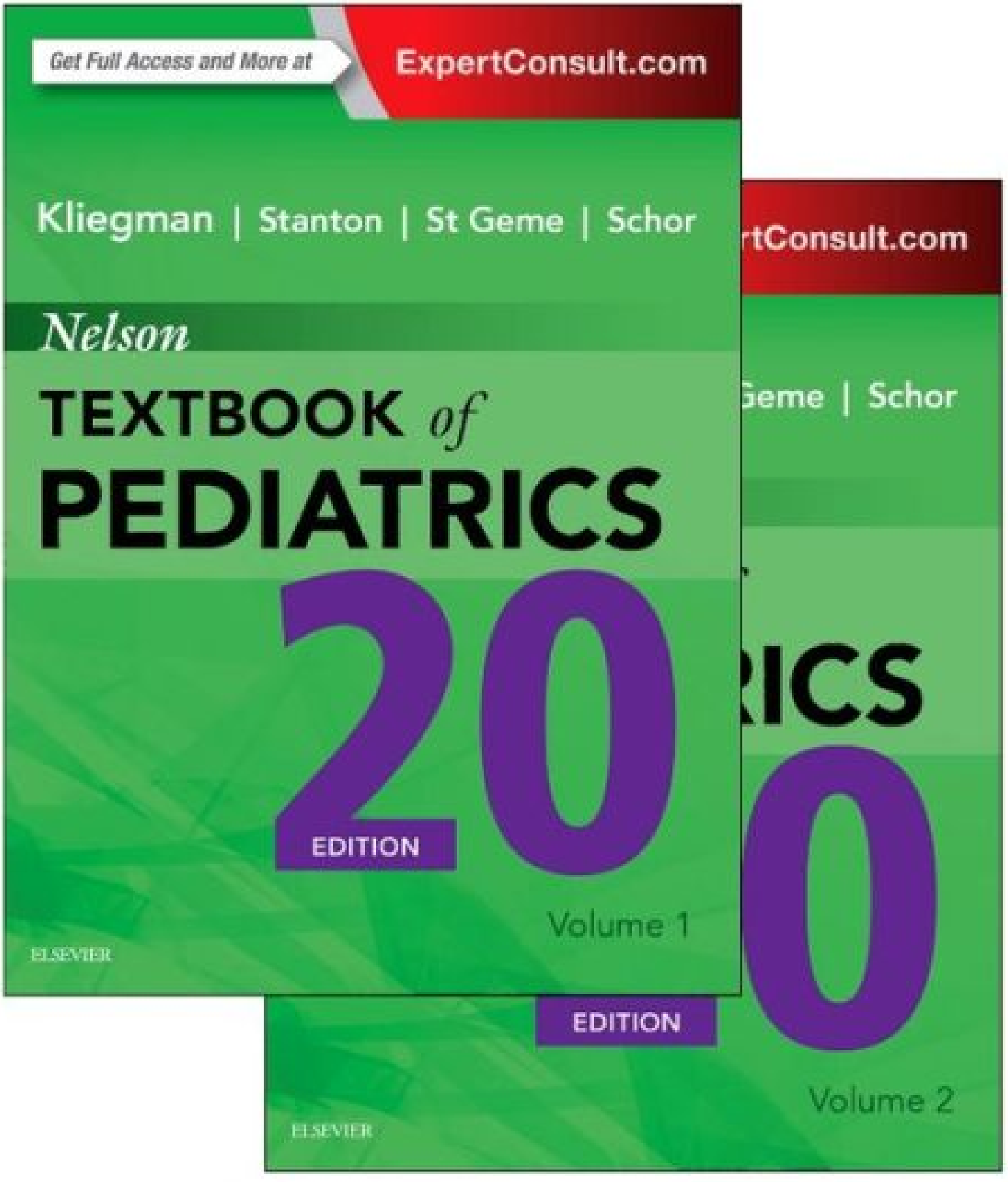
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To the Child's Physician and especially to those who through their expressed confidence in past editions of this book have provided the stimulus for this revision.
Waldo E. Nelson, 9/e, 1969

This is as true in 2015 as it was in 1969.
R.M. Kliegman, 20/e, 2015

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Pediatric Emergencies and Resuscitation
Shock

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Physiology of Puberty
Disorders of Pubertal Development

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Defects in Metabolism of Carbohydrates

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Rickets Associated with Renal Tubular Acidosis
Bone Structure, Growth, and Hormonal Regulation
Primary Chondrodystrophy (Metaphyseal Dysplasia)
Hypophosphatasia
Hyperphosphatasia
Osteoporosis

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Anxiety Disorders

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Morphology of the Skin
Evaluation of the Patient
Eczematous Disorders
Photosensitivity
Diseases of the Epidermis

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Ocular Allergies
Adverse Reactions to Drugs

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Development of the Hematopoietic System

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Superior Mesenteric Artery Syndrome (Wilkie Syndrome, Cast Syndrome, Arteriomesenteric Duodenal Compression Syndrome)
Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions

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Infection Prevention and Control
Other Anaerobic Infections

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Respiratory Distress and Failure
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Shigella
Escherichia coli

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Wheezing, Bronchiolitis, and Bronchitis

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Neutrophils
Disorders of Phagocyte Function

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Care of Abrasions and Minor Lacerations

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Clostridium difficile *Infection*

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Principles of Antifungal Therapy

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Ankylosing Spondylitis and Other Spondyloarthritides
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Diffuse Lung Diseases in Childhood

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Aspiration Syndromes
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Sports-Related Traumatic Brain Injury (Concussion)
Cervical Spinal Injuries

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Arthrogryposis

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Vulvovaginal and Müllerian Anomalies

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Childhood Asthma

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Respiratory Syncytial Virus
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Peptic Ulcer Disease in Children

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Autoimmune Encephalitis

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Neisseria gonorrhoeae (*Gonococcus*)

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The Foot and Toes
Leg-Length Discrepancy
Arthrogryposis

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Chancroid (Haemophilus ducreyi)
Syphilis (Treponema pallidum)
Nonvenereal Treponemal Infections
Leptospira
Relapsing Fever (Borrelia)

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Neoplasms of the Kidney

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Acute Care of the Victim of Multiple Trauma

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Hemoglobinopathies

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Assessment and Interviewing
Psychological Treatment of Children and Adolescents
Psychopharmacology
Psychotherapy
Psychiatric Hospitalization
Somatic Symptom and Related Disorders
Rumination and Pica
Motor Disorders and Habits
Mood Disorders
Suicide and Attempted Suicide
Disruptive, Impulse-Control, and Conduct Disorders
Autism Spectrum Disorder
Childhood Psychoses

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Coronaviruses

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Ascariasis (Ascaris lumbricoides)
Trichuriasis (Trichuris trichiura)
Enterobiasis (Enterobius vermicularis)
Strongyloidiasis (Strongyloides stercoralis)
Lymphatic Filariasis (Brugia malayi, Brugia timori, *and* Wuchereria bancrofti)
Other Tissue Nematodes
Toxocariasis (Visceral and Ocular Larva Migrans)
Trichinosis (Trichinella spiralis)

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Lipidoses (Lysosomal Storage Disorders)
Mucolipidoses
Disorders of Glycoprotein Degradation and Structure
The Porphyrias

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Liver and Biliary Disorders Causing Malabsorption

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Intestinal Transplantation in Children with Intestinal Failure

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Morphology of the Skin
Evaluation of the Patient
Eczematous Disorders
Photosensitivity
Diseases of the Epidermis

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Marfan Syndrome

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Tumors of the Digestive Tract

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Development and Function of the Gonads
Hypofunction of the Testes
Pseudoprecocity Resulting from Tumors of the Testes
Gynecomastia
Hypofunction of the Ovaries
Pseudoprecocity Resulting from Lesions of the Ovary
Disorders of Sex Development

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Growth and Development
Evaluation of the Child
The Hip
Common Fractures

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Marfan Syndrome

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Hormones and Peptides of Calcium Homeostasis and Bone Metabolism
Hypoparathyroidism
Pseudohypoparathyroidism (Albright Hereditary Osteodystrophy)
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Principles of Therapy (Skin)
Hyperpigmented Lesions
Diseases of Subcutaneous Tissue
Disorders of the Mucous Membranes
Cutaneous Bacterial Infections
Cutaneous Fungal Infections
Cutaneous Viral Infections
Arthropod Bites and Infestations

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The Inherited Pancytopenias

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Abused and Neglected Children

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Spotted Fever Group Rickettsioses
Scrub Typhus (Orientia tsutsugamushi)
Typhus Group Rickettsioses
Ehrlichioses and Anaplasmosis
Q Fever (Coxiella burnetii)

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Deformational Plagiocephaly

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Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

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Treatment of Rheumatic Diseases

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Vesicoureteral Reflux
Obstruction of the Urinary Tract
Anomalies of the Bladder
Neuropathic Bladder
Enuresis and Voiding Dysfunction
Anomalies of the Penis and Urethra
Disorders and Anomalies of the Scrotal Contents
Trauma to the Genitourinary Tract
Urinary Lithiasis

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Assessment of Fetal Growth and Development
The First Year
The Second Year
The Preschool Years
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Principles of Treatment (Cancer and Benign Tumors)
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Biologic Effects of Radiation on Children

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Overweight and Obesity

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Hypopigmented Lesions
Diseases of the Dermis
Acne

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Polycystic Ovary Syndrome and Hirsutism

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Deformational Plagiocephaly

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Wheezing, Bronchiolitis, and Bronchitis

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Cognitive Development: Domains and Theories

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Other Malabsorptive Syndromes

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Cystic Fibrosis

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Infections in Immunocompromised Persons

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Diagnostic Approach to Respiratory Disease
Chronic or Recurrent Respiratory Symptoms
Pulmonary Edema

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Rickets and Hypervitaminosis D
Vitamin E Deficiency
Vitamin K Deficiency
Micronutrient Mineral Deficiencies
Electrolyte and Acid-Base Disorders
Maintenance and Replacement Therapy
Deficit Therapy
Fluid and Electrolyte Treatment of Specific Disorders

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Chronic or Recurrent Respiratory Symptoms

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Abnormal Hemoglobins Causing Cyanosis
Hereditary Methemoglobinemia
Hereditary Methemoglobinemia with Deficiency of NADH Cytochrome B5 Reductase

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Vulvovaginal and Müllerian Anomalies

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Childhood-Onset Fluency Disorder: Dysfluency (Stuttering, Stammering)

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Nutritional Requirements
Feeding Healthy Infants, Children, and Adolescents

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Injury Control

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Chronic Diarrhea

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Miscellaneous Conditions Associated with Arthritis

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Hereditary Stomatocytosis
Glucose-6-Phosphate Dehydrogenase Deficiency and Related Deficiencies

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Diagnostic Approach to Respiratory Disease

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Congenital Disorders of the Nose
Acquired Disorders of the Nose
Nasal Polyps
General Considerations and Evaluation (Ear)
Hearing Loss
Congenital Malformations
External Otitis (Otitis Externa)
The Inner Ear and Diseases of the Bony Labyrinth
Traumatic Injuries of the Ear and Temporal Bone
Tumors of the Ear and Temporal Bone

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Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

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Arboviral Infections in North America
Arboviral Infections Outside North America
Dengue Fever and Dengue Hemorrhagic Fever
Yellow Fever
Ebola and Other Viral Hemorrhagic Fevers
Hantavirus Pulmonary Syndrome

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Chlamydia (Chlamydophila) pneumoniae
Chlamydia trachomatis
Psittacosis (Chlamydia psittaci)

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Diffuse Lung Diseases in Childhood

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Seizures in Childhood

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Disorders of Purine and Pyrimidine Metabolism

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Pediatric Emergencies and Resuscitation

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Non–Group A or B Streptococci
Enterococcus

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Cholestasis

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Tuberculosis (Mycobacterium tuberculosis)

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Sudden Infant Death Syndrome

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General Considerations (Bone and Joint Disorders)
Disorders Involving Cartilage Matrix Proteins
Disorders Involving Transmembrane Receptors
Disorders Involving Ion Transporters
Disorders Involving Transcription Factors
Disorders Involving Defective Bone Resorption
Disorders for Which Defects Are Poorly Understood or Unknown

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Sinusitis
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Campylobacter
Yersinia
Aeromonas *and* Plesiomonas

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Gonadal and Germ Cell Neoplasms
Neoplasms of the Liver
Benign Vascular Tumors
Melanoma
Nasopharyngeal Carcinoma
Adenocarcinoma of the Colon and Rectum
Desmoplastic Small Round Cell Tumor

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Congenital Anomalies of the Larynx, Trachea, and Bronchi
Foreign Bodies in the Airway
Laryngotracheal Stenosis and Subglottic Stenosis
Neoplasms of the Larynx, Trachea, and Bronchi

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Transitioning to Adult Care
The Breast

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The Acquired Pancytopenias

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The Hip

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General Considerations (Bone and Joint Disorders)
Disorders Involving Cartilage Matrix Proteins
Disorders Involving Transmembrane Receptors
Disorders Involving Ion Transporters
Disorders Involving Transcription Factors
Disorders Involving Defective Bone Resorption
Disorders for Which Defects Are Poorly Understood or Unknown

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Hookworms (Necator americanus *and* Ancylostoma *spp.)*

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Liver Transplantation

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Thyroid Development and Physiology
Defects of Thyroxine-Binding Globulin
Hypothyroidism
Thyroiditis
Goiter
Hyperthyroidism
Carcinoma of the Thyroid

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Polycystic Ovary Syndrome and Hirsutism

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Neoplasms of the Kidney

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Growth and Development (Eye)
Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections
Injuries to the Eye

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Gonadal and Germ Cell Neoplasms
Adenocarcinoma of the Colon and Rectum

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Principles of Therapy (Skin)

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Pyloric Stenosis and Other Congenital Anomalies of the Stomach

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Morphogenesis of the Liver and Biliary System

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Somatic Symptom and Related Disorders

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Mitochondrial Hepatopathies

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Nocardia
Tularemia (Francisella tularensis)
Brucella

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Chronic Fatigue Syndrome
Epstein-Barr Virus
Human T-Lymphotropic Viruses (1 and 2)

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Disorders of Lipoprotein Metabolism and Transport

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Congenital Anomalies of the Central Nervous System
Encephalopathies

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Monocytes, Macrophages, and Dendritic Cells
The Complement System
Disorders of the Complement System

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Vesiculobullous Disorders
Nutritional Dermatoses

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Hyperpigmented Lesions
Cutaneous Bacterial Infections
Cutaneous Fungal Infections
Cutaneous Viral Infections
Arthropod Bites and Infestations

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Fever
Fever Without a Focus

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Hypofunction of the Ovaries
Pseudoprecocity Resulting from Lesions of the Ovary

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Ascariasis (Ascaris lumbricoides)
Trichuriasis (Trichuris trichiura)
Enterobiasis (Enterobius vermicularis)
Strongyloidiasis (Strongyloides stercoralis)
Lymphatic Filariasis (Brugia malayi, Brugia timori, *and* Wuchereria bancrofti)
Other Tissue Nematodes
Toxocariasis (Visceral and Ocular Larva Migrans)
Trichinosis (Trichinella spiralis)

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Congenital Disorders of the Nose
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General Considerations and Evaluation (Ear)
Hearing Loss
Congenital Malformations
External Otitis (Otitis Externa)
The Inner Ear and Diseases of the Bony Labyrinth
Traumatic Injuries of the Ear and Temporal Bone
Tumors of the Ear and Temporal Bone

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Foreign Bodies and Bezoars

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Complementary Therapies and Integrative Medicine

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Malrotation
Meckel Diverticulum and Other Remnants of the Omphalomesenteric Duct
Intussusception
Malformations
Ascites

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Effects of War on Children

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Otitis Media

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Embryology, Anatomy, and Function of the Esophagus
Congenital Anomalies: Esophageal Atresia and Tracheoesophageal Fistula
Obstructing and Motility Disorders of the Esophagus
Dysmotility
Hiatal Hernia
Gastroesophageal Reflux Disease
Eosinophilic Esophagitis and Non–Gastroesophageal Reflux Disease Esophagitis
Esophageal Perforation
Esophageal Varices
Ingestions

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Diagnosis of Allergic Disease
Principles of Treatment of Allergic Disease

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Acute Care of the Victim of Multiple Trauma

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Blastomycosis (Blastomyces dermatitidis)

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Surgical Conditions of the Anus and Rectum

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Refeeding Syndrome
Liver Abscess
Generalized Arterial Calcification of Infancy/ Idiopathic Infantile Arterial Calcification
Arterial Calcifications Caused by Deficiency of CD73
Female Genital Mutilation/Cutting
Reflex Seizures (Stimulus Precipitated Seizures)
Nodding Syndrome

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Chlamydia (Chlamydophila) pneumoniae
Psittacosis (Chlamydia psittaci)

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Poisoning

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Severe Traumatic Brain Injury

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Yale School of Medicine
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Babesiosis (Babesia)

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Eating Disorders

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Brain Tumors in Childhood

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Neurodegenerative Disorders of Childhood

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Group B Streptococcus

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Children's National Medical Center
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Histiocytosis Syndromes of Childhood

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Thyroid Development and Physiology
Defects of Thyroxine-Binding Globulin
Hypothyroidism
Thyroiditis
Goiter
Hyperthyroidism
Carcinoma of the Thyroid

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Pulmonary Abscess

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Systemic Hypertension

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Ethel H. Wise Professor and Chair, Department of Preventive Medicine
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Chemical Pollutants

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Epidemiology and Prevention of Injuries
Heat Injuries
Female Athletes: Menstrual Problems and the Risk of Osteopenia
Performance-Enhancing Aids

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Varicella-Zoster Virus Infections

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The Knee

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Integration of Genetics into Pediatric Practice
The Genetic Approach in Pediatric Medicine
The Human Genome
Patterns of Genetic Transmission
Cytogenetics
Genetics of Common Disorders

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Brain Death

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Neurologic Evaluation
Chorea, Athetosis, Tremor

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Evaluation of Children with Suspected Intestinal Malabsorption
Enzyme Deficiencies

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The Anemias
Congenital Hypoplastic Anemia (Diamond-Blackfan Anemia)
Pearson Syndrome
Acquired Pure Red Blood Cell Anemia
Anemia of Chronic Disease and Renal Disease
Congenital Dyserythropoietic Anemias
Physiologic Anemia of Infancy
Megaloblastic Anemias

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Bronchopulmonary Dysplasia

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Atopic Dermatitis (Atopic Eczema)

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Normal Digestive Tract Phenomena
Major Symptoms and Signs of Digestive Tract Disorders
Normal Development, Structure, and Function (Stomach)
Pyloric Stenosis and Other Congenital Anomalies of the Stomach
Intestinal Atresia, Stenosis, and Malrotation
Intestinal Duplications, Meckel Diverticulum, and Other Remnants of the Omphalomesenteric Duct
Motility Disorders and Hirschsprung Disease
Ileus, Adhesions, Intussusception, and Closed-Loop Obstructions
Foreign Bodies and Bezoars
Functional Abdominal Pain (Nonorganic Chronic Abdominal Pain)
Malformations
Ascites
Peritonitis

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Growth and Development (Eye)
Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections
Injuries to the Eye

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Laboratory Testing in Infants and Children
Reference Intervals for Laboratory Tests and Procedures

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Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation
Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors
Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease
Infectious Complications of Hematopoietic Stem Cell Transplantation
Late Effects of Hematopoietic Stem Cell Transplantation

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Pertussis (Bordetella pertussis *and* Bordetella parapertussis)

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*Pertussis (*Bordetella pertussis *and* Bordetella parapertussis*)*
Pleurisy, Pleural Effusions, and Empyema
Pneumothorax
Hemothorax
Chlyothorax

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Principles of Drug Therapy

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Neoplasms and Adolescent Screening for Human Papillomavirus

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Diaphragmatic Hernia
Foramen of Morgagni Hernia
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Eventration
Digestive System Disorders
Blood Disorders

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Diabetes Insipidus
Other Abnormalities of Arginine Vasopressin Metabolism and Action

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Genetic Approaches to Rare and Undiagnosed Diseases

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Lead Poisoning

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Developmental-Behavioral Screening and Surveillance

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Medical Evaluation of Immigrant (Foreign-Born) Children for Infectious Diseases
Principles of Antimycobacterial Therapy

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Diseases of the Neonate
Cutaneous Defects
Ectodermal Dysplasias
Vascular Disorders
Cutaneous Nevi
Disorders of Keratinization
Disorders of the Sweat Glands
Disorders of Hair
Disorders of the Nails
Tumors of the Skin

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Measles
Rubella
Mumps

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Mechanical Ventilation

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University of Houston
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Aspartic Acid (Canavan Disease)

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Aspartic Acid (Canavan Disease)

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Central Nervous System Infections
Brain Abscess

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Pulmonary Edema

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Loss, Separation, and Bereavement

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Pulmonary Tumors
Extrapulmonary Diseases with Pulmonary Manifestations

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Lipidoses (Lysosomal Storage Disorders)
Mucolipidoses
Disorders of Glycoprotein Degradation and Structure

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Failure to Thrive

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Hansen Disease (Mycobacterium leprae)
Mycoplasma pneumoniae
Genital Mycoplasmas (Mycoplasma hominis, Mycoplasma genitalium, *and* Ureaplasma urealyticum)

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Bleeding
Breast Concerns
Neoplasms and Adolescent Screening for Human Papillomavirus

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Seizures in Childhood
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Rhinoviruses

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The Spine

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Campylobacter
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Listeria monocytogenes
Pseudomonas, Burkholderia, *and* Stenotrophomonas

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Neurodevelopmental Function and Dysfunction in the School-Age Child

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Disorders of Lipoprotein Metabolism and Transport

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Birth Brachial Plexus Palsy

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Demyelinating Disorders of the Central Nervous System

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Leukopenia
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Fever
Fever Without a Focus

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Altitude-Associated Illness in Children (Acute Mountain Sickness)

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Diffuse Lung Diseases in Childhood

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Serum Sickness
Food Allergy and Adverse Reactions to Foods

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Nonvenereal Treponemal Infections
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Conditions That Mimic Seizures

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Growth and Development (Eye)
Examination of the Eye
Abnormalities of Refraction and Accommodation
Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
Childhood Glaucoma
Orbital Abnormalities
Orbital Infections
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Amyloidosis

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Embryology, Anatomy, and Function of the Esophagus
Congenital Anomalies: Esophageal Atresia and Tracheoesophageal Fistula
Obstructing and Motility Disorders of the Esophagus
Dysmotility
Hiatal Hernia
Gastroesophageal Reflux Disease
Eosinophilic Esophagitis and Non–Gastroesophageal Reflux Disease Esophagitis
Esophageal Perforation
Esophageal Varices
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Hemolytic Anemias Resulting from Extracellular Factors—Immune Hemolytic Anemias

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Lower Urinary Tract Causes of Hematuria
Introduction to the Child with Proteinuria
Fixed Proteinuria
Nephrotic Syndrome
Cortical Necrosis

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Introduction to Glomerular Diseases
Clinical Evaluation of the Child with Hematuria
Isolated Glomerular Diseases with Recurrent Gross Hematuria
Glomerulonephritis Associated with Infections
Glomerulonephritis Associated with Systemic Lupus Erythematosus

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Nutritional Requirements
Feeding Healthy Infants, Children, and Adolescents

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Hormones of the Hypothalamus and Pituitary
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Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
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Disorders of Vision
Abnormalities of Pupil and Iris
Disorders of Eye Movement and Alignment
Abnormalities of the Lids
Disorders of the Lacrimal System
Disorders of the Conjunctiva
Abnormalities of the Cornea
Abnormalities of the Lens
Disorders of the Uveal Tract
Disorders of the Retina and Vitreous
Abnormalities of the Optic Nerve
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Cleft Lip and Palate
Syndromes with Oral Manifestations
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Dental Trauma
Common Lesions of the Oral Soft Tissues
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Preface

Whoever saves one life it is considered as if they saved an entire world.
— Babylonian Talmud

The 20th edition of *Nelson Textbook of Pediatrics* continues in its tradition of being an essential resource for pediatricians as they diagnose and treat the infants, children, and adolescents of the 21st century. The 20th edition has been thoroughly revised, updated, and edited to keep up with the growing data accumulated from basic, clinical, and population-based research. The promise that translational medicine will improve the lives of all children is greater than ever. Knowledge of human development, behavior, and diseases from the molecular to sociologic levels is increasing at fantastic rates, leading to greater understanding of health and illness in children and substantial improvements in health quality for those who have access to health care. These exciting scientific advances also provide hope to effectively address prevention and treatment of new and emerging diseases threatening children and their families.

The field of pediatrics encompasses advocacy for all children throughout the world and must address societal inequalities of important resources required for normal development, as well as protection from natural and manmade disasters. Unfortunately, many children throughout the world have not benefited from the significant advances in the prevention and treatment of health-related problems, primarily because of a lack of political will and misplaced priorities. For our increasing knowledge to benefit all children and youth, medical advances and good clinical practice must always be coupled with effective advocacy.

This new edition of *Nelson Textbook of Pediatrics* attempts to provide the essential information that practitioners, house staff, medical students, and other care providers involved in pediatric health care throughout the world need to understand to effectively address the enormous range of biologic, psychologic, and social problems that our children and youth may face. Our goal is to be comprehensive yet concise and reader friendly, embracing both the new advances in clinical science and the time-honored art of pediatric practice.

The 20th edition is reorganized and revised from the previous edition. There are many additions of new diseases and new chapters, as well as substantial expansion or significant modification of others. In addition many more tables, photographs, imaging studies, and illustrative figures, as well as up-to-date references, have been added. Although, to an ill child and his or her family and physician, even the rarest disorder is of central importance, all health problems cannot possibly be covered with the same degree of detail in one general textbook of pediatrics. Thus, leading articles and subspecialty texts are referenced and should be consulted when more information is desired.

The outstanding value of the 20th edition of the textbook is due to its expert and authoritative contributors. We are all indebted to these dedicated authors for their hard work, knowledge, thoughtfulness, and good judgment. Our sincere appreciation also goes to Kate Dimock and Jennifer Shreiner at Elsevier and to Carolyn Redman at the Pediatric Department of the Medical College of Wisconsin. In addition, we thank Barbara Ruggeri for her excellent library science skills and for keeping us up to date with the literature. We have all worked hard to produce an edition that will be helpful to those who provide care for children and youth and to those desiring to know more about children's health worldwide.

In this edition we have had informal assistance from many faculty and house staff of the departments of pediatrics at the Medical College of Wisconsin, Wayne State University School of Medicine, University of Pennsylvania School of Medicine, and University of Rochester School of Medicine. The help of these individuals and of the many practicing pediatricians from around the world who have taken the time to offer thoughtful feedback and suggestions is always greatly appreciated and helpful.

Last and certainly not least, we especially wish to thank our families for their patience and understanding, without which this textbook would not have been possible.

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VIDEOS

Video **304-1** Live *Echinococcus granulosus* protoscole,

Video **598-1** Severely limited level of consciousness and movement disorder in a patient with anti-NMDAR encephalitis after herpes simplex encephalitis

Video **598-2** Improved level of consciousness in patient shown in Video 598-1 following immunotherapy

Video **598-3** Intact cognition in patient shown in Videos 598-1 and 598-2 after immunotherapy and prolonged follow-up

Nelson TEXTBOOK *of* PEDIATRICS

The Field of Pediatrics

PART I

Chapter 1

Overview of Pediatrics

Bonita F. Stanton and Richard E. Behrman

Pediatrics is the only discipline dedicated to all aspects of the well-being of infants, children, and adolescents, including their health; their physical, mental, and psychologic growth and development; and their opportunity to achieve full potential as adults. Pediatricians must be concerned not only with particular organ systems and biologic processes, but also with environmental, social, and political influences, which have a major impact on the health and well-being of children and their families.

Children cannot advocate for themselves. As the professionals whose entire purpose is to advance the well-being of children, pediatricians must be advocates for the individual child and for all children, irrespective of culture, religion, gender, race, or ethnicity or of local, state, or national boundaries. The more politically, economically, or socially disenfranchised a population or a nation is, the greater the need for advocacy for children. The young are often among the most vulnerable or disadvantaged in society and thus their needs require special attention. As divides between nations blur through modern transportation, communication and economics, through global climate change, through contemporary means of warfare, and through uneven development within and across countries, a global, rather than a national, perspective for the field of pediatrics becomes both a reality and a necessity. The interrelation of health issues across the globe has achieved widespread recognition in the wake of the SARS (severe acute respiratory syndrome) and AIDS epidemics, expansions in the pandemics of cholera and West Nile virus, war and bioterrorism, the tsunami of 2004, the global recession beginning in 2008, the "Arab Spring" beginning in 2010, and the growing severity of hurricanes and cyclones.

More than a century ago, pediatrics emerged as a medical specialty in response to increasing awareness that the health problems of children differ from those of adults and that a child's response to illness and stress varies with age. In 1959, the United Nations issued the Declaration of the Rights of the Child, articulating the universal presumption that children everywhere have fundamental needs and rights.

VITAL STATISTICS ABOUT CHILD HEALTH
(See Also Chapter 1.1)

From 1990 to 2010, the world population grew at an annual rate of 1.3% per yr, down from 1.8% annually during the prior 20 yr. The annual growth rate from 2010 to 2030 is expected to further decline to 0.9%. Worldwide, children younger than age 18 yr account for 2.2 billion (30%) of the world's 7.02 billion persons. In 2010, there were an estimated 135 million births worldwide, 121 million (90%) of which were in developing countries. India, with 27.2 million births annually, is home to the largest number, followed by China at 16.5 million.

Despite global interconnectedness, the health problems of children and youth vary widely between and within populations in the nations of the world depending on a number of often interrelated factors. These factors include (1) economic considerations (economic disparities); (2) educational, social, and cultural considerations; (3) the prevalence and ecology of infectious agents and their hosts; (4) climate and geography; (5) agricultural resources and practices (nutritional resources); (6) stage of industrialization and urbanization; (7) the gene frequencies for some disorders; (8) the health and social welfare infrastructure available within these countries; and (9) political focus and stability. The state of health of any community is defined by the incidence of illness and by data from studies that show the changes that occur with time and in response to programs of prevention, case finding, therapy, and surveillance. To ensure that the needs of children and adults across the globe were not obscured by local needs, in 2000 the international community established 8 Millennium Development Goals (MDGs) to be achieved by 2015 (http://www.countdown2015mnch.org). Although all 8 MDGs impact child well-being, MDG 4 ("Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate") is exclusively focused on children.

Great strides have been made toward achieving the MDGs. Globally, there has been a reduction in under-5 mortality since 1990 from 90 to 48 deaths per 1,000 live births, with a reduction from 15 to 6 deaths in developed countries and from 99 to 53 deaths in developing countries. With the exception of sub-Saharan Africa and Oceania, all global regions reduced their under-5 mortality rate by more than half from 1990 to 2012. There were nearly 13 million under-5 deaths in 1990; 2006 marked the first year that there were fewer than 10 million deaths (9.7 million), which further decreased to 9.0 million in 2007, 8.8 million in 2008, 7.6 million in 2010, and 6.6 million in 2012. Despite these substantial successes, the annual rate of reduction in the global under-5 mortality rate of 3.9% remains below the MDG targeted rate of 4.4%, necessary to achieve the goal of a ⅔ reduction in the 1990 rate by 2015 (Fig. 1-1).

The infant mortality rate (deaths of children <1 yr) accounts for 83% of the under-5 mortality rate in industrialized countries, but only 64% of the rate in the least-developed nations. Neonatal (<1 mo) death contributes substantially to the under-5 mortality rate, growing in proportion as the under-5 death rate decreases. The neonatal mortality rate has been slower to decline. Globally, the neonatal mortality rate of 23 per 1,000 live births represents 57% of the infant mortality rate of 40 per 1,000 live births and 40% of the under-5 death rate (up from 37% in 1990). The neonatal mortality rate is responsible for 50% of the under-5 mortality rate in industrialized nations, 40% of the rate in developing countries, but only 33% in the least-developed countries. Most of the decline in infant mortality in the United States and other industrialized countries since 1970 is attributable to a decrease in the birthweight-specific infant mortality rate related to neonatal intensive care, not to the prevention of low-birthweight births (see Chapter 93).

Across the globe, there are significant variations in infant mortality rates by nation, by region, by economic status, and by level of industrial development, the categorizations employed by the World Bank and the United Nations (Table 1-1; see also Figs. 1-8 and 1-9). As of 2012 three nations in the world still have an under-5 mortality rate of ≥150 per 1,000 live births (Sierra Leone, 182; Angola, 164, Chad, 150), with an additional 13 nations having ≥100 deaths per 1,000 live births. Although these 3 nations are among the poorest in the world, many of their economic matches have enjoyed greater improvements in child survival in recent years, demonstrating that economics are important but that other factors, such as political will, are also important. Similarly, in 2012, the United States, with one of the 10 highest gross national incomes in the world, had an under-5 mortality rate of 7 per 1,000 live births; 39 nations had lower under-5 mortality rates, with 9 countries having a rate of 3 and 2 countries having a rate of 2 per 1,000 live births.

Causes of under-5 mortality differ markedly between developed and developing nations. In developing countries, 66% of all deaths resulted from infectious and parasitic diseases. Among the 42 countries having

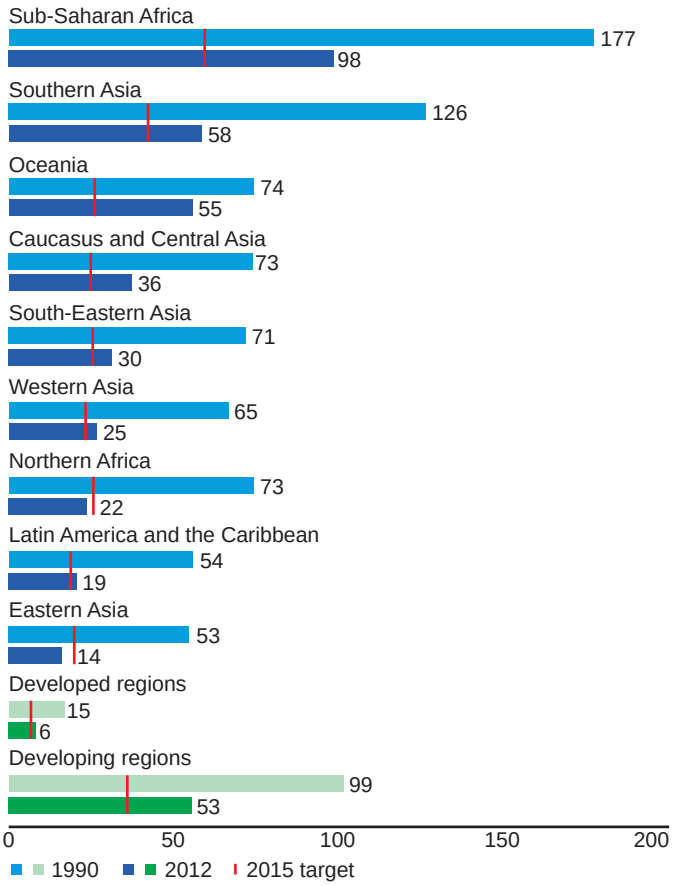


Figure 1-1 Despite substantial progress, the world is still falling short of the MDG child mortality target. Under-5 mortality rate per 1,000 live births, 1990 and 2012 (deaths per 1,000 live births). *(From* Millennium Development Goals Report, 2014. *New York, 2014, United Nations, p. 24.)*

90% of childhood deaths, diarrheal disease accounted for 22% of deaths, pneumonia 21%, malaria 9%, AIDS 3%, and measles 1%. Neonatal causes contributed to 33%. The contribution for AIDS varies greatly by country, being responsible for a substantial proportion of deaths in some countries and negligible amounts in others. Likewise, there is substantial co-occurrence of infections; a child may die with HIV, malaria, measles, and pneumonia. Infectious diseases are still responsible for much of the mortality in developing countries. In the United States, pneumonia (and influenza) accounted for only 2% of under-5 deaths, with only negligible contributions from diarrhea and malaria. Unintentional injury is the most common cause of death among U.S. children ages 1-4 yr, accounting for approximately 33% of deaths, followed by congenital anomalies (11%), homicides (9%), and malignant neoplasms (8%). Other causes accounted for <5% of total mortality within this age group (Table 1-2). Although unintentional injuries in developing countries are proportionately less important causes of mortality than in developed countries, their absolute rates and their contributions to morbidity are substantially greater.

Just as economic status of a country as a whole is closely correlated with child survival, so too is relative wealth within a country. Poorer children in nations worldwide have higher death rates than their wealthier national counterparts (Fig. 1-2).

Causes of death vary by developmental status of the nation. In the United States, the 3 leading causes of death among infants were congenital anomalies, disorders related to gestation and low birthweight, and sudden infant death (see Table 1-2). By contrast, in developing countries, the majority of infant deaths are caused by infectious diseases; even in the neonatal period, 24% of deaths are caused by severe infections and 7% by tetanus. Although immunization rates remain higher in industrialized nations compared to developing nations, this gap is closing. In 2010, immunization percentage rates against diphtheria, pertussis, tetanus, measles, and polio were in the mid-90s; comparable levels in developing countries were in the mid-80s, with rates in the least-developed countries very close. In developing countries, 29% of neonatal deaths are caused by birth asphyxia and 24% are caused by complications of prematurity.

A consistently robust predictor of infant mortality across the globe is a poor level of maternal education (consequently, another of the MDGs addresses the need for universal access to schooling for girls; Fig. 1-3). Other maternal risk characteristics, such as unmarried status, adolescence, and high parity, correlate with increased risk of postneonatal mortality and morbidity and low birthweight.

Table 1-1 Child Health Indicators Worldwide by Region

	Mortality Rate by Yr Per 1,000 Live Births					GROSS NATIONAL PER CAPITA INCOME	LIFE EXPECTANCY AT BIRTH	PRIMARY SCHOOL ATTENDANCE
	UNDER-5		INFANT MORTALITY		NEONATAL MORTALITY			
	1990	2012	1990	2012	2012	2012	2012	2008-2011
Sub-Saharan Africa	177	98	107	64	32	$1,397	56 yr	77%
Eastern and Southern Africa	163	77	101	51	28	$1,729	59 yr	87%
West and Central Africa	195	118	115	76	37	$1,071	54 yr	68%
Middle East and North Africa	71	30	53	24	15	—	71 yr	90%
South Asia	129	60	92	47	32	$1,440	67 yr	93%
East Asia and Pacific	58	20	44	17	11	$5,592	74 yr	97%
Latin America and Caribbean	54	19	43	16	10	$9,212	75 yr	95%
CEE/CIS	47	19	38	16	9	$8,727	70 yr	96%
Least-developed countries	172	85	107	58	30	$779	61 yr	81%
World	90	48	63	35	21	$10,132	71 yr	91%

CEE/CIS, Central and Eastern Europe/Commonwealth of Independent States (formerly the USSR).
Adapted from UNICEF: The state of the world's children 2014: Statistical Table, *New York, 2012, UNICEF, Table 1, p. 35.*

Table 1-2 Leading Causes of Death and Numbers of Deaths, According to Age: United States, 2010

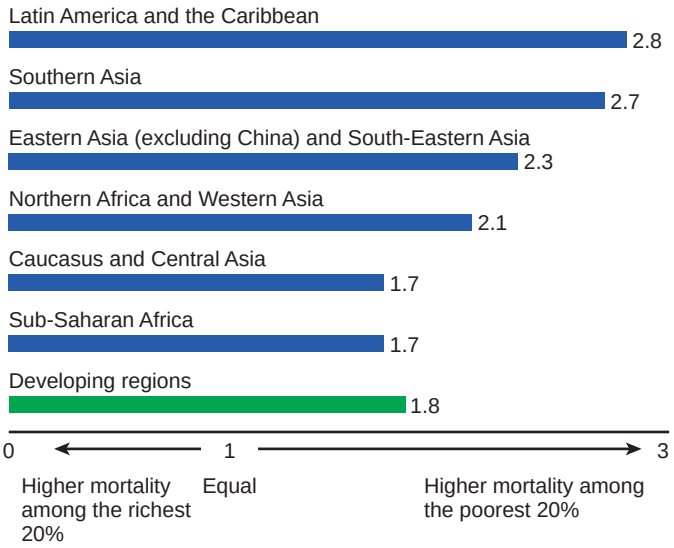
AGE AND RANK ORDER	CAUSE OF DEATH	NUMBER	PERCENT OF TOTAL DEATHS
Under 1 yr	All causes	24,586	100%
	Congenital malformations, deformations, and chromosomal abnormalities	5,107	21%
	Disorders related to short gestation and low birthweight, not elsewhere classified	4,148	17%
	Sudden infant death syndrome	2,063	8%
	Newborn affected by maternal complications of pregnancy	1,561	6%
	Unintentional injuries	1,110	5%
	Newborn affected by complications of placenta, cord, and membranes	1,030	4%
	Bacterial sepsis of newborn	583	2%
	Respiratory distress of newborn	514	2%
	Diseases of the circulatory system	507	2%
	Newborn affected by maternal complications of pregnancy	472	2%
1-4 yr	All causes	4,316	100%
	Unintentional injuries	1,394	32%
	Congenital malformations, deformations, and chromosomal abnormalities	507	12%
	Homicide	385	9%
	Malignant neoplasms	346	8%
	Diseases of heart	159	4%
	Influenza and pneumonia	91	1%
	Septicemia	62	1%
	In situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior	59	1%
	Certain conditions originating in the perinatal period	52	1%
	Chronic lower respiratory diseases	51	1%
5-14 yr	All causes	5,279	100%
	Unintentional injuries	1,643	31%
	Malignant neoplasms	916	17%
	Congenital malformations, deformations, and chromosomal abnormalities	298	6%
	Suicide	274	5%
	Homicide	261	5%
	Diseases of heart	185	4%
	Chronic lower respiratory diseases	133	3%
	Cerebrovascular diseases	90	2%
	In situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behavior	82	2%
	Influenza and pneumonia	71	1%
15-24 yr	All causes	29,551	100%
	Unintentional injuries	12,341	30%
	Homicide	4,678	16%
	Suicide	4,600	16%
	Malignant neoplasms	1,604	5%
	Diseases of heart	1,028	3%
	Congenital malformations, deformations, and chromosomal abnormalities	412	1%
	Cerebrovascular diseases	190	<1%
	Influenza and pneumonia	181	<1%
	Diabetes mellitus	165	<1%
	Pregnancy, childbirth, and the puerperium	163	<1%

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs. *Hyattsville, MD, 2014, Department of Health and Human Services, Table 23, p. 98.*

THE CHANGING PEDIATRIC WORLD

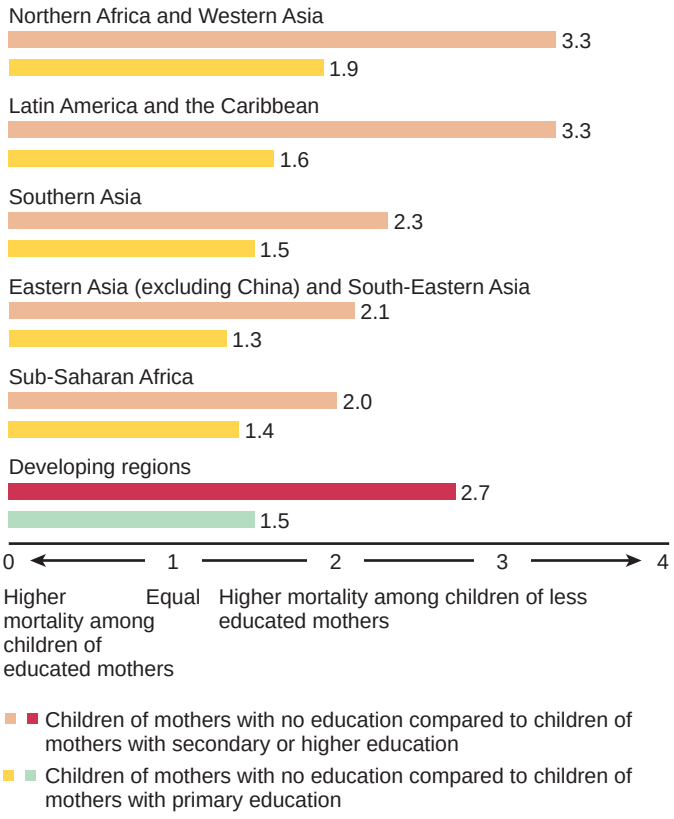
A profound improvement in child health within industrialized nations occurred in the 20th century with the introduction of antibacterial disinfectants, antibiotic agents, and vaccines. Efforts to control infectious diseases were complemented by better understanding of nutrition. In the United States, Canada, and parts of Europe, new and continuing discoveries in these areas led to establishment of public well-child clinics for low-income families. Although the timing of control of infectious disease was uneven around the globe, this focus on control was accompanied by significant decreases in morbidity and mortality in all countries. The smallpox eradication program of the 1970s resulted in the global eradication of smallpox in 1977. The introduction in the 1970s of the Expanded Program of Immunizations (universal vaccination against polio, diphtheria, measles, tuberculosis, tetanus, and pertussis) by the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) has resulted in an estimated annual reduction of 1-2 million deaths per year globally. Recognizing the importance of prevention of infectious diseases to the health of children, several countries among the 50 ranked by the World Bank as among the poorest nations (per capita income <$750/yr) have invested heavily in infectious disease control through the development of internal vaccine production capability. From 2000 to 2010, globally there was a 74% decline (with sub-Saharan Africa witnessing an 85% decline) in deaths caused by measles as a result of increased vaccination. As diarrheal diseases continued through the mid-1970s to account for ≈25% of infant and childhood deaths in developing countries (~4 million deaths per year at that time), attention turned to the development and utilization of oral resuscitation fluids to sustain children through potentially life-threatening episodes of acute diarrheal diseases. Oral rehydration solutions are largely credited with the current reduction of diarrheal deaths annually to 1.5 million. Substantial improvements have been witnessed in malaria control (global decrease of incidence by 17% and mortality rate by 25% since 2000). There have been substantial increases in the percent of households having insecticide-treated bed nets and in treatment of children with fever in endemic areas receiving antimalarial drugs.

In the later 20th century, with improved control of infectious diseases (including the elimination of polio in the Western hemisphere)



Note: Analysis is based on 73 developing countries with data on under-five mortality rate by household's wealth quintile, accounting for 71 percent of total births in developing countries in 2010.

Figure 1-2 Ratio of under-5 mortality rate for children from the poorest 20% quintile of households to children from the richest 20% of households, 2000/2010. *(From* Millennium Development Goals Report, 2012. *New York, 2012, United Nations, p. 28.)*



Note: Analysis is based on 78 developing countries with data on under-five mortality rates by mother's education, accounting for 75 percent of total births in developing countries in 2010.

Figure 1-3 Ratio of under-5 mortality rate of children of mothers with no education compared to the rate of children of mothers with higher education. *(From* Millennium Development Goals Report, 2012. *New York, 2012, United Nations, p. 28.)*

through both prevention and treatment, pediatric medicine in industrialized nations increasingly turned its attention to a broad spectrum of conditions. These included both potentially lethal conditions and temporarily or permanently handicapping conditions; among these disorders were leukemia, cystic fibrosis, diseases of the newborn infant, congenital heart disease, mental retardation, genetic defects, rheumatic diseases, renal diseases, and metabolic and endocrine disorders.

Increasing attention has also been given to behavioral and social aspects of child health, ranging from reexamination of child-rearing practices to creation of major programs aimed at prevention and management of abuse and neglect of infants and children. Developmental psychologists, child psychiatrists, neuroscientists, sociologists, anthropologists, ethnologists, and others have brought us new insights into human potential, including new views of the importance of the environmental circumstances during pregnancy, surrounding birth, and in the early years of child rearing. The later 20th century witnessed the beginning of nearly universal acceptance by pediatric professional societies of attention to normal development, child rearing, and psychosocial disorders across the continents. In the past decade, irrespective of level of industrialization, nations have developed programs addressing not only causes of mortality and physical morbidity (such as infectious diseases and protein-calorie malnutrition), but also factors leading to decreased cognition and thwarted psychosocial development, including punitive child-rearing practices (whether at home or in school) and wife abuse, child labor, undernutrition, war, and poor-quality schooling. Obesity is recognized as a major health risk not only in industrialized nations, but increasingly in transitional countries. Progress at the turn of the 21st century in unraveling the human genome offers for the first time the realization that significant genetic screening, individualized pharmacotherapy, and genetic manipulation will be a part of routine pediatric treatment and prevention practices in the future. The prevention implications of the genome project give rise to the possibility of reducing costs for the care of illness but also increase concerns about privacy issues (see Chapter 3).

Although local famines and disasters, and regional and national wars have periodically disrupted the general trend for global improvement in child health indices, it was not until the advent of the AIDS epidemic in the later 20th century that the first substantial global erosion of progress in child health outcomes occurred. This erosion resulted in ever-widening gaps between childhood health indices in sub-Saharan Africa compared to the rest of the world. From 1990 to 2002, life expectancy in sub-Saharan Africa decreased from 50 yr to 46 yr. However, as of 2008, it had returned to 52 yr and in 2012 was 56 yr. Wide distribution of effective antiretroviral therapy (Fig. 1-4), aggressive HIV prevention education, and increased access to antitubercular drugs have been important in these successes, but continued successes will require sustained international support. Despite this positive news, children with HIV remain the least-likely group to receive antiretroviral treatment. Despite these gains, diseases once confined to limited geographic niches, including West Nile virus, and diseases previously uncommon among humans, such as the avian flu virus, increased awareness of the interconnectedness of health around the world and the impact of global warming. Formerly perceived as a problem of industrialized nations, motor vehicle crashes are now recognized as a major cause of mortality in developing countries.

MORBIDITIES AMONG CHILDREN

Adequately addressing special healthcare needs is important in all countries, both to minimize loss of life and to maximize the potential of each individual.

In the United States, ≈70% of all pediatric hospital bed days are for chronic illnesses; 80% of pediatric health expenditures are for 20% of children. Approximately 14% of U.S. children have special healthcare needs, ranging from 10% to 19.8% across the 50 states and the District of Columbia. One in 5 households with children had ≥1 children with special healthcare needs (see Chapter 42). Significantly, more poor children and minority children have special healthcare needs.

Although there are numerous chronic conditions and the prevalence of these disorders vary by population, 2 of these morbidities—asthma

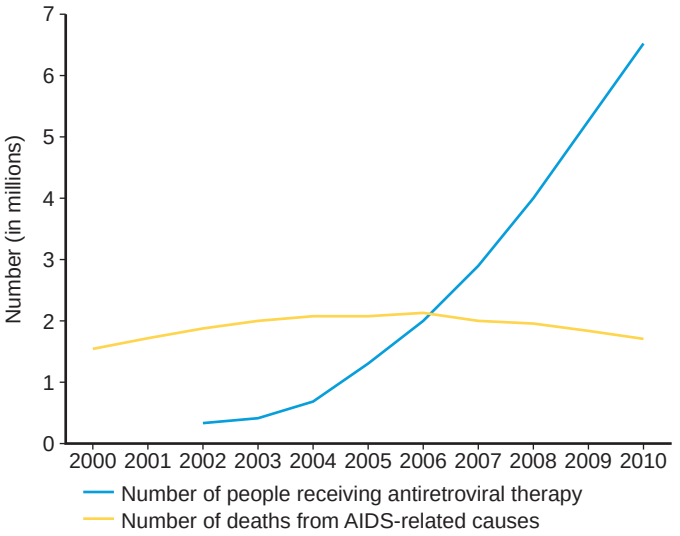


Figure 1-4 Number of persons receiving antiretroviral therapy and deaths caused by HIV over time. *(From* Millennium Development Goals Report, 2012. *New York, 2012, United Nations, p. 41.)*

and nutrition disorders—have an increasing presence worldwide and are associated with substantial health consequences and costs.

More than 80% of **asthma-related deaths** occur among children living in developing countries. The Centers for Disease Control and Prevention estimated that 10% of U.S. children have asthma, with particularly high rates among Puerto Rican and black children. Between 2001 and 2009, the prevalence of asthma increased by 50% among black children. The International Study of Asthma and Allergies in Childhood has presented evidence for a substantial global burden of childhood asthma, although rates vary substantially between and within countries. The highest annual prevalence rates are in the United Kingdom, Australia, New Zealand, and Ireland, with the lowest rates in Eastern European countries, Indonesia, China, Taiwan, India, and Ethiopia (see Chapter 144).

Chronic disorders of nutrition occur in a variety of forms. Long recognized as a major threat to child welfare, malnutrition (undernutrition) has been steadily decreasing over the past decades. Children in industrialized countries have greatly benefitted from a wide range of supplemental feeding programs (see Chapters 45 and 46); malnutrition in such nations is generally a result of selected deficiencies rather than overall undernutrition. An estimated 1% of children in the United States have some form of malnutrition. Moderate and severe malnutrition continue to impact children in developing nations. Although great progress has been made in this regard over the past several decades, children in the poorest nations and children whose families are in the lower economic quintile in a broader range of countries continue to struggle. In the period 2011–2013, 14% of children younger than age 5 yr in developing countries and 25% of those in the least-developed countries suffer from moderate/severe malnutrition; South Asia and West/Central Africa suffer from the highest rates of moderate/severe malnutrition at 42% and 23%, respectively. Rates of stunting (>2 SD below median height for age) are higher, at 29% and 41%, for children in developing and the least-developed countries, respectively (see Chapter 46).

The global epidemic of **overweight/obesity** is also significant. In the United States, 30% of children and adolescents are overweight or obese, representing a 3-fold increase over the past 30 yr. Rates of obesity for boys whose parents did not graduate from high school are 3-fold higher than those whose parents received at least a bachelor's degree; for girls, the difference is 2-fold. Similar rates have been reported from Australia and multiple countries in Europe, Egypt, Chile, Peru, and Mexico (see Chapter 47). The WHO estimates that globally 42 million children younger than the age of 5 yr are overweight; ~35 million of these live in developing countries.

Chronic cognitive morbidities represent another substantial problem. Although different diagnostic criteria have been applied, attention-deficit/hyperactivity disorder has been identified in 5-12% of children in countries across the globe, with a worldwide estimated prevalence of 5.29%. Rates exceeding 10% have been reported in the United States, New Zealand, Australia, Spain, Italy, Colombia, and Great Britain. Variations in cultural tolerance and/or differences in screening approaches or tools may account for some of the differences in prevalence of the disorder by country, but genetic and gene–environmental interactions may also play a role. Despite variations in rate, the condition is universal. Beyond the personal and familial stress caused by the disorder, costs to the educational systems are considerable. In countries where they are available, drug costs are considerable; in the United States, annual costs for drug treatments for attention-deficit/hyperactivity disorder are estimated to exceed $4 billion. In developing countries without resources for special education, these children are unlikely to fulfill their academic potential (see Chapter 33).

Mental retardation affects ≈1-3% of children in the United States, with ~80% of these children having mild retardation. Rates are several fold higher among very-low birthweight infants. In the United States, there is substantial variation in rates of mild retardation by socioeconomic status (9-fold higher in the lowest compared to the highest socioeconomic stratum), but relatively equivalent rates of severe retardation. A similar income-related distribution is found in other countries, including some of the most impoverished countries, such as Bangladesh. Lower overall rates have been reported in some countries, including countries ranging from Saudi Arabia to Sweden to China; the difference is primarily in the prevalence of mild retardation (see Chapter 36).

Posttraumatic stress disorder (PTSD) in children remains underrecognized. PTSD can follow violent attacks and witnessed violence, sexual abuse, natural disasters, motor vehicle accidents, kidnapping, and domestic violence. Female gender, prior exposure to violence, other psychologic disturbances, and low social support are also associated with its appearance after an exposure. The prevalence of childhood PTSD varies considerably around the globe, but in children with substantial exposure to violence, the rates appear to be very high. After the attacks on the World Trade Center towers and the Pentagon in 2001, 33% of U.S. children had experienced 1 or more symptoms of PTSD. The prevalence of PTSD among children and adolescents exposed to the tsunami of 2004 were 57%, 46%, 31%, 10%, and 7% 6 wk, 6 mo, 1 year, 18 mo, and 2 yr post exposure, respectively. Children hit by the waves had significantly higher rates of PTSD.

SITUATIONAL SPECIAL-RISK POPULATIONS

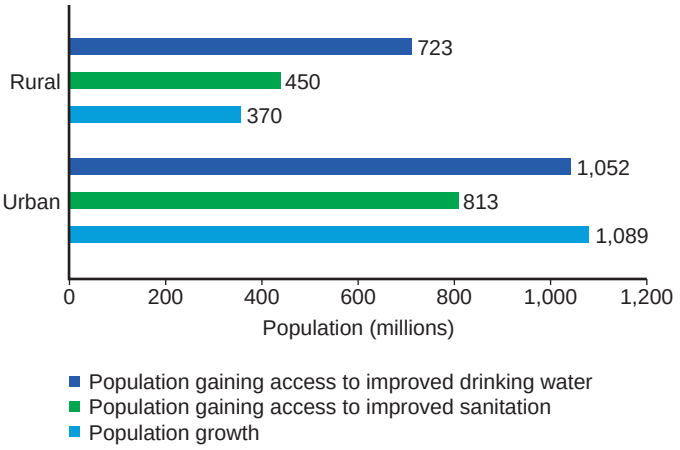
Children at situational special risk have had their futures compromised by actions or policies arising from their families, schools, communities, nations, or the international community. These problems have several causes, whether the end result is homeless children, runaway children, children in foster care, or children in other disadvantaged groups.

Children in Urban Settings

Over half of the world's population is urban dwellers. Although urban settings historically have offered educational, medical, recreational, and employment opportunities, an increasing number of urban dwellers are living in marginal communities with a growing gap in access to clean water, adequate sanitation or dependable electricity as the urban population rapidly increases (Fig. 1-5). As has been seen in Port-au-Prince, Haiti, after the devastating earthquake of 2010, national disasters exact an especially high toll on children and families living in makeshift homes on lands that are not intended for housing.

Children in Poverty

Family income is central to the health and well-being of children. Children living in poor families, especially those located in poor communities, are much more likely than children living in upper- or middle-class families to experience material deprivation and poor health, die during childhood, score lower on standardized tests, be



Source: WHO/UNICEF Joint Monitoring Programme, 2010.

Figure 1-5 In urban areas, access to improved water and sanitation is not keeping pace with population growth. *(From UNICEF,* The state of the world's children, 2012: children in an urban world, *New York, 2012, United Nations, p. 5.)*

retained in a grade or drop out of school, have out-of-wedlock births, experience violent crime, end up as poor adults, and suffer other undesirable outcomes. As of 2010, worldwide, 22% of the population lives below the international poverty line of U.S. $1.25 per capita per day; 47% of sub-Saharan and 50% of the least-developed nations live below this amount. Poverty rates are higher for children than adults and are highest for infants and toddlers. Higher in general in developing countries, within each country, the rate of infant mortality among the poorest quintile of the population is about twice that of the wealthiest quintile (see Fig. 1-2).

In the United States, from 1990 to 2000, the percentage of children <18 yr living below the poverty line had decreased from 21% to 16%. In 2010, 2 yr after the start of the recession, the rate had risen to 22%. Black and Hispanic children consistently have had higher poverty rates than Asian and white children. In 2010, 39% of black children and 35% of Hispanic children lived in poverty, compared to 14% of Asian children and 12% of white children. Sixty-six percent of black and Hispanic children compared to only 33% of Asian and 29% of white children lived below 200% of the poverty level. Children who are poor have higher-than-average rates of death and illness from almost all causes (exceptions being suicide and motor vehicle crashes, which are most common among white, nonpoor children). Many factors associated with poverty are responsible for these illnesses: crowding, poor hygiene and healthcare, poor diet, environmental pollution, poor education, and stress.

Poverty and economic loss diminish the capacity of parents to be supportive, consistent, and involved with their children. Clinicians at all times, but especially in the context of a national or global recession, need to be especially alert to the development and behavior of children whose parents have lost their jobs or who live in permanent poverty. Fathers who become unemployed frequently develop psychosomatic symptoms, and their children often develop similar symptoms. Young children who grew up in the Great Depression in the United States and whose parents were subject to acute poverty suffered more than older children, especially if the older ones were able to take on responsibilities for helping the family economically. Such responsibilities during adolescence seem to give purpose and direction to an adolescent's life. The younger children, faced with parental depression and unable to do anything to help, suffered a higher frequency of illness and a diminished capacity to lead productive lives even as adults.

The pediatric team should ask parents about their economic resources, adverse changes in their financial situation, and the family's attempts to cope. Encouraging concrete methods of coping, suggesting ways to reduce stressful social circumstances while increasing social networks that are supportive, and referring patients and their families to appropriate welfare, job training, and family agencies can significantly improve the health and functioning of children at risk when their families live in poverty. In many cases, special services, especially social services, need to be added to the traditional medical services; outreach is required to find and encourage parents to use health services and bring their children into the healthcare system. Pediatricians also have the responsibility to contribute to, and advocate for, safety net services for impoverished children within and outside the boundaries of their own country. An increasing number of programs are available to help children of greatest need worldwide, such as Project Smile, CARE, Project Hope, and Doctors Without Borders.

Children of Immigrants and Racial Minority Groups Including U.S. Native Americans

Immigrants comprise >15% of the population in >50 countries, including many Western European countries. Thirteen percent of the U.S. population is foreign-born; 24% of all children in the United States <17 yrs have immigrant parents. The United States is experiencing a wave of immigration larger than that occurring in the early 20th century. Until the mid-20th century, emigrants to the United States were primarily white and from Europe. Such individuals now represent only approximately 10% of immigrants; the remainder are overwhelmingly of color and from throughout the world, including 29% from Mexico, 5% from China, and 4% each from India and the Philippines. Although immigrants in the United States have faced discrimination and oppression throughout history, the potential for such discrimination is compounded by the racial differences represented in the current immigrant pool. In the United States, about 240,000 children legally immigrate each year, and, through 2010, an estimated 50,000/yr entered the country illegally. In recent years the number of children from Latin American countries entering illegally has greatly increased, with estimates of more than 90,000 such children entering in 2014 alone. An estimated 5.5 million children have at least 1 illegal immigrant parent; this number doubled from 2000 to 2010.

The immigrant population constitutes a substantial proportion of the low-wage labor market. Immigrants represent 16% of all U.S. workers but 20% of low-wage workers. Immigrants are twice as likely as U.S.–born citizens to earn less than minimum wage. The poverty rate of children in immigrant families is 50% greater than in U.S.–born families; over the past decade children with 2 immigrant parents consistently have a 15% greater likelihood of living below the poverty line than children in nonimmigrant families. Contributing to the lack of access to higher salaried jobs is the lack of proficiency in English (≈52% of immigrants) and the lack of education (40% have not completed high school). Immigrants account for 29% of the uninsured in the United States.

Families of different origins obviously bring different health problems and different cultural backgrounds, which influence health practices and use of medical care. To provide appropriate services, clinicians need to understand these influences (see Chapter 4). The high prevalence of hepatitis among women from Southeast Asia makes use of hepatitis B vaccine essential for their newborns. Children from Southeast Asia and South America have growth patterns that are generally below the norms established for children of Western European origin, as well as high rates of hepatitis, parasitic diseases, and nutritional deficiencies and high degrees of psychosocial stress. Foreign-born children may surpass American-born children in some health outcomes, but their health deteriorates as they become acculturated (see Chapter 4).

Refugee children who escape from war or political violence and whose families have been subjected to extreme stress represent a subset of immigrant children who have faced severe trauma. These children have a particularly high incidence of mental and behavioral problems (see Chapter 39). Armed conflicts in 2011 resulted in an especially high (4 million) number of refugees worldwide.

Linguistically isolated households, in which no one older than 14 yr of age speaks English, often present significant obstacles to providing quality healthcare to children because of difficulties in understanding and communicating basic concerns and instructions, avoiding

compromising privacy and confidentiality interests, and obtaining informed consent (see Chapter 4).

The United States is home to multiple minority populations, including the 2 largest groups, Latinos and African-Americans. The nonwhite minority groups will constitute >50% of the U.S. population by 2050. Nonwhite children in the United States disproportionately experience adverse child health outcomes (Tables 1-3 and 1-4). Infants that are born to African-American mothers experience low birthweight and infant mortality rates twice those with white mothers (see Chapter 93). Rates of these 2 adverse health outcomes are also substantially higher among some groups of Hispanic infants and children, the rates are particularly high among those of Puerto Rican descent (≈1.5 times the rates for white infants). In 2010, the overall infant mortality rate was 6.4 per 1,000 live births, whereas that for non-Hispanic African-America infants was 11.7; for Native Americans, 8.3; and Puerto Ricans, 7.1. Mexicans, Asians, Pacific Islanders, Central and South Americans, and Cubans were below the national average. Latino, Native American, and African-American children are substantially more likely to live in poverty than are white children.

There are approximately 5.1 million Native Americans (including those with mixed races/ethnicities) and 566 federally recognized tribes. The Native American population increased by 26% from 2000 to 2010 compared to a national increase of only 9.7%. Approximately 60% of Native Americans live in urban areas, not on or near native lands. Like their minority immigrant counterparts, they have faced social and economic discrimination. The unemployment and poverty levels of Native Americans are, respectively, 3-fold and 4-fold that of the white population, and far fewer Native Americans graduate from high school or go to college. The rate of low birthweight among Native Americans is more than the white rate but less than the black rate. The neonatal and the postneonatal mortality rates are higher for Native Americans living in urban areas than for urban white Americans. Deaths in the first year of life from sudden infant death syndrome, pneumonia, and influenza are higher than the average in the United States, whereas deaths as a result of congenital anomalies, respiratory distress syndrome, and disorders relating to short gestation and low birthweight are similar.

Unintended injury deaths among Native Americans occur at twice the rate for other U.S. populations; deaths caused by malignant

Table 1-3 Deaths Rates for All Causes Among Children and Young Adults According to Sex, Race, Hispanic Origin, and Age: 2010

	Deaths Per 100,000 Resident Population			
	UNDER 1 yr	1-4 yr	5-14 yr	15-24 yr
All persons	623.4	26.5	12.9	67.7
Male	680.2	29.6	14.6	97.6
Female	564.0	23.3	11.1	36.4
MALES				
White	584.3	27.4	13.8	91.8
Black male (African-American)	1206.5	42.9	19.6	142.8
American Indian or Alaska Native	542.5	34.3	18.1	116.4
Asian or Pacific Islander	434.4	19.3	8.4	43.0
Hispanic or Latino	556.8	25.0	11.4	79.4
White not Hispanic or Latino	594.4	29.3	15.0	100.8
FEMALES				
White	575.9	27.5	14.3	93.4
Black (African-American)	488.0	21.6	10.6	36.2
American Indian or Alaska Native	366.4	24.4	10.5	43.6
Asian or Pacific Islander	341.8	16.3	7.9	17.0
Hispanic or Latino	462.9	20.2	8.9	26.3
White not Hispanic or Latino	480.4	21.8	10.9	38.4

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs, *Hyattsville, MD, 2014, Department of Health and Human Services, Table 25, pp. 103–106.*

Table 1-4 Infant, Neonatal, and Postnatal Deaths and Mortality Rates by Specified Race or Origin of Mother: United States, 2009 and 2010

		Mortality Rate Per 1,000 Live Births		
RACE OF MOTHER	YEAR(S)	INFANT	NEONATAL	POSTNATAL
All races	2007	6.4	4.2	2.2
	2008	6.1	4.0	2.1
White	2007	5.3	3.5	1.9
	2008	5.2	3.5	1.8
Black or African American	2007	12.1	8.0	4.2
	2008	11.2	7.3	3.9
American Indian or Alaska Native	2007	8.3	4.3	4.0
Asian or Pacific Islander	2007	4.3	3.0	1.3
Hispanic or Latino	2007	5.3	3.6	1.7
Mexican	2007	5.1	3.5	1.6
Puerto Rican	2007	7.1	4.8	2.3
Cuban	2007	3.8	2.9	2.1*
Central and South American	2007	4.4	3.0	1.4
Other and unknown Hispanic or Latino	2007	6.1	4.0	2.1
Not Hispanic or Latino				
White	2007	5.2	3.4	1.8
Black or African American	2007	11.5	7.5	4.0

Adapted from National Center for Health Statistics: Health, United States, 2013: with special feature on prescription drugs, *Hyattsville, MD, 2014, Department of Health and Human Services, Tables 11, p. 98, and 17, p. 71.*

*2009.

neoplasms are lower. During adolescence and young adulthood, suicide and homicide are the second and third causes of death in this population and occur at about twice the rates of the rest of the population. There may be significant underreporting of deaths of Native American children.

As many as 75% of Native American children have recurrent otitis media and high rates of hearing loss, resulting in learning problems. Tuberculosis and gastroenteritis, formerly much more common among Native Americans, now occur at about the national average. Psychosocial problems are more prevalent in these populations than in the general population: depression, alcoholism, drug abuse, out-of-wedlock teenage pregnancy, school failure and dropout, and child abuse and neglect.

An estimated 300 million indigenous persons live in 70 countries (50% in Asia) and speak ≈4,000 languages. Such children endure lower vaccination rates, lower school entry and higher dropout rates, higher rates of poverty, and lower access to justice. Indigenous children in Latin America account for 66% of the deaths of children younger than age 2 yr.

Children of Migrant Workers

Families facing economic hardship have been forced to leave their land and homes in search of better opportunities; such migrations are often within a country or between neighboring countries.

In the United States, the number of migrant and seasonal farm workers is estimated to exceed 3 million, with 68% born in Mexico; 52% are parents, often accompanied by their children as they travel from site to site. The families experience poor housing, frequent moves, and a socioeconomic system controlled by a crew boss who arranges the jobs, provides transportation, and often, together with the farm owners, provides food, alcohol, and drugs under a "company store" system that leaves migrant families with little money or in debt. Children often go without schooling. English skills are limited, with 35% speaking no English and 27% "a little." The average family income is $17,500 to $19,999. Only 8% report receiving health insurance.

The medical problems of children of migrant farm workers are similar to those of children of homeless families: increased frequency of infections (including HIV), trauma, poor nutrition, poor dental care, low immunization rates, exposures to animals and toxic chemicals, anemia, and developmental delays.

Homeless Children

The number of homeless children in the United States has increased by more than 35% since the recession began in 2007. An estimated 1.6 million children are homeless, living in shelters, with other relatives or on the streets.

Homeless children have an increased frequency of illness, including intestinal infections, anemia, neurologic disorders, seizures, behavioral disorders, mental illness, and dental problems, as well as increased frequency of trauma and substance abuse. Homeless children are admitted to U.S. hospitals at a much higher rate than the national average. They have higher school failure rates, and the likelihood of their being victims of abuse and neglect is much higher. The limited research on homeless children suggests high rates of developmental delays, severe depression, or learning disorders. The increased frequency of maternal psychosocial problems, especially depression, in homeless households has a significant untoward impact on the mental and physical health of these children. Because families tend to break apart under the strain of poverty and homelessness, many homeless children end up in foster care. If their families remain intact, frequent moves make it very difficult for them to receive continuity of medical care or schooling.

Provision of adequate housing, job retraining for the parents, and mental health and social services are necessary to prevent homelessness from occurring. Physicians can have an important role in motivating society to adopt the social policies that will prevent homelessness from occurring by educating policymakers that these homeless children are at greater risk of becoming burdens both to themselves and to society if their special health needs are not met.

Runaway and Thrown-Away Children

Annually in the United States, an estimated 1.6-2.8 million youth run away. Several hundred thousand of these children have no secure and safe place to stay. Black and Hispanic youth, as well as lesbian, homosexual, bisexual, and transgender youth, are disproportionately represented in these numbers. The usual definition of a *runaway* is a youth younger than 18 yr who is gone for at least 1 night from his or her home without parental permission; ~70% of these youth endangers their physical well-being during the runaway episode. Most runaways leave home only once, stay overnight with friends, and have no contact with the police or other agencies. This group is no different from their "healthy" peers in terms of psychological status. A smaller but unknown number become multiple or permanent "runners" and are significantly different from the one-time runners, with less-favorable long-term outcomes.

Thrown-aways include children told directly to leave the household, children who have been away from home and are not allowed to return, abandoned or deserted children, and children who run away but whose caretakers make no effort to recover them or do not appear to care if they return. The same constellation of causes common to many of the other special-risk groups is characteristic of permanent runaways and thrown-aways, including environmental problems (family dysfunction, abuse, poverty) and personal problems of the young person (poor impulse control, psychopathology, substance abuse, or school failure). Thrown-aways experience more violence and conflicts in their families.

In the United States, it is a minority of runaway youths who become homeless street people. These youths have a high frequency of problem behaviors, with 75% engaging in some type of criminal activity and 50% engaging in prostitution. A majority of permanent runaways have serious mental problems; more than 33% are the product of families who engage in repeated physical and sexual abuse (see Chapter 40). These children also have a high frequency of medical problems, including hepatitis, sexually transmitted infections, and drug abuse. Although runaways often distrust most social agencies, they will come to and use medical services. Medical care may become the point of reentry into mainstream society and the path to needed services. U.S. parents who seek a physician's advice about a runaway child should be asked about the child's history of running away, the presence of family dysfunction, and personal aspects of the child's development. If the youth contacts the physician, the latter should examine the youth and assess the youth's health status, as well as willingness to return home. If it is not feasible for the youth to return home, foster care, a group home, or an independent living arrangement should be sought by referral to a social worker or a social agency. Although legal considerations involved in the treatment of homeless minor adolescents may be significant, most states, through their "Good Samaritan" laws and definitions of emancipated minors, authorize treatment of homeless youths. Legal barriers should not be used as an excuse to refuse medical care to runaway or thrown-away youths.

The issue of runaway youths is very complex in many developing nations, where in many instances the youth may be orphaned and/or leaving situations of forced sex or other abusive situations. It is estimated that there are tens of millions of such youth worldwide. Natural disasters such as the 2010 earthquake devastating Haiti also contribute to growing numbers of orphaned children. In 2012, there were an estimated 17.8 million HIV orphans globally, with 14.8 > 15 million in Africa. With school attendance <50% in many parts of sub-Saharan Africa, children who are orphaned are 17% less likely to attend school. Humanitarian and international organizations have begun to focus on this very vulnerable group of youths across the globe. Rates are often uncertain, and in many countries, these children have not even been recognized as an at-risk group, so great is the social chaos and so massive are the unmet needs.

Children Directly Affected By War and Other Forms of Direct Violence

See Chapter 39.2.

There have been ~250 major wars (defined as armed combat with more than 1,000 casualties) since the end of the Second World War.

The majority of these conflicts have been civil wars, many of which have lasted longer than a decade. Sixteen of the world's poorest 20 countries have endured a civil war in the past 20 yr. Poorer countries are more likely to engage in war; a country whose median income is at the 50th percentile is one-half as likely to engage in a civil war as a country whose median income is at the 10th percentile. The distinction between intentional and unintentional injury loses its meaning in such situations; in modern wars, 70-80% of casualties are among women and children. Direct mortality and morbidity to children account for only a portion of war's destructive impact on children. In 1996 the United Nations commissioned a report addressing the full consequences of war on children entitled "Promotion and Protection of the Rights of Children: Impact of Armed Conflict on Children" including (1) the disruption of basic educational and child health pediatric care and services; (2) hardships endured as a result of refugee status; (3) the abuse of the 250,000-300,000 children younger than age 18 yr who are soldiers; and (4) the impact on children when 1 or both parents are deployed to serve.

A growing number of children worldwide are facing acts of violence with a broad reach outside of the context of war, including religious crusades (such as suicide bombers in countries not always engaged in war), countries with extraordinarily high rates of violence (such as certain cities in South Africa and Mexico) and as a result of individuals with uncertain or confused personal motives, such as the mass shooting in an elementary school in Sandy Hook, Connecticut. While the direct consequences of such nonwar violence impact far fewer children than do those from war, the reach of such random acts of violence is increasingly touching a wider swath of our globe.

Inherent Strengths in Vulnerable Children and Interventions

By age 20-30 yr, many children in the United States and other developed countries who were at special risk will have made moderate successes of their lives. Teenage mothers and children who were born prematurely or in poverty demonstrate that, by this age, the majority have made the transition to stable marriages and jobs and are accepted by their communities as responsible citizens. As the numbers of risk factors increases for an individual, the odds for a successful adulthood decline.

Certain biologic characteristics are associated with success, such as being born with an accepting temperament. Avoidance of additional social risks is even more important. Premature infants or preadolescent boys with conduct disorders and poor reading skills, who must also face a broken family, poverty, frequent moves, and family violence, are at much greater risk than children with only 1 of these risks. Perhaps most important are the protective buffers that have been found to enhance children's resilience because these can be aided by an effective healthcare system and community. Children generally do better if they can gain social support, either from family members or from a nonjudgmental adult outside the family, especially an older mentor or peer. Providers of medical services should develop ways to "prescribe" supportive "other" persons for children who are at risk. Promotion of self-esteem and self-efficacy is a central factor in protection against risks. It is essential to promote competence in some area of these children's lives.

A team is needed because it is rare for 1 individual to be able to provide the multiple services needed for high-risk children. Successful programs are characterized by at least 1 caring person who can make personal contact with these children and their families. Most successful programs are relatively small (or are large programs divided into small units) and nonbureaucratic but are intensive, comprehensive, and flexible. They work not only with the individual, but also with the family, school, community, and at broader societal levels. Introduction of remedial programs to children at the youngest possible age appears to increase the chance of success across multiple problem areas. It is also important for services to be continued over a long period.

Global Warming

Global climate change is occurring and will impact everyone; its impact will be harder felt on children and hardest felt are certain categories of vulnerable child, including those living in areas threatened by variations in rainfall, temperatures or hurricanes and cyclones (Fig. 1-6).

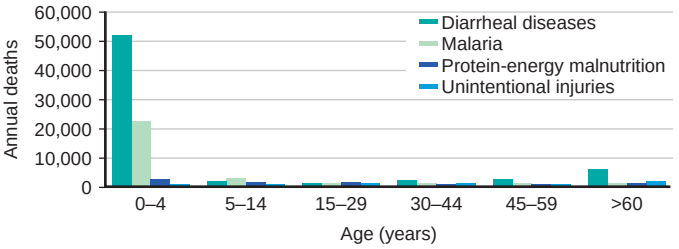


Figure 1-6 Deaths attributable to global climate change: 2004 annual data in total numbers divided by age categories. *(Data from* WHO Global burden of disease: 2004 update. *2008. Available at* http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. *Image from Sheffield PE, Landrigan PJ. Global climate change and children's health: threats and strategies for prevention.* Environ Health Perspect *2011;119:291.)*

The Challenge to Pediatricians

Concerns about the aforementioned problems of children throughout the world have generated 3 sets of goals. The *first set* includes that all families have access to adequate perinatal, preschool, and family planning services; that international and national governmental activities be effectively coordinated at the global, regional, national, and local levels; that services be so organized that they reach populations at special risk; that there be no insurmountable or inequitable financial barriers to adequate care; that the healthcare of children have continuity from prenatal through adolescent age periods; and that every family ultimately have access to all necessary services, including developmental, dental, genetic, and mental health services. A *second set* of goals addresses the need for reducing unintended injuries and environmental risks, for meeting nutritional needs, and for health education aimed at fostering health-promoting lifestyles. A *third set* of goals covers the need for research in biomedical and behavioral science, in fundamentals of bioscience and human biology, and in the particular problems of mothers and children.

PATTERNS OF HEALTHCARE

Healthcare utilization and organization differs significantly among nations, reflecting differences in the geography and wealth of the country; the priority placed on healthcare versus other competing needs and interests within a nation and by the international community; philosophy regarding prevention versus curative care; and the balance between child and adult healthcare needs. An interesting analysis of 2 industrialized countries (United States and Japan) revealed that for comparable symptoms, Japanese children were 2.5 times more likely to visit a community physician's office or emergency clinic, and 11 times more likely to visit a hospital-based outpatient clinic. In most countries, hospitals are sources of both routine and intensive child care, with medical and surgical services that may range from immunization and developmental counseling to open heart surgery and renal transplantation. Clinical conditions and procedures requiring intensive care are also likely to be clustered in university-affiliated centers serving as regional resources—if these resources exist.

In developing countries, external forces may also contribute greatly to the organization of healthcare and possibly to healthcare utilization. This relationship is complex. The significant declines in infant and child mortality enjoyed in many of the developing countries in the past 4 decades have occurred in the context of support from the international community, including agencies such as UNICEF, WHO, and the World Bank; bilateral donors (the aid provided from 1 country to another); and nongovernmental agencies to develop integrated, universal primary pediatric care with an emphasis on primary (vaccination) and selected secondary (oral rehydration solution [ORS], treatment of pneumonia and malaria) prevention strategies. But, as

healthcare systems become dependent on such external support, their populations are increasingly vulnerable to changes in political will over which they have little or no influence.

In the United States, pediatricians report an average of 50 preventive care visits per wk, 33% for infants. The visits average 17-20 min, increasing in length as children become adolescents. The principal diagnoses, accounting for ≈40% of these visits, are well-child visits (15%), middle-ear infections (12%), and injuries (10%). Ambulatory visits by children and youth decrease with age. The opposite occurs with adults. Nonwhite children are more likely than white children to use hospital facilities (including the emergency room) for their ambulatory care; the number of well-child visits annually is almost 80% higher among white infants than black infants. Children with private insurance are more likely than children with public insurance who, in turn, are more likely than uninsured children to receive non–emergency room care. Insurance coverage increases outpatient utilization and receipt of preventive care by approximately 1 visit per year for children. Between 70 and 90 children per 1,000 children are hospitalized per year. These rates are less than those of adults up to age 65 yr, except for the first year of life. Children represent <7% of the total acute hospital discharges; in children's hospitals, ≈70% of admissions are for chronic conditions, and 10-12% of pediatric hospitalizations are related to birth defects and genetic diseases. White children are less likely to be hospitalized than black or Hispanic children, but more likely than Asian children. Poor children are nearly twice as likely as nonpoor children to be hospitalized. Insurance coverage also appears to reduce hospital admissions that are potentially manageable in an ambulatory setting.

PLANNING AND IMPLEMENTING A SYSTEM OF CARE

Access to at least a basic level of quality services to promote health and treat illness is a right of every person. Having health insurance, whether private or governmental, is strongly associated with access to primary care. Efforts to make the delivery of healthcare more efficient and effective have led to the creation of new categories of healthcare providers, such as pediatric nurse practitioners in industrialized nations and trained birth attendants in developing countries, and to participate in new organizations for providing care to children, such as various managed care arrangements.

The U.S. Patient Protection and Affordable Care Act passed in 2010 and upheld by the United States Supreme Court in 2012, contains provisions specific to children, including a requirement that all preexisting conditions be covered and (effective 2014) pregnancy and newborn care be covered, as well as vision and dental care for children.

Health Services for At-Risk Populations

In the United States, the largest vulnerable group is children living in poverty, representing approximately 22% of U.S. children. Substantial proportions of children in other industrialized countries are also living in poverty. The approach to addressing the needs of this group in the United States has been the establishment of a targeted insurance program, Medicaid, which became law in 1965 as a jointly funded cooperative venture between the federal and state governments to assist states in the provision of adequate medical care to eligible needy persons. The federal statute identifies >25 different eligibility categories for which federal funds are available. These statutory categories can be classified into 5 broad coverage groups: children, pregnant women, adults in families with dependent children, individuals with disabilities, and individuals ≥65 yr old. Pediatric care in the United States is highly dependent on Medicaid; however, only a relatively small proportion of the Medicaid funds actually go to child healthcare, with the remainder serving older adults. Following broad national guidelines, each state establishes its own eligibility standards; determines the type, amount, duration, and scope of services; sets the rate of payment for services; and administers its own program. Although Medicaid has made great strides in enrolling low-income children, significant numbers of children remain uninsured. From 1988 to 1998, the proportion of children insured through Medicaid increased from 15.6% to 19.8%, but the percentage of children without health insurance increased from 13.1% to 15.4%. Minority children were disproportionately among those without insurance. The Balanced Budget Act of 1997 created a new children's health insurance program called the State Children's Health Insurance Program (SCHIP). This program gave each state permission to offer health insurance for children, up to age 19 yr, who are not already insured. SCHIP is a state-administered program and each state sets its own guidelines regarding eligibility and services. There is great variation by state, but in many states, the SCHIP program has begun to reduce racial inequities in access to healthcare for children. In 2009, the percent of children without insurance had decreased to 9%.

Many industrialized nations have adapted different "safety net" systems to assure adequate coverage of all youth. Many of these programs provide health insurance for all children, regardless of income, hoping to avoid problems with children losing insurance coverage and access to healthcare as a result of changes in eligibility by providing a single form of insurance that all providers accept. The response of developing countries to the issue of universal access to care for children has been uneven, with some providing no safety net, but many having limited universal or safety net services.

To address the special needs of Native Americans in the United States, the Indian Health Service, established in 1954, has been the responsibility of the Public Health Service, but the 1975 Indian Self-Determination Act gave tribes the option of managing Native American health services in their communities. The Indian Health Service is managed through local administrative units, and some tribes contract outside the Indian Health Service for healthcare. Much of the emphasis is on adult services: treatment for alcoholism, nutrition and dietetic counseling, and public health nursing services. There are also >40 urban programs for Native Americans, with an emphasis on increasing access of this population to existing health services, providing special social services, and developing self-help groups. In an effort to accommodate traditional Western medical, psychologic, and social services to the Native American cultures, such programs include the "Talking Circle," the "Sweat Lodge," and other interventions based on Native American culture (see Chapter 4). The efficacy of any of these programs, especially those to prevent and treat the sociopsychological problems particular to Native Americans, has not been determined.

Recognizing the health needs of migrants in the United States, the U.S. Public Health Service initiated in 1964 the Migrant Health Program to provide funds for local groups to organize medical care for migrant families. Many migrant health projects that were initially staffed by part-time providers and were open for only part of the year have been transformed into community healthcare centers that provide services not only for migrants but also for other local residents. As of 2012, there are >700 Migrant Health Centers and satellite sites operating in 42 states. Health services for migrant farm workers often need to be organized separately from existing primary care programs because the families are migratory. Special record-keeping systems that link the healthcare provided during winter months in the south with the care provided during the migratory season in the north are difficult to maintain in ordinary group practices or individual physicians' offices. Outreach programs that take medical care to the often remote farm sites are necessary, and specially organized Head Start, early education, and remedial education programs should also be provided. Approaches in other countries have also focused on business initiatives for migrant populations to enable them to overcome the cycle of financial dependency on their migratory lifestyle.

The United States has spent >$14 billion through the 1987 McKinney-Vento Act to provide emergency food, shelter, and healthcare; to finance help for young runaways; to aid homeless people in making their way back into the housing market; and to place homeless children in school. Mobile vans, with a team consisting of a physician, nurse, social worker, and welfare worker, have been shown to provide effective comprehensive care, ensure delivery of immunizations, link the children to school health services, and bring the children and their families into a stable relationship with the conventional medical system. Special record-keeping systems have been introduced to enhance continuity and to provide a record of care once the family has moved to a

permanent location. Because of the high frequency of developmental delays in this group, linkage of preschool homeless children to Head Start programs is an especially important service. The Runaway Youth Act, Title III of the Juvenile Justice and Delinquency Prevention Act of 1974 (Public Law 93-414) and its amended version (Public Law 95-509) have supported shelters and provide a toll-free 24 hr telephone number (1-800-621-4000) for youths who wish to contact their parents or request help after having run away.

Other nations have expanded the reality of the "health safety net" for children. In Belgium, Finland, the Netherlands, Portugal, and Spain, the right to housing has been incorporated into the national constitutions. The Finnish government has devised a multifaceted response to the problem, including house building, social welfare and healthcare services, and the obligation to provide a home of minimum standards for every homeless person. The number of homeless in Finland has been reduced by 50%.

Evaluation of Healthcare

The Institute of Medicine issued a report, "Crossing the Quality Chasm: A New Health System for the 21st Century" in 2001. This report, challenging American physicians to renew efforts to focus not just on access and cost, but also on quality of care, has been furthered in several pediatric initiatives, including, but not limited to, specific initiatives for monitoring child health outlined in the Institute of Medicine report "Children's Health, the Nation's Wealth"; challenge/demonstration grants funded by the Robert Wood Johnson Foundation; and the National Initiative for Children's Healthcare Quality. Importantly, each of these initiatives is calling for the establishment of measurable standards for assessment of quality of care and for the establishment of routine plans for periodic reassessment thereof. Efforts have been initiated at some medical centers to establish evidence-based clinical pathways for disorders (such as asthma) where there exists sound evidence to advise these guidelines. Pediatricians have developed tools to evaluate the content and delivery of pediatric preventive "anticipatory guidance," the cornerstone of modern pediatrics (see Chapter 5).

THE INFORMATION EXPLOSION OF THE 21ST CENTURY

There is no touchstone through which physicians can ensure that the process of their own continuing education will keep them abreast of advancing knowledge in the field, but the requirement for "Maintenance of Certification" as opposed to the former practice of lifelong certification by specialty boards actively addresses this issue (see Chapter 2). An essential element of this process may be for physicians to take an active role, such as participating in medical student and resident education. Efforts in continuing self-education will also be fostered if clinical problems can be made a stimulus for a review of standard literature, alone or in consultation with an appropriate colleague or consultant. This continuing review will do much to identify those inconsistencies or contradictions that will indicate, in the ultimate best interest of patients that things are not what they seem or have been said to be. These difficulties may be exacerbated by commercially sponsored education programs and research projects that may, on occasion, put profit before the patient's best interests. Physicians still learn most from their patients, but this will not be the case if they fall into the easy habit of accepting their patients' problems casually or at face value because the problems appear to be simple.

The tools that physicians must use in dealing with the problems of children and their families fall into 3 main categories: *cognitive* (up-to-date factual information about diagnostic and therapeutic issues, available on recall or easily found in readily accessible sources, and the ability to relate this information to the pathophysiology of their patients in the context of individual biologic variability), *interpersonal or manual* (the ability to carry out a productive interview, execute a reliable physical examination, perform a deft venipuncture, or manage cardiac arrest or resuscitation of a depressed newborn infant), and *attitudinal* (the physician's unselfish commitment to the fullest possible implementation of knowledge and skills on behalf of children and their families in an atmosphere of empathic sensitivity and concern). With regard to this last category, it is important that children participate with their families in informed decision making about their own healthcare in a manner appropriate to their stage of development and the nature of the particular health problem.

The workday needs of professional persons for knowledge and skills in care of children vary widely. Primary care physicians need depth in developmental concepts and in the ability to organize an effective system for achieving quality and continuity in assessing and planning for healthcare during the entire period of growth. They may often have little or no need for immediate recall of esoterica. On the other hand, consultants or subspecialists not only need a comfortable grasp of both common and uncommon facts within their field and perhaps within related fields, but also must be able to cope with controversial issues with flexibility that will permit adaptation of various points of view to the best interest of their unique patient.

At whatever level of care (primary, secondary, or tertiary) or in whatever position (student, pediatric nurse practitioner, resident pediatrician, practitioner of pediatrics or family medicine, or pediatric or other subspecialist), professional persons dealing with children must be able to identify their roles of the moment and their levels of engagement with a child's problem; each must determine whether his or her experience and other resources at hand are adequate to deal with this problem and must be ready to seek other help when they are not.

ORGANIZATION OF THE PROFESSION AND THE GROWTH OF SPECIALIZATION

The 20th century witnessed the formation of professional societies of pediatricians around the globe. Some of these societies, such as the European Board of Pediatrics and the American Board of Pediatrics, are concerned with education and the awarding of credentials certifying competence and the continuing maintenance of competence as a pediatrician and/or a pediatric subspecialist to the public. From its inception in 1933 through the beginning of 2014, the American Board of Pediatrics certified 108,879 general pediatricians.

The amount of information relevant to child healthcare is rapidly expanding, and no person can become master of it all. Physicians are increasingly dependent on one another for the highest quality of care for their patients. Approximately 25% of pediatricians in the United States claim an area of special knowledge and skill, including >20,000 who have board certification in 1 of the 14 pediatric subspecialties with board certification. Each year approximately 10% of the ≈3,000 pediatric residents training in the United States are enrolled in a dual-residency training program that will lead to eligibility for board certification in both pediatrics and internal medicine.

In the United States, most subspecialists practice in academic settings or children's hospitals. Likewise, specialists are growing in number in other industrialized countries and in developing nations that are becoming industrialized. Reflecting the diverse cultures, organization of medical care, economic circumstances and the history of medicine within each of the ~200 countries across the globe, is the great diversity in role of pediatricians within the healthcare delivery system to children in each country; Figure 1-7 illustrates the resultant variations in pediatricians per population among some European countries.

Beyond certifying bodies, there are other pediatric societies primarily concerned with organizing members of the profession in their country or region to dedicate their efforts, advocacy and resources toward children. In the United States, the American Academy of Pediatrics currently has a membership of ≈60,000 child health specialists in both academic and private practice. Most general pediatricians in the United States enter private practice; ≈66% are in group practices, 5% enter solo practice, and 5% work in a health maintenance organization. The American Academy of Pediatrics provides a variety of continuing educational services to pediatricians in multiple national and regional settings and tracks the professional activities and practices of its members. A comparable group in India, the Indian Academy of Pediatrics, was formed in 1963, and now has ~16,500 members and 16 subspecialty chapters. Likewise, the Pakistani Pediatrics Association was founded in 1967, the Malaysian

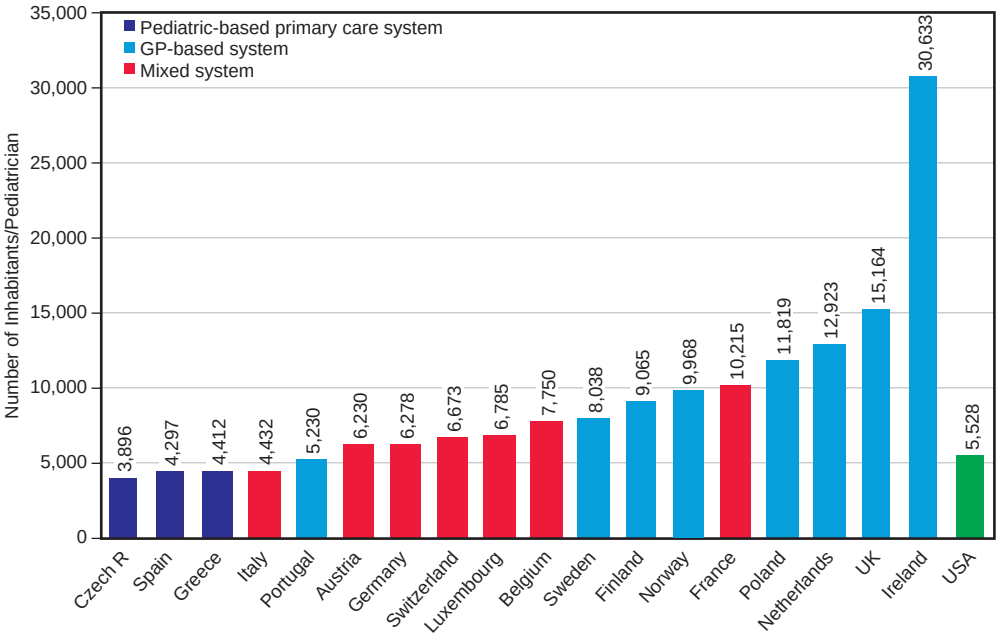


Figure 1-7 Number of inhabitants per pediatrician in some European countries as a function of the differences in primary health care delivery systems, population, and pediatric work force, compared to the current situation in the United States. *(Courtesy of Dr. Alfred Tenore, European Academy of Paediatrics and Chair of Global Pediatric Education Consortium.)*

Pediatric Association was started in 1985, and the Canadian Pediatric Society was founded in 1922. Established in 1974, the Asian Pacific Pediatric Association includes 20 member pediatric societies from throughout eastern Asia, and the International Pediatric Association established in 1910 includes 144 national pediatric societies from 139 countries, 10 regional pediatric societies, and 11 international pediatric specialty societies. The European Academy of Pediatrics is the pediatric specialist organization for the member countries of the European Union and the European Free Trade Association, and the Pediatric Council of the Arab Board of Medical Specializations is the comparable institution for 19 of the world's Arab nations These societies represent but a few of the many national and regional pediatric professional organizations around the world who seek to identify and bring treatments and approaches supporting child well-being to pediatricians worldwide.

Bibliography is available at Expert Consult.

1.1 Innovations in Addressing Child Health and Survival in Low-Income Settings

Zulfiqar Ahmed Bhutta

GLOBAL BURDEN AND MORTALITY TRENDS

The current global burden of neonatal and child death is largely concentrated in Central and sub-Saharan Africa and South Asia (Figs. 1-8 and 1-9; see also Fig. 1-1 and Table 1-1). Ten countries have almost ⅔ of the global burden of maternal and newborn deaths as well as stillbirths.

It is estimated that 6.2 million children younger than 5 yr died in 2012, a 63% reduction from 16.9 million in 1970. However, there are still wide disparities and in 2012, child mortality rates range from a high of 182 per 1,000 in Sierra Leone to 2 per 1,000 in Iceland and Luxembourg. Progress in this regard has been variable, and despite global progress, of the 75 countdown countries that have almost 98% of all maternal and under-5 child deaths, only 13 are on track to reach MDG targets for child mortality. Other global estimates from the Institute of Health Metrics and Evaluation indicate that only 31 developing countries will reach MDG 4 targets by 2015.

From 1990 to 2013, annual rates of decline ranged from 6.7% to –0.9%. In 2013, neonatal deaths account for 41.3% of under-5 deaths, up from 37.6% in 1990. Comparing 2013 with 1990, rising numbers of births, particularly in sub-Saharan Africa, were associated with an additional 1.5 million child deaths. Neonatal mortality reduction has been much slower than that for maternal and child (1-59 mo) mortality, and slowest in the highest burden countries, especially in Africa. The sobering realization is that even in countries that would reach their MDGs 4 and 5 targets, many would still have high numbers of deaths with much scope for improvement.

CAUSES OF NEWBORN AND CHILD DEATHS

The Child Health Epidemiology Reference Group estimated that 40.3% of 7.6 million under-5 deaths in 2010 occurred in the newborn period; 2013 figures from the Institute of Health Metrics and Evaluation corroborate these estimates.

Among newborn deaths, major causes include preterm birth complications (14.1%; 1.078 million), intrapartum-related complications, previously labeled as birth asphyxia (717,000 deaths; 9.4%), and sepsis or meningitis (393,000; 5.4%) neonatal deaths. Among older children, the leading causes of deaths included pneumonia (14.1%; 1.071 million), diarrhea (9.9%; 751,000), and malaria (7.4%; 564,000) (Fig. 1-10*A*). Existing data suggest broadly comparable figures for under-5 deaths (Fig. 1-10*B*), although some categories are different, notably higher proportion of malaria deaths among under-5 children in the Global Burden of Disease study 2010 estimates and lower numbers for pneumonia deaths.

An unaddressed burden of stillbirths exists globally and is not included in the current Global Burden of Disease study estimates. Of an estimated 2.64 million stillbirths worldwide in 2009, 76.2% occurred in south Asia and sub-Saharan Africa, mostly among rural populations. An estimated 45% of these stillbirths occur in the intrapartum period, reflecting a clear extension of the neonatal deaths related to intrapartum events, previously labeled as birth asphyxia deaths. The highest risk time is around birth, when more than 40% of maternal deaths and combined stillbirths during labor and neonatal deaths occur. These deaths occur rapidly, requiring urgent response by healthcare workers. Table 1-5 lists the top 10 countries for risks of intrapartum stillbirths and newborn deaths on the first day of life.

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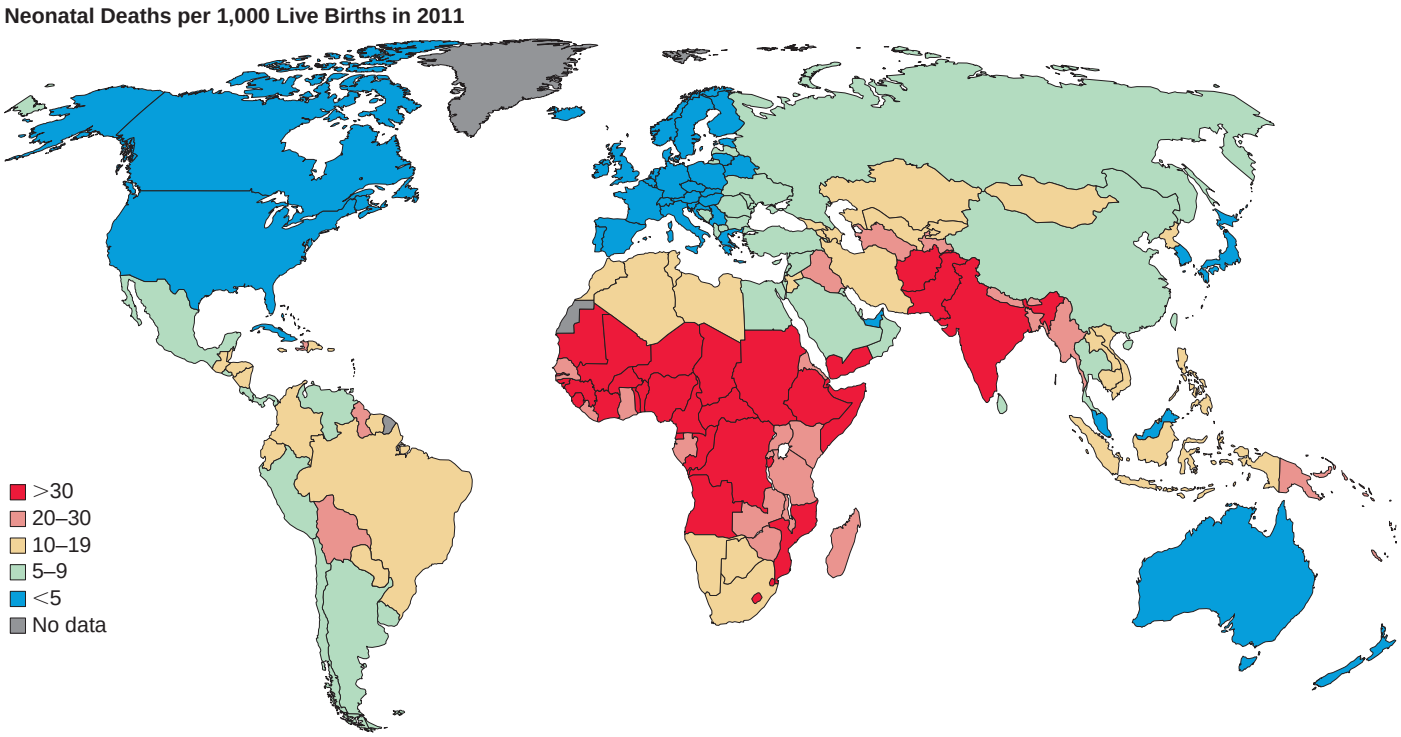

Figure 1-8 Neonatal deaths by country (rates). *(From Bhutta ZA, Black RE. Global maternal, newborn, and child health—so near and yet so far.* N Engl J Med *2013;369:2226–2235.)*

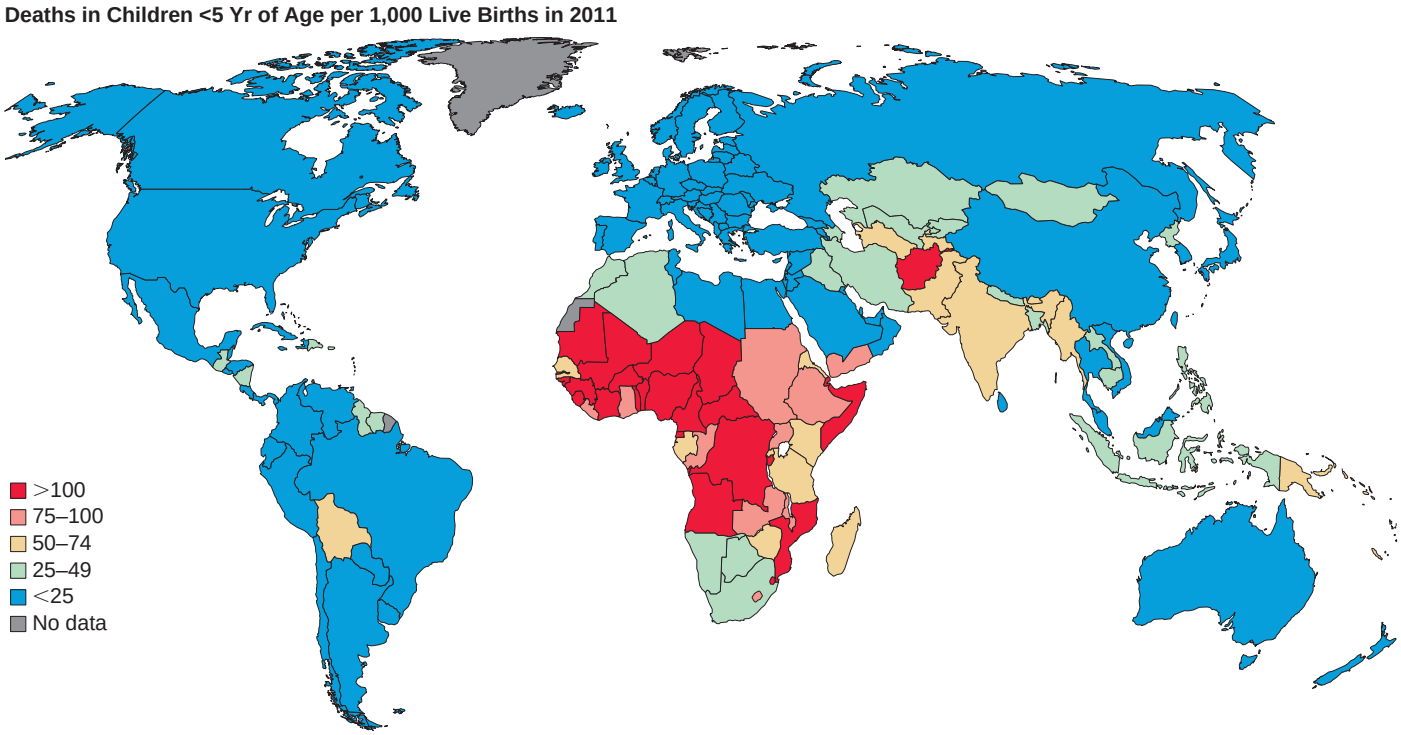

Figure 1-9 Child (1-4 yr) deaths per 1,000 live births. *(From Bhutta ZA, Black RE. Global maternal, newborn, and child health—so near and yet so far.* N Engl J Med *2013;369:2226–2235.)*

Being born small, because of preterm birth or small for gestational age (SGA) or both, is the leading risk factor for neonatal deaths and carries increased risk for postneonatal mortality, growth failure, and adult-onset noncommunicable conditions (see Chapter 97). South Asia has the highest SGA rates and sub-Saharan Africa has the highest preterm birth rates. Babies who are term SGA low birthweight face risks for stunting, and adult-onset metabolic conditions. Fifteen million preterm births, especially those <32 wk gestation, are at highest risk of neonatal death, with ongoing postneonatal mortality risk, significant risk of long-term neurodevelopmental impairment, and stunting, as well as noncommunicable conditions. Four million neonates annually have other life-threatening conditions, including intrapartum-related

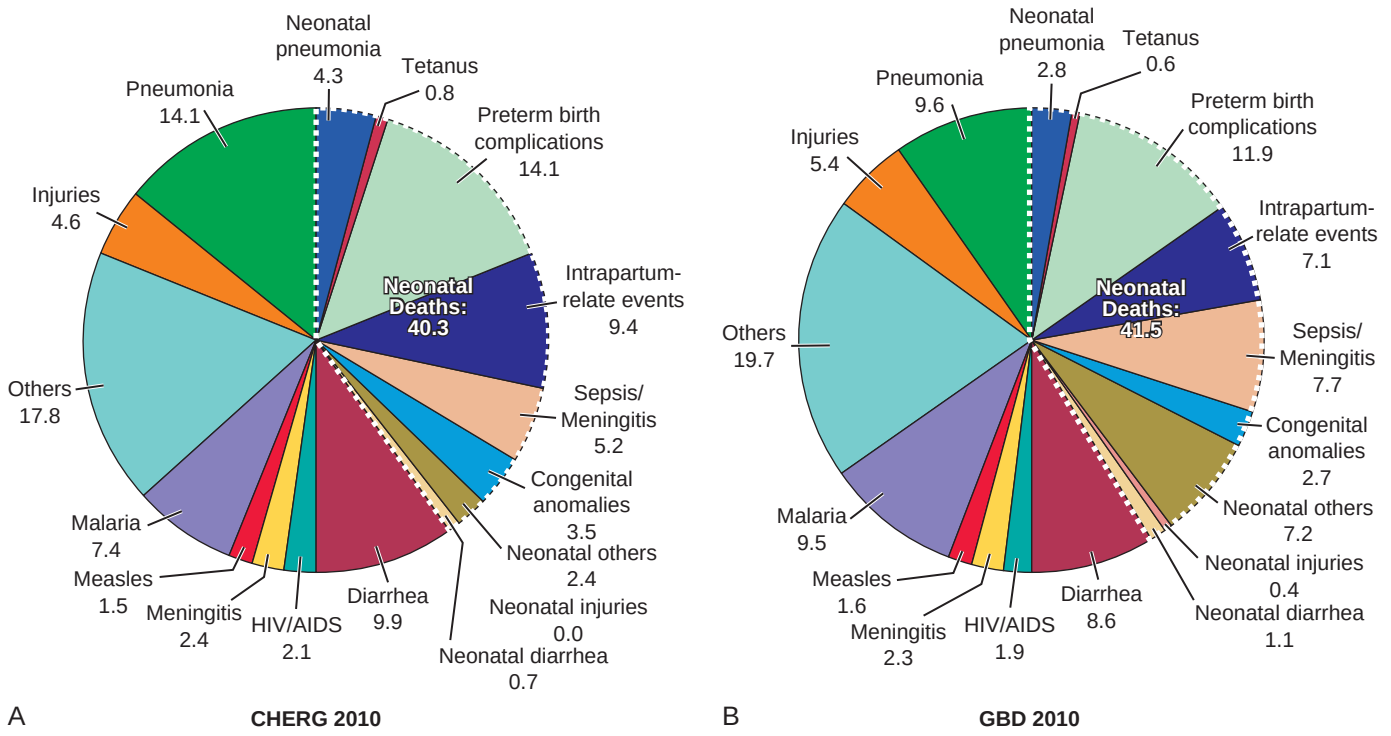

Figure 1-10 Global causes of child deaths. *CHERG, Child Health Epidemiology Reference Group; GBD, Global Burden of Disease study.*

Table 1-5 Ten Countries with the Highest Rate of First-Day Deaths and Stillbirths During Labor

COUNTRY	RISK OF NEONATAL DEATH ON DAY OF BIRTH (PER 1,000 LIVE BIRTHS)	INTRAPARTUM STILLBIRTH RATE (PER 1,000 TOTAL BIRTHS)	INTRAPARTUM STILLBIRTHS AND NEONATAL DEATHS ON DAY OF BIRTH (PER 1,000 TOTAL BIRTHS)
Pakistan	15	26.4	40.7
Nigeria	14	19.4	32.7
Sierra Leone	18	13.9	30.8
Somalia	16	14.0	29.7
Guinea-Bissau	16	13.7	29.4
Afghanistan	13	16.6	29
Bangladesh	9	20.6	28.9
Democratic Republic of Congo	15	13.3	28.3
Lesotho	16	11.8	27.5
Angola	16	11.7	27.4

brain injury, severe bacterial infection, and pathologic jaundice, with 1.4 million neonates surviving with long-term neurodevelopmental impairment. The consequences of not acting to improve birth outcomes by 2035 are estimated at 116 million deaths, 99 million with disability or lost development potential, and many millions of adults with noncommunicable disease following being born SGA and or prematurely.

UNDERSTANDING SOCIAL DETERMINANTS AND BARRIERS FOR CARE

Understanding the causes of deaths allows for better planning and targeting of interventions. Between 2000 and 2010, the bulk of the reduction in under-5 child mortality related to decreases in pneumonia, measles, and diarrhea deaths, whereas corresponding reductions in neonatal causes of deaths other than tetanus (notably those associated with prematurity and intrapartum related events) was minimal.

Poverty is a huge barrier and affects all levels of care because much of the burden of maternal and child mortality and ill health is concentrated among the poorest countries of sub-Saharan Africa and South Asia. In many of these countries, the bulk of the mortality is clustered among the poor, frequently residing in remote and rural populations with limited access to healthcare services. A sizeable proportion of deaths also occur among the urban poor living in slum conditions with limited social support networks and poor living conditions. Other determinants, such as environmental factors (e.g., overcrowding, poor air quality and sanitary conditions), may be much worse in urban slums than in many rural populations. Lack of trained human resources and transportation facilities in rural populations, as well as quality of care in existing primary care settings are also problems. Figures 1-11 and 1-12 illustrate some of the inequities observed across key evidence-based maternal and child interventions across and within large number of developing countries. Interventions that have a relatively narrow

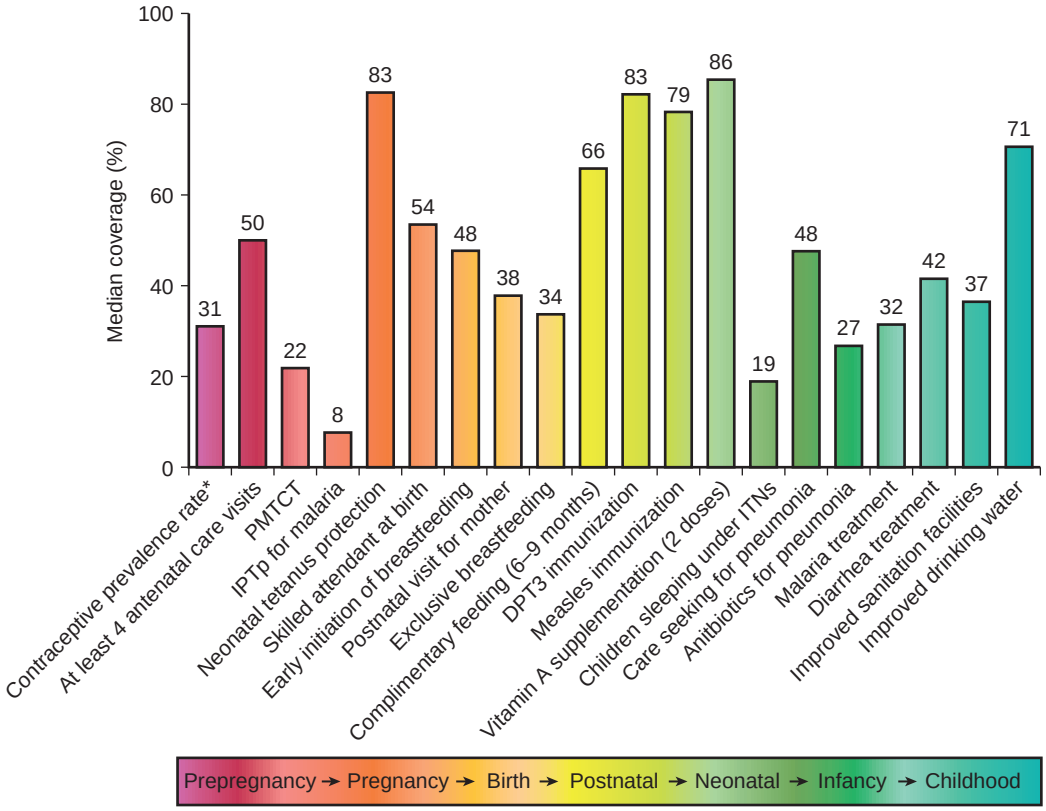

Figure 1-11 Global coverage for 75 countdown countries with 98% of maternal and child deaths. *(From Bhutta ZA, Chopra M, Axelson H, et al: Countdown to 2015 decade report [2000–10]: taking stock of maternal, newborn, and child survival. Lancet 375:2032–2044, 2010, Fig. 2.)*

delivery channel and mandates such as immunizations do achieve high coverage, whereas those that require functional health systems and facilities, such as skilled birth attendance and postnatal care, hardly reach half of the population in need. For others, such as the appropriate use of zinc, ORS, and antibiotics for the treatment of childhood diarrhea or pneumonia, current coverage rates are very low.

Estimates of the impact of various factors on child survival between 1990 and 2013 indicate that while rising numbers of births, particularly in sub-Saharan Africa, led to 1.5 million more child deaths, rising income per capita and maternal education led to 774,000 and 2.4 million fewer deaths, respectively. Technology change alone led to 4.0 million fewer deaths. In 23 developing countries, there is evidence that declines since 2000 have been faster than predicted on the basis of income, education, and technology shift alone.

EVIDENCE-BASED INTERVENTIONS AND INNOVATIONS TO ADDRESS INEQUITIES

There is a range of preventive, promotive and therapeutic interventions that can affect newborn and child survival (Table 1-6).

These services require **appropriate delivery platforms** for scaling up coverage, especially in circumstances where there is widespread **shortage of health workers**, and the **removal of financial barriers** that preclude care seeking and access where such care is not freely available within the public health system. There is also the need to **improve quality of care** within facilities and ensure availability of life saving commodities by well trained and motivated care providers.

COMMUNITY HEALTH WORKERS FOR NEWBORN AND CHILD HEALTH

The global shortage of a skilled health work force has been a key barrier to effective coverage and in many instances policy makers and planners resort to the use of community health workers (CHWs) who are provided basic training in preventive and promotive strategies. Such task-shifting strategies have been shown to yield beneficial results in diverse settings, frequently in malaria and HIV management. Communities should take active part in improving their own health, and the dynamic role of CHWs in delivery of health-related care are well recognized. CHWs work in liaison with frontline health workers and are fastened across the primary healthcare for better success in reaching the goals (Fig. 1-13).

A growing array of interventions delivered by CHWs can significantly improve neonatal and child health and survival; behavioral interventions to promote healthy behavior; preventive interventions, such as immunization; and more complex tasks, such as case management of childhood illnesses (e.g., pneumonia, malaria, and neonatal sepsis). The active involvement and empowerment of communities through CHWs have positive effects on health by changing health beliefs and improving care seeking for illnesses. CHWs increase the proportion of people who receive healthcare and increase the number of children with up-to-date immunization statuses. CHWs who provide some amount of support of breastfeeding, as well as care during pregnancy, help reduce child mortality through various antenatal interventions, including pregnancy surveillance, vitamin supplementation, and promotion of birth preparedness. CHW programs are also dependent upon basic tool kits and a steady and reliable supply of key commodities. Lack of adequate supplies and frequent stock outs are a major impediment to effective programs and implementation.

Women's and community support groups which are largely formulated and facilitated by CHWs have shown reductions in neonatal mortality and morbidity and improvement in domiciliary practices, such as early initiation of breastfeeding and healthcare seeking for their illnesses. These participatory activities empower mothers, emphasize safe delivery practices and encourage care seeking behavior.

Home visits by CHWs may improve coverage of key newborn care practices such as early initiation of breastfeeding, exclusive breastfeeding, skin-to-skin contact, delayed bathing and attention to hygiene, such as hand washing with soap and water, clean umbilical cord care, immunization and early diagnosis, detection of complications,

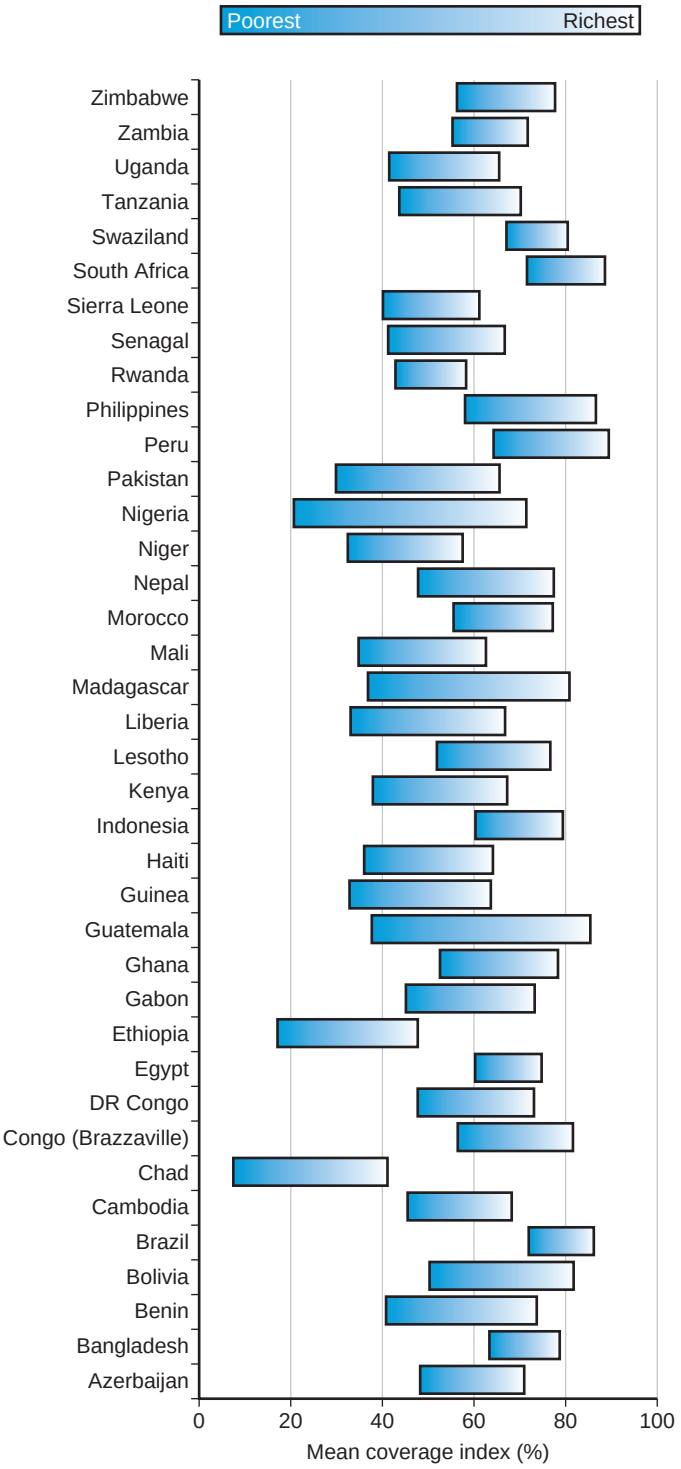

Figure 1-12 Inequities in maternal and child interventions from 38 countdown countries. *(From Bhutta ZA, Chopra M, Axelson H, et al: Countdown to 2015 decade report [2000–10]: taking stock of maternal, newborn, and child survival. Lancet 375:2032–2044, 2010,Fig. 7.)*

and appropriate referrals. Home-based newborn care consisting of therapeutic interventions, case management and referrals, and preventive interventions such as health education have shown reductions in neonatal mortality and in stillbirths.

Implementation of an essential newborn care package along with administration of home-based antibiotic therapy for suspected neonatal sepsis by CHWs has resulted in a 62% reduction in the neonatal mortality rate when 93% of the newborns in the intervention area were provided treatment. In a meta-analysis of trials of community-based case-management of pneumonia all-cause neonatal mortality was 27% lower in the intervention group, whereas pneumonia-specific neonatal mortality in the intervention group was reduced by an even greater amount. Case management of children suffering from pneumonia, malaria, and diarrhea may be the potential way forward in the low-income setting. Case management of pneumonia by CHWs could result in a 70% reduction in mortality from pneumonia in children <5 yr of age. Community-based interventions correlate to a 13% and 9% increase in care seeking for pneumonia and diarrhea, respectively. Case management is associated with increased uptake of ORS and zinc for management of diarrhea. These interventions also lead to a 32% reduction in pneumonia-specific mortality. CHWs can also be trained to perform rapid diagnostic tests for malaria, and manage test-positive children with antimalarials.

CHWs can also play a role in improving the use of anthelminthics in children. Interventions such as preventive chemotherapy, health education to promote general hygiene and sanitation, iron and β-carotene supplementation, construction of latrines, removing cattle from residential areas, staff training and community mobilization can have significant impacts on prevention and management of worm infestations. Evidence suggests that school-based delivery of anthelminthics can significantly reduce soil-transmitted helminthes prevalence, schistosomiasis prevalence, and anemia. Interventions related to handwashing counseling (for individuals or groups) suggested a 30% reduction in the risk of diarrhea as well.

THE ROLE OF INFORMATION TECHNOLOGY AND mHEALTH PLATFORMS

Mobile health, or mHealth, is the use of mobile information and communication technologies for improving health. It can be used for a wide range of purposes, including health promotion and illness prevention, healthcare delivery, training and supervision, electronic payments, and information systems. This is widely regarded as a great equalizer across social strata in increasing access to information and empower health workers to reach marginalized populations. In the simplest forms SMS/text-based campaigns can be an effective way to share health information with people who lack reliable Internet access and in other instances telemedicine can permit specialist access and consultations which were hitherto not possible because of geographic constraints and limitations. mHealth is of particular interest in low- and middle-income countries, where widespread mobile networks and access to devices are connecting people, leap-frogging older technologies to dramatically improve information flow, data collection, social and behavior change, and emergency response.

CASH TRANSFERS TO REDUCE POVERTY BARRIERS AND IMPROVE CHILD HEALTH

Out of pocket expenses by households form the major share of total health expenditure in most low income countries and a substantial share in middle income countries. Financial incentives are becoming widely used to improve healthcare coverage, alleviate poverty and improve access to child health services. Some support platforms have a dual purpose of reducing financial barriers and also strengthening service delivery. Financial incentive programs may include conditional/unconditional cash transfers, conditional/unconditional microcredit, conditional/unconditional voucher, user fee removal and health insurances. Financial incentive programs targeting child health generally focus on breastfeeding practices; vaccination; healthcare use; management of diarrheal diseases; and other preventive health interventions including preventive deworming, vitamin A and iron supplementation. These programs are also directed toward education improvement by improving school enrollment, attendance, and occasionally some measure of performance.

OTHER TECHNOLOGIES AND INNOVATIONS

There has been a massive increase in global knowledge and potential of low-cost technologies to improve diagnosis and care of sick newborn infants and children. These span bedside tools to assess risk of severe

Table 1-6 Evidence-based Interventions to Address Newborn and Child Health and Undernutrition

NEWBORN	NUTRITION	DIARRHEA	PNEUMONIA
Breastfeeding promotion including initiation			
	Improved water source, sanitation, and hygiene Preventive vitamin A supplementation Preventive zinc supplementation		
Periconceptional folic acid supplementation or fortification Multiple micronutrient/iron-folate supplementation in pregnancy Maternal balanced energy protein supplementation Maternal calcium supplementation			
ORS Antibiotics for dysentery		ORS Antibiotics for dysentery	
Case management of pneumonia			Case management of pneumonia
IPTp case management, Syphilis detection and treatment Tetanus toxoid vaccination Diabetes case management Fetal growth restriction detection Hypertensive disease prevention and case management Induction of labor for pregnancies after 41 weeks Active management of the third stage of labor Clean birth practices Labor and delivery management ANS for preterm labor Antibiotics for preterm premature rupture of membranes Immediate assessment and stimulation Neonatal resuscitation Thermal care Chlorhexidine cord application Clean postnatal practices Hospital care of preterm babies including Kangaroo mother care	Appropriate complementary feeding Management of moderate acute malnutrition Management of severe acute malnutrition	Zinc for treatment of diarrhea Rotavirus vaccine	Hib vaccine Pneumococcal vaccine

ANS, antenatal corticosteroid treatment; Hib, *Haemophilus influenzae* type b; IPTp, intermittent preventive treatment of malaria for pregnant women.

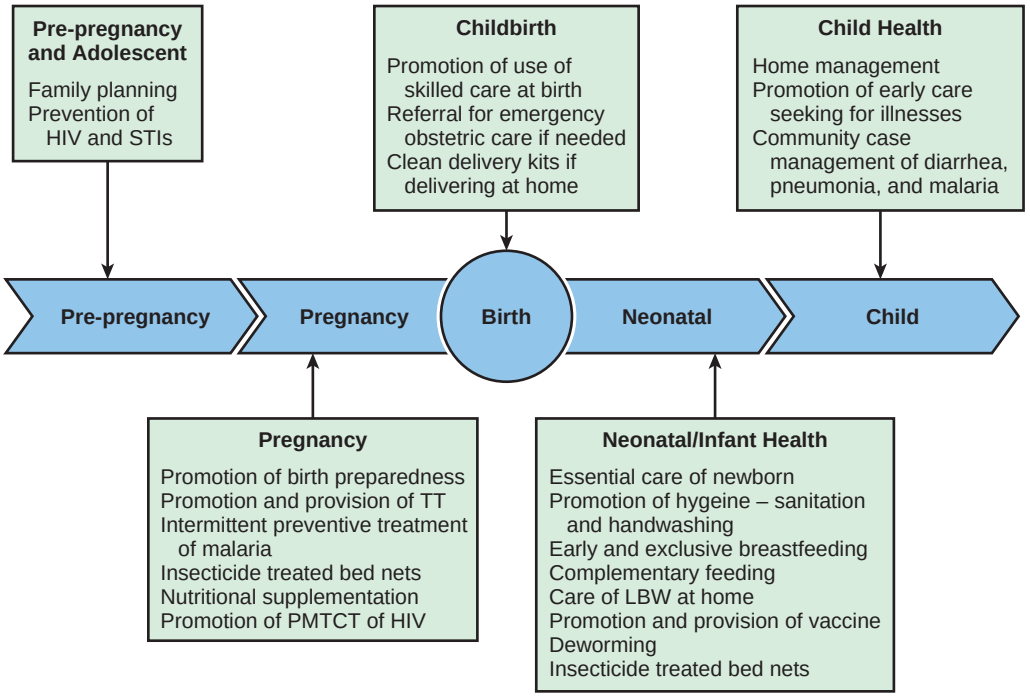

Figure 1-13 Neonatal and child health interventions: delivered by community health workers.

illness such as handheld pulse oximetry devices for children with respiratory infections, development of 4% chlorhexidine gel for prevention of cord infections in newborns, and injection devices to aid health workers such as Uniject systems.

There has been considerable work to achieve consensus across a range of UN agencies, academic bodies, and professional groups on key essential evidence-based interventions for maternal and child health that need implementation and scaling up within health systems.

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Chapter 2

Quality and Safety in Healthcare for Children

Ramesh C. Sachdeva

THE NEED FOR QUALITY IMPROVEMENT

There is a significant quality gap between known, recommended evidence-based care and the actual care that is delivered. Adults receive recommended care slightly higher than 50% of the time, whereas children receive recommended care only approximately 46% of the time. This quality gap exists because of a chasm between knowledge and practice—a chasm made wider by variations in practice and disparities in care from doctor to doctor, institution to institution, geographic region to geographic region, and socioeconomic group to socioeconomic group.

Historically, success in medicine was viewed as advances in technology, identification of new treatments, and the generation of new evidence to improve care. Although these facets of medical advances continue to be important, it is estimated that it takes about 17 yr for new knowledge and research findings to be adopted into clinical practice. Further, the Institute of Medicine's (IOM) report, "To Err is Human: Building a Safer Health System," highlights that ~44,000-98,000 patients die in U.S. hospitals each year because of preventable medical errors. These errors were more likely to occur in environments such as operating rooms, emergency departments, and intensive care units. Preventable medical errors have an economic cost of $17-$29 billion per year. These gaps in quality and related high costs will only be solved when physicians and healthcare systems adopt the emerging new science of **Quality Improvement (QI).**

The need for QI is expanding even further. With the growing concerns of healthcare costs and also the implementation of the Affordable Care Act, the scope of QI has expanded from the level of individual patients to include the notion of the **Triple Aim** proposed by the Institute for Healthcare Improvement–improving the care for *individual patients*, improving the care *for populations*, and improving the *cost effectiveness for healthcare delivery*. Recently, there has been a recognition that QI needs to shift from the sphere of process improvement toward outcomes improvement, and to ensure value from the standpoint of the patient.

WHAT IS QUALITY?

The IOM defines quality of healthcare as the degree to which healthcare services for individuals and populations increases the likelihood of desired health outcomes and are consistent with current professional knowledge. This definition incorporates 2 key concepts related to healthcare quality: the direct relationship between the provision of healthcare services and health outcomes, and the need for healthcare services to be based on current evidence.

To measure healthcare quality, the IOM has identified Six Dimensions of Quality all of which relate to quality of care. The Six Dimensions of Quality are **effectiveness, efficiency, equity, timeliness, patient safety,** and **patient-centered care.** Quality of care needs to be effective, which means that healthcare services should result in benefits and outcomes. Healthcare services also need to be efficient, which incorporates the idea of avoiding waste and improving system cost efficiencies. Healthcare quality should improve patient safety, which incorporates the concept of patient safety as one of the key elements within the Six Dimensions of Quality. Healthcare quality must be timely, thus incorporating the need for appropriate access to care. Healthcare quality should be equitable, which highlights the importance of minimizing variations as a result of ethnicity, gender, geographic location, and socioeconomic status. Healthcare quality should be patient-centered, which underscores the importance of identifying and incorporating individual patient needs, preferences, and values in clinical decision making.

The IOM framework of the Six Dimensions of Quality emphasizes the concept that all Six Dimensions of Quality need to be met for the provision of high quality healthcare. These concepts can be viewed as the overall *value* proposition—that is, the value created for a patient. From the standpoint of the practicing physician, these Six Dimensions of Quality can be categorized into clinical quality and operational quality. To provide high-quality care to children, both aspects of quality—clinical and operational—must be met. Historically, physicians have viewed quality to be limited in scope to clinical quality with the goal of improving clinical outcomes, and have considered efficiency optimization and access as the role of healthcare plans, hospitals, and insurers. Healthcare organizations, which are subject to regular accreditation requirements, viewed the practice of clinical care delivery as the responsibility of physicians and limited their efforts to improve quality largely to process improvement to enhance efficiencies. This is further magnified as many office-based pediatricians have independent clinical practices and interact with hospitals only when they care for hospitalized children.

This traditional perspective is changing. The evolving healthcare system requires physicians, healthcare providers, healthcare organizations, and hospitals to partner together to measure, demonstrate, and improve the overall quality of care to the patients they serve. With many regulatory and accreditation changes such as **Maintenance of Certification (MOC)** requirements of the **American Board of Pediatrics** and the planned Maintenance of Licensure by U.S. state licensing bodies, physicians will be required to understand and implement QI principles into their clinical practice and report the quality of their care delivered by them in a transparent manner.

The recently implemented Patient Protection and Affordable Care Act has at its core quality measurement and QI. The Affordable Care Act aims at enhancing access to care which is a quality dimension. Quality measurement is integral to ensuring transparency and choice across health plans. An important concept for quality within the Affordable Care Act relates to expanding the conventional scope of quality to population health.

Definitions of Quality-Related Terms

Quality includes many concepts—quality measurement, quality reporting and benchmarking, process improvement, performance, and outcomes improvement using quality initiatives (Table 2-1).

FRAMEWORK FOR QUALITY

Quality is broader in scope than QI. As adopted by the *American Academy of Pediatrics*, the approach to quality includes 4 building blocks (Fig. 2-1). First, the standard for quality must be defined (i.e., developing evidence based guidelines, best practices, or policies that guide the clinician for the specific clinical situation). These guidelines should change based upon new evidence. For example, in 2000-2001, the American Academy of Pediatrics had published guidelines for care

Table 2-1 Definitions of Quality-Related Terms

Quality	"…the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge." *U.S. Institute of Medicine*
Quality Initiative	"…systematic, data-guided activities designed to bring about immediate improvements in healthcare delivery in particular settings." *Hastings Center*
Performance Measure	"…yardsticks by which all healthcare providers and organizations can determine how successful they are in delivering recommended care and improving patient outcomes." *U.S. Institute of Medicine*
Performance Management	"…a systematic process by which an organization involves its employees in improving the effectiveness of the organization and achieving the organization's mission and strategic goals. By improving performance and quality, public health systems can save lives, cut costs, and get better results by managing performance." *Public Health Foundation*
Process Improvement	"… the systematic approach to closing of process or system performance gaps through streamlining and cycle time reduction, and identification and elimination of causes of below specifications quality, process variation, and non–value-adding activities." *BusinessDictionary.com*

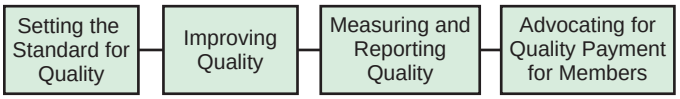

Figure 2-1 The American Academy of Pediatrics model for quality.

of children with attention-deficit/hyperactivity disorder. Subsequently, in 2011, these were updated to highlight a greater emphasis on behavioral interventions rather than pharmacologic options. Second, quality needs to be improved to close the quality gap. The quality gap refers to the difference between the recommended care and the actual care delivered to a patient. This can be achieved by using principles from improvement and implementation science. Improvement science relates to the methods and tools for achieving change. Methods can include learning collaboratives where groups of individuals share their experiences creating a community of learners. With the growth of new technology, including social media, virtual collaboratives are increasingly gaining popularity. Tools for QI can include techniques such as the Improvement Model, LEAN, Six Sigma, and Management Sciences. Implementation science is different than improvement science and relates to the study of methods to successfully spread the improvement to new settings and sustain it in these settings. Third, quality needs to be measured. Quality measures can be developed as measures for accountability and measures for improvement. Accountability measures are developed with a high level of demonstrated rigor as these are used at the macro level for measuring the quality of care at the state level, and for regional use by health plans and health systems. Efforts are ongoing to link such measures to *pay-for-performance (P4P)* for reimbursement at the hospital and individual physician level. In contrast, improvement measures are metrics that can demonstrate the improvement accompanying a QI initiative. These need to be locally relevant and typically have not had rigorous field testing. Finally, the quality measurement effort has to be linked to advocacy. Advocacy should be aimed at ensuring that there is adequate investment in early childhood from a preventive standpoint that will result in significant savings in adulthood from a healthcare perspective.

DEVELOPING GUIDELINES TO ESTABLISH THE STANDARD FOR QUALITY

Guidelines need to be developed based upon accepted recommendations, such as the Grades of Recommendation Assessment, Development and Evaluation system for rating the quality of the evidence and strength of evidence which is crucial for guideline development. Guidelines must adopt a high level of transparency in the development process. This is particularly relevant in the pediatric setting where there may be limited research using methods such as randomized controlled trials which would have a high level of rating from an evidence standpoint. As guidelines and policies related to quality need to be interpreted for specific settings, they should not be interpreted as standards of care.

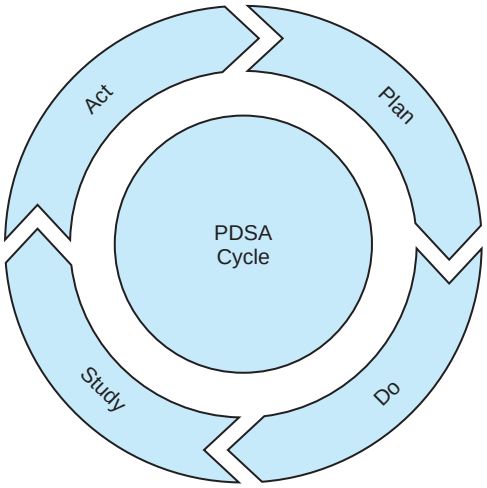

Figure 2-2 The plan-do-study-act cycle. *(From Langley GJ: The improvement guide: a practical guide to enhancing organizational performance, San Francisco, 1996, Jossey-Bass. © 1996 by Gerald J. Langley, Kevin M. Nolan, Thomas W. Nolan, L. Norman, and Lloyd P. Provost.)*

IMPROVING QUALITY

Achieving QI requires the adoption of a 3-step model: "Data → Information → Improvement." Quality needs to be measured. Quality data obtained from the measurement then needs to be converted into meaningful information that can be compared and reported. This quality measurement must also be actionable to achieve improvements in clinical practice. QI is a rapidly growing science. There are currently 4 techniques available for QI.

Model for Improvement

The *Model for Improvement* can be implemented using a framework of rapid cycle improvement also known as the *plan-do-study-act (PDSA) cycle* (Fig. 2-2). The PDSA cycle is typically aimed at testing small changes and then studying the results to plan and implement the next cycle of change (i.e., multiple PDSA cycles build on previous learning from PDSAs). Valuable information can be obtained from PDSA cycles that are successful, and those that are not, to help plan the next iteration of the PDSA cycle. The PDSA cycle specifically requires that improvements be data driven. This is important because many clinicians attempt to make changes for improvement in their practice but do not emphasize the importance of data collection.

The Model for Improvement has been successfully used in the **Vermont Oxford Network (VON)** to achieve improvements in care in

the **neonatal intensive care unit (NICU)** setting. The VON is a global network of collaborating NICUs involved in several studies that have favorably impacted the care of newborns. An example of a successful VON QI effort is a project aimed at reducing rates of chronic lung disease in extremely low birthweight infants. Clinical teams participating in this improvement effort used special reports from the VON database, reviewed the available evidence with content faculty experts, and then identified improvement goals. The teams received QI training through conference calls and emails for a period of 1 year. This effort resulted in a 37% increase in early surfactant administration for preterm infants achieving a high degree of QI.

Another example of a successful QI collaborative using the improvement model relates to the reduction of **catheter-associated bloodstream infections (CA-BSIs)** in the **pediatric intensive care unit (PICU)** setting. Similar to the VON experience, this effort included a group of PICUs that collaborated to impact a serious preventable problem in the PICU—*CA-BSIs*. National content experts and local PICU quality champions monitored and provided performance data at the local level in an almost real-time basis to ensure continued learning and improvement. The engagement of the entire PICU team—physicians, trainees, nurses, respiratory therapists, and others created a culture of quality and accountability. There was a strong emphasis on team learning across the participating institutions. This national collaborative sponsored by the Children's Hospital Association and the American Board of Pediatrics has resulted in a significant measurable reduction in CA-BSI rates across PICUs in the United States and is now in subsequent iterations of the PDSA cycle.

Six Sigma

Six Sigma relates to the reduction in *undesirable variation in processes* (Fig. 2-3). Every process has some level of inherent variation built into it. There are 2 types of variations in a process. *Random variation* relates to the variation that is inherent in the process simply because the process is being performed by humans. A physician completing a history and physical for a patient more than once may have a slightly different process each time, even though it is the same patient and the same physician. Random variation in processes is acceptable. In contrast, *special cause variation* relates to nonrandom variation that can adversely affect a process; when tracking infection rates in a nursery, a sudden increase in the infection rates may be secondary to poor handwashing techniques by a new healthcare provider in the system. This would represent a special cause variation (i.e., once this practice is improved, the infection rates will likely go back to the baseline level). Six Sigma attempts to provide a structured approach to unwanted variations in healthcare processes (Fig. 2-4). Six Sigma approaches have been successfully used in healthcare to improve processes in both the clinical and nonclinical settings.

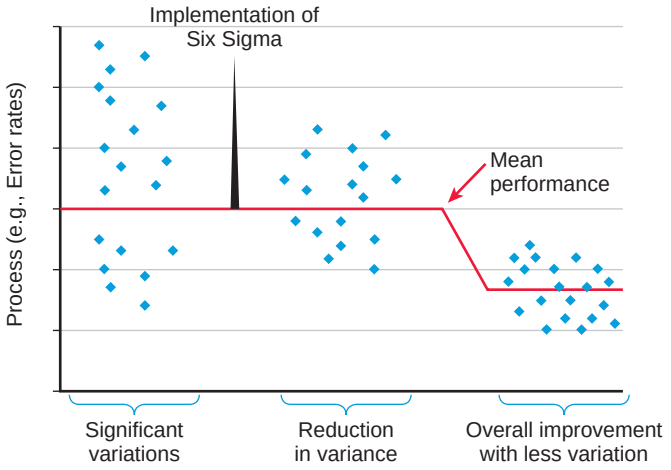

Figure 2-3 Improving quality by reducing variation and shifting the mean.

LEAN

Lean methodology, which stems from the Toyota Production System, aims at reducing waste within a process in a system. Figure 2-5*A* illustrates the steps in the process of a patient coming to the emergency department. After the initial registration, the patient is seen by a nurse and then the physician. In a busy emergency department, a patient may need to wait for hours before registration is complete and the patient is placed in the examination room. This wait time is a waste from the perspective of the patient and the family. By incorporating the registration process after placing the patient in the physician examination room, time can be saved and waste minimized (Fig. 2-5*B*). Lean

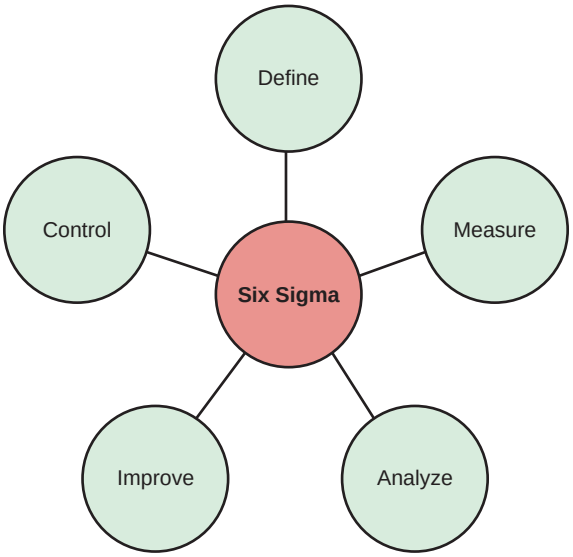

Figure 2-4 Six Sigma DMAIC (define, measure, analyze, improve, control) method.

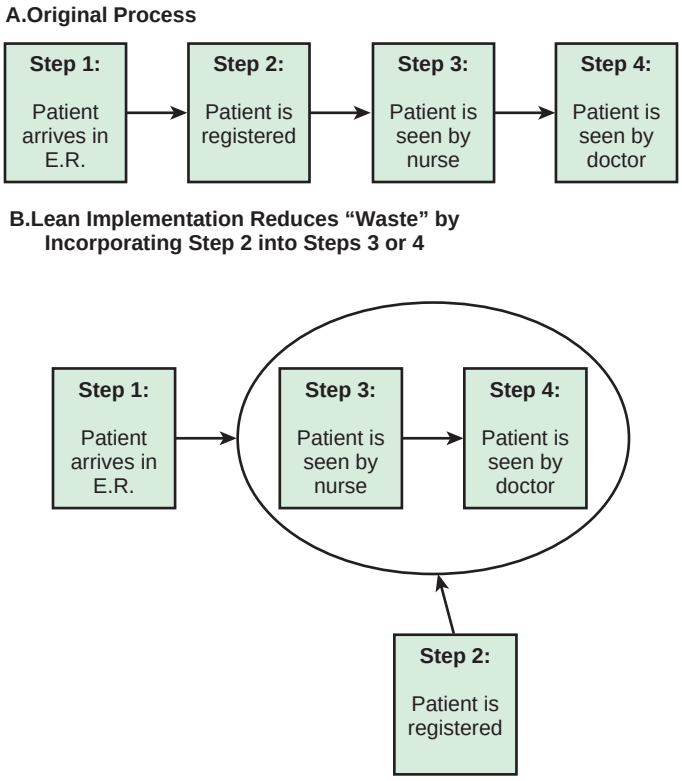

Figure 2-5 **A** and **B,** Lean—waste reduction.

methods have been successfully used in several outpatient and inpatient settings with resulting improvements in efficiency. Lean principles have also been adopted as a core strategy for children's hospitals with the goal of improving efficiencies and reducing waste.

Management Sciences

Management sciences, also known as *operations management*, stems from operations research and relates to the use of mathematical principles to maximize efficiencies within systems. Management sciences has been successfully used in many non–healthcare settings, such as airlines and the military. Management sciences principles have been successful in many European healthcare settings to optimize efficiencies in outpatient primary care office settings, inpatient acute care hospital settings, surgical settings including operating rooms, and also for effective planning of transport and hospital expansion policies. Management sciences principles are being explored for use in the U.S. healthcare system. One of the techniques for management sciences, *discrete event simulation* was used at the Children's Hospital of Wisconsin to effectively plan the expansion of the pediatric critical care services with the goal of improving quality and safety. The discrete event simulation model illustrated in Figure 2-6 depicts the various steps of the process in a PICU. Patients stratified across 3 levels of severity (low, medium, high) are admitted to the PICU, are initially seen by a nurse and physician, then stay in the PICU with ongoing care being provided by physicians and nurses, and are finally discharged from the PICU. The discrete event simulation model is a computer model developed using real estimates of numbers of patients, numbers of physicians and nurses in a PICU, and patient outcomes. Discrete event simulation models are created using real historical data, which allows testing the "what if" scenarios, such as the impact on patient flow and throughput by increasing the number of beds and/or changing nurse and physician staffing.

Another management sciences technique developed in Europe relates to the concept of *cognitive mapping*. Cognitive mapping aims at measuring the soft aspects of management sciences as illustrated in Figure 2-7. Cognitive mapping highlights the importance of perceptions and constructs of healthcare providers and how these constructs are linked in a hierarchical manner. Goals and aspirations of individual healthcare providers are identified by structured interviews and are mapped to strategic issues and problems, and options. By using specialized computer software, complex relationships can be identified to better understand the relationships between different constructs in a system. A discrete event simulation model views patient throughput based on numbers of beds, physicians, and nurses, and accounts for differences in patient mix. It does not account for many other factors, such as individual unit characteristics related to culture. By interviewing healthcare providers, cognitive maps can be developed that can help to better inform decision making.

MEASURING QUALITY

Robust quality indictors should have clinical and statistical relevance. Clinical relevance ensures that the indicators are meaningful in patient care from the standpoint of patients and clinicians. Statistical relevance ensures that the indicators have measurement properties to allow an acceptable level of accuracy and precision. These concepts are captured in the national recommendations that quality measures must meet the criteria of being valid, reliable, feasible, and usable (Table 2-2). Validity of quality measures relates to the notion that the measure is estimating the true concept of interest. Reliability relates to the notion that the measure is reproducible and provides the same result if retested. It is important that quality measures are feasible in practice. Quality measures must be useable, which means that they should be clinically meaningful. The **Agency for Healthcare Research and Quality** and the **National Quality Forum** have provided specific criteria to be considered when developing quality measures.

Quality indicators can be aimed at measuring the performance within 3 components of healthcare delivery: structure, process, and outcome (Fig. 2-8). Structure relates to the organizational characteristics in healthcare delivery. Examples of organizational characteristics are the number of physicians and nurses in an acute care setting and the availability and use of systems such as electronic health records. Process-related measures estimate how services are provided. Examples of a process measures are the percent of families of children with asthma who receive an asthma action plan as part of their office visit or the percent of hospitalized children who have documentation of

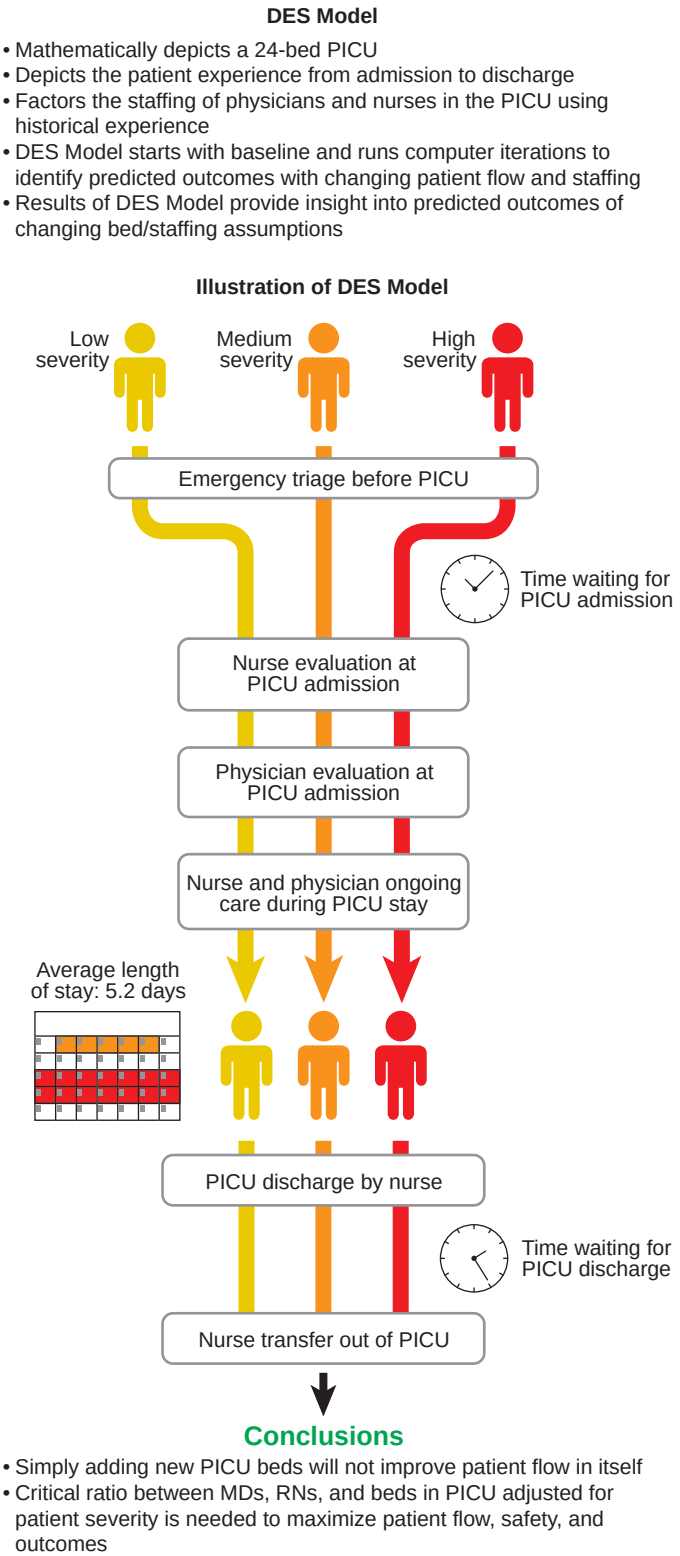

Figure 2-6 Management sciences—discrete event stimulation. PICU, pediatric intensive care unit.

pain assessments as part of their care. Outcome measures relate to the final health status of the child. Examples of outcome measures are risk adjusted survival in an intensive care unit setting, birthweight-adjusted survival in the NICU setting, and functional status of children with chronic conditions such as cystic fibrosis.

It is important to distinguish between measures for accountability and measures for improvement. As illustrated in Figure 2-9, measures, particularly measures for accountability that may be linked to attribution and payment, must be based upon a rigorous process. This can be resource intensive and time-consuming. In contrast, measures for improvement serve a different purpose—to track incremental improvements linked to specific QI efforts. These may not undergo rigorous testing, but they have limited applicability beyond the specific QI setting.

Quality data can be quantitative and qualitative. Quantitative data includes numerical data, which can be continuous (patient satisfaction scores represented as a percentage with higher numbers indicating better satisfaction) or categorical (patient satisfaction scores obtained from a survey where a Likert scale is used indicating satisfactory, unsatisfactory, good, or superior care). Data can also be qualitative in nature, which includes nonnumeric data. Examples of qualitative data can include results from open-ended surveys related to the satisfaction of care in a clinic or hospital setting. It is important to be sensitive to the source and quality of data being obtained to ensure data quality.

Data measuring quality of care can be obtained from a variety of sources, which include chart reviews, patient surveys, existing administrative data sources (billing data from hospitals), disease and specialty databases, and patient registries, which track individual patients over time.

It is important to distinguish between *databases* and *data registries*. Databases are data repositories that can be as simple as a Microsoft Excel spreadsheet or as complex as relational databases using sophisticated servers and information technology platforms. Databases can provide a rich source of aggregated data for both quality measurement and research. Data registries allow tracking individual patients over time; this dynamic and longitudinal characteristic is important for population health management and QI.

Table 2-2 Properties of Robust Quality Measures

ATTRIBUTE	RELEVANCE
Validity	Indicator accurately captures the concept being measured.
Reliability	Measure is reproducible.
Feasibility	Data can be collected using paper or electronic records.
Usability	Measure is useful in clinical practice.

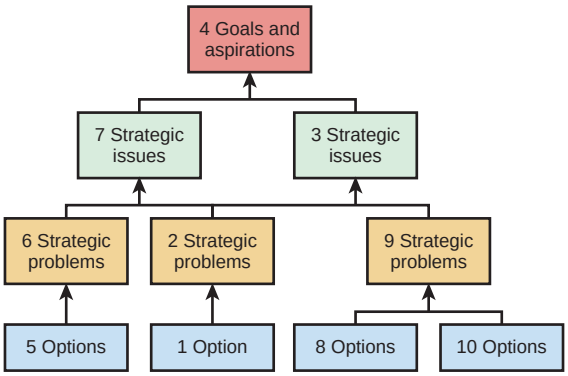

Figure 2-7 Management sciences—cognitive mapping.

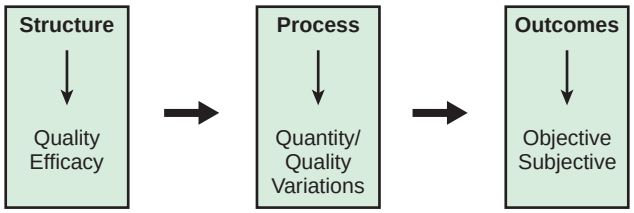

Figure 2-8 Donabedian model.

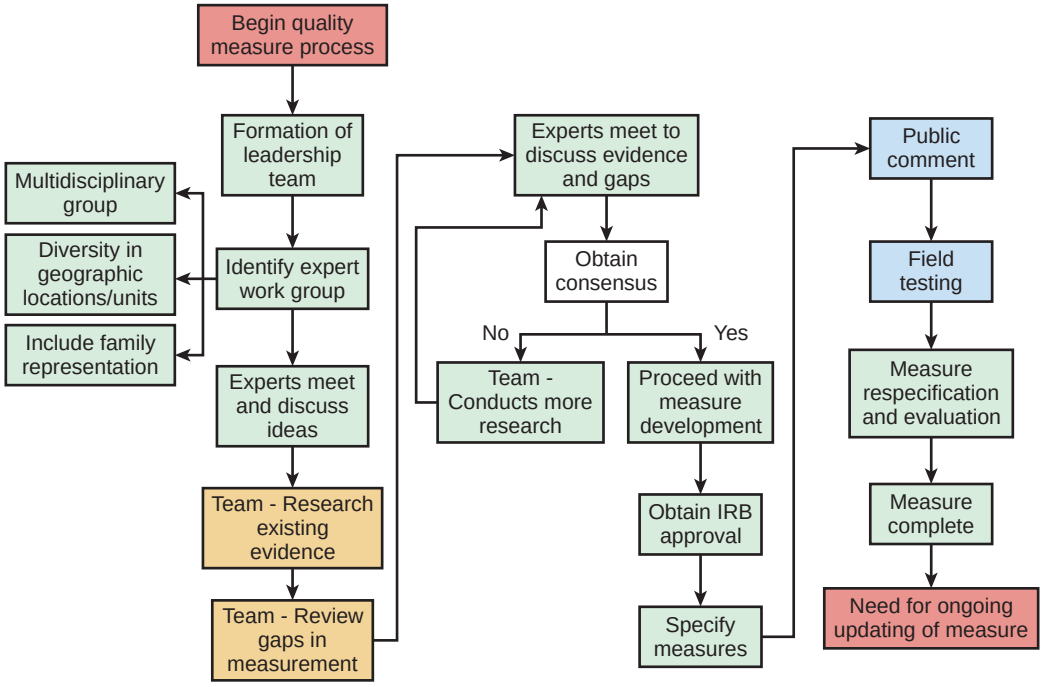

Figure 2-9 Development of a quality measure.

Data quality can become a significant impediment when using data from secondary sources, which can adversely impact the overall quality evaluation. Once data on the quality indicator has been collected, quality measurement can occur at 3 levels: (1) measuring quality status at 1 point in time (e.g., percent of children seen in a primary care office setting who received the recommended 2-year immunizations); (2) tracking performance over time (e.g., change in immunization rates in the primary care office setting for children 2 yr of age); and (3) comparing performance across clinical settings after accounting for epidemiologic confounders (e.g., immunization rates for children <2 yr of age in a primary care office setting stratified by race and socioeconomic status as compared to the rates of other practices in community and rates at national levels).

Pediatric quality measures are being developed nationally. Table 2-3 lists some of the important currently endorsed pediatric national quality indicators.

ANALYZING QUALITY DATA

Three approaches have been used for analyzing and reporting data. The classic approach from a research paradigm has been applied to quality data for statistically comparing trends over time, and differences before and after an intervention. P-values are interpreted as being significant if ≤0.05, which suggests that the likelihood of seeing a difference as extreme as observed has a probability of ≤5% (type I error). Another approach from an improvement science paradigm uses techniques such as run charts and control charts to identify special-cause variation. Special-cause variation attempts to capture observations that are unlikely to reflect random variation. Finally, quality data also has been reported on an individual patient level. This has gained popularity in the patient safety arena where identifying individual patient events in the form of descriptive analysis ("stories") may be more powerful in motivating a culture of change, rather than statistical reporting of aggregate data in the form of rates of adverse patient safety events.

COMPARING AND REPORTING QUALITY

There is an increasing emphasis on quality reporting in the United States. Many states have mandatory policies for the reporting of quality data. This reporting may be tied to reimbursement using the policy of P4P. P4P implies that reimbursements by insurers to hospitals and physicians will be partially based on the quality metrics. P4P can include both incentives and disincentives. Incentives relate to additional payments for meeting certain quality thresholds. Disincentives relate to withholding certain payments for not meeting those quality thresholds. An extension of the P4P concept relates to the implementation of the policy of **nonreimbursable hospital-acquired conditions**, formerly called "never events" by the **Centers for Medicare and Medicaid.** The Centers for Medicare and Medicaid has identified a list of hospital-acquired conditions, which are specific quality events that will result in no payment for care provided to patients (e.g., wrong site surgery, CA-BSI, and decubitus ulcers acquired in the hospital).

Quality reporting is also being used in a voluntary manner as a business growth strategy. Leading children's hospitals across the United States actively compete to have high ratings in national quality evaluations that are reported in publications such as *Parents* (formerly *Child)* magazine and *US News & World Report*. Many children's hospitals have also developed their own websites for voluntarily reporting their quality information for greater transparency. Although greater transparency may provide a competitive advantage to institutions, the underlying goal of transparency is to improve the quality of care being delivered, and for families to be able to make informed choices in selecting hospitals and physicians for their children.

Quality measures may also be used for purposes of certifying individual physicians as part of the MOC process. In the past, specialty and

Table 2-3 Examples of National Pediatric Quality Measures

NQF PEDIATRIC QUALITY INDICATORS	NQF-ENDORSED INPATIENT MEASURES AMONG PICUs	NQF-ENDORSED INPATIENT PEDIATRIC CARE MEASURES	NQF-ENDORSED OUTPATIENT PEDIATRIC CARE MEASURES
Neonatal bloodstream infection rate	PICU standardized mortality ratio	CAC-1 relievers for inpatient asthma	Appropriate testing for children with pharyngitis
Transfusion reaction	PICU severity-adjusted length of stay PICU unplanned readmission rate	CAC-2 systemic corticosteroids for inpatient asthma Admit decision time to ED departure time for admitted patients Follow-up after hospitalization for mental illness (FUH) NHSN Catheter-Associated Urinary Tract Infection (CAUTI) outcome measure NHSN Central Line-Associated Bloodstream Infection (CLABSI) outcome measure Percent of residents or patients assessed and appropriately given the pneumococcal vaccine (short stay) Restraint prevalence (vest and limb) Validated familycentered survey questionnaire for parents' and patients' experiences during inpatient pediatric hospital stay	CAHPS clinician/group surveys (adult primary care, pediatric care, and specialist care surveys) Child and adolescent major depressive disorder: diagnostic evaluation Child and adolescent major depressive disorder: suicide risk assessment Follow-up after hospitalization for mental illness (FUH) Initiation and engagement of alcohol and other drug dependence treatment Median time from ED Arrival to ED departure for discharged ED patients Pediatric symptom checklist (PSC)
Gastroenteritis admission rate		Initiation and engagement of alcohol and other drug dependence treatment (IET) Nursing hours per patient day Preventive care and screening: screening for clinical depression and follow-up plan Skill mix (RN, LVN/LPN, UAP, and contract)	

CAC, Children's Asthma Care; CAHPS, Consumer Assessment of Healthcare Providers and Systems; ED, emergency department; HBIPS, hospital-based inpatient psychiatric services; LVN/LPN, licensed vocational/practical nurse; NHSN, National Healthcare Safety Network; NQF, National Quality Forum; PICU, pediatric intensive care unit; RACHS-1, risk adjustment for congenital heart surgery; RN, registered nurse; UAP, unlicensed assistive personnel.

subspecialty certification in medicine, including pediatrics, was largely based on demonstrating a core fund of knowledge by being successful in an examination. No specific evidence of competency in actual practice needed to be demonstrated beyond successful completion of a training program. There continues to be significant variations in practice patterns even among physicians who are board certified, which highlights the concept that medical knowledge is important, but not sufficient for the delivery of high-quality care. Subsequently, the **American Board of Medical Specialties,** including its member board, the American Board of Pediatrics, implemented the MOC process in 2010. Within the MOC process, there is a specific requirement (Part IV of MOC) for the physician to demonstrate the assessment of quality of care and implementation of improvement strategies as part of recertification in pediatrics and subspecialties. Lifelong learning and the translation of learning into practice are the basis for the MOC process and for an essential competency for physicians professionalism. There are also discussions to adopt a similar requirement for Maintenance of Licensure for physicians by state medical regulatory boards.

The **Accreditation Council for Graduate Medical Education** requires residency programs to incorporate QI curriculum to ensure that systems-based practice and QI are part of the overall competencies within accredited graduate medical training programs. One form of **continuing medical education**, the **performance improvement** continuing medical education, is used for ongoing physician education. These initiatives require physicians to measure the quality of care they deliver to their patients, to compare their performance to peers or known benchmarks, and to work toward improving their care by leveraging QI methods. This forms a feedback loop for continued learning and improvement in practice.

Prior to comparing quality measures data both within and across clinical settings, it is important to perform risk adjustment to the extent that is feasible. **Risk adjustment** is the statistical concept that utilizes measures of underlying severity or risk so that the outcomes can be compared in a meaningful manner. The importance of risk adjustment was highlighted in the PICU setting many years ago. The unadjusted mortality rate for large tertiary care centers was significantly higher than that for smaller hospital settings. By performing severity of illness risk adjustment it was subsequently shown that the risks in tertiary care large PICUs were higher because patients had higher levels of severity of illness. These patients were sicker than other patients, which would explain the higher mortality rate. Although this concept is now intuitive for most clinicians, the use of severity of illness models in this study allowed a mathematical estimate of patient severity using physiologic and laboratory data, which allowed for the statistical adjustment of outcomes. This permits meaningful comparisons of the outcomes of large and small critical care units. Severity of illness models and the concepts of statistical risk adjustment are most developed in pediatric critical care, but these concepts are relevant for all comparisons of outcomes in the hospital settings where sicker patients may be transferred to the larger institutions for care and, therefore, would be expected to have poorer outcomes as compared to other settings with less sick patients.

Risk adjustment can be performed at 3 levels. First, patients who are sicker can be excluded from the analysis, thereby allowing the comparisons to be within homogenous groups. Although this approach is relatively simple to use, it is limited in that it would result in patient groups being excluded from the analysis. Second, risk stratification can be performed using measures of patient acuity. An example of this relates to the use of the **All-Patient Refined Diagnosis-Related Group** system where patients can be grouped or stratified into different severity criteria based on acuity weights. This approach may provide relatively homogenous strata within which comparisons can be performed, but it is not able to predict the overall outcomes within patient risk groups. Third, severity of illness risk adjustment relates to the use of clinical data to predict the outcomes of patient groups. An example of a clinical severity of illness risk adjustment process is the use of the **Pediatric Risk of Mortality (PRISM)** scoring system in the PICU setting. The PRISM score, and its subsequent iterations, composed of a combination of physiologic and laboratory perimeters that are weighted on a statistical logistic scale to predict the risk of mortality within that PICU stay. By comparing the observed and expected outcomes (i.e., mortality or survival), a quantitative estimate of the performance of that PICU can be established which can then be used to compare outcomes with other PICUs (standardized mortality ratio).

Risk-adjustment systems have been effectively incorporated into specialty databases. An example of such a system is the **Virtual Pediatric Intensive Care Unit System (VPS)**, which represents the pediatric critical care database system in the United States. The VPS, comprising more than 100 PICUs and cardiac PICUs across the United States, as well as international PICUs, currently has more than 300,000 patients within its database. The VPS database emphasizes data quality, both data validity and reliability, to ensure that the resulting data are accurate. Data validity has been established using standard data definitions with significant clinical input. Data reliability is established using interrater reliability to ensure that the manual data collection that involves several data collectors within pediatric institutions is consistent. The PRISM scoring system is programmed into the VPS software to allow the rapid estimation of the severity of illness of individual patients. This, in turn, allows risk adjustment of the various outcomes that are compared within institutions over time and across institutions for purposes of QI.

QUALITY AND PATIENT SAFETY

Safety is an important dimension of quality, and errors in healthcare are a leading cause of death and injury. Approximately 3-4% of hospitalized adult patients are harmed by the care that is supposed to help them, and 7% are exposed to a serious medication error that harms or could harm them. Multiple factors contribute to errors: an increasingly complex healthcare system with diffuse accountability; a culture of attributing errors to individuals, which overlooks problematic systems; lack of allegiance between physicians and hospitals, which detracts from patient-centered practices; and reimbursement policies that frequently discourage safety measures.

Medical Errors in Children's Healthcare

Few epidemiologic data are available regarding medication errors in the pediatric setting, and the *potential* for pediatric inpatient medical errors is substantial. This may be partly a result of children having unique clinical experiences that are prone to error. These unique risk factors or safety issues, the "4 Ds," are **developmental change, dependence on adults, different disease epidemiology,** and **demographic characteristics.** *Developmental change* might refer to the unique susceptibility of neonates to infections or the need for weight-based dosing with growth. Children's *dependence on adults* puts them at heightened risk for experiencing medical errors because children do not usually manage their own treatments or provide their own medical history and may not have the insight to question their own care. *Different disease epidemiology* refers to the unique illnesses and medical needs that predispose children to unique safety events as compared with adults (e.g., birth trauma and screening for metabolic abnormalities). Children have distinct *demographic characteristics* and are more likely to live in poverty than any other segment of the population.

Adverse drug events (ADEs) may occur in pediatric patients at a similar rate as in adult patients; the potential ADE rate may be 3 times higher in children. A *potential* ADE is one that is intercepted before causing harm. Most potential ADEs occur at the stage of drug ordering and involve incorrect dosing, antiinfective drugs, and intravenous medications. In an ambulatory setting, 13% of prescriptions for children had potential medication errors. These errors are more common for infants and toddlers, children obtaining multiple prescriptions at the same time, and prescriptions for analgesics/narcotics. Technology software does not always address issues specific to children, such as pediatric dosing calculations and age-based normal ranges. It is estimated that inpatient nonmedication errors involving children result in more than $1 billion in reconciliation costs per year and are associated with significant increases in length of stay, charges, and in-hospital deaths.

Key Issues in Patient Safety

Making care safer requires the identification and control of things that could cause harm to patients. Several key concepts regarding patient safety are summarized in the following sections and are available in curriculum overviews at www.patientsafety.gov, www.npsf.org, and www.va.gov.

Systems Approach

The majority of healthcare errors result from faults intrinsic to the processes by which healthcare is delivered, rather than individual mistakes. This systems approach compels organizations to respond to adverse events not by blaming individuals, but by improving the conditions under which individuals work. An error is viewed as a symptom of trouble in a process that offers an opportunity for improvement and the potential to implement safeguards.

Developing a Culture of Safety

The biggest challenge in making the health system safer is changing the culture from one of treating errors as personal failures to one of treating errors as opportunities to improve the system. Organizations need to foster a culture of learning in which each individual will feel accountable for ensuring a safe and quality program, communication is open, and teamwork is valued. Reporting of errors should be valued, reports of adverse events should be handled confidentially, and those who report errors should be protected from discovery. Developing a culture of learning involves the compassionate and appropriate disclosure of system failures and medical errors to patients and families. It has also been shown that utilizing multiple approaches to identify adverse events may be effective.

Communication. Good communication among the healthcare team is essential for patient safety. Healthcare involves the safe transfer of responsibility for patient care and the transfer of patient information. Poor communication or miscommunication creates the opportunity for incorrect or incomplete transfer of vital information during the transfer of responsibility for patient care from one provider to another, thus placing the patient at risk for serious medical error. The potential for harm is increased when the healthcare team and the patient do not share a native language. Errors in medical interpretation are common, with omissions being the most frequent. Ad hoc interpreters are significantly more likely to commit errors with harmful clinical consequences than are hospital interpreters.

Teamwork and Authority Gradients. Ensuring a systems approach to healthcare safety involves a paradigm shift. Healthcare has tended to be a hierarchical endeavor, with physicians in leadership roles that allowed significant amounts of autonomy. This authority gradient can predispose to communication failures: junior team members may be hesitant to speak up and senior members may resist feedback. A medical student or nursing assistant may be hesitant to inform an attending physician of a potential error. In a culture of safety, team members with different positions of authority must interact to facilitate optimal patient care; all are empowered to voice a safety concern. The composition of the teams may vary day to day because of shifting schedules. Senior leaders must be able to engender trust rapidly among team members, accept that human error is inevitable, and encourage behaviors that prevent or mitigate the harm that results from errors. Healthcare can learn important lessons for safety from industry. Experiences from industries that have standardized and achieved a high level of safety and reliability (e.g., the airline and nuclear industries) can help inform future healthcare systems in both developing and industrialized nations.

Human Factors Engineering. **Human factors engineering (HFE)** is a discipline concerned with the design of tools, machines, and systems that take into account human capabilities, limitations, and characteristics. It builds on ergonomics and utilizes what is known about human performance and system interaction. HFE can play an important role in the optimal design of equipment, the development of effective processes, monitoring for unintended consequences, and the planning for and introduction of new technologies. HFE techniques used to identify hazards or areas for improving safety can be proactive (addressing complex areas of healthcare before implementing an intervention) or reactive (reviewing reports of "close calls" or injuries). Computerized physician order entry, an example of HFE in healthcare, has been shown to decrease the rate of medication errors in pediatric inpatient settings.

The role of a team based approach along with the need to consider human factors requires the creation of systems that are designed to improve outcomes. Recent studies from the nursing literature has identified the positive impact of continuity of nursing care on patient outcomes in high-risk settings, and also the potential detrimental impact on patient outcomes with unduly long nursing shifts in the inpatient acute care setting for children.

Reliability. Reliability in healthcare is defined as the measurable capability of a process, procedure, or health service to perform its intended function in the required time under commonly occurring conditions (i.e., providing intended care on a consistent basis). Most healthcare organizations currently perform at *Level 1 reliability*, which means that processes are performed with only an 80-90% success rate. To achieve *Level 2 performance* (≤5 failures/100 opportunities), processes must be *intentionally designed* with tools and concepts based on the principles of HFE. Performance at *Level 3* (≤5 failures/1,000 opportunities), requires a well-designed system with low variation and cooperative relationships and a state of what has been called "mindfulness," where attention is paid to processes, structure, and their relationship to outcomes. Cincinnati Children's Hospital Medical Center used reliability science and the Model for Improvement to institute a ventilator-associated pneumonia protocol that led to an 87% reduction in ventilator-associated pneumonias per 1,000 ventilator days (from a fiscal year average of 7.5 to an average of only 0.95).

Such efforts are now expanding from individual institutions to the regional level. The Solutions for Patient Safety is a new collaboration of multiple pediatric institutions at a state level to share quality and safety data in a transparent manner, and to create a culture of shared learning.

IMPLICATIONS OF THE U.S. HEALTHCARE REFORM FOR QUALITY

In 2010, the Affordable Care Act was enacted into law. This significant health care legislation attempting to achieve the vision of universal health care includes an emphasis on access to health care, the implementation of consumer protections (e.g., preexisting conditions), and improving quality and lowering the cost of health care.

Regarding quality and safety in health care for children, health care reform has three key implications. First, universal coverage optimizes access and includes expanding coverage for young adults to age 26 yr. Second, various initiatives related to quality, safety, patient-centered outcomes research, and innovation were implemented and funded. For example, the Agency for Healthcare Research and Quality (AHRQ) has funded a national effort to establish seven centers of excellence through the Pediatric Quality Measurement Program (PQMP) to improve existing pediatric quality measures and create new measures that can be used by states and in a variety of other settings to evaluate quality of care for children. Third, a paradigm shift in the existing model of health care delivery system has been vertically integrated toward a model of horizontal integration. This has led to the creation and rapid growth of integrated delivery systems and risk-sharing relationships of accountable care organizations (ACOs).

Accomplishing this strategic direction is resulting in three new areas of rapid growth in the quality arena. "Big Data" relates to the notion of linking potentially disparate sources of data to generate new knowledge, accelerate innovation, and improve outcomes. Big Data is unique in that it aims to link structured and unstructured data sources, including data emerging from databases, registries, clinical records, and social media. A key strength of using a large volume of data across multiple sources by linking it to create Big Data is a significant increase in power for early prediction and new knowledge generation that can be rapidly implemented.

Another area of increasing emphasis is the notion of population health. This is important because it expands the traditional role of

physicians to improve quality of care for individual patients to also improve the quality of care for larger populations. Populations can be defined by geographic constraints or disease/patient condition. The notion of population health is integral for achieving the "triple aim" vision of quality of care. Efforts to link payment and reimbursement for care delivery by physicians and health systems are being increasingly tied to measurable improvements in population health. To achieve a meaningful improvement in population outcome, physician practices will need to embrace the emerging paradigm of practice transformation. Practice transformation has many facets, including the adoption of a "medical home," the seamless connectivity across the primary care and subspecialty continuum, and a strong connection between the medical and social determinants of health care delivery. To implement successful practice transformation, hospitals are increasingly adopting a broader view to evolve into health care systems that serve children across the entire range of the care continuum, including preventive and primary care, acute hospital care, and partnerships with community organizations for enhancing the social support structure. In addition, new risk-sharing payment models are evolving, resulting in the growth of entities such as ACOs, which represent a financial risk-sharing model across primary and subspecialty care and hospitals, resulting in an unprecedented level of health care integration to improve quality of care.

THE EVOLUTION OF QUALITY TO OUTCOMES TO VALUE

Most efforts at QI tend to emphasize enhancements in the process of healthcare delivery with the assumption that this will lead to improvements in outcomes. With the growing adoption of electronic health records that can allow tracking patients across the continuum of care, it will be possible to measure outcomes. Efforts at quality and outcomes must move toward creating value from the perspective of patients and families. Healthcare delivery systems must be developed based upon patient needs. Healthcare providers should lead this initiative to create value and that outcomes being measured should matter to patients.

INFORMATION TECHNOLOGY AND QUALITY IMPROVEMENT

The underlying goal of the HIT movement is to improve quality and safety. HIT includes electronic health records, personal health records, and health information exchange. The purpose of a well-functioning electronic health record is to allow collection and storage of patient data in an electronic form, to allow this information to be provided to clinicians and healthcare providers, to have the ability to allow clinicians to enter patient care orders through the **computerized physician order entry,** and to have the infrastructure to provide clinical decision support which will improve physician decision making at the level of individual patients. Personal health records will allow patients and families to be more actively engaged in managing their own health by monitoring their clinical progress and laboratory information, and also be able to communicate with their physicians for appointments, obtaining medications, and getting their questions answered. Appropriate, timely, and seamless sharing of patient information across physician networks and healthcare organizations is critical to quality care and to achieve the full vision of a *medical home* for children. Health information exchange would allow the sharing of healthcare information in an electronic format to facilitate the appropriate connections between providers and healthcare organizations within a community or region. However, significant cost and time barriers remain for adoption of HIT. The entire field of HIT as a mechanism to improve quality is likely to continue to be in the forefront of the quality journey for physicians and healthcare organizations for the next several years.

Despite the emphasis on HIT and data, it is important to understand that data does not lead to improvement in itself. Improvement is an affirmative choice and requires translating data (measurement) into clinically relevant information (data that has context and relevance) that is actionable for QI.

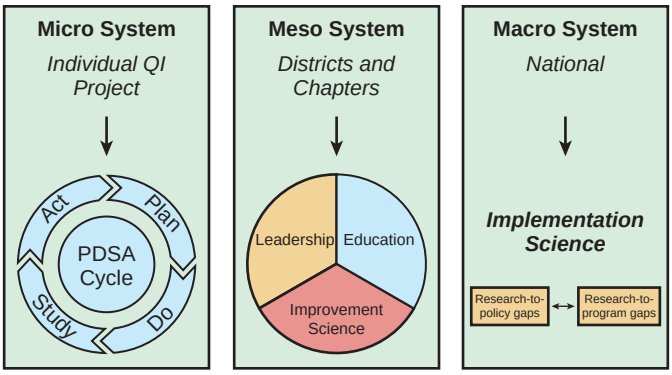

Figure 2-10 Success ingredients for large-scale quality improvement.

QUALITY IMPROVEMENT OR RESEARCH?

Research aims at generating new knowledge. QI aims at implementing the new knowledge into practice. Whereas research aims at developing new generalizable knowledge, QI aims at adopting the available evidence into practice at a local level. With the growing interest of research in the field of QI and efforts to expand the generalizability of QI initiatives, there can be situations in which research and QI overlap. In the future, the gap between QI and research will likely narrow to allow a continuum of active knowledge transfer from research into practice using QI methods.

EXPANDING INDIVIDUAL QUALITY IMPROVEMENT INITIATIVES TO SCALE

Despite the success of individual QI and patient safety projects, the overall progress to achieve large-scale improvements to reach all children across the spectrum of geographic location and socioeconomic status remains limited. This contributes to the health disparities that persist for children with significant differences in access and quality of care. A potential factor that limits the full impact of QI is the lack of strategic alignment of improvement efforts with hospitals, health systems, and across states.

This challenge can be viewed from a system standpoint in being able to conduct and expand QI from a micro level (individual projects), to the meso level (regional), to the macro level (national and international). The learning from individual QI projects for addressing specific challenges can be expanded to the regional level by ensuring that there is optimal leadership, opportunity for education, and adoption of improvement science (Fig. 2-10). To further expand the learning to a national and international level, it is important to leverage implementation science to allow a strategic approach to identification of the key success ingredients to expand the improvement strategy. To fully leverage the synergies to impact the quality of care delivered to children, it is important for national and international healthcare organizations to effectively collaborate from a knowledge management and improvement standpoint (Table 2-4).

INTERNATIONAL EFFORTS FOR QUALITY IMPROVEMENT

The implications of QI for healthcare delivery systems are equally relevant to international venues as to the United States. Many developing and industrialized countries are in the process of expanding their pediatric care delivery systems to have a greater presence of tertiary and quaternary care delivery. The understanding and adoption of QI principles during the early phase of expansion will result in the efficient use of resources with the greatest potential for favorably impacting health outcomes in children. Pediatric clinical practices in many developing countries have already adopted several unique, innovative approaches to allow delivery and creation of healthcare systems despite limited resources. These local innovations need to be expanded to allow for learning across countries. QI provides a unique strategy that can result in linking of a global community for the care of children including real-time learning and sharing of innovative best practices

Table 2-4 National Organizations Involved in Pediatric Quality Improvement

ORGANIZATION	ROLE	ACTIVITIES
American Academy of Pediatrics (AAP)	Represents more than 60,000 pediatricians and pediatric subspecialists worldwide	Resources for QI to improve health for all children, best practices, advocacy, policy, research and practice, and medical home
American Board of Pediatrics (ABP)	Certifying board for pediatrics and pediatric subspecialties	Certification policies and resources for activities such as Maintenance of Certification (MOC)
American Medical Association (AMA)	Physician member association	Physician Consortium for Performance Improvement (PCPI)—physician-led initiative
Children's Hospital Association (CHA)	Formerly the National Association of Children's Hospitals and Related Institutions; and the Child Health Corporation of America	Databases, QI collaboratives, and policy
Institute for Healthcare Improvement (IHI)	QI organization for adult and pediatric care	QI collaboratives, QI educational workshops and materials
National Initiative for Child Health Quality (NICHQ)	QI organization for pediatric care	QI training, improvement networks
Joint Commission	Hospital accreditation organization	Unannounced surveys to evaluate quality of care in hospitals
National Committee for Quality Assurance (NCQA)	QI organization	Healthcare Effectiveness Data and Information Set (HEDIS) and quality measures for improvement
National Quality Forum (NQF)	Multidisciplinary group including healthcare providers, purchases, consumers, and accrediting bodies	Endorsing national quality measures, convening expert groups, and setting national priorities

across the developing and industrialized worlds. Many international efforts to improve QI are already in progress. For example, the World Health Organization (WHO) has highlighted the global progress in adoption of HIT in many countries. A survey performed by WHO between 2005 and 2006 identified that nearly half of 112 countries responding to the survey already have national task forces or related groups to provide the national direction for e-health strategies. Pediatricians have the unique opportunity to provide leadership to evolving governmental-private-public partnerships in designing the next generation of pediatric healthcare delivery systems.

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Chapter 3

Ethics in Pediatric Care

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Pediatric ethics is the branch of bioethics that analyzes moral aspects of decisions made relating to the healthcare of children. In general terms, the **autonomy**-driven framework of adult medical ethics is replaced by a **beneficent** paternalism (or parentalism) in pediatrics. Pediatric ethics is distinctive because the pediatric clinician has an independent fiduciary obligation to act in a younger child's **best interest** that takes moral precedence over the wishes of the child's parent(s). For older children, the concept of **assent** suggests that the voice of the patient must be heard. These factors create the possibility of conflict among child, parent, and clinician. The approach to the ethical issues that arise in pediatric practice ***must*** include respect for parental responsibility and authority balanced with a child's developing capacity and autonomy. Heterogeneity of social, cultural, and religious views about the role of children adds complexity.

ASSENT AND PARENTAL PERMISSION

The doctrine of informed consent has limited direct application to children and adolescents who lack decisional capacity. The capacity for informed decision making in healthcare involves the ability to understand and communicate, to reason and deliberate, and to analyze conflicting elements of a decision using a set of personal values. The age at which a competent patient may legally exercise voluntary and informed consent for medical care varies from state to state and may be limited to specific conditions (sexually transmitted infections, family planning, drug or alcohol abuse).

In contrast to decisions about one's own care, a parent's right to direct a child's medical care is more limited. For this reason, the term *parental consent* is misleading. The concept of parental permission (rather than consent) reflects a *surrogate* or *proxy* decision made by a parent on behalf of a child. It is constrained both by the child's best interest and the independent obligation of clinicians to act in the child's best interest, even if this places them in conflict with a parent. In any given instance, the decision of what is or is not in a child's best interest may be difficult, especially given the diverse views of acceptable child rearing and child welfare. Parents are (and should be) granted wide discretion in raising their children. In cases involving a substantial risk of harm, the moral focus should be on avoiding or preventing harm to the child, not on a parental right to decide. While the term "best" interests may be too high of a threshold requirement, a minimum standard of "basic" interests is ethically obligatory.

Respect for children must account for both a child's vulnerability and developing capacity. This respect encompasses both the protective role of parental permission and the developmental role of **child assent** (the child's affirmative agreement). Understanding the concept of assent is one of the major conceptual challenges in pediatric ethics. The dissent (or disagreement) of a child is the opposite of assent and is also morally relevant. Pediatric ethics ***requires*** clinicians and parents to override a child's dissent when a proposed intervention is essential to the child's welfare. Otherwise, assent should be solicited and dissent should be honored. In seeking younger children's assent, a clinician should help them understand their condition, tell them what they can expect, assess their understanding and whether they feel pressured to assent, and solicit their willingness to participate. All efforts must be made to delineate situations in which the test or procedure will be done regardless of the child's assent/dissent, and in such cases the charade

of soliciting assent should be avoided. There is an important distinction between soliciting assent and respectfully informing a child that a test or procedure will take place regardless of the child's decision. Optimally, an educational process can transpire (if time allows) to gain the trust and assent of the child-patient. When this cannot occur, pediatric ethics requires that clinicians apologize to a child for acting to override dissent.

Older children or adolescents may have the cognitive and emotional capacity to fully participate in healthcare decisions. If so, the adolescent should be provided with the same information as would be given to an adult patient. In cases like this, the patient may be able to provide informed consent ethically but not legally. The adolescent's parent(s) remain in a guiding and protective role. The process of communication and negotiation will be more complex should disagreement arise between the parent and adolescent.

TREATMENT OF CRITICALLY ILL CHILDREN

Infants, children, and adolescents who become critically ill may recover fully, may die, or may survive with new or worsened limitations of function. Uncertainty about outcomes can make planning goals of care difficult, or if misunderstandings between patient, families, and medical staff occur, may drive conflict over treatment proposals. Ethical issues that arise during critical illness include balancing benefits, burdens, and harms of therapy in the face of uncertainty; maintaining a helpful degree of transparency and communication about medical standards of care at an institution; understanding and respecting religious and cultural differences that impact requests for or refusal of treatments; defining limits of therapy based on assessments of medical futility; recognizing the moral equivalence of not starting an ineffective treatment and stopping (although the 2 acts may feel very different to families and providers); and controversies such as withholding medically administered nutrition and hydration.

Transitioning the Goals of Care

Most acutely ill children who die in an ICU do so after a decision has been made to either forgo or withdraw **life-sustaining medical treatment (LSMT)**, and the same may apply in the chronically ill population. LSMT is justified when the anticipated benefit outweighs the burdens to the patient; the availability of technology does not in and of itself obligate its use. Decisions to use, limit, or withdraw LSMT should be made after careful consideration of all pertinent factors recognizable by both family and medical staff, including medical likelihood of particular outcomes, burdens on the patient and family, religious and cultural decision-making frameworks, and input by the patient when possible. Although fear of legal repercussions may sometimes drive treatment and medical advice, ultimate decisions should be based on what is thought to be best for the patient rather than based on fears of litigation.

The concept of **futility** has been used to support unilateral forgoing of LSMT against the wishes of patients and families by holding that clinicians should not provide futile (or useless) interventions. If medical futility is defined narrowly as the impossibility of achieving a desired physiologic outcome, then forgoing a particular intervention is ethically justified. However, this approach may not adequately engage professionals and families in understanding facts and values that might allow the same therapy to reach other goals, and may leave medical and family stakeholders in permanent conflict. If agreement cannot be reached through clear and compassionate communication efforts, further input can be sought from an ethics consultant or committee.

Communication about life-threatening or life-altering illness is challenging, and requires skills learned through both modeling and practice. These skills include choosing a setting conducive to what may become 1 or more long conversations; listening carefully to children's and families' hopes, fears, understanding, and expectations; explaining medical information and uncertainties simply and clearly without complicated terms and concepts; conveying concern and openness to discussion; and being willing to share the burdens of decision-making with families by giving clear recommendations. Discussing difficult topics with children requires an understanding of child development, and can be aided by professionals such as child psychologists or child life specialists. Such conversations and their outcomes have a major impact on the future care of the patient, on families, and on medical staff. For this reason, ongoing evaluation of goals and communication about them is needed with families and within complex medical teams as the course of the illness unfolds.

Experts recognize that good medical care involves providing for communication, symptom management, and a range of supportive services from the onset of acute illness. In this way, if an illness proves to be life-limiting in spite of aggressive therapies, the elements of palliative care are already in place. This concept has had difficulty gaining traction, especially in critical care settings, because of the mistaken conflation of broadly defined palliative measures with hospice care. Palliative care interventions focus on the relief of symptoms and conditions that may detract from quality of life regardless of the impact on a child's underlying disease process, and as such are important whether care is focused on cure or on transitioning to end-of-life care (see Chapter 43). Some interventions regarded as life-sustaining, such as chemotherapy, may be ethically acceptable in the end-of-life setting if their use decreases pain and suffering rather than results only in prolonging death.

Withholding and Withdrawing Life-Sustaining Treatment

Limitation of interventions or withdrawal of existing therapies are ethically acceptable if they are congruent with a plan of care focused on comfort and improved quality at the end of life rather than cure. The prevailing view in Western, traditional medical ethics is that there is no moral distinction between withholding or withdrawing interventions that are not medically indicated. Uncertainty in predicting a child's response to treatment may drive the initiation and continuation of interventions that are no longer supportive of shared goals of care. It is necessary to continually evaluate the results of these treatments and the evolution of the illness to recognize whether such interventions continue to be the best medical and moral choices. Maintaining the focus on the child rather than on the interests of parents or medical staff will help guide decision making.

The decision about whether or not to attempt **cardiopulmonary resuscitation** may become an issue to discuss with parents of children living with life-threatening or terminal conditions. All elements of end-of-life care approaches, including resuscitation status, should be supportive of agreed-on goals of care. It is imperative that decisions and plans are effectively communicated to all caregivers in order to avoid denying medically effective interventions and measures to ensure comfort. Orders about resuscitation status should clarify the plan regarding intubation and mechanical ventilation, the use of cardiac medications, chest compressions, and cardioversion. Because goals of care may change over time, a medical order regarding resuscitation is not irrevocable. Clinicians may assume that the absence of a do-not-attempt-resuscitation (DNAR) order obligates them to perform a prolonged resuscitation. This action may not be ethically supportable if resuscitative efforts will not achieve the desired physiologic endpoint. In all cases, treatments should be tailored to the child's clinical condition, balancing benefits and burdens to the patient. Resuscitation should not be performed solely to mollify parental distress at the tragic time of the loss of their child.

Advance Directives. An advance directive (AD) is a mechanism that allows patients and/or appropriate surrogates to designate the desired medical interventions under applicable circumstances. Discussion and clarification of resuscitation status should be included in advance care planning, and for children attending school in spite of advanced illness, may need to be addressed in that setting. Decisions regarding resuscitation status in the out-of-hospital setting can be an important component of providing comprehensive care.

The 1991 federal Patient Self-Determination Act requires that healthcare institutions ask adult (>18 yr) patients whether they have completed an AD and, if not, inform them of their right to do so. Few states support creation of broad ADs for minors because ADs are

traditionally created by persons with legal decision-making capacity, but some have moved in this direction because it is recognized that minors may be capable of participating in decision making, especially if they have been dealing with chronic disease. However, surrogate decision makers may participate in advance care planning for their children. Most states have approved the implementation of prehospital or portable DNAR orders, through which adults may indicate their desire not to be resuscitated by emergency personnel. On a state-by-state basis, portable orders regarding resuscitation status may also apply to children. If DNAR orders exist for an infant or a child, it is important to communicate effectively about their intent among all potential caregivers, because nonmedical stakeholders such as teachers or sitters may not wish to be in the position of interpreting or honoring them. Some institutions have established local policies and procedures by which an appropriately executed outpatient DNAR order can be honored upon a child's arrival in the emergency department. Key features may include a standardized document format, review by an attending physician, ongoing education, and involvement of a pediatric palliative medicine service.

In cases involving prenatal diagnosis of a lethal or significantly burdensome anomaly, parents may choose to carry their fetus/unborn child to term in order to cherish a short time with the infant after birth, but do not feel that resuscitation or certain other aggressive measures would support their well-considered goals of care. In this setting, a birth plan explaining the reasons for each choice can be developed by the parents and medical staff prior to delivery and shared with involved medical staff. This approach gives staff a chance to find other caregivers if they are uncomfortable with the approach, without abandoning the care of the child. If, after evaluation at birth, the infant's condition is as had been expected, honoring the requested plan is ethically supportable and should be done in a way that optimizes comfort of the infant and family.

Many states utilize **Physician Orders for Life-Sustaining Treatment** or **Medical Orders for Life-Sustaining Treatment** approaches to communicating a patient or surrogates wishes regarding advance care planning. It is important for pediatricians to learn which pathways for communicating goals of care are available in their own states.

Artificial Hydration and Nutrition. Issues surrounding withholding or withdrawing artificial hydration and nutrition are controversial, and interpretations are affected by parental, religious, and medical beliefs. Any adult or child who is fully dependent on the care of others will die as a result of not receiving hydration and nutrition. Case law has supported the withholding of artificially administered nutrition and hydration in the setting of adult vegetative or permanently unconscious patients who can be shown to have previously expressed a wish not to be maintained in such a state. This requires a valid AD, or for a surrogate decision maker to speak on behalf of the patient's known wishes. Because infants and many children have not reached a developmental stage in which such discussions would have been possible, decisions about stopping artificially administered nutrition and hydration as a limitation of treatment are more problematic. These decisions should be based on what families and caregivers decide best support comfort. In the child who is imminently dying, unaware of hunger, does not tolerate enteral feedings, and in whom family and staff agree that IV nutrition and hydration only prolong the dying process, it may be ethically supportable to withhold or withdraw these treatments based on a benefit–burden analysis.

The Doctrine of Double Effect. Treatment decisions at the end of life may include limitations of certain LSMT, or may involve the use of analgesic or sedative medications that some fear may shorten life, thereby causing death. The doctrine of double effect holds that an action with both good and bad effects is morally justifiable if the good effect is the only one intended, and the bad effect is foreseen and accepted, but not desired. In pediatrics, it is most commonly applied in end-of-life cases, when upward titration of medication (opiates) necessary to relieve pain, anxiety, or air hunger can be expected to result in a degree of respiratory depression. In such cases, meeting a provider's obligation to relieve suffering is the intended effect, and this obligation to the patient outweighs the acknowledged but unavoidable side effect. Choosing medications that adequately relieve symptoms with minimal adverse effects would be ethically preferable, but the obligation to provide comfort at the end of life outweighs the foreseeable occurrence of unavoidable side effects. Hastening death as a primary intention is not considered to be morally acceptable.

Providing pain medication guided by the doctrine of double effect should not be confused with active euthanasia. The distinction is clear:

- In active euthanasia, causing death is chosen as a means of relieving the symptoms that cause suffering.
- Under the doctrine of double effect, adequate management of pain, anxiety, or air hunger is recognized as an obligation to dying patients, and is provided by careful titration of medications in response to symptoms. If death occurs sooner as a result, this is accepted.

In both cases the patient dies and in both cases suffering ends, but immediate death is the intended consequence only in the case of euthanasia. Codes of ethics and legislation in many states support the obligation to provide pain and symptom relief at the end of life, even if this requires increasing doses of medication.

CARE OF DISABLED NEWBORNS

In 1982, an infant with Down syndrome and esophageal atresia was allowed to die at 6 days of age at the parents' request. Prior to this case becoming public, prevailing opinion was that withholding aggressive treatments from infants who were predicted to be significantly disabled from conditions such as Down syndrome or meningomyelocele was ethically acceptable, and was being done on advice of physicians who felt that they and families should be able to decide what was best for an individual infant. The public legal controversy resulted in federal legislation called the "Baby Doe Regulations," prohibiting the withholding of medically beneficial treatment from disabled infants except under conditions of permanent unconsciousness, "futile" treatment, and "virtually futile" treatment that imposes excessive burdens on the infant. Today, treatment options and potential outcomes have improved, attitudes toward and social supports for disabled children have evolved, and initial aggressive treatment of infants with severe disabilities has become more common. Studies done since the Baby Doe Regulations went into effect indicate that most pediatricians supported parental rather than government control of such decisions, and felt that they were now constrained to institute treatments that served neither patients nor families well.

One consequence of the legislation was a shift from potential undertreatment to widespread overtreatment (LSMT that does not serve the interests of the child) of severely disabled newborns. The legislation has been difficult to enforce, and subsequent case law has upheld the right of a parent to decide to forgo LSMT in certain instances. The 2002 "Born Alive Act" defined a human being as any infant born alive at any stage of development. It has been thought by some to pose a risk to the ethical practice of providing palliative care for newborns, though many believe that no changes in patient management are necessary.

Active euthanasia of severely suffering disabled newborns has been legalized in the Netherlands, using a protocol designed to minimize risk of abuse and maximize transparency. Although there may be some controversy over the subject in the United States, there is consensus that active euthanasia is not ethically acceptable in the care of infants and children.

DECLARING DEATH AND ORGAN DONATION

Donation of solid organs necessary to support life can occur after a patient is declared dead based on either irreversible cessation of neurologic function of the brain and brainstem (death by neurologic criteria, or "brain death") or a predetermined period of cardiac asystole called "circulatory death." To avoid a potential conflict of interest by surgeons or others caring for a potential organ recipient, the request for organ donation should be separated from the clinical discussion of either brain death or withdrawal of LSMT. Although clinicians may be

the first providers to enter discussion about death and organ donation with family members during conversations about outcomes and options, detailed discussion of organ donation should be done by other individuals who are specifically trained for this purpose. This "decoupling" of clinical decision making from a request for organ donation by trained individuals, perhaps by providing families with expert information without a perceived conflict of interest, has been associated with improved donation rates.

Death by Neurologic Criteria

Death by neurologic criteria (DBNC), commonly referred to as brain death, may be difficult for families to understand when the child appears to be breathing (albeit on a ventilator), pink, and warm to the touch, and when language such as life support is used at the bedside by staff. Studies also document clinician misunderstanding of the diagnosis of DBNC. For these reasons, strict criteria adhering to nationally accepted guidelines must be used to determine when irreversible cessation of brain and brainstem function has occurred, and to adequately document these findings (see Chapter 68.1).

The states of New York and New Jersey allow families to object on religious grounds to the declaration of DBNC. In that situation, the clinical determination of the DBNC sets the stage for a discussion of forgoing LSMT, rather than the death of the patient. A unilateral decision not to initiate new or escalate existing interventions is ethically supportable under these circumstances, given the documented death of the patient. Even though it would seem to follow that a similar unilateral decision to withdraw existing interventions would also be supportable, this act is not in accordance with the intent of the state laws. Institutional procedures for conflict resolution, including involvement of the courts if necessary, should be followed.

Circulatory Death

Protocols allowing for organ donation after determination of circulatory death (DDCD) rather than after DBNC have been developed. DDCD can occur under either controlled (after planned withdrawal of LSMT) or uncontrolled (after failed CPR) circumstances, but in both cases require rapid removal of organs in order for subsequent transplantation to be successful. An increasing number of programs are pursuing DDCD protocols after federal legislation began requiring accredited hospitals to address the issue in hopes of decreasing organ shortages. Hospitals can make policy that either allows or disallows the process. In adults, consent for donation by either means can be obtained from patients or surrogates; for children, parents or guardians would make the decision to donate.

Ethical concerns about DDCD protocols focus on two principles that have served as the basis for organ donation: (1) the "dead donor rule" limiting the donation of vital organs to those who are irreversibly dead (either by circulatory or neurologic criteria, not both), and (2) the absence of conflict of interest between clinical care and organ procurement. With DDCD protocols, irreversibility has been declared at varying times after asystole occurs (usually 2-5 min), to avoid spontaneous return of circulation after forgoing CPR. To avoid a potential conflict of interest during the DDCD process, there is a requirement for strict decoupling of end-of-life care after discontinuation of LSMT and presence of the transplant team. Unlike in the setting of DBNC, a patient who is being considered for DDCD remains alive until after asystole has occurred. Careful evaluation by the transplantation team and organ procurement agency is performed before discontinuation of LSMT. Then, in most DDCD protocols the medical caregivers from the ICU continue to care for the patient until after death by cardiac criteria has been declared, and only then is the surgical transplant team allowed into the room to procure organs.

It is ***ethically imperative*** to correctly diagnose the state of death, whether by neurologic criteria or prior to organ donation after cardiac death. Doing so avoids the danger of removing life-sustaining organs from a living person. Strict adherence to an ethically sound protocol is the best way to prevent both the perception and the potential reality of mistakes related to the pronunciation of death and organ procurement.

RELIGIOUS OR CULTURAL OBJECTIONS TO TREATMENT

Differences in religious beliefs or ethic-based cultural norms may lead to conflict between patients, families, and medical caregivers over the approach to medical care. Pediatricians need to remain sensitive to and maintain an attitude of respect for these differences, yet recognize that an independent obligation exists to provide effective medical treatment to the child. An adult with decision-making capacity is recognized as having the right to refuse treatment on religious or cultural grounds, but children who have not yet developed this capacity are considered a vulnerable population that has a right to treatment. In situations that threaten the life of the child or that may result in substantial harm, legal intervention should be sought if reasonable efforts toward collaborative decision making are ineffective. If a child's life is imminently threatened, medical intervention is ethically justified despite parental objections.

PEDIATRIC ETHICS COMMITTEES AND ETHICS CONSULTATION

Most hospitals have institutional ethics committees to assist with policy development, education, and case consultation. When these committees serve institutions caring for children, they may be referred to as *pediatric ethics committees*. Because of the important differences in approach between adult and pediatric ethics, member expertise on this committee should include those with special insight into the unique ethical issues arising in the care of children. Such committees generally provide ethics consultation advice without mandating action or being determinative. For the vast majority of decisions involving the medical treatment of children (including forgoing LSMT), pediatric clinicians and parents are in agreement about the desirability of the proposed intervention. Because of the ethical importance of assent, the views of older children should also be given considerable weight.

Pediatric ethics committees typically perform at least 3 different functions: (1) the drafting and review of institutional policy on such issues as DNAR orders and forgoing LSMT; (2) the education of healthcare professionals, patients, and families about ethical issues in healthcare; and (3) case consultation and conflict resolution. Although the process of case consultation may vary, ideally the committee (or consultant) should adopt a collaborative approach that uncovers all the readily available and relevant facts, takes into account the values of those involved, and balances the relevant interests, while arriving at a recommendation based on a consistent ethical analysis. One helpful approach involves consideration of the 4 following elements: (1) medical indications, (2) patient preferences, (3) quality of life, and (4) contextual features. Another framework based on principles would suggest attention to respect for persons, beneficence/nonmaleficence, and justice. Pediatric ethics committees often play a constructive role when parents and medical staff cannot agree on the proper course of action. Over the past several decades, these committees have acquired considerable influence and are increasingly recognized by state courts as an important aid in decision making. The membership, policies, and procedures of a pediatric ethics committee should conform to accepted professional standards.

NEWBORN SCREENING AND GENETIC TESTING

The *Oxford Dictionary of Public Health* defines **screening** as "the identification of a previously unrecognized disease or disease precursor, using procedures or tests that can be conducted rapidly and economically on large numbers of people with the aim of sorting them into those who may have the condition(s)…and those who are free from evidence of the condition(s)." Several programs, such as newborn screening for inborn errors of metabolism (see Chapter 84; e.g., phenylketonuria and hypothyroidism), are rightly counted among the triumphs of contemporary pediatrics. The success of such programs sometimes obscures serious ethical issues that continue to arise in proposals to screen for other conditions for which the benefits, risks, and costs have not been clearly established. Advances in genetics and technology have led to exponential growth in the number of conditions

for which screening programs might be considered, with insufficient opportunity to study each proposed testing program (see Chapter 78).

The introduction of screening efforts should be done in a carefully controlled manner that allows for the evaluation of the costs (financial, medical, and psychologic) and benefits of screening, including the effectiveness of follow-up and treatment protocols. New programs should be considered experimental until the risks and benefits can be carefully evaluated. Screening tests that identify candidates for treatment need to have demonstrated sensitivity, specificity, and high predictive value, lest individuals be falsely labeled and subject to possibly toxic treatments or to psychosocial risks. As newborn screening tests are being developed, parents should be given the opportunity to exercise informed parental permission or refusal. However, once a particular screening test has been clearly demonstrated to benefit the individual or public health, a formal, active parental permission process may not be ethically obligatory.

A persistent ethical issue is whether screening should be (1) voluntary ("opt in"), (2) routine, with the ability to "opt out" or refuse, or (3) mandatory. A voluntary approach entails an informed decision by parents before screening. Concern is often expressed that seeking parental permission is ethically misguided for tests of clear benefit, such as phenylketonuria screening, because refusal would constitute neglect. Routine testing with an opt-out approach requires an explicit refusal of screening by parents who object to this intervention. The principal ethical justification for mandatory screening is the claim that society's obligation to promote child welfare through early detection and treatment of selected conditions supersedes any parental right to refuse this simple and low-risk medical intervention. Parental permission is clearly required when there is a research agenda (i.e., for incorporating experimental tests into established screening programs).

Genetic testing of young children for late-onset disorders such as the *BRCA1* and *BRCA2* breast cancer risk genes has been the subject of some ethical controversy. Knowledge of increased risk status may lead to lifestyle changes that can reduce morbidity and the risk of mortality, or may precipitate adverse emotional and psychologic responses and discrimination. Because many adults choose not to be tested for late-onset disorders, one cannot assume that a child would want or will benefit from similar testing. Genetic testing of young children for late-onset disorders is generally inappropriate unless such testing will result in interventions that have been shown to reduce morbidity and mortality when initiated in childhood. Otherwise, such testing should be deferred until the child has the capacity to make an informed and voluntary choice. This ethical approach is founded on the work of philosopher Joel Feinberg's writing on the "child's right to an open future."

ADOLESCENT HEALTHCARE

Adolescent Assent and Consent

Many adolescents are more like adults than children in their capacity to understand healthcare issues and to relate them to their life goals (see Chapter 110). Teenagers may lack legally defined competency, yet they may have developed the capacity meet the elements of informed consent for many aspects of medical care (see Chapter 112). There are also public health reasons for allowing adolescents to consent to their own healthcare with regard to reproductive decisions, such as contraception, abortion, and treatment of sexually transmitted infections. Strict requirements for parental permission may deter adolescents from seeking healthcare, with serious implications for their health and other community interests.

Counterbalancing these arguments are legitimate parental interests to maintain responsibility and authority for child rearing, including the opportunity to influence the sexual attitudes and practices of their children. Others claim that access to treatment such as contraception, abortion, or needle exchange programs implicitly endorses sexual activity or drug use during adolescence. Pediatricians should not impose their own moral beliefs in these disputes. Rather, they should provide unbiased evidence-based information and nonjudgmental support. One guiding principle should be encouragement of children and adolescents to begin taking responsibility, with guidance, for their own health. This requires some input from parents or guardians but also some privacy during decision making as they achieve developmentally anticipated separation from parental control.

Chronic Illness

The normal process of adolescent development involves gradually separating from parents, establishing self-confidence, asserting individuality, developing strong peer relationships, solidifying an ability to function independently outside the family, and taking on increasing autonomy in healthcare decisions. Most developmentally normal children older than age 14 yr understand the implications of well-explained medical options as well as the average adult, and their input into their own care should be respected. For children living with chronic illness, the ability to make medical decisions for themselves may either occur earlier than for those who have been previously healthy, or may occur later if, because of illness, they have not been able to achieve normal developmental milestones or psychological maturity. The clinician's role involves assessment of the individual adolescent patient's ability to understand the medical situation, to support the patient's efforts to express wishes regarding medical treatment, to value and encourage parental support and involvement, and to foster cooperation and mutual understanding. This may be difficult in situations in which parents and adolescents disagree about life-sustaining treatments such as organ transplantation or chemotherapy, but many such conflicts may be resolved by exploring the reasons for the disagreement. Overriding an adolescent's wishes should be done very infrequently, and only after careful consideration of the potential consequences of unwanted interventions.

Decisions in Terminally Ill Adolescents

Most adolescents share end-of-life decision making with family members, although communication may be challenging because of a growing sense of independence. Open communication and flexibility about treatment preferences may help teens cope with fears and uncertainties. Development of an age-appropriate AD may support the patient's emerging autonomy by clarifying the adolescent's wishes, while fostering a collaborative process among the patient, family, and medical caregivers. From the time of diagnosis of a life-threatening condition through the end-of-life phase, children should be included in a developmentally tailored process of communication and shared decision-making that builds a foundation of mutual respect and trust.

RESEARCH

The central ethical challenge of pediatric research is the need to balance protection of children from research risk against the ethical imperative of conducting studies to better the lives of future children. Research is defined in the federal regulations as "a systematic investigation designed to develop or contribute to generalizable knowledge." For any research to be performed, the risks should be minimized and reasonable with respect to any anticipated benefits to the subjects and the importance of the resulting knowledge. The fact that some children derive a direct benefit from participation in research must also be considered, making it important to distinguish research with the prospect of direct benefit from nontherapeutic pediatric research. ***Because children are a vulnerable population, there are restrictions on the research risks to which a child may be exposed*** that contrast with the risk level acceptable for research with consenting adults. These restrictions function by limiting the kind of research institutional review boards (IRBs) are permitted to approve and by specifying the conditions under which parent(s) have the moral and legal authority to permit a child to participate in research.

Nontherapeutic research in children is the most ethically controversial because it holds no expected direct benefit for the subject. The prohibition against using a person (especially a child) solely as a means to an end has led some to argue that children should never be used in nontherapeutic research. The more widely held opinion is that children may be exposed to a limited degree of risk with IRB approval, parental permission, and assent if the child is capable. The federal regulations allow healthy children to participate in minimal-risk research regardless of the potential benefit to the child-subject. More

controversially, the regulations also state that children with a disorder or condition may be exposed to slightly more than minimal risk in nontherapeutic research if the child's experience is similar to everyday life with that condition and the anticipated knowledge is of vital importance for understanding that condition.

In pediatric research with the prospect of direct benefit, the risks must be justified by the anticipated benefit to the child, and the balance of anticipated benefit to the risk should be at least as favorable as that presented by available alternatives. ***The welfare of an individual child must always come before the scientific goals of the research study.***

The regulations in the United States for the protection of human research subjects rest on 2 foundations: (1) independent review of the ethics and science of the research by an IRB **prior to** (2) voluntary and informed consent of the subject/participant. Although it is not amenable to regulation, the integrity of the investigator is probably the most important element contributing to the protection of human research subjects. The standard for informed consent in a research setting is higher than for clinical care because the risks and benefits are typically less clear, the investigator has a conflict of interest, and humans have historically been subjected to unauthorized risks when strict requirements for consent were not respected.

Adolescents who are competent may sometimes consent to be research subjects. Younger children may participate in a process of assent, but this does not imply that a child's signature on an assent document is necessarily a legal or ethical requirement. Children should be given the opportunity to dissent, particularly for nontherapeutic research, when there cannot be a claim that participation is in the child's interest. In the United States, national regulations require that reasonable efforts be made at least to inform children who are capable of understanding that participation is not part of their care and that, therefore, they are free to refuse to participate. In the rare case that the research offers a direct benefit to the child that would not otherwise be available, the regulations do not require child assent but only parental permission.

In addition to the protection that informed consent/parental permission is intended to provide, virtually all research involving human subjects in the United States is reviewed by an IRB, required by federal regulations for institutions receiving federal research funds and for drug research regulated by the U.S. Food and Drug Administration. For research that carries more than a minor increase over minimal risk without prospect of benefit to the child such that a local IRB cannot provide approval, there is a process for federal review of research that "presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." Ultimately, the U.S. Secretary of Health and Human Services has the authority to approve such research.

BALANCING MATERNAL AND FETAL INTERESTS

Some situations require balancing of maternal health and well-being with those of the fetus/unborn child to reach an ethically sound decision. For instance, innovative surgical treatment of a prenatally diagnosed anomaly may help the fetus/unborn child survive, but in the process place the mother at risk of injury or of loss of the pregnancy. Alternatively, a pregnant woman may object to delivery by caesarian section for various reasons in spite of advice that it may protect the fetus/unborn child during birth. A third important situation involves risk-taking behaviors during pregnancy that are known to injure the developing fetus/unborn child, such as drug or alcohol use. These issues raise conflicts over clinicians' responsibility to the living, competent decision-maker—the pregnant mother—as opposed to the interests of the fetus/unborn child.

In certain cases, courts in the United States have decided that a woman can be required to undergo caesarian section against her will when the risk to her health is minimal and the benefit to the otherwise normal, near-term fetus/unborn child is clear, for example, in a case of placenta previa. Other factors, such as prematurity, have led to the opposite legal conclusion in otherwise similar situations because the benefit of intervention was less clear. In general, a clinician should not oppose a pregnant woman's refusal of a recommended intervention unless (1) the risk to the pregnant woman is minimal, (2) the intervention is clearly effective, and (3) the harm to the fetus/unborn child without the intervention would be certain, substantial, and irrevocable. Attempts should be made to persuade the pregnant woman to comply with recommendations in the interest of the fetus/unborn child when these 3 conditions exist, using support strategies such as the influence of other trusted caregivers, clergy, and/or ethics consultation/committee involvement. If these approaches fail and there is time, a clinician may seek judicial intervention as a last resort in the attempt to prevent harm to the fetus/unborn child.

Obstetricians and pediatricians may consider reporting women under child abuse or neglect statutes if ingesting alcohol or illicit drugs during pregnancy is felt to place the fetus/unborn child at risk of injury. However, clinicians must consider the likelihood of benefit from reporting, the harm to the child as well as to the mother if criminal charges or custody changes are sought, and the possible effects that reporting may have on driving pregnant women away from prenatal or postnatal care. The U.S. Supreme Court has held that drug testing of pregnant women without consent was a violation of the Fourth Amendment, which provides protection from unreasonable searches.

JUSTICE AND PEDIATRIC ETHICS

The most serious ethical problem in healthcare in the United States may be inequality in access to healthcare. Children are particularly vulnerable to this disparity, and pediatricians have a moral obligation to advocate for children as a class. Because children do not vote and do not have financial resources at their disposal, they are subject to a greater risk of being uninsured or underinsured. This lack of adequate and affordable healthcare has serious consequences in terms of death, disability, and suffering. The Affordable Care Act may help to ameliorate these problems in the United States. The per capita proportion of healthcare funding spent on adults greatly exceeds that spent on children, and Medicare is available to all adults who turn 65 yr old whereas Medicaid is limited to those beneath a specific income level. Federal dollars intended to support healthcare for children are generally administered and supplemented with state funds, which can create additional barriers. Pediatricians should be familiar with policy issues around the economics of child healthcare so that they will be better able to advocate for their own patients (see Chapter 1).

EMERGING ISSUES

The ready availability of information on the Internet has encouraged parents to become more involved in advocating for specific approaches to the healthcare of their children, requiring physicians to remain aware of the quality of these sources of information in order to adequately counsel parents on treatment choices. Because the range of aggressive, innovative, or exceedingly expensive therapies has increased, without necessarily providing clear benefit to the patient, pediatricians must exercise care and judgment before agreeing to pursue these interventions. A growing number of parents are refusing to immunize their children because of fear of adverse reaction to vaccine. This raises the ethical problem of the "free rider," in which a child may benefit from herd immunity because others have been immunized without contributing to this public good. Outbreaks of preventable infectious disease have been detected in communities where vaccine refusal is prevalent. Pediatricians should manage this issue with ethical sensitivity, educating parents about the safety profile of vaccines and encouraging appropriate immunization. More confrontational approaches are not generally effective or ethically warranted. A second emerging issue relates to children as stem cell or solid organ donors. Here the risk:benefit balance should be carefully weighed, but in general, a permissive policy with regard to stem cell donation and a more restrictive approach to solid-organ donation are ethically justified. Finally, controversial medical and surgical interventions, such as growth attenuation of children with severe cognitive impairment in hopes of prolonging ability to care for them in the home setting, and disorders of sexual development require careful ethical consideration. Attitudes about emerging technologies and treatments

may be influenced by media coverage, special interest groups, and efforts by understandably desperate families to help their children. The clinician attempting to practice ethically must carefully consider all relevant facts in each case, and try to focus families and caregivers on a reasonable best interest assessment for the child. The tension between finding optimal policy for groups of children and doing the right thing for an individual child raises formidable ethical challenges in this context. Ethics consultation may be helpful to frame the issues and design ethically supportable approaches to care.

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Chapter 4

Cultural Issues in Pediatric Care

Linda Kaljee and Bonita F. Stanton

Pediatricians live and work in a multicultural world. Among the world's 7 billion people residing in >200 countries, >6,000 languages are spoken. As the global population becomes more mobile and integrated, ethnic and economic diversity increases in all countries. From 1970 to 2000, the foreign-born population in the United States increased 3-fold. In the 2000 U.S. census, 25-30% of Americans self-identified as belonging to an ethnic or racial minority group. In 2010, 13% of the population was foreign born and 1 or both parents of 24% of children under age 17 yr is foreign born; the 40 million immigrants represents a 28% increase over the number in 2000. Whereas in 1920, 97% of immigrant families in the United States were from Europe or Canada as of 2010 more than 90% of immigrant families are from Asia and Latin America. Nonwhite children are projected to outnumber white children in the United States by the year 2030. Increased migration and diversity in the migrant pool is not limited to the United States; immigrants account for more than 15% of the population in >50 nations.

THE IMPORTANCE OF CULTURE TO MEDICAL PRACTICE

The concept of culture includes the ways in which a group of people share and understand their history, beliefs, and values, and engage in behaviors reflective of these shared worldviews. Although culture is not synonymous with language, ethnicity, nationality, or socioeconomic status, groups with similar backgrounds with respect to these characteristics often share cultural norms and beliefs.

Within cultures, there are frameworks for classifying and organizing kin (family), assigning roles and responsibilities based on age, gender, and other social groupings, and defining concepts such as prosperity, success, knowledge, causes of disease, and health. Disease typology, prevention and intervention efforts, and health practitioners are culturally defined. Health-related cultural-beliefs and practices are integrated within pluralistic health systems that include both biomedicine and traditional medicine.

Tables 4-1 to 4-3 display some cultural values associated with 4 populations in the United States: Latinos, Muslims, Native Americans, and African-Americans, illustrating both areas of significant overlap and great variation that are relevant to health perceptions and health seeking. Latinos may subscribe to the importance of "personalismo," placing great importance on politeness in the face of stress and adversity. Thus expectations may include a display of warmth from their physician, including physical touching such as handshaking, placing hands on the shoulder, and occasionally hugging. By contrast, in the Muslim culture, for a person to touch the body of a member of the opposite gender, including on the arm or a pat on the shoulder, is considered highly inappropriate.

Despite the existence of shared values within a defined population group, there may be substantial variations within subgroups, such as the Latino national subgroups (e.g., Cuban, Puerto Rican, Dominican, Mexican), resulting in great variation in specific health-seeking behaviors. Likewise, within an overarching culture ("American"), persons who are economically and/or politically disenfranchised may use resistance, inverting the values of the dominant socioeconomic group. Such a reaction may include distrust of recommendations regarding healthcare from members of the perceived dominant or controlling group or class. Immunizations have been viewed with distrust among the poor in countries around the globe, as they were believed to be a form of birth control or sterilization and were often offered through institutions associated with "Western" and postcolonial rule. Within cultures, socially constructed categories of gender, sexuality, and age affect perceptions of an individual's vulnerability to a particular disease or condition, as well as the individual's access to health system resources. Adolescents girls living in cultures with strong taboos against premarital sexual relationships (e.g., Chinese, Muslim, Vietnamese) may not have social access to disease and birth control protection (e.g., condoms) resulting in increased risks for HIV, other sexually transmitted infections, and unwanted pregnancies.

There may also be significant generational differences between foreign-born parents and their American-raised children, particularly as these children go through adolescence. Such disparate experiences and cultural identities can result in a generational gap that decreases parent–child communication and subsequently lessens the important positive effects of communication on reducing substance use and engagement in sexual risk behaviors among youth.

Other values may be shared across disparate cultural groups. Multiple ethnic groups, including Latinos and Muslims, as well as Sudanese and Bengalis, share a cultural belief of fatalism, with strong implications for health-seeking behavior.

The perceived role of the physician may also differ between cultures. Pediatricians are trained to offer advice on child rearing, and studies have shown that parents look to pediatricians for this advice. However, parents of differing cultural backgrounds may not desire or may be reluctant to accept such advice.

NEWLY RECOGNIZED CULTURAL GROUPS

Groups that may or may not traditionally have been recognized as distinct cultural groups, (adolescents, gay/lesbian youth, transgender youth, street youth, deaf youth, etc.) have shared values which frequently have implications for health and health seeking. Failure on the part of the pediatrician to recognize accepted language and frame of reference of these groups may result in the unintentional use of offensive terminology or assumptions, leading to loss of the physician's credibility or noncompliance from the patient.

THE CULTURE OF THE MEDICAL PROFESSION

The profession of medicine also has a distinct culture. Like other cultural groups, physicians have a distinct "language" and share a common history, admiring the same role models, sharing the same preparatory courses that must be mastered for entrance into training for the profession, and subscribing to a common meaning of "competence" in medical practice. Physicians learn a new way to describe health and illness, requiring a new vocabulary and a prescribed pattern to the narrative history, which is not shared by those outside medicine. Physician reliance on "evidence-based practice" carries the implication that it is synonymous with truth or real knowledge. Of particular importance in the relationship with patients has been the lack of physician insight into the existence of a physician culture and the potential biases that may be inherent to that culture.

Although physicians around the world recognize the great strides that have been made in child survival through the use of oral rehydration therapy in the treatment of dehydrating diarrheal diseases, parents are often anxious because the treatment does not stop the diarrhea. Physicians may be dependent on a particular style of communication

Table 4-1 Cultural Values* Relevant to Health and Health-Seeking Behavior

CULTURAL GROUP	RELEVANT CULTURAL NORMS	
	Description of Norm	**Consequences of Failure to Appreciate**
Latino	*Fatalismo:* Fate is predetermined, reducing belief in the importance of screening and prevention	Less preventive screening
	Simpatia: Politeness/kindness in the face of adversity—expectation that the physician should be polite and pleasant, not detached	Nonadherence to therapy, failure to make follow-up visits
	Personalismo: Expectation of developing a warm, personal relationship with the clinician, including introductory touching	Refusal to divulge important parts of medical history, dissatisfaction with treatment
	Respecto: Deferential behavior on the basis of age, social stature, and economic position, including reluctance to ask questions	Mistaking a deferential nod of the head/not asking questions for understanding; anger at not receiving due signs of respect
	Familismo: Needs of the extended family outrank those of the individual, and thus family may need to be consulted in medical decision making	Unnecessary conflict, inability to reach a decision
Muslim	*Fasting* during the holy month of Ramadan: fasting from sunrise to sundown, beginning during the teen years. Women are exempted during pregnancy, lactation, and menstruation, and there are exemptions for illness, but an exemption may be associated with a sense of personal failure	Inappropriate therapy; will not take medicines during daytime misinterpreted as noncompliance; misdiagnosed
	Modesty: Women's body including hair, body, arms, and legs not to be seen by men other than in immediate family. Female chaperone and/or husband must be present during exam and only that part of the body being examined should be uncovered	Deep personal outrage, seeking alternative care
	Touch: Forbidden to touch members of the opposite sex other than close family. Even a handshake may be inappropriate	Patient discomfort, seeking care elsewhere
	After death, body belongs to God: Postmortem exam will not be permitted unless required by law; family may wish to perform after-death care	Unnecessary intensification of grief and loss
	Cleanliness essential before prayer: Individual must perform ritual ablutions before prayer, especially elimination of urine and stool. Nurse may need to assist in cleaning if patient is incapable	Affront to religious beliefs
	God's will: God causes all to happen for a reason, and only God can bring about healing	Allopathic medicine will be rejected if it conflicts with religious beliefs, family may not seek healthcare
	Patriarchal, extended family: Older male typically is head of household, and family may defer to him for decision making	Child's mother or even both parents may not be able to make decisions about child's care; emergency decisions may require additional time
	Halal (permitted) vs. *harem* (forbidden) foods and medications: Foods and medicine containing alcohol (some cough and cold syrups) or pork (some gelatin-coated pills) are not permitted	Refusal of medication, religious effrontery
Native American	*Nature* provides the spiritual, emotional, physical, social, and biologic means for human life; by caring for the earth, Native Americans will be provided for. Harmonious living is important	Spiritual living is required of Native Americans; if treatments do not reflect this view, they are likely not to be followed
	Passive forbearance or right of the individual to choose his or her path: Another family member cannot intervene	Mother's failure to intervene in a child's behavior and/or use of noncoercive disciplinary techniques may be mistaken for neglect
	Natural unfolding of the individual: Parents further the development of their children by limiting direct interventions and viewing their natural unfolding	Many pediatric preventive practices will run counter to this philosophy
	Talking circle format to decision-making: Interactive learning format including diverse tribal members	Lecturing, excluding the views of elders is likely to result in advice that will be disregarded
African-American	Great heterogeneity in beliefs and culture among African-Americans	Risk of stereotyping and/or making assumptions that do not apply to a specific patient or family
	Extended family and variations in family size and child care arrangements are common; matriarchal decision making regarding healthcare	Advice/instructions given only to the parent and not to others involved in health decision making may not be effective
	Parenting style often involves stricter adherence to rules than seen in some other cultures	Advice regarding discipline may be disregarded if it is inconsistent with perceived norms; other parenting styles may not be effective
	History-based widespread mistrust of medical profession and strong orientation toward culturally specific alternative/complementary medicine	In patient noncompliance, physicians will be consulted as a last resort
	Greater orientation toward others; the role of an individual is emphasized as it relates to others within a social network	Compliance may be difficult if the needs of 1 individual are stressed above the needs of the group
	Spirituality/religiosity important; church attendance central in most African-American families	Loss of opportunity to work with the church as an ally in healthcare

Table 4-1 Cultural Values* Relevant to Health and Health-Seeking Behavior—cont'd

CULTURAL GROUP	RELEVANT CULTURAL NORMS	
	Description of Norm	Consequences of Failure to Appreciate
East and Southeast Asian	Long history of eastern medicines (e.g., Chinese medicine) as well as more localized medical traditions	May engage with multiple health systems (Western biomedical and traditional) for treatment of symptoms and diseases
	Extended families and care networks. Grandparents may provide day-to-day care for children while parents work outside of the home	Parents may not be the only individuals a physician needs to communicate with in regard to symptoms, follow-through on treatments, and preventive behaviors
	Sexually conservative. Strong taboos for premarital sexual relationships, especially for women	Adolescents may be reluctant to talk about issues of sexuality, pregnancy, birth control with physicians. Recent immigrants or native populations may have less knowledge regarding pregnancy prevention, sexually transmitted infections, and HIV.
	Infant/child feeding practices may overemphasize infant's or child's need to eat a certain amount of food to stay "healthy"	Guidelines for child nutrition and feeding practices may not be followed out of concern for child's well-being
	Saving face. This is a complex value whereby an individual may lose prestige or respect of a third party when a second individual says negative or contradictory statements	Avoid statements that are potentially value laden or imply a criticism of an individual. Use statements such as "We have now found that it is better to …" rather than criticizing a practice

*Adherence to these or other beliefs will vary among members of a cultural group based on nation of origin, specific religious sect, degree of acculturation, age of patient, etc.

Table 4-2 Examples of Disease Beliefs or Practices

CULTURAL GROUP	EXAMPLES
Latino	Use of traditional medicines (nopales or cooked prickly pear cactus as a hypoglycemic agent) along with allopathic medicine Recognition of disorders not recognized in Western allopathic medicine (*empacho*, in which food adheres to the intestines or stomach), which are treated with folk remedies but also brought to the pediatrician Cultural interpretation of disease (*caida de mollera* or fallen fontanel) as a cultural interpretation of severe dehydration in infants
Muslim	Female genital mutilation: practiced in some Muslim countries; the majority do not practice it and it is not a direct teaching of the Koran Koranic faith healers: use verses from the Koran, holy water, and specific foods to bring about recovery
Native American	Traditional "interpreters" or "healers" interpret signs and answers to prayers. Their advice may be sought in addition or instead of allopathic medicine Dreams are believed to provide guidance; messages in the dream will be followed
East and Southeast Asian	Concepts of "hot" and "cold," whereby a combination of hot and cold foods and other substances (e.g., coffee, alcohol) combine to cause illness. One important aspect is that Western medicines are considered hot by Vietnamese and, therefore, nonadherence may occur if it is perceived that too much of a medicine will make their child's body hot. *Note:* Hot and cold do not refer to temperatures, but are a typology of different foods; for example, fish is hot and ginger is cold. Foods, teas, and herbs are also important forms of medicine because they provide balance between hot and cold

and they may miss information from patients using alternative narrative styles. Likewise, the physician–researcher forms questions through the prism of the physician–researcher's own beliefs and literature, thereby reducing the likelihood of exploring alternative explanations or questions. Even though vast segments of the world's population understand disease as an imbalance of "hot" and "cold," this belief system has not been well-represented in contemporary medical research.

CULTURAL COMPETENCE

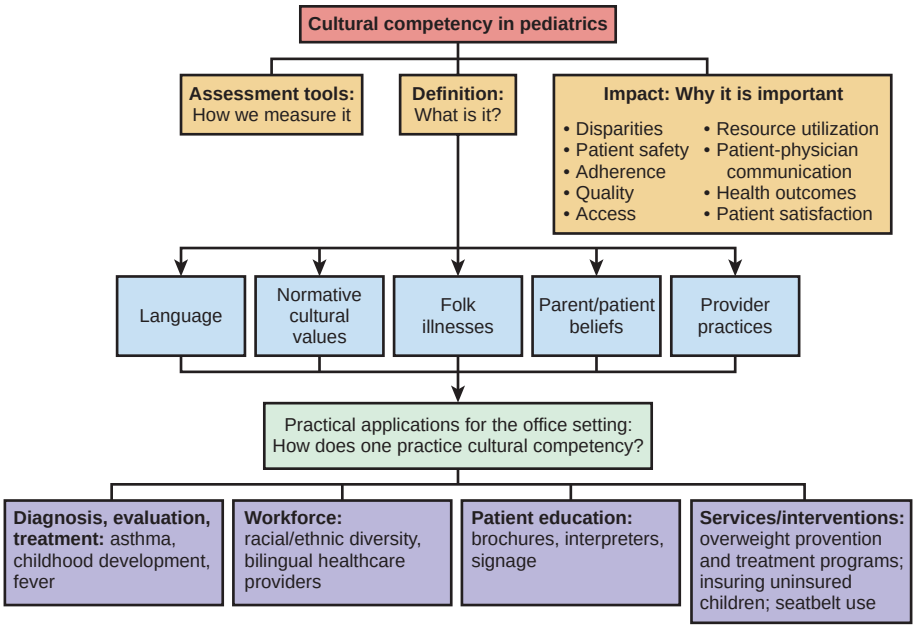
Physicians and patients bring to their interaction personal and professional values from multiple cultural systems that have significant implications for the delivery of healthcare. Consequently, physician "cultural competence" is critical to a successful patient–provider interaction (Fig. 4-1). Campinha-Bacote's model for understanding and assessing culturally competency is frequently used in education and research: (1) learning to value and understand other cultures, in part through self-awareness of one's own cultural values ("cultural awareness"); (2) learning basic fundamentals about other cultures, particularly those of the patients with whom the physician will interact ("cultural knowledge"); (3) developing the ability to apply cultural knowledge in patient encounters ("cultural skills"); (4) seeking exposure to cross-cultural interactions ("cultural encounters"); and (5) being motivated to achieve all of the previous ("cultural desire"). This framework provides an important guide to pediatric education and practice and, thus, will serve as the outline for the remainder of this chapter.

Cultural Awareness

Recognition of the importance of differing cultural expectations and explanations is critical to a pediatrician's successful interactions with patients. Among many cultures (e.g., Muslim), kinship is of great importance and decision making may involve the extended family. The erroneous belief on the part of a physician that a mother may execute independent decision making in relation to her child's healthcare (when in fact she may not be entitled to such a role in her family or culture) may result in an apparent noncompliance on the part of the mother.

Cultural Knowledge

Physicians and patients have differing definitions of health and illness and differing concepts of the origins of disease and therapeutic responses. Understanding the patient perspective will both increase



Conceptual framework for cultural competency in pediatrics: (1) what is known about the impact of cultural competency on general pediatric care; (2) the domains of cultural competency; and (3) practical applications of cultural competency for general pediatricians

Figure 4-1 Components of cultural competency in pediatric practice. *(From Brotanek JM, Seeley CE, Flores G: The importance of cultural competency in general pediatrics,* Curr Opin Pediatr *20:711–718, 2008, Fig. 1, p. 712.)*

Table 4-3 Home Remedies for Fever, Colic, and Teething Among African-Americans

CONDITION	REMEDY	KNOWLEDGE, % (*N* = 107)	USE, % (*N* = 107)
Fever	Acetaminophen*	98	77.6
	Cool bath*	85	48.3
	Isopropyl alcohol*	71	38.3
	Cool drinks/popsicles†	11.2	0
	Undress child†	10.3	0
	Ibuprofen†	10.3	0
	Warm feet†	8.4	0
	Potatoes or onions in socks†	6.5	0
Colic	Catnip*	34.6	8.4
	Senna extract*	25.2	4.7
	Other (asafetida, paregoric, or bicarbonate)†	13.1	0
	Chamomile*	7.5	0
	Walk†	6.5	0
	Cigarette smoke†	5.6	0
	Simethicone drops†	4.7	0
	Vacuum/steam†	3.7	0
	Cover head†	3.7	0
	Massage†	2.8	0
	Gripe water*	1.9	0
Teething	Nonprescription benzocaine gel*	97.2	57
	Teething object†	35.2	7.5
	Whiskey*	34.6	1.9
	Penny*	16.8	0
	Ice cubes/popsicles†	13.3	0
	Egg†	11.4	0
	Spices (asafetida, cloves, or vanilla)†	4.8	0

*Responses given in closed-ended questions.
†Responses given in open-ended questions.
From Smitherman LC, Janisse J, Mathur A: The use of folk remedies among children in an urban black community: remedies for fever, colic and teething, Pediatrics 115:297–304, 2005, Table 2.

the likelihood of correct diagnosis and patient adherence to therapy and decrease the possibility of misdiagnosis. The belief that becoming chilled causes dysentery is common among rural Chinese, and medical advice that directly challenges or runs contrary to this belief may be disregarded. Likewise, diarrhea among Bangladeshi children during teething may be regarded as normal and would not be identified as a health issue. Thus, asking the parent if the child has been ill might not reveal the presence of diarrhea. Rubbing a coin against a child's skin is thought by some parents in Asia to reduce fever. Failure by the pediatrician to recognize the practice of *coining* could lead to the erroneous

diagnosis of a rash or child abuse. In some instances, particularly in relation to developmental and emotional disorders, the manifestation of symptoms and/or recognition of symptoms by parents or other caregivers may be culturally defined. Autism is a condition characterized by communication and socializing disabilities. Yet expectations of children's language and social skills development are culturally defined, resulting in potentially later identification by family members of a child's disabilities and subsequently delayed treatment seeking.

Cultural Skill

Describing a diagnostic or therapeutic course of action that respects cultural beliefs but is consistent with good medical practice can be challenging. Common among many Latino groups is the belief of *empacho,* a condition wherein food is "stuck" to the stomach or intestinal wall, resulting in obstruction. The condition is believed to cause nausea, vomiting, diarrhea, and anorexia. Although many Latino parents would take a child with *empacho* to the physician for treatment, in Western settings, a pediatrician diagnosing the condition as viral gastroenteritis might only advise supportive management, leaving the parents perplexed and with no option but to seek independent treatment from an alternative or traditional healer. A culturally skilled pediatrician might suggest partnering with the traditional healer in such a situation. Likewise, in response to parents subscribing to a belief in fatalism and, consequently, a notion that preventive medicine or screening is not necessary, a skilled pediatrician might suggest that screening is the mechanism through which their destiny is intended to be reached. Referrals for services may also be affected by a patient's culture and history. The need for psychologic services may be rejected because of cultural stigmas regarding psychological disorders. Likewise, referrals for HIV or sexually transmitted infection testing may be more likely rejected by gay adolescent men from cultures in which homosexuality is highly stigmatized.

Central to "cultural skill" is the employment of language fully comprehended by the child's parents. This goal is best realized if the pediatrician is at least conversant in the parent's language, and thus a requirement for a second language is a reasonable goal for physicians. Familiarity with a language should not be confused with fluency or even competency. Professional interpreters should be available and accessed to overcome the language barriers. Ad hoc use of individuals at the workplace who are known to possess skill in the indicated language and/or use of telephone interpreter services may suffice if a professional interpreter is not available. A genuinely bilingual family member or friend may be helpful, but issues of confidentiality, disruption of social roles, and uncertain or inaccurate translation of medical terms may pose serious problems. Medical errors occur at a significantly higher rate among non–English speaking patients when nonprofessional translators (e.g., family members) are used to obtain a history or give medical advice.

Cultural Encounters

Although cultural knowledge may be acquired through didactic training, the development of cultural skills requires experience that can only be gained through repeated "cultural encounters." Nonminority clinicians provide lower quality of care to Latino and African-American patients, with these children being less likely to receive analgesia and/or nebulizers for asthma. Latino mothers have reported clinician attitudes as a major barrier to seeking care for their children. Participation by physicians in diverse medical educational settings and experience in community clinics has been shown to predict increased cultural knowledge. Cultural knowledge and participation in diverse educational settings, and Latino ethnicity and bilingual skills likewise predict cultural awareness, Cultural awareness predicts culturally competent actions. Consistent with observations that cultural competence may not be valued in the traditional medical culture is the observation that *higher* specialty training (e.g., subspecialty training among internists compared to general physicians, family medicine, or internal medicine generalists) predicted *less* cultural awareness. Children who receive care from practice sites with the highest cultural competence scores are less likely to underutilize preventive asthma medications.

Cultural Desire

Cultural competence is not something that can be achieved and retained in the absence of continued effort. The recognition that culture is integral to health and healing, and to disease and sickness, is central to the concept of "cultural competence." Understanding of the role of culture in health outcomes is nascent; it is not yet known why less acculturated Latinos in the United States demonstrate significantly lower rates of low birthweight, depression, tobacco use, illicit drug use, and older age for sexual debut compared to those who are more acculturated. Likewise, less acculturation among Asian children is associated with lower prevalence of chronic illness. Such findings expose the complexities between individuality, environment, cultures, and biology, and how these integrated factors can affect health-related behaviors and health outcomes.

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Chapter 5

Maximizing Children's Health: Screening, Anticipatory Guidance, and Counseling

Joseph F. Hagan Jr. and Paula M. Duncan

Routine, scheduled care of well infants, children, and adolescents is an essential prevention effort for children and youth worldwide. Children's constantly changing development lends added value to regular and periodic encounters between children and their families and practitioners of pediatric healthcare. Health supervision visits from birth to age 21 yr are the platform for a young person's healthcare. The provision of well care in the medical home, fosters strong relationships between the clinic or practice and the child and family, enabling the provision of appropriate surveillance, screening, and sick care.

To assure the optimal health of the developing child, pediatric care in the United States and other countries evolved into regularly scheduled visits to assure adequate nutrition, detect and immunize against infectious diseases, and observe the child's development. Assessment of immunizations, nutrition and developmental status remain essential elements of the well-child health supervision visit, but changes in the population's health have led to the addition of other components to the content of today's well-child encounter. Preventive care for children and youth is a component of contemporary U.S. health reform activities; this approach offers great opportunity for health cost savings.

A healthy economy requires educated and healthy workers. For children to have a successful educational experience, they must have both physical and emotional health. Educational success is also tied to early childhood developmental competence. Thus health supervision well-child care plays a vital role in promoting adult health, a concept endorsed by business leaders.

Adversity impairs development and adverse factors in life experience increase the risk of disease. Adults who experienced abuse, violence, or other stressors as children have an increased risk for depression, heart disease, and other morbidities. Biology informs us that stress leads to increased heart rate and blood pressure, and increased levels of inflammatory cytokines, cortisol, and other stress hormones, all of which impair brain activity, immune status, and cardiovascular function. There are both a causal model and evidence that

adverse childhood events, including those that could have been prevented, adversely impact the life course.

PERIODICITY

The frequency and content for well-child care activities are derived from evidence-based practice and research. In addition, federal agencies and professional organizations, such as the American Academy of Pediatrics (AAP), have developed evidence informed, expert consensus guidelines for care. The Recommendations for Preventive Pediatric Health Care or Periodicity Schedule (Fig. 5-1) is a compilation of recommendations listed by age-based visits. It is intended to guide practitioners of pediatric primary care to perform certain services and make observations at age-specific visits and it designates the standard for preventive services for children and youth according to the U.S. health reform legislation, the Affordable Care Act of 2010.

GUIDELINES

Comprehensive guides for care of well infants, children, and adolescents have been developed, based on the Periodicity Schedule, which expand and further recommend how practitioners might accomplish the tasks outlined in the Periodicity Schedule. In the United States, the current guideline standard is *The Bright Futures Guidelines for Health Supervision of Infants, Children, and Adolescents,* 4th edition. These guidelines were developed by the AAP under the leadership of the Maternal Child Health Bureau of the U.S. Department of Health and Human Services, in collaboration with the National Association of Pediatric Nurse Practitioners, the American Academy of Family Physicians, the American Medical Association, the American Academy of Pediatric Dentistry, Family Voices, and others.

TASKS OF WELL-CHILD CARE

The well-child encounter intends to promote the physical and emotional well-being of children and youth. Child health professionals, including pediatricians, family medicine physicians, nurse practitioners, and physician assistants, take advantage of the opportunity well-child visits provide to elicit parental questions and concerns, gather relevant family and individual health information, perform a physical examination, and initiate screening tests.

The tasks of each well-child visit include:

- Disease detection
- Disease prevention
- Health promotion
- Anticipatory guidance

To achieve these outcomes, healthcare professionals employ techniques to screen for disease, screen for risk of disease, and provide advice about healthy behaviors. These activities lead to the formulation of appropriate anticipatory guidance and health advice.

Clinical detection of disease in the well-child encounter is accomplished by both surveillance and screening. In well-child care, surveillance occurs in every health encounter and is enhanced by repeated visits and observations with advancing developmental stages. It relies on the experience of a skilled clinician over time. Screening is a more formal process utilizing some form of tool that has been validated and has known sensitivity and specificity. For example, anemia surveillance is accomplished through taking a dietary history and seeking signs of anemia in the physical examination. Anemia screening is done by hematocrit or hemoglobin tests. Developmental surveillance relies on the observations of parents and the watchful eyes of providers of pediatric healthcare who are experienced in child development. Developmental screening uses a structured developmental screening tool by personnel trained in its use or in the scoring and interpretation of parent report questionnaires.

The second essential action of the well-child encounter, *disease prevention,* may include both *primary prevention* activities applied to a whole population and *secondary prevention* activities aimed at patients with specific factors of risk. For example, counseling about reducing fat intake is appropriate for all children and families. Counseling is intensified for overweight and obese youth or in the presence of a family history of hyperlipidemia and its sequelae. The child and adolescent healthcare professional needs to individualize disease prevention strategies to the specific patient, family, and community.

Health promotion and **anticipatory guidance** activities distinguish the well-child health supervision visit from all other encounters with the healthcare system. Disease detection and disease prevention activities are germane to all interactions of children with physicians and other healthcare providers, but health promotion and anticipatory guidance shift the focus to wellness and to the strengths of the family (e.g., what is being done well and how this might be improved). This approach is an opportunity to help the family address relationship issues, broach important safety topics, access community services, and engage with extended family, school, neighborhood, and church.

It is not possible to cover all the topics suggested by comprehensive guidelines such as *Bright Futures* in the average 18 min well-child visit. Child health professionals must prioritize the most important topics to cover. Consideration should be given to a discussion of:

- The agenda the parent or child brings to the health supervision visit.
- The topics where evidence suggests counseling is effective in behavioral change.
- The topics where there is a clear rationale for the issue's critical importance to health, for example, sleep environment to prevent sudden infant death syndrome or attention to diet and physical activity.
- A summary of the child's progress in emotional and social development, physical growth, and strengths.
- Issues that address the questions, concerns, or specific health problems relevant to the individual family.
- Community-specific problems that could significantly impact the child's health (e.g., neighborhood violence from which children need protection or absence of bike paths that would promote activity).

It is important to note that this approach is directed at all children, including those with special health needs. Children with special health needs are no different from other children in their need for guidance about healthy nutrition, physical activity, progress in school, connection with friends, a healthy sense of self-efficacy, and avoidance of risk-taking behaviors. The coordination of specialty consultation, medication monitoring, and functional assessment, which should occur in their periodic visits, needs to be balanced with a discussion of the child's unique ways of accomplishing the emotional, social, and developmental tasks of childhood and adolescence. Comprehensive integrated care planning for children and youth with special healthcare needs supports partnerships between medical homes and families and youth through goal setting and negotiating next steps. In this process, chronic condition management and health surveillance (including adolescent engagement and planning for transition to adult care) occur within an effective patient care relationship, partnering to improve health outcomes and efficiencies of care provision.

INFANCY AND EARLY CHILDHOOD

Nutrition, physical activity, sleep, safety, and emotional, social, and physical growth, along with parental well-being, are critical for all children. For each well-child visit, there are topics that are specific to individual children based on their age, family situation, chronic health condition, or a parental concern, for example, sleep environment to prevent sudden infant death syndrome, activities to lose weight, and fences around swimming pools. Attention should also be focused on the family milieu, including screening for parental depression (especially maternal postpartum depression) and other mental illness, family violence, substance abuse, nutritional inadequacy, or lack of housing. These issues are essential to the care of young children.

Answering parents' questions is the most important priority of the well-child visit. Promoting family-centered care and partnership with parents increases the ability to elicit parent concerns, especially about their child's development, learning, and behavior. It is important to identify children with developmental disorders as early as possible. Developmental surveillance at every visit combined with a structured developmental screening, neuromuscular screening and autism screening at some visits is a way to improve diagnosis, especially for some of

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2014 Recommendations for Preventive Pediatric Health Care

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Bright Futures

Each child and family is unique; therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving competent parenting, have no manifestations of any important health problems, and are growing and developing in satisfactory fashion. Additional visits may become necessary if circumstances suggest variations from normal.

Developmental, psychosocial, and chronic disease issues for children and adolescents may require frequent counseling and treatment visits separate from preventive care visits.

These guidelines represent a consensus by the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to emphasize the great importance of continuity of care in comprehensive health supervision and the need to avoid fragmentation of care.

Refer to the specific guidance by age as listed in *Bright Futures* guidelines (Hagan JF, Shaw JS, Duncan PM, eds. *Bright Futures Guidelines for Health Supervision of Infants, Children and Adolescents*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008).

The recommendations in this statement do not indicate an exclusive course of treatment or standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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	INFANCY								EARLY CHILDHOOD							MIDDLE CHILDHOOD						ADOLESCENCE										
AGE[1]	Prenatal[2]	Newborn[3]	3-5 d[4]	By 1 mo	2 mo	4 mo	6 mo	9 mo	12 mo	15 mo	18 mo	24 mo	30 mo	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y	14 y	15 y	16 y	17 y	18 y	19 y	20 y	21 y
HISTORY Initial/Interval	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
MEASUREMENTS																																	
Length/Height and Weight		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Head Circumference		●	●	●	●	●	●	●	●	●	●	●																					
Weight for Length		●	●	●	●	●	●	●	●	●	●																						
Body Mass Index[5]												●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood Pressure[6]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
SENSORY SCREENING																																	
Vision		★	★	★	★	★	★	★	★	★	★	★	★	●[7]	●	●	●	★	●	★	●	★	●	★	★	●	★	★	●	★	★	★
Hearing		●[8]	★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	★	●	★	●	★	★	★	★	★	★	★	★	★	★	★	★
DEVELOPMENTAL/BEHAVIORAL ASSESSMENT																																	
Developmental Screening[9]								●			●		●																				
Autism Screening[10]											●	●																					
Developmental Surveillance		●	●	●	●	●	●		●	●		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Psychosocial/Behavioral Assessment		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Alcohol and Drug Use Assessment[11]																						★	★	★	★	★	★	★	★	★	★	★
Depression Screening[12]																						●	●	●	●	●	●	●	●	●	●	●
PHYSICAL EXAMINATION[13]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
PROCEDURES[14]																																	
Newborn Blood Screening[15]		←—	●	—→																													
Critical Congenital Heart Defect Screening[16]		●																															
Immunization[17]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hematocrit or Hemoglobin[18]						★			●	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Lead Screening[19]							★	★	● or ★[20]		★	● or ★[20]		★	★	★	★															
Tuberculosis Testing[21]				★			★		★			★		★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Dyslipidemia Screening[22]												★			★		★		★	←—	●	—→	★	★	★	★	★	★	←—	—	●	—→
STI/HIV Screening[23]																						★	★	★	★	★	←—	●	—→	★	★	★
Cervical Dysplasia Screening[24]																																●
ORAL HEALTH[25]							★	★	● or ★		● or ★	● or ★	● or ★	●			●															
ANTICIPATORY GUIDANCE	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

1. If a child comes under care for the first time at any point on the schedule, or if any items are not accomplished at the suggested age, the schedule should be brought up to date at the earliest possible time.
2. A prenatal visit is recommended for parents who are at high risk, for first-time parents, and for those who request a conference. The prenatal visit should include anticipatory guidance, pertinent medical history, and a discussion of benefits of breastfeeding and planned method of feeding, per the 2009 AAP statement "The Prenatal Visit" (http://pediatrics.aappublications.org/content/124/4/1227.full).
3. Every infant should have a newborn evaluation after birth, and breastfeeding should be encouraged (and instruction and support should be offered).
4. Every infant should have an evaluation within 3 to 5 days of birth and within 48 to 72 hours after discharge from the hospital to include evaluation for feeding and jaundice. Breastfeeding infants should receive formal breastfeeding evaluation, and their mothers should receive encouragement and instruction, as recommended in the 2012 AAP statement "Breastfeeding and the Use of Human Milk" (http://pediatrics.aappublications.org/content/129/3/e827.full). Newborn infants discharged less than 48 hours after delivery must be examined within 48 hours of discharge, per the 2010 AAP statement "Hospital Stay for Healthy Term Newborns" (http://pediatrics.aappublications.org/content/125/2/405.full).
5. Screen, per the 2007 AAP statement "Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity: Summary Report" (http://pediatrics.aappublications.org/content/120/Supplement_4/S164.full).
6. Blood pressure measurement in infants and children with specific risk conditions should be performed at visits before age 3 years.
7. If the patient is uncooperative, rescreen within 6 months, per the 2007 AAP statement "Eye Examination in Infants, Children, and Young Adults by Pediatricians" (http://pediatrics.aappublications.org/content/111/4/902.abstract).
8. All newborns should be screened, per the AAP statement "Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs" (http://pediatrics.aappublications.org/content/120/4/898.full).
9. See 2006 AAP statement "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (http://pediatrics.aappublications.org/content/118/1/405.full).
10. Screening should occur per the 2007 AAP statement "Identification and Evaluation of Children with Autism Spectrum Disorders" (http://pediatrics.aappublications.org/content/120/5/1183.full).
11. A recommended screening tool is available at http://www.cesar.boston.org/CRAFFT/index.php.
12. Recommended screening using the Patient Health Questionnaire (PHQ)-2 or other tools available in the GLAD-PC toolkit and at http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf.
13. At each visit, age-appropriate physical examination is essential, with infant totally unclothed and older children undressed and suitably draped. See 2011 AAP statement "Use of Chaperones During the Physical Examination of the Pediatric Patient" (http://pediatrics.aappublications.org/content/127/5/991.full).
14. These may be modified, depending on entry point into schedule and individual need.
15. The Recommended Uniform Newborn Screening Panel (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/uniformscreeningpanel.pdf), as determined by The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and state newborn screening laws/regulations (http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/hbsdisorders.pdf), establish the criteria for and coverage of newborn screening procedures and programs. Follow-up must be provided, as appropriate, by the pediatrician.
16. Screening for critical congenital heart disease using pulse oximetry should be performed in newborns, after 24 hours of age, before discharge from the hospital, per the 2011 AAP statement "Endorsement of Health and Human Services Recommendation for Pulse Oximetry Screening for Critical Congenital Heart Disease" (http://pediatrics.aappublications.org/content/129/1/190.full).
17. Schedules, per the AAP Committee on Infectious Diseases, are available at: http://aapredbook.aappublications.org/site/resources/izschedules.xhtml. Every visit should be an opportunity to update and complete a child's immunizations.
18. See 2010 AAP statement "Diagnosis and Prevention of Iron Deficiency and Iron Deficiency Anemia in Infants and Young Children (0-3 Years of Age)" (http://pediatrics.aappublications.org/content/126/5/1040.full).
19. For children at risk of lead exposure, see the 2012 CDC Advisory Committee on Childhood Lead Poisoning Prevention statement "Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention" (http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf).
20. Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high prevalence areas.
21. Tuberculosis testing per recommendations of the Committee on Infectious Diseases, published in the current edition of *AAP Red Book: Report of the Committee on Infectious Diseases*. Testing should be performed on recognition of high-risk factors.
22. See AAP-endorsed 2011 guidelines from the National Heart Blood and Lung Institute, "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents" (http://www.nhlbi.nih.gov/guidelines/cvd_ped/index.htm).
23. Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the *AAP Red Book: Report of the Committee on Infectious Diseases*. Additionally, all adolescents should be screened for HIV according to the AAP statement (http://pediatrics.aappublications.org/content/126/5/1023.full) once between the ages of 16 and 18, making every effort to preserve confidentiality of the adolescent. Those at increased risk of HIV infection, including those who are sexually active, participate in injection drug use, or are being tested for other STIs, should be tested for HIV and reassessed annually.
24. See USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm). Indications for pelvic examinations prior to age 21 are noted in the 2010 AAP statement: "Gynecologic Examination for Adolescents in the Pediatric Office Setting" (http://pediatrics.aappublications.org/content/126/3/583.full).
25. Refer to a dental home, if available. If not available, perform a risk assessment (http://www2.aap.org/oralhealth/docs/RiskAssessmentTool.pdf). If primary water source is deficient in fluoride, consider oral fluoride supplementation. For those at high risk, consider application of fluoride varnish for caries prevention. See 2008 AAP statement "Preventive Oral Health Intervention for Pediatricians" (http://pediatrics.aappublications.org/content/122/6/1387.full) and 2009 AAP statement "Oral Health Risk Assessment Timing and Establishment of the Dental Home" (http://pediatrics.aappublications.org/content/111/5/1113.full).

KEY ● = to be performed ★ = risk assessment to be performed with appropriate action to follow, if positive ←— ● —→ = range during which a service may be provided

Figure 5-1 Recommendations for preventive pediatric healthcare. *(From Bright Futures/American Academy of Pediatrics. Copyright 2014, American Academy of Pediatrics, Elk Grove Village, IL.)*

the more subtle delays or autism spectrum disorders where early intervention is believed to be associated with reduced morbidity.

MIDDLE CHILDHOOD AND ADOLESCENCE

As the child enters school-age years, additional considerations emerge. Attention to developing autonomy requires fostering a clinician–patient relationship separate from the clinician–child-family relationship with increasing needs for privacy and confidentiality as the child ages.

The 6 health behaviors that most significantly impact adolescent and adult morbidity and mortality are inadequate physical activity, poor nutrition, sexuality-related behaviors, substance use and abuse (including tobacco), unintentional injury-related behaviors, and intentional injury-related behaviors. Emotional well-being and early diagnosis and treatment of mental health problems are equally important, with attention to the developmental tasks of adolescence (competence at school and other activities, connection to friends and family, autonomy, empathy, and a sense of self-worth).

OFFICE INTERVENTION FOR BEHAVIORAL AND MENTAL HEALTH ISSUES

One-fifth of primary care encounters with children are for a behavioral or mental health problem, or are sickness visits complicated by a mental health issue. Pediatricians require increased knowledge for diagnosis, treatment, and referral criteria for attention-deficit/hyperactivity disorder (see Chapter 33), depression and other mood disorders (see Chapter 26), anxiety (see Chapter 25), and conduct disorder (see Chapter 29), as well as an understanding of the pharmacology of the frequently prescribed psychotropic medications. Familiarity with available local mental health services and clinicians and knowledge of the types of services indicated are important for effective consultation or referral. Encouragement of behavioral change is also an important responsibility of the clinician. Motivational interviewing provides a structured approach that has been designed to help patients and parents identify the discrepancy between their desire for health and their behavioral choices. It also allows the clinician to use proven strategies that lead to a patient-initiated plan for change.

STRENGTH-BASED APPROACHES AND FRAMEWORK

Questions about school or extracurricular accomplishments or competent personal characteristics should be integrated into the content of the well child visit. Such inquiries set a positive context for the visit, deepen the partnership with the family, acknowledge the child's healthy development, and facilitate discussing social–emotional development with children and their parents. There is a strong relationship between appropriate social–emotional development (e.g., children's strong connection to their family, social friends, and mentors; competence; empathy; and appropriate autonomy) and decreased participation in all the risk behaviors of adolescence (related to drugs, sex, and violence). An organized approach to the identification and encouragement of a child's strengths during health supervision visits provides both the child and parent with an understanding of how to promote healthy achievement of the developmental tasks of childhood and adolescence. Children with special health needs often have a different timetable, but they have an equal need to be encouraged to develop strong family and peer connections, competence in a variety of arenas, ways to do things for others, and appropriate independent decision making.

OFFICE SYSTEM CHANGE FOR QUALITY IMPROVEMENT

Some of the office strategies to improve the preventive services delivered to children and youth include screening schedules and parent handouts, flow sheets, registries, and the use of parent and youth previsit questionnaires. Such tools are available in *The Bright Futures Guidelines Toolkit* and online previsit tools are under construction. These efforts are part of a larger national effort that is built on a coordinated team approach in the office setting and the use of continuous measurement for improvement.

EVIDENCE

Available evidence should be utilized in developing health-promotion and disease-detection recommendations. Revisions to the AAP's *Periodicity Schedule* undergo rigorous evidence assessment; however, many highly valued well-child care activities have not been evaluated for efficacy. Lack of evidence is most often related to absence of study and does not define lack of benefit. Thus the clinical encounter with the well child is also guideline- and recommendation-driven and requires the integration of clinician goals, family needs, and community realities in seeking better health for the child. The rationale for well-child care activities is a balance of evidence from research, clinical practice guidelines, professional recommendations, expert opinion, experience and knowledge of the needs of the patient population in the context of community assets and challenges. Clinical or counseling decisions and recommendations may also be based on legislation (seat belts), on common sense measures not likely to be studied experimentally (lowering water heater temperatures), or on the basis of relational evidence (television watching associated with violent behavior in young children). Most important, sound clinical and counseling decisions are responsive to family needs and desires, and support "patient-centered decision making."

CARING FOR THE CHILD AND YOUTH IN THE CONTEXT OF THE FAMILY AND COMMUNITY

A successful primary care practice for children incorporates families, is family centered, and embraces the concept of the medical home. A medical home is defined by the AAP as primary care that is accessible, continuous, comprehensive, family centered, coordinated, compassionate, and culturally effective. In a medical home, a pediatrician works in partnership with the family and patient to assure that all medical and nonmedical needs of the child are met. Through this partnership, the child healthcare professional helps the family/patient access and coordinate specialty care, educational services, out-of-home care, family support, and other public and private community services that are important to the overall health of the child and family.

Ideally, health promotion activities occur not only in the medical home, but also in partnership with community members and other health and education professionals. This rests on a clear understanding of the important role that the community plays in supporting healthy behaviors among families. Communities where children and families feel safe and valued, and have access to positive activities and relationships, provide the important base that the healthcare professional can build on and refer to for needed services that support health but are outside the realm of the healthcare system or primary care medical home. It is important for the medical home and community agencies to identify mutual resources, communicate well with families and each other, and partner in designing service delivery systems. This interaction is the practice of community pediatrics, whose unique feature is its concern for all of the population: those who remain well but need preventive services, those who have symptoms but do not receive effective care, and those who do seek medical care either in a physician's office or in a hospital.

Bibliography is available at Expert Consult.

5.1 Injury Control

Frederick P. Rivara and David C. Grossman

In all high-income countries of the world, and in many low- and middle-income countries, injuries are the most common cause of death during childhood and adolescence beyond the first few months of life and represent 1 of the most important causes of preventable pediatric morbidity and mortality in the United States (see Table 1-2 in Chapter 1 and Fig. 5-2). The identification of risk factors for injuries has led to the development of successful programs for prevention and control. Strategies for injury prevention and control should be pursued

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by the pediatrician in the office, emergency department, hospital, and community setting and be done in a multidisciplinary, multifaceted fashion.

INJURY CONTROL (FORMERLY CALLED ACCIDENT PREVENTION)

Injuries have defined risk and protective factors that can be used to define prevention strategies. The term *accidents* implies an event occurring by chance, without pattern or predictability. In fact, most injuries occur under fairly predictable circumstances to high-risk children and families. Most injuries are preventable.

The reduction of morbidity and mortality from injuries can be accomplished not only through primary prevention (averting the event or injury in the first place), but also through secondary and tertiary prevention. The latter 2 approaches include appropriate emergency medical services for injured children; regionalized trauma care for the child with multiple injuries, severe burns, or traumatic brain injury; and specialized pediatric rehabilitation services that attempt to return children to their previous level of functioning.

Injury control also encompasses intentional injuries (assaults and self-inflicted injuries). These injuries are important in adolescents and young adults, and in some populations, they rank first or second as causes of death in these age groups. Many of the same principles of injury control can be applied to these problems; for example, limiting access to firearms may reduce both unintentional shootings and suicides.

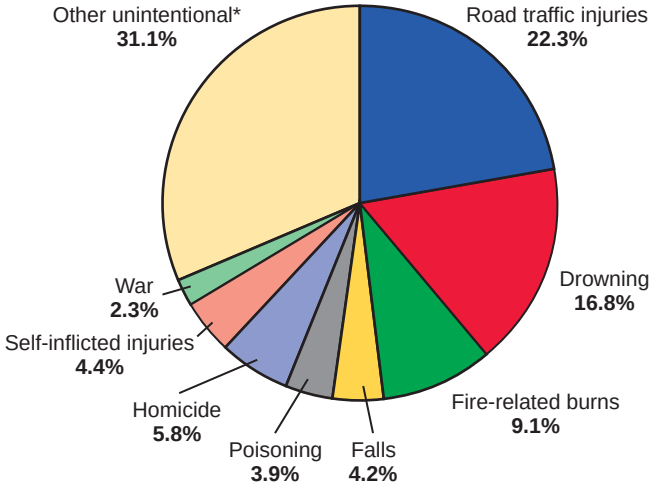

Figure 5-2 Worldwide distribution of global child injury deaths by cause, 0-17 yr of age, 2004. *"Other intentional" includes categories such as smothering, asphyxiation, choking, animal and venomous bites, hypothermia, and hyperthermia, as well as natural disasters. *(From WHO 2008, Global Burden of Disease: 2004 update. www.who.int/violence_injury_prevention/child/injury/wold_report/en/)*

SCOPE OF THE PROBLEM

Mortality

In the United States, injuries cause 41% of deaths among 1-4 yr old children and 3.5 times more deaths than the next leading cause, congenital anomalies. For the rest of childhood and adolescence up to the age of 19 yr, 63% of deaths are a result of injuries, more than all other causes combined. In 2010, injuries caused 13,819 deaths (16 deaths per 100,000) among individuals 19 yr old and younger in the United States (Table 5-1), resulting in more years of potential life lost than any other cause. Unintentional injuries remained the leading cause of death among those <24 yr in 2014 (see Table 1-2).

Motor vehicle injuries lead the list of injury deaths among school-age children and adolescents, and are the second leading cause of injury death for those ages 1-4 yr. In children and adults, motor vehicle **occupant** injuries account for the majority of these deaths. During adolescence, occupant injuries are the leading cause of injury death, accounting for >50% of unintentional trauma mortality in this age group.

Drowning ranks second overall as a cause of unintentional trauma deaths among those ages 1-14 yr, with peaks in the preschool and later teenage years (see Chapter 74). In some areas of the United States, drowning is the leading cause of death from trauma for preschool-age children. The causes of drowning deaths vary with age and geographic area. In young children, bathtub and swimming pool drowning predominate, whereas in older children and adolescents, drowning occurs predominantly in natural bodies of water while the victim is swimming or boating.

Fire and burn deaths account for 8% of all unintentional trauma deaths and 14% in those younger than 5 yr of age (see Chapter 75).

Table 5-1 Injury Deaths in the United States, 2010* [N (Rate per 100,000)]

CAUSE OF DEATH	YOUNGER THAN 1 Yr	1-4 Yr	5-9 Yr	10-14 Yr	15-19 Yr	0-19 Yr
ALL CAUSES	24,586 (623.35)	4316 (26.55)	2330 (11.45)	2949 (14.26)	10887 (49.40)	45068 (54.12)
ALL INJURIES	1529 (38.77)	1862 (11.45)	905 (4.45)	1341 (6.49)	8182 (37.12)	13819 (16.60)
All unintentional	1110 (28.14)	1264 (7.78)	758 (3.73)	885 (4.28)	4537 (20.58)	8684 (10.43)
Motor vehicle occupant	22 (0.56)	95 (0.58)	116 (0/57)	143 (0.69)	1065 (4.83)	1441 (1.73)
Pedestrian	12 (0.30)	206 (1.27)	96 (0.47)	115 (0.56)	315 (1.43)	744 (0.89)
Drowning	39 (0.99)	436 (2.68)	134 (0.66)	117 (0.57)	301 (1.37)	1027 (1.23)
Fire and burn	41(1.04)	281 (1.73)	174 (0.86)	89 (0.47)	102 (0.46)	687 (0.83)
Poisoning	25 (0.63)	65 (0.40)	21 (0.10)	58 (0.28)	938 (4.26)	1107 (1.33)
Bicycle	0	2 (0.01)	17 (0.08)	39 (0.19)	54 (0.25)	112 (0.13)
Firearm	11 (0.28)	71 (0.44)	73 (0.36)	225 (1.09)	2331 (10.58)	2711 (3.26)
Fall	12 (0.30)	25 (0.15)	12 (0.06)	20 (.10)	108 (0.49)	177 (0.21)
Suffocation	959 (24.31)	165 (1.02)	51 (0.25)	239 (1.16)	842 (3.82)	2256 (2.71)
All intentional	311 (7.89)	386 (2.37)	118 (0.58)	418 (2.02)	3508 (15.92)	4741 (5.69)
Suicide	0	0	7 (0.03)	267 (1.29)	1659 (7.53)	1933 (2.32)
Firearm suicide	0	0	1 (—)	80 (0.39)	688 (3.03)	749 (0.90)
Homicide	311 (7.89)	385 (2.37)	111 (0.55)	150 (0.73)	1832 (8.31)	2789 (3.35)
Firearm homicide	11 (0.28)	43 (0.26)	58 (0.29)	107 (0.52)	1554 (7.05)	1773 (2.13)
Undetermined intent	108 (2.74)	82 (0.50)	29 (0.14)	38 (0.18)	137 (0.62)	394 (0.47)

*Injury data from Centers for Disease Control and Prevention: Web-based Injury Statistics Query and Reporting System (WISQARS) (website). National Center for Injury Prevention and Control, Centers for Disease Control and Prevention (producer). Available at http://www.cdc.gov/injury/wisqars/index.html.

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Most of these are a result of house fires; deaths are caused by smoke inhalation and asphyxiation rather than severe burns. Children and the elderly are at greatest risk for these deaths because of difficulty in escaping from burning buildings.

Suffocation accounts for approximately 86% of all unintentional deaths in children younger than 1 yr of age. The majority of these deaths result from choking on food items, such as hot dogs, candy, grapes, and nuts. Nonfood items that can cause choking include undersize infant pacifiers, small balls, and latex balloons. However, some of these deaths may represent misclassification of children dying from sudden infant death syndrome (see Chapter 375).

Homicide is the third leading cause of injury death in children 1-4 yr of age and the second leading cause of injury death in adolescents (15-19 yr old). Homicide in the pediatric age group falls into 2 patterns: infantile and adolescent. Child homicide involves children younger than age 5 yr and represents child abuse (see Chapter 40). The perpetrator is usually a caretaker; death is generally the result of blunt trauma to the head and/or abdomen. The adolescent pattern of homicide involves peers and acquaintances and is caused by firearms in 85% of cases. The majority of these deaths involve handguns. Children between these 2 age groups experience homicides of both types.

Suicide is rare in children younger than age 10 yr; only 1% of all suicides occur in children younger than age 15 yr. The suicide rate increases markedly after the age of 10 yr, with the result that suicide is now the third leading cause of death for 15-19 yr olds. Native American teenagers are at the highest risk, followed by white males; black females have the lowest rate of suicide in this age group. Approximately 40% of teenage suicides involve firearms (see Chapter 27).

In the last decade, there has been a substantial increase in unintentional poisoning deaths among teens and young adults; in 2010 unintentional poisonings were the third leading cause of injury deaths among 15-24 year olds. Many of these were from prescription analgesic and opioid medications.

Nonfatal Injuries

Most childhood injuries do not result in death. Approximately 12% of children and adolescents receive medical care for an injury each year in hospital emergency departments, and at least an equal number are treated in physicians' offices. Of these, 2% require inpatient care and 55% have at least short-term temporary disability as a result of their injuries.

The distribution of these nonfatal injuries is very different from that of fatal trauma (Fig. 5-3). Falls are the leading cause of both emergency department visits and hospitalizations. Bicycle-related trauma is the most common type of sports and recreational injury, accounting for approximately 300,000 emergency department visits annually. Nonfatal injuries, such as anoxic encephalopathy from near-drowning, scarring and disfigurement from burns, and persistent neurologic deficits from head injury, may be associated with severe morbidity, leading to substantial changes in the quality of life for victims and their families.

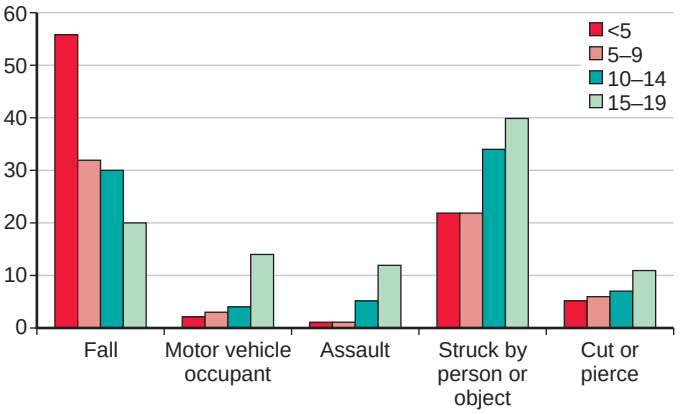

Figure 5-3 Emergency department visits for injuries, 2011. *(Data from NEISS All Injury Program operated by the Consumer Product Safety Commission for numbers of injuries. Bureau of Census for population estimates.)*

Global Child Injuries

Child injuries are a global public health issue and prevention efforts are necessary in low-, middle-, and high-income countries. Between 1990 and 2010 there was a 53% decrease in death rates of people of all ages from communicable, maternal, neonatal, and nutritional disorders whereas injury mortality rates decreased by only 16%. Worldwide, nearly 1 million children and adolescents die from injuries and violence each year, and more than 90% of these deaths are in low- and middle-income countries. As child mortality undergoes an epidemiologic transition because of better control of infectious diseases and malnutrition, injuries have and will increasingly become the leading cause of death for children in the developing world as it now is in all industrialized countries. Drowning is now the 5th most common cause of death for 5-9 yr old children globally, and in some countries, such as Bangladesh, it is the leading cause of death among children beyond the first year of life, with a rate 22 times greater than that in the Americas. An estimated 1 billion people do not currently have access to roads; as industrialization and motorization spreads, the incidence of motor vehicle crashes, injuries, and fatalities will climb. The rate of child injury death in low- and middle-income countries is 3-fold higher than that in high-income countries, and reflects both a higher incidence of many types of injuries as well as a much higher case-fatality ratio in those injured because of a lack of emergency and surgical care. As in high-income countries, prevention of child injuries and consequent morbidity and mortality is feasible with multifaceted approaches, many of which are low cost and of proven effectiveness.

PRINCIPLES OF INJURY CONTROL

Injury prevention once centered on attempts to pinpoint the innate characteristics of a child that result in greater frequency of injury. Most discount the theory of the *accident-prone child.* Although longitudinal studies have demonstrated an association between hyperactivity and impulsivity and increased rates of injury, the sensitivity and specificity of these traits for injury are extremely low. The concept of *accident proneness* is counterproductive in that it shifts attention away from potentially more modifiable factors, such as product design or the environment. It is more appropriate to examine the physical and social environment of children with frequent rates of injury than to try to identify particular personality traits or temperaments, which are difficult to modify. Children at high risk for injury are likely to be relatively poorly supervised, to have disorganized or stressed families, and to live in hazardous environments.

Efforts to control injuries include education or persuasion, changes in product design, and modification of the social and physical environment. Efforts to persuade individuals, particularly parents, to change their behaviors have constituted the greater part of injury control efforts. Speaking with parents specifically about using child car-seat restraints and bicycle helmets, installing smoke detectors, and checking the tap water temperature is likely to be more successful than offering well-meaning but too-general advice about supervising the child closely, being careful, and "childproofing" the home. This information should be geared to the developmental stage of the child and presented in moderate doses in the form of anticipatory guidance at well-child visits. Table 5-2 lists important topics to discuss at each developmental stage.

The most successful injury-prevention strategies generally are those involving changes in product design. These passive interventions protect all individuals in the population, regardless of cooperation or level of skill, and are likely to be more successful than active measures that require repeated behavior change by the parent or child. For some types of injuries, effective passive interventions are not available or feasible; we must rely heavily on attempts to change the behavior of individuals. The most important and effective product changes have been in motor vehicles. Turning down the water heater temperature,

Table 5-2 Injury Prevention Topics for Anticipatory Guidance by the Pediatrician

NEWBORN Car seats Tap water temperature Smoke detectors
INFANT Car seats Tap water temperature Bath safety
TODDLER AND PRESCHOOLER Car seats and booster seats Water safety Poison prevention Fall prevention
PRIMARY SCHOOL CHILD Pedestrian skills training Water skills training Booster seats and seat belts Bicycle helmets Safe storage of firearms
MIDDLE SCHOOL CHILD Seat belts Safe storage of firearms Water skills training
HIGH SCHOOL AND OLDER ADOLESCENT Seat belts Alcohol and drug use, especially while driving and swimming Mobile phone use while driving Safe storage of firearms Occupational injuries

installing smoke detectors, and using child-resistant caps on medicines and household products are other examples of effective product modifications. Many interventions require both active and passive measures. Smoke detectors provide passive protection when fully functional, but behavior change is required to ensure periodic battery changes and proper testing.

Modification of the environment often requires greater changes than individual product modification, but may be very effective in reducing injuries. Safe roadway design, decreased traffic volume and speed limits in neighborhoods, and elimination of guns from households are examples of such interventions. Included in this concept are changes in the social environment through legislation, such as laws mandating child seat restraint and seatbelt use, bicycle helmet use, and graduated driver licensing laws.

Prevention campaigns combining 2 or more of these approaches have been particularly effective in reducing injuries. The classic example is the combination of legislation and education to increase child seat restraint and seatbelt use; other examples are programs to promote bike helmet use among school-aged children and improvements in occupant protection in motor vehicles.

RISK FACTORS FOR CHILDHOOD INJURIES

Major factors associated with an increased risk of injuries to children include age, sex, race and ethnicity, socioeconomic status, rural–urban location, and the environment.

Age

Toddlers are at the greatest risk for burns, drowning, and falling. Poisonings become another risk as these children acquire mobility and exploratory behavior. Young school-age children are at greatest risk for pedestrian injuries, bicycle-related injuries (the most serious of which usually involve motor vehicles), motor vehicle occupant injuries, burns, and drowning. During the teenage years, there is a markedly increased risk from motor vehicle occupant trauma, a continued risk from drowning and burns, and the new risk of intentional trauma. Work-related injuries associated with child labor, especially for 14-16 yr olds, are an additional risk.

Injuries occurring at a particular age represent a window of vulnerability during which a child or an adolescent encounters a new task or hazard that the adolescent may not have the developmental skills to handle successfully. Toddlers do not have the judgment to know that medications can be poisonous or that some houseplants are not to be eaten; they do not understand the hazard presented by a swimming pool or an open second-story window. For young children, parents may inadvertently set up this mismatch between the skills of the child and the demands of the task. Many parents expect young school-age children to walk home from school, the playground, or the local convenience store, tasks for which most children are not developmentally ready. Likewise, the lack of skills and experience to handle many tasks during the teenage years contributes to an increased risk of injuries, particularly motor vehicle injuries. The high rate of motor vehicle crashes among 15-17 yr old teens is caused in part by inexperience, but also appears to reflect their level of development and maturity. Alcohol, other drugs, and mobile phone use substantially add to these limitations.

Age also influences the severity of injury and the risk of long-term disability. Young school-age children have an incompletely developed pelvis. In a motor vehicle crash, the seatbelt does not anchor onto the pelvis, but rides up onto the abdomen, resulting in the risk of serious abdominal injury. Age also interacts with vehicle characteristics in that most children ride in the rear seat, which in the past was equipped only with lap belts and not with lap-shoulder harnesses. Proper restraint for 4-8 yr old children requires the use of booster seats. Children younger than the age of 2 yr have much poorer outcomes from traumatic brain injuries than do older children and adolescents.

Gender

Beginning at 1-2 yr of age and continuing throughout the life span, males have higher rates of fatal injury than females. During childhood, this does not appear to be primarily a result of developmental differences between the sexes, differences in coordination, or differences in muscle strength. Variation in exposure to risk may account for the male predominance in some types of injuries. Although boys in all age groups have higher rates of bicycle-related injuries, adjusting for exposure reduces this excess rate. Boys may have higher rates of injuries because they use bicycles more frequently or for more hours. Sex differences in rates of pedestrian injuries do not appear to be caused by differences in the amount of walking, but rather reflect differences in behavior between young girls and boys. Greater risk-taking behavior, combined with greater frequency of alcohol use, may lead to the disproportionately high rate of motor vehicle crashes among teenage males. The rate of violence related injuries is higher among males because of their risk taking behavior.

Race and Ethnicity

Native Americans have the highest death rate from unintentional injuries. African-American children and adolescents have higher rates of fatal injuries than whites, whereas Asians have lower rates; rates for Hispanic children and adolescents are intermediate between those for African-Americans and those for whites. These discrepancies are even more pronounced for some injuries. The homicide rate for African-Americans age 15-19 yr was 29.6/100,000 in 2010, compared with 6.4/100,000 for American Indians and Alaskan Natives and 4.0/100,000 for whites and 2.0/100,000 for Asians. The suicide rate for Native American youth was 2.2 times the rate for whites and 4.4-fold greater than that for African-Americans. The rate of firearm homicide deaths for African-American youth ages 15-19 is nearly 9-fold higher than that for whites and 21 times that of Asian American youth.

These disparities appear to be primarily related to poverty, the educational status of parents, and the presence of hazardous environments. Homicide rates among African-Americans are nearly equivalent to those among whites, when adjusted for socioeconomic status. It is important to understand racial disparities in injury rates, but

Table 5-3 Recommended Child Restraint Methods

	INFANTS	TODDLERS (1-3)	YOUNG CHILDREN
Recommended age/ weight requirements	*Birth to 1 yr or below weight limit of seat*	*Older than 1 yr and 20-40 lb*	*40-80 lb and under 4'9" in height; generally between 4 and 8 yr of age*
Type of seat	Infant only or rear-facing convertible	Convertible or forward-facing harness seat	Belt positioning booster seat
Seat position	Rear-facing only. Place in back seat of vehicle	Can be rear-facing until 30 lb if seat allows; generally forward-facing. Place in back seat of vehicle	Forward-facing. Place in back seat of vehicle
Notes	Children should use rear-facing seat until at least 1 yr and at least 20 lb Harness straps should be at or below shoulder level	Harness straps should be at or above shoulder level Most seats require top strap for forward-facing use	Belt positioning booster seats must be used with both lap and shoulder belts Make sure the lap belt fits low and tightly across the lap/upper thigh area and the shoulder belt fits snugly, crossing the chest and shoulder to avoid abdominal injuries

Data from http://www.safercar.gov/parents/CarSeats.htm.

inappropriate to ascribe the etiology of these differences to race or ethnicity.

Socioeconomic Status

Poverty is one of the most important risk factors for childhood injury. Mortality from fires, motor vehicle crashes, and drowning is 2-4 times higher in poor children. Death rates among both African-Americans and whites have an inverse relationship to income level: the higher the income level, the lower the death rate. Native Americans have especially high rates. Other factors are single-parent families, teenage mothers, multiple care providers, family stress, and multiple siblings; these are primarily a function of poverty rather than independent risk factors.

Rural–Urban Location

Injury rates are generally higher in rural than in urban areas. Homicide rates are higher in urban areas, as is violent crime in general. Case fatality from injury is generally twice as high in rural areas than in urban areas, reflecting both the increased severity of some injuries (such as motor vehicle crashes occurring at higher speeds) and poorer access to emergency medical services and definitive trauma care in rural areas. Some injuries are unique to rural areas, such as agricultural injuries to children and adolescents.

Environment

Poverty increases the risk of injury to children, at least in part through its effect on the environment. Children who are poor are at increased risk for injury because they are exposed to more hazards in their living environments. They may live in poor housing, which is more likely to be dilapidated and less likely to be protected by smoke detectors. The roads in their neighborhoods are more likely to be major thoroughfares. Their neighborhoods are more likely to experience higher levels of violence, and they are more likely to be victims of assault than are children and adolescents living in the suburbs. The focus on the environment is also important because it directs attention away from relatively immutable factors, such as family dynamics, poverty, and race, and directs efforts toward factors that can be changed through interventions.

MECHANISMS OF INJURY

Motor Vehicle Injuries

Motor vehicle injuries are the leading cause of serious and fatal injuries for children and adolescents. Large and sustained reductions in motor vehicle crash injuries can be accomplished by identifiable interventions.

Occupants

Injuries to passenger vehicle occupants are the predominant cause of motor vehicle deaths among children and adolescents. The peak injury and death rate for both males and females in the pediatric age group occurs between 15 and 19 yr of age (see Table 5-1). Proper restraint use in vehicles is the single most effective method for preventing serious or fatal injury. Table 5-3 shows the recommended restraints at different ages. Figure 5-4 provides examples of car safety seats.

Much attention has been given to child occupants younger than 8 yr of age. Use of child restraint devices, infant car seats, and booster seats can be expected to reduce fatalities by 71% and the risk of serious injuries by 67% in this age group. All 50 states and the District of Columbia have laws mandating their use, although the upper age limit for booster seat requirements varies by state. Physician reinforcement of the positive benefits of child seat restraints has been successful in improving parent acceptance. Pediatricians should point out to parents that toddlers who normally ride restrained behave better during car trips than children who ride unrestrained.

A detailed guide and list of acceptable devices is available from the AAP (http://www.healthychildren.org/english/safety-prevention/on-the-go/pages/car-safety-seats-information-for-families.aspx) and the National Highway Traffic Safety Administration (http://www.safecar.gov/parents/carseats.htm). Children weighing < 20 lb may use an infant seat or be placed in a convertible infant-toddler child-restraint device. Infants and toddlers younger than 1 to 2 yr or if less than manufacturer's weight limit should be placed in the rear seat facing backward; older toddlers and young children can be placed in the rear seat in a forward-facing child harness seat until it is outgrown. Emphasis must be placed on the correct use of these seats, including placing the seat in the right direction, routing the belt properly, and ensuring that the child is buckled into the seat correctly. Government regulations have made the fit between car seats and the car easier, quicker, and less prone to error. *Children younger than age 13 yr should never sit in the front seat. Inflating airbags can be lethal to infants in rear-facing seats and to small children in the front passenger seat.*

Older children are often not adequately restrained. Many children ride in the rear seat restrained with lap belts only. Booster seats have been shown to decrease the risk of injury by 59%, and should be used by children who are between 40 lb (≈4 yr of age) and 80 lb, are <8 yr of age, and are <4 ft 9 in (145 cm) tall. Many states have extended their car seat laws to include children of booster seat age as well. Shoulder straps placed behind the child or under the arm do not provide adequate crash protection and may increase the risk of serious injury. The use of lap belts alone has been associated an increased risk of seatbelt-related injuries, especially fractures of the lumbar spine and hollow-viscous injuries of the abdomen. These flexion-distraction injuries of the spine are usually accompanied by injuries to the abdominal organs.

The rear seat is clearly much safer than the front seat for both children and adults. One study of children younger than the age of 15 yr found that the risk of injury in a crash was 70% lower for children in the rear seat compared with those sitting in the front seat. Frontal

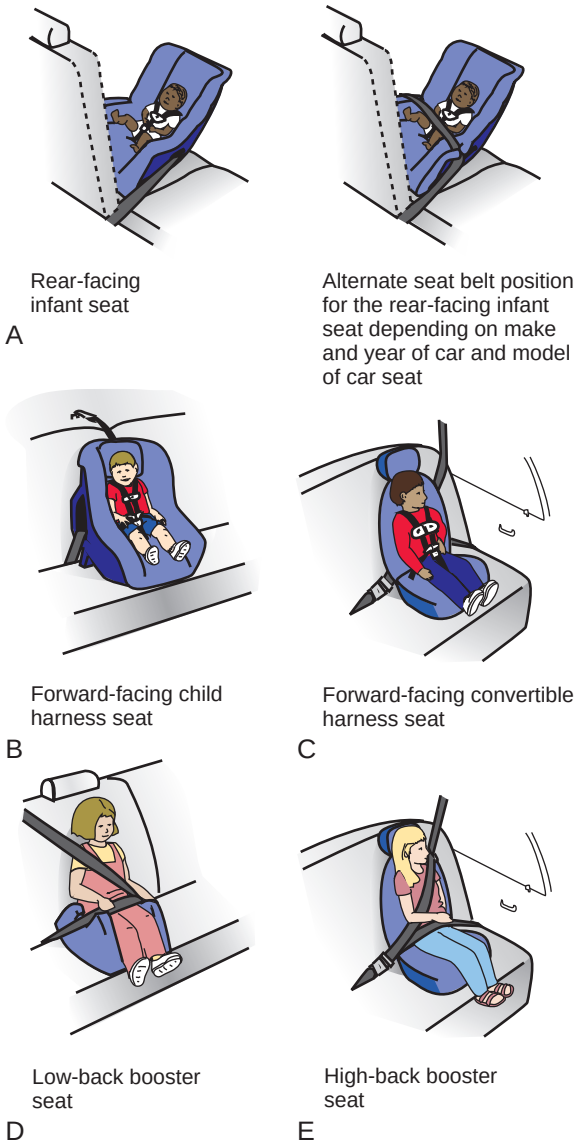

Figure 5-4 Car safety seats. **A,** Rear-facing infant seat. **B,** Forward-facing child harness seat. **C,** Forward-facing convertible harness seat. **D,** Low-back booster seat. **E,** High-back booster seat. *(From Ebel BE, Grossman DC: Crash proof kids? An overview of current motor vehicle child occupant safety strategies, Curr Probl Pediatr Adolesc Health Care 33:33–64, 2003. Source: NHTSA.)*

airbags appear to offer little protection to children in crashes and also present a risk of serious or fatal injury from the airbag itself. Side airbags also pose a risk for children who are in the front seat and are leaning against the door at the time of a crash. The safest place for children is in the rear middle seat, properly restrained for their age and size. Educational and legislative interventions to increase the number of children traveling in the rear seat have been successful.

Transportation of **premature infants** presents special problems. The possibility of oxygen desaturation, sometimes associated with bradycardia, among premature infants while in child seat restraints has led the AAP to recommend an observed trial of infants born at <37 wk of gestational age in the seat before discharge and the use of oxygen or alternative restraints for infants who experience desaturation or bradycardia, such as seats that can be reclined and used as a car bed. Car seats should only be used for travel and not as a general use infant seat around the home.

Children riding in the rear bed of pickup trucks are at special risk for injury because of the possibility of ejection from the truck and resultant serious head injury.

Teenage Drivers

Drivers 15-17 yr of age have more than twice the rate of collisions compared with motorists 18 yr of age and older. Formal driver education courses for young drivers appear to be ineffective as a primary means of decreasing the number of collisions, and in fact may increase risk by allowing younger teens to drive. The risk of serious injury and mortality is directly related to the speed at the time of the crash and inversely related to the size of the vehicle. Small, fast cars greatly increase the risk of a fatal outcome in the event of a crash.

The number of passengers traveling with teen drivers influences the risk of a crash. The risk of death for 17 yr old drivers is 50% greater when driving with 1 passenger compared with driving alone; this risk is 2.6-fold higher with 2 passengers and 3-fold higher with 3 or more passengers. The risk is also increased if the driver is male and the passengers are younger than age 30 yr.

Teens driving at night are overrepresented in crashes and fatal crashes, with nighttime crashes accounting for >33% of teen motor vehicle fatalities. Almost 50% of fatal crashes involving drivers younger than age 18 yr occur in the 4 hr before or after midnight. Teens are 5-10 times more likely to be in a fatal crash while driving at night compared with driving during the day. The difficulty of driving at night combined with the inexperience of teen drivers appears to be a deadly combination.

Another risk factor for motor vehicle crashes for people of all ages, including teens, is distracted driving from the use of mobile devices for texting or talking. In 2011, ⅓ of high school students reported they had texted or emailed while driving in the last 30 days. Dialing on a cell phone increases the risk of a crash nearly 3-fold, and texting may increase the risk as much as 6-fold. Although 44 states have banned text messaging for all drivers, the effect of state laws on prohibiting such behavior well driving is unknown. Parents should set limits on the use of these devices by their teens; technological interventions that can block cell phone signals in a moving vehicle may also be available.

Graduated licensing laws (GLLs) consist of a series of steps over a designated period before a teen can get full, unrestricted driving privileges. In a 3-stage graduated license, the student driver must first pass vision and knowledge-based tests. This is followed by obtaining a learner's permit and once a specific age has been achieved and driving skills advanced, the student driver is eligible to take the driving test. Once given the provisional license, the new driver will have a specified time to do low-risk driving. GLLs usually place initial restrictions on the number of passengers (especially teenaged) allowed in the vehicle and restrict driving during nighttime. There is a decrease in the number of crashes of 10-30% among the youngest drivers in states with a GLL system. The characteristics of GLLs vary substantially across states.

Alcohol use is a major cause of motor vehicle trauma among adolescents. The combination of inexperience in driving and inexperience with alcohol is particularly dangerous. Approximately 20% of all deaths from motor vehicle crashes in this age group are the result of alcohol intoxication, with impairment of driving seen at blood alcohol concentrations as low as 0.05 g/dL. Approximately 30% of adolescents report riding with a driver who had been drinking and approximately 10% report driving after drinking. All states have adopted a zero tolerance policy, which defines any measurable alcohol content as legal intoxication, to adolescent drinking while driving. All adolescent motor vehicle injury victims should have their blood alcohol concentration measured in the emergency department and be screened for high-risk alcohol use with a validated screening test (such as the CRAFFT or Alcohol Use Disorders Identification Test [AUDIT] screening tools) to identify those with alcohol abuse problems (see Chapter 114.1). Individuals who have evidence of alcohol abuse should not leave the emergency department or hospital without plans for appropriate alcohol abuse treatment. Interventions for problem drinking can be effective in decreasing the risk of subsequent motor vehicle crashes. Even brief interventions in the emergency department using motivational interviewing can be successful in decreasing adolescent problem drinking.

Another cause of impaired driving is marijuana use. In 2011, nearly one-quarter of high school students reported using marijuana in the prior 30 days. Marijuana use doubles the risk of a crash; as with alcohol,

this effect may be more pronounced with less experienced drivers. As of this writing, two states (Washington and Colorado) have legalized the sale of marijuana for adults; the effects of this on adolescent injury remains to be determined.

All-Terrain Vehicles. All-terrain vehicles (ATVs) in many parts of the country are an important cause of injuries to children and adolescents. These vehicles can attain high speeds and are prone to rollover because of their high center of gravity. Orthopedic and head injuries are the most common serious injuries seen among children involved in ATV crashes. Helmets can significantly decrease the risk and severity of head injuries among ATV riders, but current use is very low. Voluntary industry efforts to decrease the risk of injuries appear to have had little effect in making ATVs safer. The AAP recommends that children younger than 16 yr of age should not ride on ATVs.

Bicycle Injuries. Each year in the United States, approximately 300,000 children and adolescents are treated in emergency departments for bicycle-related injuries, making this one of the most common reasons that children with trauma visit emergency departments. The majority of severe and fatal bicycle injuries involve head trauma. A logical step in the prevention of these head injuries is the use of helmets. Helmets are very effective, reducing the risk of all head injury by 85% and the risk of traumatic brain injury by 88%. Helmets also reduce injuries to the mid and upper face by as much as 65%. Pediatricians can be effective advocates for the use of bicycle helmets and should incorporate this advice into their anticipatory guidance schedules for parents and children. Appropriate helmets are those with a firm polystyrene liner that fit properly on the child's head. Parents should avoid buying a larger helmet to give the child "growing room."

Promotion of helmet use can and should be extended beyond the pediatrician's office. Community education programs spearheaded by coalitions of physicians, educators, bicycle clubs, and community service organizations have been successful in promoting the use of bicycle helmets to children across the socioeconomic spectrum, resulting in helmet use rates of 60% or more with a concomitant reduction in the number of head injuries. Passage of bicycle helmet laws also leads to increased helmet use.

Consideration should also be given to other types of preventive activities, although the evidence supporting their effectiveness is limited. Bicycle paths are a logical method for separating bicycles and motor vehicles.

Pedestrian Injuries. Pedestrian injuries are an important of traumatic death for children and adolescents in the United States and in most high-income countries. In low-income countries, a much higher proportion of motor vehicle fatalities are pedestrians, especially among 5-14 year olds. Although case fatality rates are <5%, serious nonfatal injuries constitute a much larger problem, resulting in 60,000 emergency department visits annually for children and adolescents. Pedestrian injuries are the most important cause of traumatic coma in children and a frequent cause of serious lower extremity fractures, particularly in school-age children.

Most injuries occur during the day, with a peak in the after-school period. Improved lighting or reflective clothing would be expected to prevent few injuries. Surprisingly, approximately 30% of pedestrian injuries occur while the individual is in a marked crosswalk, perhaps reflecting a false sense of security and decreased vigilance in these areas. The risk of pedestrian injury is greater in neighborhoods with high traffic volumes, speeds greater than ≈25 mph, absence of play space adjacent to the home, household crowding, and low socioeconomic status.

One important risk factor for childhood pedestrian injuries is the developmental level of the child. Children < 5 yr are at risk for being run over in the driveway. Few children < 9 or 10 yr of age have the developmental skills to successfully negotiate traffic 100% of the time. Young children have poor ability to judge the distance and speed of traffic and are easily distracted by playmates or other factors in the environment. Many parents are not aware of this potential mismatch between the abilities of the young school-age child and the skills needed to cross streets safely. The use of mobile phones and devices has become increasingly common while walking, and can increase the risk of being struck by a motor vehicle.

Prevention of pedestrian injuries is difficult, but should consist of a multifaceted approach. Education of the child in pedestrian safety should be initiated at an early age by the parents and continue into the school-age years. Younger children should be taught never to cross streets when alone; older children should be taught (and practice how) to negotiate quiet streets with little traffic. Major streets should not be crossed alone until the child is at least 10 yr of age or older and has been observed to follow safe practices.

Legislation and police enforcement are important components of any campaign to reduce pedestrian injuries. Right-turn-on-red laws increase the hazard to pedestrians. In many cities, few drivers stop for pedestrians in crosswalks, a special hazard for young children. Engineering changes in roadway design are extremely important as passive prevention measures. Most important are measures to slow the speed of traffic and to route traffic away from schools and residential areas; these efforts are endorsed by parents and can decrease the risk of injuries and death by 10-35%. Other modifications include networks of 1-way streets, proper placement of transit or school bus stops, sidewalks in urban and suburban areas, edge stripping in rural areas to delineate the edge of the road, and curb parking regulations. Comprehensive traffic "calming" schemes using these strategies have been very successful in reducing child pedestrian injuries in Sweden, the Netherlands, Germany, and increasingly, the United States.

Ski- and Snowboard-Related Head Injuries. The increasing use of helmets in snow sports, such as skiing and snowboarding, is encouraging .since head injuries are the most common cause of death in these sports, and helmets reduce the risk of head injury by 50% or more. Use of helmets does not result in skiers or snow boarders taking more risks and should be encouraged in all snow sports.

Fire- and Burn-Related Injuries. See Chapter 75.

Poisoning. See Chapter 63.

Drowning. See Chapter 74.

Traumatic Brain Injury. See Chapter 68.

Firearm Injuries. Injuries to children and adolescents involving firearms occur in 3 different situations: unintentional injury, suicide attempt, and assault. The injury induced may be fatal or may result in permanent sequelae.

Unintentional firearm injuries and deaths have continued to decrease and accounted for 134 deaths in 2010, representing only a very small fraction of all firearm injuries among children and adolescents. The majority of these deaths occur to teens during hunting or recreational activities. **Suicide** is the third most common cause of death from all causes in both males and females ages 10-19 yr. During the 1950s to 1970, suicide rates for children and adolescents more than doubled; firearm suicide rates peaked in 1994 and decreased by 59% from this peak by 2010. The difference in the rate of suicide death between males and females is related to the differences in method used during attempts. Women die less often in suicide attempts, partly because they use less-lethal means (mainly drugs) and perhaps have a lower degree of intent. The use of firearms in a suicidal act usually converts an attempt into a fatality.

Homicides are second only to motor vehicle crashes among causes of death in teenagers older than 15 yr. In 2010, 1,832 adolescents age 15-19 yr were homicide victims; African American teenagers accounted for 52% of the total, making homicides the most common cause of death among African-American teenagers. Hispanic teenagers accounted for nearly 17% of the homicide deaths in this age group. In 2010, 85% of homicides among teenage males involved firearms, the majority of which are handguns.

In the United States, approximately 34% of households owned guns in 2012. Handguns account for approximately 30% of the firearms in use today, yet they are involved in 80% of criminal and other firearm misuse. Home ownership of guns increases the risk of adolescent suicide 3- to 10-fold and the risk of adolescent homicide up to 4-fold. In homes with guns, the risk to the occupants is far greater than the chance that the gun will be used against an intruder; for every death

occurring in self-defense, there may be 1.3 unintentional deaths, 4.6 homicides, and 37 suicides.

Of all firearms, handguns pose the greatest risk to children and adolescents. Access to handguns by adolescents is surprisingly common and is not restricted to those involved in gang or criminal activity. Stricter approaches to reduce youth access to handguns, rather than all firearms, would appear to be the most appropriate focus of efforts to reduce shooting injuries in children and adolescents.

Locking and unloading guns as well as storing ammunition locked in a different location substantially reduces the risk of a suicide or unintentional firearm injury among youth by up to 73%. Because up to 30% of handgun-owning households have at least 1 firearm stored unsafely, 1 potential approach to reducing these injuries could focus on improving household firearm storage practices where children and youth reside or visit. The evidence regarding the effectiveness of office-based counseling to influence firearm storage practice is mixed.

Adolescents with mental health conditions and alcoholism are at particularly high risk for firearm injury. In the absence of conclusive evidence, physicians should continue to work with families to eliminate access to guns in these households.

Falls. Falls are the leading cause of nonfatal injury in children and adolescents. Altogether, there were 2.9 million falls that led to emergency department visits in 2011 for children and adolescents; approximately 1.7% of these visits led to a hospitalization. There have been relatively few in-depth analytic studies of falls, except in particular circumstances, such as playground injuries. Strategies to prevent falls depend on the environmental circumstances and social context in which they occur. Window falls have been successfully prevented with the use of devices that prevent egress, and injuries from playground falls can be mitigated through the use of proper surfacing, such as woodchips or other soft, energy-absorbing materials. Alcohol may also contribute to falls among teenagers, and these injuries can be reduced by general strategies to reduce teen alcohol use.

Violent Behavior and Aggression. Although the current rates of homicide are much lower than they were at their peak in the late 1980s and early 1990s, the problem of violence and assault is still large. The origins of adult and teen violence occur during childhood. Adults who commit violent acts usually have a history of violent behavior during childhood or adolescence. Longitudinal studies following groups of individuals from birth have found that aggression occurs among infants and that most children learn to control this aggression early in childhood. Children who later become violent adolescents and adults do not learn to control this aggressive behavior.

The most successful interventions for violence target young children and their families. These include home visits by nurses and paraprofessionals beginning in the prenatal period and continuing for the first few years of life to provide support and guidance to parents, especially parents without other resources. Enrollment in early childhood education programs (e.g. Head Start) starting at age 3 yr has been shown to be effective in improving school success, keeping children in school, and decreasing the chance that the child will be a delinquent adolescent. School-based interventions, including curricula to increase the social skills of children and improve the parenting skills of caregivers, have long-term effects on violence and risk-taking behavior. Early identification of behavior problems by primary care pediatricians can best be accomplished through the routine use of formal screening tools. Interventions in adolescence, such as family therapy, multisystemic therapy, and therapeutic foster care, can decrease problem behavior and a subsequent decline into delinquency and violence.

Psychosocial Consequences of Injuries

Many children and their parents have substantial psychosocial sequelae from trauma. Studies in adults indicate that 10-40% of hospitalized injured patients will have posttraumatic stress disorder (PTSD; see Chapter 25). Among injured children involved in motor vehicle crashes, 90% of families will have symptoms of acute stress disorder after the crash, although the diagnosis of acute stress disorder is not predictive of later PTSD. Standardized questionnaires that collect data from the child, the parents, and the medical record at the time of initial injury can serve as useful screening tests for later development of PTSD. Early mental health intervention, with close follow-up, is important for the treatment of PTSD and for minimizing its effect on the child and family.

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Growth, Development, and Behavior

PART II

Chapter 6

Overview and Assessment of Variability

Susan Feigelman

The field of pediatrics is dedicated to optimizing the growth and development of each child. Pediatricians require knowledge of normal growth, development, and behavior in order to effectively monitor children's progress, identify delays or abnormalities in development, obtain needed services, and counsel parents and caretakers. To alter factors that increase or decrease risk, pediatricians need to understand how biologic and social forces interact within the parent-child relationship, within the family, and between the family and the larger society. Growth is an indicator of overall well-being, status of chronic disease, and interpersonal and psychologic stress. By monitoring children and families over time, pediatricians are uniquely situated to observe the interrelationships between physical growth and cognitive, motor, and emotional development. Observation is enhanced by familiarity with developmental theory and understanding of developmental models which describe normal patterns of behavior and provide guidance for prevention of behavior problems.

BIOPSYCHOSOCIAL MODEL AND ECOBIODEVELOPMENTAL FRAMEWORK: MODELS OF DEVELOPMENT

The medical model presumes that a patient presents with signs and symptoms and a physician focuses on diagnosing and treating diseases of the body. This model neglects the psychologic aspect of a person who exists in the larger realm of the family and society. In the **biopsychosocial model**, higher-level systems are simultaneously considered with the lower-level systems that make up the person and the person's environment (Fig. 6-1). A patient's symptoms are examined and explained in the context of the patient's existence. This basic model can be used to understand health and both acute and chronic disease.

With the advances in neurology, genomics including epigenetics, molecular biology and the social sciences, a more accurate model, the **ecobiodevelopmental framework** has emerged. This framework emphasizes how the ecology of childhood (social and physical environments) interacts with biologic processes to determine outcomes and life trajectories. Early influences, particularly those producing toxic levels of stress, affect the individual through modification of gene expression, without change in DNA sequencing. These **epigenetic changes**, such as DNA methylation and histone acetylation, are a result of environmental insults. Stress responses may produce alterations in brain structure and function, leading to disruption of later coping mechanisms. These changes will produce long-lasting effects on the health and well-being of the individual and may be passed on to future generations (Fig. 6-2).

Critical to learning and remembering (and therefore development) is **neuronal plasticity**, which permits the central nervous system to reorganize neuronal networks in response to environmental stimulation, both positive and negative. An overproduction of neuronal precursors eventually leads to about 100 billion neurons in the adult brain. Each neuron develops on average 15,000 synapses by 3 yr of age. Synapses in frequently used pathways are preserved, whereas less-used ones atrophy, through neuronal "pruning." Changes in the strength and number of synapses and reorganization of neuronal circuits also play important roles in brain plasticity. Increases or decreases in synaptic activity result in persistent increases or decreases in synaptic strength. Thus experience (**environment**) has a direct effect on the physical and therefore functional properties of the brain (**genetics**). Children with different talents and temperaments (already a combination of genetics and environment) further elicit different stimuli from their (differing) environments.

Periods of behavioral development generally correlate with periods of great changes in synaptic numbers in relevant areas of the brain. Accordingly, sensory deprivation during the time when synaptic changes should be occurring has profound effects. The effects of strabismus leading to amblyopia in 1 eye may occur quickly during early childhood; likewise, patching the eye with good vision to reverse amblyopia in the other eye is less effective in late childhood (see Chapter 621). Early experience is particularly important because learning proceeds more efficiently along established synaptic pathways. Traumatic experiences also create enduring alterations in the neurotransmitter and endocrine systems that mediate the stress response, with effects noted later in life. Positive and negative experiences do not determine the total outcome, but shift the probabilities by influencing the child's ability to respond adaptively to future stimuli. The plasticity of the brain continues into adolescence, with further development of the prefrontal cortex, which is important in decision-making, future planning, and emotional control; neurogenesis persists in adulthood in certain areas of the brain, including the subventricular zone of the lateral ventricles and in portions of the hippocampus.

Biologic Influences

Biologic influences on development include genetics, in utero exposure to teratogens, the long-term negative effects of low birthweight (neonatal morbidities plus increased rates of obesity, coronary heart disease, stroke, hypertension, and type 2 diabetes), postnatal illnesses, exposure to hazardous substances, and maturation. Adoption and twin studies consistently show that heredity accounts for approximately 40% of the variance in IQ and in other personality traits, such as sociability and desire for novelty, whereas shared environment accounts for another 50%. The negative effects on development of prenatal exposure to teratogens, such as mercury and alcohol, and of postnatal insults, such as meningitis and traumatic brain injury, have been extensively studied (see Chapters 96 and 99). Any chronic illness can affect growth and development, either directly or through changes in nutrition, parenting, or peer interactions.

The age at which children walk independently is similar around the world, despite great variability in child-rearing practices. The attainment of other skills, such as the use of complex sentences, is less tightly bound to a maturational schedule. Maturational changes also generate behavioral challenges at predictable times. Decrements in growth rate and sleep requirements around 2 yr of age often generate concern about poor appetite and refusal to nap. Although it is possible to accelerate many developmental milestones (toilet training a 12 mo old or teaching a 3 yr old to read), the long-term benefits of such precocious accomplishments are questionable.

In addition to physical changes in size, body proportions, and strength, maturation brings about hormonal changes. Sexual differentiation, both somatic and neurologic, begins in utero. Both stress and reproductive hormones affect brain development as well as behavior throughout development.

Temperament describes the stable, early-appearing individual variations in behavioral dimensions, including emotionality (crying, laughing, sulking), activity level, attention, sociability, and persistence. The classic theory proposes 9 dimensions of temperament (Table 6-1). These characteristics lead to 3 common constellations: (1) the easy, highly adaptable child, who has regular biologic cycles; (2) the difficult child, who withdraws from new stimuli and is easily frustrated; and (3) the slow-to-warm-up child, who needs extra time to adapt to new circumstances. Various combinations of these clusters also occur. Temperament has long been described as biologic or "inherited." Monozygotic twins are rated by their parents as temperamentally similar more often than are dizygotic twins. Estimates of heritability suggest that genetic differences account for approximately 20-60% of the variability of temperament within a population. The remainder of the variance is attributed to the child's environment. Maternal prenatal stress and anxiety is associated with child temperament, possibly through stress hormones. However, certain polymorphisms of specific genes moderate the influence of maternal stress on infant temperament (specifically irritability) illustrating the interplay between genes and environment. Longitudinal twin studies of adult personality indicate that changes in personality over time largely result from non-shared environmental influences, whereas stability of temperament appears to result from genetic factors.

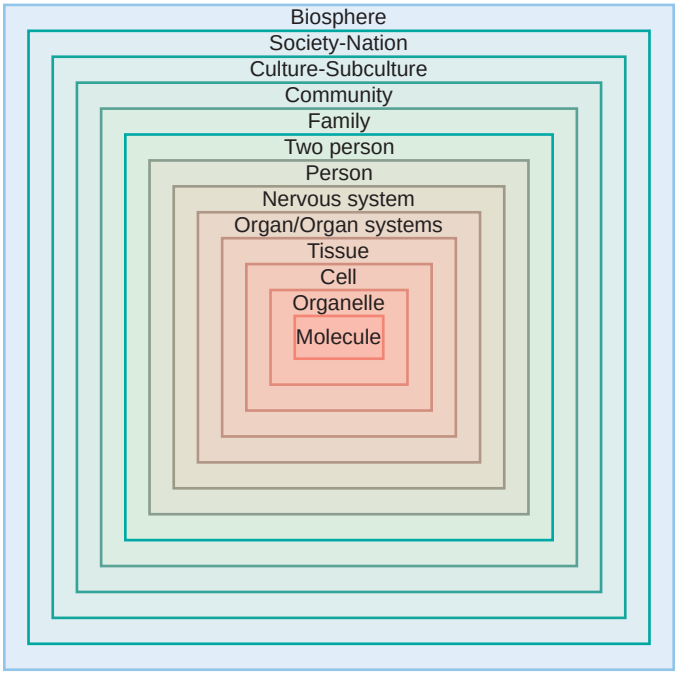

Figure 6-1 Continuum and hierarchy of natural systems in the biopsychosocial model. *(From Engel GL: The clinical application of the biopsychosocial model,* Am J Psychiatry *137:535–544, 1980.)*

The concept of temperament can help parents understand and accept the characteristics of their children without feeling responsible for having caused them. Children who have difficulty adjusting to change may have behavior problems when a new baby arrives or at the time of school entry. In addition, pointing out the child's temperament may allow for adjustment in parenting styles. Behavioral and emotional problems may develop when the temperamental characteristics of children and parents are in conflict.

Psychologic Influences: Attachment and Contingency

The influence of the child-rearing environment dominates most current models of development. Infants in hospitals and orphanages, devoid of opportunities for attachment, have severe developmental deficits. **Attachment** refers to a biologically determined tendency of a young child to seek proximity to the parent during times of stress and also to the relationship that allows securely attached children to use

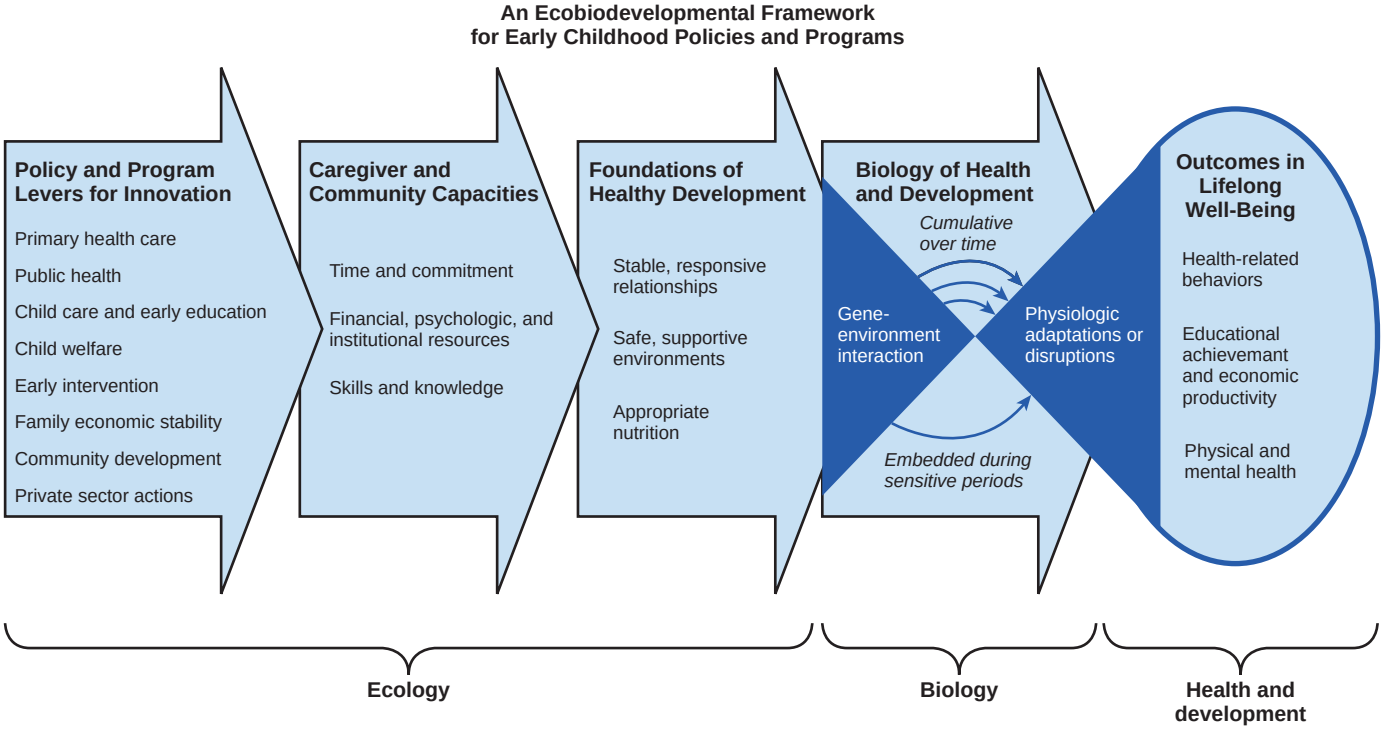

Figure 6-2 An ecobiodevelopmental framework for early childhood policies and programs. *(Adapted from Center on the Developing Child at Harvard University. The foundations of lifelong health are built in early childhood. Available at:* http://developingchild.harvard.edu/index.php/resources/reports_and_working_papers/foundations-of-lifelong-health/ *and published in* Pediatrics*: Shonkoff JP, Garner AS, The Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section of Developmental and Behavioral Pediatrics: The lifelong effects of early childhood adversity and toxic stress.* Pediatrics *129(1):e232–e246, 2012.)*

Table 6-1 Temperamental Characteristics: Descriptions and Examples

CHARACTERISTIC	DESCRIPTION	EXAMPLES*
Activity level	Amount of gross motor movement	"She's constantly on the move." "He would rather sit still than run around."
Rhythmicity	Regularity of biologic cycles	"He's never hungry at the same time each day." "You could set a watch by her nap."
Approach and withdrawal	Initial response to new stimuli	"She rejects every new food at first." "He sleeps well in any place."
Adaptability	Ease of adaptation to novel stimulus	"Changes upset him." "She adjusts to new people quickly."
Threshold of responsiveness	Intensity of stimuli needed to evoke a response (e.g., touch, sound, light)	"He notices all the lumps in his food and objects to them." "She will eat anything, wear anything, do anything."
Intensity of reaction	Energy level of response	"She shouts when she is happy and wails when she is sad." "He never cries much."
Quality of mood	Usual disposition (e.g., pleasant, glum)	"He does not laugh much." "It seems like she is always happy."
Distractibility	How easily diverted from ongoing activity	"She is distracted at mealtime when other children are nearby." "He doesn't even hear me when he is playing."
Attention span and persistence	How long a child pays attention and sticks with difficult tasks	"He goes from toy to toy every minute." "She will keep at a puzzle until she has mastered it."

*Typical statements of parents, reflecting the range for each characteristic from very little to very much.
Based on Chess S, Thomas A: Temperament in clinical practice, *New York, 1986, Guilford.*

their parents to reestablish a sense of well-being after a stressful experience. Insecure attachment may be predictive of later behavioral and learning problems.

At all stages of development, children progress optimally when they have adult caregivers who pay attention to their verbal and nonverbal cues and respond accordingly. In early infancy, such contingent responsiveness to signs of overarousal or underarousal helps maintain infants in a state of quiet alertness and fosters autonomic self-regulation. **Contingent responses** (reinforcement depending on the behavior of the other) to nonverbal gestures create the groundwork for the shared attention and reciprocity that are critical for later language and social development. Children learn best when new challenges are just slightly harder than what they have already mastered, a degree of difficulty dubbed the "zone of proximal development." Psychologic forces, such as attention problems (see Chapter 33) or mood disorders (see Chapter 26), will have profound effects on many aspects of an older child's life.

Social Factors: Family Systems and the Ecologic Model

Contemporary models of child development recognize the critical importance of influences outside of the mother–child dyad. Fathers play critical roles, both in their direct relationships with their children and in supporting mothers. As traditional nuclear families become less dominant, the influence of other family members (grandparents, foster and adoptive parents, same-sex partners) becomes increasingly important. Children are increasingly raised by unrelated caregivers while parents work or while they are in foster care.

Families function as systems, with internal and external boundaries, subsystems, roles, and rules for interaction. In families with rigidly defined parental subsystems, children may be denied any decision-making, exacerbating rebelliousness. In families with poorly defined parent–child boundaries, children may be required to take on responsibilities beyond their years, or may be recruited to play a spousal role.

Family systems theory recognizes that individuals within systems adopt implicit roles. One child may be the troublemaker, whereas another is the negotiator and another is quiet. Birth order may have profound effects on personality development, through its influence on family roles and patterns of interaction. Families are dynamic. Changes in one person's behavior affect every other member of the system; roles shift until a new equilibrium is found. The birth of a new child, attainment of developmental milestones such as independent walking, the onset of nighttime fears, and the death of a grandparent are all changes that require renegotiation of roles within the family and have the potential for healthy adaptation or dysfunction.

The family system, in turn, functions within the larger systems of extended family, subculture, culture, and society. Bronfenbrenner's ecologic model depicts these relationships as concentric circles, with the parent–child dyad at the center (with associated risks and protective factors) and the larger society at the periphery. Changes at any level are reflected in the levels above and below. The shift from an industrial economy to one based on service and information is an obvious example of societal change with profound effects on families and children.

Unifying Concepts: The Transactional Model, Risk, and Resilience

The **transactional model** proposes that a child's status at any point in time is a function of the interaction between biologic and social influences. The influences are bidirectional: Biologic factors, such as temperament and health status, both affect the child-rearing environment and are affected by it. A premature infant may cry little and sleep for long periods; the infant's depressed parent may welcome this good behavior, setting up a cycle that leads to poor nutrition and inadequate growth. The child's failure to thrive may reinforce the parent's sense of failure as a parent. At a later stage, impulsivity and inattention associated with early, prolonged undernutrition may lead to aggressive behavior. The cause of the aggression in this case is not the prematurity, the undernutrition, or the maternal depression, but the interaction of all these factors (Fig. 6-3). Conversely, children with biologic risk factors may nevertheless do well developmentally if the child-rearing environment is supportive. Premature infants with electroencephalographic evidence of neurologic immaturity may be at increased risk for cognitive delay. This risk may only be realized when the quality of parent–child interaction is poor. When parent–child interactions are optimal, prematurity carries a reduced risk of developmental disability.

Children growing up in poverty experience multiple levels of developmental risk: increased exposure to biologic risk factors, such as environmental lead and undernutrition, lack of stimulation in the home, and decreased access to interventional education and therapeutic experiences. As they respond by withdrawal or acting out, they further discourage positive stimulation from those around them.

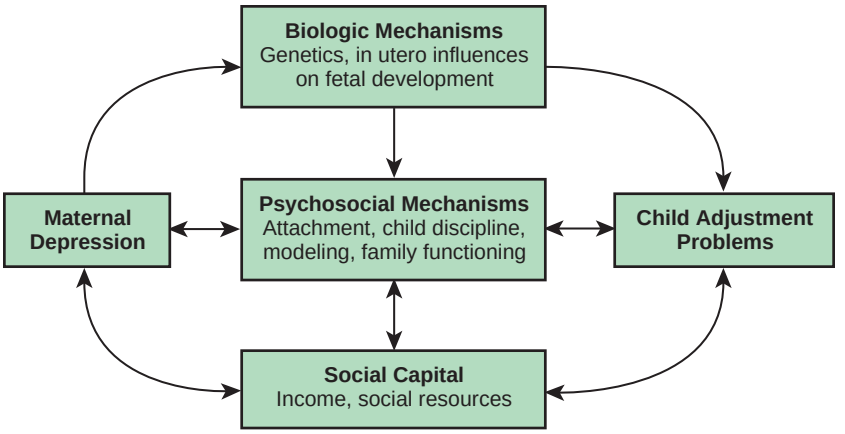

Figure 6-3 Theoretical model of mutual influences on maternal depression and child adjustment. *(From Elgar FJ, McGrath PJ, Waschbusch DA, et al: Mutual influences on maternal depression and child adjustment problems,* Clin Psychol Rev *24:441–459, 2004.)*

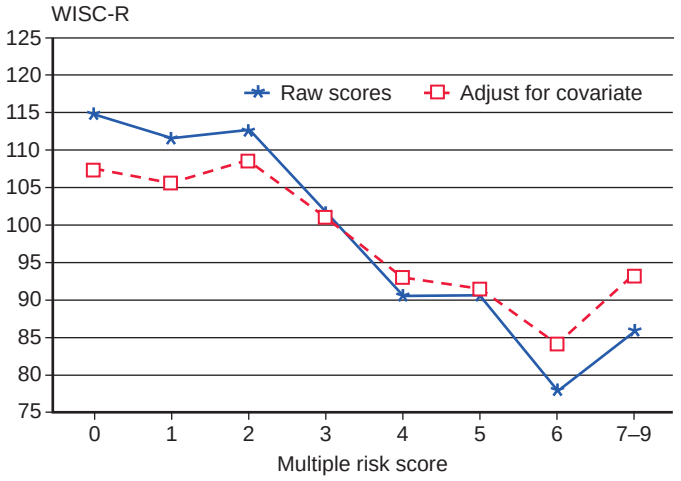

Figure 6-4 Relationship between mean IQ scores at 13 yr (both raw and adjusted for covariation of mother's IQ), as related to the number of risk factors. *WISC-R,* Wechsler Intelligence Scale-Revised. *(From Sameroff AJ, Seifer R, Baldwin A, et al: Stability of intelligence from preschool to adolescence; the influence of social and family risk factors,* Child Dev *64:80–97, 1993.)*

Children of adolescent mothers are also at risk. When early intervention programs provide timely, intensive, comprehensive, and prolonged services, at-risk children show marked and sustained upswings in their developmental trajectory. Early identification of children at developmental risk, along with early intervention to support parenting, is critically important.

An estimate of developmental risk can begin with a tally of risk factors, such as low income, limited parental education, and lack of neighborhood resources. There is a direct relationship between developmental outcome at age 13 yr and the number of social and family risk factors at age 4 yr (Fig. 6-4). Both individual stress and community-level poverty and disorder are associated with shortened telomeres in salivary samples, a link to health disparities. Protective (resilience) factors must also be considered. These factors, like risk factors, may be either biologic (temperamental persistence, athletic talent) or social. The personal histories of children who overcome poverty often include at least 1 trusted adult (parent, grandparent, teacher) with whom the child has a special, supportive, close relationship.

Developmental Domains and Theories of Emotion and Cognition

Child development can also be tracked by the child's developmental progress in particular domains, such as gross motor, fine motor, social, emotional, language, and cognition. Within each of these categories are developmental lines or sequences of changes leading up to particular attainments. Developmental lines in the gross motor domain, leading from rolling to creeping to independent walking, are obvious. Others, such as the line leading to the development of conscience, are more subtle.

The concept of a developmental line implies that a child passes through successive stages. Several psychoanalytic theories are based on stages as qualitatively different epochs in the development of emotion and cognition (Table 6-2). In contrast, behavioral theories rely less on qualitative change and more on the gradual modification of behavior and accumulation of competence.

Psychoanalytic Theories

At the core of **Freudian theory** is the idea of body-centered (or, broadly, "sexual") drives; the emotional health of both the child and the adult depends on adequate resolution of these conflicts. Although Freudian ideas have been challenged, they opened the door to subsequent theories of development.

Erikson recast Freud's stages in terms of the emerging personality (see Table 6-2). The child's sense of basic trust develops through the successful negotiation of infantile needs. As children progress through these psychosocial stages, different issues become salient. It is predictable that a toddler will be preoccupied with establishing a sense of autonomy, whereas a late adolescent may be more focused on establishing meaningful relationships and an occupational identity. Erikson recognized that these stages arise in the context of Western European societal expectations; in other cultures, the salient issues may be quite different.

Erikson's work calls attention to the intrapersonal challenges facing children at different ages in a way that facilitates professional intervention. Knowing that the salient issue for school-age children is industry vs inferiority, pediatricians inquire about a child's experiences of mastery and failure and (if necessary) suggest ways to ensure adequate successes.

Cognitive Theories

Cognitive development is best understood through the work of **Piaget**. A central tenet of Piaget's work is that cognition changes in quality, not just quantity (see Table 6-2). During the sensorimotor stage, an infant's thinking is tied to immediate sensations and a child's ability to manipulate objects. The concept of "in" is embodied in a child's act of putting a block into a cup. With the arrival of language, the nature of thinking changes dramatically; symbols increasingly take the place of objects and actions. Piaget described how children actively construct knowledge for themselves through the linked processes of assimilation (taking in new experiences according to existing schemata) and accommodation (creating new patterns of understanding to adapt to new information). In this way, children are continually and actively reorganizing cognitive processes.

Table 6-2 Classic Stage Theories

	INFANCY (0-1 YR)	TODDLERHOOD (2-3 YR)	PRESCHOOL (3-6 YR)	SCHOOL AGE (6-12 YR)	ADOLESCENCE (12-20 YR)
Freud: psychosexual	Oral	Anal	Phallic/oedipal	Latency	Genital
Erikson: psychosocial	Basic trust vs mistrust	Autonomy vs shame and doubt	Initiative vs guilt	Industry vs inferiority	Identity vs role diffusion
Piaget: cognitive	Sensorimotor	Sensorimotor	Preoperational	Concrete operations	Formal operations
Kohlberg: moral	—	Preconventional: avoid punishment/obtain rewards (stages 1 and 2)	Conventional: conformity (stage 3)	Conventional: law and order (stage 4)	Postconventional: moral principles

Piaget's basic concepts have held up well. Challenges have included questions about the timing of various stages and the extent to which context may affect conclusions about cognitive stage. Children's understanding of cause and effect may be considerably more advanced in the context of sibling relationships than in the manipulation and perception of inanimate objects. In many children, logical thinking appears well before puberty, the age postulated by Piaget. Of undeniable importance is Piaget's focus on cognition as a subject of empirical study, the universality of the progression of cognitive stages, and the image of a child as actively and creatively interpreting the world.

Piaget's work is of special importance to pediatricians for 3 reasons: (1) Piaget's observations provide insight into many puzzling behaviors of infancy, such as the common exacerbation of sleep problems at 9 and 18 mo of age. (2) Piaget's observations often lend themselves to quick replication in the office, with little special equipment. (3) Open-ended questioning, based on Piaget's work, can provide insights into children's understanding of illness and hospitalization.

Based on cognitive development, **Kohlberg** developed a theory of moral development in 6 stages, from early childhood through adulthood. Preschoolers' earliest sense of right and wrong is egocentric, motivated by externally applied controls. In later stages, children perceive equality, fairness, and reciprocity in their understanding of interpersonal interactions through perspective-taking. Most youth will reach stage 4, conventional morality, by mid to late adolescence. The basic theory has been modified to distinguish morality from social conventions. Whereas moral thinking considers interpersonal interactions, justice, and human welfare, social conventions are the agreed-on standards of behavior particular to a social or cultural group. Within each stage of development, children are guided by the basic precepts of moral behavior, but also may take into account local standards, such as dress code, classroom behavior, and dating expectations. Additional studies have even demonstrated some protomorality in infants.

Behavioral Theory

This theoretical perspective distinguishes itself by its lack of concern with a child's inner experience. Its sole focus is on observable behaviors and measurable factors that either increase or decrease the frequency with which these behaviors occur. No stages are implied; children, adults, and, indeed, animals all respond in the same way. In its simplest form, the behaviorist orientation asserts that behaviors that are positively reinforced occur more frequently; behaviors that are negatively reinforced or ignored occur less frequently. The strengths of this position are its simplicity, wide applicability, and conduciveness to scientific verification. A behavioral approach lends itself to interventions for various common problems, such as temper tantrums, aggressive preschool behavior, and eating disorders in which behaviors are broken down into discrete units. In cognitively limited children and children with autism spectrum disorders (see Chapter 30), behavioral interventions using **applied behavior analysis** approaches have demonstrated their ability to teach new, complex behaviors. Applied behavior analysis has been particularly useful in the treatment of early-diagnosed autism (see Chapter 30.1). However, in cases in which misbehavior is symptomatic of an underlying emotional, perceptual, or family problem, an exclusive reliance on behavior therapy risks leaving the cause untreated. Behavioral approaches can be taught to parents to apply at home.

Theories Commonly Employed in Behavioral Interventions

An increasing number of programs or interventions (within and outside of the physician's office) are designed to influence behavior; some of these models are based on behavioral or cognitive theory or may have attributes of both. The most commonly employed models are the Health Belief Model, Theory of Reasoned Action, Theory of Planned Behavior, Social Cognitive Theory, and the Transtheoretical Model, which is also known as Stages of Change Theory. Pediatricians should be aware of these models; Table 6-3 shows the similarities and differences between these models. Interventions based on these theories have been designed for children and adolescents in community, clinic, and hospital-based settings.

Motivational interviewing is a technique often used in clinical settings to bring about behavior change, rather than a behavioral theory. The goal in using the technique is to enhance an individual's motivation to change behavior by exploring and removing ambivalence. This may be practiced by an individual practitioner and is taught in some pediatric residency programs. Motivational interviewing emphasizes the importance of the therapist (which may be a pediatrician, other physician, psychologist, social worker, etc.) understanding the client's perspective and displaying unconditional support. The therapist is a partner rather than an authority figure and recognizes that, ultimately, the patient has control over the patient's choices.

Statistics Used in Describing Growth and Development

(See Chapters 15 and 16.)

In everyday use, the term *normal* is synonymous with *healthy*. In a statistical sense, *normal* means that a set of values generates a normal (bell-shaped or gaussian) distribution. This is the case with anthropometric quantities, such as height and weight, and with many developmental milestones, such as the age of independent standing. For a **normally distributed measurement**, a histogram with the quantity (height, age) on the *x*-axis and the frequency (the number of children of that height, or the number who stand on their own at that age) on the *y*-axis generates a bell-shaped curve. In an ideal bell-shaped curve, the peak corresponds to the arithmetic mean (average) of the sample and to the median and the mode as well. The **median** is the value above and below which 50% of the observations lie; the mode is the value having the highest number of observations. Distributions are termed *skewed* if the mean, median, and mode are not the same number.

The extent to which observed values cluster near the mean determines the width of the bell and can be described mathematically by the **standard deviation (SD)**. In the ideal normal curve, a range of values extending from 1 SD below the mean to 1 SD above the mean includes approximately 68% of the values, and each "tail" above and

Table 6-3 Similar or Identical Elements Within 5 Health-Behavior Theories

CONCEPT	GENERAL TENET OF THE CONCEPT "ENGAGING IN THE BEHAVIOR IS LIKELY IF ..."	HEALTH BELIEF MODEL	THEORY OF REASONED ACTION	THEORY OF PLANNED BEHAVIOR	SOCIAL COGNITIVE THEORY	TRANSTHEORETICAL MODEL
ATTITUDINAL BELIEFS						
Appraisal of the positive and negative aspects of the behavior and expected outcome of the behavior	The positive aspects outweigh the negative aspects	Benefits, barriers/ health motive	Behavioral beliefs and evaluation of those beliefs (attitudes)	Behavioral beliefs and evaluation of those beliefs (attitudes)	Outcome expectations/ expectancies	Pros, cons (decisional balance)
SELF-EFFICACY BELIEFS/BELIEFS ABOUT CONTROL OVER THE BEHAVIOR						
Belief in one's ability to perform the behavior; confidence	One believes in their ability to perform the behavior	Self-efficacy	—	Perceived behavioral control	Self-efficacy	Self-efficacy/temptation
NORMATIVE AND NORM-RELATED BELIEFS AND ACTIVITIES						
Belief that others want you to engage in the behavior (and one's motivation to comply); may include actual support of others	One believes that people important to one want one to engage in the behavior; person has others' support	Cues from media, friends (cues to action)	Normative beliefs and motivation to comply (subjective norms)	Normative beliefs and motivation to comply (subjective norms)	Social support	Helping relationships (process of change)
Belief that others (e.g., peers) are engaging in the behavior	One believes that other people are engaging in the behavior	—	—	—	Social environment/ norms; modeling	Social liberation (process of change)
Responses to one's behavior that increase or decrease the likelihood one will engage in the behavior; may include reminders	One receives positive reinforcement from others or creates positive reinforcements for one's self	Cues from media, friends (cues to action)	—	—	Reinforcement	Reinforcement management/stimulus control (processes of change)
RISK-RELATED BELIEFS AND EMOTIONAL RESPONSES						
Belief that one is at risk if one does not engage in the behavior, and that the consequences may be severe; may include actually experiencing negative emotions or symptoms and coping with them	One feels at risk with regard to a negative outcome or disease	Perceived susceptibility/ severity (perceived threat)	—	—	Emotional coping responses/ expectancies about environmental cues	Dramatic relief (process of change)
INTENTION/COMMITMENT/PLANNING						
Intending or planning to perform the behavior; setting goals or making a commitment to perform the behavior	One has formed strong behavioral intentions to engage in the behavior; one has set realistic goals or made a firm commitment to engage in the behavior	—	Behavioral intentions	Behavioral intentions	Self-control/ self-regulation	Contemplation/ preparation (stages of change); self-liberation (process of change)

From Noar SM, Zimmerman RS: Health behavior theory and cumulative knowledge regarding health behaviors: are we moving in the right direction? Health Educ Res *20:275–290, 2005, Table 1.*

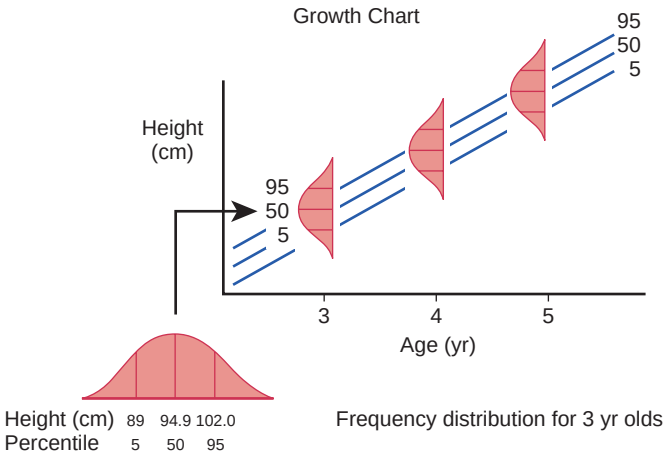

Figure 6-5 Relationship between percentile lines on the growth curve and frequency distributions of height at different ages.

Table 6-4 Relationship Between SD and Normal Range for Normally Distributed Quantities

OBSERVATIONS INCLUDED IN THE NORMAL RANGE		PROBABILITY OF A "NORMAL" MEASUREMENT DEVIATING FROM THE MEAN BY THIS AMOUNT	
SD	**%**	**SD**	**%**
±1	68.3	≥1	16.0
±2	95.4	≥2	2.3
±3	99.7	≥3	0.13

below that range contains 16% of the values. A range encompassing ±2 SD includes 95% of the values (with the upper and lower tails each comprising approximately 2.5% of the values), and ±3 SD encompasses 99.7% of the values (Table 6-4 and Fig. 6-5).

For any single measurement, its distance away from the mean can be expressed in terms of the number of SDs (also called a *z score*); one can then consult a table of the normal distribution to find out what percentage of measurements fall within that distance from the mean. Software to convert anthropometric data into z scores for epidemiologic purposes is available. A measurement that falls "outside the normal range"—arbitrarily defined as 2, or sometimes 3, SDs on either side of the mean—is atypical, but not necessarily indicative of illness. The further a measurement (say, height, weight, or IQ) falls from the mean, the greater the probability that it represents not simply normal variation, but rather a different, potentially pathologic, condition.

Another way of relating an individual to a group uses percentiles. The **percentile** is the percentage of individuals in the group who have achieved a certain measured quantity (e.g., a height of 95 cm) or a developmental milestone (e.g., walking independently). For anthropometric data, the percentile cutoffs can be calculated from the mean and SD. The 5th, 10th, and 25th percentiles correspond to −1.65 SD, −1.3 SD, and −0.7 SD, respectively. Figure 6-4 demonstrates how frequency distributions of a particular parameter (height) at different ages relate to the percentile lines on the growth curve.

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Chapter 7

Cognitive Development: Domains and Theories

Alison Gopnik

From Freud to Skinner to Piaget, philosophers, psychologists, and psychiatrists used to think that babies and young children were solipsistic and egocentric, precausal and illogical, concrete and superficial, restricted to the immediate here and now. That is still the picture most parents and many pediatricians have of babies and young children.

But 3 decades of research shows that just the opposite is true. Even the youngest babies both know more and learn more than we would ever have thought. There are still many controversies about exactly what babies and children know and when they know it. There also are competing theories about how and why children know and learn so much.

METHODOLOGIES

Much of this new understanding is the result of new techniques. Psychoanalysts asked adults to remember their childhood, behaviorists extrapolated from experiments on animals, and even Jean Piaget, the founder of the field of cognitive development, relied on observing the spontaneous behavior of babies, or on clinical interviews in which he asked children to say what they thought about mind and body or life and death. We now have experimental techniques that let children tell us what they know in their own language.

One group of methods involves seeing what babies prefer to look at (visual preferences), or listen to, or even smell. Babies have a choice of two stimuli, such as a mother's voice playing in one speaker, while a stranger's plays in another. We can see if babies turn toward one stimuli or the other.

Other methods use the fact that babies pay more attention to things that are unexpected than to those that are more predictable or familiar. Babies are *habituated* to a stimulus; they look or listen until their attention wanders, and when they see a variant of that stimulus they focus attention to the new stimulus if it is different. In *violation-of-expectation* studies, experimenters present babies with events that are surprising from an adult point of view, for example, one object apparently moving through another, and see whether babies look longer at those events than at similar unsurprising events.

These *looking-time* techniques have a drawback: it is difficult to tell just how babies interpret the stimulus by simply recording whether they look at it. Other technologies have made it possible to actually track babies' eye movements as they look at a stimulus. We can also look at what babies do as well as at what they attend to. Watching where babies reach or what they point to can be highly informative. Babies begin to imitate other people literally from birth and seeing how that imitation unfolds has proved to be a particularly useful tool.

As children grow older their attention patterns become less predictable. On the other hand, we can listen to what toddlers and preschoolers say. Large databases that record and analyze children's spontaneous language are becoming increasingly sophisticated, and can be an invaluable source of insight.

Asking preschoolers what they think often produces a sort of stream-of-consciousness poem, and has undoubtedly contributed to the impression that preschoolers are irrational. Children behave much more intelligently when you ask them about restricted, highly detailed scenarios. Instead of asking "Can someone believe something that isn't true?," researchers tell children a specific story—Max sees some

chocolate in the yellow cupboard, but then it is transferred to the blue cupboard without his knowledge. Preschoolers are even likely to respond to open-ended questions with silence or irrelevance. But they will consistently pick one option over the other when you ask them to choose between them. Four-year-olds can say that Max will look for the chocolate in the blue cupboard rather than the yellow one.

PHYSICAL KNOWLEDGE DEVELOPMENT

From the time infants are very young they understand some of the basic properties of physical objects. In the first few months of life, they know that objects are 3-dimensional and extended in space, that they can't pass through other objects, and that they continue to exist when they move behind a screen. They also have a basic concept of numbers, at least up to 3. In one experiment, infants see a toy disappear behind a screen, and then see another toy move behind the screen. The screen is lifted and 1, 2, or 3 toys appear. The babies look longer if 1 or 3, rather than 2, toys appear.

Infants also have a surprisingly early understanding of relationships that cross sensory modalities. They recognize parallelisms between lip movements and vocal sounds, between the feel of a pacifier and the way it looks, or between the visual image of a bouncing ball and the sound it makes.

Babies also have a surprisingly early and sophisticated understanding of statistics and probability. Before they are 1 yr old, they expect that a ball taken at random from a box of 80 red and 20 white balls is more likely to be red than white. Infants can also recognize statistical patterns in both visual and auditory sequences. You can play babies a string of syllables or tones or show them a sequence of pictures that have a particular pattern. For example "pa" may always follow "ti" but only follow "ko" 75% of the time. Babies seem to figure out these statistical patterns. Later they use them to isolate words or objects or other meaningful units from the torrent of sounds and sights they perceive.

In their second year, babies have a basic understanding of spatial relationships like gravity and containment. They can also categorize objects, recognizing that animals, for example, go together and are different from artifacts. They also gradually come to understand how to use simple tools to accomplish what they want, although they may still make interesting mistakes, like pulling a blanket to try to get a toy even when the toy is beside the blanket instead of on top of it.

Preschoolers continue to learn about the physical world, but they also begin to learn about the biologic world. Three and 4 yr olds are *essentialists*. They assume that categories of animals or plants, such as birds or daisies, will have the same insides and the same *essence* even if they are perceptually diverse. Contrary to conventional wisdom, preschoolers are not restricted to superficial perceptual categories. Preschoolers also have a first understanding of basic biologic ideas like inheritance, growth, and illness, and don't confuse these with psychologic ideas; they are not animists as Piaget thought. However, they still have difficulty understanding biologic concepts in a unified way, and they have little understanding of death.

By 5 yr of age, preschoolers have a more unified concept of something like a *life force*. They believe that the presence of this force makes living things grow and thrive, and its absence leads to illness and death. Interestingly, disadvantaged rural children, for example, Native American children on Indian reservations, who may have more experience of the living world, may develop an understanding of biology earlier than more privileged middle-class children.

Preschoolers also have a much more sophisticated understanding of causal relationships than we previously thought. Infants even understand something about the way physical objects move and interact with other objects. Older children understand the mechanics of simple physical systems.

They can also learn about new causal relationships. We can give young children evidence about how a novel machine works, showing them for instance that a box lights up and plays music only when you put a specific combinations of blocks on it. Children as young as 2 yr of age can figure out how the machine works and can use that information to invent novel ways to make it go. By 4 yr, they can figure out a machine that involves complex interactions of 3 different gears and switches. They can even propose invisible unobserved causes, when that is the best explanation for the pattern of evidence. In fact, they use forms of inductive causal reasoning that are basic to science and that are used in computer learning.

SOCIAL KNOWLEDGE DEVELOPMENT

Some of the most impressive kinds of early knowledge and learning involve children's understanding of other people. These *theory-of-mind* abilities are particularly important for social interaction and appear to be specifically impaired in children with autism. From the time they are born, infants treat people as special. Within the 1st mo infants prefer to look at human faces and listen to human voices, and rapidly prefer the face, voice, and even smell of their caregivers. Newborn infants also imitate facial expressions. To do this they must link what they see on the face of another person and how it feels to be them inside.

Within the 1st yr babies develop an even richer understanding of others. Seven-month-olds appreciate that human actions are directed towards particular goals. You can show the babies a ball and a teddy bear on a table. A hand reaches in and grasps the ball. Now you switch the locations of the 2 toys, so that the teddy bear is where the ball was and vice-versa. Seven-month-olds look longer when the hand goes to the teddy bear instead of the ball. They don't do this if a stick, rather than a hand, touches one object or the other.

One-year-olds don't just imitate actions; they reproduce the results of those actions. A 1 yr old child walks into the lab and sees the experimenter tap his head on a box, making the box light up. A week later she returns to the lab and sees the box on the table. She'll immediately use her own head to get the box to light.

Eighteen-month-olds can imitate in an even more sophisticated way. You can show them an experimenter touching her head to the box, but now she has a blanket wrapped around her so that her hands aren't available. If the other person's hands are free the babies will tap their own heads on the machine. But if she's wrapped up in the blanket and she taps the machine with her head, the babies will instead use their own hands. They've figured out that you would use your hands if you could, but because you can't, you're using your head instead.

In their second year, children also start to understand that their own perceptions, attention, and emotion may be shared by others. At this age babies start to engage in *joint attention behaviors*; they will follow the gaze or point of another person and they will point to objects themselves. They also start to understand that closing your eyes or wearing a blindfold may make it more difficult to see. In *social referencing*, babies will react appropriately to the emotional expression of another person that is directed at an object; if 1 yr olds see someone react to an ambiguous object with fear they will avoid the object themselves.

Babies are also sensitive to the contingency between their own actions and the actions of others, and use contingency patterns to differentiate people and things. If 1 yr olds see a machine that blinks and chirps in coordination with their own actions, they will treat it like a person, following its gaze if it turns toward an object. They will not do this if the machine makes the same noises, but they are not contingent on the baby's actions.

Eighteen-month-olds also start to show an understanding of love. *Attachment* researchers have long noted that different babies behave differently when they are separated from their caregivers and then reunited. *Secure* babies are distressed at separation but are quickly comforted when the caregiver returns. *Avoidant* babies seem to repress their distress; they ignore the caregiver both when she leaves and returns. *Anxious* babies are very distressed and take a long time to comfort.

Secure and insecure babies seem to have different theories of love. In one experiment, 18 mo old babies saw an animated film of a mother figure, a big circle, and a baby figure, which was a small circle that emitted a realistic cry. Then the babies either saw that the mother move toward the baby or move away from the baby. The secure babies expected that the mother would return to the baby and looked longer when she did not. The insecure babies had just the opposite theory; they looked longer when the mother changed course and returned.

From 2-6 yr of age, children discover further fundamental facts about how their own minds and the minds of others work. Even 18 mo olds already seem to understand something about the ways that people's minds might differ. You can show 14 mo olds and 18 mo olds 2 bowls of food: raw broccoli and Goldfish crackers. Then the experimenter tastes a bit of food from each bowl and acts as if she likes the broccoli but not the crackers. She puts out her hand and says, "Can you give me some." Fourteen-month-olds give the experimenter the crackers, but the 18 mo olds give the experimenter broccoli.

Slightly older children can understand the complex causal interactions between desire, perception, and emotion; they can predict all the possible actions that might stem from different psychologic combinations.

Preschoolers also, against conventional wisdom, can understand the difference between the physical and the mental, reality and fantasy, from a very young age. Preschoolers may be intensely emotionally affected by the products of fantasy, from imaginary friends to monsters in the closet. Nevertheless, they recognize the distinction between imaginations, which are private and intangible, and reality, which is public and verifiable.

In addition, around 5 yr of age children start to understand the relationship between our beliefs and the world around us. For example, suppose you show a child a candy box that turns out to be full of pencils. The children are very surprised when they see the pencils. But if you ask them what they thought was in the box 3 yr olds confidently report that they thought there were pencils in there. You see the same thing in the "Max" experiment described earlier. Though 4 yr olds accurately report where Max will look for the chocolate, 3 yr olds say that Max will look for the chocolate where it actually is instead of where he thinks it is.

Similarly, 3 yr olds have difficulty understanding the sources of their beliefs. If you ask them how they learned something, they are likely to think that they saw it directly, even when they actually heard it from someone else—an important consideration in child testimony. In their spontaneous language children only start explaining actions in terms of thoughts and beliefs, especially false thoughts and beliefs, when they are around 4 yr old. There are somewhat controversial studies that suggest that some implicit and unconscious understanding of belief may even be in place earlier, but there are clearly important changes in children's conscious understanding of the mind between 3 and 5 yr of age.

Understanding the mind also allows children to act to change the minds of others. Children who can explain actions in terms of a theory of mind also seem to be more adept, for good or ill, at altering other people's minds. They are more socially skillful, but they are also better liars.

Understanding minds actually also allows us to change our own minds as well as the minds of others. Between 3 and 5 yr of age, children also start to develop capacities for what psychologists call *executive control*, which is the ability to control your own actions, thoughts, and feelings. These capacities seem to be specifically related to *theory-of-mind* abilities. Understanding how your own mind works may help you to control and regulate it.

THEORIES OF COGNITIVE DEVELOPMENT

Several alternative theories have been proposed to explain these developmental processes. The basic conundrum of cognitive development is that even the youngest babies seem to have abstract, highly structured, hierarchical knowledge of the world; knowledge that lets them make wide-ranging new inferences. And yet as children experience more of the world, these representations change in systematic ways; it appears that young children are learning from their experiences.

One classic approach, often called *nativism* suggests that much of this abstract structure is in place innately; babies are born knowing about crucial aspects of the world. Learning is largely just a matter of filling in details. Although babies are far from being blank slates, there also seem to be significant changes in their understanding of the world.

The alternative approach, *empiricism,* suggests that all of children's knowledge is simply the result of a process of associating or combining particular sensory experiences, or detecting the statistics of the environment. Although children are able to associate particular experiences and to detect statistics, those abilities don't seem to be sufficient to explain their remarkable growth of knowledge.

Piaget originally articulated *constructivism* as an alternative to both nativism and empiricism. But Piaget had little to say in detail about how constructivist processes could take place; many of his empirical claims have been disproved. The *theory theory* is the more current version of constructivism. The idea is that children develop their knowledge of the world by constructing every day or intuitive theories, much like scientific theories. The *theory theory*, unlike empiricism, proposes that even babies may be born with innate theories of the world, but unlike nativism, it proposes that those theories may be radically transformed as children learn more about the world. Most recently, *rational constructivism*, a more rigorous and precise version of the *theory theory*, was formulated. It uses mathematical ideas about probabilistic models and bayesian inference to explain how even very young children can learn so much from the evidence they encounter.

Within the constructivist approach, an exciting new set of studies and theoretical ideas confirms something that parents and preschool teachers and others have long thought intuitively: Very young children's play, both their exploratory play and their imaginative and pretend play, contributes greatly to their early learning.

Nativism, empiricism, and constructivism all focus on the process of learning from evidence. Two other approaches describe other factors that contribute to cognitive development. Information-processing approaches stress the development of general abilities to process and organize information, such as memory or attention. Indeed, children do develop such abilities in the first few years of life and those developments contribute to the development of their knowledge.

Sociocultural approaches emphasize the contribution that *expert adults* can make to children's knowledge. There is growing evidence that from very early in infancy babies are specifically and powerfully tuned to information that comes to them from their caregivers. By preschool, what is sometimes called *implicit* or *intuitive* pedagogy plays an increasingly important role in children's learning. Preschoolers tend to give grownup testimony the benefit of the doubt, but they can also distinguish between reliable and unreliable teachers.

However, preschoolers sensitivity to implicit teaching can be a double-edged sword. Some studies show that children are less likely to engage in wide-ranging exploration when adults provide them with answers. Preschoolers left to their own resources are often able to solve complex problems (see Chapter 7.1). In addition because play is such an important component of a preschool-age child's learning process, the learning environment may need to be less structured, more child-focused, and with less emphasis on traditional academic instruction. Sociocultural approaches are especially relevant to the many kinds of learning where there is no right answer such as learning the particular traditions, mythologies, or values of your cultural or ethnic group.

All these factors, innate structure, association and statistics, theory formation and play, information-processing abilities, and cultural transmission, must somehow combine to allow children to learn as much as they do.

Bibliography is available at Expert Consult.

7.1 The Reggio Emilia Educational Approach and Child Development and Learning

Naama Zoran and Rivkie Spalter

Maria Montessori was the first to bring the message of children as competent, and was followed by Loris Malaguzzi who had the same philosophy and developed his approach in Reggio Emilia, a city in Italy. Malaguzzi believed that education is a lifetime experience that has 3

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Box 7-1 Example of Creating an Educational Environment That Recognizes the Child's Social–Emotional Well-Being

The K3 children were working on building an igloo in the playground. When they realized the task was bigger than they anticipated, they decided to invite their parents to help.

M (4 yr old) shared that his dad could not come because he was in the hospital. The teacher dialogued with the child, and together they thought about ways for the father to be part of the process. The decision was to create a book for his father with the story of the igloo. The strong message given to the child was that he has the tools for coping with the situation. This empowered him to approach the situation with joy and creativity. One of the child's ideas was to add some photos of his father's previous visits at school to the book. Seen as competent, he chose the pictures that would go into the pages.

M was so proud of his book. He asked every person who visited our school, whether adult or child, to read his book with him. In addition this book brought emotional stability to a family going through a difficult and scary time. The book was a tool for father and son to communicate and share meaningful conversation.

major elements: the emotional component, the ethical component, and the aesthetic component.

THE EMOTIONAL COMPONENT

Malaguzzi believed that the concept of well-being leads the educational approach. Well-being, especially in early childhood, is the leading developmental task that every child from birth is thriving for as part of each child's sense of self establishment. Creating an educational environment that recognizes the child's social–emotional well-being means creating a place where every child is valued and respected as an individual and as an equal member of a group. Malaguzzi believed that every moment should be enjoyable and satisfactory (Box 7-1).

THE ETHICAL COMPONENT

The following points characterize the Reggio Emilia ethical code:

- Education is not just a technique but is a shared process for revealing values.
- The school is a place that transmits and constructs culture through experiences. The reciprocal relations between transmission and construction gives schools and teachers a responsibility and an active role in sustaining and generating a culture that is based on the past, yet looking ahead to the future.
- The school should focus not only on knowledge but also on concepts, ideas, and values.
- The educator influences the future, and as such needs to generate the connections between the individual and the world.
- Children are born with myriad ways to construct and process knowledge. Those ways are defined as *100 languages*; language is defined as the different ways through which any human being represents, communicates, and expresses thoughts, feelings, concepts, and symbols (Box 7-2).

THE AESTHETIC COMPONENT

Education must focus on the aesthetics because the child knows how to value beauty and is able to interact with all the expressive languages. Malaguzzi's innovative idea for approaching and embracing the expressive–aesthetic aspects to early childhood education was the *atelier*. The atelier is a statement about the importance of imagination, creativity, expression, and aesthetics in the learning and knowledge construction processes. Because children do not separate different disciplinary fields, and because they learn in an interrelated and interdisciplinary way, the learning environment should connect between aesthetics and ways of knowing. The expressive languages and the arts are ways to break the conformist thinking about children and their learning, and to move toward elaborating the opportunities that are given to children while they are exploring, researching, and constructing knowledge.

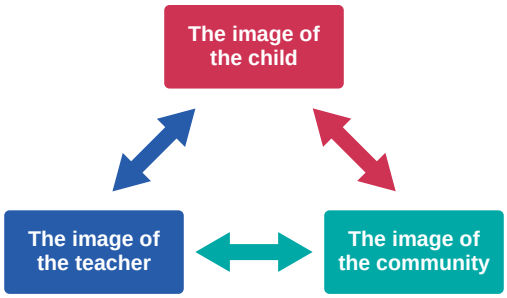

Figure 7-1 Pedagogic thinking: core concepts around 3 major areas.

Box 7-2 Example of Children Processing Information and Solving Problems

When the K4 teacher had an idea to have senior citizens as pen pals for the K4 kids, she thought about a correspondence that might take place every once in a while.

One cold winter day the bus arrived with the seniors for the monthly visit, but the driver notified the school that the bus needed to leave because the lift to lower the seniors off the bus was jammed. When the children heard about the situation, they immediately thought about a way to solve it. They decided as a group to board the bus with the activities that they had planned. They put on their coats and hats and brought the bingo and the brownies, and for the next 2 hr, the children and seniors had an enjoyable afternoon together. It was a moment when we realized that our children have internalized the value of working with seniors and from that place found the appropriate solution to the issue at hand.

PEDAGOGIC THINKING: CORE CONCEPTS AROUND 3 MAJOR AREAS

One of the cornerstones of this approach is the concept of **images** (Fig. 7-1).

An image is a cognitive structure that serves as a container. It keeps and holds all of the tools we have to perceive and interpret the world around us. All of the perceptions and interpretations are organized into clusters that serve as our inner compass and navigate our way in the personal and social–cultural life that we share with others.

When it comes to education, the images play a crucial and determinative role as is reflected in the following quote from Carla Rinaldi: "Everyone (you, us, each parent…) has his or her own image of the child, and, consequently, we have our own educational theories that we develop based on personal, social, cultural, and political experience, and that we construct or acquire as part of our society and culture. Whether we are aware of it or not, we cannot live without theories." Yet, as educators we have a profound responsibility for the awareness level that guides us when we make choices for children.

It is important to note that each person has his or her own image of the child. By saying image we mean personal interpretation that is subjective and unique. The focus is on which point of view being used when thinking about a child. Our points of view about the world around us are dynamic and are consistently changing. We are structuring the impressions we are getting on any concept or experience to create a holistic image in our mind.

The Image of the Child

Loris Malaguzzi said "Each has inside ourselves an image of the child that directs you as you begin to relate to a child. This theory within you pushes you to behave in certain ways." It orients you when you listen to the child, observe the child. It is very difficult for you to act contrary to this internal image.

It is important to emphasize the impact of the image to the awareness of the teachers, as only the awareness would enable the teacher to follow the desired image of children; one that sees and accepts the

Box 7-3 Example of Relating to a Child as a Competent Partner

One day, a child who was questioning about how he is seen by his teacher began to cry, saying, "I cannot do it," referring to pulling on his pants. The teacher who understood it was a question more than a statement about his incompetence, said: "Show me what you **can** do." Her focusing on her perception of the child as competent met the child's inner question and empowered the child to focus on what the child could accomplish. The child was able to complete the task on his own.

child as an active competent partner, plentiful with potential and capabilities. Usually the strength and the talents of children are underestimated and schools tend to suppress the child's potential by creating an environment of transmission, instead of exploration. The environment should be collaborative between teachers and children; they partner together rather than the teacher determining all activities or interactions.

The concept of a "blank slate," first mentioned by the philosopher John Locke, is presented here as a characterizing traditional point of view in education that does not believe in the child's abilities and leaves no room for the child's feelings, thoughts, imagination, and creativity. It also reflects the belief that the child is waiting for the school and society to "write" on, nourish, and fill his or her slate.

Choosing an image calls for a *sense of responsibility*, as we need to commit to the image that was chosen. The chosen image then becomes a compass that guides us in every interaction or practice we are having with the child. Reggio educators believe that the image of **child as competent** brings a point of view that sees children as structuring their sense of self, they generate and construct values, and they establish their rights; the first one is the right that acknowledges and accepts the role childhood has and the unique contribution each person brings to it.

The child is born as a *researcher* that is looking for relationships, hypotheses, and provocations in anything the child is exploring. The choice to see the child as a researcher has major pedagogic implications. The first guiding implication is the understanding that the child is **never** waiting for the adult to actuate the child's need to research, yet the child needs the adult as a **context** for the child's revelations (Box 7-3).

The Image of the Educator

The core component in the image of the teacher is the understanding that to be a high-quality teacher, the educator needs to perceive himself or herself also as a learner. The most meaningful place for learning how to teach is within the educational setting. You learn how to teach by being with children and by reflecting on the processes you have experienced with them; the best key for learning and teaching is **reciprocity**.

The role of the teacher in the above image encompasses the following aspects:

- To define and create the context within which all learning/teaching processes would occur. The context enables the landscape of learning to emerge and develop.
- To think and plan using symbols and concepts
- To interpret the child concepts and symbols with the group
- To elaborate on the experiences and the interpretations done with the children.
- To review with the children a second round of experiences built on the previous day.
- To add improvisations according to the previous learning processes.

There are reciprocal relationships between the image of the child and the image of the teacher, and each is complementary and bound to the other.

Teachers should never think of the child in the abstract. When we think about a child, that child is already tightly connected and linked to a certain reality. Children have relationships and experiences that they bring to any new environment. Similarly, the teacher brings pieces of his or her life to the educational environment (Box 7-4).

Box 7-4 Example of Reciprocal Relationships Between the Image of the Child and the Image of the Teacher

One morning a child was brought to school and was not willing to take his coat off. The mother did not know how to convince him to take the coat off; the teacher kept asking him to take the coat off; and the child was crying and determined not to take the coat off.

It was only when the teacher changed her **point of view** and was willing to accept the child and meet him where he was that the child stopped crying and was able to join his class activities.

We see this example as a compass for remembering that it is only when you leave your preconceived notions and see yourself as a **place** where children feel that they are seen and heard as equal, active, and competent partners that the quality of relationships you create is elevated and becomes clear and coherent.

The Image of the Contextual Community

The concept at the core of the educational communal life is the idea of the "other" that is the essence of the Reggio Emilia pedagogic approach. The "other" might be the child, the family, or a colleague—in a sense, any person who is interacting with the educational system. All members together, through the relations that are constructed among all, are part of creating a sense of belonging for the system and for its members. The feeling of belonging serves as a foundation for the community life. When people who are part of the system feel they are seen, heard, and known, a culture of participation can be developed. The culture of participation arises out of the integration of the concept of feeling a part of, and its complementary aspect of taking part, and is shared among all children, parents, and teachers.

The focus was and is to develop relationships with the other, with the other's uniqueness and originality, with the other's point of view, and to reach the place where the subjectivity of each partner is open to entering an intersubjective field for a real meeting. The basic assumption is that each family shares its culture with the others.

The idea of crossing the *boundaries of the subjectivity* to arrive at the intersubjective landscape emerges from a very important declaration that the school sends to the community: A declaration of a place that has a defined and solid identity that is based on the perception that the school by nature is a multicultural place, and as such embraces every inhabitant, including each inhabitant's background and culture, knowing that the school point of view is partial, and each is invited to share their points of view, as the school invites each partner to add their point of view for strengthening, elaborating, and accommodating the shared identity of the school.

Concepts like welcoming, plurality, dialog, and intercultural dynamics are explored and new meanings are attributed to them, as a realization that every word/concept or value could have different meanings. That realization creates a place for reworking of the ideas, a place where new questions are generated and discussed.

THE DEVELOPMENTAL THEORIES OF GREENSPAN, VYGOTSKY, AND MALAGUZZI

Greenspan on Well-Being and the Sense of Self

Stanley Greenspan (1941–2010), a psychiatrist, was a leading researcher on the prevention and treatment of emotional and developmental disorders in infants and children. He believed that when you observe or interact with a child, you should take into account not just the child's developmental functioning level, but also the child's background, personal and familial history, and, especially, the quality of relationships the child is experiencing in his or her home and school environment.

Greenspan believed that it is the quality of the interactions children have with meaningful figures that determines the quality of the social–emotional experiences and the level of success in achieving the developmental tasks that are required in every developmental sequence. Greenspan developed a model that shows how in every developmental phase, 2 different processes are possible. Simply stated, high-quality responsive parenting leads to high-quality achievement of the

Table 7-1 Comparison of Greenspan and Malaguzzi Developmental Theories

DEVELOPMENTAL PRINCIPLE	GREENSPAN	MALAGUZZI (REGGIO)
Self-regulation	The ability to reach an inner and outer harmony. The harmony represents the skills needed to create the initial understanding of being in the world.	The school environment is designed and organized in ways that support the concept of being in harmony. In Malaguzzi's words, an "amiable environment."
Attachment and bonding	The ability to create a meaningful, special bond with another; plant the seeds for the notion of to love and be loved.	Well-being is the fountain for all the relationships, and the school is the landscape of well-being that is ready to embrace all kinds of relationships.
Differentiation	The ability to differentiate oneself from any other person is crucial for the sense of separation and uniqueness.	The child is seen as a unique individual, who is at all times an active and equal member of the school community.
Initiation and internalization	The ability to navigate oneself in the world in an active, participatory way, that empowers and leads to the internalization of the sense of self.	One of the core concepts that defines curricular planning and guides teachers' practical choices is the ability of the school to define the educational intents in visible and declarative ways that support the curricular initiatives and their impact on the school community.
Representational thinking	The ability to represent all of the above in a verbal, conceptual, socially and emotionally appropriate way.	The concept of the "hundred languages of children" is a message that there are a hundred ways to represent the knowledge and understanding that was achieved in any learning experience.

developmental tasks needed; and low-quality parenting skills lead to low-quality achievement of the developmental tasks at hand.

The above point of view matches Malaguzzi's concept of the **pedagogy of relationships**. The concept of *pedagogy of relationships* has an extra value for the early childhood period because the early childhood years are considered the most critical period in our lives; the **self** that is the entity that is the core of our being establishes its essential structure in these early years.

Greenspan defined the leading developmental tasks that are connected to the development of the sense of self and that continue to deepen and elaborate throughout life: self-regulation processes, attachment and bonding, differentiation, initiative and internalization, and representational symbolic thinking (Table 7-1).

Vygotsky and the Reggio Emilia Approach

Vygotsky's concept of the **zone of proximal development** states that in any given moment, the person (child or adult) finds himself between 2 developmental points—the *actual* and the *potential* points of development that represent the idea of human competence. Vygotsky saw the actual point of development as the place that reflects the already existing skills in all areas of development, and the potential point of development as the place for the skills on which the person works at that given time. Between those 2 points of development is the land of development, where each of us is using what we already have in order to develop what is potentially waiting to unfold.

Vygotsky believed that the teacher's role is to be with children in a very conscious and attentive way. To use the child's actual point of development as the launching place for challenges that would encourage further exploration and learning.

Malaguzzi believed that being with children in their developmental journey calls for deep engagement and attentiveness by the teacher in order to meet all children individually and in small groups in terms of where they are in their interests, exploration, and research. The main goal is to create the most meaningful learning environment that supports the actualization of their potential. According to Malaguzzi, the level of engagement of the teachers is not narrowed only to their actions but includes investment in observations, interpretations, and reflections that are the grounds for the practical actions.

Vygotsky's social constructive is known for its relevance to the educational field. One of Vygotzky's leading concepts is the scaffolding process that defines a specifi interaction between teachers and learners in which the teacher supports the learning process in situations where the learner cannot explore or research alone. Connected to the scaffolding concept is the question of the relations between scaffolding and giving **help** when it comes to relationships with children. Vygotsky's scaffolding concept highlights the difference between authentic and nonauthentic support of children's learning processes and focuses on giving only the support that would enable the child to move toward the child's potential point of development, according to the child's developmental pace. This was interpreted by Malaguzzi as *things that children can do by themselves should not be done for them*.

Box 7-5 Example of Giving Only the Support That Enables a Child to Move Toward the Child's Potential Point of Development, According to the Child's Developmental Pace

The children were playing with a large box that was brought to the school. One of the kids climbed in and suddenly realized he was stuck and could not climb out. The child began to cry. The teacher asked him what he could do to solve the problem, and his response was: "I will ask my friends." He called his friends and they began giving him ideas.

One child tried to pull him out, but the box was too tall. Two other friends came, brought a chair, and tried to pull him out, but still the box was too tall.

Then a fourth child joined and suggested putting a chair INSIDE the box. The children brought a chair that was put inside, and their friend climbed out happy and empowered.

It is only when the child needs the bridge between the child's current place and the child's destination that adults should step in delicately and consciously and provide help (Box 7-5).

Reggio Approach and Relationships with Parents

In the Reggio approach, the image of the parent parallels the image of the child. In other words, as the child is seen as an equal, active, and competent partner, the parent is also perceived as a competent, active partner to the educational endeavor. The core of the relationship is the value of parent participation with 2 cornerstones. First is the idea of taking part in the different ways parents can participate in school life. Second is the emotional attitude parents establish toward the school. The integration of those 2 cornerstones creates a way of being in the schools that represents a democratic approach to citizenship with solidarity and shared responsibility as core guidelines.

The ethical code for the participatory approach is that each member in the educational process brings his or her forms of knowing, points of view, interpretations of different experiences, and culture. The participation sets the ground to discussions and rich exchanges among the parents and the school that open the door for wide-ranging discussions

and collaborations. The uniqueness of the participatory way of being in the Reggio Emilia approach is the belief that only by accepting other persons from a humanistic point of view, can real acceptance and acknowledgement arise. The parent usually has his or her own image of the child that is based on the relationships, culture, and family traditions, history, and characteristics. The deep relationship with the school enables the parent to gain a different image of his or her child. The opportunity to widen the personal image and to integrate the personal image with the school image opens a door for a wider and deeper relationship between parents and their children.

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Chapter 8

Assessment of Fetal Growth and Development

Susan Feigelman

Table 8-1 Milestones of Prenatal Development

WK	DEVELOPMENTAL EVENTS
1	Fertilization and implantation; beginning of *embryonic* period
2	Endoderm and ectoderm appear (bilaminar embryo)
3	First missed menstrual period; mesoderm appears (trilaminar embryo); somites begin to form
4	Neural folds fuse; folding of embryo into human-like shape; arm and leg buds appear; crown-rump length 4-5 mm
5	Lens placodes, primitive mouth, digital rays on hands
6	Primitive nose, philtrum, primary palate
7	Eyelids begin; crown-rump length 2 cm
8	Ovaries and testes distinguishable
9	*Fetal* period begins; crown-rump length 5 cm; weight 8 g
12	External genitals distinguishable
20	Usual lower limit of viability; weight 460 g; length 19 cm
25	Third trimester begins; weight 900 g; length 24 cm
28	Eyes open; fetus turns head down; weight 1,000-1,300 g
38	Term

The developing fetus is affected by social and environmental influences, including maternal nutritional status; substance use (both legal and illicit); and psychologic trauma. Correspondingly, the psychologic alterations experienced by the parents during the gestation profoundly impact the lives of all members of the family. Growing evidence implicates the importance of these and other maternal and paternal experiences that occur during and prior to the pregnancy (and even among members of earlier generations) on the subsequent development of the individual (*epigenetic effects*). The complex interplay between these forces and the somatic and neurologic transformations occurring in the fetus influence growth and behavior at birth, through infancy, and potentially throughout the individual's life.

SOMATIC DEVELOPMENT

Embryonic Period

Table 8-1 lists milestones of prenatal development. By 6 days postconception age, as implantation begins, the embryo consists of a spherical mass of cells with a central cavity (the *blastocyst*). By 2 wk, implantation is complete and the uteroplacental circulation has begun; the embryo has 2 distinct layers, *endoderm* and *ectoderm*, and the amnion has begun to form. By 3 wk, the 3rd primary germ layer *(mesoderm)* has appeared, along with a primitive neural tube and blood vessels. Paired heart tubes have begun to pump.

During wk 4-8, lateral folding of the embryologic plate, followed by growth at the cranial and caudal ends and the budding of arms and legs, produces a human-like shape. Precursors of skeletal muscle and vertebrae (somites) appear, along with the branchial arches that will form the mandible, maxilla, palate, external ear, and other head and neck structures. Lens placodes appear, marking the site of future eyes; the brain grows rapidly. By the end of wk 8, as the embryonic period closes, the rudiments of all major organ systems have developed; the crown-rump length is 3 cm.

Fetal Period

From the 9th wk on (fetal period), somatic changes consist of rapid body growth as well as differentiation of tissues, organs, and organ systems. Figure 8-1 depicts changes in body proportion. By wk 10, the face is recognizably human. The midgut returns to the abdomen from the umbilical cord, rotating counterclockwise to bring the stomach, small intestine, and large intestine into their normal positions. By wk 12, the gender of the external genitals becomes clearly distinguishable. Lung development proceeds, with the budding of bronchi, bronchioles, and successively smaller divisions. By wk 20-24, primitive alveoli have formed and surfactant production has begun; before that time, the absence of alveoli renders the lungs useless as organs of gas exchange.

During the 3rd trimester, weight triples and length doubles as body stores of protein, fat, iron, and calcium increase.

NEUROLOGIC DEVELOPMENT

During the 3rd wk, a neural plate appears on the ectodermal surface of the trilaminar embryo. Infolding produces a neural tube that will become the central nervous system and a neural crest that will become the peripheral nervous system. Neuroectodermal cells differentiate into neurons, astrocytes, oligodendrocytes, and ependymal cells, whereas microglial cells are derived from mesoderm. By the 5th wk, the 3 main subdivisions of forebrain, midbrain, and hindbrain are evident. The dorsal and ventral horns of the spinal cord have begun to form, along with the peripheral motor and sensory nerves. Myelinization begins at midgestation and continues for years.

By the end of the embryonic period (wk 8), the gross structure of the nervous system has been established. On a cellular level, neurons migrate outward to form the 6 cortical layers. Migration is complete by the 6th mo, but differentiation continues. Axons and dendrites form synaptic connections at a rapid pace, making the central nervous system vulnerable to teratogenic or hypoxic influences throughout gestation. Figure 8-2 shows rates of increase in DNA (a marker of cell number), overall brain weight, and cholesterol (a marker of myelinization). The prenatal and postnatal peaks of DNA probably represent rapid growth of neurons and glia, respectively. By the time of birth, the structure of the brain is complete. Synapses will be pruned back substantially and new connections will be made, largely as a result of experience. Many psychiatric and developmental disorders are thought to result at least in part from disruptions in the **functional connectivity** of brain networks. Disorders of connectivity may begin during fetal life; MRI studies provide a developmental timetable for such connections that lend support to the possible role of disruptions in the establishment of such connections during fetal life.

BEHAVIORAL DEVELOPMENT

No behavioral evidence of neural function is detectable until the 3rd mo. Reflexive responses to tactile stimulation develop in a craniocaudal sequence. By wk 13-14, breathing and swallowing motions appear. The grasp reflex appears at 17 wk and is well developed by 27 wk. Eye

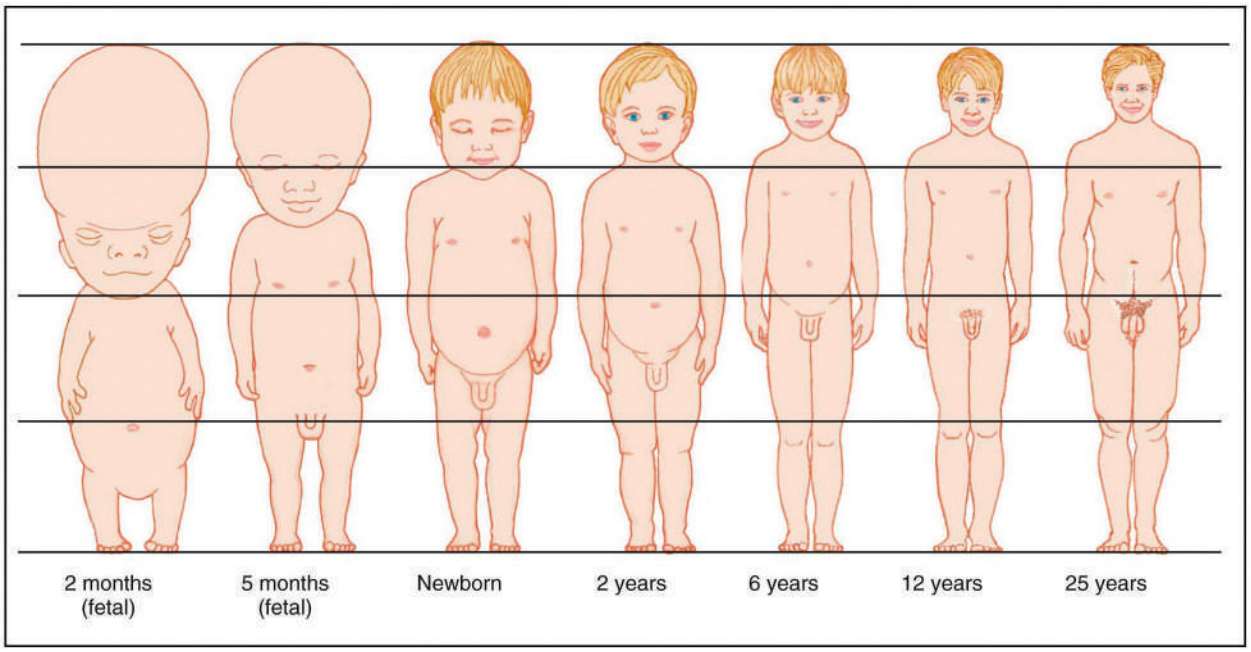

Figure 8-1 Changes in body proportions. Approximate changes in body proportions from fetal life through adulthood are shown. *(From Leifer G:* Introduction to maternity & pediatric nursing, *Philadelphia, 2011, WB Saunders, pp 347–385, Fig. 15-2.)*

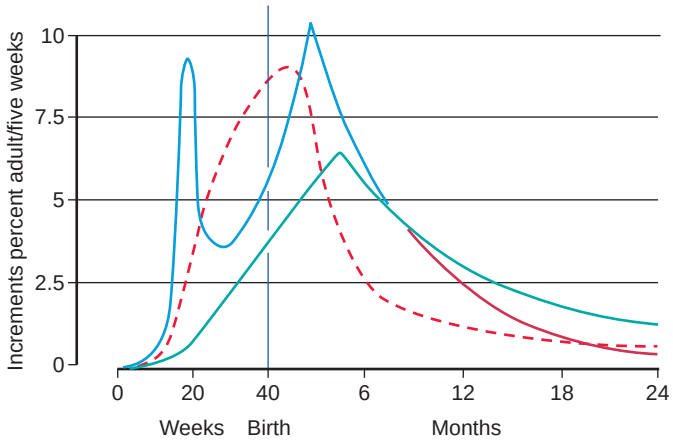

Figure 8-2 Velocity curves of the various components of human brain growth. Solid line with two peaks, DNA; dashed line, brain weight; solid line with a single peak, cholesterol. *(From Brasel JA, Gruen RK. In Falkner F, Tanner JM, editors:* Human growth: a comprehensive treatise, *New York, 1986, Plenum Press, pp 78–95.)*

opening occurs around 26-28 wk. By midgestation, the full range of neonatal movements can be observed.

During the 3rd trimester, fetuses respond to external stimuli with heart rate elevation and body movements (see Chapter 96). As with infants in the postnatal period, reactivity to auditory (vibroacoustic) and visual (bright light) stimuli vary, depending on their behavioral state, which can be characterized as quiet sleep, active sleep, or awake. Individual differences in the level of fetal activity are commonly noted by mothers and have been observed ultrasonographically. Fetal behavior is affected by maternal medications and diet, increasing after ingestion of caffeine. Behavior may be entrained to the mother's diurnal rhythms: asleep during the day, active at night. Abnormal fetal movement patterns are found in neonates with subsequent muscular or neurologic abnormalities.

Fetal movement increases in response to a sudden auditory tone, but decreases after several repetitions. This demonstrates **habituation,** a basic form of learning in which repeated stimulation results in a response decrement. If the tone changes in pitch, the movement increases again, which is evidence that the fetus distinguishes between a familiar, repeated tone and a novel tone. Habituation improves in older fetuses, and decreases in neurologically impaired or physically stressed fetuses. Similar responses to visual and tactile stimuli have been observed.

PSYCHOLOGIC CHANGES IN PARENTS

Many psychologic changes occur during pregnancy. An unplanned pregnancy may be met with anger, denial, or depression. Ambivalent feelings are the norm, whether or not the pregnancy was planned. Elation at the thought of producing a baby and the wish to be the perfect parent compete with fears of inadequacy and of the lifestyle changes that mothering will impose. Parents of an existing child feel protective for the existing child, worried that the existing child may feel less valued. Old conflicts may resurface as a woman psychologically identifies with her own mother and with herself as a child. The father-to-be faces similar mixed feelings, and problems in the parental relationship may intensify.

Tangible evidence that a fetus exists as a separate being, whether as a result of ultrasonic visualization or awareness of fetal movements (at approximately 20 wk), often heightens a woman's feelings. Parents worry about the fetus's healthy development and mentally rehearse what they will do if the child is malformed, including their response to evidence of abnormality through ultrasound, amniocentesis or other fetal laboratory tests. Toward the end of pregnancy, a woman becomes aware of patterns of fetal activity and reactivity and begins to ascribe to her fetus an individual personality and an ability to survive independently. Appreciation of the psychologic vulnerability of the expectant parents and of the powerful contribution of fetal behavior facilitates supportive clinical intervention.

THREATS TO FETAL DEVELOPMENT

Mortality and morbidity are highest during the prenatal period (see Chapter 93). An estimated 50% of all pregnancies end in spontaneous abortion, including 10-20% of all clinically recognized pregnancies. The vast majority occur in the 1st trimester. Some occur as a result of chromosomal or other abnormalities.

Teratogens associated with gross physical and mental abnormalities include various infectious agents (toxoplasmosis, rubella, syphilis); chemical agents (mercury, thalidomide, antiepileptic medications, and ethanol), high temperature, and radiation (see Chapters 96 and 718).

Teratogenic effects may also result in decreased growth and cognitive or behavioral deficits that only become apparent later in life. Nicotine has vasoconstrictor properties and may disrupt dopaminergic and serotonergic pathways. Prenatal exposure to cigarette smoke is associated with lower birthweight, shorter length, and smaller head circumference, as well as changes in neonatal neurodevelopmental assessments. Later, these children are at increased risk for learning problems, externalizing behavior disorders, and long-term health effects. The effects of prenatal exposure to cocaine, also occurring through alternations in placental blood flow and in direct toxic effects to the developing brain, have been followed in several cohorts and are less dramatic than previously believed. Exposed adolescents show small but significant effects in behavior and functioning, but may not show cognitive impairment. The associated risk factors including other prenatal exposures (alcohol and cigarette co-use) as well as "toxic" postnatal environments frequently characterized by instability, multiple caregivers, and violence exposure remain significant (see Chapters 39 and 40).

The association between an inadequate nutrient supply to the fetus and low birthweight has been recognized for decades; this adaptation on the part of the fetus presumably increases the likelihood that the fetus will survive until birth. For any potential fetal insult, the extent and nature of its effects are determined by characteristics of the host as well as the dose and timing of the exposure. Inherited differences in the metabolism of ethanol, timing of exposure, and the mother's diet may explain the variability in fetal alcohol effects. Organ systems are most vulnerable during periods of maximum growth and differentiation, generally during the 1st trimester (organogenesis). http://www2.epa.gov/children/children-are-not-little-adults details critical periods and specific developmental abnormalities.

Fetal adaptations or responses to an adverse situation in utero (referred to as *fetal programming* or *developmental plasticity*) have lifelong implications for the individual. Fetal programming may prepare the fetus for an environment that matches that experienced in utero. Fetal programming in response to some environmental and nutritional signals in utero increase the risk of cardiovascular disease, diabetes, and obesity in later life. These adverse long-term effects appear to represent a mismatch between fetal and neonatal environmental conditions and the conditions that the individual will confront later in life; a fetus deprived of adequate calories may or may not as a child or teenager face famine. One proposed mechanism for fetal programming is **epigenetic imprinting**, in which two genes are inherited but one is turned off through environmentally induced epigenetic modification (see Chapters 80 and 81.1). Imprinted genes play a critical role in fetal growth and thus may be responsible for the subsequent lifelong effects on growth and related disorders.

Just as the fetal adaptations to the in utero environment may increase the likelihood of later metabolic conditions, the fetus adapts to the mother's psychologic distress. In response to the stressful environment, physiologic changes involving the hypothalamic–pituitary–adrenal axis and the autonomic nervous system occur. Dysregulation of the hypothalamic–pituitary–adrenal axis and autonomic nervous system may explain the associations observed in some but not all studies between maternal distress and negative infant outcomes, including low birthweight, spontaneous abortion, prematurity, and decreased head circumference. In addition, children born to mothers experiencing high stress levels have been found to have higher rates of inattention, impulsivity, conduct disorders, and cognitive changes. Although these changes may have been adaptive in primitive cultures, they are maladaptive in modern societies, leading to psychopathology. Genetic variability, timing of stress during sensitive periods, and the quality of postnatal parenting can attenuate or exacerbate these associations.

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Chapter 9

The Newborn

John M. Olsson

(See also Chapter 94.)

Regardless of gestational age, the newborn (neonatal) period begins at birth and includes the 1st mo of life. During this time, marked physiologic transitions occur in all organ systems, and the infant learns to respond to many forms of external stimuli. Because infants thrive physically and psychologically only in the context of their social relationships, any description of the newborn's developmental status has to include consideration of the parents' role as well.

PARENTAL ROLE IN MOTHER–INFANT ATTACHMENT

Parenting a newborn infant requires dedication because a newborn's needs are urgent, continuous, and often unclear. Parents must attend to an infant's signals and respond empathically. Many factors influence parents' ability to assume this role.

Prenatal Factors

Pregnancy is a period of psychologic preparation for the profound demands of parenting. Women may experience ambivalence, particularly (but not exclusively) if the pregnancy was unplanned. If financial worries, physical illness, prior miscarriages or stillbirths, or other crises interfere with psychologic preparation, the neonate may not be welcomed. For adolescent mothers, the demand that they relinquish their own developmental agenda, such as an active social life, may be especially burdensome.

The early experience of being mothered may establish unconsciously held expectations about nurturing relationships that permit mothers to "tune in" to their infants. These expectations are linked with the quality of later infant–parent interactions. Mothers whose early childhoods were marked by traumatic separations, abuse, or neglect may find it especially difficult to provide consistent, responsive care. Instead, they may reenact their childhood experiences with their own infants, as if unable to conceive of the mother–child relationship in any other way. Bonding may be adversely affected by several risk factors during pregnancy and in the postpartum period that undermine the mother–child relationship and may threaten the infant's cognitive and emotional development (Table 9-1).

Social support during pregnancy, particularly support from the father and close family members, is also important. Conversely, conflict with or abandonment by the father during pregnancy may diminish the mother's ability to become absorbed with her infant. Anticipation

Table 9-1 Prenatal Risk Factors for Attachment

Recent death of a loved one
Previous loss of or serious illness in another child
Prior removal of a child
History of depression or serious mental illness
History of infertility or pregnancy loss
Troubled relationship with parents
Financial stress or job loss
Marital discord or poor relationship with the other parent
Recent move or no community ties
No friends or social network
Unwanted pregnancy
No good parenting model
Experience of poor parenting
Drug and/or alcohol abuse
Extreme immaturity

From Dixon SD, Stein MT: Encounters with children: pediatric behavior and development, *ed 3, St. Louis, 2000, Mosby, p 74.*

of an early return to work may make some women reluctant to fall in love with their babies because of anticipated separation. Returning to work should be delayed for at least 6 wk, by which time feeding and basic behavioral adjustments have been established.

Many decisions have to be made by parents in anticipation of the birth of their child. One important choice is that of how the infant will be nourished. Among the important benefits of breastfeeding is its promotion of bonding. Providing breastfeeding education for the parents at the prenatal visit by the pediatrician and by the obstetrician during prenatal care can increase maternal confidence in breastfeeding after delivery and reduce stress during the newborn period (see Chapter 45).

Peripartum and Postpartum Influences

The continuous presence during labor of a woman trained to offer friendly support and encouragement (a **doula**) results in shorter labor, fewer obstetric complications (including cesarean section), and reduced postpartum hospital stays. Early skin-to-skin contact between mothers and infants immediately after birth may correlate with an increased rate and longer duration of breastfeeding. Most new parents value even a brief period of uninterrupted time in which to get to know their new infant, and increased mother–infant contact over the 1st days of life may improve long-term mother–child interactions. Nonetheless, early separation, although predictably very stressful, does not inevitably impair a mother's ability to bond with her infant. Early discharge home from the maternity ward may undermine bonding, particularly when a new mother is required to resume full responsibility for a busy household.

Postpartum depression may occur in the 1st wk or up to 6 mo after delivery and can adversely affect neonatal growth and development. Screening methods are available for use during neonatal and infant visits to the pediatric provider (Table 9-2). Referral for care will greatly accelerate recovery.

THE INFANT'S ROLE IN MOTHER–INFANT ATTACHMENT

The in utero environment contributes greatly but not completely to the future growth and development of the fetus. Abnormalities in maternal–fetal placental circulation and maternal glucose metabolism or the presence of maternal infection can result in abnormal fetal growth. Infants may be small or large for gestational age as a result. These abnormal growth patterns not only predispose infants to an increased requirement for medical intervention, but also may affect their ability to respond behaviorally to their parents.

Physical Examination

Examination of the newborn should include an evaluation of growth and an observation of behavior. The average term newborn weighs approximately 3.4 kg (7.5 lb); boys are slightly heavier than girls. Average weight does vary by ethnicity and socioeconomic status. The average length and head circumference are about 50 cm (20 in) and 35 cm (14 in), respectively, in term infants. Each newborn's growth parameters should be plotted on growth curves specific for that infant's gestational age to determine the appropriateness of size. Likewise specific growth charts for conditions associated with variations in growth patterns have also been developed. The infant's response to being examined may be useful in assessing its vigor, alertness, and tone. Observing how the parents handle their infant, their comfort and affection, is also important. The order of the physical examination should be from the least to the most intrusive maneuver. Assessing visual tracking and response to sound and noting changes of tone with level of activity and alertness are very helpful. Performing this examination and sharing impression with parents is an important opportunity to facilitate bonding (see Chapter 94).

Interactional Abilities

Soon after birth, neonates are alert and ready to interact and nurse. This first alert-awake period may be affected by maternal analgesics and anesthetics or fetal hypoxia. Neonates are nearsighted, having a fixed focal length of 8-12 inches, approximately the distance from the breast to the mother's face, as well as an inborn visual preference for faces. Hearing is well developed, and infants preferentially turn toward a female voice. These innate abilities and predilections increase the likelihood that when a mother gazes at her newborn, the baby will gaze back. The initial period of social interaction, usually lasting about 40 minutes, is followed by a period of somnolence. After that, briefer periods of alertness or excitation alternate with sleep. If a mother misses her baby's first alert-awake period, she may not experience as long a period of social interaction for several days. The hypothalamic–midbrain–limbic–paralimbic–cortical circuit of the parents interact to support responses to the infants that are critical for effective parenting (e.g., emotion, attention, motivation, empathy, and decision making).

Modulation of Arousal

Adaptation to extrauterine life requires rapid and profound physiologic changes, including aeration of the lungs, rerouting of the circulation, and activation of the intestinal tract. The necessary behavioral changes are no less profound. To obtain nourishment, to avoid hypo- and hyperthermia, and to ensure safety, neonates must react appropriately to an expanded range of sensory stimuli. Infants must become aroused in response to stimulation, but not so overaroused that their behavior becomes disorganized. Underaroused infants are not able to feed and interact; overaroused infants show signs of **autonomic instability,** including flushing or mottling, perioral pallor, hiccupping, vomiting, uncontrolled limb movements, and inconsolable crying.

Behavioral States

The organization of infant behavior into discrete behavioral states may reflect an infant's inborn ability to regulate arousal. *Six states* have been described: quiet sleep, active sleep, drowsy, alert, fussy, and crying. In the **alert state,** infants visually fixate on objects or faces and follow them horizontally and (within a month) vertically; they also reliably turn toward a novel sound, as if searching for its source. When overstimulated, they may calm themselves by looking away, yawning, or sucking on their lips or hands, thereby increasing parasympathetic activity and reducing sympathetic nervous activity. The behavioral state determines an infant's muscle tone, spontaneous movement, electroencephalogram pattern, and response to stimuli. In **active sleep,** an infant may show progressively less reaction to a repeated heel stick (habituation), whereas in the **drowsy state,** the same stimulus may push a child into fussing or crying.

Mutual Regulation

Parents actively participate in an infant's state regulation, alternately stimulating and soothing. In turn, they are regulated by the infant's signals, responding to cries of hunger with a letdown of milk (or with a bottle). Such interactions constitute a system directed toward furthering the infant's physiologic homeostasis and physical growth. At the same time, they form the basis for the emerging psychologic relationship between parent and child. Infants come to associate the presence of the parent with the pleasurable reduction of tension (as in feeding) and show this preference by calming more quickly for their mother than for a stranger. This response, in turn, strengthens a mother's sense of efficacy and her connection with her baby.

IMPLICATIONS FOR THE PEDIATRICIAN

The pediatrician can support healthy newborn development in several ways.

Optimal Practices

A prenatal pediatric visit allows pediatricians to assess potential threats to bonding (a tense spousal relationship) and sources of social support. Supportive hospital policies include the use of birthing rooms rather than operating suites and delivery rooms; encouragement for the father or a trusted relative or friend to remain with the mother during labor or the provision of a professional doula; the practice of giving the newborn infant to the mother immediately after drying and a brief assessment; placement of the newborn in the mother's room rather

Table 9-2 Edinburgh Postnatal Depression Scale

INSTRUCTIONS FOR USERS

1. The mother is asked to underline the response that comes closest to how she has been feeling in the previous 7 days.
2. All 10 items must be completed.
3. Care should be taken to avoid the possibility of the mother discussing her answers with others.
4. The mother should complete the scale herself, unless she has limited English or has difficulty with reading.
5. The Edinburgh Postnatal Depression Scale may be used at 6-8 wk to screen postnatal women. The child health clinic, a postnatal checkup, or a home visit may provide a suitable opportunity for its completion.

Edinburgh Postnatal Depression Scale
Name:
Address:
Baby's age:
Because you have recently had a baby, we would like to know how you are feeling. Please underline the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.
Here is an example, already completed.
I have felt happy:
Yes, all the time
<u>Yes, most of the time</u>
No, not very often
No, not at all
This would mean: "I have felt happy most of the time" during the past week. Please complete the other questions in the same way.
In the past 7 days:

1. I have been able to laugh and see the funny side of things
   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all
2. I have looked forward with enjoyment to things
   As much as I ever did
   Rather less than I used to
   Definitely less than I used to
   Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   Yes, most of the time
   Yes, some of the time
   Not very often
   No, never

4. I have been anxious or worried for no good reason
   No, not at all
   Hardly ever
   Yes, sometimes
   Yes, very often

*5. I have felt scared or panicky for no very good reason
   Yes, quite a lot
   Yes, sometimes
   No, not much
   No, not at all

*6. Things have been getting on top of me
   Yes, most of the time I haven't been able to cope at all
   Yes, sometimes I haven't been coping as well as usual
   No, most of the time I have coped quite well
   No, I have been coping as well as ever

*7. I have been so unhappy that I have had difficulty sleeping
   Yes, most of the time
   Yes, sometimes
   Not very often
   No, not at all

*8. I have felt sad or miserable
   Yes, most of the time
   Yes, quite often
   Not very often
   No, not at all

*9. I have been so unhappy that I have been crying
   Yes, most of the time
   Yes, quite often
   Only occasionally
   No, never

*10. The thought of harming myself has occurred to me
   Yes, quite often
   Sometimes
   Hardly ever
   Never

Response categories are scored 0, 1, 2, and 3 according to increased severity of the symptom. Items marked with an asterisk (*) are reverse scored (i.e., 3, 2, 1, and 0). The total score is calculated by adding the scores for each of the 10 items. Users may reproduce the scale without further permission providing they respect copyright (which remains with the *British Journal of Psychiatry*) by quoting the names of the authors, the title, and the source of the paper in all reproduced copies.
From Currie ML, Rademacher R: The pediatrician's role in recognizing and intervening in postpartum depression, Pediatr Clin North Am *51:785–801, 2004.*

than in a central nursery; and avoiding in-hospital distribution of infant formula. Such policies ("Baby Friendly Hospital") have been shown to significantly increase breastfeeding rates (see Chapter 94.3). After discharge, home visits by nurses and lactation counselors can reduce early feeding problems and identify emerging medical conditions in either mother or baby. Infants requiring transport to another hospital should be brought to see the mother first, if at all possible. On discharge home, fathers can shield mothers from unnecessary visits and calls and take over household duties, allowing mothers and infants time to get to know each other without distractions. The first office visit should occur during the 1st 2 wk after discharge to determine how smoothly the mother and infant are making the transition to life at home. Babies who are discharged early, those who are breastfeeding, and those who are at risk for jaundice should be seen 1-3 days after discharge.

Assessing Parent–Infant Interactions

During a feeding or when infants are alert and face-to-face with their parents, it is normal for the dyad to appear absorbed in one another. Infants who become overstimulated by the mother's voice or activity may turn away or close their eyes, leading to a premature termination of the encounter. Alternatively, the infant may be ready to interact, but the mother may appear preoccupied. Asking a new mother about her own emotional state, and inquiring specifically about a history of depression, facilitates referral for therapy, which may provide long-term benefits to the child. Pediatricians may detect **postpartum depression** using the Edinburgh Postnatal Depression Scale at well-child visits during the 1st yr (see Table 9-2).

Teaching About Individual Competencies

The Newborn Behavior Assessment Scale (NBAS) provides a formal measure of an infant's neurodevelopmental competencies, including state control, autonomic reactivity, reflexes, habituation, and orientation toward auditory and visual stimuli. This examination can also be used to demonstrate to parents an infant's capabilities and vulnerabilities. Parents might learn that they need to undress their infant to increase the level of arousal or to swaddle the infant to reduce overstimulation by containing random arm movements. The NBAS can be

used to support the development of positive early parent-infant relationships. Demonstration of the NBAS to parents in the 1st wk of life has been shown to correlate with improvements in the caretaking environment months later.

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Chapter 10

The First Year

Susan Feigelman

The prenatal period and the 1st yr of life provide the platform for remarkable growth and development, setting the trajectory for a child's life. Neural plasticity, the ability of the brain to be shaped by experience, both positive and negative, is at its peak. Total brain volume doubles in the 1st yr of life and increases by an additional 15% over the 2nd yr. Total brain volume at age 1 mo is approximately 36% of adult volume but by age 1 yr is approximately 72% (83% by 2 yr) (Fig. 10-1). The acquisition of seemingly "simple" skills, such as swallowing, reflect a series of intricate and highly coordinated processes involving multiple levels of neural control distributed among several physiologic systems whose nature and relationships mature throughout the 1st yr of life. Substantial learning of the basic tools of language (phonology, word segmentation) occurs during infancy. Speech processing in older individuals requires defined and precise neuronal networks; the infant brain possesses a structural and functional organization similar to that of adults, suggesting that structural neurologic processing of speech may guide infants to discover the properties of his or her native language. Myelination of the cortex begins at 7-8 mo gestation and continues into adolescence and young adulthood. It proceeds in a posterior to anterior fashion, allowing progressive maturation of sensory, motor, and finally associative pathways. Given the importance of iron, cholesterol, and other nutrients in myelination, adequate stores throughout infancy are critical (see Chapter 45). Inadequate dietary intake, insufficient interactions with caregivers or the wider environment may alter experience-dependent processes that are critical to brain structure development and function during infancy. Although some of these processes may be delayed, as the periods of plasticity close during the rapid developmental changes occurring in infancy, more permanent deficits may result.

The infant acquires new competences in all developmental domains. The concept of developmental trajectories recognizes that complex skills build on simpler ones; it is also important to realize how development in each domain affects functioning in all of the others. All growth parameters should be plotted using the World Heath Organization charts which show how children from birth through 72 mo "should" grow under optimal circumstances (see Figs. 11-1 and 11-2). Table 10-1 presents an overview of key milestones by domain; Table 10-2 presents similar information arranged by age. Table 10-3 presents age at time of appearance on x-ray of centers of ossification. Parents often

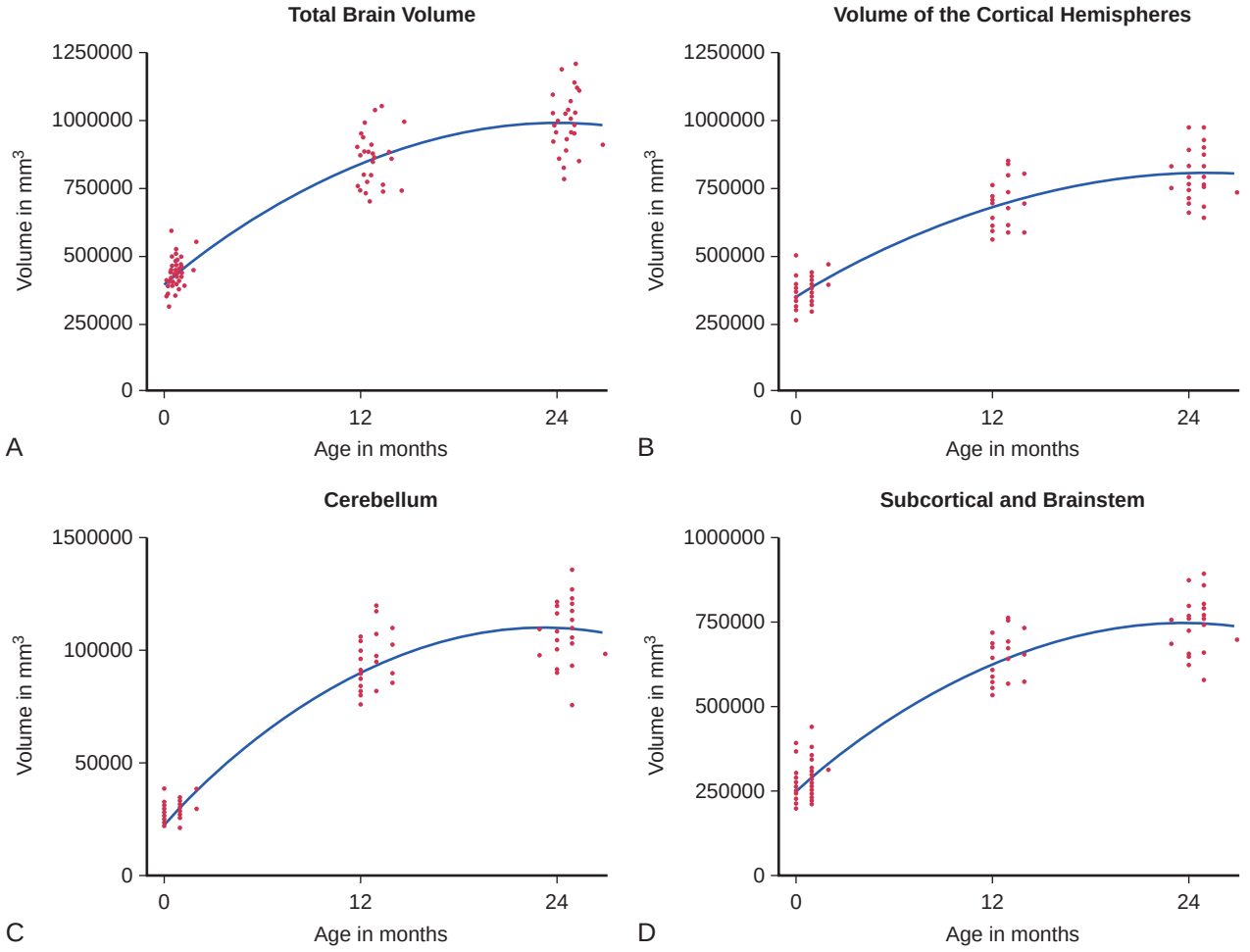

Figure 10-1 Scatterplots showing brain growth in the 1st 2 yr of life. **A,** Total brain volume by age at scan. **B,** Cortical hemispheres. **C,** Cerebellum. **D,** Subcortical region and brainstem. *(From Knickmeyer RC, Gouttard S, Kang C, et al: A structural MRI study of human brain development from birth to 2 years.* J Neurosci *28(47):12176–12182, 2008, Fig. 2.)*

Table 10-1 Developmental Milestones in the 1st 2 Yr of Life

MILESTONE	AVERAGE AGE OF ATTAINMENT (MO)	DEVELOPMENTAL IMPLICATIONS
GROSS MOTOR		
Holds head steady while sitting	2	Allows more visual interaction
Pulls to sit, with no head lag	3	Muscle tone
Brings hands together in midline	3	Self-discovery of hands
Asymmetric tonic neck reflex gone	4	Can inspect hands in midline
Sits without support	6	Increasing exploration
Rolls back to stomach	6.5	Truncal flexion, risk of falls
Walks alone	12	Exploration, control of proximity to parents
Runs	16	Supervision more difficult
FINE MOTOR		
Grasps rattle	3.5	Object use
Reaches for objects	4	Visuomotor coordination
Palmar grasp gone	4	Voluntary release
Transfers object hand to hand	5.5	Comparison of objects
Thumb-finger grasp	8	Able to explore small objects
Turns pages of book	12	Increasing autonomy during book time
Scribbles	13	Visual–motor coordination
Builds tower of 2 cubes	15	Uses objects in combination
Builds tower of 6 cubes	22	Requires visual, gross, and fine motor coordination
COMMUNICATION AND LANGUAGE		
Smiles in response to face, voice	1.5	More active social participant
Monosyllabic babble	6	Experimentation with sound, tactile sense
Inhibits to "no"	7	Response to tone (nonverbal)
Follows one-step command with gesture	7	Nonverbal communication
Follows one-step command without gesture	10	Verbal receptive language (e.g., "Give it to me")
Says "mama" or "dada"	10	Expressive language
Points to objects	10	Interactive communication
Speaks first real word	12	Beginning of labeling
Speaks 4-6 words	15	Acquisition of object and personal names
Speaks 10-15 words	18	Acquisition of object and personal names
Speaks 2-word sentences (e.g., "Mommy shoe")	19	Beginning grammatization, corresponds with 50 word vocabulary
COGNITIVE		
Stares momentarily at spot where object disappeared	2	Lack of object permanence (out of sight, out of mind [e.g., yarn ball dropped])
Stares at own hand	4	Self-discovery, cause and effect
Bangs 2 cubes	8	Active comparison of objects
Uncovers toy (after seeing it hidden)	8	Object permanence
Egocentric symbolic play (e.g., pretends to drink from cup)	12	Beginning symbolic thought
Uses stick to reach toy	17	Able to link actions to solve problems
Pretend play with doll (e.g., gives doll bottle)	17	Symbolic thought

seek information about "normal development" during this period and should be directed to reliable sources, including the American Academy of Pediatrics website (www.AAP.org).

AGE 0-2 MONTHS

In the full-term infant, myelination is present by the time of birth in the dorsal brainstem, cerebellar peduncles, and posterior limb of the internal capsule. The cerebellar white matter acquires myelin by 1 mo of age and is well myelinated by 3 mo of age. The subcortical white matter of the parietal, posterior frontal, temporal, and calcarine cortex is partially myelinated by 3 mo of age. In this period, the infant experiences tremendous growth. Physiologic changes allow the establishment of effective feeding routines and a predictable sleep–wake cycle. The social interactions that occur as parents and infants accomplish these tasks lay the foundation for cognitive and emotional development.

Physical Development

A newborn's weight may initially decrease 10% below birthweight in the 1st wk as a result of excretion of excess extravascular fluid and limited nutritional intake. Nutrition improves as colostrum is replaced by higher-fat breast milk, as infants learn to latch on and suck more efficiently, and as mothers become more comfortable with feeding techniques. Infants regain or exceed birthweight by 2 wk of age and should grow at approximately 30 g (1 oz)/per day during the 1st mo (see Table 15-1). This is the period of fastest postnatal growth. Arms are held to the sides. Limb movements consist largely of uncontrolled writhing, with apparently purposeless opening and closing of the hands. Smiling occurs involuntarily. Eye gaze, head turning, and sucking are under better control and thus can be used to demonstrate infant perception and cognition. An infant's preferential turning toward the mother's voice is evidence of recognition memory.

Six behavioral states have been described (see Chapter 9). Initially, sleep and wakefulness are evenly distributed throughout the 24 hr day (Fig. 10-2). Neurologic maturation accounts for the consolidation of sleep into blocks of 5 or 6 hr at night, with brief awake, feeding periods. Learning also occurs; infants whose parents are consistently more interactive and stimulating during the day learn to concentrate their sleeping during the night.

Cognitive Development

Infants can differentiate among patterns, colors, and consonants. They can recognize facial expressions (smiles) as similar, even when they appear on different faces. They also can match abstract properties of stimuli, such as contour, intensity, or temporal pattern, across sensory modalities. Infants at 2 mo of age can discriminate rhythmic patterns in native vs non-native language. Infants appear to seek stimuli actively,

Table 10-2 Emerging Patterns of Behavior During the 1st Yr of Life*

NEONATAL PERIOD (1ST 4 WK)	
Prone:	Lies in flexed attitude; turns head from side to side; head sags on ventral suspension
Supine:	Generally flexed and a little stiff
Visual:	May fixate face on light in line of vision; "doll's-eye" movement of eyes on turning of the body
Reflex:	Moro response active; stepping and placing reflexes; grasp reflex active
Social:	Visual preference for human face
AT 1 MO	
Prone:	Legs more extended; holds chin up; turns head; head lifted momentarily to plane of body on ventral suspension
Supine:	Tonic neck posture predominates; supple and relaxed; head lags when pulled to sitting position
Visual:	Watches person; follows moving object
Social:	Body movements in cadence with voice of other in social contact; beginning to smile
AT 2 MO	
Prone:	Raises head slightly farther; head sustained in plane of body on ventral suspension
Supine:	Tonic neck posture predominates; head lags when pulled to sitting position
Visual:	Follows moving object 180 degrees
Social:	Smiles on social contact; listens to voice and coos
AT 3 MO	
Prone:	Lifts head and chest with arms extended; head above plane of body on ventral suspension
Supine:	Tonic neck posture predominates; reaches toward and misses objects; waves at toy
Sitting:	Head lag partially compensated when pulled to sitting position; early head control with bobbing motion; back rounded
Reflex:	Typical Moro response has not persisted; makes defensive movements or selective withdrawal reactions
Social:	Sustained social contact; listens to music; says "aah, ngah"
AT 4 MO	
Prone:	Lifts head and chest, with head in approximately vertical axis; legs extended
Supine:	Symmetric posture predominates, hands in midline; reaches and grasps objects and brings them to mouth
Sitting:	No head lag when pulled to sitting position; head steady, tipped forward; enjoys sitting with full truncal support
Standing:	When held erect, pushes with feet
Adaptive:	Sees raisin, but makes no move to reach for it
Social:	Laughs out loud; may show displeasure if social contact is broken; excited at sight of food
AT 7 MO	
Prone:	Rolls over; pivots; crawls or creep-crawls (Knobloch)
Supine:	Lifts head; rolls over; squirms
Sitting:	Sits briefly, with support of pelvis; leans forward on hands; back rounded
Standing:	May support most of weight; bounces actively
Adaptive:	Reaches out for and grasps large object; transfers objects from hand to hand; grasp uses radial palm; rakes at raisin
Language:	Forms polysyllabic vowel sounds
Social:	Prefers mother; babbles; enjoys mirror; responds to changes in emotional content of social contact
AT 10 MO	
Sitting:	Sits up alone and indefinitely without support, with back straight
Standing:	Pulls to standing position; "cruises" or walks holding on to furniture
Motor:	Creeps or crawls
Adaptive:	Grasps objects with thumb and forefinger; pokes at things with forefinger; picks up pellet with assisted pincer movement; uncovers hidden toy; attempts to retrieve dropped object; releases object grasped by other person
Language:	Repetitive consonant sounds ("mama," "dada")
Social:	Responds to sound of name; plays peek-a-boo or pat-a-cake; waves bye-bye
AT 1 YR	
Motor:	Walks with one hand held; rises independently, takes several steps (Knobloch)
Adaptive:	Picks up raisin with unassisted pincer movement of forefinger and thumb; releases object to other person on request or gesture
Language:	Says a few words besides "mama," "dada"
Social:	Plays simple ball game; makes postural adjustment to dressing

*Data are derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others.
Data from Knobloch H, Stevens F, Malone AF: Manual of developmental diagnosis, *Hagerstown, MD, 1980, Harper & Row.*

as though satisfying an innate need to make sense of the world. These phenomena point to the integration of sensory inputs in the central nervous system. Caretaking activities provide visual, tactile, olfactory, and auditory stimuli; all of these support the development of cognition. Infants habituate to the familiar, attending less to repeated stimuli and increasing their attention to novel stimuli.

Emotional Development

The infant is dependent on the environment to meet his or her needs. The consistent availability of a trusted adult to meet the infant's urgent needs creates the conditions for secure attachment. Basic trust vs mistrust, the first of Erikson's psychosocial stages (see Chapter 6), depends on attachment and reciprocal maternal bonding. Crying occurs in response to stimuli that may be obvious (a soiled diaper), but are often obscure. Infants who are consistently picked up and held in response to distress cry less at 1 yr and show less-aggressive behavior at 2 yr. Cross-cultural studies show that in societies in which infants are carried close to the mother, babies cry less than in societies in which babies are only periodically carried. Crying normally peaks at about 6 wk of age, when healthy infants may cry up to 3 hr/day, then decreases to 1 hr or less by 3 mo. Infants cry in response to the cry of another infant, which has been interpreted as an early sign of empathy development.

Crying/fussiness is present in 20% of infants younger than 2 mo of age and although in most it is a transient and normal behavioral activity, it is often associated with parental concern and distress. Excessive

Table 10-3 Time of Appearance in X-Rays of Centers of Ossification in Infancy and Childhood

BOYS—AGE AT APPEARANCE*	BONES AND EPIPHYSEAL CENTERS	GIRLS—AGE AT APPEARANCE*
HUMERUS, HEAD		
3 wk		3 wk
CARPAL BONES		
2 mo ± 2 mo	Capitate	2 mo ± 2 mo
3 mo ± 2 mo	Hamate	2 mo ± 2 mo
30 mo ± 16 mo	Triangular†	21 mo ± 14 mo
42 mo ± 19 mo	Lunate†	34 mo ± 13 mo
67 mo ± 19 mo	Trapezium†	47 mo ± 14 mo
69 mo ± 15 mo	Trapezoid†	49 mo ± 12 mo
66 mo ± 15 mo	Scaphoid†	51 mo ± 12 mo
No standards available	Pisiform†	No standards available
METACARPAL BONES		
18 mo ± 5 mo	II	12 mo ± 3 mo
20 mo ± 5 mo	III	13 mo ± 3 mo
23 mo ± 6 mo	IV	15 mo ± 4 mo
26 mo ± 7 mo	V	16 mo ± 5 mo
32 mo ± 9 mo	I	18 mo ± 5 mo
FINGERS (EPIPHYSES)		
16 mo ± 4 mo	Proximal phalanx, 3rd finger	10 mo ± 3 mo
16 mo ± 4 mo	Proximal phalanx, 2nd finger	11 mo ± 3 mo
17 mo ± 5 mo	Proximal phalanx, 4th finger	11 mo ± 3 mo
19 mo ± 7 mo	Distal phalanx, 1st finger	12 mo ± 4 mo
21 mo ± 5 mo	Proximal phalanx, 5th finger	14 mo ± 4 mo
24 mo ± 6 mo	Middle phalanx, 3rd finger	15 mo ± 5 mo
24 mo ± 6 mo	Middle phalanx, 4th finger	15 mo ± 5 mo
26 mo ± 6 mo	Middle phalanx, 2nd finger	16 mo ± 5 mo
28 mo ± 6 mo	Distal phalanx, 3rd finger	18 mo ± 4 mo
28 mo ± 6 mo	Distal phalanx, 4th finger	18 mo ± 5 mo
32 mo ± 7 mo	Proximal phalanx, 1st finger	20 mo ± 5 mo
37 mo ± 9 mo	Distal phalanx, 5th finger	23 mo ± 6 mo
37 mo ± 8 mo	Distal phalanx, 2nd finger	23 mo ± 6 mo
39 mo ± 10 mo	Middle phalanx, 5th finger	22 mo ± 7 mo
152 mo ± 18 mo	Sesamoid (adductor pollicis)	121 mo ± 13 mo
HIP AND KNEE		
Usually present at birth	Femur, distal	Usually present at birth
Usually present at birth	Tibia, proximal	Usually present at birth
4 mo ± 2 mo	Femur, head	4 mo ± 2 mo
46 mo ± 11 mo	Patella	29 mo ± 7 mo
FOOT AND ANKLE‡		

Values represent mean ± standard deviation, when applicable.

*To nearest month.

†Except for the capitate and hamate bones, the variability of carpal centers is too great to make them very useful clinically.

‡Standards for the foot are available, but normal variation is wide, including some familial variants, so this area is of little clinical use.

The norms present a composite of published data from the Fels Research Institute, Yellow Springs, OH (Pyle SI, Sontag L: AJR Am J Roentgenol *49:102, 1943), and unpublished data from the Brush Foundation, Case Western Reserve University, Cleveland, OH, and the Harvard School of Public Health, Boston, MA. Compiled by Lieb, Buehl, and Pyle.*

crying (longer than 3 hr/day, longer than 3 days/wk lasting longer than 1 wk) and more often crying/fussiness persisting longer than 3-5 mo might be associated with child abuse, behavioral problems when an older child (anxiety, aggression, hyperactivity), decreased duration of breastfeeding and postnatal depression (uncertain which is the cause or effect). Most infants with crying/fussiness do not have gastroesophageal reflux, lactose intolerance, or cow-milk protein allergy. Some researchers believe excessive crying may be an early manifestation of migraines.

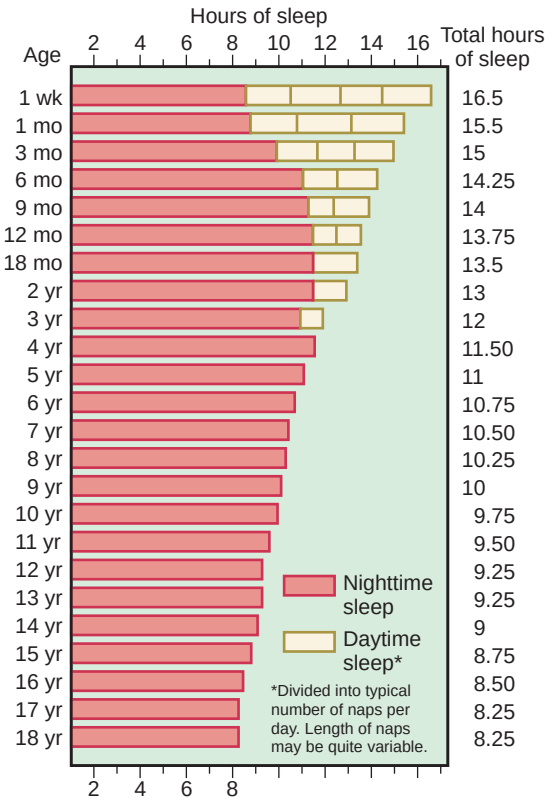

Figure 10-2 Typical sleep requirements in children. *(From Ferber R: Solve your child's sleep problems, New York, 1985, Simon & Schuster.)*

Infants have various signals for their needs and for getting attention from a caregiver. These behaviors progressively increase in intensity in many infants from changes in breathing and color, to postural and movement cures, and then to calm vocalizations. These precry cues, if not attended to, will eventually lead to active crying. Some infants may go directly to crying, perhaps based on temperament; these infants may be less easily consolable and may have feeding problems like refusal of feeds. Sensory integration issues may also be involved with the child being over responsive or sensory deprived.

Management of crying/fussiness should include teaching caregivers about precry cues and responding to the signal for feeding in a calm relaxed manner. If sensory overstimulation is a factor, creating a non-distracting, calm environment may help as well as swaddling. When lack of sensory stimulation is present, mother–infant skin-to-skin contact, and carrying the infant may be beneficial. In all situations, reassurance that this is both normal and transient, with only 5% of infants persisting beyond 3 mo of age, helps the family cope.

The emotional significance of any experience depends on both the individual child's temperament and the parent's responses (see Table 6-1); differing feeding schedules produce differing reactions. Hunger generates increasing tension; as the urgency peaks, the infant cries, the parent offers the breast or bottle and the tension dissipates. Infants fed "on demand" consistently experience this link between their distress, the arrival of the parent, and relief from hunger. Most infants fed on a fixed schedule quickly adapt their hunger cycle to the schedule. Those who cannot because they are temperamentally prone to irregular biologic rhythms experience periods of unrelieved hunger as well as unwanted feedings when they already feel full. Similarly, infants who are fed at the parents' convenience, with neither attention to the infant's hunger cues nor a fixed schedule, may not consistently experience feeding as the pleasurable reduction of tension. Infants with early dysregulation often show increased irritability and physiologic instability (spitting, diarrhea, poor weight gain) as well as later behavioral problems.

Implications for Parents and Pediatricians

Success or failure in establishing feeding and sleep cycles determines parents' feelings of efficacy. When things go well, the parents' anxiety and ambivalence, as well as the exhaustion of the early weeks, decrease. Infant issues (colic) or familial conflict will prevent this from occurring. With physical recovery from delivery and hormonal normalization, the mild postpartum depression that affects many mothers passes. If the mother continues to feel sad, overwhelmed, and anxious, the possibility of moderate to severe postpartum depression, found in 10-15% of postpartum women, needs to be considered. Major **depression** that arises during pregnancy or in the postpartum period threatens the mother–child relationship and is a risk factor for later cognitive and behavioral problems. The pediatrician may be the first professional to encounter the depressed mother and should be instrumental in assisting her in seeking treatment (see Chapter 9).

AGE 2-6 MONTHS

At about age 2 mo, the emergence of voluntary (social) smiles and increasing eye contact mark a change in the parent–child relationship, heightening the parents' sense of being loved reciprocally. During the next months, an infant's range of motor and social control and cognitive engagement increases dramatically. Mutual regulation takes the form of complex social interchanges, resulting in strong mutual attachment and enjoyment. Routines are established. Parents are less fatigued.

Physical Development

Between 3 and 4 mo of age, the rate of growth slows to approximately 20 g/day (see Table 15-1 and Figs. 11-1 and 11-2). By age 4 mo, birth weight is doubled. Early reflexes that limited voluntary movement recede. Disappearance of the asymmetric tonic neck reflex means that infants can begin to examine objects in the midline and manipulate them with both hands (see Chapter 590). Waning of the early grasp reflex allows infants both to hold objects and to let them go voluntarily. A novel object may elicit purposeful, although inefficient, reaching. The quality of spontaneous movements also changes, from larger writhing to smaller, circular movements that have been described as "fidgety." Abnormal or absent fidgety movements may constitute a risk factor for later neurologic abnormalities.

Increasing control of truncal flexion makes intentional rolling possible. Once infants can hold their heads steady while sitting, they can gaze across at things rather than merely looking up at them, opening up a new visual range. They can begin taking food from a spoon. At the same time, maturation of the visual system allows greater depth perception.

In this period, infants achieve stable state regulation and regular sleep–wake cycles. Total sleep requirements are approximately 14-16 hr/24 hr, with about 9-10 hr concentrated at night and 2 naps/day. Approximately 70% of infants sleep for a 6-8 hr stretch by age 6 mo (see Fig. 10-2). By 4-6 mo, the sleep electroencephalogram shows a mature pattern, with demarcation of rapid eye movement and 4 stages of non–rapid eye movement sleep. The sleep cycle remains shorter than in adults (50-60 min vs approximately 90 min). As a result, infants arouse to light sleep or wake frequently during the night, setting the stage for behavioral sleep problems (see Chapter 19).

Cognitive Development

The overall effect of these developments is a qualitative change. At 4 mo of age, infants are described as "hatching" socially, becoming interested in a wider world. During feeding, infants no longer focus exclusively on the mother, but become distracted. In the mother's arms, the infant may literally turn around, preferring to face outward.

Infants at this age also explore their own bodies, staring intently at their hands, vocalizing, blowing bubbles, and touching their ears, cheeks, and genitals. These explorations represent an early stage in the understanding of cause and effect as infants learn that voluntary muscle movements generate predictable tactile and visual sensations. They also have a role in the emergence of a sense of self, separate from the mother. This is the 1st stage of personality development. Infants come to associate certain sensations through frequent repetition. The proprioceptive feeling of holding up the hand and wiggling the fingers always accompanies the sight of the fingers moving. Such self sensations are consistently linked and reproducible at will. In contrast, sensations that are associated with "other" occur with less regularity and in varying combinations. The sound, smell, and feel of the mother sometimes appear promptly in response to crying, but sometimes do not. The satisfaction that the mother or another loving adult provides continues the process of attachment.

Emotional Development and Communication

Babies interact with increasing sophistication and range. The primary emotions of anger, joy, interest, fear, disgust, and surprise appear in appropriate contexts as distinct facial expressions. When face-to-face, the infant and a trusted adult can match affective expressions (smiling or surprise) approximately 30% of the time. Initiating games (singing, hand games) increases social development. Such face-to-face behavior reveals the infant's ability to share emotional states, the 1st step in the development of communication. Infants of depressed parents show a different pattern, spending less time in coordinated movement with their parents and making fewer efforts to reengage. Rather than anger, they show sadness and a loss of energy when the parents continue to be unavailable.

Implications for Parents and Pediatricians

Motor and sensory maturation makes infants at 3-6 mo exciting and interactive. Some parents experience their 4 mo old child's outward turning as a rejection, secretly fearing that their infants no longer love them. For most parents, this is a happy period. Most parents excitedly report that they can hold conversations with their infants, taking turns vocalizing and listening. Pediatricians share in the enjoyment, as the baby coos, makes eye contact, and moves rhythmically. Infants who do not show this reciprocal language and movements are at risk for autism spectrum disorders (see Chapter 30). If this visit does not feel joyful and relaxed, causes such as social stress, family dysfunction, parental mental illness, or problems in the infant–parent relationship should be considered. Parents can be reassured that responding to an infant's emotional needs cannot spoil the infant. Giving vaccines and drawing blood while the child is seated on the parent's lap or nursing at the breast increases pain tolerance.

AGE 6-12 MONTHS

With achievement of the sitting position, increased mobility, and new skills to explore the world around them, 6-12 mo old infants show advances in cognitive understanding and communication, and there are new tensions around the themes of attachment and separation. Infants develop will and intentions, characteristics that most parents welcome, but still find challenging to manage.

Physical Development

Growth slows more (see Table 15-1 and Figs. 11-1 and 11-2). By the 1st birthday, birth weight has tripled, length has increased by 50%, and head circumference has increased by 10 cm. The ability to sit unsupported (6-7 mo) and to pivot while sitting (around 9-10 mo) provides increasing opportunities to manipulate several objects at a time and to experiment with novel combinations of objects. These explorations are aided by the emergence of a thumb–finger grasp (8-9 mo) and a neat pincer grasp by 12 mo. Voluntary release emerges at 9 mo. Many infants begin crawling and pulling to stand around 8 mo, followed by cruising. Some walk by 1 yr. Motor achievements correlate with increasing myelinization and cerebellar growth. These gross motor skills expand infants' exploratory range and create new physical dangers, as well as opportunities for learning. Tooth eruption occurs, usually starting with the mandibular central incisors. Tooth development reflects skeletal maturation and bone age, although there is wide individual variation (see Table 10-3 and Chapter 307).

Cognitive Development

The 6 mo old infant has discovered his hands and will soon learn to manipulate objects. At first, everything is mouthed. In time, novel

objects are picked up, inspected, passed from hand to hand, banged, dropped, and then mouthed. Each action represents a nonverbal idea about what things are for (in Piagetian terms, a *schema;* see Chapter 6). The complexity of an infant's play, how many different schemata are brought to bear, is a useful index of cognitive development at this age. The pleasure, persistence, and energy with which infants tackle these challenges suggest the existence of an intrinsic drive or mastery motivation. Mastery behavior occurs when infants feel secure; those with less secure attachments show limited experimentation and less competence.

A major milestone is the achievement by 9 mo of **object permanence** (**constancy**), the understanding that objects continue to exist, even when not seen. At 4-7 mo of age, infants look down for a yarn ball that has been dropped but quickly give up if it is not seen. With object constancy, infants persist in searching. They will find objects hidden under a cloth or behind the examiner's back. Peek-a-boo brings unlimited pleasure as the child magically brings back the other player. Events seem to occur as a result of the child's own activities.

Emotional Development

The advent of object permanence corresponds with qualitative changes in social and communicative development. Infants look back and forth between an approaching stranger and a parent, and may cling or cry anxiously, demonstrating **stranger anxiety**. Separations often become more difficult. Infants who have been sleeping through the night for mo begin to awaken regularly and cry, as though remembering that the parents are in the next room.

A new demand for autonomy also emerges. Poor weight gain at this age often reflects a struggle between an infant's emerging independence and parent's control of the feeding situation. Use of the 2-spoon method of feeding (1 for the child and 1 for the parent), finger foods, and a high chair with tray table can avert potential problems. Tantrums make their first appearance as the drives for autonomy and mastery come in conflict with parental controls and the infants' still-limited abilities.

Communication

Infants at 7 mo of age are adept at nonverbal communication, expressing a range of emotions and responding to vocal tone and facial expressions. Around 9 mo of age, infants become aware that emotions can be shared between people; they show parents toys as a way of sharing their happy feelings. Between 8 and 10 mo of age, babbling takes on a new complexity, with multisyllabic sounds ("ba-da-ma"); babies can discriminate between languages. Infants in bilingual homes learn the characteristics and rules that govern 2 different languages. Social interaction (attentive adults taking turns vocalizing with the infant) profoundly influences the acquisition and production of new sounds. The first true word (i.e., a sound used consistently to refer to a specific object or person) appears in concert with an infant's discovery of object permanence. Picture books now provide an ideal context for verbal language acquisition. With a familiar book as a shared focus of attention, a parent and child engage in repeated cycles of pointing and labeling, with elaboration and feedback by the parent. The addition of sign language may support infant development while enhancing mother–infant communication.

Implications for Parents and Pediatricians

With the developmental reorganization that occurs around 9 mo of age, previously resolved issues of feeding and sleeping reemerge. Pediatricians can prepare parents at the 6 mo visit so that these problems can be understood as the result of developmental progress and not regression. Parents should be encouraged to plan ahead for necessary, and inevitable, separations (e.g., babysitter, daycare). Routine preparations may make these separations easier. Although controversial, the stability that comes with dual parent employment may be beneficial for long-term social emotional outcomes. Introduction of a **transitional object** may allow the infant to self-comfort in the parents' absence. The object cannot have any potential for asphyxiation or strangulation.

Infants' wariness of strangers often makes the 9 mo examination difficult, particularly if the infant is temperamentally prone to react negatively to unfamiliar situations. Initially, the pediatrician should avoid direct eye contact with the child. Time spent talking with the parent and introducing the child to a small, washable toy will be rewarded with more cooperation. The examination can be continued on the parent's lap when feasible.

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Chapter 11

The Second Year

Susan Feigelman

The toddler's newly found ability to walk allows separation and independence; however, the toddler continues to need secure attachment to the parents. At approximately 18 mo of age, the emergence of symbolic thought and language causes a reorganization of behavior, with implications across many developmental domains.

AGE 12-18 MONTHS

Physical Development

The toddler continues to experience considerable brain growth and myelination in the 2nd yr, resulting in an increase in head circumference of 2 cm over the year (Fig. 11-1; see also Fig. 10-1). Toddlers have relatively short legs and long torsos, with exaggerated lumbar lordosis and protruding abdomens. Growth in length continues at a steady rate (Fig. 11-2).

Most children begin to walk independently at around 12-15 mo of age. Early walking is not associated with advanced development in other domains. Infants initially toddle with a wide-based gait, with the knees bent and the arms flexed at the elbow; the entire torso rotates with each stride; the toes may point in or out, and the feet strike the floor flat. The appearance is that of genu varus (bowleg). Subsequent refinement leads to greater steadiness and energy efficiency. After several months of practice, the center of gravity shifts back and the torso stabilizes, while the knees extend and the arms swing at the sides for balance. The feet are held in better alignment, and the child is able to stop, pivot, and stoop without toppling over (see Chapters 672 and 673).

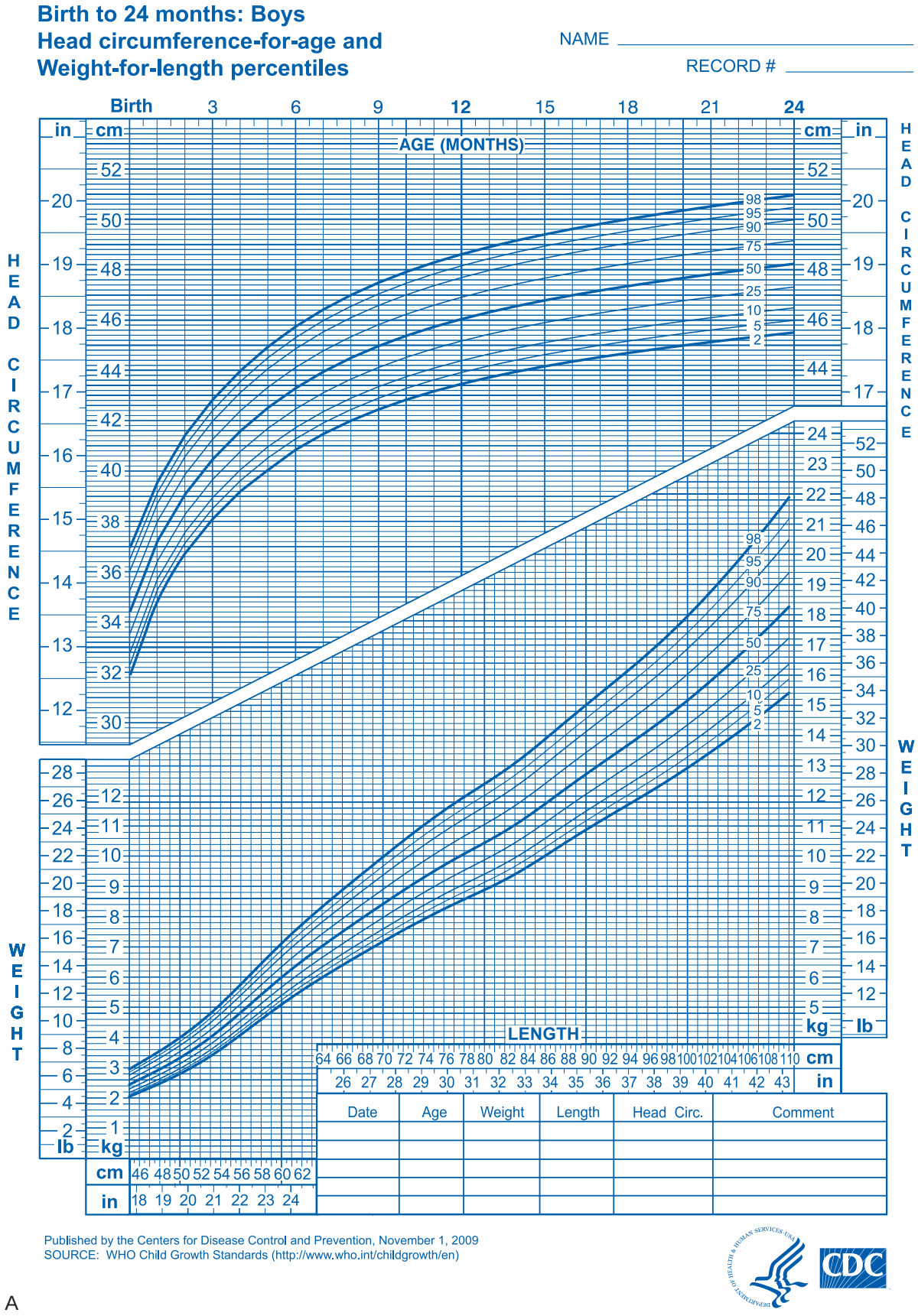
Cognitive Development

Exploration of the environment increases in parallel with improved dexterity (reaching, grasping, releasing) and mobility. Learning follows the precepts of Piaget's sensorimotor stage (see Chapter 6). Toddlers manipulate objects in novel ways to create interesting effects, such as stacking blocks or putting things into a computer disk drive. Playthings are also more likely to be used for their intended purposes (combs for hair, cups for drinking). Imitation of parents and older siblings or other children is an important mode of learning. Make-believe (symbolic) play centers on the child's own body (pretending to drink from an empty cup) (Table 11-1; also see Table 10-1).

Emotional Development

Infants who are approaching the developmental milestone of taking their first steps may be irritable. Once they start walking, their predominant mood changes markedly. Toddlers are described as "intoxicated" or "giddy" with their new ability and with the power to control the distance between themselves and their parents. Exploring toddlers orbit around their parents, moving away and then returning for a reassuring touch before moving away again. A securely attached child will

Text continued on p. 75



A

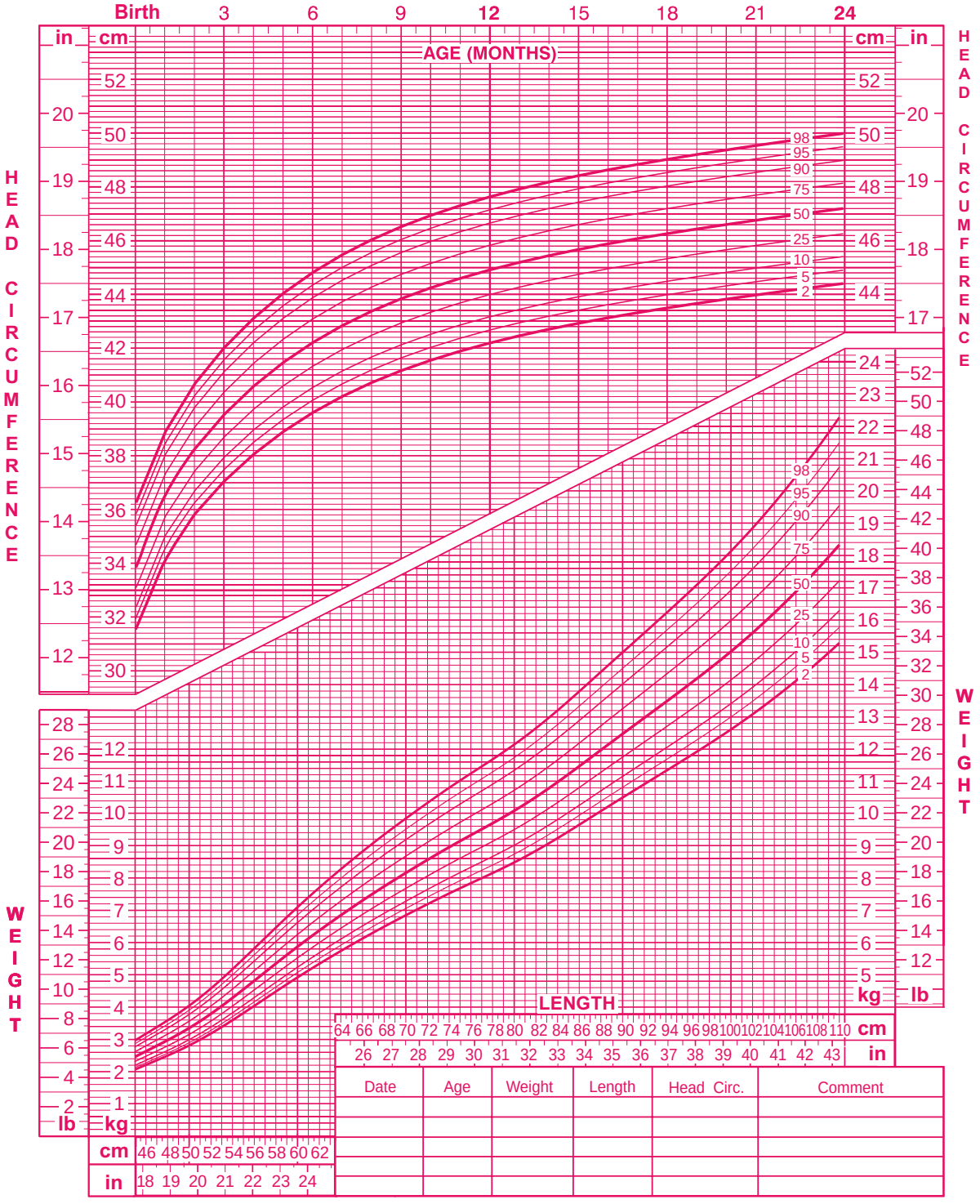
Figure 11-1 The World Health Organization Growth Charts. Weight/length and head circumference for boys **(A)** and girls **(B).** *(Courtesy of the World Health Organization: WHO Child Growth Standards, 2014.* http://www.who.int/childgrowth/standards/en/.*)*

Continued

Birth to 24 months: Girls
Head circumference-for-age and
Weight-for-length percentiles

NAME _____

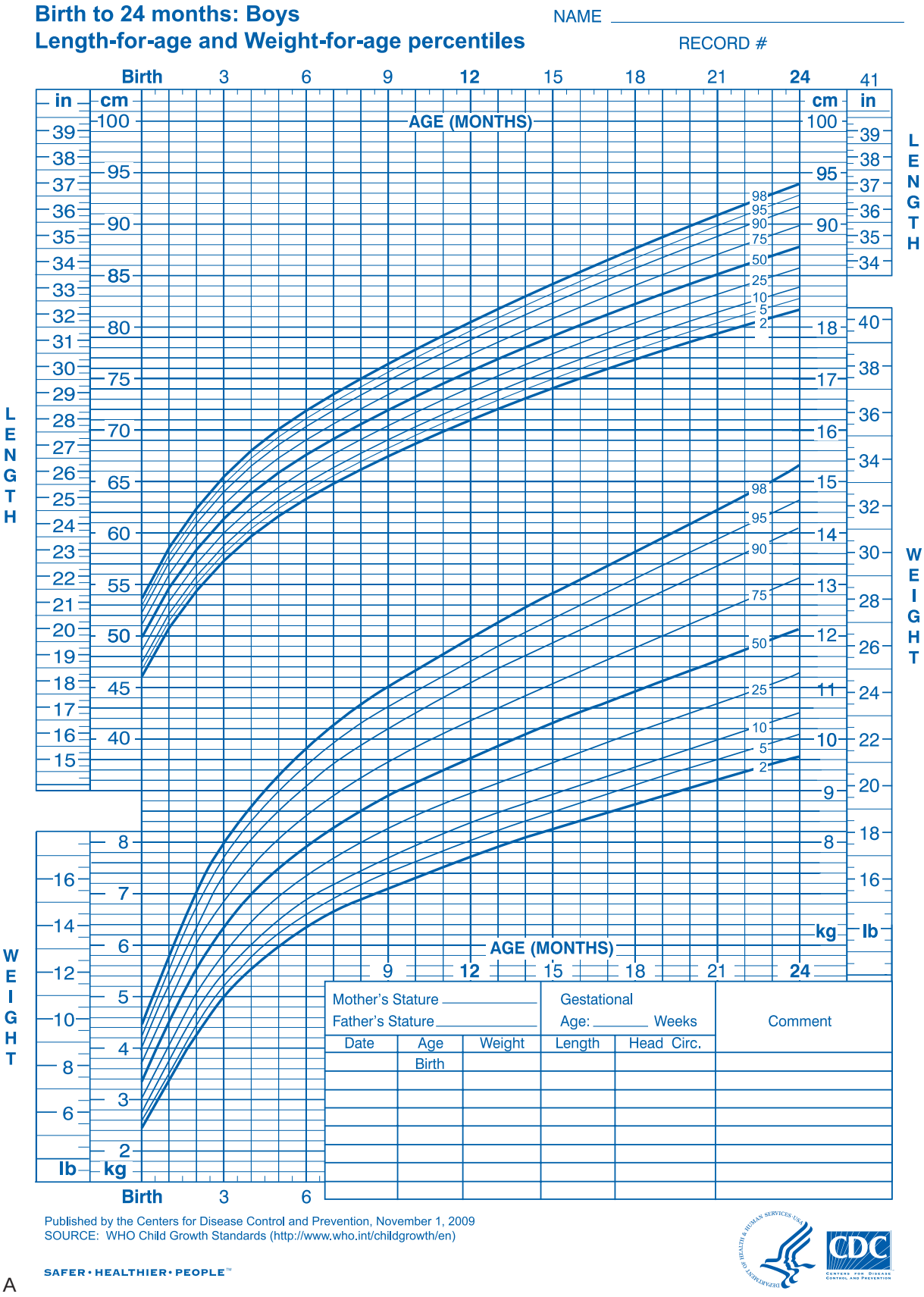
RECORD # _____



Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

B

Figure 11-1, cont'd



A

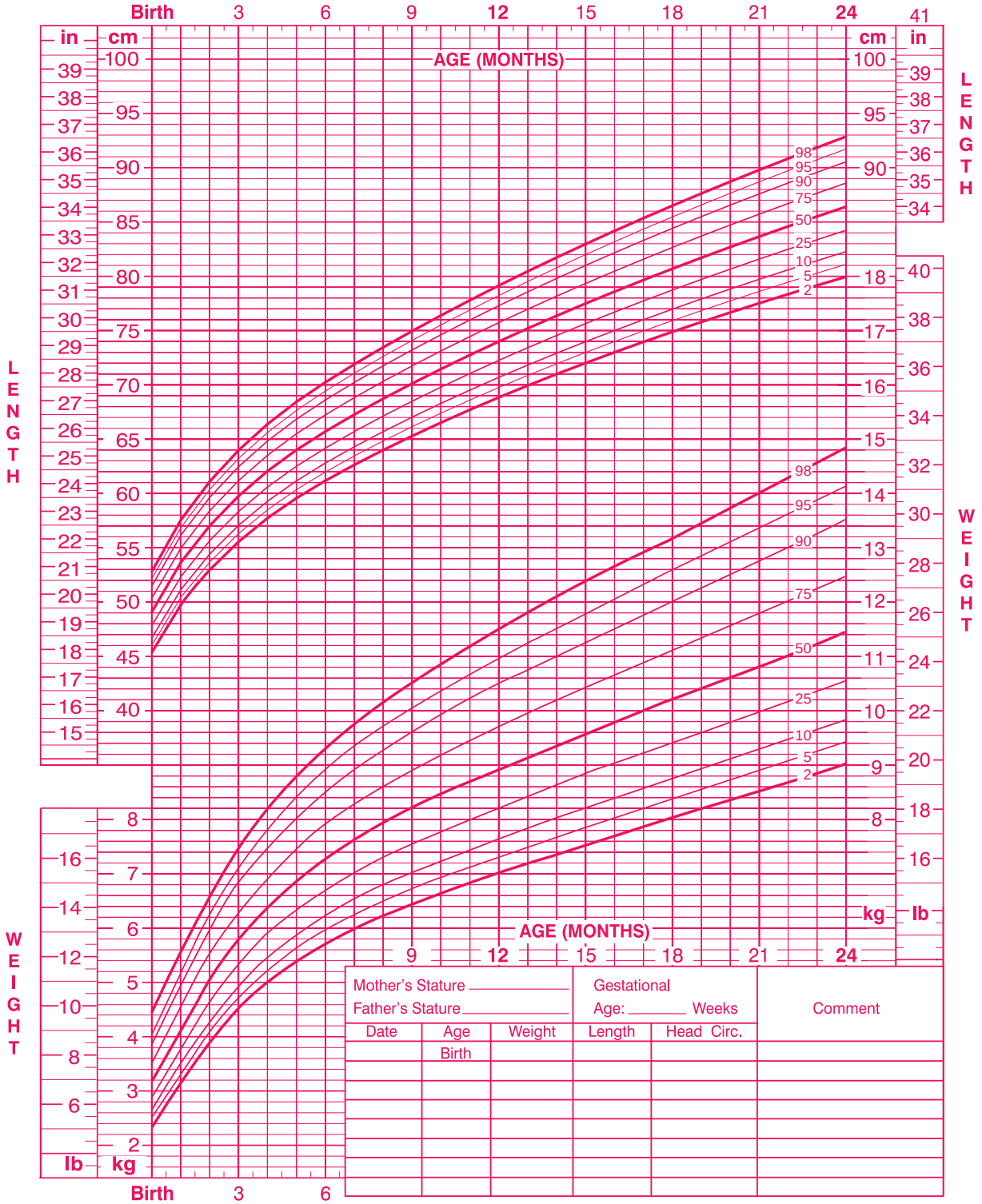
Figure 11-2 The World Health Organization Growth Charts. Length for age and weight for age for boys **(A)** and girls **(B)**. *(Courtesy of the World Health Organization: WHO Child Growth Standards, 2014.* http://www.who.int/childgrowth/standards/en/*.)*

Continued

Birth to 24 months: Girls
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD #



Mother's Stature _____ Father's Stature _____			Gestational Age: _____ Weeks		Comment
Date	Age	Weight	Length	Head Circ.	
	Birth				

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

B

Figure 11-2, cont'd

Table 11-1 Emerging Patterns of Behavior from 1-5 Yr of Age*

15 MO	
Motor:	Walks alone; crawls up stairs
Adaptive:	Makes tower of 3 cubes; makes a line with crayon; inserts raisin in bottle
Language:	Jargon; follows simple commands; may name a familiar object (e.g., ball); responds to his/her name
Social:	Indicates some desires or needs by pointing; hugs parents
18 MO	
Motor:	Runs stiffly; sits on small chair; walks up stairs with 1 hand held; explores drawers and wastebaskets
Adaptive:	Makes tower of 4 cubes; imitates scribbling; imitates vertical stroke; dumps raisin from bottle
Language:	10 words (average); names pictures; identifies 1 or more parts of body
Social:	Feeds self; seeks help when in trouble; may complain when wet or soiled; kisses parent with pucker
24 MO	
Motor:	Runs well, walks up and down stairs, 1 step at a time; opens doors; climbs on furniture; jumps
Adaptive:	Makes tower of 7 cubes (6 at 21 mo); scribbles in circular pattern; imitates horizontal stroke; folds paper once imitatively
Language:	Puts 3 words together (subject, verb, object)
Social:	Handles spoon well; often tells about immediate experiences; helps to undress; listens to stories when shown pictures
30 MO	
Motor:	Goes up stairs alternating feet
Adaptive:	Makes tower of 9 cubes; makes vertical and horizontal strokes, but generally will not join them to make cross; imitates circular stroke, forming closed figure
Language:	Refers to self by pronoun "I"; knows full name
Social:	Helps put things away; pretends in play
36 MO	
Motor:	Rides tricycle; stands momentarily on 1 foot
Adaptive:	Makes tower of 10 cubes; imitates construction of "bridge" of 3 cubes; copies circle; imitates cross
Language:	Knows age and sex; counts 3 objects correctly; repeats 3 numbers or a sentence of 6 syllables; most of speech intelligible to strangers
Social:	Plays simple games (in "parallel" with other children); helps in dressing (unbuttons clothing and puts on shoes); washes hands
48 MO	
Motor:	Hops on 1 foot; throws ball overhand; uses scissors to cut out pictures; climbs well
Adaptive:	Copies bridge from model; imitates construction of "gate" of 5 cubes; copies cross and square; draws man with 2-4 parts besides head; identifies longer of 2 lines
Language:	Counts 4 pennies accurately; tells story
Social:	Plays with several children, with beginning of social interaction and role-playing; goes to toilet alone
60 MO	
Motor:	Skips
Adaptive:	Draws triangle from copy; names heavier of 2 weights
Language:	Names 4 colors; repeats sentence of 10 syllables; counts 10 pennies correctly
Social:	Dresses and undresses; asks questions about meaning of words; engages in domestic role-playing

*Data derived from those of Gesell (as revised by Knobloch), Shirley, Provence, Wolf, Bailey, and others. After 6 yr, the Wechsler Intelligence Scales for Children (WISC-IV) and other scales offer the most precise estimates of developmental level. To have their greatest value, they should be administered only by an experienced and qualified person.

use the parent as a secure base from which to explore independently. Proud of her or his accomplishments, the child illustrates Erikson's stage of autonomy and separation (see Chapter 6). The toddler who is overly controlled and discouraged from active exploration will feel doubt, shame, anger, and insecurity. All children will experience tantrums, reflecting their inability to delay gratification, suppress or displace anger, or verbally communicate their emotional states. The quality of the parent–child relationship may moderate negative effects of childcare arrangements when parents work.

Linguistic Development

Receptive language precedes expressive language. By the time infants speak their first words around 12 mo of age, they already respond appropriately to several simple statements, such as "no," "bye-bye," and "give me." By 15 mo, the average child points to major body parts and uses 4-6 words spontaneously and correctly. Toddlers also enjoy **polysyllabic** jargoning (see Tables 10-1 and 11-1), but do not seem upset that no one understands. Most communication of wants and ideas continues to be nonverbal.

Implications for Parents and Pediatricians

Parents who cannot recall any other milestone tend to remember when their child began to walk, perhaps because of the symbolic significance of walking as an act of independence and/or because of the new demands that the ambulating toddler places on his or her parent. All toddlers should be encouraged to explore their environments; a child's ability to wander out of sight also increases the risks of injury and the need for supervision.

In the office setting, many toddlers are comfortable exploring the examination room, but cling to the parents under the stress of the examination. Performing most of the physical examination in the parent's lap may help allay fears of separation. Infants who become more, not less, distressed in their parents' arms or who avoid their parents at times of stress may be insecurely attached. Young children who, when distressed, turn to strangers rather than parents for comfort are particularly worrisome. Children raised in "toxic" stressful environments have increased vulnerability to disease. The conflicts between independence and security manifest in issues of discipline, temper tantrums, toilet training, and changing feeding behaviors. Parents should be counseled on these matters within the framework of normal development.

Parents may express concern about poor food intake as growth slows. The growth chart should provide reassurance. Most children still take two daytime naps, although the duration steadily decreases (see Fig. 10-1).

AGE 18-24 MONTHS

Physical Development

Motor development during this period is reflected in improvements in balance and agility and the emergence of running and stair climbing. Height and weight increase at a steady rate during this year, with a gain of 5 in and 5 lb. By 24 mo, children are about half of their ultimate adult height. Head growth slows slightly. Eighty-five percent of adult head circumference is achieved by age 2 yr, with just an additional 5 cm gain over the next few years (see Fig. 11-1 and Table 15-1).

Cognitive Development

At approximately 18 mo of age, several cognitive changes coalesce, marking the conclusion of the sensory-motor period. These can be observed during self-initiated play. *Object permanence* is firmly established; toddlers anticipate where an object will end up, even though the object was not visible while it was being moved. *Cause and effect* are better understood, and toddlers demonstrate flexibility in problem solving (e.g., using a stick to obtain a toy that is out of reach, figuring out how to wind a mechanical toy). *Symbolic transformations* in play are no longer tied to the toddler's own body, so that a doll can be "fed" from an empty plate. Like the reorganization that occurs at 9 mo (see Chapter 10), the cognitive changes at 18 mo correlate with important changes in the emotional and linguistic domains (see Table 11-1).

Emotional Development

The relative independence of the preceding half-year often gives way to increased clinginess around 18 mo. This stage, described as "rapprochement," may be a reaction to growing awareness of the possibility of separation. Many parents report that they cannot go anywhere without having a small child attached to them. **Separation anxiety** will be manifest at bedtime. Many children use a special blanket or stuffed toy as a **transitional object,** which functions as a symbol of the absent parent. The transitional object remains important until the transition to symbolic thought has been completed and the symbolic presence of the parent has been fully internalized. Despite the attachment to the parent, the child's use of "no" is a way of declaring independence. Individual differences in temperament, in both the child and the parents play a critical role in determining the balance of conflict vs cooperation in the parent–child relationship. As effective language emerges, conflicts become less frequent.

Self-conscious awareness and internalized standards of behavior first appear at this age. Toddlers looking in a mirror will, for the first time, reach for their own face rather than the mirror image if they notice something unusual on their nose. They begin to recognize when toys are broken and may hand them to their parents to fix. Language becomes a means of impulse control, early reasoning, and connection between ideas. When tempted to touch a forbidden object, they may tell themselves "no, no." This is the very beginning of the formation of a conscience. The fact that they often go on to touch the object anyway demonstrates the relative weakness of internalized inhibitions at this stage.

Linguistic Development

Perhaps the most dramatic developments in this period are linguistic. Labeling of objects coincides with the advent of symbolic thought. After the realization that words can stand for things occurs, a child's vocabulary balloons from 10-15 words at 18 mo to between 50 and 100 at 2 yr. After acquiring a vocabulary of about 50 words, toddlers begin to combine them to make simple sentences, the beginning of grammar. At this stage, toddlers understand **2-step commands,** such as "Give me the ball and then get your shoes." Language also gives the toddler a sense of control over the surroundings, as in "night-night" or "bye-bye." The emergence of verbal language marks the end of the sensory-motor period. As toddlers learn to use symbols to express ideas and solve problems, the need for cognition based on direct sensation and motor manipulation wanes.

Implications for Parents and Pediatricians

With children's increasing mobility, physical limits on their explorations become less effective; words become increasingly important for behavior control as well as cognition. Children with delayed language acquisition often have greater behavior problems and frustrations due to problems with communication. Language development is facilitated when parents and caregivers use clear, simple sentences; ask questions; and respond to children's incomplete sentences and gestural communication with the appropriate words. Television viewing, as well as television as background noise, decreases parent–child verbal interactions, whereas looking at picture books and engaging the child in 2-way conversations stimulate language development.

In the office setting, certain procedures may lessen the child's **stranger anxiety.** Avoid direct eye contact initially. Perform as much of the examination as feasible with the child on the parent's lap. Pediatricians can help parents understand the resurgence of problems with separation and the appearance of a treasured blanket or teddy bear as a developmental phenomenon. Parents must understand the importance of exploration. Rather than limiting movement, parents should place toddlers in safe environments or substitute 1 activity for another. Methods of discipline, including corporal punishment, should be discussed; effective alternatives will usually be appreciated. Helping parents to understand and adapt to their children's different temperamental styles can constitute an important intervention (see Table 6-1). Developing daily routines is helpful to all children at this age. Rigidity in those routines reflects a need for mastery over a changing environment.

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Chapter 12

The Preschool Years

Susan Feigelman

The emergence of language and exposure of children to an expanding social sphere represent the critical milestones for children ages 2-5 yr. As toddlers, children learn to walk away and come back to the secure adult or parent. As preschoolers, they explore emotional separation, alternating between stubborn opposition and cheerful compliance, between bold exploration and clinging dependence. Increasing time spent in classrooms and playgrounds challenges a child's ability to adapt to new rules and relationships. Emboldened by their growing array of new skills and accomplishments, preschool children also are increasingly cognizant of the constraints imposed on them by the adult world and their own limited abilities.

STRUCTURAL DEVELOPMENT OF THE BRAIN

The preschool brain experiences dramatic changes in its anatomical and physiologic characteristics, with increases in cortical area, decreases in cortical thickness, and changing cortical volume. These changes are not uniform across the brain, but vary by region. Gray and white matter tissue properties change dramatically, including diffusion properties in the major cerebral fiber tracts. Dramatic increases occur in the brain metabolic demands. In general, a greater number of brain regions are required among younger compared to older children to complete the same cognitive task. This duplication has been interpreted as a form of "scaffolding," which is discarded with increasing age. The preschool brain is characterized by growth and expansion, that will be followed in later years by pruning.

PHYSICAL DEVELOPMENT

Somatic and brain growth slows by the end of the 2nd yr of life, with corresponding decreases in nutritional requirements and appetite, and the emergence of "picky" eating habits (see Table 15-1). Increases of approximately 2 kg (4-5 lb) in weight and 7-8 cm (2-3 in) in height per year are expected. Birthweight quadruples by 2.5 yr of age. An average 4 yr old weighs 40 lb and is 40 in tall. The head will grow only an additional 5-6 cm between ages 3 and 18 yr. Current growth charts, with growth parameters, can be found on the Centers for Disease Control and Prevention website (http://www.cdc.gov/growthcharts/) and in Chapter 15. Children with early adiposity rebound (increase in body mass index) are at increased risk for adult obesity.

Growth of sexual organs is commensurate with somatic growth. The preschooler has genu valgum (knock-knees) and mild pes planus (flat-foot). The torso slims as the legs lengthen. Physical energy peaks, and the need for sleep declines to 11-13 hr/24 hr, with the child eventually dropping the nap (see Fig. 10-1). Visual acuity reaches 20/30 by age 3 yr and 20/20 by age 4 yr. All 20 primary teeth have erupted by 3 yr of age (see Chapter 307).

Most children walk with a mature gait and run steadily before the end of their 3rd yr (see Table 11-1). Beyond this basic level, there is wide variation in ability as the range of motor activities expands to include throwing, catching, and kicking balls; riding on bicycles; climbing on playground structures; dancing; and other complex pattern behaviors. Stylistic features of gross motor activity, such as

tempo, intensity, and cautiousness, also vary significantly. Although toddlers may walk with different styles, toe walking should not persist.

The effects of such individual differences on cognitive and emotional development depend in part on the demands of the social environment. Energetic, coordinated children may thrive emotionally with parents or teachers who encourage physical activity; lower-energy, more cerebral children may thrive with adults who value quiet play.

Handedness is usually established by the 3rd yr. Frustration may result from attempts to change children's hand preference. Variations in fine-motor development reflect both individual proclivities and different opportunities for learning. Children who are restricted from drawing with crayons, for example, develop a mature pencil grasp later.

Bowel and bladder control emerge during this period, with "readiness" for toileting having large individual and cultural variation. Girls tend to train faster and earlier than boys. Bed-wetting is normal up to age 4 yr in girls and age 5 yr in boys (see Chapter 23.3). Many children master toileting with ease, particularly once they are able to verbalize their bodily needs. For others, toilet training can involve a protracted power struggle. Refusal to defecate in the toilet or potty is relatively common and can lead to constipation and parental frustration. Defusing the issue with a temporary cessation of training (and a return to diapers) often allows toilet mastery to proceed.

Implications for Parents and Pediatricians

The normal decrease in appetite at this age may cause parental concern about nutrition; growth charts should reassure parents that the child's intake is adequate. Children normally modulate their food intake to match their somatic needs according to feelings of hunger and satiety. Daily intake fluctuates, at times widely, but intake during the period of a week is relatively stable. A complete multivitamin can be used to assure adequate vitamin and mineral intake. Parents should provide a predictable eating schedule, with 3 meals and 2 snacks per day, allowing the child to choose how much to eat.

Highly active children face increased risks of injury, and parents should be counseled about safety precautions. Parental concerns about possible hyperactivity may reflect inappropriate expectations, heightened fears, or true overactivity. Children who engage in impulsive activity with no apparent regard for personal safety should be evaluated further.

LANGUAGE, COGNITION, AND PLAY

These 3 domains all involve symbolic function, a mode of dealing with the world that emerges during the preschool period.

Language

Our understanding of the acquisition of language is evolving. Preschool children command significant computational skills and understanding of statistical patterns that allow them to learn about both language and causation. The 2 and 3 yr old child employs frequency distributions to identify phonetic units distinguishing words in his or her native language from other languages.

Language development occurs most rapidly between 2 and 5 yr of age. Vocabulary increases from 50-100 words to more than 2,000. Sentence structure advances from telegraphic phrases ("Baby cry") to sentences incorporating all of the major grammatical components. As a rule of thumb, between the ages of 2 and 5 yr, the number of words in a typical sentence equals the child's age (2 by age 2 yr, 3 by age 3 yr, and so on). By 21-24 mo, most children are using possessives ("My ball"), progressives (the "-ing" construction, as in "I playing"), questions, and negatives. By age 4 yr, most children can count to 4 and use the past tense; by age 5 yr, they can use the future tense. Children do not use figurative speech; they will only comprehend the literal meaning of words. Referring to an object as "light as a feather" may produce a quizzical look on a child.

It is important to distinguish between *speech* (the production of intelligible sounds) and *language,* which refers to the underlying mental act. Language includes both expressive and receptive functions. Receptive language (understanding) varies less in its rate of acquisition than does expressive language; therefore, it has greater prognostic importance (see Chapters 16 and 35).

Language acquisition depends critically on environmental input. Key determinants include the amount and variety of speech directed toward children and the frequency with which adults ask questions and encourage verbalization. Children raised in poverty typically perform lower on measures of language development compared to children from economically advantaged families.

Although experience influences the rate of language development, many linguists believe that the basic mechanism for language learning is "hard-wired" in the brain. Children do not simply imitate adult speech; they abstract the complex rules of grammar from the ambient language, generating implicit hypotheses. Evidence for the existence of such implicit rules comes from analysis of grammatical errors, such as the overgeneralized use of "-s" to signify the plural and "-ed" to signify the past ("We seed lots of mouses.").

Language is linked to both cognitive and emotional development. Language delays may be the first indication that a child has an intellectual disability, has an autism spectrum disorder, or has been maltreated. Language plays a critical part in the regulation of behavior through internalized "private speech" in which a child repeats adult prohibitions, first audibly and then mentally. Language also allows children to express feelings, such as anger or frustration, without acting them out; consequently, language-delayed children show higher rates of tantrums and other externalizing behaviors.

Preschool language development lays the foundation for later success in school. Approximately 35% of children in the United States may enter school lacking the language skills that are the prerequisites for acquiring literacy. Children from socially and economically disadvantaged backgrounds have an increased risk of school problems, making early detection, along with referral and enrichment, important. Although children typically learn to read and write in elementary school, critical foundations for literacy are established during the preschool years. Through repeated early exposure to written words, children learn about the uses of writing (telling stories or sending messages) and about its form (left to right, top to bottom). Early errors in writing, like errors in speaking, reveal that literacy acquisition is an active process involving the generation and revision of hypotheses. Programs such as Head Start are especially important for improving language skills for children from bilingual homes. Such parents should be reassured that although bilingual children do initially lag behind their monolingual peers in acquiring language, they learn the differing rules governing both languages. Bilingual children do not follow the same course of language development as monolingual children, but create a different system of language cues. Several cognitive advantages have been repeatedly demonstrated among bilingual compared to monolingual children.

Picture books have a special role not only in familiarizing young children with the printed word but also in the development of verbal language. Children's vocabulary and receptive language improve when their parents or caregivers consistently read to them. Reading aloud with a young child is an interactive process in which a parent repeatedly focuses the child's attention on a particular picture, asks questions, and then gives the child feedback (**dialogic reading**). The elements of shared attention, active participation, immediate feedback, repetition, and graduated difficulty make such routines ideal for language learning. Programs in which physicians provide books to preschool children have shown improvement in language skills among the children.

The period of rapid language acquisition is also when **developmental dysfluency** and **stuttering** are most likely to emerge; these can be traced to activation of the cortical motor, sensory, and cerebellar areas. Common difficulties include pauses and repetitions of initial sounds. Stress or excitement exacerbates these difficulties, which generally resolve on their own. Although 5% of preschool children will stutter, it will resolve in 80% of those children by age 8 yr. Children with stuttering should be referred for evaluation if it is severe, persistent, or associated with anxiety, or if parental concern is elicited. **Treatment** includes guidance to parents to reduce pressures associated with speaking.

Cognition

The preschool period corresponds to Piaget's preoperational (prelogical) stage, characterized by **magical thinking**, **egocentrism**, and **thinking that is dominated by perception**, not abstraction (see Table 6-2). Magical thinking includes confusing coincidence with causality, animism (attributing motivations to inanimate objects and events), and unrealistic beliefs about the power of wishes. A child might believe that people cause it to rain by carrying umbrellas, that the sun goes down because it is tired, or that feeling resentment toward a sibling can actually make that sibling sick. Egocentrism refers to a child's inability to take another's point of view and does not connote selfishness. A child might try to comfort an adult who is upset by bringing the adult a favorite stuffed animal. After 2 yr of age, the child develops a concept of herself or himself as an individual and senses the need to feel "whole."

Piaget demonstrated the dominance of perception over logic. In one experiment, water is poured back and forth between a tall, thin vase and a low, wide dish, and children are asked which container has more water. Invariably, they choose the one that looks larger (usually the tall vase), even when the examiner points out that no water has been added or taken away. Such misunderstandings reflect young children's developing hypotheses about the nature of the world as well as their difficulty in attending simultaneously to multiple aspects of a situation.

Recent work indicating that preschool children do have the ability to understand causal relationships has modified our understanding of the ability of preschool children to engage in abstract thinking. (see Chapter 7)

Imitation, central to the learning experience of preschool children, is now being recognized as a complex act because the of differences in the size of the operators (the adult and the child), different levels of dexterity, and even different outcomes. A child who watches an adult unsuccessfully attempt a simple act (unscrew a lid) will imitate the action—but often with the intended outcome, not the demonstrated but failed outcome. Thus "imitation" goes beyond the mere repetition of observed movements.

By age 3, children have self-identified their sex, and are actively seeking understanding of the meaning of gender identification. There is a developmental progression from rigidity (boys and girls have strict gender roles) in the early preschool years to a more flexible realistic understanding (boys and girls can have a variety of interests).

Play

Play involves learning, physical activity, socialization with peers, and practicing adult roles. Play increases in complexity and imagination, from simple imitation of common experiences, such as shopping and putting baby to bed (2 or 3 yr of age), to more extended scenarios involving singular events, such as going to the zoo or going on a trip (3 or 4 yr of age), to the creation of scenarios that have only been imagined, such as flying to the moon (4 or 5 yr of age). By age 3 yr, cooperative play is seen in activities such as building a tower of blocks together; later, more structured role-play activity, as in playing house, is seen. Play also becomes increasingly governed by rules, from early rules about asking (rather than taking) and sharing (2 or 3 yr of age), to rules that change from moment to moment, according to the desires of the players (4 and 5 yr of age), to the beginning of the recognition of rules as relatively immutable (5 yr of age). Electronic forms of play (games) are best if interactive and educational.

Play also allows for resolution of conflicts and anxiety and for creative outlets. Children can vent anger safely (spanking a doll), take on superpowers (dinosaur and superhero play), and obtain things that are denied in real life (a make-believe friend or stuffed animal). Creativity is particularly apparent in drawing, painting, and other artistic activities. Themes and emotions that emerge in a child's drawings often reflect the emotional issues of greatest importance for the child.

Difficulty distinguishing fantasy from reality colors a child's perception of what the child views in the media, through programming and advertising. One fourth of young children have a television set in their bedroom; a TV in the bedroom is associated with more hours of watching. The number of hours that preschoolers watch TV exceeds guidelines. Interactive quality educational programming in which children develop social relationships with the characters can increase learning. However, exposure to commercial television with violent content is associated with later behavior problems and because children younger than 8 yr are not able to comprehend the concept of persuasive intent, they are more vulnerable to television advertising.

Implications for Parents and Pediatricians

The significance of language as a target for assessment and intervention cannot be overestimated because of its central role as an indicator of cognitive and emotional development and a key factor in behavioral regulation and later school success. As language emerges, parents can support emotional development by using words that describe the child's feeling states ("You sound angry right now.") and urging the child to use words to express, rather than act out, feelings. Active imaginations will come into play when children offer explanations for misbehavior. A parent's best way of dealing with untruths is to address the event, not the child, and have the child participate in making things right.

Parents should have a regular time each day for reading or looking at books with their children. Programs such as Reach Out and Read, in which pediatricians give out picture books along with appropriate guidance during primary care visits, have been effective in increasing reading aloud and thereby promoting language development, particularly in lower-income families. Television and similar media should be limited to 2 hr/day of quality programming, and parents should be watching the programs with their children and debriefing their young children afterward. At-risk children, particularly those living in poverty, can better meet future school challenges if they have early high-quality experiences, such as Head Start.

Preoperational thinking constrains how children understand experiences of illness and treatment. Children begin to understand that bodies have "insides" and "outsides." Children should be given simple, concrete explanations for medical procedures and given some control over procedures if possible. Children should be reassured that they are not to blame when receiving a vaccine or venipuncture. An adhesive bandage will help to make the body whole again in a child's mind.

The active imagination that fuels play and the magical, animist thinking characteristic of preoperational cognition can also generate intense fears. More than 80% of parents report at least 1 fear in their preschool children. Refusal to take baths or to sit on the toilet may arise from the fear of being washed or flushed away, reflecting a child's immature appreciation of relative size. Attempts to demonstrate rationally that there are no monsters in the closet often fail, inasmuch as the fear arises from prerational thinking. However, this same thinking allows parents to be endowed with magical powers that can banish the monsters with "monster spray" or a night light. Parents should acknowledge the fears, offer reassurance and a sense of security, and give the child some sense of control over the situation. Use of the Draw-a-Person, in which a child is asked to draw the best person the child can, may help elucidate a child's viewpoint.

EMOTIONAL AND MORAL DEVELOPMENT

Emotional challenges facing preschool children include accepting limits while maintaining a sense of self-direction, reining in aggressive and sexual impulses, and interacting with a widening circle of adults and peers. At 2 yr of age, behavioral limits are predominantly external; by 5 yr of age, these controls need to be internalized if a child is to function in a typical classroom. Success in achieving this goal relies on prior emotional development, particularly the ability to use internalized images of trusted adults to provide a secure environment in times of stress. The love a child feels for important adults is the main incentive for the development of self-control.

Children learn what behaviors are acceptable and how much power they wield vis-à-vis important adults by testing limits. Testing increases when it elicits attention, even though that attention is often negative, and when limits are inconsistent. Testing often arouses parental anger or inappropriate solicitude as a child struggles to separate, and it gives rise to a corresponding parental challenge: letting go. Excessively tight

limits can undermine a child's sense of initiative, whereas overly loose limits can provoke anxiety in a child who feels that no one is in control.

Control is a central issue. Young children cannot control many aspects of their lives, including where they go, how long they stay, and what they take home from the store. They are also prone to lose internal control, that is, to have temper tantrums. Fear, overtiredness, inconsistent expectations, or physical discomfort can also evoke tantrums. Tantrums normally appear toward the end of the 1st yr of life and peak in prevalence between 2 and 4 yr of age. Tantrums lasting more than 15 min or regularly occurring more than 3 times/day may reflect underlying medical, emotional, or social problems.

Preschool children normally experience complicated feelings toward their parents that can include strong attachment and possessiveness toward the parent of the opposite sex, jealousy and resentment of the other parent, and fear that these negative feelings might lead to abandonment. These emotions, most of which are beyond a child's ability to comprehend or verbalize, often find expression in highly labile moods. The resolution of this crisis (a process extending over years) involves a child's unspoken decision to identify with the parents rather than compete with them. Play and language foster the development of emotional controls by allowing children to express emotions and role play.

Curiosity about genitals and adult sexual organs is normal, as is masturbation. Excessive masturbation interfering with normal activity, acting out sexual intercourse, extreme modesty, or mimicry of adult seductive behavior all suggests the possibility of sexual abuse or inappropriate exposure (see Chapter 40.1). Modesty appears gradually between 4 and 6 yr of age, with wide variations among cultures and families. Parents should begin to teach children about "private" body areas before school entry.

Moral thinking is constrained by a child's cognitive level and language abilities, but develops as the child continues her or his identity with the parents. Beginning before the 2nd birthday, the child's sense of right and wrong stems from the desire to earn approval from the parents and avoid negative consequences. The child's impulses are tempered by external forces; the child has not yet internalized societal rules or a sense of justice and fairness. Over time, as the child internalizes parental admonitions, words are substituted for aggressive behaviors. Finally, the child accepts personal responsibility. Actions will be viewed by damage caused, not by intent. Empathic responses to others' distress arise during the 2nd yr of life, but the ability to consider another child's point of view remains limited throughout this period. In keeping with a child's inability to focus on more than 1 aspect of a situation at a time, fairness is taken to mean equal treatment, regardless of circumstance. A 4 yr old will acknowledge the importance of taking turns, but will complain if he or she didn't get enough time. Rules tend to be absolute, with guilt assigned for bad outcomes, regardless of intentions.

Implications for Parents and Pediatricians

The importance of the preschooler's sense of control over his or her body and surroundings has implications for practice. Preparing the patient by letting the child know how the visit will proceed is reassuring. Tell the child what will happen, but don't ask permission unless you are willing to deal with a "no" answer. A brief introduction to "private parts" is warranted before the genital examination.

The visit of the 4 or 5 yr old should be entertaining, because of the child's ability to communicate, as well as the child's natural curiosity. Physicians should realize that all children are occasionally difficult. Guidance emphasizing appropriate expectations for behavioral and emotional development and acknowledging normal parental feelings of anger, guilt, and confusion should be part of all visits at this time. Parents should be queried about daily routines and their expectations of child behavior. Providing children with choices (all options being acceptable to the parent) and encouraging independence in self-care activities (feeding, dressing, and bathing) will reduce conflicts.

Although some cultures condone the use of corporal punishment for disciplining of young children, it is not an effective means of behavioral control. As children habituate to repeated spanking, parents have to spank ever harder to get the desired response, increasing the risk of serious injury. Sufficiently harsh punishment may inhibit undesired behaviors, but at great psychologic cost. Children mimic the corporal punishment that they receive; children who are spanked will have more aggressive behaviors later. Whereas spanking is the use of force, externally applied, to produce behavior change, **discipline** is the process that allows the child to internalize controls on behavior. Alternative discipline strategies should be offered, such as the "countdown," along with consistent limit setting, clear communication of rules, and frequent approval. Discipline should be immediate, specific to the behavior, and time-limited. Time-out for approximately 1 min/yr of age is very effective. A kitchen timer allows the parent to step back from the situation; the child is free when the timer rings.

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Chapter 13

Middle Childhood

Susan Feigelman

Middle childhood (6-11 yr of age) is the period in which children increasingly separate from parents and seek acceptance from teachers, other adults, and peers. Children begin to feel under pressure to conform to the style and ideals of the peer group. Self-esteem becomes a central issue, as children develop the cognitive ability to consider their own self-evaluations and their perception of how others see them. For the first time, they are judged according to their ability to produce socially valued outputs, such as getting good grades, playing a musical instrument, or hitting home runs.

PHYSICAL DEVELOPMENT

Growth occurs **discontinuously,** in 3-6 irregularly timed spurts each year, but varies both within and among individuals. Growth during the period averages 3-3.5 kg (6.6-7.7 lb) and 6-7 cm (2.4-2.8 in) per year (Fig. 13-1). The head grows only 2 cm in circumference throughout the entire period, reflecting a slowing of brain growth. Myelinization continues into adolescence, with peak gray matter at 12-14 yr. Body habitus is more erect than previously, with long legs compared with the torso.

Growth of the midface and lower face occurs gradually. Loss of deciduous (baby) teeth is a more dramatic sign of maturation, beginning around 6 yr of age. Replacement with adult teeth occurs at a rate of about 4 per year, so that by age 9 yr, children will have 8 permanent incisors and 4 permanent molars. Premolars erupt by 11-12 yr of age (see Chapter 307). Lymphoid tissues hypertrophy, often giving rise to impressive tonsils and adenoids.

Muscular strength, coordination, and stamina increase progressively, as does the ability to perform complex movements, such as dancing or shooting baskets. Such higher-order motor skills are the result of both maturation and training; the degree of accomplishment reflects wide variability in innate skill, interest, and opportunity.

Physical fitness has declined among school-age children. Sedentary habits at this age are associated with increased lifetime risk of obesity, cardiovascular disease, academic achievement, and lower self-esteem (see Chapter 47). The number of overweight children and the degree of overweightness have been increasing, although recently at a slower rate (see Chapter 47). Only 15% of middle and junior high schools require physical education class at least 3 days/wk. One quarter of youth do not engage in any free-time physical activity, despite the recommendation for 1 hr of physical activity per day.

Perceptions of body image develop early during this period; children as young as 5 and 6 yr express dissatisfaction with their body image; by ages 8 and 9 yr many of these youth report trying to diet, often using

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

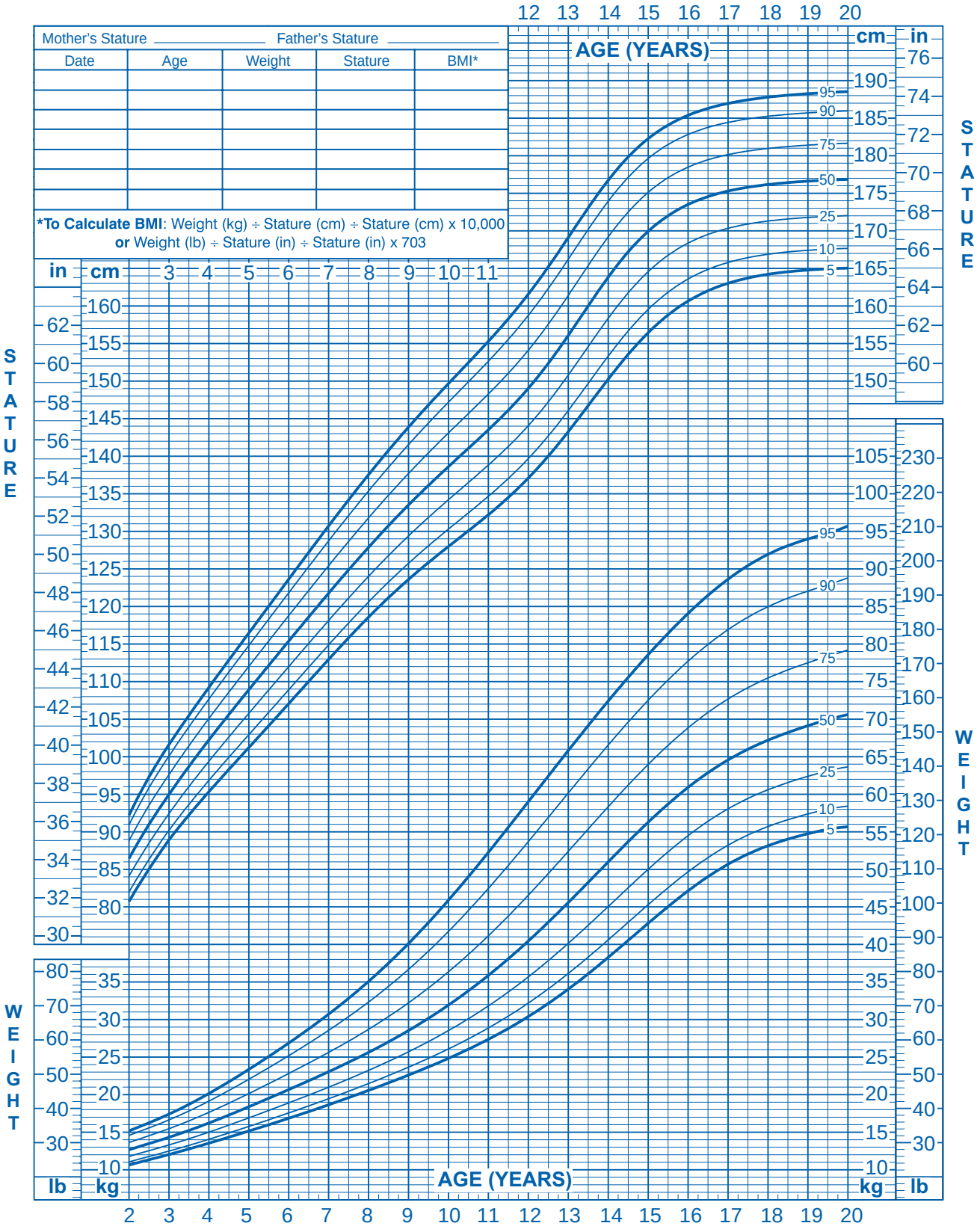
NAME _____

RECORD # _____

Mother's Stature _____ Father's Stature _____

Date	Age	Weight	Stature	BMI*

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

SAFER • HEALTHIER • PEOPLE™

Figure 13-1 Stature (height) for age and weight for boys **(A)** and girls **(B)** ages 2 to 20 years. *(Courtesy the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000. http://www.cdc.gov/growthcharts.)*

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

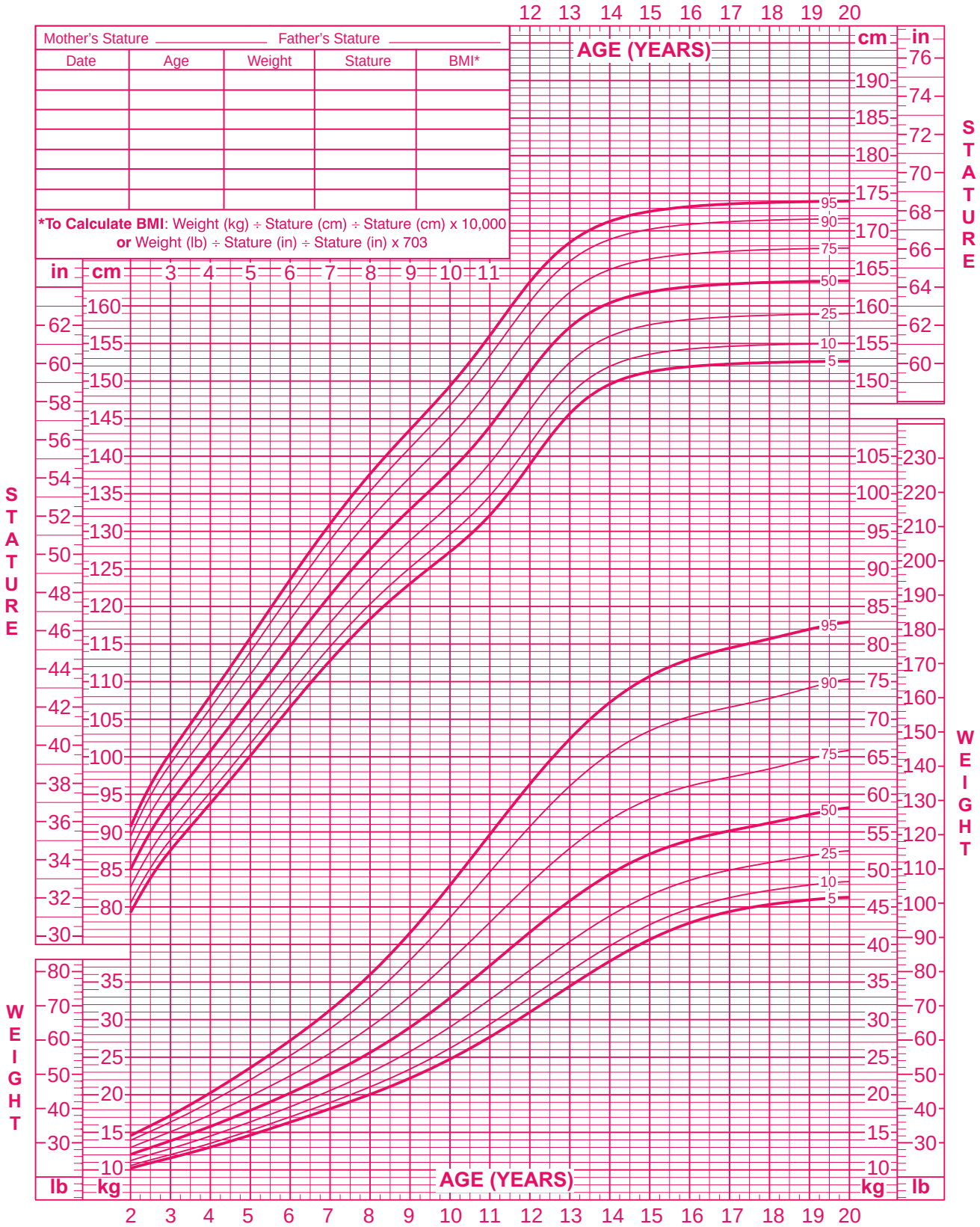
NAME _____

RECORD # _____

Mother's Stature _____ Father's Stature _____

Date	Age	Weight	Stature	BMI*

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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Figure 13-1, cont'd

ill-advised regimens. Loss of control (binge) eating occurs among approximately 6% of children of this age.

Prior to puberty, the sensitivity of the hypothalamus and the pituitary changes, leading to increased gonadotropin synthesis. Interest in gender differences and sexual behavior increases progressively until puberty. Although this is a period when sexual drives are limited, masturbation is common, and children may be interested in differences between genders. Sexual maturity occurs earlier for both genders in the United States. Rates of maturation differ by geography, ethnicity, and country. These differences in maturation have implications for differing expectations of others about them based on sexual maturation.

Implications for Parents and Pediatricians

Middle childhood is generally a time of excellent health. However, children have variable sizes, shapes, and abilities. Children of this age compare themselves with others, eliciting feelings about their physical attributes and abilities. Fears of being "abnormal" can lead to avoidance of situations in which physical differences might be revealed, such as gym class or medical examinations. Children with actual physical disabilities may face special stresses. Medical, social, and psychologic risks tend to occur together.

Children should be asked about risk factors for obesity. Participation in physical activity, including organized sports or other organized activities can foster skill, teamwork, and fitness, as well as a sense of accomplishment, but pressure to compete when the activity is no longer enjoyable has negative effects. Counseling on establishing healthy eating habits and limited screen time should be given to all families. Prepubertal children should not engage in high-stress, high-impact sports, such as power lifting or tackle football, because skeletal immaturity increases the risk of injury (see Chapter 693).

COGNITIVE DEVELOPMENT

The thinking of early elementary school-age children differs qualitatively from that of preschool children. In place of magical, egocentric, and perception-bound cognition, school-age children increasingly apply rules based on observable phenomena, factor in multiple dimensions and points of view, and interpret their perceptions using physical laws. Piaget documented this shift from *preoperational* to *concrete logical operations*. When 5 yr olds watch a ball of clay being rolled into a snake, they might insist that the snake has "more" because it is longer. In contrast, 7 yr olds typically reply that the ball and the snake must weigh the same because nothing has been added or taken away or because the snake is both longer and thinner. This cognitive reorganization occurs at different rates in different contexts. In the context of social interactions with siblings, young children often demonstrate an ability to understand alternate points of view long before they demonstrate that ability in their thinking about the physical world. Understanding time and space constructs occurs in the later part of this period.

The concept of "**school readiness**" has evolved. The American Academy of Pediatrics recommends following an "interactional relational" model in which the focus is on the child, the environment and the interactions therein. This model aid explicitly asserts that all children can learn and that the educational process is reciprocal between the child and the school. The model is developmentally based as it recognizes the importance of early experiences for later development. Rather than delaying school entry, high quality early education programs may be the key to ultimate school success.

School makes increasing cognitive demands on the child. Mastery of the elementary curriculum requires that a large number of perceptual, cognitive, and language processes work efficiently (Table 13-1), and children are expected to attend to many inputs at once. The 1st 2-3 yr of elementary school are devoted to acquiring the fundamentals: reading, writing, and basic mathematics skills. By 3rd grade, children need to be able to sustain attention through a 45 min period and the curriculum requires more complex tasks. The goal of reading a paragraph is no longer to decode the words, but to understand the content; the goal of writing is no longer spelling or penmanship, but composition. The volume of work increases along with the complexity.

Cognitive abilities interact with a wide array of attitudinal and emotional factors in determining classroom performance. These factors include external rewards (eagerness to please adults and approval from peers) and internal rewards (competitiveness, willingness to work for a delayed reward, belief in one's abilities, and ability to risk trying when

Table 13-1 Selected Perceptual, Cognitive, and Language Processes Required for Elementary School Success

PROCESS	DESCRIPTION	ASSOCIATED PROBLEMS
PERCEPTUAL		
Visual analysis	Ability to break a complex figure into components and understand their spatial relationships	Persistent letter confusion (e.g., between *b, d,* and *g*); difficulty with basic reading and writing and limited "sight" vocabulary
Proprioception and motor control	Ability to obtain information about body position by feel and unconsciously program complex movements	Poor handwriting, requiring inordinate effort, often with overly tight pencil grasp; special difficulty with timed tasks
Phonologic processing	Ability to perceive differences between similar sounding words and to break down words into constituent sounds	Delayed receptive language skill; attention and behavior problems secondary to not understanding directions; delayed acquisition of letter-sound correlations (phonetics)
COGNITIVE		
Long-term memory, both storage and recall	Ability to acquire skills that are "automatic" (i.e., accessible without conscious thought)	Delayed mastery of the alphabet (reading and writing letters); slow handwriting; inability to progress beyond basic mathematics
Selective attention	Ability to attend to important stimuli and ignore distractions	Difficulty following multistep instructions, completing assignments, and behaving well; problems with peer interaction
Sequencing	Ability to remember things in order; facility with time concepts	Difficulty organizing assignments, planning, spelling, and telling time
LANGUAGE		
Receptive language	Ability to comprehend complex constructions, function words (e.g., if, when, only, except), nuances of speech, and extended blocks of language (e.g., paragraphs)	Difficulty following directions; wandering attention during lessons and stories; problems with reading comprehension; problems with peer relationships
Expressive language	Ability to recall required words effortlessly (word finding), control meanings by varying position and word endings, and construct meaningful paragraphs and stories	Difficulty expressing feelings and using words for self-defense, with resulting frustration and physical acting out; struggling during "circle time" and in language-based subjects (e.g., English)

success is not ensured). Success predisposes to success, whereas failure impacts self-esteem and reduces self-efficacy, diminishing a child's ability to take future risks.

Children's intellectual activity extends beyond the classroom. Beginning in the 3rd or 4th grade, children increasingly enjoy strategy games and wordplay (puns and insults) that exercise their growing cognitive and linguistic mastery. Many become experts on subjects of their own choosing, such as sports trivia, or develop hobbies, such as special card collections. Others become avid readers or take on artistic pursuits. Whereas board and card games were once the usual leisure time activity of youth, video, computer and other electronic games currently fill this need.

Implications for Parents and Pediatricians

Pediatricians have an important role in preparing their patients for school entrance by promoting health through immunizations, adequate nutrition, appropriate recreation and screening for physical, developmental, and cognitive disorders. The American Academy of Pediatrics recommends that pediatric providers promote the "5 Rs" of early education: (1) reading as a daily family activity; (2) rhyming, playing, and cuddling together; (3) routines and regular times for meals, play, and sleep; (4) reward through praise for successes; and (5) reciprocal nurturing relationships,

Concrete operations allow children to understand simple explanations for illnesses and necessary treatments, although they may revert to prelogical thinking when under stress. A child with pneumonia may be able to explain about white cells fighting the "germs" in the lungs, but still secretly harbors the belief that the sickness is a punishment for disobedience.

As children are faced with more abstract concepts, academic and classroom behavior problems emerge and come to the pediatrician's attention. Referrals may be made to the school for remediation or to community resources (medical or psychologic) when appropriate. The causes may be one or more of the following: deficits in perception (vision and hearing); specific learning disabilities; global cognitive delay (mental retardation); primary attention deficit; and attention deficits secondary to family dysfunction, depression, anxiety, or chronic illness (see Chapters 16 and 32). Children whose learning style does not fit the classroom culture may have academic difficulties and need assessment before failure sets in. Simply having a child repeat a failed grade rarely has any beneficial effect and often seriously undercuts the child's self-esteem. In addition to finding the problem areas, identifying each child's strengths is important. Educational approaches that value a wide range of talents ("multiple intelligences") beyond the traditional ones of reading, writing, and mathematics may allow more children to succeed.

The change in cognition allows the child to understand "if/when" clauses. Increased responsibilities and expectations accompany increased rights and privileges. Discipline strategies should move toward negotiation and a clear understanding of consequences, including removal of privileges for infringements.

SOCIAL, EMOTIONAL, AND MORAL DEVELOPMENT

Social and Emotional Development

In this period, energy is directed toward creativity and productivity. Changes occur in 3 spheres: the home, the school, and the neighborhood. Of these, the home and family remain the most influential. Increasing independence is marked by the first sleepover at a friend's house and the first time at overnight camp. Parents should make demands for effort in school and extracurricular activities, celebrate successes, and offer unconditional acceptance when failures occur. Regular chores, associated with an allowance, provide an opportunity for children to contribute to family functioning and learn the value of money. These responsibilities may be a testing ground for psychologic separation, leading to conflict. Siblings have critical roles as competitors, loyal supporters, and role models.

The beginning of school coincides with a child's further separation from the family and the increasing importance of teacher and peer relationships. Social groups tend to be same-sex, with frequent changing of membership, contributing to a child's growing social development and competence. Popularity, a central ingredient of self-esteem, may be won through possessions (having the latest electronic gadgets or the right clothes), as well as through personal attractiveness, accomplishments, and actual social skills. Children are aware of racial differences and are beginning to form opinions about racial groups that impact their relationships.

Some children conform readily to the peer norms and enjoy easy social success. Those who adopt individualistic styles or have visible differences may be teased. Such children may be painfully aware that they are different, or they may be puzzled by their lack of popularity. Children with deficits in social skills may go to extreme lengths to win acceptance, only to meet with repeated failure. Attributions conferred by peers, such as funny, stupid, bad, or fat, may become incorporated into a child's self-image and affect the child's personality, as well as school performance. Parents may have their greatest effect indirectly, through actions that change the peer group (moving to a new community or insisting on involvement in structured after-school activities).

In the neighborhood, real dangers, such as busy streets, bullies, and strangers, tax school-age children's common sense and resourcefulness. Interactions with peers without close adult supervision call on increasing conflict resolution or pugilistic skills. Media exposure to adult materialism, sexuality, substance use and violence may be frightening, reinforcing children's feeling of powerlessness in the larger world. Compensatory fantasies of being powerful may fuel the fascination with heroes and superheroes. A balance between fantasy and an appropriate ability to negotiate real-world challenges indicates healthy emotional development.

Moral Development

Although by age 6 yr most children will have a conscience (internalized rules of society), they vary greatly in their level of moral development. For the younger youth, many still subscribe to the notion that, rules are established and enforced by an authority figure (parent or teacher) and decision-making is guided by self-interest (avoidance of negative and receipt of positive consequences). The needs of others are not strongly considered in decision-making. As they grow older, most will recognize not only their own needs and desires, but also those of others, although personal consequences are still the primary driver of behavior. Social behaviors that are socially undesirable are considered to be wrong. By age 10-11 yr the combination of peer pressure, a desire to please authority figures as well as an understanding of reciprocity (treat others as you wish to be treated) shapes the child's behavior.

Implications for Parents and Pediatricians

Children need unconditional support as well as realistic demands as they venture into a world that is often frightening. A daily query from parents over the dinner table or at bedtime about the good and bad things that happened during the child's day may uncover problems early. Parents may have difficulty allowing the child independence or may exert excessive pressure on their children to achieve academic or competitive success. Children who struggle to meet such expectations may have behavior problems or psychosomatic complaints.

Many children face stressors that exceed the normal challenges of separation and success in school and the neighborhood. Divorce affects nearly 50% of children. Domestic violence, parental substance abuse, and other mental health problems may also impair a child's ability to use home as a secure base for refueling emotional energies. In many neighborhoods, random violence makes the normal development of independence extremely dangerous. Older children may join gangs as a means of self-protection and a way to attain recognition and belong to a cohesive group. Children who bully others, and/or are victims of bullying, should be evaluated, since this behavior is associated with mood disorders, family problems, and school adjustment problems. Parents should reduce exposure to hazards where possible. Because of the risk of unintentional firearm injuries to children, parents should be encouraged to ask parents of playmates whether a gun is kept in

their home and, if so, how it is secured. The high prevalence of adjustment disorders among school-age children attests to the effects of such overwhelming stressors on development.

Pediatrician visits are infrequent in this period; therefore each visit is an opportunity to assess children's functioning in all contexts (home, school, neighborhood). Maladaptive behaviors, both internalizing and externalizing, occur when stress in any of these environments overwhelms the child's coping responses. Due to continuous exposure and the strong influence of media (programming and advertisements) on children's beliefs and attitudes, parents must be alert to exposures from the television and Internet. An average American youth spends over 6 hr/day with a variety of media, and $\frac{2}{3}$ of these children have a television in their bedrooms. Parents should be advised to remove the television from their children's rooms, limit viewing to 2 hr/day, and monitor what programs children watch. The Draw-a-Person (for ages 3-10 yr, with instructions to "draw a complete person") and Kinetic Family Drawing (beginning at age 5 yr, with instructions to "draw a picture of everyone in your family doing something") are useful office tools to assess a child's functioning.

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Chapter 14

Adolescence

See Part XIII, Chapter 110, Adolescent Development.

Chapter 15

Assessment of Growth

Virginia A. Keane

Many biophysiologic and psychosocial problems can adversely affect growth, and aberrant growth may be the first sign of an underlying problem. The most powerful tool in growth assessment is the growth chart (see Figs. 11-1, 11-2, 13-1, and 15-1) used in combination with accurate measurements of height, weight, head circumference, and calculation of the body mass index (BMI).

PROCEDURES FOR ACCURATE MEASUREMENT

Growth assessment requires accurate measurement. Weight, in pounds or kilograms, must be determined using an accurate scale. For infants and toddlers, weight, length, and head circumference are obtained. These measures should be performed with the infant naked, and ideally, repeated measures should be performed on the same equipment. Head circumference is determined using a flexible tape measure run from the supraorbital ridge to the occiput in the path that leads to the largest possible measurement. Length is most accurately measured by 2 examiners (1 to position the child), with the child supine on a measuring board. For older children, the measure is stature or height, taken without shoes, using a stadiometer. Measurements obtained in alternative manners, such as marking examination paper at the foot and head of a supine infant, or using a simple wall growth chart with a book or ruler on the head can lead to inaccuracy that may render the measurement useless. It is essential to compare measurements with previous growth trends, repeat any that are inconsistent, and plot results longitudinally.

DERIVATION AND INTERPRETATION OF GROWTH CHARTS

In 2000, the Centers for Disease Control and Prevention (CDC) published new growth charts, replacing the 1977 version. Modifications since then have not changed the data points. Set 1 includes the 5th to 95th percentiles; set 2, the 3rd to 97th percentiles. These charts contain data from national surveys conducted by the National Center for Health Statistics between 1963 and 1994. Data are representative of the U.S. population, both demographically and in terms of breastfeeding prevalence. Methodologic steps have assured that the increase in the prevalence of obesity has not unduly raised the upper limits of normal. Several deficiencies of the older charts have been corrected, such as the overrepresentation of bottlefed infants and the reliance on a local data set for the infant charts. The disjunction between length and height, when moving from the infant curves to those for older children, no longer exists. The charts include curves for plotting BMI for ages 2-20 yr rather than weight for height, facilitating identification of obesity.

The data are presented in 5 standard gender-specific charts: (1) weight for age; (2) height (length and stature) for age; (3) head circumference for age; (4) weight for height (length and stature) for infants; and (5) BMI for age for children over 2 yr of age (see Fig. 15-1; also see Figs. 11-1, 11-2, and 13-1). The charts are available at http://www.cdc.gov/growthcharts/.

Each chart is composed of percentile curves, representing the cross-sectional distribution of weight, length, stature, head circumference, weight for length, or BMI at each age. The percentile curve indicates the percentage of children at a given age on the *x*-axis whose measured value falls below the corresponding value on the *y*-axis. On the weight chart for boys 0-36 mo of age (see Fig. 11-2*A*), the 9 mo age line intersects the 25th percentile curve at 8.6 kg, indicating that 25% of the 9 mo old boys in the National Center for Health Statistics sample weigh less than 8.6 kg (75% weigh more). Similarly, a 9 mo old boy weighing more than 11.2 kg is heavier than 95% of his peers. The median or 50th percentile is also termed the *standard value,* in the sense that the standard height for a 7 mo old girl is 67 cm (see Fig. 11-2*B*). The weight-for-height charts (see Fig. 11-1) are constructed in an analogous fashion, with length or stature in place of age on the *x*-axis; the median or standard weight for a girl measuring 110 cm is 18.6 kg.

For infants, the revised CDC charts represent observed but not necessarily optimal growth because they still incorporate data from many bottlefed infants. Rates of initiation of breastfeeding in the United States have more than doubled from 26% in 1970 to 74% in 2005, but nationally only 49% continue to breastfeed at 6 mo, and only 27% continue until 12 mo. Compared with current standards, an exclusively breastfed infant would be expected to plot higher for weight in the 1st 6 mo, but relatively lower in the second half of the 1st yr. Awareness of this growth difference should prevent overidentification of growth problems in breastfed infants.

In an effort to set an internationally usable standard for optimal growth in children, the World Health Organization (WHO) released growth charts based on the Multicenter Growth Reference Study for young children in 2006 and for children 5-19 in 2007. Rather than describing the growth of typical children, the Multicenter Growth Reference Study describes the growth of children who are predominantly breastfed and raised under optimal conditions. Six study sites representing 5 continents were included: United States, Brazil, Norway, Ghana, Oman, and India. Use of the WHO charts in developing nations results in identification of many more children as malnourished and eligible for therapeutic feeding programs. Their use in the United States generally results in many fewer infants being identified as underweight (comparison of curves shown in Fig. 15-2), although studies have found overidentification of poor growth even using these curves. The CDC recommends the use of WHO charts for U.S. children from birth to 24 mo. Adoption of these charts in the United States has been slow. Charts are available online at http://www.who.int/childgrowth/standards/en/.

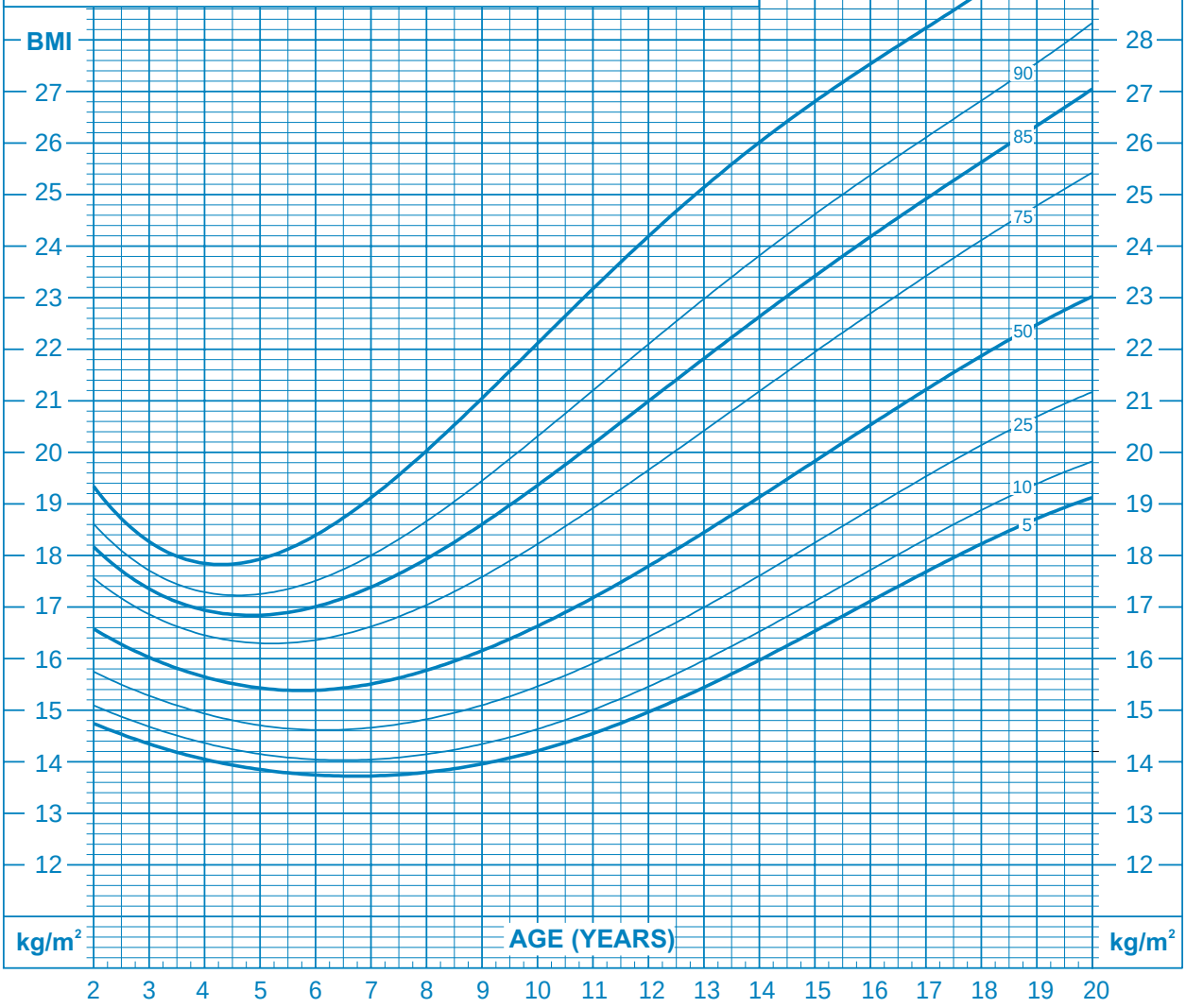
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

A

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Figure 15-1 Body mass index (BMI) percentiles for boys **(A)** and girls **(B)** ages 2-20 yr. *(Official Centers for Disease Control [CDC] growth charts, as described in this chapter. The 85th to 95th percentile is at risk for overweight; >95th percentile is overweight; <5th percentile is underweight. Technical information and interpretation and management guides are available at* www.cdc.gov/nchs. *Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, 2000.* http://www.cdc.gov/growthcharts*)*

Continued

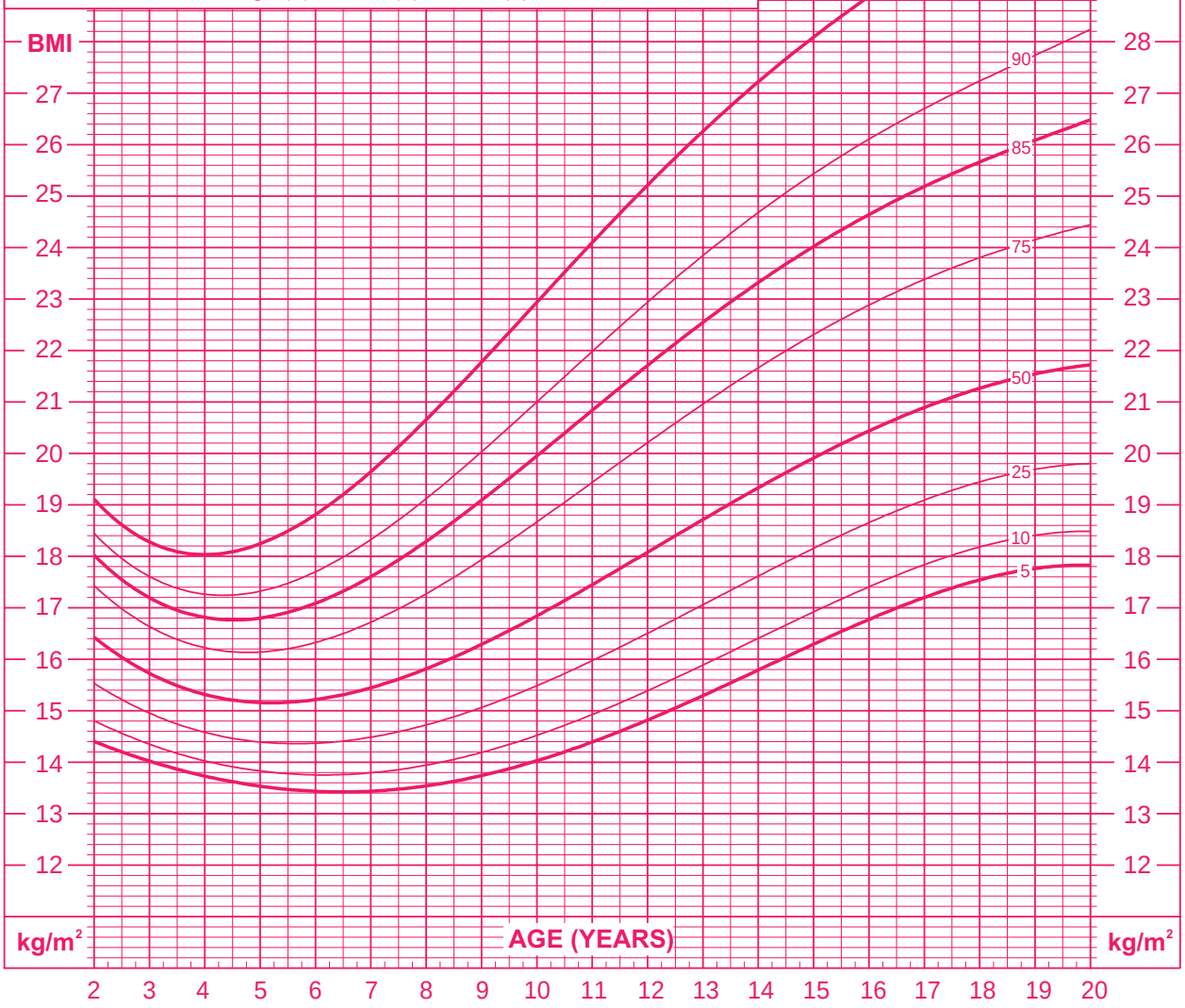
2 to 20 years: Girls
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

B

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Figure 15-1, cont'd

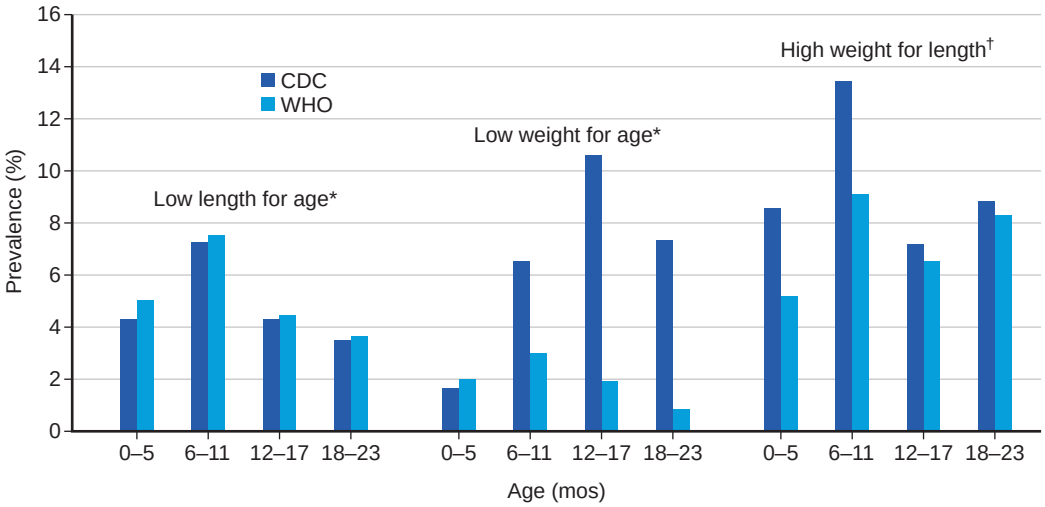

Figure 15-2 Comparison of the WHO and CDC growth chart prevalences of low length for age, low weight for age, and high weight for length among children ages younger than 24 months–United States, 1999-2004. *, ≤5th percentile on the CDC charts; ≤2.3rd percentile on the WHO charts. †, ≥95th percentile on the CDC charts; ≥97.7th percentile on the WHO charts. *(Data from the National Health and Nutrition Examination Survey, 1999-2004; from Grummer-Strawn LM, Reinold C, Krebs NF, Centers for Disease Control and Prevention, Use of World Health Organization and CDC growth charts for children aged 0-59 months in the United States.* MMWR Recomm Rep *59 (RR-9):1-15, 2010, Fig. 6.)*

Table 15-1 Growth and Caloric Requirements

AGE	APPROXIMATE DAILY WEIGHT GAIN (g)	APPROXIMATE MONTHLY WEIGHT GAIN	GROWTH IN LENGTH (cm/mo)	GROWTH IN HEAD CIRCUMFERENCE (cm/mo)	RECOMMENDED DAILY ALLOWANCE (kcal/kg/day)
0-3 mo	30	2 lb	3.5	2.00	115
3-6 mo	20	1.25 lb	2.0	1.00	110
6-9 mo	15	1 lb	1.5	0.50	100
9-12 mo	12	13 oz	1.2	0.50	100
1-3 yr	8	8 oz	1.0	0.25	100
4-6 yr	6	6 oz	3 cm/yr	1 cm/yr	90-100

Adapted from National Research Council, Food and Nutrition Board: Recommended daily allowances, *Washington, DC, 1989, National Academy of Sciences; Frank D, Silva M, Needlman R: Failure to thrive: myth and method,* Contemp Pediatr *10:114, 1993.*

For adolescents, caution must be used in applying cross-sectional charts. Growth during adolescence is linked temporally to the onset of puberty, which varies widely. By using cross-sectional data based on chronological age, the charts combine youth who are at different stages of maturation. Normal variations in the timing of the growth spurt can lead to misdiagnosis of growth abnormalities. The data for 12 yr old boys include both early-maturing boys who are at the peak of their growth spurts and late-maturing ones who are still growing at their prepubertal rate. The net result is to artificially level off the growth peak, making it appear that adolescents grow more gradually and for a longer period than they do. When additional precision is necessary, growth charts derived from longitudinal data, such as the height velocity charts of Tanner and colleagues, are recommended.

Specialized charts have been developed for U.S. children with various conditions, including very-low birthweight and prematurity; Down, Turner, and Klinefelter syndromes; cerebral palsy; and achondroplasia. In addition, growth charts for children of distinct ethnic groups or nationalities may be found on the World Wide Web.

BMI for age complements the standard growth charts for children older than 2 yr of age. BMI can be calculated as weight in kilograms/(height in meters)^2 or weight in pounds/(height in inches)$^2 \times 703$, with fractions of pounds and inches expressed as decimals. Values may be plotted on standard BMI charts (see Fig. 15-1). These calculations can be easily performed electronically using a variety of desktop and handheld devices. BMI percentile varies with age over childhood: a 6 yr old girl with a BMI of 21 is overweight, whereas a 16 yr old girl with the same BMI is just above the 50th percentile.

Electronic medical records (EMRs) include growth charts and usually calculate and plot BMIs. However, the origin of the growth charts that are included in the EMRs used by a pediatrician may be unknown to the pediatrician; consequently, pediatricians are cautioned to contact their EMR company and assure that the CDC and WHO growth charts are available in the EMRs to assure accurate assessment.

Height velocity charts, which evaluate the rate of growth per year, are considered by many to give a more sensitive and specific indicator of abnormal growth. They are used primarily by pediatric endocrinologists. Although many parents think it is important to see growth charts, parents may misinterpret their meaning. Clinicians are cautioned to provide clear interpretation when using growth charts as visual aids.

ANALYSIS OF GROWTH PATTERNS

Growth is a process rather than a static quality. An infant at the 5th percentile of weight for age may be growing normally, may be failing to grow, or may be recovering from growth failure, depending on the trajectory of the growth curve. Infants may lose up to 10% of their birth weight in the 1st wk of life and regain it by the end of the 2nd wk. They will then gain steadily at a rate of 20-30 g/day for the 1st 3 mo. Table 15-1 gives typical growth and calorie requirements for children through age 6 yr. Formulas are available for the estimation of average height

and weight and height for children of various ages, but given their complexity and the easy availability of growth charts, use of the latter is preferable.

Despite the facts that the National Center for Health Statistics charts represent cross-sectional rather than longitudinal data and that children tend to grow in spurts, most children tend to track along a percentile, referred to as *following the curve*. A normal exception commonly occurs between 6 and 18 mo of life. For full-term infants, size at birth reflects the influence of the uterine environment; however, size at 2 yr correlates with mean parental height, reflecting the influence of genes. Between 6 and 18 mo of age, infants may shift percentiles upward or downward toward their genetic potential. Thereafter, most children will track along a growth percentile, with variation within 2 large percentile bands (a small infant might track between the 5th and 25th percentiles, a large one between the 75th and 95th). This tracking often represents the midparental height and a corresponding weight, where **midparental height** is calculated in inches as follows:

- Boys: [(maternal height + 5) + paternal height]/2
- Girls: [maternal height + (paternal height − 5)]/2
- 13 cm (instead of ± 5 in) if using metric units

It is important to correct for various factors in plotting and interpreting growth charts. For **premature infants**, overdiagnosis of growth failure can be avoided by using growth charts developed specifically for this population. A cruder method, subtracting the weeks of prematurity from the postnatal age when plotting growth parameters, does not capture the variability in growth velocity that very-low birthweight infants demonstrate. Although very-low birthweight infants may continue to show catchup growth through early school age, most achieve weight catchup during the 2nd yr and height catchup by 2.5 yr, barring medical complications (see Chapter 97). For children with particularly tall or short parents, there is a risk of overdiagnosing growth disorders if parental height is not taken into account or, conversely, of underdiagnosing growth disorders if parental height is accepted uncritically as the explanation.

The analysis of growth patterns and the detection of aberrant growth patterns provide critical information for the detection of pathologic conditions. Calculation of daily and monthly growth, such as weight gain in g/day (see Table 15-1), allows more precise comparison of growth rate to the norm. Weight loss, or failure to gain normally, is often the first sign of pathology.

The diagnosis of **failure to thrive** (see Chapter 41), usually a diagnosis of children younger than 3 yr of age, is considered if a child's weight is below the 5th percentile, if it drops down more than 2 major percentile lines, or if weight for height is less than the 5th percentile. Weight for height below the 5th percentile remains the single best growth chart indicator of acute undernutrition. A BMI less than the 5th percentile also indicates that a child is underweight. Brief periods of weight loss or poor weight gain are usually rapidly corrected and do not permanently affect size. Children who have been chronically malnourished may be short (stunted) as well as thin, so that their weight-for-height curves may appear relatively normal. Chronic, severe undernutrition in infancy may depress head growth, which may be an ominous predictor of later cognitive disability. Low weight for age or height or weight loss may be referred to as wasting. When growth parameters fall below the 5th percentile, values can be expressed as percentages of the median, or standard, value. A 12 mo old girl weighing 7.1 kg is at 75% of the median weight (9.5 kg) for her age.

Another way to evaluate weight is to determine the ideal body weight for height and compare the current weight to the ideal body weight for length or height. A 15 mo old boy who is 79 cm is at the 50th percentile. The ideal weight is 12 kg. If he weighs 8 kg (<5th percentile), he is 67% of ideal body weight, an indication of severe wasting. Table 15-2 provides interpretation of percent ideal body weight from obese to severe wasting.

Extremes of height or weight can also be expressed in terms of the age for which they would represent the standard or median. For instance, a 30 mo old girl who is 79 cm (<5%) is at the 50th percentile for a 16 mo old. Thus the height age is 16 mo. Weight age can also be expressed this way.

Table 15-2 Interpretation of Percent of Ideal Body Weight

>120%	Obese
110-120%	Overweight
90-110%	Normal variation
80-90%	Mild wasting
70-80%	Moderate wasting
<70%	Severe wasting

Linear growth deficiency (stunting) is more likely to be a result of congenital, constitutional, familial, or endocrine causes than caused by nutritional deficiency (see Chapter 46). In endocrine disorders, length or height declines first or at the same time as weight; weight for height is normal or elevated. In nutritional insufficiency, weight declines before length, and weight for height is low (unless there has been chronic stunting). Figure 15-3 depicts typical growth curves for 4 classes of decreased linear growth. In congenital pathologic short stature, an infant is born small and growth gradually tapers off throughout infancy. Causes include chromosomal abnormalities (Turner syndrome, trisomy 21; see Chapter 81), perinatal infection, extreme prematurity, and teratogens (phenytoin, alcohol) (see Chapter 96). In constitutional growth delay, weight and height decrease near the end of infancy, parallel the norm through middle childhood, and accelerate toward the end of adolescence. Adult size is normal. In familial short stature, both the infant and the parents are small; growth runs parallel to and just below the normal curves.

Obesity affects large numbers of children. Growth charts can confirm an impression of obesity if the weight for height exceeds 120% of the standard (median) weight for height. According to the CDC, a BMI over the 95th percentile indicates obesity and a BMI between the 85th and 95th percentiles indicates overweight. Although widely accepted as the best clinical measure of under- and overweight, BMI may not provide an accurate index of adiposity, because it does not differentiate lean tissue and bone from fat. Measurement of the triceps, subscapular, and suprailiac skinfold thickness can be used to estimate adiposity; considerable experience is needed for accuracy. The *American Academy of Pediatrics Nutrition Handbook,* 6th edition, questions the use of fat folds to estimate total body fat, noting that the method has not been validated in young children and that basic assumptions of the method, that subcutaneous fat is a marker of total fat and that measured sites represent average skin fat thickness, are not true. Other methods of measuring fat, such as hydrodensitometry, bioelectrical impedance, and total body water measurement are used in research, but not in clinical evaluation.

OTHER INDICES OF GROWTH

Body Proportions

Body proportions follow a predictable sequence of changes with development. The head and trunk are relatively large at birth, with progressive lengthening of the limbs throughout development, particularly during puberty. The **lower-body segment** is defined as the length from the symphysis pubis to the floor, and the **upper-body segment** is the height minus the lower-body segment. The ratio of upper-body segment divided by lower-body segment (U/L ratio) equals approximately 1.7 at birth, 1.3 at 3 yr of age, and 1.0 after 7 yr of age. Higher U/L ratios are characteristic of short-limb dwarfism or bone disorders, such as rickets.

Skeletal Maturation

Reference standards for bone maturation facilitate estimation of bone age (see Table 10-3). Bone age correlates well with stage of pubertal development and can be helpful in predicting adult height in early- or late-maturing adolescents. In familial short stature, the bone age is normal (comparable to chronological age). In constitutional delay,

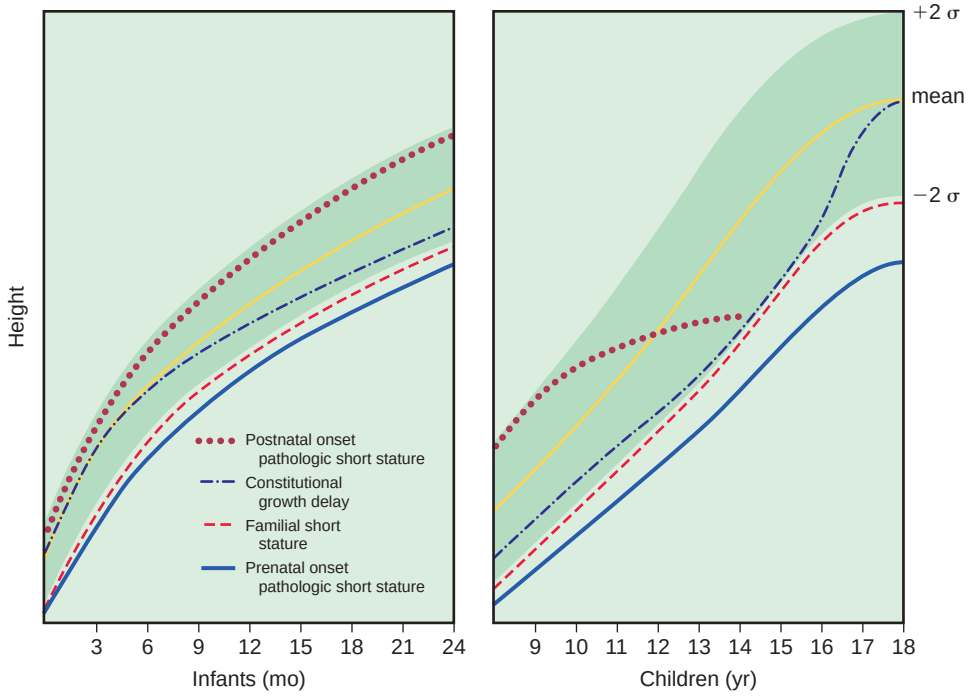

Figure 15-3 Height-for-age curves of the 4 general causes of proportional short stature: postnatal onset pathologic short stature, constitutional growth delay, familial short stature, and prenatal onset short stature. *(From Mahoney CP: Evaluating the child with short stature, Pediatr Clin North Am 34:825, 1987.)*

Table 15-3 Chronology of Human Dentition of Primary or Deciduous and Secondary or Permanent Teeth

	Calcification		Age at Eruption		Age at Shedding	
	BEGINS AT	COMPLETE AT	MAXILLARY	MANDIBULAR	MAXILLARY	MANDIBULAR
PRIMARY TEETH						
Central incisors	5th fetal mo	18-24 mo	6-8 mo	5-7 mo	7-8 yr	6-7 yr
Lateral incisors	5th fetal mo	18-24 mo	8-11 mo	7-10 mo	8-9 yr	7-8 yr
Cuspids (canines)	6th fetal mo	30-36 mo	16-20 mo	16-20 mo	11-12 yr	9-11 yr
First molars	5th fetal mo	24-30 mo	10-16 mo	10-16 mo	10-12 yr	10-12 yr
Second molars	6th fetal mo	36 mo	20-30 mo	20-30 mo	10-12 yr	11-13 yr
SECONDARY TEETH						
Central incisors	3-4 mo	9-10 yr	7-8 yr	6-7 yr		
Lateral incisors	Max, 10-12 mo Mand, 3-4 mo	10-11 yr	8-9 yr	7-8 yr		
Cuspids (canines)	4-5 mo	12-15 yr	11-12 yr	9-11 yr		
First premolars (bicuspids)	18-21 mo	12-13 yr	10-11 yr	10-12 yr		
Second premolars (bicuspids)	24-30 mo	12-14 yr	10-12 yr	11-13 yr		
First molars	Birth	9-10 yr	6-7 yr	6-7 yr		
Second molars	30-36 mo	14-16 yr	12-13 yr	12-13 yr		
Third molars	Max, 7-9 yr Mand, 8-10 yr	18-25 yr	17-22 yr	17-22 yr		

Mand, Mandibular; Max, maxillary.
Adapted from a chart prepared by P.K. Losch, Harvard School of Dental Medicine, who provided the data for this table.

endocrinologic short stature, and undernutrition, the bone age is low and comparable to the height age. Skeletal maturation is linked more closely to sexual maturity rating than to chronological age. It is more rapid and less variable in girls than in boys.

Dental Development

Dental development includes mineralization, eruption, and exfoliation (Table 15-3). Initial mineralization begins as early as the 2nd trimester (mean age for central incisors, 14 wk) and continues through 3 yr of age for the primary (deciduous) teeth and 25 yr of age for the permanent teeth. Mineralization begins at the crown and progresses toward the root. Eruption begins with the central incisors and progresses laterally. Exfoliation begins at about 6 yr of age and continues through 12 yr of age. Eruption of the permanent teeth may follow exfoliation immediately or may lag by 4-5 mo. The timing of dental development is poorly correlated with other processes of growth and maturation. **Delayed eruption** is usually considered when there are no teeth by approximately 13 mo of age (mean + 3 SD). Common causes include hypothyroid, hypoparathyroid, familial, and (the most common) idiopathic. Individual teeth may fail to erupt because of mechanical blockage (crowding, gum fibrosis). Causes of **early exfoliation** include histiocytosis X, cyclic neutropenia, leukemia, trauma, and idiopathic factors. Nutritional and metabolic disturbances, prolonged illness, and certain medications (tetracycline) commonly result in discoloration or malformations of the dental enamel. A discrete line of pitting on the enamel suggests a time-limited insult.

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Chapter 16

Developmental-Behavioral Screening and Surveillance

Frances Page Glascoe, Kevin P. Marks, and Nerissa S. Bauer

The term *developmental–behavioral* refers to children's language, motor, cognitive/academic, self-help, and social–emotional status (a term that also embraces conduct, mental health, attention, and well-being). At well-child visits, development and behavior are the most common topic in parent–professional discussions. Early developmental–behavior problems are common (20-25%) but not benign. Left untreated, early deficits often burgeon into school failure and secondary mental health problems. The consequences include leaving high school before graduating (with rates in inner cities and among minority youth ranging as high as 50%), unemployment, incarceration, and teen pregnancy.

To prevent and address problems, clinicians must screen for existing limitations and risks.

MEASURABLE DELAYS

Among the many types of developmental–behavioral conditions, language problems are the most common (17.5% at 30-36 mo) (see Chapter 35). Delays in language development are often overlooked by healthcare providers, particularly when accurate screening/surveillance tools are not used. Other common conditions are social–emotional/behavioral/mental health disorders (9.5-14.2%), attention-deficit/hyperactivity disorder (7.8%) (see Chapter 33), learning disabilities (6.5%), intellectual disabilities (1.2%) (see Chapter 36), and autism spectrum disorders (0.6-1.1%) (see Chapter 30). Less common conditions include cerebral palsy and other orthopedic/motor impairments (0.23%) (see Chapter 598.1), hearing impairment (0.12%) (see Chapters 636-643), vision impairment (0.8%) (see Chapters 618-635), and conditions associated with disabilities (e.g., Down syndrome and fragile X syndrome [see Chapter 81], traumatic brain injury [see Chapter 68]).

PSYCHOSOCIAL RISK

Many children at risk for school failure lack measurable deficits in early childhood but have markers in the form of multiple risk factors that are strong predictors of future problems. Psychosocial risks include parents with less than a high school education; parental mental health problems such as depression or anxiety; housing or food instability; ethnic or linguistic minority; single parent; 3 or more children in the home; and parenting styles that are neglectful or authoritarian (e.g., highly directive, punitive, limited verbal communication such as talking about children's interests or book-sharing). Such risks eventually lead to developmental–behavioral delays, and result in children entering kindergarten behind their peers, being held back in grade, dropping out of high school, etc. Although psychosocial risk factors are common in children with a history of abuse or neglect, children in many other families are also at-risk.

EARLY INTERVENTION SERVICES AND ELIGIBILITY CRITERIA

If intervention is instituted prior to school entrance, many problems can be prevented and all can be ameliorated. Early intervention takes many forms, requiring varying degrees of intensity.

Developmental–behavioral promotion in primary care is one form of intervention and recommended at all visits. Clinicians identify and intervene with difficulties (e.g., with parent–child interactions and children's behavior), address parents' concerns and provide guidance on child-rearing and other issues. Role-playing, coaching, and verbal advice coupled with take-home information handouts are optimal approaches, although follow-up is needed to determine whether parents capitalized on directives or whether more intensive parent education is needed (e.g., parenting classes). Early intervention in primary care also involves identifying delays, risk factors for future delays, and referring for services more intensive than brief in-office counseling;

For children with psychosocial risk factors but without measurable delays, referrals are needed to a range of services such as Head Start/Early Head Start or quality daycare programs. Families often benefit from parent training classes or mental health interventions and referrals to social work services (e.g., for housing and food assistance, help with domestic violence). Older children with risk factors, benefit from dropout prevention assistance, including after-school tutoring, Boys and Girls Club, summer school, and mentoring programs.

For children with measurable delays (and those at extreme risk such as children in foster care) **referrals are needed to services funded by the Individuals with Disabilities Education Act** (IDEA). Very young children with delays, (i.e., birth to 3 yr of age) are eligible under the broad category of "developmental delay," defined as a single 40% departure or two 25% departures from typical performance in various developmental domains (e.g., receptive language, expressive language, fine motor, gross motor, social–emotional, cognitive/preacademic, and behavior). Because screening measures identify probable strengths and weaknesses but not the extent of deficits, clinicians should refer to IDEA programs for free evaluations to determine eligibility. When children are 3 yr of age, IDEA programs (administered by the public schools) provide detailed evaluations leading to definitive diagnoses and to a range of special education services and adjunctive therapies.

PRIMARY CARE CHALLENGES IN EARLY DETECTION

Despite the serious long-term consequences of psychosocial risk factors, delays and disabilities, only approximately 30% of children with developmental–behavioral problems are detected by primary care providers prior to school entrance, which means that most children with problems miss opportunities for early intervention. There are several reasons for underdetection in primary care:

- **Overconfidence in the effectiveness of informal identification methods** (e.g., ad-hoc questions to parents and milestones checklists such as those embedded in age-specific encounter forms, even if items are drawn from lengthier standardized measures such as the Denver Developmental Screening Test). Informal approaches are of little benefit to patients (or clinicians) because they lack validity, proof of accuracy, and definitive criteria for making referral decisions;
- **Overdependence on clinical judgment and failure to scrutinize the seemingly asymptomatic**. Dysmorphology and organicity are not present in the majority of children with disabilities;
- **Overfocusing on symptoms and thus missing underlying issues**. For example, behavior problems are often the presenting complaint, but many children with developmental deficits act out in frustration due to difficulties understanding what is being asked or expressing thoughts, desires, and feelings in words;
- **Lack of familiarity with and deployment of accurate screening tools effective for busy primary care settings**;
- **An erroneous sense that quality measures take more time than informal approaches**;
- **Excessive optimism about the effectiveness of brief in-office advice when children have measured delays**, and thus deferring rather than referring. Children rarely outgrow developmental–behavioral problems in the absence of intervention;
- **Discomfort at delivering difficult news**. Clinicians require skill at conducting interviews in which difficult news is delivered in a manner that is supportive, positive, and impels families to follow through with recommendations.

POLICIES OF THE AMERICAN ACADEMY OF PEDIATRICS

The American Academy of Pediatrics (AAP) recommends a combination of screening and surveillance at all well-visits.

Screening refers to the administration of brief, standardized, and validated instruments shown to have high sensitivity in detecting children with probable problems and high specificity in determining when children probably do not have problems. Screening for delays should occur across all domains: language (expressive and receptive), motor (gross and fine), cognitive/academic (including features of autism spectrum disorder), self-help, and social–emotional skills (including conduct, attention, and mental health).

Repeated screening compensates for underdetection. Developmental–behavioral problems are a "moving target" and thus require ongoing measurement. Although AAP policies identify specific ages when formal screening should occur (e.g., 9-, 18-, 24- or 30-mo), clinicians should not interpret AAP recommendations to mean that screening/surveillance can cease after 30 mo. Problems (such as language or school readiness) may still be emerging and will not be fully manifested in very young children. The AAP policy states that screening/surveillance should be provided at all well visits and is actively advocating for payers to reimburse for identification efforts with older children.

Although clinicians are often concerned about overidentification, most children with false-positive screens, although ineligible for special education services, have moderate delays in areas predictive of future school failure, that is, language, intelligence, and academic/preacademic skills, along with elevated psychosocial risk. Such children are in need of referrals to other types of intervention programs (e.g., Head Start, after-school tutoring, summer school, and quality preschool or daycare).

Use of accurate screens provides a focus for other well-visit activities. For example, screens relying on parents' concerns identify specific topics for developmental–behavioral promotion. The presence of delays prompts clinicians to conduct a particularly careful physical exam; repeat hearing and vision screening; thoughtfully observe parent–child interactions; take an especially detailed family medical/social history; and similar actions.

Deployment of quality screens provides decision support for the types of interventions needed, including whether clinical advice is sufficient, whether more intensive hands-on services are required, and/or subspecialty medical referrals are needed.

Surveillance refers to ongoing monitoring (tracking over time) of such issues as parental concerns, children's progress with milestones, psychosocial risk and resilience factors, providers' efforts to both detect and address problems, and follow-up regarding child/family outcomes. Surveillance also refers to use of clinical acumen in decision making via the incorporation of screening test results, child/family medical histories, and the physical exam. Repeated accurate screening also serves the tasks of surveillance, but with efficiency and effectiveness. Informal approaches to surveillance are known to be ineffective and of little benefit to families.

OVERCOMING LOGISTICAL CHALLENGES IN PRIMARY CARE EARLY DETECTION AND INTERVENTION

The lists of potential developmental-behavioral topics to be covered at well-child visits are extensive—far more than could be covered in the 14-18 min allotted for such encounters. It is essential to cull topics to those of greatest interest to parents so as to create "the teachable moment" wherein parents are primed to learn most from clinicians' recommendations. Solutions include posters in waiting rooms listing the range of topics on which providers can advise; previsit checklists on which parents indicate topics of interest (and which topics have already been covered in prior visits); and use of use quality screening tests eliciting parents' specific concerns and providing decision support, that is, when advice is probably sufficient vs when referrals are needed.

Clinicians are not always aware of the plethora of services available to families. Approaches to overcome this problem include creating a list of community programs to post in each exam room so that options are visible to parents and providers and encouraging non-medical services to provide prompt feedback on the status of referrals (e.g., establishing two-way consent forms for information sharing), evaluation results and recommendations. Implementing quality screens and patient education in practices requires thoughtful planning and generating enthusiasm among clinic staff who must aid in the process. Clinic flow templates and implementation worksheets are useful tools for establishing efficient implementation procedures.

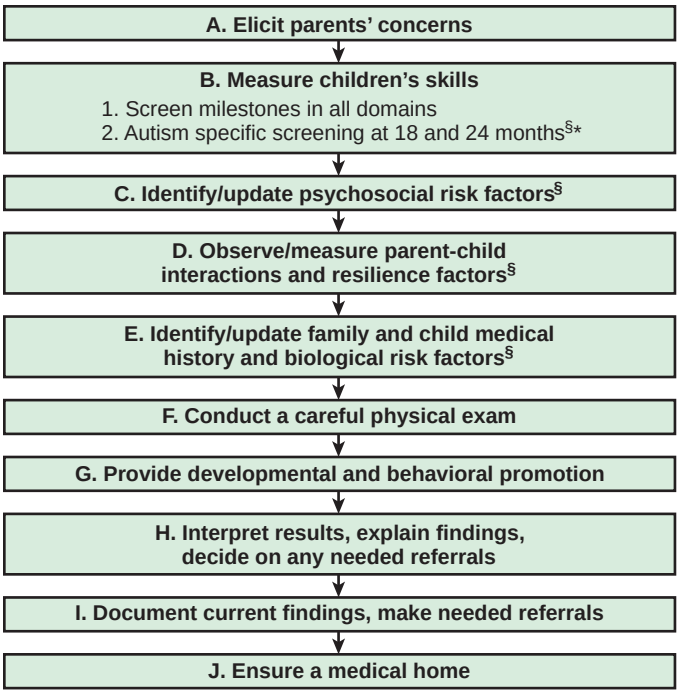

Figure 16-1 Developmental-behavioral surveillance/screening at well-visits with children from birth to 6 yr of age: step-by-step. *(Adapted with permission from Glascoe FP, Marks KP, Poon JK, Macias MM:* Identifying and addressing developmental-behavioral problems: a practical guide for medical and non-medical professionals, trainees, researchers and advocates. *Nolensville, TN, 2013, PEDStest.com, LLC;* http://www.pedstest.com. *Copyright 2013.)*

Evidence-Based Tools

Table 16-1 shows a range of measures useful for early detection of psychosocial risk and resilience, and developmental–behavioral problems, including autism spectrum disorders. Because well-child visits are brief and have enormous agendas (physical exams, immunizations, anticipatory guidance, safety and injury prevention, developmental promotion, and developmental–behavioral screening/surveillance), tools relying on information from parents are ideal because they can be completed in advance of appointments, either online or in writing, whether at home, or while waiting for the encounter to begin. If tools are scored in advance of the patient encounter, clinicians can enter the exam room armed with needed information (e.g., parenting handouts, descriptions of services).

A Workable Process: Step-By-Step

The process of surveillance/screening as drawn from AAP policies is depicted in Figure 16-1 with a description provided in Table 16-2. Many tasks are staggered across visits so that each visit is only minimally burdened with measurement. Red flags are noted in Table 16-3 but are not a substitute for evidence-based screening. Asymptomatic children are those most in need of screening. Those with obvious symptoms simply need referral.

Table 16-2 mentions a range of tools by abbreviations as denoted Table 16-1. The Resources Section (Table 16-4) provides guidance on finding supportive information, practice tools, and the like.

Bibliography is available at Expert Consult.

Table 16-1 Print and Online Tools for Developmental–Behavioral Screening and Surveillance

The following chart is a list of measures meeting standards for screening test accuracy, meaning that they correctly identify, at all ages, at least 70-80% of children with disabilities while also correctly identifying at least 70-80% of children without disabilities. All listed measures were standardized on national samples, proven to be reliable, and validated against a range of diagnostic measures and diagnosed conditions. Not included are measures that fail to meet psychometric standards (limited standardization, absent validation, problematic sensitivity and specificity) such as Denver-II.

The first column provides publication information and the cost of purchasing a specimen set. The "Purpose and Description" column provides details about content and information on alternative ways, if available, to administer measures (e.g., waiting rooms). "Scoring" shows the types of results rendered. The "Accuracy" column shows the percentage of patients with and without problems identified correctly. The "Time Frame/Costs" column shows the costs of materials per visit, along with the costs of professional time (using an average salary of $60/hr) needed to administer each measure, but does not include time needed for generating referral letters. For parent self-report tools, administration time reflects not only scoring of test results, but also the relationship between each test's reading level and the percentage of parents with less than a high school education (who may or may not be able to complete measures in waiting rooms because of literacy problems and thus will need interview administrations).

SCREENS FOR PRIMARY CARE

BEHAVIORAL AND/OR DEVELOPMENTAL SCREENS RELYING ON INFORMATION FROM PARENTS	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Ages & Stages Questionnaires, Third Edition (ASQ-3) (2009). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285. (800-638-3775) ($295.00) www.agesandstages.com. **Training Options:** DVDs for purchase, case examples, and live training **Electronic Options:** See below	1-66 mo	**Purpose:** Screening and surveillance of developmental milestones **Description:** Parents indicate children's developmental skills on 30 items plus overall concerns. The ASQ has a different form (5-8 pages) for each age interval. Written at the 4th–6th grade level. Can be used in mass mail-outs for child-find programs. Manual contains detailed instructions for organizing child-find programs and includes activity handouts for parents. The ASQ-3 is available in English and Spanish; the ASQ-2 is also available in French and Korean with additional translations underway. The ASQ-3 Learning Activities kit is helpful for developmental promotion	Cutoff scores set at 2 SD below the mean, in 5 developmental domains; indicate need for referral or monitoring	**By age:** Sensitivity: 82-89% Specificity: 77-92% **By domain:** Sensitivity: 83% Specificity: 91% **By disabilities:** i.e., cerebral palsy, visual and hearing impairment: Sensitivity: 87%	Scoring time: 2 min Scoring cost: $2.40 Materials: ~$0.36-$0.48 **Total Self-Report: $2.76-$2.88** Interview Time: 12 min. Interview Cost: $14.40 Scoring/Materials: $2.76-$2.88 **Total Interview: $17.28**
Parents' Evaluations of Developmental Status (PEDS). (2013) PEDSTest.com, LLC, 1013 Austin Court, Nolensville, TN 37135 (615-776-4121) ($36.00) www.pedstest.com **Training Options:** offers through its website self-training/train-the-trainer support via downloadable slide shows with notes, case examples, pre-/posttest questions, FAQs, participant handouts, website discussion list (covering all screens), short videos, with some live training available **Electronic Options:** See below	Birth-8 yr	**Purpose:** Screening/surveillance of development/social–emotional/behavior/mental health via parents' concerns **Description:** 10 questions eliciting parents' (and providers') concerns in English, Spanish, Vietnamese and many other languages. Items written at the 5th grade level. Longitudinal Score and Interpretation Forms, assign risk levels, track decision making and offer specific guidance on how to address concerns. Provides screening, longitudinal surveillance, and triage for both developmental and behavioral/social–emotional/mental health problems. PEDS can be used in conjunction with the PEDS:DM (below) for compliance with AAP policies on screening and surveillance, i.e., eliciting and addressing parents' concerns and monitoring milestones	Identifies when to refer and what types of referrals are needed; advise parents; monitor vigilantly; screen further (or refer for screening); or reassure	**By age:** Sensitivity: 91-97% Specificity: 73-86% **By disabilities,** i.e., learning, intellectual, language, mental health, and autism spectrum disorders: Sensitivity: 71-87%	Scoring time: 1 min Scoring cost: $1.20 Materials: $0.39 **Total Self-Report: $1.59** Interview Time: 2 min Interview Cost: $2.40 Scoring/Materials: $1.59 **Total Interview: $3.99**

PEDS: Developmental Milestones (Screening Version) (2008) PEDSTest.com, LLC, 1013 Austin Court, Nolensville, TN 37135 (615-776-4121) ($275.00) *www.pedstest.com* **Training Options:** offers through its website self-training/train-the-trainer support via downloadable slide shows with notes, case examples, pre-/posttest questions, participant handouts, FAQs, website discussion list (covering all screens), short videos, with some live training available. The PEDS:DM manual includes extensive suggestions for training medical students, residents, and nurses **Electronic Options:** See below	Birth-8 yr	**Purpose:** Screening/surveillance of developmental and social–emotional/mental health milestones **Description:** PEDS-DM is designed to replace informal milestones checklists (such as key items from other measures) with evidence. It consists of 6-8 items at each age level. Each item taps a different domain: fine/gross motor, self-help, academics, expressive/receptive language, social-emotional. The PEDS:DM provides screening, triage, and surveillance via a longitudinal score form for tracking milestones progress. Written at the 2nd-3rd grade level and can be completed by self-report, interview, or administered directly to children. Forms are laminated and completed with a dry erase marker. Supplemental measures focused on AAP policy include the M-CHAT, Family Psychosocial Screen, Pictorial PSC-17, the SWILS, the Vanderbilt ADHD scale, and the Brigance Parent-Child Interactions Scale. When combined with PEDS, ensures full compliance with AAP policy. In English, Spanish, Taiwanese, and Portuguese, with other languages in process. The PEDS:DM manual and website contain developmental–behavioral promotion handouts	Pass/fail cutoffs tied to performance above and below the 16th percentile for each item and its domain	**By age:** Sensitivity: 70-94%; Specificity: 77-93% **By developmental domain:** Sensitivity: 75-87%; Specificity: 71-88%	Scoring time: 1 min Scoring cost: $1.20 Materials: $0.02 Total Self-Report: $1.22 Interview Time: 3 min Scoring/Materials: $1.22 Total Interview: $3.82 Direct Admin: 4 min Scoring/Materials: $1.22 Total Direct Admin: $6.10

Parent-report narrow-band screens (for social–emotional/behavioral/mental health, psychosocial risk, and autism spectrum disorder). These are valuable adjuncts in primary care and in other settings but only when preceded by a broadband screen. Narrowband tools should *not* be used as the sole measure of developmental–behavioral status).

NARROWBAND SCREENS RELYING ON INFORMATION FROM PARENTS	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Modified Checklist for Autism in Toddlers (M-CHAT) (1999). Freely downloadable in multiple languages along with the Follow-up Interview at www.mchatscreen.com Also included in print in PEDS: Developmental Milestones. Commercial software vendors must pay a licensing fee **Training Options:** the site contains a guide to the needed follow-up interview for missed items, and houses research papers and reviews on autism spectrum disorder (ASD) screening **Electronic options:** see below	18-47 mo	**Purpose:** Screening for ASDs **Description:** Parent report of 23 yes-no questions written at 4th-6th grade reading level. Screens for ASD. Downloadable scoring template and Excel files for automated scoring. Requires a follow-up interview for failed items (which can be requested by referral sources). Available in multiple languages	Pass/fail scores based on failing at least 2 critical items, or 3 or more noncritical items	**By age and disability**: i.e., autism spectrum disorders: Sensitivity: 90%; Specificity: 99%	Scoring Time: 2 min Scoring costs: $2.40 Materials: $0.06 **Total (Self-Report): $2.46** Interview Time: 5 min (excluding follow-up on any failed items) Interview Cost: $6.00 Scoring/Materials: $2.46 **Total (Interview): $8.46**

Continued

Table 16-1 Print and Online Tools for Developmental–Behavioral Screening and Surveillance—cont'd

NARROWBAND SCREENS RELYING ON INFORMATION FROM PARENTS	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Brief-Infant-Toddler Social-Emotional Assessment (BITSEA) (2006) Pearson/ Psych Corp, Inc.19500 Bulverde Road, San Antonio, TX 78259 (800-627-7271) ($113.75) www.pearsonassessments.com **Training Options:** none **Electronic Options:** None	12-36 mo	**Purpose:** Screening and surveillance of milestones in social–emotional and mental health **Description:** 42 item parent-report measure (with separate forms if clinical observation is needed). Identifies social–emotional/ behavioral. problems and delays in competence. Written at the 4th-6th grade level. Can be followed by the more detailed ITSEA. Available in Spanish, French, Dutch, Hebrew. Has a CD-ROM for ease of scoring and generating reports and referral letters	Cutpoints based on child age and sex show presence/ absence of problems and competence	**By age and disability**: i.e., internalizing, externalizing, and autism spectrum disorders: Sensitivity: 80-95% Specificity: 80%	Scoring Time: 3 min Scoring costs: $3.60 Materials: $1.56 **Total (Self-Report): $5.16** Interview Time: 6 min Interview Costs: $7.20 Scoring/Materials: $5.16 **Total (Interview): $12.36**
Infant-Toddler Checklist (2002). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285. (800-638-3775) ($99.95) www.brookespublishing.com **Training Options:** live training and research support, downloadable slide shows, abstracts, videos, and references at http://firstwords.fsu.edu **Electronic options**: None	6-24 mo	**Purpose:** Screening and surveillance of language and social milestones **Description:** Parents complete the Checklist's 24 multiple-choice questions. Focuses on screening for language, social communication. Examiners are encouraged to observe child to verify parents' answers via brief observation. Reading level is ~ 3rd grade. Can serve as an entry point into the assessment-level CSBS and also as a monitoring tool. Does not screen for motor milestones. In English, Spanish, Slovenian, Chinese, and German	Cutoff scores for each domain: social, speech and symbolic	**By age and disability**: i.e., developmental disabilities: Sensitivity: 78% Specificity: 84%	Scoring time: ~10 min (by hand), ~3 with CD-ROM Observation time: ~5 min Scoring Costs: $3.60-$12.00 Observation Costs: $6.00 Material Costs: $0.12 **Total (Self-Report/Observation)**: $9.72-$18.12 Interview Time: 8 min Interview Costs: $9.60 Scoring/Materials + Observation: $9.72-$18.12 **Total Interview Costs**: $19.32-$28.72
Ages & Stages Questionnaires: Social–Emotional (ASQ:SE) (2002). Paul H. Brookes Publishing Co., Inc., P.O. Box 10624, Baltimore, MD 21285 (800-638-3775) ($225.00) www.agesandstages.com **Training Options**: training DVD live training, webinars, supporting research on website **Electronic options:** See below	3-66 mo	**Purpose:** Screening and surveillance of milestones in social-emotional and mental health **Description:** Companion measure to ASQ-3. ASQ:SE consists of 8 age-specific forms (each 4-6 pages long) with 22-36 items. Items focus on self-regulation, compliance, communication, adaptive functioning, autonomy, affect, and interaction with people. Readability is 5th-6th grade. Includes activities sheets for families. In English and Spanish	Single cutoff score indicating when a referral is needed	**By age and disability:** i.e., social–emotional problems: Sensitivity: 71-85% Specificity: 90-98%	Scoring Time: 2 min Scoring Cost: $2.40 Material Costs: $0.24-$0.36 **Total (Self-Report): $2.64-$2.76** Interview Time: 10 min Interview Cost: $12.00 Scoring/Materials:$2.64-$2.76 **Total (Interview):** $14.64-$14.76
Psychosocial Risk and Resilience Tools: Not all of the measures below are screens (meaning they do not provide definitive cutoffs) but instead assess a broad array of environmental risk and protective/resilience factors that may affect children's developmental/mental health trajectory—well before delays become obvious. Lack of resilience factors or presence of risk factors, even if all aspects of development are typical at the moment, serve as a call to lower thresholds for referral and to consider a wide-range of community services (e.g., Head Start, parent training, parent mental health programs/parents' own healthcare providers, social services)					

SURVEILLANCE TOOLS FOR RESILIENCE, RISK AND MENTAL HEALTH	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Family Psychosocial Screen (FPS) (2000) Included within the AAP Pediatric Intake Form (http://www.brightfutures.org), within PEDS: Developmental Milestones, and freely downloadable at www.pedstest.com/TheBook/Chapter10 **Training Options:** none **Electronic Options:** none	Parent	**Purpose:** screening and surveillance of family psychosocial risk **Description:** A 2-page clinic measure of psychosocial risk factors associated with developmental problems, often used for clinic intake. More than 4 risk factors is associated with developmental delays. The FPS also includes: (a) a 4 item screen for parental history of physical abuse as a child; (b) a 6 item measure of parental substance abuse; (c) a 4 item screen for domestic violence; and (d) a 3 item measure of maternal depression. Can be used along with the Brigance Parent-Child Interaction Scale to view parenting risk and resilience. Readability is 4th grade. In English and Spanish	Refer/no refer to available community resources for each of the 4 screens' risk factors	By condition, i.e., parental depression, substance abuse, etc. Depression (3 items): Sensitivity: 100% Specificity: 88% Parental Substance Abuse (7 items): (a) alcohol abuse sensitivity ~90%; (b) drug abuse sensitivity ~88% Parent history of abusive punishment as a child (4 items): Sensitivity: 92-95%; Specificity: 87-92%	Scoring Time: 3 min Scoring Cost: $3.60 Material Costs: photocopied: $0.12 Laminated: $0.00 **Total (Self-Report): $3.60-$3.72**
Brigance Parent-Child Interaction Scale (BPCIS) (2007) PEDSTest.com, LLC. The BPCIS is included in PEDS: Developmental Milestones and in the Brigance Infant and Toddler Screen. It can be freely downloaded at: http://www.pedstest.com/TheBook/Chapter10 **Training Options:** none **Electronic Options:** none	0-30 mo	**Purpose**: Surveillance of parenting behaviors associated with resilience vs psychosocial risk **Description:** Administered by parent-self report or examiner observation, the 18-19 multiple choice items tap whether parents read and talk with their child, enjoy talking with their child, and perceive him/her as interested in communication, whether parents actively teach their child new things, etc. Certain items are associated with resilience while others are associated with accumulating delays (which start to become visible at 6 mo of age and are striking by 12-18 mo)	Item analysis—discrete sets of items reflect resilience factors associated with typical development while others items reflect limited resilience associated with future or current delays	Not applicable	Scoring Time: 1 min Scoring Costs: $1.20 Materials ~$0.06 **Total (Self-Report): $1.26** Interview/Observation Administration time: ~5 min Interview Admin Costs: $6.00 Materials/Scoring ~$1.26 **Total (Direct Admin): $7.26**
Strengths and Difficulties Questionnaire (SDQ) http://www.sdqinfo.org freely downloadable in multiple languages **Training options:** none **Electronic options:** none	4-17 yr	**Purpose:** Resilience and psychosocial risk for mental health/social–emotional, behavioral skills **Description:** 25 items (youth self-report vs parent or teacher report) tapping positive and negative attributes. Generates indicators for conduct problems, hyperactivity, emotional symptoms, peer problems and prosocial behavior. Produces a total strengths vs total difficulties score. Guidance is available on how to aggregate results for epidemiologic and needs-assessment studies. Cross-cultural research and translations are abundant and norming studies have been conducted in Great Britain, the United States and otherwise in European countries	Comparison of factors	Not applicable	Scoring Time: 5 min Scoring Cost: $6.00 Materials: ~$0.12 **Total (Self-Report): $6.12** Interview time: ~5 min Interview Admin costs: $6.00 Materials/Scoring: ~$0.12 **Total (Direct Admin): $12.12**

Continued

Table 16-1 Print and Online Tools for Developmental–Behavioral Screening and Surveillance—cont'd

SCREENS FOR OLDER CHILDREN (These screens focus on academic skills and mental health, including ADHD screening)

SCREENS FOR OLDER CHILDREN	AGE RANGE	PURPOSE AND DESCRIPTION	SCORING	ACCURACY	TIME FRAME/COSTS
Safety Word Inventory and Literacy Screener (SWILS). From PEDSTest.com, LLC with items courtesy of Curriculum Associates, Inc. The SWILS is included in PEDS: Developmental Milestones (PEDS: DM) and is freely downloadable at: http://www.pedstest.com/TheBook/Chapter9 **Training Options:** none **Electronic Options**: none	6-14 yr	**Purpose**: Screening and surveillance of academic skills **Description:** Children are asked (by parents or professionals) to read 29 common safety words (e.g., high voltage, wait, poison) aloud. The number of correctly read words is compared to a cutoff score. Results predict performance in math, written language, and a range of reading skills. Test content may serve as a springboard to injury prevention counseling and can be used to screen for parental literacy. Because even non-English speakers living in the United States need to read safety words in English, the measure is only available in English	Single cutoff score by age, indicating the need for a referral	**By age/academic deficits**: Sensitivity: 73-88% Specificity: 77-88%	Scoring Time: 1 min Scoring Costs: $1.20 Materials ~$0.06 **Total (Self-Report): $1.26** Administration time: ~7 min Admin/Scoring Costs: $8.40 Materials/Scoring ~$1.26 **Total (Direct Admin): $9.66**
Pediatric Symptom Checklist (PSC) (1991). Freely downloadable in multiple languages in its 30 question version at http://psc.partners.org **The Pictorial PSC** is useful with low-income Spanish and English speaking families and is included in its 17 item factorable version in PEDS: Developmental Milestones and is available at http://www.pedstest.com/TheBook/Chapter9 **Training Options**: none **Electronic Options:** see below	6-18 yr	**Purpose:** Screening and surveillance of emotional/mental health, and conduct. Serves as a necessary prescreen for sorting attention problems from competing conditions **Description:** Administered by youth/parent self-report or by interview. The PSC/Pictorial PSC are 35 short statements of problem behaviors capturing various mental health challenges. The PSC-17/Pictorial PSC-17 are 17 item versions producing cutoffs for attentional, internalizing (meaning depression or anxiety) and externalizing problems (conduct, impulsivity, etc.) Readability is ~2nd grade. In English, Spanish, Portuguese, Chinese, Dutch, Filipino, French, Somali, and several other languages	For the PSC, a single refer/nonrefer score; for the PSC-17/Pictorial PSC-17, cutoffs for attention, internalizing, and externalizing factors	**PSC/Pictorial PSC by disability:** i.e., mental problems of any kind, across numerous studies: Sensitivity: 80-95% Sensitivity: 68-100% **PSC-17/Pictorial PSC-17 by specific disability:** i.e., ADHD: Sensitivity: 58% Specificity: 91% Internalizing Disorders: Sensitivity: 52-73% Specificity: 74% Externalizing Disorders: Sensitivity: 62% Specificity: 89%	Scoring time: 3 min Scoring Cost: $3.60 Materials ~$0.06 **Total (Self-Report): $3.66** Interview Time: 3 min Interview Cost: $3.60 Materials/Scoring: $3.66 **Total (Interview): $7.26**
CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble): (2009). Freely downloadable from the Center for Adolescent Substance Abuse Research http://www.ceasar-boston.org **Training options:** none **Electronic options:** none	Adolescents (11-21 yr)	**Purpose:** To identify substance use (tobacco, alcohol or other drug abuse) in adolescents **Description:** self-/youth-report questionnaire that contains 3 initial screening questions (A1, A2, A3). If the first 3 questions are all answered "no," then providers should routinely ask 1 more question (B1). If 1 or more of the first 3 screening questions is positive/answered "yes," then the provider should ask 6 more questions (CRAFFT: B1, B2, B3, B4, B5 and B6). If the CRAFFT score is 0 or 1 (0 or 1 item answered "yes"), then give brief advice only. If the CRAFFT score is >2, then this is a positive screen and a brief assessment is needed	For scoring, refer to "description" Note: The AAP has published a recommended algorithm for substance abuse screening, assessment and intervention. Must be completed by youth confidentially	Sensitivity: 76-93% Specificity: 76-94% (positive predictive value [PPV] 29-83%) (negative predictive value [NPV] 91-98%) However, there is no cross cultural data (similar to the PSC and Pictorial PSC)	Scoring time: 1-2 min Scoring cost: $1.20-$2.40 Materials ~$0.06 **Total (Self-Report): $1.26-$2.46** Interview time: 3 min Interview cost: $3.60 Materials/Scoring: $3.66 **Total (Interview):** $4.86-$6.06 but higher if further counseling and intervention is needed

ELECTRONIC RECORDS OPTIONS FOR SCREENING AND SURVEILLANCE WITH QUALITY TOOLS

Essential definitions are:

- Tablet PC—approaches that typically require a stylus to select among multiple-choice answers only;
- Keyboards—approaches enabling users select multiple-choice responses but also type in text-based answers to questions
- Touch-screens applications—these often allow parents to listen to questions and response options and then touch a simple response box (e.g., yes/no) thus reducing literacy demands;
- Online—meaning hosted on a website and thus requiring an Internet connection, preferably high speed;
- PDA—personal digital assistant such as a Palm Pilot or Blackberry usually requiring users to be online, with or without a keyboard
- CD-ROM—offline but still electronic, and requiring installation on the user's computer;
- Parent Portal—online applications wherein parents can complete measures but do not see results; instead, these are sent to a different office computer for retrieval/inclusion in electronic records
- Telephony—automated calling, often along with appointment reminder systems through which multiple-choice screens can be administered;
- Data Aggregation—almost all electronic applications create a database either online or on individuals' computers (in the case of CD-ROMs) where all administered screens can be viewed, overall results summarized, etc. Some web-based scoring services provide exported files; (e.g., Excel compatible) to allow users to view overall results. In all such applications, an administrator of multiple sites can view all results
- Webcasts/webinars—These are training options online, either live on a specific day and, eventually constantly available on publishers' websites.

COMPANY/OFFERINGS	TRAINING/SUPPORT OPTIONS	DESCRIPTION AND PRICING
CHADIS: http://www.chadis.com **ASQ, M-CHAT, PSC, and other measures online for touch-screen, tablet PCs, keyboards, telephony and parent portal methods). Spanish language applications coming soon**	Downloadable guides, live training at exhibits, and other training services on request	CHADIS includes decision support for more than 75 both diagnostic and parent/family focused measures, such as the Vanderbilt ADHD Diagnostic Rating Scale, and various parent and adolescent depression, substance abuse, domestic violence and other inventories. CHADIS offers integration with existing electronic healthcare records (EHRs), works with a range of equipment/applications, and automatically generates reports. Pricing is via site license and ~$695 per year per full-time provider. Includes options for Maintenance of Certification (MOC), quality improvement (QI) credit, and e-chapters for clinicians
PEDS Online: http://www.pedstest.com/online PEDS, PEDS:DM, M-CHAT online (for keyboards) in English and Spanish	Slide shows, website FAQs, email support, online videos, discussion list	This site offers PEDS, PEDS:DM, and the MCHAT for keyboard applications (allowing for actual comments from parents). Offers a parent portal (wherein families do not see the results). Scoring is automated as are summary reports for parents, referral letters when needed, and ICD-9/procedure codes. In English and Spanish. Health Level Seven (HL7)/Health Insurance Portability and Accountability Act (HIPPA)/Family Educational Rights and Privacy Act (FERPA) compliant integration with electronic records is available as is data export and aggregate views of records. $2.00-$2.75 per encounter (depending on volume)
Patient Tools: http://www.patienttools.com (M-CHAT, ASQ, ASQ:SE and other measures online for tablet, i.e., touch-screen PCs)	Webcasts/webinars, live support by phone, email	Patient Tools offers the ASQ (with audio option), ASQ:SE (with audio option), MCHAT, PEDS (in a survey version, i.e., closed-ended questions), PSC, the Vanderbilt ADHD Scales and a wide range of behavioral/mental health measures in multiple languages for adolescents and adults. A practice-based approach provides access in the office via dedicated Survey Tablet equipment, wireless tablet PCs and kiosk PC; or online from home with results available in the office. Access fees are $58.00/mo for ongoing hosting, data storage, reporting, custom programming, telephone technical and installation support. Uses client's PCs or alternately Survey Tablet equipment, including rentable docking stations, lease-purchasing arrangements, or software purchase ($1,525) plus hosting and installation ($58.00/mo) with additional licensing fees for some measures
Ages and Stages-3 and ASQ:SE: http://www.ASQonline.com **Online administration and separately on a CD-ROM for offline administration with keyboards and tablet PCs**	Live training, online training	Web-based management system offers automated scoring, reporting, referral tracking, and customizable letters for parents/providers for ASQ-3 and ASQ:SE. ASQ Pro is designed for single-site programs ($149.95 annual subscription, plus quarterly billing for screens used) and ASQ Enterprise is designed for multisite programs ($499.95 annual subscription, plus quarterly billing for screens used). Online questionnaire completion available through ASQ Family Access ($349.95 annual subscription). ASQ Family Access provides secure, customizable website for parent completion of questionnaires, i.e., a parent portal ($349.95 for an annual subscription plus $79.95 for annual support)

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Table 16-2 Annotated Description of Screening/Surveillance in Primary Care

A. **Elicit Parents' Concerns**

At every visit, it is crucial to identify the parent/patient agenda, preferably prior to the encounter, so that clinicians can best prepare for the topics at hand. Informal questions to parents are rarely effective at eliciting their unique issues and do not render the decision support needed to discern which concerns are predictive of problems and which can be addressed with information and monitoring. It is best to use a standardized, validated screening/surveillance measure such as PEDS which is also known to reduce problematic "oh, by the way" concerns, increase the likelihood of attendance at subsequent well-visits, and encourage referral uptake.

B. **Measure/Monitor Children's Skills**

1. Use a broadband milestones-focused screen such as the ASQ or PEDS:DM starting at 6-9 mo and at subsequent well-visits.
2. Use an autism-specific screen such as the M-CHAT at 18 and 24 mo and whenever clinical observation or parents' concerns are worrisome. The requisite M-CHAT Follow-Up Interview (used after a failed M-CHAT) can become a request to referral sources.

Note 1: If using a broadband milestones-focused screen such as the ASQ that does not cover social–emotional/mental health skills, additional screens (e.g., ASQ:SE) should be administered when problems arise and otherwise periodically. When time is limited, referral sources can assist with further evaluations.

Note 2: Use of accurate parent-completed tools prior to the visit is particularly efficient (e.g., from home via electronic screening services, on waiting or exam room computers, paper-pencil, or by staff/clinician interview). As with eliciting parents' concerns, having results available before the encounter gives clinicians an opportunity to prepare referral and/or patient education information.

C. **Measure/Monitor Psychosocial Risk Factors**

At the initial/intake visit (typically the 1st wk of life), a measure such as the Family Psychosocial Screen (FPS) is useful for identifying psychosocial and other risk factors (e.g., substance abuse, domestic violence, housing and food instability, parents' education levels, parental mental health and social support). Four or more risk factors, in the absence of intervention, generally lead to substantial declines in developmental–behavioral status. The FPS also contains a 3-item parental depression screen that should be readministered twice in the 6-15 mo age range to identify and address issues with postpartum dysthymia.

D. **Measure/Monitor Parent–Child Interactions (Resilience Factors)**

Protective (also called resilience) factors are the positive parent–child interactions that promote developmental and behavioral skills (e.g., when parents actively and age-appropriately teach children new things, label objects of interest, share books, and converse with their child [including back-and-forth sound play in infancy, playing peek-a-boo, etc.]). Positive interactions often eclipse psychosocial risk factors and so it is helpful to measure both at the same time. A dearth of positive interactions takes a long-term toll on developmental–behavioral status with marked differences appearing as early as 12-mo of age. Although clinicians sometimes have opportunities to observe parent–child interactions, it is often easier to ask parents to complete a measure such as the Brigance Parent-Child Interactions Scale (BPCIS). Administration at 6 and again at 15 mo is recommended, along with parenting guidance and referrals for parent training when parents have not benefited from in-office advice.

E. **Identify/Update Family and Child Medical History and Biologic Risk Factors**

Child's Medical History: Note in utero exposure to teratogenic/harmful substance, Apgar score less than 5 at 5 min, late or moderate preterm (>32 0/7 to 36 6/7 wk gestational age), very preterm (<32 wk gestational age, low birthweight (<2,500 g), very-low birthweight (<1,500 g), small for gestational age, in utero growth retardation; child's history of: obesity, diabetes, or hypertension, congenital hydrocephalus, meningomyelocele, interventricular hemorrhage (grade III or IV), respiratory distress syndrome, anoxic brain injury, encephalopathy, genetic, metabolic or neurodevelopmental disorder with a high probability of a developmental delay, failure to thrive, iron-deficiency anemia, elevated blood lead level, vision or hearing impairment, HIV, congenital heart disease, obstructive sleep apnea, seizure disorder, etc.

Family Medical/Developmental History: Note any family history of language impairment, learning or intellectual disabilities, autism spectrum disorders, motor disorder, fragile X syndrome, attention-deficit/hyperactivity disorder, mental illness including anxiety disorder, major depression, bipolar disorder, history of deafness, genetic or metabolic disorder**s**, cataract, retinoblastoma, retinal dysplasia, or glaucoma.

In most states, children are automatically eligible for IDEA services if they have a diagnosed condition involving biologic/medical risk factors. In some states, IDEA programs serve children whose parents are mentally ill, intellectually disabled, as well as children in foster care because of a history of abuse or neglect.

F. **Conduct a Careful Physical Exam**

Identify any chronic respiratory or allergic illness, recurrent otitis, head trauma, and sleep problems including symptoms of obstructive sleep apnea. Attend to known symptoms of developmental–behavioral problems, including growth parameters, head shape, and circumference, especially in light of prior visits (e.g., failure to thrive, microcephaly or markedly decelerating head circumference, markedly accelerating head circumference or macrocephaly), facial and other body dysmorphology symptomatic of genetic conditions, eye findings (e.g., cataracts in various inborn errors of metabolism), vascular markings, testicular volume, and signs of neurocutaneous disorders (e.g., >6 café-au-lait spots in neurofibromatosis, hypopigmented macules in tuberous sclerosis), Lisch nodules, ash leaf macules, etc. Neurodevelopmental assessment should include muscle strength, joint laxity, tone, presence of abnormal reflexes, and disturbance of movement.

Focus carefully on physical findings suggestive of abuse or neglect and ensure prompt referrals to social work services.

Newborn hearing screening is essential but even the asymptomatic need follow-up with otoacoustic emissions (OAE) beginning at 6-mo of age and thereafter, as well as tympanometry to evaluate of middle ear pathology. Failed OAEs regardless of middle ear status require an axiomatic referral to an audiologist.

Assess vision at every visit: (a) Abnormal red reflex (may indicate cataract, glaucoma, retinoblastoma, retinal abnormality, or strabismus, or unequal or high refractive error); (b) abnormal ocular alignment (i.e., strabismus) or asymmetrical corneal light reflex; (c) pupillary asymmetry of ≥1 mm (suggestive of neurologic condition); (d) corneal asymmetry (suggestive of glaucoma); (e) unilateral ptosis or other lesions obstructing the visual axis (e.g., eyelid hemangioma), which may cause amblyopia; and (f) nystagmus. For children 3-4 yr of age, measures of visual acuity are needed for which the Lea Symbols are helpful because letter naming is not required. At age 5-6 yr, Snellen Eye Charts can be used. Prompt referral to a pediatric ophthalmologist is warranted when acuity is less than 20/40 in children ages 3-5 yr, or 20/30 in children >6 yr.

Lead screening should be provided whenever developmental–behavioral problems arise, but preferably for all children. Lead screening should be repeated at several points during the 0-6 yr age range. Children living in older homes, near busy streets, with pica, or recently immigrated are at particular risk, as are those who play with adult makeup.

Many of the above findings will automatically qualify children for IDEA Part C programs (birth-3) and so referral for early intervention should be axiomatic in such cases.

Table 16-2 Annotated Description of Screening/Surveillance in Primary Care—cont'd

G. **Provide Developmental–Behavioral Promotion**

Whether or not screening/surveillance identifies problems, parents always need suggestions for what to do at home. The specifics of their concerns should be addressed with parenting information, advice on age-appropriate activities, and anticipatory guidance focused on how developmental changes affect health and safety (e.g., a baby about to crawl will find, mouth, and probably swallow small objects left under furniture). All parents need to be encouraged to promote their child's language and preacademic/academic development. This is most easily accomplished with written patient education materials, by encouraging parents to visit websites with quality information, participating in Reach and Read, or by parent training classes, group well visits, or social work services. A well-organized system for filing and retrieving parent-focused materials is essential (see Table 16-3 for resources). Follow up with families, in 6-8 wk to assess the effectiveness of promotion activities, especially in-office advice about behavior and social skills. If less than successful, encourage parents to engage in more intensive services (e.g., parenting classes, family therapy). Information and referral resources are listed under the Resources section for this chapter.

H. **Interpret Results, Explain Findings, Decide on Any Needed Referrals**

Refer those at psychosocial risk and those with an absence of protective factors for Head Start/Early Head Start, quality daycare, or evidence-based parent-training programs. For all children with positive screens, refer to IDEA programs. Additionally, refer to autism specialty clinics if indicated.

Consider whether medical subspecialty referrals are needed. Electroencephalograms and neuroimaging are not routinely indicated but might be used if there is clinical suspicion of a seizure disorder, hydrocephalus, micro- or macrocephaly, encephalopathy, neurofibromatosis, tuberous sclerosis, brain tumor, or other neurologic problem (not including autism). Extreme handedness at an early age and persistence of fisting after 4 mo is another indicator of potential neuron migration disorders requiring imaging. Uncommonly, surveillance may indicate a need for additional metabolic screens, such as serum electrolytes and glucose, venous blood gas, serum ammonia, urine glycosaminoglycans, endocrine screens (e.g., thyroid-stimulating hormone, free thyroxine), creatinine kinase (CK), genetic testing (chromosomal analysis, DNA for fragile X, etc.), or screens for an infectious disease (e.g., HIV antibody testing, TORCH [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex] infection testing). Because of the need to discern which tests are needed, referral to a developmental–behavioral or neurodevelopmental pediatrician is wise.

Gather referral information and then explain results to families. Sit down with them and describe referrals in a positive light (e.g., "There is much we can do to help."). Avoid diagnostic labels because in all cases, further evaluation will be provided by referral services. Use euphemisms (e.g., "seems behind others," "seems to be having difficulty with") but use language strong enough that parents will take your concerns seriously. If at all possible, provide a take-home summary report. Most online screening services generate these automatically.

I. **Document Findings and Make Referrals**

A carefully constructed well-visit age-specific encounter form should have space to indicate measures administered and results. A longitudinal problem checklist should be used to briefly document results over time, intervention recommendations, (and will also help identify which measures are needed and when). Billing and coding for optimal reimbursement is essential (in many states, developmental–behavioral screening when coded properly, incurs separate reimbursement). A referral letter is also needed that can be shared with other programs. Be sure to document not only screens administered, results and observations but also health, hearing, and vision status; IDEA requires such information before evaluating children further. Online screening services generate referral letters and thus save a great deal of practice time and expense. If at all possible, make appointments for families because this greatly increases uptake. For examples of age-specific encounter forms, referral letters, and take-home parent summary reports, see www.pedstest.com/thebook.

J. **Ensure a Medical Home**

Children with health and developmental–behavioral problems often receive splintered care with little oversight from primary care providers who, in fact, should be the center of care coordination. Many families do not seek services in a timely manner and so it is critical to establish follow-up dates (e.g., on a longitudinal problem checklist) to determine whether recommendations were followed and whether additional screening or other encouragement is needed.

Establishing communication mechanisms with IDEA and other referral services is helpful so that personnel offer prompt updates on whether appointments were kept, results of further testing, and eligibility for services. Be aware that some referrals will not result in service eligibility due to deficits of insufficient severity. Note that in some, but not all states, IDEA programs for the birth-3 yr age-range can provide ongoing monitoring of ineligible children and suggest to parents other helpful resources. Prompt feedback on the issue of eligibility and ongoing monitoring is needed so that clinicians can refer to other types of intervention programs (e.g., quality daycare, Head Start, parenting training).

In any case, make sure to collaborate with non-medical services by establishing 2-way consent forms for sharing information. Clinicians should also identify communication preferences (e.g., by email, fax, or telephone [including available hours]) and the kind of information to be sent (e.g., evaluation reports, status updates, individual educational plans). Collaboration is facilitated if providers agree to advise intervention programs about medical conditions and medical interventions that may be needed at school.

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Table 16-3 Red Flags in Developmental Screening and Surveillance

These indicators suggest that development is seriously disordered and that the child should be promptly referred to a developmental or community pediatrician.
Note: Most children do not have "red flags" and thus require quality screening to detect any problems.

POSITIVE INDICATORS (THE PRESENCE OF ANY OF THE FOLLOWING)
Loss of developmental skills at any age
Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment at any age (simultaneous referral to pediatric ophthalmology)
Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose, and throat assessment)
Persistently low muscle tone or floppiness
No speech by 18 mo, especially if the child does not try to communicate by other means such as gestures (simultaneous referral for urgent hearing test)
Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone
Persistent toe walking
Complex disabilities
Head circumference above the 99.6th centile or below 0.4th centile. Also, if circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to parental head circumference
An assessing clinician who is uncertain about any aspect of assessment but thinks that development may be disordered

NEGATIVE INDICATORS (ACTIVITIES THAT THE CHILD CANNOT DO)
Sit unsupported by 12 mo
Walk by 18 mo (boys) or 2 yr (girls) (check creatine kinase urgently)
Walk other than on tiptoes
Run by 2.5 yr
Hold object placed in hand by 5 mo (corrected for gestation)
Reach for objects by 6 mo (corrected for gestation)
Point at objects to share interest with others by 2 yr

From Bellman M, Byrne O, Sege R: Developmental assessment of children. BMJ *346:31–36, 2013.*

Table 16-4 Resources for Developmental–Behavioral Screening/Surveillance in Primary Care

DEVELOPMENTAL–BEHAVIORAL PROMOTION AND PARENT TRAINING
Kids' Health
From the Nemours Foundation, this site has a well-visit guide for each age, anticipatory guidance information, and an easily searchable database for handouts (in English and Spanish) on health and safety, emotional and social development and positive parenting for babies through adolescence.
Reach Out and Read
Offers parenting handouts on how to share books, literacy milestones, and guidance for professionals. Tabs within the site include: Parents and Educators Home, Importance of Reading Aloud, Literacy Milestones, Reading Tips, Books for Children, and Books for Parents.
American Academy of Pediatrics (Information for Families)
The AAP has numerous handouts that can be downloaded for free and available in multiple languages. Provides information on a variety of topics including health conditions, safety and prevention, mental health issues from birth through adolescence.
American Academy of Child and Adolescent Psychiatry
AACAP was one of the first professional organizations to develop handouts for families. These are freely downloadable and cover a wide range of topics as divorce, sleep problems, specific mental health diagnoses, help for military families, and how and where to find a psychiatrist. Handouts are written in many different languages including Spanish, Malaysian, Urdu, Arabic, Icelandic, Polish, and Hebrew. Other site research reviews for professionals, video clips, and links to other resources.

REFERRAL LINKS
American Academy of Pediatrics: Find a Pediatrician
Helps locate developmental–behavioral, neurodevelopmental, general and other subspecialty pediatricians.
Individuals with Disabilities Education Act
Provides links to state, regional and local early intervention programs under the Individuals with Disabilities Education Act, and testing services for young children with suspected or known to have disabilities go to
Early Head Start and Head Start
Provides links to local programs including services for migrant workers, tribal councils, etc.

INTERVENTION SERVICES FOR OLDER CHILDREN
To refer children 3 yr of age and older for evaluations, contact the school district's department of psychology or special education.
For after school/tutoring programs, check with the child's school of zone, and see the websites of the **Boys and Girls Club** and the **YWCA.**

TRAINING AND IMPLEMENTATION PLANNING
Medical Home Initiative
From the AAP and focused on coordinated care for children with special healthcare needs, the site has training materials, rating scales, an e-mail announcement list for providers, how-to information, etc. Medical Home also sponsors several conferences each year.
Harvard University
Includes a helpful video showing providers who, although reluctant to try quality screening, found use of tools far more sensitive and less than time-consuming. The site also provides a helpful implementation guide.
PEDStest.org
Includes downloadable implementation planning forms, workflow charts, two-way consent forms, longitudinal problem checklists, age-specific encounter forms, training guides, slide shows, freely downloadable risk and resilience measures, mental health and academic screens for older children, videos offering a rationale for screening, information about tools, guidance on billing and coding, and links to parenting resources in multiple languages.

Table 16-4 Resources for Developmental–Behavioral Screening/Surveillance in Primary Care—cont'd

ADDITIONAL RESOURCES

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Chapter 17

Childcare: How Pediatricians Can Support Children and Families

Laura Stout Sosinsky and Walter S. Gilliam

In the United States, 61% of all children younger than 5 yr—12.5 million children—were in regular childcare in 2011. Large proportions of young children are in childcare at all ages, with more children entering care as they get older; the majority of children 3 yr of age or older are in regular childcare. Young children of employed mothers spend on average 36 hr per wk in a childcare arrangement.

Childcare is affected by many factors, which derive from family demand, childcare supply, and child and family policy. With increasing movement of mothers into the workplace across the globe, the prime reason most families use childcare is to support maternal employment. At childbirth, unpaid maternity leave is the typical solution among U.S. mothers. The U.S. federal leave program allows for 12 wk of unpaid job-protected leave during pregnancy or after childbirth, but only covers approximately 50% of the workforce, as companies with <50 employees, part-time employees, and those working in informal labor markets are exempt. Four states and the District of Columbia have passed paid family leave laws. In part because of the financial burden of an unpaid maternity leave, many mothers return to work and their children begin childcare very young, sometimes in the 1st few wk after birth. In a 2000 Family and Medical Leave Act survey, only 10% of respondents reported taking more than 60 days for maternity leave. Approximately 44% of mothers in 2005-2007 were working by the time their first child was 3-4 mo of age, and approximately 63% of mothers were working by the time their first child was 12 mo of age. Some mothers face work requirements if they are receiving public benefits given the reforms to welfare passed by Congress in 1996. Many mothers feel strong financial motivation or even pressure to work, especially in single-parent households, or have strong incentive to work for short- and long-term financial security, interest and preference, or all of these. Maternal employment is not the only factor driving childcare use, as young children of unemployed mothers spend on average 21 hr per wk in childcare. Many parents want their children to have childcare experiences for the potential benefits early learning environments can give to their children, particularly preschoolers. Given these realities, childcare quality is of great concern, yet the quality of childcare and early education environments varies widely and the supply of high-quality childcare is largely deemed inadequate.

PROVISION AND REGULATION OF CHILDCARE IN AMERICA

Childcare Settings

Childcare settings vary widely and fall into 4 broad categories, here listed from the least to the most formal:

- Relative care;
- In-home nonrelative care such as nannies, babysitters, or au pairs;
- Family childcare, in which the caregiver provides care in her own home for up to 6 young children often including children of mixed ages, siblings, or the provider's own children; and
- Center-based care, provided in nonresidential facilities for children grouped by age.

Parents more often utilize home-based care for infants and toddlers, partly because of greater preference, flexibility, and availability, and sometimes because of lower cost. Use of center-based childcare is greater among preschoolers (children 3-5 yr old). Childcare centers and early education programs are administered by a wide array of businesses and organizations, including for-profit independent companies and chains, religious organizations, public and private schools, community organizations, cooperatives, and public agencies. Preschool programs (e.g., Head Start, prekindergarten) also may play an important role in childcare. Although early education programs may have a greater focus on educational activities and often only provide limited hours of care per days, the health and safety issues involved with preschool programs are similar to those presented by other group childcare settings.

Childcare Licensing, Regulation, and Accreditation

Licensing and regulatory requirements for the most part mandate basic health and safety standards, such as sanitary practices, child and provider vaccinations, access to a healthcare professional, and facilities and equipment safety, as well as basic structural and caregiver characteristics, such as the ratio of children to staff, group sizes, and minimum caregiver education and training requirements. Most childcare centers and preschools and many family daycare providers are subject to state licensing and regulation. As of this writing, with the exception of Idaho, all states regulate centers, as does the District of Columbia (for the most recent data, see http://www.naralicensing.org/Licensing). Most states also regulate family childcare providers, although some states only license specific types of family childcare homes, and 3 states do not license these providers at all (Idaho, Louisiana, and New Jersey). Seven states (Arizona, Idaho, Louisiana, New Jersey, Ohio, South Dakota, and Virginia) do not license small family childcare homes, and 11 states (Arkansas, Idaho, Kentucky, Louisiana, Maryland, Maine, North Carolina, New Jersey, Vermont, Washington, and Wisconsin) and the District of Columbia do not license large/group family childcare homes. Louisiana has a registration process for family childcare homes with no more than 6 children, but registration is only required when the provider cares for children subsidized by the federal Childcare and Development Fund (which assists low-income families receiving temporary public assistance, or those needing childcare in order to work or receiving training to transition off of public assistance). New Jersey has a voluntary registration process for family childcare homes that is operated by childcare resource and referral agencies in the state.

Many providers are legally exempt from licensing standards. Exemptions for various types of programs vary state to state. The smallest homes (3-4 children in care) are typically license-exempt, encompassing relative, friend, and neighbor caregivers as well as babysitters, nannies and au pairs. These providers fall outside of any regulatory scrutiny, and some may not even think of themselves as offering "childcare"; 31% of 9 mo olds and 22% of 2 yr olds may be in small home-based care settings (3 or fewer children). Fewer are cared for in large home-based settings (4 or more children), typically by nonrelatives. Small family childcare homes are exempt if there are a small number of children in care in 26 states, and large/group family childcare homes are exempt if they are open part-day in 11 states. Unlike exemption rules for homecare providers, which typically are based on size, centers are often exempted if overseen by other organizations such as schools, churches, or local governments, and thus have some external oversight. Many of these entities provide part-day or part-week Head Start or preschool programs, and about half of the states also explicitly exempt such part-time programs. Just 9% of 9 mo olds and 17% of 2 yr olds were cared for in centers. In contrast to care for 4 yr olds (when more than half of children are in center care), few centers caring for younger children were exempt from licensing (35% of centers caring for 4 yr olds were not licensed in contrast to 2% of centers caring for 2 yr olds).

Homes and centers that fall under state licensing guidelines face very different requirements. Size differs greatly between the 2 types of contexts, and such size differences are built into regulations in terms of the maximum number of children that can be cared for in a group and the number of adults that must be present. The most common state-required maximum group size in centers is 8 for infants, 12 for toddlers, and 20 for preschoolers; centers may have numerous classrooms of these sizes. For centers, regulations explicitly state an allowable ratio of children to adults. The most common ratios are 4:1 for infants, 6:1 for toddlers, and 10:1 for preschoolers, meaning that typically there would be 2 adults in a group. States license homes in 2 categories, small and large, with typical maximums of 6 and 12 in the 2 categories (including the provider's own children). More than three-quarters of licensed homes fall within the small category. Thus the total size of a typical home is smaller than just 1 classroom in a center. States less often explicitly lay out child-to-adult ratios for homes, given that many homes involve 1 provider caring for all of the children. Some states restrict the number of younger children that may be in care, or explicitly provide ratios (especially for large homes), although these restrictions vary greatly across states.

Health and safety conditions may be unsatisfactory in unlicensed settings. In most states, licensing and regulatory standards have been found to be inadequate to promote optimal child development, and in many states standards are so low as to endanger child health and safety. Therefore, even licensed providers may be providing care at quality levels far below professional recommendations. A small portion of providers become accredited by National Association for the Education of Young Children (NAEYC), National Association for Family Child Care (NAFCC), or other organizations by voluntarily meeting high-quality, developmentally appropriate, professionally recommended standards. The accreditation process goes far beyond health and safety practices and structural and caregiver characteristics to examine the quality of child–caregiver interactions, which are crucial for child development, as described in the next section. Evidence indicates that childcare programs that complete voluntary accreditation through NAEYC improve in quality and provide an environment that better facilitates children's overall development. Only 10% of childcare centers and 1% of family childcare homes are accredited; this is partly the result of a lack of knowledge, resources, and incentives for providers to improve quality, but it may also be partly because of expenses providers incur in the process of becoming accredited.

State childcare licensing agencies are playing a larger role in various initiatives designed to improve the quality of childcare, working through the infrastructure of the early care and education system. Several states' licensing agencies are part of quality initiatives called quality ratings and improvement systems, such as tiered quality strategies (e.g., tiered reimbursement systems for participating providers who achieve levels of quality beyond basic licensing requirements), public funding to facilitate accreditation, professional development systems, and program assessments and technical assistance.

Sick Children

When children are ill, they may be excluded from out-of-home arrangements, and settings under state licensure are required to exclude children with certain conditions. Guidelines for health and safety in out-of-home care from the American Academy of Pediatrics, the American Public Health Association, and the National Resource Center for Health and Safety in Child Care and Early Education offer recommendations regarding the conditions under which sick children should and should not be excluded from group programs (Table 17-1). State laws typically mirror these guidelines but may be stricter in some states.

Most families need to make arrangements to keep sick children at home (such as staying home from work or having backup plans with an alternative caregiver). Alternative care arrangements outside the home for sick children are relatively rare but may include either (1) care in the child's own center, if it offers special provisions designed for the care of ill children (sometimes called the infirmary model or sick daycare), or (2) care in a center that serves only children with illness or temporary conditions. Although it is important that such arrangements emphasize preventing further spread of disease, one study found no occurrence of additional transmission of communicable disease in children attending a sick center. The impact of group care of ill children on their subsequent health and on the health of their families and community is unknown.

CHILDCARE'S ROLE IN CHILD HEALTH AND DEVELOPMENT

Characteristics of Childcare and Associations with Child Developmental Outcomes

High-quality childcare is characterized by warm, responsive, and stimulating interactions between children and caregivers. In high-quality interactions, caregivers express positive feelings toward their children; are emotionally involved, engaged, and aware of the child's needs and sensitive and responsive to their initiations; speak directly with children in a manner that is elaborative and stimulating while being age-appropriate; and ask questions and encourage children's ideas and verbalizations. Structural quality features of the setting, including ratio of children to adults, group size, and caregiver education and training, act indirectly on child outcomes by facilitating high-quality child–caregiver interactions. It would be difficult for even the most sensitive and stimulating provider to engage in high-quality interactions with each child, if the provider was the sole caregiver of 10 toddlers.

The quality, quantity, type of setting, and stability of childcare experienced by young children contribute to child development. Childcare use by itself does not affect mother–child attachment. Only when combined with low maternal sensitivity and responsiveness does poor-quality childcare, larger quantities of childcare, or multiple childcare arrangements predict greater likelihood of insecure attachment.

Adjusting for family factors (i.e., parental income, education, race/ethnicity, family structure, parental sensitivity) the quality of childcare has a unique and consistent, albeit small, association with child outcomes across most domains of development. The type of childcare setting has unique effects, controlling for quality, with results from numerous studies demonstrating that center-based care is associated with better language and preacademic performance than home-based care. Quantity of care (hours per week) may also have unique effects, but findings are mixed, with some studies demonstrating small associations between greater quantity and elevated behavior problems, and other studies finding no associations for most children. Instability in childcare—over the course of a day, such as with rotating staff or multiple arrangements, or over time, with frequent changes in arrangements—does have negative effects on children's language and internalizing problems. Also, as childcare settings naturally have packages of quality characteristics, which are a mix of lower- and

Table 17-1 Conditions That Do and Do Not Require Exclusion from Group Childcare Settings

CONDITIONS THAT REQUIRE EXCLUSION	COMMENTS
If any of these 3 key criteria for exclusion of children who are ill are met, the child should be temporarily excluded, regardless of the type of illness:	
Illness preventing the child from participating comfortably in activities as determined by the childcare provider	Providers should specify in their policies, approved by the facilities' healthcare consultant, what severity level of illness the facility can manage, and how much and what types of illness will be addressed: • Severity level 1 consists of children whose health condition is accompanied by high interest and complete involvement in activity associated with an absence of symptoms of illness (such as children recovering from pinkeye, rash, or chickenpox), but who need further recuperation time • Severity level 2 encompasses children whose health condition is accompanied by a medium activity level because of symptoms (such as children with low-grade fever, children at the beginning of an illness, and children in the early recovery period of an illness) • Severity level 3 is composed of children whose health condition is accompanied by a low activity level because of symptoms that preclude much involvement
Illness resulting in a greater need for care than the childcare staff can provide without compromising the health and safety of the other children as determined by the childcare provider	
Illness that poses a risk of spread of harmful diseases to others	
In addition to the above key criteria, temporary exclusion is recommended when the child has any of the following conditions:	
Fever (temperature above 38°C [101°F] orally, above 38.9°C [102°F] rectally, or above 37.8°C [100°F] or higher taken axillary [armpit] or measured by an equivalent method) and behavior change or other signs and symptoms (e.g., sore throat, rash, vomiting, diarrhea)	Accompanied by behavior changes or other signs or symptoms of illness until medical professional evaluation finds the child able to be included at the facility
Acute change in behavior including lethargy/lack of responsiveness, inexplicable irritability or persistent crying, difficult breathing, or having a quickly spreading rash	Until evaluation by a medical professional finds the child able to be included at the facility
Diarrhea (defined by watery stools or decreased form of stool that is not associated with changes of diet). Exclusion is required for all diapered children whose stool is not contained in the diaper and toilet-trained children if the diarrhea is causing soiled pants or clothing	Readmission after diarrhea can occur when diapered children have their stool contained by the diaper (even if the stools remain loose) and when toilet-trained children are continent. Special circumstances that require specific exclusion criteria include the following: • Toxin-producing *Escherichia coli* or *Shigella* infection, until stools are formed and test results of 2 stool cultures obtained from stools produced 24-hr apart do not detect these organisms • *Salmonella* serotype Typhi infection, until diarrhea resolves and, in children younger than age 5 yr, 3 negative stool cultures obtained with 24-hr-intervals are obtained
Blood or mucus in stool	Not explained by dietary change, medication, or hard stools
Vomiting illness	More than 2 times in the previous 24 hr, unless the vomiting is determined to be caused by a noninfectious condition and the child remains adequately hydrated
Abdominal pain	Persistent (continues more than 2 hr) or intermittent associated with fever or other signs or symptoms
Mouth sores with drooling	Unless the child's primary care provider or local health department authority states that the child is noninfectious
Rash with fever or behavior changes	Until the primary care provider has determined that the illness is not an infectious disease
Active tuberculosis	Until the child's primary care provider or local health department states child is on appropriate treatment and can return
Impetigo	Until treatment has been started
Streptococcal pharyngitis (i.e., strep throat or other streptococcal infection)	Until 24 hr after treatment has been started
Purulent conjunctivitis	Defined as pink or red conjunctiva with white or yellow eye discharge, until after treatment has been initiated
Pediculosis (head lice)	Until after the first treatment *Note:* Exclusion is not necessary before the end of the program day
Scabies	Until after treatment has been given

Continued

Table 17-1 Conditions That Do and Do Not Require Exclusion from Group Childcare Settings—cont'd

CONDITIONS THAT REQUIRE EXCLUSION	COMMENTS
Varicella-zoster (chickenpox)	Until all lesions have dried or crusted (usually 6 days after onset of rash)
Rubella	Until 6 days after onset of rash
Pertussis	Until 5 days of appropriate antibiotic treatment
Mumps	Until 5 days after onset of parotid gland swelling
Measles	Until 4 days after onset of rash
Hepatitis A virus	Until 1 wk after onset of illness or jaundice if the child's symptoms are mild or as directed by the health department
Any child determined by the local health department to be contributing to the transmission of illness during an outbreak	
CONDITIONS THAT DO NOT REQUIRE EXCLUSION	**COMMENTS**
Common colds, runny noses	Regardless of color or consistency of nasal discharge
A cough not associated with an infectious disease or a fever	
Watery, yellow or white discharge or crusting eye discharge without fever, eye pain, or eyelid redness	
Presence of bacteria or viruses in urine or feces in the absence of illness symptoms, like diarrhea	Exceptions include children infected with highly contagious organisms capable of causing serious illness
Pink eye (bacterial conjunctivitis) indicated by pink or red eyelids after sleep	If 2 unrelated children in the same program have conjunctivitis, the organism causing the conjunctivitis may have a higher risk for transmission and a child healthcare professional should be consulted.
Fever without any signs or symptoms of illness in children who are older than 6 mo regardless of whether acetaminophen or ibuprofen was given	If the child is behaving normally but has a fever of below 38.9°C (102°F) rectally or the equivalent, the child should be monitored, but does not need to be excluded for fever alone
Rash without fever and without behavioral changes	
Lice or nits	Exclusion for treatment of an active lice infestation may be delayed until the end of the day
Ringworm	Exclusion for treatment may be delayed until the end of the day
Molluscum contagiosum	Do not require exclusion or covering of lesions
Thrush (i.e., white spots or patches in the mouth or on the cheeks or gums)	
Fifth disease	Once the rash has appeared
Methicillin-resistant *Staphylococcus aureus* (MRSA) without an infection or illness that would otherwise require exclusion	Known MRSA carriers or colonized individuals should not be excluded
Cytomegalovirus infection	
Chronic hepatitis B infection	
HIV infection	
Asymptomatic children who have been previously evaluated and found to be shedding potentially infectious organisms in the stool	Children who are continent of stool or who are diapered with formed stools that can be contained in the diaper may return to care
Children with chronic infections conditions that can be accommodated in the program according to the legal requirement of federal law in the Americans with Disabilities Act	The act requires that childcare programs make reasonable accommodations for children with disabilities and/or chronic illnesses, considering each child individually

Adapted from American Academy of Pediatrics, American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education: Stepping stones to caring for our children: national health and safety performance standards: guidelines for early care and education programs, third edition, *Elk Grove Village, IL, 2013, Authors, pp 46–52, available at:* http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/

higher-quality indicators, the bundle of features in a childcare arrangement may be another meaningful way for a parent to consider the potential effects of an arrangement on their child.

When a healthcare provider talks with a parent about the parent's child's childcare arrangement, it is also important to consider the individual child's characteristics, health concerns, dispositions, and even physiologic responses to the environment. Like all environments, childcare is experienced differently by different children. An average environment can often sufficiently compensate for the typical regulatory capacities of most children, but when an environment lacks adequate support for a child's unique needs, healthy development can be further compromised. Some children may be more vulnerable to bad childcare (or particularly responsive to good childcare), such as children with difficult or fearful temperaments, especially if their home environments are characterized by more risk factors, such as poverty or high conflict with a parent.

Several large studies have found that most U.S. childcare is of "poor to mediocre" quality. In one study, only 14% of centers (8% of

center-based infant care) were found to provide developmentally appropriate care, while 12% scored at minimal levels that compromised health and safety (40% for infant care). In another study, 58% of family daycare homes provided adequate or custodial care, and only 8% provided good care. Children with the greatest amount of family risk may be the most likely to receive childcare that is substandard in quality. Many children from lower-risk families also receive lower-quality care, and despite their advantages at home, these children may not be protected from the negative effects of poor-quality care.

Affordable, accessible, high-quality childcare is hard to find. Middle-class families spend approximately 6% of their annual income on childcare expenses, whereas poor families spend approximately 33% (on par with housing expenses). Infant and toddler care is particularly expensive with fewer available slots. For a married couple with children, the average cost of full-time center care for 1 infant ranges from 7% to approximately 19% of the state median income, depending on the state, and the average cost of center care for one 4 yr old exceeds 10% of the median household income in 21 states and the District of Columbia. For single parents, the average cost of center-based infant care exceeds 25% of median income in every state. The average cost of family childcare is only slightly lower.

In addition to the stress of meeting such a high expense, many parents worry that their child will feel unhappy in group settings, will suffer from separation from the parents, or will be subjected to neglect or abuse. This worry is especially likely among low-income parents with more risk factors, fewer resources, and fewer high-quality options available. Parents are the purchasers but not the recipients of care, and are not in the best position to judge its quality. Many parents are first-time purchasers of childcare with little experience and very immediate needs, selecting care in a market that does little to provide them with useful information about childcare arrangements. In many states, efforts are underway to improve quality and provide parents with quality information, but several states do not have a quality rating and information system, and programs in states that do are still emerging, and testing of effectiveness is still underway. To inform their care decisions, parents may turn to their child's pediatrician as the only professional with expertise in child development with whom they have regular and convenient contact.

Childcare and Child Health

A disproportionate number of sudden infant death syndrome (SIDS) deaths occur in childcare centers or family-based childcare homes (approximately 20%). Infants who are back-sleepers at home, but are put to sleep on their fronts in childcare settings, have a higher risk of SIDS. Providers and parents should be made aware of the importance of placing infants on their backs to sleep (see Chapter 375).

Children enrolled in childcare are also of an age that places them at increased risk for acquiring infectious diseases. Participation in group settings elevates exposure. Children enrolled in such settings have a higher incidence of illness (upper respiratory tract infections, otitis media, diarrhea, hepatitis A infections, skin conditions, and asthma) than those cared for at home, especially in the preschool years; these illnesses have no long-term adverse consequences. Childcare providers that follow childcare licensure guidelines for handwashing, diapering, and food handling, and that manage child illness appropriately, can reduce communicable illnesses.

There is debate about whether childcare exposure serves as a risk or protective factor for asthma. One cross-sectional study found that preschoolers in childcare had increased risk of the common cold and otitis media, and children who began childcare before the age of 2 yr had increased risk of developing recurrent otitis media and asthma. However, a longitudinal study found that children who were exposed to older children at home or to other children at childcare during the 1st 6 mo of life were less likely to have frequent wheezing from age 6-13 yr, suggesting that childcare exposure may protect against the development of asthma and frequent wheezing later in childhood. A 10 yr follow-up of a birth cohort found no association between childcare attendance and respiratory infections, asthma, allergic rhinitis, or skin prick test reactivity. Another study found that in the 1st yr of elementary school, children who had attended childcare had fewer absences from school, half as many episodes of asthma, and less acute respiratory illness than their peers who had never attended childcare. These results are perhaps related to protection against respiratory illness as a result of early exposure or a shift in the age-related peak of illness, though selection of illness-prone children into home care may play a role. Other factors may also be relevant to this issue, such as children in childcare potentially being less exposed to passive smoking than children at home.

Childcare and Children with Special Needs

The needs of children with mental, physical, or emotional disabilities who, because of their chronic illness, require special care and instruction may require particular attention when it comes to their participation in most childcare settings. Guiding principles of services for children with disabilities advocate supporting children in natural environments, including childcare. Furthermore, the Americans with Disabilities Act and Section 504 of the Rehabilitation Act of 1973 prohibit discrimination against children and adults with disabilities by requiring equal access to offered programs and services.

Although many childcare providers and settings are unprepared to identify or administer services for children with special needs, childcare could be utilized for delivery of support services to these children and/or for linking families to services, such as early intervention and doctor referrals. Furthermore, pediatricians can draw upon childcare providers to help provide important evaluative data regarding a child's well-being, as these providers have extensive daily contact with the child and may have broad, professional understanding of normative child development. A childcare provider may be the first to identify a child's potential language delay. Childcare providers are also necessary and valuable partners in the development and administration of early intervention service plans.

Children with special needs may be eligible for services under the Individuals with Disabilities Education Act (IDEA) (see Chapter 36). The purpose of this law is to provide "free appropriate public education," regardless of disability or chronic illness, to all eligible children, birth to 21 yr, in a natural and/or least-restrictive environment. Eligible children include those with mental, physical, or emotional disabilities who, because of their disability or chronic illness, require special instruction to learn. As a part of these services, a formal plan of intervention is to be developed by the service providers, families, and the children's healthcare providers. Federal funds are available to implement a collaborative early intervention system of services for eligible infants and toddlers between the ages of birth and 3 yr and their families. These services include screening, assessment, service coordination, and collaborative development of an **individualized family service plan (IFSP).** The IFSP describes early intervention services for the infant or toddler and family, including family support and the child's health, therapeutic, and educational needs. An understanding of the child's routines and real-life opportunities and activities, such as eating, playing, interacting with others, and working on developmental skills, is crucial to enhancing a child's ability to achieve the functional goals of the IFSP. Therefore it is critical that childcare providers be involved in IFSP development or revision, with parental consent. Childcare providers should also become familiar with the child's IFSP and understand the providers' role and the resources available to support the family and childcare provider.

Additionally, IDEA provides support for eligible preschool age children to receive services through the local school district. This includes development of a written **individualized education program (IEP)**, with implementation being the responsibility of the local education agency in either a public or private preschool setting. As with IFSPs, childcare providers should become familiar with the preschooler's special needs as identified in the IEP and may become involved, with parental consent, in IEP development and review meetings. In cases where children may have or be at risk of developmental delays, a diagnosis is important for obtaining and coordinating services and further evaluation. To this end, pediatricians can partner with childcare providers to screen and monitor children's behavior and development.

Table 17-2 Childcare Information Resources

ORGANIZATION	SPONSOR	WEBSITE AND CONTACT INFORMATION
Child Care Aware	Child Care Aware of America (formerly National Association of Child Care Resource and Referral Agencies)	http://www.childcareaware.org
Healthy Child Care America	American Academy of Pediatrics (AAP)	http://www.healthychildcare.org
National Association for the Education of Young Children (NAEYC)		http://www.naeyc.org
National Association for Sick Child Daycare (NASCD)		http://www.nascd.com
National Association for Family Child Care (NAFCC)		http://www.nafcc.org
National Resource Center for Health and Safety in Child Care and Early Education (NRC)		http://www.nrckids.org For the 2013 report from the AAP, APHA, and NRC, *Stepping Stones to Caring for Our Children: National Health and Safety Performance Standards: Guidelines for Early Care and Education Programs*, Third Edition, go to: http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/
Office of Child Care (OCC)	U.S. Department of Health and Human Services, Administration for Children & Families	http://www.acf.hhs.gov/programs/occ
Office of Child Care Technical Assistance Network (CCTAN)	U.S. Department of Health and Human Services, Administration for Children & Families, Office of Child Care	https://childcare.gov/

ROLE OF PEDIATRIC PROVIDERS IN CHILDCARE

Advising Parents on Childcare Selection

Organized professional guidance in choosing childcare is insufficient. Pediatricians can help parents understand the importance for their child's development of selecting high-quality care by describing how it looks and providing referrals and tips on how to find and select high-quality childcare (Table 17-2). In addition, pediatricians can help parents determine how to adjust childcare arrangements to best meet their child's specific needs (e.g., allergies, eating and sleeping habits, temperament and stress-regulation capacities). For most parents, finding childcare that they can afford, access, manage, and accept as a good environment for their child is a very difficult process and one many parents find distressing. Many parents are also worried about how their child will fare in childcare (e.g., Will their child feel distressed by group settings, suffer from separation from the parents, or even be subjected to neglect or abuse?). These worries are especially likely among low-income parents with fewer family and community resources to draw upon. A few parents may think of childcare only as babysitting, and may not consider the consequences for their child's cognitive, linguistic, and social development, focusing solely on whether the child is safe and warm. These parents may be less likely to select a high-quality childcare arrangement, which is especially problematic if the family is facing socioeconomic challenges that already place them at risk of receiving lower-quality care for their children. For these parents, it is vital to stress the importance of quality and its implications for their child's cognitive, language, and behavioral development and school readiness.

Advising Parents on Childcare Health Issues

Parents of infants should be advised to ensure that childcare providers put infants on their back to sleep to prevent SIDS. Also, pediatricians should emphasize the importance of following vaccination schedules; most states require compliance for children to participate in licensed group childcare settings.

When children are ill, parents should be advised to follow guidelines for inclusion and exclusion (see Table 17-1). Parents may disagree with childcare staff about whether a child meets or does not meet the exclusion criteria. However, professional guidelines state that "if … the reason for exclusion relates to the child's ability to participate or the caregiver's/teacher's ability to provide care for the other children, the caregiver/teacher should not be required to accept responsibility for the care of the child." (http://nrckids.org/index.cfm/products/stepping-stones-to-caring-for-our-children-3rd-edition-ss3/).

Helping Children with Special Needs

Pediatricians should work with parents and communicate with other service providers and early intervention staff to identify problems, remove access barriers, and coordinate service delivery for children with special needs. They should also encourage involvement of parents and childcare providers in IFSP or IEP plan development.

Consulting and Partnering with Childcare Providers

Most state regulations mandate that licensed programs have a formal relationship with a healthcare provider. Additional state efforts include mental health consultation models to support providers, who are often not well trained in managing child behavior, and build capacity to raise quality for all children. Early childhood mental health consultation links a mental health professional with an early education and care provider in an ongoing problem-solving and capacity-building relationship.

Pediatricians can provide consultation to childcare providers about measures to protect and maintain the health and safety of children and staff. This may include consultation regarding promoting practices to prevent SIDS; preventing and reducing the spread of communicable disease; reducing allergen, toxin, and parasite exposure; ensuring vaccinations for children and staff; removing environmental hazards; and preventing injuries.

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Chapter 18

Loss, Separation, and Bereavement

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All children will experience involuntary separations, whether from illness, death, or other causes, from loved ones at some time in their lives. Relatively brief separations of children from their parents, such as vacations, usually produce minor transient effects, but more enduring and frequent separation may cause sequelae. The potential impact of each event must be considered in light of the age and stage of development of the child, the particular relationship with the absent person, and the nature of the situation.

SEPARATION AND LOSS

Separations may be from temporary causes, such as vacations, parental job restrictions, natural disasters, or parental or sibling illness requiring hospitalization. More long-term separations occur as a result of divorce, placement in foster care, or adoption, whereas permanent separation may occur because of death. The initial reaction of young children to separation of any duration may involve crying, either of a tantrum-like, protesting type, or of a quieter, sadder type. Children's behavior may appear subdued, withdrawn, fussy, or moody, or they may demonstrate resistance to authority. Specific problems may include poor appetite, behavior issues such as acting against caregiver requests, reluctance to go to bed, sleep problems, or regressive behavior, such as requesting a bottle or bed-wetting. School-age children may experience impaired cognitive functioning and poor performance in school. Some children may repeatedly ask for the absent parent and question when the absent parent will return. The child may go to the window or door or out into the neighborhood to look for the absent parent; a few may even leave home or their place of temporary placement to search for their parents. Other children may not refer to the parental absence at all.

A child's response to reunion may surprise or alarm an unprepared parent. A parent who joyfully returns to the family may be met by wary or cautious children. After a brief interchange of affection, children may seem indifferent to the parent's return. This response may indicate anger at being left and wariness that the event will happen again, or the child may feel, as a result of magical thinking, as if the child caused the parent's departure. If the mother who frequently says "Stop it, or you'll give me a headache" is hospitalized, the child may feel at fault and guilty. As a result of these feelings, children may seem to be more closely attached to the other present parent than to the absent one, or even to the grandparent or babysitter who cared for them during their parent's absence. Some children, particularly younger ones, may become more clinging and dependent than they were before the separation, while continuing any regressive behavior that occurred during the separation. Such behavior may engage the returned parent more closely and help to reestablish the bond that the child felt was broken. Such reactions are usually transient and within 1-2 wk, children will have recovered their usual behavior and equilibrium. Recurrent separations may tend to make children more wary and guarded about reestablishing the relationship with the repeatedly absent parent, and these traits may affect other personal relationships. Parents should be advised not to try to ameliorate a child's behavior by threatening to leave.

DIVORCE

More sustained experiences of loss, such as divorce or placement in foster care, can give rise to the same kinds of reactions noted earlier, but they are more intense and possibly more lasting. Currently in the United States, approximately 40% of marriages end in divorce. Divorce has been found to be associated with negative parent functioning, such as parental depression and feelings of incompetence, negative child behavior, such as noncompliance and whining, and negative parent–child interaction, such as inconsistent discipline, decreased communication, and decreased affection. Greater childhood distress is associated with greater parental distress. Continued parental conflict and loss of contact with the noncustodial parent, usually the father, is common. Two of the most important factors that contribute to morbidity of the children in a divorce include parental psychopathology and disrupted parenting before the separation. The year following the divorce is the period when problems are most apparent; these problems tend to dissipate over the next 2 yr. Depression may be present 5 yr later, and educational or occupational decline may occur even 10 yr later. It is difficult to sort out all of the confounding factors. Children may suffer when exposed to parental conflict that continues after divorce, and in some cases may escalate. The degree of interparental conflict may be the most important factor associated with child morbidity. A continued relationship with the noncustodial parent, as long as there is minimal interparental conflict, was a factor associated with more positive outcomes.

School-age children may respond with evident depression, may seem indifferent, or may be markedly angry. Other children appear to deny or avoid the issue, behaviorally or verbally. Most children cling to the hope that the actual placement or separation is not real and are only temporary. The child may experience guilt by feeling that the loss, separation, or placement represents rejection and perhaps punishment for misbehavior. Children may protect a parent and assume guilt, believing that their own "badness" caused the parent to depart. Outwardly blaming parents may be perceived by a child as emotionally risky; parents who discover that a child harbors resentment might punish the child further for these thoughts or feelings. Children who feel that their misbehavior caused their parents to separate or become divorced have the fantasy that their own trivial or recurrent behavioral patterns caused their parents to become angry at each other. Some children have behavioral or psychosomatic symptoms and unwittingly adopt a "sick" role as a strategy for reuniting their parents.

In response to divorce of parents and the subsequent separation and loss, older children and adolescents commonly show intense anger. Five yr after the breakup, approximately ⅓ of children report intense unhappiness and dissatisfaction with their lives and their reconfigured families, another ⅓ show clear evidence of a satisfactory adjustment, whereas the remaining ⅓ demonstrate a mixed picture, with good achievement in some areas and faltering achievement in others. After 10 yr, approximately 45% do well, but 40% may have academic, social, and/or emotional problems. As adults, some are reluctant to form intimate relationships, fearful of repeating their parents' experience. Parental divorce has a moderate long-term negative impact on the adult mental health status of children who had experienced it, even after controlling for changes in economic status and problems before divorce. Good adjustment of children after a divorce is related to ongoing involvement with 2 psychologically healthy parents who minimize conflict, and to the siblings and other relatives who provide a positive support system. Divorcing parents should be encouraged to avoid adversarial processes and to use a trained mediator to resolve disputes if needed. Joint custody arrangements may reduce ongoing parental conflict, but children in joint custody may feel overburdened by the demands of maintaining a strong presence in 2 homes.

When the primary care provider is asked about the effects of divorce, parents should be informed that different children may have different reactions, but that the parents' behavior and the way they interact with each other will have a major and long-term effect on the child's adjustment. The continued presence of both parents in the child's life, with minimal interparental conflict, is most beneficial to the child.

MOVE/FAMILY RELOCATION

A significant proportion of the population of the United States changes residence each year. The effects of this movement on children and families are frequently overlooked. For children, the move is essentially involuntary and out of their control. When such changes in family

structure as divorce or death precipitate moves, children face the stresses created by both the precipitating events and the move itself. Parental sadness surrounding the move may transmit unhappiness to the children. Children who move lose their old friends, the comfort of a familiar bedroom and house, and their ties to school and community. They not only must sever old relationships but also are faced with developing new ones in new neighborhoods and new schools. Children may enter neighborhoods with different customs and values, and because academic standards and curricula vary among communities, children who have performed well in one school may find themselves struggling in a new one. Frequent moves during the school years are likely to have adverse consequences on social and academic performance.

Migrant children and children who emigrate from other countries present with special circumstances. These children not only need to adjust to a new house, school, and community but also need to adjust to a new culture and, in many cases, a new language. Because children have faster language acquisition than adults, they may function as translators for the adults in their families. This powerful position may lead to role reversal and potential conflict within the family. In the evaluation of migrant children and families, it is important to ask about the circumstances of the migration, including legal status, violence or threat of violence, conflict of loyalties, and moral, ethical, and religious differences.

Parents should prepare children well in advance of any move and allow them to express any unhappy feelings or misgivings. Parents should acknowledge their own mixed feelings and agree that they will miss their old home while looking forward to a new one. Visits to the new home in advance are often useful preludes to the actual move. Transient periods of regressive behavior may be noted in preschool children after moving, and these should be understood and accepted. Parents should assist the entry of their children into the new community, and whenever possible, exchanges of letters and visits with old friends should be encouraged.

SEPARATION BECAUSE OF HOSPITALIZATION

Potential challenges for hospitalized children include coping with separation, adapting to the new hospital environment, adjusting to multiple caregivers, seeing very sick children, and sometimes experiencing the disorientation of intensive care, anesthesia, and surgery. To help mitigate potential problems, a preadmission visit to the hospital is important to allow the child to meet the people who will be offering care and ask questions about what will happen. Parents of children younger than 5-6 yr of age should room with the child if feasible. Older children may also benefit from parents staying with them while in the hospital, depending on the severity of their illness. Creative and active recreational or socialization programs with child life specialists, chances to act out feared procedures in play with dolls or mannequins, and liberal visiting hours, including visits from siblings, are all helpful. Sensitive, sympathetic, and accepting attitudes toward children and parents by the hospital staff are very important. Healthcare providers need to remember that parents have the best interest of their children at heart and know their children the best. Whenever possible, school assignments and tutoring for the hospitalized children should be available in order to engage the child intellectually and prevent them from falling behind in their scholastic achievements.

The psychologic aspects of illness should be evaluated from the outset, and physicians should act as a model for parents and children by showing interest in a child's feelings, allowing them a venue for expression, and demonstrating that it is possible and appropriate to communicate discomfort in verbal, symbolic language. Continuity of medical personnel may be reassuring to the child and family.

MILITARY FAMILIES

More than 2 million children live in military families in the United States, and approximately 50% of them obtain medical care in the community rather than at a military medical facility.

Children whose parents are serving in the military may experience loss and separation in multiple ways. These include frequent relocations, relocation to foreign countries, and duty-related separation from parents. In recent years, the most impactful experiences have been repeated wartime deployments of parents and of the deaths of parents during military service.

All branches of the military have increased their focus on preparing and supporting military families for a service member's deployment to improve family coping. Military families composed of young parents and young children are at risk for child maltreatment in the context of repeated or prolonged deployments.

PARENTAL/SIBLING DEATH

Approximately 5-8% of U.S. children will experience parental death; rates are much higher in other parts of the world that are more directly affected by war, AIDS, and natural disasters. Anticipated deaths from chronic illness may place a significant strain on a family, with frequent bouts of illness, hospitalization, disruption of normal home life, absence of the ill parent, and perhaps more responsibilities placed on the child. Additional strains include changes in daily routines, financial pressures, and the need to cope with aggressive treatment options.

Children can and should continue to be involved with the sick parent or sibling, but they need to be prepared for what they will see in the home or hospital setting. The stresses that a child will face include visualizing the physical deterioration of the family member, helplessness, and emotional lability. Forewarning the child that the family member may demonstrate physical changes, such as appearing thinner or losing hair will help the child to adjust. These warnings, combined with simple yet specific explanations of the need for equipment, such as a nasogastric tube for nutrition, an oxygen mask, or a ventilator, will help lessen the child's fear. Children should be honestly informed of what is happening, in language they can understand, allowing them choices, but with parental involvement in decision making. They should be encouraged, but not forced, to see their ill family member. Parents who are caring for a dying spouse or child may be too emotionally depleted to be able to tend to their healthy child's needs or to continue regular routines. Children of a dying parent may suffer the loss of security and belief in the world as a safe place, and the surviving parent may be inclined to impose his or her own need for support and comfort onto the child. However, the well parent and caring relatives must keep in mind that children need to be allowed to remain children, with appropriate support and attention. Sudden, unexpected deaths lead to more anxiety and fear, because there was no time for preparation and uncertainty as to explanations.

GRIEF AND BEREAVEMENT

Grief is a personal, emotional state of bereavement or an anticipated response to loss, such as a death. Common reactions include sadness, anger, guilt, fear, and at times, relief. The normality of these reactions needs to be emphasized. Most bereaved families remain socially connected and expect that life will return to some new, albeit different, sense of normalcy. The pain and suffering imposed by grief should never be automatically deemed "normal" and thus neglected or ignored. In uncomplicated grief reactions, the steadfast concern of the pediatrician can help promote the family's sense of well-being. In more distressing reactions (such as those seen in traumatic grief of sudden deaths), the pediatrician may be a major, first-line force in helping children and families address their loss.

Participation in the care of a child with a life-threatening or terminal illness is a profound experience. Parents experience much anxiety and worry during the final stages of their child's life. In 1 study at a children's hospital, 45% of children dying from cancer died in the pediatric intensive care unit, and parents report that 89% of their children suffered "a lot" or "a great deal" during the last month of life. Physicians consistently underreport children's symptoms in comparison to parents' reports. Better ways are needed to provide for dying children, and to maintain honest and open communication, provide appropriate pain management, and meet the families' wishes as to the preferred location of the child's death, in some cases in their own home. Inclusion of multiple disciplines, such as hospice, clergy, nursing, pain service, child life specialists, and social work, often helps to fully support families during this difficult experience.

The practice of withholding information from children and parents regarding a child's diagnosis and prognosis has generally been abandoned because physicians have learned that protecting parents and patients from the seriousness of their child's condition does not alleviate concerns and anxieties. Even very young children may have a real understanding of their illness. Children who have serious diseases and are undergoing aggressive treatment and medication regimens, but are told by their parents that they are okay, are not reassured by their parents. These children understand that something serious is happening to them, and they are often forced to suffer in silence and isolation because the message they have been given by their parents is to not discuss it and to maintain a cheerful demeanor. Children have the right to know their diagnosis and should be informed early in their treatment. The content and depth of the discussion needs to be tailored to the child's personality and developmental level of understanding. Parents have choices as to how to orchestrate the disclosure. Parents may want to be the ones to inform the child themselves, may choose for the pediatric healthcare provider to do so, or may do it in partnership with the pediatrician.

A death, especially the death of a family member, is the most difficult loss for a child. Many changes in normal patterns of functioning may occur, including loss of love and support from the deceased family member, a change in income, the possible need to relocate, less emotional support from surviving family members, altering of routines, and a possible change in status from sibling to only child. Relationships between family members may become strained, and children may blame themselves or other family members for the death of a parent or sibling. Bereaved children may exhibit many of the emotions discussed earlier as a result of the loss, in addition to behaviors of withdrawal into their own world, sleep disturbances, nightmares, and symptoms such as headache, abdominal pains, or possibly similar to those of the family member who has died. Children 3-5 yr of age who have experienced a family bereavement may show regressive behaviors such as bed-wetting and thumb sucking. School-age children may exhibit nonspecific symptoms, such as headache, abdominal pain, chest pain, fatigue, and lack of energy. Children and adolescents may also demonstrate enhanced anxiety should these symptoms resemble those of the family member who died. The presence of secure and stable adults who can meet the child's needs and who permit discussion about the loss is most important in helping a child to grieve. The pediatrician should help the family understand this necessary presence and encourage the protective functioning of the family unit. More frequent visits to the healthcare professional may be necessary to address these symptoms and provide reassurance when appropriate.

Death, separation, and loss as a result of natural catastrophes and human-made disasters have become increasingly common events in children's lives. Exposure to such disasters occurs either directly or indirectly, where the event is experienced through the media. Examples of indirect exposure include televised scenes of earthquakes, hurricanes, tsunamis, tornadoes and the terrorist attacks at the Boston Marathon in 2013 and in New York on September 11, 2001, with the subsequent news stories about anthrax and heightened states of alert. Children who experience personal loss in disasters tend to watch more television coverage than children who do not. Children without a personal loss watch as a way of participating in the event and may thus experience repetitive exposure to traumatic scenes and stories. The loss and devastation for a child who personally lives through a disaster is significant; the effect of the simultaneous occurrence of disaster and personal loss complicates the bereavement process as grief reactions become interwoven with posttraumatic stress symptoms (see Chapter 25). After a death that occurs as a result of aggressive or traumatic circumstances, access to expert help may be required. Under conditions of threat and fear, children seek proximity to safe, stable, protective figures.

It is important for parents to grieve with their children. Some parents want to protect their children from their grief, so they put on an outwardly brave front or do not talk about the deceased family member. Instead of the desired protective effect, the child receives the message that demonstrating grief or talking about death is wrong, leading the child to feel isolated, to grieve privately, or to delay grieving. The child may also conclude that the parents didn't really care about the deceased because they have forgotten the deceased so easily or demonstrate no emotion. The parents' efforts to avoid talking about the death may cause the parents to isolate themselves from their children at a time when the children most need them. Children need to know that their parents love them and will continue to protect them. Children need opportunities to talk about their relative's death and associated memories. A surviving sibling may feel guilty simply because he or she survived, especially if the death was the result of an accident that involved both children. Siblings' grief, especially when compounded by feelings of guilt, may be manifested by regressive behavior or anger. Parents should be informed of this possibility and encouraged to discuss the possibility with their children.

DEVELOPMENTAL PERSPECTIVE

Children's responses to death reflect the family's current culture, their past heritage, experiences, and the sociopolitical environment. Personal experience with terminal illness and dying may also facilitate children's comprehension of death and familiarity with mourning. Developmental differences in children's efforts to make sense of and master the concept and reality of death do exist and profoundly influence their grief reactions.

Children **younger than 3 yr** of age have little or no understanding of the concept of death. Despair, separation anxiety, and detachment may occur at the withdrawal of nurturing caretakers. Young children may respond in reaction to observing distress in others, such as a parent or sibling who is crying, withdrawn, or angry. Young children also express signs and symptoms of grief in their emotional states, such as irritability or lethargy, and in severe cases, mutism. If the reaction is severe, failure to thrive may occur.

Preschool children are in the preoperational cognitive stage, in which communication takes place through play and fantasy (see Chapter 6). They do not show well-established cause-and-effect reasoning. They feel that death is reversible, analogous to someone going away. In attempts to master the finality and permanence of death, preschoolers frequently ask unrelenting, repeated questions about when the person who died will be returning. This makes it difficult for parents, who may become frustrated because they don't understand why the child keeps asking and do not like the constant reminders of the person's death. The primary care provider has a very important role in helping families understand the child's struggle to comprehend death. Preschool children typically express magical explanations of death events, sometimes resulting in guilt and self-blame ("He died because I wouldn't play with him." "She died because I was mad at her."). Some children have these thoughts, but do not express them verbally because of embarrassment or guilt. Parents and primary care providers need to be aware of magical thinking and must reassure preschool children that their thoughts had nothing to do with the outcome. Children of this age are often frightened by prolonged, powerful expressions of grief by others. Children conceptualize events in the context of their own experiential reality, and therefore consider death in terms of sleep, separation, and injury. Young children express grief intermittently and show marked affective shifts over brief periods. Regression, accompanied by longing, sadness, and anger, may accompany grief.

Younger school-age children think concretely, recognize that death is irreversible, but believe it will not happen to them or affect them, and begin to understand biologic processes of the human body ("You'll die if your body stops working"). Information gathered from the media, peers, and parents forms lasting impressions. Consequently, they may ask candid questions about death that adults will have difficulty addressing ("He must have been blown to pieces, huh?").

Children 9 yr of age and older do understand that death is irreversible and that it may involve them or their families. These children tend to experience more anxiety, overt symptoms of depression, and somatic complaints than do younger children. School-aged children are often left with anger focused on the loved one, those who could not save the deceased, or those presumed responsible for the death. Contact with

the pediatrician may provide great reassurance, especially for the child with somatic symptoms, and particularly when the death followed a medical illness. School and learning problems may also occur, and these reactions are often linked to difficulty concentrating or preoccupation with the death. Close collaboration with the child's school may provide important diagnostic information and offer opportunities to mobilize intervention or support.

At 12-14 yr of age, children begin to use symbolic thinking, reason abstractly, and analyze hypothetical, or "what if," scenarios systematically. Death and the end of life become concepts, rather than events. Teenagers are often ambivalent about dependence and independence and may withdraw emotionally from surviving family members, only to mourn in isolation. Adolescents begin to understand complex physiologic systems in relationship to death. Since they are often egocentric, they may be more concerned about the impact of the death on themselves than about the deceased or other family members. Fascination with dramatic, sensational, or romantic death sometimes occurs and may find expression in copycat behavior, such as cluster suicides, as well as competitive behavior to forge emotional links to the deceased person ("He was my best friend."). Somatic expression of grief may revolve around highly complex syndromes (eating disorders or conversion reactions) as well as symptoms limited to the more immediate perceptions, as with younger children (stomachaches). Quality of life takes on meaning, and the teenager develops a focus on the future. Depression, resentment, mood swings, rage, and risk-taking behaviors can emerge as the adolescent seeks answers to questions of values, safety, evil, and fairness. Alternately, the adolescent may seek philosophical or spiritual explanations ("being at peace") to ease their sense of loss. The death of a peer may be especially traumatic.

Families often struggle with how to inform their children of the death of a family member. The answer depends on the child's developmental level. It is best to avoid misleading euphemisms and metaphor. A child who is told that the relative who died "went to sleep" may become frightened of falling asleep, resulting in sleep problems or nightmares. Children can be told that the person is "no longer living" or "no longer moving or feeling." Using examples of pets that have died sometimes can help children gain a more realistic idea of the meaning of death. Parents who have religious beliefs may comfort their children with explanations, such as "Your sister's soul is in heaven" or "Grandfather is now with God," provided those beliefs are honestly held. If these are not religious beliefs that the parents share, children will sense the insincerity and experience anxiety rather than the hoped-for reassurance. Children's books about death can provide an important source of information, and when read together, these books may help the parent to find the right words, while addressing the child's needs.

ROLE OF THE PEDIATRICIAN IN GRIEF

The pediatrician has an important role in assisting grieving families, because the death of a child has become an uncommon experience in our society. The pediatric healthcare provider who has had a longitudinal relationship with the family will be an important source of support in the disclosure of bad news and critical decision making, during both the dying process and the bereavement period.

The involvement of the healthcare provider may include being present at the time the diagnosis is disclosed, at the hospital or home at the time of death, being available to the family by phone during the bereavement period, sending a sympathy card, attending the funeral, and/or scheduling a follow-up visit. Attendance at the funeral sends a strong message that the family and their child are important, respected by the healthcare provider, and can also help the pediatric healthcare provider to grieve and reach personal closure about the death. A family meeting 1-3 mo later may be helpful because parents may not be able to formulate their questions at the time of death. This meeting allows the family time to ask questions, share concerns, and review autopsy findings (if one was performed), and allows the healthcare provider to determine how the parents and family are adjusting to the death.

Instead of leaving the family feeling abandoned by a healthcare system that they have counted on, this visit allows them to have continued support. This is even more important when the healthcare provider will be continuing to provide care for surviving siblings. The visit can be used to determine how the mourning process is progressing, detect evidence of marital discord, and evaluate how well surviving siblings are coping. This is also an opportunity to evaluate whether referrals to support groups or mental health providers may be of benefit. Continuing to recognize the child who has died is important. Families appreciate the receipt of a card on their child's birthday or the anniversary of their child's death.

The healthcare provider needs to be an educator about disease, death, and grief. The pediatrician can offer a safe environment for the family to talk about painful emotions, express fears, and share memories. By giving families permission to talk and modeling how to address children's concerns, the pediatrician demystifies death. Parents often request practical help. The healthcare provider can offer families resources, such as literature (both fiction and nonfiction), referrals to therapeutic services, and tools to help them learn about illness, loss, and grief. In this way, the physician reinforces the sense that other people understand what they are going through and helps to normalize their distressing emotions. The pediatrician can also facilitate and demystify the grief process by sharing basic tenets of grief therapy. There is no single right or wrong way to grieve. Everyone grieves differently; mothers may grieve differently than fathers, and children mourn differently than adults. Helping family members to respect these differences and reach out to support each other is critical. Grief is not something to "get over," but a lifelong process of adapting, readjusting, and reconnecting.

Parents may need help in knowing what constitutes normal grieving. Hearing, seeing, or feeling their child's presence may be a normal response. Vivid memories or dreams may occur. The pediatrician can help parents to learn that, although their pain and sadness may seem intolerable, other parents have survived similar experiences, and their pain will lessen over time.

Pediatricians are often asked whether children should attend the funeral of a parent or sibling. These rituals allow the family to begin their mourning process. Children older than 4 yr of age should be given a choice. If the child chooses to attend, the child should have a designated, trusted adult, who is not part of the immediate family, stay with the child, offer comfort, and be willing to leave with the child if the experience proves to be overwhelming. If the child chooses not to attend, the child should be offered additional opportunities to share in a ritual, go to the cemetery to view the grave, tell stories about the deceased, or obtain a keepsake object from the deceased family member as a remembrance.

In the era of regionalized tertiary care medicine, the primary care provider and medical home staff may not be informed when one of their patients dies in the hospital. Yet, this communication is critically important. Families assume their pediatrician has been notified, and often feel hurt when they don't receive some symbol of condolence. Because of their longitudinal relationship with the family, primary care providers may offer much needed support. There are practical issues, such as the need to cancel previously made appointments and the need to alert office and nursing staff so that they are prepared should the family return for a follow-up visit or for ongoing health maintenance care with the surviving siblings. Even minor illnesses in the surviving siblings may frighten children. Parents may contribute to this anxiety because their inability to protect the child who has died may leave them with a sense of guilt or helplessness. They may seek medical attention sooner or may be hypervigilant in the care of the siblings because of guilt over the other child's death, concern about their judgment, or the need for continued reassurance. A visit to the pediatrician can do a lot to allay their fears.

Clinicians must remain vigilant for risk factors in each family member and in the family unit as a whole. Primary care providers, who care for families over time, know bereft patients' premorbid functioning and can identify those at current or future risk for physical and psychiatric morbidity. Providers must focus on symptoms that interfere with a patient's normal activities and compromise a child's attainment of developmental tasks. Symptom duration, intensity, and severity, in context with the family's culture, can help identify

complicated grief reactions in need of therapeutic attention. Descriptive words, such as "unrelenting," "intense," "intrusive," or "prolonged," should raise concern. Total absence of signs of mourning, specifically, an inability to discuss the loss or express sadness, also suggests potential problems.

No specific sign, symptom, or cluster of behaviors identifies the child or family in need of help. Further assessment is indicated if the following occur: (1) persistent somatic or psychosomatic complaints of undetermined origin (headache, stomachache, eating and sleeping disorders, conversion symptoms, symptoms related to the deceased's condition, hypochondriasis); (2) unusual circumstances of death or loss (sudden, violent, or traumatic death; inexplicable, unbelievable, or particularly senseless death; prolonged, complicated illness; unexpected separation); (3) school or work difficulties (declining grades or school performance, social withdrawal, aggression); (4) changes in home or family functioning (multiple family stresses, lack of social support, unavailable or ineffective functioning of caretakers, multiple disruptions in routines, lack of safety); (5) concerning psychologic factors (persistent guilt or blame, desire to die or talk of suicide, severe separation distress, disturbing hallucinations, self-abuse, risk-taking behaviors, symptoms of trauma such as hyperarousal or severe flashbacks, grief from previous or multiple deaths). Children who are intellectually impaired may require additional support.

TREATMENT

Suggesting interventions outside the natural support network of family and friends can often prove useful to grieving families. Bereavement counseling should be readily offered if needed or requested by the family. Interventions that enhance or promote attachments and security, as well as give the family a means of expressing and understanding death, help to reduce the likelihood of future or prolonged disturbance, especially in children. Collaboration between pediatric and mental health professionals can help determine the timing and appropriateness of services.

Interventions for children and families who are struggling to cope with a loss in the community include gestures such as sending a card or offering food to the relatives of the deceased and teaching children the etiquette of behaviors and rituals around bereavement and mutual support. Performing community service or joining charitable organizations, such as fund-raising in memory of the deceased, may be useful. In the wake of a disaster, parents and older siblings can give blood or volunteer in search and recovery efforts. When a loss does not involve an actual death (e.g., parental divorce or geographic relocation), empowering the child to join or start a "divorced kids' club" in school or planning a "new kids in town" party may help. Participating in a constructive activity helps move the family away from a sense of helplessness and hopelessness and helps them to find meaning in their loss.

Psychotherapeutic services may benefit the entire family or individual members. Many support or self-help groups focus on specific types of losses (sudden infant death syndrome, suicide, widow/widowers, or AIDS) and provide an opportunity to talk with other people who have experienced similar losses. Family, couple, sibling or individual counseling may be useful, depending on the nature of the residual coping issues. Combinations of approaches may work well for children or parents with evolving needs. A child may participate in family therapy to deal with the loss of a sibling and use individual treatment to address issues of personal ambivalence and guilt related to the death.

The question of pharmacologic intervention for grief reactions often arises. Explaining that medication does not cure grief and often does not reduce the intensity of some symptoms (separation distress) can help. Although medication can blunt reactions, the psychologic work of grieving still must occur. The pediatrician must consider the patient's premorbid psychiatric vulnerability, current level of functioning, other available supports, and the use of additional therapeutic interventions. Medication, as a first line of defense, rarely proves useful in normal or uncomplicated grief reactions. In certain situations (severe sleep disruption, incapacitating anxiety, or intense hyperarousal), use of an anxiolytic or antidepressant medication for symptom relief and to provide the patient with the emotional energy to mourn may help. Medication used in conjunction with some form of psychotherapy, and in consultation with a psychopharmacologist, has optimal results.

Children who are refugees and may have experienced war, violence, or personal torture, while often resilient, may experience post-traumatic stress disorder if exposures were severe or repeated. Sequelae such as depression, anxiety, and grief need to be addressed, and mental health therapy is indicated. Cognitive behavioral treatment, use of journaling and narratives to bear witness to the experiences, and use of translators may be essential.

SPIRITUAL ISSUES

Responding to patients' and families' spiritual beliefs can help in comforting them during family tragedies. Offering to call members of pastoral care teams or their own spiritual leader can be a real support to them and aid in decision-making. Families have found it important to have their beliefs and their need for hope acknowledged in end-of-life care. The majority of patients report welcoming discussions on spirituality, which may help individual patients cope with illness, disease, dying, and death. In addressing spirituality, physicians need to follow certain guidelines, including maintaining respect for the patient's beliefs, following the patient's lead in exploring how spirituality affects the patient's decision making, acknowledging the limits of their own expertise and role in spirituality, and maintaining their own integrity by not saying or doing anything that violates their own spiritual or religious views. Healthcare providers should not impose their own religious or antireligious beliefs on patients, but rather should listen respectfully to their patients. By responding to spiritual needs, physicians may better aid their patients and families in end-of-life care and bereavement and take on the role of healers.

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Chapter 19

Sleep Medicine

Judith A. Owens

Sleep regulation is also referred to as the *2-process* sleep system because it requires the simultaneous operation of 2 basic, highly coupled processes that govern sleep and wakefulness. The **homeostatic process** ("Process S"), regulates the length and depth of sleep, and may be related to the accumulation of adenosine and other sleep-promoting chemicals ("somnogens"), such as cytokines, during prolonged periods of wakefulness. This sleep pressure appears to build more quickly in infants and young children, thus limiting the duration that wakefulness can be sustained during the day and necessitating periods of daytime sleep (i.e., naps). The endogenous **circadian rhythms** ("Process C"), influence the internal organization of sleep and timing and duration of daily sleep–wake cycles, and govern predictable patterns of alertness throughout the 24 hr day. The "master circadian clock" that controls sleep–wake patterns, of which melatonin secretion is the principal biomarker, is located in the suprachiasmatic nucleus in the ventral hypothalamus. The "circadian clocks" govern the timing of multiple other physiologic systems in the body (e.g., cardiovascular reactivity, hormone levels, renal and pulmonary functions). Because the human circadian clock is actually slightly longer than 24 hr, intrinsic circadian rhythms must be synchronized or "entrained" to the 24 hr day cycle by environmental cues called **zeitgebers**. The **dark–light cycle** is the most powerful of the zeitgebers; light signals are transmitted to the suprachiasmatic nucleus via the circadian photoreceptor system within the retina (functionally and anatomically separate from the visual system), which switch the body's production of the hormone melatonin off

(light) or on (dark) by the pineal gland. Circadian rhythms are also synchronized by other external time cues, such as timing of meals and alarm clocks.

Sleep propensity (the relative level of sleepiness) or alertness experienced at any given time during a 24 hr period is partially determined by the homeostatic *sleep drive*, which, in turn, depends upon the duration and quality of previous sleep and the amount of time awake since the last sleep period. Interacting with this *sleep homeostat* is the 24 hr cyclic pattern or rhythm characterized by clock-dependent periods of maximum sleepiness (*circadian troughs*) and maximum alertness (*circadian nadirs*). There are 2 periods of maximum sleepiness, 1 in the late afternoon (3:00-5:00 PM) and 1 toward the end of the night (3:00-5:00 AM), and 2 periods of maximum alertness, 1 in mid-morning and 1 in the evening, just prior to sleep onset (the so-called forbidden zone or second-wind phenomenon).

There are significant consequences of the failure to meet basic sleep needs, termed insufficient/inadequate sleep or **sleep loss**. Sufficient sleep is a biologic imperative, necessary for optimal functioning and apparently for life. **Slow-wave sleep** (SWS) (i.e., N3, delta, or deep sleep) appears to be the most restorative form of sleep; it is entered into relatively quickly after sleep onset, it is preserved in the face of reduced total sleep time, and it increases (rebounds) after a night of restricted sleep. **Rapid eye movement** (REM) sleep (Stage R or "dream" sleep) appears to be involved in (1) completing vital cognitive functions, such as the consolidation of memory; (2) promoting the plasticity of the central nervous system (CNS); and (3) protecting the brain from injury. Sufficient amounts of both of these sleep stages are necessary for optimal cognitive functioning. Partial sleep loss (sleep restriction) on a chronic basis accumulates in what is termed a **sleep debt** and produces deficits equivalent to those seen under conditions of total sleep deprivation. If the sleep debt becomes large enough and is not voluntarily repaid by obtaining sufficient recovery sleep, the body may respond by overriding voluntary control of wakefulness. This results in periods of decreased alertness, dozing off, and unplanned napping, recognized as excessive daytime sleepiness. The sleep-restricted individual may also experience very brief (several seconds) repeated daytime microsleeps of which the individual may be completely unaware, but which, nonetheless, may result in significant lapses in attention and vigilance. There is also a relationship between the amount of sleep restriction and performance on cognitive tasks, particularly those requiring sustained attention and higher level cognitive skills (*executive functions*), with a decay in performance correlating with declines in sleep amounts.

Both insufficient quantity and poor quality of sleep in children and adolescents usually result in excessive daytime sleepiness and decreased daytime alertness levels. Sleepiness in children may be recognizable as drowsiness, yawning, and other classic "sleepy behaviors," but can also be manifested as mood disturbance, including complaints of moodiness, irritability, emotional lability, depression, and anger; fatigue and daytime lethargy, including increased somatic complaints (headaches, muscle aches); cognitive impairment, including problems with memory, attention, concentration, decision making, and problem solving; daytime behavior problems, including hyperactivity, impulsivity, and noncompliance; and academic problems, including chronic tardiness related to insufficient sleep and school failure resulting from chronic daytime sleepiness.

To evaluate sleep problems, it is important to have an understanding of what constitutes "normal" sleep in children and adolescents. Sleep disturbances, as well as many characteristics of sleep itself, have some distinctly different features in children from sleep and sleep disorders in adults. Changes in sleep architecture and the evolution of sleep patterns and behaviors reflect the physiologic/chronobiologic, developmental, and social/environmental changes that are occurring across childhood. These trends may be summarized as the gradual assumption of more adult sleep patterns as children mature:

1. Sleep is *the* primary activity of the brain during early development; for example, by age 2 yr, the average child has spent 9500 hr (~13 months) asleep compared to 8000 hr awake, and between 2 and 5 yr, the time asleep is equal to the time awake.
2. There is a gradual decline in the average 24 hr sleep duration from infancy through adolescence, which involves a decrease in both diurnal and nocturnal sleep amounts. The decline in daytime sleep (scheduled napping) results in termination of naps typically by around 5 yr of age. There is also a gradual continued decrease in nocturnal sleep amounts into late adolescence; however, the typical adolescent still requires 9-9.25 hr of sleep per night.
3. There is also a decline in the relative percentage of REM sleep from birth (50% of sleep) through early childhood into adulthood (25-30%), and a similar initial predominance of SWS that peaks in early childhood, drops off abruptly after puberty (40-60% decline), and then further decreases over the life span. This SWS preponderance in early life has clinical significance; for example, the high prevalence of partial arousal parasomnias (sleepwalking and sleep terrors) in preschool and early school-age children is related to the relative increased percentage of SWS in this age group.
4. The within-sleep ultradian cycle lengthens from about 50 minutes in the term infant to 90-110 minutes in the school-age child. This, again, has clinical significance in that there is typically a brief arousal or awakening during the night at the termination of each ultradian cycle. As the length of the cycles increase, there is a concomitant decrease in the number of these end-of-cycle arousals ("night wakings").
5. A gradual shift in the circadian sleep–wake rhythm to a delayed (later) sleep onset and offset time, linked to pubertal stage rather than chronological age, begins in middle childhood and accelerates in early to mid-adolescence. This biologic phenomenon often coincides with environmental factors, which further delay bedtime and advance wake time and result in insufficient sleep duration, including exposure to electronic "screens" (i.e., television and computer) in the evening, social networking, academic and extracurricular demands, and early (before 8 AM) high school start times.
6. Increasing irregularity of sleep–wake patterns is typically observed across childhood into adolescence; this is characterized by increasingly larger discrepancies between school night and non–school night bedtimes and wake times, and increased "weekend oversleep" in an attempt to compensate for chronic weekday sleep insufficiency. This practice not only fails to adequately address performance deficits associated with insufficient sleep on school nights, but further exacerbates the normal adolescent phase delay and results in additional circadian disruption (analogous to that experienced by shift workers).

Table 19-1 lists normal developmental changes in children's sleep.

COMMON SLEEP DISORDERS

Childhood sleep problems may be conceptualized as resulting from either inadequate duration of sleep for age and sleep needs (insufficient sleep quantity) or disruption and fragmentation of sleep (poor sleep quality) as a result of frequent, repetitive, and brief arousals during sleep. Less common but important causes of sleep disturbance in childhood involve inappropriate timing of the sleep period (as occurs in circadian rhythm disturbances), or primary disorders of excessive daytime sleepiness (central hypersomnias such as narcolepsy). Insufficient sleep is usually the result of difficulty initiating (delayed sleep onset) and/or maintaining sleep (prolonged night wakings), but, especially in older children and adolescents, may also represent a conscious lifestyle decision to sacrifice sleep in favor of competing priorities, such as homework and social activities. The underlying causes of sleep onset delay/prolonged night wakings or sleep fragmentation may, in turn, be related to primarily behavioral factors (e.g., bedtime resistance resulting in shortened sleep duration) and/or medical causes (e.g., obstructive sleep apnea causing frequent, brief arousals).

Certain pediatric populations are relatively more vulnerable to acute or chronic sleep problems. These include children with medical problems, including chronic illnesses or pain conditions, such as cystic fibrosis, asthma, and rheumatoid arthritis, and acute illnesses, such as otitis media; children taking medications or ingesting substances with

Table 19-1 Normal Developmental Changes in Children's Sleep

AGE CATEGORY	SLEEP DURATION AND SLEEP PATTERNS	ADDITIONAL SLEEP ISSUES	SLEEP DISORDERS
Newborn (0-2 mo)	Total sleep: 10-19 hr per 24 hr (average = 13-14.5 hr), may be higher in premature babies Bottlefed babies generally sleep for longer periods (2-5 hr bouts) than breastfed babies (1-3 hr) Sleep periods are separated by 1-2 hr awake No established nocturnal–diurnal pattern in the 1st few wk; sleep is evenly distributed throughout the day and night, averaging 8.5 hr at night and 5.75 hr during the day	The American Academy of Pediatrics issued a formal recommendation in 2005 advocating against bed sharing in the 1st yr of life, instead encouraging proximate but separate sleeping surfaces for mother and infant. Safe sleep practices for infants: • Place the baby on his or her back to sleep at night and during nap times • Place the baby on a firm mattress with a well-fitting sheet in a safety-approved crib • Do not use pillows or comforters • Cribs should not have corner posts over 1/16 in high or decorative cutouts • Make sure the baby's face and head stay uncovered and clear of blankets and other coverings during sleep	Most sleep issues that are perceived as problematic at this stage represent a discrepancy between parental expectations and developmentally appropriate sleep behaviors Newborns who are noted by parents to be extremely fussy and persistently difficult to console are more likely to have underlying medical issues, such as colic, gastroesophageal reflux, and formula intolerance
Infant (2-12 mo)	Total sleep: average is 12-13 hr (note that there is great individual variability in sleep times during infancy) Nighttime: average is 9-10 hr Naps: average is 3-4 hr	Sleep regulation or self-soothing involves the infant's ability to negotiate the sleep–wake transition, both at sleep onset and following normal awakenings throughout the night. The capacity to self-soothe begins to develop in the 1st 12 wk of life, and is a reflection of both neurodevelopmental maturation and learning Sleep consolidation, or "sleeping through the night," is usually defined by parents as a continuous sleep episode without the need for parental intervention (e.g., feeding, soothing) from the child's bedtime through the early morning. Infants develop the ability to consolidate sleep between 6 wk and 3 mo	Behavioral insomnia of childhood; sleep onset association type Sleep-related rhythmic movements (head banging, body rocking)
Toddler (1-3 yr)	Total sleep: average is 11-13 hr Nighttime: average is 9.5-10.5 hr Naps: average is 2-3 hr; decrease from 2 naps to 1 at average age of 18 mo	Cognitive, motor, social, language developmental issues impact on sleep Nighttime fears develop; transitional objects, bedtime routines important	Behavioral insomnia of childhood, sleep onset association type Behavioral insomnia of childhood, limit setting type
Preschool (3-5 yr)	Nighttime: average is 9-10 hr Naps decrease from 1 nap to no nap Overall, 26% of 4 yr olds and just 15% of 5 yr olds nap	Persistent cosleeping tends to be highly associated with sleep problems in this age group Sleep problems may become chronic	Behavioral insomnia of childhood, limit setting type Sleepwalking Sleep terrors Nighttime fears/nightmares Obstructive sleep apnea
Middle childhood (6-12 hr)	9-11 hr	School and behavior problems may be related to sleep problems Media and electronics, such as television, computer, video games, and the Internet increasingly compete for sleep time Irregularity of sleep–wake schedules reflects increasing discrepancy between school and non–school night bedtimes and wake times	Nightmares Obstructive sleep apnea Insufficient sleep
Adolescence (>12 yr)	Average sleep duration 7-7.5 hr; only 20% of adolescents overall get the recommended 9-9.25 hr of sleep Later bedtimes; increased discrepancy sleep patterns weekdays/weekends	Puberty-mediated phase delay (later sleep onset and wake times), relative to sleep-wake cycles in middle childhood Earlier required wake times Environmental competing priorities for sleep	Insufficient sleep Delayed sleep phase disorder Narcolepsy Restless legs syndrome/periodic limb movement disorder

stimulant (e.g., psychostimulants, caffeine), sleep-disrupting (e.g., corticosteroids), or daytime-sedating (some anticonvulsants, α-agonists) properties; hospitalized children; and children with a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD), depression, bipolar disorder, and anxiety disorders. Children with neurodevelopmental disorders such as blindness, mental retardation, some chromosomal syndromes (e.g., Smith-Magenis, fragile X), and autism spectrum disorders have especially high rates of sleep disturbances for a wide variety of reasons. They may be on sleep-disrupting medications, they are often more prone to nocturnal seizures, they may be less easily entrained by environmental cues and thus more vulnerable to circadian disruption, and are more likely to have

comorbid psychiatric and behavioral conditions which that further predispose them to disrupted sleep.

Insomnia of Childhood

Insomnia is difficulty initiating and/or maintaining sleep that occurs despite age-appropriate time and opportunity for sleep and results in some degree of impairment in daytime functioning for the child and/or family (ranging from fatigue, irritability, lack of energy, and mild cognitive impairment to effects on mood, school performance, and quality of life). Insomnia may be of a short-term and transient nature (usually related to an acute event), or may be characterized as long-term and chronic. Insomnia is a set of *symptoms* with a large number of possible etiologies (e.g., pain, medication, medical and psychiatric conditions, learned behaviors). Insomnia, like many behavioral issues in children, is often primarily defined by parental concerns rather than by objective criteria, and therefore should be viewed in the context of family (i.e., maternal depression, stress), child (i.e., temperament, developmental level), and environmental (i.e., cultural practices, sleeping space) considerations.

One of the most common presentations of insomnia found in infants and toddlers is the **sleep-onset association type.** In this situation, the child learns to fall asleep only under certain conditions or associations, which typically require parental presence, such as being rocked or fed, and does not develop the ability to self-soothe. During the night, when the child experiences the type of brief arousal that normally occurs at the end of an ultradian sleep cycle or awakens for other reasons, the child is not able to get back to sleep without those same associations being present. The infant then "signals" the parent by crying (or coming into the parents' bedroom, if the child is ambulatory) until the necessary associations are provided. The presenting complaint is typically one of prolonged night waking resulting in insufficient sleep (for both child and parent).

Management of night wakings should include establishment of a set sleep schedule and bedtime routine, and implementation of a behavioral program. The treatment approach typically involves a program of rapid withdrawal (extinction) or more gradual withdrawal (graduated extinction) of parental assistance at sleep onset and during the night. Extinction ("cry it out") involves putting the child to bed at a designated bedtime, "drowsy but awake" to maximize sleep propensity. and then systematically ignoring any protests by the child until a set time the next morning. Although it has considerable empirical support, extinction is often not an acceptable choice for families. Graduated extinction involves gradually weaning the child from dependence on parental presence; typically, the parent leaves the room at "lights out" and then returns or "checks" periodically at fixed or successively longer intervals during the sleep–wake transition to provide brief reassurance until the child falls asleep. The exact time interval between checks is generally determined by the parents' tolerance for crying and the child's temperament. The goal is to allow the infant or child to develop skills in self-soothing during the night, as well as at bedtime. In older infants, the introduction of more appropriate sleep associations that will be readily available to the child during the night (transitional objects, such as a blanket or toy), in addition to positive reinforcement (i.e., stickers for remaining in bed), is often beneficial. If the child has become habituated to awaken for nighttime feedings (learned hunger), then these feedings should be slowly eliminated. Parents must be consistent in applying behavioral programs to avoid inadvertent, intermittent reinforcement of night wakings; they should also be forewarned that crying behavior often temporarily escalates at the beginning of treatment (*postextinction burst*).

Bedtime problems, including stalling and refusing to go to bed, are more common in preschool-age and older children. This type of insomnia is frequently related to inadequate **limit setting** and is often the result of parental difficulties in setting limits and managing behavior in general, and the inability or unwillingness to set consistent bedtime rules and enforce a regular bedtime in particular. The situation may be exacerbated by the child's oppositional behavior. In some cases the child's resistance at bedtime is the result of an underlying problem in falling asleep that is caused by other factors (medical conditions, such as asthma or medication use; a sleep disorder, such as restless legs syndrome; or anxiety) or a mismatch between the child's intrinsic circadian rhythm ("night owl") and parental expectations regarding an "appropriate" bedtime.

Table 19-2 Basic Principles of Healthy Sleep for Children

1. **Have a set bedtime and bedtime routine** for your child.
2. **Bedtime and wake-up time should be about the same time on school nights and non–school nights.** There should not be more than about an hour difference from one day to another.
3. **Make the hour before bed shared quiet time.** Avoid high-energy activities, such as rough play, and stimulating activities, such as watching television or playing computer games, just before bed.
4. **Don't send your child to bed hungry.** A *light* snack (such as milk and cookies) before bed is a good idea. Heavy meals within an hour or 2 of bedtime, however, may interfere with sleep.
5. **Avoid products containing caffeine for at least several hours before bedtime.** These include caffeinated sodas, coffee, tea, and chocolate.
6. **Make sure your child spends time outside every day,** whenever possible, and is involved in regular exercise.
7. **Keep your child's bedroom quiet and dark.** A low-level night light is acceptable for children who find completely dark rooms frightening.
8. **Keep your child's bedroom at a comfortable temperature** during the night (<24°C [75°F]).
9. **Don't use your child's bedroom for time-out or punishment.**
10. **Keep the television set out of your child's bedroom.** Children can easily develop the bad habit of "needing" the television to fall asleep. It's also much more difficult to control your child's viewing if the set is in the bedroom.

Successful treatment of limit-setting sleep problems generally involves a combination of parent education regarding appropriate limit setting, decreased parental attention for bedtime-delaying behavior, establishment of bedtime routines, and positive reinforcement (sticker charts) for appropriate behavior at bedtime; other behavioral management strategies that have empirical support include bedtime fading (temporarily setting the bedtime closer to the actual sleep onset time and then gradually advancing the bedtime to an earlier target bedtime). Older children may benefit from being taught relaxation techniques to help themselves fall asleep more readily. Following the principles of healthy sleep practices for children is essential (Table 19-2).

When the insomnia is not primarily a result of parent behavior or secondary to another sleep disturbance, or to a psychiatric or medical problem, it is often referred to as **psychophysiologic** or **primary** or **learned insomnia**. Primary insomnia occurs largely in adolescents and is characterized by a combination of learned sleep-preventing associations and heightened physiologic arousal resulting in a complaint of sleeplessness and decreased daytime functioning. A hallmark of primary insomnia is excessive worry about sleep and an exaggerated concern of the potential daytime consequences. The physiologic arousal can be in the form of cognitive hypervigilance, such as "racing" thoughts; in many individuals with insomnia an increased baseline level of arousal is further intensified by this secondary anxiety about sleeplessness. Treatment usually involves educating the adolescent about the principles of healthy sleep practices (Table 19-3), institution of a consistent sleep–wake schedule, avoidance of daytime napping, instructions to use the bed for sleep only and to get out of bed if unable to fall asleep (stimulus control), restricting time in bed to the actual time asleep (sleep restriction), addressing maladaptive cognitions about sleep, and teaching relaxation techniques to reduce anxiety. Hypnotic medications are rarely needed.

Obstructive Sleep Apnea

Sleep-disordered breathing (**SDB**) in children encompasses a broad spectrum of respiratory disorders that occur exclusively in or are

Table 19-3 Basic Principles of Healthy Sleep for Adolescents

1. **Wake up and go to bed at about the same time** every night. Bedtime and wake-up time should not differ from school to non–school nights by more than approximately 1 hr.
2. **Avoid sleeping in on weekends** to "catch up" on sleep. This makes it more likely that you will have problems falling asleep.
3. If you take **naps**, they should be **short** (no more than 1 hr) and **scheduled in the early to midafternoon**. However, if you have a problem with falling asleep at night, **napping** during the day may make it worse and should be avoided.
4. **Spend time outside** every day. Exposure to sunlight helps to keep your body's internal clock on track.
5. **Exercise regularly.** Exercise may help you fall asleep and sleep more deeply.
6. **Use your bed for sleeping only.** Don't study, read, listen to music, watch television, etc., on your bed.
7. Make the 30-60 minutes before a **quiet or wind-down time**. Relaxing, calm, enjoyable activities, such as reading a book or listening to calm music, help your body and mind slow down enough to let you get to sleep. Don't study, watch exciting/scary movies, exercise, or get involved in "energizing" activities just before bed.
8. Eat regular meals and **don't go to bed hungry**. A light snack before bed is a good idea; eating a full meal in the hour before bed is not.
9. **Avoid** eating or drinking products containing **caffeine** from dinner time on. These include caffeinated sodas, coffee, tea, and chocolate.
10. **Do not use alcohol.** Alcohol disrupts sleep and may cause you to awaken throughout the night.
11. **Smoking disturbs sleep.** Don't smoke at least 1 hr before bed (and preferably, not at all!).
12. Don't use **sleeping pills, melatonin**, or other **nonprescription sleep aids** to help you sleep unless specifically recommended by your doctor. These can be dangerous, and the sleep problems often return when you stop taking the medicine.

exacerbated by sleep, and includes primary snoring and upper airway resistance syndrome, as well as apnea of prematurity (see Chapter 101.2) and central apnea (see Chapter 418). **Obstructive sleep apnea (OSA)**, the most important clinical entity within the SDB spectrum, is a respiratory disorder that is characterized by repeated episodes of prolonged upper airway obstruction during sleep despite continued or increased respiratory effort, resulting in complete (apnea) or partial (hypopnea; ≥30% reduction in airflow accompanied by ≥3% O_2 desaturation and/or arousal) cessation of airflow at the nose and/or mouth, as well as in disrupted sleep. Both intermittent hypoxia and the multiple arousals resulting from these obstructive events likely contribute to significant metabolic, cardiovascular, and neurocognitive/neurobehavioral morbidity.

Primary snoring is defined as snoring without associated ventilatory abnormalities on overnight polysomnogram (e.g., apneas or hypopneas, hypoxemia, hypercapnia) or respiratory-related arousals, and is a manifestation of the vibrations of the oropharyngeal soft tissue walls that occur when an individual attempts to breathe against increased upper airway resistance during sleep. Although generally considered nonpathologic, primary snoring in children with may still be associated with subtle breathing abnormalities during sleep, including evidence of increased respiratory effort, which, in turn, may be associated with adverse neurodevelopmental outcomes.

Etiology

OSA results from an anatomically or functionally narrowed upper airway; this typically involves some combination of decreased upper airway patency (upper airway obstruction and/or decreased upper airway diameter), increased upper airway collapsibility (reduced pharyngeal muscle tone), and decreased drive to breathe in the face of reduced upper airway patency (reduced central ventilatory drive) (Table 19-4). Upper airway obstruction varies in degree and level (i.e., nose, nasopharynx/oropharynx, hypopharynx) and is most commonly caused by adenotonsillar hypertrophy, although tonsillar size does not necessarily correlate with degree of obstruction, especially in older children. Other causes of airway obstruction include allergies associated with chronic rhinitis/nasal obstruction; craniofacial abnormalities, including hypoplasia/displacement of the maxilla and mandible; gastroesophageal reflux with resulting pharyngeal reactive edema (see Chapter 323); nasal septal deviation (see Chapter 376); and velopharyngeal flap cleft palate repair. Reduced upper airway tone may result from neuromuscular diseases, including hypotonic cerebral palsy and muscular dystrophies (see Chapter 609), or hypothyroidism (see Chapter 565). Reduced central ventilatory drive may be present in some children with Arnold-Chiari malformation (see Chapter 418), rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation, and meningomyelocele (see Chapter 591). In other situations, the etiology is mixed; individuals with Down syndrome (see Chapter 81), by virtue of their facial anatomy, hypotonia, macroglossia, and central adiposity, as well as the increased incidence of hypothyroidism, are at particularly high risk for OSA, with some estimates of as great as 70% prevalence.

Table 19-4 Anatomic Factors That Predispose to Obstructive Sleep Apnea and Hypoventilation in Children

NOSE
Anterior nasal stenosis
Choanal stenosis/atresia
Deviated nasal septum
Seasonal or perennial rhinitis
Nasal polyps, foreign body, hematoma, mass lesion
NASOPHARYNGEAL AND OROPHARYNGEAL
Adenotonsillar hypertrophy
Macroglossia
Cystic hygroma
Velopharyngeal flap repair
Cleft palate repair
Pharyngeal mass lesion
CRANIOFACIAL
Micrognathia/retrognathia
Midface hypoplasia (e.g., trisomy 21, Crouzon, Apert syndrome)
Mandibular hypoplasia (Pierre Robin sequence, Treacher Collins, Cornelia de Lange)
Craniofacial trauma
Skeletal and storage diseases
Achondroplasia
Storage diseases (e.g., glycogen, Hunter, Hurler syndrome)

Although many children with OSA are of normal weight, an increasingly large percentage are overweight or obese, and many of these children are school-age and younger (see Chapter 47). There is a significant correlation between weight and SDB (e.g., habitual snoring, OSA, sleep-related hypoventilation). Although adenotonsillar hypertrophy also plays an important etiologic role in overweight/obese children with OSA, mechanical factors related to an increase in the amount of adipose tissue in the throat (pharyngeal fat pads), neck (increased neck circumference), and chest wall and abdomen can create increased upper airway resistance, worsen gas exchange, and increased work of breathing, particularly in the supine position and during REM sleep. There may be a component of blunted central ventilatory drive in response to hypoxia/hypercapnia and hypoventilation as well (see Chapter 418.3), particularly in children with morbid or syndrome-based (e.g., Prader-Willi) obesity. Overweight and obese children and adolescents are at a particularly high risk for metabolic and cardiovascular complications of SDB, such as insulin resistance and systemic hypertension; morbidly obese children are also be at increased risk for postoperative complications as well as residual OSA following adenotonsillectomy.

Epidemiology

Overall prevalence of parent-reported snoring in the pediatric population is approximately 8%; "always" snoring is reported in 1.5-6%, and "often" snoring in 3-15%. When defined by parent-reported symptoms, the prevalence of OSA is 4-11%. The prevalence of pediatric OSA as documented by overnight sleep studies utilizing ventilatory monitoring procedures (e.g., in-lab polysomnography [PSG], home studies) is 1-4% overall, with a reported range of 0.1-13%. Prevalence is also affected by the demographic characteristics, such as age (increased prevalence between 2 and 8 yr), gender (more common in boys, especially after puberty), race/ethnicity (increased prevalence in African-American and Asian children), history of prematurity, and family history of OSA.

Pathogenesis

The upregulation of inflammatory pathways, as indicated by an increase in peripheral markers of inflammation such as C-reactive protein, appear to be linked to metabolic dysfunction (e.g., insulin resistance, dyslipidemia) in both obese and nonobese children with OSA. Both systemic inflammation and arousal-mediated increases in sympathetic autonomic nervous system activity with altered vasomotor tone may be key contributors to increased cardiovascular risk in both adults and children with OSA. Mechanical stress on the upper airway induced by chronic snoring may also result in both local mucosal inflammation of adenotonsillar tissues and subsequent upregulation of inflammatory molecules, most notably leukotrienes. Another potential mechanism that may mediate cardiovascular sequelae in both adults and children with OSA is altered endothelial function.

One of the primary mechanisms by which OSA is believed to exert negative influences on cognitive function appears to involve repeated episodic arousals from sleep leading to sleep fragmentation and resulting sleepiness. An equally important role may be intermittent hypoxia that leads directly to systemic inflammatory vascular changes in the brain. Levels of inflammatory markers such as C-reactive protein and cytokine interleukin-6 are elevated in children with OSA and are also associated with cognitive dysfunction.

Clinical Manifestations

The clinical manifestations of OSA may be divided into sleep-related and daytime symptoms. The most common nocturnal manifestations of OSA in children and adolescents are loud, frequent, and disruptive snoring, breathing pauses, choking or gasping arousals, restless sleep, and nocturnal diaphoresis. Many children who snore do not have OSA, but very few children with OSA do not snore. Children, like adults, tend to have more frequent and more severe obstructive events in REM sleep and when sleeping in the supine position. Children with OSA may adopt unusual sleeping positions, keeping their necks hyperextended to maintain airway patency. Frequent arousals associated with obstruction may result in nocturnal awakenings, but are more likely to cause fragmented sleep.

Daytime symptoms of OSA include mouth breathing and dry mouth, chronic nasal congestion/rhinorrhea, hyponasal speech, morning headaches, difficulty swallowing, and poor appetite. Children with OSA may have secondary enuresis, which has been postulated to result from the disruption of the normal nocturnal pattern of antidiuretic hormone or atrial natriuretic peptide secretion. Partial arousal parasomnias (sleepwalking and sleep terrors) may occur more frequently in children with OSA, related to the frequent associated arousals and an increased percentage of SWS.

One of the most important but frequently overlooked sequelae of OSA in children is the effect on mood, behavior, learning, and academic functioning. The neurobehavioral consequences of OSA in children include daytime sleepiness with drowsiness, difficulty in morning waking, and unplanned napping or dozing off during activities, although evidence of frank hypersomnolence tends to be less common in children compared to adults with OSA (except in very obese children). Mood changes include increased irritability, mood instability and emotional dysregulation, low frustration tolerance, and depression/anxiety. Behavioral issues include both "internalizing" (i.e., increased somatic complaints and social withdrawal) and "externalizing" behaviors, including aggression, impulsivity, hyperactivity, oppositional behavior, and conduct problems. There is a substantial overlap between the clinical impairments associated with OSA and the diagnostic criteria for ADHD, including inattention, poor concentration, and distractibility (see Chapter 33). There may be a selective impact of OSA specifically on "executive functions," which include cognitive flexibility, task initiation, self-monitoring, planning, organization, and self-regulation of affect and arousal; executive function deficits are also a hallmark of ADHD.

Many of the studies that have looked at changes in behavior and neuropsychologic functioning in children following treatment (usually adenotonsillectomy) for OSA have largely documented significant improvement in outcomes, in both the short and long term, of OSA syndrome posttreatment, including daytime sleepiness, mood, behavior, academics, and quality of life. However, most studies failed to find a dose-dependent relationship between OSA in children and specific neurobehavioral/neurocognitive deficits, suggesting that other factors may influence neurocognitive outcomes, including individual genetic susceptibility, racial/ethnic background, environmental influences such as passive smoking exposure, and comorbid conditions, such as obesity, shortened sleep duration, and the presence of other sleep disorders. In adults, cognitive functions impacted by OSA include deficits in attention, long-term visual and verbal memory, visuospatial functioning, and executive function while language and psychomotor function do not appear to be impacted.

Diagnosis

The 2012 revised American Academy of Pediatrics clinical practice guidelines provide excellent information for the evaluation and management of uncomplicated childhood OSA (Table 19-5). There are no physical examination findings that are truly pathognomonic for OSA, and most healthy children with OSA appear normal; certain physical examination findings may suggest OSA. Growth parameters may be abnormal (obesity or, less commonly, failure to thrive), and there may be evidence of chronic nasal obstruction (hyponasal speech, mouth breathing, septal deviation, "adenoidal facies"), as well as signs of atopic disease (i.e., "allergic shiners"). Oropharyngeal examination may reveal enlarged tonsils, excess soft tissue in the posterior pharynx, and a narrowed posterior pharyngeal space. Any abnormalities of the facial structure, such as retrognathia and/or micrognathia, midfacial hypoplasia, best appreciated by inspection of the lateral facial profile, increase the likelihood of OSA and should be noted. In very severe cases, there may be evidence of pulmonary hypertension, right-sided heart failure, and cor pulmonale; systemic hypertension may occur, especially in obese children.

Because no combination of clinical history and physical findings can accurately predict which children with snoring have OSA, the gold standard for diagnosing OSA remains an in-lab overnight **polysomnogram**.

Overnight PSG is a technician-supervised, monitored study that documents physiologic variables during sleep; sleep staging, arousal measurement, cardiovascular parameters, and body movements (electroencephalography, electrooculography, chin and leg electromyography, electrocardiogram, body position sensors, and video recording), and a combination of breathing monitors (oronasal thermal sensor and nasal air pressure transducer for airflow), chest/abdominal monitors (e.g., inductance plethysmography for respiratory effort, pulse oximeter for O_2 saturation, end-tidal or transcutaneous CO_2 for CO_2 retention, snore microphone). The polysomnographic parameter most commonly used in evaluating for sleep disordered breathing is the apnea-hypopnea index (AHI), which indicates the number of apneic and hypopneic events per hour of sleep. It should be noted that currently there are no universally accepted polysomnographic normal reference values and parameters for diagnosing OSA in children, and it is still unclear which parameters best predict morbidity. Normal preschool and school-age children generally have a total AHI of less than 1.5 (obstructive AHI <1), and this is the most widely used cutoff value for OSA in children 12 yr and below; in older adolescents, the adult cutoff of an AHI ≥5 is generally used. In cases in which the AHI

Table 19-5 American Academy of Pediatrics Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome (September 2012)

Key Action Statement 1: Screening for OSAS As part of routine health maintenance visits, clinicians should inquire whether the child or adolescent snores. If the answer is affirmative or if a child or adolescent presents with signs or symptoms of OSAS, clinicians should perform a more focused evaluation. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 2A: Polysomnography If a child or adolescent snores on a regular basis and has any of the complaints or findings of OSAS, clinicians should either (1) obtain a polysomnogram (Evidence Quality A; Key Action strength: Recommendation) *or* (2) refer the patient to a sleep specialist or otolaryngologist for a more extensive evaluation (Evidence quality D; Key Action strength: Option). (Evidence Quality: Grade A for polysomnography, Grade D for specialist referral; Recommendation Strength: Recommendation.)
Key Action Statement 2B: Alternative Testing If polysomnography is not available, then clinicians may order alternative diagnostic tests, such as nocturnal video recording, nocturnal oximetry, daytime nap polysomnography, or ambulatory polysomnography. (Evidence Quality: Grade C; Recommendation Strength: Option.)
Key Action Statement 3: Adenotonsillectomy If a child is determined to have OSAS, has a clinical examination consistent with adenotonsillar hypertrophy, and does not have a contraindication to surgery, the clinician should recommend adenotonsillectomy as the first line of treatment. If the child has OSAS but does not have adenotonsillar hypertrophy, other treatment should be considered (see Key Action Statement 6). Clinical judgment is required to determine the benefits of adenotonsillectomy compared with other treatments in obese children with varying degrees of adenotonsillar hypertrophy. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 4: High-Risk Patients Undergoing Adenotonsillectomy Clinicians should monitor high-risk patients undergoing adenotonsillectomy as inpatients postoperatively. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5: Reevaluation Clinicians should clinically reassess all patients with OSAS for persisting signs and symptoms after therapy to determine whether further treatment is required. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 5B: Reevaluation of High-Risk Patients Clinicians should reevaluate high-risk patients for persistent OSAS after adenotonsillectomy, including those who had a significantly abnormal baseline polysomnogram, have sequelae of OSAS, are obese, or remain symptomatic after treatment, with an objective test (see Key Action Statement 2) or refer such patients to a sleep specialist. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 6: CPAP Clinicians should refer patients for CPAP management if symptoms/signs or objective evidence of OSAS persists after adenotonsillectomy or if adenotonsillectomy is not performed. (Evidence Quality: Grade B; Recommendation Strength: Recommendation.)
Key Action Statement 7: Weight Loss Clinicians should recommend weight loss in addition to other therapy if a child/adolescent with OSAS is overweight or obese. (Evidence Quality: Grade C; Recommendation Strength: Recommendation.)
Key Action Statement 8: Intranasal Corticosteroids Clinicians may prescribe topical intranasal corticosteroids for children with mild OSAS in whom adenotonsillectomy is contraindicated or for children with mild postoperative OSAS. (Evidence Quality: Grade B; Recommendation Strength: Option.)

Adapted from Marcus CL, Brooks LJ, Draper KA, et al: Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics* 130:576-584, 2012.

is between 1 and 5 obstructive events per hour, clinical judgment regarding risk factors for SDB, evidence of daytime sequelae, and the technical quality of the overnight sleep study should determine further management.

Treatment

There are presently no universally accepted guidelines regarding the indications for treatment of pediatric SDB (i.e., including primary snoring and OSA). Current recommendations largely emphasize weighing what is known about the potential cardiovascular, metabolic, and neurocognitive sequelae of SDB in children in combination with the individual healthcare professional's clinical judgment. The decision of whether and how to treat OSA specifically in children is contingent on a number of parameters, including severity (nocturnal symptoms, daytime sequelae, sleep study results), duration of disease, and individual patient variables such as age, comorbid conditions, and underlying etiologic factors. Figure 19-1 presents a guide to decision making. In the case of moderate (AHI 5-10) to severe disease (AHI >10), the decision to treat is usually straightforward, and most pediatric sleep experts recommend that any child with an apnea hypopnea index >5 should be treated. However, a large randomized trial of early adenotonsillectomy vs watchful waiting with supportive care, 46% of the control group children normalized on PSG (compared to 79% of the early adenotonsillectomy group) during the 7 mo observation period.

In the majority of cases of pediatric OSA, adenotonsillectomy is the first-line treatment in any child with significant adenotonsillar hypertrophy, even in the presence of additional risk factors such as obesity. Adenotonsillectomy in uncomplicated cases generally (70-90% of children) results in complete resolution of symptoms; regrowth of adenoidal tissue after surgical removal occurs in some cases. Groups considered high-risk include young children (<3 yr old), as well as those with severe OSA documented by PSG, significant clinical sequelae of OSA (e.g., failure to thrive), or associated medical conditions, such as craniofacial syndromes, morbid obesity, and hypotonia. All patients should be reevaluated postoperatively to determine whether additional evaluation, a repeat polysomnogram and/or treatment are required. The American Academy of Sleep Medicine recommends that in high-risk groups (children with obesity, craniofacial anomalies, Down syndrome or moderate-severe OSA) or in children with continued symptoms of OSA, a follow-up sleep study at least 6 wk postadenotonsillectomy is indicated.

Additional treatment measures that may be appropriate include weight loss, positional therapy (attaching a firm object, such as a tennis ball, to the back of a sleep garment to prevent the child from sleeping in the supine position), and aggressive treatment of additional risk factors when present, such as asthma, seasonal allergies, and gastroesophageal reflux; there is evidence that intranasal corticosteroids and leukotriene inhibitors may be helpful in reducing upper airway inflammation in mild OSA. Other surgical procedures, such as

Algorithm for the Diagnosis and Treatment of Pediatric OSA

Step 1. Child is at risk for OSA (one or more):

- Parents report symptoms of OSA
- Physician identifies symptoms of OSA using structured questionnaire
- Conditions predisposing to OSA are present (adenotonsillar hypertrophy-allergic rhinitis, obesity, craniofacial abnormalities, neuromuscular disorders)
- History of prematurity
- Family history of OSA

Step 2a. OSA-related morbidity is recognized (one or more):

- Systolic or diastolic blood pressure >95th percentile for gender, age and height, or pulmonary hypertension
- Daytime sleepiness, hyperactivity, inattention, academic difficulties
- Inadequate somatic growth
- Enuresis

Step 2b. Conditions frequently coexisting with OSA are identified (one or more):

- Recurrent otitis media, tympanostomy tubes
- Recurrent wheezing
- Oral-motor dysfunction
- Metabolic syndrome

Step 3. Factors predicting OSA persistence are present (at least one):

- Male gender
- Increasing Body Mass Index percentile, development of obesity

Step 4. Objective evaluation for OSA severity:

- Overnight polysomnography
- If not available: nocturnal pulse oximetry

Step 5. Child is a potential candidate for treatment if at risk for OSA (step 1) and at least one criterion:

- AHI >5 episodes/h
- AHI 1–5 and OSA morbidity present (step 2a)
- AHI 1–5 and risk factor for OSA persistence (step 3)
- AHI 1–5 and neuromuscular disorder or craniofacial abnormalities present (step 1)
- ≥3 SpO_2 drops <90% and ≥3 clusters of desaturation events or alternatively, desaturation (≥3%) index ≥3.5 episodes/h

Or if polysomnography or oximetry not available:

- Frequently or almost always loud snoring and male gender
- Frequently or almost always loud snoring and sleepiness
- Frequently or almost always loud snoring and learning problems

Priority for treatment increases if coexisting OSA-related conditions are present that may also improve with treatment (step 2b)

Step 6. Stepwise treatment approach:

1. Weight control for obesity
2. Trial of nasal corticosteroids for adenoidal hypertrophy prior to adenoidectomy
3. Adenotonsillectomy for adenotonsillar hypertrophy
4. Orthodontic devices for mandibular malpositioning, narrow maxilla
5. nCPAP for: i) residual OSA after adenotonsillectomy; ii) OSA related to obesity, neuromuscular disorders or craniofacial abnormalities and unresponsive to other measures
6. Craniofacial surgery or tracheostomy if other treatment modalities fail

Notes

1. Information collected in steps 1–4 is used to identify children requiring treatment for OSA (step 5) and to determine the appropriate therapeutic modalities (step 6). Please refer to the text for details.
2. Step 6 represents a hierarchical approach to OSA treatment.

Figure 19-1 Algorithm for the diagnosis and treatment of pediatric OSA. *(From Kaditis A, Kheirandish-Gozal L, Gozal D: Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers,* Sleep Med *13(3):217–227, 2012, Figure 1.)*

uvulopharyngopalatoplasty, and maxillofacial surgery (e.g., mandibular distraction osteogenesis), are seldom performed in children. Oral appliances, such as mandibular advancing devices and palatal expanders, may be considered in select cases; consultation with a pediatric dentist/orthodontist is recommended. Exercises to address abnormal tongue position and low upper airway tone (i.e., myofunctional therapy) have been shown to be of some benefit in mild cases of OSA.

Continuous or bilevel positive airway pressure is the most common treatment for OSA in adults and can be used successfully in children and adolescents. Positive airway pressure may be recommended if removing the adenoids and tonsils is not indicated, if there is residual disease following adenotonsillectomy, or if there are major risk factors that are not amenable to treatment with surgery (obesity, hypotonia). Positive airway pressure delivers humidified, warmed air through an interface (mask, nasal pillows) that, under pressure, effectively "splints" the upper airway open. Optimal pressure settings (that abolish or significantly reduce respiratory events without increasing arousals or central apneas) are determined in the sleep lab during a full night positive airway pressure titration. Careful attention should be paid to education of the child and family and desensitization protocols should be implemented in most cases to increase the likelihood of adherence. Efficacy studies at the current pressure and retitrations should be conducted periodically with long-term use (at least annually or in association with significant weight changes or resumption of SDB symptoms).

Parasomnias

Parasomnias are episodic nocturnal behaviors that often involve cognitive disorientation and autonomic and skeletal muscle disturbance. Parasomnias may be further characterized as occurring primarily during non-REM sleep (partial arousal parasomnias) or in association with REM sleep, including nightmares, hypnogogic hallucinations, and sleep paralysis; other common parasomnias include sleep-talking and hypnic jerks or "sleep starts" (Fig. 19-2). Sleep-related movement disorders, including restless legs syndrome/periodic limb movement disorder (RLS/PLMD) and rhythmic movement disorder (head banging, body rocking), are reviewed in "Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder and Rhythmic Movements" below.

Etiology

Partial arousal parasomnias, which include **sleepwalking, sleep terrors**, and **confusional arousals** are more common in preschool and school-age children because of the relatively higher percentage of SWS in younger children. They typically occur when SWS predominates (i.e., in the first third of the night); in contrast, nightmares, which are much more common than the partial arousal parasomnias but are often confused with them, are concentrated in the last third of the night, when REM sleep is most prominent. Any factor that is associated with an increase in the relative percentage of SWS (certain medications, previous sleep restriction) may increase the frequency of events

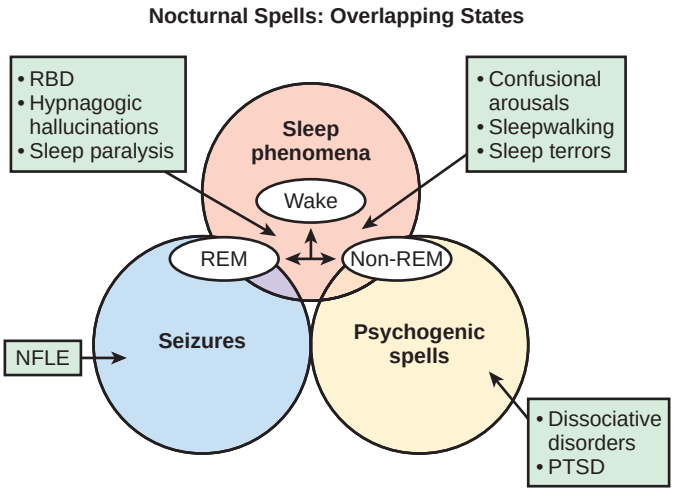

Figure 19-2 Overlapping states of being. Parasomnias are explainable on the basic notion that sleep and wakefulness are not mutually exclusive states but may dissociate and oscillate rapidly. The abnormal admixture of the 3 states of being (non-REM sleep, REM sleep, and wakefulness) may overlap, giving rise to parasomnias. REM parasomnias occur because of the abnormal intrusion of wakefulness into REM sleep and likewise non-REM parasomnias, such as sleepwalking, occur because of abnormal intrusions of wakefulness into non-REM sleep. Other nocturnal spells that may be confused with parasomnias include NFLE and psychogenic spells such as posttraumatic stress disorder (PTSD), dissociated disorders. AHI, Apnea–hypopnea index (mean number of central + mixed + obstructive apneas and hypopneas per hour of total sleep); NFLE, nocturnal frontal lobe epilepsy; RBD, REM behavior disorder. *(Modified from Mahowald MW, Schenck CH. Non-rapid eye movement sleep parasomnias.* Neurol Clin *23(4):1078, vii, 2005.)*

in a predisposed child. There appears to be a genetic predisposition for both sleepwalking and night terrors. Partial arousal parasomnias may also be difficult to distinguish from nocturnal seizures. Table 19-6 summarizes similarities and differences among these nocturnal arousal events.

Epidemiology

Many children (15-40%) **sleepwalk** on at least 1 occasion; the prevalence of children who regularly sleepwalk is approximately 17%, and 3-4% have frequent episodes. Sleepwalking (somnambulism) may persist into adulthood, with the prevalence in adults of approximately 4%. The prevalence is approximately 10 times greater in children with a family history of sleepwalking. Approximately 1-3% of children experience **sleep terrors**, primarily during the preschool and elementary school yr, and the age at onset is usually between 4 and 12 yr. Because of the common genetic predisposition, the prevalence of sleep terrors in children who sleepwalk is approximately 10%. Although sleep terrors can occur at any age from infancy through adulthood, most individuals outgrow sleep terrors by adolescence. **Confusional arousals** (sleep drunkenness, sleep inertia) commonly co-occur with sleepwalking and sleep terrors; prevalence rates have been estimated to be upward of 15% in children ages 3-13 yr.

Clinical Manifestations

The partial arousal parasomnias have several features in common. Because they typically occur at the transition out of "deep" or SWS, partial arousal parasomnias have clinical features of both the awake (ambulation, vocalizations) and the sleeping (high arousal threshold, unresponsiveness to the environment) states; there is usually amnesia for the events. The duration is typically a few minutes (sleep terrors) to 30-40 minutes (confusional arousals). Sleep terrors are sudden in onset and characteristically involve a high degree of autonomic arousal (i.e., tachycardia, dilated pupils), whereas confusional arousals typically arise more gradually from sleep, may involve thrashing around but usually not displacement from bed, and are often accompanied by slow mentation, disorientation and confusion on forced arousal from SWS or upon waking in the morning. Sleepwalking may be associated with safety concerns (e.g., falling out of windows, wandering outside). Avoidance of, or increased agitation with, comforting by parents or attempts at awakening are also common features of all partial arousal parasomnias.

REM sleep behavior disorder, is characterized by episodes of arousal during REM sleep, loss of REM atonia, and acting out of dreams including vocalizations during night-time sleep or naps. Some patients have CNS lesions (tumors), narcolepsy, seizures, neuropsychiatric medications, or neurodegenerative diseases.

Treatment

Management of partial arousal parasomnias involves some combination of parental education and reassurance, healthy sleep practices, and avoidance of exacerbating factors such as sleep restriction and caffeine. Particularly in the case of sleepwalking, it is important to institute safety precautions such as use of gates in doorways and at the top of staircases, locking of outside doors and windows, and installation of parent notification systems such as bedroom door alarms. Scheduled awakenings, a behavioral intervention that involves having the parent wake the child approximately 15-30 min before the time of night that the first parasomnia episode is most likely to be successful in situations in which partial arousal episodes occur on a nightly basis. Pharmacotherapy is rarely necessary, but may be indicated in cases of frequent or severe episodes, high risk of injury, violent behavior, or serious disruption to the family; the primary pharmacologic agents used are potent SWS suppressants, primarily benzodiazepines and tricyclic antidepressants.

Sleep-Related Movement Disorders: Restless Legs Syndrome/Periodic Limb Movement Disorder and Rhythmic Movements

RLS (Willis Ekbom syndrome) is a chronic neurologic disorder, characterized by an almost irresistible urge to move the legs, often accompanied by uncomfortable sensations in the lower extremities. Both the urge to move and the sensations are usually worse at rest and in the evening and are at least partially relieved by movement, including walking, stretching, and rubbing, but only as long as the motion continues. RLS is a clinical diagnosis that is based on the presence of these key symptoms. PLMD is characterized by periodic, repetitive, brief (0.5-10 sec), and highly stereotyped limb jerks typically occurring at 20-40 sec intervals. These movements occur primarily during sleep, most commonly occur in the legs, and frequently consist of rhythmic extension of the big toe and dorsiflexion at the ankle. The diagnosis of **periodic limb movements** (PLMs) requires overnight PSG to document the characteristic limb movements with anterior tibialis electromyography leads.

Etiology

"Early-onset" RLS (i.e., onset of symptoms before 35-40 yr of age), often termed "primary" RLS, appears to have a particularly strong genetic component, with a 6-7 fold increase in prevalence in first-degree relatives of RLS patients. The mode of inheritance is complex and several genetic loci have been identified (*MEIS1, BTBD9, MAP2K5*). Low serum iron levels in both adults and children may be an important etiologic factor for the presence and severity of both RLS symptoms and PLMs. As a marker of decreased iron stores, serum ferritin levels in both children and adults with RLS are frequently low (i.e., less than 50 μg/mL). The underlying mechanism that has been postulated is related to the role of iron as a cofactor in tyrosine hydroxylation, a rate-limiting step in dopamine synthesis; in turn, dopaminergic dysfunction has been implicated as playing a key role particularly in the genesis of the sensory component of RLS, as well as in PLMD. Certain medical conditions, including diabetes mellitus, end-stage renal disease, cancer, rheumatoid arthritis, hypothyroidism, and pregnancy, may also be associated with RLS/PLMD, as are specific medications

Table 19-6 Key Similarities and Differentiating Features Between Non-REM and REM Parasomnias as Well as Nocturnal Seizures

	CONFUSIONAL AROUSALS	SLEEP TERRORS	SLEEPWALKING	NIGHTMARES	RBD	NOCTURNAL SEIZURES
Time	Early	Early	Early-Mid	Late	Late	Any
Sleep stage	SWA	SWA	SWA	REM	REM	Any
EEG discharges	–	–	–	–	–	+
Scream	–	++++	–	++	+	+
Autonomic activation	+	++++	+	+	+	+
Motor activity	–	+	+++	+	++++	++++
Awakens	–	–	–	+	+	+
Duration (minutes)	0.5–10	1–10	2–30	3–20	1–10	5–15
Postevent confusion	+	+	+	–	–	+
Age	Child	Child	Child	Child–Young Adult	Older Adult	Adolescent, Young Adult
Genetics	+	+	+	–	–	±
Organic CNS lesion	–	–	–	–	++	++++

EEG, Electroencephalogram; RBD, REM behavior disorder; REM, rapid eye movement; SWA, slow-wave arousal
From Avidan A, Kaplish N: The parasomnias: epidemiology, clinical features and diagnostic approach. Clin Chest Med *31:353–370, 2010.*

(e.g., antihistamines such as diphenhydramine, antidepressants, and H_2 blockers such as cimetidine) and substances (notably, caffeine).

Epidemiology

Previous studies found prevalence rates of RLS in the pediatric population ranging from 1-6%; approximately 2% of 8-17 yr olds meet the criteria for "definite" RLS. Prevalence rates of PLMs greater than 5 per hour in clinical populations of children referred for sleep studies range from 5-27%; in survey studies of PLM symptoms, rates are 8-12%. Several studies in referral populations have found that PLMs occur in as much as 25% of children diagnosed with ADHD.

Clinical Manifestations

In addition to the urge to move the legs and the sensory component, most RLS episodes begin or are exacerbated by rest or inactivity, such as lying in bed to fall asleep or riding in a car for prolonged periods. A unique feature of RLS is that the timing of symptoms also appears to have a circadian component, in that they often peak in the evening hours. Some children may complain of "growing pains," although this is considered a nonspecific feature. Because RLS symptoms are usually worse in the evening, bedtime struggles and difficulty falling asleep are 2 of the most common presenting complaints. In contrast to patients with RLS, individuals with PLMs are usually unaware of these movements, but children may complain of morning muscle pain or fatigue; these movements may result in arousals during sleep and consequent significant sleep disruption. Parents of children with RLS/PLMD may report that their child is a restless sleeper, moves around or even falls out of bed during the night.

Treatment

The decision of whether and how to treat RLS depends on the level of severity (intensity, frequency, and periodicity) of sensory symptoms, the degree of interference with sleep, and the impact of daytime sequelae in a particular child or adolescent. With PLMs, for an index (PLMs per hour) less than 5, usually no treatment is recommended; for an index greater than 5, the decision to specifically treat PLMs should be based on the presence or absence of nocturnal symptoms (restless or nonrestorative sleep) and daytime clinical sequelae. The acronym AIMS represents a comprehensive approach to the treatment of RLS: A = avoidance of exacerbating factors such as caffeine and drugs which increase symptoms, I = iron supplementation when appropriate, M = muscle activity (increased physical activity, muscle relaxation, application of heat/cold compresses), and S = sleep (regular sleep schedule and sufficient sleep for age). Iron supplements should be instituted if serum ferritin levels are <50; it should be kept in mind that ferritin is an acute-phase reactant and thus may be falsely elevated (i.e., normal) in the setting of a concomitant illness. The recommended dose of ferrous sulfate is typically in the range of 3-6 mg/kg/day for a duration of 3 mo. Medications that increase dopamine levels in the CNS, such as ropinirole and pramipexole, have been found to be effective in relieving RLS/PLMD symptoms in adults; data in children are extremely limited.

Sleep-related rhythmic movements, including head banging, body rocking, and head rolling, are characterized by repetitive, stereotyped, and rhythmic movements or behaviors that involve large muscle groups. These behaviors typically occur with the transition at sleep at bedtime, but also at nap times and following nighttime arousals. Children typically engage in these behaviors as a means of soothing themselves to (or back to) sleep; they are much more common in the 1st yr of life and usually disappear by preschool age. In most instances, rhythmic movement behaviors are benign, because sleep is not significantly disrupted as a result of these movements and associated significant injury is rare. These behaviors typically occur in normally developing children, and in the vast majority of cases their presence does not indicate that there is some underlying neurologic or psychologic problem. Usually, the most important aspect in management of sleep-related rhythmic movements is reassurance to the family that this behavior is normal, common, benign, and self-limited.

Narcolepsy

Hypersomnia is a clinical term that is used to describe a group of disorders characterized by recurrent episodes of **excessive daytime sleepiness (EDS)**, reduced baseline alertness, and/or prolonged nighttime sleep periods that interfere with normal daily functioning. It is important to recognize that there are many potential causes of EDS, which may be broadly grouped as "extrinsic" (e.g., secondary to insufficient and/or fragmented sleep) or "intrinsic" (e.g., resulting from an increased need for sleep). **Narcolepsy** is a chronic lifelong CNS disorder, typically presenting in adolescence and early adulthood, that is characterized by profound daytime sleepiness and resultant significant functional impairment. Other symptoms frequently associated with narcolepsy, including cataplexy (sudden and temporary loss of muscle tone), hypnogogic/hypnopompic (immediately before falling asleep/awakening) hallucinations, and sleep paralysis, may be conceptualized

as representing the "intrusion" of REM sleep features into the waking state (see further descriptions below).

Etiology

The genesis of narcolepsy with cataplexy (type 1) is thought to be related to a specific deficit in the hypothalamic orexin/hypocretin neurotransmitter system. The underlying pathogenesis of narcolepsy involves selective loss of cells that secrete hypocretin/orexin in the lateral hypothalamus; it has been postulated that autoimmune mechanisms, possibly triggered by viral infections, in combination with a genetic predisposition and environmental factors, may be involved. Human leukocyte antigen testing also shows a strong association with narcolepsy; however, the vast majority of individuals with this antigen do not have narcolepsy, and most (90%), but not all, patients with narcolepsy with cataplexy are HLA-DQB1*0602–positive. Patients with narcolepsy without cataplexy (type 2) are increasingly thought to have a significantly different pathophysiology; they are much less likely to be HLA-DQB1*0602–positive. Although the majority of cases of narcolepsy are considered idiopathic, "secondary" narcolepsy with cataplexy is associated with CNS insults, including hypothalamic tumors and cranial irradiation, and specific genetic syndromes (Prader-Willi [see Chapter 81.8] and Niemann-Pick type C [see Chapter 86.4]). Narcolepsy has been reported in Finnish children after immunization with the AS03 adjuvanted AH1N1 influenza vaccine.

Epidemiology

The prevalence of narcolepsy is reported to be between 3 and 16 per 10,000, with the prevalence of narcolepsy with cataplexy approximately 0.2-0.5/10,000. The risk of developing narcolepsy with cataplexy in a 1st-degree relative of a narcoleptic patient is estimated at 1-2%; this represents an increase of 10-40–fold compared to the general population.

Clinical Manifestations and Diagnosis

The typical onset of symptoms of narcolepsy is in adolescence and early adulthood, although symptoms may initially present in school-age and even younger children. The early manifestations of narcolepsy are often ignored, misinterpreted, or misdiagnosed as other medical, neurologic, and psychiatric conditions, and the appropriate diagnosis is frequently delayed for a number of years.

The most prominent clinical manifestation of narcolepsy is profound daytime sleepiness, characterized by both an increased baseline level of daytime drowsiness and by the repeated occurrence of sudden and unpredictable sleep episodes. These "**sleep attacks**" are often described as "irresistible" in that the child or adolescent is unable to stay awake despite considerable effort, and they occur even in the context of normally stimulating activities (e.g., during meals, in the middle of a conversation). Very brief (several seconds) sleep attacks may also occur in which the individual may "stare off," appear unresponsive, or continue to engage in an ongoing activity (automatic behavior). EDS may also be manifested by increased nighttime sleep needs and extreme difficulty waking in the morning or after a nap. **Cataplexy** is considered pathognomonic for narcolepsy. Cataplexy is rarely the first symptom of narcolepsy, but it often develops within the 1st yr of the onset of EDS. It is described as an abrupt, bilateral, partial (especially knees and head/jaw) or complete loss of muscle tone, without loss of consciousness, classically triggered by an intense positive emotion (e.g., laughter, surprise). The cataplectic attacks are typically brief (seconds to minutes) but in children may last for hours or days ("status cataplecticus"), and they are fully reversible, with complete recovery of normal tone when the episode ends. "Cataplectic facies" is a clinical feature unique to the pediatric population and is characterized by slack facial musculature, a protruding tongue, and slurred speech. **Hypnogogic/hypnopompic hallucinations** involve vivid visual, auditory, and sometimes tactile sensory experiences occurring during transitions between sleep and wakefulness, primarily at sleep offset (hypnopompic) and sleep onset (hypnogogic). **Sleep paralysis** is the inability to move or speak for a few seconds or minutes at sleep onset or offset, and often accompanies the hallucinations. Other symptoms associated with narcolepsy include disrupted nocturnal sleep, impaired cognition, inattention, and behavioral and mood dysregulation.

Overnight PSG followed by a multiple sleep latency test are strongly recommended components of the evaluation of a patient with profound unexplained daytime sleepiness or suspected narcolepsy. The purpose of the overnight PSG is to evaluate for primary sleep disorders, such as OSA that may cause EDS. The multiple sleep latency test involves a series of 5 opportunities to nap (20 min long), during which narcoleptics demonstrate a pathologically shortened mean sleep onset latency (typically less than 5 minutes) as well as at least 2 periods of REM sleep occurring immediately after sleep onset.

Treatment

An individualized narcolepsy treatment plan usually involves education, good sleep hygiene, behavioral changes, and medication. Scheduled naps are often helpful. Medications such as psychostimulants and modafinil are often prescribed to control the EDS, whereas antidepressants (serotonin reuptake inhibitors, venlafaxine) may also be used to reduce cataplexy. Sodium oxybate is a drug that appears to both positively impact daytime sleepiness and REM-associated phenomena, such as cataplexy, hypnogogic hallucinations, and sleep paralysis. Most of these medications are not approved for use in children. The goal should be to allow the fullest possible return of normal functioning in school, at home, and in social situations.

Delayed Sleep Phase Disorder

Delayed sleep phase disorder (DSPD), a circadian rhythm disorder, involves a significant, persistent, and intractable phase shift in sleep–wake schedule (later sleep onset and wake time) that conflicts with the individual's normal school, work, and/or lifestyle demands. DSPD may occur at any age, but is most common in adolescents and young adults.

Etiology

Individuals with DSPD often start out as night owls; that is, they have an underlying predisposition or circadian preference for staying up late at night and sleeping late in the morning, especially on weekends, holidays, and summer vacations. The underlying pathophysiology of DSPD is still unknown, although some authors have theorized that it involves an intrinsic abnormality in the circadian oscillators that govern the timing of the sleep period.

Epidemiology

Studies indicate that the prevalence of DSPD may be as high as 7-16% in adolescents and young adults.

Clinical Manifestations

The most common clinical presentation is sleep initiation insomnia when the individual attempts to fall asleep at a "socially acceptable" desired bedtime, accompanied by extreme difficulty getting up in the morning even for desired activities, and daytime sleepiness. Sleep maintenance is generally not problematic, and no sleep onset insomnia is experienced if bedtime coincides with the preferred sleep onset time (e.g., on weekends, school vacations). School tardiness and frequent absenteeism with a decline in academic performance are often present.

Treatment

The treatment of DSPD usually has 3 components, all directed toward the goals of shifting the sleep–wake schedule to an earlier more desirable time, and maintaining the new schedule. The initial step involves shifting the sleep–wake schedule to the desired earlier times, usually with gradual (i.e., in 15-30 min increments every few days) advancement of bedtime in the evening and rise time in the morning; more significant phase delays (i.e., difference between current sleep onset and desired bedtime) may require "chronotherapy," which involves delaying bedtime and wake time by 2-3 hr every 24 hr "forward around the clock" until the target bedtime is reached. Because melatonin secretion is highly sensitive to light, exposure to light in the morning (either natural light or a "light box," which typically produces predominantly

blue light) and avoidance of evening light exposure are often beneficial. Exogenous oral melatonin supplementation may also be used; larger mildly sedating doses (i.e., 5 mg) are typically given at bedtime, but some studies have suggested that physiologic doses of oral melatonin (0.3-0.5 mg) administered in the afternoon or early evening (i.e., 5-7 hr before the habitual sleep onset time) seem to be most effective in advancing the sleep phase.

HEALTH SUPERVISION

It is especially important for pediatricians to both screen for and recognize sleep disorders in children and adolescents during health encounters. The well-child visit is an opportunity to educate parents about normal sleep in children and to teach strategies to prevent sleep problems from developing (primary prevention) or from becoming chronic, if problems already exist (secondary prevention). Developmentally appropriate screening for sleep disturbances should take place in the context of every well child visit and should include a range of potential sleep problems; one Table 19-7 outlines a simple sleep screening algorithm, the "BEARS." Because parents may not always be aware of sleep problems, especially in older children and adolescents, it is also important to question the child directly about sleep concerns. The recognition and evaluation of sleep problems in children requires both an understanding of the association between sleep disturbances and daytime consequences, such as irritability, inattention, and poor impulse control, and familiarity with the developmentally appropriate differential diagnoses of common presenting sleep complaints (difficulty initiating and maintaining sleep, episodic nocturnal events). In particular, an assessment of sleep patterns and possible sleep problems should be part of the initial evaluation of every child presenting with behavioral and/or academic problems, especially ADHD.

Effective preventive measures include educating parents of newborns about normal sleep amounts and patterns. The ability to regulate sleep, or control internal states of arousal to fall asleep at bedtime and to fall back asleep during the night, begins to develop in the 1st 8-12 wk of life. Thus, it is important to recommend that parents put their 2-4 mo old infants to bed "drowsy but awake" if they wish to avoid dependence on parental presence at sleep onset and foster the infants' ability to self-soothe. Other important sleep issues include discussing the importance of regular bedtimes, bedtime routines, and transitional objects for toddlers, and providing parents and children with basic information about healthy sleep practices, recommended sleep amounts at different ages, and education regarding signs that a child is not getting sufficient sleep (i.e., wakes with difficulty in the morning, sleeps longer when allowed on weekends and vacation days).

The cultural and family context within which sleep problems in children occur should be considered; for example, cosleeping of infants and parents is a common and accepted practice in many racial/ethnic groups and the goal of independent self-soothing in young infants may not be shared by these families. Anticipatory guidance needs to balance cultural awareness with the critical importance of "safe sleep" conditions in sudden infant death syndrome prevention (i.e., sleeping in the supine position, avoidance of bed-sharing but encouragement of room-sharing in the 1st yr of life) (see Chapter 375). On the other hand, the institution of cosleeping by parents as an attempt to address a child's underlying sleep problem (so-called reactive cosleeping), rather than as a conscious family decision, is likely to yield only a temporary respite from the problem and may set the stage for more significant sleep issues.

EVALUATION OF PEDIATRIC SLEEP PROBLEMS

The clinical evaluation of a child presenting with a sleep problem involves obtaining a careful medical history to assess for potential medical causes of sleep disturbances, such as allergies, concomitant medications, and acute or chronic pain conditions. A developmental history is important because of the aforementioned increased risk of sleep problems in children with neurodevelopmental disorders.

Table 19-7 BEARS Sleep Screening Algorithm

The BEARS instrument is divided into 5 major sleep domains, providing a comprehensive screen for the major sleep disorders affecting children 2-18 yr old. Each sleep domain has a set of age-appropriate "trigger questions" for use in the clinical interview.
B = Bedtime problems
E = Excessive daytime sleepiness
A = Awakenings during the night
R = Regularity and duration of sleep
S = Snoring

	Examples of Developmentally Appropriate Trigger Questions		
	TODDLER/PRESCHOOL CHILD (2-5 YR)	SCHOOL-AGED CHILD (6-12 YR)	ADOLESCENT (13-18 YR)
1. Bedtime problems	Does your child have any problems going to bed? Falling asleep?	Does your child have any problems at bedtime? (P) Do you any problems going to bed? (C)	Do you have any problems falling asleep at bedtime? (C)
2. Excessive daytime sleepiness	Does your child seem overtired or sleepy a lot during the day? Does your child still take naps?	Does your child have difficulty waking in the morning, seem sleepy during the day, or take naps? (P) Do you feel tired a lot? (C)	Do you feel sleepy a lot during the day? In school? While driving? (C)
3. Awakenings during the night	Does your child wake up a lot at night?	Does your child seem to wake up a lot at night? Any sleepwalking or nightmares? (P) Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)	Do you wake up a lot at night? Do you have trouble getting back to sleep? (C)
4. Regularity and duration of sleep	Does your child have a regular bedtime and wake time? What are they?	What time does your child go to bed and get up on school days? Weekends? Do you think your child is getting enough sleep? (P)	What time do you usually go to bed on school nights? Weekends? How much sleep do you usually get? (C)
5. Snoring	Does your child snore a lot or have difficulty breathing at night?	Does your child have loud or nightly snoring or any breathing difficulties at night? (P)	Does your teenager snore loudly or nightly? (P)

C, child; P, parent.

Assessment of the child's current level of functioning (school, home) is a key part of evaluating possible mood, behavioral, and neurocognitive sequelae of sleep problems. Current sleep patterns, including the usual sleep duration and sleep–wake schedule, are often best assessed with a sleep diary, in which a parent (or adolescent) records daily sleep behaviors for an extended period (1-2 wk). A review of sleep habits, such as bedtime routines, daily caffeine intake, and the sleeping environment (e.g., temperature, noise level) may reveal environmental factors that contribute to the sleep problems. Nocturnal symptoms that may be indicative of a medically based sleep disorder, such as OSA (loud snoring, choking or gasping, sweating) or PLMs (restless sleep, repetitive kicking movements), should be elicited. An overnight sleep study is not routinely warranted in the evaluation of a child with sleep problems unless there are symptoms suggestive of OSA or periodic leg movements, unusual features of episodic nocturnal events, or daytime sleepiness that is unexplained.

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Behavioral and Psychiatric Disorders

PART III

Chapter 20

Assessment and Interviewing

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It is estimated that 13-20% of children living in the United States experience a mental illness in a given year, at a cost of nearly $300 billion. In children, mental illness is more prevalent than leukemia, diabetes, and AIDS combined; more money is spent on mental disorders than on any other childhood illness, including asthma, trauma, upper respiratory infections, and infectious diseases. Although nearly 1 in 5 youths suffers from a psychiatric disorder, 75-80% do not receive needed mental health services. Those who do, primarily receive services in nonspecialty sectors (primary care, schools, child welfare, juvenile justice) where mental health expertise may be limited. Untreated or inadequately treated psychiatric disorders are associated with significant adverse sequelae, including increased morbidity and mortality, failure to achieve mastery in life's developmental tasks (education, occupation, marriage, child-rearing), cross-generational transmission of disadvantage, and substantial costs to society. Psychiatric disorders negatively affect the course of physical illness, adherence to treatment regimens, and use of medical resources. The strong continuity into adulthood of child psychiatric disorders further underscores the importance of early identification and treatment.

AIMS OF ASSESSMENT

A psychosocial assessment in the pediatric setting should determine whether there are signs and symptoms of cognitive, developmental, emotional, behavioral, or social difficulties and characterize these signs and symptoms sufficiently to determine their appropriate management. The focus of the assessment varies with the nature of the presenting problem and the clinical setting. Under emergency circumstances, the focus may be limited to an assessment of dangerousness to self or others for the purpose of determining the safest level of care. In routine circumstances (well-child visits), the focus may be broader, involving a screen for symptoms and functional impairment in all major psychosocial domains. The challenge for the pediatric practitioner will be to determine as accurately as possible whether the presenting signs and symptoms are likely to meet criteria for a psychiatric disorder and whether the severity and complexity of the disorder suggests referral to a mental health specialist or management in the pediatric setting.

PRESENTING PROBLEMS

Infants are presented for clinical attention because of problems with eating and/or sleep regulation, concerns about failure to gain weight and length, poor social responsiveness, limited vocalization, apathy or disinterest, and response to strangers that is excessively fearful or overly familiar. Psychiatric disorders most commonly diagnosed during this period are rumination and reactive attachment disorders.

Toddlers are assessed for concerns about sleep problems, language delay, motor hyperactivity, extreme misbehavior, extreme shyness, inflexible adherence to routine, difficulty separating from parents, struggles over toilet training, dietary issues, and testing limits. Developmental delays and more subtle physiologic, sensory, and motor processing problems can be presented as concerns. Problems with goodness of fit between the child's temperament and the parents' expectations can create relationship difficulties that also require assessment. Psychiatric disorders most commonly diagnosed during this period are autism spectrum and reactive attachment disorders.

Presenting problems in *preschoolers* include elimination difficulties, sibling jealousy, lack of friends, self-destructive impulsiveness, multiple fears, nightmares, refusal to follow directions, somatization, speech that is difficult to understand, and temper tantrums. Psychiatric disorders most commonly diagnosed in this period are autism spectrum, communication, disruptive, attention-deficit/hyperactivity, anxiety (separation, selective mutism), reactive attachment, gender dysphoria, and sleep disorders.

Older children are brought to clinical attention because of concerns about angry or sad mood, bedwetting, overactivity, impulsiveness, distractibility, learning problems, arguing, defiance, nightmares, school refusal, bullying or being bullied, worries and fears, somatization, communication problems, tics, and withdrawal or isolation. Psychiatric disorders most commonly diagnosed during this period are attention-deficit/hyperactivity, disruptive, anxiety (generalized, phobias), elimination, somatic symptom, specific learning, and tic disorders.

Adolescents are assessed for concerns about the family situation, experimentation with sexuality and drugs, delinquency and gang involvement, friendship patterns, issues of independence, identity formation, self-esteem, and morality. Psychiatric disorders most commonly diagnosed during this period are anxiety (panic, social anxiety), depressive, bipolar, psychotic, obsessive-compulsive, impulse control, conduct, substance-related, and eating disorders.

GENERAL PRINCIPLES OF THE PSYCHOSOCIAL INTERVIEW

Psychosocial interviewing in the context of a routine pediatric visit requires adequate time and privacy. The purpose of this line of inquiry should be explained to the child and parents ("to make sure things are going OK at home, at school, and with friends"), along with the limits of confidentiality. Thereafter, the first goal of the interview is to build rapport with both the child and the parents.

With the parents, this rapport is grounded in respect for the parents' knowledge of their child, their role as the central influence in their child's life, and their desire to make a better life for their child. Parents often feel anxious or guilty because they believe that problems in a child imply that their parenting skills are inadequate. Parents' experiences of their own childhood influence the meaning a parent places on a child's feelings and behavior. A good working alliance allows mutual discovery of the past as it is active in the present and permits potential distortions to be modified more readily. Developmentally appropriate overtures can facilitate rapport with the child. Examples include playing peek-a-boo with an infant, racing toy cars with a preschooler, commenting on sports with a child who is wearing a baseball cap, and discussing music with a teenager who is wearing a rock music t-shirt.

After an overture with the child, it is helpful to begin with family-centered interviewing, in which the parent is invited to present any psychosocial concerns (development, thinking, feelings, behavior, peer relationships) about the child. With adolescent patients, it is important to conduct a separate interview to give the adolescent an opportunity to confirm or refute the parent's presentation and to present the problem from his or her perspective. Following the family's undirected presentation of the primary problem, it is important to shift to direct questioning to clarify the duration, frequency, and severity of symptoms, associated distress or functional impairment, and the developmental and environmental context in which the symptoms occur.

Because of the high degree of comorbidity of psychosocial problems in children, after eliciting the presenting problem, the pediatric practitioner should then briefly screen for problems in all of the major

Table 20-1 Mental Health Action Signs

- Feeling very sad or withdrawn for more than 2 weeks
- Seriously trying to harm or kill yourself, or making plans to do so
- Sudden overwhelming fear for no reason, sometimes with a racing heart or fast breathing
- Involvement in many fights, using a weapon, or wanting to badly hurt others
- Severe out-of-control behavior that can hurt yourself or others
- Not eating, throwing up, or using laxatives to make yourself lose weight
- Intense worries or fears that get in the way of your daily activities
- Extreme difficulty in concentrating or staying still that puts you in physical danger or causes school failure
- Repeated use of drugs or alcohol
- Severe mood swings that cause problems in relationships
- Drastic changes in your behavior or personality

From The Action Signs Project, Center for the Advancement of Children's Mental Health at Columbia University.

developmentally appropriate categories of cognitive, developmental, emotional, behavioral, and social disturbance, including problems with mood, anxiety, attention, behavior, thinking and perception, substance use, social relatedness, eating, elimination, development, language, and learning. This can be preceded by a transition statement such as, "Now I'd like to ask about some other issues that I ask all parents and kids about."

A useful guide for this area of inquiry is provided by the "11 Action Signs" (Table 20-1), which was designed to give frontline clinicians the tools needed to recognize early symptoms of mental disorders. Functional impairment can be assessed by inquiring about symptoms and function in the major life domains, including home and family, school, peers, and community. These domains are included in the HEADSS (home, education, activities, drugs, sexuality, suicide/depression) interview guide, often used in the screening of adolescents (Table 20-2).

The nature and severity of the presenting problem(s) can be further characterized through the use of a standardized self-, parent-, or teacher-informant rating scale (Table 20-3 lists some of the scales in the public domain). A rating scale is a type of measure that provides a relatively rapid assessment of a specific construct with an easily derived numerical score that is readily interpreted. The use of rating scales can ensure systematic coverage of relevant symptoms, quantify symptom severity, and document a baseline against which treatment effects can be measured.

Clinical experience and methodologic studies suggest that parents and teachers are more likely than the child to report externalizing problems (disruptive, impulsive, overactive, or antisocial behavior). Children may be more likely to report anxious or depressive feelings, including suicidal thoughts and acts, of which the parents may be unaware. Functional impairment also can be assessed with self and other rating scales. Although concerns have been raised about children's competence as self-reporters (because of limitations in linguistic skills; self-reflection; emotional awareness; ability to monitor behavior, thoughts, and feelings; and tendency toward social desirability), children and adolescents can be reliable and valid self-reporters.

Clinicians are encouraged to become familiar with the psychometric characteristics and appropriate use of at least 1 broad-based measure of psychosocial problems, such as the *Strengths and Difficulties Questionnaire* (SDQ) (http://www.sdqinfo.org/py/sdqinfo/b0.py), the *Pediatric Symptom Checklist* (PSC) (http://www.brightfutures.org/mentalhealth/pdf/professionals/ped_sympton_chklst.pdf), or the *Swanson, Nolan, and Pelham–IV* (SNAP-IV) (http://psychiatryassociatespc.com/doc/SNAP-IV_Parent&Teacher.pdf). These measures are available in multiple languages. If the interview or broad-based rating scale suggests difficulties in one or more specific symptom areas, the clinician can follow with a psychometrically sound, appropriate narrow-band instrument such as the *Vanderbilt ADHD Diagnostic Rating Scale* for attention, behavior, and learning problems, the *Center for Epidemiological Studies Depression Scale for Children* (CES-DC) or *Mood and Feelings Questionnaire* (MFQ) for depression, or the *Screen for Child Anxiety Related Emotional Disorders* (SCARED) for anxiety.

Table 20-2 HEADSS Screening Interview for Taking a Rapid Psychosocial History

PARENT INTERVIEW

Home
- How well does the family get along with each other?

Education
- How well does your child do in school?

Activities
- What does your child like to do?
- Does your child do anything that has you really concerned?
- How does your child get along with peers?

Drugs
- Has your child used drugs or alcohol?

Sexuality
- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/depression
- Has your child ever been treated for an emotional problem?
- Has your child ever intentionally tried to hurt him-/herself or made threats to others?

ADOLESCENT INTERVIEW

Home
- How do you get along with your parents?

Education
- How do you like school and your teachers?
- How well do you do in school?

Activities
- Do you have a best friend or group of good friends?
- What do you like to do?

Drugs
- Have you used drugs or alcohol?

Sexuality
- Are there any issues regarding sexuality or sexual activity that are of concern to you?

Suicide/depression
- Everyone feels sad or angry some of the time. How about you?
- Did you ever feel so upset that you wished you were not alive or so angry you wanted to hurt someone else badly?

HEADSS, home, education, activities, drugs, sexuality, suicide/depression.
From Cohen E, MacKenzie RG, Yates GL: HEADSS, a psychosocial risk assessment instrument: implications for designing effective intervention programs for runaway youth, J Adolesc Health *12:539–544, 1991.*

Children and adolescents scoring above standardized cutpoints in most cases should be referred to a qualified mental health professional for assessment and treatment, because scores in this range are highly correlated with clinically significant psychiatric disorders. Youths scoring just below or slightly above cutpoints (e.g., subsyndromal or mild mood, anxiety, or disruptive behavior disorders) may be appropriate for management in the pediatric setting, as may youths scoring well above cutpoints for certain neurodevelopmental disorders (attention-deficit/hyperactivity, autism spectrum, tic).

The safety of the child in the context of the home and community is of paramount importance. The interview should sensitively assess whether the child has been exposed to any frightening events, including abuse, neglect, bullying, marital discord, or domestic or community violence; whether the child shows any indication of dangerousness to self or others or a severely altered mental status (psychosis, intoxication, rage, hopelessness); or whether the child (if age-appropriate) has been involved in any risky behavior, including running away, staying out without permission, truancy, gang involvement, experimentation with substances, and unprotected sexuality. The interview also should assess the capacity of the parents to adequately provide for the child's

Table 20-3 Select List of Mental Health Rating Scales in the Public Domain

INSTRUMENTS	FOR AGES (yr)	INFORMANT: NUMBER OF ITEMS	TIME TO COMPLETE (min)	AVAILABLE AT
BROAD BAND				
Pediatric Symptom Checklist (PSC)	3-18	Parent: 35, 17 Youth: 35, 17	5-10	www.massgeneral.org/psychiatry
SNAP-IV Rating Scale	6-18	Parent, Teacher: 90	10	www.adhd.net
Strengths & Difficulties Questionnaire (SDQ)	16 4-17	Parent, Teacher, Child: 25	5	www.sdqinfo.com
NARROW BAND				
Anxiety				
Self-Report for Childhood Anxiety Related Emotional Disorders (SCARED)	8-18	Parent, Child: 41	5	www.wpic.pitt.edu/research
Attention and Behavior				
Vanderbilt ADHD Diagnostic Rating Scale	6-12	Parent: 55 Teacher: 43	10	www.brightfutures.org
Autism				
Modified Checklist for Autism in Toddlers (M-CHAT)	16-30 months	Parent: 23	5-10	https://www.m-chat.org/index.php
Depression				
Center for Epidemiological Studies Depression Scale for Children (CES-DC)	6-18	Child: 20	5	www.brightfutures.org
Mood and Feelings Questionnaire (MFQ) Short Version	7-18	Parent: 34 Child: 33	<5	www.devepi.duhs.duke.edu/mfq.html

physical, emotional, and social needs or whether parental capacity has been diminished by psychiatric disorder, family dysfunction, or the sequelae of disadvantaged socioeconomic status. Any indications of threats to the child's safety should be immediately followed by thorough assessment and protective action.

INDICATIONS FOR REFERRAL

There is variability in the level of confidence pediatric practitioners perceive in diagnosing psychosocial problems in children and adolescents. Pediatric practitioners who have familiarity with psychiatric diagnostic criteria may feel confident diagnosing certain disorders, particularly the neurodevelopmental and other biologically based disorders (attention-deficit/hyperactivity, autism spectrum, and tic disorders, enuresis, encopresis, insomnia, anorexia). The disorders about which pediatric practitioners might have less diagnostic confidence include the disruptive/impulse control/conduct, depressive, bipolar, anxiety, psychotic, obsessive-compulsive, trauma-related, somatic symptom, and substance-related disorders. Pediatric practitioners should refer to a qualified mental health practitioner whenever they experience diagnostic uncertainty with a child who has distressing or functionally impairing psychosocial symptoms. Children who upon initial assessment are found to have indicators of dangerousness always should be immediately referred to a qualified mental health professional.

PSYCHIATRIC DIAGNOSTIC EVALUATION

The objectives of the psychiatric diagnostic evaluation of the child and adolescent are to determine whether psychopathology or developmental risk is present and if so, to establish an explanatory formulation and a differential diagnosis, and to determine whether treatment is indicated and if so, to develop a treatment plan and facilitate the parents' and child's involvement in the plan. The aims of the diagnostic evaluation are to clarify the reasons for the referral; to obtain an accurate accounting of the child's developmental functioning and the nature and extent of the child's psychosocial difficulties, functional impairment, and subjective distress; and to identify potential individual, family, or environmental factors that might account for, influence, or ameliorate these difficulties. The issues relevant to diagnosis and treatment planning can span genetic, constitutional, and temperamental factors; individual psychodynamics; cognitive, language, and social skills; family patterns of interaction and child- rearing practices; and community, school, and socioeconomic influences.

The focus of the evaluation is developmental; it seeks to describe the child's functioning in various realms and to assess the child's adaptation in these areas relative to that expected for the child's age and phase of development. The developmental perspective extends beyond current difficulties to vulnerabilities that can affect future development and as such are important targets for preventive intervention. Vulnerabilities may include subthreshold or subsyndromal difficulties that, especially when manifold, often are accompanied by significant distress or impairment and as such are important as potential harbingers of future problems.

Throughout the assessment, the clinician focuses on identifying a realistic balance of vulnerabilities and strengths in the child, in the parents, and in the parent–child interactions. From this strength-based approach, over time a hopeful family narrative is co-constructed to frame the child's current developmental progress and predict the child's ongoing progress within the scope of current risk and protective factors.

Although the scope of the evaluation will vary with the clinical circumstance, the full *psychiatric diagnostic evaluation* has 12 major components: the presenting problem(s) and the context in which they occur; a review of psychiatric symptoms; a risk assessment; a history of psychiatric treatment; a medical history, a developmental history; an educational history; a family history; a mental status examination; a biopsychosocial clinical formulation; a *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) diagnosis; and a treatment plan. For infants and young children, the presenting problem and historical information is derived from parents and other informants. As children mature, they become increasingly important contributors to the information base, and they become the primary source of information in later adolescence. Information relevant to formulation and differential diagnosis is derived in multiple ways, including directive and nondirective questioning, interactive play, and observation of the child alone and together with the caregiver(s).

The *explication of the presenting problem(s)* includes information about onset, duration, frequency, and severity of symptoms, associated

distress and/or functional impairment, and predisposing, precipitating, perpetuating, and ameliorating contextual factors. The *symptom review* assesses potential comorbidity in the major domains of child and adolescent psychopathology, including problems with intellectual, communication, motor, learning, and developmental capabilities; attention deficits; angry, sad, or elated mood; anxiety; obsessions or compulsions; trauma or stress reactions; somatic symptoms; eating, elimination, sleep, or gender disturbances; disruptive, impulse-control, or conduct problems; psychosis; or substance abuse or addiction. The *risk assessment* includes a careful assessment of risk status, including suicidality, homicidality, assaultiveness, self-injuriousness, and involvement in risky behavior or situations. The *history of psychiatric treatment* includes gathering information about prior emergency mental health assessments, psychiatric hospitalizations, day treatment, psychotherapy, pharmacotherapy, and nontraditional treatments.

The *medical history* includes information about the source of primary care, the frequency of health supervision, past and current medical illnesses and treatments, and the youth and family's history of adherence to medical treatment. A systematic review of organ or functional systems facilitates the identification of abnormalities that require investigation or monitoring by the pediatric practitioner, as well as the identification of cautionary factors related to the prescription of psychotropic medication. The *developmental history* includes information about the circumstances of conception, pregnancy, or adoption; pre-, peri-, or postnatal insults; attachment and temperament; cognitive, motor, linguistic, emotional, social, and moral development; health habits, sexuality, and substance use (as age-appropriate), coping and defensive structure, future orientation, and perceived strengths. The *educational history* includes schools attended; typical grades, attendance, and behavior; special education services; disciplinary actions; social relationships; extracurricular activities; and barriers to learning. The *family history* assesses family composition; sociodemographic and neighborhood characteristics; domiciliary arrangements; parenting capacities; family function; medical and psychiatric histories of family members; and cultural/religious affiliations. The *mental status examination* assesses appearance, relatedness, cognition, communication, mood, affective expression, behavior, memory, orientation, and perception.

The evaluation culminates in a *biopsychosocial formulation and diagnosis*. The *biopsychosocial formulation* is derived from an assessment of vulnerabilities and strengths in the biologic, psychologic, and social domains and serves to identify targets for intervention and treatment. In the biologic domain, major vulnerabilities include a family history of psychiatric disorder and personality or behavior problems, and a personal history of pre-, peri-, or postnatal insults; cognitive or linguistic impairments; physical illness; and a difficult temperament. In the psychological domain, major vulnerabilities include failure to achieve developmental tasks and maladaptive coping and defensive styles. In the social domain, major vulnerabilities include parental incapacity; unskilled parenting; family dysfunction; social isolation; unfavorable school setting; unsupportive community structures; and sociodemographic disadvantage. Major strengths include cognitive and linguistic capability; physical health and attractiveness; stable, moderate temperamental characteristics; and stable and supportive parenting, family, peer, and community structures. The biopsychosocial formulation can be organized to reflect predisposing, precipitating, perpetuating, and protective (ameliorating) factors (the "4 Ps") influencing the development of the observed psychopathology.

The *diagnosis* must be made in accordance with the nomenclature in the DSM-5. This nomenclature categorizes cross-sectional phenomenology into discrete clinical syndromes and seeks to improve diagnostic accuracy at the expense of theories of causation and dimensional presentations. By DSM-5 convention, if diagnostic criteria are met, the diagnosis is given (except where hierarchical rules apply); consequently psychiatric comorbidity is a common occurrence.

The psychiatric diagnostic evaluation culminates in a *treatment plan* that brings the broad array of targeted psychosocial interventions to the service of the child. Diagnoses drive the choice of evidence-based psychotherapeutic and psychopharmacologic treatments. The formulation drives the selection of interventions targeted at biologic, psychologic, and social vulnerabilities and strengths. Many of these treatments and interventions are described in the succeeding chapters.

SPECIAL CONSIDERATIONS IN THE DIAGNOSTIC EVALUATION OF INFANTS AND YOUNG CHILDREN

Psychiatric evaluation of infants and young children includes the domains of physiology, temperament, motor behavior, affective behavior, social behavior, and communication. Although much of the information in these domains will be derived from parent report, much also can be gleaned from nonverbal behavior and observation of the parent-child interaction. Observations should include predominant affective tone of parent and child (positive, negative, apathetic); involvement in the situation (curiosity, disinterest); social responsiveness (mutuality of gaze, auditory responsiveness); and reactions to transitions (including separation).

A screen for maternal depression (see http://www.medicalhomeportal.org/clinical-practice/screening-and-prevention/maternal-depression for several examples) is critical at this stage, as is an assessment of the mother's (or other caregiver's) ability to rapidly respond on a contingent basis to the child's expressed needs, regulate the child's rapid shifts of emotion and behavior, and provide a stimulus shelter to prevent the child from being overwhelmed.

Standardized screening instruments *(Bayley Scales of Infant Development)* designed for this age group can be helpful in systematizing the evaluation. In addition, the *Infant, Toddler and Preschool Mental Status Exam* (ITP-MSE) is a reference tool that describes how traditional categories of the mental status exam can be adapted to observations of young children. Additional categories, including sensory and state regulation, have been added that reflect important areas of development in young children.

Diagnostic systems that are more age-appropriate than DSM-5 have been developed for infants and young children. These systems include the *Research Diagnostic Criteria—Preschool Age* (RDC-PA) and the *Zero to Three Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood-Revised* (DC: 0-3R). The DC: 0-3R includes relationship classification that assesses the range of interactional adaptation in each parent–child relationship and regulation disorders of sensory processing that identify a range of constitutionally and maturationally based sensory reactivity patterns, motor patterns, and behavior patterns that together can dysregulate a child internally and the child's interactions with caregivers.

Bibliography is available at Expert Consult.

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Chapter 21

Psychological Treatment of Children and Adolescents

David R. DeMaso and Heather J. Walter

Three-quarters of children with mental health problems are seen in primary care. About half of the treatment for psychiatric disorders is provided in primary care settings and most psychotropic prescriptions for youth are written by primary care practitioners. Barriers that prevent children and their families from obtaining needed mental health services include stigma, shortages of mental health

professionals, inadequate coverage of mental health services in public and private health insurance programs, inadequately trained clinicians, inadequate time for primary care providers to identify mental health issues, and fragmented service delivery systems.

The provision of supportive counseling, anticipatory guidance, and parent psychoeducation about mental health problems combined with medication management of neurodevelopmental (attention-deficit/hyperactivity [ADHD], autism spectrum, tic), sleep, and elimination disorders are commonly undertaken by the pediatric practitioner. Youth with other psychiatric disorders (psychotic, bipolar, depressive, anxiety, obsessive-compulsive, trauma-related, somatic symptom, dissociative, gender dysphoric, disruptive/impulse-control/conduct, and substance-related) require initial evaluation, treatment planning, and stabilization by child-trained mental health clinicians. However, the pediatric practitioner often resumes the care of these youth once stabilized.

Barriers to providing mental health services in the primary care setting include lack of mental health training for staff, insufficient time, lack of knowledge about community mental healthcare resources, and inadequate reimbursement. In the face of these challenges, safe and effective mental healthcare of children and adolescents requires effective collaboration between pediatric and mental health practitioners. Several models of effective collaboration in the primary care setting have been advanced; most converge in recommending the following components: (1) screening for and early detection of mental health problems; (2) triage/referral to appropriate mental health treatment; (3) timely access to mental health consultation and direct mental health assessment (in-person or via telepsychiatry); (4) care coordination (by a designated care coordinator in the primary care setting); (5) access to specialty mental health treatment services; and (6) education of primary care practitioners around the accurate assessment and safe and effective treatment of child and adolescent psychiatric disorders.

Bibliography is available at Expert Consult.

Table 21-1 Best Principles for Use of Psychotropic Medications

1. Before initiating pharmacotherapy, a psychiatric evaluation is completed.
2. Before initiating pharmacotherapy, a medical history is obtained and a medical evaluation is considered when appropriate.
3. The prescriber communicates with other professionals to obtain collateral history and collaborate in the monitoring of outcome and side effects during the medication trial.
4. The prescriber develops a psychosocial and psychopharmacological treatment plan based upon the best available evidence.
5. The prescriber develops a plan to monitor the patient during the medication trial.
6. The prescriber is cautious when the medication trial cannot be appropriately monitored.
7. The prescriber educates the patient and family about the patient's diagnosis and treatment plan.
8. The prescriber obtains and documents informed consent before initiating the medication trial and at appropriate intervals during the trial.
9. The informed consent process focuses on the risks and benefits of the proposed and alternative treatments.
10. The medication trial should involve an adequate dose of medication for an adequate duration.
11. The prescriber reassesses the patient if the patient fails to respond to the medication trial as expected.
12. The prescriber has a clear rationale for using medication combinations.
13. The prescriber has a specific plan for medication discontinuation.

Modified from American Academy of Child and Adolescent Psychiatry: Practice parameter on the use of psychotropic medication in children and adolescents. J Am Acad Child Adolesc Psychiatry *48(9):961–973, 2009.*

21.1 Psychopharmacology

David R. DeMaso and Heather J. Walter

Data are available regarding the safety and efficacy for the use of *single* psychotropic medications for the treatment of a number of childhood psychiatric disorders, including depressive, obsessive-compulsive, ADHD, anxiety, bipolar, psychotic, and tic disorders. Evidence also supports the use of psychotropic medications for agitation, aggression and serious problems with impulse control in disruptive/impulse-control/conduct and autism spectrum disorders.

The evidence for using multiple psychotropic medications at the same time is much smaller. Combinations of medications are used to address complex comorbid conditions, manage side effects, increase treatment response, and/or address symptoms hypothesized to be associated with multiple underlying neurotransmitter abnormalities (dopamine agonists for hyperactivity and serotonin agonists for anxiety).

To ensure safe and appropriate use of psychotropic medications, prescribers should follow best practice principles that underlie medication prescribing (Table 21-1). The use of medication involves a series of interconnected steps, including performing an assessment, deciding on treatment and a monitoring plan, obtaining treatment assent and/or consent, and implementing treatment. Cognitive, emotional, and/or behavior symptoms are targets for medication intervention when there is no response to available evidence-based psychosocial interventions, there is a significant risk of harm, and/or there is significant distress or functional impairment. Commonly encountered target symptom domains include agitation, aggression, anxiety, depression, hyperactivity, inattention, impulsivity, mania, and psychosis (Table 21-2).

Table 21-2 Target Symptom Approach to Psychopharmacologic Management

TARGET SYMPTOM	MEDICATION CONSIDERATIONS
Agitation	Atypical antipsychotic Typical antipsychotic Anxiolytic (e.g., benzodiazepine)
Aggression	Stimulant Atypical antipsychotic
Anxiety	Antidepressant Anxiolytic
Depression	Antidepressant
Hyperactivity, inattention, impulsivity	Stimulant Atomoxetine Alpha-agonist
Mania	Atypical antipsychotic
Psychosis	Atypical antipsychotic

Modified from Shaw RJ, DeMaso DR: Clinical manual of pediatric psychosomatic medicine: mental health consultation with physically ill children and adolescents, *Washington, DC, 2006, American Psychiatric Press, p. 306.*

STIMULANTS AND OTHER ADHD MEDICATIONS

Stimulants are sympathomimetic drugs that act both in the central nervous system and peripherally by enhancing dopaminergic and noradrenergic transmission (Table 21-3). There is strong evidence for the effectiveness of these medications for the treatment of ADHD (***number needed to treat*** [**NNT**] approximates 4) as well as aggression (NNT approximates 4), and moderate evidence for the treatment of hyperactivity in autism spectrum disorder. In some cases, stimulants are used as an adjunct in the treatment of depression and for fatigue

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Table 21-3 Medications for ADHD Symptoms

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE RANGE
STIMULANTS				
Long Acting				
Methylphenidate (Concerta)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	6-12: 18-54 mg >12: 18-72 mg	6-12: 54 mg >12: 72 mg
Dexmethylphenidate (Focalin XR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	Child: 5-30 mg	Child: 30 mg
Amphetamine combination (Adderall XR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	6-12: 5-10 mg >12: 10-20 mg	6-12: 30 mg >12: 40 mg
Dextroamphetamine (Dexedrine Spansule)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	5-40 mg	40 mg
Intermediate Acting				
Methylphenidate (Metadate CD, Metadate ER, Ritalin LA, Ritalin SR)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	10-60 mg	60 mg
Short Acting				
Dexmethylphenidate (Focalin)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	2.5-20 mg	20 mg
Methylphenidate (Ritalin, Methylin)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	5-30 mg	60 mg
Amphetamine combination (Adderall)	ADHD (3 and up)	Inattention Hyperactivity Impulsivity	3-5: 2.5-40 mg >6: 5-40 mg	40 mg
Dextroamphetamine (Dexedrine)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	2.5-40 mg	40 mg
SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR				
Atomoxetine (Strattera)	ADHD (6 and up)	Inattention Hyperactivity Impulsivity	<70 kg: 0.5-1.2 mg/kg >70 kg: 40-80 mg	<70 kg: 1.4 mg/kg >70 kg: 100 mg
α-AGONISTS				
Clonidine (Catapres)	Not approved for ADHD in children & adolescents	Inattention Hyperactivity Impulsivity	27-40.5 kg: 0.05-0.2 mg 40.5-45 kg: 0.05-0.3 mg >45 kg: 0.05-0.4 mg	27-40.5 kg: 0.2 mg 40.5-45 kg: 0.3 mg >45 kg: 0.4 mg
Clonidine (Kapvay)	ADHD (6-17)	Inattention Hyperactivity Impulsivity	0.1-0.4 mg/day	0.4 mg
Guanfacine (Tenex)	Not approved for ADHD in children & adolescents	Inattention Hyperactivity Impulsivity	27-40.5 kg: 0.5-2 mg 40.5-45 kg: 0.5-3 mg >45 kg: 0.5-4 mg	27-40.5 kg: 2 mg 40.5-45 kg: 3 mg >45 kg: 4 mg
Guanfacine (Intuniv)	ADHD (6-17)	Inattention Hyperactivity Impulsivity	1-4 mg	4 mg

ADHD, attention-deficit/hyperactivity disorder.

or malaise associated with chronic physical illnesses. There is a range of stimulant options, including those with short half-lives (typically 4 hr) and those with long half-lives (8-12 hr). The most commonly reported side effects are appetite suppression and sleep disturbances. Nervousness, headaches, abdominal pain, dizziness, palpitations, tachycardia have also been reported. More serious reactions include psychosis, mania, hypertension, dependency, and abuse. Anorexia and weight loss have been noted with controversy about their impact on ultimate height attainment.

Sudden death has been reported in association with the use of stimulants in children, although a large study did not find an increased rate of serious cardiac events.. Currently, no routine pretreatment cardiology evaluation is indicated unless the patient has a structural cardiac abnormality and/or cardiac-related symptoms; in this situation, cardiology clearance is recommended.

Atomoxetine is a selective inhibitor of presynaptic norepinephrine transporters; it increases dopamine and norepinephrine in the prefrontal cortex. It is effective in treating ADHD for 24 hr despite a plasma half-life of 4 hr. Common side effects include headache, abdominal pain, insomnia, somnolence, erectile dysfunction, irritability, fatigue, weight loss, and dizziness along with nonclinical increases in heart rate and blood pressure. More serious reactions include psychosis, mania, aggressive behavior, suicidal ideation, depression, seizures, and hepatoxicity.

The α-adrenergic agents (clonidine and guanfacine) are presynaptic adrenergic agonists that appear to stimulate inhibitory presynaptic autoreceptors in the central nervous system. These medications (see Table 21-5) have moderate evidence for the treatment of ADHD and ADHD with oppositional defiant disorder, and weak evidence for the treatment of agitation in autism. Two longer-acting preparations of each agent (Kapvay and Intuniv) have recently received FDA approval for use in ADHD. Sedation, hypotension, dry mouth, depression, and confusion are potential side effects. Abrupt withdrawal can result in rebound hypertension. Guanfacine appears to be less sedating and to have a longer duration of action than clonidine.

ANTIDEPRESSANTS

Antidepressant drugs act on pre- and postsynaptic receptors affecting the release and reuptake of brain neurotransmitters, including norepinephrine, serotonin, and dopamine (Table 21-4). There is strong evidence for the effectiveness of antidepressant medications in the treatment of anxiety and obsessive-compulsive disorders (NNT approximates 3 and 6, respectively), and weaker evidence for the treatment of depressive disorders (NNT approximates 10). Suicidal

Table 21-4 Medications for Depression and Anxiety Symptoms

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
SELECTIVE SEROTONIN REUPTAKE INHIBITORS				
Citalopram (Celexa)	Not approved for anxiety & depression in children & adolescents	Depression Anxiety Obsessions/compulsions	20-40 mg	40 mg
Escitalopram (Lexapro)	Depression (12-17)	Depression Anxiety Obsessions/compulsions	10-20 mg	20 mg
Fluoxetine (Prozac)	Depression (8-17) OCD (7-17)	Depression Anxiety Obsessions/compulsions	10-60 mg	60 mg
Sertraline (Zoloft)	OCD (6-17)	Depression Anxiety Obsessions/compulsions	25-200 mg	200 mg
TRICYCLIC ANTIDEPRESSANTS				
Clomipramine (Anafranil)	OCD (10-17)	Obsessions/compulsions	25-100 mg	Lesser of 200 mg or 3 mg/kg
ATYPICAL ANTIDEPRESSANTS				
Bupropion (Wellbutrin XL)	Not approved for depression in children & adolescents	Depression	150-300 mg	450 mg
Venlafaxine (Effexor XR)	Not approved for anxiety & depression in children & adolescents	Depression Anxiety	75-225 mg	225 mg
ANXIOLYTIC AGENTS				
Lorazepam (Ativan)	Not approved for anxiety	Anxiety	0.5-6 mg	10 mg
Clonazepam (Klonopin)	Not approved for panic in children & adolescents	Panic	0.5-1 mg	4 mg
Buspirone (BuSpar)	Not approved for anxiety & depression in children & adolescents	Anxiety	15-30 mg	60 mg
Hydroxyzine (Atarax, Vistaril)	Anxiety	Anxiety	50 mg >6: 50-100 mg	<6: 2 mg/kg 50 mg >6: 100 mg

ADHD: attention-deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder.

Table 21-5 Medications for Psychosis and Agitation

NAME	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
ATYPICAL ANTIPSYCHOTICS				
Aripiprazole (Abilify)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (6-17)	Psychosis Mania Irritability Aggression Agitation	2-30 mg qd	30 mg Autism: 15 mg
Olanzapine (Zyprexa)	Bipolar disorder (13-17) Schizophrenia (13-17)	Psychosis Mania Agitation	2.5-10 mg qd	20 mg
Quetiapine (Seroquel)	Bipolar disorder (10-17) Schizophrenia (13-17)	Psychosis Mania Agitation	Bipolar: 400-600 mg Schizophrenia: 400-800 mg	Bipolar: 600 mg Schizophrenia: 800 mg
Risperidone (Risperdal)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Psychosis Mania Aggression Agitation Irritability	0.5-6 mg Autism: 15-20 kg: 0.25 mg-0.5 mg >20 kg: 0.5-1 mg	Bipolar & Schizophrenia: 6 mg Autism: 3 mg
Ziprasidone (Geodon)	Not approved for psychosis, mania, aggression, or agitation in children & adolescents	Psychosis Mania Agitation	40-160 mg	200 mg
TYPICAL ANTIPSYCHOTICS				
Haloperidol (Haldol)	Psychosis (3-17) Tourette (3-17) Severe behavioral disorders (3-17) Agitation (3-17)	Psychosis Mania Aggression Agitation	3-12: 0.05-0.15 mg/kg >12: 0.5-5 mg Agitation: 3-12: 0.01-0.03 mg/kg >12: 0.5-10 mg	3-12: 0.15 mg/kg/day >12: maximum 100 mg for severe refractory cases

thoughts have been reported during treatment with all antidepressant medications. The overall risk difference of suicidal ideation/attempts across all randomized controlled antidepressant trials and indications has been reported to be 0.7%, corresponding to a ***number needed to harm*** of 143.

The ***selective serotonin reuptake inhibitors*** **(SSRIs)**, which, as their name suggests, inhibit the reuptake of serotonin, have a large margin of safety with no appreciable cardiovascular effects. Side effects include irritability, insomnia, appetite changes, gastrointestinal symptoms, headaches, diaphoresis, restlessness, behavioral activation, and sexual dysfunction. Withdrawal symptoms are more common in short-acting SSRIs (sertraline, citalopram, escitalopram), leading to a recommendation for divided doses if these medications are used.

The ***tricyclic antidepressants*** **(TCAs)** have mixed mechanisms of action (e.g., clomipramine is primarily serotonergic; imipramine is both noradrenergic and serotonergic). With the advent of the SSRIs, the lack of efficacy studies (particularly in depression), and more serious side effects, the use of TCAs in children has declined. They continue to be used in the treatment of some anxiety disorders (particularly obsessive-compulsive disorder) and, unlike the SSRIs, can be helpful in pain disorders. They have a narrow therapeutic index, with overdoses being potentially fatal (see Chapter 63). Anticholinergic symptoms (e.g., dry mouth, blurred vision, and constipation) are the most common side effects. TCAs can have cardiac conduction effects in doses higher than 3.5 mg/kg. Blood pressure and electrocardiographic monitoring is indicated at doses above this level.

The **atypical antidepressants** include bupropion and venlafaxine (see Table 21-4); because of their sparse evidence base, they are third-line medications (after fluoxetine and the other SSRIs) for anxiety and depressive disorders. Bupropion has also been used for smoking cessation and ADHD. Bupropion appears to have an indirect mixed agonist effect on dopamine and norepinephrine transmission. Common side effects include irritability, nausea, anorexia, headache, and insomnia. Venlafaxine has both serotonergic and noradrenergic properties. Side effects are similar to SSRIs, including irritability, insomnia, headaches, anorexia, nervousness, dizziness, and blood pressure changes.

Anxiolytic agents (including lorazepam, clonazepam, buspirone, and hydroxyzine) have all been effectively used for acute situational anxiety (see Table 21-4). Their efficacy as chronic medication is poorer, particularly when used as a monotherapy agent.

ANTIPSYCHOTICS

Based on their mechanism of action, antipsychotic medications can be divided into typical (blocking dopamine D_2 receptors) and atypical (mixed dopaminergic and serotoninergic [5-HT_2] activity) agents (Table 21-5).

The **atypical antipsychotics** have relatively strong antagonistic interactions with 5-HT_2 receptors and perhaps more variable activity at central adrenergic, cholinergic, and histaminic sites, which might account for varying side effects noted among these agents. These medications have strong evidence for the treatment of agitation in autism (NNT approximates 2-7), and for the treatment of schizophrenia (NNT approximates 4-10), bipolar disorder (NNT approximates 3-4), and aggression (NNT approximates 2-5). Risperidone and aripiprazole are 2 of the most well-studied and commonly used medications in this class.

The atypical antipsychotics have significant side effects including extrapyramidal symptoms (e.g., restlessness and dyskinesias), weight gain, metabolic syndrome, diabetes, hyperlipidemia, hyperprolactinemia, hematologic adverse effects (e.g., leukopenia or neutropenia), seizures, hepatotoxicity, neuroleptic malignant syndrome, and cardiovascular effects. For all atypical antipsychotics, body mass index, blood pressure, fasting blood glucose, fasting lipid profiles, and abnormal movements should be closely monitored. If there is a family or personal history suggestive of cardiac disease, electrocardiograms should also be monitored.

Table 21-6 Medications for Mania

	FDA APPROVED (AGE RANGE IN YEARS)	TARGET SYMPTOMS	USUAL DAILY DOSAGE RANGE	SUGGESTED TOP END OF DAILY DOSAGE
MOOD STABILIZERS				
Lithium carbonate (Eskalith, Eskalith CR, Lithobid)	Bipolar disorder (12-17)	Mania Depression	<22 kg: 600 mg 22-41 kg: 900 mg >41 kg: 1200 mg	1800 mg
Divalproex (Depakote, Depakote ER)	Not approved for mania in children & adolescents	Mania	Teen: 10-60 mg/kg *(Blood valproic acid level 50-100 μg/mL)*	60 mg/kg
ATYPICAL ANTIPSYCHOTICS				
Aripiprazole (Abilify)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (6-17)	Irritability Psychosis Mania Aggression Agitation	2-30 mg	30 mg Autism: 15 mg
Risperidone (Risperdal)	Bipolar disorder (10-17) Schizophrenia (13-17) Irritability in autism (5-17)	Psychosis Mania Aggression Agitation Irritability	0.5-6 mg Autism: 15-20 kg: 0.25 mg-0.5 mg >20 kg: 0.5-1 mg	Bipolar & Schizophrenia: 6 mg Autism: 3 mg

Haloperidol is a high-potency butyrophenone that is the typical antipsychotic most commonly used. This medication is useful in psychosis, Tourette disorder, and severe agitation. Side effects include anticholinergic effects, weight gain, drowsiness, and extrapyramidal symptoms (dystonia, rigidity, tremor, and akathisia). There is a risk of tardive dyskinesia (see Chapter 597.3) with chronic administration.

MOOD STABILIZERS

Because of their limited evidence of effectiveness and concerns about safety, mood stabilizer medications (Table 21-6) have limited use in the treatment of child and adolescent psychiatric disorders. For the treatment of bipolar mania in adolescents, atypical antipsychotics are considered first-line therapy.

Lithium's mechanism of action is not well understood; proposed theories relate to neurotransmission, endocrine effects, circadian rhythm, and cellular processes. Common side effects include polyuria and polydipsia and central nervous system symptoms (tremor, somnolence, and memory impairment). Periodic monitoring of lithium levels along with thyroid and renal function is needed. Lithium serum levels of 0.8-1.2 mEq/L are targeted for acute episodes and 0.6-0.9 mEq/L are targeted for maintenance therapy.

Valproic acid is an anticonvulsant with a therapeutic plasma concentration range of 50-100 μg/mL. Common side effects include sedation, gastrointestinal symptoms, and hair thinning. Idiosyncratic bone marrow suppression and liver toxicity have been reported, necessitating monitoring of blood counts as well as liver and kidney function.

MEDICATION USE IN PHYSICAL ILLNESS

There are special considerations in the use of psychotropic medications with physically ill children. Between 80% and 95% of psychotropic medications are protein bound, with the exceptions being lithium (0%), methylphenidate (10-30%), venlafaxine (25-30%), gabapentin (0-3%), and topiramate (9-17%). As a result, psychotropic levels may be directly affected because albumin binding is reduced in many physical illnesses. Metabolism is primarily through the liver and gastrointestinal tract, with excretion via the kidney. Therefore, dosages may need to be adjusted in children with hepatic or renal impairment.

Hepatic Disease

Lower doses of medications may be required in in patients with hepatic disease. Initial dosing of medications should be reduced and titration should proceed slowly. In steady-state situations, changes in protein binding can result in elevated unbound medication, resulting in increased drug action even in the presence of normal serum drug concentrations. Because it is often difficult to predict changes in protein binding, it is important to maintain attention to the clinical effects of psychotropic medications and not rely exclusively on serum drug concentrations.

In acute hepatitis, there is generally no need to modify dosing because metabolism is only minimally altered. In chronic hepatitis and cirrhosis, hepatocytes are destroyed and doses may need to be modified.

Medications with high baseline rates of liver clearance (e.g., haloperidol, sertraline, venlafaxine, TCAs) are significantly affected by hepatic disease. For drugs that have significant hepatic metabolism, intravenous administration may be preferred because parenteral administration avoids first-pass liver metabolic effects and the dosing and action of parenteral medications are similar to those in patients with normal hepatic function. Valproic acid can impair the metabolism of the hepatocyte disproportionate to the degree of hepatocellular damage. In patients with valproate-induced liver injury, low albumin, high prothrombin, and high ammonia may be seen without significant elevation in liver transaminases.

Gastrointestinal Disease

Medications with anticholinergic side effects can slow gastrointestinal motility, affecting absorption and causing constipation. SSRIs increase gastric motility and can cause diarrhea. SSRIs have the potential to increase the risk of gastrointestinal bleeding, especially when they are co-administered with nonsteroidal anti-inflammatory drugs. Extended-release or controlled-release preparations of medications can reduce gastrointestinal side effects, particularly where gastric distress is related to rapid increases in plasma drug concentrations.

Kidney Disease

With the exceptions of lithium and gabapentin, psychotropic medications do not generally require significant dosing adjustments in kidney failure. It is important to monitor serum concentrations in renal insufficiency, particularly for medications with a narrow therapeutic index; cyclosporine can elevate serum lithium levels by decreasing lithium excretion. Patients with kidney failure and those on dialysis appear to be more sensitive to TCA side effects, possibly because of the accumulation of hydroxylated tricyclic metabolites.

Because most psychotropic medications are highly protein-bound, they are not significantly cleared by dialysis. Lithium, gabapentin, and topiramate are essentially completely removed by dialysis, and the common practice is to administer these medications after dialysis. Patients on dialysis often have significant fluid shifts and are at risk for dehydration, with neuroleptic malignant syndrome being more likely in these situations.

Heart Disease

Cardiovascular effects of psychotropic medications can include orthostatic hypotension, conduction disturbances, and arrhythmias. Orthostatic hypotension is one of the most common cardiovascular side effects of TCAs. Trazodone can cause orthostatic hypotension and exacerbate myocardial instability; SSRIs and bupropion are preferred as antidepressant agents in patients with heart disease.

There is the potential for increased morbidity and mortality in patients with preexisting cardiac conduction problems. Some of the calcium channel-blocking agents (e.g., verapamil) can slow atrioventricular conduction and can theoretically interact with a TCA. Patients with Wolff-Parkinson-White syndrome (see Chapter 435.3) who have a short PR interval (<0.12 sec) and widened QRS interval associated with paroxysmal tachycardia are at high risk for life-threatening ventricular tachycardia that may be exacerbated by the use of a TCA. Quinidine-like effects of TCAs and the antipsychotic agents can lead to prolongation of the QTc interval, with increased risk of ventricular tachycardia and ventricular fibrillation, particularly in patients with structural heart disease. Patients with a baseline QTc interval of >440 msec should be considered at particular risk. The range of normal QTc values in children is 400 msec ± 25-30 msec. A QTc value that exceeds 2 SD (>450-460 msec) is considered too long and may be associated with increased mortality. An increase in the QTc from baseline of >60 msec is also associated with increased mortality.

Respiratory Disease

Anxiolytic agents can increase the risk of respiratory suppression in patients with pulmonary disease. SSRIs and buspirone are good alternative medications for treating anxiety. Consideration should be given to possible airway compromise due to acute laryngospasm when dopamine-blocking agents such as antipsychotic or antiemetic medications are used.

Neurologic Disease

Psychotropic medications can be used safely with epilepsy following consideration of potential interactions between the psychotropic medication, the seizure disorder, and the anticonvulsant medication. Any behavioral toxicity of anticonvulsants used either alone or in combination should be considered before proceeding with psychotropic treatment. Simplification of combination anticonvulsant therapy or a change to another agent can result in a reduction of behavioral or emotional symptoms and obviate the need for psychotropic intervention. Clomipramine and bupropion possess significant seizure-inducing properties and should be avoided when the risk of seizures is present.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is a rare and potentially fatal reaction that can occur during treatment with antipsychotic agents (see Chapter 176). The syndrome generally manifests with fever, muscle rigidity, autonomic instability, and delirium. It is associated with elevated serum creatine phosphokinase levels, a metabolic acidosis, and high end-tidal CO_2 excretion. It has been estimated to occur in 0.2-1% of patients treated with dopamine-blocking agents. Malnutrition and dehydration in the context of an organic brain syndrome and simultaneous treatment with lithium and antipsychotic agents can increase the risk. Mortality rates may be as high as 20-30% as a result of dehydration, aspiration, kidney failure, and respiratory collapse. Differential diagnosis of neuroleptic malignant syndrome includes infections, heat stroke, malignant hyperthermia, lethal catatonia, agitated delirium, thyrotoxicosis, serotonin syndrome, drug withdrawal, and anticholinergic or amphetamine, ecstasy, salicylate toxicity.

Serotonin Syndrome

Serotonin syndrome is characterized by a triad of mental status changes, autonomic hyperactivity, and neuromuscular abnormalities (see Chapter 63). It is the result of an excess agonism of the central and peripheral nervous system serotonergic receptors and can be caused by a range of drugs including SSRIs, valproate, and lithium. Drug-drug interactions that can cause serotonin syndrome include linezolid (an antibiotic that has monoamine oxidase inhibitor properties) and antimigraine preparations used with an SSRI, as well as combinations of SSRI, trazodone, buspirone, and venlafaxine. It is generally self-limited and can resolve spontaneously after the serotonergic agents are discontinued. Severe cases require the control of agitation, autonomic instability, and hyperthermia as well as the administration of 5-HT_{2A} antagonists (e.g., cyproheptadine).

Bibliography is available at Expert Consult.

21.2 Psychotherapy

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Psychotherapy in children may also be effective in reducing patient symptomatology. Effect sizes in research studies range from 0.71 to 0.84, which are as large as or larger than the effects of psychiatric medications or medicines for many physical illnesses. Despite benefit, only a minority of patients achieve the same level of functioning as average children, because in community settings the effect size of psychotherapy approaches zero. This poor response might reflect the fact that treatment in real-world community settings involves complex and co-occurring disorders, as opposed to the research or academic setting, where comorbid conditions are often excluded.

A variety of psychotherapeutic approaches exist with varying levels of evidence regarding their effectiveness. Differences between therapeutic approaches may be less pronounced in practice than in theory. The quality of the therapist–patient alliance consistently has been shown to be the strongest predictor of treatment outcome. A positive therapeutic relationship, expecting change to occur, facing problems assertively, increasing mastery, and attributing change to the participation in the therapy have all been connected to effective therapy.

The use of psychotherapy involves a series of interconnected steps including performing an assessment, deciding upon treatment and a monitoring plan, obtaining treatment assent or consent, and implementing treatment. Cognitive, emotional, and/or behavioral symptoms are identified that become the targets for evidence-based psychotherapeutic interventions. Psychotherapists ideally develop a treatment plan by combining known evidence-based practices about specific interventions with their clinical judgment to arrive at a specific intervention plan for the individual patient. It is not unusual for the psychotherapist to use elements from more than one treatment approach, including psychopharmacology.

BEHAVIOR THERAPY

Behavior therapy is based upon both classic (pavlovian) and operant (skinnerian) conditioning. Both of these approaches do not concern themselves with the inner motives of the individual, but instead address the antecedent stimuli and consequent responses. The treatment begins with a behavioral assessment with interview, observation, diary, and rating scale components, along with a functional analysis of the setting context, immediately preceding external events, and real-world consequences of the behavior. A treatment plan is then developed to modify the maladaptive functions of the behavior, using tools such as positive and negative reinforcement, social and tangible rewards, shaping, modeling, and prompting to increase positive behavior, and extinction, stimulus control, punishment, response cost, overcorrection, differential reinforcement of incompatible behavior, graded exposure/

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systematic desensitization, flooding, modeling, and role playing to decrease negative behavior.

Behavior therapy has shown applicability to anxiety disorders, obsessive-compulsive and related disorders, posttraumatic stress disorder, behavior disorders, ADHD, nocturnal enuresis, autism spectrum disorder, and intellectual disability.

COGNITIVE-BEHAVIORAL THERAPY

Cognitive-behavioral therapy (CBT) is based on social and cognitive learning theories and extends behavior therapy to address the influence of cognitive processes on behavior. These cognitive processes include social information processing (automatic and controlled), fixed patterns of thinking or beliefs (cognitive schema), and emotional effects mediating cognitive attributions and behavior. CBT is problem-oriented treatment that seeks to identify and change cognitive distortions (e.g., learned helplessness or irrational fears), identify and avoid distressing situations, and identify and practice distress-reducing behavior. Self-monitoring (daily thought record), self-instruction (brief sentences asserting thoughts that are comforting and/or adaptive), and self-reinforcement (rewarding oneself) are key tools used to facilitate achievement of the CBT treatment goals.

CBT has shown applicability to the treatment of behavior, depressive, and anxiety disorders. Specially modified versions of CBT have shown applicability to the treatment of other disorders. ***Trauma-focused CBT*** involves a combination of psychoeducation, teaching effective relaxation, affective modulation, and cognitive coping and processing skills, engaging in a trauma narrative, mastering trauma reminders, and enhancing future safety and development, and is considered the first-line treatment for posttraumatic stress disorder. ***Dialectical behavioral therapy*** combines standard CBT with concepts of distress tolerance, emotional regulation, interpersonal effectiveness, and mindfulness drawn from Buddhist meditative practice. Dialectical behavioral therapy has shown promise for the treatment of borderline personality disorder, bipolar disorder, suicidal behavior, and other manifestations of emotional and behavioral dysregulation.

FAMILY THERAPY

Although family therapy covers a broad range of approaches, the core idea in family therapy is that the cause of problems in individuals is thought to lie in patterns of family interaction, with other family members helping to maintain the problem. Family dysfunction can take a variety of forms, including enmeshment, disengagement, role-reversal or confusion, and maladaptive communication patterns. Family therapy begins with an assessment of the family system, including observing patterns of interaction, assessing family beliefs and the meanings attached to behaviors, defining social and cultural contexts, exploring the presenting problem in the context of individual and family development, assessing the family's style of dealing with problems, and identifying family strengths and weaknesses. Family therapy techniques are drawn from 2 major theoretical models: structural and behavioral. Structural family therapy develops capacities believed to foster well-functioning families, including clear and flexible boundaries between individuals, well-defined roles, and an appropriate balance between closeness and independence. Behavioral family therapy focuses on behavioral sequences that occur in daily life, and attempts to interrupt unhelpful patterns and strengthen positive patterns through effective communication and problem solving.

Family therapy has shown applicability to anorexia and substance abuse, and for these disorders is the treatment of choice. For other disorders (e.g., depressive, anxiety, obsessive-compulsive, and behavior), the evidence is more limited.

PSYCHODYNAMIC PSYCHOTHERAPY

At the core of psychodynamic psychotherapy lies a *dynamic* interaction between different parts or aspects of the mind. This approach is based on the belief that much of one's mental activity occurs outside one's awareness. The patient is often unaware of internal conflicts because threatening or painful emotions, impulses, and memories are repressed. Behavior is then controlled by what the patient does not know about himself or herself. Therapy objectives are to increase self-understanding, increase acceptance of feelings, shift to mature defense mechanisms, and develop realistic relationships between self and others. This therapy is nondirective to allow the patient's characteristic patterns to emerge so that self-understanding and a corrective emotional experience can then be fostered by the therapist.

Psychodynamic psychotherapy has shown applicability for the treatment of emotional problems (e.g., anxiety, depression) as well as maladaptive aspects of personality. Limited applicability has been shown for behavior, eating, and trauma-related disorders. Brief, time-limited psychodynamic psychotherapy can be appropriate for youth who are in acute situational distress, while long-term therapy can be appropriate when the biological or social factors destabilizing the child's adaptation and development are chronic, or the psychological difficulties due to comorbidities are complex, or entrenched conflicts and developmental interferences are present.

SUPPORTIVE PSYCHOTHERAPY

Supportive psychotherapy aims to minimize levels of emotional distress through the provision of individual and contextual support. Treatment is focused on the here and now. The therapist is active and helpful in providing the patient with symptomatic relief by containing anxiety, sadness, and anger. The therapist provides education and encouragement to bolster a patient's existing coping mechanisms. The therapist also facilitates problem solving and social and instrumental support for contextual symptom-generating problems.

PARENTING INTERVENTIONS

Parenting interventions are based upon attachment and social learning theory. Attachment theory proposes that the quality of care provided to the child, particularly sensitivity and responsiveness, leads to a secure or insecure attachment, which in turn influences the development of internal working models of self and others. A history of consistent and sensitive care by a parent is expected to lead to the child developing a model of self as lovable and others as loving and helpful. Social learning theory hypothesizes that children's real-life experiences and exposures directly or indirectly shape behavior, and that new positive experiences and exposures can change behavior favorably.

Parenting interventions seek to address both attachment and social learning deficits by improving both the parent–child relationship and parenting skills. Core attachment skills include spending quality time with the child, increasing verbal interaction, showing physical affection, providing contingent praise, and engaging in child-directed play. Core parenting skills include increasing reinforcement of positive behaviors, decreasing reinforcement of negative behaviors, applying consequences for dangerous/destructive behavior, and making parental response predictable, contingent, and immediate.

Parenting interventions have shown applicability for the behavior disorders and ADHD.

Bibliography is available at Expert Consult.

21.3 Psychiatric Hospitalization

David R. DeMaso and Heather J. Walter

Psychiatric hospital programs are meant to address the serious risks and severe impairments caused by the most acute and complex forms of psychiatric disorder that cannot be managed effectively at any other level of care. Their goal is to produce rapid clinical stabilization that allows an expeditious, safe, and appropriate treatment transition to a less-intensive level of mental healthcare outside of the hospital.

High levels of illness severity combined with significant functional impairment signal a need for hospitalization. Admission criteria must include significant signs and symptoms of active psychiatric disorder(s). Functional admission indicators generally include a significant risk of self-harm and/or harm to others, although in some cases the patient is unable to meet basic self-care or healthcare needs, jeopardizing

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well-being. Serious emotional disturbances that prevent participation in family, school, or community life can also rise to a level of global impairment that can only be addressed on an inpatient basis.

Discharge planning begins at the time of admission, when efforts are made to coordinate care with services and resources that are already in place for the child or adolescent in the community. Step-down care might be needed in partial hospital or residential settings if integrated services in a single location remain indicated after sufficient clinical stabilization has occurred in the hospital setting. Transition from the hospital entails active collaboration and communication with pediatric practitioners in the child's medical home.

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Chapter 22

Somatic Symptom and Related Disorders

Patricia I. Ibeziako and David R. DeMaso

Pediatric psychosomatic medicine deals with the relation between physiologic and psychological factors in the causation or maintenance of disease states. The process whereby distress is experienced and/or expressed in physical symptoms is referred to as ***somatization*** or ***psychosomatic illness***. Even though somatic symptoms are present in virtually every psychiatric disorder, they are most prominent in the various somatic symptom disorders.

In the *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), illnesses previously referred to as somatoform disorders are defined as ***somatic symptom disorders***. Somatic symptom disorders are classified on the basis of distressing physical symptoms and excessive thoughts, feelings or behaviors in relation to these symptoms rather than the absence of a medical explanation for somatic symptoms. These disorders form a continuum that can range from pain to disabling neurological symptoms and they generally interfere with school, home life and peer relationships. The DSM-5 Somatic Symptom and Related Disorders category includes the following disorders related to children and adolescents: ***conversion disorder*** (or functional neurologic symptom disorder), ***somatic symptom disorder***, ***factitious disorder***, ***psychological factors affecting other medical conditions***, and ***other specified/unspecified somatic symptom disorders*** (Tables 22-1 through 22-5 identify the DSM-5 diagnostic criteria).

Multiple terms used to describe somatic symptom disorders include "functional," "psychosomatic," or "medically unexplained symptoms." Additionally, most patients are seen by general practitioners and specialists and may receive specialty-specific syndrome diagnoses such as visceral hyperalgesia, irritable bowel syndrome, chronic fatigue syndrome, or noncardiac chest pain. The diagnostic heterogeneity that exists across the different medical specialists contributes to the different diagnostic labels. Studies indicate a significant overlap in the symptoms and presentation of patients with somatic symptoms who have received different diagnoses from different specialties.

Moreover, functional syndromes share similarities in etiology, pathophysiology, neurobiology, psychological mechanisms, patient characteristics, and management and treatment response, which is indicative of a single spectrum of disorders. It is helpful for healthcare providers to avoid the dichotomy of approaching illness using a medical model in which diseases are considered as being either organic

Table 22-1 DSM-5 Diagnostic Criteria for Conversion Disorder or Functional Neurologic Symptom Disorder

A. One or more symptoms or deficits affecting voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurologic or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.
D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type: weakness or paralysis, abnormal movements, swallowing symptoms, speech symptom, attacks/seizures, or anesthesia/sensory loss, special sensory symptom (visual, olfactory, or hearing), or mixed symptoms.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 318.

Table 22-2 DSM-5 Diagnostic Criteria for Somatic Symptom Disorder

A. One or more somatic symptoms that are distressing or result in significant disruption of daily life.
B. Excessive thoughts, feelings or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
   1. Disproportionate and persistent thoughts about the seriousness of one's symptoms.
   2. Persistent high level of anxiety about health and symptoms.
   3. Excessive time and energy devoted to these symptoms or health concerns.
C. Although any 1 somatic symptom may not be continuously present, the state of being symptomatic is persistent.

Specify if:

With predominant pain (previously known as pain disorder in DSM IV-TR): for individuals whose somatic symptoms predominantly involve pain.

Persistent: A persistent course is characterized by severe symptoms, marked impairment, and long duration (more than 6 mo).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 311.

Table 22-3 DSM-5 Diagnostic Criterial for Psychological Factors Affecting Other Medical Conditions

A. A medical symptom or condition (other than a mental disorder) is present.
B. Psychological or behavioral factors adversely affect the medical condition in 1 of the following ways:
   1. The factors have influenced the course of the medical condition as shown by a close temporal association between the psychological factors and the development or exacerbation of, or delayed recovery from, the medical condition.
   2. The factors interfere with the treatment of the medical condition (e.g., poor adherence).
   3. The factors constitute additional well-established health risks for the individual.
   4. The factors influence the underlying pathophysiology, precipitating or exacerbating symptoms or necessitating medical attention.
C. The psychological and behavioral factors in Criterion B are not better explained by another mental disorder (e.g., panic disorder, major depressive disorder, posttraumatic stress disorder).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 322.

Table 22-4 DSM-5 Diagnostic Criteria for Factitious Disorders

Factitious Disorder Imposed on Self

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.
B. The individual presents himself or herself to others as ill, impaired, or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Factitious Disorder Imposed on Another (Previously Factitious Disorder by Proxy)

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another, associated with identified deception.
B. The individual presents another individual (victim) to others as ill, impaired or injured.
C. The deceptive behavior is evident even in the absence of obvious external rewards.
D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

Note: The perpetrator, not the victim, receives this diagnosis

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 324.

Table 22-5 DSM-5 Diagnostic Criteria for Other Specified/Unspecified Somatic Symptom and Related Disorders

Other Specified

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet full criteria for any of the disorders in the somatic symptom and related disorders diagnostic class.

Examples of presentations that can be specified using the "other specified" designation include the following:

1. Brief somatic symptom disorder: Duration of symptoms is <6 mo.
2. Brief illness anxiety disorder: Duration of symptoms is <6 mo.
3. Illness anxiety disorder without excessive health-related behaviors: Criterion D for illness anxiety disorder is not met.
4. Pseudocyesis: A false belief of being pregnant that is associated with objective signs and reported symptoms of pregnancy.

Unspecified

This category applies to presentations in which symptoms characteristic of a somatic symptom and related disorder that cause clinically significant distress or impairment in functioning predominate but do not meet criteria for any of the other disorders in the somatic symptom and related disorders diagnostic class.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 327.

or psychologically based. In contrast, a biobehavioral continuum of disease characterizes illness as occurring across a spectrum ranging from a biologic etiology on one end to predominantly a psychosocial etiology on the other.

EPIDEMIOLOGY

Between 10% and 30% of children worldwide experience physical symptoms that are described as "functional" or unexplained by a physical illness. Estimated prevalence varies greatly between studies based on the type of symptoms and the study methodology. The frequency and heterogeneity of complaints increase with age with symptoms occurring more frequently in females.

The majority of children with persistent complaints of abdominal pain meet criteria for functional abdominal pain or somatic symptom disorder with predominant pain in DSM-5. In a prospective study, patients with functional abdominal pain carry long-term vulnerability to anxiety that begins in childhood and persists into late adolescence and early adulthood, even if abdominal pain resolves.

Headaches, back pain, limb pain and chest pain, as well as other gastrointestinal symptoms, are also frequently occurring pain symptoms in adolescents. Prevalence rates of conversion disorder in adolescents are 0.3-10%. Nonepileptic seizures, loss of consciousness, and motor conversion symptoms are common somatic neurologic complaints across cultures.

RISK FACTORS

Family and Environmental

Genetic

A possible genetic etiology in somatization disorders is suggested by findings of a 29% concordance rate in monozygotic twin studies and 10-20% of 1st-degree relatives of patients meeting criteria for this disorder. Further evidence is seen in studies showing a familial link between somatic symptom disorders and other psychiatric disorders (e.g., higher rates of anxiety and depression in the family members).

Symptom Modeling

Multiple studies have found evidence that a significant proportion of patients with somatic symptom disorders had recently encountered similar symptoms in their local environment or live with family members who complain of similar physical symptoms (e.g., a child with nonepileptic seizures who has a parent or sibling with a seizure disorder).

Parental Responses

Parent beliefs about the significance of symptoms influence the amount of symptoms the child reports. Having a somatic complaint may be more acceptable or noticed in some households than the expression of strong emotions (e.g., anxiety, fear or anger). In such an environment, a child may garner minimal attention for emotional distress, but obtain more attention and sympathy for physical symptoms. Multiple studies have shown that parental protectiveness predicts child functional disability and parental responses (e.g., discouraging activity, expressing concern, and providing comfort) may serve to inadvertently reinforce and maintain illness behaviors.

School and Family Stressors

External environmental factors (e.g., school stress or change in family situation) are common in children presenting with somatic symptom disorders. Common school stressors include bullying, beginning the school year, fear of academic failure, or participation in extracurricular school activities. Dysfunction and less support within the family system are common in somatic symptom disorders. A transition within the family system including death of a family member, birth of a sibling, parental divorce, physical punishment by parents and an increase in the number of arguments between parents have all been linked to somatic symptoms. Nevertheless, there is a significant minority of patients with somatic symptom disorders who do not appear to have obvious psychosocial precipitants for their symptoms. It is unclear whether the absence of recorded stressful events in these patients is because they were unwilling or unable to report relevant stressors or if they were simply absent.

Trauma

Elevated rates of childhood trauma (e.g., childhood sexual, physical, or emotional abuse) have been found in patients with somatic symptom disorders although the trauma prevalence rates in studies vary widely.

Individual

Childhood Physical Illness

There does appear to be a connection between childhood physical illness and the later development of somatization. Many children with somatic symptom disorders have other medical conditions. An antecedent history (e.g., of an accident, viral illness) may trigger onset of symptoms and lead to prolonged recovery or recurrence of symptoms after illness should have subsided. Children who tend to somatize may have a tendency to experience normal somatic sensations as "intense, noxious and disturbing," referred to as *somatosensory amplification*. Children with somatic symptom disorders may also have histories of disabling and poorly explained physical symptoms.

Temperament/Coping Styles

Somatic symptoms have been found to be more common in children who are conscientious, sensitive, insecure, internalizers, anxious, and in those who strive for high academic achievement. Somatization may also occur in youngsters who are unable to verbalize emotional distress. Somatic symptoms are often seen as a form of psychological defense against intrapsychic distress that allows the child to avoid confronting anxieties or conflicts, a process referred to as *primary gain*. "Primary gain" is obtained by keeping the conflict from consciousness and minimizing anxiety. The symptoms may also lead to what is described as "secondary gain" if the symptom results in the child being allowed to avoid unwanted responsibilities or consequences.

Learned Behavior

Somatic complaints may be reinforced (e.g., through a decrease in responsibilities or expectations by others and/or through receiving attention and sympathy as a result of the physical symptoms). Many youngsters may have an antecedent underlying general medical condition that may then be reinforced by parental and/or peer attention as well as additional medical attention in the form of unnecessary tests and investigations.

Psychiatric Comorbidity

There is an association between somatization and other psychiatric illness, in particular depressive and anxiety disorders.

Other Biologic Factors

Research into the pathophysiology of somatic symptom disorders has suggested some unifying mechanisms, including aberrant functions of efferent neural pathways, such as the autonomic nervous system and the hypothalamic–pituitary axis, and alterations in central processing of sensory input. Hyperactivity of the anterior cingulate cortex has been found in patients with conversion disorder, along with impaired activity of the dorsolateral prefrontal cortex. In studies of chronic pain, including migraine and tension type headache, there appears to be progressive loss of gray matter density in brain structures involved in registering pain such as the somatosensory cortex, anterior cingulate cortex and insula. Additionally when there is a strong expectation of pain, the anterior insular cortex is activated in proportion to this expectation.

ASSESSMENT

The majority of patients with somatic symptom and related disorders present in the pediatric rather than mental health settings. It is important for pediatricians to make their diagnosis on the basis of positive symptoms and signs (distressing somatic symptoms plus abnormal thoughts, feelings, and behaviors in response to these symptoms) rather than the absence of a medical explanation. As such, the evaluation of suspected disorders should include an assessment of biologic, psychological, social, and developmental realms both separately and in relation to each other. An integrated approach where both pediatric and mental health clinician are involved in the assessment, management, and treatment is indicated.

Medical

The presence of a physical illness does not exclude the possibility of somatization playing an important role in the child's presentation. Somatic symptoms early in a disease course that can be directly attributed to a specific physical illness (e.g., acute respiratory illness) may evolve into psychologically based symptoms, particularly in situations in which the child may experience benefit from adopting the sick role. Somatic symptoms may also occur in excess of what would be expected of the symptoms experienced in an existing physical illness. Physical findings may occur secondary to the effects of the somatic symptom disorder, especially when chronic and/or severe (e.g., deconditioning, disuse atrophy and contractures from prolonged immobilization, nutritional deficiency, gastroparesis and constipation from chronic poor oral intake.)

A comprehensive medical work-up to rule out serious physical illness must be carefully balanced with efforts to avoid unnecessary and potentially harmful tests and procedures. The physical examination will find that the child's symptoms may fluctuate in different contexts, may be anatomically inconsistent or may be in excess of what would be expected from the physical findings.

Psychological

If somatization is suspected, psychiatric consultation should be included early in the diagnostic workup. The reason for consultation should be carefully explained to the family to help avoid the perception that their child's symptoms are not being taken seriously by the pediatric team (i.e., "it's in her head"). It should be explained that a complete work-up involves a thorough assessment of the physical and psychological domains of the child and the psychiatric consultation can provide further understanding of the origins of the child's distress, what perpetuates it and which treatments are likely to be most effective.

The mental health interview should include a careful assessment of the psychological and social stressors and risk factors including a thorough family psychiatric and medical history. The nature of current physical symptoms and any history of prior episodes of somatic symptoms should be included in the assessment, in addition to the child's emotional, social and academic functioning, coping strategies and family functioning. The evaluation should provide the clinical team with a biopsychosocial explanation of the child's symptoms, which will inform the treatment plan.

Differential Diagnoses

The primary differential diagnosis is between that of somatic symptom disorder and a physical illness. It is important, however, to be aware that these disorders are not mutually exclusive and often coexist. Mood and anxiety disorders frequently include the presence of physical symptoms which tend to remit with treatment of the primary mood or anxiety symptoms and which appear distinct from physical complaints seen in somatic symptom disorders. Chronic pain syndromes may be caused by fibromyalgia and small fiber autonomic neuropathy (see Chapter 168).

MANAGEMENT

With the completion of medical and psychological assessments, a multidisciplinary team meeting of medical and mental health clinicians should be arranged to review all the specialty evaluations and tests, discuss the formulation, diagnostic impressions and treatment recommendations. This should occur to ensure that a consensus has been reached regarding the diagnosis and treatment plan and to facilitate adequate and consistent communication among all providers.

An informing meeting or conference with the family should be facilitated after the above meeting to convey the multidisciplinary team's diagnostic impressions and treatment recommendations to the patient/family. Medical and mental health clinicians together should communicate the diagnosis (or diagnoses) in a way that families can understand using a comprehensive biopsychosocial formulation. Medical and psychiatric findings should be acknowledged and discussed. Patients and families with somatic symptom disorders often present with the belief that there is primarily a medical cause for their problem and psychosocial contributors are often resisted. Following exhaustive medical investigations which do not yield any unifying

results, labeling the symptoms as "psychiatric" can effectively shift the search for the cause onto family functioning, resulting in youngsters and parents feeling blamed for the symptoms. The team should help the family move towards an understanding of the mind–body connection and shift their approach from searching for the cause of the symptoms to increasing functioning. Providing education about the benefits of treatment and risks of nontreatment is helpful to move the family through the treatment steps.

Treatment

An integrated multidisciplinary rehabilitation model is the most suitable for patients with somatic symptom disorders. A rehabilitation model approach provides a useful framework for the treatment that shifts the focus away from finding a cure for symptoms, and instead emphasizes a return to normal adaptive functioning. This includes increased activities of daily living, improved nutrition, enhanced mobility, return to school and socialization with peers.

Cognitive behavioral interventions are evidence-based treatments of choice. Cognitive behavioral interventions modify symptom experience including pain perception and restore central nervous system abnormalities that are linked with functional impairment. Components of cognitive behavioral techniques (e.g., relaxation training, biofeedback, and hypnosis) can be used to teach patients the control they can have over certain physiological processes such as autonomic system activity. Cognitive restructuring is effective in addressing and altering dysfunctional thoughts regarding symptoms and their implications for functioning. Treatments that encourage active coping strategies, emotional expression and modulation and limit adolescent reliance on emotional support provided by parents are particularly helpful to more effectively reduce symptoms and improve functioning. Modifying parental response patterns that are overly protective and potentially reinforcing (e.g., allowing the child to sleep late or to stay home from school in response to symptoms) help to decrease disability.

Psychopharmacologic treatment may be considered when other psychiatric disorders are co-occurring, specifically depressive and anxiety disorders. A combination of pharmacotherapy, physical therapy, and psychological interventions in multicomponent management programs has been shown to be effective.

Treatment Setting

The majority of patients can be managed in the outpatient setting with appropriate mental health follow-up. Scheduled follow up visits with the primary care provider (PCP) and other specialists are important to maintain alliance and investment in treatment, prevent doctor shopping, and avoid unnecessary invasive tests and procedures.

Because of the nature of their symptoms, most patients with somatic symptom disorders do not present in mental health settings for their physical complaints and only patients displaying prominent emotional symptoms or who have a concurrent mental disorder are referred to psychiatric services. Medical specialists treat "their own" specialty functional somatic syndrome within their service as a natural consequence of the large number of patients with these disorders presenting at their clinics. The management in these clinics is often monodisciplinary and with primarily medically based treatments and interventions. The existence of various syndrome-specific clinics perpetuates the separate, specialty-dominated approach to somatic symptom disorders and can perpetuate fragmented care rather than moving toward a more integrated model. Although specialized clinics play an important role in the provision of the expertise needed in the evaluation of these patients, they are often not prepared to manage patients who have symptoms involving multiple organ systems. These patients may attend several clinics simultaneously and receive several, parallel, uncoordinated treatments.

A medical home model with mental health clinicians working in collaboration with PCPs and/or different medical specialists may prove to be the most suitable approach for patients with somatic symptom disorders. Collocated medical and mental health services improve communication, decrease fragmentation of services, and decrease the stigma and resistance some families may have with attending psychiatric clinics. The efficacy of a treatment program with comprehensive multidisciplinary services and cognitive behavioral treatment has been studied in a randomized, controlled trial, and the results showed immediate, clinically relevant benefits that were sustained at the 1-year follow-up.

Patients with profound and pervasive functional impairment likely will need more intensive psychiatric treatment (e.g., a medical-psychiatric partial hospital program or inpatient unit). Multidisciplinary inpatient rehabilitation programs have a great deal to offer these patients as they are designed to support both physical and psychological recovery. Families feel reassured that multidisciplinary staff can continue to monitor symptoms, thus ensuring that any missed diagnoses will be recognized quickly.

Children with a high level of impairment often miss a significant amount of school; communication with the school in such cases is often crucial in helping a successful transition back and improving overall functioning. In addition to discussions with the school guidance counselor and nurse, a letter for the school providing education and recommended approaches for patient's symptoms is often beneficial. Ongoing communication between the school and PCP for monitoring of further symptoms is recommended.

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Chapter 23

Rumination and Pica

Emily R. Katz, Robert L. Kitts, and David R. DeMaso

23.1 Rumination Disorder

Emily R. Katz, Robert L. Kitts, and David R. DeMaso

Rumination disorder is the repeated regurgitation of food, where the regurgitated food may be rechewed, reswallowed, or spit out, for a period of at least 1 mo following a period of normal functioning. Regurgitation is typically frequent and daily; it does not occur during sleep. It is not caused by an associated gastrointestinal illness or other medical condition (e.g., gastroesophageal reflux or pyloric stenosis). It does not occur exclusively during the course of anorexia nervosa, bulimia nervosa, binge-eating disorder, or avoidant/restrictive food intake disorder. If the symptoms occur in the context of an intellectual developmental disorder or another neurodevelopmental disorder, they must be sufficiently severe to warrant additional clinical attention.

Weight loss and failure to make expected weight are common features in infants with rumination disorder. Infants may display a characteristic position of straining and arching the back with the head held back, making sucking movements with their tongue. In infants and older individuals with intellectual disability, the rumination behavior may appear to have a self-soothing or self-stimulating function. Malnutrition may occur in older children and adults, particularly when the regurgitation is associated with restricted food intake (which may be designed to avoid regurgitation in front of others). They may attempt to hide the regurgitation behavior or avoid eating among others.

EPIDEMIOLOGY

Originally thought of as a disorder predominantly seen in infants and those with intellectual disability, rumination disorder has also been recognized in healthy individuals across the life span. Prevalence data

for rumination disorder are inconclusive. In otherwise healthy children, this disorder typically appears in the first year of life, generally between the ages of 3 and 12 mo. The disorder can have an episodic course or occur continuously until treatment is initiated. In infants, the disorder frequently remits spontaneously, but can be protracted with problematic and even life-threatening malnutrition. Additional complications related to the secondary effects of malnutrition included growth delay and negative effect on development and learning potential.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

Risk factors for rumination disorder in infants and young children include a disturbed relationship with primary caregivers, lack of an appropriately stimulating environment, neglect, stressful life situations, learned behavior reinforced by pleasurable sensations, distraction from negative emotions, and/or inadvertent reinforcement (attention) from primary caregivers. The differential diagnosis includes congenital gastrointestinal system anomalies, pyloric stenosis (see Chapter 329), Sandifer syndrome (see Chapter 323), gastroparesis, hiatal hernia (see Chapter 322), increased intracranial pressure, diencephalic tumors, adrenal insufficiency, and inborn errors of metabolism. Older children and adults with anorexia nervosa or bulimia nervosa may also engage in regurgitation because of concerns about weight gain. The diagnosis of rumination disorder is appropriate only when the severity of the disturbance exceeds that routinely associated with a concurrent physical illness or mental disorder.

TREATMENT

This first step in treatment begins with a behavioral analysis to determine if the disorder serves as a self-stimulation purpose and/or is socially motivated. The behavior may begin as self-stimulation, but it subsequently becomes reinforced and maintained by the social attention given to the behavior. The central focus of behavioral treatment is to reinforce correct eating behavior while minimizing attention to rumination. Diaphragmatic breathing and postprandial gum chewing when used as a competing response have been shown to be helpful. Aversive conditioning techniques (e.g., withdrawal of positive attention) are considered when a child's health is jeopardized.

Successful behavioral treatment requires the child's primary caregivers to be involved in the intervention. The caretakers need education and counseling around responding adaptively to the child's behavior as well as altering any maladaptive responses. There is no current evidence supporting a psychopharmacologic intervention for this disorder. In more severe or intractable cases (e.g., severe dehydration and malnutrition), an intensive integrated medical-behavioral treatment program afforded on a medical or medical-psychiatric unit may be necessary.

Bibliography is available at Expert Consult.

23.2 Pica

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Pica involves the persistent eating of nonnutritive, nonfood substances (e.g., paper, soap, plaster, charcoal, clay, wool, ashes, paint, earth) over a period of at least 1 mo. The eating behavior is inappropriate to the developmental level (e.g., the normal mouthing and tasting of objects in infants and toddlers) and, therefore, a minimum age of 2 yr is suggested. The eating behavior is not part of a culturally supported or socially normative practice. A diagnosis of pica may be assigned in the presence of any other feeding and eating disorder.

EPIDEMIOLOGY

Pica can occur throughout the lifetime, but occurs most commonly in childhood. It appears to be more common in those with intellectual disability and autism spectrum disorders, and to a lesser degree in obsessive-compulsive and schizophrenic disorders. The prevalence of pica is unclear, although it appears to increase with the severity of an intellectual disability. It usually remits in childhood but can continue into adolescence and adulthood. *Geophagia* (eating earth) is associated with pregnancy and is not seen as abnormal in some cultures (e.g., rural or preindustrial societies in parts of Africa and India). Children with pica are at increased risk for lead poisoning (see Chapter 721), iron-deficiency anemia (see Chapter 455), mechanical bowel problems, intestinal obstruction, intestinal perforations, dental injury, and parasitic infections. It can be fatal based on substances ingested.

ETIOLOGY AND DIFFERENTIAL DIAGNOSIS

Numerous etiologies have been proposed but not proved, ranging from psychosocial causes to physical ones. They include nutritional deficiencies (e.g., iron, zinc, and calcium), low socioeconomic factors (e.g., lead paint exposure), child abuse and neglect, family disorganization (e.g., poor supervision), mental disorder, learned behavior, underlying (but undetermined) biochemical disorder, and cultural and familial factors. The differential diagnosis includes anorexia nervosa (see Chapter 28), factitious disorder, and nonsuicidal self-injury in personality disorders. A separate diagnosis of pica should be made only if the eating behavior is sufficiently severe enough to warrant additional clinical attention.

TREATMENT

Combined behavioral, social, and medical approaches are generally indicated for pica. Assessment for neglect and family supervision combined with a psychiatric assessment for cooccurring mental disorders and developmental delay are important in developing an effective intervention strategy for pica. Behavioral treatment interventions, particularly applied behavioral analysis in patients with intellectual disability or autism spectrum disorders, have increasing evidence for being helpful. The sequelae related to an ingested item can require specific treatment (e.g., lead toxicity, iron-deficiency anemia, parasitic infestation). Ingestion of hair can require medical or surgical intervention for a gastric bezoar (see Chapter 334.2).

Bibliography is available at Expert Consult.

23.3 Enuresis (Bed-Wetting)

See Chapter 543.

23.4 Encopresis

See Chapter 332.2.

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Chapter 24

Motor Disorders and Habits

Colleen A. Ryan, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

Motor disorders are interrelated sets of psychiatric symptoms characterized by abnormal motor movements and associated phenomena. In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), motors disorders include tic, stereotypic movement, and developmental coordination disorders. Tic disorders (Tourette, persistent motor or vocal tic, provisional tic) and stereotypic movement

disorder will be addressed in this chapter. Although not DSM-5 motor disorders, habits present as repetitive and often problematic motor behaviors (specifically thumb sucking and teeth grinding).

24.1 Tic Disorders

Colleen A. Ryan, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

Tourette disorder **(TD)**, ***persistent (chronic) motor or vocal tic*** **(PTD),** and provisional tic disorders (Table 24-1) are characterized by involuntary, rapid, repetitive, single or multiple motor and/or vocal/phonic tics that wax and wane in frequency but have persisted for more than 1 year since first tic onset (<1 year for provisional tic disorder). PTD is differentiated from TD in that PTD is limited to either motor or vocal tics (not both), whereas TD has both motor and vocal tics at some point in the illness (although not necessarily concurrently). The tic disorders are hierarchical in order (i.e., TD followed by PTD followed by provisional tic disorder), such that once a tic disorder at one level of the hierarchy is diagnosed, a lower hierarchy diagnosis cannot be made.

DESCRIPTION

Tics are sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations. Simple motor tics (e.g., eye blinking, neck jerking, shoulder shrugging, extension of the extremities) are fast, brief movements involving one or a few muscle groups, while complex motor tics involve sequentially and/or simultaneously produced relatively coordinated movements that can seem purposeful (e.g., brushing back one's hair bangs, tapping the foot, imitating someone else's movement [echopraxia], or making a sexual or obscene gesture [copropraxia]). Simple vocal tics (e.g., throat clearing, sniffing, coughing) are solitary, meaningless sounds and noises, whereas complex vocal tics (e.g., partial words [syllables], words out of context, coprolalia [obscenities or slurs], palilalia [repeating one's own sounds or words], or echolalia [repeating the last heard word or phrase]) are meaningful utterances and verbalizations.

Sensory phenomena (premonitory urges) that precede and trigger the urge to tic have been described. Individuals with tics can suppress them for varying periods of time, particularly when external demands exert their influence, when deeply engaged in a focused task or activity, or during sleep. Tics are often suggestible and are worsened by anxiety, excitement, or exhaustion. Although parents have described increasing frequency of tics at the end of the day, research has not supported volitional suppressing of tics leading to tic rebound.

Table 24-1 DSM-5 Diagnostic Criteria for Tic Disorders

Note: A tic is a sudden, rapid, recurrent, nonrhythmic motor movement or vocalization.

TOURETTE'S DISORDER
A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).

PERSISTENT (CHRONIC) MOTOR OR VOCAL TIC DISORDER
A. Single or multiple motor or vocal tics have been present during the illness, but not both motor and vocal.
B. The tics may wax and wane in frequency but have persisted for more than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder.
Specify if:
With motor tics only
With vocal tics only

PROVISIONAL TIC DISORDER
A. Single or multiple motor and/or vocal tics.
B. The tics have been present for less than 1 year since first tic onset.
C. Onset is before age 18 years.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., cocaine) or another medical condition (e.g., Huntington's disease, postviral encephalitis).
E. Criteria have never been met for Tourette's disorder or persistent (chronic) motor or vocal tic disorder.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 81.

CLINICAL COURSE

Onset of tics is typically between ages 4 and 6 yr. Peak severity occurs between ages 10 and 12 yr, with marked attenuation of tic severity in most individuals (65%) by age 18-20 yr. A small percentage will have worsening tics into adulthood. New onset of tics in adulthood is very rare and most often is associated with exposure to drugs or insults to the central nervous system. Tics manifest similarly in all age groups and change in affected muscle groups and vocalizations over time. Some individuals may have tic-free periods of weeks to months.

EPIDEMIOLOGY

Prevalence rates for all tics range from 6-18% for boys and 3-11% for girls, with the rate of TD alone estimated as 0.3-0.8%. In general, PTD/TD has a male preponderance with a gender ratio varying from 2:1 to 4:1. Evidence supports higher rates in white compared to African-American or Hispanic youth.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes the repetitive movements of childhood (Table 24-2). Tics may be difficult to differentiate from stereotypies. Although stereotypies may resemble tics, stereotypies are typically rhythmic movements and do not demonstrate the change in body location or movement type over time that is typical of tics. Compulsions may be difficult to differentiate from tics when tics have premonitory urges. Tics should be differentiated from a variety of developmental and benign movement disorders (e.g., benign paroxysmal torticollis, Sandifer syndrome, benign jitteriness of newborns, and shuddering attacks). Tics may present in various neurologic illnesses (e.g., Wilson disease, neuroacanthocytosis, Huntington syndrome, and a variety of frontal-subcortical brain lesions); it is rare for tics to be the only manifestation of these disorders. Individuals presenting with tics in the context of declining motor or cognitive function should be referred for neurologic assessment. Some substances/medications that are reported to worsen tics include stimulants, selective serotonin reuptake inhibitors, lamotrigine, and cocaine. If tics develop in close temporal relationship to the use of a substance/medication and then remit when use of the substance is discontinued, a causal relationship is possible. Although a long-time clinical concern, there is no scientific evidence in controlled studies that stimulants increase tics.

COMORBIDITIES

Co-occurring psychiatric disorders are common, often with both the patient and family viewing the accompanying condition as more problematic than the tics per se. There is a bidirectional association between PTD/TD (especially TD) and obsessive-compulsive disorder (OCD; see Chapter 25), with 20-60% of TD patients meeting OCD criteria and 20-40% of OCD patients reporting tics (Fig. 24-1). Attention-deficit/hyperactivity disorder (ADHD; see Chapter 33) co-occurs in approximately 50% of all childhood PTD/TD, but estimates

Table 24-2 Repetitive Movements of Childhood

	DESCRIPTION	TYPICAL DISORDERS WHERE PRESENT
Tics	Sudden rapid, recurrent, nonrhythmic, stereotyped, vocalization or motor movement	Transient tics, Tourette disorder, persistent tic disorder
Dystonia	Involuntary, sustained, or intermittent muscle contractions that cause twisting and repetitive movements, abnormal postures, or both	DYT1 Gene, Wilson, myoclonic dystonia, extrapyramidal symptoms caused by dopamine blocking agents
Chorea	Involuntary, random, quick, jerking movements, most often of the proximal extremities, that flow from joint to joint. Movements are abrupt, nonrepetitive, and arrhythmic and have variable frequency and intensity	Sydenham chorea, Huntington chorea
Stereotypies	Stereotyped, rhythmic, repetitive movements or patterns of speech, with lack of variation over time	Autism, stereotypic movement disorder, intellectual disability
Compulsions	A repetitive, excessive, meaningless activity or mental exercise that a person performs in an attempt to avoid distress or worry	Obsessive-compulsive disorder, anorexia, body dysmorphic disorder, trichotillomania, excoriation disorder
Myoclonus	Shock-like involuntary muscle jerk that may affect a single body region, one side of the body, or the entire body; may occur as a single jerk or repetitive jerks	Hiccups, hypnic jerks, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, mitochondrial encephalopathies, metabolic disorders
Akathisia	Unpleasant sensations of "inner" restlessness, often prompting movements in an effort to reduce the sensations	Extrapyramidal adverse effects from dopamine blocking agents; anxiety
Volitional behaviors	Behavior that may be impulsive or due to boredom like tapping peers, making sounds (animal noises)	Attention-deficit/hyperactivity disorder, oppositional defiant disorder, sensory integration disorders

Adapted from Murphy TK, Lewin AB, Storch EA, et al: Practice parameter for the assessment and treatment of children and adolescents with chronic tic disorders, J Am Acad Child Adolesc Psychiatry *52(12):1341–1359, 2013.*

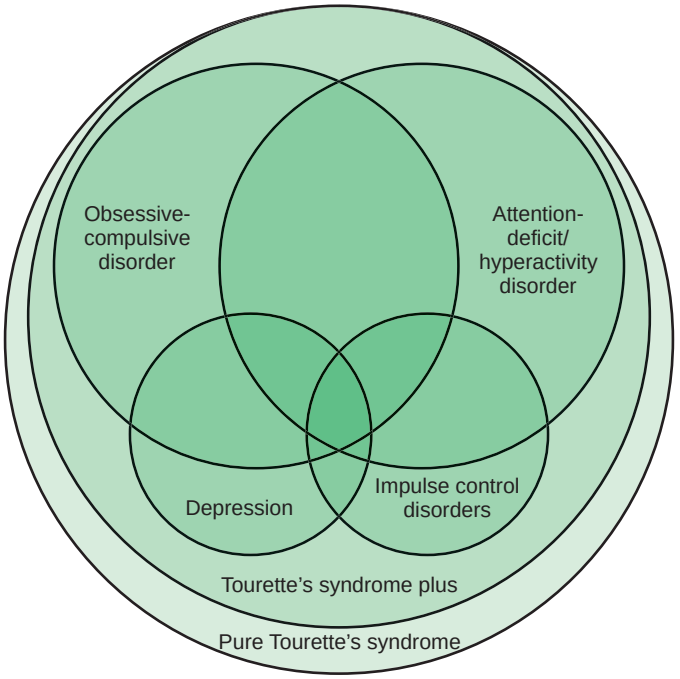

Figure 24-1 **Schematic representation of the behavioral spectrum in Tourette syndrome.** The size of each area is proportional to the estimated prevalence of the symptoms; the background color intensity is proportional to the complexity of the clinical presentation. *From Cavanna AE, Seri S: Tourette's syndrome. BMJ 347:f4964, 2013.*

in clinically referred patients suggest much higher rates (60-80%). PTD/TD is often accompanied by behavior problems including poor frustration tolerance, temper outbursts, and oppositionality. Learning disabilities have been found in more than 20% of these patients. The co-occurrence of anxiety and depression also has been observed. Some patients with PTD/TD will display symptoms of ***autism spectrum disorders*** **(ASDs**; see Chapter 30); careful assessment is required to determine which disorder is primary.

ETIOLOGY

Tics are proposed to be the result of dysfunctional corticostriatal–thalamocortical motor pathways in the basal ganglia, striatum, and frontal lobes associated with abnormalities in the dopamine, serotonin and norepinephrine neurotransmitter systems. Male predominance in PTD/TD may be attributable to influences of sex hormones on the neurodevelopment of these motor pathways, as reflected by the effects of antiandrogens in the treatment of TD.

Family studies suggest a 10-100–fold increase in the risk of PTD/TD among 1st-degree relatives compared to rates in the general population. Twin studies also support a genetic link, with approximately 80% of monozygotic twins and 30% of dizygotic twins showing concordance for PTD/TD. To date, candidate-gene association and nonparametric linkage studies have not shown specific susceptibility genes for PTD/TD.

Autoimmune mediated mechanisms have been hypothesized as having a potential etiologic role in some tic disorders. The ***pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection*** **(PANDAS**; see Chapter 183) designation has been used to describe cases of acute childhood onset of OCD and/or tics following a streptococcal infection. More recently, **PANS *(pediatric acute-onset neuropsychiatric syndrome)*** has been used to describe a subtype of acute childhood onset OCD (tics are not a required feature) in which a link to a prior streptococcal infection is not evident suggesting that other infectious agents may also be responsible (Table 24-3). In addition to a diagnosis of OCD and/or tics, children with PANS/PANDAS have been reported to have symptoms of separation anxiety, nightmares, personality change, oppositional behaviors, and deterioration in math skills and handwriting. Although some studies suggest a prior history of infections may increase the risk for developing tic disorder, this remains controversial.

Premorbid stress has been hypothesized to act as a sensitizing agent in the pathogenesis of TD among susceptible individuals by affecting

Table 24-3 Diagnostic Criteria Proposed for Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS)

CRITERION	DESCRIPTION
I.	Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
II.	Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least 2 of the following 7 categories (see text for full description): 1. Anxiety 2. Emotional lability and/or depression 3. Irritability, aggression and/or severely oppositional behaviors 4. Behavioral (developmental) regression 5. Deterioration in school performance 6. Sensory or motor abnormalities 7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency
III.	Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder or others. *Note:* The diagnostic work-up of patients suspected of PANS must be comprehensive enough to rule out these and other relevant disorders. The nature of the co-occurring symptoms will dictate the necessary assessments, which may include MRI scan, lumbar puncture, electroencephalogram or other diagnostic tests.

From Swedo SE, Leckman JF, Rose NR: From research subgroup to clinical syndrome: modifying the PANDAS criteria to describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome). Pediatr Therapeut *2:113, 2012, Table 2.*

stress responsive biologic systems such as the hypothalamic–pituitary–adrenal axis.

SEQUELAE

Many individuals with mild to moderate tics express little to no distress or functional impairment and may even be unaware of their tics. Even individuals with moderate to severe tics can experience little functional impairment, but psychological distress may occur. Uncommonly, the presence of tics can lead to social isolation, social victimization, inability to work or attend school, or impaired quality of life.

SCREENING

Pediatricians should routinely screen for unusual movements and vocalizations. As an adjunct to a verbal screen, commonly used broadband symptom rating scales such as the *Child Behavior Checklist* (CBCL) and the *Swanson, Nolan, and Pelham* (SNAP) include specific tic questions. Often families are unaware that frequent sniffing, coughing, or blinking may be indicative of tics, attributing these behaviors to medical problems (e.g., allergies, visual problems). A careful assessment of the timing, triggers, and specific characteristics may differentiate tics from other medical problems. If differentiation is difficult, a referral to a pediatric specialist in the affected system is warranted.

ASSESSMENT

If the screening suggests the presence of a tic disorder, a more comprehensive evaluation should ensue, including the age of onset, types of tics, tic frequency, alleviating and aggravating factors, and a family history of tics. Symptom rating scales specific for tics (e.g., the *Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey* [MOVES], *Tic Self Report Scale*, *Tourette's Disorder Scale*, *Parent Tic Questionnaire* (PTQ; hppt://www.uab.edu/ot/practice/tourette-syndrome-clinic/parent-tic-questionnaire), and the *Child Tourette's Disorder Impairment Scale–Parent Version* can supplement the assessment. For clinician-rated tic severity, the most commonly used instrument is the *Yale Global Tic Severity Scale* (YGTSS); the *Tourette Syndrome Severity Scale* (TSSS), and the *Tourette Syndrome Global Scale* (TSGS) also can be useful.

A medical workup should be considered for new-onset tics, particularly for presentations characterized by sudden onset, atypicality, or mental status abnormalities. Basic laboratory measures (hemogram, renal/hepatic function panel, thyroid panel and ferritin along with urine drug screen for adolescents) should be considered. For new sudden (overnight) onset or severe symptom exacerbation, pediatricians may assess for co-occurring acute infection (e.g., culture, rapid viral tests, etc.). Electroencephalogram and brain imaging are not routinely recommended and should be reserved for cases with other neurologic findings that might suggest an autoimmune encephalitis syndrome (limbic encephalitis) (see Chapter 598.4). Cooccurring psychiatric disorders (e.g., OCD, ADHD, ASD) should be investigated.

TREATMENT

The decision to treat tics is made with the child and family based upon the level of impairment and distress caused by the tics. If tics are mild in severity, there may be no need for intervention after psychoeducation is provided.

Psychoeducation should include common symptom presentations, implications of co-occurring conditions, course and prognosis, and treatment options (including no treatment). The youth's typical exacerbating and alleviating factors should be reviewed. The clinician can direct the family and youth to informational websites, including the Tourette Syndrome Association (www.tsa-usa.org) or the Tourette Syndrome "Plus" website (www.tourettesyndrome.net).

Nearly 75% of children with TD/PTD receive some form of classroom accommodation (most often ignoring the tics and permission to leave the room as needed). The accommodations may need to be formalized in an ***Individualized Education Plan*** **(IEP)** or 504 Plan.

Referral to a behavioral treatment specialist should be considered when tics are distressing or functionally impairing. The behavioral intervention with the strongest empirical support is ***habit reversal therapy*** **(HRT)**. The typical components of HRT include premonitory urge awareness training, building a competing response to the urge to tic, and social support. In a large randomized trial comparing an HRT protocol to a psychosocial control, the effect size favoring the intervention was 0.64; nearly all intervention subjects were also prescribed medication. To date, there are no studies comparing HRT to medication or combined (medication plus HRT) therapy.

Behavioral treatment may also address less-adaptive coping strategies (e.g., avoidance, social withdrawal) that develop secondary to tics and contribute to impairment. Skill-based therapies such as cognitive-behavioral therapy can be beneficial in reducing maladaptive coping strategies, anxiety, and compulsive behavior.

Medications should be considered when the tics are causing severe impairment in the quality of life, or when medication-responsive psychiatric comorbidities are present that target both tic symptoms and comorbid conditions. The only 2 FDA-approved medications to treat TD are haloperidol and pimozide, although most clinicians use atypical antipsychotics (risperidone) before the FDA-approved agents because of the more favorable side-effect profile of the atypicals. Others use α_2-agonists as 1st-line agents because of their less-adverse side-effect profile compared to the antipsychotics.

The α_2-adrenergic agonists (clonidine and guanfacine) have demonstrated an effect size of 0.5 for amelioration of tics. A meta-analysis found that agonist trials enrolling subjects with comorbid ADHD demonstrated a much higher effect size (0.68) than trials enrolling subjects without comorbid ADHD (0.15). The starting dose for clonidine is 0.025-0.05 mg/day with gradual increases up to 0.1-0.4 mg/day, administered in divided doses (3-4 times a day). A transdermal patch of clonidine is available, as is a sustained-release formulation that has been FDA-approved for the treatment of ADHD, but has not been studied for the treatment of tics. Sedation and low blood pressure are

common side effects that require careful monitoring, particularly when initiating treatment. The role of guanfacine, which is a less-sedating α_2-agonist, has not been firmly established but trials are underway.

The D_2 dopamine receptor-blocking medications (haloperidol and pimozide) are effective in reducing tics, but the side-effect burden (e.g., extrapyramidal symptoms) have limited their use as 1st-line treatment. Risperidone, an atypical antipsychotic medication, has appeared in 4 randomized control trials to be an effective treatment, although concerns for neuromotor and metabolic side effects exist. The starting dose for risperidone is 0.125-0.5 mg/day with a usual dose range of 0.75-3.0 mg/day.

The side effects of all antipsychotic medications warrant close monitoring: abnormal movements should be monitored periodically using a standardized methodology (such as the *Abnormal Involuntary Movement Scale [AIMS] checklist*); blood pressure, body mass index and fasting glucose and lipids should be checked at baseline and at regular intervals thereafter, according to standard guidelines. Consideration of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds 90th percentile body mass index for age, or a change of 5 body mass index units occurs in youths who were obese at the beginning of treatment. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Children with tic disorders may benefit from selective serotonin reuptake inhibitors (SSRIs) for the treatment of comorbid OCD, anxiety, or depressive disorders. Augmentation of SSRIs with an atypical antipsychotic medication has been a consideration in patients with co-occurring tic disorders and OCD responding poorly to an SSRI alone. The presence of tics does not preclude the use of stimulants to address comorbid ADHD. However, close clinical monitoring is required for possible exacerbation of tics during stimulant treatment. Anger and rage outbursts are not uncommon among youth with tics (up to 80% in clinically referred samples). Behavioral therapies that address anger management may be useful. There are no controlled pharmacologic studies in youth with tics disorders with anger outbursts. There also is no scientific evidence to support the use of deep brain stimulation, repetitive magnetic stimulation, and dietary supplements in the treatment of TD/PTD.

24.2 Stereotypic Movement Disorder

Colleen A. Ryan, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

In DSM-5, ***stereotypic movement disorder*** **(SMD)** is defined as a neurodevelopmental disorder characterized by repetitive, seemingly driven, and apparently purposeless motor behavior (stereotypy) that interferes with social, academic, or other activities that may result in self-injury. The onset of SMD is the early developmental period (often before age 3 yr), and the symptoms are not attributable to the physiologic effects of a substance or neurologic condition and are not better explained by another neurodevelopmental or mental disorder. The disorder is considered mild if symptoms are easily suppressed by sensory stimulus or distraction, and severe if continuous monitoring and protective measures are required to prevent serious injury, with moderate falling between mild and severe.

DESCRIPTION

Examples of stereotypic movements include hand shaking or waving, body rocking, head banging, self-biting, and hitting one's own body. The presentation depends on the nature of the stereotypic movement and level of the child's awareness of the behavior. Among typically developing children, the repetitive movements may be stopped when attention is directed to them or when the child is distracted from performing them. Among children with neurodevelopmental disorders, the behaviors are typically less responsive to such efforts. Each individual presents with his or her own uniquely patterned behavior. Stereotypic movements may occur many times during a day, lasting a few seconds to several minutes or longer. The behaviors may occur in multiple contexts, including when the individual is excited, stressed, fatigued, or bored.

CLINICAL COURSE

Stereotypic movements typically begin within the first 3 yr of life. In children who develop complex motor stereotypies, the great majority exhibit symptoms before 24 mo of age. In most typically developing children, these movements resolve over time. Among individuals with intellectual disability, the stereotyped behaviors may persist for years, although the pattern may change over time.

EPIDEMIOLOGY

Simple stereotypic movements (e.g., rocking) are common in typically developing young children. Self-injurious habits, such as self-biting or head banging, can occur in up to 25% of typically developing toddlers, but they are almost invariably associated with developmental delay in children older than age 5 yr. Complex stereotypic movements are much less common (occurring in approximately 3-4% of children). Between 4% and 16% of individuals with intellectual disability engage in stereotypic movements.

COMORBIDITY

Stereotypic movements are a common manifestation of a variety of neurogenetic disorders, such as Lesch-Nyhan syndrome, Rett syndrome (see Chapter 599), fragile X syndrome (see Chapter 81), Cornelia de Lange syndrome, and Smith-Magenis syndrome.

DIFFERENTIAL DIAGNOSIS

According to DSM-5, stereotypic movements must be differentiated from normal development, **ASDs**, tic disorders, **OCDs**, and other neurologic and medical conditions. Simple stereotypic movements occurring in the context of normal development usually resolve with age. Stereotypic movements may be a presenting symptom of ASD, but SMD does not include the deficits in social communication characteristic of ASD. When ASD is present, SMD is diagnosed only when there is self-injury or when the stereotypic behaviors are sufficiently severe to become a focus of treatment. Typically, SMD has an earlier age of onset than the tic disorders, and the movements are fixed in their pattern. SMD is distinguished from OCD by the absence of obsessions as well as the nature of the repetitive behaviors, which in OCD are purposeful (e.g., in response to obsessions). The diagnosis of stereotypic movements requires the exclusion of habits, mannerisms, paroxysmal dyskinesias, and benign hereditary chorea. A neurologic history and examination are required to assess features suggestive of other disorders, such as myoclonus, dystonia, and chorea.

ETIOLOGY

There is a possible evolutionary link between repetitive abnormal grooming-like behaviors and early human experience with adversity. Brain regions implicated in this model (e.g., amygdala and hippocampus) are those involved in navigating human experience through unpredictable, anxiety-provoked emotional states as well as regions (e.g., nucleus accumbens) related to pleasure and reward seeking. The latter involves the hypothesis that individuals experience some level of gratification from performing the habit behavior.

Social isolation with insufficient stimulation (e.g., severe neglect; see Chapter 40) is a risk factor for self-stimulation that may progress into stereotypies (particularly repetitive rocking or spinning). Environmental stress may trigger stereotypic behaviors. Repetitive self-injurious behavior may be a behavioral phenotype in neurogenetic syndromes (e.g., Lesch-Nyhan, Rett, and Cornelia de Lange syndromes). Lower cognitive functioning is also linked to greater risk of stereotypic behaviors.

TREATMENT

The initial approach to helping children with mild stereotypy is for parents to ignore the undesired behavior, encourage substitute behavior, and not convey worry to their child. These behaviors may disappear with time and elimination of attention in young children. However, in children with neurodevelopmental disorders, stereotypies are more refractory to treatment than in normally developing children, and may necessitate referral to a behavioral psychologist and/or child and adolescent psychiatrist for behavioral and/or psychopharmacologic management. The pediatrician should consider and rule out neglect of the child, which can be associated with repetitive rocking, spinning, or other stereotypic movements.

Behavior therapy is the mainstay of treatment, using a variety of strategies including habit reversal, relaxation training, self-monitoring, contingency management, competing responses, and negative practice. The environment should also be modified to reduce risk of injury to those engaging in self-injurious behavior.

Atypical antipsychotic medications appear to be helpful in reducing stereotypic movements in youth with ASD. Patients with co-occurring with anxiety and obsessive-compulsive behaviors treated with SSRIs for these disorders may show improvement in their stereotypic movements.

HABITS

Habits involve an action or pattern of behavior that is repeated often. Habits are common in childhood and range from benign and transient (thumb sucking, nail biting) to more problematic (trichotillomania, bruxism). In DSM-5, habits are not included as a diagnostic category as they are not viewed as disorders causing clinically significant distress or impairment in functioning. Treatment with HRT has been effective as a 1st-line approach (Table 24-4).

Table 24-4 Components of Habit Reversal Procedure

Increase Individual's Awareness of Habit
Response description—have individual describe behavior to therapist in detail while reenacting the behavior and looking in a mirror.
Response detection—inform individual of each occurrence of the behavior until each occurrence is detected without assistance.
Early warning—have individual practice identifying earliest signs of the target behavior.
Situation awareness—have individual describe all situations in which the target behavior is likely to occur.
Teach Competing Response to Habit
The competing response must result in isometric contraction of muscles involved in the habit, be capable of being maintained for 3 min, and be socially inconspicuous and compatible with normal ongoing activities but incompatible with the habit (e.g., clenching one's fist, grasping and clenching an object). For vocal tics and stuttering, deep relaxed breathing with a slight exhale before speech has been used as the competing response.
Sustain Compliance
Habit inconvenience review—have individual review in detail all problems associated with target behavior.
Social support procedure—family members and friends provide high levels of praise when a habit-free period is noted.
Public display—individual demonstrates to others that he or she can control the target behavior in situations in which the behavior occurred in the past.
Facilitate Generalization—Symbolic Rehearsal Procedure
For each situation identified in situation awareness procedure, individual imagines himself or herself beginning the target behavior but stopping and engaging in the competing response.

From Carey WB, Crocker AC, Coleman WL, Elias ER, Feldman HM, editors: Developmental-behavioral pediatrics, *ed 4, Philadelphia, 2009, Elsevier/Saunders, Table 65-4, p. 639.*

Thumb Sucking

Thumb sucking is common in infancy and in as many as 25% of children age 2 yr and 15% of children age 5 yr. Thumb sucking beyond 5 yr may be associated with sequelae (paronychia, anterior open bite). Like other rhythmic patterns of behavior, thumb sucking is self-soothing. Basic behavioral management, including encouraging parents to ignore thumb sucking and instead focus on praising the child for substitute behaviors, is often effective treatment. Simple reminders and reinforcers, such as giving the child a sticker (or other rewards) for each block of time that he or she does not suck the thumb can also be considered. Although some suggest the use of noxious agents (bitter salves) this approach should rarely be necessary.

Bruxism

Bruxism or teeth grinding is common (5-30% of children), can begin in the first 5 yr of life, and may be associated with daytime anxiety. Persistent bruxism can manifest as muscular or temporomandibular joint pain. Untreated bruxism can cause problems with dental occlusion. Helping the child find ways to reduce anxiety might relieve the problem; bedtime can be made more relaxing by reading or talking with the child and allowing the child to discuss fears. Praise and other emotional support are useful. Persistent bruxism requires referral to a dentist given the risk for dental occlusion.

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Chapter 25

Anxiety Disorders

David R. Rosenberg and Jennifer A. Chiriboga

Anxiety, defined as dread or apprehension is not considered pathologic, is seen across the life span, and can be adaptive (e.g., the anxiety one might feel during an automobile crash). Anxiety has both a cognitive and behavioral component, expressed in worrying and wariness, and a physiologic component, mediated by the autonomic nervous system. Anxiety disorders are characterized by pathologic anxiety in which anxiety becomes disabling, interfering with social interactions, development, and achievement of goals or quality of life, and can lead to low self-esteem, social withdrawal, and academic underachievement. The average age of onset of anxiety disorder is 11 yr. Diagnosis of a particular anxiety disorder in a child requires significant interference in the child's psychosocial and/or academic or occupational functioning, which can occur even with subthreshold symptoms that do not meet criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Anxiety may have physical manifestations such as weight loss, pallor, tachycardia, tremors, muscle cramps, paresthesias, hyperhidrosis, flushing, hyperreflexia, and abdominal tenderness.

Separation anxiety disorder (**SAD**), childhood-onset social phobia or social anxiety disorder, generalized anxiety disorder (**GAD**), obsessive-compulsive disorder (**OCD**), phobias, posttraumatic stress disorder (**PTSD**), and panic disorder (**PD**) are all defined by the occurrence of either diffuse or specific anxiety, often related to predictable situations or cues. Anxiety disorders are the most common psychiatric disorders of childhood; they occur in 5-18% of all children and adolescents, prevalence rates comparable to physical disorders such as asthma and diabetes. Anxiety disorders are often comorbid with other psychiatric and medical disorders (including a second anxiety disorder); significant impairment in day-to-day functioning is common. High levels of fear in adolescence are also a significant risk factor for experiencing later episodes of major depression in adulthood. Anxiety

and depressive disorder in adolescence predict increased risk of anxiety and depressive symptoms (including suicide attempts) in adulthood, underscoring the need to diagnose and treat these underreported, yet prevalent, conditions early.

Because anxiety is both a normal phenomenon and, when highly activated, strongly associated with impairment, the pediatrician must be able to differentiate normal anxiety from abnormal anxiety across development. Anxiety has an identifiable developmental progression for most children; most infants exhibit stranger wariness or anxiety beginning at 7-9 mo of age. Behavioral inhibition to the unfamiliar (withdrawal or fearfulness to novel stimuli associated with physiologic arousal) is evident in approximately 10-15% of the population at 12 mo of age and is moderately stable. Most children who show behavioral inhibition do not develop impairing levels of anxiety. A family history of anxiety disorders and maternal over involvement or enmeshment predicts later clinically significant anxiety in behaviorally inhibited infants. The infant who is excessively clingy and difficult to calm during pediatric visits should be followed for signs of increasing levels of anxiety.

Preschoolers typically have specific fears related to the dark, animals, and imaginary situations, in addition to normative separation anxiety. Preoccupation with orderliness and routines (*just right* phenomena) often takes on a quality of anxiety for preschool children. Parents' reassurance is usually sufficient to help the child through this period. Although most school-age children abandon the imaginary fears of early childhood, some replace them with fears of bodily harm or other worries (Table 25-1). In adolescence, general worrying about school performance and worrying about social competence are common and remit as the teen matures.

Table 25-1 DSM-5 Diagnostic Criteria for Specific Phobia

Diagnostic Criteria

A. Marked fear or anxiety about a specific object or situation (e.g., flying, heights, animals, receiving an injection, seeing blood).

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, or clinging.

B. The phobic object or situation almost always provokes immediate fear or anxiety.

C. The phobic object or situation is actively avoided or endured with intense fear or anxiety.

D. The fear or anxiety is out of proportion to the actual danger posed by the specific object or situation and to the sociocultural context.

E. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

F. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

G. The disturbance is not better explained by the symptoms of another mental disorder, including fear, anxiety and avoidance or situations associated with panic-like symptoms or other incapacitating symptoms (as in agoraphobia); objects or situations related to obsessions (as in obsessive-compulsive disorder); remainders of traumatic events (as in posttraumatic stress disorder); separation from home or attachment figures (as in separation anxiety disorder); or social situations (as in social anxiety disorder).

Specify if:

Code based on the phobic stimulus:

Animal (e.g., spiders, insects, dogs).

Natural environment (e.g., heights, storms, water).

Blood-injection-injury (e.g., needles, invasive medical procedures).

Situational (e.g., airplanes, elevators, enclosed places).

Other (e.g., situations that may lead to choking or vomiting; in children, e.g., loud sounds or costumed characters).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 197–198.

Genetic or temperamental factors contribute more to the development of some anxiety disorders, whereas environmental factors are closely linked to the cause of others. Specifically, behavioral inhibition appears to be a heritable tendency and is linked with social phobia, generalized anxiety, and selective mutism. OCD and other disorders associated with OCD-like behaviors, such as Tourette syndrome and other tic disorders, tend to have high genetic risk as well (see Chapter 24.1). Environmental factors, such as parent–infant attachment and exposure to trauma, contribute more to SAD and PTSD. Parental anxiety disorder is associated with an increased risk of anxiety disorder in offspring. Differences in the size of the amygdala and hippocampus are noted in patients with anxiety symptoms.

SAD is one of the most common childhood anxiety disorders with a prevalence of 3.5-5.4%. Approximately 30% of children presenting to an outpatient anxiety disorder clinic have SAD as a primary diagnosis. Separation anxiety is developmentally normal when it begins about 10 mo of age and tapers off by 18 mo. By 3 yr of age, most children can accept the temporary absence of their mother or primary caregiver.

SAD is more common in prepubertal children, with an average age of onset of 7.5 yr. Girls are more commonly affected than boys. SAD is characterized by unrealistic and persistent worries about separation from the home or a major attachment figure. Concerns include possible harm befalling the affected child or the child's primary caregivers, reluctance to go to school or to sleep without being near the parents, persistent avoidance of being alone, nightmares involving themes of separation, numerous somatic symptoms, and complaints of subjective distress. The first clinical sign might not appear until 3rd or 4th grade, typically after a holiday or a period where the child has been home because of illness, or when the stability of the family structure has been threatened by illness, divorce, or other psychosocial stressor.

Symptoms vary depending on the child's age: Children younger than 8 yr often have associated school refusal and excessive fear that harm will come to a parent; children 9-12 yr have excessive distress when separated from a parent; and those 13-16 yr often have school refusal and physical complaints. SAD may be more likely to develop in children with lower levels of psychosocial maturity. Parents are often unable to be assertive in returning the child to school. Mothers of children with SAD often have a history of an anxiety disorder. In these cases, the pediatrician should screen for parental depression or anxiety. Often referral for parental treatment or family therapy is necessary before SAD and concomitant school refusal can be successfully treated.

Comorbidity is common in SAD. In children with comorbid tic disorders and anxiety, SAD is especially associated with tic severity. SAD is a predictor for early onset of PD. Children with SAD compared to those without SAD are 3 times more likely to develop PD in adolescence.

When a child reports recurring acute severe anxiety, antidepressant or anxiolytic medication is often necessary. Controlled studies of tricyclic antidepressants (imipramine) and benzodiazepines (clonazepam) show that these agents are not generally effective. Data support the use of cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) (see Table 21-4 in Chapter 21). One study of children 7-17 yr of age with a primary diagnosis of SAD compared 12 wk of treatment with CBT, the SSRI sertraline, their combination, and placebo. Nearly 81% of those treated with combination therapy improved, 55% for SSRI alone, 60% for CBT. All treatments were superior to placebo (24% response rate). The SSRI was well tolerated and had few side effects; adverse events, including suicidal and homicidal ideation, did not differ between the SSRI and placebo groups and there were no attempted suicides. CBT was associated with less insomnia, fatigue, sedation, and restlessness than SSRI. Combining SSRI with CBT may be the best approach to achieving a positive response; long-term SSRI treatment can provide additional benefit. Findings from this study are consistent with a meta-analysis of published and unpublished randomized controlled trials of antidepressants for pediatric patients with SAD, social phobia, or GAD.

Childhood-onset social phobia (social anxiety disorder) is characterized by excessive anxiety in social settings (including the presence

Table 25-2 DSM-5 Diagnostic Criteria for Social Anxiety Disorder (Social Phobia)

Diagnostic Criteria

A. Marked fear or anxiety about 1 or more social situations in which the individual is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation, meeting unfamiliar people), being observed (e.g., eating or drinking), and performing in front of others (e.g., giving a speech).
B. The individual fears that he or she will act in a way or show anxiety symptoms that will be negatively evaluated (i.e., will be humiliating or embarrassing; will lead to rejection or offend others).
C. The social situations almost always provoke fear or anxiety.

Note: In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking, or failing to speak in social situations.

D. The social situations are avoided or endured with intense fear or anxiety.
E. The fear or anxiety is out of proportion to the actual threat posed by the social situation and to the sociocultural context.
F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.
G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
H. The fear, anxiety, or avoidance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
I. The fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder, such as panic disorder, body dysmorphic disorder, or autism spectrum disorder.
J. If another medical condition (e.g., Parkinson disease, obesity, disfigurement from burns or injury) is present, the anxiety or avoidance is clearly unrelated or is excessive.

Specify if:

Performance only: If the fear is restricted to speaking or performing in public.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 202–203.

of unfamiliar peers, or unfamiliar adults) or performance situations, leading to social isolation (Table 25-2) and is associated with social scrutiny and fear of doing something embarrassing. Fear of social settings can also occur in other disorders, such as GAD. Avoidance or escape from the situation usually dissipates anxiety in **social phobia (SP),** unlike GAD, where worry persists. Children and adolescents with SP often maintain the desire for involvement with family and familiar peers. When severe, the anxiety can manifest as a panic attack.

SP is associated with a decreased quality of life, with increased likelihood of having failed at least 1 grade, and a 38% likelihood of not graduating from high school. Its onset is typically during or before adolescence and is more common in girls. A family history of SP or extreme shyness is common. Approximately 70-80% of patients with SP have at least 1 comorbid psychiatric disorder. Most shy patients do not have a SP.

Social effectiveness therapy for children (SET-C), alone or with SSRIs, is considered the treatment of choice for SP (see Table 21-4 in Chapter 21). SSRI and SET-C are superior to placebo in reducing social distress and behavioral avoidance and increasing general functioning. SET-C may be better than SSRI in reducing these symptoms. SET-C, but not SSRI, may be superior to placebo in improving social skills, decreasing anxiety in specific social interactions, and enhancing social competence. SSRIs have a maximum effect by 8 wk; SET-C provides continued improvement through 12 wk. A combination of SSRI and CBT is superior to either treatment alone in reducing severity of anxiety in children with SP and other anxiety disorders. β-Adrenergic blocking agents are used to treat SP, particularly the subtype with performance anxiety and stage fright. β-Blockers are not FDA approved for SP.

School refusal, which occurs in approximately 1-2% of children, is associated with anxiety in 40-50% of cases, depression in 50-60% of cases, and oppositional behavior in 50% of cases. Younger anxious children who refuse to attend school are more likely to have SAD, whereas older anxious children usually refuse to attend school because of SP. Somatic symptoms, especially abdominal pain and/or headaches, are common. There may be increasing tension in the parent–child relationship or other indicators of family disruption (domestic violence, divorce, or other major stressors) contributing to school refusal.

Management of school refusal typically requires parent management training and family therapy. Working with school personnel is always indicated; anxious children often require special attention from teachers, counselors, or school nurses. Parents who are coached to calmly send the child to school and to reward the child for each completed day of school are usually successful. In cases of ongoing school refusal, referral to a child and adolescent psychiatrist and psychologist is indicated. SSRI treatment may be helpful. Young children with affective symptoms have a good prognosis, whereas adolescents with more insidious onset or with significant somatic complaints have a more guarded prognosis.

Selective mutism is conceptualized as a disorder that overlaps with SP. Children with selective mutism talk almost exclusively at home, although they are reticent in other settings, such as school, daycare, or even relatives' homes. The mutism must be present for ≥1 mo. Often, 1 or more stressors, such as a new classroom or conflicts with parents or siblings, drive an already shy child to become reluctant to speak. It may be helpful to obtain history of normal language use in at least 1 situation to rule out any communication disorder (fluency disorder), neurologic disorder, or pervasive developmental disorder (autism, schizophrenia) as a cause of mutism. Fluoxetine in combination with behavioral therapy is effective for children whose school performance is severely limited by their symptoms (see Chapter 35). Other SSRIs may also be effective.

PD is a syndrome of recurrent, discrete episodes of marked fear or discomfort in which patients experience abrupt onset of physical and psychologic symptoms called *panic attacks* (Table 25-3). Physical symptoms can include palpitations, sweating, shaking, shortness of breath, dizziness, chest pain, and nausea. Children can present with acute respiratory distress but without fever, wheezing, or stridor, ruling out organic causes of the distress. The associated psychologic symptoms include fear of death, impending doom, loss of control, persistent concerns about having future attacks, and avoidance of settings where attacks have occurred (agoraphobia, Table 25-4).

PD is uncommon before adolescence, with the peak age of onset at 15-19 yr of age, occurring more often in girls. The postadolescence prevalence of PD is 1-2%. Early-onset PD and adult-onset PD do not differ in symptom severity or social functioning. Early-onset PD is associated with greater comorbidity, which can result from greater familial loading for anxiety disorders in the early-onset subtype. Children of parents with PD are much more likely to develop PD. A predisposition to react to autonomic arousal with anxiety may be a specific risk factor leading to PD. Twin studies suggest that 30-40% of the variance is attributed to genetics. The increasing rates of panic attack are also directly related to earlier sexual maturity. Cued panic attacks can be present in other anxiety disorders and differ from the uncued "out-of-the-blue" attacks in PD.

No randomized controlled trials have evaluated the effectiveness of antidepressant medication in youth with PD. Open-label studies with SSRIs appear to show effectiveness in the treatment of adolescents (see Table 21-4 in Chapter 21). CBT may also be helpful. The recovery rate is approximately 70%.

GAD occurs in children who often experience unrealistic worries about different events or activities for at least 6 mo (Table 25-5) with at least 1 somatic complaint. The diffuse nature of the anxiety symptoms differentiates it from other anxiety disorders. Worries in children with GAD commonly center around concerns about competence and performance in school and athletics. GAD often manifests with somatic symptoms including restlessness, fatigue, problems concentrating, irritability, muscle tension, and sleep disturbance. Given the somatic

Table 25-3 DSM-5 Diagnostic Criteria for Panic Disorder

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time 4 (or more) of the following symptoms occur:

Note: The abrupt surge can occur from a calm state or an anxious state.

1. Palpitations, pounding heart, or accelerated heart rate.
2. Sweating
3. Trembling or shaking.
4. Sensations of shortness of breath or smothering.
5. Feelings of choking.
6. Chest pain or discomfort.
7. Nausea or abdominal distress.
8. Feeling dizzy, unsteady, light-headed, or faint.
9. Chills or heart sensations.
10. Paresthesias (numbness or tingling sensations).
11. Derealizations (feeling or unreality) or depersonalization (being detached from one-self).
12. Fear of losing control or "going crazy."
13. Fear of dying.

Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. Such symptoms should not count as 1 of the 4 required symptoms.

B. At least 1 of the attacks has been followed by 1 mo (or more) of 1 or both of the following:
   1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, "going crazy").
   2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., the panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive-compulsive disorder; or in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 208–209.

Table 25-4 DSM-5 Diagnostic Criteria for Agoraphobia

A. Marked fear or anxiety about 2 (or more) if the following 5 situations:
   1. Using public transportation (e.g., automobiles, buses, trains, ships, planes).
   2. Being in open spaces (e.g., parking lots, marketplaces, bridges).
   3. Being in enclosed places (e.g., shops, theaters, cinemas).
   4. Standing in line or being in a crowd.
   5. Being outside of the home alone.

B. The individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of a developing panic-like symptoms or other incapacitating or embarrassing symptoms (e.g., fear or falling in the elderly, fear of incontinence).

C. The agoraphobic situations almost always provoke fear or anxiety.

D. The agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety.

E. The fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context.

F. The fear, anxiety, or avoidance is persistent, typically lasting for 6 mo or more.

G. The fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational or other important area of functioning.

H. If another medical condition (e.g., inflammatory bowel disease, Parkinson disease) is present, the fear, anxiety, or avoidance is clearly excessive.

I. The fear, anxiety, or avoidance is not better explained by the symptoms or another mental disorder—for example, the symptoms are not confined to specific phobia, situational type; do not involve only social situations (as in social anxiety disorder); and are not related exclusively to obsessions (as in obsessive-compulsive disorder), reminders or traumatic events (as in posttraumatic stress disorder), or fear of separation (as in separation anxiety disorder).

Note: Agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 217–218.

symptoms characteristic of GAD, the differential diagnosis must consider other medical causes. Excessive use of caffeine or other stimulants in adolescence is common and should be determined with a careful history. When the history or physical exam is suggestive, the pediatrician should rule out hyperthyroidism, hypoglycemia, lupus, and pheochromocytoma.

Children with GAD are markedly self-conscious and perfectionistic and struggle with more intense distress than is evident to parents or others around them. They often have other anxiety disorders, such as simple phobia and PD. Onset may be gradual or sudden, although GAD does not often become manifest until puberty. Boys and girls are equally affected before puberty, when GAD becomes more prevalent in girls. The prevalence of GAD ranges from 2.5-6% of children. Hypermetabolism in frontal precortical area and increased blood flow in the right dorsolateral prefrontal cortex may be present.

Children with GAD are good candidates for CBT, an SSRI, or their combination (see Table 21-4 in Chapter 21). Buspirone may be used as an adjunct to SSRI therapy. Combination of CBT and SSRI often results in a superior response in pediatric patients with anxiety disorders, including GAD. The recovery rate is approximately 80%.

It is important to distinguish children with GAD from those who present with specific repetitive thoughts that invade consciousness **(obsessions)** or repetitive rituals or movements that are driven by anxiety **(compulsions)**. The most common obsessions are concerned with bodily wastes and secretions, the fear that something calamitous will happen, or the need for sameness. The most common compulsions are hand washing, continual checking of locks, and touching. At times of stress (bedtime, preparing for school), some children touch certain objects, say certain words, or wash their hands repeatedly. OCD is diagnosed when the thoughts or rituals cause distress, consume time, or interfere with occupational or social functioning (Table 25-6). In the DSM-5, OCD and related disorders (such as trichotillomania, excoriation, body dysmorphic disorder, and hoarding) are listed separately and are no longer included under anxiety disorders.

OCD is a chronically disabling illness characterized by repetitive, ritualistic behaviors over which the patient has little or no control. OCD has a lifetime prevalence of 1-3% worldwide, and as many as 80% of all cases have their onset in childhood and adolescence. Common obsessions include contamination (35%) and thoughts of harming loved ones or oneself (30%). Washing and cleaning compulsions are common in children (75%), as are checking (40%) and straightening (35%). Many children are observed to have visuospatial irregularities, memory problems, and attention deficits, causing academic problems not explained by OCD symptoms alone.

Table 25-5 DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with 3 (or more) of the following 6 symptoms (with at least some symptoms having been present for more days than not for the past 6 mo):
Note: Only 1 item is required in children.
1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
D. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or other medical condition (e.g., hyperthyroidism).
F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, remainders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 222.

Table 25-6 DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder

A. Presence of obsessions, compulsions, or both:
Obsessions are defined by (1) and (2):
1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress.
2. The individual attempts to ignore or suppress such thoughts, urges or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion).
Compulsions are defined by (1) and (2):
1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly.
2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.
B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hr per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The obsessive-compulsive symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating disorder, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilic disorders; impulses, as in disruptive, impulse-control and conduct disorders; guilty ruminations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).
Specify if:
With good or fair insight: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true.
With poor insight: The individual thinks obsessive-compulsive disorder beliefs are probably true.
With absent insight/delusional beliefs: The individual is completely convinced that obsessive-compulsive disorder beliefs are true.
Specify if:
Tic-related: The individual has a current or past history of a tic disorder.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 237.

The Children's Yale-Brown Obsessive-Compulsive Scale (C-YBOCS) and the Anxiety Disorders Interview Schedule for Children (ADIS-C) are reliable and valid methods for identifying children with OCD. The C-YBOCS is helpful in following the progression of symptoms with treatment. The Leyton Obsessional Inventory (LOI) is a self-report measure of OCD symptoms that is quite sensitive. Patients with OCD have consistently identified abnormalities in the frontostriatal-thalamic circuitry associated with severity of illness and treatment response. Comorbidity is common in OCD, with 30% of patients having comorbid tic disorders, 26% having comorbid major depression, and 24% having comorbid developmental disorders.

Consensus guidelines recommend that children and adolescents with OCD begin treatment with either CBT alone or CBT in combination with SSRI, when symptoms are moderate to severe (YBOCS >21). In OCD patients with comorbid tics, SSRIs are no more effective than placebo, and combination of CBT and SSRI is superior to CBT; CBT alone is superior to placebo. Pediatric OCD patients with comorbid tics should begin treatment with CBT alone or the combination of CBT and SSRI. Pediatric patients with OCD who have a family history of OCD may be significantly less responsive to CBT alone than patients without a family history of OCD.

There are 4 FDA-approved medications for pediatric OCD: fluoxetine, sertraline, fluvoxamine, and clomipramine. Clomipramine, a heterocyclic antidepressant and nonselective serotonin and norepinephrine reuptake inhibitor, is only indicated when a patient has failed 2 or more SSRI trials. There may be a role for glutamate-modulating medications in the treatment of OCD. The glutamate inhibitor riluzole (Rilutek) is FDA-approved for amyotrophic lateral sclerosis (see Chapter 612.3) and has a good safety record. The most common adverse event with riluzole is transient increase in liver transaminases. Riluzole in children with treatment-resistant OCD may be beneficial and is well tolerated. Other glutamate-modulating agents, such as memantine, *N*-acetyl-cysteine, and D-cycloserine, have been used with some success in patients with OCD. Referral of patients with OCD to a mental health professional is always indicated.

In 10% of children with OCD, symptoms are triggered or exacerbated by group A β-hemolytic streptococcal infection (see Chapter 183). Group A β-hemolytic streptococcal bacteria trigger antineuronal antibodies that cross-react with basal ganglia neural tissue in genetically susceptible hosts, leading to swelling of this region and resultant obsessions and compulsions. This subtype of OCD, called **pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS),** is characterized by sudden and dramatic onset or exacerbation of OCD or tic symptoms, associated neurologic findings, and a recent streptococcal infection. Increased

antibody titers of antistreptolysin O and antideoxyribonuclease B correlates with increased basal ganglia volumes. Plasmapheresis is effective in reducing OCD symptoms in some patients with PANDAS and also decreasing enlarged basal ganglia volume. OCD has also followed episodes of acute disseminated encephalomyelitis (see Chapter 600.3) The pediatrician should be aware of the infectious cause of some cases of tic disorders, attention-deficit disorder, and OCD and follow management guidelines (see Chapter 24).

Children with **phobias** avoid specific objects or situations that reliably trigger physiologic arousal (e.g., dogs or spiders) (see Table 25-1). The fear is excessive and unreasonable and can be cued by the presence or anticipation of the feared trigger, with anxiety symptoms occurring immediately. Neither obsessions nor compulsions are associated with the fear response; phobias only rarely interfere with social, educational, or interpersonal functioning. Assault by a relative and verbal aggression between parents can influence the onset of specific phobias. The parents of phobic children should remain calm in the face of the child's anxiety or panic. Parents who become anxious themselves may reinforce their children's anxiety, and the pediatrician can usefully interrupt this cycle by calmly noting that phobias are not unusual and rarely cause impairment. The prevalence of specific phobias in childhood is 0.5-2%.

Systematic desensitization is a form of behavior therapy that gradually exposes the patient to the fear-inducing situation or object, while simultaneously teaching relaxation techniques for anxiety management. Successful repeated exposure leads to extinguishing anxiety for that stimulus. When phobias are particularly severe, SSRIs can be used with behavioral intervention. Low-dose SSRI treatment may be especially effective for some children with severe, refractory choking phobia.

PTSD (see Chapter 39) is typically precipitated by an extreme stressor. PTSD is an anxiety disorder resulting from the long- and short-term effects of trauma that cause behavioral and physiologic sequelae in toddlers, children, and adolescents (Table 25-7). Another

Table 25-7 DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder

POSTTRAUMATIC STRESS DISORDER

Note: The following criteria apply to adults, adolescents, and children older than 6 yr. For children 6 yr and younger, see corresponding criteria below.

A. Exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others.
   3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
   4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., 1st responders collecting human remains; police officers repeatedly exposed to details of child abuse).

Note: Criterion A4 does not apply to exposure through electronic media, television, movies or pictures, unless this exposure is work related.

B. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: In children older than 6 yr, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

   2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

Note: In children, there may be frightening dreams without recognizable content.

   3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the more extreme expression being a complete loss or awareness of present surroundings.)

Note: In children, trauma-specific reenactment may occur in play.

   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
   5. Marked physiologic reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by 1 or both of the following:
   1. Avoidance of or efforts to avoid distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).
   2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that around distressing memories, thoughts or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:
   1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
   2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
   3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
   4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
   5. Markedly diminished interest or participation in significant activities.
   6. Feelings of detachment or estrangement from others.
   7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:
   1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed by verbal or physical aggression toward people or objects.
   2. Reckless or self-destructive behavior.
   3. Hypervigilance.
   4. Exaggerated startle response.
   5. Problems with concentration.
   6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 mo.

G. The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning.

H. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication, alcohol) or another medical condition.

Continued

Table 25-7 DSM-5 Diagnostic Criteria for Posttraumatic Stress Disorder—cont'd

Specify whether

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: to use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

POSTTRAUMATIC STRESS DISORDER FOR CHILDREN 6 YR AND YOUNGER

A. In children 6 yr and younger, exposure to actual or threatened death, serious injury, or sexual violence in 1 (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others, especially primary caregivers.

Note: Witnessing does not include events that are only in electronic media, television, movies, or pictures.

   3. Learning that the traumatic event(s) occurred to a parent or caregiving figure.

B. Presence of 1 (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

Note: Spontaneous and intrusive memories may not necessarily appear distressing and may be expressed as play reenactment.

   2. Recurrent distressing dreams in which the content and/or affect of the dream is related to the traumatic event(s).

Note: It may not be possible to ascertain that the frightening content is related to the traumatic event.

   3. Dissociative reactions (e.g., flashbacks) in which the child feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Such trauma-specific reenactment may occur in play.
   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. One (or more) of the following symptoms, representing either persistent avoidance of stimuli associated with the traumatic event(s) or negative alterations in cognitions and mood associated with the traumatic event(s), must be present, beginning after the event(s) or worsening after the event(s):

Persistent Avoidance of Stimuli

   1. Avoidance of or efforts to avoid activities, places, or physical reminders that arouse recollections or the traumatic event(s).
   2. Avoidance of or efforts to avoid people, conversations, or interpersonal situations that around recollections of the traumatic event(s).

Negative Alterations in Cognitions

   3. Substantially increased frequency of negative emotional states (e.g., fear, guilt, sadness, shame, confusion).
   4. Markedly diminished interest or participation in significant activities, including constriction of play.
   5. Socially withdrawn behavior.
   6. Persistent reduction in expression of positive emotions.

D. Alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by 2 (or more) of the following:
   1. Irritable behavior and angry outbursts (with little or no provocation), typically expressed as verbal and physical aggression toward people or objects (including extreme temper tantrums).
   2. Hypervigilance.
   3. Exaggerated startle response.
   4. Problems with concentration.
   5. Sleep disturbance (e.g., difficulty falling asleep or staying asleep or restless sleep).

E. The duration of the disturbance is more than 1 mo.

F. The disturbance causes clinically significant distress or impairment in relationships with parents, siblings, peers, or other caregivers or with school behavior.

G. The disturbance is not attributable to the physiologic effects of a substance (e.g., medication or alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: to use this subtype, the dissociative symptoms must not be attributable to the physiologic effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 mo after the event (although the onset and expression of some symptoms may be immediate).

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diagnostic category, **acute stress disorder**, reflects the fact that traumatic events often cause acute symptoms that may or may not resolve. Previous trauma exposure, a history of other psychopathology, and symptoms of PTSD in parents predict childhood-onset PTSD. Many adolescent and adult psychopathologic conditions, such as conduct disorder, depression, and some personality disorders, might relate to previous trauma. PTSD is also linked to mood disorders and disruptive behavior. Separation anxiety is common in children with PTSD. The lifetime prevalence of PTSD by age 18 yr is approximately 6%. Up to 40% show symptoms, but do not fulfill the diagnostic criteria.

Events that pose physical injury, harm, or death to the child, to the child's caregiver, or to others close to the child and that produce considerable stress, fear, and/or helplessness are required to make the diagnosis of PTSD. Three clusters of symptoms are also essential for diagnosis: reexperiencing, avoidance, and hyperarousal. Persistent reexperiencing of the stressor through intrusive recollections, nightmares, and reenactment in play are typical responses in children. Persistent avoidance of reminders and numbing of emotional responsiveness, such as isolation, amnesia, and avoidance, constitute the second cluster of behaviors. Symptoms of hyperarousal, such as hypervigilance, poor concentration, extreme startle responses, agitation, and sleep problems, complete the symptom profile of PTSD. Occasionally, children regress in some of their developmental milestones after a traumatic event. Avoidance symptoms are commonly observable in younger children, whereas older children may be more able to describe reexperiencing and hyperarousal symptoms. Repetitive play involving the event, psychosomatic symptoms, and nightmares may also be observed.

Initial interventions after a trauma should focus on reunification with a parent and attending to the child's physical needs in a safe place. Aggressive treatment of pain might decrease the likelihood of PTSD, and facilitating a return to comforting routines, including regular sleep, is indicated. Long-term treatment may include individual, group, school-based, or family therapy, as well as pharmacotherapy, in selected cases. Individual treatment involves transforming the child's concept of himself or herself as victim to that of survivor and can occur through play therapy, psychodynamic therapy, or CBT. Group work is also helpful for identifying which children might need more intensive assistance. Goals of family work include helping the child establish a sense of security, validating the child's emotions, and anticipating situations when the child will need more support from the family. Clonidine or guanfacine may be helpful for sleep disturbance, persistent arousal, and exaggerated startle response. Recent randomized controlled trials in children and adolescents with PTSD did not find a significant difference between SSRI and placebo. SSRIs may be considered in pediatric patients with PTSD who have comorbid conditions responsive to SSRIs, for example, depression, affective numbing, and anxiety (see Table 21.4 in Chapter 21). As for many other anxiety disorders, CBT is the psychotherapeutic intervention with the most empiric support.

ANXIETY ASSOCIATED WITH MEDICAL CONDITIONS

It is prudent to rule out organic conditions such as hyperthyroidism, caffeinism (carbonated beverages), hypoglycemia, central nervous system disorders (delirium, encephalopathy, brain tumors), migraine, asthma, lead poisoning, cardiac arrhythmias, and, rarely, pulmonary embolism, hyperparathyroidism, systemic lupus erythematosus, anaphylaxis, porphyria or pheochromocytoma, before making a diagnosis of an anxiety disorder. Some prescription drugs with side effects that can mimic anxiety include antiasthmatic agents, steroids, sympathomimetics, SSRIs (initiation), anticholinergic agents, and antipsychotics. Nonprescription drugs causing anxiety include diet pills, antihistamines, stimulate drugs of abuse, drug withdrawal, and cold medicines.

Chronic illness is also an underlying cause of anxiety. Children are not often emotionally and cognitively competent to understand the implications of a serious and prolonged illness. In addition to the physiologic implications of illness they must also attend to the hospitalizations, procedures and medications that permeate their everyday schedule. This experience affects their schooling, friendships, activities, and dynamics of the nuclear family including the experiences of their well siblings.

School issues surrounding both prolonged absences and school re-entry following a medical condition can cause, or reinforce and escalate existing anxiety. School is a foundation not only for learning, but it is central to children's social experiences and feelings of normalcy. It is often impeded and stunted by illness. Academic struggles can result from missing classes, medication and emotional status. Children with chronic conditions are also socially disadvantaged with friendship networks hampered by unstable attendance or by social rejection for being different. Consulting with the school psychologist can be beneficial in preparing teachers and classmates before the child returns to school. An agreement between the student and school staff should be implemented outlining a plan for taking medication, needing rest or consulting on other needs. If the child and family wish, an informational meeting with students and teachers can normalize the situation. Explaining the condition makes it less scary for children who catastrophize or worry about contagion. Classmates and teachers are a natural and accessible resource and can be an incredible support and community. Medication may also be warranted to supplement social supports.

The experiences of the siblings of children with chronic illness are often forgotten with familial resources focused on medical and financial consequences, and the emotional and physical functioning of the ill child. It is not uncommon for the siblings of ill children to experience depression and anxiety as well. Assessing their social support systems, communication opportunities with parents and emotional outlets are critical to maintaining healthy functioning. Maintaining a redefined schedule of after-school activities and social engagements are helpful in allowing siblings to continue in school.

SAFETY AND EFFICACY CONCERNS ABOUT SSRIS

No empiric evidence suggests the superiority of one SSRI over another. Data are limited as far as combining medications are concerned. SSRIs are usually well tolerated by most children and adolescents. The FDA issued a black box warning of increased agitation and suicidality among adolescents and children on these medications. This warning was based on review of studies in children and adolescents with major depression and not anxiety disorders. Close monitoring is always warranted.

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Chapter 26

Mood Disorders

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Mood disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in emotional self-regulation. Classically, the mood disorders have been divided into depressive and bipolar disorders, representing the 2 emotional polarities (dysphoric ["low"] and euphoric ["high"] mood).

26.1 Major and Other Depressive Disorders

Heather J. Walter, Lovern R. Moseley, and David R. DeMaso

The depressive disorders include major depressive, persistent depressive, disruptive mood dysregulation, other specified/unspecified

Table 26-1 DSM-5 Diagnostic Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   1. Depressed most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
   2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
   3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gain.
   4. Insomnia or hypersomnia nearly every day.
   5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   6. Fatigue or loss of energy nearly every day.
   7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
   9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 125–126.

Table 26-2 DSM-5 Diagnostic Criteria for Persistent Depressive Disorder

A. Depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 yr.

Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr.

B. Presence, while depressed, of 2 (or more) of the following:
   1. Poor appetite or overeating.
   2. Insomnia or hypersomnia.
   3. Low energy or fatigue.
   4. Low self-esteem.
   5. Poor concentration or difficulty making decisions.
   6. Feelings of hopelessness.

C. During the 2 yr period (1 yr for children or adolescents) of the disturbance, the individual has never been without the symptoms in Criteria A and B for more than 2 mo at a time.

D. Criteria for a major depressive disorder may be continuously present for 2 yr.

E. There has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder.

F. The disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.

G. The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hypothyroidism).

H. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Note: Because the criteria for a major depressive episode include 4 symptoms that are absent from the symptom list for persistent depressive disorder (dysthymia), a very limited number of individuals will have depressive symptoms that have persisted longer than 2 yr but will not meet criteria for persistent depressive disorder. If full criteria for a major depressive episode have been met at some point during the current episode of illness, they should be given a diagnosis of major depressive disorder. Otherwise, a diagnosis of other specified depressive disorder or unspecified depressive disorder is warranted.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 168–169.

depressive, premenstrual dysphoric, and substance/medication-induced disorders, as well as depressive disorder caused by another medical condition.

DESCRIPTION

Major depressive disorder (**MDD**) is characterized by a distinct period of at least 2 wk (an episode; Table 26-1) in which there is a depressed or irritable mood and/or loss of interest or pleasure in almost all activities that is present for most of the day, nearly every day. Major depression is associated with characteristic vegetative and cognitive symptoms, including disturbances in appetite, sleep, energy, and activity level; impaired concentration; thoughts of worthlessness or guilt; and suicidal thoughts or actions. Major depression is considered to be mild if few or no, symptoms in excess of those required to make the diagnosis are present, and the symptoms are mildly distressing and manageable and result in minor functional impairment. Major depression is considered to be severe if symptoms substantially in excess of those required to make the diagnosis are present, and the symptoms are highly distressing and unmanageable and markedly impair function. Moderate major depression is intermediate in severity between mild and severe.

Persistent depressive disorder (dysthymia) (Table 26-2) is characterized by depressed or irritable mood for more days than not, for at least 1 yr (in children/adolescents). As with major depression, this chronic form of depression is associated with characteristic vegetative and cognitive symptoms; however, the cognitive symptoms of persistent depression are less severe (e.g., low self-esteem rather than worthlessness, hopelessness rather than suicidality). In the same way as major depression, persistent depressive disorder is characterized as mild, moderate, or severe.

Overall, the clinical presentation of major and persistent depressive disorders in children and adolescents is similar to that in adults. The prominence of the symptoms can change with age: irritability and somatic complaints may be more common in children, and energy, activity level, appetite, and sleep disturbances may be more common in adolescents. Because of the cognitive and linguistic immaturities of young children, symptoms of depression in that age group may be more likely to be observed than self-reported.

The core feature of ***disruptive mood dysregulation disorder*** (**DMDD**) (Table 26-3) is severe, persistent irritability evident for at least 12 mo in multiple settings (at home, at school, with peers). This irritability is characterized by frequent and severe temper outbursts (verbal and/or physical) and a persistently irritable or angry mood that is present for most of the day, nearly every day. This diagnosis is intended to more accurately characterize the extreme irritability heretofore considered by some investigators to be a developmental presentation of bipolar disorder (see Chapter 26.2), and to distinguish extreme irritability from the milder presentations characteristic of oppositional defiant and intermittent explosive disorders (see Chapter 29).

Table 26-3 DSM-5 Diagnostic Criteria for Disruptive Mood Dysregulation Disorder

A. Severe recurrent temper outbursts manifested verbally (e.g., verbal rages) and/or behaviorally (e.g., physical aggression toward people or property) that are grossly out of proportion in intensity or duration to the situation or provocation.
B. The temper outbursts are inconsistent with developmental level.
C. The temper outbursts occur, on average, 3 or more times per week.
D. The mood between temper outbursts is persistently irritable or angry most of the day, nearly every day, and is observable by others (e.g., parents, teachers, peers).
E. Criteria A-D have been present for 12 or more months. Throughout that time, the individual has not had a period lasting 3 or more consecutive months without all of the symptoms in Criteria A-D.
F. Criteria A and D are present in at least 2 of 3 settings (i.e., at home, at school, with peers) and are severe in at least 1 of these.
G. The diagnosis should not be made for the first time before age 6 yr or after age 18 yr.
H. By history or observation, the age at onset of Criteria A-E is before 10 yr.
I. There has never been a distinct period lasting more than 1 day during which the full symptom criteria, except duration, for a manic or hypomanic episode have been met.

Note: Developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation, should not be considered as a symptom of mania or hypomania.

J. The behaviors do not occur exclusively during an episode of major depressive disorder and are not better explained by another mental disorder (e.g., autism spectrum disorder, posttraumatic stress disorder, separation anxiety disorder, persistent depressive disorder [dysthymia]).

Note: The diagnosis cannot coexist with oppositional defiant disorder, intermittent explosive disorder, or bipolar disorder, though it can coexist with others, including major depressive disorder, attention-deficit/hyperactivity disorder, conduct disorder, and substance use disorders. Individuals whose symptoms meet criteria for both disruptive mood dysregulation disorder and oppositional defiant disorder should only be given the diagnosis of disruptive mood dysregulation disorder. If an individual has ever experienced a manic or hypomanic episode, the diagnosis of disruptive mood dysregulation disorder should not be assigned.

K. The symptoms are not attributable to the physiologic effects of a substance or to another medical or neurologic condition.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 156.

Other specified/unspecified depressive disorder (subsyndromal depressive disorder) applies to presentations in which symptoms characteristic of a depressive disorder are present and cause clinically significant distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class.

EPIDEMIOLOGY

The overall prevalence of parent-reported diagnosis of depressive disorder in the United States (excluding DMDD) among 3-17 yr old children is ~2.1% (current) and ~3.9% (ever); the prevalence rate increases to ~12.8% (lifetime) for 12-17 yr olds. The male : female ratio (excluding DMDD) approximates 1 : 1 during childhood and beginning in early adolescence rises to 1 : 1.5-3.0 in adulthood.

Based upon rates of chronic and severe persistent irritability, which is the core feature of DMDD, the overall 6 mo to 1 yr prevalence has been estimated to fall within the 2-5% range. In 3 community samples, the 3 mo prevalence rate of DMDD ranged from 0.8-3.3%, with the highest rates occurring in preschoolers. Approximately 5-10% of children and adolescents are estimated to have subsyndromal (unspecified) depression.

CLINICAL COURSE

Major depression may first appear at any age, but the likelihood of onset increases markedly with puberty. Incidence appears to peak in the 20s. The median duration of a major depressive episode approximates 5-8 mo for clinically referred youth and 3-6 mo for community samples. The course is quite variable in that some individuals rarely or never experience remission, whereas others experience many years with few or no symptoms between episodes. Persistent depressive disorder often has an early and insidious onset, and by definition, a chronic course (average untreated duration in both clinical and community samples: 3.5 yr).

Prepubertal depressive disorders exhibit more heterotypic than homotypic continuity; depressed children appear to be more likely to develop nondepressive psychiatric disorders in adulthood than depressive disorders. Adolescents exhibit greater homotypic continuity, with the probability of recurrence of depression reaching 50%-70% after 5 yr. The persistence of even mild depressive symptoms during remission is a powerful predictor of recurrence; other negative prognostic factors include more severe symptoms, longer time to remission, history of maltreatment, and comorbid psychiatric disorders. Up to 20% of depressed adolescents develop a bipolar disorder; the risk is higher among adolescents who have a high family loading for bipolar disorder, who have psychotic depression, or who have had pharmacologically induced mania.

DIFFERENTIAL DIAGNOSIS

A number of psychiatric disorders, general medical conditions, and medications can generate symptoms of depression or irritability and must be distinguished from the depressive disorders. The psychiatric disorders include autism spectrum (see Chapter 30), attention-deficit/hyperactivity (ADHD; see Chapter 33), bipolar, anxiety (see Chapter 25), trauma- and stressor-related, disruptive/impulse control/conduct, and substance-related disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, failure to thrive, chronic fatigue disorder, and pain disorder. Medications include narcotics, chemotherapy agents, β-blockers, corticosteroids, and contraceptives. The diagnosis of a depressive disorder should be made after these other explanations for the observed symptoms have been ruled out.

COMORBIDITY

Major and persistent depressive disorders often co-occur with other psychiatric disorders. Depending on the setting and source of referral, 40-90% of youths with a depressive disorder have other psychiatric disorders, and up to 50% have 2 or more comorbid diagnoses. The most common comorbid diagnosis is an anxiety disorder and as such may reflect a common diathesis; other common comorbidities include ADHD and disruptive behavior, eating, and substance use disorders. The development of depressive disorders can both lead and follow the development of the comorbid disorders.

Preliminary data suggests the co-occurrence of DMDD with other psychiatric disorders, including other depressive disorders, ADHD, conduct disorder, and substance use disorders, from 60-90% of the time. Because the symptoms of DMDD overlap in part with symptoms of bipolar disorder (see Chapter 26.2), oppositional defiant disorder (see Chapter 29), and intermittent explosive disorder (see Chapter 29), by *Diagnostic Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) convention hierarchical diagnostic rules apply (i.e., bipolar disorder takes precedence over DMDD if a manic/hypomanic episode has ever occurred; DMDD takes precedence over oppositional defiant disorder and intermittent explosive disorder if full criteria for DMDD are met).

SEQUELAE

Approximately 60% of youths with MDD report thinking about suicide, and 30% actually attempt suicide. The risk of suicidal behavior increases if there is a history of suicide attempts, exposure to adverse psychosocial circumstances, a family history of suicidal behavior, or comorbid psychiatric disorders. Youths with depressive disorders are also at high

risk of substance abuse, impaired family and peer relationships, early pregnancy, legal problems, educational and occupational underachievement, and poor adjustment to life stressors, including physical illness.

Children with DMDD have displayed elevated rates of social impairments, school suspension, and service use. Irritability in adolescence has predicted the development of major depressive and dysthymic disorders and generalized anxiety disorder (but not bipolar disorder) 20 yr later, as well as lower educational attainment and income.

ETIOLOGY AND RISK FACTORS

Current models of vulnerability to depressive disorders are grounded in gene by environment pathways. Genetic studies have repeatedly demonstrated the heritability of depressive disorders, with monozygotic twin studies finding concordance rates of 40-65%. In families, both bottom-up (children to parents) and top-down (parents to children) studies have shown a 2-4–fold bidirectional increase in depression among 1st-degree relatives. The exact nature of genetic expression remains unclear. Cerebral variations in structure and function (particularly serotonergic), the function of the hypothalamic–pituitary–adrenal axis, difficult temperament/personality (i.e., negative affectivity), and ruminative, self-devaluating cognitive style have been implicated as components of biologic vulnerability. The great majority of depressive disorders arise in youth with long-standing psychosocial difficulties, among the most predictive of which are physical/sexual abuse, neglect, chronic illness, school difficulties (bullying, academic failure), social isolation, family or marital disharmony, divorce/separation, parental psychopathology, and domestic violence. Longitudinal studies demonstrate the greater importance of environmental influences in children who become depressed compared to adults who become depressed. Factors shown to be protective against the development of depression include a positive relationship with a parent, better family function, closer parental supervision/monitoring/involvement, a prosocial peer group, higher IQ, and greater educational aspirations.

PREVENTION

Numerous experimental trials have sought to demonstrate the effectiveness of psychological or educational strategies in preventing the onset of depressive disorders in children and adolescents. These programs generally have provided information about the link between depressed mood and depressogenic thoughts and behaviors, and training in skills intended to modify these thoughts and behaviors. A meta-analytic review found small to moderate effects of these programs at both postintervention and follow-up (overall mean effect size: 0.16), with selective programs (targeted at high-risk groups) performing better than universal programs. A Cochrane review found some evidence that depression prevention programs may have a small favorable effect compared with no intervention, but no effect compared to attention controls.

SCREENING/CASE FINDING

Adolescents presenting in the primary care setting should be queried, along with their parent(s), about depressed mood as part of the routine clinical interview. A typical screening question would be "Everyone feels sad or angry some of the time, how about you (or your teen)?" The parents of younger children can be queried about overt signs of depression, such as tearfulness, irritability, boredom, or social isolation. A number of standardized broadband screening instruments widely used in the primary care setting (e.g., *Pediatric Symptom Checklist*, *Strengths and Difficulties Questionnaire*, *Vanderbilt ADHD Diagnostic Rating Scales*) have items specific to sad mood, and as such can be used to focus the interview.

The role of universal depression screening using standardized narrowband (depression-specific) instruments is unclear. A Cochrane review found that the use of depression screening in primary care has little or no impact on the recognition, management, or outcome of depression. The United States Preventive Services Task Force recommends the use of depression screening instruments only among adolescents, and only when systems are in place to ensure adequate follow-up. Targeted screening of known high-risk groups (e.g., youth who are homeless, refugees, attracted to the same sex, involved with child welfare or juvenile justice) or of youth experiencing known psychosocial adversities (see "Etiology/Risk Factors" above) or self-reporting a dysphoric mood may be a higher-yield case-finding strategy than universal screening (Fig. 26-1).

STEPPED MANAGEMENT

Because of the high rates of response to placebo and attention comparators as well as to brief therapy in the treatment of pediatric depression, clinical practice guidelines increasingly are advocating a stepped approach to the management of depressed youth. The stepped approach involves active case finding and initial management in the primary care setting if appropriate, with referral to increasingly intensive and specialized interventions as indicated by the clinical status of the patient.

EARLY INTERVENTION

Youth and/or their parents presenting in the primary care setting who self-report, or respond affirmatively to queries about, a distressing life experience or a depressed or irritable mood, should be offered the opportunity to talk about the situation with the pediatric practitioner (in private with the older youth as indicated). By engaging in active listening (e.g., "I hear how upset you have been feeling, tell me more about what happened to make you feel that way"), the pediatric practitioner can begin to assess the onset, duration, context, and severity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., suicidality, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 wk to conduct a depression assessment. At this follow-up visit, to assist with decision making around appropriate level of care, a depression screening instrument can be administered (Table 26-4) and additional risk factors (see "Etiology/Risk Factors" above) can be explored.

For mild symptoms (manageable and not functionally impairing) and in the absence of major risk factors (e.g., suicidality, psychosis, substance use, history of depression, mania, or traumatic exposures, parental psychopathology [particularly depression]) or severe family dysfunction), guided self-help (anticipatory guidance) with watchful waiting may suffice. Guided self-help can include provision of educational materials (e.g., pamphlets, books, workbooks, internet sites) that provide information to the youth about dealing with stressful situations; and advice to parents about strengthening the parent-child relationship and modifying adverse environmental exposures (e.g., taking action against bullying, increasing opportunities for social interaction/support, protecting the child from exposure to marital discord) as depressogenic buffers. During the period of guided self-help, additional follow-up visits should be scheduled.

For youth who continue to have mild depression after a few weeks of guided self-help, supportive therapy by a mental health professional (ideally colocated in the primary care, school, or community setting) may be an appropriate subsequent step. Supportive psychotherapy, which can be delivered in individual or group formats, focuses on teaching thoughts (e.g., positive self-talk) and behaviors (e.g., pleasurable activities, relaxation, problem-solving, effective communication) known to ameliorate depressive symptoms, as well as providing concrete social or material problem-solving assistance to the youth or family as needed.

TREATMENT

For youth who have not responded to approximately 4-8 wk of supportive psychotherapy, or who from the outset exhibit moderate to severe, comorbid, or recurrent depression or suicidality, or who have a history of mania, traumatic exposures or severe family dysfunction or psychopathology, assessment and treatment in the specialty mental health setting by a child-trained mental health clinician should be provided (see Chapter 20). The mental health clinician should be

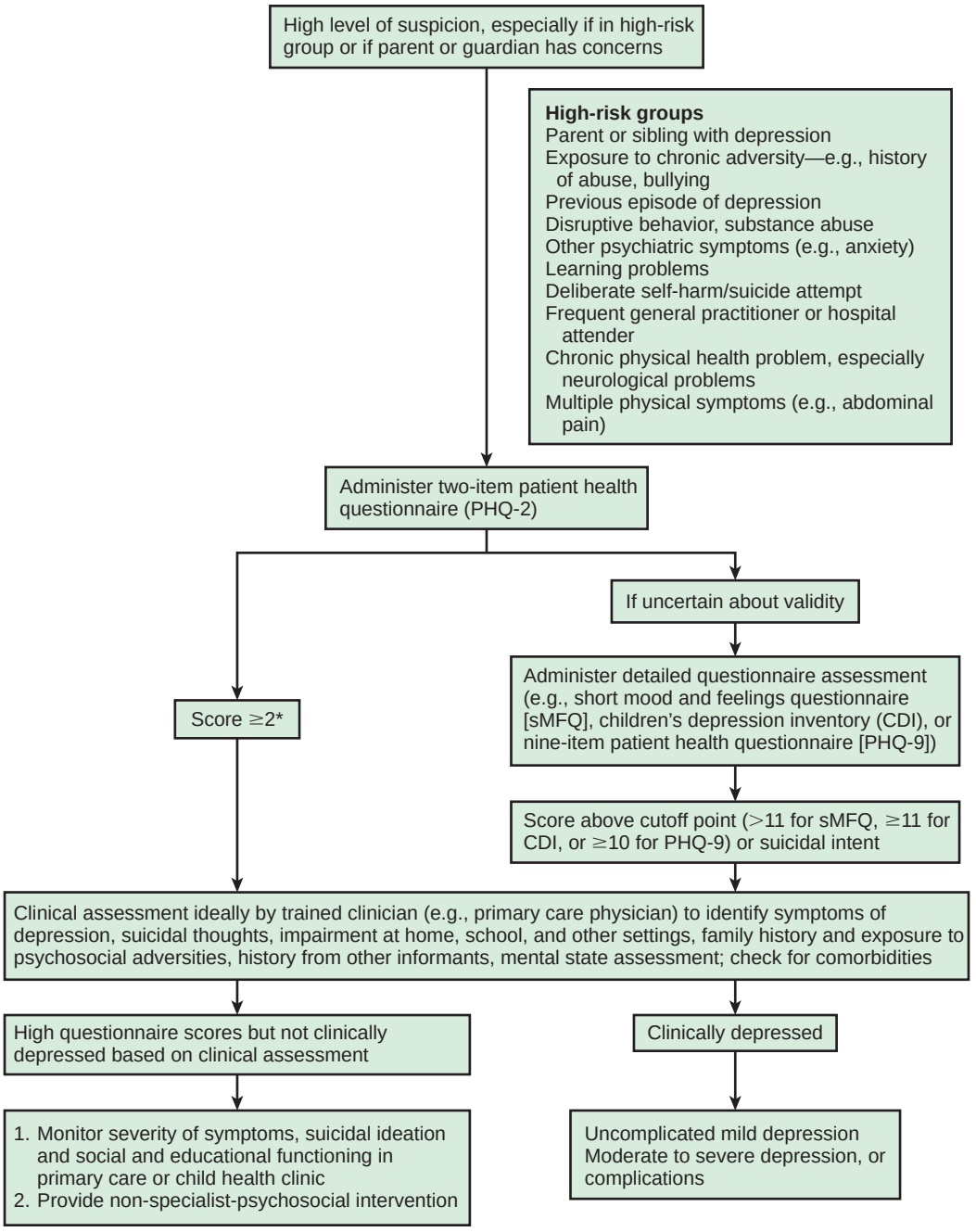

Figure 26-1 Detection of depression in adolescents in nonspecialist settings. *If patient scores < 2, generally no further action is needed. *(From Thapar A, Collishaw S, Pine DS, Thapar AK: Depression in adolescence.* Lancet *379:1056–1066, 2012. Fig. 1.)*

trained to the appropriate level of competence in the specific services he/she is asked to provide.

For moderate to severe depression, specific manualized psychotherapies, antidepressant medication, or a combination of the two should be provided. At present, there is insufficient evidence upon which to base definitive conclusions about the relative effectiveness of these treatments. The main goal of the acute treatment phase is to achieve response, which typically is defined as at least a 50% reduction in depressive symptoms as assessed by a standardized rating scale (see Table 26-4). Full recovery (i.e., absence of a depressive diagnosis) should be the ultimate treatment goal.

Clinical trials of acute treatments have generated support for the efficacy of ***cognitive-behavioral therapy*** **(CBT)** and ***interpersonal therapy*** as monotherapies in depressed youth, but effect sizes are modest (0.35 and 0.26, respectively). CBT focuses on identifying and correcting cognitive distortions that may lead to depressed mood and teaches problem-solving, behavior activation, social communication, and emotional regulation skills to combat depression. interpersonal therapy focuses on enhancing interpersonal problem solving and social communication to decrease interpersonal conflicts. Each of these therapies typically involves approximately 8-12 weekly visits.

Limited evidence suggests that family therapy may be more effective than no treatment on decreasing depression and improving family functioning. Because of the heterogeneity of the evidence base, however, the use of better supported therapies would at this time seem to be preferable over family therapy.

Two ***selective serotonin reuptake inhibitors*** **(SSRIs),** fluoxetine and escitalopram, are the only antidepressants approved by the FDA

Table 26-4 Depression-Specific Screening Instruments

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE	NUMBER OF ITEMS
Preschool Feelings Checklist	Parent	3-5.6 yr	20
Preschool Symptom	Self-Report Youth, Parent, Teacher	3-5 yr	25
Center for Epidemiologic Studies-Depression-Children	Youth	6-18 yr	20
Children's Depression Rating Scale-Revised	Youth, Parent, Clinician	6-18 yr	47
Children's Depression Inventory-Second Edition	Youth, Parent, Teacher	7-17 yr	28/17/12
Depression Self-Rating Scale	Youth	7-13 yr	18
Beck Depression Inventory for Youth	Youth	7-14 yr	20
Mood and Feelings Questionnaire	Youth, Parent	7-18 yr	33-34
Reynolds Child Depression Scale	Youth	8-13 yr	30
Reynolds Adolescent Depression Scale-Second Edition	Youth	11-20 yr	30
Beck Depression Inventory	Youth	13+ yr	21
Patient Health Questionnaire-9	Youth	13-17 yr	9

for the treatment of depression, and fluoxetine alone is approved for preadolescents (see Chapter 21.1). These agents should be 1st-line for pharmacotherapy of pediatric depression, unless other factors (e.g., comorbidities, side-effect profiles, personal or family history of response to a specific medication) favor an alternative SSRI (preferably sertraline or citalopram). Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist.

Randomized controlled trials **(RCTs)** of the effectiveness of antidepressants are mixed. Based on a large meta-analysis of RCTs, approximately 60% of youths with depression respond to antidepressants (vs. 50% for placebo), yielding a ***number needed to treat*** of 10, but only around 30% of medicated depressed youth experience symptom remission. Fluoxetine has consistently demonstrated greater efficacy, with a number needed to treat of 6, and is the only SSRI separating from placebo in studies of depressed preadolescents. Studies of other classes of antidepressant medications have not demonstrated clear superiority over placebo, and tricyclic medications and paroxetine in particular are not currently recommended for use in youth because of their clearly unfavorable risk : benefit profiles. The absolute risk for suicidal thoughts in youth with major depression approximates 3% (treated with antidepressant) versus 2% (given placebo), translating to a ***number needed to harm*** of 112.

Clinical severity, comorbidity, family conflict, low drug concentration, nonadherence, anhedonia, sleep difficulties, subsyndromal manic symptoms, and child maltreatment have all been related to treatment resistance. Approximately 50% of depressed youth failing to respond to the first SSRI respond after switching to a second antidepressant medication plus CBT, versus approximately 40% who respond to a second medication alone. For youth with psychotic depression, augmenting the antidepressant with an atypical antipsychotic medication should be considered, while monitoring closely for side effects.

The SSRIs have been well tolerated by children and adolescents. The most common side effects include irritability, gastrointestinal symptoms, sleep disturbance, restlessness, diaphoresis, headaches, changes in appetite, dizziness, dry mouth, and sexual dysfunction. Approximately 5% of youths, particularly children, develop increased impulsivity, agitation, and irritability (behavioral activation) on SSRIs, but the symptoms quickly resolve when the medication dose is reduced or the medication is discontinued. More rarely, the use of antidepressants has been associated with serotonin toxicity, increased predisposition to bleeding, abnormal heart rhythms (citalopram causes dose-dependent QT-interval prolongation and should not be prescribed at doses greater than 40 mg/day) and increased suicidal thoughts.

The initial dose of SSRI medication should be approximately one-half of the adult dose (e.g., 10 mg of fluoxetine). Some studies have reported that the half-lives of SSRIs other than fluoxetine are much shorter in children than in adults; therefore daily withdrawal side effects can be observed with these medications if they are administered once daily. Clinical response, tolerability, and emergence of behavioral activation, mania, or suicidal thoughts should be assessed frequently (preferably weekly) for the first 4 wk. If the youth has safely tolerated the antidepressant, the initial dose may be doubled at 4 wk if an adequate response (at least 50% reduction in symptom severity as measured by standardized rating scales) has not been achieved, with biweekly monitoring recommended. Patients who have responded by 8 wk can then be monitored less frequently (up to monthly) until remission (no longer meets diagnostic criteria) has been achieved. Patients treated in the primary care setting who have not responded by 8 wk or remitted by 12 wk should be referred to the specialty mental health setting for advanced care.

Because of the high rate of recurrence, successful treatment should continue for 6-12 mo. At the conclusion of treatment, all antidepressants should be discontinued gradually to avoid withdrawal symptoms (gastrointestinal upset, disequilibrium, sleep disruption, flu-like symptoms, sensory disturbances). Patients with recurrent (2 or more), chronic, or severe major depression can require treatment beyond 12 mo.

Table 26-5 summarizes screening, assessment, and treatment recommendations for depression.

LEVEL OF CARE

Most children and adolescents with mild to moderate depressive disorders can be safely and effectively treated as outpatients, provided that a clinically appropriate schedule of visits can be maintained through the phases of treatment. Inpatient treatment should be considered for youth who present with a high risk of suicide, serious self-harm, or self-neglect, or when the family is not able to provide an appropriate level of supervision or follow-up with outpatient treatment recommendations, or when comprehensive assessment for diagnostic clarity is needed. When considering inpatient admission for a young person with depression, the benefits of inpatient treatment needs to be balanced against potential detrimental effects, such as the loss of family and community support.

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Table 26-5 Screening and Treatment for Major Depressive Disorder in Youths

RECOMMENDATION	ADOLESCENTS (12-18 Yr)	CHILDREN (7-11 Yr)
Screening	Screen (when systems for diagnosis, treatment, and follow-up are in place) Grade B	No recommendations Grade I (insufficient evidence)
Risk assessment	Risk factors for major depressive disorder include parental depression, having comorbid mental health or chronic medical conditions, and having experienced a major negative life event	
Screening tests	The following have been shown to do well in teens in primary care settings: Patient Health Questionnaire for Adolescents (PHQ-A) Beck Depression Inventory—Primary Care version (BDI-PC)	Screening instruments perform less well in younger children
Treatments	Among pharmacotherapies, fluoxetine, a SSRI, has been found efficacious. However, because of risk of suicidality, SSRIs should be considered only if clinical monitoring is possible. Various modes of psychotherapy, and pharmacotherapy combined with psychotherapy, have been found efficacious	Evidence on the balance of benefits and harms of treatment of younger children is insufficient for a recommendation

For a summary of the evidence systematically reviewed in making these recommendations, the full recommendation statement, and supporting documents, please go to http://www.AHRQ.gov/clinic/USPSTF/USPSCHDEPR.htm.

26.2 Bipolar and Related Disorders

Heather J. Walter, Natalija Bogdanovic, and David R. DeMaso

DESCRIPTION

The bipolar and related disorders include bipolar I, bipolar II, cyclothymic, and other specified/unspecified bipolar and related disorders, as well as bipolar and related disorder caused by another medical condition.

A manic episode (Table 26-6) is characterized by a distinct period of at least 1 wk in which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy that is present for most of the day, nearly every day (or any duration if hospitalization is necessary). The episode is associated with characteristic cognitive and behavioral symptoms, including disturbances in self-regard, speech, attention, thought, activity, impulsivity, and sleep. To diagnose ***bipolar I disorder***, criteria must be met for at least 1 manic episode, and the episode must not be better explained by a psychotic disorder. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes. Bipolar I disorder is rated as mild, moderate, or severe in the same way as the depressive disorders (see Description section of Chapter 26.1).

To diagnose **bipolar II disorder,** criteria must be met for at least 1 hypomanic episode and at least 1 major depressive episode. A hypomanic episode is similar to a manic episode, but is briefer (at least 4 days) and less severe (causes less impairment in functioning, is not associated with psychosis, and would not require hospitalization). In bipolar II disorder, there must never have been a manic disorder, the episodes must not be better explained by a psychotic disorder, and the symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania must cause clinically significant distress or functional impairment. Bipolar II disorder is rated as mild, moderate, or severe in the same way as bipolar I disorder.

Cyclothymic disorder is characterized by a period of at least 1 yr (in children and adolescents) in which there are numerous periods with hypomanic and depressive symptoms that do not meet criteria for a hypomanic episode or a major depressive episode, respectively.

Other specified/unspecified bipolar and related disorders (subsyndromal bipolar disorder) applies to presentations in which symptoms characteristic of a bipolar and related disorder are present and cause distress or functional impairment, but do not meet the full criteria for any of the disorders in this diagnostic class. Although this diagnosis (formerly known as bipolar disorder, not otherwise specified)

Table 26-6 DSM-5 Diagnostic Criteria for a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, 3 (or more) of the following symptoms (4 if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hr of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
D. The episode is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiologic effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least 1 lifetime manic episode is required for the diagnosis of bipolar I disorder.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 124.

heretofore had frequently been applied to children with severe and chronic mood and behavioral dysregulation who did not precisely fit other diagnostic categories, the empiric support for the validity of this practice has been sparse. Many children who formerly received this diagnosis will meet criteria for DMDD (see Chapter 26.1).

In adolescents, the clinical manifestations of bipolar disorder are similar to those in adults, and psychosis (delusions, hallucinations) often is an associated symptom. Mood in a manic episode is often described as euphoric, excessively cheerful, high, or "feeling on top of the world." During the episode, the adolescent may engage in multiple new projects that are initiated with little knowledge of the topic and often at unusual hours (in the middle of the night). Inflated self-esteem is usually present, ranging from uncritical self-confidence to marked grandiosity, and may reach delusional proportions. The adolescent may sleep little if at all for days at a time and nonetheless feel rested and full of energy. Speech can be rapid, pressured, and loud and characterized by jokes, puns, amusing irrelevancies, and theatricality. Frequently there is a flight of ideas evidenced by a nearly continuous flow of accelerated speech, with abrupt shifts from one topic to another. Distractibility is evidenced by an inability to censor irrelevant extraneous stimuli, which often prevents an individual with mania from engaging in a rational conversation. The expansive mood, grandiosity, and poor judgment often lead to reckless involvement in activities with high potential for personal harm.

There is controversy about the applicability of the bipolar diagnostic criteria to prepubertal children. It may be developmentally normal for children to be elated, expansive, grandiose, or talkative, reducing the specificity of these symptoms to this disorder. In addition, the distractibility, overactivity, and impulsivity formerly ascribed to bipolar disorder by some investigators may be better explained by a diagnosis of ADHD. The presentations of severe irritability formerly diagnosed as bipolar disorder may be better captured by the diagnosis of DMDD.

EPIDEMIOLOGY

The lifetime prevalence of the bipolar disorders among adults approximates 1-3%; rates among youth generally have been less than 1%. For bipolar I, the male : female ratio approximates 1.1 : 1.

CLINICAL COURSE

The mean age of onset of the first manic episode is approximately 18 yr for bipolar I disorder. Premorbid problems are common in bipolar disorder, especially difficulties with mood and behavioral regulation. Premorbid anxiety also is common. The early course of adolescent-onset bipolar disorder appears to be more chronic and refractory to treatment than adult-onset bipolar disorder. Comorbidity predicts functional impairment and age at onset predicts duration of episodes. Sleep impairment and family conflict are inversely related to favorable treatment response, suggesting important targets for treatment. The bipolar disorders are highly recurrent, and more than 80% of bipolar I patients go on to have additional mood episodes. Recurrent episodes can approximate 4 in 10 yr, with the interepisode interval shortening as the patient ages. Although the majority of patients with bipolar I return to a fully functional level between episodes, approximately one-third continue to be symptomatic and functionally impaired between episodes. In a 14 yr follow-up study, children 4-16 yr of age exceeding the clinical cutpoint for the dysregulation ("bipolar") profile on the Child Behavior Checklist were found to have increased rates of anxiety, mood, disruptive behavior, and substance abuse disorders in adulthood.

DIFFERENTIAL DIAGNOSIS

A number of psychiatric disorders, general medical conditions, and medications can generate manic-like symptoms and must be distinguished from the bipolar and related disorders. The psychiatric disorders include ADHD, oppositional defiant, intermittent explosive, posttraumatic stress, depressive, anxiety, substance abuse, and borderline personality disorders. Medical conditions include neurologic disorders, endocrine disorders, infectious diseases, tumors, anemia, uremia, and vitamin deficiencies. Medications include androgens, bronchodilators, cardiovascular medications, corticosteroids, chemotherapy agents, thyroid preparations, and certain psychiatric medications (benzodiazepines, antidepressants, stimulants). The diagnosis of a bipolar disorder should be made after these other explanations for the observed symptoms have been ruled out.

COMORBIDITY

Nearly 75% of individuals with bipolar disorders have co-occurring anxiety disorders, and nearly 50% have co-occurring attention, disruptive/impulse control/conduct, and substance use disorders.

SEQUELAE

The lifetime risk of suicide in individuals with bipolar disorder is estimated to be at least 15 times that of the general population. Youths with bipolar disorders are also at high risk for substance abuse, antisocial behavior, impaired academic performance, impaired family and peer relationships, and poor adjustment to life stressors.

ETIOLOGY/RISK FACTORS

Twin studies suggest the heritability of bipolar disorder is greater than 60%. Offspring of parents with bipolar disorders are at high risk for early-onset bipolar disorders, and there is an average 10-fold increased risk among adult relatives of individuals with bipolar disorder, with the magnitude of risk increasing with the degree of kinship. Bipolar disorder and schizophrenia likely share a genetic origin, reflected in familial co-aggregation of the two disorders.

Dysthymic (sad), cyclothymic (labile), or hyperthymic (irritable) temperaments may presage eventual bipolar disorder. Premorbid anxiety and dysphoria also are common, and approximately 20% of youth with major depression go on to experience manic episodes by adulthood. Similar to findings in adults, factors that predict the eventual development of mania in depressed youth include a depressive episode characterized by rapid onset, psychomotor retardation, and psychotic features, a family history of affective disorders, especially bipolar disorder, and a history of mania or hypomania after treatment with antidepressants.

PREVENTION

Although empiric support is sparse, 1 randomized controlled study demonstrated the effectiveness of family-focused treatment versus an educational control in hastening and sustaining recovery from mood symptoms in a high familial risk cohort of youth with subsyndromal symptoms of mania. Family-focused treatment is a manualized psychoeducational intervention designed to reduce family stress, conflict, and affective arousal by enhancing communication and problem-solving between youth and their caregivers. Pharmacologic interventions for subsyndromal mania have produced equivocal results.

CASE FINDING

Cardinal manic symptoms of elation and grandiosity occurring in adolescents as a discrete episode should alert pediatric practitioners to the possibility of a bipolar or related disorder. Because of the complexity of these disorders, any suspected cases should be referred to the specialty mental health setting for comprehensive assessment (see Chapter 20) and treatment (see Chapter 21).

TREATMENT

For mania in bipolar I disorder, medication is the primary treatment. Among traditional mood stabilizer medications (lithium carbonate, divalproex sodium, carbamazepine), only lithium is approved by the FDA for the treatment of bipolar disorder from age 12 yr (see Chapter 21.1). At present lithium has only open-label empirical support, with an overall response rate approximating 40%. There is no RCT evidence supporting the efficacy of divalproex sodium or carbamazepine. No other anticonvulsant medications sometimes used for the treatment of mania (oxcarbazepine, lamotrigine, topiramate) have FDA approval or RCT evidence of efficacy. In contrast, atypical antipsychotic medications (e.g., quetiapine, aripiprazole, ziprasidone, risperidone, olanzapine) have an overall 66% response with significant separation from placebo/active comparator in RCTs, and as such are considered to be

1st-line treatments for mania. The FDA has approved aripiprazole, risperidone, and quetiapine for the treatment of bipolar disorder from age 10 yr, and olanzapine from age 13 yr (see Chapter 21.1). The choice of antipsychotic medication is based upon factors such as side-effect profiles, adherence considerations, and a positive response of a family member.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6-8 wk) to determine the agent's effectiveness. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Because all of these medications are associated with significant side effects, careful monitoring of baseline and follow-up indices is imperative. Side effects of lithium include reduced urine concentrating ability, hypothyroidism, hyperparathyroidism, weight gain, and renal failure. Acute overdose (level > 1.5 mEq/L) manifests with neurologic symptoms (tremor, ataxia, nystagmus, hyperreflexia, myoclonus, slurred speech, delirium, coma, seizures), and altered renal function. Toxicity is enhanced when dehydrated or with drugs that affect renal function (nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibition) Neuroleptic malignant syndrome has been reported in patients also taking antipsychotic drugs. Atypical antipsychotics cause weight gain, metabolic aberrations (diabetes, hyperlipidemia), and cardiac effects. Withdrawal of medication has been associated with increased risk of relapse.

The regimen needed to stabilize acute mania should be maintained for 12-24 mo. Maintenance therapy is often needed for adolescents with bipolar I disorder, and some patients need lifelong medication. Any attempts to discontinue prophylactic medication should be done gradually, while closely monitoring the patient for relapse.

For depression in bipolar II disorder, antidepressant medication may be used once a mood-stabilizing medication has been initiated. Lamotrigine as adjunctive or monotherapy also may be helpful for adolescents with bipolar depression. Comorbid ADHD can be treated with stimulant medication once a mood-stabilizing medication has been initiated.

Psychotherapy is a potentially important adjunctive treatment for the bipolar disorders. However, a Cochrane review of 7 RCTs of family interventions found only heterogeneous evidence of effectiveness, precluding definitive conclusions about their use. Factors known to adversely influence response to therapy include high-conflict families and sleep impairment, suggesting the importance of targeting these factors in treatment.

LEVEL OF CARE

Most youths with bipolar disorders can be safely and effectively treated as outpatients, provided that an appropriate schedule of visits and laboratory monitoring can be maintained through the course of treatment. Youths who are suicidal or psychotic typically require inpatient care.

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Chapter 27

Suicide and Attempted Suicide

David R. DeMaso, Heather J. Walter, and Elizabeth A. Wharff

Youth suicide is a major and tragic public health problem. For youth between the ages of 15 and 24 yr in the United States, suicide is the 3rd leading cause of death, with approximately 4,600 lives lost each year. Globally, suicide rates for youth ages 15-19 yr are 7.4/100,000 persons, the 4th leading cause of death for males and the 3rd for females. There are a number of psychiatric, social, cultural, and environmental risk factors for suicidal behavior, and knowledge of these risk factors can facilitate identification of youths at highest risk (Fig. 27-1).

EPIDEMIOLOGY

Suicidal Ideation and Attempts

Based on the 2011 Youth Risk Behavior Survey, almost one-third of 9th through 12th grade students nationwide in the United States felt so sad or hopeless almost every day for 2 or more wk in a row during the previous year that they stopped doing some usual activities. During that same time period, nearly 16% of the students reported that they had seriously considered attempting suicide and 8% reported that they had actually attempted suicide. A suicide attempt in the previous year that resulted in an injury, poisoning, or overdose that had to be treated by a doctor or nurse was reported by more than 2% of students.

It is estimated that for every completed youth suicide, as many as 200 suicide attempts are made. Ingestion of medication is the most common method of attempted suicide. The 15-19 yr old age group is the most likely to intentionally harm themselves by ingestion, receive treatment in emergency departments, and survive. Attempts are more common in adolescent females than males (approximately 4:1), and in Hispanic females compared to their non-Hispanic counterparts. Gay, lesbian, bisexual, and transgender youths also have disproportionately high rates of suicide attempts. Attempters who have made prior suicide attempts, who used a method other than ingestion, and who still want to die are at increased risk for completed suicide.

Suicide Completions

In the United States, completed suicide is very rare before puberty. Rates of completed suicide increase steadily across adolescence into young adulthood, peaking in the early 20s. In the past 60 yr, the suicide rate has quadrupled among 15-24 year old males and has doubled for females of the same age. The male:female ratio for completed suicide rises with age from 3:1 in children to approximately 4:1 in 15-24 yr olds, and to greater than 6:1 among 20-24 yr olds.

Native Americans/Alaska Natives have highest rates of completed suicide of all ethnic groups, with nearly 21 deaths per 100,000. White youth are the next highest at almost 12 deaths per 100,000. The ethnic groups with the lowest risk are African-Americans, Hispanics, Asians, and Pacific Islanders. Over time the suicide rate among African-American, Hispanic, and other minority males has increased, while the rate among white males has remained steady.

Access to means has been linked to suicide rates among different groups in the population and different geographical areas of the world (Fig. 27-2). Firearms are the most common method used to complete suicide in the United States, and account for 56% of male suicides and 30% of female suicides. In females, poisonous ingestions, especially overdoses of medications, are the most common method used to complete suicide, and account for 37% of female suicides, compared to only 12% of male suicides. Hanging is the third most common method used to complete suicide and accounts for 25% of male and female suicides. Firearms are the most lethal method of suicide completion; the death rate with respect to firearms is approximately 80-90%, whereas the death rate is only 1.5-4% for overdoses.

RISK FACTORS

In addition to age, race/ethnicity, and a history of a previous suicide attempt, there are multiple risk factors that predispose youths to suicide (Table 27-1).

Preexisting Mental Disorder

Approximately 90% of youths who complete suicide have a preexisting psychiatric illness, most commonly major depression (see Chapter 26.1). Among females, chronic anxiety, especially panic disorder, also is associated with suicide attempts and completion (see Chapter 25).

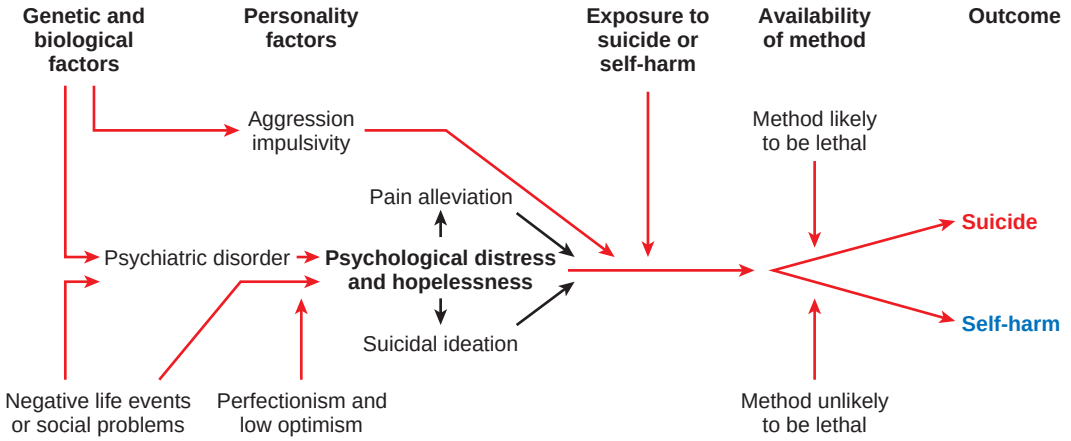


Figure 27-1 Key risk factors for adolescent self-harm and suicide. *(From Hawton K, Saunders KEA, O'Connor RC: Self-harm and suicide in adolescents.* Lancet *379:2373–2380, 2012, Fig. 2.)*

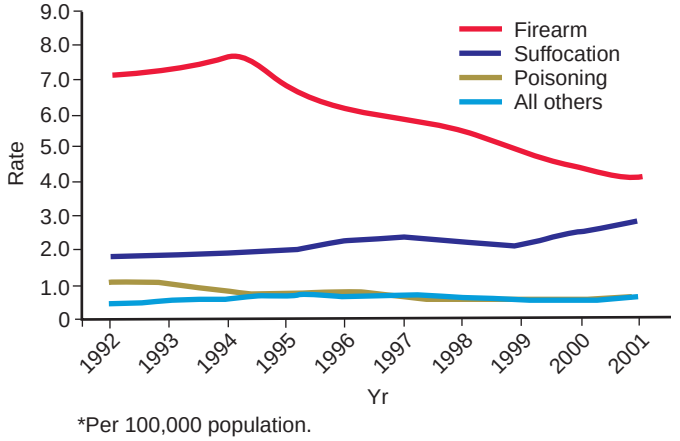


Figure 27-2 Annual suicide rates among persons age 15-19 yr, by year and method, United States, 1992-2001. *(From Centers for Disease Control and Prevention: Methods of suicide among persons aged 10-19 years, United States, 1992-2001.* MMWR Morb Mortal Wkly Rep *53:471-474, 2004.)*

Among males, conduct disorder and substance use convey increased risk. Comorbidity of a substance use disorder (see Chapter 114), a depressive disorder (see Chapter 26.1), and conduct disorder (see Chapter 29.1) are linked to suicide by firearm. Schizophrenia spectrum disorders (see Chapter 31) are linked to suicide attempts and completions.

Cognitive Distortions

Negative self-attributions can contribute to the hopelessness that is commonly associated with suicidality; hopelessness may contribute to approximately 55% of the explained variance in continued suicidal ideation. Many youth who are suicidal hold negative views of their own competence, have poor self-esteem, and have difficulty identifying sources of support or reasons to live. Many youngsters lack the coping strategies necessary to manage strong emotions and instead tend to catastrophize and engage in all-or-nothing thinking.

Biologic Factors

Postmortem studies show that there are observable differences between the brains of individuals who have completed suicide and those who died from other causes. The brain systems that may be related to suicide completion are the serotonergic system, adrenergic system, and the hypothalamic–pituitary axis. Family history of mental disorders also is linked to completed suicide.

Table 27-1 Risk Factors for Self-Harm and Suicide in Adolescents

SOCIODEMOGRAPHIC AND EDUCATIONAL FACTORS
Sex (female for self-harm and male for suicide)—most countries*
Low socioeconomic status*
Lesbian, gay, bisexual, or transgender sexual orientation
Restricted educational achievement*
INDIVIDUAL NEGATIVE LIFE EVENTS AND FAMILY ADVERSITY
Parental separation or divorce*
Parental death*
Adverse childhood experiences*
History of physical or sexual abuse
Parental mental disorder*
Family history of suicidal behavior*
Marital or family discord
Bullying
Interpersonal difficulties*
PSYCHIATRIC AND PSYCHOLOGICAL FACTORS
Mental disorder,* especially depression, anxiety, attention deficit hyperactivity disorder
Drug and alcohol misuse*
Impulsivity
Low self-esteem
Poor social problem-solving
Perfectionism
Hopelessness*

All the factors in the panel have been shown to be related to self-harm.
*Shown to be related to suicide.
From Hawton K, Saunders KEA, O'Connor: Self-harm and suicide in adolescents. Lancet *379:2373–2380, 2012, Panel 1, p. 2375.*

Social, Environmental, and Cultural Factors

Of youths who attempt suicide, 65% can name a precipitating event for their action. Most adolescent suicide attempts are precipitated by stressful life events (e.g., academic or social problems, being bullied, trouble with the law, family instability, questioning one's sexual orientation, a newly diagnosed medical condition, or a recent or anticipated loss).

Suicide attempts may also be precipitated by exposure to news of another person's suicide or by reading about or viewing a suicide portrayed in a romantic light in the media. Media coverage of suicide is linked to fluctuating incidence rates of suicides, particularly among adolescents. Glorification or sensationalization of suicide in the media has found to be associated with an increase in suicides. When media coverage includes a detailed description of specific means used, the use of that particular method may increase in the overall population.

For some immigrants, suicidal ideation can be associated with high levels of acculturative stress, especially in the context of family separation and limited access to supportive resources. Physical and sexual abuse can also increase one's risk of suicide with 15-20% of female suicide attempters having had a history of abuse. There is a general association between family conflict and suicide attempts; this association is strongest in children and early adolescents. Family psychopathology and a family history of suicidal behavior convey excess risk. The lack of supportive social relations with peers, parents, and school personnel have an interactive relationship in increasing the risk of suicide among youth.

Protective Factors

Protective factors can provide a counterbalance for those contemplating suicide. They may include a sense of family responsibility, life satisfaction, social support, coping and problem-solving skills, religious faith, intact reality testing, and solid therapeutic relationships (e.g., pediatrician, teacher, therapist).

ASSESSMENT AND INTERVENTION

Pediatric practitioners should consider suicide potential and the need for mental health assessment in the context of adverse information elicited in child/parent psychosocial histories (e.g., HEADSS Psychosocial Risk Assessment; see Table 20-2 in Chapter 20), screening measure scores out of the normal range (e.g., Pediatric Symptom Checklist), or self-reported statements or behaviors from patients and/or parents.

All suicidal ideation and attempts should be taken seriously and require a thorough assessment by a child-trained mental health clinician to evaluate the youth's current state of mind, underlying psychiatric conditions, and ongoing risk of harm. Emergency mental health assessment is needed for immediate threat to self (i.e., suicidal intent and plan); urgent mental health assessment (48-72 hr) is needed for severe psychiatric symptoms, significant change in overall functioning, and/or suicidal ideation without intent or plan. Routine mental health assessment is appropriate for mild to moderate psychiatric symptoms without suicidal ideation.

Pediatric practitioners should expect the mental health clinician to evaluate the presence and degree of suicidality and underlying risk factors. The reliability and validity of child interviewing is affected by the child's level of cognitive development and well as their understanding of the relationship between their emotions and behavior. Confirmation of the youth's suicidal behavior can be obtained from information gathered by interviewing others who know the child or adolescent. It is not unusual for there to be a discrepancy between patient and parent reports, with both children and adolescents being more likely to disclose suicidal ideation and suicidal actions than their parents.

In the mental health assessment, suicidal ideation can be assessed by explicit questions posed in a nonjudgmental, noncondescending, matter-of-fact approach. The *Ask Suicide-Screening Questionnaire* is a validated 4-item measure that has been shown in the emergency room setting to have high sensitivity and negative predictive value in identifying youth at risk for suicide ideation and behavior: *(1) In the past few weeks, have you felt that you or your family would be better off if you were dead? (2) In the past few weeks, have you wished you were dead? (3) In the past weeks, have you been having thoughts about killing yourself? (4) Have you ever tried to kill yourself*?

The assessment of a suicidal attempt should include a detailed exploration of the hours immediately preceding the attempt to identify precipitants as well as the circumstances of the attempt itself so as to fully understand the patient's intent and potential lethality. The calculation of the level of suicide concern is complex requiring a determination across a spectrum of risk (Fig. 27-3). At the low end of the risk spectrum are youth with thoughts of death or wanting to die, but without suicidal thoughts, intent, or a plan. Those with highly specific suicide plans, preparatory acts or suicide rehearsals, and clearly articulated intent are at the high end. A suicidal history, presently impaired judgment (as seen in altered mental states including depression, mania, anxiety, intoxication, substance abuse, psychosis, trauma-reactive, hopelessness, rage, humiliation, impulsivity) as well as poor social support further exacerbates the heightened risk. Among adolescents who consider self-harm, those who carry out (enactors) self-injury are more likely to have family or friends (or think that their peers) engaged in self harm, and are more impulsive than those who only have thoughts of self-harm (ideators).

For youth who are an imminent danger to themselves, inpatient level of psychiatric care is necessary to ensure safety, clarify diagnoses, and comprehensively plan treatment. These patients can be hospitalized voluntarily or involuntarily. It is helpful for the pediatric practitioner to have an office protocol to follow in these situations. This protocol should take into consideration state laws regarding involuntary hospitalization, transportation options, nearest emergency assessment site, necessary forms for hospitalization, and available emergency mental health consultants.

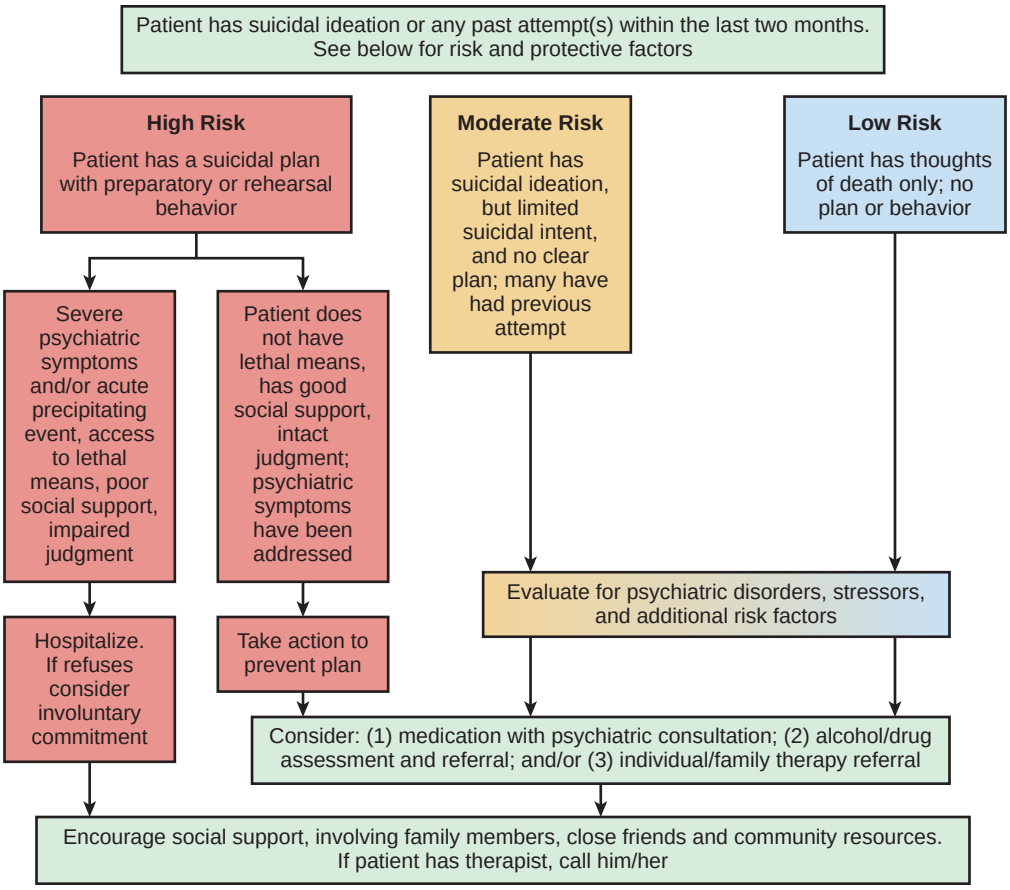
For those youth suitable for treatment in the outpatient setting, an appointment should be scheduled within a few days with a mental health clinician. Ideally, this appointment should be scheduled before leaving the assessment venue, as nearly 50% of those who attempt suicide fail to follow through with the mental health referral. A procedure should be in place to contact the family if the family fails to complete the referral.

Through follow-up office visits, pediatric practitioners can help support and facilitate the implementation of psychotherapies (e.g., cognitive-behavioral therapy, dialectical behavioral therapy, interpersonal therapy, and/or family therapy) that target the specific psychiatric disorders and the emotional dysphoria or behavioral dysregulation that accompany suicidal ideation or behavior. In conjunction with a child and adolescent child psychiatrist, psychotropic medications may be used as indicated to treat underlying psychiatric disorders. Pediatric practitioners also can encourage social connectedness to peers and to community organizations (e.g., school or church), as well as promote help-seeking (e.g., talking to a trusted adult when distressed) and wellness (e.g., sleep, exercise, relaxation, nutrition) behaviors. In the unfortunate circumstance of a completed suicide, pediatricians can offer support to the family, particularly by monitoring for adverse bereavement responses in siblings and parents.

PREVENTION

Suicide prevention is of high global importance. Yet, even in high-risk populations suicide is a comparatively rare event. Even the aforementioned risk factors associated with suicide are relatively common and individually not strong predictors of suicide. The assessment is complicated by patients that may attempt to conceal their suicide thoughts and by those who express suicidal thoughts without serious intent. Suicide screening has been challenging because most screening instruments have variable sensitivity and specificity. In addition, the burden of follow-up mental health evaluations for those who screen positive has been daunting. Although primary care–feasible screening tools may be help to identify some adults at increased risk for suicide, they have, to date, demonstrated limited ability to detect suicide risk in adolescents.

Prevention strategies in the pediatric medical home include training staff to recognize and respond to the warning signs of suicide, screening for and treating depression, educating patients/parents about warning signs for suicide, and restricting access to modes of lethal self-harm. Youth have increased rates of suicide attempts and completions if they live in homes where firearms are present and available. When recommended by their primary care providers, most parents restrict access of their children to guns and medications. Pediatric practitioners should consider counseling parents to either remove firearms from the home entirely or securely lock guns and ammunition in separate locations. Anecdotal evidence suggests youth frequently know where guns and keys to gun cabinets are kept, even though parents may think they do not. The same recommendation applies to restricting access to potentially lethal prescription and nonprescription



Risk Factors

- **Suicidal behavior:** history of prior suicide attempts, aborted suicide attempts, or self-injurious behavior.
- **Family history:** of suicide, attempts, or psychiatric diagnoses, especially those requiring hospitalization.
- **Current/past psychiatric disorders:** especially mood disorders (e.g., depression, bipolar disorder), psychotic disorders, alcohol/substance abuse, TBI, PTSD, personality disorders (e.g., borderline PD). ***Co-morbidity*** *with other psychiatric and/or substance abuse disorders and recent onset of illness increase risk.*
- **Key symptoms:** anhedonia, impulsivity, hopelessness, anxiety/panic, insomnia, command hallucinations, intoxication, oppositionality, and conduct problems.
- **Precipitants/stressors:** triggering events leading to humiliation, shame or despair (i.e., loss of relationship, financial, or health status – real or anticipated).
- **Chronic medical illness** (esp. CNS disorders, pain)
- **History of current abuse or neglect.**

Protective Factors

Protective factors, even if present, may not counteract significant acute risk.

- **Internal:** ability to cope with stress, religious beliefs, frustration tolerance.
- **External:** responsibility to family, positive therapeutic relationships, social supports

Figure 27-3 Assessment and interventions with potentially suicidal patients. *(Adapted from Suicide Prevention Resource Center, WICHE Center for Mental Health Program.* Suicide prevention primer. *Available at* http://www.sprc.org/sites/sprc.org/files/primer.pdf.*)*

medications (e.g., containers of more than 25 acetaminophen tablets) and alcohol. *These approaches emphasize the importance of restriction of access to means for suicide to prevent self-harm.*

Screening for suicide in schools is also fraught with problems related to low specificity of the screening instrument and paucity of referral sites, as well as poor acceptability among school administrators. Gatekeeper (e.g., student support personnel) training appears effective in improving skills among school personnel and is highly acceptable to administrators but has not been shown to prevent suicide. School curricula (e.g., *Signs of Suicide*) have shown some preventive potential by teaching students to recognize the signs of depression and suicide in themselves and others, and to provide students with specific action steps necessary for responding to these signs. Peer helpers have not generally been shown to be efficacious.

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Chapter 28

Eating Disorders

Richard E. Kreipe

Eating disorders (EDs) are characterized by body dissatisfaction related to overvaluation of a thin body ideal associated with dysfunctional patterns of cognition and weight-control behaviors that result in significant biologic, psychological, and social complications. Although largely affecting white, adolescent girls, EDs also affect boys and cross all racial, ethnic, and cultural boundaries. Early intervention in EDs improves outcome.

Table 28-1 DSM-5 Diagnostic Criteria for Anorexia Nervosa

A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B. Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Specify whether:

Restricting type (ICD-10-CM code F50.01): During the last 3 mo, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

Binge-eating/purging type (ICD-10-CM code F50.02): During the last 3 mo, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Specify if:

In partial remission: After full criteria for anorexia nervosa were previously met, Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met.

In full remission: After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based, for adults, on current body mass index (BMI) (see below) or, for children and adolescents, on BMI percentile. **The ranges below are derived from World Health Organization categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used.** The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

Mild: BMI ≥ 17 kg/m^2
Moderate: BMI 16–16.99 kg/m^2
Severe: BMI 15–15.99 kg/m^2
Extreme: BMI < 15 kg/m^2

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 338–339.

Table 28-2 DSM-5 Diagnostic Criteria for Bulimia Nervosa

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   1. Eating, in a discrete period of time (e.g., within any 2 hr period), an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
   2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).
B. Recurrent inappropriate compensatory behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise.
C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo.
D. Self-evaluation is unduly influenced by body shape and weight.
E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify if:

In partial remission: After full criteria for bulimia nervosa were previously met, some, but not all, of the criteria have been met for a sustained period of time.

In full remission: After full criteria for bulimia nervosa were previously met, none of the criteria have been met for a sustained period of time.

Specify current severity:

The minimum level of severity is based on the frequency of inappropriate compensatory behaviors (see below). The level of severity may be increased to reflect other symptoms and the degree of functional disability.

Mild: An average of 1-3 episodes of inappropriate compensatory behaviors per week.
Moderate: An average of 4-7 episodes of inappropriate compensatory behaviors per week.
Severe: An average of 8-13 episodes of inappropriate compensatory behaviors per week.
Extreme: An average of 14 or more episodes of inappropriate compensatory behaviors per week.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 345.

DEFINITIONS

Anorexia nervosa (AN) involves significant overestimation of body size and shape, with a relentless pursuit of thinness that typically combines excessive dieting and compulsive exercising in the **restrictive** subtype; in the **binge-purge** subtype, patients might intermittently overeat and then attempt to rid themselves of calories by vomiting or taking laxatives, still with a strong drive for thinness (Table 28-1). **Bulimia nervosa (BN)** is characterized by episodes of eating large amounts of food in a brief period, followed by compensatory vomiting, laxative use, and exercise or fasting to rid the body of the effects of overeating in an effort to avoid obesity (Table 28-2).

Children and adolescents with EDs may not fulfill criteria for AN or BN in the new *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) but fall into a new subcategory of **Atypical AN,** or a new category of **Avoidant Restrictive Food Intake Disorder (ARFID)** (Table 28-3), that includes a group of conditions in which food intake is restricted or avoided due to adverse feeding or eating experiences or the sensory qualities of food, resulting in significant nutritional deficiencies and problems with social interactions. **Binge eating disorder (BED)**, in which binge eating is not followed regularly by any compensatory behaviors (vomiting, laxatives) is a stand-alone category in DSM-5 but shares many features with obesity (see Chapter 47). ED-NOS, often called "disordered eating," can worsen into full syndrome EDs.

EPIDEMIOLOGY

The classic features of AN include a white, early to middle adolescent girl of above-average intelligence and socioeconomic status, who is a conflict-avoidant, risk-aversive, perfectionist struggling with disturbances of anxiety and/or mood. BN tends to emerge in later adolescence, sometimes evolving from AN, and is typified by impulsivity and features of borderline personality disorder that are associated with depression and mood swings. The 0.5-1% and 3-5% incidence rates among younger and older adolescent females for AN and BN, respectively, probably reflect ascertainment bias in sampling and underdiagnosis in cases not fitting the typical profile. The same may be true of the significant gender disparity, in which female patients account for approximately 90% of patients with diagnosed EDs. Ten percent or more of some adolescent female populations have ED-NOS.

No single factor causes the development of an ED; sociocultural studies indicate a complex interplay of culture, ethnicity, gender, peers, and family. The gender dimorphism is presumably related to females having a stronger relationship between body image and self-evaluation, as well as the influence of the Western culture's thin body ideal on the development of EDs. Race and ethnicity appear to moderate the

Table 28-3 DSM-5 Diagnostic Criteria for Avoidant/Restrictive Food Intake Disorder

A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:
   1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children).
   2. Significant nutritional deficiency.
   3. Dependence on enteral feeding or oral nutritional supplements.
   4. Marked interference with psychosocial functioning.
B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.
C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.
D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Specify if:

In remission: After full criteria for avoidant/restrictive food intake disorder were previously met, the criteria have not been met for a sustained period of time.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 334.

association between risk factors and disordered eating, with African-American and Caribbean females reporting lower body dissatisfaction and less dieting than Hispanic and non-Hispanic white females. Because peer acceptance is central to healthy adolescent growth and development, especially in early adolescence when AN tends to have its initial prevalence peak, the potential influence of peers on EDs is significant, as are the relationships among peers, body image, and eating. Teasing by peers or by family members (especially male) may be a contributing factor for overweight females.

Family influence in the development of EDs is even more complex because of the interplay of environmental and genetic factors; shared elements of the family environment and immutable genetic factors account for significant (about equal) variance in disordered eating. There are associations between parents' and children's eating behaviors; dieting and physical activity levels suggest parental reinforcement of body-related societal messages. The influence of inherited genetic factors on the emergence of EDs during adolescence is also significant, but not in a direct fashion. Rather, the risk for developing an ED appears to be mediated through a genetic predisposition to anxiety (see Chapter 25), depression (see Chapter 26), or obsessive-compulsive traits that may be modulated through the internal milieu of puberty. There is little evidence that parents "cause" an ED in their child or adolescent; the importance of parents in treatment and recovery cannot be overestimated.

PATHOLOGY AND PATHOGENESIS

The emergence of EDs coinciding with the processes of adolescence (e.g., puberty, identity, autonomy, cognition) indicates the central role of development. A history of sexual trauma is not significantly more common in EDs than in the population at large, but when present it makes recovery more difficult and is more common in BN. EDs may be viewed as a final common pathway, with a number of *predisposing* factors that increase the risk of developing an ED, *precipitating* factors often related to developmental processes of adolescence triggering the emergence of the ED, and *perpetuating* factors that cause an ED to persist. EDs often begin with dieting but gradually progress to unhealthy habits that lessen the negative impact of associated psychosocial problems to which the affected person is vulnerable because of premorbid biologic and psychologic characteristics, family interactions, and social climate. When persistent, the biologic effects of starvation and malnutrition (e.g., true loss of appetite, hypothermia, gastric atony, amenorrhea, sleep disturbance, fatigue, weakness, and depression) combined with the psychologic rewards of increased sense of mastery and reduced emotional reactivity, actually maintain and reward pathologic ED behaviors. This positive reinforcement of behaviors and consequences, generally viewed by parents and others as negative, helps to explain why affected persons characteristically deny that a problem exists and resist treatment. Although noxious, purging can be reinforcing owing to a reduction in anxiety triggered by overeating; purging also can result in short-term, but reinforcing, improvement in mood that is related to changes in neurotransmitters. In addition to an imbalance in neurotransmitters, most notably serotonin and dopamine, there are also alterations in functional anatomy that support the concept of EDs as brain disorders. The cause-and-effect relationship in central nervous system alterations in EDs is not clear, nor is their reversibility.

CLINICAL MANIFESTATIONS

A central feature of EDs is the overestimation of body size, shape or parts (e.g., abdomen, thighs) leading to weight-control practices intended to reduce weight (AN) or prevent weight gain (BN). Associated practices include severe restriction of caloric intake and behaviors intended to reduce the effect of calories ingested, such as compulsive exercising or purging by inducing vomiting or taking laxatives. Eating and weight loss habits commonly found in EDs can result in a wide range of energy intake and output, the balance of which leads to a wide range in weight from extreme loss of weight in AN to fluctuation around a normal to moderately high weight in BN. Reported eating and weight-control habits (Table 28-4) thus inform the initial primary care approach.

Although weight-control patterns guide the initial pediatric approach, an assessment of commonly reported symptoms and findings on physical examination is essential to identify targets for intervention. When reported symptoms of excessive weight loss (feeling tired and cold; lacking energy; orthostasis; difficulty concentrating) are explicitly linked by the clinician to their associated physical signs (hypothermia with acrocyanosis and slow capillary refill, loss of muscle mass, bradycardia with orthostasis), it becomes more difficult for the patient to deny that a problem exists. Furthermore, awareness that bothersome symptoms can be eliminated by healthier eating and activity patterns can increase a patient's motivation to engage in treatment. Tables 28-5 and 28-6 detail common symptoms and signs that should be addressed in a pediatric assessment of a suspected ED.

DIFFERENTIAL DIAGNOSIS

In addition to identifying symptoms and signs that deserve targeted intervention for patients who have an ED or disordered eating, a comprehensive history and physical examination are required in the assessment of a suspected ED to rule out other conditions in the differential diagnosis. Weight loss can occur with any condition in which there is increased catabolism (e.g., malignancy or occult chronic infection) or malabsorption (e.g., inflammatory bowel disease or celiac disease), but these illnesses are generally associated with other findings and are not usually associated with decreased caloric intake. Patients with inflammatory bowel disease can reduce intake to minimize abdominal cramping; eating can cause abdominal discomfort and early satiety in AN because of gastric atony associated with significant weight loss, not malabsorption. Likewise, signs of weight loss in AN might include hypothermia, acrocyanosis with slow capillary refill, and neutropenia suggesting overwhelming sepsis, but the overall picture in EDs is one of relative cardiovascular stability compared to sepsis. Endocrinopathies are also in the differential of EDs. With BN, voracious appetite in the face of weight loss might suggest diabetes mellitus, but blood glucose levels are normal or low in EDs. Adrenal insufficiency mimics

Table 28-4 Eating and Weight Control Habits Commonly Found in Children and Adolescents with an Eating Disorder

	Prominent Feature		Clinical Comments Regarding Eating Disorder Habits	
HABIT	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**	**ANOREXIA NERVOSA**	**BULIMIA NERVOSA**
Overall intake	Inadequate energy (calories), although volume of food and beverages may be high because of very low caloric density of intake as a result of "diet" and nonfat choices	Variable, but calories normal to high; intake in binges often "forbidden" food or drink that differs from intake at meals	Consistent inadequate caloric intake leading to wasting of the body is an essential feature of diagnosis	Inconsistent balance of intake, exercise and vomiting, but severe caloric restriction is short-lived
Food	Counts and limits calories, especially from fat; Emphasis on "healthy food choices" with reduced caloric density Monotonous, limited "good" food choices, often leading to vegetarian or vegan diet Strong feelings of guilt after eating more than planned leads to exercise and renewed dieting	Aware of calories and fat, but less regimented in avoidance than AN Frequent dieting interspersed with overeating, often triggered by depression, isolation, or anger	Obsessive-compulsive attention to nutritional data on food labels and may have "logical" reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder	Choices less structured, with more frequent diets
Beverages	Water or other low- or no-calorie drinks; nonfat milk	Variable, diet soda common; may drink alcohol to excess	Fluids often restricted to avoid weight gain	Fluids ingested to aid vomiting or replace losses
Meals	Consistent schedule and structure to meal plan Reduced or eliminated caloric content, often starting with breakfast, then lunch, then dinner Volume can increase with fresh fruits, vegetables, and salads as primary food sources	Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode	Rigid adherence to "rules" governing eating leads to sense of control, confidence, and mastery	Elimination of a meal following a binge-purge only reinforces the drive for binge later in the day
Snacks	Reduced or eliminated from meal plan	Often avoided in meal plans, but then impulsively eaten	Snack foods removed early because "unhealthy"	Snack "comfort foods" can trigger a binge
Dieting	Initial habit that becomes progressively restrictive, although often appearing superficially "healthy" Beliefs and "rules" about the patient's idiosyncratic nutritional requirements and response to foods are strongly held	Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being "weak" or "lazy"	Distinguishing between healthy meal planning with reduced calories and dieting in ED may be difficult	Dieting tends to be impulsive and short-lived, with "diets" often resulting in unintended weight gain
Binge eating	None in restrictive subtype, but an essential feature in binge-purge subtype	Essential feature, often secretive Shame and guilt prominent afterward	Often "subjective" (more than planned but not large)	Relieves emotional distress, may be planned
Exercise	Characteristically obsessive-compulsive, ritualistic, and progressive May excel in dance, long-distance running	Less predictable May be athletic, or may avoid exercise entirely	May be difficult to distinguish active thin vs. ED	Males often use exercise as means of "purging"
Vomiting	Characteristic of binge-purge subtype May chew, then spit out, rather than swallow, food as a variant	Most common habit intended to reduce effects of overeating Can occur after meal as well as a binge	Physiologic and emotional instability prominent	Strongly "addictive" and self-punishing, but does not eliminate calories ingested—many still absorbed
Laxatives	If used, generally to relieve constipation in restrictive subtype, but as a cathartic in binge-purge subtype	Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect	Physiologic and emotional instability prominent	Strongly "addictive," self-punishing, but ineffective means to reduce weight (calories are absorbed in the small intestine, but laxatives work in the colon)
Diet pills	Very rare, if used; more common in binge-purge subtype	Used to either reduce appetite or increase metabolism	Use of diet pills implies inability to control eating	Control over eating may be sought by any means

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder.

Table 28-5 Symptoms Commonly Reported by Patients with an Eating Disorder

SYMPTOMS	Diagnosis: ANOREXIA NERVOSA	Diagnosis: BULIMIA NERVOSA	CLINICAL COMMENTS REGARDING ED SYMPTOMS
Body image	Feels fat, even with extreme emaciation, often with specific body distortions (e.g., stomach, thighs); Strong drive for thinness, with self-efficacy closely tied to appraisal of body shape, size, and/or weight	Variable body image distortion and dissatisfaction, but drive for thinness is less than the desire to avoid gaining weight	Challenging a patient's body image is both ineffective and counter-therapeutic clinically Accepting the patient's expressed body image but noting its discrepancy with symptoms and signs reinforces concept that patient can "feel" fat but also "be" too thin and unhealthy
Metabolism	Hypometabolic symptoms include feeling cold, tired, and weak and lacking energy May be both bothersome and reinforcing	Variable, depending on balance of intake and output and hydration	Symptoms are evidence of body's "shutting down" in an attempt to conserve calories with an inadequate diet Emphasizing reversibility of symptoms with healthy eating and weight gain can motivate patients to cooperate with treatment
Skin	Dry skin, delayed healing, easy bruising, goose flesh Orange-yellow skin on hands	No characteristic symptom, self-injurious behavior may be seen	Skin lacks good blood flow and the ability to heal in low weight Carotenemia with large intake of β-carotene foods; reversible
Hair	Lanugo-type hair growth on face and upper body Slow growth and increased loss of scalp hair	No characteristic symptom	Body hair growth conserves energy Scalp hair loss can worsen during refeeding "telogen effluvium" (resting hair is replaced by growing hair) Reversible with continued healthy eating
Eyes	No characteristic symptom	Subconjunctival hemorrhage	Caused by increased intrathoracic pressure during vomiting
Teeth	No characteristic symptom	Erosion of dental enamel erosion Decay, fracture, and loss of teeth	Intraoral stomach acid resulting from vomiting etches dental enamel, exposing softer dental elements
Salivary glands	No characteristic symptom	Enlargement (no to mild tenderness)	Caused by chronic binge eating and induced vomiting, with parotid enlargement more prominent than submandibular; reversible
Heart	Dizziness, fainting in restrictive subtype Palpitations more common in binge-purge subtype	Dizziness, fainting, palpitations	Dizziness and fainting due to postural orthostatic tachycardia and dysregulation at hypothalamic and cardiac level with weight loss, as a result of hypovolemia with binge-purge Palpitations and arrhythmias often caused by electrolyte disturbance Symptoms reverse with weight gain and/or cessation of binge-purge
Abdomen	Early fullness and discomfort with eating Constipation Perceives contour as "fat," often preferring well-defined abdominal musculature	Discomfort after a binge Cramps and diarrhea with laxative abuse	Weight loss is associated with reduced volume and tone of GI tract musculature, especially the stomach Laxatives may be used to relieve constipation or as a cathartic Symptom reduction with healthy eating can take weeks to occur
Extremities and musculoskeletal	Cold, blue hands and feet	No characteristic symptoms Self-cutting or burning on wrists or arms	Energy-conserving low body temperature with slow blood flow most notable peripherally Quickly reversed with healthy eating
Nervous system	No characteristic symptom	No characteristic symptom	Neurologic symptoms suggest a diagnosis other than an ED
Mental status	Depression, anxiety, obsessive-compulsive symptoms, alone or in combination	Depression; PTSD; borderline personality disorder traits	Underlying mood disturbances can worsen with dysfunctional weight control practices and can improve with healthy eating AN patients might report emotional "numbness" with starvation, preferable to emotionality associated with healthy eating

AN, anorexia nervosa; BN, bulimia nervosa; ED, eating disorder; GI, gastrointestinal; PTSD, posttraumatic stress disorder.

Table 28-6 Signs Commonly Found in Patients with Eating Disorders Relative to Prominent Feature of Weight Control

PHYSICAL SIGN	Prominent Feature: RESTRICTIVE INTAKE	Prominent Feature: BINGE EATING/PURGING	CLINICAL COMMENTS RELATED TO EATING DISORDER SIGNS
General appearance	Thin to cachetic, depending on balance of intake and output Might wear bulky clothing to hide thinness and might resist being examined	Thin to overweight, depending on the balance of intake and output through various means	Examine in hospital gown Weight loss more rapid with reduced intake and excessive exercise Binge eating can result in large weight gain, regardless of purging behavior Appearance depends on balance of intake and output and overall weight control habits
Weight	Low and falling (if previously overweight may be normal or high); may be falsely elevated if patient drinks fluids or adds weights to body before being weighed	Highly variable, depending on balance of intake and output and state of hydration Falsification of weight is unusual	Weigh in hospital gown with no underwear, after voiding (measure urine SG) Remain in gown until physical exam completed to identify possible fluid loading (low urine SG, palpable bladder) or adding weights to body
Metabolism	Hypothermia: temp < 35.5°C (95.9°F), pulse < 60 beats/min Slowed psychomotor response with very low core temperature	Variable, but hypometabolic state is less common than in AN	Hypometabolism related to disruption of hypothalamic control mechanisms as a result of weight loss Signs of hypometabolism (cold skin, slow capillary refill, acrocyanosis) most evident in hands and feet, where energy conservation is most active
Skin	Dry Increased prominence of hair follicles Orange or yellow hands	Calluses over proximal knuckle joints of hand (Russell's sign)	Carotenemia with large intake of β-carotene foods Russell's sign: maxillary incisors abrasion develops into callus with chronic digital pharyngeal stimulation, usually on dominant hand
Hair	Lanugo-type hair growth on face and upper body Scalp hair loss, especially prominent in parietal region	No characteristic sign	Body hair growth conserves energy Scalp hair loss "telogen effluvium" can worsen weeks after refeeding begins, as hair in resting phase is replaced by growing hair
Eyes	No characteristic sign	Subconjunctival hemorrhage	Increased intrathoracic pressure during vomiting
Teeth	No characteristic sign	Eroded dental enamel and decayed, fractured, missing teeth	Perimolysis, worse on lingual surfaces of maxillary teeth, is intensified by brushing teeth without preceding water rinse
Salivary glands	No characteristic sign	Enlargement, relatively nontender	Parotid > submandibular involvement with frequent and chronic binge eating and induced vomiting
Throat	No characteristic sign	Absent gag reflex	Extinction of gag response with repeated pharyngeal stimulation
Heart	Bradycardia, hypotension, and orthostatic pulse differential > 25 beats/min	Hypovolemia if dehydrated	Changes in AN resulting from central hypothalamic and intrinsic cardiac function Orthostatic changes less prominent if athletic, more prominent if associated with purging
Abdomen	Scaphoid, organs may be palpable but not enlarged, stool-filled left lower quadrant	Increased bowel sounds if recent laxative use	Presence of organomegaly requires investigation to determine cause Constipation prominent with weight loss
Extremities and musculoskeletal system	Cold, acrocyanosis, slow capillary refill Edema of feet Loss of muscle, subcutaneous, and fat tissue	No characteristic sign, but may have rebound edema after stopping chronic laxative use	Signs of hypometabolism (cold) and cardiovascular dysfunction (slow capillary refill and acrocyanosis) in hands and feet Edema, caused by capillary fragility more than hypoproteinemia in AN, can worsen in early phase of refeeding
Nervous system	No characteristic sign	No characteristic sign	Water loading before weigh-ins can cause acute hyponatremia
Mental status	Anxiety about body image, irritability, depressed mood, oppositional to change	Depression, evidence of PTSD, more likely suicidal than AN	Mental status often improves with healthier eating and weight; SSRIs only shown to be effective for BN

AN, anorexia nervosa; BN, bulimia nervosa; PTSD, posttraumatic stress disorder; SG, specific gravity; SSRI, selective serotonin reuptake inhibitor.

many physical symptoms and signs found in restrictive AN but is associated with elevated potassium levels and hyperpigmentation. Although thyroid disorders are often considered, because of changes in weight and other symptoms in AN, the overall presentation includes symptoms of both underactive and overactive thyroid, such as hypothermia, bradycardia, and constipation, as well as weight loss and excessive physical activity, respectively.

In the central nervous system, craniopharyngiomas and Rathke pouch tumors can mimic some of the findings of AN, such as weight loss and growth failure, and even some body image disturbances, but the latter are less fixed than in typical EDs and are associated with other findings, including evidence of increased intracranial pressure. Mitochondrial neurogastrointestinal encephalomyopathy, caused by a mutation in the *TYMP* gene, presents with gastrointestinal dysmotility, cachexia, ptosis, peripheral neuropathy, ophthalmoplegia, and leukoencephalopathy. Symptoms begin during the second decade of life and are often initially diagnosed as AN. Early satiety, vomiting, cramps, constipation, and pseudoobstruction result in weight loss often before the neurologic features are noticed.

Any patient with an atypical presentation of an ED, based on age, sex, or other factors not typical for AN or BN deserves a scrupulous search for an alternative explanation. Patients can have both an underlying illness and an ED. The core features of dysfunctional eating habits—body image disturbance and change in weight—can coexist with conditions such as diabetes mellitus, where patients might manipulate their insulin dosing to lose weight.

LABORATORY FINDINGS

Because the diagnosis of an ED is made clinically, there is no confirmatory laboratory test. Laboratory abnormalities, when found, are the result of malnutrition, weight-control habits used, or medical complications; studies should be chosen based on history and physical examination. A routine screening battery typically includes complete blood count, erythrocyte sedimentation rate (should be normal), and biochemical profile. Common abnormalities in ED include low white blood cell count with normal hemoglobin and differential; hypokalemic, hypochloremic metabolic alkalosis with severe vomiting; mildly elevated liver enzymes, cholesterol, and cortisol levels; low gonadotropins and blood glucose with marked weight loss; and generally normal total protein, albumin, and renal function. An electrocardiogram may be useful when profound bradycardia or arrhythmia is detected; the electrocardiogram usually has low voltage, with nonspecific ST or T wave changes. Although prolonged QTc has been reported, prospective studies have not found an increased risk for this.

COMPLICATIONS

No organ is spared the harmful effects of dysfunctional weight-control habits, but the most concerning targets of medical complications are the heart, brain, gonads, and bones. Some **heart** findings in EDs (e.g., sinus bradycardia and hypotension) are *physiologic* adaptations to starvation that conserve calories and reduce afterload. Cold, blue hands and feet with slow capillary refill that can result in tissue perfusion insufficient to meet demands also represent energy-conserving responses associated with inadequate intake. All of these acute changes are reversible with restoration of nutrition and weight. Significant orthostatic pulse changes, prolonged corrected QT interval, ventricular dysrhythmias, or reduced myocardial contractility reflect myocardial impairment that can be lethal. In addition, with extremely low weight, **refeeding syndrome** (a result of the rapid drop in serum phosphorous, magnesium, and potassium with excessive reintroduction of calories, especially carbohydrates), is associated with acute heart failure and neurologic symptoms. With long-term malnutrition, the myocardium appears to be more prone to tachyarrhythmias, the second most common cause of death after suicide. In BN, dysrhythmias can also be related to electrolyte imbalance.

Clinically, the primary **brain** area affected acutely in EDs, especially with weight loss, is the hypothalamus. Hypothalamic dysfunction is reflected in problems with thermoregulation (warming and cooling), satiety, sleep, autonomic cardioregulatory imbalance (orthostasis), and endocrine function (reduced gonadal and excessive adrenal cortex stimulation), all of which are reversible. Anatomic studies of the brain in ED have focused on AN, with the most common finding being increased ventricular and sulcal volumes that normalize with weight restoration. Persistent gray-matter deficits following recovery, related to the degree of weight loss, have been reported. Elevated medial temporal lobe cerebral blood flow on positron emission tomography similar to that found in psychotic patients, suggests that these changes may be related to body image distortion. Also, visualizing high-calorie foods is associated with exaggerated responses in the visual association cortex that are similar to those seen in patients with specific phobias. Patients with AN might have an imbalance between serotonin and dopamine pathways related to neurocircuits in which dietary restraint reduces anxiety.

Reduced **gonadal** function occurs in male and female patients; it is clinically manifested in AN as amenorrhea in female patients and erectile dysfunction in males. It is related to understimulation from the hypothalamus as well as cortical suppression related to physical and emotional stress. Amenorrhea precedes significant dieting and weight loss in up to 30% of females with AN, and most adolescents with EDs perceive the absence of menses positively. The primary health concern is the negative effect of decreased ovarian function and estrogen on **bones**. Decreased bone mineral density (BMD) with osteopenia or the more severe osteoporosis is a significant complication of EDs (more pronounced in AN than BN). Data do not support the use of sex hormone replacement therapy because this alone does not improve other causes of low BMD (low body weight, lean body mass, and insulin-like growth factor-1; high cortisol).

TREATMENT

Principles Guiding Primary Care Treatment

The approach in primary care should facilitate the acceptance by the patient (and parents) of the diagnosis and initial treatment recommendations. A **nurturant–authoritative** approach using the **biopsychosocial** model is useful. A pediatrician who explicitly acknowledges that the patient may disagree with the diagnosis and treatment recommendations and be ambivalent about changing eating habits, while also acknowledging that recovery requires strength, courage, will-power and determination, demonstrates *nurturance*. Parents also find it easier to be nurturant once they learn that the development of an ED is neither a willful decision by the patient nor a reflection of bad parenting. Framing the ED as a coping mechanism for a complex variety of issues with both positive and negative aspects avoids blame or guilt and can prepare the family for professional help that will focus on strengths and restoring health, rather than on the deficits in the adolescent or the family.

The **authoritative** aspect of a physician's role comes from expertise in health, growth, and physical development. A goal of primary care treatment should be attaining and maintaining health—not merely weight gain—although weight gain is a means to the goal of wellness. Providers who frame themselves as consultants to the patient with *authoritative* knowledge about health can avoid a countertherapeutic authoritarian stance. Primary care health-focused activities include monitoring the patient's physical status, setting limits on behaviors that threaten the patient's health, involving specialists with expertise in EDs on the treatment team, and continuing to provide primary care for health maintenance, acute illness, or injury.

The **biopsychosocial** model uses a broad ecologic framework, starting with the biologic impairments of physical health related to dysfunctional weight control practices, evidenced by symptoms and signs. Explicitly linking ED behaviors to symptoms and signs can increase motivation to change. In addition, there are usually unresolved psychosocial conflicts in both the intrapersonal (self-esteem, self-efficacy) and interpersonal (family, peers, school) domains. Weight-control practices initiated as coping mechanisms become reinforced because of positive feedback. That is, external rewards (e.g., compliments about improved physical appearance) and internal rewards (e.g., perceived mastery over what is eaten or what is done to minimize the effects of overeating through exercise or purging) are more powerful to maintain

behavior than negative feedback (e.g., conflict with parents, peers, and others about eating) is to change it. Thus, when definitive treatment is initiated, more productive alternative means of coping must be developed.

Nutrition and Physical Activity

The primary care provider generally begins the process of prescribing nutrition, although a dietitian should be involved eventually in the meal planning and nutritional education of patients with AN or BN. Framing food as fuel for the body and the source of energy for daily activities emphasizes the health goal of increasing the patient's energy level, endurance, and strength. For patients with AN and low weight, the nutrition prescription should work toward gradually increasing weight at the rate of about 0.5-1 lb/wk, by increasing energy intake by 100-200 kcal increments every few days toward a target of approximately 90% of average body weight for sex, height, and age. Weight gain will not occur until intake exceeds output, and eventual intake for continued weight gain can exceed 4,000 kcal/day, especially for patients who are anxious and have high levels of thermogenesis from nonexercise activity. Stabilizing intake is the goal for patients with BN, with a gradual introduction of forbidden foods while also limiting foods that might trigger a binge.

When initiating treatment of an ED in a primary care setting, the clinician should be aware of common cognitive patterns. Patients with AN typically have all-or-none thinking (related to perfectionism) with a tendency to overgeneralize and jump to catastrophic conclusions, while assuming that their body is governed by rules that do not apply to others. These tendencies lead to the dichotomization of foods into good or bad categories, having a day ruined because of 1 unexpected event, or choosing foods based on rigid self-imposed restrictions. These thoughts may be related to neurocircuitry and neurotransmitter abnormalities related to executive function and rewards.

A standard nutritional balance of 15-20% calories from protein, 50-55% from carbohydrate, and 25-30% from fat is appropriate. The fat content may need to be lowered to 15-20% early in the treatment of AN because of continued fat phobia. With the risk of low BMD in patients with AN, calcium and vitamin D supplements are often needed to attain the recommended 1,300 mg/day intake of calcium. Refeeding can be accomplished with frequent small meals and snacks consisting of a variety of foods and beverages (with minimal diet or fat-free products), rather than fewer high-volume high-calorie meals. Some patients find it easier to take in part of the additional nutrition as canned supplements (medicine) rather than food. Regardless of the source of energy intake, the risk for refeeding syndrome (acute tachycardia and heart failure with neurologic symptoms associated primarily with acute decline in serum phosphate and magnesium) increases with the degree of weight loss and the rapidity of caloric increases. Therefore, if the weight has fallen below 80% of expected weight for height, refeeding should proceed cautiously, possibly in the hospital (Table 28-7).

Patients with AN tend to have a highly structured day with restrictive intake, in contrast to BN, which is characterized by a lack of structure, resulting in chaotic eating patterns and binge-purge episodes. All patients with AN, BN, or ED-NOS benefit from a daily structure for healthy eating that includes 3 meals and at least 1 snack a day, distributed evenly over the day, based on balanced meal planning. Breakfast deserves special emphasis because it is often the first meal eliminated in AN and is often avoided the morning after a binge-purge episode in BN. In addition to structuring meals and snacks, patients should plan structure in their activities. Although overexercising is common in AN, completely prohibiting exercise can lead to further restriction of intake or to surreptitious exercise; inactivity should be limited to situations in which weight loss is dramatic or there is physiologic instability. Also, healthy exercise (once a day, for no more than 30 minutes, at no more than moderate intensity) can improve mood and make increasing calories more acceptable. Because patients with AN often are unaware of their level of activity and tend toward progressively increasing their output, exercising without either a partner or supervision is not recommended.

Table 28-7 Indications for Inpatient Medical Hospitalization of Patients with Anorexia Nervosa

PHYSICAL AND LABORATORY
Heart rate < 50 beats/min
Other cardiac rhythm disturbances
Blood pressure < 80/50 mm Hg
Postural hypotension resulting in a >10 mm Hg drop or a >25 beats/min increase
Hypokalemia
Hypophosphatemia
Hypoglycemia
Dehydration
Body temperature < 36.1°C (97°F)
<80% healthy body weight
Hepatic, cardiac, or renal compromise
PSYCHIATRIC
Suicidal intent and plan
Very poor motivation to recover (in family and patient)
Preoccupation with ego-syntonic thoughts
Coexisting psychiatric disorders
MISCELLANEOUS
Requires supervision after meals and while using the restroom
Failed day treatment

Primary Care Treatment

Follow-up primary care visits are essential in the management of EDs; close monitoring of the response of the patient and the family to suggested interventions is required to determine which patients can remain in primary care treatment (patients with early, mildly disordered eating), which patients need to be referred to individual specialists for co-management (mildly progressive disordered eating), and which patients need to be referred for interdisciplinary team management (EDs). Between the initial and subsequent visits, the patient can record daily caloric intake (food, drink, amount, time, location), physical activity (type, duration, intensity), and emotional state (e.g., angry, sad, worried) in a journal that is reviewed jointly with the patient in follow-up. Focusing on the recorded data helps the clinician to identify dietary and activity deficiencies and excesses as well as behavioral and mental health patterns, and the patient to become objectively aware of the relevant issues to address in recovery.

Given the tendency of patients with AN to overestimate their caloric intake and underestimate their activity level, before reviewing the journal record it is important at each visit to measure weight, without underwear, in a hospital gown after voiding; urine specific gravity; temperature; and blood pressure and pulse in supine, sitting, and standing positions as objective data. In addition, a targeted physical examination focused on hypometabolism, cardiovascular stability, and mental status, as well as any related symptoms, should occur at each visit to monitor progress (or regression).

Referral to Mental Health Services

In addition to referral to a registered dietitian, mental health services are an important element of treatment of EDs. Depending on availability and experience, these services can be provided by a psychiatric social worker, psychologist, or psychiatrist, who should team with the primary care provider. Although patients with AN often are prescribed a selective serotonin reuptake inhibitor (SSRI) because of depressive symptoms, there is no evidence of efficacy for patients at low weight; food remains the initial treatment of choice to treat depression in AN. SSRIs, very effective in reducing binge-purge behaviors regardless of depression, are considered a standard element of therapy in BN. SSRI dosage in BN, however, may need to increase to an equivalent of more than 60 mg of fluoxetine to maintain effectiveness.

Cognitive-behavioral therapy, which focuses on restructuring "thinking errors" and establishing adaptive patterns of behavior, is more effective than interpersonal or psychoanalytic approaches.

Dialectical behavioral therapy, in which distorted thoughts and emotional responses are challenged, analyzed, and replaced with healthier ones, with an emphasis on "mindfulness," requires adult thinking skills and is useful for older patients with BN. **Group therapy** can provide much needed support, but it requires a skilled clinician. Combining patients at various levels of recovery who experience variable reinforcement from dysfunctional coping behaviors can be challenging if group therapy patients compete with each other to be "thinner" or take up new behaviors such as vomiting.

The younger the patient, the more intimately the parents need to be involved in therapy. The only treatment approach with evidence-based effectiveness in the treatment of AN in children and adolescents is **family-based treatment**, exemplified by the Maudsley approach. This 3-phase intensive outpatient model helps parents play a positive role in restoring their child's eating and weight to normal, then returns control of eating to the child who has demonstrated the ability to maintain healthy weight, and then encourages healthy progression in the other domains of adolescent development. Features of effective family treatment include an agnostic approach in which the cause of the disease is unknown and irrelevant to weight gain, emphasizing that parents are *not* to blame for EDs; parents being actively nurturing and supportive of their child's healthy eating while reinforcing limits on dysfunctional habits, rather than an authoritarian food police or complete hands-off approach; and reinforcement of parents as the best resource for recovery for almost all patients, with professionals serving as consultants and advisors to help parents address challenges.

Referral to an Interdisciplinary Eating Disorder Team

The treatment of a child or adolescent diagnosed with an ED is ideally provided by an interdisciplinary team (physician, nurse, dietitian, mental health provider) with expertise treating pediatric patients. Because such teams, often led by specialists in adolescent medicine at medical centers, are not widely available, the primary care provider might need to convene such a team. Adolescent medicine–based programs report encouraging treatment outcomes, possibly related to patients entering earlier into care and the stigma that some patients and parents may associate with psychiatry-based programs. Specialty centers focused on treating EDs are generally based in psychiatry and often have separate tracks for younger and adult patients. The elements of treatment noted earlier (cognitive-behavioral therapy, dialectical behavioral therapy, and family-based therapy), as well as individual and group treatment should all be available as part of interdisciplinary team treatment. Comprehensive services ideally include intensive outpatient and/or partial hospitalization as well as inpatient treatment. Regardless of the intensity, type, or location of the treatment services, the patient, parents, and primary care provider are essential members of the treatment team. A recurring theme in effective treatment is helping patients and families re-establish connections that are disrupted by the ED.

Inpatient medical treatment of EDs is generally limited to patients with AN, to stabilize and treat life-threatening starvation and to provide supportive mental health services. Inpatient medical care may be required to avoid refeeding syndrome in severely malnourished patients, provide nasogastric tube feeding for patients unable or unwilling to eat, or initiate mental health services, especially family-based treatment, if this has not occurred on an outpatient basis (see Table 28-7). Admission to a general pediatric or hospital unit is advised only for short-term stabilization in preparation for transfer to a medical unit with expertise in treating pediatric EDs. Inpatient psychiatric care of EDs should be provided on a unit with expertise in managing the often challenging behaviors (e.g., hiding or discarding food, vomiting, surreptitious exercise) and emotional problems (e.g., depression, anxiety). Suicidal risk is small, but patients with AN might threaten suicide if made to eat or gain weight in an effort to get their parents to back off.

An ED **partial hospital program** offers outpatient services that are less intensive than round-the-clock inpatient care. Generally held 4-5 days a wk for 6 to 9 hr each session, partial hospital program services typically are group-based and include eating at least 2 meals as well as opportunities to address issues in a setting that more closely approximates "real life" than inpatient treatment. That is, patients sleep at home and are free-living on weekends, exposing them to challenges that can be processed during the 25-40 hr in program, also sharing group and family experiences.

Supportive Care

In relation to pediatric EDs, support groups are primarily designed for parents. Because their daughter or son with an ED often resists the diagnosis and treatment, parents often feel helpless and hopeless. Because of the historical precedent of blaming parents for causing EDs, parents often express feelings of shame and isolation (www.maudsleyparents.org). Support groups and multifamily therapy sessions bring parents together with other parents whose families are at various stages of recovery from an ED in ways that are educational and encouraging. Patients often benefit from support groups after intensive treatment or at the end of treatment because of residual body image or other issues after eating and weight have normalized.

PROGNOSIS

With early diagnosis and effective treatment, 80% or more of youth with AN recover: They develop normal eating and weight control habits, resume menses, maintain average weight for height, and function in school, work, and relationships, although some still have poor body image. With weight restoration, fertility returns as well, although the weight for resumption of menses (approximately 92% of average body weight for height) may be lower than the weight for ovulation. The prognosis for BN is less-well established, but outcome improves with multidimensional treatment that includes SSRIs and attention to mood, past trauma, impulsivity, and any existing psychopathology. Atypical AN and ED-NOS may still have significant morbidity.

PREVENTION

Given the complexity of the pathogenesis of EDs, prevention is difficult. Targeted preventive interventions can reduce risk factors in older adolescents and college-age women. Universal prevention efforts to promote healthy weight regulation and discourage unhealthy dieting have not shown effectiveness in middle-school students. Programs that include recovered patients or focus on the problems associated with EDs can inadvertently normalize or even glamorize EDs and should be discouraged.

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Chapter 29

Disruptive, Impulse-Control, and Conduct Disorders

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The disruptive, impulse-control, and conduct disorders are interrelated sets of psychiatric symptoms characterized by a core deficit in self-regulation of anger, aggression, defiance, and antisocial behaviors. The disruptive, impulse-control, and conduct disorders include oppositional defiant, intermittent explosive, conduct, other specified/unspecified disruptive, impulse control, and conduct, and antisocial personality disorders, as well as pyromania and kleptomania.

Table 29-1 DSM-5 Diagnostic Criteria for Oppositional Defiant Disorder

A. A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 mo as evidenced by at least 4 symptoms from any of the following categories, and exhibited during interaction with at least 1 individual who is not a sibling.

Angry/Irritable Mood
1. Often loses temper.
2. Is often touchy or easily annoyed.
3. Is often angry and resentful.

Argumentative/Defiant Behavior
4. Often argues with authority figures or, for children and adolescents, with adults.
5. Often actively defies or refuses to comply with requests from authority figures or with rules.
6. Often deliberately annoys others.
7. Often blames others for his or her mistakes or misbehavior.

Vindictiveness
8. Has been spiteful or vindictive at least twice within the past 6 mo.

Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic. For children younger than 5 yr, the behavior should occur on most days for a period of at least 6 mo unless otherwise noted (Criterion A8). For individuals 5 yr or older, the behavior should occur at least once per week for at least 6 mo, unless otherwise noted (Criterion A8). While these frequency criteria provide guidance on a minimal level of frequency to define symptoms, other factors should be considered, such as whether the frequency and intensity of the behaviors are outside a range that is normative for the individual's developmental level, gender, and culture.

B. The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning.

C. The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 462–463.

Table 29-2 DSM-5 Diagnostic Criteria for Intermittent Explosive Disorder

A. Recurrent behavioral outbursts representing a failure to control aggressive impulses as manifested by either of the following:
1. Verbal aggression (e.g., temper tantrums, tirades, verbal arguments or fights) or physical aggression toward property, animals, or other individuals, occurring twice weekly, on average, for a period of 3 mo. The physical aggression does not result in damage or destruction of property and does not result in physical injury to animals or other individuals.
2. Three behavioral outbursts involving damage or destruction of property and/or physical assault involving physical injury against animals or other individuals occurring with a 12-mo period.

B. The magnitude of aggressiveness expressed during the recurrent outbursts is grossly out of proportion to the provocation or to any precipitating psychosocial stressors.

C. The recurrent aggressive outbursts are not premeditated (i.e., they are impulsive and/or anger-based) and are not committed to achieve some tangible objective (e.g., money, power, intimidation).

D. The recurrent aggressive outbursts cause either marked distress in the individual or impairment in occupational or interpersonal functioning, or as associated with financial or legal consequences.

E. Chronological age is at least 6 yr (or equivalent developmental level).

F. The recurrent aggressive outbursts are not better explained by another mental disorder (e.g., major depressive disorder, bipolar disorder, disruptive mood dysregulation disorder, a psychotic disorder, antisocial personality disorder, borderline personality disorder) and are not attributable to another medical condition (e.g., head trauma, Alzheimer disease) or to the physiologic effects of a substance (e.g., a drug of abuse, a medication). For children ages 6-18 yr, aggressive behavior that occurs as part of an adjustment disorder should not be considered for this diagnosis.

Note: This diagnosis can be made in addition to the diagnosis of attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, or autism spectrum disorder when recurrent impulsive aggressive outbursts are in excess of those usually seen in these disorders and warrant clinical attention.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 466.

DESCRIPTION

Oppositional defiant disorder **(ODD)** is characterized by a pattern lasting at least 6 mo of angry, irritable mood, argumentative/defiant behavior, or vindictiveness exhibited during interaction with at least 1 individual who is not a sibling (Table 29-1). For preschool children, the behavior must occur on most days whereas in school-age children, the behavior must occur at least once a week. The severity of the disorder is considered to be mild if symptoms are confined to only 1 setting (e.g., at home, at school, at work, with peers), moderate if symptoms are present in at least 2 settings, and severe if symptoms are present in 3 or more settings.

Intermittent explosive disorder **(IED)** is characterized by recurrent verbal or physical aggression that is grossly disproportionate to the provocation or to any precipitating psychosocial stressors (Table 29-2). The outbursts, which are impulsive and/or anger-based rather than premeditated and/or instrumental, typically last for less than 30 min and commonly occur in response to a minor provocation by a close intimate.

Conduct disorder **(CD)** is characterized by a repetitive and persistent pattern over at least 12 mo of serious rule-violating behavior in which the basic rights of others or major societal norms or rules are violated (Table 29-3). The symptoms of CD are divided into 4 major categories: *aggression to people and animals*, *destruction of property*, *deceitfulness or theft*, and *serious rule violations* (e.g., truancy, running away). Three subtypes of CD (which have different prognostic significance) are based on the age of onset: *childhood-onset type*, *adolescent onset type*, and *unspecified*. A small proportion of individuals with CD exhibit characteristics (lack of remorse/guilt, callous/lack of empathy, unconcerned about performance, shallow/deficient affect) that qualify for the "*with limited prosocial emotions*" specifier. CD is classified as mild if few if any symptoms in excess of those required for the diagnosis are present, and the symptoms cause relatively minor harm to others. CD is classified as severe if many symptoms in excess of those required for the diagnosis are present, and the symptoms cause considerable harm to others. Moderate severity is intermediate between mild and severe.

Other specified/unspecified disruptive, impulse-control, and CD (subsyndromal disorder) applies to presentations in which symptoms characteristic of the disorders in this class are present and cause clinically significant distress or functional impairment, but do not meet full diagnostic criteria for any of the disorders in this class.

EPIDEMIOLOGY

The prevalence of ODD approximates 3% and in preadolescents is more common in males than females (1.4:1). One-year prevalence rates for IED and CD approximate 3% and 4%, respectively. For CD, prevalence rates rise from childhood to adolescence and are higher

Table 29-3 DSM-5 Diagnostic Criteria for Conduct Disorder

A. A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least 3 of the following 15 criteria in the past 12 mo from any of the categories below, with at least 1 criterion present in the past 6 mo:

Aggression to People and Animals
1. Often bullies, threatens, or intimidates others.
2. Often initiates physical fights.
3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).
4. Has been physically cruel to people.
5. Has been physically cruel to animals.
6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery).
7. Has forced someone into sexual activity.

Destruction of Property
8. Has deliberately engaged in fire setting with the intention of causing serious damage.
9. Has deliberately destroyed others' property (other than by fire setting).

Deceitfulness or Theft
10. Has broken into someone else's house, building, or car.
11. Often lies to obtain good or favors or to avoid obligations (i.e., "cons" others).
12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).

Serious Violations of Rules
13. Often stays out at night despite parental prohibitions, beginning before age 13 yr.
14. Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period.
15. Is often truant from school, beginning before age 13 yr.

B. The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning.

C. If the individual is age 18 yr or older, criteria are not met for antisocial personality disorder.

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among males than among females. The prevalence of these disorders has been shown to be higher in lower socioeconomic classes.

CLINICAL COURSE

Oppositional behavior can occur in all children and adolescents from time to time, particularly during the toddler and early teenage periods when autonomy and independence are normative developmental tasks. Oppositional behavior becomes a concern when it is intense, persistent, and pervasive and when it affects the child's social, family, and academic life.

Some of the earliest manifestations of oppositionality are stubbornness (3 yr), defiance and temper tantrums (4-5 yr), and argumentativeness (6 yr). Approximately 65% of children with ODD exit from the diagnosis after a 3 yr follow-up; earlier age at onset of oppositional symptoms conveys a poorer prognosis. ODD often precedes the development of CD (approximately 30% higher likelihood with comorbid attention-deficit/hyperactivity disorder [ADHD; see Chapter 33]), but also increases the risk for the development of depressive and anxiety disorders. The defiant and vindictive symptoms carry most of the risk for CD, whereas the angry-irritable mood symptoms carry most of the risk for anxiety and depression.

IED most commonly begins in late childhood or adolescence and appears to follow a chronic and persistent course over many years.

The onset of CD may occur as early as the preschool years, but the first significant symptoms usually emerge during the period from middle childhood through middle adolescence; onset is rare after age 16 yr. Symptoms of CD vary with age as the individual develops increased physical strength, cognitive abilities, and sexual maturity. Symptoms that emerge first tend to be less serious (e.g., lying), while those emerging later tend to be more severe (e.g., sexual or physical assault). Severe behaviors emerging at an early age convey a poor prognosis. In the majority of individuals, the disorder remits by adulthood; in a substantial fraction, antisocial personality disorder develops. Individuals with CD also are at risk for the later development of mood, anxiety, posttraumatic stress, impulse control, psychotic, somatic symptom, and substance-related disorders.

DIFFERENTIAL DIAGNOSIS

The disorders in this diagnostic class share a number of characteristics with each other as well as with disorders from other classes, and as such must be carefully differentiated. ODD can be distinguished from CD by the absence of physical aggression and destructiveness, and by the presence of angry/irritable mood; ODD can be distinguished from IED by the lack of serious aggression (physical assault). IED can be distinguished from CD by the lack of predatory aggression and other nonaggressive symptoms of CD.

The oppositionality seen in ODD must be distinguished from that seen in ADHD, depressive and bipolar disorders (including ***disruptive mood dysregulation disorder*** [see Chapter 26]), language disorders and intellectual disability, and social anxiety disorder. ODD should not be diagnosed if the behaviors occur exclusively during the course of a psychotic, substance use, depressive or bipolar disorder, and if criteria are met for disruptive mood dysregulation disorder. IED should not be diagnosed if the behavior can be better explained by a depressive, bipolar, disruptive mood dysregulation, psychotic, antisocial personality, or borderline personality disorder. The aggression seen in CD must be distinguished from that seen in ADHD and intermittent explosive, depressive, bipolar, and adjustment disorders.

COMORBIDITY

Rates of ODD are much higher in children with ADHD, which suggests shared temperamental risk factors. Depressive, anxiety, and substance use disorders are most commonly comorbid with IED. ADHD and ODD are both common in individuals with CD, and this comorbid presentation predicts worse outcomes. CD also may co-occur with anxiety, depressive, bipolar, learning, language, and substance-related disorders.

SEQUELAE

The disruptive, impulse-control, and CDs are associated with a wide range of psychiatric disorders in adulthood and with many other adverse outcomes, such as suicidal behavior, physical injury, delinquency and criminality, legal problems, substance use, unplanned pregnancy, social instability, marital failure, and academic and occupational underachievement.

ETIOLOGY AND RISK FACTORS

At the individual level, a number of neurobiologic markers (lower heart rate and skin conductance reactivity, reduced basal cortisol reactivity, abnormalities in the prefrontal cortex and amygdala, serotonergic abnormalities) have been variously associated with aggressive behavior disorders. Other biologic risk factors include pre-, peri-, and postnatal insults, cognitive and linguistic impairment (particularly language-based learning deficits); difficult temperamental characteristics (particularly negative affectivity, poor frustration tolerance, impulsivity); certain personality characteristics (novelty seeking, reduced harm avoidance, and reward dependence); and certain cognitive characteristics (cognitive rigidity, hostile attributions for ambiguous social cues).

At the family level, a consistently demonstrated risk factor is ineffective parenting. Parents of behaviorally disordered children have been found to be more inconsistent in their use of rules; to issue more and unclear commands; to be more likely to respond to their child on the basis of their mood rather than the child's behavior; to be less

Table 29-4 Anger/Aggression-Specific Screening Instruments

NAME OF INSTRUMENT	INFORMANT(S)	AGE RANGE	NUMBER OF ITEMS
Children's Aggression Scale	Parent, Teacher	5-18 y	33 (P), 23 (T)
Eyberg Child Behavior Inventory	Parent	2-16 y	36
Outburst Monitoring Scale	Parent	12-17 y	20
Sutter-Eyberg Student Behavior Inventory–Revised	Teacher	2-16 y	38

likely to monitor their children's whereabouts; and to be relatively unresponsive to their children's prosocial behavior. Complicating this association is the consistent finding that temperamentally difficult children are more likely to elicit negative parenting responses, including physical punishment, which can exacerbate anger and oppositionality in the child. Other important family-level influences include impaired parent–child attachment, child maltreatment (physical and sexual abuse), exposure to marital conflict and domestic violence, family poverty and crime, and family genetic liability (family histories of the disorders in this class as well as substance use, depressive, bipolar, schizophrenic, somatization, and personality disorders, as well as ADHD, have all been shown to be associated with the development of behavior disorders).

Peer-level influence on the development of behavior problems include peer rejection in childhood and antisocial peer groups, while neighborhood influences include social processes such as collective efficacy and social control.

PREVENTION

A number of studies have assessed the efficacy of programs targeted at the prevention of problem behaviors in children. One of the best researched programs is *Fast Track* (http://fasttrackproject.org), which is a multicomponent school-based intervention comprising a classroom curriculum targeted at conflict resolution and interpersonal skills, parent training, and interventions targeted at the school environment. Implemented in 1st through 10th grade, outcomes at grade 12 demonstrated that intervention decreased the lifetime prevalence of CD, ODD, and ADHD, but only among those at highest initial risk. Another well-researched program, the *Seattle Social Development Project* (http://ssdp-tip.org/SSDP/index.html), also is a multicomponent school-based intervention made up of teacher, parent, and student components targeting classroom management, interpersonal problem-solving skills, child behavior management skills, and academic support skills. Implemented in 1st through 6th grades, outcomes at age 18 yr demonstrated that the intervention decreased school misbehavior and disciplinary actions and violent delinquent acts, as well as demonstrating other favorable academic and behavioral outcomes.

SCREENING/CASE FINDING

The parents of children presenting in the primary care setting should be queried about angry mood or aggressive, defiant, or antisocial behavior as part of the routine clinical interview. A typical screening question would be "Does [name] have a lot of trouble controlling [his/her] anger or behavior?" A number of standardized broad-band screening instruments widely used in the primary care setting *(Pediatric Symptom Checklist*, *Strengths and Difficulties Questionnaire*, *Vanderbilt ADHD Diagnostic Rating Scales)* have items specific to angry mood and/or aggressive behavior, and as such can be used to focus the interview.

Stepped Management

Because of the high rates of response to brief interventions, including bibliotherapy (use of books and other printed material to address emotional or behavioral issues with or without psychotherapy) and other media interventions, clinical practice guidelines increasingly are advocating a stepped approach to the management of youth with behavior problems. The stepped approach involves active case finding and initial management in the primary care setting if appropriate, with referral to increasingly intensive and specialized interventions as indicated by the clinical status of the patient.

Early Intervention

Youth and/or their parents presenting in the primary care setting who self-report or respond affirmatively to queries about difficulties managing angry mood or aggressive or antisocial behavior should be afforded the opportunity to talk about the situation with the pediatric practitioner (in private with the older youth as indicated). By engaging in active listening (e.g., "I hear how you have been feeling. Tell me more about what happened to make you feel that way"), the pediatric practitioner can begin to assess the onset, duration, context, and severity of the symptoms, and associated dangerousness, distress, and functional impairment. In the absence of acute dangerousness (e.g., homicidality, assaultiveness, psychosis, substance abuse) and significant distress or functional impairment, the pediatric practitioner can schedule a follow-up appointment within 1-2 wk to conduct a behavior assessment. At this follow-up visit, to assist with decision making around appropriate level of care, a behavior screening instrument can be administered (Table 29-4) and additional risk factors (see "Etiology/Risk Factors" above) can be explored.

For mild symptoms (manageable by the parent and not functionally impairing) and in the absence of major risk factors (homicidality, assaultiveness, psychosis, substance use, child maltreatment, parental psychopathology, or severe family dysfunction), guided self-help (anticipatory guidance) with watchful waiting may suffice. Guided self-help can include provision of educational materials (pamphlets, books, DVDs, workbooks, Internet sites) that provide information to the youth about dealing with anger-provoking situations, and advice to parents about strengthening the parent–child relationship, effective parenting strategies, and the effects of adverse environmental exposures on the development of behavior problems. An example of a self-help program for parents is the *Positive Parenting Program* (Triple P; www.triplep.net), self-directed version, in which parents are provided with a workbook outlining a 10 wk self-guided program that includes readings and homework tasks. In a Cochrane review, media-based parenting interventions were found to have a moderate, if variable, effect on child behavior problems. If the problematic behavior is occurring predominantly at school, the parent can be advised about the role of a special education evaluation in the assessment and management of the child's misbehavior, including the development of a behavioral intervention plan. During the period of guided self-help, follow-up visits should be scheduled.

If a mental health clinician has been colocated or integrated into the primary care setting, all parents of young children (universal prevention) as well as the parents of youth with behavior problems (indicated prevention) can be provided with a brief version of parent training. For example, *Incredible Years* has a 6-8 session universal prevention version designed for the parents of 2-6 yr old children, and the Triple P program has a universal prevention communications system (print and electronic media) for the parents of youth from birth to the teenage years. For children with behavior problems, the Triple P program has seminar (three 90 min sessions), brief (15-30 min consultations), and primary care (four 20-30 min consultations) versions for the parents

of youth from birth to the teenage years that have been specifically designed for implementation in the primary care setting. These brief interventions focus on strengthening the parent–child relationship, identifying and monitoring the frequency of a problem behavior, and implementing and reviewing the effects of a targeted behavior plan.

Treatment

For youth who continue to have mild to moderate behavior problems after several weeks of guided self-help or a brief course of parent training, or who from the outset exhibit moderate to severe or comorbid aggression, homicidality, assaultiveness, psychosis, or substance use, or who have a history of child maltreatment or severe family dysfunction or psychopathology, assessment (see Chapter 20) and treatment (see Chapter 21) in the specialty mental health setting by a child-trained mental health clinician should be provided. The mental health clinician should be trained to the appropriate level of competence in the specific services the clinician is asked to provide.

The youth's problem behavior may predominantly occur at home, at school, with peers, or in the community, or it may be pervasive. If possible, interventions need to address each context specifically, rather than assuming generalizability of treatment. Thus, for behaviors mostly manifested in the home setting, parent training would be the treatment of choice, whereas for behaviors manifested mostly at school, consultation with the teacher and recommendation of a special education evaluation for service eligibility can be useful. When there are pervasive problems, including aggression toward peers, anger management training can be employed in addition to the other interventions.

Parent training has been extensively studied for the treatment of youth problem behavior. These programs, typically 10-15 wk in duration, focus on some combination of the following components: understanding social learning principles, developing a warm, supportive relationship with the child, encouraging child-directed interaction and play, providing a predictable, structured household environment, setting clear and simple household rules, consistently praising and materially rewarding positive behavior, consistently ignoring annoying behavior (followed by praise when the annoying behavior ceases), and consistently giving consequences (such as time out or loss of privileges) for dangerous or destructive behavior. Other important targets for parenting training include understanding developmentally appropriate moods and behavior, managing difficult temperamental characteristics, fostering the child's social and emotional development, and protecting the child from traumatic exposures. Several of these programs have demonstrated moderate to large effect sizes (0.5-0.8) in multiple randomized trials for short-term reductions in behavior problems. A Cochrane review found group parenting programs to be effective and cost-effective for improving child behavior problems (***standardized mean difference* [SMD]:** −0.53 to −0.72), parental mental health (SMD: −0.36), and parenting skills (SMD: −0.47 to −0.53) among parents of 3-12 yr old children. An earlier Cochrane review concluded that parenting programs can be effective in improving the emotional and behavioral adjustment of 0-3 yr old children.

Parenting programs with effect sizes exceeding 0.20 include *Parent–Child Interaction Therapy*, Triple P, *Helping the Noncompliant Child, Incredible Years,* and *Parent Management Training Oregon*. Parenting programs have been found to be effective in disadvantaged community settings as well as in DVD format (Incredible Years) and over the Internet (Triple P Online), and for some programs effects have been found to be durable over a number of years. Predictors of nonresponse to these interventions have included greater initial symptom severity as well as involvement of the parent with child protection services.

Adherence to the complete treatment regimen has limited the effectiveness of parent training programs. Estimates of premature termination are as high as 50-60%, and termination within 5 treatment sessions is not uncommon. Predictors of premature termination of parent training programs have included single parent status, low family income, low parental education levels, young maternal age, minority group status, and life stresses.

Anger management training programs for misbehaving youth also have been extensively studied. These programs, typically 16-20 weekly sessions in duration, focus on some combination of the following components: emotion awareness, perspective taking, anger management, social problem solving, and goal settings. Among the programs with effect sizes exceeding 0.20 include *Coping Power* and *Problem-Solving Skills Training*.

Multicomponent treatments for serious behavior disorders (such as CD) that target the broader social context include ***Multidimensional Treatment Foster Care*** and ***Multisystemic Therapy*.** Multidimensional Treatment Foster Care, delivered in a foster care setting for 6-9 mo, typically includes foster parent training and support; family therapy for biologic parents; youth anger management, social skills, and problem-solving training; school-based behavioral interventions and academic support; and psychiatric consultation and medication management, when needed. Multisystemic Therapy, typically lasting 3-5 mo, generally includes social competence training, parent and family skills training, medications, academic engagement and skills building, school interventions and peer mediation, mentoring and after-school programs, and involvement of child-serving agencies. These multicomponent programs have been designated probably efficacious because of the limited rigorous supporting evidence. Predictors of nonresponse to multicomponent treatments have included higher frequency of rule-breaking behavior and predatory aggression, higher psychopathy scores, and comorbid mood disorders.

Two classes of medication, stimulants and atypical antipsychotics, have strong evidence for the management of impulsive, anger-driven aggressive behavior, although neither are FDA approved for this indication. Resource limitations may necessitate provision of pharmacotherapy in the primary care setting; the safety and efficacy of this practice can be enhanced by regular consultation with a child and adolescent psychiatrist.

In a meta-analysis of pharmacologic treatments for aggression in youth, stimulants had a pooled mean effect size of 0.78. In a systematic review of placebo-controlled efficacy of stimulants for rating-scale assessed aggression, stimulants had a pooled effect size of 0.6 and a ***number needed to treat*** of 4. The doses of stimulants used for aggression are similar to those used for ADHD (average dose for methylphenidate: approximately 1 mg/kg/day).

Stimulants have been well-tolerated by children and adolescents, and all formulations have similar adverse event profiles. The most common (generally dose-dependent) side effects include headache, stomachache, appetite suppression, weight loss, blood pressure and heart rate increases, and delayed sleep onset. Rare side effects include irritability (particularly in younger children) and hallucinations. The cardiac effects of stimulants have been extensively studied, the most recent of which has demonstrated a hazard ratio for serious cardiovascular events of 0.75. Stimulants should be avoided in the presence of structural cardiac abnormalities and patient symptoms (syncope, palpitations, arrhythmias), or family history (e.g., unexplained sudden death) suggestive of cardiovascular disease, without cardiology consultation.

In studies of risperidone in youth with aggressive behavior, the mean effect size for aggression was 0.72. For maintenance treatment, mean effect size was 0.40. The usual daily dose of risperidone for aggression has been suggested to be 1.5-2 mg for children and 2-4 mg for adolescents. The initial starting doses have been suggested to be 0.25 mg for children and 0.5 mg for adolescents, titrating upward to the usual daily dose as indicated and tolerated.

Side effects of antipsychotic medications include sedation, extrapyramidal side effects, withdrawal dyskinesia, hyperprolactinemia, elevated liver transaminases, weight gain, cardiovascular effects, and metabolic abnormalities (elevated glucose and lipids). Ziprasidone is associated with the lowest weight gain followed by aripiprazole, quetiapine, risperidone, and olanzapine. However, ziprasidone has not been recommended for use in children and adolescents due to lack of efficacy data. The excessive weight gain associated with olanzapine precludes its choice as a 1st-line agent.

The side effects of antipsychotic medications warrant close monitoring: abnormal movements should be monitored periodically using a standardized methodology (such as the Abnormal Involuntary

Movement Scale [AIMS] checklist); blood pressure, body mass index and fasting glucose and lipids should be checked at baseline and at regular intervals thereafter, according to standard guidelines. Consideration of weight management interventions and increased monitoring of blood glucose and lipid levels should be implemented if weight gain exceeds 90th percentile body mass index for age, or a change of 5 body mass index units occurs in youths who were obese at the beginning of treatment. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Medication trials should be systematic, and the duration of trials should be sufficient (generally 6-8 wk) to determine the agent's effectiveness. The immediate goal of treatment is to achieve at least a 50% reduction in aggressive symptoms as assessed by a standardized rating scale (see Table 29-4). A second medication of the same class can be considered if there is insufficient evidence of response to the maximal tolerated dose by 8 wk. Care should be taken to avoid unnecessary polypharmacy, in part by discontinuing agents that have not demonstrated significant benefit. Discontinuation of the medication should be considered after a symptom-free interval.

LEVEL OF CARE

Most children and adolescents with a behavior disorder can be safely and effectively treated in the outpatient setting. Youths with intractable CD may benefit from residential or specialized foster care treatment, where more intensive treatments can be provided.

Bibliography is available at Expert Consult.

29.1 Age-Specific Behavioral Disturbances

Lovern R. Moseley, Heather J. Walter, and David R. DeMaso

INFANCY AND TODDLERHOOD

Temper tantrums and breath-holding spells are common during the first years of life and are age-typical expressions of frustration or anger. Parents who respond to toddler defiance with punitive anger can reinforce oppositional behavior. Parents are best advised to attempt to avert defiance by giving the child choices; once the child has begun a tantrum, the child can be given a timeout. It is useful to advise parents to tell their child, once he or she is calm, that the reasons for frustration are understandable, but that defiance is not acceptable.

Parents are occasionally concerned about **breath-holding spells.** Although some children hold their breath until they lose consciousness, sometimes leading to a brief seizure, there is no increased risk of seizure disorders in children who have had a seizure during a breath-holding spell. Parents are best advised to ignore breath holding once it has started. Without sufficient reinforcement, breath holding generally disappears.

Subtypes of breath holding spells include cyanotic, pallid, or mixed episodes. Cyanotic are the dominant type and may include a brief loss of consciousness and a very brief tonic-clonic seizure. Pallid spells may be similar to vasovagal related syncopal events in older children and initiated from similar stimuli (see Chapter 69). Iron deficiency with or without anemia may be present and some children with breath-holding spells respond to iron therapy. Medical conditions to consider should include seizures, Chiari crisis, dysautonomia, cardiac arrhythmias, and central nervous system lesions.

The first key to the office management of temper tantrums and breath-holding spells is to help parents to intercede before the child is highly distressed. The pediatrician should advise parents to intercede early in defiant behavior by calmly placing the child in timeout for a period of time approximating 1 min for each year of age. When breath holding does not respond to the parent's coaching or is accompanied by head banging or high levels of aggression, referral for a mental health evaluation is indicated.

If behavioral measures such as timeout fail, pediatricians must assess how the parents handle anger before making further recommendations about how to approach the child. Children can be frightened by the intensity of their own angry feelings and by angry feelings they arouse in their parents. Parents should model the anger control that they wish their children to exhibit. Some parents are unable to see that they lose control themselves; their own angry behavior does not help their children to internalize controls. Advising parents to calmly provide simple choices will help the child to feel more in control and to develop a sense of autonomy. Providing the child with options also typically helps reduce the child's feelings of anger and shame, which can later have adverse effects on social and emotional development.

Lying can be used by 2-4 yr olds as a method of playing with the language. By observing the reactions of parents, preschoolers learn about expectations for honesty in communication. Lying can also be a form of fantasy for children, who describe things as they wish them to be rather than as they are. To avoid an unpleasant confrontation, a child who has not done something that a parent wanted may say that it has been done. The child's sense of time and reason does not permit the realization that this only postpones a confrontation.

CHILDHOOD AND ADOLESCENCE

Lying

In **school-age children,** lying is generally an effort to cover up something that the child does not want to accept in his or her own behavior. The lie is invented to achieve a temporary good feeling and to protect the child against a loss of self-esteem. Habitual lying also can be promoted by poor adult modeling. Many adolescents lie to avoid adults' disapproval; lying may be used as a method of rebellion. Chronic lying can occur in combination with several other antisocial behaviors and is a sign of underlying psychopathology or family dysfunction.

Regardless of age or developmental level, when lying becomes a common way of managing conflict, intervention is warranted. Initially, the parents should confront the child to give a clear message of what is acceptable. Sensitivity and support combined with limit-setting are necessary for a successful intervention. If this behavior cannot be resolved through the parents' understanding of the situation and the child's understanding that lying is not a reasonable alternative, a mental health evaluation is indicated.

Stealing

Many children **steal** something at some point in their lives. When preschoolers and school-age children steal more than once or twice, the behavior may be a response to stressful environmental circumstances. Stealing can be an expression of anger or revenge for perceived frustrations with parents. In some instances, stealing becomes 1 way the child or adolescent can manipulate and attempt to control the child's or adolescent's world. Stealing also can be learned from adults.

It is important for parents to help the child undo the theft by returning the stolen articles or by rendering their equivalent either in money that the child can earn or in services. When stealing is part of a pattern of conduct problems, referral for a mental health evaluation is warranted.

Truancy and Running Away

Truancy and running away are never developmentally appropriate. Truancy may represent disorganization within the home, caretaking needs of younger siblings, developing conduct problems, or emotional problems including depression or anxiety. Whereas younger children may threaten to run away out of frustration or a desire to get back at parents, older children who run away are almost always expressing a serious underlying problem within themselves or their family, including violence, abuse, and neglect. Adolescent runaways are at high risk for substance abuse, unsafe sexual activity, and other risk-taking behaviors. Youth exhibiting truancy or running away should be referred for a mental health evaluation.

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Fire Setting

Although interest in fire is common in early childhood, unsupervised **fire setting** is always inappropriate because of its extreme dangerousness. School-age children may set fires accidentally, or because of curiosity or latent hostility. These young children usually set fires by themselves within their homes. In adolescence, fire setting can be a sign of delinquency or a signal of traumatic experiences. Fire setting always requires intervention by a mental health clinician. A thorough mental health evaluation is necessary to plan the components of a successful treatment program.

Aggression and Bullying

See also Chapter 39.1.

Aggression and bullying are serious symptoms and are associated with significant morbidity and mortality. Children might not grow out of this behavior; early intervention is indicated for persistent aggressive behavior. Aggressive tendencies are heritable, although environmental factors can promote aggression in susceptible children. Both enduring and temporary stressors affecting a family can increase aggressive behavior in children. Aggression in childhood is correlated with a chaotic and impoverished family home that could be the result of chronic unemployment, family discord, exposure to community and domestic violence, criminality and psychiatric disorders as well as births to teenage mothers and those with limited resources and support. Boys are almost universally reported to be more aggressive than girls. A difficult temperament and later aggressiveness are related, although there is evidence that these children elicit punitive caregiving within the family environment, setting up a cycle of increasing aggression. Aggressive children often misperceive social cues and react with inappropriate hostility toward peers and parents.

Clinically, it is important to differentiate the causes and motives for childhood aggression. Intentional aggression may be primarily instrumental, to achieve an end, primarily hostile, to inflict physical or psychologic pain, or primarily angry and impulsive. Children who are callous and not empathetic and who are often aggressive require mental health intervention. These children are at high risk for suspension from school and eventual school failure. Learning disorders are common, and aggressive children should be screened. Other forms of psychopathology may be present; in particular, aggressive children might have ADHD, ODD, IED, CD, and/or disruptive mood dysregulation disorder.

Aggressive behavior in boys is relatively consistent from the preschool period through adolescence; a boy with a high level of aggressive behavior at 3-6 yr of age has a high probability of carrying this behavior into adolescence, especially without effective intervention. The developmental progression of aggression among girls is less-well studied. There are fewer girls with physically aggressive behavior in early childhood; interpersonal coercive behavior, especially in peer relationships, is not uncommon among girls and may be related to the development of more physical aggression in adolescence (fighting, stealing).

Children exposed to aggressive models on television, in video games, or in play show more aggressive behavior compared with children not exposed to these models. Parents' anger and aggressive or harsh punishment model behavior that children might imitate when they are physically or psychologically hurt. Parents' abuse may be transmitted to the next generation by several modes: children imitate aggression that they have witnessed, abuse can cause brain injury (which itself predisposes the child to violence), and internalized rage often results from abuse.

Cutting and Other Self-Injurious Behaviors

Cutting and other self-injurious behaviors have been occurring in increased rates among children as young as age 11 yr through adolescence. Rates are higher in girls than boys, but cutting and other self-injurious behaviors do occur in both. The behavior involves the deliberate carving, cutting, scratching, or burning of the skin with fingernails or other objects sharp enough to cause injury (razors, scissors, broken glass, hard plastic, knives, staples, fire). Oftentimes the behavior does not occur with the intention of suicide but can be associated with it and can unintentionally result in significant harm or even death. Youth often report that they have friends who "cut" and have reported that it is a way to feel better and so they have tried it as well. There is increased access to message boards and websites on the internet where youth have shared their stories of self-injury; these postings may have contributed to experimentation. The behavior is usually triggered by psychological distress and is also correlated with depression, anxiety, peer victimization, low self-esteem, substance abuse, eating disorders, impulsivity, delinquency, and neglectful or highly punitive parenting practices, as well as a history of physical or sexual abuse. Parents should be advised to monitor their children's media access and be aware of their peer group. Learning that their child has been engaging in this behavior can be very frightening for parents as they are unsure of what to do or the reasons why their child is engaging in this behavior. It is imperative that they seek mental healthcare for their child.

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Chapter 30

Autism Spectrum Disorder

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The essential features of ***autism spectrum disorder*** **(ASD)** are persistent impairment in reciprocal social communication and interaction, and restricted, repetitive patterns of behavior or interests (Table 30-1). ASD encompasses disorders previously referred to as early infantile autism, childhood autism, Kanner autism, high functioning autism, atypical autism, Asperger disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. These specific diagnoses are not reliably distinguishable or consistently applied across different treatment centers. Individuals diagnosed with one of these previous diagnoses should be given the diagnosis of ASD.

DESCRIPTION

Social Communication and Interaction Deficits

Aberrant development of social communication and impaired ability to engage in reciprocal social interactions are hallmark symptoms of ASD. Deficits in social–emotional reciprocity (the ability to engage with others and share thoughts and feelings) are evident early in children with ASD who show little or no initiation of social interaction and little or no sharing of emotions or imitative behaviors. Children may present with abnormal social approach, failure of back-and-forth conversation, and difficulties processing and responding to complex social cues. Infants <6 mo of age may or may not demonstrate features typical of ASD.

Impairments in nonverbal social communication are manifested by absent, reduced, or atypical use of eye contact, gestures, facial expressions, body orientation, or speech intonation. Youth may fail to smile, orient to name, or use gestures to point or show. Abnormal eye contact with failure to follow someone's pointing or eye gaze is characteristic. In patients with fluent language, poorly integrated verbal and nonverbal communication may result in odd, wooden, or exaggerated body language during social interactions (Table 30-2).

Children with ASD may demonstrate absent, reduced, or atypical social interest, manifested by rejection of others, passivity, or inappropriate approaches that seem aggressive and disruptive. In young children, lack of shared, age-appropriate flexible pretend and symbolic play is seen, with children often insistent on playing by very fixed rules.

Table 30-1 DSM-5 Diagnostic Criteria for Autism Spectrum Disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
   1. Deficits in social-emotional reciprocity.
   2. Deficits in nonverbal communicative behaviors used for social interaction.
   3. Deficits in developing, maintaining, and understanding relationships.
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
   1. Stereotyped or repetitive motor movements, use of objects, or speech.
   2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior.
   3. Highly restricted, fixated interests that are abnormal in intensity or focus.
   4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment.
C. Symptoms must be present in the early developmental period (may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, pp. 50–51.

Children with ASD may prefer solitary activities and interactions with much younger or older people. A desire to establish friendships without complete understanding of the components of friendship (one-sided friendships based solely on shared special interests) can be seen in some children, while an absence of interest in peers may be seen in others. Some youth show deficits in empathy and understanding what another person might be thinking.

Restricted and Repetitive Patterns

The second core characteristic of ASD is restricted, repetitive patterns of behavior, interests, or activities. These include stereotyped movements (hand flapping, finger flicking), repetitive use of objects (spinning coins, lining up toys), repetitive and abnormal speech (echolalia [delayed or immediate parroting of heard words], pronoun reversal, nonsense rhyming, idiosyncratic phrases); insistence on sameness and inflexible adherence to routines or ritualized patterns of behavior (distress at small changes, insistence on adherence to rules, rituals and routines, rigid thinking, repetitive questioning); highly restricted and fixed interests of abnormal intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests); and hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., extreme responses to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects, apparent indifference to pain, heat, or cold) (see Table 30-2).

The symptoms of ASD must be present in the early developmental period, must cause clinically significant functional impairment, and must not be better explained by intellectual disability or global developmental delay.

Severity

The severity of ASD is based on evaluations of impairment caused by both deficits in social communication and in restricted, repetitive behaviors. Within these 2 categories, severity is rated levels 1-3, with level 3 implying most severe deficit with a need for the most substantial support (Table 30-3).

Specifiers/Associated Features

ASD is specified as occurring with or without accompanying intellectual and language impairment, and associated with a known medical or genetic condition, environmental factor, or other neurodevelopmental, mental, or behavioral disorder. Children with ASD vary in their verbal abilities. Language level in individuals with ASD "without accompanying language impairment" may speak in full sentences or have fluent speech. ASD specified "with accompanying language impairment" can range from nonverbal speech to single word or phrase speech (capable of imitating songs, rhymes, or television commercials). Receptive language may lag behind expressive language development in ASD. Early abnormal language concerns include absent babbling or gestures by 12 mo, absent single words by 16 mo, and absent 2-word purposeful phrases by 24 mo, as well as any loss of language or social skills at any time. Language, if present, is often one-sided, lacking social reciprocity, idiosyncratic, repetitive, and used to request or label rather than comment, share feelings, or converse.

Intellectual functioning can vary from intellectual impairment (intellectual developmental disorder) to superior intellectual functioning in select areas (splinter skills, savant behavior) ("with or without accompanying intellectual impairment"). Some children show typical development in certain skills and can even show areas of strength in specific areas (puzzles, art, or music). The intellectual profile of an individual may be uneven, with gaps in verbal and nonverbal learning ability and intellectual and adaptive functional skills.

Motor deficits, including odd gait, clumsiness, dyspraxia, and other abnormal motor signs (e.g., walking on tiptoes) are often present. Stereotypic movement or tic disorders may go unnoticed given aforementioned restricted behavioral patterns. Self-injury (head banging, biting the wrist) may occur. Some youth develop catatonic-like motor behavior (slowing and "freezing" mid-action) though most do not go onto develop a full episode with mutism, posturing, grimacing, and waxy flexibility.

Epilepsy is a common comorbidity, and any type of seizure may be observed in ASD. Epilepsy is associated with greater intellectual disability and lower verbal ability. Mutations in the *BCKD-kinase* gene is a syndrome associated with autism, epilepsy and intellectual disability. Youth with ASD are also prone to anxiety and depression as well as abnormalities in attention and hyperactivity.

Language, social, or a mixed pattern of regression may occur in the first 1-2 years. In some, a diagnosis of Landau Kleffner syndrome is identified; in others regression may be due to the onset of epilepsy or abnormal EEG findings in the absence of clinical seizures. Levetiracetam also causes a reversible autistic regression syndrome.

EPIDEMIOLOGY

The Centers for Disease Control and Prevention estimates the prevalence of ASD in the United States as 11.3/1,000 (prior estimated prevalence range: 0.7/10,000 to 72.6/10,000 across 36 earlier surveys). Recent higher reported rates of the disorder appear to be related to differences in diagnostic criteria and practices, inclusion of subthreshold cases, age of children screened, and location of the study. The male : female ratio is estimated to be 4 : 1. The incidence of ASD may be higher in immigrant populations.

ETIOLOGY/RISK FACTORS

Genetic and Familial Factors

There is a high recurrence risk (2-19%) for ASD among siblings, as well as a higher concordance rate (37-90%) in twin studies. Closer spacing of pregnancies, advanced maternal or paternal age, and extremely premature birth (<26 wk gestational age) as well as family members with learning problems, psychiatric disorders, and social disability, have been identified as risk factors. Multiple genes are viewed as involved in autism with studies supporting a role for both common (>5% of general population) and rare genetic variations contributing to the disorder. For example, Timothy syndrome, characterized by

Table 30-2 Signs and Symptoms of Possible Autism in Preschool Children (or Equivalent Mental Age)

Social interaction and reciprocal communication behaviors

Spoken language
- Language delay (in babble or words—for example, using fewer than 10 words by the age of 2 yr)
- Regression in or loss of use of speech
- Spoken language (if present) may include unusual features, such as: vocalizations that are not speech-like; odd or flat intonation; frequent repetition of set words and phrases (echolalia); reference to self by name or "you" or "she" or "he" beyond age 3 yr
- Reduced and/or infrequent use of language for communication—for example, use of single words, although able to speak in sentences

Responding to others
- Absent or delayed response to name being called, despite normal hearing
- Reduced or absent responsive social smiling
- Reduced or absent responsiveness to other people's facial expressions or feelings
- Unusually negative response to the requests of others ("demand avoidance" behavior)
- Rejection of cuddles initiated by parent or carer, although the child himself or herself may initiate cuddles

Interacting with others
- Reduced or absent awareness of personal space, or unusually intolerant of people entering their personal space
- Reduced or absent social interest in others, including children of his or her own age—may reject others; if interested in others, he or she may approach others inappropriately, seeming to be aggressive or disruptive
- Reduced or absent imitation of others' actions
- Reduced or absent initiation of social play with others, plays alone
- Reduced or absent enjoyment of situations that most children like—for example, birthday parties
- Reduced or absent sharing of enjoyment

Eye contact, pointing, and other gestures
- Reduced or absent use of gestures and facial expressions to communicate (although may place an adult's hand on objects)
- Reduced and poorly integrated gestures, facial expressions, body orientation, eye contact (looking at people's eyes when speaking), and speech used in social communication
- Reduced or absent social use of eye contact (assuming adequate vision)
- Reduced or absent "joint attention" (when 1 person alerts another to something by means of gazing, finger pointing, or other verbal or nonverbal indication for the purpose of sharing interest). This would be evident in the child from lack of:
  - Gaze switching
  - Following a point (looking where the other person points to—may look at hand)
  - Using pointing at or showing objects to share interest

Ideas and imagination
- Reduced or absent imagination and variety of pretend play

Unusual or restricted interests and/or rigid and repetitive behaviors
- Repetitive "stereotypical" movements such as hand flapping; body rocking while standing; spinning; finger flicking
- Repetitive or stereotyped play—for example, opening and closing doors
- Over focused or unusual interests
- Excessive insistence on following own agenda
- Extremes of emotional reactivity to change or new situations; insistence on things being "the same"
- Over-reaction or under-reaction to sensory stimuli, such as textures, sounds, smells
- Excessive reaction to the taste, smell, texture, or appearance of food, or having extreme food fads

From Baird G, Douglas HR, Murphy MS: Recognizing and diagnosing autism in children and young people: summary of NICE guidance. BMJ 343:d6360, 2011, Box 1, p. 901.

Table 30-3 DSM-5 Severity Levels for Autism Spectrum Disorder

SEVERITY LEVEL	SOCIAL COMMUNICATION	RESTRICTED, REPETITIVE BEHAVIORS
Level 3 "Requiring very substantial support"	Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. *For example*, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches	Inflexibility of behavior, extreme difficulty coping with change, or other restricted/repetitive behaviors markedly interfere with functioning in all spheres. Great distress/difficulty changing focus or action.
Level 2 "Requiring substantial support"	Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. *For example*, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd nonverbal communication	Inflexibility of behavior, difficulty coping with change, or other restricted/repetitive behaviors appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 "Requiring support"	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social interactions, and clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions. *For example*, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful	Inflexibility of behavior causes significant interference with functioning in one or more contexts. Difficulty switching between activities. Problems of organization and planning hamper independence.

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association, p. 52.

dysmorphic facies, congenital heart disease, prolonged QT interval, and developmental delay, is caused by a mutation in the L-type calcium channel $Ca_v1.2$ and also has ASD features. In addition, ASD is associated with multiple abnormalities of mitochondrial DNA.

Neurobiologic Factors

The high rates of seizure disorder suggest a role for neurobiologic factors in ASD. The number of different areas of the brain affected by autism suggests a diverse and widely distributed set of affected neural systems. Postmortem studies reveal various abnormalities, particularly within the limbic system. Structural MRI reveals an overall increase of brain size, and diffusion tensor imaging studies suggest aberrations in white matter tract development. Functional MRI identifies difficulties in tasks involving social and affective judgments and differences in the processing of face and nonface stimuli. Poor neuronal connectivity in various brain regions also is reported. Elevated peripheral levels of serotonin are a replicated neurochemical finding of unclear significance. A role for dopamine is suggested given the problems with overactivity and stereotyped mannerisms and the positive response of such behaviors to antipsychotic medications.

Neuropsychological correlates of ASD include impairments in executive functioning (e.g., simultaneously engaging in multiple tasks), weak central coherence (integrating information into meaningful wholes), and deficits in theory of mind tasks (taking the perspective of another person). The empathizing-systemizing personality theory describes the autistic mind in terms of impaired empathy alongside intact or even superior systemizing (the drive to analyze or construct systems).

Environmental exposures early in the 1st trimester of pregnancy that have been linked to ASD in epidemiologic studies include thalidomide, misoprostol, rubella infection, valproic acid, and the organophosphate insecticide chlorpyrifos. Prenatal folic acid supplementation may reduce the risk of ASD. There has been concern about vaccines as a postnatal environmental cause for ASD. The focus has been on either the measles-mumps-rubella vaccine or the thimerosal preservative as a causative factor. All available data have not supported either hypothesis.

Neuropathology Factors

The head circumference in ASD is normal or slightly smaller than normal at birth until 2 mo of age. Afterward, children with ASD show an abnormally rapid increase in head circumference from 6-14 mo of age, increased brain volume in 2-4 yr olds, increased volume of the cerebellum, cerebrum, and amygdala, and marked abnormal growth in the frontal, temporal, cerebellar, and limbic regions of the brain. Early, accelerated brain growth during the first several years of life is followed by abnormally slow or arrested growth, resulting in areas of underdeveloped and abnormal circuitry in parts of the brain. Areas of the brain responsible for higher-order cognitive, language, emotional, and social functions are most affected.

CLINICAL COURSE

ASD symptoms are typically recognized during the 2nd yr of life but can been seen earlier than 12 mo if developmental delays are severe. Initial symptoms most frequently involve delayed language accompanied by lack of social interest or odd play patterns. During the 2nd yr, odd and repetitive behaviors and the absence of typical play become more apparent. It is typical for parents to report that there was no period of normal development or that there was a history of unusual behaviors. Less commonly (in 20-40% of cases), a period of apparently normal development is reported before a loss of skills. In adolescence, a small number of individuals with ASD make marked developmental gains; another subgroup will deteriorate (self-injury, aggression).

DIFFERENTIAL DIAGNOSIS

ASD must be differentiated from communication disorders (especially social communication disorder), intellectual disability (see Chapter 36), sensory impairments (especially deafness), reactive attachment disorder, obsessive-compulsive and related disorders, anxiety disorders (see Chapter 25) including selective mutism, schizophrenia (see Chapter 31), stereotypic movement disorder (see Chapter 24.2), attention-deficit/hyperactivity disorder (ADHD), and Rett syndrome (see Chapter 599).

Autistic-like behavior has been noted in many metabolic syndromic and genetic disorders. These include adenylosuccinate lyase deficiency, PKU, glucose-6-phosphatase deficiency, adenosine deaminase deficiency, succinic semialdehyde dehydrogenase deficiency, disorders of creatine transport and metabolism, propionic acidemia, MELAS and other mitochondrial disorders, Danan disease, tuberous sclerosia, fragile X syndrome, Smith Lemli Opitz syndrome, myotonic dystrophy, dystrophinopathies, Cohen and Myhre syndromes, muscle-eye-brain disease, and various genetic microdeletions or duplications, including deletion 22q11.2.

Developmental language disorders and intellectual disability have an impact on socialization and may be mistaken for ASD. The distinction is particularly difficult in preschool children. When an individual shows impairment in social communication and social interactions but without abnormal nonverbal communication or restricted, repetitive patterns of behavior, a diagnosis of *social communication disorder* should be considered. If there is no apparent discrepancy between the level of social-communicative skills and other intellectual skills, a diagnosis of intellectual disability should be considered.

Children with reactive attachment disorder (typically occurring in the face of emotional neglect; see Chapter 40) may exhibit deficits in attachment and therefore inappropriate social responsivity, but these usually improve substantially if adequate caretaking is provided. Obsessive-compulsive disorder (see Chapter 25) has a later onset than ASD, is not typically associated with social and communicative impairments, and is characterized by repetitive patterns of behavior that are ego dystonic. Symptoms that characterize anxiety disorders, such as excessive worry, the need for reassurance, the inability to relax, and feelings of self-consciousness are also seen in ASD, particularly among higher functioning individuals. However, the 2 conditions can be differentiated by the prominent social and communicative impairments seen in ASD but not anxiety disorders, and the developed social insight of children with anxiety disorders, which is not seen in ASD. Differentiating childhood schizophrenia from autism can be difficult, as both are characterized by social impairments and odd patterns of thinking; florid delusions and hallucinations are rarely seen in autism.

Motor stereotypies are among the diagnostic criteria for ASD, so an additional diagnosis of stereotypic movement disorder should not be given if the movements are better explained by ASD. However when stereotypies cause self-injury and become a focus of treatment, both diagnoses may be appropriate. Similarly, an additional diagnosis of ADHD should only be given when attentional difficulties or hyperactivity exceed those typically observed in children of comparable mental age.

During the regressive phase of Rett syndrome (ages 1-4 yr), disruptive social interaction may be observed and affected children may meet diagnostic criteria for ASD. After this phase, social communication improves and an additional diagnosis of ASD should be considered only if all criteria for ASD are met.

COMORBIDITIES

Given difficulties in communication (mutism) and cognitive impairment, issues of comorbidity in ASD can be quite complex. The process of diagnostic overshadowing (the tendency to fail to diagnosis other comorbid conditions when a more noticeable condition is present) may occur. Most studies do show increased rates of anxiety and attentional disorders.

In most epidemiologically based samples of persons with autistic disorder, approximately 50% exhibit severe or profound intellectual disability, 35% exhibit mild to moderate intellectual disability, and the remaining 20% have IQs in the normal range. Verbal skills are typically more impaired than nonverbal skills. Intellectual impairment is not an essential diagnostic feature of autism; it is necessary and important for the diagnosis of intellectual disability to be made.

Neurologic comorbidities include epilepsy, sleep dysfunction, motor delay, dyspraxia, incoordination, and gait disturbances.

A range of behavioral difficulties can be observed in ASD including hyperactivity, obsessive compulsive phenomena, self-injury, aggression, stereotypies, tics, and affective symptoms. The issue of whether these qualify as additional disorders is complex. Affective symptoms are frequently observed and include lability, inappropriate affective responses, anxiety, and depression. Impairments in emotion regulation processes can lead to under- and overreactivity. Overt clinical depression is sometimes observed, and this may be particularly true for adolescents. Case reports and case series suggest possible associations with bipolar disorders and tic disorders. Attentional difficulties (ADHD) are also frequent in autism, reflecting cognitive, language, and social problems.

SEQUELAE

Most persons with ASD remain within the spectrum as adults, and regardless of their intellectual functioning, continue to experience problems with independent living, employment, social relationships, and mental health. Some children, especially those with communication abilities, can grow up to live self-sufficient lives in the community with employment. Others remain dependent on their family or require placement in facilities outside the home. Because early, intensive therapy can improve language and social function, delayed diagnosis can lead to a poorer outcome. A better prognosis is associated with higher intelligence, functional speech, and less-bizarre symptoms and behavior. The symptom profile for some children might change as they grow older, and risk of seizures or self-injurious behavior becomes more common. ASD is not a degenerative disorder and it is typical for learning and compensation to continue throughout life.

SCREENING/CASE FINDING

All children should receive autism-specific screening at 18 and 24 mo of age, in addition to broad developmental screening at 9, 18, and 24 mo (Fig. 30-1). In some instances screening may be relevant to older children, such as those who are more intellectually able and whose

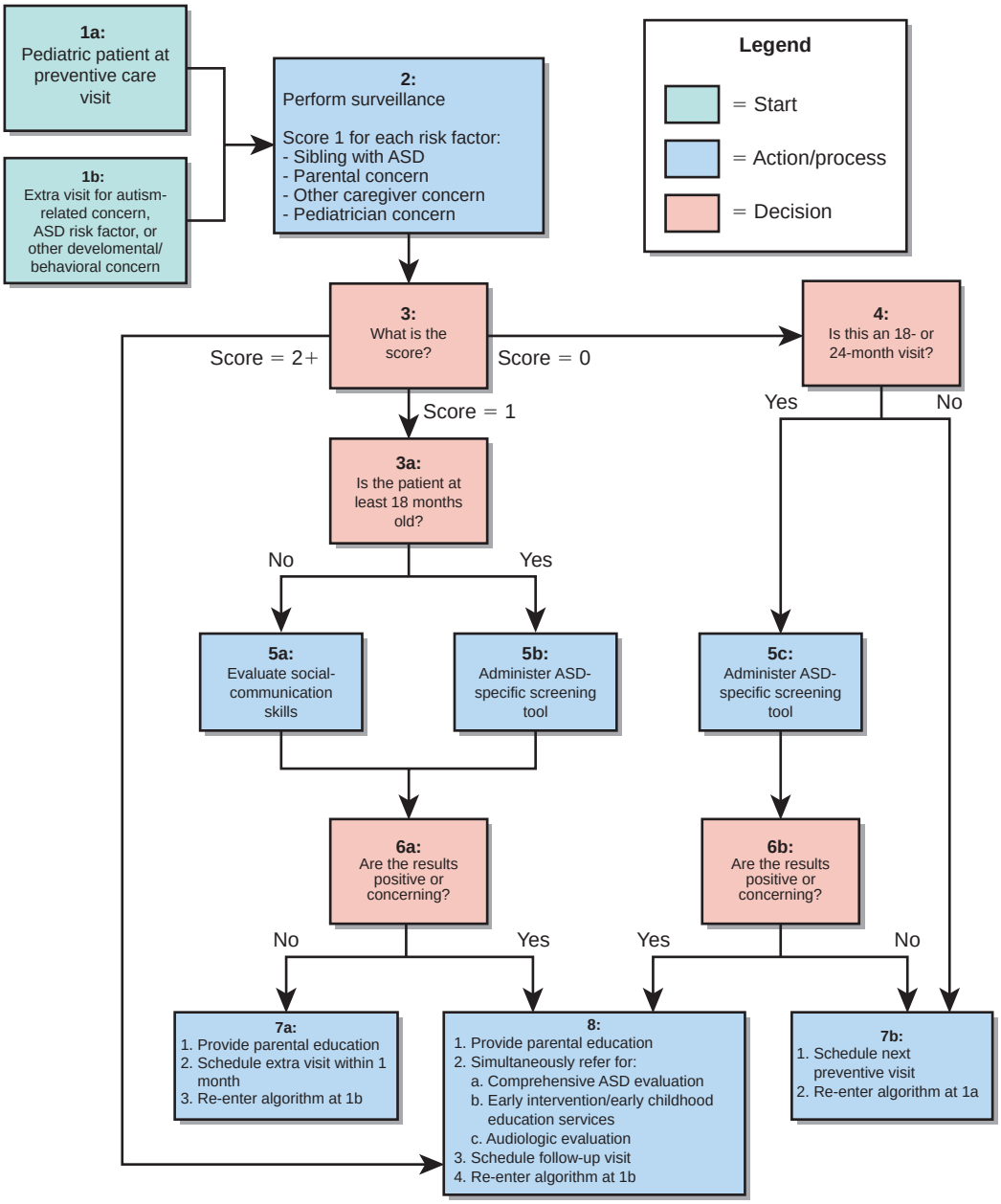

Figure 30-1 Surveillance and screening algorithm: autism spectrum disorders (ASDs). *(From Plauche Johnson C, Myers SM, Council on Children with Disabilities: Identification and evaluation of children with autism spectrum disorders, Pediatrics 120:1183–1215, 2007.)*

1a: Pediatric patient at preventive care visit

1a - Developmental concerns, including those about social skill deficits should be included as one of several health topics addressed at each pediatric preventive care visit through the first 5 years of life. *(Go to step 2)*

1b: Extra visit for autism-related concern, asd risk factor, or other developmental/ behavioral concern

1b - At the parents' request, or when a concern is identified in a previous visit, a child may be scheduled for a "problem-targeted" clinic visit because of concerns about ASD. Parent concerns may be based on observed behaviors, social or language deficits, issues raised by other caregivers, or heightened anxiety produced by ASD coverage in the media. *(Go to step 2)*

2:
Perform surveillance

Score 1 for each risk factor:
- Sibling with ASD
- Parental concern
- Other caregiver concern
- Pediatrician concern

2 - Developmental surveillance is a flexible, longitudinal, continuous, and cumulative process whereby health care professionals identify children who may have developmental problems. There are 5 components of developmental surveillance: eliciting and attending to the parents' concerns about their child's development, documenting and maintaining a developmental history, making accurate observations of the child, identifying the risk and protective factors, and maintaining an accurate record and documenting the process and findings. The concerns of parents, other caregivers, and pediatricians all should be included in determining whether surveillance suggests that the child may be at risk of an ASD. In addition, younger siblings of children with an ASD should also be considered at risk, because they are 10 times more likely to develop symptoms of an ASD than children without a sibling with an ASD. Scoring risk factors will help determine the next steps, *(Go to step 3)*

For more information on developmental surveillance, see "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (Pediatrics 2006; 118:405-420).

3: What is the score?

3 - Scoring risk factors:
- If the child does not have a sibling with an ASD and there are no concerns from the parents, other caregivers, or pediatrician: Score = 0 *(Go to step 4)*
- If the child has only 1 risk factor, either a sibling with ASD or the concern of a parent, caregiver, or pediatrician: Score = 1 *(Go to step 3a)*
- If the child has 2 or more risk factors: Score = 2+ *(Go to step 8)*

3a: Is the patient at least 18 months old?

3a -
- If the child's age is <18 months, *(Go to step 5a)*
- If the child's age is ≥18 months, *(Go to step 5b)*

4: Is this an 18-or 24-month visit?

4 - In the absence of established risk factors and parental/provider concerns (score = 0), a level-1 ASD-specific tool should be administered at the 18- and 24-month visits. *(Go to step 5c)* If this is not an 18- or 24-month visit, *(Go to step 7b)*.

Note: In the AAP policy, "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening", a general developmental screen is recommended at the 9-, 18-, and 24-or 30-month visits and an ASD screening is recommended at the 18-month visit. This clinical report also recommends an ASD screening at the 24-month visit to identify children who may regress after 18 months of age.

5a: Evaluate social-communication skills

5a - If the child's age is <18 months, the pediatrician should use a tool that specifically addresses the clinical characteristics of ASDs, such as those that target social-communication skills. *(Go to step 6a)*

5b: Administer ASD-specific screening tool

5b - If the child's age is ≥18 months, the pediatrician should use an ASD-specific screening tool. *(Go to step 6a)*

5c: Administer ASD-specific screening tool

5c - For all children ages 18 or 24 months, (regardless of risk factors), the pediatrician should use an ASD-specific screening tool. *(Go to step 6b)*

AAP-recommended strategies for using ASD screening tools: "Autism: Caring for Children with Autism Spectrum Disorders: A Resource Toolkit for Clinicians" (in press)*

6a: Are the results positive or concerning?

6a - When the result of the screening is *negative*, *Go to step 7a*

When the result of the screening is *positive*, *Go to step 8*

6b: Are the results positive or concerning?

6b - When the result of the ASD screening (at 18- and 24-month visits) is *negative*, *Go to step 7b*

When the result of the ASD screening (at 18- and 24-month visits) is *positive*, *Go to step 8*

7a:
1. Provide parental education
2. Schedule extra visit within 1 month
3. Re-enter algorithm at 1b

7a - If the child demonstrates risk but has a negative screening result, information about ASDs should be provided to parents. The pediatrician should schedule an extra visit within 1 month to address any residual ASD concerns or additional developmental/behavioral concerns after a negative screening result. The child will then re-enter the algorithm at 1b. A "wait-and-see" approach is discouraged. If the only risk factor is a sibling with an ASD, the pediatrician should maintain a higher index of suspicion and address ASD symptoms at each preventive care visit, but an early follow-up within 1 month is not necessary unless a parental concern subsequently arises.

7b:
1. Schedule next preventive visit
2. Re-enter algorithm at 1a

7b - If this is not an 18- or 24-month visit, or when the result of the ASD screening is *negative*, the pediatrician can inform the parents and schedule the next routine preventive visit. The child will then re-enter the algorithm at 1a.

8:
1. Provide parental education
2. Simultaneously refer for:
   a. Comprehensive ASD evaluation
   b. Early intervention/early childhood education services
   c. Audiologic evaluation
3. Schedule follow-up visit
4. Re-enter algorithm at 1b

8 - If the screening result is *positive* for possible ASD in step 6a or 6b, the pediatrician should provide peer reviewed and/or consensus-developed ASD materials. Because a positive screening result does not determine a diagnosis of ASD, the child should be referred for a comprehensive ASD evaluation, to early intervention/early childhood education services (depending on child's age), and an audiologic evaluation. A categorical diagnosis is not needed to access intervention services. These programs often provide evaluations and other services even before a medical evaluation is complete. A referral to intervention services or school also is indicated when other developmental/behavioral concerns exist, even though the ASD screening result is negative. The child should be scheduled for a follow-up visit and will then re-enter the algorithm at 1b. All communication between the referral sources and the pediatrician should be coordinated.

AAP information for parents about ASDs includes: "*Is Your One-Year-Old Communicating with You?**" and "*Understanding Autism Spectrum Disorders.**"

*Available at www.aap.org

Figure 30-1, cont'd

social disability is therefore more likely to be detected later. A number of screening instruments for ASD have been developed that may be helpful to the pediatric practitioner. For example, the Modified Checklist for Autism in Toddlers (M-CHAT) is a free online 23-item autism screening tool designed to identify children 16-30 mo of age who should receive a more thorough assessment for possible early signs of ASD or developmental delay (https://www.m-chat.org/index.php).

ASSESSMENT

If screening indicates ASD symptomatology, a thorough diagnostic assessment should be performed to determine whether full criteria are met. Multidisciplinary assessment is optimal in facilitating early diagnosis, treatment, and coordinated multiagency collaboration. Evaluations from various professionals, including a developmental pediatrician or pediatric neurologist, medical geneticist, child and adolescent psychiatrist, speech-language pathologist, occupational or physical therapist, or medical social worker may be indicated. The *Autism Diagnostic Observation Schedule* (ADOS), which is a semistructured interactive examination by a professional trained in its administration, is the standard diagnostic tool. *The use of such instruments supplements, but does not replace, informed clinical judgment*.

All children with ASD should have a medical assessment, which typically includes a physical examination, a hearing screen, a Wood's lamp examination for signs of tuberous sclerosis (see Chapter 596.2), and genetic testing, which should include ***chromosomal microarray* (CMA)**. In a community sample of children with ASD, diagnostic yield 0.57% for fragile X testing, and 24% for CMA. CMA is recommended by medical geneticists as the standard of care for the initial evaluation of children with ASD, but does not always detect fragile X or Rett syndromes.

Unusual features in the child (dysmorphology, staring spells) should prompt additional evaluations. The categories of potential organic etiologies includes infectious (encephalitis or meningitis), endocrinologic (hypothyroidism), metabolic (homocystinuria, phenylketonuria), traumatic (head injury), toxic (fetal alcohol syndrome), or genetic (chromosomal abnormality). Certain developmental disorders, most notably Landau-Kleffner syndrome, should be ruled out (characterized by a highly distinctive electroencephalogram abnormality and marked aphasia). Neuroimaging, electroencephalography, and additional laboratory tests should be obtained when relevant, based on examination or history (testing for the *MeCP2* gene in females for possible Rett disorder). Table 30-4 summarizes potential medical tests in the assessment of ASD.

Psychological assessments that clarify cognitive ability and adaptive skills are indicated for treatment planning. Deficits in language and socialization often make it difficult to obtain an accurate estimate of a child's intellectual potential. Some children with ASD perform adequately on nonverbal tests, and those with developed speech can show adequate intellectual capacity. Communication assessment, including measures of both receptive and expressive vocabulary as well as language use (particularly social or pragmatic), is also helpful relative to diagnosis and treatment planning. Occupational and physical therapy evaluations may be needed to evaluate sensory and/or motor difficulties. Sleep is also an important variable to assess.

Table 30-4 Medical and Genetic Evaluation of Children with Autism Spectrum Disorder

Recommended evaluations
Careful physical examination to identify dysmorphic physical features
Macrocephaly
Wood's lamp examination for tuberous sclerosis
Formal audiologic evaluation
Lead test; repeat periodically in children with pica
Chromosomal microarray
Consider if results of above evaluation are normal and if accompanying intellectual impairment
FISH test for region 15q11q13 to rule out duplications in Prader-Willi/Angelman syndrome
Fluorescence in situ hybridization (FISH) test for telomeric abnormalities
Test for mutations in *MECP2* gene (Rett syndrome) in females
DNA testing for fragile X syndrome
Metabolic testing to consider based on clinical features (emesis, hypotonia, lethargy, ataxia, coarse facial features of a storage disease, multiple organs involved)
Fasting blood glucose
Plasma amino acids
Ammonia and lactate
Fatty acid profile, paroxysmal
Carnitine
Acylcarnitine, quantitative
Homocysteine
Urine amino acids
Urine organic acids
Urine purine/pyrimidines
Urine acylglycine, random
Plasma 7-dehydrocholesterol (Smith-Lemli-Opitz disease screening)
Medical testing to consider based on clinical features
Complete blood cell count
Liver enzymes
Biotinidase
Thyroxine, thyroid-stimulating hormone
Ceruloplasmin/serum copper
EEG if the following clinical features are noted
Clinically observable seizures
History of significant regression in social or communication functioning

Adapted from Barbaresi WJ, Katusic SK, Voigt R. Autism: A review of the state of the science for pediatric primary care clinicians, Arch Pediatr Adolesc Med *160:1169-1175, 2006.*

TREATMENT

The pediatric practitioner should aim to foster a long-term collaborative relationship with the family that will vary in intensity over time. For young children, diagnosis and identification of treatment programs will generally be the major focus, whereas for school age children behavioral and medication issues will often become a priority. Vocational training along with future self-sufficiency planning becomes critical in adolescence and early adulthood. It is helpful to the family for the pediatric practitioner to maintain an active role in long-term treatment planning, providing family support, and navigating the healthcare and educational systems.

Psychosocial Interventions

Structured behavioral, educational, and communication interventions are effective for many children with ASD and are associated with better outcomes. Several comprehensive treatment approaches are effective for certain groups of children, although none of the approaches has clearly emerged as superior.

***Applied behavioral analysis* (ABA)** is a behavioral intervention that is informed by basic and empirically supported learning principles. A widely disseminated comprehensive ABA program is *Early Intensive Behavioral Intervention*. Early Intensive Behavioral Intervention is intensive and highly individualized with up to 40 hr per week of one-to-one direct teaching, initially using discrete trials to teach simple skills and progressing to more complex skills such as initiating verbal behavior. ABA techniques have efficacy for specific problem behaviors and to be effective when applied to academic tasks, adaptive living skills, communication, social skills, and vocational skills.

Older children and adolescents with relatively higher intelligence, but with poor social skills and psychiatric symptoms, can benefit from more intensive behavioral or cognitive-behavioral therapy and/or supportive psychotherapy. The focus is on achieving social communication competence, emotional and behavioral regulation, and functional adaptive skills necessary for independence.

Children with ASD need a structured educational approach with explicit teaching. Effective programs typically involve planned, intensive, individualized intervention with an experienced, interdisciplinary

Table 30-5 Level of Evidence for Pharmacologic Treatment of Target Symptoms in Autism Spectrum Disorder

CLASS	AGENT	PRIMARY TARGET SYMPTOM(S)	LEVEL OF EVIDENCE
α_2-Agonist	Clonidine	Hyperactivity	Insufficient
	Guanfacine	Hyperactivity	Insufficient
Antipsychotics	Aripiprazole	Irritability, hyperactivity, stereotypy	Established
	Haloperidol	Behavioral symptoms	Established
	Risperidone	Irritability, hyperactivity	Established
	Risperidone	Repetitive behavior, stereotypy	Preliminary
	Olanzapine	Global functioning	Insufficient
Mood stabilizers	Divalproex sodium/Valproic acid	Irritability, repetitive behavior	Insufficient
	Lamotrigine	Irritability, social behavior	Insufficient
	Levetiracetam	Irritability	Insufficient
Norepinephrine reuptake inhibitors	Atomoxetine	Hyperactivity	Preliminary
Serotonin reuptake inhibitors	Citalopram	Repetitive behavior	Insufficient
	Fluoxetine	Repetitive behavior	Insufficient
	Clomipramine	Repetitive behavior, stereotypy, irritability, hyperactivity	Insufficient
Stimulants	Methylphenidate	Hyperactivity	Promising
Miscellaneous	Amantadine	Hyperactivity, irritability	Insufficient
	Naltrexone	Social behavior, communication, Indiscriminant learning, SIB	Insufficient
	Naltrexone	Hyperactivity	Preliminary
	Pentoxifylline	Irritability, social withdrawal	Preliminary

Established, >2 strong studies or >4 adequate studies in separate settings; Insufficient, lack of research or mixed outcomes; Preliminary, >1 adequate study; Promising, >2 adequate studies.

Adapted from Siegel M, Beaulieu AA. Psychotropic medications in child with autism spectrum disorders: A systematic review and synthesis for evidenced based practice. J Autism Dev Disord *42(8):1592–1605, 2012.*

team of providers, and family involvement to ensure generalization of skills. Two structured educational models with demonstrated efficacy include the *Early Start Denver Model* and the *Treatment and Education of Autism and related Communication handicapped Children* (TEACCH) program. The ***individualized educational plan* (IEP)** should reflect an accurate assessment of the child's strengths and vulnerabilities with an explicit description of services to be provided, goals and objectives, and procedures for monitoring effectiveness. Development of an appropriate IEP is central in providing effective service to the child and family.

Communication is generally addressed in the child's IEP in coordination with the speech-language pathologist. Children who do not yet use words can be helped through use of alternative communication modalities such as sign language, electronic communication boards, visual supports, picture exchange, and other forms of augmentative communication. For individuals with fluent speech, the focus should be on pragmatic (social) language skills training.

There is a lack of evidence for most other forms of psychosocial intervention. Studies of sensory-oriented interventions, such as auditory integration training, sensory integration therapy, and touch therapy/massage have contained methodologic flaws and have yet to show replicable improvements. There is also limited evidence thus far for what are usually termed developmental, social-pragmatic models of intervention. Children with ASD are psychiatrically hospitalized at substantially higher rates than the non-ASD population. The efficacy of this level of care is unknown, although there is preliminary evidence for the efficacy of hospital psychiatry units that specialize in this population.

Pharmacotherapy

Pharmacologic interventions (Table 30-5) may increase the ability of children with ASD to benefit from educational and other interventions as well as to remain in less-restrictive environments through the management of challenging behavior. Common targets for pharmacologic intervention include associated comorbid conditions (anxiety, depression) and problematic target symptoms (e.g., irritability, hyperactivity, repetitive behavior, stereotypy, self-injurious behavior).

The FDA has approved risperidone (ages 5-16 yr) and aripiprazole (ages 6-17 yr) for the treatment of irritability in ASD, as evidenced by physical aggression, self-injury, and severe tantrum behavior. In youth weighing < 20 kg, the initial dose of risperidone is 0.25 mg/day with a target dose of 0.5 mg/day, and maximum does of 3 mg/day. In those weighing ≥ 20 kg, the initial dose of risperidone is 0.5 mg/day with a target dose of 1 mg/day, and maximum dose of 3 mg/day. For aripiprazole, the initial dose is 2 mg/day with a target dose of 5-10 mg/day, and maximum dose of 15 mg/day.

The atypical antipsychotic agents also reduce hyperactivity in ASD, though stimulants and atomoxetine appear to be promising for hyperactivity. There is also evidence that repetitive behaviors and stereotypies in ASD may respond to the antipsychotics. Selective serotonin reuptake inhibitors do not have evidence supporting their use for repetitive behaviors or irritability in ASD; they may have efficacy for the treatment of co-occurring depressive and anxiety disorders. The doses of these latter medications would parallel clinical prescribing practices for the specific target symptom (hyperactivity) and/or mental disorders. There is insufficient evidence to support the use of mood stabilizers.

Combining medication with parent training appears to be moderately more efficacious than medication alone for reducing serious behavioral disturbance, and modestly more efficacious for adaptive functioning. Individuals with ASD may be non-verbal, so response to medication is often judged by caregiver report. While this may help assess the effectiveness of the selected medication, it must be remembered that the overall goal of pharmacotherapy is to facilitate the child's adjustment and engagement with behavioral, educational, and communication interventions.

Intranasal oxytocin (IO) is a novel approach to treating ASD. In preliminary studies, IO leads to increased social interactions, better speech comprehension, reduced repetitive behaviors, and functional MRI evidence of improved social attunement. There is currently a large clinical trial testing the efficacy of IO.

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Chapter 31

Childhood Psychoses

Giuseppe J. Raviola, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

Psychosis is a severe disruption of thought, perception, and behavior resulting in **loss of reality testing.** Delusions, hallucinations, disorganized thinking, grossly disorganized behavior, and negative symptoms are key features that define psychotic disorders. **Delusions** are fixed, unchangeable, false beliefs even in light of conflicting evidence. They may include a variety of themes (persecutory, referential, somatic, religious, or grandiose). Delusions are considered bizarre if they are clearly implausible. **Hallucinations** are vivid and clear perception-like experiences that occur without external stimulus and have the full force and impact of normal perceptions. They may occur in any sensory modality; auditory hallucinations are the most common. **Disorganized thinking** is typically inferred from an individual's speech (loose associations, tangentiality, or incoherence). **Grossly disorganized behavior** may range from child-like silliness to catatonic behavior. **Negative symptoms** include diminished emotional expression, avolition, alogia (lack of speech), anhedonia (inability to experience pleasure), and asociality. They generally account for a substantial portion of the morbidity associated with schizophrenia.

31.1 Schizophrenia Spectrum and Other Psychotic Disorders

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Schizophrenia spectrum and other psychotic disorders include brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, substance/medication-induced psychotic disorder (see Chapter 114), psychotic disorder caused by another medical condition, catatonia associated with another mental disorder, catatonic disorder caused by another medical condition, unspecified catatonia, delusional disorder, schizotypal personality disorder, and other specified/unspecified schizophrenia spectrum and other psychotic disorders.

DESCRIPTION

The schizophrenia spectrum and other psychotic disorders are primarily characterized by the active (or positive) symptoms of psychosis, specifically delusions, hallucinations, disorganized speech, or grossly disorganized behavior. **Brief psychotic disorder** is characterized by the sudden onset (within 2 wk from baseline function) of these symptoms in the context of emotional turmoil or overwhelming confusion, followed by complete resolution (Table 31-1). Although brief, the level of impairment in this disorder may be severe enough that supervision may be required to ensure that basic needs are met and the individual is protected from the consequences of poor judgment and cognitive impairment.

If the psychotic symptoms persist for up to 6 mo, the condition is called **schizophreniform disorder** (Table 31-2), whereas in **schizophrenia**, there are continuous signs of the disturbance for at least 6 mo (Table 31-3). Active symptoms must have been present for a significant portion of time during a 1 mo period, and the level of psychosocial functioning must be markedly below the level achieved prior to the onset (or there is failure in children to achieve the expected level of functioning).

Table 31-1 DSM-5 Diagnostic Criteria for Brief Psychotic Disorder

A. Presence of 1 (or more) of the following symptoms. At least 1 of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.

   Note: Do not include a symptom if it is a culturally sanctioned response.
B. Duration of an episode of the disturbance is at least 1 day but less than 1 mo, with eventual full return to premorbid level of functioning.
C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With marked stressor(s) (brief reactive psychosis): If symptoms occur in response to events that, singly or together, would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

Without marked stressor(s): If the symptoms do not occur in response to events that, singly or together, would be would be markedly stressful to almost anyone in similar circumstances in the individual's culture.

With postpartum onset: If onset is during pregnancy or within 4 wk postpartum.

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Table 31-2 DSM-5 Diagnostic Criteria for Schizophreniform Disorder

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least 1 of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (i.e., diminished emotional expression or avolition).
B. An episode of the disorder lasts at least 1 mo but less than 6 mo. When the diagnosis must be made without waiting for recovery, it should qualified as "provisional."
C. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
D. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

Specify if:

With good prognostic features: This specifier requires the presence of at least 2 of the following features: onset of prominent psychotic symptoms within 4 wk of the first noticeable change in usual behavior or functioning; confusion or perplexity; good premorbid social and occupational functioning; and absence of blunted or flat affect.

Without good prognostic features: This specifier is applied if 2 or more of the above features have not been present.

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Table 31-3 DSM-5 Diagnostic Criteria for Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least 1 of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g., frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in 1 or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 mo. This 6 mo period must include at least 1 mo of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least a month (or less if successfully treated).

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Schizophrenia is a heterogeneous clinical syndrome with a range of cognitive, behavioral, and emotional dysfunctions. Prodromal symptoms often precede the active phase, in which individuals may express a variety of unusual or odd beliefs and may have unusual perceptual experiences; their speech may be generally understandable but vague; and their behavior may be unusual but not grossly disorganized. Individuals who had been socially active may become withdrawn.

Individuals with schizophrenia can display inappropriate affect, dysphoric moods, disturbed sleep patterns, and lack of interest in eating or food refusal. Depersonalization, derealization, somatic concerns, and anxiety and phobias are common. Cognitive deficits are observed, including decrements in declarative memory, working memory, language function, and other executive functions, as well as slower processing speed. These individuals may have no insight or awareness of their disorder, which is a predictor of nonadherence to treatment, higher relapse rates, and poorer illness course. Hostility and aggression can be associated with schizophrenia, although spontaneous or random assault is uncommon. Aggression is more frequent for younger males and for individuals with a past history of violence, non-adherence with treatment, substance abuse, and impulsivity.

The essential features of schizophrenia are the same in childhood, but it is more difficult to make the diagnosis. In children, delusions and hallucinations may be less elaborate, and visual hallucinations may be more common. Disorganized speech and behavior occur in many childhood onset psychiatric disorders, and should not be attributed to schizophrenia unless more common disorders are ruled out.

Table 31-4 Medical Conditions Associated with Psychotic-like Behavior

Medications (steroids, β-blocking agents, cyclosporine)
Drugs of abuse (intoxication, overdose or withdrawal)
Central nervous system infections
Autoimmune encephalitis (anti–*N*-methyl-D-aspartate [NMDA] receptor/limbic/paraneoplastic)
Acute disseminated encephalomyelitis (ADEM)
Systemic lupus erythematosus (SLE)
Syndromes (fragile X, trisomy 21, tuberous sclerosis)
Wilson disease
Porphyria
Nonconvulsive status (seizures)
Hyper-/hypoparathyroidism
Hyper-/hypothyroidism
Hyper-/hypoadrenalism
Hypoglycemia
Thiamine deficiency
Vitamin B_{12} deficiency
Inborn errors of metabolism (see Table 31-5)

EPIDEMIOLOGY

Brief psychotic disorders have been reported to account for 9% of cases of first-onset psychosis in the United States with a 2 : 1 ratio in favor of females. The incidence of schizophreniform disorders in the United States and other developed countries appears as much as 5-fold less than that of schizophrenia, whereas in developing countries the incidence is higher (approaching that of schizophrenia), particularly when associated with good prognostic features.

The lifetime prevalence of schizophrenia is approximately 0.3-0.7%, although there are reported variations by race/ethnicity, across countries, and by geographic origin for immigrants. The male : female ratio is approximately 1.4 : 1. Males generally have a worse premorbid adjustment, lower educational achievement, more prominent negative symptoms, and more cognitive impairment than females.

CLINICAL COURSE

Brief psychotic disorder may appear in adolescence or early adulthood, with the average age of onset in the mid-30s. By definition, a diagnosis of brief psychotic disorder requires full remission within 1 mo of onset. The development of schizophreniform disorder is similar to that of schizophrenia. About one-third of individuals with an initial diagnosis of schizophreniform disorder recover within a 6 mo period; the majority of the remaining two-thirds will eventually receive a diagnosis of schizophrenia or schizoaffective disorder.

Schizophrenia typically develops between the late teens and the mid-30s; onset prior to adolescence is rare. The peak age at onset for the first psychotic episode is in the early to mid-20s for males and in the late-20s for females. The onset may be abrupt or insidious, but the majority of individuals manifest a slow and gradual development, with around one-half of individuals complaining of depressive symptoms. The predictors of course and outcome are largely unexplained. The course appears to be favorable in approximately 20% of cases, and a small number of individuals are reported to recover completely. Most individuals require daily living supports. Psychotic symptoms tend to diminish over time, while negative symptoms are the most persistent, along with cognitive deficits.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the psychotic disorders is broad, and includes substances/medications (dextromethorphan, LSD, hallucinogenic mushrooms, psilocybin, peyote, cannabis, stimulants, and inhalants; corticosteroids, anesthetics, anticholinergics, antihistamines, amphetamines), other medical conditions (Tables 31-4 and 31-5), other disorders within the same class, depressive and bipolar disorders

Table 31-5 Psychiatric Signs in Inborn Errors of Metabolism in Adolescents and Adults: Review of the Literature and Personal Experience

	CONFUSION	MENTAL RETARDATION	BEHAVIORAL DISTURBANCES	CATATONIA	VISUAL HALLUCINATIONS	PSYCHOSIS (SCHIZOPHRENIA)	DEPRESSION
Urea cycle defects	+	+/–	+	+	+	+	+
Cbl (C, G)	+	+	+		+		+
MTHFR deficiency	+	+	+	+	+	+	+
Porphyria	+		+	+		+	+
Wilson disease		+/–	+	+		+/–	+
CBS deficiency		+	+			+/–	+
CTX		+	+	+		+	
MLD			+			+	
GM_2 gangliosidosis			+	+	+	+	+
NPC			+	+	+	+	+
α-Mannosidosis		+	+		+	+	
β-Mannosidosis		+	+				
ALDc			+			+	+
Nonketotic hyperglycinemia		+	+				
Monoamine oxidase A deficiency		+	+				
Creatine transporter deficiency		+	+				
Succinic semialdehyde dehydrogenase deficiency		+	+				

+, Frequently reported; +/–, unusual; empty cell, not reported; ALDc, cerebral adrenoleukodystrophy; CBS, cystathionine β-synthase; CTX, cerebrotendinous xanthomatosis; MLD, metachromatic leukodystrophy; MTHFR, methylene tetrahydrofolate reductase; NPC, Niemann-Pick type C.

From Sedel F, Baumann N, Turpin JC, et al: Psychiatric manifestations revealing inborn errors of metabolism in adolescent and adults. J Inherit Metab Dis *30:631–641, 2007, Table 3, p. 635.*

(see Chapter 26), malingering and factitious disorders, obsessive-compulsive (see Chapter 25) and body dysmorphic disorder, posttraumatic stress disorder (see Chapter 25), autism spectrum disorder (see Chapter 30) or other communication disorders (see Chapter 35), and personality disorders.

Autoimmune encephalitis caused by anti–*N*-methyl-D-aspartate (NMDA) receptor or other autoantibodies may manifest with psychosis, anxiety, depression, agitation, aggression, delusions, catatonia, hallucinations, and paranoia in combination with sleep disturbances, autonomic dysfunction (hypoventilation), dyskinesias, movement disorders, seizures, and a depressed level of consciousness. The electroencephalogram (EEG), cerebral spinal fluid, and MRI are usually, but not always, abnormal. The constellation of psychosis and encephalitic features should suggest the diagnosis; however, at presentation behavioral problems may be the dominant feature (see Chapter 598.4).

Differentiating medical from psychiatric causes of abnormal behavior may be difficult. In general, medical causes are often associated with abnormalities in vital signs and the neurologic exam (including level of consciousness). In medical causes of abnormal behavior, there may not be a positive family history or a prior personal history of psychiatric illness. Furthermore, in medical causes, there are often impairments in attention, orientation, recent memory, and intellectual function. Hallucinations may be present with medical disease, but they are often tactile, visual, or olfactory rather than auditory (noted in psychiatric disease). Medical patients may be able to reality test about their hallucinations, stating they are aware they are not real.

The diagnosis of a psychotic disorder should be made only after these other explanations for the observed symptoms have been ruled out. Most children who report hallucinations do not meet criteria for the schizophrenia spectrum disorders, and most do not have psychosis. Normative childhood experiences, including overactive imaginations and vivid fantasies, can be mistaken for psychosis.

COMORBIDITY

Rates of comorbidity with substance-related disorders are high in schizophrenia. Other common comorbidities are anxiety disorders and obsessive-compulsive disorders.

SEQUELAE

Follow-up studies of early onset schizophrenia suggest moderate to severe impairment across the life span. Poor outcome is predicted by low premorbid functioning, insidious onset, higher rates of negative symptoms, childhood onset, and low intellectual functioning. When followed into adulthood, youth with schizophrenia demonstrated greater social deficits, lower levels of employment, and were less likely to live independently, relative to those with other childhood psychotic disorders.

Approximately 5-6% of individuals with schizophrenia die by suicide, approximately 20% attempt suicide on 1 or more occasions, and many more have suicidal ideation. Life expectancy is reduced in individuals with schizophrenia because of associated medical conditions; a shared vulnerability for psychosis and medical disorders may explain some of the medical comorbidity of schizophrenia.

ETIOLOGY AND RISK FACTORS

Etiologic evidence for schizophrenia supports a neurodevelopmental and neurodegenerative model with multiple genetic and environmental exposures playing important roles. It has been hypothesized that while psychotic disorders likely have their origins in early development, but it is not until they are in their mid-teens that the underlying neural structures manifest the disabling functional deficits and resultant psychotic symptoms.

Genetic Factors

The lifetime risk of developing schizophrenia is 5-20 times higher in 1st-degree relatives of affected probands compared to the general population. Concordance rates of 40-60% and 5-15% have been reported, respectively, in monozygotic and dizygotic twins. Genome-wide association studies, using large collaborative international cohorts, have implicated different genomic loci and genes, including the major histocompatibility complex (6p21.1), MIR137, and ZNF804a. Structural mutations arising at genomic "hotspots," including 1q21.1, 15q13.3, and 22q11.2, may be responsible for 0.5-1.0% of cases.

Childhood schizophrenia appears to be associated with a higher rate of large cytogenetic abnormalities and rare structural variants than reported in adults. The majority of rare copy number errors detected in affected persons are found at different genetic loci, and many are unique to 1 individual or family.

Environmental Factors

In utero exposure to maternal famine, advanced paternal age, prenatal infections, obstetric complications, marijuana use and immigration have been hypothesized to contribute to the development of schizophrenia. Environmental exposures may mediate disease risk via direct neurologic damage, gene by environment interactions, epigenetic effects and/or de novo mutations. There is no evidence that psychological or social factors cause schizophrenia. Rather, environmental factors may potentially interact with biologic risk factors to mediate the timing of onset, course, and severity of the disorder. Expressed emotion within the family setting can influence the onset and/or exacerbation of acute episodes and relapse rates.

Neuroanatomical Abnormalities

Increased lateral ventricle volumes along with reductions in hippocampus, thalamus, and frontal lobe volumes have been reported in schizophrenia. Youth in particular have reductions in grey matter volumes and reduced cortical folding. Neurotransmitter systems, particularly central nervous system dopamine circuits, are hypothesized to have a key role in the pathophysiology of schizophrenia. The dopamine hypothesis is derived in part from the identification of D_2 receptor blockade as the mechanism for the action of antipsychotic medications.

PREVENTION

There has been significant interest in prospectively identifying youth at risk for schizophrenia spectrum and other psychotic disorders in an effort to provide early intervention prior to the development of a full-blown psychotic disorder. Various names including ***attenuated psychosis syndrome*** **(APS)**, psychosis risk syndrome, ultrahigh risk, clinical high risk, at-risk mental state, and prodromal stage have been used to describe patients that present with troubling symptoms suggestive of early psychosis.

APS is characterized by the presence of delusions, hallucinations, or disorganized speech in an attenuated form, with relatively intact reality testing, but of sufficient frequency to warrant clinical attention. The symptoms are described as being present at least once per week for the past month and have begun/worsened over the past year. The symptoms are less severe and more transient than a psychotic disorder, although nearly 20-40% with these attenuated symptoms appear to go on to a psychotic disorder within 3 yr of symptom presentation. There is evidence that premorbid lower cognitive and social skills as well as a history of substance abuse contribute to the risk of developing a full-blown psychotic disorder in individuals with APS.

There is some evidence that antipsychotic medication may delay conversion of attenuated to full-blown psychosis and ameliorate attenuated symptoms in active treatment, yet there appear to be no lasting effects after the medication is withdrawn. In addition, there is concern that the long-term use of even low-dose antipsychotic medication may cause heightened sensitization of brain dopamine receptors, which, in turn, could lead to a rapid-onset of psychosis following discontinuation of the medication.

Antidepressants have been associated with symptomatic improvement in adolescents with APS. In a randomized control trial, omega-3 fish oils reduced attenuated positive, negative, and general symptoms. Psychological interventions (social skills, cognitive, and interaction training programs, as well as psychoeducational family interventions and cognitive-behavioral therapy) are reported to improve symptoms and psychosocial functioning in youth with early symptoms.

Despite improvements in diagnostic predictive validity, significant concern remains regarding a high false-positive rate (identifying an individual as prodromal who does not go on to develop psychosis) that may cause individuals to be stigmatized or exposed to unnecessary treatment. In this context, youth with early symptoms suggestive of psychosis should be referred to a child and adolescent psychiatrist and/or a specialized research program.

SCREENING/CASE FINDING

Pediatric practitioners can make general inquiries of youth and their parents regarding problems with thinking or perceptions. For the older youth, questions like *"Does your mind ever play tricks on you?," "Do you hear voices talking to you when no one is there?," and/or "Does your mind ever feel confused?"* can help elicit symptoms. For younger children, the clinician must ensure that the child understands the questions. True psychotic symptoms are generally confusing to the individual, and highly descriptive, detailed, organized, and/or situation-specific reports are less likely to represent true psychosis. Overt signs of the illness should be evident on mental status exam; without overt evidence of psychosis, the validity of symptom reports needs to be carefully scrutinized. For youth presenting with what could be psychosis, assessment and treatment in the specialty mental health setting by a child and adolescent psychiatrist should be provided.

ASSESSMENT

The diagnostic assessment of schizophrenia in youth is uniquely complicated and misdiagnosis is common. Most children who report hallucinations do not meet criteria for schizophrenia, and many do not have a psychotic illness. Normative childhood experiences, including overactive imaginations and vivid fantasies, can be misinterpreted as psychosis. Expertise in childhood psychopathology and experience in assessing reports of psychotic symptoms in youth are important prerequisite skills for clinicians evaluating youth for possible psychosis. Comprehensive diagnostic assessments, which reconcile mental status findings with the rigorous application of diagnostic criteria, help improve accuracy.

There are no neuroimaging, psychological or laboratory tests that establish a diagnosis of schizophrenic spectrum disorders. The medical evaluation focuses on ruling out nonpsychiatric causes of psychosis, while also establishing baseline laboratory parameters for monitoring medication therapy. Routine laboratory testing typically includes blood counts, basic metabolic panel, liver and renal functions, metabolic parameters, and thyroid functions. More extensive evaluation is indicated for atypical presentations, such as a gross deterioration in cognitive and motor abilities, focal neurologic symptoms, or delirium. Neuroimaging may be indicated when neurologic symptoms are present, or an EEG is indicated for a clinical history suggestive of seizures. Toxicology screens are indicated for acute onset or exacerbations of psychosis, when exposure to drugs of abuse cannot be ruled out. Genetic testing is indicated if there are associated dysmorphic or syndromic features. Tests to rule out specific syndromes or diseases (e.g., amino acid screens for inborn errors of metabolism, ceruloplasmin for Wilson disease [see Chapter 357.2], porphobilinogen for acute intermittent porphyria [see Chapter 91]) are indicated for clinical presentations suggestive of a specific syndrome. Neuropsychological testing cannot establish the diagnosis, but may be important for documenting cognitive deficits for academic planning.

TREATMENT

There are hallmark phases important to recognize in the assessment and management of schizophrenia. In the prodrome phase, most patients experience functional deteriorations (i.e., social withdrawal, idiosyncratic preoccupations, unusual behaviors, academic failure, deteriorating self-care skills, and/or dysphoria) prior to the onset of psychotic symptoms. The acute phase is characterized by prominent positive symptoms and deterioration in functioning. The recuperative/recovery phase is marked by a several-month period of impairment and predominantly negative symptoms. The residual phase (if reached) has no positive symptoms though negative symptoms may contribute to some level of impairment.

Treatment goals include decreasing psychotic symptomology, directing the child toward a developmentally typical trajectory, and reintegrating the child into the home and community. Children and families facing schizophrenia spectrum disorders require an array of mental health services to address their psychological, social, educational, and cultural needs. Given the insidious onset and chronic course of these disorders, the patient must be followed longitudinally, with periodic reassessment to hone diagnostic accuracy and tailor services to meet the patient's and family's needs. Integrated psychopharmacologic, psychotherapeutic, psychoeducational, and case-management services are often necessary.

Psychoeducation about the illness with an assessment of the potential role of stigma in treatment participation is critical for improving adherence with treatment recommendations. Assessing a child's strengths and vulnerabilities as well as available environmental resources is critical in devising an effective treatment plan. School and community liaison work to develop and maintain a day-to-day schedule for the patient is important. Specialized educational programs should be considered within the school system. Cognitive remediation has shown some promising results in planning ability and cognitive flexibility. Effective and collaborative communication among the family, the pediatrician, a child and adolescent psychiatrist, and other mental health providers increases the potential for the patient's optimal functioning.

Pharmacotherapy

First-generation (typical) and second-generation (atypical) antipsychotic medications have been shown to be effective in reducing psychotic symptoms with the latter the preferred medication choice (see Chapter 21). Haloperidol, risperidone, aripiprazole, quetiapine, paliperidone, and olanzapine are FDA approved for treating schizophrenia in ages 13 yr and older. The choice of which agent to use first is typically based on FDA approval status, side-effect profile, patient and family preference, clinician familiarity, and cost. Depot antipsychotics have not been studied in pediatric age groups and have inherent risks with long-term exposure to side effects. Although clozapine is effective in treating both positive and negative symptoms, its risk for agranulocytosis and seizures limits its use to those patients with treatment-resistant disorders.

Most patients require long-term treatment and are at significant risk to relapse if their medication is discontinued. The goal is to maintain the medication at the lowest effective dose so as to minimize potential adverse events. Many patients will continue to experience some degree of positive or negative symptoms, requiring ongoing treatment. Patients should maintain regular physician contact so as to monitor symptom course, side effects, and adherence.

Individuals prescribed antipsychotic medications need to be systematically monitored for side effects, including sedation, abnormal movements, weight gain, hyperprolactinemia, elevated liver transaminases, diabetes, hyperlipidemia, hematologic effects (leukopenia or neutropenia), seizures, neuroleptic malignant syndrome, and cardiovascular effects. For atypical antipsychotics, body mass index, fasting blood glucose, fasting triglycerides/cholesterol, waist circumference, high-density lipoprotein/low-density lipoprotein, blood pressure, and symptoms of diabetes should be checked at baseline and at regular intervals thereafter. Regular physical activity and nutritional balance should be part of a comprehensive treatment plan.

Abnormal movements (dystonia, akathisia, tardive dyskinesia) need periodic assessment preferably using a standardized instrument such as the *Abnormal Involuntary Movement Scale* (AIMS). The need for antiparkinsonian agents may be a consideration for patients, particularly those at risk for acute dystonia or who have a previous history of dystonic reactions. In patients with a personal or family history of cardiac abnormalities, including syncope, palpitations, arrhythmias, or sudden unexplained death, a baseline electrocardiogram with subsequent monitoring should be considered, along with cardiology consultation. Alternative pharmacology should be considered if the resting

heart rate exceeds 130 beats/min, or the PR, QRS, and QTc exceed 200, 120, and 460 msec, respectively.

Electroconvulsive therapy (ECT) may be used with severely impaired adolescents if medications are either not helpful or cannot be tolerated. It has not been systematically studied in children.

Bibliography is available at Expert Consult.

31.2 Psychosis Associated with Epilepsy

David R. DeMaso

Schizophrenia spectrum and other psychotic disorders include *psychotic disorder due to another medical condition* (Table 31-6). *Psychosis associated with epilepsy* has been reported in children and adults. Also called *schizophrenic-like psychosis of epilepsy*, the disorder manifests with delusions or hallucinations, along with poor insight. The characterization is complicated by the fact that anticonvulsant drugs can present with psychosis and antipsychotic drugs can lower the seizure threshold, producing seizures.

Psychosis associated with epilepsy can be further differentiated into ictal, interictal, and postictal psychosis. Ictal-induced psychosis is a form of **nonconvulsive status epilepticus**, usually complex partial status that can last for hours to days and is associated with periods of impaired consciousness. Brief interictal psychosis can last days to weeks and is associated with paranoia, delusions, and auditory hallucinations. Chronic interictal psychosis resembles schizophrenia and manifests with paranoia, visual hallucinations, and catatonia. Postictal psychosis is the most common type (observed in 2-7% of patients with epilepsy); it lasts up to 1 wk and then spontaneously remits.

The diagnosis requires a strong index of suspicion and EEG monitoring. Treatment requires appropriate anticonvulsant drugs and, if the psychosis persists, initiating low-dose antipsychotic medication.

Bibliography is available at Expert Consult.

31.3 Catatonia in Children and Adolescents

Bonita F. Stanton

Catatonia is a poorly defined state presenting as an unusual manifestation of decreased or increased muscle tone and decreased responsiveness (although agitation may be present) occurring in association with a broad array of conditions affecting children, adolescents and adults. These conditions include psychosis, autism spectrum disorder, developmental disorders, drug-induced conditions, affective disorders and a wide range of medical disorders (Table 31-7). Not surprising given the ill-defined nature of the condition, the prevalence of catatonia in children and adolescents is unknown, although it is generally believed to be significantly underdiagnosed. Recognition of catatonia by a clinician is very important because the disorder is generally very responsive to treatment with benzodiazepines and/or ECT.

DIAGNOSIS AND TREATMENT

Catatonia is defined as 3 or more of the 12 symptoms listed in Table 31-8. An important next step is the evaluation and possible elimination of medications being administered to the child for their potential to induce catatonic symptoms, a not-infrequent side effect of many medical and psychiatric medications. Of particular importance, antipsychotic agents should be discontinued as they have been associated with an increased incidence of malignant catatonia or neuroleptic malignant syndrome (see Chapter 21).

Benzodiazepams (typically lorazepam) and **ECT** are effective in adults and appear to be effective in children. A treatment algorithm using a lorazepam challenge test (by mouth, intravenous, or intramuscular administration of lorazepam 1-2 mg) is shown in Figure 31-1. If the challenge test does reverse symptoms, increasing doses of lorazepam are indicated, with careful monitoring to avoid side effects. ECT may be indicated alone (if no improvement with lorazepam) or in combination with lorazepam if some but incomplete improvement is noted.

Table 31-6 DSM-5 Diagnostic Criteria for Psychotic Disorder Due to Another Medical Condition

A. Prominent hallucinations or delusions.
B. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of another medical condition.
C. The disturbance is not better explained by another mental disorder.
D. The disturbance does not occur exclusively during the course of a delirium.
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify whether:
With delusions: If delusions are the predominant symptom.
With hallucinations: If hallucinations are the predominant symptom.

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Table 31-7 Conditions Associated with Catatonia

Psychotic disorders
  Paranoid schizophrenia, catatonic schizophrenia, psychosis, autism, Prader-Willi syndrome, intellectual impairment
Mood disorders
  Bipolar disorder- manic or mixed episodes
Major depressive disorder
Medical conditions
  Endocrine abnormalities, infections, electrolyte imbalances
Neurologic conditions
  Epilepsy, strokes, traumatic brain injury, multiple sclerosis, encephalitis
Drugs
  Withdrawal: Benzodiazepines, L-dopa, gabapentin
  Overdose: LSD, phencyclidine (PCP), cocaine, Ecstasy, disulfiram, levetiracetam

Adapted from Weder ND, Muralee S, Penland H, Tampi RR: Catatonia: a review. Ann Clin Psychiatry *20(2):97–107, 2008, Table 2.*

Table 31-8 Diagnostic Criteria of Catatonia in the DSM-5

Catatonia is defined as the presence of 3 or more of the following
1. Catalepsy (i.e., passive induction of a posture held against gravity)
2. Waxy flexibility (i.e., slight and even resistance to positioning by examiner)
3. Stupor (no psychomotor activity; not actively relating to environment)
4. Agitation, not influenced by external stimuli
5. Mutism (i.e., no, or very little, verbal response [*Note:* not applicable if there is an established aphasia])
6. Negativism (i.e., opposing or not responding to instructions or external stimuli)
7. Posturing (i.e., spontaneous and active maintenance of a posture against gravity)
8. Mannerisms (i.e., odd caricature of normal actions)
9. Stereotypies (i.e., repetitive, abnormally frequent, non–goal-directed movements)
10. Grimacing
11. Echolalia (i.e., mimicking another's speech)
12. Echopraxia (i.e., mimicking another's movements)

From Tandon R, Heckers S, Bustillo J, et al: Catatonia in DSM-5. Schizophr Res *150(1):26-30, 2013, Table 1.*

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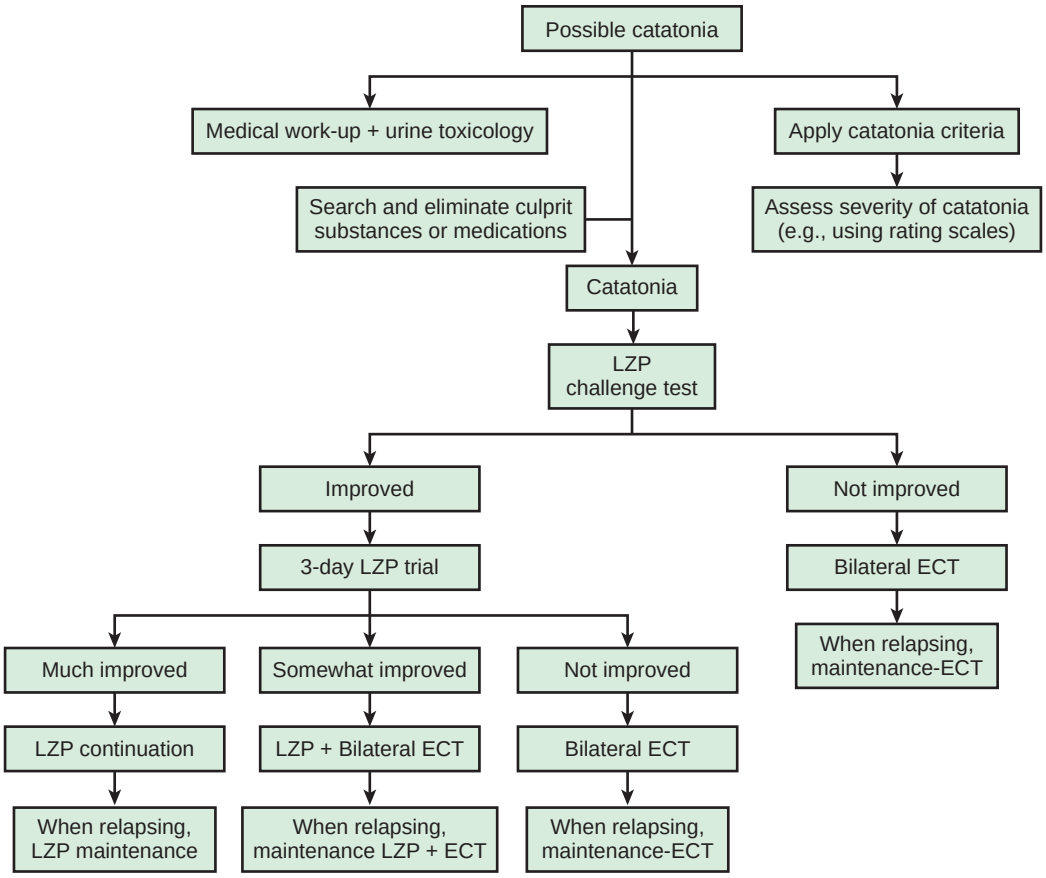

Figure 31-1 Evaluation, diagnosis and treatment of catatonia in children and adolescents. ECT, electroconvulsive therapy; LZP, lorazepam. *(From Dhossche DM, Wilson C, Wachtel LE: Catatonia in childhood and adolescents: implications for the DSM-5. Prim Psychiatry 17(4):23–26, 2010.)*

The outlook for catatonia is greatly impacted by that of the associated condition(s). The long-term outcome for individuals treated with ECT is unknown, but mortality rates in catatonic patients declined after the introduction of ECT in treatment.

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31.4 Acute Phobic Hallucinations of Childhood

Giuseppe J. Raviola, Michael L. Trieu, David R. DeMaso, and Heather J. Walter

Among adults, hallucinations are viewed as synonymous with psychosis and as harbingers of serious psychopathology. In children, hallucinations can be part of normal development or can be associated with nonpsychotic psychopathology, psychosocial stressors, drug intoxication, or physical illness. The first clinical task in evaluating youth who report hallucinations is to sort out those that are associated with severe mental illness from those that derive from other causes (Fig. 31-2).

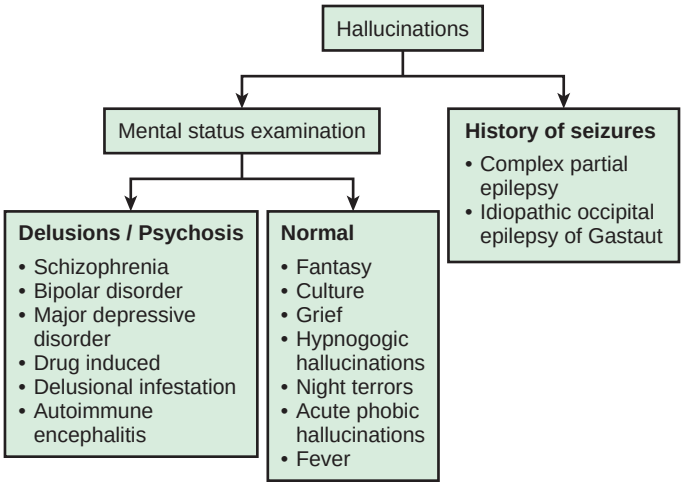

Figure 31-2 Evaluation of hallucinations.

CLINICAL MANIFESTATIONS

Hallucinations are perceptions (typically auditory, visual, tactile, or olfactory) that occur in the absence of identifiable external stimuli. Hallucinations can be further categorized as nondiagnostic (hearing footsteps, knocking, or one's name) and diagnostic (hearing 1 or more voices saying words other than one's own name).

In children with nonpsychotic hallucinations, the symptoms of psychosis are absent. Nonpsychotic hallucinations commonly occur in the context of severe traumatic stress, developmental difficulties, social and emotional deprivation, parents whose own psychopathology promotes a breakdown in the child's sense of reality, cultural beliefs in mysticism, and unresolved mourning. Auditory hallucinations of voices telling the child to do bad things may be more often associated with disruptive behavior disorders than with psychotic diagnoses. Hearing a voice invoking suicide is often associated with depression. Trauma-related auditory hallucinations are commonly associated with posttraumatic stress disorder or a brief psychotic disorder with marked stressors. The content of the hallucinations may be relevant in understanding the underlying psychopathology and/or developmental issues.

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DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute phobic hallucinations are benign and common and occur in previously healthy preschool children. The hallucinations are often visual or tactile, last 10-60 minutes, and occur at any time but most often at night. The child is quite frightened and might complain that bugs or snakes are crawling over him or her and attempt to remove them. The cause is unknown. The differential diagnosis includes drug overdose or poisoning, high fever, encephalitis, and psychosis. The child's fear is not alleviated by reassurance by the parents or physician, and the child is not amenable to reason. Findings on physical and mental status examinations are otherwise normal. Symptoms can persist for 1-3 days, slowly abating over 1-2 wk.

The differential diagnosis of hallucinations comprises a broad range of mental disorders, including diagnoses in which hallucinations are not the hallmark feature, but may be viewed as associated symptoms (posttraumatic stress disorder, nonpsychotic mood disorders, and disruptive, impulse-control, and conduct disorders); diagnoses that are defined by psychotic features (brief psychotic disorder, schizophrenia, major depressive or bipolar disorder with psychotic features); and at-risk clinical states (poor reality testing). In addition, other medical conditions can manifest with hallucinations, including drug intoxications (cannabis, LSD, cocaine, amphetamines, barbiturates), medication side effects (e.g., steroids, anticholinergic medications, stimulant medications), and physical illnesses (e.g., thyroid, parathyroid, and adrenal disorders; Wilson disease; electrolyte imbalances; infections; migraines; seizures; and neoplasms).

TREATMENT

The evaluation of the underlying condition directs the type of treatment needed. Nonpsychotic hallucinations suggest the need for disorder-specific psychotherapy (e.g., trauma-focused cognitive behavioral therapy for posttraumatic stress disorder) and perhaps adjunctive medication (e.g., an antidepressant for depression or anxiety, or a brief trial of antipsychotic medication for agitation). Cognitive-behavioral therapy focused on helping the youth understand the origin of the hallucinations and on developing coping strategies for stressful situations may be helpful for older children and adolescents. True psychotic hallucinations suggest the need for antipsychotic medication.

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Learning Disorders

PART IV

Chapter 32

Neurodevelopmental Function and Dysfunction in the School-Age Child

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TERMINOLOGY AND EPIDEMIOLOGY

A **neurodevelopmental function** is a basic brain process needed for learning and productivity. **Neurodevelopmental variation** refers to differences in neurodevelopmental functioning. Wide variations in these functions exist within and between individuals. These differences can change over time and need not represent pathology or abnormality.

Neurodevelopmental dysfunctions reflect disruptions of neuroanatomic structure or psychophysiologic function and place a child at-risk for developmental, cognitive, emotional, behavioral, psychosocial and adaptive challenges. For the school-age child, an area of particular focus is academic skill development. Academic disorders have been diagnostically classified as **Specific Learning Disorder** (SLD) by the revised *Diagnostic and Statistical Manual of Mental Disorder Fifth Edition* (DSM-5). Changes in DSM-5 (compared to DSM-IV) involve a broadening of the diagnostic criteria in an effort to recognize factors that may interrupt the effective acquisition of academic skills that include **reading**, **written language, spelling** and **mathematics.** The *International Classification of Diseases* (ICD) of the World Health Organization, 10th Edition (ICD-10) categorizes **Specific Developmental Disorders of Scholastic Skills** that include **Reading Disorder, Spelling Disorder, Disorder of Arithmetical Skills,** and **Mixed Disorder of Scholastic Skills**. **Dyslexia** (reading disorder) is included in ICD-10 in a separate category of symbolic dysfunction. The terms, **Dyscalculia** (mathematics disorder), and **Dysgraphia** (written language disorder) are also used by investigators and clinicians, but their inclusion in diagnostic classification systems has been inconsistent and a source of some disagreement among experts.

Traditionally, the educational system has identified SLDs through the process of psychoeducational testing. Through this process, students experiencing academic problems would be evaluated psychometrically. Typical testing batteries have usually included measures of overall intelligence and academic skills. A student exhibiting a significant discrepancy between scores on tests of intelligence and tests of academic achievement could be classified as a student with an SLD, and would subsequently be eligible for Special Education Services. The degree of discrepancy required for such classification often differed between states and even between school districts. In a marked change in approach to the identification of SLDs, the reauthorization of the Individuals with Disabilities Education Act (IDEA) in 2004 introduced the Response to Intervention (RTI) model, which does not necessitate that schools use the discrepancy model for determining if a student has an SLD. Instead, schools may employ research-based intervention approaches and monitor a student's response to that intervention before initiating psychoeducational testing. This approach has been met with some disapproval, as those who challenge its effectiveness argue that the RTI model, in and of itself, should not be used to identify children with SLD. The underlying view behind this objection rests with the notion that children may fail to respond to RTI for a variety of reasons (e.g., underlying neurocognitive weakness), not just because a SLD exists.

Overall estimates of the prevalence of SLD's range from 3-10%. Some data indicate that approximately 8% of children 3-17 yr of age have, at one point, been identified as having a SLD. Prevalence estimates can vary owing to numerous factors, including differences in definitions and criteria used for classification and diagnosis, as well as differences in methods of assessment.

ETIOLOGY AND PATHOGENESIS

Neurodevelopmental dysfunction may present for any number of reasons. These include pre-/perinatal, genetic, medical, psychologic, environmental and sociocultural influences. Genes that contribute to neurodevelopmental dysfunction have been identified. Reading disorders can be both familial and heritable, and studies have linked some reading disabilities to specific gene loci on chromosomes 6 and 15. Chromosomal abnormalities can lead to unique patterns of dysfunction, such as visual–spatial deficits in girls diagnosed with Turner syndrome or language deficits in children with fragile X syndrome (see Chapter 81). Chromosome 22q11.2 deletion syndrome (DiGeorge or velocardiofacial syndrome [see Chapter 125]) is associated with predictable patterns of neurodevelopmental dysfunction, including a higher prevalence of intellectual disability, and deficits in visual–spatial processing, executive function, attention, working memory, verbal learning, arithmetic, and language with relative strengths in selected reading and spelling skills. Investigations of the neuroanatomical substrates have also yielded important information about the underlying causes of neurodevelopmental dysfunction. Multiple investigations have identified differences in the left parietotemporal and left occipitotemporal brain regions of individuals with dyslexia compared to those without reading difficulties (see Chapter 34). Studies also describe the neural circuitry, primarily in the parietal cortex, underlying mathematical competencies such as the processing of numerical magnitude, and mental arithmetic investigations support a broader role for the white matter in active learning and memory than was previously estimated.

Perinatal risk factors that are associated with neurodevelopmental dysfunction include very-low birthweight, severe intrauterine growth restriction, perinatal hypoxic–ischemia encephalopathy, and prenatal exposure to substances such as alcohol and drugs (see Chapter 96). Increased risk of academic and frontal lobe disorders also is associated with environmental toxins, including lead (see Chapter 721); drugs such as cocaine; infections such as meningitis and HIV; and brain injury secondary to intraventricular hemorrhage, periventricular leukomalacia, or head trauma.

Early psychologic trauma can result in both structural and neurochemical changes in the developing brain, which may contribute to neurodevelopmental dysfunction. Findings suggest that the effects of exposure to trauma (see Chapter 39) and/or abuse (see Chapter 40) early in the developmental course can induce disruption of the brain's regulatory system with connections in the orbitofrontal cortex, and may influence right-hemisphere function with associated risk for problems with information processing, memory, and frontal lobe related operations (e.g., focus and self-regulation). Environmental and sociocultural deprivation can lead to, or potentiate, neurodevelopmental dysfunction, which most often results from a combination of contributing factors, rather than a single cause.

CORE NEURODEVELOPMENTAL FUNCTIONS

The neurodevelopmental processes that are critical for academic success may best be understood as falling within **core neurodevelopmental domains**.

Sensory and Motor Development

Sensory development (e.g., auditory, visual, tactile, proprioceptive) begins well before birth. This neurodevelopmental process is crucial in helping children experience, understand, and manipulate their environments. Through sensory experiences, children's brains mature as new neuronal pathways are created and existing pathways are strengthened. Any interruption of this process may result in sensory-motor deficits and delays (e.g., apraxia) that can interfere with early development and academic performance.

Sensory development for the school-age child progresses in association with environmental exposure and with the development of other cognitive processes such as motor development.

There are 3 distinct, yet related, forms of neuromotor ability: graphomotor, fine motor, and gross motor coordination.

Graphomotor function refers to the specific motor aspects of written output. Several subtypes of graphomotor dysfunction significantly impede writing. Some children harbor weaknesses of visualization during writing. They have trouble picturing the configurations of letters and words as they write (orthographics). Their written output tends to be poorly legible, with inconsistent spacing between words. Others have weaknesses in orthographic memory, which interferes with their ability to recall and/or reproduce letter and number forms rapidly and accurately. They may labor over individual letters and prefer printing (manuscript) to cursive writing. Some exhibit signs of finger agnosia or weak graphomotor feedback; they have trouble localizing their fingers while they write. As a result, they need to keep their eyes very close to the page and tend to apply excessive pressure to the pencil. Others struggle with graphomotor production deficits. For these children, trouble producing the highly coordinated motor sequences needed for writing results in difficulty assigning writing roles to specific muscle groups in their hands. This phenomenon has also been described as **dyspraxic dysgraphia.** It is important to emphasize that a child may show excellent fine motor dexterity (as revealed in mechanical or artistic domains) but very poor graphomotor fluency (with labored or poorly legible writing).

For the school-age child, problems with **fine motor function** can disrupt their ability to communicate in written form, to excel in artistic and crafts activities, and can interfere with learning a musical instrument or mastering a computer keyboard. The term **dyspraxia** relates to difficulty in developing an ideomotor plan and activating coordinated and integrated visual motor actions to complete a task or solve a motor problem, such as assembling a model.

Some children exhibit **gross motor incoordination.** They have problems in processing "outer spatial" information to guide gross motor actions. Affected children may be inept at catching or throwing a ball because they cannot form accurate judgments about trajectories in space. Others demonstrate diminished body position sense. They do not efficiently receive or interpret proprioceptive and kinesthetic feedback from peripheral joints and muscles. They are likely to evidence difficulties when activities demand balance and ongoing tracking of body movement. Others are unable to satisfy the motor praxis demands of certain gross motor activities. It may be hard for them to recall or plan complex motor procedures such as those needed for dancing, gymnastics, or swimming. Children with gross motor problems can incur considerable embarrassment in physical education classes. Gross motor weaknesses can lead to social rejection, withdrawal, and generalized feelings of inadequacy.

Language

Language is one of the most critical and complex cognitive functions and can be broadly divided into **receptive** (auditory comprehension/understanding) and **expressive** (speech and language production and/or communication) functions. Children who primarily experience receptive language problems may have difficulty understanding verbal information, following instructions and explanations, and interpreting what they hear. Expressive language weaknesses can result from problems with speech production and/or problems with higher level language development (see Chapter 35). Speech production difficulties include oromotor problems affecting articulation, verbal fluency, and naming. Some children have trouble with sound sequencing within words. Others find it hard to regulate the rhythm or prosody of their verbal output. Their speech may be dysfluent, hesitant, and inappropriate in tone. Problems with word retrieval can result in problems in finding exact words when needed (as in a class discussion) or substituting definitions for words (circumlocution). Children who evidence higher level expressive language impediments have trouble formulating sentences, using grammar acceptably, and organizing spoken (and possibly written) narratives.

In considering disordered language, whether in reception or expression, it is vital to ascertain the potential underlying difficulties that are contributing. Some children, for example, have particular problems with **phonology** (see Chapter 35). Commonly, a weak phonologic sense has a negative effect not only on language processing, but also on the development of reading, writing and even mathematics (e.g., word problems). Children with **semantic deficits** have trouble learning the meaning of words, and as a result, may use words improperly (e.g., out of context). Other common language deficiencies include difficulty with **syntax** (word order), problems with **discourse** (paragraphs and passages), an underdeveloped sense of **metalinguistics** (the ability to think about and analyze how language works), and trouble with drawing appropriate inferences (supplying missing information) from language. Difficulty with language **pragmatics**, or the social understanding and application of language, can be another significant impediment.

Language weaknesses not only contribute to problems with reading, writing and math, but can also manifest in the content areas, such as the sciences, which necessitate the processing of dense verbal material in textbooks and the rapid convergent recall of facts, and social studies courses that often entail the use of sophisticated language and verbal abstract concepts (e.g., democracy). Learning foreign languages can be a serious problem. In contrast, children who possess strong language skills are often able to make use of their linguistic facility to compensate for any academic problems; it may be possible to verbalize one's way through a mathematics curriculum, thereby circumventing a tendency to be confused by predominantly nonverbal concepts (e.g., ratio, equation, and diameter).

To one degree or another, all academic skills are taught largely through language, and thus it is not surprising that children who experience language dysfunction often experience problems with academic performance. In fact, some studies suggest that up to 80% of children who present with a SLD also experience language-based weaknesses.

Visual–Spatial/Visual–Perceptual Function

The process of visual development begins well before birth, with continued development and refinement throughout childhood (see Chapter 621). Important structures involved in the development and function of the visual system, beyond the eyes themselves, include the retina, optic cells (e.g., rods and cones), the optic chiasm, the optic nerves, the brainstem (control of automatic responses like pupil dilation), the thalamus (e.g., lateral geniculate nucleus for form, motion, color), and the primary (visual space and orientation) and secondary (color perception) visual processing regions located in and around the occipital lobe. Other brain areas, considered to be outside of the primary visual system, are also important to visual function, helping to process *what* (temporal lobe) is seen and *where* it is located in space (parietal lobe). The left and right cerebral hemispheres interact considerably in visual processes, with each hemisphere possessing more specialized functions, including left hemisphere mediated processing of details, patterns, and linear information, and right hemisphere processing of the gestalt and overall form.

Some of the more critical aspects of visual processing to develop in the school-age child include **spatial relations**—the ability to accurately perceive objects in space in relation to other objects; **visual**

discrimination—the ability to differentiate and identify objects based on their individual attributes such as size, shape, color, form, and position; and, **visual closure**—the ability to recognize or identify an object even when the entire object cannot be seen.

Children with subtle visual deficits are often misidentified and/or missed completely. Indications of visual processing deficits in the school-age child may include difficulty learning to draw and write, and problems with art activities. These children might also have trouble discriminating between left and right. They might encounter problems recognizing letters and words, resulting in delayed reading, spelling, and writing.

Visual–spatial processing dysfunctions are not a common cause of chronic reading disorders, but more recent investigations have established that deficits in orthographic coding (visual–spatial analysis of character-based systems) can contribute to reading disorders. Spelling and writing can emerge as a weakness because children with visual processing problems commonly have trouble with the precise visual configurations of words. In mathematics, these children often have difficulty with visual–spatial orientation, with resultant difficulty aligning digits in columns when performing calculations and/or difficulty managing geometric material. In the social realm, intact visual processing allows a child to make use of visual or physical cues when communicating and interpreting the paralinguistic aspects of language. Secure visual functions are also necessary to process proprioceptive and kinesthetic feedback and to coordinate movements during physical activities. Children with visual processing deficits are thus susceptible to problems such as social isolation and withdrawal and consequent behavioral and/or emotional difficulties.

Intellectual Function

The concept of intellectual function, or intelligence, has had many definitions and theoretical models, and achieving a consensus on the subject has been challenging. Well-known theories include Spearman's unitary concept of "the g-factor," the "verbal and nonverbal" theories (e.g., Binet, Thorndike), the 2-factor theory from Catell (crystallized vs fluid intelligence), Luria's simultaneous and successive processing model, and more recent models that view intelligence as a global construct composed of more-specific cognitive functions (e.g., auditory and visual–perceptual processing, spatial abilities, processing speed, and working memory). A useful definition of **intellectual function** is the capacity to think in the abstract, reason, problem solve and comprehend.

The expression of intellect is mediated by many factors, including language development, sensorimotor abilities, genetics, heredity, environment, and neurodevelopmental dysfunction or neuropathology. When an individual's intelligence is measured at a standard score of 70 or lower, and significant weaknesses in adaptive skills are indicated, consideration of the diagnosis of Intellectual Disability would be warranted. In DSM-5, the previous diagnostic term of Mental Retardation has been changed to **Intellectual Disability**. DSM-5 also includes the term **Intellectual Developmental Disorder** to indicate weaknesses in intellectual functioning that begin during the early developmental period (Chapter 36).

The clinical assessment of intellectual functioning has proved useful in identifying intellectual disability, informing treatment strategies, and in predicting future functionality (e.g., academic, occupational and social). Notwithstanding, intelligence test scores (e.g., IQ) reflect only part of an individual's ability profile. Functionally, there are some common characteristics that distinguish children with deficient intellectual functioning from those with average or above average abilities. Typically, those at the lowest end of the spectrum (e.g., profound or severe intellectual deficiencies) are incapable of independent function, and require a highly structured environment with constant aid and supervision (see Chapter 36). At the other end of the spectrum are those with unusually well-developed intellect (e.g., gifted). Although this level of intellectual functioning offers many opportunities, it can also be associated with functional challenges related to socialization, learning style, and communication and perceptual differences. Individuals whose intellect falls in the below average range (sometimes referred to as the "borderline" or "*slow learner" range*) tend to experience greater difficulty processing and managing information that is abstract, making connections between concepts and ideas, and generalizing information (e.g., may be able to comprehend a concept in one setting but are unable to carry it over and apply it in different situation). In general, these individuals tend to do better when information is presented in more concrete and explicit terms, and when working with rote information (e.g., memorizing specific material). Stronger intellect is associated with better-developed concept formation, critical thinking, problem solving, understanding and formulation of rules, brainstorming and creativity, and metacognition (the ability to "think about thinking")

Frontal Lobe Functioning

Attention

Most brain processes are heavily dependent on functional arousal, alertness, and attention. Any malfunction within or across these systems will likely cause some degree of breakdown in other cognitive processes. Functional attention subsumes intact neuroanatomic and neurochemical brain systems. Structurally, brain regions involved include subcortical, cortical, and association areas throughout the brain. Primary structures involved include brainstem regions (e.g., basal ganglia), the limbic system (e.g., amygdala and hippocampus), and the frontal lobes (e.g., prefrontal cortex). The neurotransmitter dopamine, along with its neuronal pathways, has been identified as a major chemical modulator of attention. It is through the cognitive mechanisms of attention and executive functions that the child's brain acquires, organizes, and processes information. These mechanisms also allow the child to regulate, plan, and monitor their behaviors and thoughts. Children with attention dysfunction comprise a widely heterogeneous group who show various patterns of impairment of these systems (see Chapter 33). The resulting symptoms not only affect behavior, learning, and academic skills development, but also have an impact on the child's emotional, social, and adaptive development and functioning.

Attention is far from a unitary, independent, or specific function. This may be illustrated best through the phenotype associated with **Attention-Deficit/Hyperactivity Disorder (ADHD).** ADHD is not only a disorder of impaired focus, but also includes a host of symptoms related to problems with vigilance, distractibility, impulsivity in thought and behavior, hyperactivity, and flexibility. Disordered attention can occur owing to faulty mechanisms in and/or across subdomains of attention. These subdomains include **selective attention** (the ability to focus attention to a particular stimulus and to discriminate relevant from irrelevant information), **divided attention** (the ability to orient to more than one stimulus at a given time), **sustained attention** (the ability to maintain one's focus), and **alternating attention** (the capacity to shift focus between stimuli).

Attention problems in school-age children can manifest at any point in the process, from arousal through output. Children with diminished alertness and arousal can exhibit signs of mental fatigue in a classroom or when engaged in any activity requiring sustained focus. They might yawn, stretch, fidget, and daydream. They can become overactive in an effort to attain or maintain a higher level of arousal. They are apt to have difficulty allocating and sustaining their concentration, and their efforts may be erratic and unpredictable, with extreme performance inconsistency. These children can also have difficulty discriminating between important and unimportant information. Such weaknesses of determining saliency often result in focusing on the wrong stimuli, at home, in school, and socially, and can result in the child's missing important information and can impede their ability to take notes, to summarize information, or to recognize what to study for a test. In the social context, poor attention may result in inept social interaction (e.g., because of factors such as not "hearing" what others say). Some children present with what has been termed *sluggish cognitive tempo*. Children with sluggish cognitive tempo have many inattentive features without a history of significant hyperactivity and/or impulsiveness. Some researchers believe that sluggish cognitive tempo may be a different disorder from ADHD, with its own characteristics, including hypoactivity, lethargy, confusion, and mental "fogginess."

Distractibility can take the form of listening to extraneous noises instead of a teacher, staring out the window, or constantly thinking about the future. These children often show evidence of superficial concentration, where their level of focus is not of sufficient intensity to capture specific information. As a result, these children are often described as "forgetful" because directions and explanations need to be repeated and details (e.g., changes in operational signs in mathematics) may be missed. These children can also exhibit difficulties with cognitive activation and generalization, passively processing and not linking information with prior knowledge and experience, or over-relying on prior experience.

Attention dysfunction can affect the output of work, behavior, and/or social activity. These children have a tendency to perform or act without previewing a likely outcome or thinking through the potential consequences of what they are about to do or say. Their impulsivity can lead to careless mistakes in academic work and unintended misbehavior. It is important to appreciate that most children with attentional dysfunction also harbor other forms of neurodevelopmental dysfunction that can be associated with academic disorders (with some estimates suggesting up to 60% comorbidity).

Executive Functioning

There is considerable overlap between attention and **executive functioning**. Additions to the ICD classification system include a code for *Frontal Lobe and Executive Function Deficit* (799.55). Executive functioning is an umbrella term used to describe specific cognitive processes involved in regulating, guiding, organizing, and monitoring of thoughts and actions (cognitive, behavioral, and emotional functions) to achieve a specific goal. Processes considered to be executive in nature include inhibition control, flexibility (the ability to shift between activities or thoughts), emotional control, initiation skills, planning, organization, working memory, and self-monitoring.

Studies indicate that executive functioning can be strengthened in children as young as age 4 yr, which suggests that executive functioning is actively developing in the preschool-age child.

Executive function deficits that have particular impact on school function include **inhibition**, or **inhibitory control**, the ability to control a response, whether it be cognitive or behavioral. Children with inhibitory control deficits may answers questions prematurely and fail to check their work. Behaviorally, these children may speak without first considering the impact of what they say. In the social context, disinhibited children may interrupt others and demonstrate other impulsive behaviors that often interfere with interpersonal relationships (see Chapter 33).

The function of **working memory** has been the focus of significant research efforts. Working memory can be defined as the ability to hold, manipulate, and store information for short periods. In its simplest form, working memory involves the interaction of short-term verbal and visual processes (e.g., memory, phonologic, awareness and spatial skills) with a centralized control mechanism that is responsible for coordinating all of the cognitive processes involved (e.g., temporarily suspending information in memory while working with it). Developmentally, working memory capacity can double or triple between the preschool years and adolescence. A child with working memory dysfunction might carry a number and then forget what it was that the child intended to do after carrying that number. Working memory is an equally important underlying function for reading, where it enables the child to remember the beginning of a paragraph when the child arrives at the end of it. In writing, working memory helps children remember what they intend to express in written form while they are performing another task, like placing a comma or working on spelling a word correctly. Working memory also enables the linkage between new incoming information in short-term memory with prior knowledge or skills held in longer-term memory (Table 32-1).

Table 32-1 Symptom Expression of Executive Dysfunction

EXECUTIVE FUNCTION DEFICIT	SYMPTOM EXPRESSION
Disinhibition	Impulsivity/poor behavioral regulation Interrupts "Blurts" things out
Shifting	Problems with transitioning from one task/activity to another Unable to adjust to unexpected change Repeats unsuccessful problem-solving approaches
Initiation	Difficulty independently beginning tasks/activities Lacks initiative Difficulty developing ideas or making decisions
Working memory	Challenges following multistep instruction (e.g., only completes 1 of 3 steps) Forgetfulness
Organization and planning	Fails to plan ahead Work is often disorganized Procrastinates and does not complete tasks "Messy" child
Self-monitoring	Fails to recognize errors and check work Does not appreciate impact of actions on others Poor self-awareness
Affect control	Experiences behavioral and emotional outbursts (e.g., tantrums) Easily upset/frustrated Frequent mod changes

Memory

Memory is a term used to describe the cognitive mechanism by which information is acquired, retained, and recalled. Structurally, some major brain areas involved in memory processing include the hippocampus, the fornix, the temporal lobes, and the cerebellum, with connections in and between most brain regions. The memory system can be partitioned into subsystems based on processing sequences; the form, time span, and method of recall; whether memories are conscious or unconsciously recalled; and the types of memory impairments that can occur.

Once information has been identified (through auditory, visual, tactile, and/or other sensory processes), it needs to be **encoded and registered,** a mental process that constructs a representation of the information into the memory system. The period of time (typically seconds) during which this information is being held and/or manipulated for registration, and ultimately encoded, consolidated, and retained, is referred to as **working memory** (see above). Other descriptors include **short-term memory** and **immediate memory**. **Consolidation** and **storage** represent the process by which information in short-term memory is transferred into **long-term memory**. Information in long-term memory can be available for hours or as long as a life span. Long-term memories are generally thought to be housed, in whole or in part, in specific brain regions (e.g., the cortex, cerebellum). Ordinarily, consolidation in long-term memory is accomplished in 1 or more of 4 ways: pairing 2 bits of information (such as a group of letters and the English sound it represents); storing procedures (consolidating new skills, such as the steps in solving mathematics problems); classifying data in categories (filing all insects together in memory); and linking new information to established rules, patterns, or systems of organization (rule-based learning).

Once information finds its way into long-term memory, it must be accessed. In general, information can be retrieved spontaneously (a process known as **free recall**) or with the aid of cues (**cued or recognition recall**). Some other common descriptors of memory include **anterograde memory** (the capacity to learn from a single point in time

forward), **retrograde memory** (the capacity to recall information that was already learned), and **explicit memory** (conscious awareness of recall), **implicit memory** (subconscious recall: no awareness that the memory system is being activated), **procedural memory** (memory for how to do things), and **prospective memory** or *remembering to remember*.

As children proceed through school, the demands for the efficient use of memory progressively increase. By secondary school, rapid and precise recall is heavily emphasized. Children can have trouble with 1 or more memory mechanisms. They might struggle with the initial registration of information in short-term memory. Others might have difficulty storing newly introduced information. Other children might have difficulty accessing (retrieving) information, despite having registered and stored it effectively. Children can experience frustration in their efforts at consolidating information into long-term memory and/or encounter difficulty with simultaneous recall (retrieval of several facts or procedures at once). Some students exhibit delayed **automatization:** not enough of what they have learned in the past is accessible to them instantaneously and with no expenditure of effort. Such skills as forming letters, mastering mathematical facts, and decoding words must ultimately become automatic if students are to make good academic progress.

Weaknesses with memory processing can be highly specific and/or dependent on the material. Some children struggle to learn visual-spatial material, whereas others may be deficient in learning auditory information. Some have difficulty processing linear data or sequential information. Some can experience difficulty with rote data (e.g., word lists) yet have little or no difficulty registering information in context (e.g., a narrative). Although in-depth examination (e.g., neuropsychologic testing) is often necessary to differentiate potential memory weaknesses and their impact on the child's overall functioning, screening for memory problems should be part of any well-child examination.

Social Cognition

For the school-age child, the development and effective use of social skills is of immeasurable importance. It is heavily dependent on secure **social cognition**, which is composed of mental processes that allow an individual to understand and interact with the social environment. Although some evidence shows that social cognition exists as a discrete area of neurodevelopmental function, multiple cognitive processes are involved with social cognition. These include the ability to recognize, interpret, and make sense of the thoughts, communications (verbal and nonverbal), and actions of others, the ability to understand that others' perceptions, perspectives, and intentions might differ from our own (commonly referred to as "theory of mind"), the ability to use language to communicate with others socially (pragmatic language), and the ability to make inferences about others and/or the environment based on contextual information. It can also be argued that social cognition involves processes associated with memory and executive functions like flexibility.

CLINICAL MANIFESTATIONS

School-age children with neurodevelopmental dysfunctions vary widely with regard to clinical presentations. Their specific patterns of academic performance and behavior represent final common pathways, the convergence of many forces, including interacting cognitive strengths and deficits; environmental, social, or cultural factors; temperament; educational experience; and intrinsic resilience (Table 32-2). Symptoms of academic disorders differ with age. Children in preschool or kindergarten might present with delayed language development, including problems with articulation, vocabulary development, word finding and rhyming. They often experience early challenges with learning colors, shapes, letters and numbers, the alphabet, and days of the week. Difficulty following instructions, overactivity, and distractibility may be early symptoms of emerging attention and inhibitory control weaknesses. Difficulties with fine motor development (e.g., grasping crayons and pencils, coloring or drawing) and social interaction are not uncommon. As these children enter elementary school, they can evidence problems integrating and associating letters and sounds and problems with semantic knowledge such as mixing up their words (like go and eat). While learning to read and spell, challenges with reversals (b/d), inversions (m/w), transpositions (felt/left), and substitutions (house/home) might persist. Reading comprehension may be weak.

Table 32-2 Neurodevelopmental Dysfunction Underlying Academic Disorders

ACADEMIC DISORDER	POTENTIAL UNDERLYING NEURODEVELOPMENTAL DYSFUNCTION
Reading	Language • Phonologic processing • Verbal fluency • Syntactic and semantic skills Memory • Working memory Sequencing Visual–spatial Attention
Written expression, spelling	Language • Phonologic processing • Syntactic and semantic skills Graphomotor Visual–spatial Memory • Working memory Sequencing Attention
Mathematics	Visual–spatial Memory • Working memory Language Sequencing Graphomotor Attention

Isolated neurodevelopmental dysfunction can lead to a specific academic disorder, but more often there is a combination of factors underlying weak academic performance. In addition to the dysfunction in neurodevelopmental domains as listed in the table, the clinician must also consider the possibility of limitations of intellectual and cognitive abilities or associated social and emotional problems.

Children with early signs of a mathematics weakness might have difficulty with concepts of quantity or with adding or subtracting without using concrete representation (e.g., their fingers when calculating). Difficulty learning time concepts and confusion with directions (right/left) might also be observed. Sequencing problems are noted in reading, spelling and writing, and mathematics. Poor fine motor control and coordination and poor planning can lead to spelling and writing problems. Attention and behavioral regulation weaknesses observed earlier can continue, and together with executive functioning weaknesses (e.g., organization, initiation skills), further complicate the child's ability to acquire and generalize new knowledge.

Middle school brings with it a significant shift in cognitive, academic, and regulatory demands, as children in this age group are expected to be increasingly independent, causing further difficulties for a child with existing attention, inhibitory, and/or executive challenges. In reading and writing, middle school children might present with transposition and sequencing errors; might struggle with root words, prefixes, and suffixes; might have difficulty with written expression; and might avoid reading and writing altogether. Challenges completing word problems in math are common. Difficulty with recall of information might also be experienced. Although observable in both lower and more advanced grades, behavioral, emotional, and/or social difficulties tend to become more salient in middle school children who experience cognitive and/or academic problems.

Many of these challenges continue well into high school. High school students can present with deficient reading comprehension, written expression, and slower processing efficiency. Trouble answering

open-ended questions, dealing with abstract information, and producing executive control (e.g., self-monitoring, organization, planning, and self-starting) is often reported.

Reading

Reading disorders (see Chapter 34), also termed **dyslexia,** can stem from any number of neurodevelopmental dysfunctions as described earlier (see Table 32-2). Most commonly, language and/or auditory processing weaknesses are present as evidenced by poor **phonologic processing.** Challenges with phonologic processing often result in deficiencies at the level of decoding individual words and, consequently, a delay in automaticity (e.g., acquiring a repertoire of words they can identify instantly) that causes reading to be slow, laborious, and frustrating. Without effective identification and intervention, reading comprehension, and ultimately the acquisition of knowledge may be seriously compromised. Deficits in other core neurodevelopmental domains might also be present. Weak working memory might make it difficult for a child to hold sounds and/or symbols in mind while breaking down words into their component sounds or might cause reading comprehension problems. Some children experience temporal-ordering weaknesses and struggle with reblending phonemes into correct sequences. Memory dysfunction can cause problems with recall and summarization of what was read. Some children with higher-order cognitive deficiencies have trouble understanding what they read because they lack a strong grasp of the concepts in a text. Although relatively rare as a cause of reading difficulty, problems with visual–spatial functions (e.g., visual perception) can cause children difficulty in recognizing letters. It is not unusual for children with reading problems to avoid reading practice, and a delay in reading proficiency becomes increasingly pronounced and difficult to remediate.

Spelling and Writing

Spelling and writing impairments share many related underlying processing deficits with reading, so it is not surprising that the 2 disorders often occur simultaneously in school-age children (see Table 32-2). Core neurodevelopmental weaknesses can include phonologic and decoding difficulties, **orthographic** problems (coding letters and words into memory), and **morphologic** deficits (use of suffixes, prefixes, and root words). Problems in these areas can manifest as phonetically poor, yet visually comparable approximations to the actual word (*faght* for *fight*), spelling that is phonetically correct but visually incorrect (*fite* for *fight*), and inadequate spelling patterns (*played* as *plade).* Children with memory disorders might misspell words because of coding weaknesses. Others misspell because of poor auditory working memory that interferes with their ability to process letters. Sequencing weaknesses often result in transposition errors when spelling. Overall, the careful analysis of a child's errors can provide valuable insights into the nature of their spelling problems. As children proceed through school, demands increase for large amounts of well-organized written output.

Writing difficulties have been classified as **disorder of written expression**, or **dysgraphia** (see Table 32-2). Although many of the same dysfunctions described for reading and spelling can contribute to problems with writing, written expression is the most complex of the language arts, requiring synthesis of many neurodevelopmental functions (e.g., auditory, visual–spatial, memory, executive). Deficits in any of these domains can be problematic. Even when a child's phonologic and/or orthographic skills are functional, the child can experience writing problems owing to weaknesses with language, attention, sequencing and/or fine motor development. These weaknesses can occur in written output that is difficult to comprehend, disjointed, and/or poorly organized. The child with working memory challenges can lose track of what the child intended to write. Attention deficits can make it hard for a child to mobilize and sustain the mental effort, pacing, and self-monitoring demands necessary for writing. In many cases, writing is laborious because of an underlying graphomotor dysfunction (e.g., fluency does not keep pace with ideation and language production). Thoughts may also be forgotten or underdeveloped during writing because the mechanical effort is so taxing.

Mathematics

Delays in mathematical ability, known as **mathematics disorder** or **dyscalculia,** can be especially refractory to correction, partly because math involves the assimilation of both procedural knowledge (e.g., calculations) and higher-order cognitive processes (e.g., working memory) (see Table 32-2). A school-based study found that no student who was delayed for longer than 6 mo in mathematics in 6th grade ever caught up; another study found persistence of severe arithmetic disorder in half of affected preteen children. Factors associated with persistence of difficulties included the disorder's severity and heritability. Significant mathematical weaknesses can become virtually insurmountable because the subject is so cumulative in its structure.

Some children experience mathematics failure because of weaknesses in reasoning and problem solving (e.g., intellectual functioning). It may be hard for them to grasp and apply concepts effectively and/or systematically. Good mathematicians are able to use both verbal and perceptual conceptualization to understand such concepts as fractions, percentages, equations, and proportion. Children with language dysfunctions have difficulty in mathematics because they have trouble understanding their teachers' verbal explanations of quantitative concepts and operations and are likely to experience frustration in solving word problems and in processing the vast network of technical vocabulary in math. Mathematics also relies on visualization. Children who have difficulty forming and recalling visual imagery may be at a disadvantage in acquiring mathematical skills. They might experience problems writing numbers correctly, placing value locations, and processing geometric shapes or fractions. Children with attention, inhibitory control, or executive deficits (e.g., working memory) may be unable to focus on fine detail (such as operational signs), might take an impulsive approach to problem solving, engage in little or no self-monitoring, forget components of the same problem, or commit careless errors. When a child's memory system is weak, the child might have difficulty recalling appropriate procedures and automatizing mathematical facts (e.g., multiplication tables). Moreover, it is not unusual for children with mathematical disabilities to have superimposed mathematics phobias. Anxiety over mathematics can be especially debilitating.

Nonacademic Problems

Neurodevelopmental dysfunctions commonly have effects that extend far beyond academic performance. These effects may be related to the dysfunctions themselves or to secondary sequelae (e.g., persistent failure and frustration). The impulsivity and lack of effective self-monitoring of children with attention and impulse-control deficits can lead to unacceptable actions that were unintentional. Children with neurodevelopmental dysfunctions can experience excessive performance anxiety or clinical depression, and sadness, self-deprecatory comments, declining self-esteem, chronic fatigue, loss of interests, and even suicidal ideation can ensue. Some children lose motivation. They tend to give up and exhibit learned helplessness, a sense that they have no control over their destiny. Therefore, they feel no need to exert effort and develop future goals. These children may be easily led toward dysfunctional interpersonal relationships, detrimental behaviors (e.g., delinquency), and the development of mental health and personality disorders, such as mood disorders (see Chapter 26) or antisocial personality disorder.

ASSESSMENT AND DIAGNOSIS

The primary care pediatrician has a critical role in identifying and evaluating the child with an academic disorder. A system of screening and surveillance should be incorporated into routine office visits to promote early identification of academic difficulties. The pediatrician should be aware of a family medical history that includes a parent who still struggles with reading or time management, or an older sibling who has failed at school. Factors in the child's medical history should be flagged, such as extreme prematurity or chronic medical conditions. Children with low birthweight and those born prematurely who appear to have been spared more serious neurologic problems might only manifest academic problems later in their school career and they

warrant particular attention. Children falling into these high risk categories should be flagged for an increased level of scrutiny at routine well-child visits as well as acute-care visits, especially if physical complaints are nonspecific. There should be a low threshold for initiating further school performance screening and assessment of these children. Warning signs might be subtle or absent and problems will not be recognized unless there is a system of eliciting and identifying school problems as part of the routine well-child visit. Parents might have concerns about their child's learning progress but be reluctant to share these with the pediatrician unless prompted such as through completion of a standard developmental screening questionnaires or direct questioning of parents regarding possible concerns about their child's school performance. Inconsistency in report from grade to grade may sometimes be caused by a difference in teaching styles or classroom demands. The type of deficit will also be influential; for example, problems with basic phonemic awareness would be more apparent earlier, while reading comprehension difficulties would emerge later.

Review of school report cards can provide useful clues to patterns of neurodevelopmental dysfunction. In addition to the patterns of grades in the various academic skill areas, it is also important to review ratings of classroom behavior, sometimes listed under headings such as deportment, behavior, conduct, effort/work habits, or citizenship. Review of standardized testing is helpful, and poor scores could be caused by a learning disorder, ADHD, anxiety, lack of motivation, or some combination thereof. Conversely, above-average scores tend to rule out learning or attention problems, but motivation or adjustment issues could then explain a discrepancy between standardized scores and classroom performance. Comparison of how long the homework should take, and how long it takes the child is recommended. Children with ADHD, learning disorders, or emotional/behavioral issues often find homework to be a contentious activity.

The primary care physician is responsible for identifying or ruling out any underlying or associated medical problems that could be impeding the academic performance of the patient who is struggling in school. Vision and hearing screening are critical components of the medical evaluation and any suspicion of sensory difficulty should warrant referral for more definitive testing. The influence of chronic medical problems or potential side effects of medications should be considered. Sleep deprivation is increasingly being recognized as a contributor to academic problems and the possibility of substance abuse must always be a consideration, especially in the adolescent who was previously achieving well at school and has manifested a rapid decline in academic performance.

The physician should be alert for dysmorphic physical features, minor congenital anomalies, or constellations of physical findings (such as cardiac anomalies and palatal anomalies in velocardiofacial syndrome) and should perform a detailed neurologic examination. Special investigations, such as electroencephalograms or brain scans, are not indicated in the absence of specific medical findings. Measures of brain function, such as functional MRI, offer insight into possible areas of neurodevelopmental dysfunction, but they largely remain only research tools with limited application in the general clinical setting at this time.

If problems emerge, the pediatrician should address medical causes or associated conditions. The pediatrician can advise and assist parents in obtaining necessary psychoeducational and/or emotional evaluations through the school or by referral to independent clinicians.

Those physicians with a particular interest in learning disorders can extend their participation in the evaluation process. They can obtain data on neurodevelopmental function through the use of questionnaires completed by the parents, the school, and (if old enough) the child, providing information about behavioral adjustment, patterns of academic performance, and traits associated with specific developmental dysfunctions. Screening instruments such as the Pediatric Symptoms Checklist and standardized behavioral questionnaires, including the Child Behavior Checklist (CBCL) and the Behavior Assessment System for Children–Second Edition (BASC-2) can aid in evaluation (see Chapter 20).

The physician may also perform an extended neurologic and developmental assessment. Available pediatric neurodevelopmental examination instruments that facilitate direct sampling of various neurodevelopmental functions, such as attention, memory, and language, include the Pediatric Early Elementary Examination (PEEX II) and the Pediatric Examination of Educational Readiness at Middle Childhood (PEERAMID II). Examinations of this type also include direct behavioral observations and assessment of minor neurologic indicators (sometimes called *soft signs*). The latter include various associated movements and other phenomena often associated with neurodevelopmental dysfunction.

A child who is functioning poorly during the school years usually requires a *multidisciplinary evaluation*, including a pediatrician, a psychologist, and, if possible, a psychoeducational specialist (sometimes called an *educational diagnostician*) who can undertake a detailed analysis of academic skills and subskills. Other professionals should become involved, as needed, in individual cases, such as a speech-language pathologist, an occupational therapist, a neurologist, and a social worker. In some cases, more in-depth examination of a child's neurocognitive status is warranted. This is particularly true for children who present with developmental or cognitive difficulties in the presence of a medical condition (e.g., epilepsy, traumatic brain injury, childhood cancers/brain tumors, genetic conditions). A neuropsychologic evaluation involves comprehensive assessment of brain function as a means of understanding brain function across domains. The goal of neuropsychologic assessment is to understand brain function via identification of a child's profile of cognitive strengths and weaknesses. Neuropsychologic data are often analyzed together with other tests (e.g., structural), such as MRIs, to look for supporting evidence of any areas of difficulty (e.g., memory weaknesses associated with temporal lobe anomalies).

Many children undergo evaluations in school. Such assessments are guaranteed in the United States under Public Law 101-476, the IDEA. In addition, children found to have attentional dysfunction and other disorders might qualify for educational accommodations under Section 504 of the Rehabilitation Act of 1973.

Multidisciplinary evaluations conducted in schools are usually very helpful, but they are focused primarily on determining whether a student meets the eligibility criteria for special education services. School budgeting constraints or lack of personnel can also affect the quality of evaluations and the extent of recommended services. Many parents seek independent evaluations or second opinions outside of the school setting, and pediatricians can facilitate such outside assessments.

Psychoeducational testing can yield relevant data, especially when such assessments include careful analyses that pinpoint where breakdowns are occurring in the processes of reading, spelling, writing, and mathematics. Input from multiple sources can be used in formulating specific recommendations for regular and special educational teachers and for interventions that can be implemented at home. A mental health specialist can be valuable in identifying family-based issues or psychiatric disorders that may be complicating or aggravating neurodevelopmental dysfunctions.

TREATMENT

There are a number of standard approaches that should be incorporated into any management plan for a student who is struggling academically. The primary physician can play an important role as a consultant in overseeing and monitoring the implementation of these steps. Management of children with neurodevelopmental dysfunctions often needs to be multidisciplinary. Most children require several of the following forms of intervention.

Demystification

Many children with neurodevelopmental dysfunctions have little or no understanding of the nature or sources of their academic difficulties. Once an appropriate descriptive assessment has been performed, it is important to explain to the child the nature of the dysfunction while delineating the child's strengths. This explanation should be provided

in nontechnical language, communicating a sense of optimism and a desire to be helpful and supportive.

Bypass Strategies (Accommodations)

Numerous techniques can enable a child to circumvent neurodevelopmental dysfunctions. Such bypass strategies are ordinarily used in the regular classroom. Examples of bypass strategies include using a calculator while solving mathematical problems, writing essays with a word processor, presenting oral instead of written reports, solving fewer mathematical problems, being seated near the teacher to minimize distraction, presenting correctly solved mathematical problems visually, and taking standardized tests untimed. These bypass strategies do not cure neurodevelopmental dysfunctions, but they minimize their academic and nonacademic effects and can provide a scaffold for more successful academic achievement.

Interventions (Remediation of Skills)

Interventions can be implemented at home and in school to strengthen the weak links in academic skills. Reading specialists, mathematics tutors, and other such professionals can use diagnostic data to select techniques that use a student's neurodevelopmental strengths in an effort to improve decoding skills, writing ability, or mathematical computation skills. Remediation need not focus exclusively on specific academic areas. Many students need assistance in acquiring study skills, cognitive strategies, and productive organizational habits.

Early identification is critical so that appropriate instructional interventions can be introduced in an effort to minimize the long-term effects of academic disorders. Any interventions should be empirically supported (e.g., phonologically based reading intervention has been shown to significantly improve reading skills in school-age children). Remediation may take place in a resource room or learning center at school and is usually limited to children who have met the educational criteria for special education resource services as described earlier.

Interventions that can be implemented at home could include drills to aid the automatization of subskills, such as arithmetic facts or letter formations, or the use of phonologically based reading programs.

There are a number of treatment/intervention approaches to strengthening executive function that have demonstrated positive findings. These include computerized training programs such as CogMed (Pearson) that has been demonstrated to strengthen working memory skills in children via a computer game model. Curriculum-based classroom programs, such as the Tools of the Mind (Tools) and PATHS (Promoting Alternative Thinking Strategies) also have accumulating research support. These programs employ approaches such as social play and target areas such as self-control and problem-solving to teach and strengthen executive functions. Aerobic exercise and martial arts such as Tae Kwon Do, which stresses discipline and emphasizes the development of self-regulation (e.g., impulse control), have demonstrated improvements that generalize in many aspects of executive functions and attention.

Developmental Therapy

Controversy exists about the efficacy of treatments to enhance weak developmental functions. Nevertheless, some forms of developmental therapy are widely accepted. Speech-language pathologists commonly offer intervention for children with various forms of language disability. Occupational therapists strive to improve the motor skills of certain students with writing problems, and physical therapists address gross motor clumsiness.

Curriculum Modifications

Many children with neurodevelopmental dysfunctions require alterations in the school curriculum to succeed, especially as they progress through secondary school. Students with memory weaknesses might need to have their courses selected for them so that they do not have an inordinate cumulative memory load in any single semester. The timing of foreign language learning, the selection of a mathematics curriculum, and the choice of science courses are critical issues for many of these struggling adolescents.

Strengthening of Strengths

Affected children need to have their affinities, potentials, and talents identified clearly and exploited widely. It is as important to augment strengths as it is to attempt to remedy deficiencies. Athletic skills, artistic inclinations, creative talents, and mechanical abilities are among the potential assets of certain students who are underachieving academically. Parents and school personnel need to create opportunities for such students to build on these assets and to achieve respect and praise for their efforts. These well-developed personal assets can ultimately have implications for the transition into young adulthood, including career or college selection.

Individual and Family Counseling

When academic difficulties are complicated by family problems or identifiable psychiatric disorders, psychotherapy may be indicated. Clinical psychologists or child psychiatrists may offer long- or short-term therapy. Such intervention may involve the child alone or the entire family. Cognitive-behavioral therapy is a technique that is increasingly popular. It is essential that the therapist have a firm understanding of the nature of a child's neurodevelopmental dysfunctions.

Controversial Therapies

A variety of treatment methods for neurodevelopmental dysfunctions have been proposed that currently have no known scientific evidence base of efficacy. This list includes dietary interventions (vitamins, elimination of food additives or potential allergens), neuromotor programs or medications to address vestibular dysfunction, eye exercises, filters, tinted lenses, and various technologic devices. Parents should be cautioned against expending the excessive amounts of time and financial resources usually demanded by these remedies. In many cases, it is difficult to distinguish the nonspecific beneficial effects of increased support and attention paid to the child from the supposed target effects of the intervention.

Medication

Psychopharmacologic agents may be especially helpful in lessening the toll of neurodevelopmental dysfunctions. Most commonly, stimulant medications are used in the treatment of children with attention deficits. Although most children with attention deficits have other associated dysfunctions (such as language disorders, memory problems, motor weaknesses, or social skill deficits), medications such as methylphenidate, dextroamphetamine, lisdexamfetamine, mixed amphetamine salts, and atomoxetine can be important adjuncts to treatment by helping some children focus more selectively and control their impulsivity. When depression or excessive anxiety is a significant component of the clinical picture, antidepressants or antianxiety drugs may be helpful. Other drugs may improve behavioral control (see Chapter 21). Children receiving medication need regular follow-up visits that include a history to check for side effects, a review of current behavioral checklists, a complete physical examination, and appropriate modifications of the medication dose. Periodic trials off medication are recommended to establish whether the medication is still necessary.

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Chapter 33

Attention-Deficit/ Hyperactivity Disorder

David K. Urion

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood and one of among the most prevalent chronic health conditions affecting school-age children. ADHD is characterized by inattention, including increased distractibility and difficulty sustaining attention; poor impulse control and decreased self-inhibitory capacity; and motor overactivity and motor restlessness (Table 33-1). Definitions vary in different countries (Table 33-2). Affected children commonly experience academic underachievement, problems with interpersonal relationships with family members and peers, and low self-esteem. ADHD often co-occurs with other emotional, behavioral, language, and learning disorders (Table 33-3). For 40-50% of affected children, the disorder appears to continue with varying manifestations into adulthood, and leads to significant under- and unemployment, social dysfunction, and an increased risk of antisocial behaviors including substance abuse, difficulties maintaining relationships, and encounters with the law.

ETIOLOGY

ADHD may be a final common pathway for a variety of complex brain developmental processes. Mothers of children with ADHD are more likely to experience birth complications, such as toxemia, lengthy labor, and complicated delivery. Maternal drug use, smoking and alcohol use during pregnancy, lead or mercury exposure (prenatal or postnatal) are commonly linked to attentional difficulties associated with the development of ADHD. Food colorings and preservatives have inconsistently been associated with hyperactivity in previously hyperactive children.

There is a very strong genetic component to ADHD. Genetic studies have primarily implicated at least 2 candidate genes, the dopamine transporter gene *(DAT1)* and a particular form of the dopamine 4 receptor gene *(DRD4),* in the development of ADHD. Additional genes that might contribute to ADHD include *DOCK2* associated with a pericentric inversion 46N inv(3)(p14:q21) involved in cytokine regulation, a sodium-hydrogen exchange gene, other dopaminergic genes *(DRD5),* serotonergic genes *(5HTT, HTR1B),* and the synaptosomal-associated protein, SNAP-25.

Abnormal brain structures are linked to an increased risk of ADHD; 20% of children with severe traumatic brain injury are reported to have subsequent onset of substantial symptoms of impulsivity and inattention. Children with head or other injury and in whom ADHD is later diagnosed might have impaired balance or impulsive behavior as part of the ADHD, thus predisposing them to injury. Structural and functional abnormalities have been identified in children with ADHD without preexisting identifiable brain injury. These include dysregulation of the frontal subcortical circuits, small cortical volumes in this region, widespread small-volume reduction throughout the brain, and abnormalities of the cerebellum, particularly midline/vermian elements. Abnormalities in neural networks or circuits have been identified with functional MRI.

Psychosocial family stressors can also contribute to or exacerbate the symptoms of ADHD, including poverty, exposure to violence, and under- or malnutrition.

EPIDEMIOLOGY

Studies of the prevalence of ADHD across the globe have generally reported that 9% of school-age children are affected, although rates vary considerably by country, perhaps partly as a result of differing sampling and testing techniques. Rates may be higher if symptoms (inattention, impulsivity, hyperactivity) are considered in the absence of functional impairment. The prevalence rate in adolescent samples is 2-6%. Approximately 2% of adults have ADHD. ADHD is often underdiagnosed in children and adolescents. Youth with ADHD are often undertreated with respect to what is known about the needed and appropriate doses of medications. Many children with ADHD also present with comorbid neuropsychiatric diagnoses, including opposition defiant disorder, conduct disorder, learning disabilities, depression, and anxiety disorders. The incidence of ADHD appears increased in children with neurologic disorders such as epilepsies, neurofibromatosis, tuberous sclerosis (see Table 33-3).

PATHOGENESIS

MRI studies indicate that a loss of normal asymmetry in the brain, in addition to smaller brain volumes of specific structures, such as the prefrontal cortex and basal ganglia, is seen in the brains of children with ADHD. Children with ADHD have approximately a 5-10% reduction in the volume of these brain structures. Functional MRI findings suggest low blood flow to the striatum. Functional MRI data also suggest deficits in a widespread functional networks for selective and tonic attention in ADHD, that include the striatum, prefrontal regions, parietal lobe, and temporal lobe. The prefrontal cortex and basal ganglia are rich in dopamine receptors. This knowledge, plus data about the dopaminergic mechanisms of action of medication treatment for ADHD, has led to the **dopamine hypothesis,** which postulates that disturbances in the dopamine system may be related to the onset of ADHD. Fluorodopa positron emission tomography scans also support the dopamine hypothesis through the identification of low levels of dopamine activity in adults.

CLINICAL MANIFESTATIONS

Development of the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (DSM-IV) criteria leading to the diagnosis of ADHD occurred mainly in field trials with children 5-12 yr of age. Fewer studies utilizing *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) criteria are available, but those that are available suggest a good correlation with data from DSM-IV criteria-based studies, despite the broadened age-based definition for onset of symptoms in DSM-5 (see Table 33-1). The current DSM-5 criteria state that the behavior must be developmentally inappropriate (substantially different from that of other children of the same age and developmental level), must begin before age 12 yr, must be present for at least 6 mo, must be present in 2 or more settings and reported as such by independent observers, and must not be secondary to another disorder. DSM-5 identifies 3 subtypes of ADHD. The first subtype, *ADHD, predominantly inattentive type,* often includes cognitive impairment and is more common in females. The other 2 subtypes, *ADHD, predominantly hyperactive-impulsive type,* and *ADHD, combined type,* are more commonly diagnosed in males. Clinical manifestations of ADHD may change with age. The symptoms may vary from motor restlessness and aggressive and disruptive behavior, which are common in preschool children, to disorganized, distractible, and inattentive symptoms, which are more typical in older adolescents and adults. ADHD is often difficult to diagnose in preschoolers because distractibility and inattention are may be considered developmental norms during this period.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A diagnosis of ADHD is made primarily in clinical settings after a thorough evaluation, including a careful history and clinical interview to rule in or to identify other causes or contributing factors; completion of behavior rating scales by different observers from at least 2 settings (e.g., teacher and parent); a physical examination; and any necessary or indicated laboratory tests which arise from conditions suspected based on history and/or physical examination. It is important to systematically gather and evaluate information from a variety of sources, including the child, parents, teachers, physicians, and, when appropriate, other caretakers, over the course of both diagnosis and subsequent management.

Table 33-1 DSM-5 Diagnostic Criteria for Attention-Deficit/Hyperactivity Disorder

DIAGNOSTIC CRITERIA

1. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):
   1. **Inattention:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
      1. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities (e.g., overlooks or misses details, work is inaccurate).
      2. Often has difficulty sustaining attention in tasks or play activities (e.g., has difficulty remaining focused during lectures, conversations, or lengthy reading).
      3. Often does not seem to listen when spoken to directly (e.g., mind seems elsewhere, even in the absence of any obvious distraction).
      4. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., starts tasks but quickly loses focus and is easily sidetracked).
      5. Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks; difficulty keeping materials and belongings in order; messy, disorganized work; has poor time management; fails to meet deadlines).
      6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (e.g., schoolwork or homework; for older adolescents and adults, preparing reports, completing forms, reviewing lengthy papers).
      7. Often loses things necessary for tasks or activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
      8. Is often easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
      9. Is often forgetful in daily activities (e.g., doing chores, running errands; for older adolescents and adults, returning calls, paying bills, keeping appointments).
   2. **Hyperactivity and impulsivity:** Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:
      - **Note:** The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (age 17 and older), at least five symptoms are required.
      1. Often fidgets with or taps hands or feet or squirms in seat.
      2. Often leaves seat in situations when remaining seated is expected (e.g., leaves his or her place in the classroom, in the office or other workplace, or in other situations that require remaining in place).
      3. Often runs about or climbs in situations where it is inappropriate. (**Note:** In adolescents or adults, may be limited to feeling restless.)
      4. Often unable to play or engage in leisure activities quietly.
      5. Is often "on the go," acting as if "driven by a motor" (e.g., is unable to be or uncomfortable being still for extended time, as in restaurants, meetings; may be experienced by others as being restless or difficult to keep up with).
      6. Often talks excessively.
      7. Often blurts out an answer before a question has been completed (e.g., completes people's sentences; cannot wait for turn in conversation).
      8. Often has difficulty waiting his or her turn (e.g., while waiting in line).
      9. Often interrupts or intrudes on others (e.g., butts into conversations, games, or activities; may start using other people's things without asking or receiving permission; for adolescents and adults, may intrude into or take over what others are doing).
2. Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.
3. Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).
4. There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.
5. The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

Specify whether:

- **Combined presentation:** If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
- **Predominantly inattentive presentation:** If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
- **Predominantly hyperactive/impulsive presentation:** If Criterion A2 (hyperactivity-impulsivity) is met and Criterion A1 (inattention) is not met for the past 6 months.

Specify if:

- **In partial remission:** When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning.

Specify current severity:

- **Mild:** Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in no more than minor impairments in social or occupational functioning.
- **Moderate:** Symptoms or functional impairment between "mild" and "severe" are present.
- **Severe:** Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning.

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Clinical Interview and History

The clinical interview allows a comprehensive understanding as to whether the symptoms meet the diagnostic criteria for ADHD. During the interview, the clinician should gather information pertaining to the history of the presenting problems, the child's overall health and development, and the social and family history. The interview should emphasize factors that might affect the development or integrity of the central nervous system or reveal chronic illness, sensory impairments, or medication use that might affect the child's functioning. Disruptive social factors, such as family discord, situational stress, and abuse or neglect, can result in hyperactive or anxious behaviors. A family history of 1st-degree relatives with ADHD, mood or anxiety disorders, learning disability, antisocial disorder, or alcohol or substance abuse might indicate an increased risk of ADHD and/or comorbid conditions.

Table 33-2 Differences Between U.S. and European Criteria for ADHD or HKD

DSM-5 ADHD	ICD-10 HKD
SYMPTOMS	
Either or both of following: At least 6 of 9 inattentive symptoms At least 6 of 9 hyperactive or impulsive symptoms	All of following: At least 6 of 8 inattentive symptoms At least 3 of 5 hyperactive symptoms At least 1 of 4 impulsive symptoms
PERVASIVENESS	
Some impairment from symptoms is present in >1 setting	Criteria are met for >1 setting

ADHD, attention-deficit/hyperactivity disorder; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; HKD, hyperkinetic disorder; ICD-10, *International Classification of Diseases, 10th edition.*

Adapted from Biederman J, Faraone S: Attention-deficit hyperactivity disorder, Lancet *366:237–248, 2005.*

Table 33-3 Differential Diagnosis of Attention-Deficit/Hyperactivity Disorder

PSYCHOSOCIAL FACTORS
Response to physical or sexual abuse
Response to inappropriate parenting practices
Response to parental psychopathology
Response to acculturation
Response to inappropriate classroom setting
DIAGNOSES ASSOCIATED WITH ADHD BEHAVIORS
Fragile X syndrome
Fetal alcohol syndrome
Pervasive developmental disorders
Obsessive-compulsive disorder
Gilles de la Tourette syndrome
Attachment disorder with mixed emotions and conduct
MEDICAL AND NEUROLOGIC CONDITIONS
Thyroid disorders (including general resistance to thyroid hormone)
Heavy metal poisoning (including lead)
Adverse effects of medications
Effects of abused substances
Sensory deficits (hearing and vision)
Auditory and visual processing disorders
Neurodegenerative disorder, especially leukodystrophies
Posttraumatic head injury
Postencephalitic disorder

Note: Coexisting conditions with possible ADHD presentation include oppositional defiant disorder, anxiety disorders, conduct disorder, depressive disorders, learning disorders, and language disorders. Presence of 1 or more of the symptoms of these disorders can fall within the spectrum of normal behavior, whereas a range of these symptoms may be problematic but fall short of meeting the full criteria for the disorder.

From Reiff MI, Stein MT: Attention-deficit/hyperactivity disorder evaluation and diagnosis: a practical approach in office practice, Pediatr Clin North Am *50:1019–1048, 2003. Adapted from Reiff MI: Attention-deficit/hyperactivity disorders. In Bergman AB, editor:* 20 Common problems in pediatrics, *New York, 2001, McGraw-Hill, p 273.*

Behavior Rating Scales

Behavior rating scales are useful in establishing the magnitude and pervasiveness of the symptoms, but are not sufficient alone to make a diagnosis of ADHD. There are a variety of well-established behavior rating scales that have obtained good results in discriminating between children with ADHD and control subjects. These measures include, but are not limited to, the Vanderbilt ADHD Diagnostic Rating Scale; the Conner Rating Scales (parent and teacher); the ADHD Index; the Swanson, Nolan, and Pelham Checklist (SNAP); and the ADD-H: Comprehensive Teacher Rating Scale (ACTeRS). Other broadband checklists, such as the Achenbach Child Behavior Checklist (CBCL) or Behavioral Assessment Scale for Children (BASC), are useful, particularly in instances where the child may be experiencing co-occurring problems in other areas (anxiety, depression, conduct problems). Some, such as the BASC, include a validation scale to help determine the reliability of a given observer's assessment of the child.

Physical Examination and Laboratory Findings

There are no standard laboratory tests available to identify ADHD in children. The presence of hypertension, ataxia, or a thyroid disorder should prompt further diagnostic evaluation. Impaired fine motor movement and poor coordination and other **subtle neurologic motor signs** (difficulties with finger tapping, alternating movements, finger-to-nose, skipping, tracing a maze, cutting paper) are common, but they are not sufficiently specific to contribute to a diagnosis of ADHD. The clinician should also identify any possible vision or hearing problems. The clinician should consider testing for elevated lead levels in children who present with some or all of the diagnostic criteria, if these children are exposed to environmental factors that might put them at risk (substandard housing, old paint, proximity to a highway which led to deposition of lead in the topsoil from automobile exhaust years ago). Behavior in the structured laboratory setting might not reflect the child's typical behavior in the home or school environment. Therefore, reliance on observed behavior in a physician's office can result in an incorrect diagnosis. Computerized attentional tasks and electroencephalographic assessments are not needed to make the diagnosis, and compared to the clinical gold standard they are subject to false-positive and false-negative errors. Nonetheless, the FDA has approved the Neuropsychiatric EEG-Based Assessment Aide (NEBA) system, which may identify an abnormal theta : beta wave ratio associated with ADHD.

Differential Diagnosis

Chronic illnesses, such as migraine headaches, absence seizures, asthma and allergies, hematologic disorders, diabetes, childhood cancer, affect up to 20% of children in the United States and can impair children's attention and school performance, either because of the disease itself or because of the medications used to treat or control the underlying illness (medications for asthma, steroids, anticonvulsants, antihistamines) (see Table 33-3). In older children and adolescents, **substance abuse** (see Chapter 114) can result in declining school performance and inattentive behavior.

Sleep disorders, including those secondary to chronic upper airway obstruction from enlarged tonsils and adenoids, often result in behavioral and emotional symptoms, although such problems are not likely to be principal contributing causes of ADHD (see Chapter 19). Periodic leg movements of sleep/restless leg syndrome is associated with attentional symptoms, and inquiry regarding this should be made during the history. Behavioral and emotional disorders can cause disrupted sleep patterns as well.

Depression and anxiety disorders (see Chapters 25 and 26) can cause many of the same symptoms as ADHD (inattention, restlessness, inability to focus and concentrate on work, poor organization, forgetfulness), but can also be comorbid conditions. Obsessive-compulsive disorder can mimic ADHD, particularly when recurrent and persistent thoughts, impulses, or images are intrusive and interfere with normal daily activities. Adjustment disorders secondary to major life stresses (death of a close family member, parents' divorce, family violence, parents' substance abuse, a move, shared social trauma such as bombings or other attacks) or parent–child relationship disorders involving conflicts over discipline, overt child abuse and/or neglect, or overprotection can result in symptoms similar to those of ADHD.

Although ADHD is believed to result from primary impairment of attention, impulse control, and motor activity, there is a high prevalence of comorbidity with other neuropsychiatric disorders (see Table 33-3). Of children with ADHD, 15-25% have learning disabilities, 30-35% have developmental language disorders, 15-20% have

diagnosed mood disorders, and 20-25% have coexisting anxiety disorders. Children with ADHD can also have co-occurring diagnoses of sleep disorders, memory impairment, and decreased motor skills.

TREATMENT

Psychosocial Treatments

Once the diagnosis of ADHD is established, the caregiver should discuss with the parents and child the ways ADHD can affect learning, behavior, self-esteem, social skills, and family function. The clinician should set goals for the family to improve the child's interpersonal relationships, develop study skills, and decrease disruptive behaviors. Parent support groups with appropriate professional consultation to such groups can be very helpful.

Behaviorally Oriented Treatments

Treatments geared toward behavioral management often occur in the time frame of 8-12 sessions. The goal of such treatment is for the clinician to identify targeted behaviors that cause impairment in the child's life (disruptive behavior, difficulty in completing homework, failure to obey home or school rules) and for the child to work on progressively improving the child's skill in these areas. The clinician should guide the parents and teachers in implementing rules, consequences, and rewards to encourage desired behaviors. In short-term comparison trials, stimulants have been more effective than behavioral treatments used alone; behavioral interventions are only modestly successful at improving behavior, but they may be particularly useful for children with complex comorbidities and family stressors, when combined with medication.

Medications

The most widely used medications for the treatment of ADHD and the treatment of choice are the presynaptic dopaminergic agonists, commonly called psychostimulant medications, including methylphenidate (Ritalin, Concerta, Metadate, Focalin, Daytrana), amphetamine, and/or various amphetamine and dextroamphetamine preparations (Dexedrine, Adderall, Vyvanse) (Table 33-4). Longer-acting, once-daily forms of each of the major types of stimulant medications are available and facilitate compliance with treatment and coverage over a longer period of time. The clinician should prescribe a stimulant treatment, either methylphenidate or an amphetamine compound. If a full range of methylphenidate dosages is used, approximately 25% of patients have an optimal response on a low (<0.5 mg/kg/day for methylphenidate, <0.25 mg/kg/day for amphetamines), 25% on medium (0.5-1.0 mg/kg/day for methylphenidate, 0.25-0.5 mg/kg/day for amphetamines), or high (1.0-1.5 mg/day for methylphenidate, 0.5-0.75 mg/kg/day for amphetamine) daily dosage; another 25% will be unresponsive or will have side effects, making that drug particularly unpalatable for the family.

Over the first 4 wk of treatment, the physician should increase the medication dose as tolerated (keeping side effects minimal to absent) to achieve maximum benefit. If this strategy does not yield satisfactory results, or if side effects prevent further dose adjustment in the presence of persisting symptoms, the clinician should use an alternative class of stimulants that was not used previously. If a methylphenidate compound is unsuccessful, the clinician should switch to an amphetamine product. If satisfactory treatment results are not obtained with the second stimulant, clinicians may choose to prescribe atomoxetine, a noradrenergic reuptake inhibitor that is superior to placebo in the treatment of ADHD in children, adolescents, and adults and that has been approved by the FDA for this indication. Atomoxetine should be initiated at a dose of 0.3 mg/kg/day and titrated over 1-3 wk to a maximum total daily dosage of 1.2-1.8 mg/kg/day. The dose should be divided into twice-daily portions. Once-daily dosing appears to be associated with a high incidence of treatment failure. Guanfacine, originally developed as an antihypertensive agent, is also FDA approved for the treatment of ADHD, although it appears to be less successful for hyperactivity and more likely to assist with impulsivity. It can also treat motor and vocal tics, and so may be a reasonable choice in a child with a comorbid tic disorder.

The clinician should recognize that careful monitoring of medication is a necessary component of treatment in children with ADHD. When physicians prescribe medications for the treatment of ADHD, they tend to use lower-than-optimal doses. Optimal treatment usually requires somewhat higher doses than those typically used in routine practice settings. All-day preparations are also useful to maximize positive effects and minimize side effects, and regular medication follow-up visits should be offered (4 or more times per year) as opposed to the twice-yearly medication visits often used in standard community-care settings.

Medication alone is not always sufficient to treat ADHD in children, particularly in instances where children have multiple psychiatric disorders or stressed home environments. When children do not respond to medication, it may be appropriate to refer them to a mental health specialist. Consultation with a child psychiatrist or psychologist can also be beneficial to determine the next steps for treatment, including adding other components and supports to the overall treatment program. Evidence suggests that children who receive careful medication management, accompanied by frequent treatment follow-up, all within the context of an educative, supportive relationship with the primary care provider, are likely to experience behavioral gains for up to 24 mo.

Stimulant drugs used to treat ADHD may be associated with an increased risk of adverse cardiovascular events, including sudden cardiac death, myocardial infarction, and stroke in young adults and rarely in children. In some of the reported cases, the patient had an underlying disorder, such as hypertrophic obstructive cardiomyopathy, which is made worse by sympathomimetic agents. These events are rare, but they nonetheless warrant consideration before initiating treatment and during monitoring of treatment with stimulant medications. Children with a positive or personal family history of cardiomyopathy, or arrhythmias, or syncope require an electrocardiogram and possible cardiology consultation before a stimulant is prescribed (Fig. 33-1).

PROGNOSIS

A childhood diagnosis of ADHD often leads to persistent ADHD throughout the life span. From 60-80% of children with ADHD continue to experience symptoms in adolescence, and up to 60% of adolescents exhibit ADHD symptoms into adulthood. In children with ADHD, a reduction in hyperactive behavior often occurs with age. Other symptoms associated with ADHD can become more prominent with age, such as inattention, impulsivity, and disorganization, and

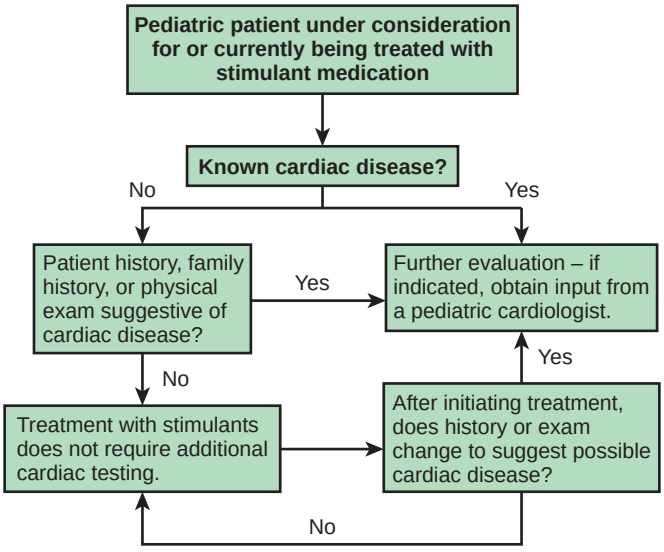

Figure 33-1 Cardiac evaluation of children and adolescents receiving or being considered for stimulant medications. *(From Perrin JM, Friedman RA, Knilans TK: Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder,* Pediatrics *122:451–453, 2008.)*

Table 33-4 Medications Used in the Treatment of Attention-Deficit/Hyperactivity Disorder

GENERIC NAME	BRAND NAME	DURATION	DOSAGE RANGE	SIDE EFFECTS
METHYLPHENIDATE				
Immediate-release	Ritalin, Methylin	3-4 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
Extended-release	Metadate ER, Methylin ER,	4-6 hr	10, 20 mg extended-release tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
	Metadate-CD	8-10 hr	10, 20, 30 mg extended-release caps	
	Ritalin LA	8-10 hr	20, 30, 40 mg caps	
	Concerta	10-12 hr	18, 27, 36, 54 mg caps	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Sustained-release	Ritalin SR, Methylphenidate SR	4-6 hr	20 mg sustained-release tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
Transdermal system	Daytrana	≥12 hr	Patch	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics, priapism
DEXMETHYLPHENIDATE				
	Focalin	4-6 hr	2.5, 5, 10 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Extended-release	Focalin XR	6-8 hr		Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
DEXTROAMPHETAMINE				
Short-acting	Dexedrine, DextroStat	4-6 hr	5, 10, 15 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Intermediate-acting	Dexedrine, Spansule	6-8 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Lisdexamfetamine	Vyvanse	≤12 hr	30 mg, 50 mg, 70 mg tablets	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
MIXED AMPHETAMINE SALTS				
Intermediate-acting	Adderall	4-6 hr	5, 10, 20 mg tabs	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
Extended-release	Adderall XR	8-12 hr	5, 10, 15, 20, 25, 30 mg caps	Moderate appetite suppression, mild sleep disturbances, transient weight loss, irritability, emergence of tics
ATOMOXETINE				
Extended-release	Strattera	12 hr	10, 18, 25, 40, 60 mg caps	Nervousness, sleep problems, fatigue, stomach upset, dizziness, dry mouth Can lead in rare cases to severe liver injury or to suicidal ideation
Bupropion	Wellbutrin	4-5 hr	100, 150 mg tabs	Difficulty sleeping, headache, seizures
Bupropion	Wellbutrin SR, Wellbutrin XL		100, 150, 200 mg tabs	
TRICYCLIC ANTIDEPRESSANTS				
Imipramine	Tofranil	Variable	See Table 21-4	Nervousness, sleep problems, fatigue, stomach upset, dizziness, dry mouth, accelerated heart rate
Desipramine*	Norpramin			
Nortriptyline	Aventyl, Pamelor			
α-AGONISTS				
Clonidine	Catapres, Kapvay	6-12 hr	3-10 μg/kg/day bid-qid	Sedation, depression, dry mouth, rebound hypertension on discontinuing, confusion
Guanfacine	Tenex, Intuniv	6-12 hr	1, 2, 3 mg tabs	Hypotension, lightheadedness

cap, capsule; tab, tablet.
*Associated with deaths from cardiac problems. Not recommended for children.

these exact a heavy toll on young adult functioning. A variety of risk factors can affect children with untreated ADHD as they become adults. These risk factors include engaging in risk-taking behaviors (sexual activity, delinquent behaviors, substance use), educational underachievement or employment difficulties, and relationship difficulties. With proper treatment, the risks associated with the disorder can be significantly reduced. It appears that consistent treatment with medication and adjuvant therapies can lower the risk of adverse outcomes, such as substance abuse.

PREVENTION

Parent training can lead to significant improvements in preschool children with ADHD symptoms, and parent training for preschool youth with ADHD can reduce oppositional behavior. To the extent that parents, teachers, physicians, and policymakers support efforts for earlier detection, diagnosis, and treatment, prevention of long-term adverse effects of ADHD on affected children's lives should be reconsidered within the lens of prevention. Given the effective treatments for ADHD now available, and the well-documented evidence about the long-term effects of untreated or ineffectively treated ADHD on children and youth, prevention of these consequences should be within the grasp of physicians and the children and families with ADHD for whom we are responsible.

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Chapter 34

Dyslexia

Sally E. Shaywitz and Bennett A. Shaywitz

Dyslexia is defined in this chapter as an *unexpected difficulty* in reading, that is, unexpected in relation to intelligence, chronological age/grade level, education, or professional status. In typical readers, development of reading and IQ are dynamically linked over time, but in dyslexic readers there is a developmental uncoupling between reading and IQ (Fig. 34-1). These findings provide an explanation for the "unexpected" nature of dyslexia and provide the long sought empirical evidence for the seeming paradox between cognition and reading in individuals with developmental dyslexia.

ETIOLOGY

Dyslexia is both familial and heritable. Dyslexia is observed in 50% of children who have a parent with dyslexia; 50% of the siblings of dyslexic persons; and 50% of the parents of dyslexics. Dyslexia reflects a multifactorial model of the interaction between genetic and environmental factors. Multiple genes can influence the disorder, with each gene individually contributing a small amount of variance and with a single etiologic factor insufficient to cause or explain dyslexia. The neural systems are the final common pathway for multiple influences, and it is unlikely that a single gene or even several genes cause or explain dyslexia.

EPIDEMIOLOGY

Dyslexia is the most common and most comprehensively studied of the **learning disabilities,** affecting 80% of children identified as learning disabled. Dyslexia may be the most common neurobehavioral disorder affecting children, with prevalence rates ranging from 5-10% in clinic- and school-identified samples to 17.5% in unselected population-based samples in the United States and other countries. Dyslexia fits a dimensional model in which reading ability and disability occur along a continuum, with dyslexia representing the lower tail of a normal distribution of reading ability. Although more boys than girls are identified by schools as dyslexic, in studies based on survey samples in which *all* children are assessed, there are no significant gender differences in dyslexia.

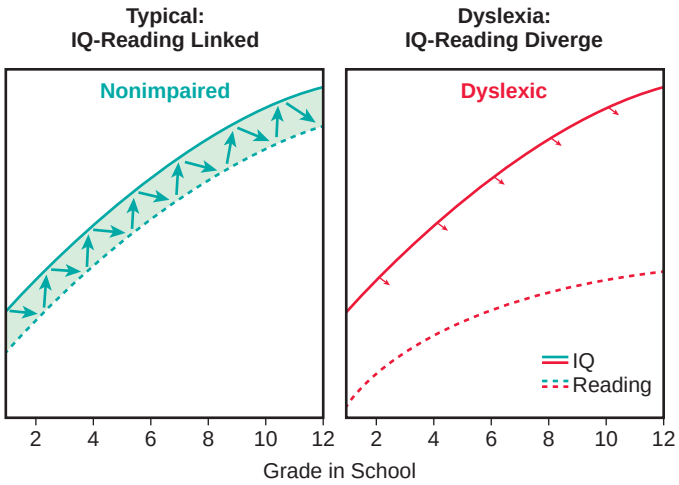

Figure 34-1 Uncoupling of reading and IQ over time: empirical evidence for a definition of dyslexia. *Left* panel shows that in typical readers, reading and IQ development are dynamically linked over time. In contrast, *right* panel, dyslexic readers, shows that reading and IQ development are dissociated and one does not influence the other. *(Data adapted from Ferrer E, Shaywitz BA, Holahan JM, et al: Uncoupling of reading and IQ over time: empirical evidence for a definition of dyslexia,* Psychol Sci *21(1):93–101, 2010.)*

PATHOGENESIS

Evidence from a number of lines of investigation indicates that dyslexia reflects deficits within the language system, and more specifically, within the phonologic component of the language system engaged in processing the sounds of speech. Dyslexic individuals have difficulty developing an awareness that spoken words can be segmented into smaller elemental units of sound **(phonemes),** an essential ability given that reading requires that the reader map or link printed symbols to sound. Increasing evidence indicates that disruption of attentional mechanisms may also play an important role in reading difficulties.

Functional brain imaging in both children with dyslexia and adult dyslexic readers demonstrates an inefficient functioning of left hemisphere posterior brain systems, a pattern referred to as the *neural signature of dyslexia* (Fig. 34-2). Although functional MRI consistently demonstrates differences between *groups* of dyslexic compared to typical readers, brain imaging is not able to differentiate an *individual* case of dyslexic reader from a typical reader and so brain imaging is not useful in diagnosing dyslexia.

CLINICAL MANIFESTATIONS

Reflecting the underlying phonologic weakness, children and adults with dyslexia manifest problems in both spoken and written language. Spoken language difficulties are typically manifest by mispronunciations, lack of glibness, speech that lacks fluency with many pauses or hesitations and "ums," word-finding difficulties with the need for time to summon an oral response and the inability to come up with a verbal response quickly when questioned; these reflect sound-based, and not semantic or knowledge-based difficulties.

Struggles in decoding and word recognition can vary according to age and developmental level. The cardinal signs of dyslexia observed in school-age children and adults are a labored, effortful approach to reading involving decoding, word recognition, and text reading. Listening comprehension is typically robust. Older children improve reading accuracy over time, albeit without commensurate gains in reading fluency; they remain slow readers. Difficulties in spelling typically reflect the phonologically based difficulties observed in oral reading. Handwriting is often affected as well.

History often reveals early subtle language difficulties in dyslexic children. During the preschool and kindergarten years, at-risk children display difficulties playing rhyming games and learning the names for letters and numbers. Kindergarten assessments of these language skills can help identify children at risk for dyslexia. Although a dyslexic child enjoys and benefits from being read to, the child might avoid reading aloud to the parent or reading independently.

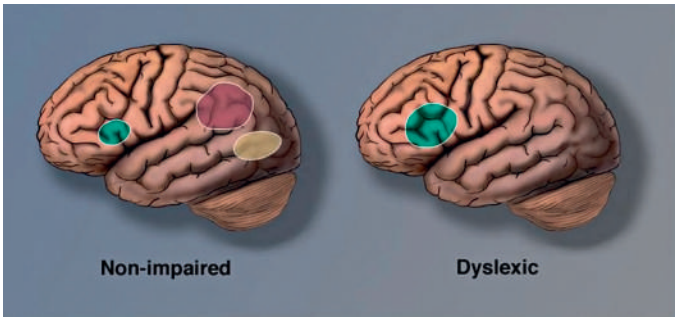

Figure 34-2 A neural signature for dyslexia. The *left* side of the figure shows a schematic of left hemisphere brain systems in in typical (non-impaired) readers. The 3 systems for reading are an anterior system in the region of the inferior frontal gyrus (Broca's area), serving articulation and word analysis, and 2 posterior systems, 1 in the occipitotemporal region serving word analysis, and a second in the occipitotemporal region (the word-form area) serving the rapid, automatic, fluent identification of words. In dyslexic readers (*right* side of figure), the 2 posterior systems are functioning inefficiently and appear underactivated. This pattern of underactivation in left posterior reading systems is referred to as the neural signature for dyslexia. *(Adapted from Shaywitz S:* Overcoming dyslexia: a new and complete science-based program for reading problems at any level. *New York, 2003, Alfred A. Knopf. Copyright 2003 by S. Shaywitz. Adapted with permission.)*

Dyslexia may co-occur with attention-deficit/hyperactivity disorder (see Chapter 33); this comorbidity has been documented in both referred samples (40% comorbidity) and nonreferred samples (15% comorbidity).

DIAGNOSIS

Dyslexia is a clinical diagnosis, and history is especially critical. The clinician seeks to determine through history, observation, and psychometric assessment, if there are unexpected difficulties in reading (based on the person's intelligence, chronological/grade, level of education or professional status) and associated linguistic problems at the level of phonologic processing. There is no single test score that is pathognomonic of dyslexia. The diagnosis of dyslexia should reflect a thoughtful synthesis of all clinical data available.

Dyslexia is distinguished from other disorders that can prominently feature reading difficulties by the unique, circumscribed nature of the phonologic deficit, one that does not intrude into other linguistic or cognitive domains. Family history, teacher and classroom observation, and tests of language (particularly phonology), reading including fluency, and spelling represent a core assessment for the diagnosis of dyslexia in children; additional tests of intellectual ability, attention, memory, general language skills, and mathematics may be administered as part of a more comprehensive evaluation of cognitive, linguistic, and academic function. Once a diagnosis has been made, dyslexia is a permanent diagnosis and need not be reconfirmed by new assessments.

For informal screening, in addition to a careful history, the primary care physician in an office setting can listen to the child read aloud from the child's own grade-level reader. Keeping a set of graded readers available in the office serves the same purpose and eliminates the need for the child to bring in schoolbooks. Oral reading is a sensitive measure of reading accuracy and fluency. The most consistent and telling sign of a reading disability in an accomplished young adult is slow and laborious reading and writing. In attempting to read aloud, most children and adults with dyslexia display an effortful approach to decoding and recognizing single words, an approach in children characterized by hesitations, mispronunciations, and repeated attempts to sound out unfamiliar words. In contrast to the difficulties they experience in decoding single words, persons with dyslexia typically possess the vocabulary, syntax, and other higher-level abilities involved in comprehension.

The failure either to recognize or to measure the lack of fluency in reading is perhaps the most common error in the diagnosis of dyslexia in older children and accomplished young adults. Simple word identification tasks will not detect dyslexia in a person who is accomplished enough to be in honors high school classes or to graduate from college or obtain a graduate degree. Tests relying on the accuracy of word identification alone are inappropriate to use to diagnose dyslexia because they show little to nothing of the struggle to read. Because they assess reading accuracy but not automaticity (speed), the kinds of reading tests commonly used for school-age children might provide misleading data on bright adolescents and young adults. The most critical tests are those that are timed; they are the most sensitive in detecting dyslexia in a bright adult. There are few standardized tests for young adult readers that are administered under timed and untimed conditions; the Nelson-Denny Reading Test is an exception. The helpful Test of Word Reading Efficiency (TOWRE) examines simple word reading under timed conditions. Any scores obtained on testing must be considered relative to peers with the same degree of education or professional training.

MANAGEMENT

The management of dyslexia demands a life-span perspective. Early on, the focus is on remediation of the reading problem. Application of knowledge of the importance of early language, including vocabulary and phonologic skills, leads to significant improvements in children's reading accuracy, even in predisposed children. As a child matures and enters the more time-demanding setting of secondary school, the emphasis shifts to the important role of providing accommodations. Based on the work of the National Reading Panel, evidence-based reading intervention methods and programs are identified. Effective intervention programs provide systematic instruction in 5 key areas: phonemic awareness, phonics, fluency, vocabulary, and comprehension strategies. These programs also provide ample opportunities for writing, reading, and discussing literature.

Taking each component of the reading process in turn, effective interventions improve **phonemic awareness:** the ability to focus on and manipulate phonemes (speech sounds) in **spoken** syllables and words. The elements found to be most effective in enhancing phonemic awareness, reading, and spelling skills include teaching children to manipulate phonemes with letters; focusing the instruction on 1 or 2 types of phoneme manipulations rather than multiple types; and teaching children in small groups. Providing instruction in phonemic awareness is necessary but not sufficient to teach children to read. Effective intervention programs include teaching **phonics,** or making sure that the beginning reader understands how letters are linked to sounds (phonemes) to form letter-sound correspondences and spelling patterns. The instruction should be explicit and systematic; phonics instruction enhances children's success in learning to read, and systematic phonics instruction is more effective than instruction that teaches little or no phonics or teaches phonics casually or haphazardly.

Fluency is of critical importance because it allows the automatic, rapid recognition of words and while it is generally recognized that fluency is an important component of skilled reading, it has proven difficult to teach. Interventions for **vocabulary development and reading comprehension** are not as well established. The most effective methods to teach reading comprehension involve teaching **vocabulary** and **strategies** that encourage active interaction between the reader and the text. Emerging science indicates that it is not only teacher content knowledge but the teacher's skill in engaging the student and focusing the student's attention on the reading task at hand that is required for effective instruction.

For those in high school, college, and graduate school, provision of accommodations most often represents a highly effective approach to dyslexia. Imaging studies now provide neurobiologic evidence for the need for extra time for dyslexic students; accordingly, college students with a childhood history of dyslexia require extra time in reading and writing assignments as well as examinations. Many adolescent and adult students have been able to improve their reading accuracy but without commensurate gains in reading speed. The accommodation of extra time reconciles the individual's often high cognitive ability and slow reading so that the exam is a measure of that person's ability rather than his disability. Another important accommodation is teaching the dyslexic student to listen to texts. Programs such as Kurzweil, WYNN, Learning Ally, and Bookshare are available, as are programs such as Dragon Dictate that provide voice-to-text conversion. Other helpful accommodations include the use of laptop computers with spelling checkers, access to lecture notes, tutorial services, and a separate quiet room for taking tests. In addition, the impact of the primary phonologic weakness mandates special consideration during oral examinations so that students are not graded on their lack of glibness or speech hesitancies but on their content knowledge. Unfortunately, often speech hesitancies or difficulties in word retrieval are wrongly confused with insecure content knowledge.

PROGNOSIS

Application of evidence-based methods to young children (kindergarten to grade 3), when provided with sufficient intensity and duration, can result in improvements in reading accuracy and, to a much lesser extent, fluency. In older children and adults, interventions result in improved accuracy, but not an appreciable improvement in fluency. Accommodations are critical in allowing the dyslexic child to demonstrate his or her knowledge. Parents should be informed that with proper support, dyslexic children can succeed in a range of future occupations that might seem out of the reach of dyslexic children including medicine, law, journalism, and writing.

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Chapter 35

Language Development and Communication Disorders

Mark D. Simms

Most children learn to communicate in their native language without specific instruction or intervention other than exposure to a language-rich environment. Normal development of speech and language is predicated on the infant's ability to hear, see, comprehend, remember, and socially interact with others. The infant must also possess sufficient motor skills to imitate oral motor movements.

NORMAL LANGUAGE DEVELOPMENT

Language can be subdivided into several essential components. **Communication** consists of a wide range of behaviors and skills. At the level of basic verbal ability, **phonology** refers the correct use of speech sounds to form words, **semantics** refers to the correct use of words, and **syntax** refers to the appropriate use of grammar to make sentences. At a more abstract level, verbal skills include the ability to link thoughts together in a coherent fashion and to maintain a topic of conversation. **Pragmatic** abilities include verbal and nonverbal skills that facilitate the exchange of ideas, including the appropriate choice of language for the situation and circumstance and the appropriate use of body language (i.e., posture, eye contact, gestures). Social pragmatic and behavioral skills also play an important role in effective interactions with communication partners (i.e., engaging, responding, and maintaining reciprocal exchanges).

It is customary to divide language skills into receptive (hearing and understanding) and expressive (talking) abilities. Language development usually follows a fairly predictable pattern and parallels general intellectual development (Table 35-1).

Receptive Language Development

The peripheral auditory system is mature by 26 wk gestation and the fetus responds to and discriminates speech sounds. Anatomical asymmetry in the *planum temporale*, the structural brain region specialized for language processing, is present by 31 wk gestation. At birth, the full-term newborn appears to have functionally organized neural networks that are sensitive to different properties of language input. The normal newborn demonstrates preferential response to human voices over inanimate sound, and recognizes the mother's voice, reacting stronger to it than to a stranger's voice. Even more remarkable is the ability of the newborn to discriminate sentences in their "native" (mother's) language from sentences in a "foreign" language. In research settings, infants of monolingual mothers showed a preference only for that language, while infants of bilingual mothers showed a preference for both exposed languages over any other language.

Between 4 and 6 mo, infants visually search for the source of sounds, again showing a preference for the human voice over other environmental sounds. By 5 mo, infants can passively follow the adult's line of visual regard, resulting in a "joint reference" to the same objects and events in the environment. The ability to share the same experience is critical to the development of further language, social, and cognitive skills as the infant "maps" specific meanings onto his or her experiences. By 8 mo, the infant can actively show, give, and point to objects. Comprehension of words often becomes apparent by 9 mo, when the infant selectively responds to his or her name and appears to comprehend the word "no." Social games, such as "peek-a-boo," "so big," and waving "bye-bye" can be elicited by simply mentioning the words. At 12 mo, many children can follow a simple, one-step request without a gesture (e.g., "Give it to me!").

Between 1 and 2 yr, comprehension of language accelerates rapidly. Toddlers can point to body parts on command, identify pictures in books when named, and respond to simple questions (e.g., "Where's your shoe?"). The 2 yr old is able to follow a 2-step command, employing unrelated tasks (e.g., "Take off your shoes, then go sit at the table"), and can point to objects described by their use (e.g., "Give me the one we drink from"). By 3 yr, children typically understand simple "wh-" question forms (e.g., who, what, where, why). By 4 yr, most children can follow adult conversation. They can listen to a short story and answer simple questions about it. Five yr olds typically have a receptive vocabulary of more than 2000 words and can follow 3- and 4-step commands.

Expressive Language Development

Cooing noises are established by 4-6 wk of age. Over the first 3 mo of life, parents may distinguish their infant's different vocal sounds for pleasure, pain, fussing, tiredness, etc. Many 3 mo old infants vocalize in a reciprocal fashion with an adult to maintain a social interaction ("vocal tennis"). By 4 mo, infants begin to make bilabial ("raspberry") sounds, and by 5 mo, monosyllables and laughing are noticeable. Between 6 and 8 mo, polysyllabic babbling ("lalala" or "mamama") is heard and the infant might begin to communicate with gestures. Between 8 and 10 mo, babbling makes a phonologic shift toward the particular sound patterns of the child's native language (i.e., they produce more native sounds than nonnative sounds). At 9-10 mo, babbling becomes truncated into specific words (e.g., "mama," or "dada") for their parents.

Over the next several months, infants learn 1 or 2 words for common objects and begin to imitate words presented by an adult. These words might appear to come and go from the child's repertoire until a stable group of 10 or more words is established. The rate of acquisition of new words is approximately 1 new word per wk at 12 mo, but it accelerates to approximately 1 new word per day by 2 yr. The first words to appear are used primarily to label objects (nouns) or to ask for objects and people (requests). By 18-20 mo, toddlers should use a minimum of 20 words and produce jargon (strings of word-like sounds) with language-like inflection patterns (rising and falling speech patterns). This jargon usually contains some embedded true words. Spontaneous 2-word phrases (pivotal speech), consisting of the flexible juxtaposition of words with clear intention (e.g., "Want juice!" or "Me down!"), is characteristic of 2 yr olds and reflects the emergence of grammatical ability (syntax).

Two-word, combinational phrases do not usually emerge until the child has acquired 50-100 words in their lexicon. Thereafter, the acquisition of new words accelerates rapidly. As knowledge of grammar increases, there is a proportional increase in verbs, adjectives, and other words that serve to define the relation between objects and people (predicates). By 3 yr, sentence length increases and the child uses pronouns and simple present tense verb forms. These 3-5 word sentences typically have a subject and verb but lack conjunctions, articles, and complex verb forms. The Sesame Street character Cookie Monster ("Me want cookie!") typifies the "telegraphic" nature of the 3 yr old's sentences. By 4-5 yr, children should be able to carry on conversations using adult-like grammatical forms and use sentences that provide details (e.g., "I like to read my books").

Variations of Normal

Language milestones have been found to be largely universal across languages and cultures, with some variations depending on the complexity of the grammatical structure of individual languages. In Italian (where verbs often occupy a prominent position at the beginning or end of sentences), 14 month-olds produce a greater proportion of verbs compared with English speaking infants. Within a given language, development usually follows a fairly predictable pattern, paralleling general cognitive development. Although the sequences are predictable, the exact timing of achievement is not. There are marked variations among normal children in the rate of development of babbling, comprehension of words, production of single words, and use of combinational forms within the first 2-3 yr of life.

Table 35-1 Normal Language Milestones

HEARING AND UNDERSTANDING	TALKING
BIRTH TO 3 MONTHS Startles to loud sounds Quiets or smiles when spoken to Seems to recognize your voice and quiets if crying Increases or decreases sucking behavior in response to sound	Makes pleasure sounds (cooing, gooing) Cries differently for different needs Smiles when sees you
4-6 MO Moves eyes in direction of sounds Responds to changes in tone of your voice Notices toys that make sounds Pays attention to music	Babbling sounds more speech-like, with many different sounds, including *p, b,* and *m* Vocalizes excitement and displeasure Makes gurgling sounds when left alone and when playing with you
7 MO-1 YEAR Enjoys games such as peekaboo and pat-a-cake Turns and looks in direction of sounds Listens when spoken to Recognizes words for common items, such as *cup, shoe,* and *juice* Begins to respond to requests *(Come here. Want more?)*	Babbling has both long and short groups of sounds, such as *tata upup bibibibi.* Uses speech or noncrying sounds to get and keep attention Imitates different speech sounds Has 1 or 2 words *(bye-bye, Dada, Mama),* although they might not be clear
1-2 YR Points to a few body parts when asked Follows simple commands and understands simple questions *(Roll the ball. Kiss the baby. Where's your shoe?)* Listens to simple stories, songs, and rhymes Points to pictures in a book when named	Says more words every month Uses some 1-2 word questions *(Where kitty? Go bye-bye? What's that?)* Puts 2 words together *(more cookie, no juice, mommy book)* Uses many different consonant sounds at the beginning of words
2-3 YR Understands differences in meaning (e.g., go–stop, in–on, big–little, up–down) Follows 2-step requests *(Get the book and put it on the table.)*	Has a word for almost everything Uses 2-3 word "sentences" to talk about and ask for things Speech is understood by familiar listeners most of the time Often asks for or directs attention to objects by naming them
3-4 YR Hears you when you call from another room Hears television or radio at the same loudness level as other family members Understands simple *who, what, where, why* questions	Talks about activities at school or at friends' homes Usually understood by people outside the family Uses a lot of sentences that have ≥4 words Usually talks easily without repeating syllables or words
4-5 YR Pays attention to a short story and answers simple questions about it Hears and understands most of what is said at home and in school	Voice sounds as clear as other children's Uses sentences that include details *(I like to read my books.)* Tells stories that stick to a topic Communicates easily with other children and adults Says most sounds correctly except a few, such as *l, s, r, v, z, ch, sh,* and *th* Uses the same grammar as the rest of the family

Adapted from American Speech-Language-Hearing Association, 2005. http://www.asha.org/public/speech/development/chart.htm.

Two basic patterns of language learning have been identified: "analytic" and "holistic." The analytic pattern is the most common and reflects the mastery of increasingly larger units of language form. As reflected in the previous discussion of milestones, the child's analytic skills proceed from simple to more complex and lengthy forms. Children who follow a holistic or gestalt learning pattern might start by using relatively large chunks of speech in familiar contexts. They might memorize familiar phrases or dialogs from movies or stories and repeat them in an over-generalized fashion. Their sentences often have a formulaic pattern, reflecting inadequate mastery of the use of grammar to flexibly and spontaneously combine words appropriately in the child's own unique utterance. Over time, these children gradually break down the meanings of phrases and sentences into their component parts, and they learn to analyze the linguistic units of these memorized forms. As this occurs, more original speech productions emerge and the child is able to assemble thoughts in a more flexible manner. Both analytic and holistic learning processes are necessary for normal language development to occur.

LANGUAGE AND COMMUNICATION DISORDERS

Epidemiology

Disorders of speech and language are very common in preschool-age children. Nearly 20% of 2 yr olds are thought to have delayed onset of speech. By age 5 yr, approximately 6% of children are identified as having a speech impairment, 5% as having both speech and language impairment, and 8% as having language impairment. Boys are nearly twice as likely to have an identified speech or language impairment as girls.

Etiology

Normal language ability is a complex function that is widely distributed across the brain through interconnected neural networks that are synchronized for specific activities. Although there are clinical similarities between acquired aphasia in adults and childhood language disorders, unilateral, focal lesions acquired in early life do not seem to have the same effects in children as in adults. Risk factors for neurologic injury are absent in the vast majority of children with language impairment.

Genetic factors appear to play a major role in influencing how children learn to talk. Language disorders cluster in families. A careful family history may identify current or past speech or language problems in up to 30% of 1st-degree relatives of proband children. Although children who are exposed to parents with language difficulty might be expected to experience poor language stimulation and inappropriate language modeling, studies of twins have shown the concordance rate for low language test score and/or a history of speech therapy to be approximately 50% in dizygotic pairs, rising to over 90% in

monozygotic pairs. A number of potential gene loci have been identified, but no consistent genetic markers have been established.

The most plausible genetic mechanism involves a disruption in the timing of early prenatal neurodevelopmental events affecting migration of nerve cells from the germinal matrix to the cerebral cortex. Chromosomal lesions and point mutations of the *FOXP2* gene and polymorphisms of the *CNTNAP2* gene are associated with an uncommon but distinct speech and language disorder characterized by difficulties in learning and producing oral movement sequences (childhood apraxia of speech). Affected children have a spectrum of impairment in expressive and receptive language as well as problems understanding grammar.

Pathogenesis

Language disorders are associated with a fundamental deficit in the brain's capacity to process complex information rapidly. Simultaneous evaluation of words (semantics), sentences (syntax), prosody (tone of voice), and social cues can overtax the child's ability to comprehend and respond appropriately in a verbal setting. Limitations in the amount of information that can be stored in verbal working memory can further limit the rate at which language information is processed. Electrophysiologic studies show abnormal latency in the early phase of auditory processing in children with language disorders. Neuroimaging studies identify an array of anatomic abnormalities in regions of the brain that are central to language processing. MRI scans in children with **specific language impairment (SLI)** may reveal white matter lesions, white matter volume loss, ventricular enlargement, focal gray matter heterotopia within the right and left parietotemporal white matter, abnormal morphology of the inferior frontal gyrus, atypical patterns of asymmetry of language cortex, or increased thickness of the corpus callosum in a minority of affected children. Postmortem studies of children with language disorders found evidence of atypical symmetry in the plana temporale and cortical dysplasia in the region of the Sylvian fissure. A high incidence of paroxysmal electroencephalogram (EEG) anomalies during sleep has been identified in children with SLI. Although these findings might represent a mild variant of the Landau-Kleffner syndrome (acquired verbal auditory agnosia), they likely represent an epiphenomenon in which paroxysmal activity is related to architectural dysplasia. In support of a genetic mechanism affecting cerebral development, a high rate of atypical perisylvian asymmetries has also been documented in the parents of children with SLI.

Clinical Manifestations

Primary disorders of speech and language development are often found in the absence of more generalized cognitive or motor dysfunction. Disorders of communication are the most common comorbid condition in persons with generalized cognitive disorders (intellectual disability or autism), structural anomalies of the organs of speech (velopharyngeal insufficiency from cleft palate), and neuromotor conditions affecting oral motor coordination (dysarthria from cerebral palsy or other neuromuscular disorders).

Classification

Each professional discipline has adopted a somewhat different classification system, based on cluster patterns of symptoms. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) organized communication disorders into: (1) language disorder (which combines expressive and mixed receptive-expressive language disorders), speech sound disorder (phonologic disorder), and childhood-onset fluency disorder (stuttering); and (2) social (pragmatic) communication disorder, which is persistent difficulties in the social uses of verbal and nonverbal communication (Table 35-2). In clinical practice, childhood speech and language disorders occur as a number of distinct entities.

Specific Language Impairment

Also referred to as **developmental dysphasia**, or developmental language disorder, SLI is characterized by a significant discrepancy between the child's overall cognitive level (typically nonverbal measures of intelligence) and functional language level. These children also follow an atypical pattern of language acquisition and use. Closer examination of the child's skills might reveal deficits in understanding and use of word meaning (semantics) and grammar (syntax). Often, children with SLI are delayed in starting to talk. Most significantly, they usually have difficulty understanding spoken language. The problem may stem from insufficient understanding of single words or from the inability to deconstruct and analyze the meaning of sentences. Many affected children show a holistic pattern of language development, repeating memorized phrases or dialog from movies or stories (echolalia). In contrast to their difficulty with spoken language, children with SLI appear to learn visually and demonstrate their ability on nonverbal tests of intelligence.

After children with SLI become fluent talkers, they are generally less proficient at producing oral narratives compared with their peers. Their stories tend to be shorter and include fewer propositions, main story ideas, or story grammar elements. Older children include fewer mental state descriptions (e.g., references to what their characters think and how they feel). Their narratives contain fewer cohesive devices and the story line may be difficult to follow.

Although they have difficulty interacting with peers who are more verbally adept, many children with SLI play appropriately with younger or older children. Despite their communication impairment, they engage in pretend play, show imagination, share emotions (affective reciprocity), and demonstrate joint referencing behaviors appropriate to their age. Of note is the high incidence of fine motor coordination difficulty found in these children. A combination of increased joint mobility and mild muscular hypotonia often results in motor clumsiness.

Many children with SLI show difficulties with social interaction, particularly with same-age peers. Social interaction is mediated by oral communication, and a child deficient in communication is at a distinct disadvantage in the social arena. Children with SLI tend to be more dependent on older children or adults, who can adapt their communication to match the child's level of function. Generally, social interaction skills are more closely correlated with language level than with nonverbal cognitive level. Using this as a guide, one usually sees a developmental progression of increasingly more sophisticated social interaction as the child's language abilities improve. In this context, social ineptitude is not necessarily a sign of asocial distancing (e.g., autism) but rather a delay in the ability to negotiate social interactions.

Higher-Level Language Disorder

As children mature, the ability to communicate effectively with others depends on mastery of a range of skills that go beyond basic understanding of words and rules of grammar. Higher-level language skills include the development of advanced vocabulary, the understanding of word relationships, reasoning skills (including drawing correct inferences and conclusions), the ability to understand things from another person's perspective, and the ability to paraphrase and rephrase with ease. In addition, higher-order language abilities include pragmatic skills that serve as the foundation for social interactions. These skills include knowledge and understanding of one's conversational partner, knowledge of the social context in which the conversation is taking place, and general knowledge of the world. Social and linguistic aspects of communication are often difficult to separate, and persons who have trouble interpreting these relatively abstract aspects of communication typically experience difficulty forming and maintaining relationships. DSM-5 Identified Social (Pragmatic) Communication Disorder (SPCD) as a category of communication disorder (Table 35-2). Symptoms of pragmatic difficulty include extreme literalness and inappropriate verbal and social interactions. Proper use and understanding of humor, slang, and sarcasm depend on correct interpretation of the meaning and the context of language and the ability to draw proper inferences. Failure to provide a sufficient referential base to one's conversational partner—to take the perspective of another person—results in the appearance of talking or behaving randomly or incoherently. SPCD often occurs in the context of SLI and autism spectrum disorder (ASD) and it has been recognized as a symptom of a wide range of disorders, including right-hemisphere damage to the

Table 35-2 DSM-5 Diagnostic Criteria for Communication Disorders

Language Disorder	A. Persistent difficulties in the acquisition and use of language across modalities (i.e., spoken, written, sign language, or other) due to deficits in comprehension or production that include the following: 1. Reduced vocabulary (word knowledge and use) 2. Limited sentence structure (ability to put words and word endings together to form sentences based on the rules of grammar and morphology). 3. Impairments in discourse (ability to use vocabulary and connect sentences to explain or describe a topic or series of events or have a conversation). B. Language abilities are substantially and quantifiably below those expected for age, resulting in functional limitations in effective communication, social participation, academic achievement, or occupational performance, individually or in any combination. C. Onset of symptoms is in the early developmental period. D. The difficulties are not attributable to hearing or other sensory impairment, motor dysfunction, or another medical or neurological condition and are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.
Speech Sound Disorder	A. Persistent difficulty with speech sound production that interferes with speech intelligibility or prevents verbal communication of messages. B. The disturbance causes limitations in effective communication that interfere with social participation, academic achievement, or occupational performance, individually or in any combination. C. Onset of symptoms is in the early developmental period. D. The difficulties are not attributable to congenital or acquired conditions, such as cerebral palsy, cleft palate, deafness or hearing loss, traumatic brain injury, or other medical or neurological conditions.
Social (Pragmatic) Communication Disorder	A. Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following: 1. Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for the social context. 2. Impairment of the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language. 3. Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction. 4. Difficulties understanding what is not explicitly stated (e.g., making inferences) and nonliteral or ambiguous meanings of language (e.g., idioms, humor, metaphors, multiple meanings that depend on the context for interpretation). B. The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination. C. The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities). D. The symptoms are not attributable to another medical or neurological condition or to low abilities in the domains of word structure and grammar, and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder.

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brain, Williams syndrome, and nonverbal learning disabilities. SPCD can also occur independently of other disorders. In school settings, children with SPCD may be socially ostracized and/or bullied.

Intellectual Disability

Most children with a mild degree of intellectual disability learn to talk at a slower-than-normal rate; they follow a normal sequence of language acquisition and eventually master basic communication skills. Difficulties may be encountered with higher-level language concepts and use. Persons with moderate to severe degrees of intellectual disability can have great difficulty in acquiring basic communication skills. About half of persons with an IQ of <50 are able to communicate using single words or simple phrases; the rest are typically nonverbal.

Autism and Pervasive Developmental Disorders

A disordered pattern of language development is one of the core features of autism and other pervasive developmental disorders (see Chapter 28). The language profile of children with autism is often indistinguishable from that in children with SLIs. The key points of distinction between these conditions are the lack of reciprocal social relationships that characterizes children with autism, limitation in the ability to develop functional, symbolic, or pretend play, and an obsessive need for sameness and resistance to change. Approximately 75-80% of children with autism are also intellectually disabled, and this can limit their ability to develop functional communication skills. Language abilities can range from absent to grammatically intact, but with limited pragmatic features and/or odd prosody patterns. Some autistic persons have highly specialized, but isolated, "savant" skills, such as calendar calculations and hyperlexia (the precocious ability to recognize written words beyond expectation based on general intellectual ability). Regression in language and social skills (**autistic regression**) occurs in approximately one-third of children with autism, usually before 2 yr of age. No explanation for this phenomenon has been identified. Once the regression has "stabilized," recovery of function does not usually occur (Fig. 35-1).

Asperger Syndrome

(See Chapter 28.2.)

Although sharing many characteristics of autism (deficits in social relatedness and restricted range of interests), individuals with Asperger syndrome typically show normal early language development (syntax and semantics). As they mature, higher-order social and language pragmatic impairments become prominent features of this disorder. Affected children have an unusually circumscribed range of interests, which are all-absorbing and interfere with learning of other skills and with social adaptation. These children may engage in long-winded, verbose monologues about their topics of special interest, with little regard to the reaction of others. Their inflection pattern (prosody) may be inappropriate to the content of their conversation, and they might not adjust their rate of speech or vocal volume to the setting.

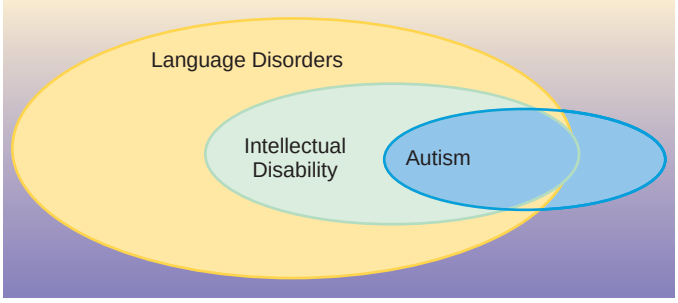

Figure 35-1 Relationship of autism, language disorders, and intellectual disability. *(From Simms MD, Schum RL: Preschool children who have atypical patterns of development,* Pediatr Rev *21:147–158, 2000.)*

Selective Mutism

Selective mutism is defined as a failure to speak in specific social situations despite speaking in other situations, and it is typically a symptom of an underlying **anxiety disorder**. Children with selective mutism can speak normally in certain settings, such as within their home or when they are alone with their parents. They fail to speak in other social settings, such as at school or at other places outside their home. Other symptoms associated with selective mutism can include excessive shyness, withdrawal, dependency on parents, and oppositional behavior. Most cases of selective mutism are not the result of a single traumatic event, but rather are the manifestation of a chronic pattern of anxiety. Mutism is not passive–aggressive behavior. Mute children report that they want to speak in social settings but are afraid to do so. It is important to emphasize that the underlying anxiety disorder is the likely origin of selective mutism. Often, one or both parents of a child with selective mutism has a history of anxiety symptoms, including childhood shyness, social anxiety, or panic attacks. This suggests that the child's anxiety represents a familial trait. For some unknown reason, the child converts the anxiety into the mute symptom. Mutism is highly functional for the child in that it reduces anxiety and protects the child from the perceived challenge of social interaction. Treatment of selective mutism should focus on reducing the general anxiety, rather than focusing only on the mute behaviors (see Chapter 25). Selective mutism reflects a difficulty of social interaction and not a disorder of language processing.

Isolated Expressive Language Disorder

More commonly seen in boys than girls, isolated expressive language disorder (late talker syndrome) is a diagnosis best made in retrospect. These children have age-appropriate receptive language and social ability. Once they start talking, their speech is clear. There is no increased risk for language or learning disability as they progress through school. A family history of other males with a similar developmental pattern is often reported. This pattern of language development likely reflects a variation of normal.

MOTOR SPEECH DISORDERS

Dysarthria

Motor speech disorders can originate from neuromotor disorders such as cerebral palsy, muscular dystrophy, myopathy, facial palsy. The resulting dysarthria affects both speech and nonspeech functions (smiling and chewing). Lack of strength and muscular control manifests as slurring of words and distorting of vowels. Speech patterns are often slow and labored. Poor velopharyngeal function can result in mixed nasal resonance (hyper- or hyponasal speech). In many cases, feeding difficulty, drooling, open mouth posture, and a protruding tongue accompany the dysarthric speech.

Childhood Apraxia of Speech

Difficulty in planning and coordinating movements for speech production can result in inconsistent distortion of speech sounds. The same word may be pronounced differently each time. Intelligibility tends to decline as the length and complexity of the child's speech increases. Consonants may be deleted and sounds transposed. As they try to talk spontaneously, or imitate other's speech, children with childhood apraxia of speech may display oral groping or struggling behaviors. Children with childhood apraxia of speech frequently have a history of early feeding difficulty, limited sound production as infants, and delayed onset of spoken words. They may point, grunt, or develop an elaborate gestural communication system in an attempt to overcome their verbal difficulty. Apraxia may be limited to oral-motor function, or it may be a more generalized problem affecting fine and/or gross motor coordination.

Phonologic Disorder

Children with phonologic speech disorder are often unintelligible, even to their parents. Articulation errors are not the result of neuromotor impairment but seem to reflect an inability to correctly process the words they hear. As a result, they lack understanding of how to fit sounds together properly to create words. In contrast to children with childhood apraxia of speech, those with phonologic disorder are fluent—although unintelligible—and produce a consistent, highly predictable pattern of articulation errors. Children with phonologic speech disorder are at high risk for later reading and learning disability.

HEARING IMPAIRMENT

Hearing loss can be a major cause of delayed or disordered language development (see Chapter 637). Approximately 16-30 per 1,000 children have mild to severe hearing loss, significant enough to affect educational progress. In addition to these "hard of hearing" children, approximately another 1 per 1,000 are deaf (profound bilateral hearing loss). Hearing loss can be present at birth or acquired postnatally. Newborn screening programs can identify many forms of congenital hearing loss, but children can develop progressive hearing loss or acquire deafness after birth.

The most common types of hearing loss are attributable to conductive (middle ear) or sensorineural deficit. Although it is not possible to accurately predict the impact of hearing loss on a child's language development, the type and degree of hearing loss, the age of onset, and the duration of the auditory impairment clearly play important roles. Children with significant hearing impairment often have problems developing facility with language and often have related academic difficulties. Presumably, the language impairment is caused by lack of exposure to fluent language models starting in infancy.

Approximately 30% of hearing-impaired children have at least one other disability that affects development of speech and language (e.g., intellectual disability, cerebral palsy, craniofacial anomalies). Any child who shows developmental warning signs of a speech or language problem should have a hearing assessment by an audiologist and an examination by a geneticist as part of a comprehensive evaluation.

HYDROCEPHALUS

Some children with hydrocephalus may be described as having "cocktail-party syndrome." Although they may use sophisticated words, their comprehension of abstract concepts is limited, and their pragmatic conversational skills are weak. As a result, they speak superficially about topics and appear to be carrying on a monologue (see Chapter 591.11).

RARE CAUSES OF LANGUAGE IMPAIRMENT

Hyperlexia

Hyperlexia is the precocious development of reading single words that spontaneously occurs in some young children (ages 2-5 yr) without specific instruction. It is often associated with children who have a pervasive developmental disorder (see Chapter 30) or SLI. It stands in contrast to precocious reading development in young children who do not have any other developmental disorders. Hyperlexia is a variation seen in young children with disordered language who do not have the social deficits or restricted or repetitive behaviors associated with autism. A typical manifestation is for a child with SLI to orally read single words, or match pictures with single words. Although hyperlexic children show early and well-developed word-decoding skills, they

usually have no precocious ability for comprehension of text. Rather, text comprehension is closely intertwined with oral comprehension, and children who have difficulty decoding the syntax of language are also at risk for having reading comprehension problems.

Landau-Kleffner Syndrome (Verbal Auditory Agnosia)

Children with Landau-Kleffner syndrome have a history of normal language development until they experience a regression in their ability to comprehend spoken language (verbal auditory agnosia). The regression may be sudden or gradual, and it usually occurs between 3 and 7 yr of age. Expressive language skills typically deteriorate, and some children may become mute. Despite their language regression, these children typically retain appropriate play patterns and the ability to interact in a socially appropriate manner. An EEG might show a distinct pattern of status epilepticus in sleep (continuous spike wave in slow-wave sleep), and up to 80% of children with this condition eventually exhibit clinical seizures. A number of treatment approaches have been reported, including antiepileptic medication, steroids, and intravenous gamma globulin, with varying results. The prognosis for return of normal language ability is uncertain, even with resolution of the EEG abnormality. Epileptic interictal discharges are more frequently found on EEGs of children with language impairments than in otherwise normally developing children, even in those without any history of language regression. However, this phenomenon is believed to represent a manifestation of an underlying disorder of brain structure or function that is distinct from the language impairment, as there has been little evidence of improvement in language function when the EEG was normalized after administration of antiepileptic medication. Unless there is a clear pattern of either seizure symptoms or regression in language ability, a routine EEG is not recommended as part of the evaluation for a child with speech and/or language impairment.

Metabolic and Neurodegenerative Disorders

(See also Part XI.)

Regression of language development may accompany loss of neuromotor function at the outset of a number of metabolic diseases including lysosomal storage disorders (metachromatic leukodystrophy), peroxisomal disorders (adrenal leukodystrophy), ceroid lipofuscinosis (Batten disease), and mucopolysaccharidosis (Hunter disease, Hurler disease). Recently, creatine transporter deficiency was identified as an X-linked disorder that manifests with language delay in boys and mild learning disability in female carriers.

Screening

Developmental surveillance at each well child visit should include specific questions about normal language developmental milestones and observations of the child's behavior. Clinical judgment, defined as eliciting and responding to parents' concerns, can detect the majority of children with speech and language problems. Many clinicians employ standardized developmental screening questionnaires and observation checklists designed for use in a pediatrics office (see Chapter 14).

The U.S. Preventive Services Task Force reviewed screening instruments for speech and language delays in young children that can be used in primary care settings. The Task Force focused on brief measures that require <10 min to complete. There was insufficient evidence that screening instruments are more effective than using physician's clinical observations and parents' concerns to identify children who require further evaluation. The Task Force noted that there is no single gold standard for screening, owing to inconsistent measures and terminology, and did not recommend the use of screening instruments. Furthermore, the Task Force determined that the use of formal measures was not time or cost efficient and deferred to pediatrician's and parents' concerns as indicators of potential problems. Table 35-3 offers guidelines for raising concerns and referring a child for specialized speech and language evaluation. Because of the high prevalence of speech and language disorders in the general population, referral to a speech-language pathologist for further evaluation should be made whenever there is a suspicion of delay.

NONCAUSES OF LANGUAGE DELAY

Twinning, birth order, "laziness," exposure to multiple languages (bilingualism), tongue-tie, or otitis media are not adequate explanations for significant language delay. Normal twins learn to talk at the same age as normal single-born children, and birth order effects on language development have not been consistently found. The drive to communicate and the rewards for successful verbal interaction are so strong that children who let others talk for them usually can't talk for themselves and are not "lazy." Toddlers exposed to more than 1 language can show a mild delay in starting to talk, and they can initially mix elements (vocabulary and syntax) of the different languages they are learning (code switching). However, they learn to segregate each language by 24-30 mo and are equal to their monolingual peers by 3 yr of age. An extremely tight lingual frenulum (tongue-tie) can affect feeding and speech articulation, but does not prevent the acquisition of language abilities. Finally, prospective studies show that frequent ear infections and/or serous otitis media in early childhood does not result in persisting language disorder.

Diagnostic Evaluation

It is important to distinguish developmental delay (abnormal timing) from developmental disorder (abnormal patterns or sequences). A child's language and communication skills must also be interpreted within the context of the child's overall cognitive and physical abilities. Finally, it is important to evaluate the child's use of language to communicate with others in the broadest sense (communicative intent). Thus, a multidisciplinary evaluation is often warranted. At a minimum this should include psychologic evaluation, neurodevelopmental pediatric assessment, and speech and language examination.

Psychologic Evaluation

There are 2 main goals for the psychologic evaluation of a young child with a communication disorder. Nonverbal cognitive ability must be assessed to determine if the child has an intellectually disability, and the child's social behaviors must be assessed to determine whether

Table 35-3 Speech and Language Screening

REFER FOR SPEECH–LANGUAGE EVALUATION IF:		
AT AGE	**RECEPTIVE**	**EXPRESSIVE**
15 mo	Does not look/point at 5-10 objects	Is not using 3 words
18 mo	Does not follow simple directions ("get your shoes")	Is not using Mama, Dad, or other names
24 mo	Does not point to pictures or body parts when they are named	Is not using 25 words
30 mo	Does not verbally respond or nod/shake head to questions	Is not using unique 2-word phrases, including noun–verb combinations
36 mo	Does not understand prepositions or action words; does not follow 2-step directions	Has a vocabulary of <200 words; does not ask for things; echolalia to questions; language regression after attaining 2-word phrases

autism spectrum disorder (ASD) is present. Additional diagnostic considerations may include emotional disorders such as anxiety, depression, mood disorder, obsessive-compulsive disorder, academic learning disorders, and attention-deficit/hyperactivity disorder (ADHD).

Cognitive Assessment

Intellectual disability is defined as deficits in cognitive abilities and adaptive behaviors. In this context, children with intellectual disability show delayed development of communication skills; however, delayed communication does not necessarily signal intellectual disability. Therefore, a broad-based cognitive assessment is an important component to the evaluation of children with language delays, including evaluation of both verbal and nonverbal skills. If a child has intellectual disability, both verbal and nonverbal scores will be low compared to norms (≤2nd percentile). In contrast, a typical cognitive profile for a child with SLI includes a significant difference between nonverbal and verbal abilities, with nonverbal IQ being greater than verbal IQ and the nonverbal score within an average range.

Evaluation of Social Behaviors

Social interest is the key difference between children with a primary language disorder (SLI) and those with a communication disorder secondary to ASD. Children with SLI have an interest in social interaction, but they may have difficulty enacting their interest because of their limitations to communication. In contrast, autistic children show little social interest. Four key nonverbal behaviors that are often shown by children with SLI—but not autistic children (especially toddlers and preschoolers)—are joint attention, affective reciprocity, pretend play, and direct imitation.

Relationship of Language and Social Behaviors to Mental Age

Cognitive assessment provides a mental age for the child, and the child's behavior must be evaluated in that context. Most 4 yr old children typically engage peers in interactive play, but most 2 yr olds are playful but primarily focused on interactions with adult caretakers. A 4 yr old with mild to moderate intellectual disability and a mental age of 2 yr might not play with peers yet because of cognitive limitation, not a lack of desire for social interaction.

Speech and Language Evaluation

A certified speech-language pathologist should perform a speech and language evaluation. A typical evaluation includes assessment of language, speech, and the physical mechanisms associated with speech production. Both expressive and receptive language is assessed by a combination of standardized measures and informal interactions and observations. All components of language are assessed, including syntax, semantics, pragmatics, and fluency. Speech assessment similarly uses a combination of standardized measures and informal observations. Assessment of physical structures includes oral structures and function, respiratory function, and vocal quality. In many settings, a speech-language pathologist works in conjunction with an audiologist, who can do appropriate hearing evaluation of the child. If an audiologist is not available in that setting, then a separate referral should be made. No child is too young for a speech and language or hearing evaluation. A referral for evaluation is appropriate whenever there is suspicion of language impairment.

Medical Evaluation

As in any developmental disorder, careful history and physical examination should focus on the identification of potential contributors to the child's language and communication difficulties. A family history of delay in talking, need for speech and language therapy, or academic difficulty can suggest a genetic predisposition to language disorders. Pregnancy history might reveal risk factors for prenatal developmental anomalies, such as polyhydramnios or decreased fetal movement patterns. Small size for gestational age at birth, symptoms of neonatal encephalopathy, or early and persistent oral-motor feeding difficulty may presage speech and language difficulty. Developmental history should focus on the age at which various language skills were mastered and the sequences and patterns of milestone acquisition. Regression or loss of acquired skills should raise immediate concern.

Physical examination should include measurement of height (length), weight, and head circumference. The skin should be examined for lesions consistent with phakomatosis (e.g., tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome) and other disruptions of pigment (hypomelanosis of Ito). Anomalies of the head and neck, such as white forelock and hypertelorism (Waardenburg syndrome), ear malformations (Goldenhar syndrome), facial and cardiac anomalies (Williams syndrome, velocardiofacial syndrome), retrognathism of the chin (Pierre-Robin anomaly), or cleft lip and/or palate, are associated with hearing and speech abnormalities. Neurologic examination might reveal muscular hypertonia or hypotonia, both of which can affect neuromuscular control of speech. Generalized muscular hypotonia, with increased range of motion of the joints, is commonly seen in children with SLI. The reason for this association is not clear but it might account for the fine and gross motor clumsiness often seen in these children. However, mild hypotonia is not a sufficient explanation for the impairments of expressive and receptive language.

No routine diagnostic studies are indicated for SLI or isolated language disorders. When language delay is a part of a generalized cognitive or physical disorder, referral for further genetic evaluation, chromosome testing (including high resolution banding karyotype, fragile X testing, and microarray comparative genomic hybridization), neuroimaging studies, and EEG may be considered, if clinically indicated.

TREATMENT

Laws emanating from the federal Individuals with Disabilities Education Act (IDEA) require that schools provide special education services to children who have learning difficulties. This includes children with speech and language disorders. Services are provided to children from birth through 21 yr of age. States have various methods for providing services, and for young children these can include Birth-to-Three, Early Childhood, and Early Learning programs. These programs provide speech–language therapy as part of public education, in conjunction with other special education resources. Children can also receive therapy from nonprofit service agencies, hospital and rehabilitation centers, and speech pathologists in private practice.

Of concern is the fact that many children with identified speech and language deficits do not receive appropriate intervention services. Population-based surveys in both the United States and Canada have found that less than half of children identified by kindergarten entry receive speech and language interventions, even when their parents have been educated about the nature of their child's condition. In one study, children with deficits in speech–sound production were much more likely to receive services (41%) than those who had problems with language alone (9%). These findings are troubling because poor educational outcome, especially in reading, social and behavioral adjustment, are more highly associated with language than with speech–sound disorders. Therefore, the children at greatest risk are least likely to receive intervention services. Boys were twice as likely to receive speech intervention as girls, regardless of their speech–language diagnosis. Social and demographic factors did not appear to influence whether identified children received interventions services.

Speech–language therapy includes a variety of goals. Sometimes both speech and language activities are incorporated in therapy. The speech goals focus on development of more intelligible speech. Language goals can focus on expanding vocabulary (lexicon) and understanding of the meaning of words (semantics), improving syntax by using proper forms or learning to expand single words into sentences, and social use of language (pragmatics). Therapy can include individual sessions, group sessions, and mainstream classroom integration. Individual sessions may use drill activities for older children or play activities for younger children to target specific goals. Group sessions can include several children with similar language goals to help them practice peer communication activities and to help them bridge the gap into more naturalistic communication situations. Classroom

integration might include the therapist team-teaching or consulting with the teacher to facilitate the child's use of language in common academic situations.

For children with severe language impairment, alternative methods of communication are often included in therapy. These may include use of manual sign language, use of pictures (e.g., Picture Exchange Communication System), and computerized devices for speech output. Often the ultimate goal is to achieve better spoken language. Early use of signs or pictures can help the child to establish better functional communication and help the child to understand the symbolic nature of words to facilitate the language process. There is no evidence that use of signs or pictures interferes with development of oral language if the child has the capacity to speak. Many clinicians believe that these alternative methods accelerate the learning of language. They also reduce frustration of parents and children who cannot communicate for basic needs.

Parents can consult with their child's speech-language therapist about home activities to enhance language development and extend therapy activities through appropriate language-stimulating activities and recreational reading. Parents' language activities should focus on emerging communication skills that are within the child's repertoire, rather than teaching the child new skills. The speech pathologist can guide parents on effective modeling and eliciting communication from their child.

Recreational reading focuses on expanding the child's comprehension of language. Sometimes the child's avoidance of reading is a sign that the parent is presenting material that is too complex for the child. The speech-language therapist can guide the parent in selecting an appropriate level of reading material.

PROGNOSIS

Children with isolated expressive language disorder ("late talkers") have an excellent prognosis for both language, learning, and social–emotional adjustment.

Over time, children with SLI respond to therapeutic/educational interventions and show a trend toward improvement of communication skills. Adults with a history of childhood language disorder continue to show evidence of impaired language ability, even when surface features of the communication difficulty have improved considerably. This suggests that many persons find successful ways of adapting to their impairment. Although the majority of children improve their communication ability with time, 50-80% of preschoolers with language delay and normal nonverbal intelligence continue to experience difficulty with language and social development up to 20 yr beyond the initial diagnosis. Language disorders often interfere with the child's ability to conceptualize the increasingly complex and ambiguous worlds of social relationship and emotions. As a consequence, in later childhood and adolescence, children with persisting symptoms of SLI are about twice as likely as their typical language peers to show clinical levels of emotional problems and twice as likely to show behavioral difficulties. A Danish study found that adults with SLI were less likely to have completed formal education beyond high school and to have lower occupational and socioeconomic success than the general population. Fifty-six percent held a paid job (vs 84% of the same age general population), of which 35% were unskilled and 40% were skilled workers. Eighty percent of the adults reported having had difficulty reading while in school and most had received remedial teaching, and 50% continued to report reading difficulty as adults (compared with 5% of Danish adults). Lower non-verbal intelligence and comorbid psychiatric and/or neurologic disorders independently contributed to a worse prognosis. These results were consistent with previous reports of adult outcomes of children with SLI from Canada and the United Kingdom.

Academic Disorders

Early language difficulty is strongly related to later reading disorder. Approximately 50% of children with early language difficulty develop reading disorder, and 55% of children with reading disorder have a history of impaired early oral language development. By the time they enter kindergarten, many children with early language deficits may have improved significantly, and they may begin to show early literacy skills, identifying and sounding out letters. However, as they progress through school, they are often unable to keep up with the increasing demands for both oral and written language. Despite their ability to read words, these children lack oral and reading comprehension and struggle with a wide range of academic subjects. This "illusory recovery" of early language skill may result in children losing speech–language services or other special education support in early grades only to be identified later with academic problems. In addition, children with subtle, but persisting language impairments may appear inattentive or anxious in language-rich classroom environments and be misdiagnosed as having an attention disorder.

A study from Australia found that at 7-9 yr of age, children with communication impairments were reported by their parents and teachers to be making slower progress in reading, writing, and overall school achievement than other children their age. The children reported a higher incidence of bullying, poorer peer relationships, and less overall enjoyment of school than their typically developing peers.

COMORBID DISORDERS

Emotional and Behavioral Difficulty

Early language disorder, particularly difficulty with auditory comprehension, appears to be a specific risk factor for later emotional dysfunction. Boys and girls with language disorder have a higher than expected rate of anxiety disorder (principally social phobia). Boys with language disorder are more likely to develop symptoms of ADHD, conduct disorder, and antisocial personality disorder compared with normally developing peers. Language disorders are common in children referred for psychiatric services, but they are often underdiagnosed, and their impact on children's behavior and emotional development is often overlooked.

Preschoolers with language difficulty commonly express their frustration through anxious, socially withdrawn, or aggressive behavior. As their ability to communicate improves, parallel improvements are usually noted in their behavior, suggesting a cause-and-effect relationship between language and behavior. However, the persistence of emotional and behavioral problems over the life span of persons with early language disability suggests a strong biologic or genetic connection between language development and subsequent emotional disorders.

The full impact of environmental and education support on these emotional and behavioral difficulties is not known at this time, but many children with SLI need psychologic support. Efforts should be made to support the child's resilience, emotional competency, and coping abilities. Parents and teachers should be encouraged to strengthen the child's prosocial behavior and to reduce noncompliant and aggressive behaviors.

Motor and Coordination Delays

Approximately one-third to one-half of children with speech and/or language disorders have some degree of motor coordination impairment that may have an important impact on their ability to carry out activities of daily living (dressing, eating, and bathing), school tasks (writing, drawing, coloring), and social/recreational activities (participation in sports and other playground activities). Motor difficulties are not related to the type of language impairment (i.e., they are found in both children with only receptive delays and in those with both expressive and receptive delays). The patterns of motor difficulties seen in children with language impairments are not distinctly "abnormal" and the motor profiles of children with language impairments resemble those of younger children, suggesting that they result from delayed maturation of motor development rather than from a neurologic impairment. Several researchers have postulated that language impairments and motor difficulties may have a common neurodevelopmental basis. Because attention may be focused on the child's language delays, the need for intervention and support for the child's comorbid motor impairment may be overlooked.

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35.1 Childhood-Onset Fluency Disorder: Dysfluency (Stuttering, Stammering)

Kenneth L. Grizzle

Fluent speech requires timely synchronization of phonatory and articulatory muscle groups. There is also an important interaction between speech and language skills. Stuttering involves involuntary frequent repetitions, lengthenings (prolongations) or arrests (blocks, pauses) of syllables, or sounds that are exacerbated by emotionally or syntactically demanding speech. The World Health Organization's definition of *stuttering* is a disorder in the rhythm of speech in which the person knows precisely what he or she wishes to say but at the same time may have difficulty saying it because of an involuntary repetition, prolongation, or cessation of sound. Table 35-4 describes the DSM-5 definition. Stuttering often leads to frustration and avoidance of speaking situations. Stuttering can lead to being bullied or teased and to speech-related anxiety and social phobia.

EPIDEMIOLOGY AND ETIOLOGY

Stuttering usually begins at 2-4 yr of age and is seen more often in boys (4:1). Approximately 3-5% of preschool children stutter to some degree; only 0.7-1% of young adults stutter. Stuttering is common in families. Genetic studies suggest genes located on chromosome 12. Stuttering may occur suddenly and often begins when word combinations are involved. Higher vocabulary at age 2 yr and higher material education may also be associated with stuttering. Girls and those with a family history of recovery are most likely to have spontaneous recovery by adolescence. This recovery is not related to the severity of the stuttering. Approximately 75% of boys stop stuttering by adolescence; approximately 90% of girls stop by adolescence.

Adolescent/young adult onset stuttering may be related to central nervous system pathology. In contrast to childhood onset, adolescents may have dysfluency with each word whereas childhood onset usually manifests stuttering on the first word or syllable of a phrase.

Stuttering may be caused by impaired timing between areas of the brain involved in language preparation and execution. Adults who stutter and those with fluent speech activate similar areas of the brain. In addition, adults who stutter overactivate parts of the motor cortex and cerebellar vermis, show right-sided laterality, and have no auditory activation on hearing their own speech.

DIAGNOSIS

Stuttering must be differentiated from the normal developmental dysfluency of preschool children (Tables 35-5 and 35-6). Developmental dysfluency is characterized by brief periods of stuttering that resolve by school age, and it usually involves whole words, with <10 dysfluencies per 100 words. Table 35-4 lists the DSM-5 diagnostic criteria for stuttering. Stuttering often improves while singing, reading aloud, or talking to pets or toys. It increases in intensity with anxiety-inducing situations such as reading or speaking in public or on the phone. Some children who stutter develop behavior routines such as eye blinking, grimacing, head turning, and arm or neck movements. Stuttering that persists and is associated with tics may be a manifestation of **Tourette syndrome** (see Chapters 24.1 and 597.4). Additional disorders in the

Table 35-4 Childhood-Onset Fluency Disorder (Stuttering)

Diagnostic Criteria

A. Disturbances in the normal fluency and time patterning of speech that are inappropriate for the individual's age and language skills, persist over time, and are characterized by frequent and marked occurrences of one (or more) of the following:
   1. Sound and syllable repetitions.
   2. Sound prolongations of consonants as well as vowels.
   3. Broken words (e.g., pauses within a word).
   4. Audible or silent blocking (filled or unfilled pauses in speech).
   5. Circumlocutions (word substitutions to avoid problematic words).
   6. Words produced with an excess of physical tension.
   7. Monosyllabic whole-word repetitions (e.g., "I-I-I-I see him").
B. The disturbance causes anxiety about speaking or limitations in effective communication, social participation, or academic or occupational performance, individually or in any combination.
C. The onset of symptoms is in the early developmental period. (Note: Later-onset cases are diagnosed as 307.0 [F98.5] adult-onset fluency disorder.)
D. The disturbance is not attributable to a speech-motor or sensory deficit, dysfluency associated with neurological insult (e.g., stroke, tumor, trauma), or another medical condition and is not better explained by another mental disorder.

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Table 35-5 Differences Between Stuttering and Developmental Dysfluency

BEHAVIOR	STUTTERING	DEVELOPMENTAL DYSFLUENCY
Frequency of syllable repetition per word	≥2	≤1
Tempo	Faster than normal	Normal
Airflow	Often interrupted	Rarely interrupted
Vocal tension	Often apparent	Absent
Frequency of prolongations per 100 words	≥2	≤1
Duration of prolongation	≥2 sec	≤1 sec
Tension	Often present	Absent
Silent pauses within a word	May be present	Absent
Silent pauses before a speech attempt	Unusually long	Not marked
Silent pauses after the dysfluency	May be present	Absent
Articulating postures	May be inappropriate	Appropriate
Reaction to stress	More broken words	No change in dysfluency
Frustration	May be present	Absent
Eye contact	May waver	Normal

Adapted with permission from Van Riper C: The nature of stuttering, *Englewood Cliffs, NJ, Prentice-Hall, 1971, p 28. From Lawrence M, Barclay DM III: Stuttering: a brief review,* Am Fam Physician *57:2175–2178, 1998.*

Table 35-6	Examples of Normal Dysfluency in Preschoolers
TYPE OF DYSFLUENCY	**EXAMPLES**
Voiced repetitions	Occasionally 2 word parts *(mi…milk)* Single-syllable words *(I…I see you)* Multisyllabic words *(Barney…Barney is coming!)* Phrases *(I want…I want Elmo.)*
Interjections	*We went to the…uh…cottage.*
Revisions: incomplete phrases	*I lost my.…Where is Daddy going?*
Prolongations	*I am Toooommy Baker.*
Tense pauses	Lips together, no sound produced

From Costa D, Kroll R: Stuttering: an update for physicians, CMAJ *162:1849–1855, 2000.*

differential diagnosis include hearing impairment, medication effects, cluttering, and in adolescent onset stuttering, central nervous system disorders.

TREATMENT

Preschool children with normal developmental dysfluency (see Table 35-6) can be observed with parental education and reassurance. Parents should not reprimand the child or create undue anxiety. Preschool or older children with stuttering should be referred to a speech pathologist. Therapy is most effective if started during the preschool period. In addition to the risks noted in Table 35-4, indications for referral include 3 or more dysfluencies per 100 syllables (*b-b-but; th-th-the; you, you, you*), avoidances or escapes (pauses, head nod, blinking), discomfort or anxiety while speaking, and suspicion of an associated neurologic or psychotic disorder.

Most preschool children respond to interventions taught by speech pathologists and to behavioral feedback by parents. Parents should not yell at the child, but should calmly praise periods of fluency ("That was smooth") or nonjudgmentally note episodes of stuttering ("That was a bit bumpy"). The child can be involved with self-correction and respond to requests ("Can you say that again?") made by a calm parent. Such treatment greatly improves dysfluency but it may never be completely eliminated.

Adolescents and adults have also been treated (off label) with risperidone or olanzapine with varying but usually positive results if behavioral speech therapy is unsuccessful. Speech therapy in adolescents may be different from that in young children and involves speech restructuring with the development of a new speech pattern.

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Chapter 36

Intellectual Disability

Bruce K. Shapiro and Mark L. Batshaw

Intellectual disability refers to a group of disorders that have in common deficits of adaptive and intellectual function and an age of onset before maturity is reached.

DEFINITION

Contemporary conceptualizations of intellectual disability emphasize functioning and social interaction rather than test scores. The definitions of intellectual disability by the World Health Organization International Classification of Diseases, Individuals with Disabilities Education Act (IDEA), the American Psychiatric Association (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [DSM-5]) and the American Association on Intellectual and Developmental Disabilities (AAIDD) all include significant impairment in general intellectual function, social skills, and adaptive behavior. This focus on the conceptual, social, and practical enables the development of individual treatment plans designed to enhance functioning. Consistent across these definitions is onset of symptoms before age 18 yr or adulthood or during childhood, even if the diagnosis is made later in life.

Significant impairment in general intellectual function refers to performance on an individually administered test of intelligence that is approximately 2 SD below the mean. For a test that has a mean of 100 and SD of 15, IQ scores below 70 would meet these criteria. If the standard error of measurement is considered, the upper limits of subaverage intellectual function may extend to an IQ of 75. Using a score of 75 to delineate intellectual disability might double the number of children with intellectual disability, but the requirement for impairment of adaptive skills limits the false positives. Children with intellectual disability often show a variable pattern of strengths and weaknesses. Not all of their partial scores on IQ tests fall into the significantly subaverage range.

Significant impairment in adaptive behavior reflects the degree that the cognitive dysfunction impairs daily function. Adaptive behavior refers to the skills that are required for people to function in their everyday lives. The AAIDD and DSM-5 classifications of adaptive behavior addresses 3 broad sets of skills: conceptual, social, and practical. Conceptual skills include language, reading and writing, money concepts, and self-direction. Social skills include interpersonal skills, personal responsibility, self-esteem, gullibility, naiveté, and ability to follow rules, obey laws, and avoid victimization. Representative practical skills are performance of activities of daily living (dressing, feeding, toileting and bathing, mobility), instrumental activities of daily living (e.g., housework, managing money, taking medication, shopping, preparing meals, using the telephone), occupational skills, and the maintenance of a safe environment. For a deficit in adaptive behavior to be present, a significant delay in 1 of the 3 areas must be present. The rationale for requiring only 1 of the 3 areas is the empirically derived finding that people with intellectual disability can have varying patterns of ability and may not have deficits in all 3 areas.

The requirement for adaptive behavior deficits is the most controversial aspect of the diagnostic formulation. The controversy centers on 2 broad areas: whether impairments in adaptive behavior are necessary for the construct of intellectual disability and what to measure. The adaptive behavior criterion may be irrelevant for many children; adaptive behavior is impaired in virtually all children who have IQ scores <50. The major utility of the adaptive behavior criterion is to confirm intellectual disability in children with IQ scores in the 65-75 range. It should be noted that deficits in adaptive behavior are often found in disorders such as autism spectrum disorders (see Chapter 30) and attention-deficit/hyperactivity disorder (ADHD) (see Chapter 33) in the presence of typical intellectual function.

The issues of measurement are important as well. The independence of the 3 domains of adaptive behavior has not been validated with research. The relationship between adaptive behavior and IQ performance is insufficiently explored. Most adults with mild intellectual disability do not have significant impairments in practical skills. It should be noted that adaptive behavior deficits must be distinguished from maladaptive behavior (e.g., aggression, inappropriate sexual contact).

Onset before age 18 yr or adulthood distinguishes dysfunctions that originate during the developmental period. The diagnosis of intellectual disability may be made after 18 yr of age or childhood, but the cognitive and adaptive dysfunction must have been manifested before age 18 or adulthood (e.g., during "childhood").

The term **mental retardation** should be cast aside because it is stigmatizing, has been used to limit the achievements of the individual, and has not met its initial objective of providing assistance to people with the disorder. The term **intellectual disability** is increasingly used

Table 36-1 Identification of Cause in Children with Severe Intellectual Disability

CAUSE	EXAMPLES	PERCENT OF TOTAL
Chromosomal disorder	Trisomies 21, 18, 13, Deletion 1p36 Klinefelter syndrome Wolf Hirschhorn syndrome	~20
Genetic syndrome	Fragile X syndrome Prader-Willi syndrome Rett syndrome	~20
Nonsyndromic autosomal mutations	Variations in copy number, de novo mutations in *SYNGAP1*, *GRIK2*, *TUSC3*, oligosaccharyl transferase, and others	~10
Developmental brain abnormality	Hydrocephalus ± meningomyelocele, lissencephaly	~8
Inborn errors of metabolism or neurodegenerative disorder	PKU, Tay-Sachs, various storage diseases	~7
Congenital infections	HIV, toxoplasmosis, rubella, CMV, syphilis, herpes simplex	~3
Familial intellectual disability	Environment, syndromic, or genetic	~5
Perinatal causes	HIE, meningitis, IVH, PVL, fetal alcohol syndrome	4
Postnatal causes	Trauma (abuse), meningitis, hypothyroidism	~4
Unknown	Cerebral palsy	20

CMV, Cytomegalovirus; HIE, hypoxic ischemic encephalopathy; HIV, human immunodeficiency virus; IVH, intraventricular hemorrhage; PKU, phenylketonuria; PVL, periventricular leukomalacia.

Modified from Stromme P, Hayberg G: Aetiology in severe and mild mental retardation: a population based study of Norwegian children, Dev Med Child Neurol *42:76–86, 2000.*

in its place, but has not been adopted universally. In the United States, some existing laws and their attendant entitlements still use the term mental retardation. In Europe, the term **learning disability** is often used to describe intellectual disability. **Global developmental delay** is a term often used to describe young children whose limitations have not yet resulted in a formal diagnosis of intellectual disability; it is often inappropriately used beyond the point when it is clear the child has intellectual disability, usually age 3 yr. Developmental delay is a classification that may be used by IDEA until age 9 yr.

ETIOLOGY

There appear to be 2 overlapping populations of children with intellectual disability: mild (IQ 50-70), which is more associated with environmental influences, and severe (IQ <50), which is more frequently linked to biologic and genetic causes. Mild intellectual disability is 4 times more likely to be found in the offspring of women who have not completed high school than in women who have graduated. This is presumably a consequence of both genetic (children can inherit an intellectual impairment) and socioeconomic (poverty, malnutrition) factors. The specific causes of mild intellectual disability are identifiable in <50% of affected individuals. The most common biologic causes of mild intellectual disability include genetic or chromosomal syndromes with multiple, major, or minor congenital anomalies (velocardiofacial syndrome, Williams syndrome, Noonan syndrome), intrauterine growth restriction, prematurity, perinatal insults, intrauterine exposure to drugs of abuse (including alcohol), and sex chromosomal abnormalities. Familial clustering is common.

In children with severe intellectual disability, a biologic cause (most commonly prenatal) can be identified in more than 75% of cases. Causes include chromosomal (e.g., Down syndrome Wolf-Hirschhorn syndrome, deletion 1p36 syndrome) and other genetic and epigenetic disorders (e.g., fragile X syndrome, Rett syndrome, Angelman and Prader-Willi syndromes), abnormalities of brain development (e.g., lissencephaly), and inborn errors of metabolism or neurodegenerative disorders (e.g., mucopolysaccharidoses) (Table 36-1). Nonsyndromic severe intellectual disability may be a result of inherited or de novo gene mutations, as well as microdeletions or microduplications not detected on standard chromosome analysis. More than 400 genes may be associated with nonsyndromic intellectual disability, with many detected by exomic sequencing. These de novo point mutations may also cause other phenotype features such as seizures or autism; the absence of these features suggests more pleotropic manifestations of genetic mutations. Consistent with the finding that disorders that alter early embryogenesis are the most common and severe, the earlier the problem occurs in development, the more severe its consequences tend to be.

EPIDEMIOLOGY

The prevalence of intellectual disability depends on the definition, the method of ascertainment, and the population. According to statistics, 2.5% of the population should have intellectual disability, and 75% of these individuals should fall into the mild to moderate range. Rates vary across populations. Globally, the prevalence of intellectual disability has been estimated to be approximately 16.41/1,000 persons in low income countries, approximately 15.94/1,000 for middle-income countries, and approximately 9.21/1,000 in high-income countries. Overall, intellectual disability occurs more in boys than in girls: 2 : 1 in mild intellectual disability and 1.5 : 1 in severe intellectual disability. In part this may be a consequence of the many X-linked disorders associated with intellectual disability, the most prominent being fragile X syndrome (see Chapter 81.5).

In 2009-2010 in the United States, approximately 463,000 or 0.9% of school-age children received services for intellectual disability in federally supported school programs. For several reasons, fewer children than predicted are identified as having mild intellectual disability. Because it is more difficult to diagnose mild intellectual disability than the more severe forms, professionals might defer the diagnosis and give the benefit of the doubt to the child. Other reasons that contribute to the discrepancy are use of instruments that underidentify young children with mild intellectual disability (Chapter 30), some children being diagnosed as having autism spectrum disorders and their intellectual disability not addressed, and a disinclination to make the diagnosis in poor or minority students because of previous overdiagnosis.

Young children might show cognitive limitations without significant delays in adaptive behavior. As a result, new cases of mild intellectual disability continue to be diagnosed among children up to 9 yr of age. Children with intellectual disability also may be incorporated into another diagnosis (e.g., autism, cerebral palsy). Furthermore, it

is possible that the number of children with mild intellectual disability is actually decreasing as a result of public health and education measures to prevent prematurity and provide early intervention and head start programs. In fact, the number of school children who receive services for intellectual disability has decreased since 1999, but if developmental delay is included, the numbers have not changed appreciably.

Unlike mild intellectual disability, where the prevalence may be decreasing, the occurrence of severe intellectual disability has not changed appreciably since the 1940s and is 0.3-0.5% of the population. Many of the causes of severe intellectual disability involve genetic or congenital brain malformations that can neither be anticipated nor treated at present. In addition, new populations with severe intellectual disability have offset the decreases in the prevalence of severe intellectual disability that have resulted from improved healthcare. Although prenatal diagnosis and subsequent pregnancy terminations have resulted in a decreased prevalence of Down syndrome (see Chapter 81), and newborn screening with early treatment has virtually eliminated intellectual disability caused by phenylketonuria and congenital hypothyroidism, an increased prevalence of maternal prenatal drug use (see Chapter 96.4) and improved survival of very-low birthweight premature infants has counterbalanced this effect.

PATHOLOGY AND PATHOGENESIS

The limitations in our knowledge of the neuropathology of intellectual disability are exemplified by the fact that 10-20% of brains of persons with severe intellectual disability appear entirely normal by standard neuropathologic study. The majority of brains of these persons show only mild, nonspecific changes that correlate poorly with the degree of intellectual disability. These changes include microcephaly, gray matter heterotopias in the subcortical white matter, unusually regular columnar arrangement of the cortex, and neurons that are more tightly packed than usual. Only a minority of the brain shows more specific changes in dendritic and synaptic organization, with dysgenesis of dendritic spines or cortical pyramidal neurons, or impaired growth of dendritic trees. The programming of the central nervous system (CNS) involves a process of induction; CNS maturation is defined in terms of genetic, molecular, autocrine, paracrine, and endocrine influences. Receptors, signaling molecules, and genes are critical to brain development. The maintenance of different neuronal phenotypes in the adult brain involves the same genetic transcripts that play a crucial role during fetal development, with activation of similar intracellular signal transduction mechanisms. Several syndromes that were thought to involve complex chromosomal abnormalities are, in fact, caused by single-gene mutations involving induction. Rubinstein-Taybi syndrome (see Chapter 81), a disorder marked clinically by broad thumbs and great toes, characteristic facies, and severe intellectual disability, results from a mutation in the gene encoding for the transcriptional coactivator CREB-binding protein (CBP), a factor important in the control of gene expression in early embryogenesis.

CLINICAL MANIFESTATIONS

Early diagnosis of intellectual disability facilitates earlier intervention, identification of abilities, realistic goal setting, easing of parental anxiety, and greater acceptance of the child in the community. Most children with intellectual disability first come to the pediatrician's attention in infancy because of dysmorphisms, associated developmental disabilities, or failure to meet age-appropriate developmental milestones. There are no specific physical characteristics of intellectual disability, but dysmorphisms may be the earliest signs that bring children to the attention of the pediatrician. They might fall within a genetic syndrome such as Down syndrome or be isolated, as in microcephaly or failure to thrive. Associated developmental disabilities include seizure disorders, cerebral palsy, hypotonia, and autism; these conditions are seen more commonly in conjunction with intellectual disability than in the general population.

Most children with intellectual disability do not keep up with their peers and fail to meet age-expected norms. In early infancy, failure to meet age-appropriate expectations can include a lack of visual or auditory responsiveness, unusual muscle tone (hypo- or hypertonia) or posture, and feeding difficulties. Between 6 and 18 mo of age, gross motor delay (lack of sitting, crawling, walking) is the most common complaint. Language delay and behavior problems are common concerns after 18 mo (Table 36-2). Earlier identification of atypical development is likely to occur with more severe impairments; and intellectual disability is usually identifiable by age 3 yr.

For some children with mild intellectual disability the diagnosis remains uncertain during the early school years. It is only after the demands of the school setting increase over the years, changing from "learning to read" to "reading to learn," that the child's limitations are clarified.

Adolescents with mild intellectual disability can present a diagnostic challenge. Typically they are up to date on current trends and are conversant as to who, what, and where. It isn't until the "why" and "how" questions are asked that their limitations become apparent. If allowed to interact at a superficial level, their mild intellectual disability might not be appreciated, even by professionals who may be their special education teachers or healthcare providers. Because of the stigma associated with intellectual disability, they may use euphemisms to avoid being thought of as "stupid" or "retarded" and refer to themselves as learning disabled, dyslexic, language disordered, or slow learners. Some people with intellectual disability emulate their social milieu to be accepted. They may be social chameleons and assume the morals of the group to which they are attached. Some would rather be thought "bad" than "incompetent."

LABORATORY FINDINGS

The most commonly used medical diagnostic testing for children with intellectual disability include neuroimaging; metabolic, genetic, and chromosomal testing; microarray analysis; and electroencephalography. These tests should not be used as screening tools for all children with an intellectual disability. In some children, there is a reasonable yield for testing, whereas in others the yield of <1% does not support its use. Decisions on diagnostic testing should be based on the medical and family history, physical examination, testing by other disciplines, and the family's wishes. Table 36-3 summarizes clinical practice guidelines that have been published and the yields of testing to assist in evaluating the child with global developmental delay or intellectual disability. Microarray analysis has replaced karyotyping as the preferred approach for children with multiple anomalies or a positive family history. Microarray analysis has the ability to discern abnormalities that are below the resolution of karyotyping. For example, deletion 1p36 syndrome, the most common subtelomeric microdeletion syndrome (1:5,000 births), accounts for approximately 1% of

Table 36-2 Common Presentations of Intellectual Disability By Age

AGE	AREA OF CONCERN
Newborn	Dysmorphic syndromes, (multiple congenital anomalies), microcephaly Major organ system dysfunction (e.g., feeding and breathing)
Early infancy (2-4 mo)	Failure to interact with the environment Concerns about vision and hearing impairments
Later infancy (6-18 mo)	Gross motor delay
Toddlers (2-3 yr)	Language delays or difficulties
Preschool (3-5 yr)	Language difficulties or delays Behavior difficulties, including play Delays in fine motor skills: cutting, coloring, drawing
School age (>5 yr)	Academic underachievement Behavior difficulties (attention, anxiety, mood, conduct, etc.)

children with developmental disabilities and is characterized by failure to thrive, microcephaly, deep-set eyes, midface hypoplasia, broad nasal bridge, heart deficits, and CNS anomalies. Noncompaction cardiomyopathy and seizures are also noted. The diagnosis is made by standard chromosomes in only approximately 20% and requires fluorescent in situ hybridization or microarray comparative genomic hybridization methods for remaining patients. Microarray analysis may identify variants of unknown significance or benign variants, and therefore should be used in conjunction with a genetic consultation. Karyotyping has a role for children whose array analysis is unrevealing and concern is present for inversions, balanced insertions, and reciprocal translocations. Fluorescent in situ hybridization and subtelomeric analysis have been largely replaced by microarray analysis but continue to be used for specific indications. If microarray analysis is not diagnostic whole exome sequencing increases the diagnostic yield in many children with nonsyndromic severe intellectual disability.

Molecular genetic testing for fragile X syndrome is appropriate for a boy with moderate intellectual disability, unusual physical features, and/or a family history of intellectual disability, or for a girl with more subtle cognitive deficits associated with severe shyness and a relevant family history. For children with a strong history of X-linked intellectual disability, specific testing of genes or the entire chromosome may be revealing. MECP2 (methyl CpG binding protein 2 [Rett syndrome]) testing should be considered in girls with moderate to severe disability.

A child with a progressive neurologic disorder, developmental regression, or acute behavioral changes needs metabolic investigation (urinary organic acids, plasma amino acids, blood lactate, lysosomal enzymes in lymphocytes), although many of these disorders are detectable as part of newborn screening; a child with seizure-like episodes should have an electroencephalography performed. Children with micro- or macrocephaly or changes in head growth trajectory or asymmetric head shapes, as well as those with new or focal neurologic findings, including seizures, should have a neuroimaging procedure.

MRI scans identify a significant number of subtle markers of cerebral dysgenesis in children with intellectual disability. Formes frustes

Table 36-3 Suggested Evaluation of the Child with Intellectual Disability/Global Developmental Delay

TEST	COMMENT
In-depth history	Includes pre-, peri-, and postnatal events (including seizures); developmental attainments; and 3-generation pedigree in family history
Physical examination	Particular attention to minor or subtle abnormalities; neurologic examination for focality and skull abnormalities Behavioral phenotype
Vision and hearing evaluation	Essential to detect and treat; can mask as developmental delay
Gene microarray analysis	A 7.8% yield overall (10% in syndromic and 6.5% in nonsyndromic intellectual disability) Better resolution than Karyotype. May identify up to twice as many abnormalities as karyotyping. Excellent in detecting de novo microdeletions or microduplications
Karyotype	Yield 4% in global developmental delay/intellectual disability Best for inversions and balanced insertions, reciprocal translocations, and polyploidy
Fragile X screen	Combined yield 2% Preselection on clinical grounds can increase yield to 7.6%
X-linked candidate intellectual disability genes	May explain up to 10% of intellectual disability Yield may be as high as 42% if there is a definite family history and as high as 17% from a possibly linked kindred
Exomic gene sequencing	Detects inherited and de novo point mutations especially in nonsyndromic severe intellectual disability
Neuroimaging	MRI preferred. Positives increased by abnormalities of skull contour or microcephaly and macrocephaly, or focal neurologic examination. Overall has a higher yield Identification of specific etiologies is rare. Most conditions that are found do not alter the treatment plan. Need to weigh risk of sedation against possible yield
Thyroid (T_4, TSH)	Near 0% in settings with universal newborn screening program
Serum lead	If there are identifiable risk factors for excessive environmental lead exposure
Metabolic testing	Yield 0.2-4.6% based on clinical indicators and tests performed Urine organic acids, plasma amino acids, ammonia, lactate, and a capillary blood gas. Focused testing based on clinical findings is warranted Tandem mass spectrometry newborn screening has allowed for identification of many disorders in perinatal period and have decreased yield in older children. Other disorders have emerged; e.g., congenital disorders of glycosylation and disorders of creatine synthesis and transport
MECP2 for Rett syndrome	1.5% of females with severe intellectual disability 0.5% of males
EEG	May be deferred in absence of history of seizures
Repeated history and physical examination	Can give time for maturation of physical and behavioral phenotype. New technology may be available for evaluation

EEG, Electroencephalogram; CGH, comparative genomic hybridization; MECP2, methyl CpG binding protein 2; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Based on Michelson DJ, Shevell MI, Sherr EH, et al: Evidence report: Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of Child Neurology. Neurology 77:1629-35, 2011; Curry CJ, Stevenson RE, Aughton D, et al: Evaluation of mental retardation: recommendations of a Consensus Conference: American College of Medical Genetics. Am J Med Genet 12:72:468-477, 1997. Shapiro BK, Batshaw ML: Mental retardation. In Burg FD, Ingelfinger JR, Polin RA, et al: Gellis and Kagan's current pediatric therapy, *ed 18, Philadelphia, 2005, WB Saunders, used with permission; and Shevell M, Ashwal S, Donley D, et al: Practice parameter: evaluation of the child with global developmental delay,* Neurology *60:367–380, 2003.*

of amino acid and organic acid disorders are associated with intellectual disability in the absence of the more commonly associated manifestations of behavior change, lethargy, and coma.

Some children with more subtle physical or neurologic findings can also have determinable biologic causes of their intellectual disability (see Chapter 83). How intensively one investigates the cause of a child's intellectual disability is based on a number of factors:

- What is the degree of intellectual disability? One is less likely to find a biologic cause in a child with mild intellectual disability than in a child with a severe intellectual disability.
- Is there a specific diagnostic path to follow? If there is a medical history or a family history, or if physical findings pointing to a specific disorder, a diagnosis is more likely to be made. In the absence of these indicators, it is difficult to choose specific tests to perform.
- Are the parents planning on having additional children? If so, one would be more likely to intensively seek disorders for which prenatal diagnosis or a specific early treatment option is available.
- What are the parents' wishes? Some parents have little interest in searching for the cause of the intellectual disability and focus exclusively on treatment. Others are so focused on obtaining a diagnosis that they have difficulty following through on interventions until a cause has been found. The entire spectrum of responses must be respected, and supportive guidance should be provided in the context of the parents' education.

DIFFERENTIAL DIAGNOSIS

One of the important roles of pediatricians is the early recognition and diagnosis of cognitive deficits. The developmental surveillance approach to early diagnosis of intellectual disability should be multifaceted. Parents' concerns and observations about their child's development should be listened to carefully, because their observations have been found to be as accurate as developmental screening tests. Medical, genetic, and environmental risk factors should be recognized. Infants at high risk (prematurity, maternal substance abuse, perinatal insult) should be registered in newborn follow-up programs in which they are evaluated periodically for developmental lags in the first 2 yr of life; they should be referred to early intervention programs as appropriate. Developmental milestones should be recorded routinely during health-care maintenance visits. The American Academy of Pediatrics has formulated a schema for developmental surveillance and screening. Whether developmental surveillance is a more effective technique for identifying than recognizing failure to meet age-appropriate milestones has not been clearly established.

Before making the diagnosis of intellectual disability, other disorders that affect cognitive abilities and adaptive behavior should be considered. These include conditions that mimic intellectual disability and others that involve intellectual disability as an associated impairment. Sensory deficits (severe hearing and vision loss), communication disorders, and poorly controlled seizure disorders can mimic intellectual disability; certain progressive neurologic disorders can appear as intellectual disability before regression is appreciated. More than half of children with cerebral palsy (see Chapter 598) or autism spectrum disorders (see Chapter 30) also have intellectual disability as an associated deficit. Differentiation of isolated **cerebral palsy** from intellectual disability relies on motor skills being more affected than cognitive skills and on the presence of pathologic reflexes and tone changes. In **autism spectrum disorders,** language and social adaptive skills are more affected than nonverbal reasoning skills, whereas in intellectual disability there are usually more equivalent deficits in social, fine motor, adaptive, and cognitive skills.

DIAGNOSTIC PSYCHOLOGIC TESTING

The formal diagnosis of intellectual disability requires the administration of individual tests of intelligence and adaptive functioning.

The Bayley Scales of Infant Development (BSID-III), the most commonly used infant intelligence scale, assesses language, visual problem-solving skills, behavior, fine motor skills, and gross motor skills in children between 1 mo and 42 mo of age. A Mental Developmental Index (MDI) and a Psychomotor Development Index (PDI, a measure of motor competence) score are derived from the results. This test permits the differentiation of infants with severe intellectual disability from typically developing infants, but it is less helpful in distinguishing between a typical child and one with mild intellectual disability.

The most commonly used psychologic tests for children older than 3 yr of age are the Wechsler Scales. The Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV) is used for children with mental ages of 2.5-7.6 yr. The Wechsler Intelligence Scale for Children, 4th edition (WISC-IV), is used for children who function above a 6 yr mental age. Both scales contain a number of subtests in the areas of verbal and performance skills. Although children with intellectual disability usually score below average on all subscale scores, they occasionally score in the average range in 1 or more performance areas.

The most commonly used test of adaptive behavior is the **Vineland Adaptive Behavior Scale** (VABS), which involves semi structured interviews with parents and/or caregivers and teachers that assess adaptive behavior in four domains: communication, daily living skills, socialization, and motor skills. Other tests of adaptive behavior include the Woodcock-Johnson Scales of Independent Behavior–Revised, the American Association on Intellectual and Developmental Disability Adaptive Behavior Scale (ABS-2nd edition), and the Adaptive Behavior Assessment System (ABAS-2nd edition). There is usually (but not always) a good correlation between scores on the intelligence and adaptive scales. Basic adaptive abilities (feeding, dressing, hygiene) are more responsive to remedial efforts than is the IQ score. Adaptive abilities are also more variable, which can relate to the underlying condition and to environmental expectations. Although persons with Prader-Willi syndrome (see Chapter 81) have stability of adaptive skills through adulthood, those with fragile X syndrome may have increasing deficits over time.

COMPLICATIONS

Children with intellectual disability have higher rates of vision, hearing, neurologic, orthopedic, and behavioral or emotional disorders than do typically developing children. These other problems are often detected later in children with intellectual disability. If untreated, the associated impairments can potentially adversely affect the individual's outcome more than the intellectual disability itself.

The most common associated deficits are motor impairments, behavioral and emotional disorders, medical complications, and seizures. The more severe the intellectual disability, the greater are the number and severity of associated impairments. Knowing the cause of the intellectual disability can help predict which associated impairments are most likely to occur. Fragile X syndrome and fetal alcohol syndrome (see Chapter 106.2) are associated with a high rate of behavioral disorders; Down syndrome has many medical complications (hypothyroidism, celiac disease, congenital heart disease, atlantoaxial subluxation). Associated impairments can require ongoing physical therapy, occupational therapy, speech-language therapy, adaptive equipment, glasses, hearing aids, and medication. Failure to identify and treat these impairments adequately can hinder successful habilitation and result in difficulties in the school, home, and/or neighborhood environment.

PREVENTION

Examples of primary programs to prevent intellectual disability include:

- Increasing the public's awareness of the adverse effects of alcohol and other drugs of abuse on the fetus
- Preventing teen pregnancy and promoting early prenatal care
- Preventing traumatic injury by encouraging the use of guards and railings to prevent falls and other avoidable injuries in the home; using appropriate seat restraints when driving and wearing a safety helmet when biking or skateboarding; teaching firearms safety
- Preventing poisonings by teaching parents about locking up medications and potential poisons

- Encouraging safe sexual practices to prevent the transmission of diseases
- Implementing immunization programs to reduce the risk of intellectual disability caused by encephalitis, meningitis, and congenital infection

Presymptomatic detection of certain disorders can result in treatment that prevents adverse consequences. State newborn screening by tandem mass spectrometry (now including >50 rare genetic disorders in most states), newborn hearing screening, and preschool lead poisoning prevention programs are examples. Thyroid screening in a child with Down syndrome is an example of presymptomatic testing in a disorder associated with intellectual disability.

TREATMENT

Although intellectual disability is not treatable, many associated impairments are amenable to intervention and therefore benefit from early identification. Most children with an intellectual disability do not have a behavioral or emotional disorder as an associated impairment, but challenging behaviors (aggression, self-injury, oppositional defiant behavior) and mental illness (mood and anxiety disorders) occur with greater frequency in this population than among children with typical intelligence. These behavioral and emotional disorders are the primary cause for out-of-home placements, reduced employment prospects, and decreased opportunities for social integration. Some behavioral and emotional disorders are difficult to diagnose in children with more severe intellectual disability because of the child's limited abilities to understand, communicate, interpret, or generalize. Other disorders are masked by the intellectual disability. The detection of ADHD (see Chapter 33) in the presence of moderate to severe intellectual disability may be difficult, as may be discerning a thought disorder (psychosis) in someone with autism and intellectual disability.

Although mental illness is generally of biologic origin and responds to medication, behavioral disorders can result from a mismatch between the child's abilities and the demands of the situation, organic problems, and/or family difficulties. They may represent attempts by the child to communicate, gain attention, or avoid frustration. In assessing the challenging behavior, one must also consider whether it is inappropriate for the child's *mental age,* rather than the *chronological age.* When intervention is needed, an environmental change, such as a more appropriate classroom setting, may improve certain behavior problems. Behavior management techniques are useful; psychopharmacologic agents may be appropriate in certain situations.

Medication is not useful in treating the core symptoms of intellectual disability; no agent has been found to improve intellectual function. Medication may be helpful in treating associated behavioral and psychiatric disorders. Psychopharmacology is generally directed at specific symptom complexes including ADHD (stimulant medication), self-injurious behavior and aggression (neuroleptics), and anxiety obsessive-compulsive disorder, and depression (selective serotonin reuptake inhibitors). Before long-term therapy with any psychopharmacologic agent is initiated, a short trial should be conducted. Even if a medication proves successful, its use should be reevaluated at least yearly to assess the need for continued treatment.

SUPPORTIVE CARE AND MANAGEMENT

Each child with intellectual disability needs a medical home with a pediatrician who is readily accessible to the family to answer questions, help coordinate care, and discuss concerns. Pediatricians can have effects on patients and their families that are still felt decades later. The role of the pediatrician includes involvement in prevention efforts, early diagnosis, identification of associated deficits, referral for appropriate diagnostic and therapeutic services, interdisciplinary management, provision of primary care, and advocacy for the child and family. The management strategies for children with an intellectual disability should be multimodal, with efforts directed at all aspects of the child's life: health, education, social and recreational activities, behavior problems, and associated impairments. Support for parents and siblings should also be provided.

Primary Care

For children with an intellectual disability, primary care has a number of important components:

- Provision of the same primary care received by all other children of similar chronological age (see Chapter 5)
- Anticipatory guidance relevant to the child's level of function: feeding, toileting, school, accident prevention, sexuality education
- Assessment of issues that are relevant to that child's disorder: e.g., examination of the teeth in children who exhibit bruxism, thyroid function in children with Down syndrome, cardiac function in Williams syndrome (see Chapter 108)

The American Academy of Pediatrics has published a series of guidelines for children with specific genetic disorders associated with intellectual disability (Down syndrome, fragile X syndrome, and Williams syndrome). Goals should be considered and programs adjusted as needed during the primary care visit. Decisions should also be made about what additional information is required for future planning or to explain why the child is not meeting expectations. Other evaluations, such as formal psychologic or educational testing, may need to be scheduled.

Interdisciplinary Management

The pediatrician has the responsibility for consulting with other disciplines to make the diagnosis of intellectual disability and coordinate treatment services. Consultant services may include psychology, speech-language pathology, physical therapy, occupational therapy, audiology, nutrition, nursing, and/or social work, as well as medical specialties such as neurodevelopmental disabilities, neurology, genetics, psychiatry, developmental-behavioral pediatricians, and/or surgical specialties. Contact with early intervention and school personnel is equally important to help prepare the child's Individual Family Service Plan/Individual Educational Plan. The family should be an integral part of the planning and direction of this process. Care should be family centered and culturally sensitive; for older children, their participation in planning and decision making should be promoted to whatever extent possible.

Periodic Reevaluation

The child's abilities and the family's needs change over time. As the child grows, more information must be provided to the child and family, goals must be reassessed, and programming needs should be adjusted. A periodic review should include information about the child's health status as well as the child's functioning at home, at school, and in other community settings. Other information, such as formal psychologic or educational testing, may be helpful. Reevaluation should be undertaken at routine intervals (6-12 mo during early childhood), at any time the child is not meeting expectations, or when the child is moving from one service delivery system to another. This is especially true during the transition to adulthood, beginning at age 14 yr as mandated by the IDEA Amendments of 2004. This transitioning should include the transfer of care to the adult healthcare system by age 21 yr.

Educational Services

Education is the single most important discipline involved in the treatment of children with an intellectual disability. The educational program must be relevant to the child's needs and address the child's individual strengths and weaknesses. The child's developmental level, the child's requirements for support, and goals for independence provide a basis for establishing an Individualized Education Program for school-age children, as mandated by federal legislation.

Leisure and Recreational Activities

The child's social and recreational needs should be addressed. Although young children with intellectual disability are generally included in play activities with children who have typical development, adolescents with intellectual disability often do not have opportunities for appropriate social interactions. Participation in sports should be encouraged, even if the child is not competitive, because it offers many benefits,

Table 36-4 Severity of Intellectual Disability and Adult Age Functioning

LEVEL	MENTAL AGE AS ADULT*	ADULT ADAPTATION
Mild	9-11 yr	Reads at 4th-5th grade level; simple multiplication and division; writes simple letter, lists; completes job application; basic independent job skills (arrive on time, stay at task, interact with coworkers); uses public transportation, might qualify for driver's license; keeps house, cooks using recipes
Moderate	6-8 yr	Sight-word reading; copies information, e.g., address from card to job application; matches written number to number of items; recognizes time on clock; communicates; some independence in self-care; housekeeping with supervision or cue cards; meal preparation, can follow picture recipe cards; job skills learned with much repetition; uses public transportation with some supervision
Severe	3-5 yr	Needs continuous support and supervision; might communicate wants and needs, sometimes with augmentative communication techniques
Profound	<3 yr	Limitations of self-care, continence, communication, and mobility; might need complete custodial or nursing care

*WHO, *International Statistical Classification of Diseases and Related Health Problems*, 10th revision, Geneva, Switzerland, 2011, World Health Organization.

including weight management, development of physical coordination, maintenance of cardiovascular fitness, and improvement of self-image. Social activities are equally important, including dances, trips, dating, and other typical social and recreational events.

Family Counseling

Many families adapt well to having a child with intellectual disability, but some have emotional or social difficulties. The risks of parents' depression and child abuse and neglect are higher in this group of children than in the general population. Among the factors that have been associated with good family coping and parenting skills are stability of the marriage, good parental self-esteem, limited number of siblings, higher socioeconomic status, lower degree of disability or associated impairments, parents' appropriate expectations and acceptance of the diagnosis, supportive extended family members, and availability of community programs and respite care services. In families in which the emotional burden of having a child with intellectual disability is great, family counseling, parent support groups, respite care, and home health services should be an integral part of the treatment plan.

PROGNOSIS

In children with severe intellectual disability, the prognosis is often evident by early childhood. Mild intellectual disability might not always be a lifelong disorder. Children might meet criteria for intellectual disability at an early age, but later the disability can evolve into a more specific developmental disorder (communication disorder, autism, slow learner, or borderline normal intelligence). Others with a diagnosis of mild intellectual disability during their school years develop sufficient adaptive behavior skills so that they no longer fit the diagnosis as adolescents, or the effects of maturation and plasticity can result in children moving from one diagnostic category to another (from moderate to mild retardation). Some children who have a diagnosis of a specific learning disability or communication disorder might not maintain their rate of cognitive growth and fall into the range of intellectual disability over time. By adolescence, the diagnosis has generally stabilized.

The apparent higher prevalence of intellectual disability in low and middle income group countries is of concern given the limitations in available resources. While community-based rehabilitation is being implemented in more than 90 countries, the efficacy of such programs has not been established.

The long-term outcome of persons with intellectual disability depends on the underlying cause, the degree of cognitive and adaptive deficits, the presence of associated medical and developmental impairments, the capabilities of the families, and the school and community supports, services, and training provided to the child and family (Table 36-4). As adults, many persons with mild intellectual disability are capable of gaining economic and social independence with functional literacy. They might need periodic supervision, especially when under social or economic stress. Most live successfully in the community, either independently or in supervised settings. Life expectancy is not adversely affected by intellectual disability itself.

For persons with moderate intellectual disability, the goals of education are to enhance adaptive abilities and "survival" academic and vocational skills so they are better able to live in the adult world (see Table 36-4). The concept of supported employment has been very beneficial to these individuals; the person is trained by a coach to do a specific job in the setting in which the person is to work. This bypasses the need for a sheltered workshop experience and has resulted in successful work adaptation in the community for many people with an intellectual disability. These persons generally live at home or in a supervised setting in the community.

As adults, people with severe to profound intellectual disability usually require extensive to pervasive supports (see Table 36-4). These individuals may have associated impairments, such as cerebral palsy, behavioral disorders, epilepsy, or sensory impairments, that further limit their adaptive functioning. They can perform simple tasks in supervised settings. Most people with this level of intellectual disability are able to live in the community with appropriate supports.

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Children with Special Needs

PART V

Chapter 37
Adoption

Samantha L. Wilson and Mark D. Simms

Adoption is a social, emotional, and legal process that provides a new family for a child when the birth family is unable or unwilling to parent. In the United States, about 1 million children <18 yr of age are adopted; 2-4% of all American families have adopted. Annually across the globe, approximately 250,000 children are adopted; approximately 30,000 of adoptions are between nations. In the United States approximately **136,000 children were adopted in 2008, a** 15% increase since 1990. Of these, approximately 40% were stepparent or relative adoptions. Of non-stepparent adoptions, approximately 60% were from the child welfare system, 25% were international, and 15% were voluntarily adoption-placed domestic infants. Public agencies support approximately 50% of total annual adoptions in the United States, private agencies facilitate approximately 25% of adoptions, and independent practitioners, for example, lawyers, handle approximately 15% of adoptions. Compared to 19% of the general population, approximately 39% of adopted children have special healthcare needs.

The Adoption and Safe Families Act (P.L. 105-89) requires children in foster care to be placed with adoptive families if they cannot be safely returned to their families within a reasonable period of time. In fiscal year (FY) 2011, there were 104,236 children waiting for adoption, including 61,361 whose biological parents' rights had been terminated. Many children awaiting adoption have "special needs" because they are of school age, part of a sibling group, members of historically oppressed racial/ethnic groups, or because they have considerable physical, emotional, or developmental needs. A number of policy efforts are aimed at increasing adoption opportunities for these children, including federal adoption subsidies, tax credits, recruitment efforts to identify ethnically diverse adults willing to adopt, increased preplacement services, and expanding adoption opportunities to single adults, gay/lesbian partners, and older couples.

Along with foster care adoptions, international adoptions are a way of providing stable, long-term care to vulnerable children throughout the world. There is concern that in some countries of origin the rapid growth of international adoption has outpaced regulation and oversight to protect vulnerable children/families. Opportunities for financial gain have led to abuses, including the sale and abduction of children, bribery, and financial coercion of families, though the extent and scope of the potential concern is difficult to ascertain. Increasing global efforts, such as the Hague Convention on Protection of Children and Co-Operation In Respect of Intercountry Adoption, have promoted political cooperation between nations and established international law to reduce potential for child abduction/trafficking and to ensure that the best interests of the child are paramount in decision making. Participating nations, including the United States, are working to address the myriad sociopolitical conditions that create the need for out-of-family care, and are working to support children within their nations' borders. International adoption is increasingly considered a measure of last resort if the child cannot be cared for within the child's birth family (including extended relatives), the immediate community, or within the larger national culture. As a result, children adopted internationally into the United States are more likely to enter their families at older ages or with complex medical/developmental/social-emotional needs.

Although the vast majority of children adopted internationally *enter* the United States for purposes of adoption, there are a small, but growing, number of children who *exit* the United States for adoption into other countries. For example, in FY 2012, 99 children exited the United States for adoption by families in other countries (e.g., Canada, Netherlands, Ireland, United Kingdom). Little is known about the circumstances surrounding these adoptions and the eventual outcomes of the children who are adopted internationally *from* the United States.

In 2012, U.S. families adopted 8,868 children from other countries (compared with a peak of 22,884 in 2004). Children from China, Ethiopia, Russia, and South Korea represented 65% of children adopted internationally into the United States in 2012; 33% were from China alone. Although individual experiences vary, most children placed for international adoption have some history of poverty and social hardship in their home countries, and approximately 65% are adopted from orphanage/institutional settings. Many young infants are placed into orphanage care shortly after birth, while some older children have experienced family disruption resulting from parental illness, war, or natural disasters. Still others enter orphanage care following determination of significant abuse/neglect within their biologic families. The effects of institutionalization and other life stresses impact all areas of early growth and development. As a result, many children require specialized support and understanding to overcome the impact of stress and early adversity and to reach their full potential.

ROLE OF PEDIATRICIANS

Preadoption Medical Record Reviews

Adoption agencies are making increased efforts to obtain biological family health information and genetic histories to share with adoptive families prior to adoption. Pediatricians can help prospective adoptive parents understand the health and developmental history of a child and available background information from birth families in order to assess actual and potential medical risk factors to support adult decision making about the family's ability to parent the waiting child. Under the Hague Convention on Protection of Children and Co-operation in Respect of Intercountry Adoption, agencies in the United States that arrange international adoptions must make efforts to obtain accurate and complete health histories on children awaiting adoption.

The nature and quality of medical and genetic information, when available, varies greatly. Poor translation and use of medical terminology and medications that are unfamiliar to U.S.-trained physicians are quite common. Results of specific diagnostic studies and laboratory tests performed outside of the United States should not be relied on and **should be repeated** once the child arrives in the United States. Paradoxically, review of the child's medical records may raise more questions than provide answers. Each medical diagnosis should be considered carefully before being rejected or accepted. Country-specific growth curves should be avoided as they may be inaccurate or reflect a general level of poor health and nutrition in the country of origin. Instead, serial growth data should be plotted on U.S. standard growth curves; they may reveal a pattern of poor growth as a consequence of malnutrition or other chronic illness. Photographs or videotapes/DVDs may provide the only "objective" information from which medical status can be determined. Full-face photographs may reveal dysmorphic features consistent with fetal alcohol syndrome (see Chapter 106.2) or findings suggestive of other congenital disorders.

Preadoptive medical record reviews are also of potential value within the context of U.S. domestic adoptions. Biological family health information and genetic histories are often shared with adoptive families prior to adoption, and such information may become increasingly

relevant to the child as the child ages. The increase in "open" domestic adoptions, which encourages some degree of communication between participating biological and adoptive family members, may provide opportunities for long-term communication about medical and genetic conditions that might affect the adopted child.

In both international and domestic adoptions, frank interpretations of available information should be shared with the prospective adoptive parents. As noted by the American Academy of Pediatrics Committee on Early Childhood, Adoption and Dependent Care (1991), "It is not the pediatrician's role to judge the advisability of a proposed adoption, but it is appropriate and necessary that the prospective parents and any involved agency be apprised clearly and honestly of any special health needs detected now or anticipated in the future."

Postadoption Medical Care

Arrival Visit–International Adoption

All children with symptoms of an acute illness should receive immediate medical care after arriving in the United States. However, a significant number of children adopted internationally have acute or chronic medical problems that are not always immediately evident, including growth deficiencies, anemia, elevated blood lead, dental decay, strabismus, birth defects, developmental delay, feeding and sensory difficulty, and social-emotional concerns (see Chapter 37.1 below). After the child is settled in the new home, pediatricians should encourage adoptive parents to seek a comprehensive assessment of the child's growth and development. The American Academy of Pediatrics recommends that all children who are adopted from other countries undergo routine screening for infectious diseases and disorders of growth, development, vision, and hearing (Tables 37-1 and 37-2). Additional tests (e.g., malaria) should be ordered depending on the prevalence of disease in the child's country of origin (see Centers for Disease Control and Prevention's interactive malaria map at http://www.cdc.gov/malaria/map/). If the child's purified protein derivative is negative, a repeat skin test should be performed in 4-6 mo; children may have false-negative tests because of poor nutrition. A positive purified protein derivative should be followed by a QuantiFERON-TB Gold test to determine if the response is the result of prior bacillus Calmette-Guérin vaccination (see Chapter 215). If they have not received hepatitis A vaccine prior to arriving in the United States, parents, other caregivers, and family members (siblings, grandparents, etc.) should also be immunized. In 1 survey, 65% of internationally adopted children had no written records of overseas immunizations; however, those with records appeared to have valid records, although doses were not necessarily acceptable according to the U.S. schedule (see Chapter 172). The diverse medical and developmental needs of internationally adopted children have led to the creation of specialty clinics throughout the United States, which may be a valuable resource for adoptive families at all stages in the adoption process.

Table 37-1 Recommended Screening Tests for International Adoptees Upon U.S. Arrival

Screening tests
- Complete blood cell count
- Hemoglobin identification
- Blood lead level
- Urinalysis
- Newborn screening (children <12 mo)
- Vision and hearing screening
- Developmental testing

Other screening tests to consider based on clinical findings and age of the child
- Detection of *Helicobacter pylori* antibody or ^{13}C-urea breath test
- Stool cultures for bacterial pathogens
- Glucose-6-phosphate dehydrogenase deficiency screening
- Sickle cell
- Urine pregnancy test

Infectious disease screening (see Table 37-2)

Developmental Delays

At the time of adoption, many children exhibit delays in at least 1 area of development, but most exhibit significant gains within the first 12 mo after adoption. Those adopted before 6 mo of age usually demonstrate typical development, whereas those adopted at older ages have more variable outcomes. In the immediate postadoption period, it may be impossible to determine with any certainty whether a child's developmental delays will be transient or long-lasting. Careful monitoring of development within the first year of adoption can identify a "developmental trend" over time that may be more predictive of long-term functioning than assessment at any specific point in time.

Growth Delays

Physical growth delays are common in both domestically and internationally adopted children, and may represent the combined result of many factors, for example, unknown/untreated medical conditions, malnutrition, and psychological deprivation. Weight and height at the time of adoption have been negatively correlated with the amount of time the child spent in adverse environments (i.e., orphanage care or in the care of highly neglectful biological families). Though most children experience a significant catch-up in physical growth following adoption, many remain shorter than their U.S. peers.

Language Development

For both domestic and international adoptees, genetic or biologic risk factors for poor language development may not have been identified preadoptively. Children adopted internationally typically have had little exposure to English, and it may not be possible to assess a child's language abilities until they have had a chance to learn English. Most internationally adopted children of pre–school-age are able to attain English language skills equal to those born in the United States within 24 mo postadoption. In older children, delays in native language skills often predict delays in English acquisition. If language concerns persist following 1-2 yr in an enriching environment, assessment by a speech-language pathologist may be warranted.

Table 37-2 Screening Tests for Infectious Diseases in International Adoptees

RECOMMENDED TESTS

Hepatitis B virus serologic testing*
- Hepatitis B surface antigen (HBsAg)
- Antibody to hepatitis B surface antigen (anti-HBs)

Hepatitis C virus serologic testing*†

Hepatitis A virus serologic testing†

Varicella virus serologic testing†

Syphilis serologic testing
- Nontreponemal test (RPR, VDRL, or ART)
- Treponemal test (MHA-TP or FTA-ABS)

Human immunodeficiency viruses 1 and 2 testing (ELISA if >18 mo, PCR if <18 mo)*

Complete blood cell count with red blood cell indices and differential (if eosinophilia, see text)

Stool examination for ova and parasites (2-3 specimens)†

Stool examination for *Giardia lamblia* and *Cryptosporidium* antigen (1 specimen)†

Tuberculin skin test (with CXR if >5 mm induration) or interferon-γ release assay*†

OPTIONAL TESTS (FOR SPECIAL POPULATIONS OR CIRCUMSTANCES)

GC/Chlamydia

Chagas disease serology

Malaria thick and thin smears

Urine for O&P for schistosomiasis, if hematuria present

*Repeat 3-6 mo after arrival.

†See text.

ART, automated reagin test; CXR, chest radiograph; ELISA, enzyme-linked immunosorbent assay; FTA-ABS, fluorescent treponemal antibody absorption; GC, gonococcus; MHA-TP, microhemagglutination test for *Treponema pallidum*; O&P, ova and parasites; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories.

Eating Concerns

Initial concerns about eating, sleep regulation, and repetitive (e.g., self-stimulating or self-soothing) behaviors are common, especially among children adopted following a high degree of neglect or developmental trauma. Feeding concerns are sometimes linked to limited exposure to textured or solid foods during later infancy/toddlerhood. Children who have experienced chronic lack of food may not have developed an awareness of satiation cues, leading to hoarding or frequent vomiting. Feeding concerns often subside gradually with introduction of age-appropriate foods and parental support for positive feeding practices. Many children who were adopted following a significant period of malnutrition may eat an excessive amount of food. Unless the child is eating to the point of vomiting (which would indicate little awareness of satiation cues), it is generally best to allow them to eat until satiation. Typically within 6 mo, the child will regulate food intake appropriately. Occasionally, additional support from a speech pathologist or feeding specialist is warranted to address possible physical/psychological concerns that could impede proper feeding.

Sleep Concerns

Sleep is often disrupted as the child reacts to changes in routines and environments. Efforts to create continuity between the preadoption and postadoption environment can be helpful. Within the first 3-6 mo, as the child's emotional self-regulation improves, many sleep concerns subside. Similarly, stereotypic behaviors, such as rocking or head banging, often diminish within the first few months following adoption.

Social and Emotional Development

Dyadic interactions between child and caretaker are a critical component to later regulatory functioning and social-emotional development. The amount and quality of individualized caretaking children have received prior to their adoption is usually unknown. In many instances, entry into a secure, stable home setting with consistent child-caring routines is sufficient to support the child's emerging social-emotional development. At times, the child's prior experiences or biologic disposition may result in behavior that is confusing to the adoptive parents. The child's reactions may be subtle or difficult to interpret, interfering with the parents' ability to respond in a sensitive manner. In these circumstances, additional support may be helpful to foster the emerging relationships and behavioral regulation in the newly formed family.

Racial Identity Development

An estimated 22% of adoptive families are interracial (where the racial background of the child differs from that of the parent/parents). In the vast majority of these adoptive placements, children of color have been adopted by white parents. Racial identity development, including ways to understand and respond to discrimination, is increasingly recognized as important in the overall development of children. Surveys of adults adopted transracially indicate that racial identity is of central importance at many ages, and tends to increase in significance during young adulthood. Integrating race/ethnicity into identity can be a complex process for all children, but it may be especially complicated when they are raised in a family where racial differences are noted. Adults raised within interracial families have noted the value of attending racially diverse schools and of having adult role models (e.g., teachers, doctors, coaches) who share their racial background. Parents who adopt transracially are often encouraged to support interactions within diverse communities and to discuss race (and associated discrimination) often within the family.

Toxic Stress

The cumulative amount of early adversity (e.g., numerous years within international orphanage care, extensive abuse/neglect prior to removal from biological family, or multiple foster care placements) experienced by a child prior to adoption, referred to as "toxic stress," can impact both immediate placement stability and long-term functioning. The degree of presumed toxic stress may be helpful in interpreting a child's behavior and supporting family functioning (see video at http://developingchild.harvard.edu/resources/multimedia/videos/three_core_concepts/toxic_stress/).

Family Support

There are unique aspects to adoptive family formation that can create familial stress and impact child and family functioning. Some adoptive families may have to address infertility, creation of a multiracial family, disclosure of adoptive status, concerns and questions the child may have about their biologic origins, and ongoing scrutiny by adoption agencies. In the case of gay/lesbian parents, there are often additional psychosocial stressors, including continued barriers to legal recognition of both parents in a gay/lesbian partnership that can negatively impact family functioning. Although most families acclimate well to adoption-related stressors, some parents experience post adoption depression and may benefit from additional support to ease the family's transition.

Adoption Narrative

Families are encouraged to speak openly and repeatedly about adoption with their child, beginning in the toddler years and continuing through adolescence. Creating a "Lifebook" for the adopted child provides a way to support family communication about the child's history and significant relationships (including birth family members) and to document the child's important life transitions (e.g., through foster care or immigration to the United States). It is common, and normal, for children to have questions about adoption and their biological family throughout their development. An increase in cognitive understanding between ages 7 and 10 yr can sometimes increase adoption-related questions and/or distress. Youth who have questions about biological family members are increasingly able to access information via web-based searching, raising the importance of ongoing open communication about adoption. Pediatricians may need to respond to increased concerns/questions when the adoptee's health and genetic history is incomplete or unknown. At any time, concerns about development, behavior, and social-emotional functioning may or may not be related to the child's adoption history.

The vast majority of adopted children and families adjust well and lead healthy, productive lives. It is not common for adoptions to disrupt; disruption rates are higher among children adopted from foster care, which research associates with their age at time of adoption and/or a history of multiple placements prior to adoption. As a result of a greater understanding of the needs of families who adopt children from foster care, agencies are placing greater emphasis on the preparation of adoptive parents and ensuring the availability of a full range of postadoption services, including physical health, mental health, and developmental services for their adopted children.

Bibliography is available at Expert Consult.

37.1 Medical Evaluation of Immigrant (Foreign-Born) Children for Infectious Diseases

Stacene R. Maroushek

More than 210,000 foreign-born children (≤16 yr old) enter the United States each year as asylees, refugees, and immigrants including international adoptees. This number does not include undocumented children living and working in the United States, the U.S.-born children of foreign-born parents, or the approximately 2.7 million nonimmigrant visitors ≤16 yr old who legally enter the United States annually with temporary visas. With the exception of internationally adopted children, pediatric guidelines for screening these newly arrived children are sparse. The diverse countries of origin and patterns of infectious disease, the possibility of previous high-risk living circumstances (e.g., refugee camps, orphanages, foster care, rural/urban poor), the

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limited availability of reliable healthcare in many economically developing countries, the generally unknown past medical histories, and interactions with parents who may have limited English proficiency, varied educational, or economic experiences, make the medical evaluation of immigrant children a challenging but important task.

Before admission into the United States, all immigrant children are required to have a medical examination performed by a physician designated by the U.S. Department of State in their country of origin. This examination is limited to completing legal requirements for screening for certain communicable diseases and examination for serious physical or mental defects that would prevent issuing a permanent residency visa. This evaluation is not a comprehensive assessment of the child's health and, except in limited circumstances, laboratory or radiographic screening for infectious diseases **is not required** for children <15 yr old. After entry into the United States, health screenings of refugees, but not other immigrants, are recommended to be done by the resettlement state. There is little tracking of refugees as they move to different cities or states. Thus, many foreign-born children have had minimal prearrival or postarrival screening for infectious diseases or other health issues.

Immunization requirements and records also vary depending on entry status. Internationally adopted children who are younger than 10 yr are exempt from Immigration and Nationality Act regulations pertaining to immunization of immigrants before arrival in the United States. Adoptive parents are required to sign a waiver indicating their intention to comply with U.S.-recommended immunizations, whereas older immigrants need only show evidence of up-to-date, not necessarily complete, immunizations before application for permanent resident (green card) status after arrival in the United States.

Infectious diseases are among the most common medical diagnoses identified in immigrant children after arrival in the United States. Children may be asymptomatic; therefore, diagnoses must be made by screening tests in addition to history and physical examination. Because of inconsistent perinatal screening for hepatitis B and hepatitis C viruses, syphilis, and HIV, and the high prevalence of certain intestinal parasites and tuberculosis, all foreign-born children should be screened for these infections on arrival in the United States. Table 37-2 lists suggested screening tests for infectious diseases. In addition to these infections, other medical and developmental issues, including hearing, vision, dental, and mental health assessments; evaluation of growth and development; nutritional assessment; lead exposure risk; complete blood cell count with red blood cell indices; microscopic urinalysis; newborn screening (this could be done in nonneonates, too) and/or measurement of thyroid-stimulating hormone concentration; and examination for congenital anomalies (including fetal alcohol syndrome) should be considered as part of the initial evaluation of any immigrant child.

Children should be examined within 1 mo of arrival in the United States or earlier if there are immediate health concerns, but foreign-born parents may not access the healthcare system with their children unless prompted by illness, school vaccination, or other legal requirements. I**t is important to assess the completeness of previous medical screenings at any first visit with a foreign-born child**.

Clinicians should be aware of potential diseases in high-risk immigrant children and their clinical manifestations. Some diseases, such as central nervous system cysticercosis, may have incubation periods as long as several years, and thus may not be detected during initial screening. On the basis of findings at the initial evaluation, consideration should be given to a repeat evaluation 6 mo after arrival. In most cases, the longer the interval from arrival to development of a clinical syndrome, the less likely the syndrome can be attributed to a pathogen acquired in the country of origin.

COMMONLY ENCOUNTERED INFECTIONS

Hepatitis B

See Chapter 350.

The prevalence of hepatitis B surface antigen (HBsAg) in international adoptees and refugee children ranges from 1-5% and 4-14%, respectively, depending on the country of origin, age, and year studied. Prevalence of markers of past hepatitis B virus (HBV) infection is higher. HBV infection is most prevalent in immigrants from Asia, Africa, and some countries in Central and Eastern Europe, as well as the former Soviet Union (e.g., Bulgaria, Romania, Russia, and Ukraine), but also occurs in immigrants born in other countries. All immigrant children, even if previously vaccinated, coming from high-risk countries (HBsAg seropositivity >2%) should undergo serologic testing for HBV infection, including both HBsAg and antibody to HBsAg (anti-HBs), to identify current or chronic infection, past resolved infection, or evidence of previous immunization. Because HBV has a long incubation period (6 wk to 6 mo), the child may have become infected at or near the time of migration and initial testing might be falsely negative. Therefore, strong consideration should be given to a repeated evaluation 6 mo after arrival for all children, especially those from highly endemic countries. Chronic HBV infection is indicated by persistence of HBsAg for more than 6 mo. Children with HBsAg-positive test results should be evaluated to identify the presence of chronic HBV infection because chronic hepatitis B infection occurs in >90% of infants infected at birth or in the first year of life, and in 30% of children exposed at ages 1-5 yr. Once identified as being infected, additional testing to assess for biochemical evidence of severe or chronic liver disease or liver cancer should take place.

Hepatitis A

See Chapter 358.

Hepatitis C

See also Chapter 358.

The decision to screen children should depend on history (e.g., receipt of blood products; traditional percutaneous procedures such as tattooing, body piercing, circumcisions, or other exposures to reused, unsterile medical devices) and the prevalence of infection in the child's country of origin. Children from Eastern Mediterranean and Western Pacific countries, Africa, China, and Southeast Asia should be considered for hepatitis C infection screening. All children coming from Egypt, which has the highest known seroprevalence (12% nationally and 40% in some villages), should be tested for hepatitis C.

Intestinal Pathogens

Fecal examinations for ova and parasites by an experienced laboratory will identify a pathogen in 15-35% of internationally adopted children; prevalence rates in immigrants and refugees range from 8-86%. The prevalence of intestinal parasites varies by country of origin, time period when studied, previous living conditions (including water quality, sanitation, and access to footwear) and the age of the child, with toddler/young school-age children being most affected. If documented predeparture treatment was given, an eosinophil count should be performed. An absolute eosinophil count of >400 cells/μL, if persistently elevated for 3-6 mo after arrival, should prompt further investigation for tissue-invasive parasites such as *Strongyloides* (see Chapter 295) and *Schistosoma* (see Chapter 300) species. If no documented predeparture treatment was given, 2 stool ova and parasite specimens obtained from separate morning stools should be examined by the concentration method, and an eosinophil count should be performed. If the child is symptomatic, including evidence of poor physical growth, but no eosinophilia is present, a single stool specimen should also be sent for *Giardia lamblia* (see Chapter 282) and *Cryptosporidium parvum* (see Chapter 283) antigen detection. All potentially pathogenic parasites found should be treated appropriately. All nonpregnant refugees >2 yr of age coming from sub-Saharan Africa and Southeast Asia should be presumptively treated with predeparture albendazole.

Tuberculosis

See also Chapter 215.

Tuberculosis (TB) commonly is encountered in immigrants from all countries because *Mycobacterium tuberculosis* infects approximately 30% of the world's population. Latent TB infection rates range from 0.6-30% in adoptees and up to 60% in some refugee children from North Africa and the Middle East. Prior to 2007, chest radiographs or

tuberculin skin tests were generally not administered in children <15 yr of age and reports indicate that 1-2% of these unscreened children may enter the United States with undiagnosed active TB disease.

Since 2007, TB Technical Instructions for Medical Evaluation of Aliens have required that children ages 2-14 yr undergo a TB skin test if they are medically screened in countries where the TB rate is 20 cases or more per 100,000 population. If the skin test is positive, a chest x-ray is required. If the chest x-ray suggests TB, cultures and 3 sputum smears are required, all before arrival in the United States. This requirement is being phased in over a number of years, and some countries with a case rate of 20 per 100,000 may not currently be screening children. Check with the Centers for Disease Control and Prevention, Division of Global Migration and Quarantine for latest information (www.cdc.gov/ncidod/dq/technica.htm).

Congenital Syphilis

See Chapter 218.

HIV Infection

See Chapter 276.

Immunizations

See Chapter 172.

Immigrant children and adolescents should receive immunizations according to the recommended schedules in the United States for healthy children and adolescents. Some immigrants will have written documentation of immunizations received in their birth or home country. Although immunizations such as bacillus Calmette-Guérin, diphtheria and tetanus toxoids, and pertussis (DTP), poliovirus, measles, and hepatitis B virus vaccines often are documented, other immunizations, such as *Haemophilus influenzae* type b, mumps, and rubella vaccines, are given less frequently, and *Streptococcus pneumoniae*, human papillomavirus, meningococcal, and varicella vaccines are given rarely. When doubt exists, an equally acceptable alternative is to reimmunize the child. Because the rate of more serious local reactions after diphtheria, tetanus toxoid, and acellular pertussis vaccine increases with the number of doses administered, serologic testing for antibody to tetanus and diphtheria toxins before reimmunizing, or if a serious reaction occurs, can decrease risk.

In children older than 6 mo with or without written documentation of immunization, testing for antibodies to diphtheria and tetanus toxoid and poliovirus may be considered to determine whether the child has protective antibody concentrations. If the child has protective concentrations, then the immunization series should be completed as appropriate for that child's age. In children older than 12 mo, measles, mumps, rubella, and varicella antibody concentrations may be measured to determine whether the child is immune; these antibody tests should not be performed in children younger than 12 mo because of the potential presence of maternal antibody.

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Chapter 38

Foster and Kinship Care

Moira Szilagyi

The placement of children in out-of-home care has served the needs of children in many societies worldwide throughout history. The institution of foster care was developed in the United States as a temporary resource for children during times of family crisis and is rooted in the principle that children fare best when raised in family settings. The 1989 United Nations Convention on the Rights of the Child, a legally binding international instrument, addresses the need for such care for all children worldwide. Regardless of its setting, the mission of foster care is to provide for the safety, permanency, and well-being of children while assisting their families with services to promote reunification.

EPIDEMIOLOGY

The number of children in foster care worldwide is unknown, although it has been estimated that 8 million may be in foster and residential care. On September 11, 2011, approximately 400,540 children in the United States resided in foster care, representing a downward trend since 1999, when the daily average of children in care was 567,000. This decrease has occurred despite an increase in maltreatment reports, as child welfare offers families more preventive services and placement with relatives or nonrelative caregivers (kinship care) as an alternative to removal, resulting in fewer admissions. Reunification rates and adoption of children from foster care have also increased. Court ordered and informal kinship care have increased, accounting for up to 7% of children.

Approximately 33% of children in foster care in the United States are younger than the age of 5 yr and 35% are older than age 12 yr. The largest subset is white (41%) with significant percentages of black (27%) and Hispanic (21%) children. The average length of stay has dropped to a mean of 23.9 mo (median: 13.5 mo), although 31% of children remain in foster care for more than 2 yr. Only approximately 52% of children achieve reunification. Approximately 8% go to relatives, while approximately 20% (50,000 children) are adopted out of foster care annually. Among remaining children, 11% emancipate, 6% enter into long-term state guardianship, 1% run away, and 2% transfer to other institutions. In 2011, there were 343 deaths in foster care.

Most children live in nonrelative foster (47%) or certified relative foster (27%) family care, and 4% reside in a preadoptive home, although this is less than 20% of the children who are awaiting adoption. Approximately 15%, mostly adolescents, live in group homes or residential settings. The average number of placements a child experiences in foster care is not included in Adoption and Foster Care Reporting System, but important predictors include severe behavioral and/or developmental problems, larger sibling group size, and longer time spent in foster care. Within 12 months, nearly all emancipated youth have at least one homeless night and, within a decade, less than half have a high school degree and most are living in poverty and have high rates of posttraumatic stress disorder and depression.

LEGISLATION IN THE UNITED STATES

In the United States, the Adoption and Safe Families Act (P.L. 105-89), passed in 1997, requires that a permanency plan be made for each child no later than 12 months after entry into foster care and that a petition to terminate parental rights typically be filed when a child has been in foster care for at least 15 of the previous 22 months. The Fostering Connections and Promoting Adoptions Act of 2009 (P.L. 110-351) focused on incentives for guardianship and adoption, supports for the young adults at the age of emancipation, and rights of Native American children to care within their tribe. This latter act also contained a clause requiring states to develop and coordinate healthcare systems for children in foster care in collaboration with Medicaid and pediatricians.

EARLY CHILDHOOD TRAUMA LEADS TO POOR HEALTH OUTCOMES

Children in foster care have high rates of early childhood trauma and adversity. More than 70% have a history of abuse, neglect, or both. More than 80% have experienced significant domestic and/or community violence. Birth parents have high rates of mental illness, criminal justice system involvement, substance abuse, unemployment, and cognitive impairment. Many children have had prenatal substance exposure, multiple caregivers of varying quality, and are from families with long involvement with child protective services.

Removal from the family of origin may compound trauma although some children experience relief at removal from a chaotic, abusive, or dangerous home. Most children miss their family, worry about their parents and siblings, and long for reunification. Separation, loss and grief, unpredictable contact with birth parents, placement changes, the process of terminating parental rights, and the sheer uncertainty of foster care may further erode a child's well-being.

Childhood trauma is correlated with poor developmental, behavioral and health outcomes. Early trauma and chronic stress adversely affect the neurobiology of the developing brain, especially those areas involved in attention, emotional regulation, memory, executive function, and cognition. As a result, shortened attention span, hyperactivity, poorer cognitive function, aggression, and memory issues are problems encountered frequently encountered among children in foster care.

HEALTH ISSUES

Multiple childhood adversities and the receipt of fragmented and inadequate health services before placement into foster care mean that children enter foster care with a high prevalence of chronic medical, mental health, developmental, dental, and educational problems (Table 38-1), and so are defined as children with special healthcare needs. The greatest single healthcare need of this population is for high-quality, evidence-based mental health services to address the impacts of prior and ongoing trauma, loss, and unpredictability. In addition, they have higher rates of asthma, growth failure, obesity, vertically transmitted infections, and neurologic conditions than the general pediatric population. Adolescents need access to reproductive health and substance abuse services. Up to 60% of children <5 yr have a developmental delay in at least 1 domain and more than 40% of school-age children qualify for special education services. Unfortunately, educational difficulties persist despite improvements in school attendance and performance after placement in foster care.

Table 38-1 | Health Issues of Children in Foster Care

CHRONIC MEDICAL PROBLEMS Affect 40-60% of children Asthma, dermatologic, neurologic, obesity, growth failure, hearing, and vision problems are most common
ABUSE AND NEGLECT >70% of children have a history of abuse and neglect at entry into foster care Monitor at all health visits for abuse or neglect
COMPLEX CHRONIC MEDICAL PROBLEMS Involves 10% of children in foster care Children may be dependent on medical technologies or have multiple disabilities
MENTAL HEALTH CONCERNS Affects 80% of children >4 yr of age Result of childhood trauma and adversity Most common diagnoses are adjustment disorder, posttraumatic stress disorder, attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder Externalizing problems are more likely to result in therapy
DEVELOPMENTAL PROBLEMS 60% of children <5 yr of age have at least 1 documented delay Commonly affect communication, cognition, problem-solving, and personal-social domains
DENTAL PROBLEMS 35% of children have significant dental disease
ADOLESCENT HEALTH ISSUES High rates of sexually transmitted infections, high-risk behaviors, and substance abuse
EDUCATIONAL PROBLEMS Half of special education placements relate to behavioral or emotional issues, not cognitive Only 32% of adolescents eventually graduate from high school; 32% obtain a General Equivalency Diploma
FAMILY RELATIONSHIP PROBLEMS 100% of children have family relationship problems

Although children in foster care are children with special healthcare needs, often they lack access to the services they need. Most public and private child welfare agencies do not have formal arrangements for accessing the needed array of health services and rely on local physicians and/or health clinics funded by Medicaid. Health histories are often sparse at admission because many have lacked regular care or their biological parents may not be available or forthcoming. Once children enter foster care, there is often a diffusion of responsibility across caregivers and child welfare. Foster parents usually receive little information about a child's healthcare needs, but they are typically expected to decide when and where children receive healthcare services. Child welfare case workers are responsible for ensuring that a child's health needs are addressed but coordination across multiple healthcare providers may be daunting. Uncertainty about who is legally responsible for making healthcare treatment decisions and who may have access to health information may delay or result in the denial of healthcare services.

HEALTHCARE FOR CHILDREN AND ADOLESCENTS IN FOSTER CARE

The American Academy of Pediatrics (AAP) and Child Welfare League of America published updated general guidelines for the healthcare of this special needs population in 2007. The AAP has published detailed healthcare standards for children in foster care, available on the *Healthy Foster Care America* website. Children should receive healthcare services in a medical home setting where they receive comprehensive healthcare that is continuous over time (Table 38-2). Compassionate, culturally competent healthcare that is trauma-informed means that health staff should understand the effects of past trauma and ongoing uncertainty and loss on a child's health and well-being, and that of their birth and foster families. Children should be seen early and often when they first enter foster care to identify all their health issues, and to support the child and foster parent through a major transition that involves considerable loss and adjustment for the child and many challenges for the foster parent.

The AAP recommends that every child in foster care have comprehensive medical, dental, developmental, and mental health assessments within 30 days of entering foster care. Almost every child in foster care deserves a full mental health evaluation to assess for the impact of trauma and loss on emotional well-being. Psychotropic medication should only be considered, if at all, after a thorough high-quality mental health evaluation by a pediatric-trained mental health professional. It is wise for the pediatrician to remember that inattention, impulsivity and hyperactivity may reflect the impact of past trauma on the developing brain rather than attention-deficit/hyperactivity disorder (see Chapter 33). Childhood trauma impairs cognition and memory (see Chapter 40) so that children <6 yr of age should receive a comprehensive developmental assessment, while older children should receive a comprehensive educational assessment. The caseworker should provide consents for healthcare and any available health history, and encourage the appropriate involvement of the birth parent. The primary care provider should help caseworkers and foster parents obtain and interpret the results of these assessments. Pediatricians, caregivers, and caseworkers should share health information.

Foster parents are the major therapeutic intervention of the foster care system, and pediatricians should provide them with appropriate education and support. Important topics include positive parenting strategies, supporting children through transitions, providing a consistent and nurturing environment, and helping children heal from past trauma and adversity (Table 38-3). Foster and birth parents may need extensive education about behavioral and emotional problems within the context of the child's trauma history to remove blame and promote healing. Minimizing conflict among caregivers is extremely important as a child ideally has affection and loyalty for all of the child's caregivers. Pediatricians should focus on both caregiver (foster and birth

Table 38-2 Pediatric Medical Home for Children in Foster Care

CHARACTERISTIC	APPLICATION IN FOSTER CARE
Comprehensive healthcare	Perform comprehensive admission assessment within 30 days of entry Ensure access to mental health, developmental, and dental evaluation and services Screen and refer as needed for abuse and neglect
Coordination of care	Make timely referrals and follow up subspecialist visits Communicate with caseworkers, foster parents, and legal professionals Maintain a comprehensive medical record despite changes in placement
Compassionate care	Understand and educate children, families, and other healthcare professionals on the impact of early childhood adversities, trauma and ongoing uncertainties of foster care on the developing child Promote positive purposeful parenting strategies and minimizing conflict among caregivers
Child-centered and family-focused care	Prioritize the needs of children first and foremost Partner with families to increase understanding of a child's needs Focus on the strengths of children and families
Continuity of care	Invite children to remain patients throughout their stay in foster care, and beyond when feasible
Cultural competence	Extend this concept to include the microculture of foster care and the multiple transitions that can further erode a child's well-being. Understand the roles of caseworkers, foster parents, law guardians, etc.
Accessibility	Create a welcoming environment for children and all of their families (birth, foster, kin, preadoptive)

Table 38-3 Anticipatory Guidance for Children in Foster Care

SITUATION	ANTICIPATORY GUIDANCE FOR FOSTER PARENTS
Preparing for visits	Educate foster/kinship parents about impact of visitation on children Send familiar object with child to visit Have child draw picture to give birth parent Reassure child that foster parent will be there when child returns from visits Advise all caregivers to minimize conflict with and negativity toward each other
Returning from visits and other transitions	Greet child warmly and help with unpacking Establish reentry rituals, such as quiet play, reading together, having a healthy snack
Relationship with birth parent(s)	Encourage caseworker to have birth parents keep child's rituals and routines consistent with those in foster home (vice versa when appropriate) Focus on birth parent's positive qualities; maintain a neutral affect
Building on child's strengths	Encourage participation in child-directed play. Encourage participation in normalizing activities (such as hobbies or sports) "Catch the child being good" Encourage specific praise Provide child with words for emotions Ignore negative behavior unless there is a safety issue
Preparing for court dates	Foster/kinship parent, caseworker or law guardian should explain purpose of court hearings to child in simple terms
School	If changing schools, visit school together a few times, and meet the teacher Check in regularly (weekly or monthly depending on need) with child's teacher
Adolescent	Decide what issues demand firm limits and guidelines (curfews, no smoking, party at a friend's house, etc.), what issues are not important and can be left up to teen (hair length and color, etc.) and what issues are ideal for negotiation (transportation to a school function, style of dress etc.) Encourage responsible decision-making by recognizing and complimenting it. Encourage after-school activities. Teach driving when age and developmentally appropriate Encourage teen to seek employment and teach job skills Help teen to identify mentors and focus on the future

parent) and child strengths. For teens and young adults in foster care, the pediatrician should provide anticipatory guidance around education, identity formation in the face of past trauma, independent decision making, health promotion, and developing the skills and competencies needed for a successful future life. The pediatrician should advocate for placement stability in a nurturing and responsive foster family where caregivers possess the appropriate skills to help children and youth heal.

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Chapter 39

Impact of Violence on Children

Marilyn C. Augustyn and Barry S. Zuckerman

The reach of violence, whether as the victim, perpetrator, or witness, whether in person or through the media, is far, deep, and long-standing across the globe (see Chapter 1). Exposure to violence disrupts the healthy development of children in a myriad of ways. Pediatric clinicians must be competent to address these issues in impacted children and families under their care and also have a wider responsibility to advocate on local, state, national, and international levels for safer environments in which all children can grow and thrive.

Witnessing violence is detrimental to children. Because their scars as bystanders are emotional and not physical, the pediatric clinician may not fully appreciate their distress and thereby miss an opportunity to provide needed interventions. For children not living in war zones, the source of first exposure to violence is often **intimate partner violence.** According to data from the National Center for Posttraumatic Stress Disorder (PTSD), 20-30% of American women will be physically abused by a partner at least once in their lifetimes. Similarly in the 2010 National Intimate Partner and Sexual Violence Survey administered by the Centers for Disease Control and Prevention (CDC), 1 in 4 women and 1 in 7 men have been the victim of severe physical violence by an intimate partner, affecting more than 12 million people each year. Slightly more than half of female victims of intimate partner violence live in households with children <12 yr of age; family violence is most likely to be perpetrated by those between the ages of 18 and 30 yr and most victims are impacting before 24 yr of age. Across studies, 7-23% of youths in general population surveys experienced exposure to intimate partner violence, 36-39% of youth in intimate partner violence cases have witnessed the violence, and 45-46% of primary caregivers in child maltreatment investigations have experienced intimate partner violence. In a national survey, 50% of the men who frequently assaulted their wives also frequently abused their children. Most of the children were injured when they intervened to protect their mother from her partner (see Chapter 40). Children who witness domestic violence are at higher risk for negative medical outcomes including increased risk of obesity, asthma, and PTSD. In addition, these children are at higher risk for other traumatic events; for example, in a sample of 120 preschool children (age 4-6 yr) exposed to intimate partner violence in the past 2 yr, 38% were exposed to additional traumatic events, including sexual assaults by family members, physical assaults, serious accidents, and/or life-threatening illnesses.

Another source of witnessed violence is **community violence.** Community violence in the United States is a serious problem that disproportionately affects children from low-income areas. According to the 2011 National Survey of Children's Exposure to Violence, approximately 22% of children had witnessed violence in their family or in their community in the year prior to the survey, and of all the horrors the survey inquired about—assaults and bullying, sexual victimization, maltreatment by a caregiver, and theft or vandalism—nearly 60% of children had experienced or witnessed one of them. Young children living in high crime and violence areas observe death more frequently and at younger ages than do children growing up in more secure surroundings. Witnessing acts of violence may be a significant stressor in children's lives. If children's coping skills are not sufficient to deal with violent situations, stress may be manifested as psychological, physical, or behavioral symptoms.

Table 39-1 Public Health Recommendations to Reduce Effects of Media Violence on Children and Adolescents

Parents should:
- Be made aware of the risks associated with children viewing violent imagery, as it promotes aggressive attitudes, antisocial behavior, fear, and desensitization
- Review the nature, extent, and context of violence in media available to their children before children view
- Assist children's understanding of violent imagery appropriate to their developmental level

Professionals should:
- Offer support and advice to parents who allow their children unsupervised access to extreme violent imagery as this could be seen as a form of emotional abuse and neglect
- Educate all young people in critical film appraisal, in terms of realism, justification, and consequences
- Exercise greater control over access to inappropriate violent media entertainment by young people in secure institutions
- Use violent film material in anger management programs under guidance

Media producers should:
- Reduce violent content and promote antiviolence themes and publicity campaigns
- Ensure that when violence is presented it is in context and associated with remorse, criticism, and penalty
- Ensure that violent action is not justified or its consequences understated

Policy makers should:
- Monitor the nature, extent, and context of violence in all forms of media and implement appropriate guidelines, standards, and penalties
- Ensure that education in media awareness is a priority and a part of school curricula

From Browne KD, Hamilton-Giachritsis C: The influence of violent media on children and adolescents: a public-health approach, Lancet *365:702-710, 2005.*

The most ubiquitous source of witnessing violence for children in the United States is **media violence.** The average child 2-5 yr of age watches 20-30 hr of television a week, hours that are increasingly filled with scenes of violence, not only on commercial television but also on news outlets. In addition, the wider array of "screen time" children are exposed to, including computer, smart phones, and video games, increases the opportunities for violent events to enter the lives of children. In particular, recent tragic events, including mass shootings and acts of terrorism, have increased the specter of fear among children. Although exposure to media violence cannot be equated to exposure to real-life violence, many studies confirm that media violence desensitizes children to the meaning and impact of violent behavior. Not all children are equally affected by media violence. Children most at risk from viewing violence may be children who are also exposed regularly to real-life violence in their homes and communities. Table 39-1 lists interventions to reduce exposure to media violence.

IMPACTS OF VIOLENCE

The violence children experience and witness also has a profound impact on health and development. In a cross-sectional analysis of a Head Start preschool-age cohort, being abused, exposure to domestic violence, and having a mother using substances were associated with a higher number of health problems. Beyond injuries, violence affects children psychologically and behaviorally; it may influence how they view the world and their place in it. Children can come to see the world as a dangerous and unpredictable place. This fear may thwart their exploration of the environment, which is essential to learning in childhood. Children may experience overwhelming terror, helplessness, and fear even if they are not immediately in danger. Preschoolers are most vulnerable to threats that involve the safety (or perceived safety) of their caretakers. High exposure to violence in older children correlates

with poorer performances in school, symptoms of anxiety and depression, and lower self-esteem. Violence, particularly domestic violence, can also teach children especially powerful early lessons about the role of violence in relationships. Violence may change the way that children view their future; they may believe that they could die at an early age and thus take more risks, such as drinking alcohol, abusing drugs, not wearing a seatbelt, and not taking prescribed medication.

Some children exposed to severe and/or chronic violence may suffer from PTSD, exhibiting constricted emotions, difficulty concentrating, autonomic disturbances, and reenactment of the trauma through play or action (see Chapters 1 and 25). Although young children may not fully meet these criteria, certain behavioral changes are commonly associated with exposure to trauma, such as sleep disturbances, aggressive behavior, new fears, and increased anxiety about separations ("clinginess"). A particular challenge in treating and diagnosing pediatric PTSD is that a child's caregiver exposed to the same trauma may be suffering from it as well.

Diagnosis and Follow-up

The simplest way to recognize whether violence has become a problem in a family is to screen both the parents and the children (after ≈8 yr of age) on a regular basis. This practice is particularly important during pregnancy and the immediate postpartum period when women may be at highest risk for being abused. It is important to assure families that they are not being singled out, but that all families are asked about their exposure to violence. A direct approach may be useful: "Violence is a major problem in our world today and one that impacts everyone in our society. Thus I have started asking all my patients and families about violence that they are experiencing in their lives. …" In other cases, beginning with general questions and then moving to the specific may be helpful. "Do you feel safe in your home and neighborhood? Has anyone ever hurt you or your child?" When violence has impacted the child, it is important to gather details about symptoms and behaviors.

The pediatric clinician can effectively counsel many parents and children who have been exposed to violence. Regardless of the type of violence to which the child has been exposed, the following components are part of the guidance: careful review of the facts and details of the event, gaining access to support services, providing information about the symptoms and behaviors common in children exposed to violence, assistance in restoring a sense of stability to the family in order to enhance the child's feelings of safety, and helping parents talk to their children about the event. When the symptoms are chronic (>6 mo in duration) or not improving, if the violent event involved the death or departure of a parent, if the caregivers are unable to empathize with the child, or if the ongoing safety of the child is a concern, it is important that the family be referred to mental health professionals for additional treatment.

Bibliography is available at Expert Consult.

39.1 Bullying, Cyberbullying, and School Violence

Douglas Vanderbilt and Marilyn C. Augustyn

BULLYING ("TRADITIONAL BULLYING")

Bullying is the assertion of power through social, emotional, or physical means of aggression that involves a bully repeatedly and intentionally targeting a weaker victim. Bullying affects a large number of children and lays the groundwork for long-term depression, suicidality, psychotic symptoms, conduct problems, and psychosomatic concerns seen in children. Children can move between being a bully, victim, bully-victim (both a bully and a victim at different times), or bystander. Bullying can be **direct,** involving physical aggression such as hitting, stealing, and threatening with a weapon or verbal aggression such as name-calling, public humiliation, and intimidation, or it can be **indirect,** involving relational aggression such as spreading rumors, social rejection, exclusion from peer groups, and ignoring. Bullying occurs most frequently at school when there is minimal supervision during breaks, recess, and lunch at playgrounds, in hallways, and en route to and from school.

CYBERBULLYING

Cyberbullying is an emerging form of bullying that takes place using electronic technology (text messaging, mass emailing, Internet chat rooms, social networking sites, etc.). In contrast to traditional bullying, it allows complete anonymity to the bully and has enormous capacity for "reach." Given its recent recognition and ongoing evolution, much remains unknown about its causes and therefore prevention strategies; what is clear is that the psychological consequences can be devastating for the victim. Victims of cyberbullying may be at higher risk for suicide (see Chapter 27) than victims of traditional bullying.

Epidemiology

Bullying is a common occurrence for schoolchildren. Bullying occurs in all countries, affecting anywhere from 9-54% of youth. Apparent rates of bullying are influenced by the manner in which questions are asked; youth are more willing to acknowledge having engaged in activities which can be categorized as forms of "bullying" than they are to respond to a question asking them if they have acted in a bullying manner or have been a bully.

The 2011 Indicators of School Crime and Safety reported that 28% of youth (31% females and 25% males) ages 12 to 18 yr had been bullied at school, 18% were ridiculed, 18% were the subject of rumors, 9% were cyberbullied, 8% were purposefully pushed, shoved, or tripped (leading to injury in about 1/5), 6% were purposefully excluded from activities, 5% were threatened with harm, and 3% had personal property that had been purposefully destroyed.

With regard to traditional bulling, the 2009 Youth Health Risk Behavior Survey (YHRBS), concurred that males and females were equally likely to report having been bullied (victims); males were 2.5 times more likely than females to report having bullied others. Rates of bullying or being bullied did not differ by race/ethnicity, except that Hispanics were less likely to report having bullied someone. Other surveys have found that students who carry weapons, smoke, and drink alcohol more than 5-6 days/wk were at greatest risk for moderate bullying. Those who carry weapons, smoke, have more than 1 alcoholic drink per day, have above-average academic performance, moderate/high family affluence, and feel irritable or bad-tempered daily were at greatest risk for frequent bullying. Negative parenting behavior is related to a moderate increase of risk for becoming a bully/victim and small to moderate effects on victim status at school.

Rates of cyberbullying victimization have ranged from 4-72% and of cyberbullying from 3-23%, in part reflecting variations in definitions and sampling design. According to the 2009 YHRBS, males and females were equally likely to experience cyberbullying, but males were >3-fold likely to report having been a cyberbully. Rates of cyberbullying (as victim or perpetrator) did not differ by race/ethnicity. Seniors were more likely to be involved in cyberbullying than youth in other grades.

A separate study conducted among 918 students in grades 6 through 12, found considerable overlap between traditional and cyberbullying/victimization; three-fourths were not involved as victim or bully in either traditional or cyberbullying. Most victims of traditional bullying were not involved in cyberbullying, but those with involvement were more likely to be victims. Most traditional bullies were not involved in cyberbullying but those who were, were generally bullies.

Health Outcomes

Involvement in bullying is associated with poorer psychosocial adjustment; bullies, victims, and bully-victims report greater health problems and poorer emotional and social adjustment. Victims tend to be either physically weak and emotionally vulnerable or provocative, with attention or conduct problems and have lower social status and higher social marginalization and isolation. Overall, **both** victim and

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National Child Traumatic Stress Network http://www.nctsn.org/.

bully-victims have been described as anxious, insecure, lonely, and lacking social skills. They may have learning disabilities, autism spectrum disorder, or poor physical skills. They have more depression, psychosomatic complaints, medication use, and suicidality. Chronic or severe victimization in childhood has been shown to be associated with psychotic symptoms in early adolescence. Long-term consequences in adulthood of being bullied as a child include depression, poor self-esteem, and abusive relationships. In the 2009 YHRBS, traditional bullying victimization was a significant predictor of depression for males and females and a direct contributor to suicidal behavior for females.

Bullies have higher rates of both conduct disorders and social standing. They have the lowest rates of adjustment problems because of their higher social status. They make friends that support their bullying behavior but other peers avoid them. Bullies who acknowledge their behavior have higher rates of depression and psychologic distress compared to those who deny their bullying behavior. In the 2009 YHRBS data, traditional bullying predicted depression in females but not in males. Depression significantly mediated the relationship between bullying and suicidal behavior among both genders. They have higher negative attitudes toward school and use more tobacco, alcohol, and other drugs. Childhood bullies have a 4-fold increase in criminal behavior by their mid-20s and are at higher risk of dropping out of school. They have lower likelihood of being employed and having stable long-term romantic relationships. The bully-victim has problems with peer relationships and high rates of depression, loneliness, alcohol use, and weapon carrying.

Less is known about the characteristics of cyber bullies or victims and their long-term consequences. In the 2009 YHRBS data, cyber victimization was associated with depression in women but not men, and contributed to suicidal behavior among women. Cyberbullying was not associated with depression among men or women. Lower academic achievement and lower self-esteem are associated with cyberbullying perpetration and victimization, and anxiety symptoms with cyberbullying perpetration.

SCHOOL VIOLENCE

Epidemiology

School violence is a common but nonnormative aspect of development occurring throughout the world. Almost 40% of U.S. schools report a least 1 violent incident to police, with more than 600,000 victims of violent crime per year. Among 9th to 12th graders, 8% were threatened or injured on school property in the last 12 mo, and 14% were involved in a physical fight over the last year. School-associated violent deaths are rare. Seventeen homicides of children ages 5-18 yr occurred at school during the 2009-2010 school year. Of all youth homicides, less than 2% occur at school. These are more likely to occur at the beginning of each semester with perpetrators previously giving warning signals. Whereas urban schools experience more episodes of violence, the episodes of rare "rampage" gun violence in rural and suburban schools demonstrate that no region is immune to lethal violence.

Risk Factors

Bullying and weapon carrying may be important precursors to more serious school violence. Among perpetrators of violent deaths at school, 20% had been bullying victims, and 6% of all students carried a weapon to school in the last 30 days. Nonlethal violence, mental health problems, racial tensions, student attacks on teachers, and the effects of rapid economic change in communities can all lead to school violence. Individual risk factors for violence include prior history of violence, drug, alcohol, or tobacco use, association with delinquent peers, poor family functioning, poor grades in school, and poverty in the community.

Family risk factors include early childbearing, low parental attachment and involvement, authoritarian or permissive parenting styles, and poverty. There is more school violence in areas with higher crime rates and more street gangs, with little improvement with additional security measures. These risks take away students' ability to learn in a safe environment and leave many children with traumatic stress and grief reactions. Behavioral genetics and developmental psychology are beginning to elucidate the bidirectional gene-environment interactions that promote these endemic episodes of violence.

TREATMENT AND PREVENTION OF BULLYING AND SCHOOL VIOLENCE

Pediatric providers are in a unique position to screen, treat, and advocate for reducing the impact of school violence by assisting those affected and seeking to prevent further occurrences. **Signs** of a child being bullied include physical complaints such as insomnia, stomachaches, headaches, and new-onset enuresis (see Chapter 23.3). **Psychologic symptoms,** such as depression (see Chapter 26), loneliness, anxiety (see Chapter 25), and suicidal ideation, may occur. **Behavioral changes,** such as irritability, poor concentration, school avoidance, and substance abuse, are common. **School problems,** such as academic failure, social problems, and lack of friends, can also occur. Additional vigilance must be made for those children with chronic medical illnesses, obesity, physical deformities, and learning disabilities or autism spectrum disorder who may be potential targets. A bully may be more difficult to identify because of the bully's desire to obscure the behavior. Children who are aggressive, overly confident, lacking in empathy, and having conduct problems may need careful screening. The physical, behavioral, psychologic, and school symptoms of bullying may overlap with other conditions such as medical illness, learning problems, and psychologic disorders.

Simple questions to ask children include **BORRIS**: Have you been **bullied** or bullied anyone? Have you **observed** bullying going on? How did you **respond**? Do you feel like you are **repetitively** singled out as a bully or a victim? Have you sent or receiving things over the **Internet** that you think may represent bullying? Do you feel **stuck** in bullying situations? And for parents **WART**: Have you **witnessed** or heard about your child being picked on or picking on other kids? Have there been any recent changes about your child's **attitude,** attention and concentration changes? What are your community **rules** about bullying? Has your child **talked** to you about being picked on or witnessing other kids being picked on?

Management of bullying and school violence involves systemic interventions with parents, victims, bullies, and the school. Interventions should include supporting families, victims, and bullies; identifying and referring those children in need of further academic and mental health services; and expecting behavioral change from the bully and social change from the school environment. The clinician should listen empathetically to the child to help empower and reassure the child. The clinician should not blame the victim or trivialize the child's concern. Suggestions should include having the child seek social support from teachers and friends and avoiding situations where the bullying may occur. Role-playing an encounter can be helpful for the child. Extracurricular activities, like drama clubs, mentoring programs, and sports, can be used to help to bolster the child's self-esteem. The clinician should identify safety issues, such as suicidal ideation and plans, substance abuse, and other high-risk behaviors.

Once a bully is identified and appropriate screening for family risk factors is completed, the clinician should educate the parents and child about the seriousness of the behavior and its potential consequences. The clinician should label the behavior as the problem and help the family and child to acknowledge the behavior as hurtful. For example: "Do you feel bad when other children hurt your feelings?" "Bullying hurts other children's feelings." The school and parents should ensure accountability for the child's subsequent behavior. Parental mental health and resource risk factors should also be addressed.

Beyond individual- and family-based interactions, providers also can advocate for systemic interventions through **school-community violence and bullying prevention programs**. Targeted school curriculums or social skills group interventions have not been found to reduce bullying in several well-done studies. Successful interventions involve whole school approaches that involve multiple disciplines. These broad-based programs simultaneously include school-wide rules and

sanctions, teacher training, classroom curriculum, conflict resolution training, and individual counseling. Mentoring programs and an increased number of social workers can also be helpful in reducing bullying. Addressing access to firearms, involving community organizations and parents, enhancing the built environment of schools and community, and supporting youth self-esteem are important in creating a safe school climate. Targeting larger societal risk promoters of violence in the neighborhood and school culture are also avenues for improving school violence. In Denmark, an intensive national-level policy has led to the reduction in school bullying prevalence from 25% to 11%.

Prevention programs for cyberbullying are at a more nascent stage, reflecting uncertainty about the prevalence of the practice, who is perpetrating it and from where, and how students respond when they are victimized. One study of approximately 800 parents and 1200 of their children found that although 80% of parents had set rules regarding conduct on the Internet, 85% of the children who had engaged in cyberbullying had done so from their homes. Therefore, if the bullying is reported to the police, the police could track the IP address to find the bully. However, rates vary tremendously by survey (and country) regarding student notification of adults when cyberbullied, with less than 10% of students in a Swedish survey, one-third in a Canadian survey, and a majority in an Austrian survey having reported the victimization to an adult. Many schools have established cyberbullying policies and are increasingly involved with teaching youth about guidelines for appropriate online interactions, and monitoring for cyberbullying problems. As of July 2013, 49 states (plus Washington, DC) have enacted legislation aimed to prevent bullying and 47 states (plus Washington, DC) have specific legislation regarding electronic harassment. Pediatric clinicians must be aware of local legislative action to support children in this difficult topic. (See http://www.cyberbullying.us/Bullying_and_Cyberbullying_Laws.pdf)

Bibliography is available at Expert Consult.

39.2 Effects of War on Children

Isaiah D. Wexler and Eitan Kerem

The adverse consequences of war on children are endless—death, pain, dismemberment and other physical and cognitive disabilities, acute and chronic psychological suffering, temporary and permanent loss of family members, rape, conscription into armed service, forced relocation, famine, drought, and a litany of other untoward consequences lasting for decades after hostilities have ceased. More than 1 billion children <18 yr live in countries involved in war. The majority of sexual victims in war-torn nations are <17 yr of age. The United Nations Children's Fund (UNICEF) estimates that of the 3.6 million people killed as a result of military conflict between the years 1990 and 2003, 90% were civilian and 50% were children.

Mortality and morbidity related to the long-term effects of war and civil strife are often higher than that occurring during actual fighting. War and violence are not listed as leading causes of childhood mortality, but the regions with the highest levels of child mortality, especially among children <5 yr of age, are the same locations involved in military conflicts. Nations, especially but not limited to the least developed, devote substantial portions of their budgets to military expenditures at the expense of the healthcare infrastructure; a substantial proportion of deaths attributed to malnutrition, environmentally related infectious disease, or inadequate immunization are related to the effects of war. For example, an analysis of postwar (2003) Iraq found that mortality rates were 5.5/1,000/yr preinvasion (occurred in March 2003), and 13.2/1,000/yr for the 40 mo postinvasion; through mid-2006, there had been an estimated 654,965 fatalities above the preinvasion death rate, of which 601,027 were from violent causes. The largest group of deaths among females occurred among those <15 yr; infant and <5 yr of age mortality rates had not returned to their 1991 pre-Gulf War levels.

Table 39-2 Impact of War on Children

PHYSICAL
Death
Rape
Injuries
Amputations and fractures
Head trauma
Ballistic wounds
Blast injuries
Burns
Chemical and biologic induced
Malnutrition and starvation
Infectious disease
Displacement
PSYCHOSOCIAL
Loss of caregivers and family members
Separation from community
Lack of education
Inappropriate socialization
Acute stress reaction
Posttraumatic stress disorder
Depression
Maladaptive behavior
EXPLOITATION
Conscription as soldiers
Coerced involvement in terrorist activities
Prostitution
Slavery
Forced adoption

During wartime, customary patterns of behavior are forced to change, overcrowding is frequent, and essential resources, such as water and food staples, may be polluted or contaminated. War is associated with plagues and epidemics and novel disease entities can develop or reemerge. African nodding disease, Konzo (cassava-associated cyanide intoxication), polio, and other epidemics have been attributed to the effects of war.

The morbidity of children exposed to conflicts is significant (Table 39-2). Many more children are physically harmed than killed. Children bear the psychological scars of war resulting from exposure to violent events, loss of primary caregivers, and forced removal from their homes. During periods of war, children are more susceptible to exploitation in the forms of forced conscription as soldiers, sexual exploitation, and slavery. There are approximately 300,000 soldiers younger than the age of 18 yr who are actively participating in military conflicts worldwide. Lacking the appropriate education and socialization, the moral compass of these children is often misaligned. They are not capable of understanding the sources of conflict or why they have been targeted. Their thought processes are more concrete; it is easier for them to dehumanize their adversaries. Children, who themselves are exposed to violence and cruelty, often become the worst perpetrators of atrocities.

After cessation of hostilities, children are still at risk for life-endangering injuries from landmines and unexploded ordnance. Prior to the signing of the international treaty to ban landmines in 1997, an estimated 20,000-25,000 casualties occurred annually from landmines. In 1999, that number had decreased to 8,807 and by 2011 to 4,286. The CDC reported for a 5 yr period ending in 2006 that of the 5,741 individuals who were killed or injured by landmines or unexploded ordnance, 47.2% were children younger than the age of 18 yr. Injuries and death tended to occur while children were either playing or involved in household chores, and in contrast to adults, a large proportion of the injuries involved upper-extremity amputation. After the end of armed conflict, the continued proliferation of small arms and light weapons, which are easily handled by children, continues to take its toll on human life and hinders stabilization in postconflict societies.

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Website Resources

www.cdc.gov/ViolencePrevention/youthviolence/schoolviolence/index.html.
www.aap.org/ConnectedKids/.
www.stopbullying.gov/index.html.
www.safeyouth.org/scripts/index.asp.
http://www.ncsl.org/issues-research/educ/cyberbullying.aspx.

SUSCEPTIBILITY OF CHILDREN IN TIMES OF WAR

Children do not have the physical or intellectual capabilities to defend themselves. It is easier for adults to victimize children than to victimize other adults. Older children's curiosity, desire for adventure, and imperfect assessment of risk often lead them to participate in dangerous behavior. Younger children, because of their small size and immature physiology, are more susceptible to disease and starvation, and are more likely to sustain fatal injuries from ballistic projectiles and explosive devices such as mines. Blast injuries, which are now the most common cause of battle-related injuries, have a more devastating impact on children as compared to adults. Specific types of military engagement can have a disproportionate effect on children. In a survey of war-related mortality in Iraq from 2003-2008, it was found that approximately 10% of the violence-related fatalities were children. Most children succumbed to either small-arms gunfire or suicide bombs (35%). When compared to adults, a proportionately higher rate of children died as a result of the usage of indiscriminant types of weaponry such as mortars, missiles, and aircraft-delivered bombs; 40% of the total casualties in these types of attacks were children.

During times of war, there is a breakdown of social inhibitions and cultural norms. Aberrant behavior such as rape, torture, and pillaging, which would be nearly inconceivable in times of peace, is common during war. Children may be attacked or used as human shields.

The changing nature of war has adversely affected children. Conventional warfare in which armies of professional soldiers representing different countries battle each other has become less common. Intrastate conflicts in the form of civil war are more frequent. Of the approximately 200 armed conflicts occurring after World War II, three-quarters have been intrastate. These conflicts are often rooted in ethnic or religious differences, and the participants are frequently nonprofessional "irregulars" who lack discipline and accountability to higher echelons, and are directed by those who do not acknowledge or respect international accords governing warfare. Often the military resources of the antagonists are disproportionate, leading the weaker protagonist to develop compensatory tactics that can include guerrilla, paramilitary, and terrorist activities, while the stronger side often resorts to the disproportionate use of force. Low-intensity conflicts have become more common. These types of conflicts are often characterized by military activities targeting civilian populations with the goal of disrupting normal routines and generating publicity for the perpetrators. Children are often victims, as this serves to maximize the impact of terrorist activity.

Terrorism and organized urban-based gang warfare violence have become more prevalent. Violence perpetrated by terrorists groups or gangs is designed to coerce and/or intimidate both individuals and entire societies. The destruction of the New York City World Trade Center Towers in 2001 and the nearly 3,000 fatalities showed that highly organized and motivated terrorists have few inhibitions and can strike anywhere. Biologic and chemical terrorism have also been realized, with the most recent example being the use of sarin gas, a deadly volatile nerve agent, in the Syrian civil war. Children are more susceptible to chemical and biologic toxins because of their higher respiratory rates, more permeable skin, and other developmental vulnerabilities (see Chapter 723).

The media has had a significant role in exacerbating the effects of war on children. Media coverage of war and terrorist events is extensive and graphic. Children, who are more impressionable than adults, often view this material in an uncontrolled fashion. Uncensored pictures of victims, unbridled violence, people in shock, or family members searching through ruins for relatives may traumatize children and even encourage inappropriate behavior. Overt broadcast propaganda glorifying war and violence may sway children to participate in militaristic or antisocial activities.

PSYCHOLOGIC IMPACT OF WAR

Exposure to war and violence can have a significant impact on a child's psychosocial development. Displacement, loss of caregivers, physical suffering, and the lack of appropriate socialization all contribute to abnormal child development (see Table 39-2). Often the reactions are age-specific (Table 39-3). Preschoolers may have an increase in somatic complaints and sleep disturbances, and have acting-out behavior such as tantrums or excessively clinging behavior. School-age children will show regressive behavior such as enuresis and thumb sucking. They, too, have an increase in somatic complaints; there is often a negative impact on school performance. For teenagers, psychological withdrawal and depression are common. Adolescents often exhibit trauma-stimulated acting-out behavior. Motivated by the desire for revenge, they may be quick to join in the violence and contribute to the continuation of conflict.

Table 39-3 Manifestations of Stress Reactions in Children and Adolescents Exposed to War, Terrorism, and Urban Violence

CHILDREN ≤6 YEARS
Excessive fear of separation
Clinging behavior
Uncontrollable crying or screaming
Freezing (persistent immobility)
Sleep disorders
Terrified affect
Regressive behavior
Expressions of helplessness and passivity
CHILDREN 7-11 YEARS
Decline in school performance
Truancy
Sleep disorders
Somatization
Depressive affect
Abnormally aggressive or violent behavior
Irrational fears
Regressive and childish behavior
Expressions of fearfulness, withdrawal, and worry
ADOLESCENTS 12-17 YEARS
Decline in school performance
Sleep disturbances
Flashbacks
Emotional numbness
Antisocial behavior
Substance abuse
Revenge fantasies
Suicidal ideation
Withdrawal

There is an increased incidence of both acute stress reactions and PTSD (see Chapter 25). The true incidence is difficult to assess because of the heterogeneous nature of war, degree of exposure to violence, and methodological challenges related to the precise characterization of PTSD. The incidence of PTSD among children and adolescents living in Middle East countries that have experienced substantial armed conflict appear to be high: 5-8% in Israel, 23-70% in Palestine, and 10-30% in Iraq. Risk factors for having a more serious psychological response to a violent event include severity of the incident, personal involvement (physical injury, proximity, loss of a relative), prior history of exposure to traumatic events, female gender, and a dysfunctional parental response to the same event. It is not unusual for children to develop PTSD many years after the traumatic event. Children do not have to be directly exposed to violent activity, and media coverage of terrorist events may be sufficient to trigger PTSD.

The trauma experienced by children during war can have lifelong effects. Studies on children imprisoned in concentration camps or evacuated from their homes in London during the Battle of Britain show that these individuals were at greater risk for PTSD, anxiety disorders, and a higher level of dissatisfaction with life. Individuals who suffered wartime trauma can pass on certain traits to their children, including a greater propensity for PTSD. However, children are resilient. With appropriate support from family and community

together with timely and intensive psychological intervention, children can recover and lead normal, productive lives despite the searing trauma that they may have experienced.

EFFORTS TO PROTECT CHILDREN FROM THE EFFECTS OF WAR

International Conventions

War and terror violate the human rights of children, including the right to life, the right to be nurtured and protected, the right to develop appropriately, the right to be with family and community, and the right to a healthy existence. Several international treaties and conventions have been ratified, beginning with the **Fourth Geneva Convention** (1949) that set forth guidelines regarding appropriate treatment of children in times of war. The **United Nations Convention on the Rights of the Child** (1990) delineated specific human rights inherent to every child (defined as any individual younger than the age of 18 yr), and the subsequent **First Optional Protocol** (2000), which prohibits conscripting or recruiting children for military activities. **The Rome Statute of the International Criminal Court,** which was enacted in 2002, declared that the conscription or enlistment of children younger than the age of 15 yr is a prosecutable war crime. As of 2010, a decade since their passage, the number of armed conflicts in which children were serving as soldiers had decreased from 36 to 16 worldwide.

Although these treaties and conventions define the extent of protection afforded to children, the means of enforcement available to the international community is limited. Individuals, motivated by religious fervor, nationalistic zeal, or ethnic xenophobia, are unlikely to curb their activities because of fear of prosecution. These treaties better serve in heightening awareness regarding the protected status of children in wartime, and perhaps deter high-ranking leaders who fear being held accountable for war crimes.

Humanitarian Efforts

Several organizations, either nongovernmental or under the auspices of the United Nations, are involved in mitigating the effects of war on children. These organizations, which include the International Red Cross, UNICEF, United Nations Refugee Agency (UNCHR), International Rescue Committee, World Health Organization, and Médicins Sans Frontières (Doctors Without Borders), have had a significant impact on reducing violence-related casualties in war-torn regions. The infusion of humanitarian aid into developing countries often improves overall mortality and morbidity by increasing the level of medical and social services available to the general population. Other organizations, such as Amnesty International, Stockholm International Peace Research Institute, and Physicians for Human Rights, actively monitor human rights abuses involving children and other civilian groups. In 2005, the United Nations Security Council approved the establishment of a monitoring and reporting system designed to protect children exposed to war. United Nations–led task forces conduct active surveillance in war-stricken regions reporting on the *6 grave violations against children during armed conflict:* the killing or injuring of children, recruitment of child soldiers, attacks directed against schools or hospitals, sexual violence against children, abduction of children, and denial of humanitarian access for children.

THE ROLE OF PEDIATRICIANS AND ALLIED HEALTH PROFESSIONALS

War is a chronic condition and health providers need to be prepared to treat childhood casualties resulting from military or terrorist activity as well as caring for children suffering from the aftermath of war or related violence. Community and hospital pediatricians need to be involved in community disaster planning. General disaster planning should not ignore the unique needs and requirements of children; in planning for a possible chemical attack, appropriate resuscitation equipment suitable for children needs to be stockpiled. The signs of biologic infection or chemical intoxication are different for children, and pediatricians and emergency personnel need to be aware of these differences (see Chapters 719 and 723). Surveys of pediatricians and other healthcare providers indicate that many feel unprepared for bioterrorism attacks. Professional organizations such as the American Academy of Pediatrics and the CDC have published position papers; there is a special section in the American Academy of Pediatrics *Red Book* that presents guidelines for treating specific pathogens likely to be utilized in biologic warfare. In regions where violent terrorist activity is likely, pediatricians, nurses, and rescue personnel should consider becoming certified in the Red Cross Basic and Advanced Trauma Life Support.

Pediatricians need to be cognizant of the effects that war and terror can have on parents and children. Parents, who themselves are under tremendous strain, may not be sensitive to the effects that the same stressors have on their children. Pediatricians should draw out both parents and children, and encourage them to talk freely about their feelings. Child healthcare providers can be instrumental in educating parents to be more aware of inappropriate responses by children to war and violence. When necessary, pediatricians can serve their families by referring them to appropriate support services.

Just as it is important to administer first aid for physical trauma, it is also critical to provide psychologic first aid to victims of trauma. An excellent source of online information for both providers and caregivers is provided by the National Child Traumatic Stress Network (www.nctsn.org). In day-to-day patient interactions, a pediatrician is most likely to confront situations related to stress reactions such as PTSD or depressive disorders. Recognition of PTSD is essential so that early treatment can be initiated. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* stipulates that for a diagnosis of PTSD, there has to be manifestations from each of four symptom clusters: intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. The DSM-V also established a special preschool subtype of PTSD which has the same four symptom clusters but with specific manifestations that are typical of preschoolers exposed to trauma (see Chapter 25). Clues to the presence of PTSD and acute anxiety reactions include changes in behavior, school performance, affect, and sleep patterns, and an increase in somatic complaints. Even when the triggering event is neither temporally nor physically proximate, it should not dissuade the pediatrician from making an appropriate referral to mental health professionals who are expert in childhood stress disorders.

Medical professional standards demand from each physician that the physician treat all patients equitably without regard to their background. Both international law and professional medical societies ban physicians from actively participating in torture or other activities that infringe on human rights, including those of children. It is difficult to countenance any situation in which a health professional, even acting as a representative of his or her country, might directly or indirectly injure a minor.

Health professionals have an important role in preventing the atrocities that occur to children. In their role as advocates for the rights of children, pediatricians can be instrumental in focusing public attention on the precarious situation of children exposed to brutality and mayhem that are part and parcel of organized violence. They can promulgate the message that war and terror should not be allowed to rob children of their childhood.

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Chapter 40

Abused and Neglected Children

Howard Dubowitz and Wendy G. Lane

The maltreatment (including abuse and neglect) of children is a pervasive problem in nations throughout the world (Fig. 40-1), with short- and long-term physical and mental health and social consequences to the child, family, community, and society at-large. In addition to the child healthcare professionals' responsibility to identify maltreated children and help ensure their protection and health, they should assume vital roles related to prevention, treatment, and advocacy. Rates and policies vary greatly among nations and often within nations. Rates of maltreatment and provision of services are affected by the overall policies of the country, province, or state governing recognition and responses to child abuse and neglect. Two broad approaches have been identified: a child and family welfare approach, with a focus on the family as a whole, and a child safety approach, with the focus on the child perceived to be at risk. The United States has primarily had a child safety approach.

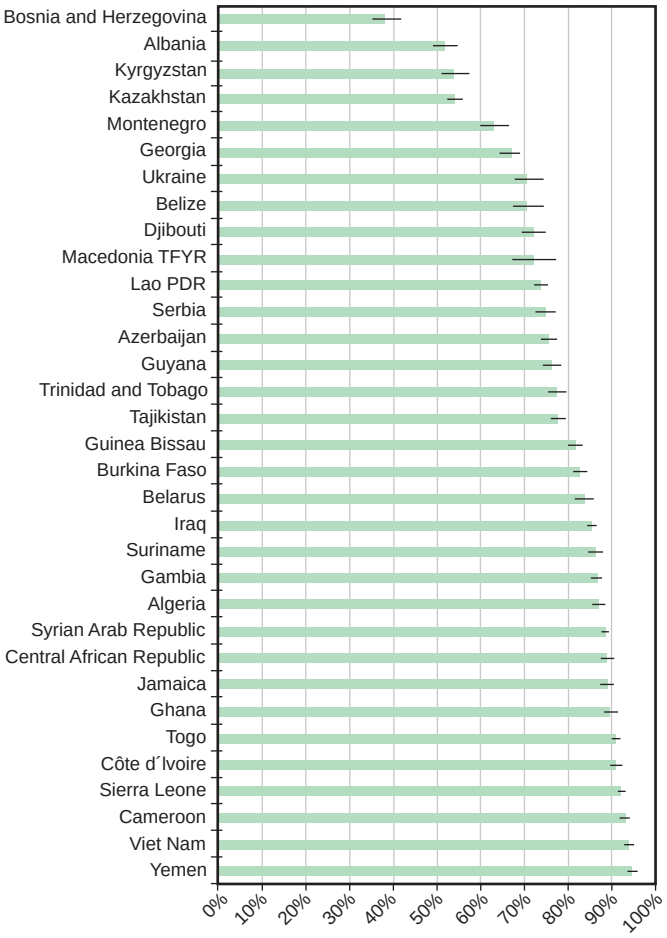

Figure 40-1 Percentage of children ages 2-14 yr who experienced any violent discipline (physical punishment and/or psychological aggression) in the past month, by country. *(From UNICEF,* Child disciplinary practices at home: evidence from a range of low- and middle-income countries, 2010. http://www.childinfo.org/discipline.html.*)*

DEFINITIONS

Abuse is defined as acts of commission and **neglect** as acts of omission. The U.S. government defines child abuse as "any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm." Some states in the United States also include other household members. Children may be found in situations in which no actual harm has occurred and no imminent risk of serious harm is evident, but potential harm may be a concern. Many states include potential harm in their child abuse laws. Consideration of potential harm enables preventive intervention, although predicting potential harm is inherently difficult. Two aspects should be considered. One is the likelihood of harm; the other is the severity of that harm.

Physical abuse includes beating, shaking, burning, and biting. Corporal punishment in any form is increasingly being prohibited. The Global Initiative to End All Corporal Punishment of Children reported that 33 countries have prohibited corporal punishment in all settings, including the home. Governments in at least an additional 18 countries are publicly committed to prohibition in all settings. The majority of countries have prohibited corporal punishment in settings outside the home—in schools (117 countries), in penal institutions (121 countries), and as a sentence of the courts (157 countries). In the United States, corporal punishment in the home is lawful in all states, but 31 states have banned corporal punishment in public schools and the Supreme Court has ruled it unlawful as punishment for a crime.

Internationally, a high proportion of children continue to experience corporal punishment. At the beginning of 2013, 33 countries had banned all corporal punishment, while in 165 some form of corporal punishment is permitted, including 41 countries in which children can be sentenced to corporal punishment for committing a crime.

The threshold for defining corporal punishment as abuse is unclear. One can consider any injury beyond transient redness as abuse. If parents spank a child, it should be limited to the buttocks, should occur over clothing, and should never involve the head and neck. When parents use objects other than a hand, the potential for serious harm increases. Acts of serious violence (e.g., throwing a hard object, slapping an infant's face) should be seen as abusive even if no injury ensues; significant risk of harm exists. Although some child healthcare professionals think that hitting is acceptable under limited conditions, almost all believe that more constructive approaches to discipline are preferable. Although many think that hitting a child should never be acceptable, and many studies have documented the potential harm, there remains a reluctance in the United States to label hitting as abuse unless there is an injury. It is clear that the emotional impact of being hit may leave the most worrisome scar, long after the bruises fade and the fracture heals.

Sexual abuse has been defined as "the involvement of dependent, developmentally immature children and adolescents in sexual activities which they do not fully comprehend, to which they are unable to give consent, or that violate the social taboos of family roles." Sexual abuse includes exposure to sexually explicit materials, oral–genital contact, genital-to-genital contact, genital-to-anal contact, and genital fondling. Any touching of "private parts" by parents or caregivers in a context other than necessary care is inappropriate.

Neglect refers to omissions in care, resulting in actual or potential harm. Omissions include inadequate healthcare, education, supervision, protection from hazards in the environment, and unmet physical needs (e.g., clothing, food) and emotional support. A preferable alternative to focusing on caregiver omissions is to instead consider the basic needs (or rights) of children (e.g., adequate food, clothing, shelter, healthcare, education, nurturance); neglect occurs when a need is not adequately met and results in actual or potential harm, whatever the reasons. A child whose health is jeopardized or harmed by not receiving necessary care experiences medical neglect. Not all such situations

necessarily require a report to **child protective services (CPS)**; less-intrusive initial efforts may be appropriate.

Psychological abuse includes verbal abuse and humiliation and acts that scare or terrorize a child. Although this form of abuse may be extremely harmful to children, resulting in depression, anxiety, poor self-esteem, or lack of empathy, CPS seldom becomes involved because of the difficulty in proving such allegations. Child healthcare professionals should still carefully consider this form of maltreatment, even if the concern fails to reach a legal or agency threshold for reporting. These children and families can benefit from counseling and social support. Many children experience more than 1 form of maltreatment; CPS may be more likely to address psychological abuse in the context of other forms of maltreatment.

Internationally, problems of **trafficking** in children, for purposes of cheap labor and/or sexual exploitation, expose children to all of the forms of abuse just noted.

INCIDENCE AND PREVALENCE

Global Situation

Child abuse and neglect are not rare and occur worldwide. Based on international studies, the World Health Organization (WHO) has estimated that approximately 20% of women and 5-10% of men report being sexually abused as children, while 25-50% of all children report being physically abused. Many children experience emotional abuse and neglect. Rates of child abuse overall and both corporal and psychological vary greatly by this sample of lower- and middle-income nations. Although more difficult to detect and therefore probably underestimated, reports of psychological abuse tend to be somewhat higher than those of physical abuse (Fig. 40-2).

Situation in the United States

Abuse and neglect mostly occur behind closed doors and often are a well-kept secret. Nevertheless, there were 3.4 million reports to CPS involving 6.2 million children in the United States in 2011. Of the 681,000 children with substantiated reports, 78.5% experienced neglect, 17.6% physical abuse, 9.1% sexual abuse, and 9% psychological maltreatment. These rates of substantiated maltreatment continue a trend where neglect has remained at a steady rate since the early 1990s, whereas both sexual and physical abuse rates have declined by approximately 50%. Medical personnel made 8.4% of all reports. The rate of hospitalized children with serious physical abuse has *not* declined in recent years, raising the possibility of CPS trends not necessarily representing a true decline.

Etiology

Child maltreatment seldom has a single cause; rather, multiple and interacting biopsychosocial **risk factors** at 4 levels usually exist. To illustrate, at the *individual level*, a child's disability or a parent's depression or substance abuse predispose a child to maltreatment. At the *familial level*, intimate partner (or domestic) violence presents risks for children. Influential *community factors* include stressors such as dangerous neighborhoods or a lack of recreational facilities. Professional inaction may contribute to neglect, such as when the treatment plan is not clearly communicated. Broad *societal factors*, such as poverty and its associated burdens, also contribute to maltreatment. WHO estimates the rate of homicide of children is approximately 2-fold higher in low-income compared to high-income countries (2.58 vs. 1.21 per 100,000 population), but clearly homicide occurs in high-income countries. Children in all social classes can be maltreated, and child healthcare professionals need to guard against biases concerning low-income families.

Protective factors, such as family supports, or a mother's concern for her child, may buffer risk factors and protect children from maltreatment. Identifying and building on protective factors can be vital to intervening effectively. One can say to a parent, for example, "I can see how much you love ____. What can we do to keep her out of the hospital?" Child maltreatment results from a complex interplay among risk and protective factors. A single mother who has a colicky baby and who recently lost her job is at risk for maltreatment, but a loving grandmother may be protective. A good understanding of factors that contribute to maltreatment, as well as those that are protective, should guide an appropriate response.

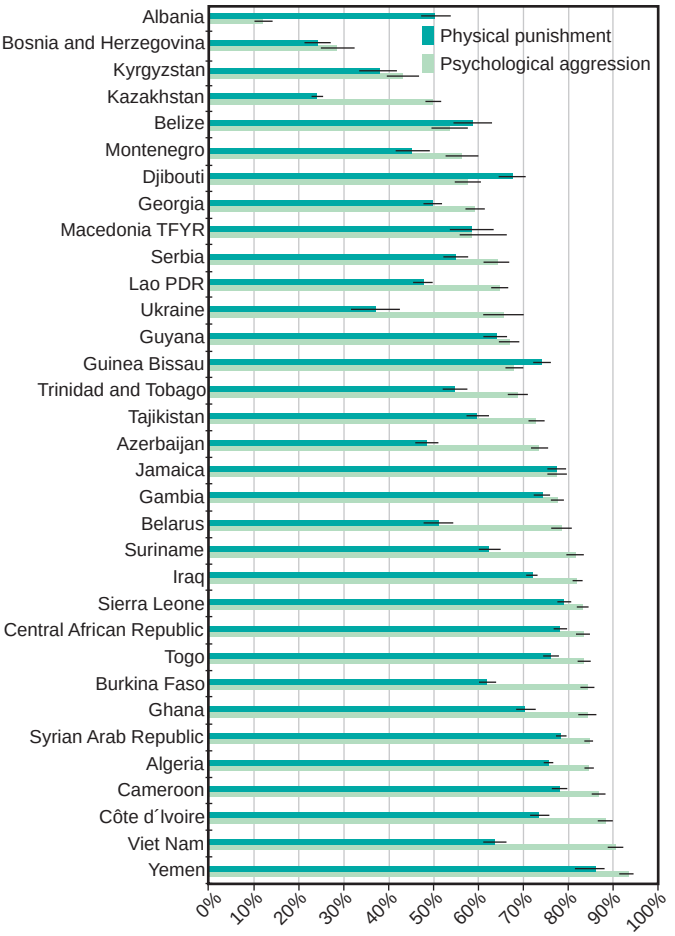

Figure 40-2 Percentage of children ages 2-14 yr who experienced psychological aggression and percentage of children ages 2-14 yr who experienced physical punishment in the past month, by country, 2005-2006. *(From UNICEF,* Child disciplinary practices at home: evidence from a range of low- and middle-income countries, 2010. http://www.childinfo.org/discipline.html.*)*

Clinical Manifestations

Child abuse and neglect can manifest in many different ways. With regard to physical abuse, a critical element is the lack of a plausible history other than inflicted trauma. Signs of abuse may precede the eventual diagnosis of child abuse. These **sentinel injuries** may be noted in approximately 25% of abused infants and may precede the diagnosis by weeks or even months from the sentinel event. Bruising and intraoral injury, in addition to symptoms of an acute life-threatening event, may be early clues of abuse. As with any medical condition, the onus is on the clinician to carefully consider the differential diagnosis and not jump to conclusions.

Bruises are the most common manifestation of physical abuse. Features suggestive of inflicted bruises include (a) bruising in a preambulatory infant (occurring in just 2% of infants), (b) bruising of padded and less-exposed areas (buttocks, cheeks, under the chin, genitalia), (c) patterned bruising or burns conforming to shape of an object or ligatures around the wrists (Table 40-1, Figs. 40-3 and 40-4), and (d) multiple bruises, especially if clearly of different ages. Earlier suggestions for estimating the age of bruises have been discredited. It is very difficult to precisely determine the ages of bruises.

Other conditions, such as birthmarks and mongolian spots can be confused with bruises and abuse. These skin markings are not tender

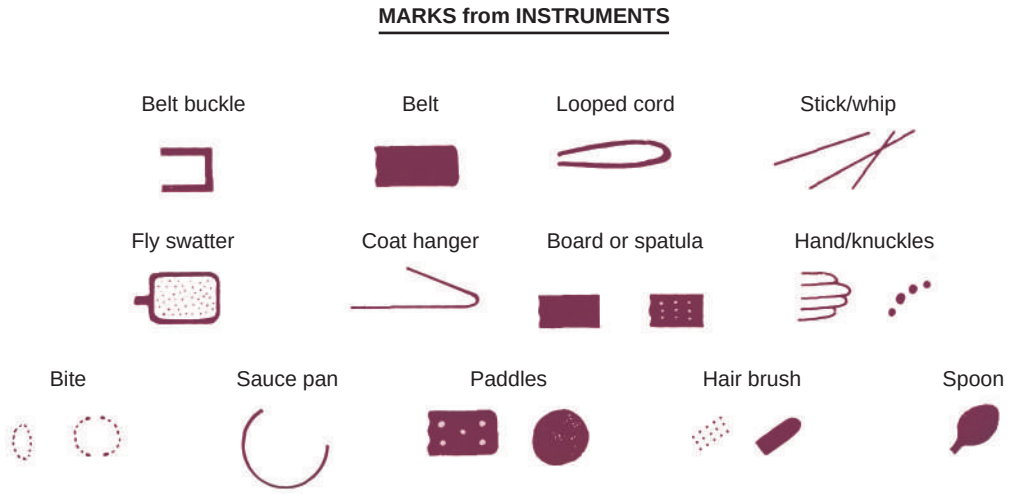

Figure 40-3 **A variety of instruments may be used to inflict injury on a child.** Often the choice of an instrument is a matter of convenience. Marks tend to silhouette or outline the shape of the instrument. The possibility of intentional trauma should prompt a high degree of suspicion when injuries to a child are geometric, paired, mirrored, of various ages or types, or on relatively protected parts of the body. Early recognition of intentional trauma is important to provide therapy and prevent escalation to more serious injury.

Table 40-1 Injury Patterns

METHOD OF INJURY/IMPLEMENT	PATTERN OBSERVED
Grip/grab	Relatively round marks that correspond with fingertips and/or thumb
Closed-fist punch	Series of round bruises that correspond with the knuckles of the hand
Slap	Parallel, linear bruises (usually petechial) separated by areas of central sparing
Belt/electrical cord	Loop marks or parallel lines of petechiae (the width of the belt/cord) with central sparing; may see triangular marks from the end of the belt, small circular lesions caused by the holes in the tongue of the belt, and/or a buckle pattern
Rope	Areas of bruising interspersed with areas of abrasion
Other objects/household implements	Injury in shape of object/implement (e.g., rods, switches, and wires cause linear bruising)
Human bite	Two arches forming a circular or oval shape, may cause bruising and/or abrasion
Strangulation	Petechiae of the head and/or neck, including mucous membranes; may see subconjunctival hemorrhages
Binding/ligature	Marks around the wrists, ankles, or neck; sometimes accompanied by petechiae or edema distal to the ligature mark Marks adjacent to the mouth if the child has been gagged
Excessive hincar (punishment by kneeling on salt or other rough substance)	Abrasions/burns, especially to knees
Hair pulling	Traumatic alopecia; may see petechiae on underlying scalp, or swelling or tenderness of the scalp (from subgaleal hematoma)
Tattooing or intentional scarring	Abusive cases have been described, but can also be a cultural phenomenon (e.g., Maori body ornamentation)

and do not rapidly change color or size. An underlying medical explanation for bruises may exist, such as connective tissue disorders or blood dyscrasias (see Chapters 476, 477, and 484). The history or examination usually provides clues to these conditions. Henoch-Schönlein purpura, the most common vasculitis in young children, may be confused with abuse. The pattern and location of bruises caused by abuse are usually different from those caused by a coagulopathy. Noninflicted bruises are characteristically anterior and over bony prominences, such as chin, ankles, elbows, shins, and forehead. The presence of a medical disorder does not preclude abuse.

Cultural practices can cause bruising. Cao gio, or *coining*, is a Southeast Asian folkloric therapy. A hard object is vigorously rubbed on the skin, causing petechiae or purpura. Cupping is another approach, popular in the Middle East. A heated glass is applied to the skin, often on the back. As it cools, a vacuum forms, leading to perfectly circular bruises. The context here is important, and such circumstances should not be considered abusive (see Chapter 4).

A careful history of bleeding problems in the patient and first degree relatives is needed. If a bleeding disorder is suspected, a complete blood count including platelet count, prothrombin time, and partial thromboplastin time should be obtained. More extensive testing, such as factors VIII, IX, and XI activity and a von Willebrand evaluation, should be considered in consultation with a hematologist.

Bites have a characteristic pattern of 1 or 2 opposing arches with multiple bruises (see Fig. 40-3). They can be inflicted by an adult, another child, an animal, or the patient. Bites by a child (younger than approximately 8 yr with primary teeth) typically have a distance of less than 2.5 cm between the canines—often the most prominent bruises.

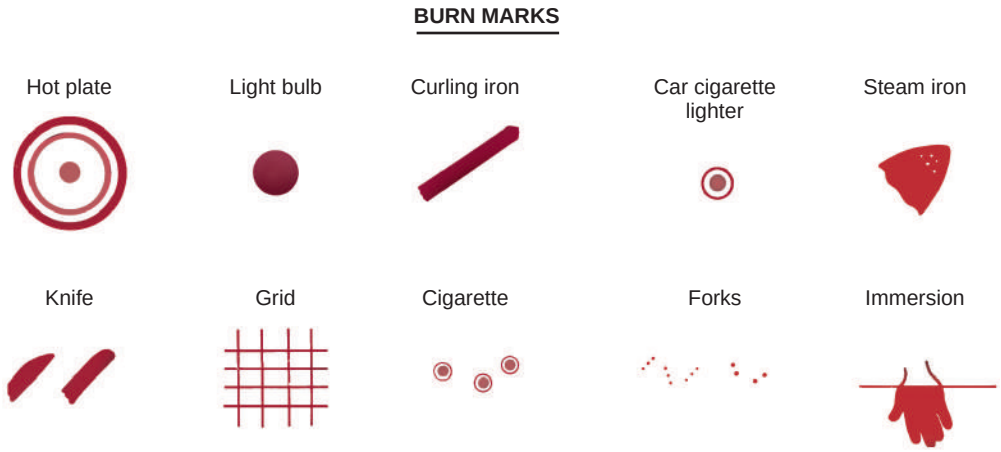

Figure 40-4 Marks from heated objects cause burns in a pattern that duplicates that of the object. Familiarity with the common heated objects that are used to traumatize children facilitates recognition of possible intentional injuries. The location of the burn is important in determining its cause. Children tend to explore surfaces with the palmar surface of the hand and rarely touch a heated object repeatedly or for a long time.

Figure 40-5 Immersion injury patterns. **A,** Sparing of the flexor creases. **B,** Immersion "stocking" burn. **C,** Immersion "glove" burn. **D,** Immersion buttocks burn. *(From Jenny C:* Child abuse and neglect: diagnosis, treatment, and evidence, *Philadelphia, 2011, Saunders, p. 225, Fig. 28-3.)*

The appearance of animal bites is variable; they usually have narrower arches than human bites and are often deep (see Chapter 724). Self-inflicted bites are on accessible areas, particularly the hands. Adult bites raise concern for abuse. Multiple bites by another child suggest inadequate supervision and neglect.

Burns may be inflicted or a result of inadequate supervision. Scalding burns may result from immersion or splash. Immersion burns, when a child is forcibly held in hot water, show clear delineation between the burned and healthy skin, and uniform depth. They may have a sock or glove distribution. Splash marks are usually absent, unlike when a child inadvertently encounters hot water. Symmetric burns are especially suggestive of abuse as are burns of the buttocks and perineum. Although most often accidental, splash burn may also result from abuse. Burns from hot objects such as curling irons, radiators, steam irons, metal grids, hot knives, and cigarettes leave patterns representing the object. A child is likely to try to rapidly escape from a hot object; thus burns that are extensive and deep reflect more than fleeting contact and are suggestive of abuse (Fig. 40-5).

Several conditions mimic abusive burns, such as brushing against a hot radiator, car seat burns, hemangiomas, and folk remedies, such as moxibustion. Impetigo may resemble cigarette burns. Cigarette burns are usually 7-10 mm across, whereas impetigo has lesions of varying size (see Chapter 665.1). Noninflicted cigarette burns are usually oval and superficial.

Neglect frequently contributes to childhood burns. Children, home alone, may be burned in house fires. A parent taking drugs may cause a fire and may be unable to protect a child. Exploring children may pull hot liquids left unattended onto themselves. Liquids cool as they flow downward so that the burn is most severe and broad proximally. If the child is wearing a diaper or clothing, the fabric may absorb the

hot water and cause burns worse than otherwise expected. Some circumstances are difficult to foresee, and a single burn resulting from a momentary lapse in supervision should not automatically be seen as neglectful parenting.

Concluding whether a burn was inflicted depends on the history, burn pattern, and the child's capabilities. A delay in seeking healthcare may result from the burn initially appearing minor, before blistering or becoming infected. This circumstance may represent reasonable behavior and should not be automatically deemed neglectful. A home investigation is often valuable (e.g., testing the water temperature).

Fractures that strongly suggest abuse include classic metaphyseal lesions, posterior rib fractures, and fractures of the scapula, sternum, and spinous processes, especially in young children (Table 40-2). These fractures all require more force than would be expected from a minor fall or routine handling and activities of a child. Rib and sternal fractures rarely result from cardiopulmonary resuscitation, even when performed by untrained adults. It is possible, however, that the recommended 2-finger or 2-thumb technique recommended for infants since 2005 may produce anterolateral rib fractures. In abused infants, rib (Fig. 40-6), metaphyseal (Fig. 40-7), and skull fractures are most common. Femoral and humeral fractures in nonambulatory infants are also highly suggestive for abuse. With increasing mobility and running, toddlers can fall with enough rotational force to cause a spiral, femoral fracture. Multiple fractures in various stages of healing are suggestive of abuse; nevertheless, underlying conditions need to be considered. Clavicular, femoral, supracondylar humeral, and distal extremity fractures in children older than 2 yr are most likely noninflicted unless they are multiple or accompanied by other signs of abuse. Few fractures are pathognomonic of abuse; all must be considered in light of the history.

Table 40-2 Skeletal Injuries from Abuse

High-specificity findings
- Classic metaphyseal corner lesions
- Posterior rib fracture
- Scapular fracture
- Sternal fracture
- Spinous process fracture
- First rib fracture

Moderate-specificity findings
- Multiple fractures
- Fractures of differing age
- Spine fracture
- Complex skull fracture
- Physeal fractures of the long bones
- Digital fractures

Low-specificity findings
- Diaphyseal fractures of the long bones
- Simple skull fractures
- Clavicle fracture

Modified from Kleinman PK. Diagnostic imaging of child abuse, *ed 2, St. Louis, 1998, Mosby.*

Figure 40-6 A high-detail oblique view of the ribs of a 6 mo old infant shows multiple healing posteromedial rib fractures (*arrowheads*). The level of detail in this image is far greater than what would be present on a standard chest radiograph. *(From Dwek JR: The radiographic approach to child abuse.* Clin Orthop Relat Res *469:776-789, 2011, p. 780, Fig. 4.)*

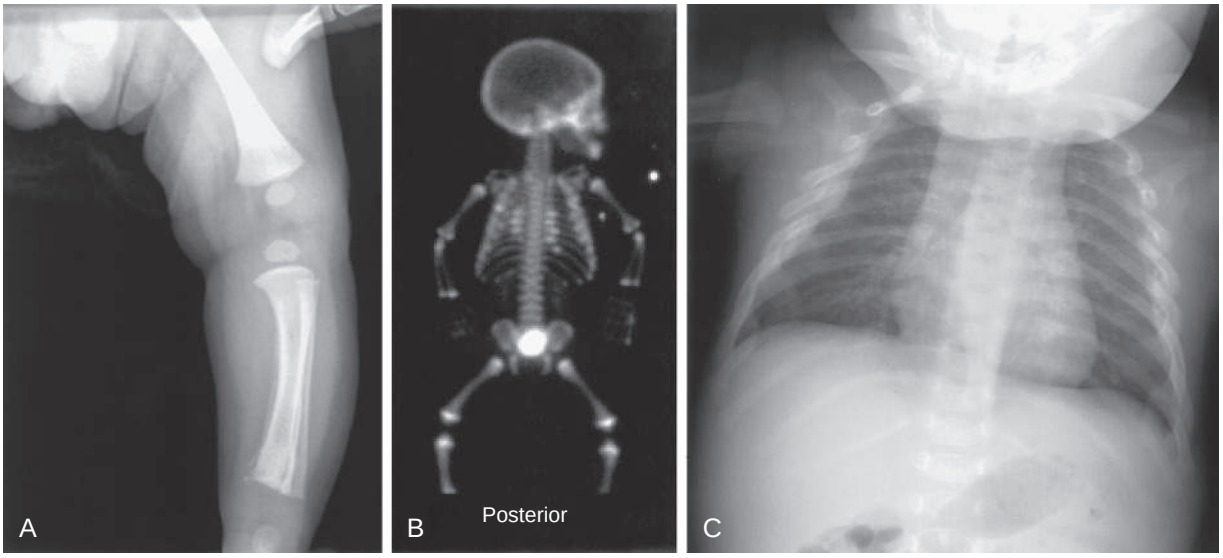

Figure 40-7 **A,** Metaphyseal fracture of the distal tibia in a 3 mo old infant admitted to the hospital with severe head injury. There is also periosteal new bone formation of the tibia, perhaps from previous injury. **B,** Bone scan of same infant. Initial chest x-ray showed a single fracture of the right posterior 4th rib. A radionuclide bone scan performed 2 days later revealed multiple previously unrecognized fractures of the posterior and lateral ribs. **C,** Follow-up radiographs 2 wk later showed multiple healing rib fractures. This pattern of fracture is highly specific for child abuse. The mechanism of these injuries is usually violent squeezing of the chest.

The *differential diagnosis* includes conditions that increase susceptibility to fractures, such as osteopenia of prematurity and osteogenesis imperfecta, metabolic and nutritional disorders (e.g., scurvy, copper deficiency, rickets), renal osteodystrophy, osteomyelitis, congenital syphilis, congenital insensitivity to pain, Caffey disease, and neoplasia. Some have pointed to possible rickets and low but subclinical levels of vitamin D as being responsible for fractures thought to be abusive. The evidence to date does not support this supposition. Features of congenital or metabolic conditions associated with nonabusive fractures include family history of recurrent fractures after minor trauma, abnormally shaped cranium, dentinogenesis imperfecta, blue sclera, wormian bones, craniotabes, ligamentous laxity, bowed legs, hernia, and translucent skin. Subperiosteal new bone formation is a nonspecific finding seen in infectious, traumatic, and metabolic disorders. In young infants, new bone formation may be a normal physiologic finding, usually bilateral, symmetric, and less than 2 mm in depth.

The evaluation of a fracture should include a skeletal survey in children <2 yr of age when abuse seems possible. Multiple films with different views are needed (Table 40-3); "babygrams" (1 or 2 films of the entire body) should be avoided. If the survey is normal, but concern for an occult injury remains, a radionucleotide bone scan should be performed to detect a possible acute injury. Follow-up films after 2 wk may also reveal fractures not apparent initially.

In corroborating the history and the injury, the age of a fracture can be crudely estimated (Table 40-4). Soft-tissue swelling subsides in 2-21 days. Periosteal new bone is visible within 4-21 days. Loss of definition of the fracture line occurs between 10-21 days. Soft callus can be visible after 10 days and hard callus between 14-90 days. These time frames are shorter in infancy and longer in children with poor nutritional status or a chronic underlying disease. Fractures of flat bones such as the skull do not form callus and cannot be aged, although soft-tissue swelling indicates approximate recency (i.e., within the prior week).

Abusive head trauma (AHT) results in the most significant morbidity and mortality. Abusive injury may be caused by direct impact, asphyxia, or shaking. Subdural hematomas (Fig. 40-8), retinal hemorrhages (Fig. 40-9), particularly when extensive and involving multiple layers, and diffuse axonal injury strongly suggest AHT, especially when they co-occur. The poor neck muscle tone and relatively large heads of infants make them vulnerable to acceleration–deceleration forces associated with shaking, leading to AHT. Children may lack external signs of injury, even with serious intracranial trauma. Signs and symptoms may be nonspecific, ranging from lethargy, vomiting (without diarrhea), changing neurologic status or seizures, and coma. In all preverbal children, an index of suspicion for AHT should exist when children present with these signs and symptoms. Asymptomatic subdural hemorrhage may occur after vaginal or cesarean birth. These resolve by 1 mo of age and prior to resolution the infant remains asymptomatic.

Skull fractures are common in abuse, reflecting impact injury. There is no specific pattern of skull fracture that is diagnostic of abuse. Acute intracranial trauma is best evaluated via initial and follow-up CT. MRIs are helpful in differentiating extra axial fluid, determining timing of injuries, assessing parenchymal injury, and identifying vascular anomalies. MRIs are best obtained 5-7 days after an acute injury. Glutaric aciduria type 1 can present with intracranial bleeding and should be considered. Other causes of subdural hemorrhage in infants include arteriovenous malformations, coagulopathies, birth trauma, tumor, or infections. When AHT is suspected, injuries elsewhere—skeletal and abdominal—should be ruled out.

Table 40-3 Skeletal Survey for Infants and Children Under 2 Yr of Age*

- Anteroposterior (AP) and lateral of skull (Townes view optional; add if any fracture seen)
- Lateral spine (C-spine may be included on skull radiographs; AP spine is included on AP chest and AP pelvis to include entire spine)
- AP, right posterior oblique, left posterior oblique of chest—rib technique
- AP pelvis
- AP of each femur
- AP of each leg
- AP of each humerus
- AP of each forearm
- Posteroanterior of each hand
- AP (dorsoventral) of each foot

*Images are checked by a radiologist before the patient leaves. Poorly positioned or otherwise suboptimal images should be repeated. Lateral views are added for positive or equivocal findings in the extremities. Coned views of positive or equivocal findings (i.e., at the ends of the long bones, ribs) may be obtained.

From Coley BD: Caffey's pediatric diagnostic imaging, *ed. 12, Vol. 2, Philadelphia, 2013, Mosby/Elsevier, p. 1588, Box 144-1.*

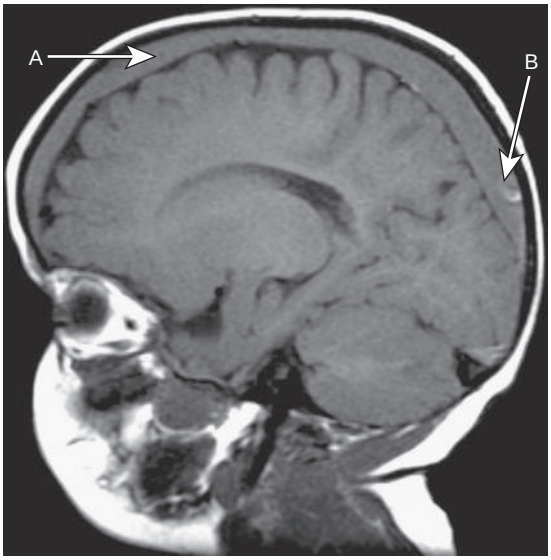

Figure 40-8 CT scan indicating intracranial bleeding. *A*, Older blood. *B*, New blood.

Table 40-4 Timetable of Radiologic Changes in Children's Fractures*

CATEGORY	EARLY	PEAK	LATE
1. Resolution of soft-tissue swelling	2-5 days	4-10 days	10-21 days
2. Subperiosteal new bone formation	4-10 days	10-14 days	14-21 day
3. Loss of fracture line definition, days		10-14 days	14-21 days
4. Soft callus		10-14 days	14-21 days
5. Hard callus	14-21 days	21-42 days	42-90 days
6. Remodeling of fracture	3 mo	1 yr	2 yr to physeal closure

*Repetitive injuries may prolong categories 1, 2, 5, and 6.

From Kleinman PK: Diagnostic imaging of child abuse, *ed. 2, St. Louis, 1998, Mosby, p. 176.*

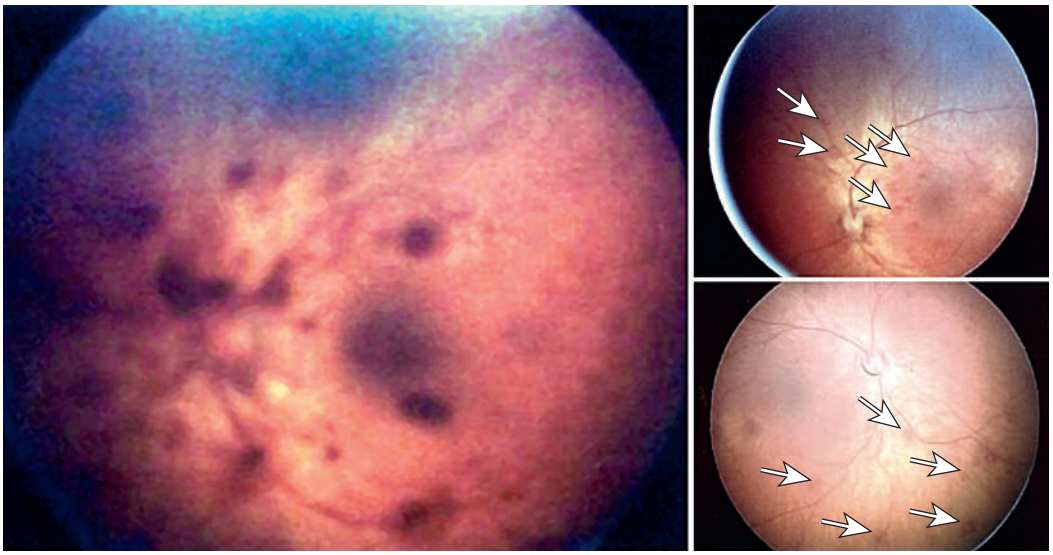

Figure 40-9 Retinal hemorrhages. Arrows point to hemorrhages of various sizes.

Retinal hemorrhages are an important marker of AHT (see Fig. 40-9). Whenever AHT is being considered, a dilated indirect eye examination by a pediatric ophthalmologist should be performed. Although retinal hemorrhages can be found in other conditions, hemorrhages that are multiple, involve more than one layer of the retina, and extend to the periphery (outside the posterior pole) are very suspicious for abuse. The mechanism is likely repeated acceleration–deceleration as a consequence of shaking. Traumatic retinoschisis points strongly to abuse.

There are other causes of retinal hemorrhages, although the pattern is usually different than that seen in child abuse. After normal spontaneous vaginal delivery, 25% of term neonates may have retinal hemorrhages (lower with caesarian section, higher with vacuum assisted delivery). These hemorrhages are in the posterior pole and are intraretinal; 80% resolve by 10 days, 100% by 6-8 wk. Coagulopathies (particularly leukemia), retinal diseases, carbon monoxide poisoning, or glutaric aciduria may be responsible. Severe noninflicted direct crush injury to the head can rarely cause an extensive hemorrhagic retinopathy. Cardiopulmonary resuscitation rarely, if ever, causes retinal hemorrhage in infants and children; if present, there a few hemorrhages in the posterior pole. Hemoglobinopathies, diabetes mellitus, routine play, minor noninflicted head trauma, and vaccinations do not appear to cause retinal hemorrhage in children. Severe coughing or seizures rarely cause retinal hemorrhages that could be confused with AHT. Retinal hemorrhages are rare in children with increased cranial pressure.

The dilemma frequently posed is whether minor, "everyday" forces can explain the findings seen in AHT. Simple linear skull fractures in the absence of other suggestive evidence can be explained by a short fall, although even that is rare (1-2%), and underlying brain injury from short falls is exceedingly rare. Timing of brain injuries in cases of abuse is not precise. In fatal cases, however, the trauma most likely occurred very soon before the child became symptomatic.

Other manifestations of AHT may be seen. "Raccoon" eyes occur in association with subgaleal hematomas after traction on the anterior hair and scalp or after a blow to the forehead. Neuroblastoma can present similarly, and should be considered (see Chapter 498). Bruises from attempted strangulation may be visible on the neck. Choking or suffocation can cause hypoxic brain injury, often with no external signs.

Abdominal trauma accounts for significant morbidity and mortality in abused children. Young children are especially vulnerable because of their relatively large abdomens and lax abdominal musculature. A forceful blow or kick can cause hematomas of solid organs (liver, spleen, kidney) from compression against the spine, as well as hematoma (duodenal) or rupture (stomach) of hollow organs. Intraabdominal bleeding may result from trauma to an organ or from shearing of a vessel. More than one organ may be affected. Children may present with cardiovascular failure or an acute condition of the abdomen, often after a delay in care. Bilious vomiting without fever or peritoneal irritation suggests a duodenal hematoma, often caused by abuse.

The manifestations of abdominal trauma are often subtle, even with severe injuries. Bruising of the abdominal wall is unusual, and symptoms may evolve slowly. Delayed perforation may occur days after the injury; bowel strictures or a pancreatic pseudocyst may occur weeks or months later. Child healthcare professionals should consider screening for occult abdominal trauma when other evidence of physical abuse exists. Screening should include liver and pancreatic enzyme levels, and testing urine for blood. Children with lab results indicating possible injury should have abdominal CT performed. CT or ultrasound should also be performed if there is concern about possible splenic, adrenal, or reproductive organ injury.

Neglect is the most prevalent form of child maltreatment, with potentially severe and lasting sequelae. It may manifest in many ways, depending on which needs are not adequately met. Nonadherence to medical treatment may aggravate the condition, as may a delay in seeking care. Inadequate food may manifest as impaired growth; inattention to obesity may compound that problem. Poor hygiene may contribute to infected cuts or lesions. Inadequate supervision contributes to injuries and ingestions. Children's needs for mental healthcare, dental care, and other health-related needs may be unmet, manifesting as neglect in those areas. Educational needs, particularly for children with learning disabilities, are often not met.

The evaluation of possible neglect requires addressing several critical questions. "Is this neglect?" "Have the circumstances harmed the child, or jeopardized the child's health and safety?" Suboptimal treatment adherence may lead to few or no clear consequences. Inadequacies in the care children receive naturally fall along a continuum, requiring a range of responses tailored to the individual situation. Legal considerations or CPS policies may discourage physicians from labeling many circumstances as neglect. Even if neglect does not meet a threshold for reporting to CPS, child healthcare professionals can still help ensure children's needs are adequately met.

GENERAL PRINCIPLES FOR ASSESSING POSSIBLE ABUSE AND NEGLECT

The heterogeneity of circumstances in situations of child maltreatment precludes specific details. The following are useful general principles.

- Given the complexity and possible ramifications of determining child maltreatment, an interdisciplinary assessment is optimal, with input from all involved professionals. Consultation with a physician expert in child maltreatment is recommended.

- A thorough history should be obtained from the parent(s) optimally via separate interviews.
- Verbal children should be interviewed separately, in a developmentally appropriate manner. Open-ended questions (e.g., "Tell me what happened") are best. Some children need more directed questioning (e.g., "How did you get that bruise?"); others need multiple choice questions. Leading questions (e.g., "Did your daddy hit you?") must be avoided.
- A thorough physical examination is necessary.
- Careful documentation of the history and physical is essential. Verbatim quotes are valuable, including the question that prompted the response. Photographs are helpful.
- For abuse: What is the evidence for concluding abuse? Have other diagnoses been ruled out? What is the likely mechanism of the injury? When did the injury likely occur?
- For neglect: Do the circumstances indicate that the child's needs have not been adequately met? Is there evidence of actual harm? Is there evidence of potential harm and on what basis? What is the nature of the neglect? Is there a pattern of neglect?
- Are there indications of other forms of maltreatment? Has there been prior CPS involvement?
- A child's safety is a paramount concern. What is the risk of imminent harm, and of what severity?
- What is contributing to the maltreatment? Consider the categories described in the section on etiology.
- What strengths/resources are there? This is as important as identifying problems.
- What interventions have been tried, with what results? Knowing the nature of these interventions can be useful, including from the parent's perspective.
- What is the prognosis? Is the family motivated to improve the circumstances and accept help, or resistant? Are suitable resources, formal and informal, available?
- Are there other children in the home who should be assessed for maltreatment?

GENERAL PRINCIPLES FOR ADDRESSING CHILD MALTREATMENT

The circumstances surrounding each child and/or incident of suspected abuse or neglect may be complex and highly variable, precluding specific steps. The following are general principles.

- Treat any medical problems.
- Help ensure the child's safety, often in conjunction with CPS; this is a priority.
- Convey concerns of maltreatment to parents, kindly but forthrightly. Avoid blaming. It is natural to feel anger or pain towards parents of maltreated children, but they need support and deserve respect.
- Have a means of addressing the difficult emotions child maltreatment can evoke in us.
- Be empathic and state interest in helping, or suggest another pediatrician.
- Know your national and state laws and/or local CPS policies on reporting child maltreatment. In the United States, the legal threshold for reporting is typically "reason to believe"; one does not need to be certain. Physical abuse and moderate to severe neglect warrant a report. In less-severe neglect, less-intrusive interventions may be an appropriate initial response. For example, if an infant's mild failure to thrive is a result of an error in mixing the formula, parent education and perhaps a visiting nurse should be tried. In contrast, severe failure to thrive may require hospitalization, and if the contributing factors are particularly serious (e.g., a psychotic mother), out-of-home placement may be needed. CPS can assess the home environment, providing valuable insights.
- Reporting child maltreatment is never easy. Parental inadequacy or culpability is at least implicit, and parents may express considerable anger. Child healthcare professionals should supportively inform families directly of the report; it can be explained as an effort to clarify the situation and provide help, as well as a professional (and legal) responsibility. Explaining what the ensuing process is likely to entail (e.g., a visit from a CPS worker and sometimes a police officer) may ease a parent's anxiety. Parents are frequently concerned that they might lose their child. Child healthcare professionals can cautiously reassure parents that CPS is responsible for helping children and families and that, in most instances, children remain with their parents. Even when CPS does not accept a report or when a report is not substantiated, they may offer voluntary supportive services such as food, shelter, homemaker services, and child care. Child healthcare professionals can be a useful liaison between the family and the public agencies, and should try to remain involved after reporting to CPS.
- Help address contributory factors, prioritizing those most important and amenable to being remedied. Concrete needs should not be overlooked; accessing nutrition programs, obtaining health insurance, enrolling children in preschool programs, and help finding safe housing can make a valuable difference. Parents may need their own problems addressed to enable them to adequately care for their children.
- Establish specific objectives (e.g., no hitting, diabetes will be adequately controlled), with measurable outcomes (e.g., urine dipsticks, hemoglobin A_{1c}). Similarly, advice should be specific and limited to a few reasonable steps. A written contract can be very helpful.
- Engage the family in developing the plan, solicit their input and agreement.
- Build on strengths; there are always some. These provide a valuable way to engage parents.
- Encourage informal supports (e.g., family, friends; invite fathers to office visits). This is where most people get their support, not from professionals. Consider support available through a family's religious affiliation.
- Consider children's specific needs. Too often, maltreated children do not receive direct services.
- Be knowledgeable about community resources, and facilitate appropriate referrals.
- Provide support, follow-up, review of progress, and adjust the plan if needed.
- Recognize that maltreatment often requires long-term intervention with ongoing support and monitoring.

OUTCOMES OF CHILD MALTREATMENT

Child maltreatment often has significant short- and long-term medical, mental health, and social sequelae. Physically abused children are at risk for many problems, including conduct disorders, aggressive behavior, decreased cognitive functioning, and poor academic performance. Neglect is similarly associated with many potential problems. Even if a maltreated child appears to be functioning well, healthcare professionals and parents need to be sensitive to the possibility of later problems. Maltreatment is associated with increased risk in adulthood for several health risk behaviors and physical and mental health problems. Maltreated children are at risk for becoming abusive parents. The neurobiologic effects of child abuse and neglect on the developing brain may partly explain some of these sequelae.

Some children appear to be resilient and may not exhibit sequelae of maltreatment, perhaps owing to protective factors or interventions. The benefits of intervention have been found in even the most severely neglected children, such as those from Romanian orphanages, who were adopted—the earlier the better.

PREVENTION OF CHILD ABUSE AND NEGLECT

An important aspect of prevention is that many of the efforts to strengthen families and support parents should promote children's health, development, and safety, as well as prevent child abuse and neglect. Medical responses to child maltreatment have typically occurred after the fact; preventing the problem is preferable. Child healthcare professionals can help in several ways. An ongoing relationship offers opportunities to develop trust and knowledge of a family's

circumstances. Astute observation of parent–child interactions can reveal useful information.

Parent and child education regarding medical conditions helps to ensure implementation of the treatment plan and to prevent neglect. Possible barriers to treatment should be addressed. Practical strategies such as writing down the plan can help. In addition, anticipatory guidance may help with child rearing, diminishing the risk of maltreatment. Hospital-based programs that educate parents about infant crying and the risks of shaking the infant may help prevent AHT.

Screening for major psychosocial risk factors for maltreatment (depression, substance abuse, intimate partner violence, major stress), and helping address identified problems, often via referrals, may help prevent maltreatment. The primary care focus on prevention offers excellent opportunities to screen briefly for psychosocial problems. The traditional organ system–focused review of systems can be expanded to probe areas such as feelings about the child, the parent's own functioning, possible depression, substance abuse, intimate partner violence, disciplinary approaches, stressors, and supports. The Safe Environment for Every Kid (SEEK) model offers a promising approach for pediatric primary care to identify and help address prevalent psychosocial problems. So doing can strengthen families, support parents, promote children's health, development and safety, and, help prevent child maltreatment.

Obtaining information directly from children or youth is also important, especially given that separate interviews with teens have become the norm. Any concerns identified on such screens require at least brief assessment and initial management, which may lead to a referral for further evaluation and treatment. More frequent office visits can be scheduled for support and counseling while monitoring the situation. Other key family members (e.g., fathers) might be invited to participate, thereby encouraging informal support. Practices might arrange parent groups through which problems and solutions are shared.

Advocacy

Child health professionals can assist in understanding what contributed to the child's maltreatment. When advocating for the best interest of the child and family, addressing risk factors at the individual, family, and community levels is optimal. At the individual level, an example of advocating on behalf of a child is explaining to a parent that an active toddler is behaving normally and not intentionally challenging the parent. Encouraging a mother to seek help dealing with a violent spouse, saying for example, "You and your life are very important," asking about substance abuse and helping parents obtain health insurance for their children are all forms of advocacy. Child abuse can and does occur even in families in which one spouse does not support or condone the abusive behavior (Fig. 40-10).

Efforts to improve family functioning, such as encouraging fathers' involvement in child care are also examples of advocacy. Remaining involved after a report to CPS and helping ensure appropriate services are provided is advocacy as well. In the community, child health professionals can be influential advocates for maximizing resources devoted to children and families. These include parenting programs, services for abused women and children, and recreational facilities. Finally, child health professionals can play an important role in advocating for policies and programs at the local, state, and national levels to benefit children and families. Child maltreatment is a complex problem that has no easy solutions.

Bibliography is available at Expert Consult.

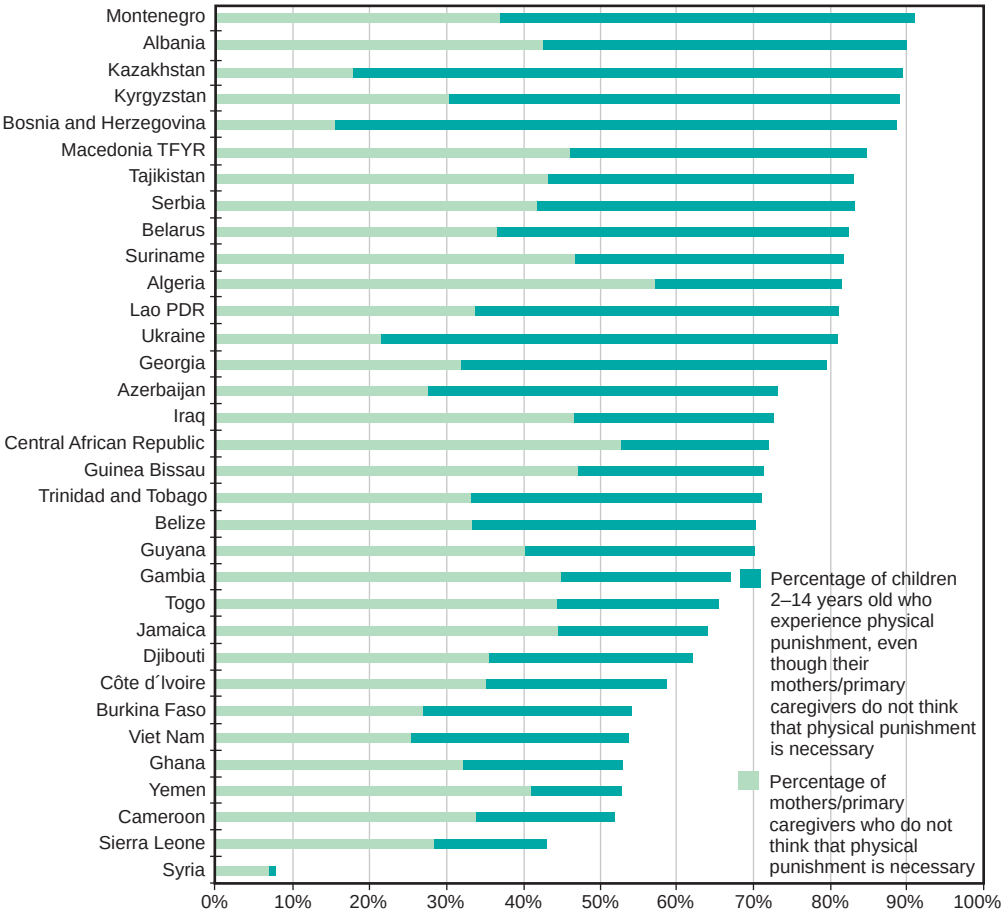

Figure 40-10 Percentage of mothers/primary caregivers who do not think that physical punishment is necessary and percentage of children 2-14 yr old who experience physical punishment, even though their mothers/primary caregivers do not think that physical punishment is necessary, in selected countries with available data. *(From UNICEF global databases 2011, from DHS, MICS and other national surveys, 2005-2006. http://www.childinfo.org/discipline.html.)*

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40.1 Sexual Abuse

Wendy G. Lane and Howard Dubowitz

See also Chapter 119, Adolescent Rape.

Approximately 25% of girls and 10% of boys in the United States will be sexually abused at some point during their childhood. Rates vary across the globe, with children in some countries experiencing even higher rates. Whether children and families share this information with their pediatrician will depend, in large part, on the pediatrician's comfort with and openness to discussing possible sexual abuse with families.

Pediatricians may play a number of different roles in addressing sexual abuse, including identification, reporting to CPS, testing for and treating sexually transmitted infections, and providing support and reassurance to children and families. Pediatricians may also play a role in the prevention of sexual abuse by advising parents and children about ways to help keep safe from sexual abuse. In many jurisdictions throughout the United States, general pediatricians will play a triage role, with the definitive medical evaluation conducted by a child abuse specialist.

DEFINITION

Sexual abuse may be defined as any sexual behavior or action toward a child that is unwanted or exploitative. Some legal definitions distinguish sexual abuse from sexual assault; the former being committed by a caregiver or household member, and the latter being committed by someone with a noncustodial relationship or no relationship with the child. For this chapter, the term *sexual abuse* encompasses both abuse and assault. Sexual abuse does *not* have to involve direct touching or contact by the perpetrator. Showing pornography to a child, filming or photographing a child in sexually explicit poses, and encouraging or forcing one child to perform sex acts on another also constitute sexual abuse.

PRESENTATION OF SEXUAL ABUSE

Caregivers may become concerned about the possibility of sexual abuse when children exhibit sexually explicit behavior. This behavior includes that which is outside the norm for a child's age and developmental level. For preschool and school-age children, sexually explicit behavior may include compulsive masturbation, attempting to perform sex acts on adults or other children, or asking adults or children to perform sex acts on them. Teenagers may become sexually promiscuous and even engage in prostitution. Older children and teenagers may respond by sexually abusing younger children. It is important to recognize that this behavior could also result from accidental exposure (e.g., the child who enters his parent's bedroom at night to find his parents having sex), or from neglect (e.g., watching pornographic movies where a child can see them).

Children who have been sexually abused sometimes provide a clear, spontaneous disclosure to a trusted adult. Often the signs of sexual abuse are much more subtle. For some children, behavioral changes are the first indication that something is amiss. Nonspecific behavior changes such as social withdrawal, acting out, increased clinginess or fearfulness, distractibility, and learning difficulties may be attributed to a variety of life changes or stressors. Regression in developmental milestones, including new-onset bedwetting or encopresis (see Chapter 23), is another behavior that caregivers may overlook as an indicator of sexual abuse. Teenagers may respond by becoming depressed, experimenting with drugs or alcohol, or running away from home. Because nonspecific symptoms are very common among children who have been sexually abused, it should nearly always be included in one's differential diagnosis of child behavior changes.

Some children may not exhibit behavioral changes or provide any other indication that something is wrong. For these children, sexual abuse may be discovered when another person witnesses the abuse or discovers evidence such as sexually explicit photographs or videos. Pregnancy may be another way that sexual abuse is identified. There are also children, with and without symptoms, who will not be identified at any point during their childhood.

THE ROLE OF THE GENERAL PEDIATRICIAN IN THE ASSESSMENT AND MANAGEMENT OF POSSIBLE SEXUAL ABUSE

Before determining where and how a child with suspected sexual abuse is evaluated, it is important to assess for and rule out any medical problems that can be confused with abuse. A number of genital findings may raise concern about abuse but often have alternative explanations. Genital redness in a prepubertal child is more often caused by nonspecific vulvovaginitis, eczema, or infection with staphylococcus, group A streptococcus, *Haemophilus*, *Neisseria*, or yeast. Lichen sclerosis is a less-common cause of redness. Vaginal discharge can be caused by sexually transmitted infections, but also by vaginal foreign body, onset of puberty, or infection with *Salmonella*, *Shigella*, or *Yersinia*. Genital ulcers can be caused by herpes simplex virus and syphilis, but also by Epstein-Barr virus, varicella-zoster, Crohn disease, and Behçet disease. Genital bleeding can be caused by urethral prolapse, vaginal foreign body, accidental trauma, and vaginal tumor.

When other medical conditions are not under consideration, have been ruled out, or are less likely than abuse, the possibility for suspected sexual abuse should be probed (Fig. 40-11). Where and how a child with suspected sexual abuse is evaluated should be determined by how long ago the last incident of abuse likely occurred, and whether the child is prepubertal or postpubertal. For the prepubertal child, if abuse has occurred in the previous 72 hr, forensic evidence collection (e.g., external genital, vaginal, anal, and oral swabs, sometimes referred to as a "rape kit") is often indicated, and the child should be referred to a site equipped to collect forensic evidence. Depending on the jurisdiction, this site may be an emergency department, a child advocacy center, or an outpatient clinic. If the last incident of abuse occurred more than 72 hr prior, the likelihood of recovering forensic evidence is extremely low, and forensic evidence collection is not necessary. For postpubertal females, many experts recommend forensic evidence collection up to 120 hr following the abuse—the same time limit as for adult women. The extended time frame is justified because some studies have demonstrated that semen can remain in the postpubertal vaginal vault for more than 72 hr.

The referral site may be different when the child does not present until after the cutoff for an acute exam. Because emergency departments may not have a child abuse expert, and can be busy, noisy, and lacking in privacy, examination at an alternate location such as a child

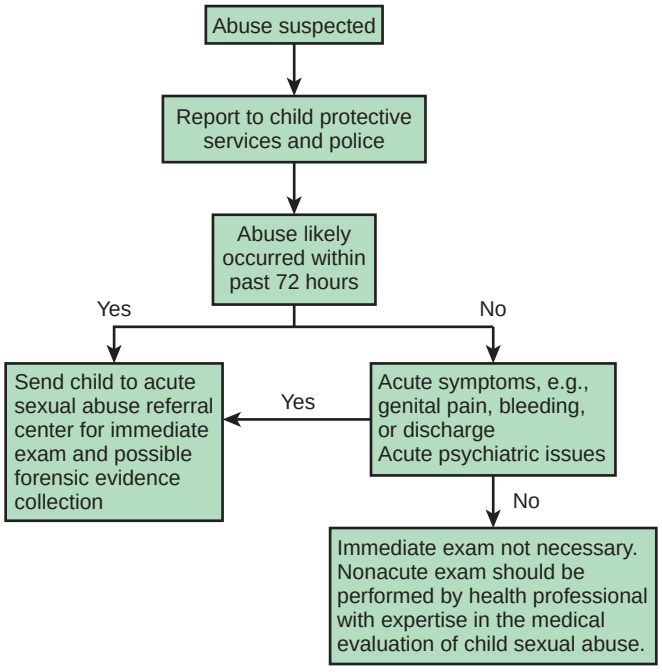

Figure 40-11 Triage protocol for children with suspected sexual abuse.

advocacy center or outpatient clinic is recommended. If the exam is not urgent, waiting until the next morning is recommended because it is easier to interview and examine a child who is not tired and cranky. Referring physicians should be familiar with the triage procedures in their communities, including the referral sites for both acute and chronic exams, and whether there are separate referral sites for prepubertal and postpubertal children.

Children with suspected sexual abuse may present to the pediatrician's office with a clear disclosure of abuse or more subtle indicators. In this situation, a private, brief conversation between pediatrician and child can provide an opportunity for the child to speak in the child's own words without the parent speaking for the child. Doing this may be especially important when the caregiver does not believe the child, or is unwilling or unable to offer emotional support and protection. Telling caregivers that a private conversation is part of the routine assessment for the child's concerns can help comfort a hesitant parent.

When speaking with the child, experts recommend establishing rapport by starting with general and open-ended questions; for example: "Who lives at home?" and "What are your favorite things to do?" Questions about sexual abuse should be nonleading. A pediatrician should explain that sometimes children are hurt or bothered by others, and that the physician wonders whether that might have happened to the child. Open-ended questions, such as "Can you tell me more about that?" allow the child to provide additional information and clarification in the child's own words. It is *not* necessary to obtain extensive information about what happened because the child will usually have a forensic interview once a report is made to CPS and an investigation begins. Very young children and those with developmental delay may lack the verbal skills to describe what happened. In this situation, the caregiver's history may provide enough information to warrant a report to CPS without interviewing the child.

All 50 U.S. states (and a growing number of other nations) mandate that professionals report suspected maltreatment to CPS. The specific criteria for "reason to suspect" are generally not defined by state law. It is clear that reporting does not require certainty that abuse has occurred. Therefore, it may be appropriate to report a child with sexual behavior concerns when no accidental sexual exposure can be identified and the child does not clearly confirm or deny abuse during your conversation with her.

PHYSICAL EXAMINATION OF THE CHILD WITH SUSPECTED SEXUAL ABUSE

Many physicians are unfamiliar with genital anatomy and examination, particularly in the prepubertal child (Figs. 40-12 and 40-13). Because approximately 95% of children who undergo a medical evaluation following sexual abuse have normal exams, the role of the primary care provider is often simply to be able to distinguish a normal exam from findings indicative of common medical concerns or trauma. The absence of physical findings can often be explained by the type of sexual contact that has occurred. Abusive acts such as fondling or even

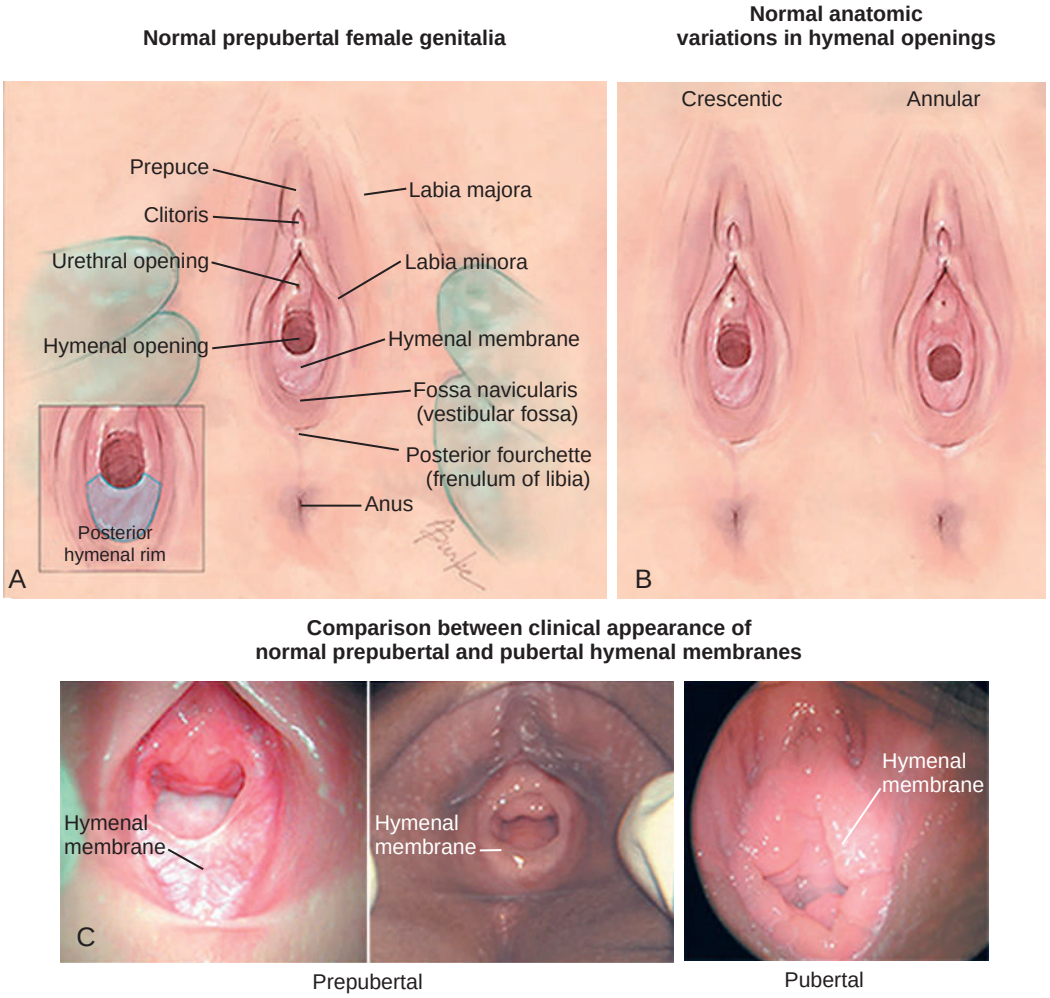

Figure 40-12 Female prepubertal genital anatomy. **A**, Inset shows the region defined as the posterior hymenal rim, between the 4 o'clock and 8 o'clock positions (*shaded blue*). **B,** There is a range of normal anatomic variations in hymenal openings. Crescentic and annular are two of the most common shapes. **C,** Photographs illustrate the range of normal prepubertal and pubertal hymenal membranes. In most children, the hymen becomes thicker and more redundant during puberty. *(From Berkoff MC, Zolotor AJ, Makoroff KL, et al: Has this prepubertal girl been sexually abused?* JAMA *300:2779-2792, 2008.)*

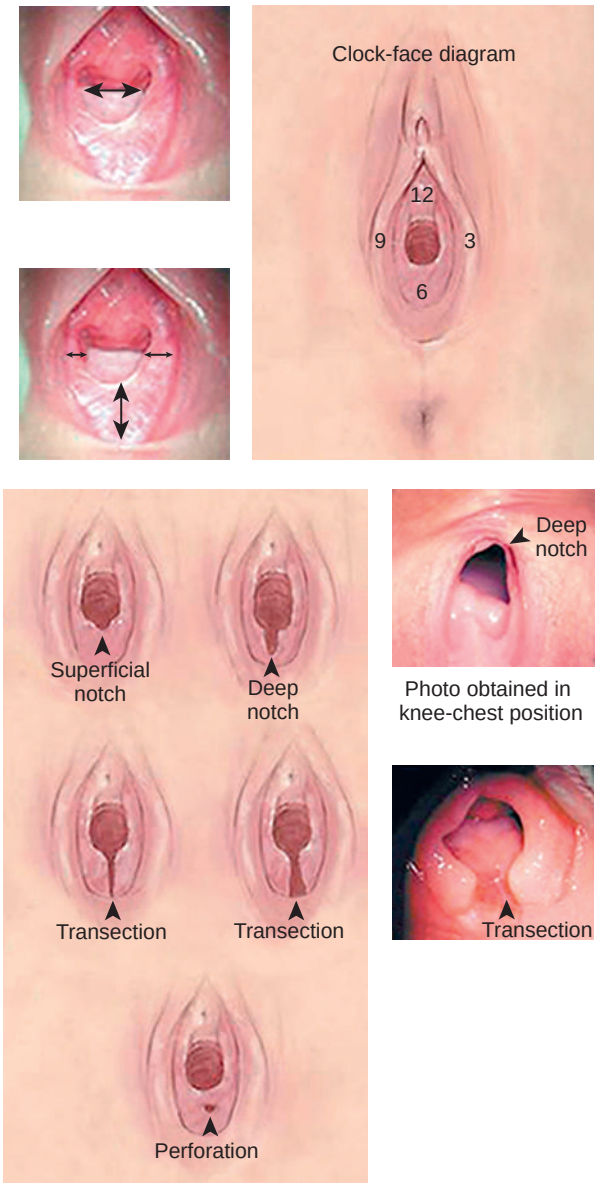

Figure 40-13 **Hymenal membrane characteristics.** When considering the possibility of sexual abuse during an examination, the examiner should document pertinent positive and negative findings. In addition to the clinical signs depicted in the figure, other possible findings include prominent hymenal vessels, bumps, tags, longitudinal intravaginal ridge, external ridge, periurethral bands, or vestibular bands. Perforation of the hymen is not a finding commonly discussed in the literature. *(From Berkoff MC, Zolotor AJ, Makoroff KL, et al: Has this prepubertal girl been sexually abused?* JAMA *300:2779-2792, 2008.)*

digital penetration can occur without causing injury. Many children do not disclose abuse until days, weeks, months, or even years after the abuse has occurred; because genital injuries can heal rapidly, injuries are often completely healed by the time a child presents for medical evaluation. A normal genital exam does not rule out the possibility of abuse, and should not influence the decision to report to CPS.

Even with the high proportion of normal genital exams, there is value in conducting a thorough physical exam. Unsuspected injuries or medical problems, such as labial adhesions, imperforate hymen, or a small urethral prolapse, may be identified. In addition, reassurance about the child's physical health may allay fears and reduce anxiety for the child and family.

Few findings on the genital examination are diagnostic for sexual abuse. In the acute time frame, lacerations or bruising of the labia, penis, scrotum, perianal tissues, or perineum are indicative of trauma. Likewise, hymenal bruising and lacerations, and perianal lacerations extending deep to the external anal sphincter indicate penetrating trauma. Several nonacute findings are also concerning for sexual abuse. A complete transection of the hymen to the base between the 4 and 8 o'clock positions (i.e., absence of hymenal tissue in the posterior rim) is considered diagnostic for trauma (see Fig. 40-13). For all of these findings, the cause of injury must be elucidated through the child and caregiver history. If there is any concern that the finding may be the result of sexual abuse, CPS should be notified and a medical evaluation should be performed by an experienced child abuse pediatrician.

Table 40-5 Situations Involving a High Risk for Transmission of Sexually Transmitted Infections

1. Child has signs or symptoms of STI, including vaginal discharge or pain, genital itching or odor, urinary symptoms, and genital ulcers or lesions.
2. The suspected perpetrator is known to have an STI, or is at high risk for having an STI because of multiple partners, substance abuse, or other reasons.
3. Any other person living in the child's household has an STI.
4. There is evidence of genital, oral, or anal penetration or ejaculation.
5. The patient or parent requests testing.

STI, sexually transmitted infection.

From Centers for Disease Control and Prevention, Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010, MMWR Recomm Rep *59(RR-12):1-114, 2010.*

Testing for sexually transmitted infections is not indicated for all children, but is warranted in the situations described in Table 40-5. Until recently, culture was considered the gold standard for the diagnosis of vaginal gonorrhea (see Chapter 192) and chlamydia (see Chapter 226) infections in children. There is growing evidence that **nucleic acid amplification testing (NAAT)** for gonorrhea and chlamydia by either vaginal swab or urine in prepubertal girls is as (or possibly more) sensitive, than culture. Current guidelines from the Centers for Disease Control and Prevention (CDC) allow for NAAT testing by vaginal swab or urine as an alternative to culture in girls. Because obtaining vaginal swabs can be uncomfortable for prepubertal children, urine testing is preferable. Culture remains the preferred method for testing of rectal and pharyngeal specimens in boys and girls. Little data on the use of urine NAAT testing in prepubertal boys is available. Therefore, the CDC continues to recommend urine or urethral culture for boys. Many child abuse experts perform urine NAAT testing on prepubertal boys because urethral swabs are uncomfortable, and there are good data to support urine NAAT testing in girls. For all NAAT testing in both genders, the child should *not* receive presumptive treatment at the time of testing. Instead, a positive NAAT test should be confirmed by culture or an alternate NAAT test prior to treatment. Because gonorrhea and chlamydia in prepubertal children do not typically cause ascending infection, waiting for a definitive diagnosis before treatment will not increase the risk for pelvic inflammatory disease.

A number of sexually transmitted infections should raise concern for abuse (Table 40-6). In a prepubertal child, a positive culture for gonorrhea beyond the neonatal period, trichomonas beyond 1 yr of age, or chlamydia beyond 3 yr of age indicates that the child has had some contact with infected genital secretions, almost always as a result of sexual abuse. Syphilis (see Chapter 218) and HIV are diagnostic for sexual abuse if other means of transmission have been excluded. Because of the potential for transmission either perinatally or through nonsexual contact, the presence of genital warts has a low specificity for sexual abuse. The possibility of sexual abuse should be considered and addressed with the family, especially in children whose warts first appear beyond 3 yr of age. Type 1 or 2 genital herpes is concerning for sexual abuse, but not diagnostic given other possible routes of

Table 40-6 Implications of Commonly Encountered Sexually Transmitted (ST) or Sexually Associated (SA) Infections for Diagnosis and Reporting of Sexual Abuse Among Infants and Prepubertal Children

ST/SA CONFIRMED	EVIDENCE FOR SEXUAL ABUSE	SUGGESTED ACTION
Gonorrhea*	Diagnostic†	Report‡
Syphilis*	Diagnostic	Report‡
HIV§	Diagnostic	Report‡
*Chlamydia trachomatis**	Diagnostic†	Report‡
Trichomonas vaginalis	Highly suspicious	Report‡
Condylomata acuminate (anogenital warts)	Suspicious	Report‡
Genital herpes*	Suspicious	Report‡¶
Bacterial vaginosis	Inconclusive	Medical follow-up

*Report if not likely to be perinatally acquired and rare nonsexual vertical transmission is excluded.

†Although culture is the gold standard, current studies are investigating the use of nucleic acid amplification tests as an alternative diagnostic method.

‡Report to the agency mandated to receive reports of suspected child abuse.

§Report if not likely to be acquired perinatally or through transfusion.

¶Report unless a clear history of autoinoculation is evident.

From MMWR 2010 STD guidelines. Adapted from Kellogg N, American Academy of Pediatrics Committee on Child Abuse and Neglect: The evaluation of sexual abuse in children, Pediatrics *116:506-512, 2005.*

transmission. For both human papillomavirus and herpes simplex virus, the American Academy of Pediatrics recommends reporting to CPS unless perinatal or horizontal transmission is considered likely.

SEXUAL ABUSE PREVENTION

Pediatricians can play a role in the prevention of sexual abuse by educating parents and children about sexual safety at well child visits. During the genital exam the pediatrician can inform the child that only the doctor and select adult caregivers should be permitted to see their "private parts," and that a trusted adult should be told if anyone else attempts to do so. Pediatricians can raise parental awareness that sometimes older kids or adults may try engage in sexual behavior with children. The pediatrician can teach parents how to minimize the opportunity for perpetrators to access children, for example, by limiting 1-adult/1-child situations and being sensitive to any adult's unusual interest in young children. In addition, pediatricians can help parents talk to children about what to do if confronted with a potentially abusive situation. Some examples include telling children to say "no," to leave, and to tell a parent and/or another adult. If abuse does occur, the pediatrician can tell parents how to recognize possible signs and symptoms, and how to reassure the child that she or he was not at fault. Finally, pediatricians can provide parents with suggestions about how to maintain open communication with their children so that these conversations can occur with minimal parent and child discomfort.

Bibliography is available at Expert Consult.

40.2 Medical Child Abuse (Factitious Disorder by Proxy, Munchausen Syndrome by Proxy)

Howard Dubowitz and Wendy G. Lane

The term *Munchausen syndrome* is used to describe situations in which adults falsify their own symptoms. In *Munchausen syndrome by proxy*, a parent, typically a mother, simulates or causes disease in her child. Several terms have been suggested to describe this phenomenon: factitious disorder by proxy, pediatric condition falsification, caregiver fabricated illness, and **medical child abuse (MCA)**. In some instances, such as partial suffocation, "child abuse" may be most appropriate.

The core dynamic is that a parent falsely presents a child for medical attention. This may be via fabricating a history, such as reporting seizures that never occurred. A parent may directly cause a child's illness by exposing a child to a toxin, medication, or infectious agent (e.g., injecting stool into an intravenous line). Signs or symptoms may also be manufactured, such as when a parent smothers a child, or alters laboratory samples or temperature measurements. Each of these actions may lead to unnecessary medical care, sometimes including intrusive tests and surgeries. The "problems" often recur repeatedly over several years. In addition to the physical concomitants of testing and treatment, there are potentially serious and lasting social and psychologic sequelae.

Child health professionals are typically misled into thinking that the child really has a medical problem. Parents, sometimes working in a medical field, may be adept at constructing somewhat plausible presentations; a convincing seizure history may be offered, and a normal electroencephalogram cannot fully rule out the possibility of a seizure disorder. Even after extensive testing fails to lead to a diagnosis or treatment proves ineffective, health professionals may think they are confronting a "new or rare disease." Unwittingly, this can lead to continued testing and interventions, thus perpetuating the MCA. Pediatricians generally rely on and trust parents to provide an accurate history. As with other forms of child maltreatment, accurate diagnosis of MCA requires that the pediatrician maintain a healthy skepticism under certain circumstances.

CLINICAL MANIFESTATIONS

As with other forms of child abuse, the presentation of MCA may vary in nature and severity. Consideration of MCA should be triggered when the reported symptoms are repeatedly noted by only one parent, appropriate testing fails to confirm a diagnosis, and seemingly appropriate treatment is ineffective. The child's symptoms, their course, or the response to treatment may be incompatible with any recognized disease. Preverbal children are usually involved, although older children may be convinced by parents that they have a particular problem and become dependent on the increased attention; this may lead to feigning symptoms.

Symptoms in young children are mostly associated with proximity of the offending caregiver to the child. The mother may present as a devoted or even model parent who forms close relationships with members of the healthcare team. While appearing very interested in her child's condition, she may be relatively distant emotionally. She may have a history of Munchausen syndrome, though not necessarily diagnosed as such. **Bleeding** is a particularly common presentation. This may be caused by adding dyes to samples, adding blood (e.g., from the mother) to the child's sample, or giving the child an anticoagulant (e.g., warfarin).

Seizures are a common manifestation, with a history easy to fabricate, and the difficulty of excluding the problem based on testing. A parent may report that another physician diagnosed seizures, and the myth may be continued if there is no effort to confirm the basis for the "diagnosis." Alternatively, seizures may be induced by toxins, medications (e.g., insulin), water, or salts. Physicians need to be familiar with the substances available to families and the possible consequences of exposure.

Apnea is another common presentation. The observation may be falsified or created by partial suffocation. A history of a sibling with the same problem, perhaps dying from it, should be cause for concern. Parents of children hospitalized for apparent life-threatening events have been videotaped attempting to suffocate their child while in the hospital.

Gastrointestinal signs or symptoms are another common manifestation. Forced ingestion of medications such as ipecac may cause chronic vomiting, or laxatives may cause diarrhea.

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The **skin**, easily accessible, may be burned, dyed, tattooed, lacerated, or punctured to simulate acute or chronic skin conditions.

Recurrent sepsis may be caused by infectious agents being administered; intravenous lines during hospitalization may provide a convenient portal. Urine and blood samples may be contaminated with foreign material, blood or stool.

DIAGNOSIS

In assessing possible MCA, several explanations should be considered in addition to a true medical problem. Some parents may be extremely anxious and genuinely concerned about possible problems. There may be many reasons underpinning this anxiety, such as a personality trait, the death of neighbor's child, or something read on the Internet. Alternatively, parents may believe something told to them by a trusted physician despite subsequent evidence to the contrary and efforts to correct the earlier misdiagnosis. Physicians may unwittingly contribute to a parent's belief that a real problem exists by, perhaps reasonably, persistently pursuing a medical diagnosis. There is a need to discern commonly used hyperbole (e.g., exaggerating the height of the fever) in order to evoke concern and perhaps justify a visit to an emergency department. In the end, a diagnosis of MCA rests on clear evidence of a child repeatedly being subjected to unnecessary medical tests and treatment, primarily stemming from a parent's actions. Determining the parent's underlying psychopathology is the responsibility of mental health professionals.

Once MCA is suspected, gathering and reviewing **all** the child's medical records is an onerous but critical first step. It is often important to confer with other treating physicians about what specifically was conveyed to the family. A mother may report that the child's physician insisted that a certain test be done when it may be the mother instead who demanded the test. It is also necessary to confirm the basis for a given diagnosis, rather than simply accepting a parent's account.

Pediatricians may face the dilemma of when to accept that all plausible diagnoses have been reasonably ruled out, the circumstances fit MCA, and further testing and treatment should cease. The likelihood of MCA must be balanced with concerns about possibly missing an important diagnosis. Consultation with a pediatrician expert in child abuse is recommended. In evaluating possible MCA, specimens should be carefully collected, with no opportunity for tampering with them. Similarly, temperature measurements should be closely observed.

Depending on the severity and complexity, hospitalization may be needed for careful observation to help make the diagnosis. In some instances, such as repeated apparent life-threatening events, covert video surveillance accompanied by close monitoring (to rapidly intervene in case a parent attempts to suffocate a child) can be valuable. It is important that there be close coordination among hospital staff, especially as some may side with the mother and resent even the possibility of MCA being raised. Parents should not be informed of the evaluation for MCA until the diagnosis is made. Doing so could naturally influence their behavior and jeopardize establishing the diagnosis. All steps in making the diagnosis and all pertinent information should be very carefully documented, perhaps using a "shadow" chart that the parent does not have access to.

TREATMENT

Once the diagnosis is established, the treatment plan should be worked out by the medical team and CPS; it may require out-of-home placement and should include mental healthcare for the offending parent as well as for older affected children. Further medical care should be carefully organized and coordinated by one primary care provider. CPS should be encouraged to meet with the family only after the medical team has informed the offending parent of the diagnosis; their earlier involvement may hamper the evaluation. Parents often respond with resistance, denial, and threats. It may be prudent to have hospital security in the vicinity.

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Chapter 41

Failure to Thrive

Heather S. McLean and David T. Price

Failure to thrive (FTT) results from inadequate usable calories necessary for a child's metabolic and growth demands. No single set of growth parameters provides the criteria for a universal definition. FTT has classically been grouped into organic and nonorganic types; this construct is outmoded and not useful to clinicians seeking to address underlying causes, which are often multifactorial. Many would consider a weight for height ratio less than 2 SD (or <3 or 5 percentile) for age and gender diagnostic of FTT; others would use weight crossing 2 major percentiles on the growth curve. Patients with FTT may either have growth deceleration, faltering growth, or even weight loss.

A biopsychosocial model helps explain the complex interplay between even minor illnesses, the mental health of caregivers, and the home environment. The interaction between the child and parent is often complex; parent expectations of child behavior and the actual temperament of the infant create a transactional model where at times it is often difficult to separate cause and effect (action and reaction). The infant brings to this model an innate temperament with behavioral domains such as activity, adaptability, distractibility, response to new stimuli, and intensity of responses. Some infants are "easy babies," whereas others are more "difficult." These behaviors may interact with different maternal expectations or understanding of child behavior. Additional maternal contributions to this model may include postpartum depression, and the mother's own history of abuse or neglect as a child, as well as home environmental issues such as family stress, poor social/emotional support, poverty, and a chaotic lifestyle. In addition, many medical causes of FTT are associated with these same psychosocial risk factors; both need to be addressed in the management of FTT.

CLINICAL MANIFESTATIONS

Inadequate weight for corrected age, weight for height, and body mass index, as well as failure to gain adequate weight over a period of time, help define FTT (see Chapter 15). Growth parameters should be measured serially and plotted on growth charts appropriate for the child's sex, age, and, if preterm, postconceptual age. Growth charts are also available for some known chromosomal abnormalities, such as Down syndrome and Turner syndrome (see Chapter 81).

ETIOLOGY AND DIAGNOSIS

The causes of insufficient growth include (1) failure of the child to ingest and utilize sufficient calories, (2) malabsorption, and (3) increased metabolic demands. Focus the diagnostic approach on the cause of undernutrition. History, physical examination, and observation of the parent–child interaction in the clinical or home environment usually suggest the most likely etiologies and thus direct appropriate workup and management. A complete history should include a detailed nutritional, family, and prenatal history; documentation of child and caregiver interaction, the quantity, quality and frequency of meals, and further information regarding the onset of the growth failure (Table 41-1).

Many children with FTT will be solely categorized because of deprivation and/or psychological problems and rarely just because of child neglect. These families often share risk factors with neglect, such as poverty, social isolation, and caregiver mental health issues.

The medical causes of FTT may involve every organ system. The clinician may approach the diagnosis in terms of cause (Tables 41-2 and 41-3) or signs and symptoms (Table 41-4). The onset of growth deficiency can indicate a cause, such as the introduction of gluten into the diet of a child with celiac disease or a coincidental psychosocial event. A chromosomal abnormality, intrauterine infection, or

Table 41-1 Historical Factors About the Period After the Neonatal Period to Be Considered in an Evaluation of Growth Failure Using a Biopsychosocial Model

BIOLOGICAL SPHERE	PSYCHOSOCIAL SPHERES
Frequency and source of routine medical care	Provision of baby care, especially feeding
Growth measurements	Maternal sleep deprivation
Immunization status	Postnatal depression or other mental illness
Medical illnesses	Type and amount of social support
Hospitalizations	Availability of respite for mother
Medications	Involvement of father and/or other intimate partner
Allergies—medications, food, other	Intimate partner violence
Surgeries	Financial resources, including money for baby supplies
Injuries, including bruises on infants	Enrollment in governmental aid programs
Feeding issues—vigorous or difficult feeder	Parental reaction to fussing/crying
Breastfeeding:	Who lives with baby
• Milk letdown	Reactions of others in the home to the baby
• Sense of fullness/emptying	Parental employment
• Frequency and duration of feedings	Use of daycare or babysitting
• Maternal observation of baby swallowing	Caregiver perception of weight gain and general appearance
• Maternal diet and medical problems while breastfeeding	
Formula feeding:	
• Type	
• Method of mixing (concentration)	
• Frequency and quantity of feedings	
Other intake in first few months of life, such as:	
• Water	
• Juice	
• Tea	
• Soda	
• Cereal	
Sleep schedule	
Baby's temperament	
Developmental milestones	
Use of alternative or complementary medicines	

From Jenny C: Child abuse and neglect: diagnosis, treatment, and evidence, *Philadelphia, 2011, Elsevier/Saunders, p. 554, Table 57-5.*

Table 41-2 Diagnostic Classification of Causes and Selected Examples of Failure to Thrive

INADEQUATE INTAKE	MALABSORPTION
Inadequate food offered	Cystic fibrosis
• Food insecurity	Celiac disease
• Poor knowledge of child's needs	Hepatobiliary disease
• Formula dilution or excessive juice	Food protein allergy, insensitivity, or intolerance
• Breastfeeding difficulties	Infection (giardiasis)
• Medical child abuse/caregiver fabricated illness (Munchausen by proxy)	Short gut syndrome
• Medical neglect	**INCREASED METABOLIC DEMAND**
• Food fads including "rice" milk as substitute for formula or cow milk	Insulin resistance (intrauterine growth restriction)
Child not taking enough food	Congenital infections (human immunodeficiency virus, TORCHES)
• Oromotor dysfunction, neurologic disease	Syndromes (Russell-Silver, Turner, Down)
• Developmental delay	Malignancy
• Behavioral feeding problem (altered oromotor sensitivity, pain and conditioned aversion)	Chronic disease (cardiac, pulmonary, renal)
• Anorexia from systemic causes	Metabolic disorders
Emesis	Immunodeficiency/autoinflammatory disorders
• Pyloric stenosis	Endocrine (diabetes mellitus, diabetes insipidus, hyperthyroidism)
• Gastroesophageal reflux	
• Eosinophilic esophagitis	
• Vascular rings	
• Malrotation with intermittent volvulus	
• Increased intracranial pressure and other neurologic disorders	
• Inborn errors of metabolism	
• Rumination	
• Cyclic vomiting	

TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex.
Data from Jaffe A: Failure to thrive: current clinical concepts, Pediatr Rev *32:100-108, 2011.*

Table 41-3 Failure to Thrive: Differential Diagnosis by System

PSYCHOSOCIAL/BEHAVIORAL Inadequate diet because of poverty/food insufficiency, errors in food preparation Poor parenting skills (lack of knowledge of sufficient diet) Child/parent interaction problems (autonomy struggles, coercive feeding, maternal depression) Food refusal Rumination Parental cognitive or mental health problems Child abuse or neglect; emotional deprivation	**GASTROINTESTINAL** Pyloric stenosis Gastroesophageal reflux Repair of tracheoesophageal fistula Malrotation Malabsorption syndromes Celiac disease Milk intolerance: lactose, protein Pancreatic insufficiency syndromes (cystic fibrosis) Chronic cholestasis Inflammatory bowel disease Chronic congenital diarrhea states Short bowel syndrome Pseudoobstruction Hirschsprung disease Food allergy
NEUROLOGIC Cerebral palsy Hypothalamic and other central nervous system tumors (diencephalic syndrome) Neuromuscular disorders Neurodegenerative disorders	**CARDIAC** Cyanotic heart lesions Congestive heart failure Vascular rings
RENAL Recurrent urinary tract infection Renal tubular acidosis Renal failure	**PULMONARY/RESPIRATORY** Severe asthma Cystic fibrosis; bronchiectasis Chronic respiratory failure Bronchopulmonary dysplasia Adenoid/tonsillar hypertrophy Obstructive sleep apnea
ENDOCRINE Diabetes mellitus Diabetes insipidus Hypothyroidism/hyperthyroidism Growth hormone deficiency Adrenal insufficiency	**MISCELLANEOUS** Collagen-vascular disease Malignancy Primary immunodeficiency Transplantation
GENETIC/METABOLIC/CONGENITAL Sickle cell disease Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease) Fetal alcohol syndrome Skeletal dysplasias Chromosomal disorders Multiple congenital anomaly syndromes (VATER, CHARGE)	**INFECTIONS** Perinatal infection (TORCHES) Occult/chronic infections Parasitic infestation Tuberculosis HIV

CHARGE, coloboma, heart disease, atresia choanae, retarded growth and retarded development and/or central nervous system anomalies, genital hypoplasia, and ear anomalies and/or deafness; TORCHES, toxoplasma, other agents, rubella, cytomegalovirus, herpes simplex; VATER, vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia.

Table 41-4 Approach to Failure to Thrive Based on Signs and Symptoms

HISTORY/PHYSICAL EXAMINATION	DIAGNOSTIC CONSIDERATION
Spitting, vomiting, food refusal	Gastroesophageal reflux, chronic tonsillitis, food allergies, eosinophilic esophagitis
Diarrhea, fatty stools	Malabsorption, intestinal parasites, milk protein intolerance, pancreatic insufficiency, celiac disease, immunodeficiency, inflammatory bowel disease
Snoring, mouth breathing, enlarged tonsils	Adenoid hypertrophy, obstructive sleep apnea
Recurrent wheezing, pulmonary infections	Asthma, aspiration, food allergy, cystic fibrosis, immunodeficiency
Recurrent infections	HIV or congenital immunodeficiency diseases, anatomic defects
Travel to/from developing countries	Parasitic or bacterial infections of the gastrointestinal tract

teratogen exposure should be considered in a child with symmetric growth failure since birth. Investigation for metabolic disorders should be considered in children with FTT accompanied by 1 of the following factors: history of acute, severe, and potentially life-threatening symptoms, recurrent vomiting, liver dysfunction, neurologic symptoms, cardiomyopathy and myopathy, impairment of special senses, renal symptoms, or distinct dysmorphic features and/or organomegaly.

The physical examination should focus on identifying chronic illnesses, recognizing syndromes that may alter growth, and documenting the effects of malnutrition (Table 41-5).

Laboratory evaluation of children with FTT should be judicious and based on findings from the history and physical. Obtaining the state's newborn screening results, a complete blood count, and urinalysis represent a reasonable initial screen. Testing for celiac disease is indicated in children if the poor growth coincided with gluten exposure (see Chapter 338).

TREATMENT

Treatment requires a multidisciplinary approach and an understanding of all the medical and psychosocial elements that contribute to a child's

Table 41-5	Approach to Physical Examination
Vital signs	Blood pressure, if over 2 yr, temperature, pulse, respirations, oxygen saturation, anthropometry (growth percentiles, body mass index)
General appearance	Activity, affect, posture
Skin	Hygiene, rashes, trauma (bruises, burns, scars)
Head	Hair whorls, color and pluckability of hair, occipital alopecia, fontanel size and patency, frontal bossing, sutures, shape, facial dysmorphisms, philtrum
Eyes	Ptosis, strabismus, fundoscopic examination where possible, palpebral fissures, conjunctival pallor, icterus, cataracts
Ears	External form, rotation, tympanic membranes
Mouth, nose, throat	Thinness of lip, hydration, dental eruption and hygiene caries, glossitis, cheilosis, gum bleeding, marked tonsillar enlargement
Neck	Hairline, masses, lymphadenopathy
Cardiovascular	Evidence of congestive heart failure, cyanosis
Abdomen	Protuberance, hepatosplenomegaly, masses
Genitalia	Malformations, hygiene, trauma
Rectum	Fissures, trauma, hemorrhoids
Extremities	Edema, dysmorphisms, rachitic changes, nails and nail beds
Neurologic	Cranial nerves, reflexes, tone, retention of primitive reflexes, quality of voluntary movement

From American Academy of Pediatrics Committee on Nutrition: Failure to thrive. In Kleinman RE, Greer FR, editors: Pediatric nutrition, *ed 7, Elk Grove Village, IL, 2014, American Academy of Pediatrics, Tab 27-3.*

growth: a child's health and nutritional status, family issues, and the parent–child interaction. An appropriate feeding atmosphere at home is important for all children with FTT.

Indications for hospitalization include severe malnutrition or failure of outpatient management. If a child requiring hospitalization has not responded after 2-3 mo of outpatient management, a specialized, multidisciplinary inpatient assessment should be considered. Inpatient care may include further diagnostic and laboratory evaluation, an assessment and implementation of adequate nutrition, and evaluation of the parent–child feeding interaction.

Children with severe malnutrition must be refed carefully, with an incremental increase in calories to avoid refeeding syndrome (see Chapter 46). The type of caloric supplementation is based on the severity of FTT and the underlying medical condition. The response to feeding depends on the specific diagnosis, medical treatment, and severity of FTT. Minimal catch-up growth should generally be 2-3 times the average weight gain for corrected age. Multivitamin supplementation should be given to all children with FTT to meet the recommended dietary allowance, because these children commonly have iron, zinc, and vitamin D deficiencies, as well as increased micronutrient demands with catch-up growth.

Therapy for the psychosocial factors should be specific for the underlying issue (maternal depression, insufficient funds for food). In addition, parent education should focus on what is normal infant development and correcting any parental misconceptions about feeding and temperament, as well as learning the infant cues for hunger, satiety, and sleep. Some children who develop feeding aversion behaviors will require treatment by a specialized feeding team. If abuse or purposeful neglect is a concern, the family should be referred to the child protective service team.

PROGNOSIS

FTT early in life, regardless of cause, is concerning because maximal postnatal brain growth occurs in the first 6 mo of life. Studies investigating the long-term sequelae of FTT in young infants and children have been conflicting, and there is no clear consensus regarding the long-term emotional, cognitive and metabolic effects. Despite inconclusive long-term outcomes in children who have FTT, investigators support early nutritional interventions for children who have poor growth. Early FTT may be associated with increased risk factors (including dyslipidemia, hypertension, and glucose intolerance) for cardiovascular disease as an adult perhaps relating to epigenetic responses to impaired nutrition and/or inflammation. The growing importance of cardiovascular disease among adults in lower and middle income nations where many children still have inadequate nutrition offers yet another reason why early FTT should be cause for concern globally.

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Chapter 42

Chronic Illness in Childhood

Lisa J. Chamberlain and Paul H. Wise

EPIDEMIOLOGY

Patterns of chronic illness in childhood are complex and dynamic. Serious chronic illness in children is less common than that among adults and widely heterogeneous. These differences have profound implications for the organization of children's health services, as pediatricians have the difficult task of identifying and caring for children with unusual and varied conditions. Child health services have become far more reliant on standardized screening programs and formal systems of referral to regional specialty care programs than are health-care systems for adults. Pediatrics has been characterized by rapid progress in preventing serious acute illnesses and extending the lives of children who previously would have succumbed to their illness early in life. These factors have made the epidemiology of childhood far more dynamic than that of the adult world.

National survey data suggest that 30% of all children have some form of chronic health condition (Table 42-1). If allergies, eczema, minor visual impairments, and other conditions not likely to generate serious consequences are excluded, then between 15% and 20% of all children have a chronic physical, learning, or developmental disorder. Boys have higher rates of chronic illness than do girls. There is considerable variation in the nature and severity of chronic illnesses in children (Table 42-2). The most common serious chronic condition is asthma, with 12% of children having received a diagnosis of asthma at some time in their lives; half of these children were reported to have experienced asthma symptoms in the prior 12 mo (see Chapter 144). Mental health and behavioral conditions represent a large and growing number of children with chronic illness. It has been estimated that almost 21% of U.S. children between 9 and 17 yr of age have a diagnosable mental or addictive disorder associated with some impairment; approximately 11% had significant impairment. Estimates suggest that 5% had major depression (see Chapter 26) and approximately 9.5% have attention-deficit/hyperactivity disorder (see Chapter 33). Overweight is not usually defined as a chronic health condition, but in 2013, the American Medical Association characterized obesity as a disease. In 2010 12% of 2-5 yr olds, 18% of 6-11 yr olds, and nearly 18% of all

Table 42-1 Prevalence and Activity Limitation for Selected Chronic Diseases in Children <18 Yr of Age: United States, 2000-2003

CONDITION	NUMBER (IN THOUSANDS)	PREVALENCE (PER 100,000 CHILDREN)	ACTIVITY LIMITATION* (% OF CHILDREN WITH CONDITION)
Asthma	9,017	12,419	6.9
ADHD/ADD	4,034	6,078	5.5
Developmental delay	2,061	3,145	16.7
Congenital and other heart conditions	957	1,318	9.76
Intellectual disability	447	677	27.7
Cerebral palsy	273	375	36.24
Autism	234	322	18.2
Sickle cell anemia	151	209	23.91
Diabetes	120	166	4.8
Down syndrome	104	141	23.9
Arthritis	73	101	37.11
Muscular dystrophy	35	48	81.3
Cystic fibrosis	29	40	33.9

*Presence of an impairment or health problem that limits the ability to crawl, walk, run, or play. Figures based on weighted and age-adjusted national sample.
ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder.
Data from National Health Interview Survey, 2000-2003. National Center for Health Statistics, Centers for Disease Control and Prevention.

Table 42-2 Quality Measures for Healthcare Received by Children with Special Healthcare Needs by Family Income: United States, 2005-2006 (Percent Meeting Quality Measure)

	MEDICAL PARTNERSHIP AND SATISFACTION WITH SERVICES*	MEDICAL HOME†	ADEQUATE INSURANCE‡	EARLY AND CONTINUOUS SCREENING§	COMMUNITY-BASED SERVICES‖	TRANSITION TO ADULT LIFE¶
<99% FPL	50.0	34.0	56.8	47.7	85.7	24.3
100-199% FPL	52.7	41.3	57.4	56.9	86.7	33.7
200-399% FPL	58.7	51.0	61.8	66.8	90.3	43.5
>399% FPL	64.8	56.2	69.1	76.8	92.0	53.7

*Families of children and youth with special healthcare needs partner in decision-making at all levels and are satisfied with the services they receive.
†Children and youth with special healthcare needs receive coordinated ongoing comprehensive care within a medical home.
‡Families of children with special healthcare needs have adequate private and/or public insurance to pay for the services they need.
§Children are screened early and continuously for special healthcare needs.
‖Community-based services for children and youth with special healthcare needs are organized so families can use them easily.
¶Youth with special healthcare needs receive the services necessary to make transitions to all aspects of adult life, including adult healthcare, work, and independence.
FPL, federal poverty line ($19,350 for family of 4 for the 48 contiguous states and the District of Columbia in 2005).
From U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau: *The national survey of children with special health care needs, chartbook 2005-2006*, Rockville, MD, 2008, U.S. Department of Health and Human Services.

children age 12 through 19 yr have a body mass index above the 95th percentile (see Chapter 47). Comorbid conditions, such as hypertension and a variety of metabolic disorders, may exist.

The severity and impact of chronic illnesses can vary significantly. Approximately 9% of all children have activity limitations as a consequence of 1 or more chronic illnesses, which has been relatively stable since 2001. Of these children, 40% have developmental or learning disorders, 35% have chronic physical conditions, and 25% report chronic mental health disorders. Approximately 2% of children have chronic conditions and activity limitation severe enough to meet eligibility criteria for the Supplemental Security Income program. Between 12% and 18% of all children meet the chronic illness and elevated service needs of the **children with special healthcare needs (CSHCN)** definition, depending on the data set that is examined.

These current prevalence figures represent a substantial increase in childhood chronic illness in the past several decades. In 2009, approximately 9% of children were reported to have a chronic health condition that limited their activities; the comparable figure in 1960 was only 2%. Although the increase in childhood chronic illness is likely partly a result of changes in survey methodologies, improvements in diagnosis, and expanded public awareness of behavioral and developmental disorders, there is strong evidence that the prevalence of certain important chronic child health conditions has increased. Asthma rates rose from <4% in 1980 to 9.5% in 2011, with the highest rates among the poorest children. The prevalence of attention-deficit/hyperactivity disorder and autism (see Chapter 30) has also increased considerably. Although improvements in the survival of infants and young children from prematurity, congenital anomalies, and genetic disorders have also

contributed to the rising prevalence rates, this source accounts for only a small portion of all chronic illness in childhood.

Chronic illness accounts for a growing portion of child healthcare expenditures, serious illness, hospitalizations, and deaths among children in the United States. Across 37 children's hospitals, 19% of admission and 23% of inpatient charges were accounted for by only 3% of patients with frequent recurrent hospitalizations. Children with a chronic illness are hospitalized approximately 4 times more often and spend more than 7 times as many days in the hospital as children without a chronic illness. Estimates suggest that chronic illness accounts for the majority of all nontraumatic hospitalizations for children, a figure that has more than doubled in the past 4 decades, and children with chronic illnesses are experiencing increasing lengths of stay. Multiple admissions in any given year have also risen substantially: a child with a chronic condition is more likely to be readmitted, particularly for children with malignancies and neurologic conditions, although up to 25% of these may be planned admissions. The majority of all non–trauma-related deaths in children are now a result of chronic disorders. This historical shift in the distribution of pediatric hospitalization and mortality reflects not only the rise in the prevalence of childhood chronic illness, but also marked reductions in the incidence of serious acute pediatric illness.

Chronic illness is also contributing more profoundly to **social disparities** in child health. There are somewhat conflicting data on the association of poverty and the prevalence of chronic disorders in children, although most studies suggest a moderate elevation among poor children. Children enrolled in welfare cash assistance programs are more likely to have a chronic illness, and poor and African-American children have greater limitations in activity because of chronic conditions. Latino school-age children have rates of chronic illness that are similar to non-Latino whites; however, there remains little information on the prevalence and impact of chronic illness and its functional impact among the different subgroups of Latino children, as well as subgroups of Asian and Pacific Islanders.

ENHANCED NEEDS OF CHILDREN WITH CHRONIC ILLNESS AND THEIR FAMILIES

Although the nature and severity of chronic illness in children is quite heterogeneous, there are important clinical considerations that are common to virtually all such conditions regardless of their specific diagnosis or specialty group.

Financial Costs

The care required by children with serious chronic illnesses is usually associated with high financial costs. Even though the majority of children with chronic illness have coverage, 38% report being inadequately insured, experiencing gaps in coverage, and having costs or services not covered. Most states have some mechanism to facilitate health insurance coverage for children, although the nature and scope of these programs can vary considerably. A growing number of private and public health insurance plans require deductibles and copayments, which can accumulate rapidly for a child with a chronic illness. Some plans offer coverage up to a designated cost, period of hospitalization, or for a certain number of specialty visits. Once this cap has been reached, a larger portion or all of the costs may be borne by the family. This financial burden has been increasing over time, more so for families with private insurance: 20% of families have out-of-pocket expenses exceeding 10% of the family's income. The Family Opportunity Act of 2005 allows families of children with disabilities who are not financially eligible for Medicaid to buy into the program on a sliding scale. This program was created to fill the gap when children are underinsured because of private insurance limiting essential services, such as durable medical equipment and uncovered prescription drugs. The implementation of this program varies widely by state. The Patient Protection and Affordable Care Act, known colloquially as the ACA or "Obamacare," protects children with serious illness by instituting new insurance industry regulations, ending the practice of denying coverage to individuals with preexisting conditions, and allowing children to remain on their parents' insurance policies to the age of 26 yr.

Of great importance for children with serious chronic disorders, many new procedures, medications, and therapeutic regimens may be considered "experimental" by some insurers and not covered. Insurance coverage policies often generate strong incentives for hospital rather than outpatient care, even if the latter is indicated. Frequent medical visits and hospitalizations can interfere with parental employment and undermine job performance and security.

Complex Clinical Management

Children with serious chronic disorders usually require intense clinical management both in community and hospital settings. Close surveillance of disease progression, symptoms and functioning, and adverse medication effects often necessitate frequent communication and office visits. Managing hospital admissions and discharge planning may also prove complex and involve a variety of clinicians and community resources. As pressure to reduce hospitalization has grown, the burden on outpatient systems has increased accordingly. An uncoordinated approach to the multitude of required clinical visits can prove highly burdensome to the family and can undermine even the most committed family's attempts to comply. New models of care including **accountable care organizations (ACOs)** link care across the continuum, from quaternary to primary care by incentivizing multidisciplinary care teams to manage patients focusing on care coordination and prevention. The ability to capture savings through decreased admissions and emergency department use has been largely derived from the experiences of adult-focused programs; the feasibility and utility of pediatric ACOs, particularly for large populations of poor children, remain unexplored. The impact of ACOs and related financial arrangements on highly regionalized specialty service systems for children is of particular concern.

Pain

Many seriously ill children suffer from chronic pain (rheumatoid arthritis, spastic cerebral palsy), recurrent pain during exacerbations of underlying disease (inflammatory bowel diseases, sickle cell anemia), or acute pain related to procedures, surgeries, or diagnostic tests. This pain can alter a child's affect and influence their academic and social development, while also decreasing the family's quality of life (see Chapter 62). Assessing pain in young children or those with developmental disorders can be difficult and should always consider sociocultural and psychologic factors as well as developmental stage. Because serious, chronic pain is relatively unusual in children, its management may require the involvement of pediatric pain subspecialists who may practice with multidisciplinary teams in regional centers. The emotional toll on parents of children experiencing chronic pain can also be profound and require close attention by medical personnel.

Behavioral and Adjustment Issues

Although chronic illness in children elevates the likelihood that they will experience psychologic and behavioral problems, most children with chronic illness will experience the same level of psychologic and behavioral issues as other children their age. Behavioral and adjustment problems are more likely to occur the earlier the onset of the illness, particularly if it emerges in infancy. The risk of psychologic and behavioral problems does not appear to be associated with the severity of the chronic illness per se. These effects can occur across all diagnoses, although they are more profound for disorders that affect the central nervous system, including cerebral palsy, head trauma, and treatment-related complications that affect the brain, such as chemotherapy for cancer. Children with higher levels of cognitive ability appear to be less likely to develop serious behavioral or adjustment problems. Familial strife and mental illness, particularly depression in the mother, have been associated with an enhanced risk for psychologic and behavioral consequences.

Impact on Families

Like all children, a child with a chronic illness usually brings a mix of challenges and joy to a family. The presence of a chronic illness can add extra burdens, which can be expressed in a variety of forms. First,

the daily requirements of care should never be underestimated, particularly when the child is unable to perform tasks such as bathing, dressing, using the toilet, and feeding. Second, the care required by the child with chronic illness may divert needed attention from siblings and strain normal family dynamics. Third, the ultimate burden faced by families of children with a chronic illness is the emotional toll exacted by the daily struggles, pain, and, occasionally, early death that chronic illness can imply. Fourth, among the most difficult attributes of childhood chronic illness is the inherent unpredictability of its course and ultimate impact. Clinicians should be sensitive to how difficult it can be living with a child whose condition can worsen at any moment and without apparent cause. If conditions worsen to the point where medical care is futile, the evolving field of pediatric palliative care (see Chapter 43) can provide critical medical services and offer comprehensive support for grieving families. Fifth, children with serious chronic illness and their parents may harbor powerful hopes for new breakthroughs or divine intervention. Clinicians should understand the importance of these hopes for the families under their care and should explore related hopes for lesser, more incremental steps, such as attending school, playing sports, or taking a special trip.

Comprehensive Care and the Medical Home

All children require a clinician who takes responsibility for their comprehensive healthcare needs. To meet this responsibility, the coordinated implementation of a series of essential practice components, often termed the **medical home,** is recommended. These services should be provided within a broader system of care that emphasizes partnering in decision making between the family and medical providers, coordination of services among medical and community service providers, adequate health insurance coverage, ongoing screening for special healthcare needs, critical educational and community-based services, and special attention to the needs of older children as they transition to adult life and healthcare systems. Innovative new models are being suggested, including linkages between **community health centers** and academic medical partnerships, which combine the subspecialist expertise, medical technology, and inpatient care of local academic medical centers with the primary care expertise of community health centers, to create a distinctive form of ACO. Evidence suggests that the extent to which these care requirements are being met for families with children with special healthcare needs is highly variable (see Table 42-1) and thus new models are needed. Although essential for all children, these practice elements take on special importance for children with chronic disorders and are outlined as follows.

Preventive Services

Primary, preventive care is an essential component of healthcare for children with chronic disease. Although overall CSHCN use preventive medical and dental services at rates similar to those of other children, primary preventive services can easily be overlooked in addressing the more specialized needs of these patients. The most common unmet healthcare need for CSHCN is dental care. Children with chronic disorders are commonly less-well immunized than their healthy counterparts. Well child care may be disrupted by visits for acute exacerbations of the chronic disorder and clinicians should carefully evaluate whether the chronic illness or its symptoms are contraindications to immunization. A family's reliance on specialty services can be so great that the need for primary care services is overlooked. Special effort may be required to ensure the provision of high-quality primary care to children with chronic illness.

Continuity of Care

Children with chronic illnesses are particularly dependent on a stable, ongoing relationship with clinicians and the healthcare system. The duration and complexity of chronic illness in children require that the clinician responsible for coordinating the child's care have a good understanding of the child's clinical history, including patterns of exacerbation and response to medications and other interventions. Continuity of care also serves as a basis for building trust and effective communication between affected families and clinicians, a prerequisite for high-quality care. Practice structures, therefore, should ensure the identification of a principal clinical provider and facilitate the provider's involvement in all necessary care. Transitioning of care as the child reaches adulthood is also critical, but is not experienced equally across the spectrum of medical need. The greatest difficulty in transitioning care occurs in youth with more complex conditions, those with cognitive impairments, and youth from racial/ethnic minority backgrounds. The transition requires planning, coordination and recognition of the emotional bonds that likely have developed between the child (and the child's family) and the practitioner (see Chapter 112.3).

Access to Urgent Care

Clinicians should expect that children with chronic illness will have enhanced requirements for urgent consultation, emergency care, and hospitalization. Practice mechanisms that ensure rapid access to medical consultation both by telephone and office visitation are essential. Procedures for urgent referral to appropriate facilities for emergency evaluation and hospitalization should also be established. This is particularly important in managed care systems that may require primary care referral or approval for care at referral sites.

Access to Specialty Care

Children with chronic illness commonly require specialized care. The need for specialty referral is particularly important in pediatrics because serious disorders are relatively rare in children. In many countries, including the United States, there is a shortage of many pediatric subspecialists. The ACA includes provisions to encourage pediatric residents to pursue pediatric subspecialty training. Regional systems of specialty referral and hospitalization have been formalized in the past several decades, particularly for perinatal care, pediatric trauma, and children with serious chronic illness. These systems of "regionalized" specialty care have been shown to reduce dramatically morbidity and mortality among affected children. It is crucial that policymakers who develop and implement health insurance products through new marketplaces or exchanges understand the need to include access to children's hospitals and pediatric subspecialists for children with special healthcare needs. Pediatricians can play a crucial role in conveying to policymakers the special dependence of modern pediatrics on established regionalized systems of care. Regionalized care heavily relies on specialty care referrals, responsive communication between primary care practices and specialty programs is essential, particularly in conveying the reasons for referral, patient history, the nature and findings of the specialty evaluation, hospital course, and the collaborative development of a follow-up management plan.

Enhanced Information Systems

Children with chronic illness often require careful monitoring of their clinical status and the rapid evaluation of exacerbations. On-call and related coverage systems must include immediate access to up-to-date medical record information for children with complex histories and management regimens. Electronic medical records and systems that permit parent or other caretakers routine access to computerized medical record information may also prove useful. Access to current medical information, laboratory results, as well as clinical protocols and decision support algorithms could prove particularly helpful for children with complex healthcare requirements.

Linkage to Schools, Support Groups, and Community Services

Children with chronic illnesses often have special educational needs and may require the active participation of teachers and school health personnel in medical care plans. An important first step in creating a care plan is to assess the level of medical expertise available at the school site because many schools no longer have a nurse present. Special mechanisms should be established to ensure close coordination with schools, including provisions for collaborative evaluations of needs, monitoring of educational performance and social interactions, and the ongoing refinement of medical and educational management

regimens. Clinicians can prevent the isolation many families feel by connecting them to support and advocacy groups composed of other parents with similarly affected children. Such connections have been facilitated by use of the Internet, which can link children and families over wide geographic areas.

Logistic Access

The difficulties that families can experience in transporting children with serious physical or behavioral disorders should never be underestimated. Particularly for older children or those requiring wheelchairs or other equipment, urban public transportation systems may be seriously impractical. In suburban and rural areas, transportation may involve traveling over great distances. For parents who have daytime employment, extended clinic hours may be required. Many communities have implemented innovative transportation programs for families in need of health and social services, particularly when available means of travel to clinical facilities is deemed unsafe or if it requires specially equipped vehicles or the assistance of trained personnel. In a growing number of areas, a variety of forms of telemedicine have enhanced access to medical and particularly, specialty care consultation.

Cultural Sensitivity and Language Concordance

See also Chapter 4.

Clinicians must possess a basic understanding of the meaning of illness and traditions of healing in the communities they serve. Cultural competency education is a required component of pediatric residency training, empowering a new generation of pediatricians with tools needed to bridge cultural divides. Although such cultural competence of individual providers is important, access also depends on creating clinical programs that respond to local perceptions and social institutions. Cultural competence not only reduces the likelihood of misunderstandings and medical errors, but also helps ensure that clinical programs can take full advantage of the many strengths that exist in culturally defined communities.

The most basic element of communication between clinicians and families of children with a chronic illness is that they share a common language. Clinicians should not overestimate their own or a parent's basic command of a language and must ensure that conveyed information is well understood. Children should not be used as interpreters despite the fact that they often have a better command of English than do their parents. Given the complex issues chronic illness can generate, it is far more useful to integrate trained interpreters into programs for chronically ill children in locations characterized by diverse language groups.

Nondiscrimination in Access and Clinical Decision Making

Clinicians who care for children with chronic illness must recognize the power of social status to define access to care. A history of inadequate service provision or different levels of service for distinct social groups can generate deep resentment and distrust for the medical system. **Family centered care**, defined in 1987 and incorporated into The Maternal and Child Health Bureau's core objectives, includes principles that build on family strengths, honor diversity, and emphasize the centrality of community-based services among others. Many studies have suggested that even when patients have adequate health insurance, poor and minority patients are less likely to be offered recommended diagnostic and therapeutic interventions. Although the precise reasons for these observations remain unclear, it is important that provider preconceptions do not replace a careful consideration of the true desires and capabilities of families, particularly in association with new, specialized, or home-based interventions. Strategies to confront these issues include implementing a family centered care approach training and recruitment of minority health providers, educational programs for clinicians, and the active assessment of clinical decision-making and family experiences at clinical facilities.

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Chapter 43

Pediatric Palliative Care

Christina Ullrich, Janet Duncan, Marsha Joselow, and Joanne Wolfe

The World Health Organization defines palliative care for children as "…the active total care of the child's body, mind and spirit, and also involves giving support to the family.…Optimally, this care begins when a life-threatening illness or condition is diagnosed and continues regardless of whether or not a child receives treatment directed at the underlying illness." Provision of palliative care applies to children with a range of acute and chronic diseases, both life-threatening and life-altering, including, but not limited to, cancer, mitochondrial disorders, cardiac disease, neurodegenerative diseases, and trauma with life-threatening sequelae (Table 43-1). In fact, medical and technological advances have resulted in children living longer, often with significant dependence on new and complex technologies. These children have complex chronic conditions across the spectrum of congenital and acquired life-threatening disorders (see Chapter 42). Children with complex chronic conditions benefit from integration of palliative care strategies. These children, who often survive near-death crises followed by the renewed need for rehabilitative and life-prolonging treatments, are best served by a system that is flexible and responsive to changing needs.

Table 43-1 Conditions Appropriate for Pediatric Palliative Care

CONDITIONS FOR WHICH CURATIVE TREATMENT IS POSSIBLE BUT MAY NOT SUCCEED
Advanced or progressive cancer or cancer with a poor prognosis
Complex and severe congenital or acquired heart disease
CONDITIONS FOR WHICH THERE IS INTENSIVE LONG-TERM TREATMENT AIMED AT PROLONGING LIFE AND MAINTAINING QUALITY OF LIFE BUT PREMATURE DEATH IS STILL POSSIBLE
Human immunodeficiency virus infection
Cystic fibrosis
Severe immunodeficiency
High-risk solid-organ transplant candidates and/or recipients such as lung or multivisceral
Chronic or severe respiratory failure
Muscular dystrophy
Primary pulmonary hypertension
PROGRESSIVE CONDITIONS FOR WHICH THERE IS NO CURATIVE OPTION AND IN WHICH TREATMENT IS ALMOST EXCLUSIVELY PALLIATIVE AFTER DIAGNOSIS
Progressive metabolic disorders (e.g. mucopolysaccharidosis, Tay Sachs)
Batten disease
Severe forms of osteogenesis imperfecta
CONDITIONS INVOLVING SEVERE, NONPROGRESSIVE DISABILITY, CAUSING EXTREME VULNERABILITY TO HEALTH COMPLICATIONS
Severe cerebral palsy with recurrent infection or difficult-to-control symptoms
Severe neurologic sequelae of infectious disease
Hypoxic or anoxic brain injury
Brain malformations such as holoprosencephaly or lissencephaly

Adapted from The Together for Short Lives (formerly the Association for Children's Palliative Care [ACT]) Life-limiting/Life-threatening Condition Categories available at http://www.togetherforshortlives.org.uk/professionals/childrens_palliative_care_essentials/approach

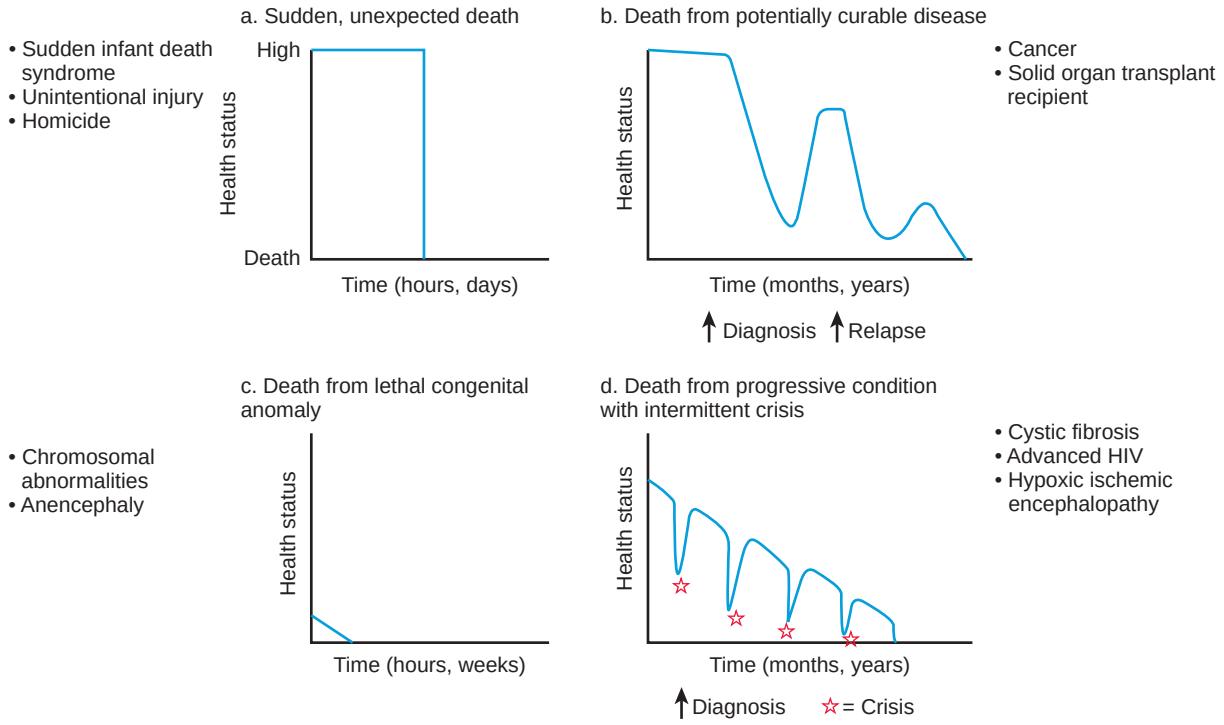

Figure 43-1 **Typical illness trajectories for children with life-threatening illness.** *(From Field M, Behrman R, editors:* When children die: improving palliative and end-of-life care for children and their families, *Washington, DC, 2003, National Academies Press, p. 74, Fig 3.1.)*

Although palliative care is often mistakenly understood as equivalent to end-of-life care, its scope and potential benefit extend before and well after end-of-life and is *applicable throughout the illness trajectory*. Palliative care emphasizes optimization of quality of life, communication, and symptom control, aims that may be congruent with maximal treatment aimed at sustaining life.

The mandate of the pediatrician and other pediatric clinicians to attend to children's physical, mental, and emotional health and development includes the provision of palliative care for those children who live with a significant possibility of death before adulthood (Fig. 43-1). Such comprehensive physical, psychological, social, and spiritual care requires an interdisciplinary approach. This is often possible with creative use of professional hospital and community-based providers.

In the United States, the healthcare and reimbursement structure combined with frequent use of medical technology (e.g., home ventilatory support) or continuous home nursing historically precluded formal enrollment of children on the hospice benefit when they were otherwise eligible (i.e., had an estimated prognosis of 6 mo or less). Section 2302 of the Patient Protection and Affordable Care Act, termed the **concurrent care for children requirement** eliminated the requirement that Medicaid patients <21 yr of age forgo curative or life-prolonging therapies to be eligible for hospice. Although Medicaid programs in every state are now required to provide concurrent curative/life-prolonging treatment and hospice services for hospice-eligible children, development of systems to make such concurrent care a reality has been slow. A limitation of the concurrent care for children requirement is that it does not expand access to hospice for children with life-threatening illness who do not meet hospice eligibility criteria (i.e., have a prognosis that cannot be estimated to be <6 mo). A number of state-based pediatric palliative care coalitions have formed in recent years to improve access to home-based pediatric hospice/palliative care services, using strategies such as Medicaid waivers or state plan amendments to increase coverage for hospice services. A growing number of home care agencies have also developed palliative care programs that serve as a bridge to hospice services for children not yet meeting hospice eligibility criteria. Provision of hospice or palliative care for children is often also limited by the availability of clinicians who have training or experience in caring for seriously ill children.

CARE SETTINGS

Pediatric palliative care should be provided across settings, including the hospital, outpatient settings, the home, pediatric nursing facilities, and inpatient hospice houses. **Home care** for the child with a life-threatening illness requires 24 hr per day access to experts in pediatric palliative care, a team approach, and an identified coordinator who serves as a link between hospitals, the community, and specialists and who may assist in preventing and/or arranging for hospital admissions, respite care, and increased home care support as needed. Adequate home care support and respite care, though very important, are often not readily available or families may feel using respite care is a personal failure, or they may worry that others cannot adequately care for their child's special needs.

At the end of life, children and families may need intensive support. About half of pediatric deaths occur in acute-care hospitals, and end-of-life care may thus be provided in the home, hospital, pediatric nursing facility or hospice house. Families need to feel safe and well cared for and given permission, if possible, to choose location of care. In tertiary care hospitals, most children die in the neonatal and pediatric ICUs. The philosophy of palliative care can be successfully integrated into a hospital setting, including the ICU, when the focus of care also includes the prevention or amelioration of suffering and improving comfort and quality of life. All interventions that affect the child and family need to be assessed in relationship to these goals. This proactive approach asks the question, "What can we offer that will improve the quality of this child's life and provide the most meaning and control for their family?" instead of, "What therapies are we no longer going to offer this patient?" Staff may benefit from education, support, and guidance as pediatric palliative care, like other types of intensive care, is an area of specialty. Regardless of the care setting, comprehensive palliative care requires an interdisciplinary approach that may include nurses, physicians, psychologists, psychiatrists, social workers, chaplains/clergy, child-life specialists, and trained volunteers.

PRIMARY AND SUBSPECIALTY PALLIATIVE CARE

Not all children with serious illness require care by a hospice and palliative medicine subspecialist or pediatric palliative care team. Basic palliative care knowledge, skills, and behaviors should be known to all clinicians who care for children with life-threatening illnesses and conditions. The role of the Hospice and Palliative Medicine subspecialist and team is to provide clinical consultation for more complex situations, to provide education and training, and to improve palliative care outcomes for all children and families through quality improvement and research.

COMMUNICATION, ADVANCE CARE PLANNING, AND ANTICIPATORY GUIDANCE

Although accurate prognostication is a particular challenge in pediatrics, the medical team often recognizes a terminal prognosis before the prognosis is understood by parents. This time delay may impede informed decision making about how the child lives at the end of life. Given the inherent prognostic uncertainty of a life-threatening diagnosis, discussions concerning resuscitation, symptom control, and end-of-life care planning should be initiated when the physician recognizes that a significant possibility of patient mortality exists. Having these conversations in the midst of a crisis is not ideal. Whenever possible, they should occur well in advance of the crisis or when the patient has recovered from a crisis, but is at high risk for others.

Patients and families are most comfortable being cared for by physicians and other care providers with whom they have an established relationship. Even in the face of long-standing and highly connected relationships, *clinicians often hold assumptions about parent prognostic awareness, and parent readiness and willingness to have such discussions*. In an attempt to protect families, clinicians may avoid conversations that they perceive as promoting hopelessness. However, parents greatly value honesty, and such conversations can promote parent hopefulness. A consultative palliative care team may provide the family with an opportunity to engage in sensitive conversations that are not as comfortably initiated with the primary team.

The population of children who die before reaching adulthood includes a disproportionate number of nonverbal and preverbal children who are developmentally unable to make autonomous care decisions. Although parents are usually the primary decision-makers, children should be as fully involved in discussions and decisions about their care as appropriate for their developmental status. Utilizing communication experts, child-life therapists, chaplains, social workers, psychologists, or psychiatrists to allow children to express themselves through art, play, music, talk, and writing will enhance the provider's knowledge of the child's understanding and hopes. Tools such as "Five Wishes" (for adults), "Voicing My Choices" (for adolescents), and "My Wishes" (for school-age children), have been useful in helping to gently introduce advance care planning to children, adolescents, and their families (http://www.agingwithdignity.org/index.php).

The Parents

From a parent's perspective, compassionate communication with medical providers who understand their child's illness, treatment options, and family beliefs and goals is the cornerstone of caring for children with life-threatening illness. During this period of time, one of the most significant relationships is that with the child's pediatrician, who often has an enduring relationship with the child and family, including healthy siblings. Parents need to know that their child's pediatrician will not abandon them as the goals of care evolve. A family's goals may change with the child's evolving clinical condition and other variable factors. A flexible approach rooted in ongoing communication and guidance that incorporates understanding of the family's values, goals, and religious, cultural, spiritual, and personal beliefs is of paramount importance.

Pediatricians should recognize the important role they have in continuing to care for the child and family as the primary goal of treatment may simultaneously be prolongation of life and comfort, relief of suffering, and promoting quality of life. Regular meetings between caregivers and the family are essential in order to reassess and manage symptoms, explore the impact of illness on immediate family members, and provide anticipatory guidance. At these meetings, important issues with lifelong implications for parents and their child may be discussed. Such discussions should be planned with care, ensuring that adequate time for in-depth conversation is allotted; a private, physical setting is arranged; devices silenced; and that both parents and/or others who might be identified by the family as primary supports are present. Strategies for facilitating conversations related to goals of care and decision-making are detailed below.

Families may look to their pediatrician for assurance that all treatment options have been explored. Assisting a patient's family to arrange a second opinion may be helpful. Listening to families and children speak about the future even in the face of poor prognosis may help keep the focus on living even while the child may be dying. Hoping for a miracle can coexist for parents even as they are facing and accepting the more likely reality of death.

Parents also need to know about the availability of home care, respite services, web-based support educational materials other media, and support groups. Responding to parent requests or need for counseling referrals for themselves, other children, or family is essential. Attending to the concrete needs of families such as financial, insurance and housing needs can be paramount in freeing them of worries that might interfere or compete with their ability to be fully present in their child's care.

When closer to end of life, while broaching the topic may seem daunting, exploration of how parents envision their child's death, addressing their previous loss experiences (most often with death of an adult relative) and any misconceptions they may have, is often a great relief to parents. Learning about cultural, spiritual, and family values regarding pain management, suffering, and the preferred place of end-of-life care is essential before death. Even raising thoughts about funeral arrangements, the possibility of autopsy, and organ/tissue donation can be helpful to give parents choices and know that these considerations can be discussed without fear.

A major worry of many parents is in how to involve and communicate with siblings as well as the child about the fact that most likely death is going to occur. Evidence shows that parents who have open conversations with their child about death and dying do not regret having done so. Clear communication around end-of-life issues, delivered with sensitivity and caring are directly correlated with ratings of high satisfaction with physician care. Such communication includes speaking directly to the child when appropriate. Communication is complicated by an assumed need for mutual protection in which the child wants to protect his or her parents and likewise the parents want to protect their child from painful information or sadness. Honoring the uniqueness of the child as well as understanding and respecting the family's communication style, values, spirituality, and culture, is critical in these highly sensitive conversations.

In communications with the child and family, the physician should avoid giving specific estimates of survival length, even when the child or family explicitly asks for them. These predictions are invariably inaccurate because population-based statistics do not predict the course for individual patients. A more honest approach may be to *explore ranges of time in general terms* ("weeks to months," "months to years"). The physician can also ask parents what they might do differently if they knew how long their child would live and then assist them in thinking through the options relating to their specific concerns (suggest celebrating upcoming holidays/important events earlier in order to take advantage of times when the child may be feeling better). It is generally wise to suggest that relatives who wish to visit might do so earlier rather than later, given the unpredictable trajectory of many conditions.

For the child and family, the integration of bad news is a process, not an event, and when done sensitively does not take away hope or alter the relationship between the family and physician. The physician should expect that some issues previously discussed may not be fully resolved for the child and parents (do-not-resuscitate [DNR] orders, artificial nutrition or hydration) and may need to be revisited over

time. Parents of a child with chronic illness may reject the reality of an impending death because past predictions may not have been accurate. Whether they are parents of a child with a chronic illness or of a child whose death is the result of accident or sudden catastrophic illness, they may experience great anxiety, guilt, or despair.

The Child

Truthful communication that takes into account the child's developmental stage and unique lived experience can help to address the fear and anxiety commonly experienced among children with life-threatening illness. Responding in a developmentally appropriate fashion (Table 43-2) to a child's questions about death, such as "What's happening to me?" or "Am I dying?" requires a careful exploration of what is already known by the child, what is really being asked (the question behind the question), and why the question is being asked at this particular time and in this setting. It may signal a need to be with someone who is comfortable listening to such unanswerable questions. Many children find nonverbal expression much easier than talking; art, play therapy, and storytelling may be more helpful than direct conversation.

A child's perception of death depends on the child's conceptual understanding of *universality* (that all things inevitably die), *irreversibility* (that dead people cannot come back to life), *nonfunctionality* (that being dead means that all biologic functions cease), and *causality* (that there are objective causes of death).

Very young children may struggle with the concepts of irreversibility and nonfunctionality. For young, school-age children, who are beginning to understand the finality of death, worries may include magical thinking in which their thoughts, wishes, or bad behavior might be the underlying cause for their illness. Older children seek more factual information to gain some control over the situation.

Table 43-2 Developmental Questions, Thoughts, and Concepts of Dying and with Responsive Strategies

TYPICAL QUESTIONS AND STATEMENTS ABOUT DYING	THOUGHTS THAT GUIDE BEHAVIOR	DEVELOPMENTAL UNDERSTANDING OF DEATH	STRATEGIES AND RESPONSES
MONTHS-3 YR *"Mommy, don't cry."* *"Daddy, will you still tickle me when I'm dead?"*	Limited understanding of events, future and past, and of the difference between living and nonliving.	May have "sense" that something is wrong. Death is often viewed as continuous with life (analogous to being awake and being asleep).	Optimize comfort, and consistency; familiar persons, objects, routines. Use soothing songs, words, and touch. *"I will always love you."* *"I will always take care of you."* *"I will tickle you forever."*
3-5 YR *"I did something bad and so I will die."* *"Can I eat anything I want in heaven?"*	Concepts are simple and reversible. Variations between reality and fantasy.	The child may see death as temporary and reversible, and not universal. May feel responsible for illness. Death may be perceived as an external force that can get you.	Assure child that illness is not the child's fault. Provide consistent caregivers. Promote honest simple language. Use books to explain the life cycle and promote questions and answers. *"You did not do anything to cause this."* *"You are so special to us and we will always love you."* *"We know (God, Jesus, Grandma, Grandpa) are waiting to see you."*
5-10 YR *"How will I die?"* *"Will it hurt?"* *"Is dying scary?"*	The child begins to demonstrate organized, logical thought. Thinking becomes less esoteric. The child begins to problem solve concretely, reason logically, and organize thoughts coherently. However, the child has limited abstract reasoning.	The child begins to understand death as real and permanent. Death means that your heart stops, your blood does not circulate, and you do not breathe. It may be viewed as a violent event. The child may not accept death could happen to himself or herself or anyone the child knows, but starts to realize that people the child knows will die.	Be honest and provide specific details if they are requested. Help and support the child's need for control. Permit and encourage the child's participation in decision making. *"We will work together to help you feel comfortable. It is very important that you let us know how you are feeling and what you need. We will always be with you so that you do not need to be afraid."*
10-18 YR *"I'm afraid if I die my mom will just break down."* *"I'm too young to die. I want to get married and have children."* *"Why is God letting this happen?"*	Abstract thoughts and logic possible. Body image is important. Need peer relationships for support and for validation. Altruistic values • staying alive for family • parents, siblings • donating organs/tissue Disbelief that he/she is dying.	Understand death as irreversible, inevitable and universal. Needs reassurance of continued care and love. Search for meaning and purpose of life.	Reinforce child/adolescent's self-esteem, sense of worth, and self-respect. Allow need for privacy, independence, access to friends and peers. Tolerate expression of strong emotions and permit participation in decision making. *"I can't imagine how you must be feeling. Despite it all, you are doing an incredible job. I wonder how I can help?"* *"What's most important to you now?"* *"What are your hopes…your worries?"* *"You have taught me so much, I will always remember you."*

Adapted from Hurwitz C, Duncan J, Wolfe J: Caring for the child with cancer at the close of life, *JAMA* 292:2141-2149, 2003.

Children's fears of death are often centered on the concrete fear of being separated from parents and other loved ones and what will happen to their parents rather than themselves. This can be true for teens and young adults as well. This fear may be responded to in different ways: some families may give reassurance that loving relatives will be waiting, while others use religious figures to refer to an eternal spiritual connection.

Even though adolescents may have a conceptual understanding of death similar to that of adults, working with the adolescent with life-threatening illness presents unique concerns and issues. The developmental work of adolescence includes separating from their parents, developing strong peer relationships, and moving towards independent adulthood. For this particular population, the teenager's developmental need to separate is complicated by the often increasing dependence both physically and emotionally on the teenager's parents. At the same time, adolescents are often asked to be part of the decision-making process without always having the emotional experience to fully understand the impact.

In addition to developmental considerations, understanding related to the child's life experiences, the length of the child's illness, the understanding of the nature and prognosis of the illness, the child's role in the family (peacemaker, clown, troublemaker, the "good" child) should be considered in communication with children.

Parents have an instinctive and strong desire to protect their children from harm. When facing the death of their child, many parents attempt to keep the reality of impending death hidden from their child with the hope that the child can be "protected" from the harsh reality. Although it is important to respect parental wishes, it is also true that most children already have a sense of what is happening to their bodies even when it has been purposely left unspoken. Children may blame themselves for their illness and the hardships that it causes for their loved ones. Perpetuating the myth that "everything is going to be all right" takes away the chance to explore fears and provide reassurance. Honest communication also allows opportunities for memory and legacy making and saying goodbye.

School is the "work" of childhood and is important in optimizing quality of life for a child seeking "normalcy" in the face of illness. Finding ways to help children and their families to maintain these connections through modification of the school day and exploring options to promote educational and social connections into the home or into the hospital room can be meaningful in the event that a child is not well enough to attend school. Video conferencing can readily be arranged from almost any setting. As with the younger child, finding ways to help the adolescent maintain peer relationships and school based programming can be important in maximizing quality of life.

The Siblings

Brothers and sisters are at special risk both during their sibling's illness and after the death. Because of the extraordinary demands placed on parents to meet the needs of their ill child and their own needs, healthy siblings may feel that their own needs are not being acknowledged or fulfilled. These feelings of neglect may then trigger guilt about their own good health and resentment toward their parents and ill sibling. Younger siblings may react to the stress by becoming seemingly oblivious to the turmoil around them. Some younger siblings may feel guilty as a result of "wishing" the affected child would die so they could get their parents back; preschool children may believe that their wishes caused the death of their sibling ("magical thinking"; see Chapter 7). Parents need to know that these are normal responses, and siblings should be encouraged to maintain the typical routines of daily living. Siblings who are most involved with their sick brothers or sisters before death usually adjust better both at the time of and after the death. Acknowledging and validating sibling feelings, being honest and open, and appropriately involving them in the life of their sick sibling provide a good foundation for the grief process. It is often helpful to identify a person in the family (such as a loving aunt) or school (such as a counselor) to offer confidential and supportive opportunities for the sibling to reflect on their family experience.

The Staff

Adequate support for the staff providing palliative care is necessary to prevent depression, emotional withdrawal, and/or other symptoms. Offering educational opportunities and emotional support for staff at various stages of caring for a child with life-threatening illness can be helpful in bettering patient/family care and preventing staff from experiencing compassion fatigue, burn out and long-term repercussions, including the possibility of leaving the field.

Goals of Care and Decision Making

In the course of a child's life-limiting illness, a series of important decisions may arise in relation to location of care, medications with risks and benefits, not starting and or discontinuing life-prolonging treatments, experimental treatments in research protocols, and the use of integrative therapies (see Chapters 3 and 64). Such family decisions are greatly facilitated by opportunities for in-depth and guided discussions around **goals of care** for their child. This is often accomplished by eliciting parent (and child) understanding of the child's condition and asking open-ended questions that explore the parent's and child's hopes, worries, and family values. Goals of care conversations include what is most important for them as a family, considerations of their child's clinical condition, and their values and beliefs, including cultural, religious, and spiritual considerations. Table 43-3 lists specific questions that can effectively guide these discussions. The conversation should also include a review of previous discussions, active listening to concerns and issues as they are raised, opportunities to repeat back elements of the discussion to ensure clarity, and provision of honest, factual answers even in areas of uncertainty.

Decision making should be focused on the goals of care, as opposed to limitations of care; "This is what we can offer" instead of "There is nothing more we can do." Instead of meeting specifically to discuss "withdrawing support" or a DNR order, a more general discussion centered on the goals of care will naturally lead to considering which interventions are in the **child's best interests and can present an opportunity for the clinicians to make recommendations based on these goals.** By offering medical recommendations based on family goals and the clinical reality, the team can decrease the burden of responsibility for decision making that parents carry.

Resuscitation Status

The legal mandate requiring attempted resuscitation for cardiorespiratory arrest unless a written DNR order is in place is a complex and confusing concept for many parents. In broaching this topic, rather than asking parents if they want to forgo cardiopulmonary resuscitation for their child (and placing the full burden of decision making on them), it is preferable to discuss whether or not resuscitative interventions are likely to benefit the child. *It is important to make recommendations based on overall goals of care and medical knowledge of potential benefit and/or harm of these interventions.* Once the goals of therapy are agreed upon, the physician is required to write a formal order. Out-of-hospital DNR verification forms are available in many states, which, if completed on behalf of the child, affirm that rather than initiating resuscitative efforts, emergency response teams are obligated to provide comfort measures when called to the scene. Some states have implemented the **physician orders for life-sustaining treatment (POLST)** system. A POLST order is completed for children with life-threatening illness, translating the expressed wishes of the parents (and

Table 43-3 Five Basic Questions to Guide Goals of Care Conversation

Tell us about your child as a person; what does your child enjoy?
What is your understanding of your child's illness/condition?
In light of your understanding, what is most important to you regarding your child's care?
What are you hoping for? What are your worries?
In the face of your child's illness/condition, what gives you strength?

in some cases, of the child) into actionable orders (www.polst.org). It may also be beneficial to write a letter delineating decisions regarding resuscitation interventions and supportive care measures to be undertaken for the child, particularly if POLST are not available. The letter should be as detailed as possible, including recommendations for comfort medications and contact information for caregivers best known to the patient. Such a letter, given to the parents, with copies to involved caregivers and institutions, can be a useful communication aid, especially in times of crisis. If a child may die in the home setting, and the parents opt to use on out-of-hospital DNR verification form or POLST, plans to pronounce the child and provide support for the family must be in place. If the child has been referred to hospice, the hospice personnel usually fulfill those responsibilities.

Conflicts in decision making can occur within families, within healthcare teams, between the child and family, and between the family and professional caregivers. For children who are developmentally unable to provide guidance in decision making (neonates, very young children, or children with cognitive impairment), parents and healthcare professionals may come to different conclusions as to what is in the child's best interests. Given the shifting boundary that separates childhood from adulthood, decision making around the care of adolescents presents specific challenges. In some families and cultures, truth telling and autonomy are secondary to maintaining the integrity of the family. (see Chapter 4). Although frequently encountered, differences in opinion are often manageable for all involved when lines of communication are kept open, team and family meetings are held, and the goals of care are clear.

Symptom Management

Intensive symptom management is another cornerstone of pediatric palliative care. Alleviation of symptoms reduces suffering of the child and family, and allows them to focus on other concerns and participate in meaningful experiences. Despite increasing attention to symptoms, and pharmacologic and technical advances in medicine, children often suffer from multiple symptoms. Table 43-4 lists key elements and general approaches to managing symptoms.

Pain is a complex sensation triggered by actual or potential tissue damage and influenced by cognitive, behavioral, emotional, social, and cultural factors. Effective pain relief is essential to prevent central sensitization, a central hyperexcitation response that may lead to escalating pain, and to diminish a stress response that may have a variety of physiologic effects. Assessment tools include self-report tools for children who are able to communicate their pain verbally, as well as tools based on behavioral cues for children who are unable to do so because of developmental delays, medical conditions or cognitive limitations. Tables 43-5 to 43-7 address management of pain (see Chapter 62).

Table 43-4 Key Elements of Effective Symptom Management

Establish and periodically revisit goals of care and ensure that goals are communicated to entire care team.
Anticipate and plan for symptoms before they occur.
Assess the child for symptoms regularly, using consistent and developmentally appropriate assessment tools.
- Utilize self-report, if the child is able to reliably report symptoms.
- Evaluate all aspects of the symptom, including quality, frequency, duration, and intensity.

Consider the holistic nature of symptoms.
- Explore the meaning that symptoms may have for families in their social, cultural, religious context.
- Assess distress caused by the symptom.
- Evaluate the degree of functional impairment from the symptom.

Understand the pathophysiology of the symptom and establish a complete differential diagnosis.
Treat the underlying cause if possible, weighing benefits and risks, in the context of goals of care.
Choose the least-invasive route for medications—by mouth whenever possible.
Prescribe regular medications for constant symptoms, and consider prn doses for breakthrough or uncontrolled symptoms.
Consider both pharmacologic and nonpharmacologic approaches.
Reassess the symptom and response to interventions regularly.
- For refractory symptoms, revisit the differential diagnosis and review potentially contributing factors.
- Effective interventions relieve the symptom and reduce distress and functional impairment.

Partner with families to identify and address any barriers to optimal control of symptoms.
Address spiritual, emotional, and existential suffering in addition to physical suffering as these are often interrelated.

Table 43-5 Guidelines for Pain Management

Utilize nonopioid analgesics as monotherapy for mild pain and together with opioids for more severe pain.
- Nonopioid analgesics include acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), salicylates, and selective cyclooxygenase (COX-2) inhibitors.

For moderate or severe pain, start with a short-acting opioid at regular intervals.
- When dose requirements have stabilized, consider converting opioid to a long-acting formulation with doses available for breakthrough or uncontrolled pain, as needed.
- For uncontrolled pain, increase opioid dose by 30-50%; for severe pain increase by 50-100%.
- Avoid codeine and opioids with mixed agonist activity (e.g., butorphanol, pentazocine).

Administer medications via the simplest, most effective, and least-distressing route.
Dispel the myth that strong medications should be saved for extreme situations or the very end of life.
- Opioids do not have a "ceiling effect," and escalating symptoms may be treated with an increase in dose.

Clarify for families the differences between tolerance, physical dependence, and addiction.
Anticipate and treat/prevent common analgesic side effects (gastritis with NSAIDs; constipation, pruritus, nausea, sedation with opioids).
- Always initiate a bowel regimen to prevent constipation when starting opioids.
- Consider a stimulant for opioid-induced somnolence.
- Pruritus rarely indicates a true allergy. If not responsive to an antihistamine, consider low-dose naloxone or switching opioids.
- Consider switching to a different opioid for intolerable side effects or neurotoxicity (e.g., myoclonus).
- Use an equianalgesic conversion table when switching opioids, and account for incomplete cross-tolerance.

Consider the use of adjuvant drugs for specific pain syndromes, and for their opioid-sparing effect:
- Antidepressants (e.g., amitriptyline, nortriptyline) and anticonvulsants (e.g., gabapentin, carbamazepine, topiramate) for neuropathic pain.
- Steroids or NSAIDs for bone pain.
- Sedatives and hypnotics for anxiety and muscle spasm.
- To enhance analgesia from opioids, consider clonidine or ketamine.
  - Use topical local anesthetics (lidocaine, prilocaine, bupivacaine) when possible.
  - Consider anesthetic blocks for regional pain.
  - Consider palliative radiation therapy.
  - Consider psychological approaches (e.g., cognitive or behavioral therapy) and integrative therapies (e.g., acupuncture, massage).

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pain—mild	Acetaminophen	15 mg/kg po q 4 hr, max 4 g/day	Available po (including liquid), pr, IV
	Ibuprofen	10 mg/kg po q 6 hr	PO (including liquid) only; avoid if risk of bleeding; use only in infants ≥6 mo. Use with caution in congestive heart failure. Chewable tablets contain phenylalanine
	Trilisate	10-15 mg/kg po tid	Trilisate may have less antiplatelet activity and therefore pose less risk for bleeding than other salicylates. Salicylates, however, have been associated with Reye syndrome in children <2 yr
Pain—moderate/severe	Morphine immediate release (i.e., MSIR)	0.3 mg/kg po q 4 hr if <50 kg; 5-10 mg po q 4 hr*†	Also available in IV/SQ formulation‡§
	Oxycodone	0.1 mg/kg po q 4 hr if <50 kg; 5-10 mg po q 4 hr if >50 kg*†	No injectable formulation‡§
	Hydromorphone	0.05 mg/kg po q 4 hr if <50 kg; 1-2 mg po q 4 hr if >50 kg*†	Also available in IV/SQ formulation. Injectable form very concentrated, facilitating subcutaneous delivery‡§
	Fentanyl	0.5-1.5 μg/kg IV/SQ q 30 min*†	Rapid infusion may cause chest wall rigidity‡§
	Methadone	Starting dose 0.1-0.2 mg/kg po bid. May give tid if needed. Recommend consultation with experienced clinician for equivalence dosing from other opioids.*†	Only opioid with immediate and prolonged effect available as a liquid; do not adjust dose more often than every 72 hr as prolonged biologic half-life > than therapeutic half-life. Knowledge of the pharmacokinetics of methadone is needed for converting to and from doses of other opioids. Also available IV/SQ. May cause QT interval prolongation (consider ECG), especially in adults on >200 mg/day or in those at risk for QT prolongation. Interacts with several antiretrovirals§
Pain—sustained release	MS Contin	Total daily dose of MSIR divided bid-tid	Do not crush MS Contin. For those unable to swallow pills, Kadian and Avinza capsules may be opened and contents mixed with food but *cannot be chewed*. Kadian contents may be mixed in 10 mL water and given via 16-French G-tube. Avoid alcohol with Avinza. Larger dose formulation may not be suitable for small children§
	Kadian (contains sustained-release pellets), Avinza (contains immediate and extended release beads)		
	Oramorph		
	OxyContin	Total daily dose of oxycodone divided bid-tid	Do not crush§
	Transdermal fentanyl patch	Divide 24-hr po morphine dose by 2 to determine starting dose of transdermal fentanyl. There is no data on the equianalgesic conversion from transdermal fentanyl to any oral opioid	Smallest patch size may be too high for small children. For children >2 yr. Apply to upper back in young children. Patch may not be cut. Typically for patients on at least 60 mg morphine/day or its equivalent. Not appropriate when dosage changes are frequent or for opioid-naïve patients. Fever >40°C results in higher serum concentrations§
Pain—neuropathic	Nortriptyline	0.5 mg/kg po at bedtime to maximum of 150 mg/day	Fewer anticholinergic side effects than amitriptyline. May cause constipation, sedation, postural hypotension, dry mouth. May cause QT interval prolongation (consider ECG). At higher doses monitor ECG and plasma levels
	Gabapentin	Start at 5 mg/kg/day at bedtime and gradually increase to 10-15 mg/kg/day divided tid; titrate up by 5 mg/kg/day every 3-4 days as needed but not to exceed 50-75 mg/kg/day (3600 mg/day)	May cause neuropsychiatric events in children (aggression, emotional lability, hyperkinesia), usually mild but may require discontinuation of gabapentin. May cause dizziness, drowsiness, tremor, nystagmus, ataxia, swelling
	Pregabalin	Start at 1 mg/kg/dose po at bedtime for 3 days, then increase to 1 mg/kg/dose bid. Increase every 3 days to 3 mg/kg/dose po bid (maximum: 6 mg/kg/dose)	
	Methadone	See previous listing	See previous listing
Dyspnea	Morphine, immediate release (i.e., MSIR)	0.1 mg/kg po q 4 hr prn*†	All opioids may relieve dyspnea. For dyspnea, the starting dose is 30% of the dose that would be administered for pain§
	Lorazepam	0.025-0.05 mg/kg IV/po q 6 hr, up to 2 mg/dose	See previous listing

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Respiratory secretions	Scopolamine patch	1.5 mg patch, change q 72 hr	Excessive drying of secretions can cause mucus plugging of airways. Good for motion-induced nausea and vomiting. Handling patch and contacting eye may cause anisocoria and blurry vision. May fold patches but do not cut them. Anticholinergic side effects possible
	Glycopyrrolate	0.04-0.1 mg/kg po q 4-8 hr	Powerful antisialagogue. Excessive drying of secretions can cause mucus plugging of airways. Anticholinergic side effects possible. Quaternary ammonium structure limits its ability to cross lipid membranes, such as the blood–brain barrier (in contrast to atropine, scopolamine and hyoscyamine sulfate), so may exert fewer central anticholinergic effects
	Hyoscyamine sulfate	4 gtt po q 4 hr prn if <2 yr; 8 gtt po q 4 hr prn if 2-12 yr; do not exceed 24 gtt/24 hr	Anticholinergic side effects possible, including sedation. May be given sublingually
	Atropine	1-2 gtt SL q 4-6 hr prn	Give 0.5% ophthalmic drops sublingually
Nausea	Metoclopramide	0.1-0.2 mg/kg/dose q 6 hr, up to 10 mg/dose (prokinetic and mild nausea dosing). For chemotherapy-associated nausea 0.5-1 mg/kg q 6 hr prn po/IV/SC, give with diphenhydramine and continue diphenhydramine for 24 hr after last dose of high-dose metoclopramide to prevent extrapyramidal reaction	Helpful when dysmotility is an issue; may cause extrapyramidal reactions, particularly in children following IV administration of high doses. Contraindicated in complete bowel obstruction or pheochromocytoma
	Ondansetron	0.15 mg/kg dose IV/po q 8 hr prn. No single intravenous dose should exceed 16 mg because of risk of QT prolongation	Significant experience in pediatrics. Good empiric therapy for nausea in palliative care population. Oral dissolving tablet contains phenylalanine. Higher doses used with chemotherapy although single 32 mg IV dose is no longer available (risk for QT prolongation). Consider ECG monitoring in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or in patients on other medications with the potential to cause QT prolongation
	Dexamethasone	0.1 mg/kg/dose tid po/IV; max dose 10 mg/day	Also helpful with hepatic capsular distention, bowel wall edema, anorexia, increased intracranial pressure. May cause mood swings or psychosis
	Lorazepam	See previous listing	See previous listing
	Dronabinol	2.5-5 mg/m^2/dose q 3-4 hr	Available in 2.5- and 5-mg capsules. May remove liquid contents from capsules for children who cannot swallow capsules. Avoid in patients with sesame oil hypersensitivity or history of schizophrenia. May cause euphoria, dysphoria or other mood changes. Tolerance to central nervous system side effects usually develops in 1-3 days of continuous use. Avoid in patients with depression or mania
	Scopolamine patch	See previous listing	See previous listing
Anxiety	Lorazepam	See previous listing	See previous listing
Agitation	Haloperidol	0.01 mg/kg po tid prn for acute onset: 0.025-0.050 mg/kg po, may repeat 0.025 mg/kg in 1 hr prn	May cause extrapyramidal reactions, which can be reversed with diphenhydramine or Cogentin. Safety not established in children <3 yr
Sleep disturbance/insomnia	Lorazepam	See previous listing	See previous listing
	Trazodone	Children 6-18 yr: 0.75-1 mg/kg/dose, given bid-tid if needed If >18 yr, start at 25-50 mg/dose, given bid-tid if needed	Potentially arrhythmogenic
Fatigue	Methylphenidate	0.3 mg/kg/dose titrated as needed, up to 60 mg/day	Rapid antidepressant effect; also improves cognition. Administer before meals to avoid appetite suppression. Use with caution in children at risk for cardiac arrhythmia. Available as liquid and chewable tablet

Continued

Table 43-6 Pharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness—cont'd

SYMPTOM	MEDICATION	STARTING DOSE	COMMENTS
Pruritus	Diphenhydramine	0.5-1 mg/kg q 6 hr IV/po (100 mg max per day)	May reverse phenothiazine-induced dystonic reactions. Topical formulation on large areas of the skin or open area may cause toxic reactions. May cause paradoxical reaction in young children
	Hydroxyzine	0.5-1 mg/kg q 6 hr IV/po (600 mg maximum per day)	
Constipation	Docusate	40-150 mg/day po in 1-4 divided doses	Stool softener available as liquid or capsule
	MiraLAX	<5 yr: ½ scoop (8.5 g) in 4 oz of water daily >5 yr: 1 scoop (17 g) in 8 oz of water daily	Tasteless powder may be mixed in beverage of choice. Now available nonprescription
	Lactulose	5-10 mL po up to q 2 hr until bowel movement	Bowel stimulant; dosing q 2 hr may cause cramping
	Senna	2.5 mL po daily (for children weighing >27 kg)	Bowel stimulant; available as granules
	Dulcolax	3-12 yr: 5-10 mg po daily >12 yr 5-15 mg po daily	Available in oral or rectal formulation
	Pediatric Fleets Enema	2.5 oz pediatric enema for children 2-11 yr; adult enema for children ≥12 yr	May repeat ×1 if needed. Do not use in neutropenic patients
	Methylnaltrexone	10-20 kg: 2 mg SC 21-33 kg: 4 mg SC 34-46 kg: 6 mg SC 47-62 kg: 8 mg SC 63-114 kg: 12 mg SC ≥155 kg: 0.15 mg/kg SC Administer 1 dose every other day as needed; maximum of 1 dose per 24 hr	A peripherally acting opioid antagonist for opioid-induced constipation. Usually works within 30-60 minutes of administration
Muscle spasm	Diazepam	0.5 mg/kg/dose IV/po q 6 hr prn; initial dose for children <5 yr is 5 mg dose; for children ≥5 yr dose is 10 mg/dose	May be irritating if given by peripheral IV
	Baclofen	5 mg po tid, increase by 5 mg/dose as needed	Helpful with neuropathic pain and spasticity; abrupt withdrawal may result in hallucinations and seizures; not for children <10 yr
Seizures	Lorazepam	0.1 mg/kg IV/po/SL/PR; repeat q 10 min ×2	
	Diazepam	0.1 mg/kg q 6 hr (max 5 mg/dose if <5 yr; max 10 mg/dose if >5 yr)	May be given pr as Diastat (0.2 mg/kg/dose q 15 minutes ×3 doses)
Neuroirritability	Gabapentin	See previous listing	
	Clonidine	Starting dose: 0.05 mg/day. May increase every 3-5 days by 0.05 mg/day to 3-5 μg/kg/day given in divided doses 3-4 times/day; maximum dose is 0.3 mg/day May switch from oral to transdermal route once optimal oral dose is established; Transdermal dose is equivalent to the total oral daily dose (e.g., if total oral dose is 0.1 mg/day, apply 1 patch (delivers 0.1 mg/day). Change patch every 7 days.	Transdermal patch may contain metal (e.g., aluminum) that may cause burns if worn during MRI scan. Remove patch prior to MRI. Patch may be cut into quarter or half fractions based on dose needed
	Clonazepam	<10 yr or <30 kg Initial dose: 0.01-0.03 mg/kg/day divided tid; ≥10 yr (≥30 kg) Initial dose: up to 0.25 mg po tid; may increase by 0.5-1 mg/day every 3 days Maintenance dose: 0.05-0.2 mg/kg/day up to 20 mg/day	
Anorexia	Megestrol acetate	10 mg/kg/day in 1-4 divided doses, may titrate up to 15 mg/kg/day or 800 mg/day	For children >10 yr. Acute adrenal insufficiency may occur with abrupt withdrawal after long-term use. Use with caution in patients with diabetes mellitus or history of thromboembolism. May cause photosensitivity
	Dronabinol	See previous listing	See previous listing
	Cyproheptadine	Children ≥2 yr and adolescents: 0.08 mg/kg po q 8 hr; if no benefit in 5 days, increase dose by 0.04-0.08 mg/kg/dose maximum daily dose: ≤6 yr: 12 mg/day; 7-14 yr: 16 mg/day; ≥15 yr: 32 mg/day	Potent antihistamine and serotonin antagonist

*Infants <6 mo should receive 25-30% of the usual opioid starting dose.
†Although the usual opioid starting dose is presented, dose may be titrated as needed. There is no ceiling/maximum dose for opioids.
‡Breakthrough dose is 10% of 24 hr dose. See Chapter 62 for information regarding titration of opioids.
§Side effects from opioids include constipation, respiratory depression, pruritus, nausea, urinary retention, physical dependence.
ECG, electrocardiogram; gtt, drops; hr, hr; IV, intravenously; po, by mouth; pr, rectally; prn, as needed; SC, subcutaneously; SL, sublingually.
Adapted from Ullrich C, Wolfe J: Pediatric pain and symptom control. In Walsh TD, Caraceni AT, Fainsinger R, et al: *Palliative medicine*, Philadelphia, 2008, Saunders, pp. 1101-1102, Table 198.3.

Table 43-7 Nonpharmacologic Approach to Symptoms Commonly Experienced by Children with Life-Threatening Illness

SYMPTOM	APPROACH TO MANAGEMENT
Pain	Prevent pain when possible by limiting unnecessary painful procedures, providing sedation, and giving pre-emptive analgesia prior to a procedure (e.g., including sucrose for procedures in neonates) Address coincident depression, anxiety, sense of fear or lack of control Consider guided imagery, relaxation, hypnosis, art/pet/play therapy, acupuncture/acupressure, biofeedback, massage, heat/cold, yoga, transcutaneous electric nerve stimulation, distraction
Dyspnea or air hunger	Suction secretions if present, positioning, comfortable loose clothing, fan to provide cool, blowing air Limit volume of IV fluids, consider diuretics if fluid overload/pulmonary edema present Behavioral strategies including breathing exercises, guided imagery, relaxation, music, distraction
Fatigue	Sleep hygiene (establish a routine, promote habits for restorative sleep) Regular, gentle exercise; Prioritize or modify activities Address potentially contributing factors (e.g., anemia, depression, side effects of medications) Aromatherapy*: peppermint, rosemary, basil
Nausea/vomiting	Consider dietary modifications (bland, soft, adjust timing/volume of foods or feeds) Aromatherapy*: ginger, peppermint, lavender acupuncture/acupressure
Constipation	Increase fiber in diet, encourage fluids, ambulation (if possible)
Oral lesions/dysphagia	Oral hygiene and appropriate liquid, solid and oral medication formulation (texture, taste, fluidity). Treat infections, complications (mucositis, pharyngitis, dental abscess, esophagitis) Oropharyngeal motility study and speech (feeding team) consultation
Anorexia/cachexia	Manage treatable lesions causing oral pain, dysphagia, or anorexia. Support caloric intake during phase of illness when anorexia is reversible. Acknowledge that anorexia/cachexia is intrinsic to the dying process and may not be reversible Prevent/treat coexisting constipation
Pruritus	Moisturize skin Trim child's nails to prevent excoriation Try specialized antiitch lotions Apply cold packs Counterstimulation, distraction, relaxation
Diarrhea	Evaluate/treat if due to obstipation Assess and treat infection Dietary modification
Depression	Psychotherapy, behavioral techniques, setting attainable daily goals Aromatherapy*: bergamot, lavender
Anxiety	Psychotherapy (individual and family), behavioral techniques Aromatherapy*: clary sage, angelica, mandarin, lavender
Agitation/terminal restlessness	Evaluate for organic or drug causes Educate family Orient and reassure child; provide calm, nonstimulating environment, use familiar music, verse, voice, touch Aromatherapy*: frankincense, ylang ylang

*Best if aromatherapy is administered by a practitioner trained in aromatherapy.
From Sourkes B, Frankel L, Brown M, et al: Food, toys, and love: pediatric palliative care, *Curr Probl Pediatr Adolesc Health Care* 35:345-392, 2005.

Many children with life-threatening illness experience pain that requires opioids for adequate relief at some point in their illness trajectory. Although it was previously recommended, prescribing codeine should generally be avoided because of its side-effect profile and lack of superiority over nonopioid analgesics. Furthermore, relatively common genetic polymorphisms in the CYP2D6 gene lead to wide variation in codeine metabolism. Specifically, 10-40% of individuals carry polymorphisms causing them to be "poor metabolizers" who cannot convert codeine to its active form, morphine, and therefore are at risk for inadequate pain control; others are "ultrametabolizers" who may even experience respiratory depression from rapid generation of morphine from codeine. It is therefore preferable to use a known amount of the active agent, morphine.

It is important to explore with families, as well as members of the care team, misconceptions that they may have regarding respiratory suppression, addiction, dependence, the symbolic meaning of starting an opioid such as methadone or morphine and/or a morphine drip, and the potential for opioids to hasten death. There is no association between administration or escalation of opioids and length of survival. Evidence supports longer survival in individuals with symptoms that are well controlled.

Children also often experience a multitude of **nonpain symptoms**. A combination of both pharmacologic (see Table 43-6) and nonpharmacologic approaches (see Table 43-7) is often optimal. **Fatigue** is one of the most common symptoms in children with advanced illness. Children may experience fatigue as a physical symptom (e.g., weakness or somnolence), a decline in cognition (e.g., diminished attention or concentration), and/or impaired emotional function (e.g., depressed mood or decreased motivation). Because of its multidimensional and incapacitating nature, fatigue can prevent children from participating in meaningful or pleasurable activities, thereby impairing quality of life. Fatigue is usually multifactorial in etiology. A careful history may reveal contributing physical factors (uncontrolled symptoms, medication side effects), psychological factors (anxiety, depression), spiritual distress, or sleep disturbance. Interventions to reduce fatigue include treatment of contributing factors, exercise, pharmacologic agents, and behavior modification strategies. Challenges to effectively addressing fatigue include the common belief that fatigue is inevitable, lack of communication between families and care teams about it, and limited awareness of potential interventions for fatigue.

Dyspnea (the subjective sensation of shortness of breath) is caused by a mismatch between afferent sensory input to the brain and the

outgoing motor signal from the brain. It may stem from respiratory causes (e.g., airway secretions, obstruction, infection) or other factors (e.g., cardiac), and may also be influenced by psychological factors (e.g., anxiety). Respiratory parameters such as respiratory rate and oxygen saturation correlate unreliably with the degree of dyspnea. Therefore, giving oxygen to a cyanotic or hypoxic child who is otherwise quiet and relaxed may relieve staff discomfort while having no impact on patient distress and may also add burden if the child cannot tolerate the mask or canula. Dyspnea can be relieved with the use of regularly scheduled *and* as-needed doses of opioids. Opioids work *directly* on the brainstem to reduce the sensation of respiratory distress, as opposed to relieving dyspnea via sedation. The dose of opioid needed to reduce dyspnea is as little as 25% of the amount that would be given for analgesia. Nonpharmacologic interventions, including guided imagery or hypnosis to reduce anxiety, or cool, flowing air, aimed toward the face, are also frequently helpful in alleviating dyspnea. While oxygen may relieve hypoxemia-related headaches, it is no more effective than blowing room air in reducing the distressing sensation of shortness of breath.

As death approaches, a buildup of secretions may result in noisy respiration sometimes referred to as a "death rattle." Patients at this stage are usually unconscious, and noisy respirations are often more distressing for others than for the child. It is often helpful to discuss this anticipated phenomenon with families in advance, and if it occurs, to point out the child's lack of distress from it. If treatment is needed, an anticholinergic medication, such as glycopyrrolate, may reduce secretions.

Neurologic symptoms include **seizures** that are often part of the antecedent illness but may increase in frequency and severity toward the end of life. A plan for managing seizures should be made in advance and anticonvulsants should be readily available in the event of seizure. Parents can be taught to use rectal diazepam at home. Increased **neuroirritability** accompanies some neurodegenerative disorders; it may be particularly disruptive because of the resultant break in normal sleep–wake patterns and the difficulty in finding respite facilities for children who have prolonged crying. Such neuroirritability may respond to gabapentin. Judicious use of sedatives, benzodiazepines, clonidine, nortriptyline, or methadone may also reduce irritability without inducing excessive sedation; such treatment can dramatically improve the quality of life for both child and caregivers. **Increased intracranial pressure** and **spinal cord compression** are most often encountered in children with brain tumors or metastatic and solid tumors. Depending on the clinical situation and the goals of care, radiation therapy, surgical interventions, and steroids are potential therapeutic options.

Feeding and hydration issues can raise ethical questions that evoke intense emotions in families and medical caregivers alike. Options that may be considered to artificially support nutrition and hydration in a child who can no longer feed by mouth include nasogastric and gastrostomy feedings or intravenous nutrition or hydration. These complex decisions require evaluating the risks and benefits of artificial feedings and taking into consideration the child's functional level and prognosis. At times, it may be appropriate to initiate a trial of tube feedings with the understanding that they may be discontinued at a later stage of the illness. A commonly held but unsubstantiated belief is that artificial nutrition and hydration are "comfort measures," without which a child may suffer from starvation or thirst. This may result in well-meaning but disruptive and invasive attempts to administer nutrition or fluids to a dying child. In dying adults, the sensation of thirst may be alleviated by careful efforts to keep the mouth moist and clean. There may also be deleterious side effects to artificial hydration in the form of increased secretions, need for frequent urination, edema and exacerbation of dyspnea. For these reasons, it is important to educate families about anticipated decreases in appetite/thirst and therefore little need for nutrition and hydration as the child approaches death. In addition, exploring the meaning that provision of nutrition and hydration may hold for families, as well as helping families anticipate the changes in their child's appearance and exploring alternative ways that they may love and nurture their child, may ease distress around this issue. **Nausea and vomiting** may be the result of a variety of causes, including medications/toxins, irritation to or obstruction of the gastrointestinal tract, motion, and emotions. Drugs such as metoclopramide, 5-hydroxytryptamine antagonists, steroids, and aprepitant may be used, and should be chosen depending on the underlying pathophysiology and neurotransmitters involved. Vomiting may accompany nausea but may also occur without nausea, such as in the instance of increased intracranial pressure. **Constipation** is commonly encountered in children with neurologic impairment or children receiving medications that impair gastrointestinal motility (most notably, opioids). Stool frequency and quantity should be evaluated in the context of the child's diet and usual bowel pattern. Children on regular opioids should routinely be placed on stool softeners (docusate) in addition to a laxative agent (e.g., senna). **Diarrhea** may be particularly difficult for the child and family and may be treated with loperamide (an opioid that does not cross the blood–brain barrier), and in some cases cholestyramine or octreotide may be indicated. Paradoxical diarrhea, a result of overflow resulting from constipation, should also be included in the differential diagnosis.

Hematologic issues include consideration of anemia and thrombocytopenia or bleeding. If the child has symptomatic anemia (weakness, dizziness, shortness of breath, tachycardia), red blood cell transfusions may be considered. Platelet transfusions may be an option if the child has symptoms of bleeding. Life-ending hemorrhage is disturbing for all concerned, and a plan involving the use of fast-acting sedatives should be prepared in advance if such an event is a possibility.

Skin care issues include primary prevention of problems by ongoing and timely assessment including observation of indwelling lines and tubes, and frequent turning and repositioning and alleviating pressure wherever possible (e.g., elevating heels with pillows). Pruritus may be secondary to systemic disorders or drug therapy. Treatment includes avoiding excessive use of drying soaps, using moisturizers, trimming fingernails, and wearing loose-fitting clothing, in addition to administering topical or systemic steroids. Oral antihistamines and other specific therapies may also be indicated (e.g., cholestyramine in biliary disease). Although opioids can cause histamine release from mast cells, this does not account for most of the pruritus caused by opioids. A trial of diphenhydramine may provide relief; alternatively, rotating opioids or instituting a low dose of opioid antagonist may be needed for refractory pruritus.

Children with life-threatening illness may experience psychological symptoms such as **anxiety** and **depression.** Such symptoms are frequently multifactorial, and sometimes interrelated with uncontrolled symptoms such as pain and fatigue. Diagnosing depression in the context of serious illness may pose challenges since neurovegetative symptoms may not be reliable indicators. Instead, expressions of hopelessness, helplessness, worthlessness, and guilt may be more useful. Pharmacologic agents such as antidepressants may be helpful, although their effect is often preceded by a significant lag phase. Because of its immediate and positive effect on mood, methylphenidate may be an effective antidepressant for children at end of life, when there may not be time for a traditional antidepressant to take effect. Interventions and opportunities for children to explore worries, hopes, and concerns in an open, supportive, and nonjudgmental setting are equally if not more important approaches to psychological distress. Skilled members from a variety of disciplines, including psychology, social work, chaplaincy, child life, and expressive therapy, among others, may help children and their families in this regard. Such opportunities may in fact create positive moments in which meaning, connection, and new definitions of hope are found.

Discussions with adolescent patients or with the parents of any ill child, about possible therapies or interventions should include **integrative therapies** such as massage therapy, Reiki, acupuncture, clinical aromatherapy, prayer, and nutritional supplements. Many families use integrative therapy, but do not bring it up with their physician unless explicitly asked (see Chapter 64). Although largely unproven, some therapies are inexpensive and provide relief to individual

patients. Other therapies may be expensive, painful, intrusive, and even toxic. By initiating conversation and inviting discussion in a nonjudgmental way, the clinician can offer advice on the safety of different therapies and may help avoid expensive, dangerous, or burdensome interventions.

Intensive Symptom Management

At end of life, when intensive efforts to relieve the symptom have been exhausted, or when efforts to address suffering are incapable of providing relief with acceptable toxicity/morbidity or in an acceptable time frame, **palliative sedation** may be considered. Palliative sedation may relieve suffering from refractory symptoms by reducing a child's level of consciousness. It is most often used for intractable pain, dyspnea, or agitation, but is not limited to these distressing indications. Palliative sedation requires opportunities for parents, staff, and primary clinicians to discuss the indication and goals for sedation, as well as questions or concerns about this therapy, both before and after initiation of sedation.

The *principle of double effect* is often invoked to justify escalation of symptom-relieving medications or palliative sedation for uncontrolled symptoms at the end of life. Use of this principle emphasizes the risk of hastening death posed by escalating opioids or sedation, which is theoretical and unproven. There is mounting evidence that patients with well-controlled symptoms live longer.

The Terminal Phase

As death seems imminent, the major task of the physician and team are to help the child have as many good days as possible and not suffer. If not already in place, a referral to **hospice** may provide the most comprehensive care for the child and family. Gently preparing the family for what to expect and offering choices, when possible, will allow them a sense of control in the midst of tragic circumstances. Before death, it can be very helpful to discuss:

- Support of siblings or other family members
- Resuscitation status
- Limiting technology when no longer beneficial to the child
- Cultural, spiritual, or religious needs
- Location of death
  - Who will pronounce if death occurs at home
- Funeral arrangements
  - Offering siblings choice and appropriate support to attend
- Autopsy and/or tissue or organ donation
  - Legacy building, benefits others, informs science and family

Offered the opportunity, families will often tolerate thinking and speaking about their hopes and fears regarding their child's end of life, and some even express relief when the door to such conversation in opened by the care team. It may help to let the family know these conversations are not about *whether* the child will die, but about *how* the child may die.

Families gain tremendous support from having a physician and team who will continue to stay involved in the child's care. If the child is at home or hospitalized, regular phone calls or visits, assisting with symptom management, and offering emotional support is invaluable for families.

In an intensive care setting, where technology can be overwhelming and put distance between the child and parent, the physician can offer discontinuation of that which is not benefiting the child or adding to quality of life. Parents may be afraid to ask about holding or sleeping next to their child. They may need reassurance and assistance in holding, touching, and speaking with their child, despite tubes and technology, even if the child appears unresponsive.

It is believed that hearing and the ability to sense touch is often present until death; all family members should be encouraged to continue interacting with their loved one through the dying process. Parents may be afraid to leave the bedside so that their child will not die alone. Offering parents other supports such as chaplaincy/clergy, social work and extended family members may be helpful. In most instances the moment of death cannot be predicted. Some propose that children wait to die until parents are "ready," an important event has passed, or until they are given permission. Caregivers need not dispute this, nor the hope for a miracle often held by families until the child takes the very last breath.

For the family, the moment of death is an event that is recalled in detail for years to come, and so enhancing opportunity for dignity and limited suffering is essential. Research suggests that improved symptom control and easing of difficult moments at the time of death may lessen the long-term distress of bereaved parents. Clinical experience has shown that families often find solace in clinician "presence," whether at home or in the hospital. After death, families should be given the option of remaining with their child for as long as they would like. During this time, physicians and other professionals may ask permission to "say goodbye." The family may be invited to bathe and dress the body as a final act of caring for the child.

The physician's decision to attend the funeral is a personal one. Participation may serve the dual purpose of showing respect as well as helping the clinician cope with a personal sense of loss. If unable to attend services, families report highly valuing the importance of receiving a card or note from the physician. To know that their child made a difference and will not be forgotten is often very important to families in their bereavement.

The Pediatrician

While optimal palliative care for children entails caregivers from a variety of disciplines, pediatricians are well-positioned to support children and their families, particularly if they have a long-standing relationship with multiple family members. A pediatrician who has cared for a family over time may already know and care for other family members, understand preexisting stressors for the family, and may be familiar with coping strategies used by family members. Pediatricians are familiar with the process of eliciting concerns and providing anticipatory guidance for parents, as well as developmentally appropriate explanations for children.

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Nutrition

PART VI

Chapter 44

Nutritional Requirements

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Nutritional intakes for infants, children, and adolescents should provide for maintenance of current weight and support normal growth and development. The infancy growth period is rapid, critical for neurocognitive development, and has the highest energy and nutrient requirements relative to body size compared with other periods of growth. It is followed by the childhood period of growth, during which 60% of total growth occurs, and is finally followed by the puberty phase. Nutrition and growth during the first 3 years of life predict adult stature and some health outcomes. The major risk period for growth stunting (impaired linear growth) is between 4 and 24 months of age. It is critical to identify nutrient deficiencies promptly and to address them aggressively early in life, because they can impart lasting adverse effects on growth and development. Dietary intake not only meets energy requirements but also provides macronutrients and micronutrients essential for sustaining the functioning of multiple vital processes. Nutrient deficiencies can limit growth, impair immune function, and increase morbidity and mortality. The significant global burden of malnutrition and undernutrition is the leading worldwide cause of acquired immunodeficiency and the major underlying factor for morbidity and mortality globally for children <5 yr of age.

The nutrition transition in many developing countries as populations change from traditional diets to the Western diet has resulted in increased life expectancy and adult stature in these populations. Unfortunately, this nutrition transition is also frequently accompanied by decreased physical activity, and in parallel to decreases in the incidence and prevalence of communicable (infectious) diseases, there are increases in the incidence and prevalence of noncommunicable diseases such as noninsulin-dependent diabetes, cardiovascular disease, obesity, inflammatory bowel disease, and certain cancers.

Consequently, it is important to view the impact of nutrition on health from various perspectives: to prevent deficiency, to promote adequacy, and to prevent or reduce the risk for acquiring diseases associated with excess intakes, such as obesity, diabetes, and cardiovascular disease. Advances in our understanding of the roles of vitamin D, polyunsaturated fatty acids (PUFAs), and total fiber have changed our focus from recommendations for deficiency to nutritional intakes associated with optimal health. In addition, the 2006 World Health Organization (WHO) growth charts, *which are recommended for all children until 2 years of age*, are not only descriptive, but are also proscriptive on how children with adequate nutrition and health care should grow. Identification and provision of appropriate and adequate nutrition in infancy and childhood are critical to not only support normal growth and development, but also to provide the foundation for lifelong health and well-being.

DIETARY REFERENCE INTAKES

The dietary reference intake (DRI) established by the Food and Nutrition Board of the Institute of Medicine provides guidance as to nutrient needs for individuals and groups across different life stages and by gender (Tables 44-1 to 44-4).

Key DRI concepts include the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL) (Fig. 44-1). The EAR is the average daily nutrient intake level estimated to meet the requirements for 50% of the population, assuming normal distribution; the RDA is an estimate of the daily average nutrient intake to meet the nutritional needs of >97% of the individuals in a population, and it can be used as a guideline for individuals to avoid deficiency in the population. When an EAR cannot be derived, an RDA cannot be calculated; therefore, an adequate intake (AI) is developed as a guideline for individuals based on the best available data and scientific consensus. The UL denotes the highest average daily intake at which no adverse health effects are associated for almost all individuals in a particular group. The relationships among EAR, RDA, and UL are characterized in Figure 44-2.

ENERGY

Energy includes both intake and expenditure. Deficits and excesses of energy intake yield undesirable health consequences. Inadequate energy intake can lead to growth faltering, catabolism of body tissues and inability to provide energy substrate, whereas excess energy intakes can increase the risk for obesity. Adequacy of energy intake in adults is associated with maintenance of a healthy weight. The 3 components of energy expenditure in adults are the basal metabolic rate, thermal effect of food (energy required for digestion and absorption), and energy for physical activity. Additional energy intake is required to support growth and development for children.

The **estimated energy requirement (EER)** is the average dietary energy intake predicted to maintain energy balance in a healthy individual and accounts for age, gender, weight, stature, and physical activity level (see Table 44-1). The Dietary Guidelines for Americans 2010 recommend 60 min of moderately intense daily activity for children >2 yr of age to maintain a healthy weight and to prevent or delay progression of chronic noncommunicable diseases such as obesity and cardiovascular disease. The EER was determined based on empirical research in healthy persons at different physical activity levels, including levels different from the recommended levels. *They do not necessarily apply to children with acute or chronic diseases*. EER is estimated by equations that account for total energy expenditure, as well as energy deposition for healthy growth. The EER for infants, relative to body weight, are approximately twice those for adults because of the increased metabolic rate and requirements for weight maintenance and tissue accretion affecting growth.

The nutrients that provide energy intake in the child's diet are fats (~9 kcal/g), carbohydrates (~4 kcal/g), and proteins (~4 kcal/g). They are referred to as **macronutrients**. Alcohol intake also contributes to energy intake (~7 kcal/g). The EER does not specify the relative energy contributions of macronutrients. Once the minimal intakes of each of the respective macronutrients are attained to meet physiologic requirements and to achieve adequacy (sufficient protein intake to meet specific amino acid requirements, fat for essential fatty acids, and neurologic development), the remainder of the intake is used to meet energy requirements with some degrees of freedom and interchangeability among fats, carbohydrates, and proteins. This forms the basis for the acceptable macronutrient distribution ranges (AMDRs) (see Table 44-2), expressed as a function of total energy intake.

Table 44-1 Equations to Estimate Energy Requirement

INFANTS AND YOUNG CHILDREN: EER (KCAL/DAY) = TEE + ED	
0-3 mo	EER = (89 × weight [kg] – 100) + 175
4-6 mo	EER = (89 × weight [kg] – 100) + 56
7-12 mo	EER = (89 × weight [kg] – 100) + 22
13-36 mo	EER = (89 × weight [kg] – 100) + 20
CHILDREN AND ADOLESCENTS 3-18 YR: EER (KCAL/DAY) = TEE + ED	
Boys	
3-8 yr	EER = 88.5 – (61.9 × age [yr] + PA × [(26.7 × weight [kg] + (903 × height [m])] + 20
9-18 yr	EER = 88.5 – (61.9 × age [yr] + PA × [(26.7 × weight [kg] + (903 × height [m])] + 25
Girls	
3-8 yr	EER = 135.3 – (30.8 × age [yr] + PA [(10 × weight [kg] + (934 × height [m])] + 20
9-18 yr	EER = 135.3 – (30.8 × age [yr] + PA [(10 × weight [kg] + (934 × height [m])] + 25

ED, energy deposition; EER, estimated energy requirement; TEE, total energy expenditure.

PA indicates the physical activity coefficient:

For boys:
- PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)
- PA = 1.13 (low active, estimated physical activity level 1.4-1.6)
- PA = 1.26 (active, estimated physical activity level 1.6-1.9)
- PA = 1.42 (very active, estimated physical activity level 1.9-2.5)

For girls:
- PA = 1.00 (sedentary, estimated physical activity level 1.0-1.4)
- PA = 1.16 (low active, estimated physical activity level 1.4-1.6)
- PA = 1.31 (active, estimated physical activity level 1.6-1.9)
- PA = 1.56 (very active, estimated physical activity level 1.9-2.5)

Adapted from Kleinman RE, editor: Pediatric nutrition handbook, *ed 6, Elk Grove Village, IL, 2009, American Academy of Pediatrics.*

FAT

Fat is the most calorically dense macronutrient, providing approximately 9 kcal/g. For infants, human milk/formula are the main dietary sources of fat, whereas older children get fat from animal products, vegetable oils, and margarine. The AMDR for fats is 30-40% of total energy intake for children 1-3 yr and 25-35% for children 4-18 yr of age. In addition to being energy-dense, fats provide essential fatty acids and play structural and functional roles; cholesterol moieties are precursors for cell membranes, hormones, and bile acids. Fat intake facilitates absorption of fat-soluble vitamins A, D, E, and K. Both roles are particularly relevant in the context of neurological and ocular development.

Table 44-2 Acceptable Macronutrient Distribution Ranges

	AMDR (% OF ENERGY)	
	Children 1-3 yr	**Children 4-18 yr**
Fat	30-40	25-35
ω6 PUFAs (linoleic acid)	5-10	5-10
ω3 PUFAs (α-linolenic acid)	0.6-1.2	0.6-1.2
Carbohydrate	45-65	45-65
Protein	5-20	10-30

AMDR, acceptable macronutrient distribution range; PUFA, polyunsaturated fatty acid.

Adapted from Otten JJ, Hellwig JP, Meyers LD, editors; Institute of Medicine: Dietary reference intakes: the essential guide to nutrient requirements, *Washington, DC, 2006, National Academies Press.*

Table 44-3 Dietary Reference Intakes: Macronutrients

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
TOTAL DIGESTIBLE CARBOHYDRATE				
RDA based on its role as the primary energy source for the brain AMDR based on its role as a source of kcal to maintain body weight	*Infants* 0-6 mo 7-12 mo *Children* >1 yr *Pregnancy* ≤18 yr 19-30 yr	 60* 95* 130 175 175	Major types: starches and sugars Grains and vegetables (corn, pasta, rice, potatoes, breads) are sources of starch Natural sugars are found in fruits and juices Sources of added sugars: soft drinks, candy, fruit drinks, desserts	No defined intake level for potential adverse effects of total digestible carbohydrate is identified, but the upper end of the AMDR was based on decreasing risk of chronic disease and providing adequate intake of other nutrients It is suggested that the maximal intake of added sugars be limited to providing no more than 25% of energy
TOTAL FIBER				
Improves laxation, reduces risk of coronary heart disease, assists in maintaining normal blood glucose levels	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr	 ND ND 190* 25* 31* 38* 38* 26* 26* 25* 28* 28*	Includes dietary fiber naturally present in grains (e.g., oats, wheat, unmilled rice) and functional fiber synthesized or isolated from plants or animals and shown to be of benefit to health	Dietary fiber can have variable compositions; therefore, it is difficult to link a specific source of fiber with a particular adverse effect, especially when phytate is also present in the natural fiber source As part of an overall healthy diet, a high intake of dietary fiber will not produce deleterious effects in healthy persons Occasional adverse GI symptoms are observed when consuming some isolated or synthetic fibers, but serious chronic adverse effects have not been observed Owing to the bulky nature of fibers, excess consumption is likely to be self-limiting; therefore, an UL was not set for individual functional fibers

Continued

Table 44-3 Dietary Reference Intakes: Macronutrients—cont'd

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
TOTAL FAT				
Energy source When found in foods, is a source of ω3 and ω6 PUFAs Facilitates absorption of fat-soluble vitamins	*Infants* 0-6 mo 7-12 mo 1-18 yr	 31* 30* Insufficient evidence to determine AI or EAR; see AMDR Table 41-4	Infants: Human milk or infant formula Older children: butter, margarine, vegetable oils, whole milk, visible fat on meat and poultry products, invisible fat in fish, shellfish, some plant products such as seeds and nuts, bakery products	UL not set because there is no defined intake of fat at which adverse effects occur. High fat intake will lead to obesity. The upper end of AMDR is also based on decreasing risk of chronic disease and providing adequate intake of other nutrients Low fat intake (with high carbohydrate) has been shown to increase plasma triacylglycerol concentrations and decrease HDL cholesterol
ω6 POLYUNSATURATED FATTY ACIDS				
Essential component of structural membrane lipids, involved with cell signaling, precursor of eicosanoids Required for normal skin function	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 yr *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr *Lactation* ≤18 yr 19-21 yr	 4.4* 4.6* 7* 10* 12* 16* 17* 10* 11* 12* 13* 13* 13* 13*	Nuts, seeds; vegetable oils such as soybean, safflower, corn oil	No defined intake of ω6 level at which adverse effects occur Upper end of the AMDR is based on the lack of evidence that demonstrates long-term safety and human in vitro studies that show increased free-radical formation and lipid peroxidation with higher amounts of ω6 fatty acids Lipid peroxidation is thought to be a component of atherosclerotic plaques
ω3 POLYUNSATURATED FATTY ACIDS				
Involved with neurologic development and growth Precursor of eicosanoids	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr 19-21 yr *Females* 9-13 yr 14-18 yr 19-21 yr *Pregnancy* ≤18 yr 19-21 yr *Lactation* ≤18 yr 19-21 yr	 0.5* 0.5* 0.7* 0.9* 1.2* 1.6* 1.6* 1.0* 1.1* 1.1* 1.1* 1.4* 1.3* 1.3*	Vegetable oils, e.g., soybean, canola, flax seed oil; fish oils, fatty fish; smaller amounts in meats and eggs	No defined intake level for potential adverse effects of ω3 PUFAs is identified Upper end of AMDR is based on maintaining the appropriate balance with ω6 fatty acids and on the lack of evidence that demonstrates long-term safety, along with human in vitro studies that show increased free-radical formation and lipid peroxidation with higher amounts of PUFAs Because the longer-chain *n*-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are biologically more potent than their precursor, linolenic acid, much of the work on the adverse effects of this group of fatty acids has been on DHA and EPA Lipid peroxidation is thought to be a component in the development of atherosclerotic plaques
SATURATED AND *TRANS* FATTY ACIDS				
The body can synthesize its needs for saturated fatty acids from other sources		No dietary requirement	Saturated fatty acids are present in animal fats (meat fats and butter fat), and coconut and palm kernel oils *Trans* fat: stick margarines, foods containing hydrogenated or partially hydrogenated vegetable shortenings	There is an incremental increase in plasma total and LDL cholesterol concentrations with increased intake of saturated or *trans* fatty acids; therefore, the intakes of each should be minimized while consuming a nutritionally adequate diet

Table 44-3 Dietary Reference Intakes: Macronutrients—cont'd

FUNCTION	LIFE STAGE GROUP	RDA OR AI* (g/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION
CHOLESTEROL		No dietary requirement	Sources: liver, eggs, foods that contain eggs, e.g., cheesecake, custard pie	
PROTEIN AND AMINO ACIDS†				
Major structural component of all cells in the body Functions as enzymes, in membranes, as transport carriers, and as some hormones During digestion and absorption, dietary proteins are broken down to amino acids, which become the building blocks of these structural and functional compounds Nine indispensable amino acids must be provided in the diet; the body can make the other amino acids needed to synthesize specific structures from other amino acids	*Infants* 0-6 mo 7-12 mo *Children* 1-3 yr 4-8 yr *Males* 9-13 yr 14-18 yr ≥19 yr *Females* 9-13 yr ≥14 yr ≤18 yr 19-21 yr	 9.1* **11.0** **13** **19** **34** **52** **56** **34** **46** **71**	Proteins from animal sources, e.g., meat, poultry, fish, eggs, milk, cheese, yogurt, provide all 9 indispensable amino acids in adequate amounts and are considered "complete proteins" Proteins from plants, legumes, grains, nuts, seeds, and vegetables tend to be deficient in ≥1 of the indispensable amino acids and are called "incomplete proteins" Vegan diets adequate in total protein content can be "complete" by combining sources of incomplete proteins, which lack different indispensable amino acids	No defined intake level for potential adverse effects of protein is identified Upper end of AMDR was based on complementing the AMDR for carbohydrate and fat for the various age groups Lower end of AMDR is set at approximately the RDA

Note: Starred numbers are AI; bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake. AMDR is the range of intake for a particular energy source that is associated with reduced risk of chronic disease while providing intakes of essential nutrients. With consumption in excess of the AMDR, there is a potential for increasing the risk of chronic diseases and/or insufficient intakes of essential nutrients. ND amounts are not determinable because of a lack of data regarding adverse effects in this age group and concern with regard to a lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*Adequate intake.

†Based on 1.5 g/kg/day for infants, 1.1 g/kg/day for 1-3 yr, 0.95 g/kg/day for 4-13 yr, 0.85 g/kg/day for 14-18 yr, 0.8 g/kg/day for adults, and 1.1 g/kg/day for pregnant (using prepregnancy weight) and lactating women.

AI, adequate intake; AMDR, acceptable macronutrient distribution range; GI, gastrointestinal; LDL, low-density lipoprotein (cholesterol); ND, not determinable; PUFA, polyunsaturated fatty acid; RDA, recommended dietary allowance; UL, upper limit.

Adapted from Food and Nutrition Board, Institute of Medicine: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids *http://www.iom.edu/Activities/Nutrition/SummaryDRIs/DRI-Tables.aspx*.

Table 44-4 Indispensable, Dispensable, and Conditionally Indispensable Amino Acids in the Human Diet

INDISPENSABLE	DISPENSABLE	CONDITIONALLY INDISPENSABLE*	PRECURSORS OF CONDITIONALLY INDISPENSABLE
Histidine† Isoleucine Leucine Lysine Methionine Phenylalanine Threonine Tryptophan Valine	Alanine Aspartic acid Asparagine Glutamic acid Serine	Arginine Cysteine Glutamine Glycine Proline Tyrosine	Glutamine/glutamate, aspartate Methionine, serine Glutamic acid/ammonia Serine, choline Glutamate Phenylalanine

*Conditionally indispensable is defined as requiring a dietary source when endogenous synthesis cannot meet metabolic need.

†Although histidine is considered indispensable, unlike the other 8 indispensable amino acids, it does not fulfill the criteria of reducing protein deposition and inducing negative nitrogen balance promptly upon removal from the diet.

Adapted from Otten JJ, Hellwig JP, Meyers LD, editors; Institute of Medicine: Dietary reference intakes: the essential guide to nutrient requirements, *Washington, DC, 2006, National Academies Press.*

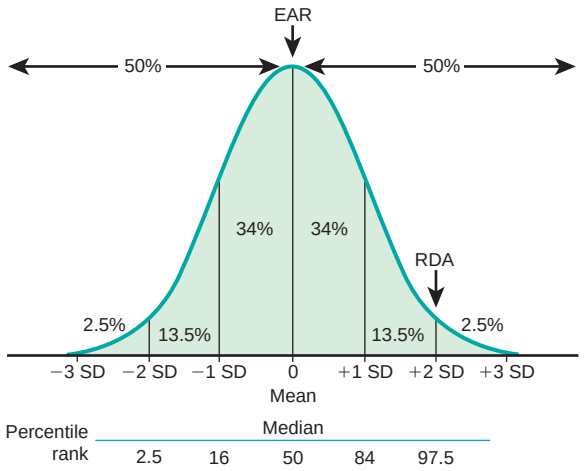

Figure 44-1 Dietary reference intakes. Normal requirement distribution of hypothetical nutrient showing percentile rank and placement of the estimated average requirement (EAR) and the recommended dietary allowance (RDA) on the distribution. SD, standard deviation.

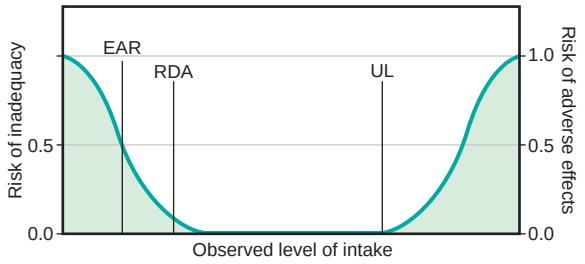

Figure 44-2 Dietary reference intakes: the relationship among the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper limit of intake (UL). This figure shows that the EAR is the intake at which the risk of inadequacy is estimated to be 0.5 (50%). The RDA is the intake at which the risk of inadequacy would be very small—only 0.02 to 0.03 (2-3%). At intakes between the RDA and the UL, the risk of inadequacy and of excess are estimated to be close to 0.0. At intakes above the UL, the potential risk of adverse effects can increase.

Triglycerides are the most common form of dietary fat and are composed of 1 glycerol molecule and 3 fatty acids. Triglycerides are found in animal and vegetable fats. Simple sugars (refined grains and high sugar drinks) are converted to triglycerides in the liver. Elevated serum triglycerides are a risk factor for cardiovascular disease and part of the metabolic syndrome. Decreasing simple sugars and increasing complex carbohydrate intake reduce serum triglyceride levels.

Dietary saturated fatty acids (found primarily in animal fat and dairy products), *trans* fats (found in hydrogenated margarines and oils), and cholesterol increase the low-density lipoprotein (LDL) fraction of serum cholesterol, a risk factor for the development of atherosclerosis. Autopsy studies demonstrate that atherosclerosis begins early in childhood, even in infancy. Therefore, dietary advice to optimize cardiovascular health should be dispensed for children starting at age 2 yr when sufficient fat intake to sustain growth and brain development is less of a concern.

Because saturated and monounsaturated fats can be synthesized endogenously to support adequate structural and physiologic requirements, there is no AI or RDA set for these dietary components. *Trans* fats have no known beneficial effects in humans; therefore, no corresponding AI or RDA has been set. Similarly, an UL has not been set for cholesterol, saturated, or *trans* fats because there is a positive linear association between intake of these fats and increased risk for cardiovascular disease, without a threshold level at which risk is increased. Diets low in saturated fats and cholesterol and without *trans* fats are therefore preferred. For optimal cardiovascular health in the general population, rather than limiting the total amount of fat intake, in most cases, advice should focus on changing the type of fat that is consumed. With respect to preventing obesity, all types of fatty acids have about the same energy content and can contribute to increasing the risk for obesity. The current dietary guidelines for children and adolescents recommend that total fat should account for <30% of total daily energy and saturated fat less than 10%, dietary cholesterol <300 mg/day, with no *trans* fat.

Humans are incapable of synthesizing the precursor omega (ω) 3 (α-linolenic acid; ALA) and ω6 (linoleic acid; LA) PUFAs, and are dependent on diet for these essential fatty acids. **Essential fatty acid (EFA) deficiency** is associated with desquamating skin rashes, alopecia, thrombocytopenia, impaired immunity, and growth deficits, but is rare in the general population. Essential fatty acids are enzymatically elongated and desaturated into longer-chain fatty acids; ALA can be converted to eicosapentaenoic (EPA) and docosahexaenoic (DHA) ω3 PUFAs. LA is converted to arachidonic acid (ARA). Long-chain PUFAs such as DHA and ARA play a variety of structural and functional roles; they influence membrane fluidity and function as well as gene expression, and modulate the inflammatory response. ARA and DHA are present in breast milk, often supplemented in infant formulas, and are required for normal growth and development. DHA is present in the retina and is involved in the visual evoked response in infants.

The conversion of ALA to EPA and DHA and of LA to ARA is influenced by many factors, including type and amounts of dietary fats and by enzymatic substrate affinity among competing ω3, ω6, ω9, saturated, and *trans* fatty acids. The efficiency in conversion of ALA to a longer-chain PUFA is minimal and variable. Approximately 0.5% of dietary ALA is converted to DHA and 5% of ALA intake converted to EPA; therefore, dietary intake of longer-chain PUFAs is an important determinant of serum and tissue long-chain PUFA status. The biologic activity and health benefits of ALA are thought to be derived via the longer-chain PUFA products EPA and DHA. Consistent with these findings of limited conversion of ALA to EPA and DHA, and that EPA and DHA appear to confer the biologic role and health benefits, the DRI stipulates that up to 10% of the AI for ω3 PUFA (ALA being the major dietary constituent) can be replaced by DHA and EPA to support normal neural development and growth.

The ratio of dietary intake of each type of PUFA influences their relative amounts in different tissue compartments. A dietary ω6:ω3 PUFA ratio of 4-5 : 1 may be beneficial in reducing risk of disease and may be associated with improved health outcomes, as compared to the current 15-30 : 1 ratio observed in the United States.

PROTEINS

Proteins and amino acids have structural and functional roles in every cell in the body. Proteins also provide approximately 4 kcal/g; however, dietary protein intake is required to replenish the turnover of proteins and to meet amino acid needs for growth. Dietary protein intake also provides energy substrate when in excess or during periods of catabolism. Inadequate energy intake and/or inadequate protein intake increases catabolism of body protein reservoirs (i.e., lean body mass) so as to provide substrate for energy and free amino acids required to support normal physiologic function. Nitrogen losses, derived from proteins, occur through urine, stool, and other bodily excretions. Increased protein intake may be required for rare hypermetabolic states, such as extensive burns. Protein energy malnutrition, although relatively rare in the noninstitutionalized U.S. population, is more common in the developing world. Protein energy malnutrition impairs brain, immune system and intestinal mucosal functions.

DRI for protein is provided in Table 44-3. An UL for protein has not been set. Intake of proteins or specific amino acids needs to be limited in some health conditions, such as renal disease and metabolic diseases, such as phenylketonuria and maple syrup urine disease, in which specific amino acids can be toxic.

The amino acid content of dietary protein is also important. Certain amino acids are **indispensable** and humans depend on dietary sources to meet adequacy and prevent deficiency. Certain amino acids are

termed **conditional essential/indispensable**, meaning they become essential in patients affected by some diseases or during a certain life stage, such as with cysteine, tyrosine and arginine in newborns because of enzymes immaturity (see Table 44-4). Human milk contains both the indispensable and conditionally indispensable amino acids and therefore meets the protein requirements for infants. Breast milk is considered the optimal source of proteins for infants and is the reference amino acid composition by which biologic quality is determined for infants. If a single amino acid in a food protein source is low or absent but is required to support normal metabolism, that specific amino acid becomes the limiting nutrient. For soy-based infant formula, supplementation with the limiting amino acid (methionine) is necessary.

To ensure appropriate growth and to promote satiety, children should consume the recommended amount of protein. Specific recommendations for appropriate dietary protein sources to meet indispensable amino acid requirements are available for groups adopting specific diets, such as vegetarians and vegans. Inclusion of legumes and corn, as well as the use of a variety of food sources to provide all of the required amino acids is a strategy advocated for vegetarians and vegans.

CARBOHYDRATES

Carbohydrates are abundant in many foods, including cereals, grains, fruits, and vegetables, and provide approximately 4 kcal/g. Dietary carbohydrates include monosaccharides, which contain 1 sugar molecule (glucose, fructose), disaccharides that contain 2 sugar molecules (sucrose, lactose), oligosaccharides, polysaccharides (which contain multiple sugar molecules in a chain or complex configuration) (starch), and sugar alcohols. Carbohydrates (glucose) serve as an essential energy source for erythrocytes and the central nervous system and a major energy source for all cells. The requirements for carbohydrates are based on the average minimum amount of glucose utilized by the brain. Chronic low carbohydrate intake results in ketosis. Although an UL for carbohydrates has not been set, a maximal intake of <25% or <10% of total energy intake from added sugars has been proposed in various dietary guidelines. Higher intakes of added sugar can displace other macro- and micronutrients and increase risk for nutrient deficiency and excessive energy intake. There is no distinct advantage or benefit obtained from discretionary calorie intake such as that provided by the consumption of added sugars.

The recommended AMDR for carbohydrates (see Table 44-2) were based upon data suggesting a risk for coronary heart disease with diets high in carbohydrates and low in fat. These diets, compared to higher fat intakes, result in high triglycerides, low high-density lipoprotein (HDL) cholesterol, and small LDL cholesterol particles and are associated with a high risk of coronary heart disease, especially in sedentary overweight individuals. Diets within the AMDR for carbohydrates and fats minimize the risks of diabetes, obesity and coronary heart disease. Diets with less than the minimum AMDR for carbohydrate most likely do not meet the AI for fiber (see Table 44-3).

The majority of carbohydrates are present as starches or sugars in food. Simple sugars (mono- and disaccharides) are often added to foods and beverages during food preparation, processing, and packaging to enhance palatability and as preservatives. Nondiet soft drinks, juice drinks, iced tea, and sport drinks are among the major contributors to added sugars in the diet of U.S. children and adolescents. Added sugars increase the risk for obesity, diabetes, and dental caries. Fructose is one such added sugar in the form of high-fructose corn syrup, which is nearly ubiquitous in the U.S. diet. Fructose increases HDL and triglyceride production in the liver and serum uric acid levels which increase systolic blood pressure and is associated with fatty liver disease and metabolic syndrome. Excessive fructose intake, such as in the form of fruit juices, is associated with diarrhea, abdominal pain, and failure to thrive in children.

The **glycemic index** is a measure of the height of blood sugar levels 2 hours following ingestion against the reference standard (a slice of white bread). The glycemic index has predictable effects on blood glucose, hemoglobin A_{1C}, insulin, triglycerides, and HDL cholesterol levels. Lower glycemic index foods are recommended and may reduce the risk of insulin resistance and cardiovascular disease.

FIBER

Fiber consists of nondigestible carbohydrates mostly derived from plant sources, such as whole grain, fruits, and vegetables, that escape digestion and reach the colon nearly 100% intact. These compounds were previously classified as being water soluble versus insoluble, which may be a relatively less meaningful distinction, although still commonly used. The DRI classification lists **dietary fiber** (nondigestible carbohydrates and lignin that are intrinsic and intact in plants), **functional fiber** (with known physiologic benefits in humans), and **total fiber** (dietary plus functional).

Although fiber intake does not contribute significantly to energy intake, it does play several important roles. The metabolic fate of fiber is influenced primarily by the colonic bacteria, which depending on the structure of the fiber, can render it susceptible to fermentation (e.g., pectin and oat bran). Common by-products of colonic fermentation include carbon dioxide, methane (in addition to other gases), **oligofructases** (also known as prebiotics-substrates that nourish beneficial commensurate gastrointestinal microbiota), and **short-chain fatty acids (SCFAs)**. The common SCFAs produced by fermentation include acetate, butyrate, and propionate. There is dynamic interplay between the colonic bacterial milieu and the diet. SCFAs influence colonic physiology by stimulating colonic blood flow and fluid and electrolyte uptake. Butyrate is the preferred fuel for the colonocyte, and it might have a role in maintaining the normal phenotype in these cells.

Dietary fiber might play an important role by diluting toxins, carcinogens, and tumor promoters; by decreasing transit time, thereby decreasing colonic mucosal exposure; and by promoting their expulsion in the fecal stream. Dietary fiber resistant to colonic degradation might also play a role in maintaining and promoting stool bulk and in the regulation of intraluminal pressure and colonic wall resistance, disordered colonic motility, or both. Lack of dietary fiber is associated with constipation and diverticulosis.

All fiber slows gastric emptying and promotes satiety, and thus may help to regulate appetite. Dietary fiber may decrease the rate of release and absorption of simple sugars, and help in the regulation of blood sugar, with lower postprandial blood sugars observed. Dietary fiber has a low glycemic index, and may have a beneficial effect on insulin sensitivity. Fiber also binds luminal cholesterol and reduces absorption and/or enterohepatic circulation of the cholesterol in bile salts (with the intake of more viscous forms of dietary fiber, such as pectin). Soluble fiber types (such as guar gum, oat products, pectin) lower serum cholesterol, while insoluble fiber may reduce serum triglycerides. However, fiber such as psyllium, resistant dextrins, and resistant starch may also have a role in lowering both serum LDL and triglycerides. Decreased fiber intake in Western society has been associated with the increasing incidence and prevalence of diabetes, obesity, cardiovascular disease, colon cancer, and inflammatory bowel disease.

Data are insufficient to establish an EAR for dietary fiber. An AI for dietary fiber has been established based on the intake levels associated with reducing risk for cardiovascular disease and in lowering or normalizing serum cholesterol (see Table 44-3). An UL has not been established for fibers, which are not thought to be harmful to human health. A general rule of thumb used for fiber intake in children is: *age (in years) + 5 = grams of fiber intake per day*.

MICRONUTRIENTS

Vitamins and trace minerals or **micronutrients** play an essential role in growth and development and contribute to a host of physiologic functions. Many U.S. children have suboptimal intake of iron, zinc, potassium, calcium, vitamin D, and vitamin K, and excess intakes of sodium. Dietary recommendations for micronutrients were originally established to prevent deficiency but also include the impact of micronutrients on long-term health outcomes (Table 44-5). Food fortification is an effective strategy to prevent some nutrient deficiencies, and

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Table 44-5 Dietary Reference Intakes for Vitamins

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Biotin	Coenzyme in synthesis of fat, glycogen, and amino acids	*Infants (µg/day)*			Liver Smaller amounts in fruits and meats	No adverse effects of biotin in humans or animals have been found; this does not mean there is no potential for adverse effects resulting from high intakes Because data on the adverse effects of biotin are limited, caution may be warranted	None
		0-6 mo	5*	ND			
		7-12 mo	6*	ND			
		Children (µg/day)					
		1-3 yr	8*	ND			
		4-8 yr	12*	ND			
		Males (µg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Females (µg/day)					
		9-13 yr	20*	ND			
		14-18 yr	25*	ND			
		19-21 yr	30*	ND			
		Pregnancy (µg/day)					
		≤18 yr	30*	ND			
		19-21 yr	30*	ND			
		Lactation (µg/day)					
		≤18 yr	35*	ND			
		19-21 yr	35*	ND			
Choline	Precursor for acetylcholine, phospholipids, and betaine	*Infants (mg/day)*			Milk, liver, eggs, peanuts	Fishy body odor, sweating, salivation, hypotension, hepatotoxicity	Patients with trimethylaminuria, renal disease, liver disease, depression, and Parkinson disease may be at risk for adverse effects with choline intakes at the UL AIs have been set for choline, but there is little data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and the choline requirement might be met by endogenous synthesis at some of these stages
		0-6 mo	125*	ND			
		7-12 mo	150*	ND			
		Children (mg/day)					
		1-3 yr	200*	1,000			
		4-8 yr	250*	1,000			
		Males (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	550*	3,000			
		19-21 yr	550*	3,500			
		Females (mg/day)					
		9-13 yr	375*	2,000			
		14-18 yr	400*	3,000			
		19-21 yr	425*	3,500			
		Pregnancy (mg/day)					
		≤18 yr	450*	3,000			
		19-21 yr	450*	3,500			
		Lactation (mg/day)					
		≤18 yr	550*	3,000			
		19-21 yr	550*	3,500			

Folate aka folic acid, folacin, pteroyl-polyglutamates given as dietary folate equivalents (DFE) 1 DFE = 1 μg food folate = 0.6 μg folate from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach	Coenzyme in the metabolism of nucleic and amino acids Prevents megaloblastic anemia	*Infants (μg/day)* 0-6 mo 65* ND 7-12 mo 80* ND *Children (μg/day)* 1-3 yr **150** 300 4-8 yr **200** 400 *Males (μg/day)* 9-13 yr **300** 600 14-18 yr **400** 800 19-21 yr **400** 1,000 *Females (μg/day)* 9-13 yr **300** 600 14-18 yr **400** 800 19-21 yr **400** 1,000 *Pregnancy (μg/day)* ≤18 yr **600** 800 19-21 yr **600** 1,000 *Lactation (μg/day)* ≤18 yr **500** 800 19-21 yr **500** 1,000	Enriched cereal, grains, dark leafy vegetables, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	Masks neurologic complications in people with vit B12 deficiency No adverse effects associated with folate from food or supplements have been reported; this does not mean that there is no potential for adverse effects resulting from high intakes Because data on adverse effects of folate are limited, caution may be warranted UL for folate applies to synthetic forms obtained from supplements and/or fortified foods	In view of evidence linking poor folate intake with neural tube defects, all women who can become pregnant should consume 400 μg/day from supplements or fortified foods in addition to intake of food folate from a varied diet
Niacin Includes nicotinic acid amide, nicotinic acid (pyridine-3 carboxylic acid), and derivatives that exhibit the biologic activity of nicotinamide Given as niacin equivalents (NE) 1 mg niacin = 60 mg tryptophan 0-6 mo = preformed niacin (not NE)	Coenzyme or cosubstrate in many biologic reduction and oxidation reactions, thus required for energy metabolism	*Infants (mg/day)* 0-6 mo 2* ND 7-12 mo 4* ND *Children (mg/day)* 1-3 yr **6** 10 4-8 yr **8** 15 *Males (mg/day)* 9-13 yr **12** 20 14-18 yr **16** 30 19-21 yr **16** 35 *Females (mg/day)* 9-13 yr **12** 20 14-18 yr **14** 30 19-21 yr **14** 35 *Pregnancy (mg/day)* ≤18 yr **18** 30 19-21 yr **18** 35 *Lactation (mg/day)* ≤18 yr **17** 30 19-21 yr **17** 35	Meat, fish, poultry, enriched and whole-grain breads and bread products, fortified ready-to-eat cereals	No evidence of adverse effects from consuming naturally occurring niacin in food Adverse effects from niacin-containing supplements can include flushing and GI distress UL for niacin applies to synthetic forms obtained from supplements, fortified food, or a combination of these	Extra niacin may be required by persons treated with hemodialysis or peritoneal dialysis or those with malabsorption syndrome

Continued

Table 44-5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Pantothenic acid	Coenzyme in fatty acid metabolism	*Infants (mg/day)*			Chicken, beef, potatoes, oats, cereals, tomato products, liver, kidney, yeast, egg yolk, broccoli, whole grains	No adverse effects associated with pantothenic acid from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intakes Because data on adverse effects of pantothenic acid are limited, caution may be warranted	None
		0-6 mo	1.7*	ND			
		7-12 mo	1.8*	ND			
		Children (mg/day)					
		1-3 yr	2*	ND			
		4-8 yr	3*	ND			
		Males (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Females (mg/day)					
		9-13 yr	4*	ND			
		14-18 yr	5*	ND			
		19-21 yr	5*	ND			
		Pregnancy (mg/day)					
		≤18 yr	6*	ND			
		19-21 yr	6*	ND			
		Lactation (mg/day)					
		≤18 yr	7*	ND			
		19-21 yr	7*	ND			
Riboflavin aka vitamin B_2	Coenzyme in numerous redox reactions	*Infants (mg/day)*			Organ meats, milk, bread products, fortified cereals	No adverse effects associated with vitamin B_2 consumption from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_2 are limited, caution may be warranted	None
		0-6 mo	0.3*	ND			
		7-12 mo	0.4*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.3**	ND			
		19-21 yr	**1.3**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.6**	ND			
		19-21 yr	**1.6**	ND			

Thiamin aka vitamin B_1, aneurin	Coenzyme in the metabolism of carbohydrates and branched-chain amino acids	*Infants (mg/day)*			Enriched, fortified, or whole-grain products, bread and bread products, mixed foods whose main ingredient is grain, ready-to-eat cereals	No adverse effects associated with vitamin B_1 consumption from food or supplements have been reported; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_1 are limited, caution may be warranted	Persons who might have increased need for vitamin B_1 include those being treated with hemodialysis or persons with a malabsorption syndrome
		0-6 mo	0.2*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	ND			
		4-8 yr	**0.6**	ND			
		Males (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.2**	ND			
		19-21 yr	**1.2**	ND			
		Females (mg/day)					
		9-13 yr	**0.9**	ND			
		14-18 yr	**1.0**	ND			
		19-21 yr	**1.1**	ND			
		Pregnancy (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
		Lactation (mg/day)					
		≤18 yr	**1.4**	ND			
		19-21 yr	**1.4**	ND			
Vitamin A Includes provitamin A carotenoids that are dietary precursors of retinol Given as retinol activity equivalents (RAEs) 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin To calculate RAEs from REs of provitamin A carotenoids in food, divide the REs by 2 For preformed vitamin A in food or supplements and for provitamin A carotenoids in supplements, 1 RE = 1 RAE	Required for normal vision, gene expression, reproduction, embryonic development, and immune function	*Infants (μg/day)*			Liver, dairy products, fish, dark-colored fruit, leafy vegetables	Teratologic effects, liver toxicity (from preformed vitamin A only)	Persons with high alcohol intake, pre-existing liver disease, hyperlipidemia, or severe protein malnutrition may be distinctly susceptible to the adverse effects of excess preformed vitamin A intake β-Carotene supplements are advised only to serve as a provitamin A source for persons at risk for vitamin A deficiency
		0-6 mo	400*	600			
		7-12 mo	500*	600			
		Children (μg/day)					
		1-3 yr	**300**	600			
		4-8 yr	**400**	900			
		Males (μg/day)					
		9-13 yr	**600**	1,700			
		14-18 yr	**900**	2,800			
		19-21 yr	**900**	3,000			
		Females (μg/day)					
		9-13 yr	**600**	1,700			
		14-18 yr	**700**	2,800			
		19-21 yr	**700**	3,000			
		Pregnancy (μg/day)					
		≤18 yr	**750**	2,800			
		19-21 yr	**770**	3,000			
		Lactation (μg/day)					
		≤18 yr	**1,200**	2,800			
		19-21 yr	**1,300**	3,000			

Continued

Table 44-5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin B_6 Comprises a group of 6 related compounds: pyridoxal, pyridoxine, pyridoxamine, and 5′-phosphates (PLP, PNP, PMP)	Coenzyme in the metabolism of amino acids, glycogen, and sphingoid bases	*Infants (mg/day)*			Fortified cereals, organ meats, fortified soy-based meat substitutes	No adverse effects associated with vitamin B_6 from food have been reported; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_6 are limited, caution may be warranted Sensory neuropathy has occurred from high intakes of supplemental forms	None
		0-6 mo	0.1*	ND			
		7-12 mo	0.3*	ND			
		Children (mg/day)					
		1-3 yr	**0.5**	30			
		4-8 yr	**0.6**	40			
		Males (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.3**	80			
		19-21 yr	**1.3**	100			
		Females (mg/day)					
		9-13 yr	**1.0**	60			
		14-18 yr	**1.2**	80			
		19-21 yr	**1.3**	100			
		Pregnancy (mg/day)					
		≤18 yr	**1.9**	80			
		19-21 yr	**1.9**	100			
		Lactation (mg/day)					
		≤18 yr	**2.0**	80			
		19-21 yr	**2.0**	100			
Vitamin B_{12} aka cobalamin	Coenzyme in nucleic acid metabolism Prevents megaloblastic anemia	*Infants (μg/day)*			Fortified cereals, meat, fish, poultry	No adverse effects have been associated with consumption of the amounts of vitamin B_{12} normally found in food or supplements; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin B_{12} are limited, caution may be warranted	Because 10-30% of older people malabsorb food-bound vitamin B_{12}, those >50 yr are advised to meet their RDA mainly by consuming foods fortified with vitamin B_{12} or a supplement containing vitamin B_{12}
		0-6 mo	0.4*	ND			
		7-12 mo	0.5*	ND			
		Children (μg/day)					
		1-3 yr	**0.9**	ND			
		4-8 yr	**1.2**	ND			
		Males (μg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Females (μg/day)					
		9-13 yr	**1.8**	ND			
		14-18 yr	**2.4**	ND			
		19-21 yr	**2.4**	ND			
		Pregnancy (μg/day)					
		≤18 yr	**2.6**	ND			
		19-21 yr	**2.6**	ND			
		Lactation (μg/day)					
		≤18 yr	**2.8**	ND			
		19-21 yr	**2.8**	ND			

Vitamin C aka ascorbic acid, dehydroascorbic acid (DHA)	Cofactor for reactions requiring reduced copper or iron metalloenzyme and as a protective antioxidant	*Infants (mg/day)*			Citrus fruit, tomatoes, tomato juice, potatoes, Brussels sprouts, cauliflower, broccoli, strawberries, cabbage, spinach	GI disturbances, kidney stones, excess iron absorption	Smokers require additional 35 mg/day of vitamin C over that needed by nonsmokers Nonsmokers regularly exposed to tobacco smoke should ensure they meet the RDA for vitamin C
		0-6 mo	40*	ND			
		7-12 mo	50*	ND			
		Children (mg/day)					
		1-3 yr	**15**	400			
		4-8 yr	**25**	650			
		Males (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**75**	1,800			
		19-21 yr	**90**	2,000			
		Females (mg/day)					
		9-13 yr	**45**	1,200			
		14-18 yr	**65**	1,800			
		19-21 yr	**75**	2,000			
		Pregnancy (mg/day)					
		≤18 yr	**80**	1,800			
		19-21 yr	**85**	2,000			
		Lactation (mg/day)					
		≤18 yr	**115**	1,800			
		19-21 yr	**120**	2,000			
Vitamin E aka α-tocopherol α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, RRS-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements	A metabolic function has not yet been identified Vitamin E's major function appears to be as a nonspecific chain-breaking antioxidant	*Infants (mg/day)*			Vegetable oil, unprocessed cereal grains, nuts, fruit, vegetables, meat	No evidence of adverse effects from consuming vitamin E naturally occurring in food Adverse effects from vitamin E–containing supplements may include hemorrhagic toxicity UL for vitamin E applies to any form of α-tocopherol obtained from supplements, fortified foods, or a combination of these	Patients on anticoagulant therapy should be monitored when taking vitamin E supplements
		0-6 mo	4*	ND			
		7-12 mo	5*	ND			
		Children (mg/day)					
		1-3 yr	**6**	200			
		4-8 yr	**7**	300			
		Males (mg/day)					
		9-13 yr	**11**	600			
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Females (mg/day)					
		9-13 yr	**11**	600			
		14-18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Pregnancy (mg/day)					
		≤18 yr	**15**	800			
		19-21 yr	**15**	1,000			
		Lactation (mg/day)					
		≤18 yr	**19**	800			
		19-21 yr	**19**	1,000			

Continued

Table 44-5 Dietary Reference Intakes for Vitamins—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	RDA OR AI	UL	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Vitamin K	Coenzyme during the synthesis of many proteins involved in blood clotting and bone metabolism	*Infants (μg/day)*			Green vegetables (collards, spinach, salad greens, broccoli), Brussels sprouts, cabbage, plant oil, margarine	No adverse effects associated with vitamin K consumption from food or supplements have been reported in humans or animals; this does not mean there is no potential for adverse effects resulting from high intake Because data on adverse effects of vitamin K are limited, caution may be warranted	Patients on anticoagulant therapy should monitor vitamin K intake
		0-6 mo	2.0*	ND			
		7-12 mo	2.5*	ND			
		Children (μg/day)					
		1-3 yr	30*	ND			
		4-8 yr	55*	ND			
		Males (μg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	120*	ND			
		Females (μg/day)					
		9-13 yr	60*	ND			
		14-18 yr	75*	ND			
		19-21 yr	90*	ND			
		Pregnancy (μg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			
		Lactation (μg/day)					
		≤18 yr	75*	ND			
		19-21 yr	90*	ND			

Note: Starred numbers are AI, and bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all members of the group, but lack of data prevents specifying with confidence the percentage covered by this intake.

UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

ND amounts are not determinable because of a lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*Adequate intake. *RDA for vitamin D in IU/day: 400 if <1 yr age, 600 if >1 yr, lactating, or pregnant.

AI, adequate intake; GI, gastrointestinal; ND, not determinable; PLP, pyridoxal phosphate; PMP, pyridoxamine phosphate; PNP, pyridoxine phosphate; RDA, recommended dietary allowance; UL, upper limit.

Adapted from Food and Nutrition Board, Institute of Medicine: Dietary reference intakes for calcium, phosphorous, magnesium, vitamin D, and fluoride *(website),* www.nap.edu/openbook.php?record_id=5776; Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline *(website),* www.nap.edu/openbook.php?record_id=6015; Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids *(website),* www.nap.edu/openbook.php?record_id=9810; *and* Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc *(website),* www.nap.edu/openbook.php?record_id=10026.

has been successfully implemented to prevent iodine and folate deficiency.

Breast milk provides optimal intake of most nutrients including iron and zinc. Although they present in lower amounts than in infant formula, they are more bioavailable and sufficient to meet infant needs until ~4-6 mo of age. After 4-6 mo of age, iron and zinc are required from complementary foods, such as iron-fortified cereal and pureed meats.

Iron requirements are higher during infancy and childhood as compared to later life stages, and are higher for menstruating females as compared to males of similar age groups (see Chapter 54). Iron present in animal protein is more bioavailable than that found in vegetables and other foods because it is already incorporated into heme moieties in blood and muscle. Iron deficiency is the most common micronutrient deficiency and is associated with iron-deficiency anemia and neurocognitive deficits. **Zinc** deficiency affects millions of children and is associated with increased risk for impaired linear growth (stunting), impaired immune function, and increased risk for respiratory and diarrheal diseases.

Breast milk is a poor source of **vitamin D** (see Chapter 51). Vitamin D insufficiency is more common than previously thought in infants and children. Vitamin D is central to calcium and bone metabolism, but is also an important determinant of various nonosseous health outcomes. Vitamin D is absorbed in the skin from sunlight and is also present naturally in some foods and fortified in all cow milk products, regardless of fat content, soy milk, almond milk, and orange juice. Sunlight exposure varies by season. Therefore, for populations residing in northern latitudes and/or who have darker skin, sunlight exposure is unlikely to meet the vitamin D needs over the year; in these groups, additional sunlight exposure and/or vitamin D supplementation may be required to achieve optimal status.

Children with darker skin and those who do not consume fortified products should be screened for vitamin D deficiency. The DRI for vitamin D is based on its effects on calcium status and bone health. The goal is to achieve serum levels of 25(OH) D levels above 50 nmol/L (30 ng/dL), which is often achieved using vitamin D supplementation. In 2010, the American Academy of Pediatrics increased total vitamin D intake recommendations to 600 IU/day for infants and children. A supplement was recommended for all breast-fed infants to ensure sufficient intake.

Calcium adequacy is determined in part as a function of bone health as measured by bone mineral content and density. The main storage organs for calcium are the bones and teeth. Bone mineral accretion occurs primarily in the pediatric age range, with peak bone mass being achieved by the 2nd to 3rd decade of life. Calcium recommendations vary by age and were also increased from AI to RDA, and the UL was increased in 9-18 yr olds (Table 44-6).

Vitamin K is an important determinant of bone health, but is also an important cofactor for coagulation factors (factors II, VII, IX, and X; protein C; and protein S) (see Chapter 53). Status can be assessed by prothrombin time, protein in the absence of vitamin K (PIVKA-II) and the vitamin K–dependent coagulation factor levels. Neonates are at risk for suboptimal vitamin K status, leading to an increased risk for hemorrhagic disease of the newborn. Vitamin K prophylaxis at birth is recommended for all newborn infants.

Potassium and sodium are the main intra- and extracellular cations, respectively, and are involved in transport of fluids and nutrients across the cellular membrane. There is an AI set for **potassium** related to its effects in maintaining a healthy blood pressure, reducing risk for nephrolithiasis, and supporting bone health. Moderate potassium deficiency can occur even in the absence of hypokalemia and can result in increased blood pressure, stroke, and other cardiovascular disease. Most American children have potassium intake below the current recommendations. African-Americans in particular are at increased risk for potassium deficiency. For people at increased risk for hypertension and who are salt sensitive, reducing sodium intake and increasing potassium intake is advised. Leafy green vegetables, vine fruit (such as tomatoes) and root vegetables are good food sources of potassium (see Table 44-6). People with impaired renal function may need to reduce potassium intake as hyperkalemia can increase risk for fatal cardiac arrhythmias among these patients.

Sodium has an AI, but given the risk of hypertension, an UL has also been set. The UL threshold may be even lower in African-Americans, who, on average, are more salt sensitive, and for those with hypertension or preexisting renal disease. Dietary sodium intake also displaces potassium intake. Elevated sodium: potassium ratios can increase the risk for nephrolithiasis. Intakes of <2,300 mg (approximately 1 tsp) per day are recommended. The average daily salt intake for most people in the United States and Canada exceeds both the AI and UL. Most dietary salt in the United States is found in processed foods, breads, condiments, and as a food preservative, and to enhance palatability. *For populations with or at risk for hypertension and renal disease, sodium intake should be decreased to <1,500 mg/day and potassium intake increased to >4,700 mg/day.* For persons with hypertension, additional dietary guidelines are available from the Dietary Approaches to Stop Hypertension (DASH) eating plan.

WATER

The water requirement and content as a proportion of body weight are highest in infants and decrease with age. Water intake is achieved with liquid and food intake, and losses include excretion in the urine and stool as well as insensible and evaporative losses through the skin and respiratory tract. An AI has been established for water (see Table 44-6). Special considerations are required by life stages and by basal metabolic rate, physical activity, body proportions (surface area to volume), environment, and underlying medical conditions. Breast milk and infant formula provide adequate water, and additional water intake is not required until complementary foods are introduced. Although water contains no calories, the concern is that water intake might actually decrease breast milk intake and displace the intake of essential nutrients during this metabolically very active life stage. The increased fluid needs of infants and young children can be explained in part by the high ratio of body surface area to volume in infancy and high respiratory rate.

The consequences of inadequate fluid intake include dehydration, impaired thermoregulation and heat dissipation, reduced activity tolerance and performance, and reduced intravascular fluid. These deficits can result in an increased compensatory heart rate, hypotension and syncope, and, if uncorrected, renal injury or nephrolithiasis. Excess free water intake is usually better tolerated by healthy adults than by younger children, who may be at increased risk for water intoxication. Hyponatremia can result from excess free water intake coupled with inadequate sodium intake. Fluid intake requirements and restrictions are also influenced by underlying renal and hormonal disorders, including diabetes, the syndrome of inappropriate antidiuretic hormone secretion, and diabetes insipidus.

MEASURING NUTRITIONAL ADEQUACY

Growth according to expected patterns can be tracked using the 2000 Centers for Disease Control and Prevention (CDC) and 2006 WHO growth charts (see Chapters 6 and 15). The WHO growth charts are derived from longitudinal and cross-sectional data obtained from a sample of healthy breast-fed infants and children (0-5 yr) who were receiving adequate nutritional intake and medical care from Brazil, Ghana, India, Norway, Oman, and the United States. Consequently, the WHO growth charts are not only descriptive of population average and distribution, but are also prescriptive regarding how adequately nourished healthy children under best-care practices should grow. The CDC and American Academy of Pediatrics recommend the use of the WHO charts to monitor growth of all infants and children (breast and bottle or infant formula fed) from birth to 2 yr of age, and the use of the CDC 2000 growth charts for children 2 to 20 yr of age.

Although the WHO and CDC growth charts are recommended for growth and nutritional assessment, a number of disease-specific charts are available. It is noteworthy that many other disease- or syndrome-specific growth charts are based on small samples of children, and include children with suboptimal nutritional status. For these patient

Text continued on p. 286

Table 44-6 Dietary Reference Intakes for Select Micronutrients and Water

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Sodium	Maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added sodium chloride (salt), benzoate, phosphate; salted meats, bread, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table Salt is ~ 40% sodium by weight	Hypertension Increased risk of cardiovascular disease and stroke	AI is set based on ability to obtain a nutritionally adequate diet for other nutrients and to meet the needs for sweat losses for persons engaged in recommended levels of physical activity Persons engaged in activity at higher levels or in humid climates resulting in excessive sweat might need more than the AI UL applies to apparently healthy persons without hypertension; it thus may be too high for persons who already have hypertension or who are under the care of a health professional
		0-6 mo	120	ND			
		7-12 mo	370	ND			
		Children					
		1-3 yr	1,000	1,500			
		4-8 yr	1,200	1,900			
		Males					
		9-13 yr	1,500	2,200			
		14-21 yr	1,500	2,300			
		Females					
		9-13 yr	1,500	2,200			
		13-21 yr	1,500	2,300			
		Pregnancy and Lactation					
		≥14 yr	1,500	2,300			
Chloride	With sodium, maintains fluid volume outside of cells and thus normal cell function	*Infants*			Processed foods with added sodium chloride (salt), benzoate, phosphate; salted meats, nuts, cold cuts; margarine; butter; salt added to foods in cooking or at the table Salt is ~60% chloride by weight	In concert with sodium, results in hypertension	Chloride is lost, usually with sodium, in sweat, as well as in vomiting and diarrhea AI and UL are equimolar in amount to sodium because most of sodium in diet comes as sodium chloride (salt)
		0-6 mo	180	ND			
		7-12 mo	570	ND			
		Children					
		1-3 yr	1,500	2,300			
		4-8 yr	1,900	2,900			
		Males					
		9-13 yr	2,300	3,400			
		14-21 yr	2,300	3,600			
		Females					
		9-13 yr	2,300	3,400			
		13-21 yr	2,300	3,600			
		Pregnancy and Lactation					
		≥14 yr	2,300	3,600			
Potassium	Maintains fluid volume inside/outside of cells and thus normal cell function; acts to blunt the rise of blood pressure in response to excess sodium intake, and decrease markers of bone turnover and recurrence of kidney stones	*Infants*			Fruits and vegetables, dried peas, dairy products, meats, nuts	None documented from food alone, but potassium from supplements or salt substitutes can result in hyperkalemia and possibly sudden death if excess is consumed by persons with chronic renal insufficiency (kidney disease) or diabetes	Persons taking drugs for cardiovascular disease such as ACE inhibitors, ARBs, or potassium-sparing diuretics should be careful not to consume supplements containing potassium and might need to consume less than the AI
		0-6 mo	400	None set			
		7-12 mo	700				
		Children					
		1-3 yr	3,000	No UL			
		4-8 yr	3,800				
		Males					
		9-13 yr	4,500				
		14-21 yr	4,700				
		Females					
		9-13 yr	4,500				
		13-21 yr	4,700				
		Pregnancy					
		≥14 yr	4,700				
		Lactation					
		≥14 yr	5,100				

Vitamin D aka calciferol **1 µg calciferol = 40 IU vitamin D** DRI values are based on absence of adequate exposure to sunlight	Maintains serum calcium and phosphorus concentrations	*Infants (µg/day)**			Fish liver oils, flesh of fatty fish, liver and fat from seals and polar bears, eggs from hens that have been fed vitamin D, fortified milk products, fortified cereals	Elevated plasma 25(OH)D concentration causing hypercalcemia	Patients on glucocorticoid therapy might require additional vitamin D
		0-6 mo	10	25			
		7-12 mo	10	38			
		*Children (µg/day)**					
		1-3 yr	15	63			
		4-8 yr	15	75			
		*Males (µg/day)**					
		9-21yr	15	100			
		*Females (µg/day)**					
		9-21 yr	15	100			
		*Pregnancy (µg/day)**					
		≤18 yr	15	100			
		Lactation (µg/day)					
		≤18 yr	15	100			
		19-21 yr	15	100			
Calcium	Essential role in blood clotting, muscle contraction, nerve transmission, and bone and tooth formation	*Infants*			Milk, cheese, yogurt, corn tortillas, calcium-set tofu, Chinese cabbage, kale, broccoli	Kidney stones, hypercalcemia, milk alkali syndrome, and renal insufficiency	Amenorrheic women (exercise- or anorexia nervosa–induced) have reduced net calcium absorption
		0-6 mo	200	1,000			
		7-12 mo	260	1,500			
		Children					
		1-3 yr	700	2,500			
		4-8 yr	1,000	2,500			
		Males					
		9-18 yr	1,300	3,000			
		19-21 yr	1,000	2,500			
		Females					
		9-18 yr	1,300	3,000			
		19-21 yr					
		Pregnancy					
		≤18 yr	1,300	3,000			
		19-21 yr	1,000	2,500			
		Lactation					
		≤18 yr	1,300	3,000			
		19-21 yr	1,000	2,500			

Continued

Table 44-6 Dietary Reference Intakes for Select Micronutrients and Water—cont'd

NUTRIENT	FUNCTION	LIFE-STAGE GROUP	AI (mg/day)	UL (mg/day)	SELECTED FOOD SOURCES	ADVERSE EFFECTS OF EXCESSIVE CONSUMPTION	SPECIAL CONSIDERATIONS
Iron	Critical component of enzymes, cytochromes, myoglobin, and hemoglobin	*Infants*			Heme sources: meat, poultry, fish Nonheme sources: dairy, eggs, plant-based foods, breads, cereals, breakfast foods	GI distress	Persons with decreased gastric acidity may be at increased risk for deficiency Cow's milk is a poor source of bioavailable iron and is not recommended for children <1 yr old Neurocognitive deficits have been reported in infants with iron deficiency RDA for females increases with menarche related to increased losses during menstruation Vegans and vegetarians might require iron supplementation or intake of iron-fortified foods GI parasites can increase iron losses via GI bleeds Iron supplements can interfere with zinc absorption and vice versa; if supplements are being used, the doses should be staggered
		0-6 mo	0.27	40			
		7-12 mo	11	40			
		Children					
		1-3 yr	7	40			
		4-8 yr	10	40			
		Males					
		9-13 yr	8	40			
		14-18 yr	11	45			
		19-21 yr	8	45			
		Females					
		9-13 yr	8	40			
		14-18 yr	15	45			
		19-21 yr	18	45			
		Pregnancy					
		≤18 yr	27	45			
		19-21 yr	27	45			
		Lactation					
		≤18 yr	10	45			
		19-21 yr	9	45			
Zinc	Essential for proper growth and development, and an important catalyst for 100 specific enzymes	*Infants*			Meats, shellfish, legumes, fortified cereals, whole grains	Acutely zinc supplements cause GI irritation and headache; chronic effects of zinc supplementation include impaired immune function, changes in lipoprotein and cholesterol levels, and reduced copper status	Zinc supplements interfere with iron absorption and vice versa; therefore, if supplements are being used, the doses should be staggered Zinc deficiency can be associated with stunting or impaired linear growth
		0-6 mo	2	4			
		7-12 mo	3	5			
		Children					
		1-3 yr	3	7			
		4-8 yr	5	12			
		Males					
		9-13 yr	8	23			
		14-18 yr	11	34			
		19-21 yr	11	40			
		Females					
		9-13 yr	8	23			
		14-18 yr	9	34			
		19-21 yr	8	40			
		Pregnancy					
		≤18 yr	12	34			
		19-21 yr	11	40			
		Lactation					
		≤18 yr	13	34			
		19-21 yr	12	40			

Water	Maintains homeostasis in the body Allows transport of nutrients to cells and removal and excretion of waste products of metabolism	*Infants (L/day)*		None set	All beverages, including water Moisture in foods High-moisture foods include watermelon, meats, soups	No UL because normally functioning kidneys can handle >0.7 L (24 oz) of fluid per hour Symptoms of water intoxication include hyponatremia, which can result in heart failure, and rhabdomyolysis (skeletal muscle tissue injury), which can lead to kidney failure	Recommended intakes for water are based on median intakes of generally healthy persons who are adequately hydrated Persons can be adequately hydrated at levels above or below the AIs provided; AIs provided are for total water in temperate climates All sources can contribute to total water needs: beverages (tea, coffee, juice, soda, and drinking water) and moisture found in foods Moisture in food accounts for ~ 20% of total water intake Thirst and consumption of beverages at meals are adequate to maintain hydration
		0-6 mo	0.7				
		7-12 mo	0.8				
		Children					
		1-3 yr	1.3				
		4-8 yr	1.7				
		Males (L/day)					
		9-13 yr	2.4				
		14-18 yr	3.3				
		≥19 yr	3.7				
		Females (L/day)					
		9-13 yr	2.1				
		14-18 yr	2.3				
		≥19 yr	2.7				
		Pregnancy (L/day)					
		≥14 yr	3.0				
		Lactation (L/day)					
		≥14 yr	3.8				

Note: Bold numbers are RDA. RDAs and AIs may both be used as goals for individual intake. RDAs are set to meet the needs of 97-98% of members in a group. For healthy breast-fed infants, the AI is the mean intake. The AI for other life-stage and gender groups is believed to cover the needs of all members of a group, but lack of data prevents specifying with confidence the percentage covered by this intake. UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Because of a lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes. ND amounts are not determinable because of a lack of data on adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

*Vitamin D RDA in IU/day: 40 if <1 yr, 600 if >1 yr of age or pregnant or lactating.

ACE, angiotensin-converting enzyme; AI, adequate intake; ARB, angiotensin receptor blocker; GI, gastrointestinal; ND, not determinable; RDA, recommended dietary allowance; UL, upper limit.

Adapted from Food and Nutrition Board, Institute of Medicine: Dietary reference intakes for water, potassium, sodium, chloride, and sulfate *(website). http://www.nap.edu/openbook.php?record_id=10925.*

groups, disease-specific charts may be helpful to use in conjunction with the WHO or CDC growth charts for comparison to children of similar age and sex from the general population. The goal should be to use this information to approximate growth as closely to that of the general population as possible in these subsets of children, where and when possible. In addition to anthropometry, other nutrient biomarkers can be used to assess status. For infants and children with specific dietary or health concerns, consultation with lactation consultants, registered dieticians, and/or physician nutrition specialists may also be indicated.

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Chapter 45

Feeding Healthy Infants, Children, and Adolescents

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Early nutrition plays an important role in the origin of adult diseases such as type 2 diabetes, hypertension, obesity, and the metabolic syndrome; therefore, appropriate feeding practices should be established in the neonatal period and continued throughout childhood and adolescence to adulthood. Healthy feeding in children requires partnerships between family members, the healthcare system, schools, the community, and the government.

FEEDING DURING THE FIRST YEAR OF LIFE

Breastfeeding

The American Academy of Pediatrics (AAP) and World Health Organization (WHO) have declared breastfeeding and the administration of human milk to be the normative practice for infant feeding and nutrition. Breastfeeding has documented short- and long-term medical and neurodevelopmental advantages (Tables 45-1 and 45-2) and rare contraindications (Table 45-3). Thus the decision to breastfeed should be considered a public health issue and not only a lifestyle choice. The AAP and the WHO recommend that infants should be exclusively breastfed or given breast milk for 6 months. Breastfeeding should be continued with the introduction of complementary foods for 1 year or longer, as mutually desired by mother and infant. The success of breastfeeding initiation and continuation depends on multiple factors, such as education about breastfeeding, hospital breastfeeding practices and policies, routine and timely follow-up care, and family and societal support (Table 45-4).

Feedings should be initiated soon after birth unless medical conditions preclude them. Mothers should be encouraged to nurse at each breast at each feeding starting with the breast offered second at the last feeding. It is not unusual for an infant to fall asleep after the first breast and refuse the second. It is preferable to empty the first breast before offering the second in order to allow complete emptying of both breasts and therefore better milk production. Table 45-5 summarizes patterns of milk supply in the 1st week.

New mothers should be instructed about infant hunger cues, correct nipple latch, positioning of the infant on the breast, and feeding frequency. It is also suggested that someone trained in lactation observe a feeding to evaluate positioning, latch, milk transfer and maternal responses, and infant satiety. Attention to these issues during the birth hospitalization allows dialogue with the mother and family and can prevent problems that could occur with improper technique or knowledge of breastfeeding. As part of the discharge teaching process, issues surrounding infant feeding, elimination patterns, breast engorgement, basic breast care, and maternal nutrition should be discussed. A follow-up appointment is recommended within 24-48 hr after hospital discharge.

Table 45-1 Selected Beneficial Properties of Human Milk Compared to Infant Formula

Secretory IgA	Specific antigen-targeted antiinfective action
Lactoferrin	Immunomodulation, iron chelation, antimicrobial action, antiadhesive, trophic for intestinal growth
κ-Casein	Antiadhesive, bacterial flora
Oligosaccharides	Prevention of bacterial attachment
Cytokines	Antiinflammatory, epithelial barrier function
Growth factors	
Epidermal growth factor	Luminal surveillance, repair of intestine
Transforming growth factor (TGF)	Promotes epithelial cell growth (TGF-β) Suppresses lymphocyte function (TGF-β)
Nerve growth factor	Promotes neural growth
Enzymes	
Platelet-activating factor-acetylhydrolase	Blocks action of platelet-activating factor
Glutathione peroxidase	Prevents lipid oxidation
Nucleotides	Enhance antibody responses, bacterial flora

Adapted from Hamosh M: Bioactive factors in human milk, Pediatr Clin North Am *48:69–86, 2001.*

Table 45-2 Conditions for Which Human Milk Has Been Suggested to Possibly Have a Protective Effect

Acute disorders	Crohn disease
Diarrhea	Childhood cancer
Otitis media	Lymphoma
Urinary tract infection	Leukemia
Necrotizing enterocolitis	Recurrent otitis media
Septicemia	Allergy
Infant botulism	Obesity and overweight
Insulin-dependent diabetes mellitus	Hospitalizations
Celiac disease	Infant mortality

Nipple Pain

Nipple pain is one of the most common complaints of breastfeeding mothers in the immediate postpartum period. Poor infant positioning and improper latch are the most common reasons for nipple pain beyond the mild discomfort felt early in breastfeeding. If the problem persists and the infant refuses to feed, consideration needs to be given to nipple candidiasis. If present the mother should be treated with an antifungal cream that is wiped away before feeding, and the infant treated with oral medication.

Engorgement

In the second stage of lactogenesis, physiologic fullness of the breast occurs. Breasts may become engorged: firm, overfilled, and painful as the pattern and volume of milk production is adjusting to the infant's feeding schedule. Incomplete removal of milk as a result of poor breastfeeding technique or infant illness can cause engorgement. Breastfeeding immediately at signs of infant hunger will eventually prevent this

Table 45-3 Absolute and Relative Contraindications to Breastfeeding Because of Maternal Health Conditions

MATERNAL HEALTH CONDITION	DEGREE OF RISK
HIV and HTLV infection	In the United States, breastfeeding is contraindicated In other settings, health risks of not breastfeeding must be weighed against the risk of transmitting virus to the infant
Tuberculosis infection	Breastfeeding is contraindicated until completion of approximately 2 wk of appropriate maternal therapy
Varicella-zoster infection	Infant should not have direct contact to active lesions Infant should receive immune globulin
Herpes simplex infection	Breastfeeding is contraindicated with active herpetic lesions of the breast
CMV infection	May be found in milk of mothers who are CMV seropositive Transmission through human milk causing symptomatic illness in term infants is uncommon
Hepatitis B infection	Infants routinely receive hepatitis B immune globulin and hepatitis B vaccine if mother is HbsAg positive No delay in initiation of breastfeeding is required
Hepatitis C infection	Breast-feeding is not contraindicated
Alcohol intake	Limit maternal alcohol intake to <0.5 g/kg/day (for a woman of average weight, this is the equivalent of 2 cans of beer, 2 glasses of wine, or 2 oz of liquor)
Cigarette smoking	Discourage cigarette smoking, but smoking is not a contraindication to breastfeeding
Chemotherapy, radiopharmaceuticals	Breastfeeding is generally contraindicated

CMV, cytomegalovirus; HbsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus.

Data from Schanler RJ, Krebs NF, Mass SB (eds): Breastfeeding handbook for physicians, *ed 2, Elk Grove Village, IL, 2014, American Academy of Pediatrics, pp 223–226.*

from occurring. To reduce engorgement, breasts should be softened prior to infant feeding with a combination of hot compresses and expression of milk. Between feedings a supportive bra should be worn, cold compresses applied, and oral nonsteroidal antiinflammatory medications administered.

Mastitis

Mastitis occurs in 2-3% of lactating women and is usually unilateral, manifesting with localized warmth, tenderness, edema, and erythema after the second postdelivery week. Sudden onset of breast pain, myalgia, and fever with fatigue, nausea, vomiting, and headache can also occur. Organisms implicated in mastitis include *Staphylococcus aureus, Escherichia coli,* group A streptococcus, *Haemophilus influenzae, Klebsiella pneumoniae,* and *Bacteroides* spp. Diagnosis is confirmed by physical examination. Oral antibiotics and analgesics, while promoting breastfeeding or emptying of the affected breast, usually resolve the infection. A breast abscess is a less common complication of mastitis, but it is a more serious infection that requires intravenous antibiotics, incision, and drainage, along with temporary cessation of feeding from that breast.

Table 45-4 Recommendations on Breastfeeding Management for Healthy Term Infants

1. Exclusive breastfeeding for about 6 months
   - Breastfeeding preferred; alternatively expressed mother's milk, or donor breast milk
   - To continue for at least the first year and beyond as long as mutually desired by mother and child
   - Complementary foods rich in iron and other micronutrients should be introduced at about 6 mo of age
2. Peripartum policies and practices that optimize breastfeeding initiation and maintenance should be compatible with the AAP and Academy of Breastfeeding Medicine Model Hospital Policy and include the following:
   - Direct skin-to-skin contact with mothers immediately after delivery until the first feeding is accomplished and encouraged throughout the postpartum period
   - Delay in routine procedures (weighing, measuring, bathing, blood tests, vaccines, and eye prophylaxis) until after the first feeding is completed
   - Delay in administration of intramuscular vitamin K until after the first feeding is completed but within 6 hr of birth
   - Ensure 8-12 feedings at the breast every 24 hr
   - Ensure formal evaluation and documentation of breastfeeding by trained caregivers (including position, latch, milk transfer, examination) at least once for each nursing shift
   - Give no supplements (water, glucose water, commercial infant formula, or other fluids) to breastfeeding newborn infants unless medically indicated using standard evidence-based guidelines for the management of hyperbilirubinemia and hypoglycemia
   - Avoid routine pacifier use in the postpartum period
   - Begin daily oral vitamin D drops (400 IU) at hospital discharge
3. All breastfeeding infants should be seen by a pediatrician within 48 to 72 hr after discharge from the hospital
   - Evaluate hydration (elimination patterns)
   - Evaluate body weight gain (body weight loss no more than 7% from birth and no further weight loss by day 5: assess feeding and consider more frequent follow-up)
   - Discuss maternal/infant issues
   - Observe feeding
4. Mother and infant should sleep in proximity to each other to facilitate breastfeeding
5. Pacifier should be offered, while placing infant in back-to-sleep-position, no earlier than 3 to 4 weeks of age and after breastfeeding has been established

From American Academy of Pediatrics: Breast-feeding and the use of human milk, Pediatrics *129:e827–e841, 2012.*

Inadequate Milk Intake

Insufficient milk intake, dehydration, and jaundice in the infant can become evident within the first week of life. Signs of insufficient milk intake include: lethargy, delayed stooling, decreased urine output, weight loss >7% of birth weight, hypernatremic dehydration, inconsolable crying and increased hunger. Insufficient milk intake may be caused by insufficient milk production, failure of established breastfeeding, and health conditions in the infant that prevent proper breast stimulation. Parents should be counseled that breastfed neonates feed 8-12 times a day with a minimum of 8 times per day. Careful attention to prenatal history can identify maternal factors that may be associated with this problem (failure of breasts to enlarge during pregnancy or within the first few days after delivery). Direct observation of breastfeeding can help identify improper technique. If a large volume of milk is expressed manually after breastfeeding, then the infant might not be extracting enough milk, eventually leading to decreased milk output. Late preterm infants (34-36 wk) are at risk for insufficient milk syndrome because of poor suck and swallow patterns or medical issues.

Jaundice

Breastfeeding jaundice is a common reason for hospital readmission of healthy breastfed infants and is largely related to insufficient fluid

Table 45-5 Patterns of Milk Supply

DAY OF LIFE	MILK SUPPLY
Day 1	Some milk (~5 mL) may be expressed
Days 2-4	Lactogenesis, milk production increases
Day 5	Milk present, fullness, leaking felt
Day 6 onward	Breasts should feel "empty" after feeding

Adapted from Neifert MR: Clinical aspects of lactation: promoting breastfeeding success, Clin Perinatol *26:281–306, 1999.*

intake during the first week of life (see Chapter 102.3). It may also be associated with dehydration and hypernatremia. **Breast milk jaundice** is a different disorder that causes persistently high serum indirect bilirubin in a thriving healthy baby that becomes evident later than breastfeeding jaundice, but which generally declines in the 2nd to 3rd wk of life. Infants with severe or persistent jaundice should be evaluated for other medical causes (see Chapter 102.3) before ascribing the jaundice to breast milk that might contain inhibitors of glucuronyl transferase or enhanced absorption of bilirubin from the gut. Persistently high bilirubin levels may require changing from breast milk to infant formula for 24-48 hr and/or treatment with phototherapy without cessation of breastfeeding. Breastfeeding should resume after the decline in serum bilirubin. Parents should be reassured and encouraged to continue collecting breast milk during the period when the infant is taking formula.

Collecting Breast Milk

The pumping of breast milk is a common practice when the mother and baby are separated for work, illness, or hospitalization of mother or infant. Good hand washing and hygiene should be emphasized. Electric breast pumps are more efficient and better tolerated by mothers than mechanical pumps or manual expression. Collection kits should be cleaned with hot soapy water, rinsed, and air dried after each use. Glass or plastic containers should be used to collect the milk, and milk should be refrigerated and then used within 48 hr. Expressed breast milk can be frozen and used for up to 6 mo. Milk should be thawed rapidly by holding under running tepid water and used completely within 24 hr after thawing. *Milk should never be microwaved.*

Growth of the Breastfed Infant

The rate of weight gain of the breastfed infant differs from that of the formula-fed infant, and the infant's risk for excess weight gain during late infancy may be associated with bottle feeding. The WHO growth charts are based on the growth of healthy breastfed infants through the 1st yr of life. These standards (http://www.who.int/childgrowth) are the result of a study in which >8,000 children were selected from 6 countries. The infants were selected based on healthy feeding practices (breastfeeding), good health care, high socioeconomic status, and nonsmoking mothers, so that they reflect the growth of breastfed infants in the optimal conditions and can be used as prescriptive rather than normative curves. Charts are available for growth monitoring from birth to age 6 yr. The Centers for Disease Control and Prevention (CDC) recommends use of the WHO growth charts for infants 0-23 months of age, and CDC growth charts for ages 24 mo to 20 yr.

Formula Feeding (Fig. 45-1)

Despite efforts to promote exclusive breastfeeding through 6 months, less than 50% of women continue to breastfeed at 6 months. Most women make their infant feeding choices early in pregnancy. Parental preference is the most common reason for using infant formula. However, infant formula is also indicated in infants whose intake of breast milk is contraindicated for infant factors (e.g. inborn errors of metabolism), and maternal factors (see Table 45-3). In addition infant formula is used as a supplement to support inadequate weight gain in breastfed infants.

Infant formulas marketed in the United States are safe and nutritionally adequate as the sole source of nutrition for healthy infants for the first 6 months of life. Infant formulas are available in ready-to-feed, concentrated liquid or powder forms. Ready-to-feed products generally provide 20 kcal/30 mL (1 oz) and approximately 67 kcal/dL. Concentrated liquid products, when diluted according to instructions, provide a preparation with the same concentration. Powder formulas come in single or multiple servings and when mixed according to instructions will result in similar caloric density.

Although infant formulas are manufactured in adherence to good manufacturing practices and are regulated by the U.S. Food and Drug Administration (FDA), there are still potential safety issues. Powder preparations are not sterile, and although the number of bacterial colony-forming units per gram of formula is generally lower than allowable limits, outbreaks of infections with *Enterobacter sakazakii* have been documented, especially in premature infants. The powder preparations can contain other coliform bacteria but have not been linked to disease in healthy term infants. Care must be taken in following the mixing instructions to avoid over- or underdilution, to use boiled or sterilized water, and to use the specific scoops provided by the manufacturer as scoop sizes vary. Water that has been boiled should be allowed to cool fully to prevent degradation of heat labile nutrients, specifically vitamin C. Well water should be tested regularly for bacteria and toxin contamination. Municipal water can contain variable concentrations of fluoride, and if the concentrations are high, bottled water that is defluoridated should be used to avoid toxicity.

Parents should be instructed to use proper handwashing techniques when preparing formula and feedings for the infant. Guidance to follow written instructions for storage should also be given. Once opened, ready-to-feed and concentrated liquid containers can be covered with aluminum foil or plastic wrap and stored in the refrigerator for no longer than 48 hr. Powder formula should be stored in a cool, dry place; once opened, cans should be covered with the original plastic cap or aluminum foil, and the powdered product can be used within 4 weeks. Once prepared, all bottles regardless of type of formula should be used within 24 hours. Formula should be used within 2 hours of removal from the refrigerator and once a feeding has started, that formula should be used within an hour or be discarded. Prepared formula stored in the refrigerator should be warmed by placing the container in warm water for ~5 min. Formula should not be heated in a microwave, because it can heat unevenly and result in burns despite appearing to be at the right temperature when tested.

Formula feedings should be ad libitum, with the goal of achieving growth and development to the child's genetic potential. The usual intake to allow a weight gain of 25-30 g/day will be 140-200 mL/kg/day in the first 3 months of life. The rate of weight gain declines from 3-12 months of age.

COW MILK PROTEIN–BASED FORMULAS

Intact cow milk–based formulas in the United States contain a protein concentration varying from 1.8 to 3 g/100 kcal or (1.45-1.6 g/dL), considerably higher than in mature breast milk (1.5 g/100 kcal). This increased concentration is designed to meet the needs of the youngest infants but leads to excess protein intake for older infants. In contrast, breastfed infants receive protein intakes that match their needs at various ages. The whey:casein ratio varies from 18:82 to 60:40; one manufacturer markets a formula that is 100% whey. The predominant whey protein is β-globulin in cow milk and α-lactalbumin in human milk. This and other differences between human milk and cow milk–based formulas result in different plasma amino acid profiles in infants on different feeding patterns, but a clinical significance of these differences has not been demonstrated.

Plant or a mixture of plant and animal oils are the source of fat in infant formulas; fat provides 40-50% of the energy in cow milk–based formulas. Fat blends are better absorbed than dairy fat and provide saturated, monounsaturated, and polyunsaturated fatty acids (PUFAs). All infant formulas are supplemented with long-chain PUFAs, docosahexaenoic acid (DHA), and arachidonic acid (ARA) at varying

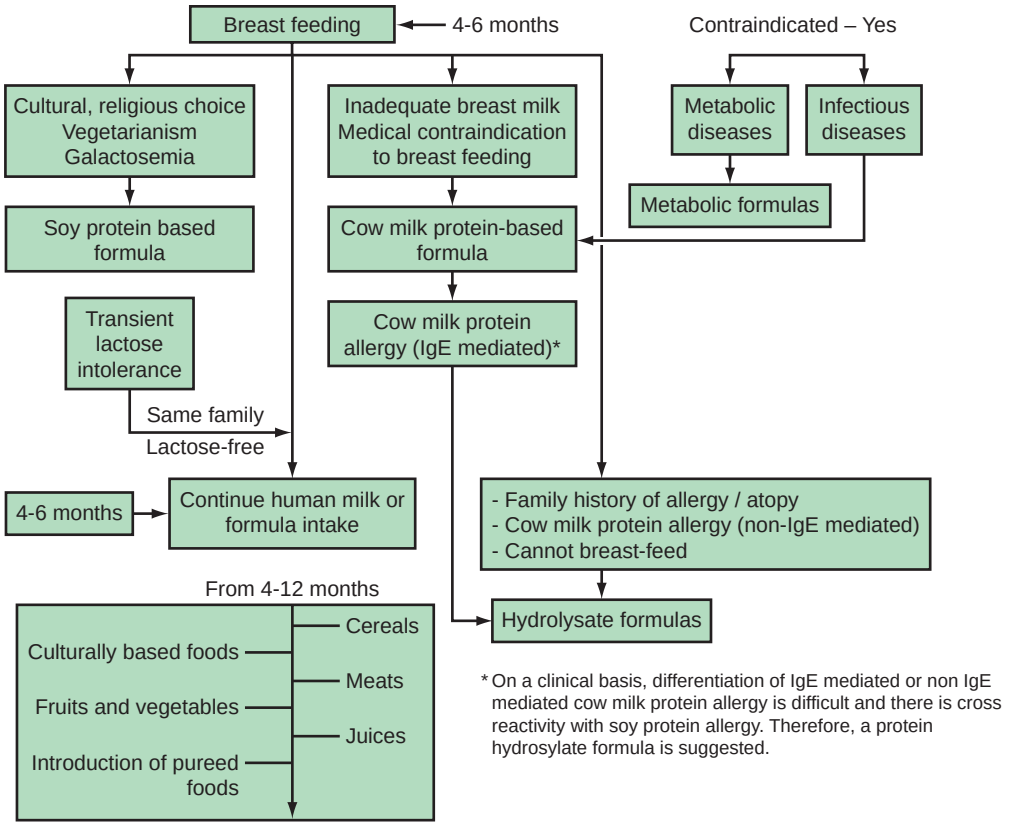

Figure 45-1 Feeding algorithm for term infants. *(From Gamble Y, Bunyapen C, Bhatia J: Feeding the term infant. In Berdanier CD, Dwyer J, Feldman EB, editors:* Handbook of nutrition and food, *Boca Raton, FL, 2008, CRC Press, pp 271–284,* Fig. 15-3.*)*

concentrations. ARA and DHA are found at varying concentrations in human milk and vary by geographic region and maternal diet. No studies in term infants have found a negative effect of DHA and ARA supplementation, and some studies have demonstrated positive effects on visual acuity and neurocognitive development. A critical review concluded that there are no consistent effects of long-chain PUFAs on visual acuity in term infants. A Cochrane review concluded that routine supplementation of milk formula with long chain PUFAs to improve the physical, neurodevelopmental, or visual outcomes of term infants cannot be recommended based on the current evidence. DHA and ARA are derived from single-cell microfungi and microalgae and are classified as generally recognized as safe for use in infant formulas at approved concentrations and ratios.

Lactose is the major carbohydrate in breast milk and in standard cow milk–based formulas for term infants. Formulas for term infants may also contain modified starch or other complex carbohydrates. Carbohydrates comprise 69-75g/L of cow milk–based formula.

SOY FORMULAS

Soy protein–based formulas on the market are all free of cow milk–based protein and lactose and use sucrose, corn syrup solids, and/or maltodextrin to provide 67 kcal/dL. They meet the vitamin, mineral, and electrolyte guidelines from the AAP and the FDA for feeding term infants. The protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide a protein content of 2.45-2.8 g per 100 kcal or 1.7-1.8 g/dL.

The quantity of specific fats varies by manufacturer and is usually similar to the manufacturer's corresponding cow milk–based formula. The fat content is 5.0-5.5 g per 100 kcal or 3.4-3.6 g/dL. The oils used in both cow milk and soy formula include soy, palm, sunflower, olein, safflower, and coconut. DHA and ARA are also added.

In term infants, although soy protein–based formulas have been used to provide nutrition resulting in normal growth patterns, there are few indications for use in place of cow milk–based formula. Indications for soy formula include galactosemia and hereditary lactase deficiency, because soy–based formulas are lactose-free; and situations in which a vegetarian diet is preferred. Most healthy infants with acute gastroenteritis can be managed after rehydration with continued use of breast milk or cow–based formulas and do not require a lactose-free formula, such as soy-based formula. However, soy protein–based formulas may be indicated when documented secondary lactose intolerance occurs. Soy protein–based formulas have no advantage over cow protein–based formulas as a supplement for the breastfed infant, unless the infant has one of the indications noted previously and are not recommended for preterm infants. The routine use of soy protein–based formula has no proven value in the prevention or management of infantile colic, fussiness, or atopic disease. Infants with documented cow protein–induced enteropathy or enterocolitis often are also sensitive to soy protein and should not be given isolated soy protein–based formula. They should be provided formula derived from extensively hydrolyzed protein or synthetic amino acids. Soy formulas contain phytoestrogens, which have been shown to have physiologic activity in rodent models but a meta-analysis of the topic done by the Center for the Evaluation of Risks to Human Reproduction concluded that there is minimal concern for adverse developmental effects in infants fed soy formula.

PROTEIN HYDROLYSATE FORMULA

Protein hydrolysate formulas may be *partially hydrolyzed*, containing oligopeptides with a molecular weight of <5000 Da, or *extensively hydrolyzed*, containing peptides with a molecular weight <3000 Da. Partially hydrolyzed proteins have fat blends similar to cow milk–based formulas, and carbohydrates are supplied by corn maltodextrin or corn syrup solids. Because the protein is not extensively hydrolyzed, these formulas should not be fed to infants who are allergic to cow protein. In studies of formula fed infants who are at high risk of developing

atopic disease there is modest evidence that childhood atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas, compared with cow milk–based formula. Comparative studies of the various hydrolyzed formulas have also indicated that not all formulas have the same protective benefit. Extensively hydrolyzed formulas may be more effective than partially hydrolyzed in preventing atopic disease. Extensively hydrolyzed formulas are recommended for infants intolerant to cow milk or soy proteins. These formulas are lactose free and can include medium-chain triglycerides, making them useful in infants with gastrointestinal malabsorption as a consequence of cystic fibrosis, short gut syndrome, prolonged diarrhea, and hepatobiliary disease.

AMINO ACID FORMULAS

Amino acid formulas are peptide-free formulas that contain mixtures of essential and nonessential amino acids. They are designed for infants with dairy protein allergy who failed to thrive on extensively hydrolyzed protein formulas. The effectiveness of amino acid formulas to prevent atopic disease has not been studied.

Milk and Other Fluids

Neither breastfed nor formula-fed infants require additional water unless dictated by high environmental temperature. Vomiting and spitting up are common in infants. When weight gain and general well-being are noted, no change in formula is necessary.

Whole cow milk should not be introduced until 12 mo of age. In children between 12 and 24 mo of age for whom being overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or cardiovascular disease, the use of reduced-fat milk is appropriate. Otherwise whole milk is recommended until age 24 months changing to 2% at 24 months, and 1% at 3 yr of age for healthy children. Regardless of the type, all milk consumed should be pasteurized. Infants and young children are particularly susceptible to infections such as *E. coli*, *Campylobacter*, and *Salmonella* found in raw or unpasteurized milk. For cultural and other reasons, such as parental preference, goat milk is sometimes given in place of formula although this is not recommended. Goat milk has been shown to cause significant electrolyte disturbances and anemia because it has low folic acid concentrations.

COMPLEMENTARY FEEDING

The timely introduction of complementary foods (solid and liquid foods other than breast milk or formula, also called weaning foods or beikost) during infancy is necessary to enable transition from milk feedings to other table foods and is important for nutritional and developmental reasons (Table 45-6). The ability of exclusive breastfeeding to meet macronutrient and micronutrient requirements becomes limiting with increasing age of the infant. The recommendation for timing of complementary feed initiation is based on the benefits on neurodevelopment and prevention of future comorbidities (see Table 45-2) from exclusive breastfeeding for 6 months. The AAP, WHO, and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition all recommend exclusive breastfeeding for the first 6 months. Similar data on the benefits of the exclusive use of formula for 6 months have not been published.

Some complementary foods are more nutritionally appropriate than others to complement breast milk or infant formula. The food consumption patterns of U.S. infants and toddlers demonstrate that nearly all infants ≤12 mo consumed some form of milk every day; infants >4 mo consumed more formula than human milk, and by 9-11 mo of age 20% consumed whole cow milk and 25% consumed nonfat or reduced-fat milk.

The most commonly fed complementary foods between 4 and 11 mo of age are infant cereals. Nearly 45% of infants between 9 and 11 mo of age consumed noninfant cereals. Infant eating patterns also vary, with up to 61% of infants 4-11 mo of age consuming no vegetables. Among those who consumed vegetables, French fries were the most common vegetables in toddlers. Positive changes in the last decade include increased duration of breastfeeding, delayed introduction of complementary foods, and decreased juice consumption. Continuing concerns included lack of fruits and vegetables, diets low in iron, essential fatty acids, fiber and whole grains, and high in saturated fat and sodium. Table 45-6 summarizes the AAP recommendations for initiating complementary foods.

The complementary foods should be varied to ensure adequate macro- and micronutrient intake. In addition to complementary foods introduced at 6 mo of age, continued breastfeeding or the use of infant formula for the entire 1st year of life should be encouraged. Overconsumption of energy-dense complementary foods can lead to excessive weight gain in infancy, resulting in an increased risk of obesity in childhood.

Table 45-6 Important Principles for Weaning

Begin at 6 mo of age
At the proper age, encourage a cup rather than a bottle
Introduce 1 food at a time
Energy density should exceed that of breast milk
Iron-containing foods (meat, iron-supplemented cereals) are required
Zinc intake should be encouraged with foods such as meat, dairy products, wheat, and rice
Phytate intake should be low to enhance mineral absorption
Breast milk should continue to 12 mo, formula or cow milk is then substituted
Give no more than 24 oz/day of cow milk
Fluids other than breast milk, formula, and water should be discouraged
Give no more than 4-6 oz/day of fruit juices; no sugar sweetened beverages

Adapted from American Academy of Pediatrics: Pediatric nutrition handbook, *ed 6, Elk Grove Village, IL, 2008, American Academy of Pediatrics.*

FEEDING TODDLERS AND PRESCHOOL-AGE CHILDREN

Toddlerhood is a period when eating behavior and healthful habits can be established and is often a confusing and anxiety-generating period. Growth after the 1st yr slows, motor activity increases, and appetite decreases. Birth weight triples during the 1st year of life and quadruples by 2 yr of age, reflecting this slowing in growth velocity. Eating behavior is erratic, and the child appears distracted as the child explores the environment. Children consume a limited variety of foods and often only "like" a particular food for a period of time and then reject the favored food. The use of growth charts to demonstrate adequate growth and to provide guidance about typical behavior and eating habits will help allay concerns of parents. Important goals of early childhood nutrition are to foster healthful eating habits and to offer foods that are developmentally appropriate.

Feeding Practices

The period starting after 6 mo until 15 mo is characterized by the acquisition of self-feeding skills because the infant can grasp finger foods, learn to use a spoon, and eat soft foods (Table 45-7). Around 12 mo of age, the child learns to drink from a cup and may still breastfeed or desire formula bottle feeding. Bottle weaning should begin around 12-15 mo and bedtime bottles should be discouraged because of the association with dental carries. Unless being used at mealtime, the sippy cup should only contain water to prevent caries. Sugar-sweetened beverages and 100% fruit juice should also be discouraged from being used in bottles in all infants at all times. Cups without a lid can be used for no more than 4-6 oz/day of 100% fruit juice for toddlers. In the 2nd year of life, self-feeding becomes a norm and provides the opportunity for the family to eat together with less stress. Self-feeding allows the child to limit the child's intake. Child feeding is an interactive process. Children receive cues regarding appropriate feeding behaviors from parents. Parents should ignore negative eating behaviors unless the behavior jeopardizes the health and safety of the child. In addition, parents should eat with their

Table 45-7 Feeding Skills Birth to 36 Months

AGE (mo)	FEEDING/ORAL SENSORIMOTOR
Birth to 4-6	Nipple feeding, breast, or bottle Hand on bottle during feeding (2-4 mo) Maintains semiflexed posture during feeding Promotion of infant–parent interaction
6-9 (transition feeding)	Feeding more in upright position Spoon feeding thin, pureed foods Both hands to hold bottle Finger feeding introduced Vertical munching of easily dissolvable solids Preference for parents to feed
9-12	Cup drinking Eats lumpy, mashed food Finger feeding for easily dissolvable solids Chewing includes rotary jaw action
12-18	Self-feeding; grasps spoon with whole hand Holds cup with 2 hands Drinking with 4-5 consecutive swallows Holding and tipping bottle
>18-24	Swallowing with lip closure Self-feeding predominates Chewing broad range food Up–down tongue movements precise
24-36	Circulatory jaw rotations Chewing with lips closed One-handed cup holding and open cup drinking with no spilling Using fingers to fill spoon Eating wide range of solid food Total self-feeding, using fork

Adapted from Arvedson JC. Swallowing and feeding in infants and young children. GI Motility online *(2006) doi:10.1038/gimo17.*

toddlers and not simply feed them in order to model positive eating behaviors.

The 2 yr old child should progress from small pieces of soft food to prepared table foods with precautions. At this stage, the child is not capable of completely chewing and swallowing foods, and particular attention should be paid to foods with a choking risk. Hard candies, nuts, and raw carrots should be avoided. Hot dogs, sausages, and grapes should be sliced length wise. Caregivers should always be vigilant and present during feeding, and the child should be placed in a high chair or booster seat. The AAP discourages eating in the presence of distractions such as television, tablets, mobile devices, and other screens, or eating in a car where an adult cannot adequately observe the child.

Young children have a natural preference for sweetened foods and beverages that begins in infancy. Reluctance to accept new foods is a common developmental phase. A new food should be offered multiple times (8-15) before being considered rejected by the child.

Toddlers need to eat 3 healthy meals and 2 snacks daily. Milk continues to be an important source of nutrition. Guidelines for vitamin D supplementation recommend a daily vitamin D intake of 600 IU/day for all infants beginning in the first few days of life, and for children and adolescents who are ingesting <1000 mL/day of vitamin D-fortified milk or formula. Toddlers and preschool children often fail to meet the recommended servings of fruits, vegetables, and fiber, whereas intakes of food with fat and added sugar are high. Giving vegetables at the beginning of the meal and increasing the portion size of vegetables served during meals can be an effective strategy for increasing vegetable consumption in preschool children.

Eating in the Daycare Setting

Many U.S. toddlers and preschool children attend daycare and receive meals and snacks in this setting. There is a wide variation in the quality of the food offered and the level of supervision during meals. Parents are encouraged to assess the quality of the food served at daycare by asking questions, visiting the center, and taking part in parent committees. Free or reduced-price snacks and meals are provided in daycare centers for low- and medium-income communities through the U.S. Department of Agriculture (USDA) Child and Adult Care Food Program. Participating programs are required to provide meals and snacks that meet the meal regulations set by the USDA, guaranteeing a certain level of food quality. However, often for monetary reasons, many daycare centers still struggle to provide high-quality meals and snacks.

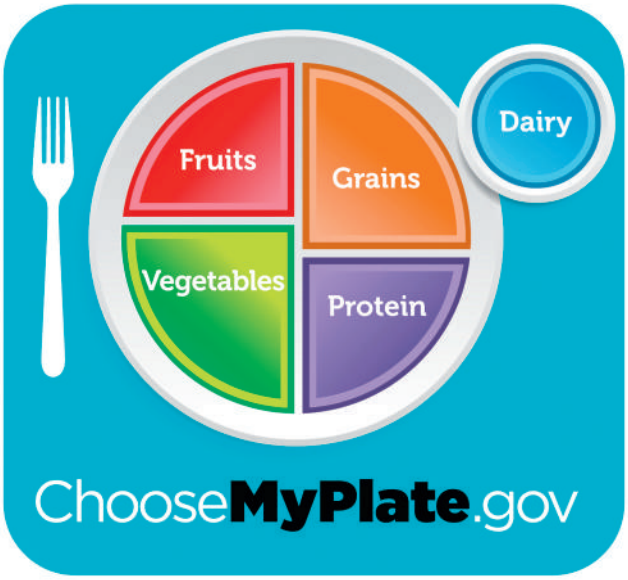

Figure 45-2 MyPlate food guide. *(From U.S. Department of Agriculture: mypyramid.gov.* http://www.choosemyplate.gov/*.)*

FEEDING SCHOOL-AGE CHILDREN AND ADOLESCENTS

MyPlate

The USDA MyPlate (www.choosemyplate.gov) is a basis for building an optimal diet for children and adults (Fig. 45-2). MyPlate is based on the *Dietary Guidelines for Americans, 2010* and replaces MyPyramid. MyPlate is aimed at the general public to provide a visual representation of the different food groups and their portion sizes. In addition to food group information, the website provides discretionary calorie information. It provides weight management strategies, and abilities to track calories and physical activity goals. A personalized eating plan based on these guidelines provide, on average over a few days, all the essential nutrients necessary for health and growth, while limiting nutrients associated with chronic disease development. MyPlate can also be used as an Internet interactive tool that allows customization of recommendations, based on age, sex, physical activity, and, for some populations, weight and height. Print material is also available for families without Internet access.

Recommendations based on MyPlate emphasize making half the plate vegetables and fruit, one half of the plate protein and grains, with protein having the smallest section. Protein replaces the meat category as many protein sources are not from animals. A separate dairy section is included. Physical activity recommendations to achieve a healthful energy balance are not visually displayed, but are provided on the website. MyPlate has removed foods that have low nutritional value, such as sweetened sugar beverages, and sweetened bakery products.

In the United States and in an increasing number of other countries, the vast majority of children and adolescents do not consume a diet that follows the recommendations of MyPlate. The intake of

discretionary calories is much higher than recommended, with frequent consumption of sweetened sugar beverages (soda, juice drinks, iced tea, sport drinks), snack foods, high-fat meat (bacon, sausage), and high-fat dairy products (cheese, ice cream). Intake of dark green and orange vegetables (as opposed to fried white potatoes), whole fruits, reduced-fat dairy products, and whole grain is typically lower than recommended. Furthermore, unhealthful eating habits such as larger-than-recommended portion sizes; food preparation that adds fat, sugar, or salt; skipping breakfast and/or lunch; grazing; or following fad diets is prevalent and associated with a poorer diet quality. MyPlate offers a helpful and customer-friendly tool to assist pediatricians counseling families on optimal eating plans for short- and long-term health.

Eating at Home

At home, much of what children and adolescents eat is under the control of their parents. Typically, parents shop for groceries and they control, to some extent, what food is available in the house. It has been demonstrated that modeling of healthful eating behavior by parents is a critical determinant of the food choices of children and adolescents. Counseling to improve diet should include guiding parents in using their influence to make healthier food choices available and attractive at home.

Regular family meals sitting at a table, as opposed to eating alone, in the living room, or watching television/screens, are associated with improved diet quality, perhaps because of increased opportunities for positive parenting during meals. Such an ideal situation is recommended but a challenge for many families who, with busy schedules and other stressors, are unable to provide such a setting. Another parenting challenge is to control the excess appetite of some children and adolescents. Encourage children to eat at a slower pace and to chew their food properly. Encourage conversation at the dinner table to prolong eating to 15 minutes. Offering vegetables while children are hungry at the beginning of the meal has been shown to increase vegetable consumption. Useful strategies, when the child is still hungry after a meal, include a 15- to 20-min pause (allow child to engage in another activity) before a second serving or offering foods that are insufficiently consumed, such as vegetables, whole grains, or fruits.

Eating at School

The National School Lunch Program and the School Breakfast Program provide low-cost meals to more than 5 billion children nationwide. Guidelines for meals are taken from the *Dietary Guidelines for Americans and the Dietary Reference, 2005*. Recommendations regarding the use of age-grade portion sizes, and amounts of vegetable and fruits, grains, and fats were included (Table 45-8). The training and equipment for school food service staff, school community engagement, parent education, and food industry involvement are among the necessary components. The year 2020 is the target year for achieving recommendations for sodium. In the meantime, while schools are working on implementing changes, parents should be encouraged to examine the weekly menu with their child and assist with their choices ahead of time. If children bring their lunch from home recommendations for what constitutes a healthy lunch should be provided by the Pediatrician. Parents can be directed to www.choosemyplate.org for healthy lunch ideas. In addition parties within classrooms should be limited to once a month.

Eating Out

The number of meals eaten outside the home or brought home from takeout restaurants has increased in all age groups of the U.S. population. The increased convenience of this meal pattern is undermined by the generally lower nutritional value of the meals, compared to home-cooked meals. Typically, meals consumed or purchased in fast-food or casual restaurants are of large portion size, are dense in calories, and contain large amounts of saturated fat, salt, and sugar, and low amounts of whole grains, fruits, and vegetables. Although still a problem currently, *trans* fat is slowing being phased out of most commercial restaurants. Although an increasing number of restaurants offer healthier alternatives, the vast majority of what is consumed at restaurants does not fit MyPlate.

With increasing age, an increasing number of meals and snacks are also consumed during peer social gatherings at friends' houses and parties. When a large part of a child's or adolescent's diet is consumed on these occasions, the diet quality can suffer, because food offerings are typically of low nutritional value. Parents and pediatricians need to guide teens in navigating these occasions while maintaining a healthful diet and enjoying meaningful social interactions. These occasions often are also opportunities for teens to consume alcohol; consequently, adult supervision is important.

Table 45-8 Revised National School Lunch Program and School Breakfast Program Recommendations

- Portion sizes of food are to be based on age-grade groups
- School lunches and breakfasts will have a minimum and maximum calorie level, maximum saturated fat content, and a maximum sodium content
- Foods must contain zero grams of trans fat per serving
- The inclusion of unsaturated vegetable oils is encouraged within calorie limits
- Vegetables and fruits are not interchangeable
- Vegetable offerings at lunch must include ½ cup equivalent of the following: dark green vegetables, bright orange vegetables, and legumes
- No more than half of fruit servings may be in the form of juice
- At least ½ of bread/grain offered must be whole grain
- Milk must be fat-free if flavored and either fat free or 1% if plain
- Students must select a fruit option at breakfast with their meal, and either a fruit or a vegetable at lunch for the meal to be reimbursable.

Adapted from IOM (Institute of Medicine): School meals: building blocks for healthy children. Washington, DC, 2010, National Academies Press.

NUTRITION ISSUES OF IMPORTANCE ACROSS PEDIATRIC AGES

Food Environment

Most families have some knowledge of nutrition and intend to provide their children with a healthful diet. The discrepancy between this fact and the actual quality of the diet consumed by U.S. children is often explained by challenges in the environment for families to make healthful food choices. Because the final food choice is made by individual children or their parents, interventions to improve diet have focused on individual knowledge and behavior changes, but have had limited success. A main determinant of food choice is taste, but other factors also influence these choices. One of the most useful conceptual frameworks for understanding the child's food environment in the context of obesity illustrates the variety of individual food and physical activity choices. Many of these determinants are not under the direct control of individual children or parents (Fig. 45-3). Understanding the context of food and lifestyle choices helps in understanding lack of changes or "poor compliance" and can decrease the frustration often experienced by the pediatricians who might "blame the victim" for behavior that is not entirely under their control.

Marketing and advertising of food to children is a particularly illustrative aspect of the food environment. Marketing includes strategies as diverse as shelf placements, association of cartoon characters with food products, coupons, and special offers or pricing, all of which influence food purchase choices. Television advertising is an important part of how children and adolescents hear about food, with an estimated 40,000 TV commercials per yr, seen by the average U.S. child, many of which are for food, as compared to the few hours of nutrition education they receive in school. Additional food advertisement increasingly occurs as brand placement in movies and TV shows, on websites, and even video games.

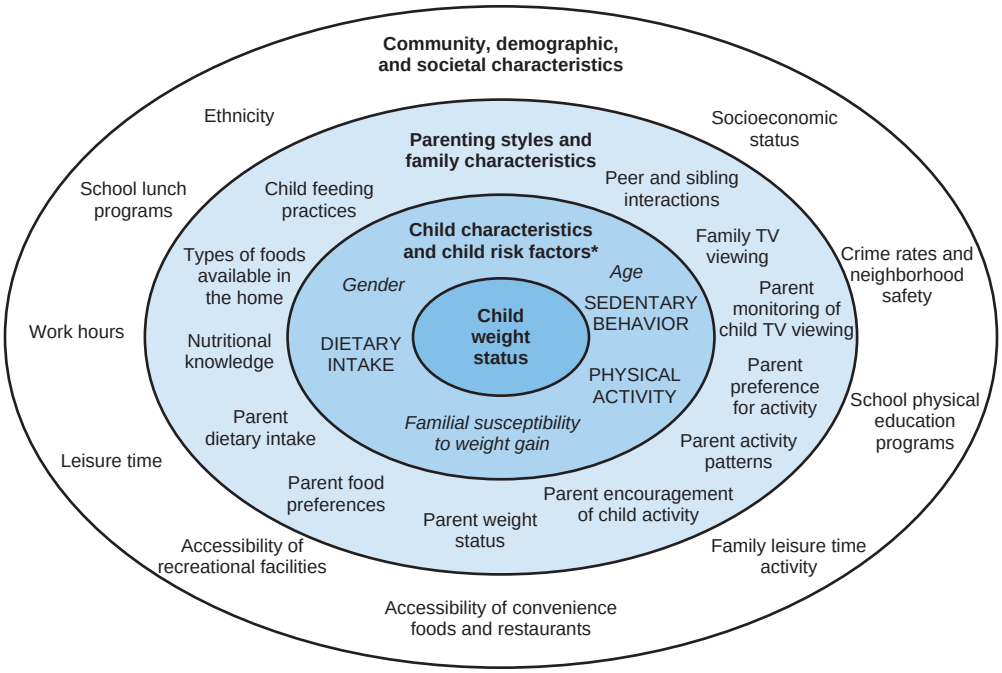

Figure 45-3 A conceptual framework of the context of food and lifestyle choices. Child risk factors (shown in uppercase lettering) refer to child behaviors associated with the development of overweight. Characteristics of the child (shown in italic lettering) interact with child risk factors and contextual factors to influence the development of overweight (i.e., moderator variables). *(From Davison KK, Birch LL: Childhood overweight: a contextual model and recommendations for future research,* Obes Rev *2:159–171, 2001. © 2001 The International Association for the Study of Obesity.)*

Using Food as Reward

It is a prevalent habit to use food as a reward or sometimes withdraw food as punishment. Most parents use this practice occasionally, and some use it almost systematically, starting at a young age. The practice is also commonly used in other settings where children spend time, such as daycare, school, or even athletic settings. Although it might be a good idea to limit some unhealthy but desirable food categories to special occasions, using food as a reward is problematic. Limiting access to some foods and making its access contingent on a particular accomplishment increases the desirability of that type of food. Conversely, encouraging the consumption of some foods renders them less desirable. Therefore, phrases such as "finish your vegetables, and you will get ice cream for dessert" can result in establishing unhealthy eating habits once the child has more autonomy in food choices. Parents should be counseled on such issues and encouraged to choose items other than food as reward, such as inexpensive toys or sporting equipment, family time, special family events, or collectable items. Similar types of behavior are also seen in schools and extra-curricular events. As opposed to rewarding or punishments of food (pizza/candy) daycare providers, teachers, and counselors should be encouraged to use alternative rewards such as minutes of free time, sitting in the teacher's chair, being the teacher helper, and homework-free nights.

Cultural Considerations in Nutrition and Feeding

Food choices, food preparation, eating patterns, and infant feeding practices all have very deep cultural roots. In fact, beliefs, attitudes, and practices surrounding food and eating are some of the most important components of cultural identity. Therefore, it is not surprising that in multicultural societies, great variability exists in the cultural characteristics of the diet. Even in a world where global marketing forces tend to reduce geographic differences in the types of food, or even brands, that are available, most families, especially during family meals at home, are still much influenced by their cultural background. Therefore, pediatricians should become familiar with the dietary characteristics of various cultures in their community, so that they can identify and address, in a nonjudgmental way and avoiding stereotypes, the potential nutritional issues related to the diet of their patients.

Vegetarianism

Vegetarianism is the practice of following a diet that excludes animal flesh foods, including beef, pork, poultry, fish, and shellfish. There are several variants of the diet, some of which also exclude eggs and/or some products produced from animal labor, such as dairy products and honey. There are many different variations in vegetarianism:

- Veganism: excludes all animal products. It may be part of a larger practice of abstaining from the use of animals products for any purpose.
- Ovovegetarianism: includes eggs but not dairy products.
- Lactovegetarianism: includes dairy products but excludes eggs.
- Lactoovovegetarianism: includes eggs and dairy products.
- Flexitarian: recent term referring to a vegetarian who will occasionally eat meat.

Another expression used for vegetarianism and veganism is "plant-based diets."

Other dietary practices commonly associated with vegetarianism include fruitarian diet (fruits, nuts, seeds, and other plant matter gathered without harm to the plant); Su vegetarian diet (a diet that excludes all animal products as well as onion, garlic, scallions, leeks, or shallots); a macrobiotic diet (whole grains and beans and, in some cases, fish); and raw vegan diet (fresh and uncooked fruits, nuts, seeds, and vegetables). The safety of these restrictive diets has not been studied in children. These diets can be very limited in macro- and micronutrients and are not recommended for children. Implementing vegetarian diets in teenage girls may be a sign of an eating disorder.

Vegetarianism is considered a healthful and viable diet; both the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) and the Dietitians of Canada have found that a properly planned and well-balanced vegetarian diet can satisfy the nutritional

goals for all stages of life. Compared with nonvegetarian diets, vegetarian diets have low levels of saturated fat, cholesterol, and animal protein, and relatively higher levels of complex carbohydrates, fiber, magnesium, potassium, folate, vitamins C and E, and phytochemicals. Vegetarians have a lower body mass index, cholesterol, and blood pressure, and are at decreased risk for cancer and ischemic heart disease.

Specific nutrients of concern in vegetarian diets include:

- **Iron:** Vegetarian diets have similar levels of iron compared to nonvegetarian diets, but the iron has lower bioavailability than iron from meat sources, and iron absorption may be inhibited by other dietary constituents, such as phytate (see Chapter 54). Iron stores are lower in vegetarians and vegans than in nonvegetarians; and iron deficiency is more common in vegetarian and vegan women and children. Foods rich in iron include iron-fortified cereals, black beans, cashews, kidney beans, lentils, oatmeal, raisins, black-eyed peas, soybeans, sunflower seeds, chickpeas, molasses, chocolate, and tempeh.
- **Vitamin B_{12}:** Plants are not a good source of B_{12} (see Chapter 49.7). Additional vitamin B_{12} can be obtained through dairy products and eggs; vegans need fortified foods or supplements. Breastfeeding by vegan mothers can place an infant at risk for vitamin B_{12} deficiency.
- **Fatty acids:** Vegetarians and vegans may be at risk for low levels of eicosapentaenoic acid (EPA) and DHA. The inclusion of sources of linolenic acid (precursor of EPA and DHA), such as walnuts, soy products, flaxseed, and canola oils, are recommended.
- **Calcium and vitamin D:** Without supplementation, vegan diets are low in calcium and vitamin D putting vegans at risk for impaired bone mineralization (see Chapter 51). *Vitamin D-OH levels should be monitored in vegans and supplemented for levels <30 dL.* Calcium sources include leafy greens (with low oxalate: broccoli, kale, or Chinese cabbage). Calcium and vitamin D are found in almond and soy milk, and fortified orange juice.
- **Zinc:** The bioavailability of zinc in plant sources tends to be low because of the presence of phytates and fiber that inhibit zinc absorption (see Chapter 54). Zinc is found in soy products, legumes, grains, cheese, and nuts.

Organic Foods

Parents may prefer organic foods to feed children secondary to concerns regarding chemical and hormonal treatment of animals and produce. The nutritional differences between organic and conventional foods may not be clinically relevant. Children consuming organic foods have lower or no detectable levels of pesticides in their urine compared to those consuming nonorganic foods. It remains unclear whether such a reduction in exposure to chemicals is clinically significant. Organic foods tend to have higher antioxidant levels and lower levels of cadmium. Similarly, despite concerns of parents, the amount of bovine growth hormone in conventional milk is thought to be neither significant nor biologically active in humans. Additionally, milk consumption from estrogen-treated cows does not result in endocrine disruptions in infants. However other chemicals in the environment, such as bisphenol-A (found in plastics), nitrates, endocrine disruptors, and phthalates, should be avoided. Organic certification of a food also suggests the food source is not from a genetically modified nutrient. Because the cost of these foods is generally higher than the cost of other foods, a prudent approach is to explain to families that the scientific basis for choosing organic foods is limited, but if it is their preference and they can afford the added cost, there is no reason not to eat organic foods.

Nutrition as Part of Complementary and Alternative Medicine, Functional Foods, Dietary Supplements, Vitamin Supplements, and Botanical and Herbal Products

The use of nutrition or nutritional supplements as complementary or alternative medicine is increasing, despite limited data on safety and efficacy, especially in children. Many parents assume that if a food or supplement is natural or organic, then there is no potential for risk and some that supplements are beneficial. However, adverse effects of some dietary supplements have been documented. It is difficult for pediatricians to compete against the aggressive marketing through multi-media sources of food supplements to families of healthy and chronically ill children. Additionally, pediatricians must compete against the word-of-mouth and advice from people without a scientific background and those with significant conflicts of interest. One reason to recommend caution to parents when it comes to dietary supplements, including botanical and herbal products, is that in the United States, unlike medications, these products are not evaluated for safety and efficacy before marketing and do not undergo the same level of quality control as medications. The potential for adverse effects or simply for inefficacy is therefore high (see Chapter 64).

Pediatricians are often asked by parents if their children need to receive a daily multivitamin. Unless the child follows a particular diet that may be poor in one or more nutrients for health, cultural, or religious reasons, or if the child has a chronic health condition that puts the child at risk for deficiency in 1 or more nutrients, multivitamins are not indicated. A diet that follows the guidelines of MyPlate contains sufficient nutrients to support healthy growth. Many children do not follow all the guidelines of MyPlate, and parents and pediatricians may be tempted to use multivitamin supplements just to make sure that nutrient deficiencies are avoided. Use of a daily multivitamin supplement can result in a false impression that the child's diet is complete and in decreased efforts to meet dietary recommendations with food rather than the intake of supplements (see Chapter 44) The average U.S. diet provides more than a sufficient amount of most nutrients, including most vitamins. Therefore, multivitamins should not be routinely recommended.

The Institute of Medicine recommends 600 IU of vitamin D per day in all children who drink less than 1,000 mL/day of vitamin D–fortified milk, representing the majority of U.S. children and adolescents. In some specific populations of children at risk for deficiency, supplements of vitamin B_{12}, iron, fat-soluble vitamins, or zinc may be considered.

Food Safety

Constantly keeping food safety issues in mind is an important aspect of feeding infants, children, and adolescents. In addition to choking hazards and food allergies, pediatricians and parents should be aware of food safety issues related to infectious agents and environmental contaminants. Food poisoning with bacteria, viruses, or their toxins are most common with raw or undercooked food, such as oysters, beef, and eggs, or cooked foods that have not been handled or stored properly. The specific bacteria and viruses involved in food poisoning are described in Chapter 340. Many chemical contaminants, such as heavy metals, pesticides, and organic compounds, are present in various foods, usually in small amounts. Because of concerns regarding their child's neurologic development and cancer risk, many questions arise from parents, especially after media coverage of isolated incidents. A recurring debate is the balance between the benefits of seafood for the growing brain and cardiovascular health and the risk of mercury contamination from consuming large predatory fish species. Pediatricians need to become familiar with reliable sources of information, such as the websites of the U.S. Environmental Protection Agency, the FDA, or the CDC. The Food Safety Modernization Act provides the FDA with authority to have stricter control over food production and distribution. The FDA can require that manufacturers develop food safety plans. A good source of information for patients and parents can be found at www.foodsafety.gov.

Nutritional Programming

Emerging epidemiologic evidence suggests that early nutrition starting during fetal development can have long-term impact on growth, and adult health. It is well established that undernutrition in early life can exert a long-term impact in terms of reduced adult height and academic achievements; other data, however, suggest that intrauterine growth restriction is associated with obesity and other adult cardiovascular risk factors. Rapid weight gain in infancy, either following intrauterine growth restriction or a period of malnutrition, is associated

with an increased risk for later obesity. The process that explains these changes has been termed "programming."

Preventive Nutrition Counseling in Pediatric Primary Care

An important part of the primary care well-child visit focuses on nutrition and growth because most families turn to pediatricians for guidance on child nutrition. Preventive nutrition is one of the cornerstones of preventive pediatrics and a critical aspect of anticipatory guidance. The first steps of nutrition counseling are nutritional status assessments, primarily done through growth monitoring and dietary intake assessment. Although dietary assessment is somewhat simple in infants who have a relatively monotonous diet, it is more challenging at older ages. The goals of dietary assessment in the primary care setting need to remain modest and include an idea of the eating patterns (time, location, and environment) and usual diet by asking the parent to describe the child's dietary intake on a typical day or in the last 24 hr. Pediatricians should encourage regularly scheduled meals and 1 or 2 snacks. Alternatively, a basic assessment of the child's consumption of vegetables, fruits, whole grains, low or nonfat dairy products, 100% fruit juice and sugar-sweetened beverages should be assessed. For more ambitious goals of dietary assessment, referral to a registered dietician with pediatric experience is recommended.

Once some understanding of the child's usual diet has been acquired, existing or anticipated nutritional problems should be addressed, such as diet quality, dietary habits, or portion size. For a few nutritional problems, a lack of knowledge can be addressed with nutrition education, but most pediatric preventive nutritional issues, such as overeating or poor food choices, are not the result of lack of parents' knowledge. Therefore, nutrition education alone is insufficient in these situations, and pediatricians need to acquire training in behavior-modification techniques or refer to specialists to assist their patients in engaging in healthy feeding and eating behaviors. The physical, cultural, and family environments in which the child lives should be kept in mind at all times, so that nutrition counseling is relevant and changes are feasible.

One important aspect of nutrition counseling is providing families with sources of additional information and behavioral change tools. Although some handouts are available from government agencies, the AAP, and other professional organizations for families without Internet access, an increasing number of families rely on the Internet to find nutrition information. Therefore, pediatricians need to become familiar with commonly used websites so that they can point families to reliable and unbiased sources of information. Perhaps the most useful websites for reliable and unbiased nutrition information for children are the USDA MyPlate website, the sites of the CDC, FDA, National Institutes of Health, and Institute of Medicine Food and Nutrition Board for government sources and the AAP, American Heart Association, and the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) for professional organization resources. Pediatricians should also be aware of sites that provide biased or even dangerous information, so that they can warn families accordingly. Examples include dieting sites, sites that openly promote dietary supplements or other food products, and the sites of "nonprofit" organizations that are mainly sponsored by food companies or that have other social or political agendas.

Food Assistance Programs in the USA

Several programs exist in the United States to ensure sufficient and high-quality nutrition for children of families who cannot always afford optimal nutrition. One of the most popular federal programs is the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). This program provides nutrition supplements to a large proportion of pregnant women, postpartum women, and children up to their 5th birthday. One of its strengths is that in order to qualify, families need to regularly visit a WIC nutritionist, who can be a useful resource for nutritional counseling. Other popular programs include school lunches, breakfasts, and after-school meals, as well as daycare and summer nutrition programs. Lower-income families are also eligible for the Supplemental Nutrition Assistance Program, formerly known as the Food Stamp Program. This program provides funds directly to families to purchase various food items in regular food stores.

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Chapter 46

Nutrition, Food Security, and Health

Ann Ashworth

MALNUTRITION AS THE INTERSECTION OF FOOD INSECURITY AND HEALTH INSECURITY

Undernutrition is usually an outcome of 3 factors, often in combination: household food supply, child-caring practices, and access to health and water/sanitation services. In famine and emergency settings, food shortage is the foremost factor, but in many countries with widespread undernutrition, food production or access to food might not be the most limiting factor. More important causes might be repeated childhood infections, especially diarrheal diseases linked with an unsafe environment and lack of exclusive breastfeeding, or inadequate complementary feeding practices, or the lack of time families have available for appropriate infant or maternal care. Figure 46-1 shows some of the many causal factors on the pathway to undernutrition and how they extend from household and community levels to national/international levels. Inequitable distribution of resources because of political, economic, and agricultural policies often denies families their right to adequate land, water, food, healthcare, education, and a safe environment, all of which can influence nutritional status.

Families with few economic resources who know how to care for their children and are enabled to do so can often use available food and health services to produce well-nourished children. If food resources and health services are not available in a community, or not utilized, or not accessible to some families, children might become undernourished. Undernutrition is not confined to low-income countries. It has been noted in chronically ill patients in neonatal and pediatric intensive care units in high-income countries and among patients with burns, HIV, tuberculosis, cystic fibrosis, chronic diarrhea syndromes, malignancies, bone marrow transplantation, and inborn errors of metabolism. Severe malnutrition has been reported in affluent communities in infants whose families believe in fad diets, and in infants with food allergies fed nutritionally inadequate foods such as rice "milk," which has a very low protein and micronutrient content (Fig. 46-2).

FOOD SECURITY

Food security exists "when all people, at all times, have access to sufficient, safe, nutritious food to maintain a healthy and active life." Four main dimensions of food security can be identified: **availability**, **access**, **utilization,** and **stability**. *Availability* refers to the supply of food (reflecting the level of food production, food stocks, and net trade). *Access* is at the household level, reflecting purchasing power, household food production, and food/cash transfers received through social safety net programs. The *utilization* dimension recognizes that even when a household has access to food it is not necessarily shared equitably within a household. *Stability* refers to being food secure at all times: Examples of situations that affect stability are the "lean seasons" before a harvest, natural disasters, political unrest, and rising food prices. To be food secure, all 4 dimensions must be met simultaneously.

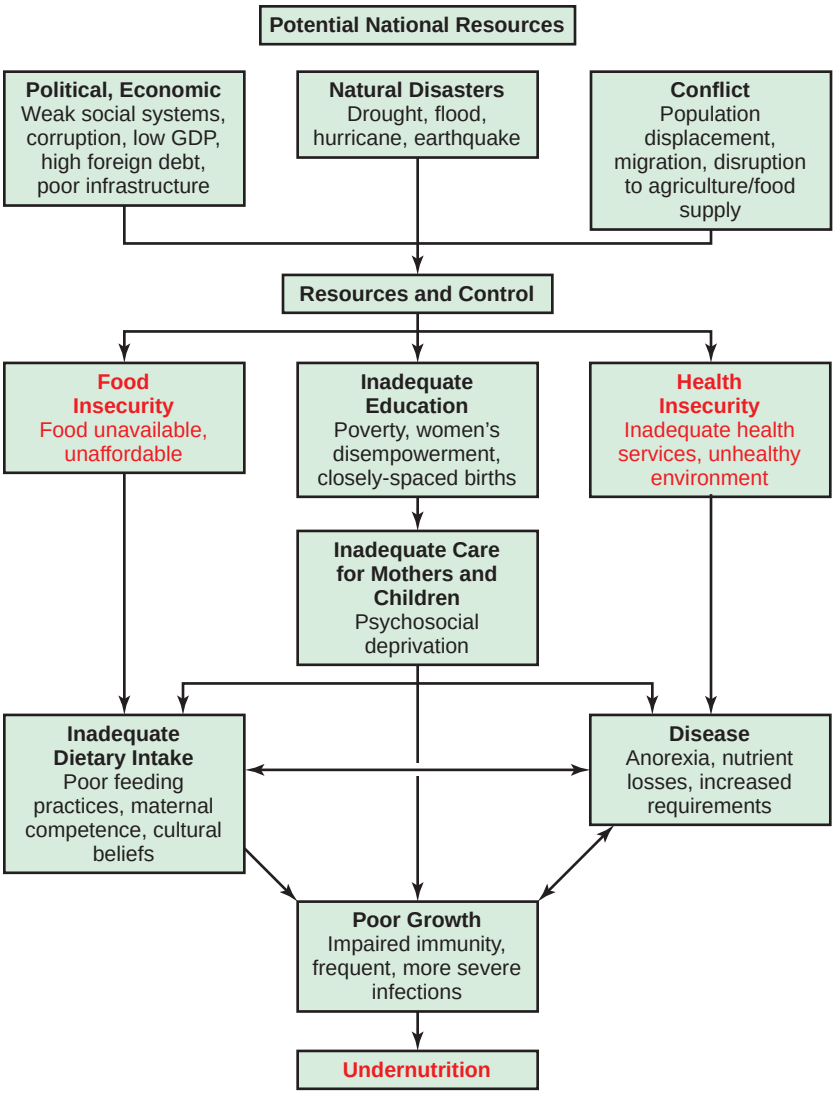

Figure 46-1 Basic, underlying, and immediate causes of undernutrition.

Measuring Food Insecurity

The most commonly used measurement of food insecurity is "undernourishment" (chronic hunger), and is the proportion of the population who are unable to meet daily energy requirements for light activities. It is an estimate calculated by the Food and Agriculture Organization (FAO) based on country-level Food Balance Sheets. It does not take nutrient adequacy into account, but has the advantage of being available for almost all countries annually (although with a time-lag) and assists in monitoring global trends. In addition, FAO measures food access by asking individuals about their experiences over the last 12 mo, such as whether they ran out of food, or skipped meals. The responses are graded from mild to severe food insecurity.

In 2011-2013, FAO estimated that about 842 million people, or 12% of the world's population, were undernourished, 98% of whom were in developing countries. The majority are rural poor subsisting on small plots of land or hired as laborers, and urban poor who lack the means to grow or buy food. Alongside the 0.84 billion people who are underfed, there are 1.5 billion who are overfed reflecting global inequalities, and the "double burden of malnutrition" in low- and middle-income countries.

Nutrition, Food Security, and Poverty

Household food security tracks income closely. With rising incomes, very poor households first increase their dietary energy intake to avert hunger. If incomes rise further there is a shift to more expensive staple foods and then to a more varied diet with a greater proportion of energy from animal sources, fruits and vegetables, fats and sugars, and less from cereals, roots and tubers. National economic growth tends to be accompanied by reductions in stunting, but economic growth can pass by the poor if they work in unaffected sectors, or are unable to take advantage of new opportunities because of lack of education, access to credit, or transportation, or if governments do not channel resources accruing from economic growth to healthcare, education, social protection, and other public services and infrastructure. There is good evidence that economic growth reduces poverty, but does not necessarily reduce undernutrition.

Food Security and Nutrition Targets

World leaders collectively agreed to 8 Millennium Development Goals (MDGs) in 2000. MDG 1 aimed to eradicate extreme poverty and hunger. The target to halve the proportion of people whose income is less than $1 per day was reached at the global level 5 yr ahead of the 2015 target. This was greatly helped by the progress made by China and India. Sub-Saharan Africa is unlikely to reach the target. The reductions in hunger are broadly consistent with those of poverty reduction, and rates of undernourishment in developing regions fell from 23.2% in 1990 to 14.3% in 2011-2013. Sub-Saharan Africa is the region least likely to achieve the target of halving undernourishment by 2015. The prevalence of underweight children (another MDG indicator of "hunger") fell from 29% in 1990 to 17% in 2012 for the

Figure 46-2 A 14 mo old girl with a "flaky paint" dermatitis. *(From Katz KA, Mahlberg MH, Honig PJ, et al: Rice nightmare: kwashiorkor in 2 Philadelphia-area infants fed Rice Dream beverage,* J Am Acad Dermatol *52(5 Suppl 1):S69–S72, 2005.)*

developing regions combined, but the rate of decline is thought insufficient to reach the global target by 2015. Rural children are almost twice as likely to be underweight as urban children, and the poorest quintile is almost 3 times as likely to be underweight as the richest quintile.

Sustainable Development Goals are expected to follow on from the MDGs. In addition, in 2012 the World Health Assembly agreed to 6 global nutrition targets to be reached by 2025, measured against a 2010 baseline, and the United Nations Secretary-General launched the Zero Hunger Challenge with 5 objectives that "would boost economic growth, reduce poverty and safeguard the environment" and "would foster peace and stability" (Table 46-1).

Table 46-1 Global Food Security and Nutrition Targets

ZERO HUNGER CHALLENGE OBJECTIVES	WORLD HEALTH ASSEMBLY GLOBAL NUTRITION TARGETS FOR 2025
• Access to an adequate and stable food supply for all • Elimination of stunting in children <2 yr and no malnutrition in pregnancy and early childhood • Sustainable food systems • Doubling of smallholder productivity and income, particularly for women • No loss or waste of food, and responsible consumption	• A 40% reduction in the number of stunted children <5 yr • A 50% reduction in anemia in women of reproductive age • A 30% reduction in low birthweight • No increase in childhood overweightness • Increase exclusive breastfeeding rates to at least 50% in the first 6 months • Reduce and maintain childhood wasting to less than 5%

Future Food Security

Between now and 2050 the world's population is expected to rise to around 9 billion, and an increase in food supply of 70-100% will be needed to feed this larger, more urban, and more affluent populace. Over this same period, the world's food supply is expected to diminish unless action is taken. Accelerating the decline in fertility rates and reducing overconsumption are basic, but difficult, actions to bridge the gap between increasing demand and diminishing supply. Equally challenging actions include limiting climate disruption, increasing the efficiency of food production, reducing waste, and reducing the demand for meat and dairy foods.

- *Limit climate disruption:* Drought, floods, and other extreme weather events are becoming more prevalent and destroy crops and livestock, often on a huge scale. Rising sea levels will lead to loss of productive land through inundation and salinization. Acidification of oceans will reduce marine harvests. Curbing greenhouse gas emissions is essential to minimize climate disruption, hence the aim to (a) cut fossil fuel use by at least half of present levels by 2050 so as to reduce CO_2 emissions and (b) change livestock husbandry and agronomic practices to reduce methane and nitrous oxide emissions.
- *Increase efficiency of food production*: Expanding the area of agricultural land to any large extent (e.g., by deforestation) is not a sustainable option because of adverse consequences on ecosystems and biodiversity, although some expansion of food production could be achieved by switching good quality land away from first-generation biofuels. For example, 40% of the U.S. corn harvest in 2010 went to biofuels. Efforts to increase the intensity of production need to be environmentally sustainable. These include optimizing yields by soil and water conservation, removal of technical and financial constraints faced by farmers, and breeding resource-efficient crops and livestock that are also climate-resilient and pest/disease-resistant.
- *Reduce waste*: Some 30-40% of food is wasted, either between harvesting and the market, or during retail, at home, and in the food service industry. Better transport and storage facilities in developing countries, less stringent sell-by dates, lower cosmetic standards for fruits and vegetables, and ending supersized portions would help reduce waste.
- *Change diets:* As wealth increases, so does the demand for processed foods, meat, dairy products, and fish. About one-third of global cereal production is fed to animals, so reducing consumption of meat from grain-fed livestock and increasing the proportion derived from the most efficient sources (pigs and poultry) would allow more people to be fed from the same amount of land.

UNDERNUTRITION

The greatest risk of undernutrition (underweight, stunting, wasting, and micronutrient deficiencies) occurs in the first 1000 days, from conception to 24 mo of age, and this early damage to growth and development can have adverse consequences in later life on health, intellectual ability, school achievement, work productivity, and earnings. Governments and agencies are therefore advised to focus interventions on this critical window of opportunity. For folate deficiency, which increases the risk of birth defects, this particular window of opportunity is before conception.

Measurement of Undernutrition

The term ***malnutrition*** encompasses both ends of the nutrition spectrum, from undernutrition to overweight. Many poor nutritional outcomes begin *in utero* and are manifest as low birthweight (LBW, <2,500 g). Preterm delivery and fetal growth restriction are the 2 main

Table 46-2 Classification of Undernutrition

CLASSIFICATION	INDEX	GRADING
Gomez (underweight)	90-75% of median weight-for-age	Grade 1 (mild)
	75-60%	Grade 2 (moderate)
	<60%	Grade 3 (severe)
Waterlow (wasting)	90-80% of median weight-for-height	Mild
	<70%	Severe
Waterlow (stunting)	95-90% of median height-for-age	Mild
	90-85%	Moderate
	<85%	Severe
WHO (wasting)	<–2 to >–3 SD weight-for-height	Moderate
	<–3	Severe
WHO (stunting)	<–2 to >–3 SD height-for-age	Moderate
	<–3	Severe
WHO (wasting) (for age group 6-59 mo)	115-125 mm mid-upper arm circumference	Moderate
	<115 mm	Severe

causes of LBW, with prematurity relatively more common in richer countries and fetal growth restriction relatively more common in poorer countries.

Nutritional status is often assessed in terms of anthropometry (Table 46-2). International standards of normal child growth under optimum conditions from birth to 5 yr have been established by the World Health Organization (WHO). To compile the standards, longitudinal data from birth to 24 mo of healthy, breastfed, term infants were combined with cross-sectional measurements of children ages 18-71 mo. The standards allow normalization of anthropometric measures in terms of *z* scores (standard deviation scores). A z-score is the child's height (weight) minus the median height (weight) for the age and sex of the child divided by the relevant standard deviation. The standards are applicable to all children everywhere, having been derived from a large multicountry study reflecting diverse ethnic backgrounds and cultural settings.

Height-for-age (or length-for-age for children <2 yr) is a measure of linear growth, and a deficit represents the cumulative impact of adverse events, usually in the first 1,000 days from conception, that result in *stunting*, or chronic malnutrition. A low height-for-age typically reflects socioeconomic disadvantage. A low **weight-for-height**, or *wasting*, usually indicates acute malnutrition. Conversely, a high weight-for-height indicates *overweight*. **Weight-for-age** is the most commonly used index of nutritional status, although a low value has limited clinical significance as it does not differentiate between wasting and stunting. Weight-for-age has the advantage of being somewhat easier to measure than indices that require height measurements. In humanitarian emergencies and some field settings, **mid-upper arm circumference** is used for screening wasted children (Fig. 46-3).

Body mass index (BMI) is calculated by dividing weight in kilograms by the square of height in meters. For children, BMI is age- and gender-specific. BMI-for-age can be used from birth to 20 yr and is a screening tool for thinness (<–2 SD), overweight (between +1 SD and +2 SD), and obesity (>+2 SD). To diagnose obesity, additional measures of adiposity are desirable as a high BMI can result from high muscularity, and not only from excess subcutaneous fat.

Micronutrient deficiencies are another dimension of undernutrition. Those of particular public health significance are vitamin A, iodine, iron, and zinc.

Vitamin A deficiency is caused by a low intake of retinol (in animal foods) or its carotenoid precursors, mainly beta-carotene (in orange-colored fruits and vegetables and dark green leaves) (see Chapter 48). The prevalence of clinical deficiency is assessed from symptoms and signs of xerophthalmia (principally night blindness and Bitot spots). Subclinical deficiency is defined as serum retinol concentration <0.70 μmol/L. Vitamin A deficiency is the leading cause of preventable blindness in children. It is also associated with a higher morbidity and mortality among young children.

Figure 46-3 Measuring mid-upper arm circumference. *(Image courtesy of Nyani Quarmyne/Panos Pictures.)*

Iodine deficiency is the main cause of preventable mental impairment (see Chapter 54). An enlarged thyroid (goiter) is a sign of deficiency. Severe deficiency in pregnancy causes fetal loss and permanent damage to the brain and central nervous system in surviving offspring (cretinism). It can be prevented by iodine supplementation before conception or during the first trimester of pregnancy. Postnatal iodine deficiency is associated with impaired mental function and growth retardation. The median urinary iodine concentration in children ages 6-12 yr is used to assess the prevalence of deficiency in the general population, and a median of <100 μg/L indicates insufficient iodine intake.

Iron-deficiency anemia is common in childhood either from low iron intakes or poor absorption, or as a result of illness or parasite infestation (see Chapter 54). Women also have relatively high rates of anemia as a result of menstrual blood loss, pregnancy, low iron intakes, poor absorption, and illness. Hemoglobin cutoffs to define anemia are 110 g/L for children 6-59 mo, 115 g/L for children 5-11 yr, and 120 g/L for children 12-14 yr. Cutoffs to define anemia for nonpregnant women are 120 g/L, 110 g/L for pregnant women, and 130 g/L for men.

Zinc deficiency increases the risk of morbidity and mortality from diarrhea, pneumonia, and possibly other infectious diseases (see Chapter 54). Zinc deficiency also has an adverse effect on linear growth. Deficiency at the population level is assessed from dietary zinc intakes.

Prevalence of Undernutrition

It is estimated that approximately 15% of births in low- and middle-income countries in 2010 were LBW. Rates of LBW are highest (26%) in southern Asia, and are twice those of sub-Saharan Africa. India accounts for approximately 40% of the world's low-weight births. Globally, in 2011 16% of children <5 yr of age were *underweight* (weight-for-age <–2 SD). The global prevalence of *stunting* (height-for-age <–2 SD) has declined from an estimated 40% to 26% over the last 20 yr, with the greatest reductions having taken place in Asia. Stunting prevalence is now highest in the African region (36% prevalence). *Wasting* (weight-for-height <–2 SD) affects 8% of children <5 yr, the prevalence having changed little over the past 2 decades. These figures represent 101 million underweight children, 165 million stunted children, and 52 million wasted children.

Asia carries 69% of the global burden of underweight children, 58% of the global burden of stunted children, and 70% of the global burden

of wasted children because of the combination of large population size and high prevalence. Africa carries most of the remaining global burden. For children <5 yr, the global prevalence is estimated to be 33% for *vitamin A deficiency,* 29% for *iodine deficiency,* 17% for *zinc deficiency,* and 18% for *iron-deficiency anemia*. Prevalence of micronutrient deficiencies tends to be highest in Africa. For pregnant women, the estimated prevalence of vitamin A deficiency is 15% and for iron-deficiency anemia 19%.

Rates of clinical deficiency of vitamin A in children <5 yr have been declining, probably as a result of high-dose vitamin A supplementation programs and measles vaccination (as measles leads to sizeable urinary loss of vitamin A), but subclinical deficiency remains widespread (more than 90 million children). Large-scale availability of iodized salt has reduced rates of iodine deficiency substantially, and iodized salt now reaches an estimated 70% of households. In contrast, progress in reducing rates of iron-deficiency anemia is slow, and rates remain largely static.

Consequences of Undernutrition

The most profound consequence of undernutrition is premature death (Table 46-3). Fetal growth restriction together with suboptimal breastfeeding in the first month of life contribute to 19% of all deaths in children <5 yr (1.3 million deaths/yr). When the effects of stunting, wasting and deficiencies of vitamin A and zinc are also considered, these 6 items jointly contribute to 45% of global child deaths (3.1 million deaths/yr), and many more are disabled or stunted for life. Anemia contributes to over one-quarter of maternal deaths.

The risk of child death from infectious diseases increases even with mild undernutrition, and as the severity of undernutrition increases, the risk increases exponentially (Table 46-4). Undernutrition impairs immune function and other host defenses, consequently childhood infections are more severe and longer lasting in undernourished children and more likely to be fatal compared with the same illnesses in well-nourished children. Also, infections can adversely affect nutritional status, and young children can quickly enter a cycle of repeated infections and ever-worsening malnutrition. Even for the survivors, physical and cognitive damage as a result of undernutrition can impact their future health and economic well-being. For girls, the cycle of undernutrition is passed on to the next generation when undernourished women give birth to LBW babies.

Fetal growth restriction and early childhood undernutrition also have consequences for adult chronic illness. LBW is associated with an increased risk of hypertension, stroke, and type 2 diabetes in adults. The increased risk is thought to reflect "fetal programming," a process by which fetal undernutrition leads to permanent changes in the structure and metabolism of organs and systems that manifest as disease in later life. The risk is exacerbated by low weight gain during the first 2 yr of life. The increased risk of adult chronic disease emanating from undernutrition in early life is a particular challenge to low-income countries with rapid economic growth.

Stunting before the age of 3 yr is associated with poorer motor and cognitive development and altered behavior in later years. The effect is

Table 46-3 Global Deaths in Children <5 yr Attributed to Nutritional Conditions

CONDITION	ATTRIBUTABLE DEATHS	% OF TOTAL DEATHS <5 YR
(a) Fetal growth restriction (<1 mo)	817,000	11.8
(b) Stunting (1-59 mo)	1,017,000	14.7
(c) Wasting (1-59 mo)	875,000	12.6
(d) Zinc deficiency (12-59 mo)	116,000	1.7
(e) Vitamin A deficiency (6-59 mo)	157,000	2.3
(f) Suboptimal breastfeeding (0-23 mo)	804,000	11.6
Joint effects of (a) + (f)	1,348,000	19.4
Joint effects of all 6 factors	3,097,000	44.7

From Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low- and middle-income countries, Lancet *382:427–451, 2013.*

Table 46-4 Hazard Ratios for All-Cause and Cause-Specific Deaths Associated with Stunting, Wasting, and Underweight in Children <5 yr

	DEATHS				
SD Score	All	Pneumonia	Diarrhea	Measles	Other Infections
Height/length-for-age					
<–3	5.5	6.4	6.3	6.0	3.0
–3 to <–2	2.3	2.2	2.4	2.8	1.9
–2 to <–1	1.5	1.6	1.7	1.3	0.9
≥–1	1.0	1.0	1.0	1.0	1.0
Weight-for-length					
<–3	11.6	9.7	12.3	9.6	11.2
–3 to <–2	3.4	4.7	3.4	2.6	2.7
–2 to <–1	1.6	1.9	1.6	1.0	1.7
≥–1	1.0	1.0	1.0	1.0	1.0
Weight-for-age					
<–3	9.4	10.1	11.6	7.7	8.3
–3 to <–2	2.6	3.1	2.9	3.1	1.6
–2 to <–1	1.5	1.9	1.7	1.0	1.5
≥–1	1.0	1.0	1.0	1.0	1.0

From Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low- and middle-income countries, Lancet *382:427–451, 2013.*

6-13 DQ (developmental quotient) points. Iodine and iron deficiencies also lead to loss of cognitive potential. Indications are that children living in areas of chronic iodine deficiency have an average reduction in IQ of 12-13.5 points compared with children in iodine-sufficient areas. Iron deficiency has a detrimental effect on the motor development of children <4 yr and on cognition of school-age children. The estimated deficit is 1.73 IQ points for each 10 g/L decrease in hemoglobin concentration.

Undernutrition can have substantial economic consequences for survivors and their families. The consequences can be quantified in 5 categories: increased costs of healthcare, either neonatal care for LBW babies or treatment of illness for infants and young children; productivity losses (and hence reduced earnings) associated with smaller stature and muscle mass; productivity losses from reduced cognitive ability and poorer school performance; increased costs of chronic diseases associated with fetal and early child malnutrition; and consequences of maternal undernutrition on future generations. The impact of nutrition on earnings appears to be independent of the effects of childhood deprivation.

Key Interventions

Interventions to address child undernutrition can be divided into those that address immediate causes (*nutrition-specific interventions*) and those that address underlying causes (*nutrition-sensitive interventions*) (Table 46-5). In the short-term, nutrition-specific interventions (e.g., salt iodization) can have substantial impacts even in the absence of economic growth, and micronutrient interventions (supplementation and fortification) are consistently ranked by economists of the Copenhagen Consensus Center as the most cost-effective investment. Increased attention is being given to nutrition-sensitive interventions as the best means of sustainably eliminating malnutrition, and to multisectoral policies that harness the synergism between the 2 types of intervention. Cross-sectoral linkages between agriculture, nutrition, and health are 1 example.

To reduce the adverse consequences of undernutrition on mortality, morbidity, and cognitive development, interventions must encompass both fetal and postnatal periods. Preventing LBW is essential, with emphasis on prevention of low maternal BMI and anemia, and in the longer term, prevention of low maternal stature. Other measures include smoking cessation, birth spacing, delaying pregnancy until after 18 yr of age, and intermittent preventive treatment of malaria. In the postnatal period, promotion and support of exclusive breastfeeding is a high priority. Although the Baby Friendly Hospital Initiative has a marked benefit on rates of exclusive breastfeeding in hospital, postnatal counseling from community workers or volunteers is needed to facilitate continuation of exclusive breastfeeding at home for 6 mo. Most studies show a lower risk of HIV transmission with exclusive breastfeeding than with mixed breastfeeding. The risk of transmission of HIV by breastfeeding is approximately 5-20% depending on duration, but can be reduced to <2% with antiretroviral drugs. Even without antiretroviral drugs, exclusively breastfed children of HIV-infected mothers in low-income countries have lower mortality than non-breastfed children, as the latter are at increased risk of death from diarrhea and pneumonia.

Interventions to improve infant feeding must be designed for the local setting and thus require careful formative research during their development. Messages should be few in number, feasible, and culturally appropriate. For complementary feeding, nutrient-rich, energy-dense mixtures of foods, and responsive feeding, are often emphasized. Where adequate complementary feeding is difficult to achieve and subclinical deficiencies are common, high-dose vitamin A supplementation every 6 mo in children <5 yr of age can reduce child mortality by 5-15% and zinc supplementation can reduce 1-4 yr mortality by 18%, diarrhea incidence by 13%, and pneumonia incidence by 19%. Monitoring of child growth provides an early alert to a nutrition or health problem but is only worthwhile if accompanied by good counseling and growth promotion activities. The impact of growth monitoring and promotion will be related to coverage, intensity of contact, health worker performance and communications skills, adequacy of resources, and the motivation and ability of families to follow agreed actions.

Table 46-5 Examples of Nutrition-Specific and Nutrition-Sensitive Interventions

NUTRITION-SPECIFIC INTERVENTIONS	NUTRITION-SENSITIVE INTERVENTIONS
• Promotion and support for exclusive breastfeeding for 6 mo, and continued breastfeeding for at least 2 yr • Promotion of adequate, timely, and safe complementary feeding from 6 mo • Increased micronutrient intake through dietary diversity • Micronutrient supplements for pregnant women (iron/folate) and young children (vitamin A, iron, zinc) in deficient areas • Zinc supplements to children during and after diarrhea (10-20 mg/day for 2 wk) • Prevention and treatment of severe acute malnutrition • Crop biofortification, food fortification, salt iodization • Reduced heavy physical activity in pregnancy	• Increased access to affordable, nutritious food; smallholder agriculture; credit and microfinance • Postharvest food processing and preservation • Vaccination against neonatal and childhood illness; access to healthcare • Improved water/sanitation and hygiene (e.g., handwashing with soap) • Education; women's empowerment; gender equality • Social protection (e.g., cash transfers) • Malaria prevention (vector control/bednets); intermittent preventive treatment during pregnancy and in children 3-59 mo • Birth spacing; delaying pregnancy until after 18 yr of age

Clinical Manifestations and Treatment of Undernutrition

Treatment of vitamin and mineral deficiencies is discussed in Chapters 48-54. Treatment of low birthweight and intrauterine growth restriction are discussed respectively in Chapter 97.

SEVERE ACUTE MALNUTRITION

Severe acute malnutrition is defined as severe wasting and/or bilateral edema.

Severe wasting is extreme thinness diagnosed by a weight-for-length (or height) below −3 SD of the WHO Child Growth Standards. In children ages 6-59 mo, a mid-upper arm circumference <115 mm also denotes extreme thinness: a color-banded tape (see Fig. 46-3) is a convenient way of screening children in need of treatment.

Bilateral edema is diagnosed by grasping both feet, placing a thumb on top of each, and pressing gently but firmly for 10 seconds. A pit (dent) remaining under each thumb indicates bilateral edema.

This definition of severe acute malnutrition distinguishes wasted/edematous children from those who are stunted, as the latter (although underweight) are not a priority for acute clinical care as their deficits in height and weight cannot be corrected in the short term. The previous name *protein-energy malnutrition* is avoided, as it oversimplifies the complex multideficiency etiology. Other terms are *marasmus* (severe wasting), *kwashiorkor* (characterized by edema), and *marasmic-kwashiorkor* (severe wasting + edema).

Children with severe acute malnutrition have had a diet insufficient in energy and nutrients relative to their needs. The magnitude of the deficits will differ depending on the duration of inadequacy, quantity and diversity of food consumed, presence of antinutrients (such as phytate), individual variation in requirements, and number and severity of coexisting infections and their duration. Infections can lead to profound nutrient deficits and imbalances: For example, amino acids are diverted to form acute-phase proteins and there are losses through diarrhea of potassium, magnesium, vitamin A, and zinc, and of glycine and taurine linked to small bowel bacterial overgrowth. Deficits can

also arise from increased nutrient utilization in response to noxae (e.g., cysteine and methionine to detoxify dietary cyanogens). Heterogeneity in the extent and nature of the deficits and imbalances, reflecting the diverse pathways to severe acute malnutrition, helps explain why affected children differ in their clinical presentation and degree of metabolic disturbance. Children who develop edematous malnutrition are more likely than nonedematous children to have been exposed to noxae that generate oxidative stress and/or to have greater deficits in free radical-scavenging antioxidants (glutathione, vitamins A, C, and E, and essential fatty acids) or cofactors (zinc, copper, selenium).

Clinical Manifestations of Severe Acute Malnutrition (Table 46-6)

Severe wasting (Fig. 46-4) is most visible on the thighs, buttocks, and upper arms, and over the ribs and scapulae where loss of fat and skeletal muscle is greatest. Wasting is preceded by failure to gain weight and then by weight loss. The skin loses turgor and becomes loose as subcutaneous tissues are broken down to provide energy. The face may retain a relatively normal appearance, but eventually becomes wasted and wizened. The eyes may be sunken from loss of retroorbital fat, and lachrymal and salivary glands may atrophy leading to lack of tears and a dry mouth. Weakened abdominal muscles and gas from bacterial overgrowth of the upper gut may lead to a distended abdomen. Severely wasted children are often fretful and irritable.

In *edematous malnutrition*, the edema is most likely to appear first in the feet and then in the lower legs. It can quickly develop into generalized edema affecting also the hands, arms, and face (Fig. 46-5). Skin changes commonly occur over the swollen limbs and include dark, crackled peeling patches (flaky paint dermatosis) with pale skin underneath that is easily infected. The hair is sparse and easily pulled out and may lose its curl. In dark-haired children, the hair may turn pale or reddish. The liver is often enlarged with fat. Children with edema are miserable and apathetic, and often refuse to eat.

Table 46-6 Clinical Signs of Malnutrition

SITE	SIGNS
Face	Moon face (kwashiorkor), simian facies (marasmus)
Eye	Dry eyes, pale conjunctiva, Bitot spots (vitamin A), periorbital edema
Mouth	Angular stomatitis, cheilitis, glossitis, spongy bleeding gums (vitamin C), parotid enlargement
Teeth	Enamel mottling, delayed eruption
Hair	Dull, sparse, brittle hair, hypopigmentation, flag sign (alternating bands of light and normal color), broomstick eyelashes, alopecia
Skin	Loose and wrinkled (marasmus), shiny and edematous (kwashiorkor), dry, follicular hyperkeratosis, patchy hyper- and hypopigmentation (crazy paving or flaky paint dermatoses), erosions, poor wound healing
Nails	Koilonychia, thin and soft nail plates, fissures, or ridges
Musculature	Muscle wasting, particularly buttocks and thighs; Chvostek or Trousseau sign (hypocalcemia)
Skeletal	Deformities, usually as a result of calcium, vitamin D, or vitamin C deficiencies
Abdomen	Distended: hepatomegaly with fatty liver; ascites may be present
Cardiovascular	Bradycardia, hypotension, reduced cardiac output, small vessel vasculopathy
Neurologic	Global developmental delay, loss of knee and ankle reflexes, impaired memory
Hematologic	Pallor, petechiae, bleeding diathesis
Behavior	Lethargic, apathetic, irritable on handling

From Grover Z, Ee LC: Protein energy malnutrition, Pediatr Clin N Am *56:1055–1068, 2009.*

Pathophysiology

When a child's intake is insufficient to meet daily needs, physiologic and metabolic changes take place in an orderly progression to conserve energy and prolong life. This process is called *reductive adaptation*. Fat stores are mobilized to provide energy. Later protein in muscle, skin, and the gastrointestinal tract is mobilized. Energy is conserved by reducing physical activity and growth, reducing basal metabolism and the functional reserve of organs and by reducing inflammatory and immune responses. These changes have important consequences:

- The liver makes glucose less readily, making the child more prone to hypoglycemia. It produces less albumin, transferrin, and other transport proteins. It is less able to cope with excess dietary protein and to excrete toxins.
- Heat production is less, making the child more vulnerable to hypothermia.
- The kidneys are less able to excrete excess fluid and sodium, and fluid easily accumulates in the circulation, increasing the risk of fluid overload.
- The heart is smaller and weaker and has a reduced output, and fluid overload readily leads to death from cardiac failure.
- Sodium builds up inside cells due to leaky cell membranes and reduced activity of the sodium/potassium pump, leading to excess body sodium, fluid retention, and edema.
- Potassium leaks out of cells and is excreted in urine, contributing to electrolyte imbalance, fluid retention, edema, and anorexia.
- Loss of muscle protein is accompanied by loss of potassium, magnesium, zinc, and copper.

Figure 46-4 Child with severe wasting.

- The gut produces less gastric acid and enzymes. Motility is reduced, and bacteria may colonize the stomach and small intestine, damaging the mucosa and deconjugating bile salts. Digestion and absorption are impaired.
- Cell replication and repair are reduced, increasing the risk of bacterial translocation through the gut mucosa.
- Immune function is impaired, especially cell-mediated immunity. The usual responses to infection may be absent, even in severe illness, increasing the risk of undiagnosed infection.

Figure 46-5 Child with generalized edema.

- Red cell mass is reduced, releasing iron which requires glucose and amino acids to be converted to ferritin, increasing the risk of hypoglycemia and amino acid imbalances. If conversion to ferritin is incomplete, unbound iron promotes pathogen growth and formation of free radicals.
- Micronutrient deficiencies limit the body's ability to deactivate free radicals, which cause cell damage. Edema and hair/skin changes are outward signs of cell damage.

When prescribing treatment it is essential to take these changes in function into account, otherwise organs and systems will be overwhelmed and death will rapidly ensue.

Principles of Treatment

Figure 46-6 shows the 10 steps of treatment, which are separated into 2 phases referred to as stabilization and rehabilitation. These steps apply to all clinical forms and all geographic locations, including North America and Europe. The aim of the stabilization phase is to repair cellular function, correct fluid and electrolyte imbalance, restore homeostasis, and prevent death from the interlinked triad of hypoglycemia, hypothermia, and infection. The aim of the rehabilitation phase is to restore wasted tissues (i.e., catch-up growth). It is essential that treatment proceeds in an ordered progression and that the metabolic machinery is repaired before any attempt is made to promote weight gain. Pushing ahead too quickly risks inducing the potentially fatal "refeeding syndrome."

Caregivers bring children to health facilities because of illness, rarely because of their malnutrition. A common mistake among healthcare providers is to focus on the illness and treat as for a well-nourished child. This approach ignores the deranged metabolism in malnourished children and can be fatal. Such children should be considered as severely malnourished with a complication, and treatment should follow the 10 steps. Two other potentially fatal mistakes are to treat edema with a diuretic and to give a high-protein diet in the early phase of treatment.

- ***Emergency treatment***: Table 46-7 summarizes the therapeutic directives for malnourished children with shock and other emergency conditions. Note that treatment of shock in these children is different (less rapid, smaller volume, different fluid) from treatment of shock in well-nourished children. This difference is because shock from dehydration and sepsis often coexist and are difficult to differentiate on clinical grounds. Thus one has to be guided by the response to treatment: children with dehydration respond to IV fluid whereas those with septic shock will not respond. Since severely malnourished children can quickly succumb to fluid overload, they must be monitored closely.
- ***Stabilization***: Table 46-8 summarizes the therapeutic directives for stabilization steps 1-7. Giving broad-spectrum antibiotics (Table 46-9) and feeding frequent small amounts of F75 (a specially formulated low-lactose milk with 75 kcal and 0.9 g protein per

	Stabilization		Rehabilitation
	Day 1–2	Day 3–7	Week 2–6
1. Prevent/treat hypoglycemia	→		
2. Prevent/treat hypothermia	→		
3. Treat/prevent dehydration	→		
4. Correct imbalance of electrolytes	→	→	→
5. Treat infections	→	→	
6. Correct deficiencies of micronutrients	no iron	no iron	with iron →
7. Start cautious feeding	→	→	
8. Rebuild wasted tissue (catch-up growth)		→	→
9. Provide loving care and play	→	→	→
10. Prepare for follow-up		→	→

Figure 46-6 The 10 steps of treatment for severe acute malnutrition and their approximate time frames.

Table 46-7 Emergency Treatment in Severe Malnutrition

CONDITION	IMMEDIATE ACTION
Shock • lethargic or unconscious and • cold hands Plus either: • slow capillary refill (longer than 3 sec) or • weak fast pulse	1. Give oxygen 2. Give sterile 10% glucose (5 mL/kg) by IV 3. Give IV fluid at 15 mL/kg over 1 hr, using: • Ringers lactate with 5% dextrose or • half-normal saline with 5% dextrose or • half-strength Darrow solution with 5% dextrose • if all of the above are unavailable, Ringer lactate 4. Measure and record pulse and respirations at the start and every 10 minutes If there are signs of improvement (pulse and respiration rates fall) repeat IV 15 mL/kg for 1 more hr. Then switch to oral or nasogastric rehydration with ReSoMal, 5-10 mL/kg in alternate hr (see Table 46-8 step 3) If there are no signs of improvement assume septic shock and: 1. Give maintenance fluid IV (4 mL/kg/hr) while waiting for blood 2. Order 10 mL/kg fresh whole blood and transfuse slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood 3. Give furosemide 1 mL/kg IV at the start of the transfusion
Hypoglycemia Blood glucose less than 3 mmol/L	See Table 46-8 step 1 for treatment
Severe dehydration	Do *not* give IV fluids except in shock See Table 46-8 step 3 for treatment
Very severe anemia Hb less than 4 g/dL	If very severe anemia (or Hb 4-6 g/dL AND respiratory distress): 1. Give whole blood 10 mL/kg slowly over 3 hr. If signs of heart failure, give 5-7 mL/kg packed cells rather than whole blood 2. Give furosemide 1 mL/kg IV at the start of the transfusion
Emergency eye care Corneal ulceration	If corneal ulceration: 1. Give vitamin A immediately (age <6 mo 50,000 IU, 6-12 mo 100,000 IU, >12 mo 200,000 IU) 2. Instill 1 drop atropine (1%) into affected eye to relax the eye and prevent the lens from pushing out

Table 46-8 Therapeutic Directives for Stabilization

STEP	PREVENTION	TREATMENT
1. Prevent/treat hypoglycemia blood glucose <3 mmol/L	Avoid long gaps without food and minimize need for glucose: 1. Feed immediately 2. Feed every 3 hr day and night (2 hr if ill) 3. Feed on time 4. Keep warm 5. Treat infections (they compete for glucose) *Note:* Hypoglycemia and hypothermia often coexist, and are signs of severe infection	If conscious: 1. 10% glucose (50 mL), or a feed (see step 7), or 1 teaspoon sugar under the tongue-whichever is quickest 2. Feed every 2 hr for at least the first day. Initially give ¼ of feed every 30 min 3. Keep warm 4. Start broad-spectrum antibiotics If unconscious: 1. Immediately give sterile 10% glucose (5 mL/kg) by IV 2. Feed every 2 hr for at least first day. Initially give ¼ of feed every 30 min. Use nasogastric (NG) tube if unable to drink 3. Keep warm. 4. Start broad-spectrum antibiotics
2. Prevent/treat hypothermia axillary <35°C (95°F); rectal <35.5°C (95.9°F)	Keep warm and dry and feed frequently 1. Avoid exposure 2. Dress warmly, including head and cover with blanket 3. Keep room hot; avoid draughts 4. Change wet clothes and bedding 5. Do not bathe if very ill 6. Feed frequently day and night 7. Treat infections	Actively rewarm 1. Feed 2. Skin-to-skin contact with carer ("kangaroo technique") or dress in warmed clothes, cover head, wrap in warmed blanket and provide indirect heat (e.g. heater; transwarmer mattress; incandescent lamp) 3. Monitor temperature hourly (or every 30 min if using heater) 4. Stop rewarming when rectal temperature is 36.5°C (97.7°F)
3. Prevent/treat dehydration	Replace stool losses 1. Give ReSoMal after each watery stool. ReSoMal (37.5 mmol Na/L) is a low-sodium rehydration solution for malnutrition	Do *not* give IV fluids unless the child is in shock 1. Give ReSoMal 5 mL/kg every 30 min for first 2 hr orally or NG tube 2. Then give 5-10 mL/kg in alternate hours for up to 10 hr. Amount depends on stool loss and eagerness to drink. Feed in the other alternate hour 3. Monitor hourly and stop if signs of overload develop (pulse rate increases by 25 beats/min and respiratory rate by 5 breaths/min; increasing edema; engorged jugular veins) 4. Stop when rehydrated (3 or more signs of hydration: less thirsty, passing urine, skin pinch less slow, eyes less sunken, moist mouth, tears, less lethargic, improved pulse and respiratory rate).

Continued

Table 46-8 Therapeutic Directives for Stabilization—cont'd

STEP	PREVENTION	TREATMENT
4. Correct electrolyte imbalance—deficit of potassium and magnesium, excess sodium		1. Give extra potassium (4 mmol/kg/day) and magnesium (0.6 mmol/kg/day) for at least 2 wk (see Table 46-12) *Note:* Potassium and magnesium are already added in Nutriset F75 and F100 packets
5. Prevent/treat infections	Minimize risk of cross-infection 1. Avoid overcrowding 2. Wash hands 3. Give measles vaccine to unimmunized children age >6 mo	Infections are often silent. Starting on the first day, give broad-spectrum antibiotics to all children. 1. For antibiotic choices/schedule see Table 46-9 2. Ensure all doses are given, and given on time 3. Cover skin lesions so they do not become infected *Note:* Avoid steroids as they depress immune function
6. Correct micronutrient deficiencies	*Note:* Folic acid, multivitamins, zinc, copper, and other trace minerals are already added in Nutriset F75 and F100 packets	Do *not* give iron in the stabilization phase 1. Give vitamin A on day 1 (under 6 mo 50,000 units; 6-12 mo 100,000 units; >12 mo 200,000 units) if child has any eye signs of vitamin A deficiency or has had recent measles. Repeat this dose on days 2 and 14 2. Folic acid 1 mg (5 mg on day 1) 3. Zinc (2 mg/kg/day) and copper (0.3 mg/kg/day).These are in the electrolyte/mineral solution and Combined Mineral Vitamin mix (CMV) and can be added to feeds and ReSoMal 4. Multivitamin syrup or CMV
7. Start cautious feeding		1. Give 8-12 small feeds of F75 to provide 130 mL/kg/day,100 kcal/kg/day and 1-1.5 g protein/kg/day 2. If gross edema, reduce volume to 100 ml/kg/day 3. Keep a 24-hr intake chart. Measure feeds carefully. Record leftovers 4. If child has poor appetite, coax and encourage to finish the feed. If unfinished, reoffer later. Use NG tube if eating 80% or less of the amount offered 5. If breastfed, encourage continued breastfeeding but also give F75 6. Transfer to F100 when appetite returns (usually within 1 wk) and edema has been lost or is reduced 7. Weigh daily and plot weight.

Table 46-9 Recommended Antibiotics*

	GIVE
If no complications	Amoxicillin oral 25 mg/kg twice daily for 5 days
If complications (shock, hypoglycemia, hypothermia, skin lesions, respiratory or urinary tract infections, or lethargy/sickly)	Gentamicin (7.5 mg/kg IV or IM) once daily for 7 days *and* Ampicillin (50 mg/kg IV or IM) every 6 hr for 2 days, then oral amoxicillin (25-40 mg/kg) every 8 hr for 5 days

*Local resistance patterns may require these to be adjusted: Ensure that there is Gram-negative cover.
If specific infections are identified, add appropriate antibiotics.
For persistent diarrhea/small bowel overgrowth, add metronidazole (7.5 mg/kg oral) every 8 hr for 7 days.

100 mL to which potassium, magnesium, and micronutrients are added), will reestablish metabolic control, treat edema, and restore appetite. The parenteral route should be avoided; children who lack appetite should be fed by nasogastric tube, as nutrients delivered within the gut lumen help in its repair. Table 46-10 gives recipes for preparing the special feeds, and their nutrient composition. Two recipes for F75 are shown: one requires no cooking, the other is cereal-based and has a lower osmolality, which may benefit children with persistent diarrhea. F75 is also available commercially in which maltodextrins replace some of the sugar and to which potassium, magnesium, minerals, and vitamins are already added.

Dehydration status is easily misdiagnosed in severely wasted children, as the usual signs (such as slow skin pinch, sunken eyes) may be present even without dehydration. Rehydration must therefore be closely monitored for signs of fluid overload. Serum electrolyte levels can be misleading because of sodium leaking from the blood into cells and potassium leaking out of cells. Keeping the intake of electrolytes and nutrients constant (see Table 46-9) allows systems to stabilize more quickly than adjusting intake in response to laboratory results.

Table 46-11 gives a recipe for the special rehydration solution used in severe malnutrition (ReSoMal). Therapeutic Combined Mineral Vitamin mix (CMV) contains electrolytes, minerals, and vitamins and is added to ReSoMal and feeds. If unavailable, potassium, magnesium, zinc, and copper can be added as an electrolyte/mineral stock solution (Table 46-12 provides a recipe) and a multivitamin supplement given separately.

◆ ***Rehabilitation***: The signals for entry to this phase are reduced/minimal edema and return of appetite.

A controlled transition over 3 days is recommended to prevent the "refeeding syndrome." After the transition,

Table 46-10 Recipes for Milk Formulas F75 and F100

	F75[b] (STARTER)	F75[c] (STARTER) (CEREAL-BASED)	F100[d] (CATCH-UP)
Dried skimmed milk (g)	25	25	80
Sugar (g)	100	70	50
Cereal flour (g)	—	35	—
Vegetable oil (g)	30	30	60
Electrolyte/mineral solution (mL)[a]	20	20	20
Water: make up to (mL)	1000	1000	1000
Content/100 mL			
Energy (kcal)	75	75	100
Protein (g)	0.9	1.1	2.9
Lactose (g)	1.3	1.3	4.2
Potassium (mmol)	4.0	4.2	6.3
Sodium (mmol)	0.6	0.6	1.9
Magnesium (mmol)	0.43	0.46	0.73
Zinc (mg)	2.0	2.0	2.3
Copper (mg)	0.25	0.25	0.25
% Energy from protein	5	6	12
% Energy from fat	32	32	53
Osmolality (mOsm/L)	413	334	419

Whisk at high speed to prevent oil from separating out.
[a]See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).
[b]A comparable F75 can be made from 35 g dried whole milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 300 mL full cream cow's milk, 100 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.
[c]This lower-osmolality formula may be helpful for children with dysentery or persistent diarrhea. Cook for 4 min.
[d]A comparable F100 can be made from 110 g dried whole milk, 50 g sugar, 30 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL; or from 880 mL full cream cow's milk, 75 g sugar, 20 g oil, 20 mL electrolyte/mineral solution, and water to 1000 mL.

Table 46-11 Recipe for Rehydration Solution for Malnutrition (ReSoMal)

INGREDIENT	AMOUNT
Water	2 L
WHO-ORS	One 1-L sachet*
Sucrose	50 g
Electrolyte/mineral solution†	mL

ReSoMal contains 37.5 mmol sodium and 40 mmol potassium/L
*Sachet contains 2.6 g sodium chloride, 2.9 g trisodium citrate, 1.5 g potassium chloride, 13.5 g glucose.
†See Table 46-12 for recipe, or use commercially available therapeutic Combined Mineral Vitamin mix (CMV).

Table 46-12 Recipe for Concentrated Electrolyte/Mineral Solution*

INGREDIENT	g	mol/20 mL
Potassium chloride: KCl	224.0	24 mmol
Tripotassium citrate	81.0	2 mmol
Magnesium chloride: $MgCl_2 . 6H_2O$	76.0	3 mmol
Zinc acetate: Zn acetate.$2H_2O$	8.2	300 µmol
Copper sulfate: $CuSO_4 . 5H_2O$	1.4	45 µmol
Water: make up to	2500 mL	

Add 20 mL when preparing 1 L of feed or ReSoMal.
*Make fresh each month. Use cooled boiled water.

unlimited amounts should be given of a high-energy, high-protein milk formula such as F100 (100 kcal and 3 g protein per 100 mL), or ready-to-use therapeutic food (RUTF), or family foods modified to have comparable energy and protein contents.

To make the transition, for 2 days replace F75 with an equal volume of F100 and then increase each successive feed by 10 mL until some feed remains uneaten (usually at around 200 mL/kg/day).

After the transition, give 150-220 kcal/kg/day and 4-6 g protein/kg/day and continue to give potassium, magnesium, and micronutrients. Add iron (3 mg/kg/day). If breastfed, encourage continued breastfeeding.

Children with severe malnutrition have developmental delays, so loving care, structured play, and sensory stimulation during and after treatment are essential to aid recovery of brain function.

Community-based treatment: Many children with severe acute malnutrition can be identified in their communities before medical complications arise. If these children have a good appetite and are clinically well, they can be rehabilitated at home through community-based therapeutic care, which has the added benefit of reducing their exposure to nosocomial infections and providing continuity of care after

recovery. It also reduces the time caregivers spend away from home and their opportunity costs, and can be cost-effective for health services.

Figure 46-7 shows the criteria for inpatient versus outpatient care. To maximize coverage and compliance, community-based therapeutic care has 4 main elements: community mobilization and sensitization; active case-finding; therapeutic care; and follow-up after discharge.

Community-based therapeutic care comprises steps 8-10, plus a broad-spectrum antibiotic (step 5). RUTF is usually provided, especially in times of food shortage. RUTF is specially designed for rehabilitating children with severe acute malnutrition at home. It is high in energy and protein and has electrolytes and micronutrients added. The most widely used RUTF is a thick paste that contains milk powder, peanuts, vegetable oil, and sugar. Pathogens cannot grow in it because of its low moisture content. Hospitalized children who have completed steps 1-7 and the transition can be transferred to community-based care for completion of their rehabilitation, thereby reducing their hospital stay to about 7-10 days.

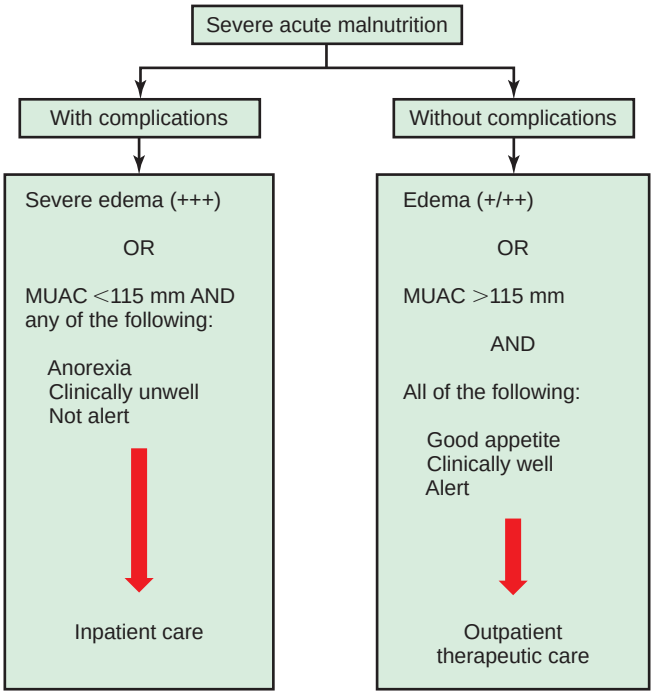

Figure 46-7 Flow diagram for inpatient and outpatient care in the child with severe acute malnutrition. MUAC, Mid upper arm circumference.

Bibliography is available at Expert Consult.

46.1 Refeeding Syndrome

Robert M. Kliegman

Refeeding syndrome can complicate the acute nutritional rehabilitation of children who are undernourished from any cause (Table 46-13). Refeeding syndrome is rare when the WHO recommendations for the treatment of malnutrition are followed (see Chapter 46); however, it may follow overly aggressive enteral or parenteral alimentation. Malnutrition usually has normal serum electrolytes but is associated with intracellular electrolyte depletion. When excessive carbohydrates are administered, the resultant increase in serum insulin levels may produce hypokalemia, hypophosphatemia, and hypomagnesemia. The hallmark of refeeding syndrome is the development of severe hypophosphatemia after the cellular uptake of phosphate during the 1st wk of starting to reefed. Serum phosphate levels of ≤0.5 mmol/L can produce weakness, rhabdomyolysis, neutrophil dysfunction, cardiorespiratory failure, arrhythmias, seizures, altered level of consciousness, or sudden death. Phosphate levels should be monitored during refeeding, and if they are low, phosphate should be administered during refeeding to treat severe hypophosphatemia (see Chapter 55.6).

Table 46-13 Clinical Signs and Symptoms of Refeeding Syndrome

HYPOPHOSPHATEMIA	HYPOKALEMIA	HYPOMAGNESEMIA	VITAMIN/THIAMINE DEFICIENCY	SODIUM RETENTION	HYPERGLYCEMIA
Cardiac Hypotension Decreased stroke volume **Respiratory** Impaired diaphragm contractility Dyspnea Respiratory failure **Neurologic** Paresthesia Weakness Confusion Disorientation Lethargy Areflexic paralysis Seizures Coma **Hematologic** Leukocyte dysfunction Hemolysis Thrombocytopenia **Other** Death	**Cardiac** Arrhythmias **Respiratory** Failure **Neurologic** Weakness Paralysis **Gastrointestinal** Nausea Vomiting Constipation **Muscular** Rhabdomyolysis Muscle necrosis **Other** Death	**Cardiac** Arrhythmias **Neurologic** Weakness Tremor Tetany Seizures Altered mental status Coma **Gastrointestinal** Nausea Vomiting Diarrhea **Other** Refractory hypokalemia and hypocalcemia Death	Encephalopathy Lactic acidosis Death	Fluid overload Pulmonary edema Cardiac compromise	**Cardiac** Hypotension **Respiratory** Hypercapnia Failure **Other** Ketoacidosis Coma Dehydration Impaired immune function

Data from Kraft MD, Btaiche IF, Sacks GS: Review of RFS, Nutr Clin Pract *20:625–633, 2005. From Fuentebella J, Kerner JA: Refeeding syndrome,* Pediatr Clin North Am *56:1201–1210, 2009.*

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Chapter 47

Overweight and Obesity

Sheila Gahagan

Obesity is an important pediatric public health problem associated with risk of complications in childhood and increased morbidity and mortality throughout adult life.

EPIDEMIOLOGY

Obesity is a global public health problem, sparing only dramatically poor regions with chronic food scarcity such as sub-Saharan Africa and Haiti. In 2008, according to the World Health Organization, more than 1.4 billion persons ≥20 yr old were overweight or obese.

In the United States, 36% of adults are obese, and an additional 35% of adults are overweight. In children, the prevalence of obesity increased 300% over approximately 40 yr. The National Health and Nutrition Examination Survey, 2009-2010, found 32% of children, 2-19 yr old to be overweight or obese, and 17% in the obese range. Children's risk varies significantly by race/ethnicity. In 2009-2010, 24% of non-Hispanic Black, 21% of Hispanic, and >20% of American Indian/Alaskan Native children and adolescents were obese compared to 14% of white children. Across all racial groups, higher maternal education confers protection against childhood obesity.

Parental obesity correlates with a higher risk for obesity in their children. Prenatal factors including high preconceptual weight, gestational weight gain, high birth weight, and maternal smoking are associated with increased risk for later obesity. Paradoxically, intrauterine growth restriction with early infant catch-up growth is associated with the development of central adiposity and adult-onset cardiovascular risk. Breastfeeding is only modestly protective for obesity. Infants with high levels of negative reactivity (temperament) are at risk for obesity. Better self-regulation is protective.

BODY MASS INDEX

Obesity or increased adiposity is defined using the body mass index (BMI), which is an excellent proxy for more direct measurement of body fat. BMI = weight in kg/(height in meters)^2. Adults with a BMI ≥30 meet the criterion for obesity, and those with a BMI 25-30 fall in the overweight range. During childhood, levels of body fat change beginning with high adiposity during infancy. Body fat levels decrease for approximately 5.5 yr until the period called *adiposity rebound,* when body fat is typically at the lowest level. Adiposity then increases until early adulthood (Fig. 47-1). Consequently, obesity and overweight are defined using BMI percentiles; children >2 yr old with a BMI ≥95th percentile meet the criterion for obesity, and those with a BMI between the 85th and 95th percentiles fall in the overweight range.

ETIOLOGY

Humans have the capacity to store energy in adipose tissue, allowing improved survival in times of famine. Furthermore, humans innately prefer sweet and salty foods and reject bitter flavors. Many vegetables are bitter. These preferences probably reflect evolutionary adaptations to avoid consuming toxic plants. Nonetheless, repeated exposure to healthy foods promotes their acceptance and liking, especially in early life. Simplistically, obesity results from an imbalance of caloric intake and energy expenditure. Even incremental but sustained caloric excess results in excess adiposity. Individual adiposity is the result of a complex interplay among genetically determined body habitus, appetite, nutritional intake, physical activity, and energy expenditure. Environmental factors determine levels of available food, preferences for types of foods, levels of physical activity, and preferences for types of activities.

Environmental Changes

Over the last 4 decades, the food environment has changed dramatically. Changes in the food industry relate in part to social changes, as extended families have become more dispersed. Fewer families routinely prepare meals. Foods are increasingly prepared by a food industry, with high levels of calories, simple carbohydrates, and fat. The price of many foods has declined relative to the family budget. These changes, in combination with marketing pressure, have resulted in larger portion sizes and increased snacking between meals. The increased consumption of high-carbohydrate beverages, including sodas, sport drinks, fruit punch, and juice, adds to these factors.

One-third of U.S. children consume fast food daily. A typical fast food meal can contain 2000 kcal and 84 g of fat. Many children consume 4 servings of high-carbohydrate beverages per day, resulting in an additional 560 kcal of low nutritional value. Sweetened beverages have been linked to increased risk for obesity because children who drink high amounts of sugar do not consume less food. The dramatic increase in the use of high-fructose corn syrup to sweeten beverages and prepared foods is another important environmental change, leading to availability of inexpensive calories.

Since World War II, levels of physical activity in children and adults have declined. Changes in the built environment have resulted in more reliance on cars and decreased walking. Work is increasingly sedentary, and many sectors of society do not engage in physical activity during leisure time. For children, budgetary constraints and pressure for academic performance have led to less time devoted to physical education in schools. Perception of poor neighborhood safety is another factor that can lead to lower levels of physical activity when children are required to stay indoors. The advent of television, computers, and video games has resulted in opportunities for sedentary activities that do not burn calories.

Changes in another health behavior, sleep, might also contribute. Over the last 4 decades, children and adults have decreased the amount of time spent sleeping. Reasons for these changes may relate to increased time at work, increased time watching television, and a generally faster pace of life. Chronic partial sleep loss can increase risk for weight gain and obesity, with the impact possibly greater in children than in adults. In studies of young, healthy, lean men, short sleep duration was associated with decreased leptin levels and increased ghrelin levels, along with increased hunger and appetite. Sleep debt also results in decreased glucose tolerance and insulin sensitivity related to alterations in glucocorticoids and sympathetic activity. Some effects of sleep debt might relate to orexins, peptides synthesized in the lateral hypothalamus that can increase feeding, arousal, sympathetic activity, and/or neuropeptide Y activity.

Genetics

Genetic determinants also have a role in individual susceptibility to obesity (Table 47-1). Findings from genome-wide association studies explain a very small portion of interindividual variability in obesity. One important example, the *FTO* gene at 16q12, is associated with adiposity in childhood, probably explained by increased energy intake (Table 47-1). Monogenic forms of obesity have also been identified, including MC4R deficiency, associated with early-onset obesity and food-seeking behavior. In addition, there are genetic conditions associated with obesity, such as Prader-Willi syndrome, which results from absence of paternally expressed imprinted genes in the 15q11.2–q13 region. Prader-Willi syndrome is characterized by insatiable appetite and food seeking. Epigenetic environmental modification of genes may have a role in the development of obesity, especially during fetal and early life.

Endocrine and Neural Physiology

Monitoring of "stored fuels" and short-term control of food intake (appetite and satiety) occurs through neuroendocrine feedback loops linking adipose tissue, the gastrointestinal tract, and the central

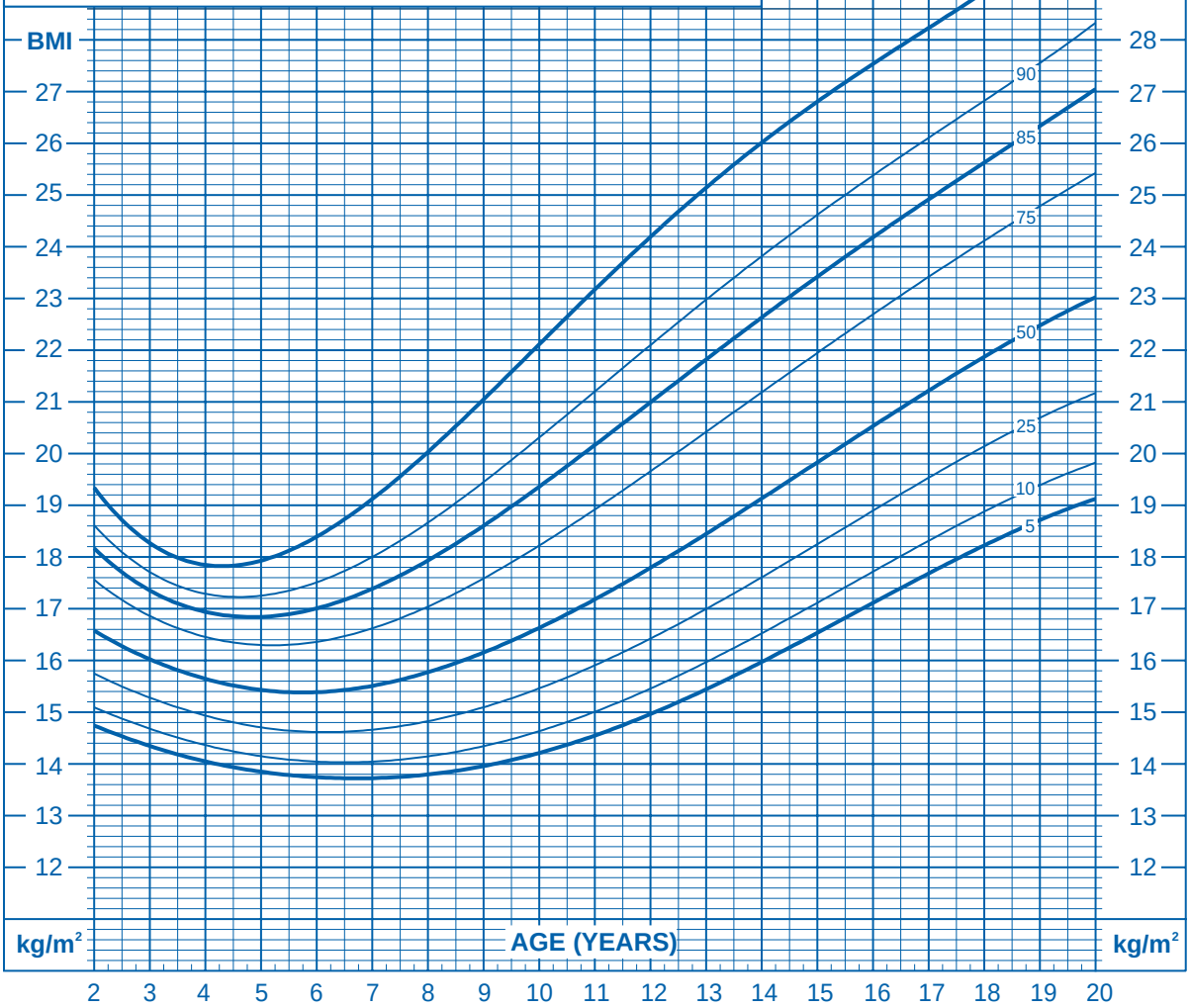
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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A

Figure 47-1 Body mass index (BMI)-for-age profiles for boys and men *(A)* and girls and women *(B)*. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). See www.cdc.gov/growthcharts

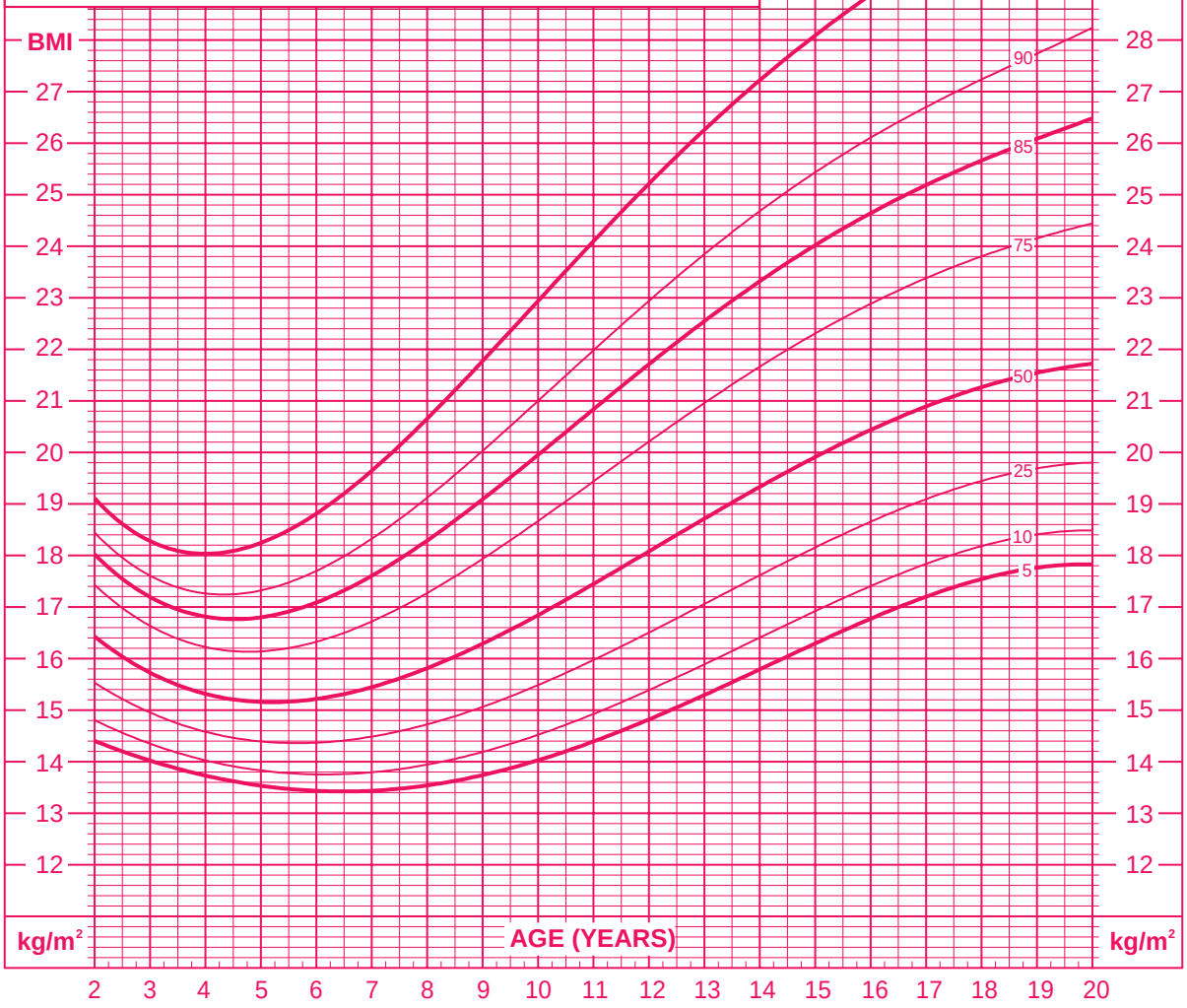
2 to 20 years: Girls
Body mass index-for-age percentiles

NAME _____

RECORD # _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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B

Figure 47-1, cont'd

Table 47-1 Endocrine and Genetic Causes of Obesity

DISEASE	SYMPTOMS	LABORATORY
ENDOCRINE		
Cushing syndrome	Central obesity, hirsutism, moon face, hypertension	Dexamethasone suppression test
GH deficiency	Short stature, slow linear growth	Evoked GH response, IGF-1
Hyperinsulinism	Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome	Insulin level
Hypothyroidism	Short stature, weight gain, fatigue, constipation, cold intolerance, myxedema	TSH, FT_4
Pseudohypoparathyroidism	Short metacarpals, subcutaneous calcifications, dysmorphic facies, mental retardation, short stature, hypocalcemia, hyperphosphatemia	Urine cAMP after synthetic PTH infusion
GENETIC		
Alstrom syndrome	Cognitive impairment, retinitis pigmentosa, diabetes mellitus, hearing loss, hypogonadism, retinal degeneration	*ALMS1* gene
Bardet-Biedl syndrome	Retinitis pigmentosa, renal abnormalities, polydactyly, hypogonadism	*BBS1* gene
Biemond syndrome	Cognitive impairment, iris coloboma, hypogonadism, polydactyly	
Carpenter syndrome	Polydactyly, syndactyly, cranial synostosis, mental retardation	Mutations in the *RAB23* gene, located on chromosome 6 in humans
Cohen syndrome	Mid-childhood-onset obesity, short stature, prominent maxillary incisors, hypotonia, mental retardation, microcephaly, decreased visual activity	Mutations in the *VPS13B* gene (often called the *COH1* gene) at locus 8q22
Deletion 9q34	Early-onset obesity, mental retardation, brachycephaly, synophrys, prognathism, behavior and sleep disturbances	Deletion 9q34
Down syndrome	Short stature, dysmorphic facies, mental retardation	Trisomy 21
ENPP1 gene mutations	Insulin resistance, childhood obesity	Gene mutation on chromosome 6q
Fröhlich syndrome	Hypothalamic tumor	
FTO gene polymorphism	Dysregulation of orexigenic hormone acyl-ghrelin, poor postprandial appetite suppression	Homozygous for *FTO* AA allele
Leptin or leptin receptor gene deficiency	Early-onset severe obesity, infertility (hypogonadotropic hypogonadism)	Leptin
Melanocortin 4 receptor gene mutation	Early-onset severe obesity, increased linear growth, hyperphagia, hyperinsulinemia Most common known genetic cause of obesity Homozygous worse than heterozygous	*MC4R* mutation
Prader-Willi Syndrome	Neonatal hypotonia, slow infant growth, small hands and feet, mental retardation, hypogonadism, hyperphagia leading to severe obesity, paradoxically elevated ghrelin	Partial deletion of chromosome 15 or loss of paternally expressed genes
Proopiomelanocortin deficiency	Obesity, red hair, adrenal insufficiency, hyperproinsulinemia	Loss-of-function mutations of the *POMC* gene
Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD)	Often confused with congenital central hypoventilation syndrome (CCHS), presentation ≥1.5 yr with weight gain, hyperphagia, hypoventilation, cardiac arrest, central diabetes insipidus, hypothyroidism, growth hormone deficiency, pain insensitivity, hypothermia, precocious puberty, neural crest tumors	Unknown genes May be a paraneoplastic disorder
Turner syndrome	Ovarian dysgenesis, lymphedema, web neck, short stature, cognitive impairment	XO chromosome

cAMP, cyclic adenosine monophosphate; FT_4, free thyroxine; GH, growth hormone; IGF, insulin-like growth factor; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

nervous system (Fig. 47-2). Gastrointestinal hormones, including cholecystokinin, glucagon-like peptide-1, peptide YY, and vagal neuronal feedback promote satiety. Ghrelin stimulates appetite. Adipose tissue provides feedback regarding energy storage levels to the brain through hormonal release of adiponectin and leptin. These hormones act on the arcuate nucleus in the hypothalamus and on the solitary tract nucleus in the brainstem and, in turn, activate distinct neuronal networks. Adipocytes secrete adiponectin into the blood, with reduced levels in response to obesity and increased levels in response to fasting. Reduced adiponectin levels are associated with lower insulin sensitivity and adverse cardiovascular outcomes. Leptin is directly involved in satiety, as low leptin levels stimulate food intake and high leptin levels inhibit hunger in animal models and in healthy human volunteers. Adiposity correlates to serum leptin levels among children and adults, with the direction of effect remaining unclear.

Numerous neuropeptides in the brain, including peptide YY, agouti-related peptide, and orexin, appear to affect appetite stimulation, whereas melanocortins and α-melanocortin–stimulating hormone are involved in satiety. The neuroendocrine control of appetite and weight involves a negative-feedback system, balanced between short-term control of appetite and long-term control of adiposity (including leptin). Peptide YY reduces food intake via the vagal–brainstem–hypothalamic pathway. Developmental changes in peptide YY are evident as infants have higher levels of peptide YY than school-age children and adults. Obese children have lower fasting levels of peptide YY compared to adults. Weight loss may restore levels of peptide YY in children even though this does not happen in adults. In addition, patients homozygous for the *FTO* obesity risk allele demonstrate poor regulation of the orexigenic hormone acyl-ghrelin and have poor postprandial appetite suppression.

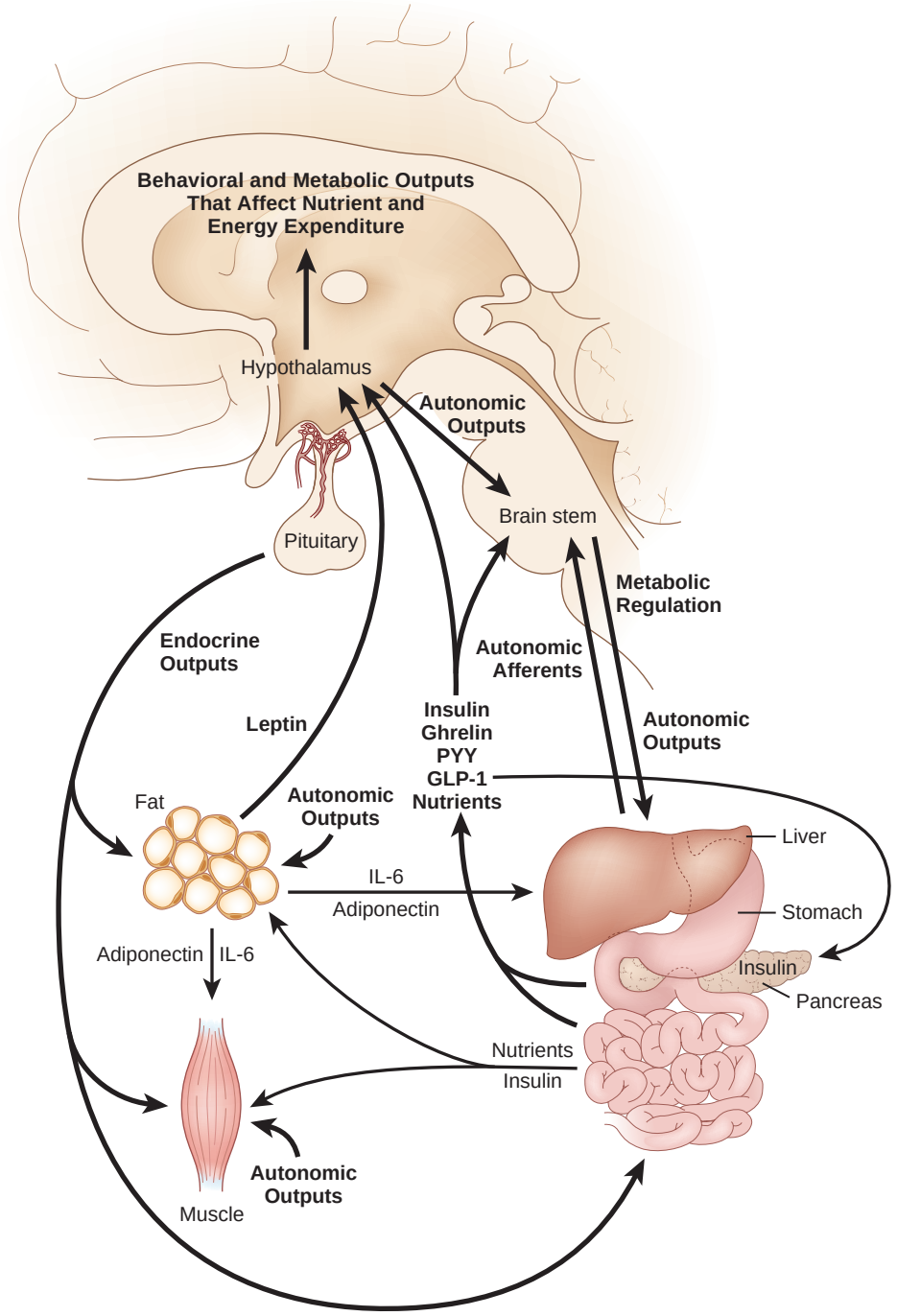

Figure 47-2 **Regulation of energy homeostasis by the brain–adipose tissue–intestinal axis.** Leptin stimulates hypothalamic anorexigenic and inhibits orexigenic neurons. Adiponectin stimulates hepatic, and muscle glucose utilization and increases insulin sensitivity, while interleukin-6 (IL-6) contributes to adipose tissue, muscle and hepatic insulin resistance. Peptide YY (PYY) inhibits orexigenic and glucagon-like peptide 1 (GLP-1) stimulates anorexigenic hypothalamic neurons. GLP-1 also augments glucose stimulated pancreatic insulin secretion and suppresses glucagon secretion. Insulin stimulates adipose tissue and muscle glucose uptake, enhances lipogenesis, suppresses hepatic glucose production, and has an inhibitory effect on the hypothalamic anorexigenic system. Ghrelin stimulates the orexigenic hypothalamic pathways. *(Modified from Melmed S, Polonsky KS, Larsen PR, Kronenberg HM:* Williams Textbook of Endocrinology, *ed 12, Philadelphia, 2011, Saunders.* Fig. 35-1.*)*

COMORBIDITIES

Complications of pediatric obesity occur during childhood and adolescence and persist into adulthood. An important reason to prevent and treat pediatric obesity is the increased risk for morbidity and mortality later in life. The Harvard Growth Study found that boys who were overweight during adolescence were twice as likely to die from cardiovascular disease as those who had normal weight. More immediate comorbidities include type 2 diabetes, hypertension, hyperlipidemia, and nonalcoholic fatty liver disease (Table 47-2). Insulin resistance increases with increasing adiposity and independently affects lipid metabolism and cardiovascular health. The metabolic syndrome (central obesity, hypertension, glucose intolerance, and hyperlipidemia) increases risk for cardiovascular morbidity and mortality. Nonalcoholic fatty liver disease (NAFLD) occurs in 10-25% of obese

Table 47-2 Obesity-Associated Comorbidities

DISEASE	POSSIBLE SYMPTOMS	LABORATORY CRITERIA
CARDIOVASCULAR		
Dyslipidemia	HDL <40, LDL >130, total cholesterol >200	Fasting total cholesterol, HDL, LDL, triglycerides
Hypertension	SBP >95% for sex, age, height	Serial testing, urinalysis, electrolytes, blood urea nitrogen, creatinine
ENDOCRINE		
Type 2 diabetes mellitus	Acanthosis nigrans, polyuria, polydipsia	Fasting blood glucose >110, hemoglobin A_{1c}, insulin level, C-peptide, oral glucose tolerance test
Metabolic syndrome	Central adiposity, insulin resistance, dyslipidemia, hypertension, glucose intolerance	Fasting glucose, LDL and HDL cholesterol
Polycystic ovary syndrome	Irregular menses, hirsutism, acne, insulin resistance, hyperandrogenemia	Pelvic ultrasound, free testosterone, LH, FSH
GASTROINTESTINAL		
Gallbladder disease	Abdominal pain, vomiting, jaundice	Ultrasound
Nonalcoholic fatty liver disease (NAFLD)	Hepatomegaly, abdominal pain, dependent edema, ↑ transaminases Can progress to fibrosis, cirrhosis	AST, ALT, ultrasound, CT, or MRI
NEUROLOGIC		
Pseudotumor cerebri	Headaches, vision changes, papilledema	Cerebrospinal fluid opening pressure, CT, MRI
Migraines	Hemicrania, headaches	None
ORTHOPEDIC		
Blount disease (tibia vara)	Severe bowing of tibia, knee pain, limp	Knee x-rays
Musculoskeletal problems	Back pain, joint pain, frequent strains or sprains, limp, hip pain, groin pain, leg bowing	X-rays
Slipped capital femoral epiphysis	Hip pain, knee pain, limp, decreased mobility of hip	Hip x-rays
PSYCHOLOGICAL		
Behavioral complications	Anxiety, depression, low self-esteem, disordered eating, signs of depression, worsening school performance, social isolation, problems with bullying or being bullied	Child Behavior Checklist, Children's Depression Inventory, Peds QL, Eating Disorder Inventory 2, subjective ratings of stress and depression, Behavior Assessment System for Children, Pediatric Symptom Checklist
PULMONARY		
Asthma	Shortness of breath, wheezing, coughing, exercise intolerance	Pulmonary function tests, peak flow
Obstructive sleep apnea	Snoring, apnea, restless sleep, behavioral problems	Polysomnography, hypoxia, electrolytes (respiratory acidosis with metabolic alkalosis)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LH, luteinizing hormone; MRI, magnetic resonance imaging; Peds QL, Pediatric Quality of Life Inventory; SBP, systolic blood pressure.

adolescents. NAFLD is now the most common chronic liver disease in U.S. children and adolescents. It can present with advanced fibrosis or nonalcoholic steatohepatitis and may result in cirrhosis and hepatocellular carcinoma. Insulin resistance is commonly associated. Furthermore, NAFLD is independently associated with increased risk of cardiovascular disease.

Obesity may also be associated with chronic inflammation. Adiponectin, a peptide with antiinflammatory properties, occurs in reduced levels in obese patients as compared to insulin-sensitive, lean persons. Low adiponectin levels correlate with elevated levels of free fatty acids and plasma triglycerides as well as a high BMI, and high adiponectin levels correlate with peripheral insulin sensitivity. Adipocytes secrete peptides and cytokines into the circulation, and proinflammatory peptides such interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) occur in higher levels in obese patients. Specifically, IL-6 stimulates production of C-reactive protein in the liver. C-reactive protein is a marker of inflammation and might link obesity, coronary disease, and subclinical inflammation.

Some complications of obesity are mechanical, including obstructive sleep apnea and orthopedic complications. Orthopedic complications include Blount disease and slipped femoral capital epiphysis (see Chapters 677, 678.4).

Mental health problems can coexist with obesity, with the possibility of bidirectional effects. These associations are modified by gender, ethnicity, and socioeconomic status. Self-esteem may be lower in obese adolescent girls compared to nonobese peers. Some studies have found an association between obesity and adolescent depression. There is considerable interest in the cooccurrence of eating disorders and obesity.

IDENTIFICATION

Overweight and obese children are often identified as part of routine medical care, and the child and family may be unaware that the child has increased adiposity. They may be unhappy with the medical provider for raising this issue and respond with denial or apparent lack of concern. It is often necessary to begin by helping the family understand the importance of healthy weight for current and future health, especially because intervention requires considerable effort by the child and the family. Forging a good therapeutic relationship is important, because obesity intervention requires a chronic disease management approach. Successful resolution of this problem necessitates considerable family and child effort over an extended period in order to change eating and activity behaviors.

EVALUATION

The evaluation of the overweight or obese child begins with examination of the growth chart for weight, height, and BMI trajectories; consideration of possible medical causes of obesity; and detailed

exploration of family eating, nutritional, and activity patterns. A complete pediatric history is used to uncover comorbid disorders. The family history focuses on the adiposity of other family members and the family history of obesity-associated disorders. The physical examination adds data that can lead to important diagnoses. Laboratory testing is guided by the need to identify comorbid conditions.

Examination of the growth chart reveals the severity, duration, and timing of obesity onset. Children who are overweight (BMI in the 85th-95th percentile) are less likely to have developed comorbid conditions than those who are obese (BMI ≥95th percentile). Those with a BMI ≥99th percentile are even more likely to have coexisting medical problems. Once obesity severity is determined, the BMI trajectory is examined to elucidate when the child became obese. Several periods during childhood are considered sensitive periods or times of increased risk for developing obesity, including infancy, adiposity rebound (when body fat is lowest at approximately age 5.5 yr), and adolescence. An abrupt change in BMI might signal the onset of a medical problem or a period of family or personal stress for the child. Examination of the weight trajectory can further expand understanding of how the problem developed. A young child might exhibit high weight and high height because linear growth can increase early in childhood if a child consumes excess energy. At some point, the weight percentile exceeds the height percentile and the child's BMI climbs into the obese range. Another example is a child whose weight rapidly increases when she reduces her activity level and consumes more meals away from home. Examination of the height trajectory can reveal endocrine problems, which often occur with slowing of linear growth.

Consideration of possible medical causes of obesity is essential, even though endocrine and genetic causes are rare (see Table 47-1). Growth hormone deficiency, hypothyroidism, and Cushing syndrome are examples of endocrine disorders that can lead to obesity. In general, these disorders manifest with slow linear growth. Because children who consume excessive amounts of calories tend to experience accelerated linear growth, short stature warrants further evaluation. Genetic disorders associated with obesity can have coexisting dysmorphic features, cognitive impairment, vision and hearing abnormalities, or short stature. In some children with congenital disorders such as myelodysplasia or muscular dystrophy, lower levels of physical activity can lead to secondary obesity. Some medications can cause excessive appetite and hyperphagia, resulting in obesity. Atypical antipsychotic medications often have this dramatic side effect. Rapid weight gain in a child or adolescent taking one of these medications might require a discontinuation of that medication. Poor linear growth and rapid changes in weight gain are indications for evaluation of possible medical causes.

Exploration of family eating and nutritional and activity patterns begins with a description of regular meal and snack times and family habits for walking, bicycle riding, active recreation, television, computer, and video game time. It is useful to request a 24-hr dietary recall with special attention to intake of fruits, vegetables, and water, as well as high-calorie foods and high-carbohydrate beverages. When possible, evaluation by a nutritionist is extremely helpful. This information will form the basis for incremental changes in eating behavior, caloric intake, and physical activity during the intervention.

Initial assessment of the overweight or obese child includes a complete review of bodily systems focusing on the possibility of comorbid conditions (see Table 47-2). Developmental delay and visual and hearing impairment can be associated with genetic disorders. Difficulty sleeping, snoring, or daytime sleepiness suggests the possibility of sleep apnea. Abdominal pain might suggest NAFLD. Symptoms of polyuria, nocturia, or polydipsia may be the result of type 2 diabetes. Hip or knee pain can be caused by secondary orthopedic problems, including Blount disease and slipped capital femoral epiphysis. Irregular menses may be associated with polycystic ovary syndrome. Acanthosis nigricans can suggest insulin resistance and type 2 diabetes (Fig. 47-3).

The family history begins with identifying other obese family members. Parental obesity is an important risk for child obesity. If all family members are obese, focusing the intervention on the entire family is reasonable. The child may be at increased risk for developing type 2 diabetes if a family history exists. Patients of African-American, Hispanic, or Native American heritage are also at increased risk for developing type 2 diabetes. Identification of a family history of hypertension, cardiovascular disease, or metabolic syndrome indicates increased risk for developing these obesity-associated conditions. If one helps the family to understand that childhood obesity increases risk for developing these chronic diseases, this educational intervention might serve as motivation to improve their nutrition and physical activity.

Figure 47-3 Acanthosis nigricans. *(From Gahagan S: Child and adolescent obesity,* Curr Probl Pediatr Adolesc Health Care *34:6–43, 2004.)*

Physical examination should be thorough, focusing on possible comorbid conditions (see Table 47-2). Careful screening for hypertension using an appropriately sized blood pressure cuff is important. Systematic examination of the skin can reveal acanthosis nigricans, suggesting insulin resistance, or hirsutism, suggesting polycystic ovary syndrome. Tanner staging can reveal premature adrenarche secondary to advanced sexual maturation in overweight and obese girls.

Laboratory testing for fasting plasma glucose, triglycerides, low-density lipoprotein and high-density lipoprotein cholesterol, and liver function tests are recommended as part of the initial evaluation for newly identified pediatric obesity (Table 47-3). Overweight children (BMI 85th-95th percentile) who have a family history of diabetes mellitus or signs of insulin resistance should also be evaluated with a fasting plasma glucose test. Other laboratory testing should be guided by history or physical examination findings.

INTERVENTION

There is evidence that some interventions result in modest but significant and sustained improvement in body mass. Based on behavior change theories, treatment includes specifying target behaviors, self-monitoring, goal setting, stimulus control, and promotion of self-efficacy and self-management skills. Behavior changes associated with improving BMI include drinking lower quantities of sugar-sweetened beverages, consuming higher-quality diets, increasing exercise, watching less TV, and self-weighing. Most successful interventions have been family based and take into account the child's developmental age. "Parent-only" treatment can be as effective as "parent–child" treatment. Because obesity is multifactorial, not all children and adolescents will respond to the same approach. For example, "loss-of-control" eating, associated with weight gain and obesity, predicts poor outcome in response to family-based treatment. Furthermore, clinical-treatment programs are expensive and not widely available. Therefore there is interest in novel approaches including Internet-based treatments and guided self-help.

It is important to begin with clear recommendations about appropriate caloric intake for the obese child (Table 47-4). Working with a dietitian is very helpful. Meals should be based on fruits, vegetables, whole grains, lean meat, fish, and poultry. Prepared foods should be chosen for their nutritional value, with attention to calories and fat. Foods that provide excessive calories and low nutritional value should be reserved for infrequent treats.

Weight-reduction diets in adults generally do not lead to sustained weight loss. Therefore, the focus should be on changes that can be maintained for life. Attention to eating patterns is helpful. Families should be encouraged to plan family meals, including breakfast. It is almost impossible for a child to make changes in nutritional intake and eating patterns if other family members do not make the same changes. Dietary needs also change developmentally, as adolescents require greatly increased calories during their growth spurts, and adults who lead inactive lives need fewer calories than active and growing children.

Table 47-3 Normal Laboratory Values for Recommended Tests

LABORATORY TEST	NORMAL VALUE
Glucose	<110 mg/dL
Insulin	<15 mU/L
Hemoglobin A_{1c}	<5.7%
AST (age 2-8 yr)	<58 U/L
AST (age 9-15 yr)	<46 U/L
AST (age 15-18 yr)	<35 U/L
ALT	<35 U/L
Total cholesterol	<170 mg/dL
LDL	<110 mg/dL
HDL	>45 mg/dL
Triglycerides (age 0-9 yr)	<75 mg/dL
Triglycerides (age 10-19 yr)	<90 mg/dL

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

From Children's Hospital of Wisconsin: The NEW (nutrition, exercise and weight management) kids program *(PDF file). http://www.chw.org/display/displayFile.asp?docid=33672&filename=/Groups/NEWKids/NewKidsReferral.PDF.*

Psychological strategies are helpful. The "traffic light" diet groups foods into those that can be consumed without any limitations (green), in moderation (yellow), or reserved for infrequent treats (red) (Table 47-5). The concrete categories are very helpful to children and families. This approach can be adapted to any ethnic group or regional cuisine. Motivational interviewing begins with assessing how ready the patient is to make important behavioral changes. The professional then engages the patient in developing a strategy to take the next step toward the ultimate goal of healthy nutritional intake. This method allows the professional to take the role of a coach, helping the child and family reach their goals. Other behavioral approaches include family rules about where food may be consumed; for example, "not in the bedroom."

Increasing physical activity without decreasing caloric intake is unlikely to result in weight loss. Nonetheless, it can increase aerobic fitness and decrease percent body fat even without weight loss. Therefore, increasing physical activity can decrease risk for cardiovascular disease, improve well-being, and contribute to weight loss. Increased physical activity can be accomplished by walking to school, engaging in physical activity during leisure time with family and friends, or enrolling in organized sports. Children are more likely to be active if their parents are active. Just as family meals are recommended, family physical activity is recommended.

Active pursuits can replace more sedentary activities. The American Academy of Pediatrics recommends that screen time be restricted to no more than 2 hr/day for children >2 yr old and that children <2 yr old not watch television. Television watching is often associated with eating, and many highly caloric food products are marketed directly to children during child-oriented television programs.

Pediatric providers should assist families to develop goals to change nutritional intake and physical activity. They can also provide the child and family with needed information. The family should not expect immediate lowering of BMI percentile related to behavioral changes but can instead count on a gradual decrease in the rate of BMI percentile increase until it stabilizes, followed by a gradual decrease in BMI percentile. Referral to multidisciplinary, comprehensive pediatric weight-management programs is ideal for obese children whenever possible.

There is no effective pharmacotherapy resulting in reversal of excess adiposity in children and adolescents. Available medications result in

Table 47-4 Recommended Caloric Intake Designated by Age and Gender

LIFE-STAGE GROUP	AGE (yr)	RELATIVELY SEDENTARY LEVEL OF ACTIVITY (kcal)	MODERATE LEVEL OF ACTIVITY (kcal)	ACTIVE (kcal)
Child	2-3	1,000	1,000-1,400	1,000-1,400
Female	4-8	1,200	1,400-1,600	1,400-1,800
	9-13	1,600	1,600-2,000	1,800-2,200
	14-18	1,800	2,000	2,400
Male	4-8	1,400	1,400-1,600	1,600-2,000
	9-13	1,800	1,800-2,200	2,000-2,600
	14-18	2,200	2,400-2,800	2,800-3,200

Adapted from U.S. Department of Agriculture: Dietary guidelines for Americans, *2005. http://www.health.gov/DIETARYGUIDELINES/dga2005/document/html/chapter2.htm.*

Table 47-5 Traffic Light Diet Plan

FEATURE	GREEN LIGHT FOODS	YELLOW LIGHT FOODS	RED LIGHT FOODS
Quality	Low-calorie, high-fiber, low-fat, nutrient-dense	Nutrient-dense, but higher in calories and fat	High in calories, sugar, and fat
Types of food	Fruits, vegetables	Lean meats, dairy, starches, grains	Fatty meats, sugar, sugar-sweetened beverages, fried foods
Quantity	Unlimited	Limited	Infrequent or avoided

modest weight loss or BMI improvement even when combined with behavioral interventions. Various classes of drugs are of interest, including those that decrease energy intake or act centrally as anorexiants, those that affect the availability of nutrients through intestinal or renal tubular reabsorption, and those that affect metabolism. The only U.S. Food and Drug Administration (FDA)-approved medication for obesity in children <16 yr old is orlistat, which decreases absorption of fat, resulting in modest weight loss. Complications include flatulence, oily stools, and spotting. This agent offers little benefit to severely obese adolescents. Because there are multiple redundant neural mechanisms that act to protect body weight, promoting weight loss is extremely difficult. For this reason, there is considerable interest in combining therapies that simultaneously target multiple weight-regulating pathways. One example, approved for adults, combines phentermine, a noradrenergic agent, with topiramate, a γ-aminobutyric acid (GABA)-ergic medication. This combination resulted in a mean 10.2-kg weight loss compared to 1.4 kg in the placebo group. Side effects are common and include dry mouth, constipation, paresthesias, insomnia, and cognitive dysfunction. Another promising example is the combination of amylin (decreases food intake and slows gastric emptying) with leptin (which has no anorexigenic effects when given alone). This combination requires injection and is in clinical trials in adults. Another FDA approved (for adults) drug is lorcaserin, a selective serotonin 2C receptor agonist. Establishing long-term safety and tolerability in children is a challenge as medications of interest have central nervous system effects or interfere with absorption of nutrients; teratologic effects must be considered for use in adolescent girls.

In some cases, it is reasonable to refer adolescents for evaluation for bariatric surgery. The American Pediatric Surgical Association Guidelines recommends that surgery be considered only in children with complete or near-complete skeletal maturity, a BMI ≥40, and a medical complication resulting from obesity, *after* they have failed 6 mo of a multidisciplinary weight management program. Surgical approaches include the Roux-en-Y and the adjustable gastric band. In obese adults, bariatric surgery reduces the risk of developing type 2 diabetes mellitus. In obese adult patients with existing type 2 diabetes, bariatric surgery improves the control of diabetes.

PREVENTION

Prevention of child and adolescent obesity is essential for public health in the United States and most other countries (Table 47-6 and 47-7). Efforts by pediatric providers can supplement national- and community-level public health programs. The National Institutes of Health and Centers for Disease Control and Prevention recommend a variety of initiatives to combat the current obesigenic environment, including promotion of breastfeeding, access to fruits and vegetables, walkable communities, and 60 min/day of activity for children. The U.S. Department of Agriculture sponsors programs promoting 5.5 cups of fruits and vegetables per day. Incentives for the food industry to promote consumption of healthier foods should be considered. Marketing of unhealthy foods to children has begun to be regulated. We expect to see changes in federal food programs including commodity foods, the Women, Infant, and Children Supplemental Food Program, and school-lunch programs to meet the needs of today's children.

Pediatric prevention efforts begin with careful monitoring of weight and BMI percentiles at healthcare maintenance visits. Attention to changes in BMI percentiles can alert the pediatric provider to increasing adiposity before the child becomes overweight or obese. All families should be counseled about healthy nutrition for their children because the current prevalence of overweight and obesity in adults is 65%. Therefore, approximately two-thirds of all children can be considered at risk for becoming overweight or obese at some time in their lives. Those who have an obese parent are at increased risk. Prevention efforts begin with promotion of exclusive breastfeeding for 6 mo and total breastfeeding for 12 mo. Introduction of infant foods at 6 mo should focus on cereals, fruits, and vegetables. Lean meats, poultry, and fish may be introduced later in the 1st year of life. Parents should be specifically counseled to avoid introducing highly sugared beverages and foods in the 1st year of life. Instead, they should expose their infants and young children to a rich variety of fruits, vegetables, grains, lean meats, poultry, and fish to facilitate acceptance of a diverse and healthy diet. Parenting matters, and authoritative parents are more likely to have children with a healthy weight than those who are authoritarian or permissive. Families who eat regularly scheduled meals together are less likely to have overweight or obese children. Child health professionals are able to address a child's nutritional status and to provide expertise in child growth and development.

Child health professionals can also promote physical activity during regular healthcare maintenance visits. Parents who spend some of their leisure time in physical activity promote healthy weight in their children. Beginning in infancy, parents should be cognizant of their child's developmental capability and need for physical activity. Because television, computer, and video game time can replace health-promoting physical activity, physicians should counsel parents to limit screen time for their children. Snacking during television watching should be discouraged. Parents can help their children to understand that television commercials intend to sell a product. Children can learn that their parents will help them by responsibly choosing healthy foods.

As obesity is determined by complex multifactorial conditions, prevention will take efforts at multiple levels of social organization. One example, EPODE (Ensemble Prévenons l'Obésité Des Enfants), is a multilevel prevention strategy, which began in France and has been adopted by more than 500 communities in 6 countries. The goal is for local environments, daycare centers, schools, recreational settings and families to adopt practices that promote healthy lifestyles for children from birth to 12 yr old. This initiative relies on 4 necessary components: political commitment to change, resources to support social marketing and changes, support services, evidence-based practices. All EPODE sites include monitoring and evaluation. Similar efforts are taking place in the United States. An example of a U.S. community effort is Shape Up Somerville, a citywide campaign to increase daily physical activity and healthy eating in Somerville, MA, which has been ongoing since 2002. This systems intervention focuses on school health curricula, healthier food in schools and restaurants, safe routes to school, walkable and bikeable streets and worksite wellness. Communitywide programs are important because neighborhood environmental factors (poverty) have been associated with obesity in its residents. Although these efforts have resulted in lower weight gain in older children and adolescents, there is considerable interest in focusing earlier in the life cycle. Beginning obesity prevention during pregnancy and engaging health systems, early childhood programs, and community systems to support healthier life cycles is an approach with tremendous promise.

Bibliography is available at Expert Consult.

Table 47-6 Proposed Suggestions for Preventing Obesity

PREGNANCY Normalize body mass index before pregnancy. Do not smoke. Maintain moderate exercise as tolerated. In gestational diabetics, provide meticulous glucose control. Gestational weight gain within the Institute of Medicine (IOM) recommendations.
POSTPARTUM AND INFANCY Breastfeeding: exclusive for 4-6 mo, continue with other foods for 12 mo. Postpone the introduction of baby foods to 4-6 mo and juices to 12 mo.
FAMILIES Eat meals as a family in a fixed place and time. Do not skip meals, especially breakfast. No television during meals. Use small plates, and keep serving dishes away from the table. Avoid unnecessary sweet or fatty foods and sugar-sweetened drinks. Remove televisions from children's bedrooms; restrict times for television viewing and video games. Do not use food as a reward.
SCHOOLS Eliminate candy and cookie sales as fundraisers. Review the contents of vending machines and replace with healthier choices; eliminate sodas. Avoid financial support for sports teams from beverage and food industries. Install water fountains and hydration stations. Educate teachers, especially physical education and science faculty, about basic nutrition and the benefits of physical activity. Educate children from preschool through high school on appropriate diet and lifestyle. Mandate minimum standards for physical education, including 60 min of strenuous exercise 5 times weekly. Encourage "the walking school bus": groups of children walking to school with adult supervision.
COMMUNITIES Increase family-friendly exercise and safe play facilities for children of all ages. Develop more mixed residential-commercial developments for walkable and bicyclable communities. Discourage the use of elevators and moving walkways. Provide information on how to shop and prepare healthier versions of culture-specific foods.
HEALTHCARE PROVIDERS Explain the biologic and genetic contributions to obesity. Give age-appropriate expectations for body weight in children. Work toward classifying obesity as a disease to promote recognition, reimbursement for care, and willingness and ability to provide treatment.
INDUSTRY Mandate age-appropriate nutrition labeling for products aimed at children (e.g., red light/green light foods, with portion sizes). Encourage marketing of interactive video games in which children must exercise in order to play. Use celebrity advertising directed at children for healthful foods to promote breakfast and regular meals. Reduce portion size (drinks and meals).
GOVERNMENT AND REGULATORY AGENCIES Classify childhood obesity as a legitimate disease. Find novel ways to fund healthy lifestyle programs (e.g., with revenues from food and drink taxes). Subsidize government-sponsored programs to promote the consumption of fresh fruits and vegetables. Provide financial incentives to industry to develop more healthful products and to educate the consumer on product content. Provide financial incentives to schools that initiate innovative physical activity and nutrition programs. Allow tax deductions for the cost of weight loss and exercise programs. Provide urban planners with funding to establish bicycle, jogging, and walking paths. Ban advertising of fast foods, nonnutritious foods, and sugar-sweetened beverages directed at preschool children, and restrict advertising to school-age children. Ban toys as gifts to children for purchasing fast foods.

Adapted from Speiser PW, Rudolf MCJ, Anhalt H, et al: Consensus statement: childhood obesity, J Clin Endocrinol Metab *90:1871–1887, 2005.*

Table 47-7 Anticipatory Guidance: Establishing Healthy Eating Habits in Children

Do not punish a child during mealtimes with regard to eating. The emotional atmosphere of a meal is very important. Interactions during meals should be pleasant and happy.
Do not use foods as rewards.
Parents, siblings, and peers should model healthy eating, tasting new foods, and eating a well-balanced meal.
Children should be exposed to a wide range of foods, tastes, and textures.
New foods should be offered multiple times. Repeated exposure leads to acceptance and liking.
Forcing a child to eat a certain food will decrease the child's preference for that food. Children's wariness of new foods is normal and should be expected. Offering a variety of foods with low-energy density helps children balance energy intake.
Parents should control what foods are in the home. Restricting access to foods in the home will increase rather than decrease a child's desire for that food.
Children tend to be more aware of satiety than adults, so allow children to respond to satiety, and stop eating. Do not force children to "clean their plate."

Adapted from Benton D: Role of parents in the determination of food preferences of children and the development of obesity, Int J Obes Relat Metab Disord *28:858–869, 2004. Copyright 2004. Reprinted by permission from Macmillan Publishers Ltd.*

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Chapter 48

Vitamin A Deficiencies and Excess

A. Catharine Ross and Libo Tan

OVERVIEW OF VITAMIN A

Vitamin A is a fat-soluble micronutrient that cannot be synthesized de novo by the mammalian body, thus it is an obligatory dietary factor. The term vitamin A is generally used to refer to a group of compounds that possess the biologic activity of *all-trans* retinol (Fig. 48-1). As a fat-soluble micronutrient, vitamin A is recognized as being essential for all vertebrates for normal vision, reproduction, cell and tissue differentiation, and functions of the immune system. Vitamin A plays critical roles in neonatal development. It is required for normal embryonic development, hematopoiesis, immune response, metabolism, and growth and differentiation of many types of cells.

Vitamin A can be obtained from the diet where its main form is as retinyl esters, such as retinyl palmitate, which are called preformed vitamin A. They are found primarily in certain foods of animal origin. Organ meats (especially liver, kidney) are very rich in vitamin A, while other meats, milk, and cheese contain moderate levels. Other sources of vitamin A include several provitamin A carotenoids, which are found naturally in many fruits and vegetables, especially yellow-orange vegetables (pumpkin, squash, sweet potato), and leafy green vegetables (chard, spinach, broccoli). One of the most abundant carotenoids is β-carotene. α-Carotene and β-cryptoxanthin also possess vitamin A activity at a lower bioactivity. In the body, these precursors are used for the synthesis of 2 essential metabolites of vitamin A. One is *all-trans* retinoic acid, the form of vitamin A required for cell differentiation and the regulation of gene transcription. It is the most bioactive form of vitamin A. The other is *11-cis* retinal, required for vision. It functions as the light-absorbing chromophore of the visual pigments rhodopsin and iodopsin.

METABOLISM OF VITAMIN A

Ingested retinyl esters must first be hydrolyzed in the intestinal lumen, a process that liberates unesterified retinol, for the absorption of vitamin A. Most of the retinol is then reesterified in the enterocytes. The absorption of preformed vitamin A is very efficient. Approximately 70-90% of dietary preformed vitamin A is absorbed as long as there is ~10 g or more fat in the meal. Chronic intestinal disorders or lipid malabsorption can result in vitamin A deficiency. Uncleaved provitamin-A carotenoids in the intestine are also incorporated into chylomicrons and delivered to various tissues. The estimated absorption efficiency of carotenoids is approximately 20-50%, and appears to be more variable among individuals than for preformed vitamin A. The efficiency of conversion of B-carotene to retinol is much lower than expected. The carotene cleavage enzyme β-carotene monooxygenase, present in the enterocyte, exhibits certain single nucleotide polymorphisms that reduce the efficiency of conversion of β-carotene to retinol.

Once retinol is esterified in the enterocyte, retinyl ester is then packaged into nascent chylomicrons, which are then secreted into the lymphatic vessels and transported via the circulation to the liver or to other tissues. When vitamin A status is adequate, most mammals, including humans, store most of their total body vitamin A in the liver, within stellate cells. When their vitamin A status is deficient, vitamin A stores can be mobilized; the released retinol can be used by extrahepatic tissues. Stored vitamin A is released from the liver into the circulation as retinol bound to its specific transport protein, retinol-binding protein (RBP), which binds to the thyroid hormone transport protein, transthyretin (TTR); this complex delivers retinol (as well as the thyroid hormone) to a large number of vitamin A target tissues. The major physiologic mediator of retinol uptake by cells in many tissues is Stra6, a widely expressed multitransmembrane domain protein that functions as a cell-surface receptor for retinol bound to RBP.

In target tissues, retinol is either esterified into retinyl esters for storage or oxidized into retinoic acid for function. In the eye, 11-*cis*-retinal is formed.

Vitamin A Status in Neonates

Neonates begin life with low levels of vitamin A, in plasma, liver, and extrahepatic tissues, compared with those in adults. Normal plasma levels of retinol are 20-50 μg/dL in infants, and increase gradually as children become older. Median serum retinol values are 1.19 μmol/L in both boys and girls ages 4-8 yr; 1.4 and 1.33 μmol/L in boys and

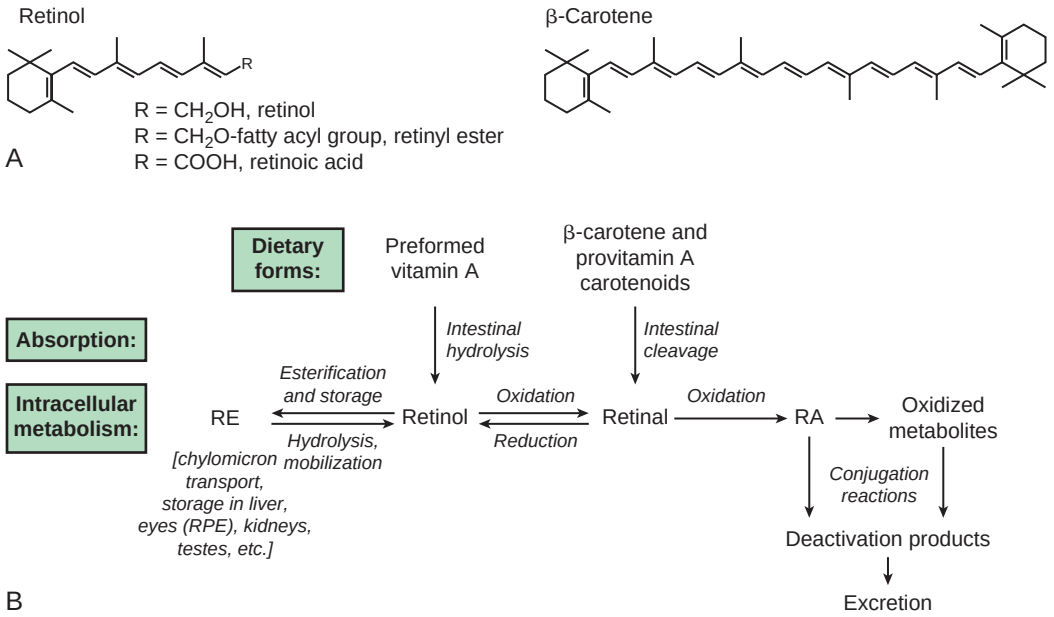

Figure 48-1 Vitamin A structures *(A)* and overview of vitamin A metabolism *(B)*.

girls, respectively, ages 9-13 yr; and 1.71 and 1.57 μmol/L in boys and girls, respectively, ages 14-18 yr (for conversion, 1 μmol/L = 28.6 μg/dL). Values of 1.96 and 1.85 μmol/L are found in 19-30 yr old adult men and women, respectively.

Retinol levels are even lower in neonates in developing countries where vitamin A intakes may be low and vitamin A deficiency is a common and significant nutritional problem. Lower vitamin A stores and plasma retinol concentrations are seen in low birthweight infants and in preterm newborns. Malnutrition, particularly protein nutrition, can cause vitamin A deficiency because of the impaired synthesis of RBP.

Inflammation as a Cause of Low Plasma Retinol

Inflammation is a cause of reduced levels of plasma retinol as a result of reduced synthesis of RBP and TTR. This condition may mimic a lack of vitamin A, but will not be corrected by supplementation. In U.S. adults, those with moderately elevated levels of C-reactive protein, indicative of mild inflammation, had lower average plasma retinol levels. The extent to which inflammation is a factor in low plasma retinol in children is uncertain but it is likely to be significant in acute infectious diseases such as measles, and possibly in chronic inflammatory conditions such as cystic fibrosis.

FUNCTIONS OF VITAMIN A AND MECHANISMS OF ACTION

Except for its role in vision, the pleiotropic actions of this micronutrient include many systemic functions that are mediated at the gene level by all-*trans*-retinoic acid (RA), which is a ligand for specific nuclear transcription factors, the retinoid receptors: RARs and RXRs. When an RAR is activated by the presence of RA, it combines with an RXR, and the resulting heterodimer binds to specific DNA sequences present in retinoid responsive genes (RAREs and RXREs, respectively) and therefore induce or repress the expression of a large number of genes. In this manner, vitamin A, via its active form, RA, regulates many genes that are involved in the fundamental biologic activities of cells, such as cell division, cell death, and cell differentiation. The term *retinoids* includes both natural and synthetic compounds with vitamin A activity and is most often used in the context of vitamin A action at the gene level. A large number of synthetic retinoids have been produced and some have gained clinical acceptance, such as in the treatment of skin disorders and certain cancers.

Retinoic acid is among the most important signaling molecules in vertebrate ontogenesis. It affects many physiologic processes, including reproduction, growth, embryonic and fetal development, and bone development, in addition to respiratory, gastrointestinal, hematopoietic, and immune functions. The role of vitamin A in immune function and host defense is particularly important in developing countries, where vitamin A supplementation or therapy reduces the morbidity and mortality rates of various diseases, such as measles (see Chapter 246).

Vitamin A plays a critical nongenomic role in vision. The human retina has 2 distinct photoreceptor systems: the rods, containing rhodopsin, which can detect low-intensity light, and the cones, containing iodopsin, which can detect different colors. The aldehyde form of vitamin A, retinal, is the prosthetic group on both visual proteins. The mechanism of vitamin A action in vision is based on the ability of the vitamin A molecule to photoisomerize (change shape when exposed to light). Thus, in the dark, low-intensity light isomerizes the rhodopsin prosthetic group, 11-*cis* retinal, to all-*trans*-retinal, generating an electrical signal that is transmitted via the optic nerve to the brain and results in visual sensation.

VITAMIN A DEFICIENCY

If the growing child has a well-balanced diet and obtains vitamin A from foods that are rich in vitamin A or provitamin-A (Table 48-1), the risk of vitamin A deficiency is small. However, even subclinical vitamin A deficiency can have serious consequences.

Deficiency states in developed countries are rare, except in some impoverished populations (see Chapter 46) or after mistakes in food preparation or with fad diets, but they are common in many developing countries and are often associated with global malnutrition (see Chapter 46). In the clinical setting, vitamin deficiencies can also occur as complications in children with various chronic disorders or diseases. Information obtained in the medical history related to dietary habits can be important in identifying the possibility of such nutritional problems. Except for vitamin A, toxicity from excess intake of vitamins is rare. Table 48-1 summarizes the food sources, functions, and deficiency and excess symptoms of the vitamins.

Clinical Manifestations of Vitamin A Deficiency

The most obvious symptoms of vitamin A deficiency are associated with the requirement of this vitamin for the maintenance of epithelial functions. In the intestines, a normal mucus-secreting epithelium (normal goblet cell function) is an effective barrier against pathogens that can cause diarrhea. Similarly, in the respiratory tract, a mucus-secreting epithelium is essential for the disposal of inhaled pathogens and toxicants. Characteristic changes as a result of vitamin A deficiency in the epithelia include a proliferation of basal cells, hyperkeratosis, and

Table 48-1 Vitamin A Characteristics

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURCES
Retinol (vitamin A_1); 1 μg retinol = 3.3 IU vitamin A = 1 RAE Provitamins A: the plant pigments α-, β-, and γ-carotenes and cryptoxanthin have partial retinol activity: 12 μg β-carotene, or 24 μg other provitamin A carotenoids = 1 μg retinol	Fat-soluble; heat-stable; destroyed by oxidation, drying Bile necessary for absorption Stored in liver Protected by vitamin E	In vision, as retinal, for synthesis of the visual pigments rhodopsin and iodopsin In growth, reproduction, embryonic and fetal development, bone growth, immune and epithelial functions, via retinoic acid as a ligand for specific nuclear transcription factors, regulating genes involved in many fundamental cellular processes	Nyctalopia Photophobia, xerophthalmia, Bitot spots, conjunctivitis, keratomalacia leading to blindness Faulty epiphyseal bone formation Defective tooth enamel Keratinization of mucous membranes and skin Retarded growth Impaired resistance to infection, anemia, reproductive failure, fetal abnormalities	Anorexia, slow growth, drying and cracking of skin, enlargement of liver and spleen, swelling and pain of long bones, bone fragility, increased intracranial pressure, alopecia, carotenemia Fetal abnormalities	Liver, fish liver oils Dairy products, except skim milk Egg yolk, fortified margarine, fortified skim milk Carotenoids from plants: green vegetables, yellow fruits, and vegetables

RAE, retinol activity equivalent.

formation of stratified cornified squamous epithelium. Squamous metaplasia of the renal pelves, ureters, vaginal epithelium, and the pancreatic and salivary ducts can lead to increased infections in these areas. In the urinary bladder, loss of epithelial integrity can result in pyuria and hematuria. Epithelial changes in the skin caused by vitamin A deficiency are manifested as dry, scaly, hyperkeratotic patches, commonly on the arms, legs, shoulders, and buttocks. The combination of defective epithelial barriers to infection, low immune response, and lowered response to inflammatory stress, all because of insufficient vitamin A, can cause poor growth and serious health problems in children.

The most characteristic and specific signs of vitamin A deficiency are eye lesions, but they may be manifest rather late in the progression of vitamin A deficiency. Lesions caused by vitamin A deficiency develop insidiously and rarely occur before 2 yr of age. An early symptom is delayed adaptation to the dark, a result of reduced resynthesis of rhodopsin; later, when vitamin A deficiency is more advanced, it leads to **night blindness** as a consequence of the absence of retinal in the visual pigment, rhodopsin, of the retina. Photophobia is a common symptom. The pigment epithelium, the structural element of the retina, keratinizes. When the pigment epithelium degenerates, the rods and cones have no support and eventually break down, resulting in blindness.

As vitamin A deficiency progresses, the corneal and conjunctival epithelial tissues of the eye become severely altered; this change results from a lack of sufficient RA for normal epithelial cell morphology and function. The cornea protects the eye from the environment and is also important in light refraction. In early vitamin A deficiency, the cornea keratinizes, becomes opaque, is susceptible to infection, and forms dry, scaly layers of cells **(xerophthalmia).** The conjunctiva keratinizes and develops plaques (**Bitot spots** [Fig. 48-2]). In later stages, infection occurs, lymphocytes infiltrate, and the cornea becomes wrinkled; it degenerates irreversibly (keratomalacia and corneal ulceration), resulting in blindness. Advanced xerophthalmia (Fig. 48-3) and xerophthalmia with permanent damage to the eye (Fig. 48-4) may develop if untreated. These eye lesions are primarily diseases of the young and are a major cause of blindness in developing countries. Although rates of xerophthalmia have fallen, the number of affected children is still too high.

Other clinical signs of vitamin A deficiency include poor overall growth, diarrhea, susceptibility to infections, anemia, apathy, mental retardation, and increased intracranial pressure, with wide separation of the cranial bones at the sutures. There may be vision problems as a consequence of bone overgrowth causing pressure on the optic nerve.

Malnutrition, particularly protein deficiency, can cause vitamin A deficiency by the impaired synthesis of retinol transport protein. In developing countries, subclinical or clinical zinc deficiency can increase the risk of vitamin A deficiency. There is also some evidence of marginal zinc intakes in children in the United States.

Diagnosis

Dark adaptation tests can be used to assess early-stage vitamin A deficiency. Although Bitot spots develop relatively early, those related to active vitamin A deficiency are usually confined to preschool-age children. Xerophthalmia is a very characteristic lesion of vitamin A deficiency. Caution must be exercised to exclude other, similar eye abnormalities from those associated with vitamin A deficiency. There are 3 useful indicators for detecting marginal vitamin A status, although they are mostly limited to research settings: conjunctival impression cytology, relative dose response, and modified relative dose response. A diet history can also be useful in suggesting or ruling out low intake as a cause. There is a relatively high prevalence of marginal vitamin A status among pregnant and lactating women. The plasma retinol level is not an accurate indicator of vitamin A status unless the deficiency is severe and liver stores are depleted, in which case low plasma retinol is likely to be evident. In children, plasma retinol values of <0.35 μmol/L are considered to be very deficient, 0.35-0.7 μmol/L are considered to be deficient, 0.7-1.05 μmol/L are considered to be marginal, and >1.05 μmol/L are considered to be adequate. It has long been thought that the liver vitamin A concentration must be 20 μg/g or higher to support a normal rate of secretion of retinol-RBP into plasma.

Epidemiology and Public Health Issues

Vitamin A deficiency and xerophthalmia still occur throughout much of the developing world and are linked to undernourishment and complicated by illness. Programs to provide periodic large doses of vitamin A have been instituted in many low-income countries in which vitamin

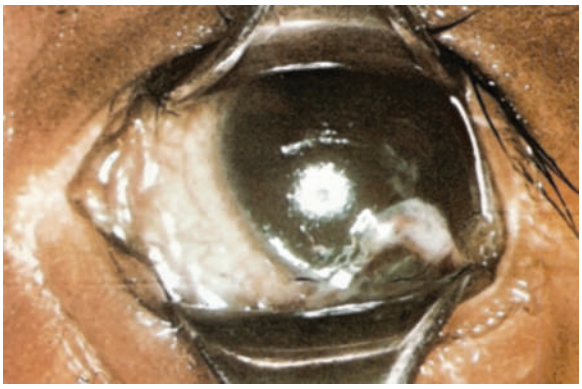

Figure 48-3 Advanced xerophthalmia with an opaque, dull cornea and some damage to the iris in a 1 yr old boy. *(From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness,* Nutr Rev *6:161–166, 1974.)*

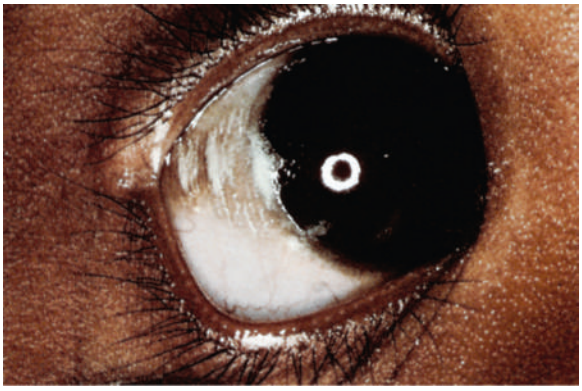

Figure 48-2 Bitot spots with hyperpigmentation seen in a 10 mo old Indonesian boy. *(From Oomen HAPC: Vitamin A deficiency, xerophthalmia and blindness,* Nutr Rev *6:161–166, 1974.)*

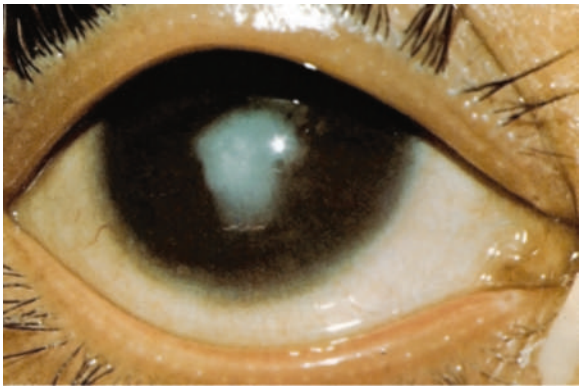

Figure 48-4 Recovery from xerophthalmia, showing a permanent eye lesion. *(From Bloch CE: Blindness and other disease arising from deficient nutrition [lack of fat soluble A factor],* Am J Dis Child *27:139, 1924.)*

Table 48-2 Dietary Reference Intakes for Vitamin A in Children

AGE RANGE	RECOMMENDED DIETARY ALLOWANCE (RDA) (μg retinol equivalents per day)	UPPER LEVEL (UL) (μg retinol equivalents per day)	COMMENTS
0-6 mo	400	600	The recommended intake for infants is an adequate intake, based on the amount of vitamin A normally present in breast milk
7-12 mo	500	600	
1-3 yr	300	600	The UL applies only to preformed vitamin A (retinol).
4-8 yr	400	900	
9-13 yr	600	1,700	
14-18 yr	900 male; 700 female	2,800	

A deficiency is still a public health problem. Vitamin A supplementation is considered part of the strategy of the World Health Organization's Millennium Development Goals to reduce <5 yr mortality. Other strategies being tested include improving the content of β-carotene in staple foods through plant breeding (biofortification).

Dietary Reference Intakes for the Healthy Population

Table 48-2 summarizes the dietary reference intakes for infants and children. Dietary reference intake values include the estimated average requirement, which is the mean biologic requirement for the nutrient in the population; the recommended dietary allowance (RDA), which is set to cover the needs of >97% of the population (thus the needs of many people are more than covered by the RDA); and the upper level (UL), an intake level above which risk of adverse effects may increase; the UL pertains only to chronic consumption of preformed vitamin A. The RDA is expressed as retinol activity equivalents (RAEs; 1 RAE = 1 μg all-*trans*-retinol; equivalents for provitamin-A in foods = 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin). From infancy to age 18 yr, the RDA increases as a consequence of increased body size, becoming higher for boys than girls during adolescence. During pregnancy, the RDA is 750-770 μg, and during lactation, the RDA is increased to 1,200-1,300 μg to ensure sufficient vitamin A content during breastfeeding.

It is noteworthy that, especially for young children, the UL is not far above the RDA, differing by only 2-fold in some age groups. This suggests that for children whose diet is good, care should be taken not to overuse dietary supplements containing preformed vitamin A and/or to avoid excessive consumption of foods that are rich in vitamin A, such as liver.

Vitamin A for Treatment of Deficiency

The safety and efficacy of vitamin A supplementation depend on the patient's state of health and the regimens of other treatments. A daily supplement of 1,500 μg of vitamin A is sufficient for treating latent vitamin A deficiency, after which intake an at RDA level should be the goal. In children without overt vitamin A deficiency, morbidity and mortality rates from viral infections, such as measles, have been reduced by administration of weekly doses equivalent to the RDA level of vitamin A, or higher doses of 30-60 mg of retinol (100,000-200,000 IU) given once or twice, under careful monitoring to avoid toxicity associated with excess vitamin A. Xerophthalmia is treated by giving 1,500 μg/kg body weight orally for 5 days followed by intramuscular injection of 7,500 μg of vitamin A in oil, until recovery.

Vitamin A is also used in preterm infants for improvement of respiratory function and prevention of the development of chronic lung disease. An analysis of 9 randomized controlled trials of vitamin A found that vitamin A appears to be beneficial in reducing death or oxygen requirement with no differences in neurodevelopmental outcomes.

HYPERVITAMINOSIS A

Chronic hypervitaminosis A results from excessive ingestion of preformed vitamin A (retinol or retinyl ester), generally for several weeks or months. The cause is often excessive use of vitamin A–containing supplements, or food faddism resulting in excessive intakes of organ meats. Toxicity can be induced in adults and children with chronic daily intakes of 15,000 μg and 6,000 μg, respectively. As there is no antidote for hypervitaminosis A, the prevention of this condition is most important. Symptoms may subside rapidly on withdrawal of the vitamin, but the rate of improvement depends on the amount of vitamin A that has built up in tissues. In extreme cases, hypervitaminosis A can be fatal. Signs of subacute or chronic toxicity can include headache; vomiting; anorexia; dry, itchy desquamating skin; seborrheic cutaneous lesions; fissuring at the corners of the mouth; alopecia and/or coarsening of the hair; bone abnormalities; swelling of the bones; enlargement of the liver and spleen; diplopia; increased intracranial pressure; irritability; stupor; limited motion; and dryness of the mucous membranes; desquamation of the palms and the soles of the feet. Radiographs may show hyperostosis affecting several long bones, especially in the middle of the shafts (Fig. 48-5). Serum levels of vitamin

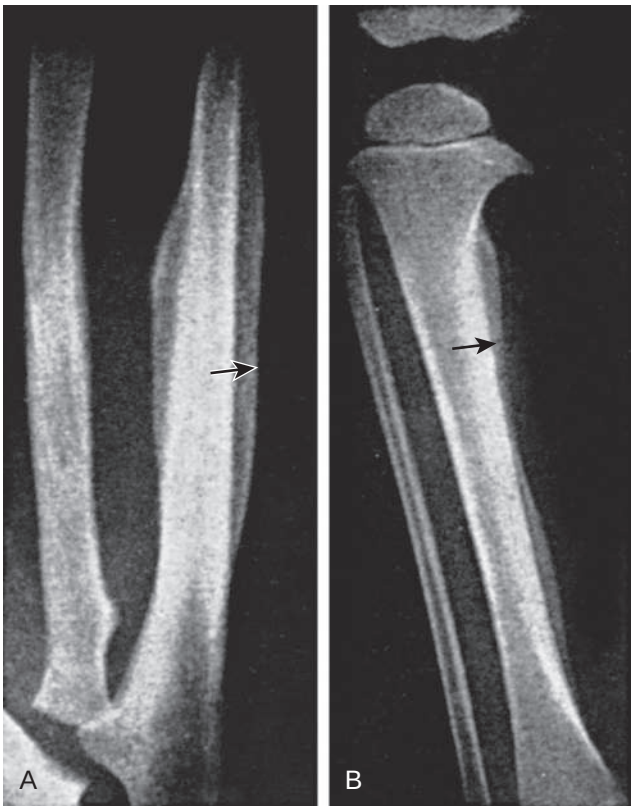

Figure 48-5 Hyperostosis of the ulna and tibia in an infant 21 mo of age, resulting from vitamin A positioning. *A*, Long, wavy cortical hyperostosis of the ulna (*arrow*). *B*, Long, wavy cortical hyperostosis of the right tibia (*arrow*), with a striking absence of metaphyseal changes. *(From Caffey J:* Pediatric x-ray diagnosis, *ed 5, Chicago, 1967, Year Book, p. 994.)*

A are elevated, mostly as retinyl ester contained in lipoproteins, which may contribute to membrane damage and symptoms, including release of liver enzymes into plasma. Hypercalcemia and/or liver cirrhosis may be present. Hypervitaminosis A is distinct from cortical hyperostosis (see Chapter 700).

In young children, toxicity is associated with vomiting and bulging fontanels. An affected child has anorexia, pruritus, and a lack of weight gain. Acute hypervitaminosis A, such as after consumption of a single large (30-60 mg dose) of vitamin A may include nausea, vomiting, and drowsiness; less-common symptoms include diplopia, papilledema, cranial nerve palsies, and other symptoms suggesting **pseudotumor cerebri.**

A syndrome of **severe congenital malformations** may occur in infants of mothers who have consumed therapeutic doses (0.5-1.5 mg/kg) of oral 13-*cis*-retinoic acid (e.g., Accutane), generally taken for the treatment of acne or cancer, during the 1st trimester of pregnancy. These malformations result in a high incidence (>20%) of spontaneous abortions and birth defects including characteristic craniofacial abnormalities. The U.S. Food and Drug Administration has increased the stringency of prescription of such drugs in women of childbearing age to attempt to reduce these birth defects.

Excessive intake of carotenoids is not associated with toxicity but can cause yellow coloration of the skin (carotenodermia) and serum (carotenemia) that disappears when intake is reduced. Children with liver disease, diabetes mellitus, or hypothyroidism are more susceptible. Food faddism including an excessive consumption of carotene-rich foods may be a cause of this condition.

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Chapter 49

Vitamin B Complex Deficiencies and Excess

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Vitamin B complex includes a number of water-soluble nutrients, including thiamine (B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), folate, cobalamin (B_{12}), biotin, and pantothenic acid. Choline and inositol are also considered part of the B complex and are important for normal body functions, but specific deficiency syndromes have not been attributed to a lack of these factors in the diet.

B-complex vitamins serve as coenzymes in many metabolic pathways that are functionally closely related. Consequently, a lack of one of the vitamins has the potential to interrupt a chain of chemical processes, including reactions that are dependent on other vitamins, and ultimately can produce diverse clinical manifestations. Because diets deficient in any one of the B-complex vitamins are often poor sources of other B vitamins, manifestations of several vitamin B deficiencies usually can be observed in the same person. It is therefore a general practice in a patient who has evidence of deficiency of a specific B vitamin to treat with the entire B-complex group of vitamins.

49.1 Thiamine (Vitamin B_1)

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Thiamine diphosphate, the active form of thiamine, serves as a cofactor for several enzymes involved in carbohydrate catabolism such as pyruvate dehydrogenase, transketolase, and α-ketoglutarate. These enzymes also play a role in the hexose monophosphate shunt that generates nicotinamide adenine dinucleotide phosphate (NADP) and pentose for nucleic acid synthesis. Thiamine is also required for the synthesis of acetylcholine and γ-aminobutyric acid, which have important roles in nerve conduction. Thiamine is absorbed efficiently in the gastrointestinal (GI) tract, and may be deficient in persons with GI or liver disease. The requirement of thiamine is increased when carbohydrates are taken in large amounts and during periods of increased metabolism, such as fever, muscular activity, hyperthyroidism, pregnancy, and lactation. Alcohol affects various aspects of thiamine transport and uptake, contributing to the deficiency in alcoholics.

Pork (especially lean), fish, and poultry are good nonvegetarian **dietary sources** of thiamine. Main sources of thiamine for vegetarians are rice, oat, wheat, and legumes. Most ready-to-eat breakfast cereals are enriched with thiamine. Thiamine is water soluble and heat labile; most of the vitamin is lost when the rice is repeatedly washed and the cooking water is discarded. The breast milk of a well-nourished mother provides adequate thiamine; breastfed infants of thiamine-deficient mothers are at risk for deficiency. Thiamine antagonists (coffee, tea) and thiaminases (fermented fish) may contribute to thiamine deficiency. Most infants and older children consuming a balanced diet obtain an adequate intake of thiamine from food and do not require supplements.

DEFICIENCY

Deficiency of thiamine is associated with severely malnourished states, including malignancy and following surgery. The disorder (or spectrum of disorders) is classically associated with a diet consisting largely of polished rice (oriental beriberi); it can also arise if highly refined wheat flour forms a major part of the diet, in alcoholics, and in food faddists (occidental beriberi). Thiamine deficiency has often been reported from inhabitants of refugee camps consuming the polished rice–based monotonous diets. Low thiamine concentrations are also noted during critical illnesses.

Thiamine-responsive megaloblastic anemia (TRMA) syndrome is a rare autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and sensorineural hearing loss, responding in varying degrees to thiamine treatment. The syndrome occurs because of mutations in the *SLC19A2* gene, encoding a thiamine transporter protein, leading to abnormal thiamine transportation and cellular vitamin deficiency. Thiamine and related vitamins may improve the outcome in children with Leigh encephalomyelopathy and type 1 diabetes mellitus.

Clinical Manifestations

Thiamine deficiency can develop within 2-3 mo of a deficient intake. Early symptoms of thiamine deficiency are nonspecific, such as fatigue, apathy, irritability, depression, drowsiness, poor mental concentration, anorexia, nausea, and abdominal discomfort. As the condition progresses, more-specific manifestations of **beriberi,** such as peripheral neuritis (manifesting as tingling, burning, paresthesias of the toes and feet), decreased deep tendon reflexes, loss of vibration sense, tenderness and cramping of the leg muscles, heart failure, and psychological disturbances, develop. Patients can have ptosis of the eyelids and atrophy of the optic nerve. Hoarseness or aphonia caused by paralysis of the laryngeal nerve is a characteristic sign. Muscle atrophy and tenderness of the nerve trunks are followed by ataxia, loss of coordination, and loss of deep sensation. Later signs include increased intracranial pressure, meningismus, and coma. The clinical picture of thiamine deficiency is usually divided into a dry (neuritic) type and a wet (cardiac) type. The disease is wet or dry depending on the amount of fluid that accumulates in the body as a result of factors such as cardiac and renal dysfunction, even though the exact cause for this edema is unknown. Many cases of thiamine deficiency show a mixture of both features and are more properly termed *thiamine deficiency with cardiopathy and peripheral neuropathy.*

The classic clinical triad of **Wernicke encephalopathy** (mental status changes, ocular signs, ataxia) is rarely reported in infants and

young children with severe deficiency secondary to malignancies or feeding of defective formula. An epidemic of life-threatening thiamine deficiency was seen in infants fed a defective soy-based formula that had undetectable thiamine levels. Manifestations included emesis, lethargy, restlessness, ophthalmoplegia, abdominal distention, developmental delay, failure to thrive, lactic acidosis, nystagmus, diarrhea, apnea, seizures, and auditory neuropathy.

Death from thiamine deficiency usually is secondary to cardiac involvement. The initial signs are cyanosis and dyspnea, but tachycardia, enlargement of the liver, loss of consciousness, and convulsions can develop rapidly. The heart, especially the right side, is enlarged. The electrocardiogram shows an increased Q-T interval, inverted T waves, and low voltage. These changes, as well as the cardiomegaly, rapidly revert to normal with treatment, but without prompt treatment, cardiac failure can develop rapidly and result in death. In fatal cases of beriberi, lesions are principally located in the heart, peripheral nerves, subcutaneous tissue, and serous cavities. The heart is dilated, and fatty degeneration of the myocardium is common. Generalized edema or edema of the legs, serous effusions, and venous engorgement are often present. Degeneration of myelin and axon cylinders of the peripheral nerves, with wallerian degeneration beginning in the distal locations, is also common, particularly in the lower extremities. Lesions in the brain include vascular dilation and hemorrhage.

Diagnosis

The diagnosis is often suspected on the basis of clinical setting and compatible symptoms. A high index of suspicion in children presenting with unexplained cardiac failure may sometimes be lifesaving. Objective biochemical tests of thiamine status include measurement of erythrocyte transketolase activity and the thiamine pyrophosphate effect. The biochemical diagnostic criteria of thiamine deficiency consist of low erythrocyte transketolase activity and high thiamine pyrophosphate effect (normal range: 0-14%). Urinary excretion of thiamine or its metabolites (thiazole or pyrimidine) after an oral loading dose of thiamine may also be measured to help identify the deficiency state. MRI changes of thiamine deficiency in infants are characterized by bilateral symmetric hyperintensities of the basal ganglia and frontal lobe, in addition to the lesions in the mammillary bodies, periaqueductal region, and thalami described in adults.

Prevention

A maternal diet containing sufficient amounts of thiamine prevents thiamine deficiency in breastfed infants, and infant formulas marketed in all developed countries provide recommended levels of intake. During complementary feeding, adequate thiamine intake can be achieved with a varied diet that includes meat and enriched or whole-grain cereals. When the staple cereal is polished rice, special efforts need to be made to include legumes and/or nuts in the ration. Thiamine and other vitamins can be retained in rice by **parboiling**, a process of steaming the rice in the husk before milling. Improvement in cooking techniques, such as not discarding the water used for cooking, minimal washing of grains, and reduction of cooking time helps to minimize the thiamine losses during the preparation of food. Thiamine supplementation should be ensured during total parenteral nutrition.

Treatment

In the absence of GI disturbances, oral administration of thiamine is effective. Children with cardiac failure, convulsions, or coma should be given 10 mg of thiamine intramuscularly or intravenously daily for the 1st wk. This treatment should then be followed by 3-5 mg of thiamine per day orally for at least 6 wk. The response is dramatic in infants and in those having predominantly cardiovascular manifestations, whereas the neurologic response is slow and often incomplete. Epilepsy, mental disability, and language and auditory problems of varying degree have been reported in survivors of severe infantile thiamine deficiency.

Patients with beriberi often have other B-complex vitamin deficiencies; therefore, all other B-complex vitamins should also be administered. Treatment of TRMA and other dependency states require higher dosages (100-200 mg/day). The anemia responds well to thiamine administration, and insulin for associated diabetes mellitus can also be discontinued in many cases of TRMA.

TOXICITY

There are no reports of adverse effects from consumption of excess thiamine by ingestion of food or supplements. A few isolated cases of pruritus and anaphylaxis have been reported in patients after parenteral administration of the vitamin.

Bibliography is available at Expert Consult.

49.2 Riboflavin (Vitamin B_2)

H.P.S. Sachdev and Dheeraj Shah

Riboflavin is part of the structure of the coenzymes flavin adenine dinucleotide (FAD) and flavin mononucleotide, which participate in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the mitochondrial respiratory chain. Riboflavin is stable to heat, but is destroyed by light. Milk, eggs, organ meats, legumes, and mushrooms are rich **dietary sources** of riboflavin. Most commercial cereals, flours, and breads are enriched with riboflavin.

DEFICIENCY

The causes of riboflavin deficiency are mainly related to malnourished and malabsorptive states, including GI infections. Treatment with some drugs, such as probenecid, phenothiazine, or oral contraceptives, can also cause the deficiency. The side chain of the vitamin is photochemically destroyed during phototherapy for hyperbilirubinemia, as it is involved in the photosensitized oxidation of bilirubin to more polar excretable compounds. Isolated **complex II deficiency**, a rare mitochondrial disease manifesting in infancy and childhood, responds favorably to riboflavin supplementation and thus can be termed a dependency state. **Brown-Vialetto-Van Laere syndrome** (BVVLS), a rare neurologic disorder characterized by progressive neurologic deterioration, hypotonia, sensorineural hearing loss, and pontobulbar palsy responds to treatment with high doses of riboflavin. Mutations in genes coding for riboflavin transporter proteins have been identified in children with BVVLS.

Clinical Manifestations

Clinical features of riboflavin deficiency include cheilosis, glossitis, keratitis, conjunctivitis, photophobia, lacrimation, corneal vascularization, and seborrheic dermatitis. Cheilosis begins with pallor at the angles of the mouth and progresses to thinning and maceration of the epithelium, leading to fissures extending radially into the skin (Fig. 49-1). In glossitis, the tongue becomes smooth, with loss of papillary structure (Fig. 49-2). Normochromic, normocytic anemia may also be seen because of the impaired erythropoiesis. A low riboflavin content of the maternal diet has been linked to congenital heart defects, but the evidence is weak.

Diagnosis

Most often, the diagnosis is based on the clinical features of angular cheilosis in a malnourished child, which responds promptly to riboflavin supplementation. A functional test of riboflavin status is done by measuring the activity of erythrocyte glutathione reductase (EGR), with and without the addition of FAD. An EGR activity coefficient (ratio of EGR activity with added FAD to EGR activity without FAD) of >1.4 is used as an indicator of deficiency. Urinary excretion of riboflavin <30 μg/24 hr also suggests low intakes.

Prevention

Table 49-1 lists the recommended daily allowance of riboflavin for infants, children, and adolescents. Adequate consumption of milk, milk products, and eggs prevents riboflavin deficiency. Fortification of

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Figure 49-1 Angular cheilosis with ulceration and crusting. *(Courtesy of National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India.)*

Figure 49-2 Glossitis as seen in riboflavin deficiency. *(From Zappe HA, Nuss S, Becker K, et al:* Riboflavin deficiency in Baltistan. http://www.rzuser.uni-heidelberg.de/%7Ecn6/baltista/ribofl_e.htm.*)*

Table 49-1 Water-Soluble Vitamins

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	RDA* BY AGE
Thiamine (vitamin B_1)	Coenzyme in carbohydrate metabolism Nucleic acid synthesis Neurotransmitter synthesis	Neurologic (dry beriberi): irritability, peripheral neuritis, muscle tenderness, ataxia Cardiac (wet beriberi): tachycardia, edema, cardiomegaly, cardiac failure	3-5 mg/day PO thiamine for 6 wk	Polished rice–based diets Malabsorptive states Severe malnutrition Malignancies Alcoholism	Meat, especially pork; fish; liver Rice (unmilled), wheat germ; enriched cereals; legumes	0-6 mo: 0.2 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Girls: 1.0 mg/day Boys: 1.2 mg/day
Riboflavin (vitamin B_2)	Constituent of flavoprotein enzymes important in oxidation-reduction reactions: amino acid, fatty acid, and carbohydrate metabolism and cellular respiration	Glossitis, photophobia, lacrimation, corneal vascularization, poor growth, cheilosis	3-10 mg/day PO riboflavin	Severe malnutrition Malabsorptive states Prolonged treatment with phenothiazines, probenecid, or OCPs	Milk, milk products, eggs, fortified cereals, green vegetables	0-6 mo: 0.3 mg/day 7-12 mo: 0.4 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 0.9 mg/day 14-18 yr: Girls: 1.0 mg/day Boys: 1.3 mg/day
Niacin (vitamin B_3)	Constituent of NAD and NADP, important in respiratory chain, fatty acid synthesis, cell differentiation, and DNA processing	Pellagra manifesting as diarrhea, symmetric scaly dermatitis in sun-exposed areas, and neurologic symptoms of disorientation and delirium	50-300 mg/day PO niacin	Predominantly maize-based diets Anorexia nervosa Carcinoid syndrome	Meat, fish, poultry Cereals, legumes, green vegetables	0-6 mo: 2 mg/day 7-12 mo: 4 mg/day 1-3 yr: 6 mg/day 4-8 yr: 8 mg/day 9-13 yr: 12 mg/day 14-18 yr: Girls: 14 mg/day Boys: 16 mg/day
Pyridoxine (vitamin B_6)	Constituent of coenzymes for amino acid and glycogen metabolism, heme synthesis, steroid action, neurotransmitter synthesis	Irritability, convulsions, hypochromic anemia Failure to thrive Oxaluria	5-25 mg/day PO for deficiency states 100 mg IM or IV for pyridoxine-dependent seizures	Prolonged treatment with INH, penicillamine, OCPs	Fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, potatoes	0-6 mo: 0.1 mg/day 7-12 mo: 0.3 mg/day 1-3 yr: 0.5 mg/day 4-8 yr: 0.6 mg/day 9-13 yr: 1.0 mg/day 14-18 yr: Girls: 1.2 mg/day Boys: 1.3 mg/day

Continued

Table 49-1 Water-Soluble Vitamins—cont'd

NAMES AND SYNONYMS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	TREATMENT OF DEFICIENCY	CAUSES OF DEFICIENCY	DIETARY SOURCES	RDA* BY AGE
Biotin	Cofactor for carboxylases, important in gluconeogenesis, fatty acid and amino acid metabolism	Scaly periorificial dermatitis, conjunctivitis, alopecia, lethargy, hypotonia, and withdrawn behavior	1-10 mg/day PO biotin	Consumption of raw eggs for prolonged periods Parenteral nutrition with infusates lacking biotin Valproate therapy	Liver, organ meats, fruits	0-6 mo: 5 μg/day 7-12 mo: 6 μg/day 1-3 yr: 8 μg/day 4-8 yr: 12 μg/day 9-13 yr: 20 μg/day 14-18 yr: 25 μg/day
Pantothenic acid (vitamin B_5)	Component of coenzyme A and acyl carrier protein involved in fatty acid metabolism	Experimentally produced deficiency in humans: irritability, fatigue, numbness, paresthesias (burning feet syndrome), muscle cramps		Isolated deficiency extremely rare in humans	Beef, organ meats, poultry, seafood, egg yolk Yeast, soybeans, mushrooms	0-6 mo: 1.7 mg/day 7-12 mo: 1.8 mg/day 1-3 yr: 2 mg/day 4-8 yr: 3 mg/day 9-13 yr: 4 mg/day 14-18 yr: 5 mg/day
Folic acid	Coenzymes in amino acid and nucleotide metabolism as an acceptor and donor of one-carbon units	Megaloblastic anemia Growth retardation, glossitis Neural tube defects in progeny	0.5-1 mg/day PO folic acid	Malnutrition Malabsorptive states Malignancies Hemolytic anemias Anticonvulsant therapy	Enriched cereals, beans, leafy vegetables, citrus fruits, papaya	0-6 mo: 65 μg/day 7-12 mo: 80 μg/day 1-3 yr: 150 μg/day 4-8 yr: 200 μg/day 9-13 yr: 300 μg/day 14-18 yr: 400 μg/day
Cobalamin (vitamin B_{12})	As deoxyadenosylcobalamin, acts as cofactor for lipid and carbohydrate metabolism As methylcobalamin, important for conversion of homocysteine to methionine and folic acid metabolism	Megaloblastic anemia, irritability, developmental delay, developmental regression, involuntary movements, hyperpigmentation	1,000 μg IM vitamin B_{12}	Vegan diets Malabsorptive states Crohn disease Intrinsic factor deficiency (pernicious anemia)	Organ meats, sea foods poultry, egg yolk, milk, fortified ready-to-eat cereals	0-6 mo: 0.4 μg/day 7-12 mo: 0.5 μg/day 1-3 yr: 0.9 μg/day 4-8 yr: 1.2 μg/day 9-13 yr: 1.8 μg/day 14-18 yr: 2.4 μg/day
Ascorbic acid (vitamin C)	Important for collagen synthesis, metabolism of cholesterol and neurotransmitters Antioxidant functions and nonheme iron absorption	Scurvy manifesting as irritability, tenderness and swelling of legs, bleeding gums, petechiae, ecchymoses, follicular hyperkeratosis, and poor wound healing	100-200 mg/day PO ascorbic acid for up to 3 mo	Predominantly milk-based (non–human milk) diets Severe malnutrition	Citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, leafy green vegetables	0-6 mo: 40 mg/day 7-12 mo: 50 mg/day 1-3 yr: 15 mg/day 4-8 yr: 25 mg/day 9-13 yr: 45 mg/day 14-18 yr: Girls: 65 mg/day Boys: 75 mg/day

*For healthy breastfed infants, the values represent adequate intakes, that is, the mean intake of apparently "normal" infants.

INH, isoniazid; NAD, nicotinamide adenine dinucleotide; NADP, nicotinamide adenine dinucleotide phosphate; OCP, oral contraceptive pill; RDA, recommended dietary allowance.

Source: Dietary Reference Intakes (DRIs): Recommended dietary allowances and adequate intakes, vitamins. *Food and Nutrition Board, Institute of Medicine, National Academies. Available from:* http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables.

cereal products is helpful for those who follow vegan diets or who are consuming inadequate amounts of milk products for other reasons.

Treatment

Treatment includes oral administration of 3-10 mg/day of riboflavin, often as an ingredient of a vitamin B–complex mix. The child should also be given a well-balanced diet, including milk and milk products.

TOXICITY

No adverse effects associated with riboflavin intakes from food or supplements have been reported, and the upper safe limit for consumption has not been established. Although the photosensitizing property of this vitamin raises the possibility for some potential risks, limited absorption in high-intake situations precludes such concerns.

Bibliography is available at Expert Consult.

49.3 Niacin (Vitamin B_3)

H.P.S. Sachdev and Dheeraj Shah

Niacin (nicotinamide or nicotinic acid) forms part of 2 cofactors, nicotinamide adenine dinucleotide and NADP, which are important in several biologic reactions, including the respiratory chain, fatty acid

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and steroid synthesis, cell differentiation, and DNA processing. Niacin is rapidly absorbed from the stomach and the intestines and can also be synthesized from tryptophan in the diet.

Major **dietary sources** of niacin are meat, fish, and poultry for nonvegetarians and cereals, legumes, and green leafy vegetables for vegetarians. Enriched and fortified cereal products and legumes also are major contributors to niacin intake. Milk and eggs contain little niacin but are good sources of tryptophan, which can be converted to nicotinamide adenine dinucleotide (60 mg tryptophan = 1 mg niacin).

DEFICIENCY

Pellagra, the classic niacin deficiency disease, occurs chiefly in populations where corn (maize), a poor source of tryptophan, is the major foodstuff. A severe dietary imbalance, such as in anorexia nervosa and in war or famine conditions, also can cause pellagra. Pellagra can also develop in conditions associated with disturbed tryptophan metabolism such as carcinoid syndrome and Hartnup disease.

Clinical Manifestations

The early symptoms of pellagra are vague: anorexia, lassitude, weakness, burning sensation, numbness, and dizziness. After a long period of deficiency, the classic triad of dermatitis, diarrhea, and dementia appears. **Dermatitis**, the most characteristic manifestation of pellagra, can develop suddenly or insidiously and may be initiated by irritants, including intense sunlight. The lesions first appear as symmetric areas of erythema on exposed surfaces, resembling sunburn, and might go unrecognized. The lesions are usually sharply demarcated from the surrounding healthy skin, and their distribution can change frequently. The lesions on the hands and feet often have the appearance of a glove or stocking (Fig. 49-3). Similar demarcations can also occur around the neck (Casal necklace) (Fig. 49-3). In some cases, vesicles and bullae develop (wet type). In others, there may be suppuration beneath the scaly, crusted epidermis; in still others, the swelling can disappear after a short time, followed by desquamation (Fig. 49-4). The healed parts of the skin might remain pigmented. The cutaneous lesions may be preceded by or accompanied by stomatitis, glossitis, vomiting, and/or diarrhea. Swelling and redness of the tip of the tongue and its lateral margins is often followed by intense redness, even ulceration, of the entire tongue and the papillae. Nervous symptoms include depression, disorientation, insomnia, and delirium.

The classic symptoms of pellagra usually are not well developed in infants and young children, but anorexia, irritability, anxiety, and apathy are common. Young patients might also have sore tongues and lips, and usually have dry and scaly skin. Diarrhea and constipation can alternate, and anemia can occur. Children who have pellagra often have evidence of other nutritional deficiency diseases.

Diagnosis

Because of lack of a good functional test to evaluate niacin status, the diagnosis of deficiency is usually made from the physical signs of glossitis, GI symptoms, and a symmetric dermatitis. Rapid clinical response to niacin is an important confirmatory test. A decrease in the concentration and/or a change in the proportion of the niacin metabolites N^1-methyl-nicotinamide and 2-pyridone in the urine provide biochemical evidence of deficiency and can be seen before the appearance of overt signs of deficiency. Histopathologic changes from the affected skin include dilated blood vessels without significant inflammatory infiltrates, ballooning of the keratinocytes, hyperkeratosis, and epidermal necrosis.

Prevention

Adequate intakes of niacin are easily met by consumption of a diet that consists of a variety of foods and includes meat, eggs, milk, and enriched or fortified cereal products. The dietary reference intake (DRI) is expressed in mg niacin equivalents (NE) in which 1 mg NE = 1 mg niacin or 60 mg tryptophan. An intake of 2 mg of niacin is considered adequate for infants 0-6 mo of age; and 4 mg is adequate for infants 7-12 mo of age. For older children, the recommended

Figure 49-3 Characteristic skin lesions of pellagra on hands and lesions on the neck (Casal necklace). *(Courtesy of Dr. J.D. MacLean, McGill Centre for Tropical Diseases, Montreal, Canada.)*

Figure 49-4 Clinical manifestations of niacin deficiency before *(A)* and after *(B)* therapy. *(From Weinsier RL, Morgan SL:* Fundamentals of clinical nutrition, *St. Louis, 1993, Mosby, p. 99.)*

intakes are 6 mg for 1-3 yr of age, 8 mg for 4-8 yr of age, 12 mg for 9-13 yr of age, and 14-16 mg for 14-18 yr of age.

Treatment

Children usually respond rapidly to treatment. A liberal and varied diet should be supplemented with 50-300 mg/day of niacin; in severe cases or in patients with poor intestinal absorption, 100 mg may be given intravenously. The diet should also be supplemented with other vitamins, especially other B-complex vitamins. Sun exposure should be avoided during the active phase of pellagra, and the skin lesions may be covered with soothing applications. Other coexisting nutrient deficiencies such as iron deficiency anemia should be treated. Even after successful treatment, the diet should continue to be monitored to prevent recurrence.

TOXICITY

There are no toxic effects associated with the intake of naturally occurring niacin in foods. Shortly after the ingestion of large doses of nicotinic acid taken as a supplement or a pharmacologic agent, a person often experiences a burning, tingling, and itching sensation as well as flushing on the face, arms, and chest. Large doses of niacin also can have nonspecific GI effects and can cause cholestatic jaundice or hepatotoxicity. Tolerable upper intake levels for children are approximately double the recommended dietary allowance.

Bibliography is available at Expert Consult.

49.4 Vitamin B_6 (Pyridoxine)

H.P.S. Sachdev and Dheeraj Shah

Vitamin B_6 includes a group of closely related compounds: pyridoxine, pyridoxal, pyridoxamine, and their phosphorylated derivatives. Pyridoxal 5′-phosphate (PLP) and, to a lesser extent, pyridoxamine phosphate function as coenzymes for many enzymes involved in amino acid metabolism, neurotransmitter synthesis, glycogen metabolism, and steroid action. If vitamin B_6 is lacking, glycine metabolism can lead to oxaluria. The major excretory product in the urine is 4-pyridoxic acid.

The vitamin B_6 content of human milk and infant formulas is adequate. Good **food sources** of the vitamin include fortified ready-to-eat cereals, meat, fish, poultry, liver, bananas, rice, and certain vegetables. Large losses of the vitamin can occur during high-temperature processing of foods or milling of cereals, whereas parboiling of rice prevents its loss.

DEFICIENCY

Because of the importance of vitamin B_6 in amino acid metabolism, high protein intakes can increase the requirement for the vitamin; the recommended daily allowances are sufficient to cover the expected range of protein intake in the population. The risk of deficiency is increased in persons taking medications that inhibit the activity of vitamin B_6 (isoniazid, penicillamine, corticosteroids, phenytoin, carbamazepine), in young women taking oral progesterone-estrogen contraceptives, and in patients receiving maintenance dialysis.

Clinical Manifestations

The deficiency symptoms seen in infants are listlessness, irritability, seizures, vomiting, and failure to thrive. Peripheral neuritis is a feature of deficiency in adults but is not usually seen in children. Electroencephalogram (EEG) abnormalities have been reported in infants as well as in young adult subjects in controlled depletion studies. Skin lesions include cheilosis, glossitis, and seborrheic dermatitis around the eyes, nose, and mouth. Microcytic anemia can occur in infants, but is not common. Oxaluria, oxalic acid bladder stones, hyperglycinemia, lymphopenia, decreased antibody formation, and infections also are associated with vitamin B_6 deficiency.

Several types of vitamin B_6 **dependence syndromes,** presumably resulting from errors in enzyme structure or function, respond to very large amounts of pyridoxine. These syndromes include pyridoxine-dependent epilepsy, a vitamin B_6–responsive anemia, xanthurenic aciduria, cystathioninuria, and homocystinuria (see Chapters 85, 456, and 601). Pyridoxine-dependent epilepsy involves mutations in the *ALDH7A1* gene causing deficiency of antiquitin, an enzyme involved in dehydrogenation of L-alpha-aminoadipic semialdehyde.

Diagnosis

The activity of the erythrocyte transaminases glutamic oxaloacetic transaminase and glutamic pyruvic transaminase is low in vitamin B_6 deficiency; tests measuring the activity of these enzymes before and after the addition of PLP may be useful as indicators of vitamin B_6 status. Abnormally high xanthurenic acid excretion after tryptophan ingestion also provides evidence of deficiency. Plasma PLP assays are being used more often, but factors other than deficiency can influence the results. Vitamin B_6 deficiency or dependence should be suspected in all infants with seizures. If more common causes of infantile seizures have been eliminated, 100 mg of pyridoxine can be injected, with EEG monitoring if possible. If the seizure stops, vitamin B_6 deficiency should be suspected. In older children, 100 mg of pyridoxine may be injected intramuscularly while the EEG is being recorded; a favorable response of the EEG suggests pyridoxine deficiency.

Prevention

Deficiency is unlikely in children consuming diets that meet their energy needs and contain a variety of foods. **Parboiling** of rice prevents the loss of vitamin B_6 from the grains. The DRIs for vitamin B_6 are 0.1 mg/day for infants up to 6 mo of age; 0.3 mg/day for ages 6 mo to 1 yr; 0.5 mg/day for ages 1-3 yr; 0.6 mg/day for ages 4-8 yr; 1.0 mg/day for ages 9-13 yr; and 1.2-1.3 mg/day for ages 14-18 yr. Infants whose mothers have received large doses of pyridoxine during pregnancy are at increased risk for seizures from pyridoxine dependence, and supplements during the 1st few weeks of life should be considered. Any child receiving a pyridoxine antagonist, such as isoniazid, should be carefully observed for neurologic manifestations; if these develop, vitamin B_6 should be administered or the dose of the antagonist should be decreased.

Treatment

Intramuscular or intravenous administration of 100 mg of pyridoxine is used to treat convulsions caused by vitamin B_6 deficiency. One dose should be sufficient if adequate dietary intake follows. For pyridoxine-dependent children, daily doses of 2-10 mg intramuscularly or 10-100 mg orally may be necessary.

TOXICITY

Adverse effects have not been associated with high intakes of vitamin B_6 from food sources. However, ataxia and sensory neuropathy have been reported with dosages as low as 100 mg/day in adults taking vitamin B_6 supplements for several months.

Bibliography is available at Expert Consult.

49.5 Biotin

H.P.S. Sachdev and Dheeraj Shah

Biotin functions as a cofactor for enzymes involved in carboxylation reactions within and outside mitochondria. These biotin-dependent carboxylases catalyze key reactions in gluconeogenesis, fatty acid metabolism, and amino acid catabolism.

There is limited information on the biotin content of foods; it is believed to be widely distributed, thus making a deficiency unlikely. Avidin found in raw egg whites acts as a biotin antagonist. Signs of biotin deficiency have been demonstrated in persons who consume large amounts of raw egg whites over long periods. Deficiency also has been described in infants and children receiving enteral and parenteral

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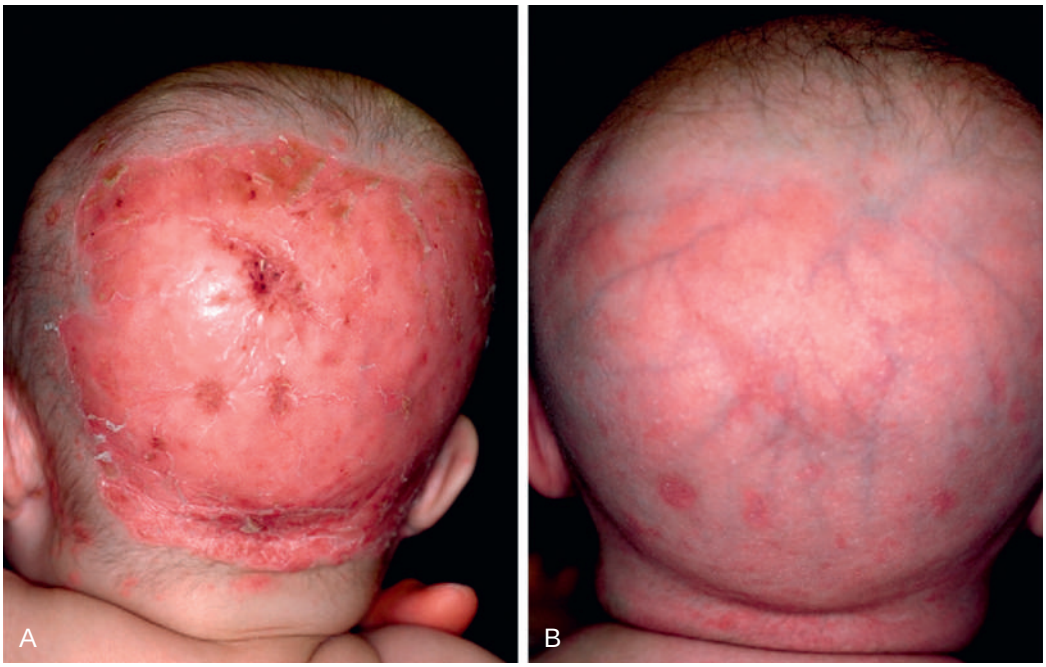

Figure 49-5 Scalp rash *(A)* Before treatment with biotin, *(B)* After 3 wk of biotin treatment. *(From Ito T, Nishie W, Fujita Y, et al: Infantile eczema caused by formula milk.* Lancet *381:1958, 2013.)*

nutrition formula that lack biotin. Treatment with valproic acid may result in a low biotinidase activity and/or biotin deficiency.

The clinical findings of biotin deficiency include scaly periorificial dermatitis, conjunctivitis, thinning of hair, and alopecia (Fig. 49-5). Central nervous system abnormalities seen with biotin deficiency are lethargy, hypotonia, seizures, ataxia, and withdrawn behavior. Biotin deficiency can be successfully treated using 1-10 mg of biotin orally daily. The adequate dietary intake values for biotin are 5 μg/day for ages 0-6 mo, 6 μg/day for ages 7-12 mo, 8 μg/day for ages 1-3 yr, 12 μg/day for ages 4-8 yr, 20 μg/day for ages 9-13 yr, and 25 μg/day for ages 14-18 yr. No toxic effects have been reported with very high doses.

Biotin responsive basal ganglia disease is a rare childhood neurologic disorder characterized by encephalopathy, seizures, and extrapyramidal manifestations. Chapter 85.6 describes conditions involving deficiencies in the enzymes holocarboxylase synthetase and biotinidase that respond to treatment with biotin.

Bibliography is available at Expert Consult.

49.6 Folate

H.P.S. Sachdev and Dheeraj Shah

Folate exists in a number of different chemical forms. Folic acid (pteroylglutamic acid) is the synthetic form used in fortified foods and supplements. Naturally occurring folates in foods retain the core chemical structure of pteroylglutamic acid but vary in their state of reduction, the single carbon moiety they bear, or the length of the glutamate chain. These polyglutamates are broken down and reduced in the small intestine to dihydro- and tetrahydrofolates, which are involved as coenzymes in amino acid and nucleotide metabolism as acceptors and donors of 1-carbon units. Folate is important for central nervous system development during embryogenesis.

Rice and cereals are rich **dietary sources** of folate, especially if enriched. Beans, leafy vegetables, and fruits such as oranges and papaya are good sources, too. The vitamin is readily absorbed from the small intestine and is broken down to monoglutamate derivatives by mucosal polyglutamate hydrolases. A high-affinity proton-coupled folate transporter (PCFT) seems to be essential for absorption of folate in intestine and in various cell types at low pH. The vitamin is also synthesized by the colonic bacteria, and the half-life of the vitamin is prolonged by enterohepatic recirculation.

DEFICIENCY

Because of its role in protein, DNA, and RNA synthesis, the risk of deficiency is increased during periods of rapid growth or increased cellular metabolism. Folate deficiency can result from poor nutrient content in diet, inadequate absorption (celiac disease, inflammatory bowel disease), increased requirement (sickle cell anemia, psoriasis, malignancies, periods of rapid growth as in infancy and adolescence), or inadequate utilization (long-term treatment with high-dose nonsteroidal antiinflammatory drugs; anticonvulsants such as phenytoin and phenobarbital; and methotrexate). Rare causes of deficiency are hereditary folate malabsorption, inborn errors of folate metabolism (methylene tetrahydrofolate reductase, methionine synthase reductase, and glutamate formiminotransferase deficiencies), and cerebral folate deficiency. A loss-of-function mutation in the gene coding for PCFT is the molecular basis for hereditary folate malabsorption. A high-affinity blocking autoantibody against the membrane-bound folate receptor in the choroid plexus preventing its transport across the blood–brain barrier is the likely cause of the infantile cerebral folate deficiency.

Clinical Manifestations

Folic acid deficiency results in megaloblastic anemia and hypersegmentation of neutrophils. Nonhematologic manifestations include glossitis, listlessness, and growth retardation not related to anemia. There is an association between low maternal folic acid status and neural tube defects, primarily spina bifida and anencephaly, and the role of periconceptional folic acid in their prevention is well established.

Hereditary folate malabsorption manifests at 1-3 mo of age with recurrent or chronic diarrhea, failure to thrive, oral ulcerations, neurologic deterioration, megaloblastic anemia, and opportunistic infections. Cerebral folate deficiency manifests at 4-6 mo of age with irritability, microcephaly, developmental delay, cerebellar ataxia, pyramidal tract signs, choreoathetosis, ballismus, seizures, and blindness as a result of optic atrophy. 5-Methyltetrahydrofolate levels are normal in serum and red blood cells (RBCs), but are markedly depressed in the cerebrospinal fluid.

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Diagnosis

The diagnosis of folic acid deficiency anemia is made in the presence of macrocytosis along with low folate levels in serum and/or RBCs. Normal serum folic acid levels are 5-20 ng/mL; with deficiency, serum folic acid levels are <3 ng/mL. Levels of RBC folate are a better indicator of chronic deficiency. The normal RBC folate level is 150-600 ng/mL of packed cells. The bone marrow is hypercellular because of erythroid hyperplasia, and megaloblastic changes are prominent. Large, abnormal neutrophilic forms (giant metamyelocytes) with cytoplasmic vacuolation also are seen.

Cerebral folate deficiency is associated with low levels of 5-methyltetrahydrofolate in the cerebrospinal fluid and normal folate levels in the plasma and RBCs. Mutations in the PCFT gene are demonstrated in the hereditary folate malabsorption.

Prevention

Breastfed infants have better folate nutrition than non–breastfed infants throughout infancy. Consumption of folate-rich foods and food-fortification programs are important to ensure adequate intake in children and in women of childbearing age. The DRIs for folate are 65 µg of dietary folate equivalents (DFE) for infants 0-6 mo of age and 80 µg of DFE for infants between 6 and 12 mo of age. (1 DFE = 1 µg food folate = 0.6 µg of folate from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach.) For older children, the DRIs are 150 µg of DFE for ages 1-3 yr; 200 µg of DFE for ages 4-8 yr; 300 µg of DFE for ages 9-13 yr; and 400 µg of DFE for ages 14-18 yr. All women desirous of becoming pregnant should consume 400-800 µg folic acid daily; the dose is 4 mg/day in those having delivered a child with neural tube defect. To be effective, supplementation should be started at least 1 mo before conception, and continued through the first 2-3 mo of pregnancy. There may be a marginal benefit of periconceptional folate supplementation in prevention of autistic spectrum disorders. Providing iron and folic acid tablets for prevention of anemia in children and pregnant women is a routine strategy in at-risk populations. Mandatory fortification of cereal flours with folic acid coupled with health-education programs has been associated with a substantial reduction in incidence of neural tube defects in many countries.

Treatment

When the diagnosis of folate deficiency is established, folic acid may be administered orally or parenterally at 0.5-1.0 mg/day. Folic acid therapy should be continued for 3-4 wk or until a definite hematologic response has occurred. Maintenance therapy with 0.2 mg of folate is adequate. Prolonged treatment with oral folinic acid is required in cerebral folate deficiency, and the response may be incomplete. Treatment of hereditary folate malabsorption may be possible with intramuscular folinic acid; some patients may respond to high-dose oral folinic acid therapy.

TOXICITY

No adverse effects have been associated with consumption of the amounts of folate normally found in fortified foods. Excessive intake of folate supplements might obscure and potentially delay the diagnosis of vitamin B_{12} deficiency. Massive doses given by injection have the potential to cause neurotoxicity.

Bibliography is available at Expert Consult.

49.7 Vitamin B_{12} (Cobalamin)

H.P.S. Sachdev and Dheeraj Shah

Vitamin B_{12}, in the form of deoxyadenosylcobalamin, functions as a cofactor for isomerization of methylmalonyl-CoA to succinyl-CoA, an essential reaction in lipid and carbohydrate metabolism. Methylcobalamin is another circulating form of vitamin B_{12}, and is essential for methyl group transfer during the conversion of homocysteine to methionine. This reaction also requires a folic acid cofactor and is important for protein and nucleic acid biosynthesis. Vitamin B_{12} is important for hematopoiesis, central nervous system myelination, and mental and psychomotor development.

Dietary sources of vitamin B_{12} are almost exclusively from animal foods. Organ meats, muscle meats, sea foods (mollusks, oysters, fish), poultry, and egg yolk are rich sources. Fortified ready-to-eat cereals and milk and their products are the important sources of the vitamin for vegetarians. Human milk is an adequate source for breastfeeding infants if the maternal serum B_{12} levels are adequate. The vitamin is absorbed from ileum at alkaline pH after binding with intrinsic factor. Enterohepatic circulation, direct absorption, and synthesis by intestinal bacteria are additional mechanisms helping to maintain the vitamin B_{12} nutriture.

DEFICIENCY

Vitamin B_{12} deficiency because of inadequate dietary intake occurs primarily in persons consuming strict vegetarian or vegan diets. Prevalence of vitamin B_{12} deficiency is high in predominantly vegetarian or lactovegetarian populations. Breastfeeding infants of B_{12}-deficient mothers are also at risk for significant deficiency. Malabsorption of B_{12} occurs in celiac disease, ileal resections, Crohn disease, *Helicobacter pylori* infection, and autoimmune atrophic gastritis (pernicious anemia). Use of proton pump inhibitors and/or histamine 2 receptor antagonists may increase the risk of deficiency. Hereditary intrinsic factor deficiency and Imerslund-Gräsbeck disease are inborn errors of metabolism leading to vitamin B_{12} malabsorption. Mutations in the hereditary intrinsic factor gene cause hereditary intrinsic factor deficiency, whereas mutations in any of the 2 subunits (cubilin and amnionless) of the intrinsic factor receptor cause Imerslund-Gräsbeck disease.

Clinical Manifestations

The hematologic manifestations of vitamin B_{12} deficiency are similar to manifestations of folate deficiency and are discussed in Chapter 454.2. Irritability, hypotonia, developmental delay, developmental regression, and involuntary movements are the common neurologic symptoms in infants and children, whereas sensory deficits, paresthesias, and peripheral neuritis are seen in adults. Hyperpigmentation of the knuckles (Fig. 49-6) and palms is another common observation with B_{12} deficiency in children. Maternal B_{12} deficiency may also be an independent risk factor for fetal neural tube defects.

Figure 49-6 Hyperpigmentation of knuckles in an infant with vitamin B_{12} deficiency and megaloblastic anemia.

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Diagnosis

See Chapter 454.2.

Treatment

The hematologic symptoms respond promptly to parenteral administration of 250-1,000 μg vitamin B_{12}. Children with severe deficiency and those with neurologic symptoms need repeated doses; daily or alternate days in first week followed by weekly for the first 1-2 mo, and then monthly thereafter. Children having only hematologic presentation recover fully within 2-3 mo, whereas those with neurologic disease need at least 6 mo of therapy. Children with continuing malabsorptive state, and those having inborn errors of vitamin B_{12} malabsorption need lifelong treatment. Prolonged daily treatment with high dose (1,000-2,000 μg) oral vitamin B_{12} preparations has also been found to be equally effective in achieving hematologic and neurologic responses in the elderly, but the data are inadequate in children and young adults.

Prevention

The DRIs are 0.4 μg/day at age 0-6 mo, 0.5 μg/day at age 6-12 mo, 0.9 μg/day at age 1-3 yr, 1.2 μg/day at age 4-8 yr, 1.8 μg/day at age 9-13 yr, 2.4 μg/day at age 14-18 yr and in adults, 2.6 μg/day in pregnancy, and 2.8 μg/day in lactation. Pregnant and breastfeeding women should ensure an adequate consumption of animal products to prevent the deficiency in infants. Strict vegetarians, especially vegans, should ensure regular consumption of vitamin B_{12}. Food fortification with the vitamin helps to prevent deficiency in predominantly vegetarian populations.

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Chapter 50

Vitamin C (Ascorbic Acid)

Dheeraj Shah and H.P.S. Sachdev

Vitamin C is important for synthesis of collagen at the level of hydroxylation of lysine and proline in precollagen. It is also involved in neurotransmitter metabolism (conversion of dopamine to norepinephrine and tryptophan to serotonin), cholesterol metabolism (conversion of cholesterol to steroid hormones and bile acids), and the biosynthesis of carnitine. Vitamin C functions to maintain the iron and copper atoms, cofactors of the metalloenzymes, in a reduced (active) state. Vitamin C is an important antioxidant (electron donor) in the aqueous milieu of the body. Vitamin C enhances nonheme iron absorption, the transfer of iron from transferrin to ferritin, and the formation of tetrahydrofolic acid and thus can affect the cellular and immunologic functions of the hematopoietic system.

DIETARY NEEDS AND SOURCES

Humans depend on dietary sources for vitamin C. An adequate intake is 40 mg for age 0-6 mo and 50 mg for age 6-12 mo. For older children, the recommended dietary allowance is 15 mg for age 1-3 yr, 25 mg for age 4-8 yr, 45 mg for age 9-13 yr, and 65-75 mg for age 14-18 yr. The recommended dietary allowances during pregnancy and lactation are 85 mg/day and 120 mg/day, respectively. The requirement for vitamin C is increased during infectious and diarrheal diseases. Children exposed to smoking or environmental tobacco smoke also require increased amounts of foods rich in vitamin C. The best food sources of vitamin C are citrus fruits and fruit juices, peppers, berries, melons, tomatoes, cauliflower, and green leafy vegetables. Vitamin C is easily destroyed by prolonged storage, overcooking, and processing of foods.

Absorption of vitamin C occurs in the upper small intestine by an active process or by simple diffusion when large amounts are ingested. Vitamin C is not stored in the body but is taken up by all tissues; the highest levels are found in the pituitary and adrenal glands. The brain ascorbate content in the fetus and neonate is manyfold higher than the content in the adult brain, a finding probably related to its function in neurotransmitter synthesis.

When a mother's intake of vitamin C during pregnancy and lactation is adequate, the newborn will have adequate tissue levels of vitamin C related to active placental transfer, subsequently maintained by the vitamin C in breast milk or commercial infant formulas. Breast milk contains sufficient vitamin C to prevent deficiency throughout infancy. Infants consuming pasteurized or boiled animal milk are at significant risk of developing deficiency if the other sources of vitamin C are also lacking in the diet. Neonates whose feeding has been delayed because of clinical condition can also suffer from ascorbic acid deficiency. For patients on total parenteral nutrition, a parenteral dose of 80 mg/day is recommended for full-term infants and a parenteral dose of 25 mg/kg/day is recommended for preterm infants. Children who choose a limited diet or those on fad diets are at risk for vitamin C deficiency.

DEFICIENCY

A deficiency of vitamin C results in the clinical presentation of **scurvy**, the oldest nutritional deficiency disease to be recognized. Children fed predominantly heat-treated (ultrahigh-temperature or pasteurized) milk or unfortified formulas and not receiving fruits and fruit juices are at significant risk for symptomatic disease. In scurvy, there is defective formation of connective tissues and collagen in skin, cartilage, dentine, bone, and blood vessels, leading to their fragility. In the long bones, osteoid is not deposited by osteoblasts, cortex is thin, and the trabeculae become brittle and fracture easily.

Clinical Features

The early manifestations are irritability, loss of appetite, low-grade fever, musculoskeletal pain, and tenderness in the legs. These signs and symptoms are followed by leg swelling—most marked at the knees and the ankles—and **pseudoparalysis**. The infant might lie with the hips and knees semiflexed and the feet rotated outward. Subperiosteal hemorrhages in the lower limb bones sometimes acutely increase the swelling and pain, and the condition might mimic acute osteomyelitis or arthritis. A "rosary" at the costochondral junctions and depression of the sternum are other typical features (Fig. 50-1). The angulation of scorbutic beads is usually sharper than the angulation of a rachitic rosary. Gum changes are seen in older children after teeth have erupted and are manifested as bluish purple, spongy swellings of the mucous membrane, especially over the upper incisors (Fig. 50-2). Anemia, a common finding in infants and young children with scurvy, is related to impaired iron absorption and coexistent hematopoietic nutrient deficiencies including iron, vitamin B_{12}, and folate. Hemorrhagic

Figure 50-1 Scorbutic rosary. *(Courtesy of Dr J.D. MacLean, McGill Centre for Tropical Diseases, Montreal.)*

Figure 50-2 Gingival lesions in advanced scurvy. *(From* Nutrition, *ed 4, Kalamazoo, MI, 1980, The Upjohn Company, p. 80. Used with permission of Pfizer, Inc.)*

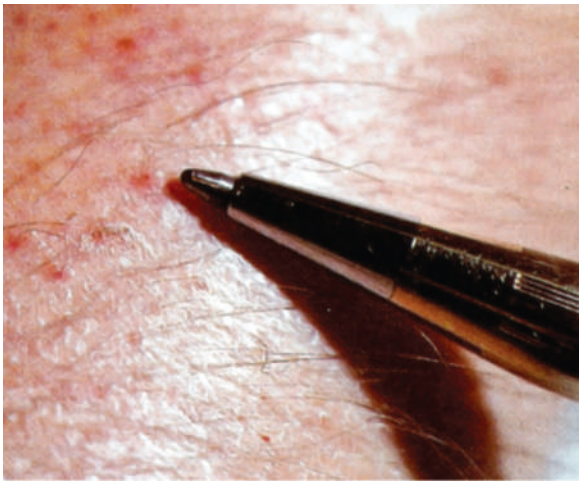

Figure 50-3 Perifollicular petechiae in scurvy. *(From Weinsier RL, Morgan SL:* Fundamentals of clinical nutrition, *St. Louis, 1993, Mosby, p. 85.)*

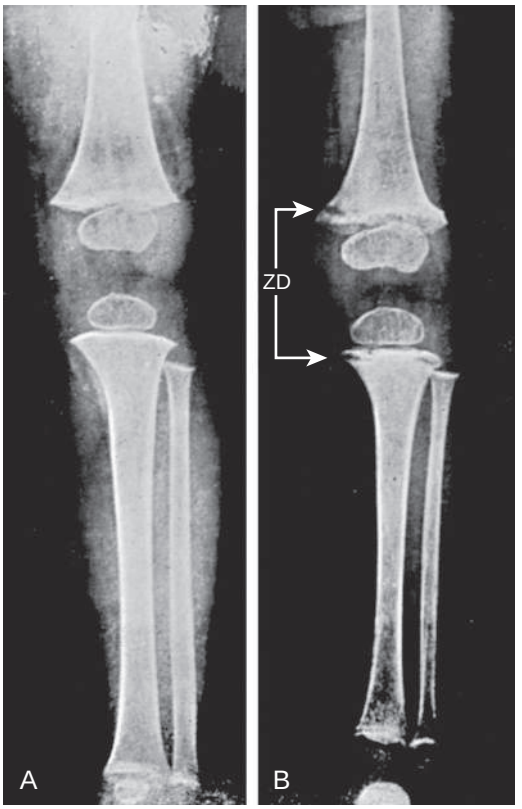

Figure 50-4 Radiographs of a leg. *A,* An early scurvy "white line" is visible on the ends of the shafts of the tibia and fibula; sclerotic rings (Wimberger sign) are shown around the epiphyses of the femur and tibia. *B,* More advanced scorbutic changes; zones of destruction (ZD) are evident in the femur and tibia. Pelkan spur is also seen at the cortical end.

manifestations of scurvy include petechiae, purpura, and ecchymoses at pressure points; epistaxis; gum bleeding; and the characteristic perifollicular hemorrhages (Fig. 50-3). Other manifestations are poor wound and fracture healing, hyperkeratosis of hair follicles, arthralgia, and muscle weakness.

Laboratory Findings and Diagnosis

The diagnosis of vitamin C deficiency is usually based on the characteristic clinical picture, the radiographic appearance of the long bones, and a history of poor vitamin C intake. The typical **radiographic changes** occur at the distal ends of the long bones and are particularly common at the knees. The shafts of the long bones have a ground-glass appearance because of trabecular atrophy. The cortex is thin and dense, giving the appearance of *pencil outlining* of the diaphysis and epiphysis. The *white line of Fränkel,* an irregular but thickened white line at the metaphysis, represents the zone of well-calcified cartilage. The epiphyseal centers of ossification also have a ground-glass appearance and are surrounded by a sclerotic ring (Fig. 50-4). The more specific but late radiologic feature of scurvy is a zone of rarefaction under the white line at the metaphysis. This zone of rarefaction *(Trümmerfeld zone),* a linear break in the bone that is proximal and parallel to the white line, represents area of debris of broken-down bone trabeculae and connective tissue. A *Pelkan spur* is a lateral prolongation of the white line and may be present at cortical ends. Epiphyseal separation can occur along the line of destruction, with either linear displacement or compression of the epiphysis against the shaft (Fig. 50-5). Subperiosteal hemorrhages are not visible using plain radiographs during the active phase of scurvy. However, during healing the elevated periosteum becomes calcified and radiopaque (Fig. 50-5), sometimes giving a dumbbell or club shape to the affected bone. MRI can demonstrate acute as well as healing subperiosteal hematomas along with periostitis, metaphyseal changes, and heterogeneous bone marrow signal intensity, even in absence of changes in plain radiographs. Gelatinous transformation of bone marrow, on aspiration, has been reported in children where the procedure was done on suspicion of a malignancy.

Biochemical tests are not very useful in the diagnosis of scurvy, because they do not reflect the tissue status. A plasma ascorbate concentration of <0.2 mg/dL usually is considered deficient. Leukocyte concentration of vitamin C is a better indicator of body stores, but this measurement is technically more difficult to perform. Leukocyte concentrations of ≤10 μg/10^8 white blood cells are considered deficient and indicate latent scurvy, even in the absence of clinical signs of deficiency. Saturation of the tissues with vitamin C can be estimated from the urinary excretion of the vitamin after a test dose of ascorbic acid. In healthy children, 80% of the test dose appears in the urine within 3-5 hr after parenteral administration. Generalized nonspecific aminoaciduria is common in scurvy, whereas plasma amino acid levels remain normal.

Differential Diagnosis

Scurvy is often misdiagnosed as arthritis, osteomyelitis, nonaccidental trauma (child abuse), or acrodynia. The early irritability and bone pain are sometimes attributed to nonspecific pains or other nutritional deficiencies. Copper deficiency results in a radiographic picture very

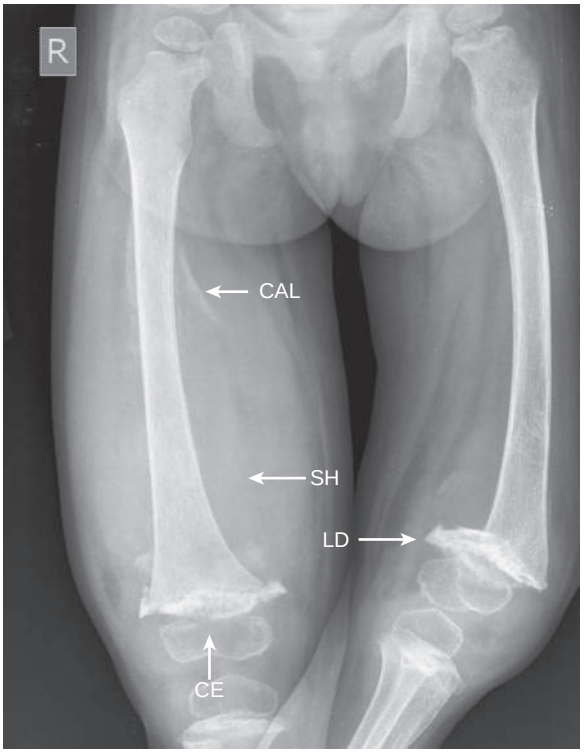

Figure 50-5 Large subperiosteal hematoma (SH) with areas of calcification (CAL) is seen along the shaft of right femur of a child with advanced scurvy. Epiphyseal separation is seen in both knees with linear displacement (LD) in left and compression (CE) against the shaft in right.

similar to that of scurvy. Henoch-Schönlein purpura, thrombocytopenic purpura, or leukemia is sometimes suspected in children presenting with hemorrhagic manifestations.

Treatment

Vitamin C supplements of 100-200 mg/day orally or parenterally ensure rapid and complete cure. The clinical improvement is seen within a week in most cases, but the treatment should be continued for up to 3 mo for complete recovery.

Prevention

Breastfeeding protects against vitamin C deficiency throughout infancy. In children consuming milk formula, fortification with vitamin C must be ensured. Children consuming heat-treated milk should consume adequate vitamin C–rich foods in infancy. Dietary or medicinal supplements are required in severely malnourished children, and chronic debilitating conditions such as malignancies and neurologic disorders.

TOXICITY

Daily intake of <2 g of vitamin C is generally without adverse effects in adults. Larger doses can cause gastrointestinal problems, such as abdominal pain and osmotic diarrhea. Megadoses of vitamin C should be avoided in patients with a history of urolithiasis or conditions related to excessive iron accumulation such as thalassemia and hemochromatosis. There is a paucity of data regarding vitamin C toxicity in children. The following values for tolerable upper intake levels are extrapolated from data for adults based on body weight differences: age 1-3 yr, 400 mg; age 4-8 yr, 650 mg; age 9-13 yr, 1,200 mg; and age 14-18 yr, 1,800 mg.

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Chapter 51

Rickets and Hypervitaminosis D

Larry A. Greenbaum

RICKETS

Bone consists of a protein matrix called *osteoid* and a mineral phase, principally composed of calcium and phosphate, mostly in the form of hydroxyapatite. Osteomalacia is present when there is inadequate mineralization of bone osteoid and occurs in children and adults. Rickets is a disease of growing bone that is caused by unmineralized matrix at the growth plates and occurs in children only before fusion of the epiphyses. Because growth plate cartilage and osteoid continue to expand but mineralization is inadequate, the growth plate thickens. There is also an increase in the circumference of the growth plate and the metaphysis, increasing bone width at the location of the growth plates and causing some of the classic clinical manifestations, such as widening of the wrists and ankles. There is a general softening of the bones that causes them to bend easily when subject to forces such as weight bearing or muscle pull. This softening leads to a variety of bone deformities.

Rickets is principally caused by vitamin D deficiency (Table 51-1) and was rampant in northern Europe and the United States during the early years of the 20th century. Although this problem was largely corrected through public health measures that provided children with adequate vitamin D, rickets remains a persistent problem in developed countries, with many cases still secondary to preventable nutritional vitamin D deficiency. It remains a significant problem in developing countries, and may be secondary to nutritional vitamin D deficiency and inadequate intake of calcium.

Etiology

There are many causes of rickets (Table 51-2), including vitamin D disorders, calcium deficiency, phosphorous deficiency, and distal renal tubular acidosis.

Clinical Manifestations

Most manifestations of rickets are a result of skeletal changes (Table 51-3). **Craniotabes** is a softening of the cranial bones and can be detected by applying pressure at the occiput or over the parietal bones. The sensation is similar to the feel of pressing into a ping-pong ball and then releasing. Craniotabes may also be secondary to osteogenesis imperfecta, hydrocephalus, and syphilis. It is a normal finding in many newborns, especially near the suture lines, but it typically disappears within a few months of birth. Widening of the costochondral junctions results in a **rachitic rosary**, which feels like the beads of a rosary as the examiner's fingers move along the costochondral junctions from rib to rib (Fig. 51-1). **Growth plate** widening is also responsible for the enlargement at the wrists and ankles. The horizontal depression along the lower anterior chest known as **Harrison groove** occurs from pulling of the softened ribs by the diaphragm during inspiration (Fig. 51-2). Softening of the ribs also impairs air movement and predisposes patients to atelectasis and pneumonia.

There is some variation in the clinical presentation of rickets based on the etiology. Changes in the lower extremities tend to be the dominant feature in X-linked hypophosphatemic rickets. Symptoms secondary to hypocalcemia occur only in those forms of rickets associated with decreased serum calcium (Table 51-4).

The chief complaint in a child with rickets is quite variable. Many children present because of skeletal deformities, whereas others have difficulty walking owing to a combination of deformity and weakness. Other common presenting complaints include failure to thrive and symptomatic hypocalcemia (see Chapter 572).

Table 51-1 Physical and Metabolic Properties and Food Sources of the Vitamins (D, E, and K)

NAMES AND SYNONYMS	CHARACTERISTICS	BIOCHEMICAL ACTION	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	SOURCES
VITAMIN D Vitamin D_3 (3-cholecalciferol), which is synthesized in the skin, and vitamin D_2 (from plants or yeast) are biologically equivalent; 1 μg = 40 IU vitamin D	Fat-soluble, stable to heat, acid alkali, and oxidation; bile necessary for absorption; hydroxylation in the liver and kidney necessary for biologic activity	Necessary for GI absorption of calcium; also increases absorption of phosphate; direct actions on bone, including mediating resorption	Rickets in growing children; osteomalacia; hypocalcemia can cause tetany and seizures	Hypercalcemia, which can cause emesis, anorexia, pancreatitis, hypertension, arrhythmias, CNS effects, polyuria, nephrolithiasis, renal failure	Exposure to sunlight (UV light); fish oils, fatty fish, egg yolks, and vitamin D–fortified formula, milk, cereals, bread
VITAMIN E Group of related compounds with similar biologic activities; α-tocopherol is the most potent and the most common form	Fat-soluble; readily oxidized by oxygen, iron, rancid fats; bile acids necessary for absorption	Antioxidant; protection of cell membranes from lipid peroxidation and formation of free radicals	Red cell hemolysis in premature infants; posterior column and cerebellar dysfunction; pigmentary retinopathy	Unknown	Vegetable oils, seeds, nuts, green leafy vegetables, margarine
VITAMIN K Group of naphthoquinones with similar biologic activities; K_1 (phylloquinone) from diet; K_2 (menaquinones) from intestinal bacteria	Natural compounds are fat-soluble; stable to heat and reducing agents; labile to oxidizing agent, strong acids, alkali, light; bile salts necessary for intestinal absorption	Vitamin K–dependent proteins include coagulation factors II, VII, IX, and X; proteins C, S, Z; matrix Gla protein, osteocalcin	Hemorrhagic manifestations; long-term bone and vascular health	Not established; analogs (no longer used) caused hemolytic anemia, jaundice, kernicterus, death	Green leafy vegetables, liver, certain legumes and plant oils; widely distributed

CNS, central nervous system; GI, gastrointestinal; UV, ultraviolet.

Table 51-2 Causes of Rickets

VITAMIN D DISORDERS
Nutritional vitamin D deficiency
Congenital vitamin D deficiency
Secondary vitamin D deficiency
Malabsorption
Increased degradation
Decreased liver 25-hydroxylase
Vitamin D–dependent rickets type 1 A and B
Vitamin D–dependent rickets type 2 A and B
Chronic kidney disease
CALCIUM DEFICIENCY
Low intake
Diet
Premature infants (rickets of prematurity)
Malabsorption
Primary disease
Dietary inhibitors of calcium absorption
PHOSPHORUS DEFICIENCY
Inadequate intake
Premature infants (rickets of prematurity)
Aluminum-containing antacids
RENAL LOSSES
X-linked hypophosphatemic rickets*
Autosomal dominant hypophosphatemic rickets*
Autosomal recessive hypophosphatemic rickets (1 and 2)*
Hereditary hypophosphatemic rickets with hypercalciuria
Overproduction of fibroblast growth factor-23
Tumor-induced rickets*
McCune-Albright syndrome*
Epidermal nevus syndrome*
Neurofibromatosis*
Fanconi syndrome
Dent disease
Distal renal tubular acidosis

*Disorders secondary to excess fibroblast growth factor-23.

Table 51-3 Clinical Features of Rickets

GENERAL
Failure to thrive
Listlessness
Protruding abdomen
Muscle weakness (especially proximal)
Fractures
HEAD
Craniotabes
Frontal bossing
Delayed fontanel closure
Delayed dentition; caries
Craniosynostosis
CHEST
Rachitic rosary
Harrison groove
Respiratory infections and atelectasis*
BACK
Scoliosis
Kyphosis
Lordosis
EXTREMITIES
Enlargement of wrists and ankles
Valgus or varus deformities
Windswept deformity (combination of valgus deformity of 1 leg with varus deformity of the other leg)
Anterior bowing of the tibia and femur
Coxa vara
Leg pain
HYPOCALCEMIC SYMPTOMS†
Tetany
Seizures
Stridor due to laryngeal spasm

*These features are most commonly associated with the vitamin D–deficiency disorders.

†These symptoms develop only in children with disorders that produce hypocalcemia (see Table 51-4).

Radiology

Rachitic changes are most easily visualized on posteroanterior radiographs of the wrist, although characteristic rachitic changes can be seen at other growth plates (Figs. 51-3 and 51-4). Decreased calcification leads to thickening of the growth plate. The edge of the metaphysis loses its sharp border, which is described as *fraying*. The edge of the metaphysis changes from a convex or flat surface to a more concave surface. This change to a concave surface is termed *cupping* and is most easily seen at the distal ends of the radius, ulna, and fibula. There is widening of the distal end of the metaphysis, corresponding to the clinical observation of thickened wrists and ankles, as well as the rachitic rosary. Other radiologic features include coarse trabeculation of the diaphysis and generalized rarefaction.

Diagnosis

Most cases of rickets are diagnosed based on the presence of classic radiographic abnormalities. The diagnosis is supported by physical examination findings (see Table 51-3) and a history and laboratory test results that are consistent with a specific etiology.

Figure 51-1 Rachitic rosary in a young infant.

Clinical Evaluation

Because the majority of children with rickets have a nutritional deficiency, the initial evaluation should focus on a dietary history, emphasizing intake of vitamin D and calcium. Most children in industrialized nations receive vitamin D from formula, fortified milk, or vitamin supplements. Along with the amount, the exact composition of the formula or milk is pertinent, because rickets has occurred in children given products that are called *milk* (e.g., soy milk) but are deficient in vitamin D and/or minerals.

Cutaneous synthesis mediated by sunlight exposure is an important source of vitamin D. It is important to ask about time spent outside, sunscreen use, and clothing, especially if there may be a cultural reason for increased covering of the skin. Because winter sunlight is ineffective at stimulating cutaneous synthesis of vitamin D, the season is an additional consideration. Children with increased skin pigmentation are at increased risk for vitamin D deficiency because of decreased cutaneous synthesis.

The presence of **maternal risk** factors for nutritional vitamin D deficiency, including diet and sun exposure, is an important consideration when a neonate or young infant has rachitic findings, especially if the infant is breastfed. Determining a child's intake of dairy products, the main dietary source of calcium, provides a general sense of calcium intake. High dietary fiber can interfere with calcium absorption.

The child's **medication** use is relevant, because certain medications, such as the anticonvulsants phenobarbital and phenytoin, increase degradation of vitamin D, and aluminum-containing antacids interfere with the absorption of phosphate.

Malabsorption of vitamin D is suggested by a history of liver or intestinal disease. Undiagnosed liver or intestinal disease should be suspected if the child has gastrointestinal (GI) symptoms, although occasionally rickets is the presenting complaint. Fat malabsorption is

Figure 51-2 Deformities in rickets showing curvature of the limbs, potbelly, and Harrison groove.

Table 51-4 Laboratory Findings in Various Disorders Causing Rickets

DISORDER	Ca	Pi	PTH	25-(OH)D	1,25-$(OH)_2$D	Alk Phos	URINE Ca	URINE Pi
Vitamin D deficiency	N, ↓	↓	↑	↓	↓, N, ↑	↑	↓	↑
Chronic kidney disease	N, ↓	↑	↑	N	↓	↑	N, ↓	↓
Dietary Pi deficiency	N	↓	N, ↓	N	↑	↑	↑	↓
Tumor-induced rickets	N	↓	N	N	RD	↑	↓	↑
Fanconi syndrome	N	↓	N	N	RD or ↑	↑	↓ or ↑	↑
Dietary Ca deficiency	N, ↓	↓	↑	N	↑	↑	↓	↑

↓, decreased; ↑, increased; ↑↑, extremely increased; 1,25-$(OH)_2$D, 1,25-dihydroxyvitamin D; 25-OHD, 25-hydroxyvitamin D; ADHR, autosomal dominant hypophosphatemic rickets; Alk Phos, alkaline phosphatase; ARHR, autosomal recessive hypophosphatemic rickets; Ca, calcium; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; N, normal; Pi, inorganic phosphorus; PTH, parathyroid hormone; RD, relatively decreased (because it should be increased given the concurrent hypophosphatemia); VDDR, vitamin D–dependent rickets; XLH, X-linked hypophosphatemic rickets.

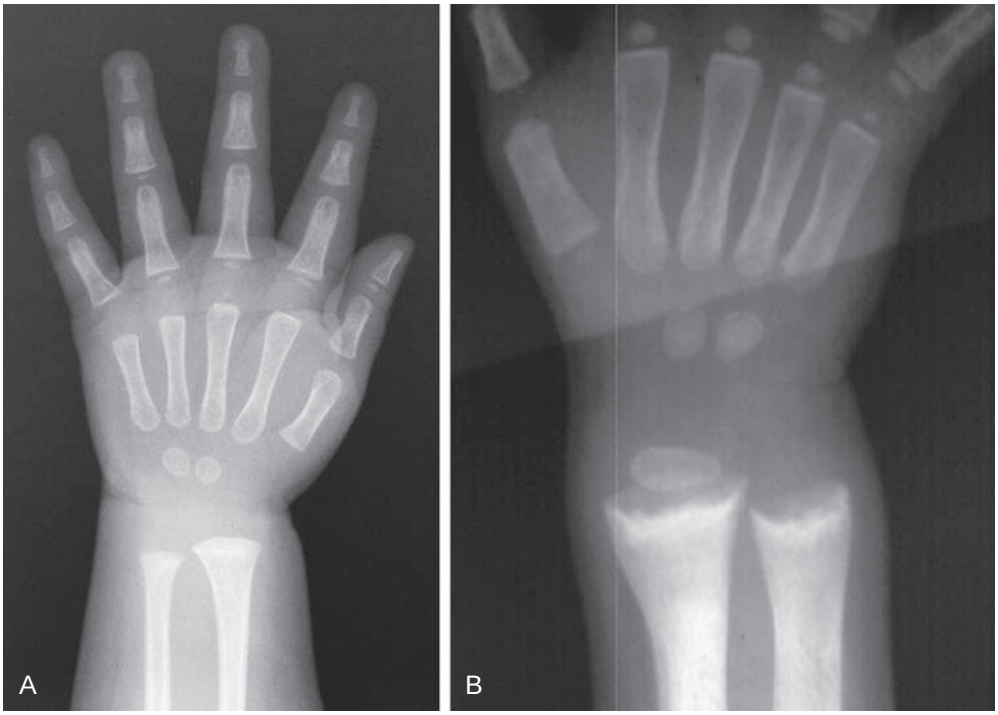

Figure 51-3 Wrist x-rays in a normal child *(A)* and in a child with rickets *(B)*. The child with rickets has metaphyseal fraying and cupping of the distal radius and ulna.

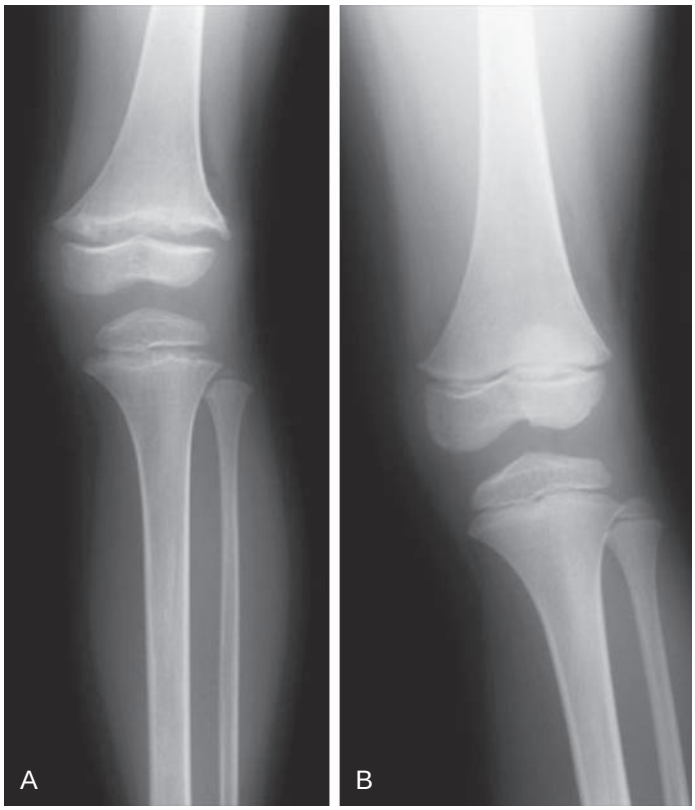

Figure 51-4 X-rays of the knees in a 7 yr old girl with distal renal tubular acidosis and rickets. *A,* At initial presentation, there is widening of the growth plate and metaphysical fraying. *B,* Dramatic improvement after 4 mo of therapy with alkali.

often associated with diarrhea or oily stools, and there may be signs or symptoms suggesting deficiencies of other fat-soluble vitamins (A, E, and K; see Chapters 48, 52, and 53).

A history of **renal disease** (proteinuria, hematuria, urinary tract infections) is an additional significant consideration, given the importance of chronic kidney disease as a cause of rickets. Polyuria can occur in children with chronic kidney disease or Fanconi syndrome.

Children with rickets might have a history of dental caries, poor growth, delayed walking, waddling gait, pneumonia, and hypocalcemic symptoms.

The family history is critical, given the large number of **genetic causes** of rickets, although most of these causes are rare. Along with bone disease, it is important to inquire about leg deformities, difficulties with walking, or unexplained short stature, because some parents may be unaware of their diagnosis. Undiagnosed disease in the mother is not unusual in X-linked hypophosphatemia. A history of a unexplained sibling death during infancy may be present in the child with cystinosis, the most common cause of Fanconi syndrome in children.

The physical examination focuses on detecting manifestations of rickets (see Table 51-3). It is important to observe the child's gait, auscultate the lungs to detect atelectasis or pneumonia, and plot the patient's growth. Alopecia suggests vitamin D–dependent rickets type 2.

The **initial laboratory** tests in a child with rickets should include serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D (1,25-D), creatinine, and electrolytes (see Tables 51-4 and 51-5 for interpretation). Urinalysis is useful for detecting the glycosuria and aminoaciduria (positive dipstick for protein) seen with Fanconi syndrome. Evaluation of urinary excretion of calcium (24 hr collection for calcium or calcium : creatinine ratio) is helpful if hereditary hypophosphatemic rickets with hypercalciuria or Fanconi syndrome is suspected. Direct measurement of other fat-soluble vitamins (A, E, and

Table 51-5 Biochemical Changes in Genetic Causes of Rickets

	SERUM BIOCHEMISTRY							URINE BIOCHEMISTRY		
	Phosphate	Calcium	PTH	250HD	1,250H_2D	FGF23	Alk Phos	Phosphate	Calcium	OTHER FEATURES
HYPOCALCEMIC VITAMIN D PATHWAY DEFECTS										
Vitamin D deficiency	Low	Variable	High	Low	Might be increased	NA	Increased	Increased	Low	Variable aminoaciduria
VDDR1B	Low	Low	High	Very low	Variable	NA	Increased	Increased	Low	250HD does not increase after vitamin D dosing
VDDR1A	Low	Low	High	Normal or high	Very low or ND	NA	Increased	Increased	Low	250HD does increase after vitamin D dosing
VDDR2A	Low	Low	High	Normal or high	High	NA	Increased	Increased	Low	—
VDDR2B	Low	Low	High	Normal or high	High	NA	Increased	Increased	Low	—
HYPOPHOSPHATEMIC RICKETS WITH RAISED FGF23										
XLH	Low	Normal	Normal or slightly high	Normal	Low	High	Increased	Increased	Variable	Urine calcium : creatinine used in monitoring therapy
ADHR	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
ARHR1	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
ARHR2	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	—
HYPOPHOSPHATEMIC RICKETS WITHOUT RAISED FGF23										
Dent's disease*	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	Low molecular weight proteinuria
HHRH	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	No loss of low molecular weight protein
αKlotho mutation	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	Variable	—
OTHER INHERITED RACHITIC DISORDERS										
HPP (severe)	High	High	Low	Normal	Normal	Normal	Very low	Normal or high	High	Raised concentrations of mineralization inhibitors
HPP (mild)	Normal or high	Normal or high	Low or normal	Normal	Normal	Normal	Low	Normal	Variable	Raised concentrations of mineralization inhibitors

From Elder CJ, Bishop NJ: Rickets. Lancet *383:1665-1674, 2014.*

PTH, parathyroid hormone; 250HD, calcidiol; 1,2SOH_2D, calcitriol; FGF23, fibroblast growth factor 23; Alk phos, alkaline phosphatase; NA, data not available; VDDR1B, vitamin D–dependent rickets due to defects in CYP2R1 encoding vitamin D 25-hydroxylase; VDDR1A, vitamin D–dependent rickets due to defects in CYP27Bl encoding 25-hydroxyvitamin D-1alpha hydroxylase; ND, not detected; VDDR2A, vitamin D–dependent rickets due to defects in VDR encoding the vitamin D receptor; VDDR2B, vitamin D–dependent rickets due to defects in *HNRNPC* encoding hnRNPC1 and hnRNPC2; XLH, X-linked hypophosphatemic rickets due to mutations in *PHEX*; ADHR, autosomal dominant hypophosphatemic rickets due to mutations in *FGF23*; ARHR1, autosomal recessive hypophosphatemic rickets due to mutations in DMP1; ARHR2, autosomal recessive hypophosphatemic rickets due to mutations in *ENPP1*; HHRH, hereditary hypophosphatemic rickets with hypercalciuria due to mutations in *SLC34A3*; HPP, hypophosphatasia.

*Dent's disease is due to mutations in $CLCN_5$.

K) or indirect assessment of deficiency (prothrombin time for vitamin K deficiency) is appropriate if malabsorption is a consideration.

VITAMIN D DISORDERS

Vitamin D Physiology

Vitamin D can be synthesized in skin epithelial cells and therefore technically is not a vitamin. Cutaneous synthesis is normally the most important source of vitamin D and depends on the conversion of 7-dehydrochlesterol to vitamin D_3 (3-cholecalciferol) by ultraviolet B radiation from the sun. The efficiency of this process is decreased by melanin; hence, more sun exposure is necessary for vitamin D synthesis in people with increased skin pigmentation. Measures to decrease sun exposure, such as covering the skin with clothing or applying sunscreen, also decrease vitamin D synthesis. Children who spend less time outside have reduced vitamin D synthesis. The winter sun away from the equator is ineffective at mediating vitamin D synthesis.

There are few natural dietary sources of vitamin D. Fish liver oils have a high vitamin D content. Other good dietary sources include fatty fish and egg yolks. Most children in industrialized countries receive vitamin D via fortified foods, especially formula and milk (both of which contain 400 IU/L) and some breakfast cereals and breads. Supplemental vitamin D may be vitamin D_2 (which comes from plants or yeast) or vitamin D_3. Breast milk has a low vitamin D content, approximately 12-60 IU/L.

Vitamin D is transported bound to vitamin D–binding protein to the liver, where 25-hydroxlase converts vitamin D into 25-hydroxyvitamin D (25-D), the most abundant circulating form of vitamin D. Because there is little regulation of this liver hydroxylation step, measurement of 25-D is the standard method for determining a patient's vitamin D status. The final step in activation occurs in the kidney, where 1α-hydroxylase adds a second hydroxyl group, resulting in 1,25-D. The 1α-hydroxylase is upregulated by PTH and hypophosphatemia; hyperphosphatemia and 1,25-D inhibit this enzyme. Most 1,25-D circulates bound to vitamin D–binding protein.

1,25-D acts by binding to an intracellular receptor, and the complex affects gene expression by interacting with vitamin D–response elements. In the intestine, this binding results in a marked increase in calcium absorption, which is highly dependent on 1,25-D. There is also an increase in phosphorus absorption, but this effect is less significant because most dietary phosphorus absorption is vitamin D independent. 1,25-D also has direct effects on bone, including mediating resorption. 1,25-D directly suppresses PTH secretion by the parathyroid gland, thus completing a negative feedback loop. PTH secretion is also suppressed by the increase in serum calcium mediated by 1,25-D. 1,25-D inhibits its own synthesis in the kidney and increases the synthesis of inactive metabolites.

Nutritional Vitamin D Deficiency

Vitamin D deficiency remains the most common cause of rickets globally and is prevalent, even in industrialized countries. Because vitamin D can be obtained from dietary sources or from cutaneous synthesis, most patients in industrialized countries have a combination of risk factors that lead to vitamin D deficiency.

Etiology

Vitamin D deficiency most commonly occurs in infancy because of a combination of poor intake and inadequate cutaneous synthesis. Transplacental transport of vitamin D, mostly 25-D, typically provides enough vitamin D for the 1st 2 mo of life unless there is severe maternal vitamin D deficiency. Infants who receive formula receive adequate vitamin D, even without cutaneous synthesis. Because of the low vitamin D content of breast milk, breastfed infants rely on cutaneous synthesis or vitamin supplements. Cutaneous synthesis can be limited because of the ineffectiveness of the winter sun in stimulating vitamin D synthesis; avoidance of sunlight because of concerns about cancer, neighborhood safety, or cultural practices; and decreased cutaneous synthesis because of increased skin pigmentation.

The effect of skin pigmentation explains why most cases of nutritional rickets in the United States and northern Europe occur in breastfed children of African descent or other dark-pigmented populations. The additional impact of the winter sun is supported by the fact that such infants more commonly present in the late winter or spring. In some groups, complete covering of infants or the practice of not taking infants outside has a significant role, explaining the occurrence of rickets in infants living in areas of abundant sunshine, such as the Middle East. Because the mothers of some infants can have the same risk factors, decreased maternal vitamin D can also contribute, both by leading to reduced vitamin D content in breast milk and by lessening transplacental delivery of vitamin D. Rickets caused by vitamin D deficiency can also be secondary to unconventional dietary practices, such as vegan diets that use unfortified soy milk or rice milk.

Clinical Manifestations

The clinical features are typical of rickets (see Table 51-3), with a significant minority presenting with symptoms of hypocalcemia; prolonged laryngospasm is occasionally fatal. These children have an increased risk of pneumonia and muscle weakness leading to a delay in motor development.

Laboratory Findings

Tables 51-4 and 51-5 summarize the principal laboratory findings. Hypocalcemia is a variable finding as a result of the actions of the elevated PTH to increase the serum calcium concentration. The hypophosphatemia is caused by PTH-induced renal losses of phosphate, combined with a decrease in intestinal absorption.

The wide variation in 1,25-D levels (low, normal, or high) is secondary to the upregulation of renal 1α-hydroxylase caused by concomitant hypophosphatemia and hyperparathyroidism. Because serum levels of 1,25-D are much lower than the levels of 25-D, even with low levels of 25-D there is still often enough 25-D present to act as a precursor for 1,25-D synthesis in the presence of an upregulated 1α-hydroxylase. The level of 1,25-D is only low when there is severe vitamin D deficiency.

Some patients have a metabolic acidosis secondary to PTH-induced renal bicarbonate wasting. There may also be generalized aminoaciduria.

Diagnosis and Differential Diagnosis

The diagnosis of nutritional vitamin D deficiency is based on the combination of a history of poor vitamin D intake and risk factors for decreased cutaneous synthesis, radiographic changes consistent with rickets, and typical laboratory findings (see Tables 51-4 and 51-5). A normal PTH level almost never occurs with vitamin D deficiency and suggests a primary phosphate disorder.

Treatment

Children with nutritional vitamin D deficiency should receive vitamin D and adequate nutritional intake of calcium and phosphorus. There are 2 strategies for administration of vitamin D. With stoss therapy, 300,000-600,000 IU of vitamin D are administered orally or intramuscularly as 2-4 doses over 1 day. Because the doses are observed, stoss therapy is ideal in situations where adherence to therapy is questionable. The alternative is daily, high-dose vitamin D, with doses ranging from 2,000-5,000 IU/day over 4-6 wk. Either strategy should be followed by daily vitamin D intake of 400 IU/day if <1 yr old or 600 IU/day if >1 yr old. It is important to ensure that children receive adequate dietary calcium and phosphorus; this dietary intake is usually provided by milk, formula, and other dairy products.

Children who have symptomatic hypocalcemia might need intravenous calcium acutely, followed by oral calcium supplements, which typically can be tapered over 2-6 wk in children who receive adequate dietary calcium. Transient use of intravenous or oral 1,25-D (calcitriol) is often helpful in reversing hypocalcemia in the acute phase by providing active vitamin D during the delay as supplemental vitamin D is converted to active vitamin D. Calcitriol doses are typically 0.05 μg/kg/day. Intravenous calcium is initially given as an acute bolus for symptomatic hypocalcemia (20 mg/kg of calcium

chloride or 100 mg/kg of calcium gluconate). Some patients require a continuous intravenous calcium drip, titrated to maintain the desired serum calcium level. These patients should transition to enteral calcium, and most infants require approximately 1,000 mg of elemental calcium.

Prognosis

Most children have an excellent response to treatment, with radiologic healing occurring within a few months. Laboratory test results should also normalize rapidly. Many of the bone malformations improve dramatically, but children with severe disease can have permanent deformities and short stature. Rarely, patients benefit from orthopedic intervention for leg deformities, although this is generally not done until the metabolic bone disease has healed, there is clear evidence that the deformity will not self-resolve, and the deformity is causing functional problems.

Prevention

Most cases of nutritional rickets can be prevented by universal administration of 400 IU of vitamin D to infants who are breastfed. Older children should receive 600 IU/day. Vitamin D may be administered as a component of a multivitamin or as a vitamin D supplement.

Congenital Vitamin D Deficiency

Congenital rickets is quite rare in industrialized countries and occurs when there is severe maternal vitamin D deficiency during pregnancy. Maternal risk factors include poor dietary intake of vitamin D, lack of adequate sun exposure, and closely spaced pregnancies. These newborns can have symptomatic hypocalcemia, intrauterine growth retardation, and decreased bone ossification, along with classic rachitic changes. More subtle maternal vitamin D deficiency can have an adverse effect on neonatal bone density and birthweight, cause a defect in dental enamel, and predispose infants to neonatal hypocalcemic tetany. Treatment of congenital rickets includes vitamin D supplementation and adequate intake of calcium and phosphorus. Use of prenatal vitamins containing vitamin D prevents this entity.

Secondary Vitamin D Deficiency

Etiology

Along with inadequate intake, vitamin D deficiency can develop due to inadequate absorption, decreased hydroxylation in the liver, and increased degradation. Because vitamin D is fat-soluble, its absorption may be decreased in patients with a variety of liver and GI diseases, including cholestatic liver disease, defects in bile acid metabolism, cystic fibrosis and other causes of pancreatic dysfunction, celiac disease, and Crohn disease. Malabsorption of vitamin D can also occur with intestinal lymphangiectasia and after intestinal resection.

Severe liver disease, which is usually also associated with malabsorption, can cause a decrease in 25-D formation as a consequence of insufficient enzyme activity. Because of the large reserve of 25-hydroxlase activity in the liver, vitamin D deficiency as a result of liver disease usually requires a loss of >90% of liver function. A variety of medications increase the degradation of vitamin D by inducing the cytochrome P450 system. Rickets as a consequence of vitamin D deficiency can develop in children receiving anticonvulsants, such as phenobarbital or phenytoin, or antituberculosis medications, such as isoniazid or rifampin.

Treatment

Treatment of vitamin D deficiency attributable to malabsorption requires high doses of vitamin D. Because of its better absorption, 25-D (25-50 μg/day or 5-7 μg/kg/day) is superior to vitamin D_3. The dose is adjusted based on monitoring of serum levels of 25-D. Alternatively, patients may be treated with 1,25-D, which also is better absorbed in the presence of fat malabsorption, or with parenteral vitamin D. Children with rickets as a result of increased degradation of vitamin D by the cytochrome P450 system require the same acute therapy as indicated for nutritional deficiency (discussed earlier), followed by long-term administration of high doses of vitamin D (e.g., 1,000 IU/day), with dosing titrated based on serum levels of 25-D. Some patients require as much as 4,000 IU/day.

Vitamin D–Dependent Rickets, Type 1

Children with vitamin D–dependent rickets type 1, an autosomal recessive disorder, have mutations in the gene encoding renal 1α-hydroxylase, preventing conversion of 25-D into 1,25-D. These patients normally present during the 1st 2 yr of life and can have any of the classic features of rickets (see Table 51-3), including symptomatic hypocalcemia. They have normal levels of 25-D, but low levels of 1,25-D (see Table 51-5). Occasionally, 1,25-D levels are at the lower limit of normal, inappropriately low given the high PTH and low serum phosphorus levels, both of which should increase the activity of renal 1α-hydroxylase and cause elevated levels of 1,25-D. As in nutritional vitamin D deficiency, renal tubular dysfunction can cause a metabolic acidosis and generalized aminoaciduria.

Treatment

These patients respond to long-term treatment with 1,25-D (calcitriol). Initial doses are 0.25-2 μg/day, and lower doses are used once the rickets has healed. Especially during initial therapy, it is important to ensure adequate intake of calcium. The dose of calcitriol is adjusted to maintain a low-normal serum calcium level, a normal serum phosphorus level, and a high-normal serum PTH level. Targeting a low-normal calcium concentration and a high-normal PTH level avoids excessive dosing of calcitriol, which can cause hypercalciuria and nephrocalcinosis. Hence, patient monitoring includes periodic assessment of urinary calcium excretion, with a target of <4 mg/kg/day.

Vitamin D–Dependent Rickets, Type 2

Patients with vitamin D–dependent rickets type 2 have mutations in the gene encoding the vitamin D receptor, preventing a normal physiologic response to 1,25-D. Levels of 1,25-D are extremely elevated in this autosomal recessive disorder (see Table 51-4). Most patients present during infancy, although rickets in less severely affected patients might not be diagnosed until adulthood. Less-severe disease is associated with a partially functional vitamin D receptor. Approximately 50-70% of children have **alopecia**, which tends to be associated with a more severe form of the disease and can range from alopecia areata to alopecia totalis. Epidermal cysts are a less common manifestation.

Treatment

Some patients respond to extremely high doses of vitamin D_2, 25-D or 1,25-D, especially patients without alopecia. This response is due to a partially functional vitamin D receptor. All patients with this disorder should be given a 3-6 mo trial of high-dose vitamin D and oral calcium. The initial dose of 1,25-D should be 2 μg/day, but some patients require doses as high as 50-60 μg/day. Calcium doses are 1,000-3,000 mg/day. Patients who do not respond to high-dose vitamin D may be treated with long-term intravenous calcium, with possible transition to very high dose oral calcium supplements. Treatment of patients who do not respond to vitamin D is difficult.

Chronic Kidney Disease (See Chapter 535.2)

With chronic kidney disease, there is decreased activity of 1α-hydroxylase in the kidney, leading to diminished production of 1,25-D. In chronic kidney disease, unlike the other causes of vitamin D deficiency, patients have hyperphosphatemia as a result of decreased renal excretion (see Table 51-4).

Treatment

Therapy requires the use of a form of vitamin D that can act without 1-hydroxylation by the kidney (calcitriol), which both permits adequate absorption of calcium and directly suppresses the parathyroid gland. Because hyperphosphatemia is a stimulus for PTH secretion, normalization of the serum phosphorus level via a combination of dietary phosphorus restriction and the use of oral phosphate binders is as important as the use of activated vitamin D.

CALCIUM DEFICIENCY

Pathophysiology

Rickets secondary to inadequate dietary calcium is a significant problem in some countries in Africa, although there are cases in other regions of the world, including industrialized countries. Because breast milk and formula are excellent sources of calcium, this form of rickets develops after children have been weaned from breast milk or formula and is more likely to occur in children who are weaned early. Rickets develops because the diet has low calcium content, typically <200 mg/day. There is little intake of dairy products or other sources of calcium. In addition, because of reliance on grains and green leafy vegetables, the diet may be high in phytate, oxalate, and phosphate, which decrease absorption of dietary calcium. In industrialized countries, rickets caused by calcium deficiency can occur in children who consume an unconventional diet. Examples include children with milk allergy who have low dietary calcium and children who transition from formula or breast milk to juice, soda, or a calcium-poor soy drink, without an alternative source of dietary calcium.

This type of rickets can develop in children who receive intravenous nutrition without adequate calcium. Malabsorption of calcium can occur in celiac disease, intestinal abetalipoproteinemia, and after small bowel resection. There may be concurrent malabsorption of vitamin D.

Clinical Manifestations

Children have the classic signs and symptoms of rickets (see Table 51-3). Presentation can occur during infancy or early childhood, although some cases are diagnosed in teenagers. Because calcium deficiency occurs after the cessation of breastfeeding, it tends to occur later than the nutritional vitamin D deficiency that is associated with breastfeeding. In Nigeria, nutritional vitamin D deficiency is most common at 4-15 mo of age, whereas calcium-deficiency rickets typically occurs at 15-25 mo of age.

Diagnosis

Laboratory findings include increased levels of alkaline phosphatase, PTH, and 1,25-D (see Table 51-4). Calcium levels may be normal or low, although symptomatic hypocalcemia is uncommon. There is decreased urinary excretion of calcium, and serum phosphorus levels may be low as a result of renal wasting of phosphate from secondary hyperparathyroidism. In some children, there is coexisting nutritional vitamin D deficiency, with low 25-D levels.

Treatment

Treatment focuses on providing adequate calcium, typically as a dietary supplement (doses of 700 [1-3 yr age], 1,000 [4-8 yr age], 1,300 [9-18 yr age] mg/day of elemental calcium are effective). Vitamin D supplementation is necessary if there is concurrent vitamin D deficiency (discussed earlier). Prevention strategies include discouraging early cessation of breastfeeding and increasing dietary sources of calcium. In countries such as Kenya, where many children have diets high in cereal with negligible intake of cow's milk, school-based milk programs have been effective in reducing the prevalence of rickets.

PHOSPHOROUS DEFICIENCY

Inadequate Intake

With the exception of starvation or severe anorexia, it is almost impossible to have a diet that is deficient in phosphorus, because phosphorus is present in most foods. Decreased phosphorus absorption can occur in diseases associated with malabsorption (celiac disease, cystic fibrosis, cholestatic liver disease), but if rickets develops, the primary problem is usually malabsorption of vitamin D and/or calcium.

Isolated malabsorption of phosphorus occurs in patients with long-term use of aluminum-containing antacids. These compounds are very effective at chelating phosphate in the GI tract, leading to decreased absorption. This decreased absorption results in hypophosphatemia with secondary osteomalacia in adults and rickets in children. This entity responds to discontinuation of the antacid and short-term phosphorus supplementation.

Fibroblast Growth Factor-23

Fibroblast growth factor-23 (FGF-23) is a humoral mediator that decreases renal tubular reabsorption of phosphate and therefore decreases serum phosphorus. FGF-23, synthesized by osteocytes, also decreases the activity of renal 1α-hydroxylase, resulting in a decrease in the production of 1,25-D. Increased levels of FGF-23 cause many of the renal phosphate-wasting diseases (see Table 51-2).

X-Linked Hypophosphatemic Rickets

Among the genetic disorders causing rickets because of hypophosphatemia, X-linked hypophosphatemic rickets (XLH) is the most common, with a prevalence of 1/20,000. The defective gene is on the X chromosome, but female carriers are affected, so it is an X-linked dominant disorder.

Pathophysiology

The defective gene is called *PHEX* because it is a **PH**osphate-regulating gene with homology to **E**ndopeptidases on the **X** chromosome. The product of this gene appears to have an indirect role in inactivating FGF-23. Mutations in the *PHEX* gene lead to increased levels of FGF-23. Because the actions of FGF-23 include inhibition of phosphate reabsorption in the proximal tubule, phosphate excretion is increased. FGF-23 also inhibits renal 1α-hydroxylase, leading to decreased production of 1,25-D.

Clinical Manifestations

These patients have rickets, but abnormalities of the lower extremities and poor growth are the dominant features. Delayed dentition and tooth abscesses are also common. Some patients have hypophosphatemia and short stature without clinically evident bone disease.

Laboratory Findings

Patients have high renal excretion of phosphate, hypophosphatemia, and increased alkaline phosphatase; PTH and serum calcium levels are normal (see Table 51-4). Hypophosphatemia normally upregulates renal 1α-hydroxylase and should lead to an increase in 1,25-D, but these patients have low or inappropriately normal levels of 1,25-D.

Treatment

Patients respond well to a combination of oral phosphorus and 1,25-D (calcitriol). The daily need for phosphorus supplementation is 1-3 g of elemental phosphorus divided into 4-5 doses. Frequent dosing helps to prevent prolonged decrements in serum phosphorus because there is a rapid decline after each dose. In addition, frequent dosing decreases diarrhea, a complication of high-dose oral phosphorus. Calcitrol is administered 30-70 ng/kg/day divided into 2 doses.

Complications of treatment occur when there is not an adequate balance between phosphorus supplementation and calcitriol. Excess phosphorus, by decreasing enteral calcium absorption, leads to secondary hyperparathyroidism, with worsening of the bone lesions. In contrast, excess calcitriol causes hypercalciuria and nephrocalcinosis and can even cause hypercalcemia. Hence, laboratory monitoring of treatment includes serum calcium, phosphorus, alkaline phosphatase, PTH, and urinary calcium, as well as periodic renal ultrasounds to evaluate patients for nephrocalcinosis. Because of variation in the serum phosphorus level and the importance of avoiding excessive phosphorus dosing, normalization of alkaline phosphatase levels is a more useful method of assessing the therapeutic response than measuring serum phosphorus. For children with significant short stature, growth hormone is an effective option. Children with severe deformities might need osteotomies, but these procedures should be done only when treatment has led to resolution of the bone disease.

Prognosis

The response to therapy is usually good, although frequent dosing can lead to problems with compliance. Girls generally have less-severe disease than boys, probably because of the X-linked inheritance. Short stature can persist despite healing of the rickets. Adults generally do well with less-aggressive treatment, and some receive calcitriol alone.

Adults with bone pain or other symptoms improve with oral phosphorus supplementation and calcitriol.

Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant hypophosphatemic rickets (ADHR) is much less common than XLH. There is incomplete penetrance and variable age of onset. Patients with ADHR have a mutation in the gene encoding FGF-23 (*FGF23*). The mutation prevents degradation of FGF-23 by proteases, leading its level to increase. The actions of FGF-23 include decreased reabsorption of phosphate in the renal proximal tubule, which results in hypophosphatemia, and inhibition of the 1α-hydroxylase in the kidney, causing a decrease in 1,25-D synthesis.

In ADHR, as in XLH, abnormal laboratory findings are hypophosphatemia, an elevated alkaline phosphatase level, and a low or inappropriately normal 1,25-D level (see Table 51-4). Treatment is similar to the approach used in XLH.

Autosomal Recessive Hypophosphatemic Rickets

Autosomal recessive hypophosphatemic rickets (ARHR), type 1 is an extremely rare disorder caused by mutations in the gene encoding dentin matrix protein 1 (*DMP1*). ARHR, type 2 occurs in patients with mutations in the *ENPP1* gene. Mutations in *ENPP1* also cause generalized arterial calcification of infancy. Both types of ARHR are associated with elevated levels of FGF-23, leading to renal phosphate wasting, hypophosphatemia, and low or inappropriately normal levels of 1,25-D. Treatment is similar to the approach used in XLH, although monitoring for arterial calcification is prudent in patients with *ENPP1* mutations.

Hereditary Hypophosphatemic Rickets with Hypercalciuria

Hereditary hypophosphatemic rickets with hypercalciuria is a rare disorder that is mainly found in the Middle East.

Pathophysiology

This autosomal recessive disorder is caused by mutations in the gene for a sodium-phosphate cotransporter in the proximal tubule (*SLC34A3*). The renal phosphate leak causes hypophosphatemia, which then stimulates production of 1,25-D. The high level of 1,25-D increases intestinal absorption of calcium, suppressing PTH. Hypercalciuria ensues as a result of the high absorption of calcium and the low level of PTH, which normally decreases renal excretion of calcium.

Clinical Manifestations

The dominant symptoms are rachitic leg abnormalities (see Table 51-3), muscle weakness, and bone pain. Patients can have short stature, with a disproportionate decrease in the length of the lower extremities. The severity of the disease varies, and some family members have no evidence of rickets but have kidney stones secondary to hypercalciuria.

Laboratory Findings

Laboratory findings include hypophosphatemia, renal phosphate wasting, elevated serum alkaline phosphatase levels, and elevated 1,25-D levels. PTH levels are low (see Table 51-4).

Treatment

Therapy relies on oral phosphorus replacement (1-2.5 g/day of elemental phosphorus in 5 divided oral doses). Treatment of the hypophosphatemia decreases serum levels of 1,25-D and corrects the hypercalciuria. The response to therapy is usually excellent, with resolution of pain, weakness, and radiographic evidence of rickets.

Overproduction of FGF-23

Tumor-induced osteomalacia is more common in adults than in children, where it can produce classic rachitic findings. Most tumors are mesenchymal in origin and are usually benign, small, and located in bone. These tumors secrete FGF-23 and produce a biochemical phenotype that is similar to XLH, including urinary phosphate wasting, hypophosphatemia, elevated alkaline phosphatase levels, and low or inappropriately normal 1,25-D levels (see Table 51-4). Curative treatment is excision of the tumor. If the tumor cannot be removed, treatment is identical to that used for XLH.

Renal phosphate wasting leading to hypophosphatemia and rickets (or osteomalacia in adults) is a potential complication in **McCune-Albright syndrome,** an entity that includes the triad of polyostotic fibrous dysplasia, hyperpigmented macules, and polyendocrinopathy (see Chapter 563.6). Affected patients have inappropriately low levels of 1,25-D and elevated levels of alkaline phosphatase. The renal phosphate wasting and inhibition of 1,25-D synthesis are related to the polyostotic fibrous dysplasia. Patients have elevated levels of FGF-23, presumably produced by the dysplastic bone. Hypophosphatemic rickets can also occur in children with isolated polyostotic fibrous dysplasia. Although it is rarely possible, removal of the abnormal bone can cure this disorder in children with McCune-Albright syndrome. Most patients receive the same treatment as children with XLH. Bisphosphonate treatment decreases the pain and fracture risk associated with the bone lesions.

Rickets is an unusual complication of **epidermal nevus syndrome** (see Chapter 651). Patients have hypophosphatemic rickets due to renal phosphate wasting and also have an inappropriately normal or low level of 1,25-D as a consequence of excessive production of FGF-23. The timing of presentation with rickets varies from infancy to early adolescence. Resolution of hypophosphatemia and rickets has occurred after excision of the epidermal nevi in some patients, but not in others. In most cases, the skin lesions are too extensive to be removed, necessitating treatment with phosphorus supplementation and 1,25-D. Rickets caused by phosphate wasting is an extremely rare complication in children with **neurofibromatosis** (see Chapter 596.1).

Fanconi Syndrome

Fanconi syndrome is secondary to generalized dysfunction of the renal proximal tubule (see Chapter 529.1). There are renal losses of phosphate, amino acids, bicarbonate, glucose, urate, and other molecules that are normally reabsorbed in the proximal tubule. Some patients have partial dysfunction, with less generalized losses. The most clinically relevant consequences are hypophosphatemia caused by phosphate losses and proximal renal tubular acidosis caused by bicarbonate losses. Patients have rickets as a result of hypophosphatemia, with exacerbation from the chronic metabolic acidosis, which causes bone dissolution. Failure to thrive is a consequence of both rickets and renal tubular acidosis. Treatment is dictated by the etiology (see Chapter 529).

Dent Disease (See Chapter 531.3)

Dent disease is an X-linked disorder usually caused by mutations in the gene encoding a chloride channel that is expressed in the kidney (CLCN5). Some patients have mutations in the *OCRL 1* gene, which can also cause Lowe syndrome (see Chapter 530.1). Affected males have variable manifestations, including hematuria, nephrolithiasis, nephrocalcinosis, rickets, and chronic kidney disease. Almost all patients have low-molecular-weight proteinuria and hypercalciuria. Other, less universal abnormalities are aminoaciduria, glycosuria, hypophosphatemia, and hypokalemia. Rickets occurs in approximately 25% of patients, and it responds to oral phosphorus supplements. Some patients also need 1,25-D, but this treatment should be used cautiously because it can worsen the hypercalciuria.

RICKETS OF PREMATURITY (See Chapter 106)

Rickets in very-low-birthweight infants has become a significant problem, as the survival rate for this group of infants has increased.

Pathogenesis

The transfer of calcium and phosphorus from mother to fetus occurs throughout pregnancy, but 80% occurs during the 3rd trimester. Premature birth interrupts this process, with rickets developing when the

premature infant does not have an adequate supply of calcium and phosphorus to support mineralization of the growing skeleton.

Most cases of rickets of prematurity occur in infants with a birthweight <1,000 g. It is more likely to develop in infants with lower birthweight and younger gestational age. Rickets occurs because unsupplemented breast milk and standard infant formula do not contain enough calcium and phosphorus to supply the needs of the premature infant. Other risk factors include cholestatic jaundice, a complicated neonatal course, prolonged use of parenteral nutrition, the use of soy formula, and medications such as diuretics and corticosteroids.

Clinical Manifestations

Rickets of prematurity occurs 1-4 mo after birth. Infants can have nontraumatic fractures, especially of the legs, arms, and ribs. Most fractures are not suspected clinically. Because fractures and softening of the ribs lead to decreased chest compliance, some infants have respiratory distress due to atelectasis and poor ventilation. This rachitic respiratory distress usually develops >5 wk after birth, distinguishing it from the early-onset respiratory disease of premature infants. These infants have poor linear growth, with negative effects on growth persisting beyond 1 yr of age. An additional long-term effect is enamel hypoplasia. Poor bone mineralization can contribute to dolichocephaly. There may be classic rachitic findings, such as frontal bossing, rachitic rosary, craniotabes, and widened wrists and ankles (see Table 51-3). Most infants with rickets of prematurity have no clinical manifestations, and the diagnosis is based on radiographic and laboratory findings.

Laboratory Findings

Because of inadequate intake, the serum phosphorus level is low or low-normal in rickets of prematurity. The renal response is appropriate, with conservation of phosphate leading to a low urine phosphate level; the tubular reabsorption of phosphate is >95%. Most patients have normal levels of 25-D, unless there has been inadequate intake or poor absorption (discussed earlier). The hypophosphatemia stimulates renal 1α-hydroxylase, so levels of 1,25-D are high or high-normal. These high levels can contribute to bone demineralization, because 1,25-D stimulates bone resorption. Serum levels of calcium are low, normal, or high, and patients often have hypercalciuria. Elevated serum calcium levels and hypercalciuria are secondary to increased intestinal absorption and bone dissolution owing to elevation of 1,25-D levels and the inability to deposit calcium in bone because of an inadequate phosphorus supply. The hypercalciuria indicates that phosphorus is the limiting nutrient for bone mineralization, although increased provision of phosphorus alone often cannot correct the mineralization defect; increased calcium is also necessary. Hence, there is an inadequate supply of calcium and phosphorus, but the deficiency in phosphorus is greater.

Alkaline phosphatase levels are often elevated, but some affected infants have normal levels. In some instances, normal alkaline phosphatase levels may be secondary to resolution of the bone demineralization because of an adequate mineral supply despite the continued presence of radiologic changes, which take longer to resolve. However, alkaline phosphatase levels may be normal despite active disease. No single blood test is 100% sensitive for the diagnosis of rickets. The diagnosis should be suspected in infants with an alkaline phosphatase level that is >5-6 times the upper limit of normal for adults (unless there is concomitant liver disease) or a phosphorus level <5.6 mg/dL. The diagnosis is confirmed by radiologic evidence of rickets, which is best seen on films of the wrists and ankles. Films of the arms and legs might reveal fractures. The rachitic rosary may be visible on chest x-ray. Unfortunately, x-rays cannot show early demineralization of bone because changes are not evident until there is >20-30% reduction in the bone mineral content.

Diagnosis

Because many premature infants have no overt clinical manifestations of rickets, screening tests are recommended. These tests should include weekly measurements of calcium, phosphorus, and alkaline phosphatase. Periodic measurement of the serum bicarbonate concentration is also important, because metabolic acidosis causes dissolution of bone. At least 1 screening x-ray for rickets at 6-8 wk of age is appropriate in infants who are at high risk for rickets; additional films may be indicated in very high risk infants.

Prevention

Provision of adequate amounts of calcium, phosphorus, and vitamin D significantly decreases the risk of rickets of prematurity. Parenteral nutrition is often necessary initially in very premature infants. In the past, adequate parenteral calcium and phosphorus delivery was difficult because of limits secondary to insolubility of these ions when their concentrations were increased. Current amino acid preparations allow higher concentrations of calcium and phosphate, decreasing the risk of rickets. Early transition to enteral feedings is also helpful. These infants should receive either human milk fortified with calcium and phosphorus or preterm infant formula, which has higher concentrations of calcium and phosphorus than standard formula. Soy formula should be avoided because there is decreased bioavailability of calcium and phosphorus. Increased mineral feedings should continue until the infant weighs 3-3.5 kg. These infants should also receive approximately 400 IU/day of vitamin D via formula and vitamin supplements.

Treatment

Therapy for rickets of prematurity focuses on ensuring adequate delivery of calcium, phosphorus, and vitamin D. If mineral delivery has been good and there is no evidence of healing, then it is important to screen for vitamin D deficiency by measuring serum 25-D. Measurement of PTH, 1,25-D, and urinary calcium and phosphorus may be helpful in some cases.

DISTAL RENAL TUBULAR ACIDOSIS

(See Chapter 530)

Distal renal tubular acidosis usually manifests with failure to thrive. Patients have a metabolic acidosis with an inability to acidify the urine appropriately. Hypercalciuria and nephrocalcinosis are typically present. There are many possible etiologies, including autosomal recessive and autosomal dominant forms. Rickets is variable, and it responds to alkali therapy (see Fig. 51-4).

HYPERVITAMINOSIS D

Etiology

Hypervitaminosis D is secondary to excessive intake of vitamin D. It can occur with long-term high intake or with a substantial, acute ingestion (see Table 51-1). Most cases are secondary to misuse of prescribed or nonprescription vitamin D supplements, but other cases have been secondary to accidental overfortification of milk, contamination of table sugar, and inadvertent use of vitamin D supplements as cooking oil. The recommended upper limits for long-term vitamin D intake are 1,000 IU for children <1 year old and 2,000 IU for older children and adults. Hypervitaminosis D can also result from excessive intake of synthetic vitamin D analogs (25-D, 1,25-D). Vitamin D intoxication is never secondary to excessive exposure to sunlight, probably because ultraviolet irradiation can transform vitamin D_3 and its precursor into inactive metabolites.

Pathogenesis

Although vitamin D increases intestinal absorption of calcium, the dominant mechanism of the hypercalcemia is excessive bone resorption.

Clinical Manifestations

The signs and symptoms of vitamin D intoxication are secondary to hypercalcemia. GI manifestations include nausea, vomiting, poor feeding, constipation, abdominal pain, and pancreatitis. Possible cardiac findings are hypertension, decreased Q-T interval, and arrhythmias. The central nervous system effects of hypercalcemia include lethargy, hypotonia, confusion, disorientation, depression, psychosis, hallucinations, and coma. Hypercalcemia impairs renal concentrating

mechanisms, which can lead to polyuria, dehydration, and hypernatremia. Hypercalcemia can also lead to acute renal failure, nephrolithiasis, and nephrocalcinosis, which can result in chronic renal insufficiency. Deaths are usually associated with arrhythmias or dehydration.

Laboratory Findings

The classic findings in vitamin D intoxication are hypercalcemia and extremely elevated levels of 25-D (>150 ng/mL). Hyperphosphatemia is also common. PTH levels are appropriately decreased owing to hypercalcemia. Hypercalciuria is universally present and can lead to nephrocalcinosis, which is visible on renal ultrasound. Hypercalcemia and nephrocalcinosis can lead to renal insufficiency.

Surprisingly, levels of 1,25-D are usually normal. This may be a result of downregulation of renal 1α-hydroxylase by the combination of low PTH, hyperphosphatemia, and a direct effect of 1,25-D. There is evidence indicating that the level of free 1,25-D may be high, owing to displacement from vitamin D–binding proteins by 25-D. Nephrocalcinosis is often visible on ultrasound or CT scan. Anemia is sometimes present; the mechanism is unknown.

Diagnosis and Differential Diagnosis

The diagnosis is based on the presence of hypercalcemia and an elevated serum 25-D level, although children with excess intake of 1,25-D or another synthetic vitamin D preparation have normal levels of 25-D. With careful sleuthing, there is usually a history of excess intake of vitamin D, although in some situations (overfortification of milk by a dairy) the patient and family may be unaware.

The **differential diagnosis** of vitamin D intoxication focuses on other causes of hypercalcemia. **Hyperparathyroidism** produces hypophosphatemia, whereas vitamin D intoxication usually causes hyperphosphatemia. **Williams syndrome** is often suggested by phenotypic features and accompanying cardiac disease. **Idiopathic infantile hypercalcemia** occurs in children taking appropriate doses of vitamin D. **Subcutaneous fat necrosis** is a common cause of hypercalcemia in young infants; skin findings are usually present. The hypercalcemia of **familial benign hypocalciuric hypercalcemia** is mild, asymptomatic, and associated with hypocalciuria. Hypercalcemia of **malignancy** is an important consideration. High intake of calcium can also cause hypercalcemia, especially in the presence of renal insufficiency. Questioning about calcium intake should be part of the history in a patient with hypercalcemia. Occasionally, patients are intentionally taking high doses of calcium and vitamin D.

Treatment

The treatment of vitamin D intoxication focuses on control of hypercalcemia. Many patients with hypercalcemia are dehydrated as a result of polyuria from nephrogenic diabetes insipidus, poor oral intake, and vomiting. Rehydration lowers the serum calcium level via dilution and corrects prerenal azotemia. The resultant increased urine output increases urinary calcium excretion. Urinary calcium excretion is also increased by high urinary sodium excretion. The mainstay of the initial treatment is aggressive therapy with normal saline, often in conjunction with a loop diuretic to further increase calcium excretion.

Normal saline, with or without a loop diuretic, is often adequate for treating mild or moderate hypercalcemia. More significant hypercalcemia usually requires other therapies. Glucocorticoids decrease intestinal absorption of calcium by blocking the action of 1,25-D. There is also a decrease in the levels of 25-D and 1,25-D. The usual dosage of prednisone is 1-2 mg/kg/24 hr.

Calcitonin, which lowers calcium by inhibiting bone resorption, is a useful adjunct, but its effect is usually not dramatic. There is an excellent response to intravenous or oral bisphosphonates in vitamin D intoxication. Bisphosphonates inhibit bone resorption through their effects on osteoclasts. Hemodialysis using a low or 0 dialysate calcium can rapidly lower serum calcium in patients with severe hypercalcemia that is refractory to other measures.

Along with controlling hypercalcemia, it is imperative to eliminate the source of excess vitamin D. Additional sources of vitamin D such as multivitamins and fortified foods should be eliminated or reduced. Avoidance of sun exposure, including the use of sunscreen, is prudent. The patient should also restrict calcium intake.

Prognosis

Most children make a full recovery, but hypervitaminosis D may be fatal or can lead to chronic kidney disease. Because vitamin D is stored in fat, levels can remain elevated for months, necessitating regular monitoring of 25-D, serum calcium, and urine calcium.

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Chapter 52

Vitamin E Deficiency

Larry A. Greenbaum

Vitamin E is a fat-soluble vitamin and functions as an antioxidant, but its precise biochemical functions are not known. Vitamin E deficiency can cause hemolysis or neurologic manifestations and occurs in premature infants, in patients with malabsorption, and in an autosomal recessive disorder affecting vitamin E transport. Because of its role as an antioxidant, there is considerable research on the potential role of vitamin E supplementation in chronic illnesses.

PATHOGENESIS

The term *vitamin E* denotes a group of 8 compounds with similar structures and antioxidant activity. The most potent member of these compounds is α-tocopherol, which is also the main form in humans. The best dietary sources of vitamin E are vegetable oils, seeds, nuts, green leafy vegetables, and margarine (see Table 51-1).

The majority of vitamin E is located within cell membranes, where it prevents lipid peroxidation and the formation of free radicals. Other antioxidants, such as ascorbic acid, enhance the antioxidant activity of vitamin E. The importance of other functions of vitamin E is still being delineated.

Premature infants are particularly susceptible to vitamin E deficiency, because there is significant transfer of vitamin E during the last trimester of pregnancy. Vitamin E deficiency in premature infants causes thrombocytosis, edema, and hemolysis potentially causing anemia. The risk of symptomatic vitamin E deficiency was increased by the use of formulas for premature infants that had a high content of polyunsaturated fatty acids (PUFAs). These formulas led to a high content of PUFAs in red blood cell membranes, making them more susceptible to oxidative stress, which could be ameliorated by vitamin E. Oxidative stress was augmented by aggressive use of iron supplementation; iron increases the production of oxygen radicals. The incidence of hemolysis as a result of vitamin E deficiency in premature infants decreased secondary to the use of formulas with a lower content of PUFAs, less-aggressive use of iron, and provision of adequate vitamin E.

Because vitamin E is plentiful in common foods, primary dietary deficiency is rare except in premature infants and in severe, generalized malnutrition. Vitamin E deficiency does occur in children with fat malabsorption secondary to the need for bile acid for vitamin E absorption. Although symptomatic disease is most common in children with cholestatic liver disease, it can occur in patients with cystic fibrosis, celiac disease, short-bowel syndrome, or Crohn disease. The autosomal recessive disorder **abetalipoproteinemia** (see Chapter 86) causes fat malabsorption, and vitamin E deficiency is a common complication.

In **ataxia with isolated vitamin E deficiency** (AVED), a rare autosomal recessive disorder, there are mutations in the gene for α-tocopherol transfer protein (*TTPA*). Patients with this disorder are unable to incorporate vitamin E into lipoproteins before their release from the liver, leading to reduced serum levels of vitamin E. There is no associated fat malabsorption, and absorption of vitamin E from the intestine occurs normally.

CLINICAL MANIFESTATIONS

A severe, progressive neurologic disorder occurs in patients with prolonged vitamin E deficiency. Clinical manifestations do not appear until after 1 yr of age, even in children with cholestasis since birth. Patients may have cerebellar disease, posterior column dysfunction, and retinal disease. Loss of deep tendon reflexes is usually the initial finding. Subsequent manifestations include limb ataxia (intention tremor, dysdiadochokinesia), truncal ataxia (wide-based, unsteady gait), dysarthria, ophthalmoplegia (limited upward gaze), nystagmus, decreased proprioception (positive Romberg test), decreased vibratory sensation, and dysarthria. Some patients have pigmentary retinopathy. Visual field constriction can progress to blindness. Cognition and behavior can also be affected. Myopathy and cardiac arrhythmias are less-common findings.

In premature infants, hemolysis as a result of vitamin E deficiency typically develops during the 2nd mo of life. Edema may also be present.

LABORATORY FINDINGS

Serum vitamin E levels increase in the presence of high serum lipid levels, even when vitamin E deficiency is present. Hence, vitamin E status is best determined by measuring the ratio of vitamin E to serum lipids; a ratio <0.8 mg/g is abnormal in older children and adults; <0.6 mg/g is abnormal in infants <1 yr. Premature infants with hemolysis caused by vitamin E deficiency also often have elevated platelet counts.

Neurologic involvement can cause abnormal somatosensory evoked potentials and nerve conduction studies. Abnormalities on electroretinography can precede physical examination findings in patients with retinal involvement.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Premature infants with unexplained hemolytic anemia after the 1st mo of life, especially if thrombocytosis is present, either should be empirically treated with vitamin E or should have serum vitamin E and lipid levels measured. Children with neurologic findings and a disease that causes fat malabsorption should have their vitamin E status evaluated.

Because children with AVED do not have symptoms of malabsorption, a correct diagnosis requires a high index of suspicion. **Friedreich ataxia** has been misdiagnosed in some patients (see Chapter 597.1). Children with unexplained ataxia should be screened for vitamin E deficiency.

TREATMENT

For correction of deficiency in neonates, the dose of vitamin E is 25-50 units/day for 1 wk, followed by adequate dietary intake. Children with deficiency as a result of malabsorption should receive 1 unit/kg/day, with the dose adjusted based on levels; ongoing treatment is necessary. Children with AVED normalize their serum vitamin E levels with high doses of vitamin E and require ongoing treatment.

PROGNOSIS

The hemolytic anemia in infants resolves with correction of the vitamin E deficiency. Some neurologic manifestations of vitamin E deficiency may be reversible with early treatment, but many patients have little or no improvement. Importantly, treatment prevents progression.

PREVENTION

Premature infants should receive sufficient vitamin E via formula or breast milk fortifier and formula without a high content of PUFAs. Children at risk for vitamin E deficiency as a result of malabsorption should be screened for deficiency and given adequate vitamin E supplementation. Vitamin preparations with high content of all of the fat-soluble vitamins are available.

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Chapter 53

Vitamin K Deficiency

Larry A. Greenbaum

Vitamin K is necessary for the synthesis of clotting factors II, VII, IX, and X; deficiency of vitamin K can result in clinically significant bleeding. Vitamin K deficiency typically affects infants, who experience a transient deficiency related to inadequate intake, or patients of any age who have decreased vitamin K absorption. Mild vitamin K deficiency can affect long-term bone and vascular health (see Chapters 103.4 and 480).

PATHOGENESIS

Vitamin K is a group of compounds that have a common naphthoquinone ring structure. Phylloquinone, called *vitamin K_1*, is present in a variety of dietary sources, with green leafy vegetables, liver, and certain legumes and plant oils having the highest content. Vitamin K_1 is the form used to fortify foods and as a medication in the United States. Vitamin K_2 is a group of compounds called *menaquinones*, which are produced by intestinal bacteria. There is uncertainty regarding the relative importance of intestinally produced vitamin K_2. Menaquinones are also present in meat, especially liver, and cheese. A menaquinone is used pharmacologically in some countries.

Vitamin K is a cofactor for γ-glutamyl carboxylase, an enzyme that performs posttranslational carboxylation, converting glutamate residues in proteins to γ-carboxyglutamate (Gla). The Gla residues, by facilitating calcium binding, are necessary for protein function.

The classic Gla-containing proteins involved in blood coagulation that are decreased in vitamin K deficiency are factors II (prothrombin), VII, IX, and X. Vitamin K deficiency causes a decrease in proteins C and S, which inhibit blood coagulation, and protein Z, which also has a role in coagulation. All of these proteins are made only in the liver, except for protein S, a product of various tissues.

Gla-containing proteins are also involved in bone biology (e.g., osteocalcin and protein S) and vascular biology (matrix Gla protein and protein S). Based on the presence of reduced levels of Gla, these proteins appear more sensitive than the coagulation proteins to subtle vitamin K deficiency. There is evidence suggesting that mild vitamin K deficiency might have a deleterious effect on long-term bone strength and vascular health.

Because it is fat soluble, vitamin K requires the presence of bile salts for its absorption. Unlike other fat-soluble vitamins, there are limited body stores of vitamin K. In addition, there is high turnover of vitamin K, and the vitamin K–dependent clotting factors have a short half-life. Hence, symptomatic vitamin K deficiency can develop within weeks when there is inadequate supply because of low intake or malabsorption.

There are 3 forms of **vitamin K–deficiency bleeding** (VKDB) of the newborn (see Chapter 103.4). Early VKDB was formerly called *classic hemorrhagic disease of the newborn* and occurs at 1-14 days of age. Early VKDB is secondary to low stores of vitamin K at birth as a result of the poor transfer of vitamin K across the placenta and inadequate intake during the 1st few days of life. In addition, there is no intestinal synthesis of vitamin K_2 because the newborn gut is sterile. Early VKDB

occurs mostly in breastfed infants as a consequence of the low vitamin K content of breast milk (formula is fortified). Delayed feeding is an additional risk factor.

Late VKDB most commonly occurs at 2-12 wk of age, although cases can occur up to 6 mo after birth. Almost all cases are in breastfed infants because of the low vitamin K content of breast milk. An additional risk factor is occult malabsorption of vitamin K, as occurs in children with undiagnosed cystic fibrosis or cholestatic liver disease (e.g., biliary atresia, α_1-antitrypsin deficiency). Without vitamin K prophylaxis, the incidence is 4-10/100,000 newborns.

The third form of VKDB of the newborn occurs at birth or shortly thereafter. It is secondary to maternal intake of medications (warfarin, phenobarbital, phenytoin) that cross the placenta and interfere with vitamin K function.

VKDB as a result of fat malabsorption can occur in children of any age. Potential etiologies include cholestatic liver disease, pancreatic disease, and intestinal disorders (celiac sprue, inflammatory bowel disease, short-bowel syndrome). Prolonged diarrhea can cause vitamin K deficiency, especially in breastfed infants. Children with cystic fibrosis are most likely to have vitamin K deficiency if they have pancreatic insufficiency and liver disease.

Beyond infancy, low dietary intake by itself never causes vitamin K deficiency. However, the combination of poor intake and the use of broad-spectrum antibiotics that eliminate the intestine's vitamin K_2-producing bacteria can cause vitamin K deficiency. This scenario is especially common in the intensive care unit. Vitamin K deficiency can also occur in patients who receive total parenteral nutrition without vitamin K supplementation.

CLINICAL MANIFESTATIONS

In early VKDB, the most common sites of bleeding are the gastrointestinal (GI) tract, mucosal and cutaneous tissue, the umbilical stump, and the postcircumcision site; intracranial bleeding is less common. GI blood loss can be severe enough to require a transfusion. In contrast, the most common site of bleeding in late VKDB is intracranial, although cutaneous and GI bleeding may be the initial manifestation. Intracranial bleeding can cause convulsions, permanent neurologic sequelae, or death. In some cases of late VKDB, the presence of an underlying disorder may be suggested by jaundice or failure to thrive. Older children with vitamin K deficiency can present with bruising, mucocutaneous bleeding, or more serious bleeding.

LABORATORY FINDINGS

In patients with bleeding as a result of vitamin K deficiency, the prothrombin time (PT) is prolonged. The PT must be interpreted based on the patient's age, because it is normally prolonged in newborns (see Chapter 476). The partial thromboplastin time is usually prolonged, but it may be normal in early deficiency; factor VII has the shortest half-life of the coagulation factors and is the first to be affected by vitamin K deficiency, but isolated factor VII deficiency does not affect the partial thromboplastin time. The platelet count and fibrinogen level are normal.

When there is mild vitamin K deficiency, the PT is normal, but there are elevated levels of the undercarboxylated forms of the proteins that are normally carboxylated in the presence of vitamin K. These undercarboxylated proteins are called *proteins induced by vitamin K absence* (PIVKA). Measurement of undercarboxylated factor II (PIVKA-II) can be used to detect mild vitamin K deficiency. Determination of blood vitamin K levels is less useful because of significant variation based on recent dietary intake; levels do not always reflect tissue stores.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is established by the presence of a prolonged PT that corrects rapidly after administration of vitamin K, which stops the active bleeding. Other possible causes of bleeding and a prolonged PT include **disseminated intravascular coagulation** (DIC), liver failure, and rare hereditary deficiencies of clotting factors. DIC, which is most commonly secondary to sepsis, is associated with thrombocytopenia, low fibrinogen, and elevated D-dimers. Most patients with DIC have hemodynamic instability that does not correct with restoration of blood volume. Severe liver disease results in decreased production of clotting factors; the PT does not fully correct with administration of vitamin K. Children with a hereditary disorder have a deficiency in a specific clotting factor (I, II, V, VII, X).

Coumarin derivatives inhibit the action of vitamin K by preventing its recycling to an active form after it functions as a cofactor for γ-glutamyl carboxylase. Bleeding can occur with overdosage of the commonly used anticoagulant warfarin or with ingestion of rodent poison, which contains a coumarin derivative. High doses of salicylates also inhibit vitamin K regeneration, potentially leading to a prolonged PT and clinical bleeding.

TREATMENT

Infants with VKDB should receive 1 mg of parenteral vitamin K. The PT should decrease within 6 hr and normalize within 24 hr. For rapid correction in adolescents, the parenteral dose is 2.5-10 mg. In addition to vitamin K, a patient with severe, life-threatening bleeding should receive an infusion of fresh-frozen plasma, which corrects the coagulopathy rapidly. Children with vitamin K deficiency as a consequence of malabsorption require chronic administration of high doses of oral vitamin K (2.5 mg twice/wk to 5 mg/day). Parenteral vitamin K may be necessary if oral vitamin K is ineffective.

PREVENTION

Administration of either oral or parenteral vitamin K soon after birth prevents early VKDB of the newborn. In contrast, a single dose of oral vitamin K does not prevent a substantial number of cases of late VKDB. However, a single intramuscular injection of vitamin K (1 mg), the current practice in the United States, is almost universally effective, except in children with severe malabsorption. This increased efficacy of the intramuscular form is thought to be the result of a depot effect. Concerns about an association between parenteral vitamin K at birth and the later development of malignancy are unsubstantiated.

Discontinuing the offending medications before delivery can prevent VKDB attributable to maternal medications. If this is not possible, administration of vitamin K to the mother may be helpful. In addition, the neonate should receive parenteral vitamin K immediately after birth. If parenteral vitamin K does not correct the coagulopathy rapidly, then the child should receive fresh frozen plasma.

Children who are at high risk for malabsorption of vitamin K should receive supplemental vitamin K and periodic measurement of the PT.

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Chapter 54

Micronutrient Mineral Deficiencies

Larry A. Greenbaum

Micronutrients include vitamins (see Chapters 48-53) and trace elements. By definition, a trace element is <0.01% of the body weight. Trace elements have a variety of essential functions (Table 54-1). With the exception of iron deficiency, trace element deficiency (see Table 54-1) is uncommon in developed countries, but some deficiencies (iodine, zinc, selenium) are important public health problems in a number of developing countries. Because of low nutritional requirements and plentiful supply, deficiencies of some of the trace elements are extremely rare in humans and typically occur in patients receiving

Table 54-1 Trace Elements

ELEMENT	PHYSIOLOGY	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS	DIETARY SOURCES
Chromium	Potentiates the action of insulin	Impaired glucose tolerance, peripheral neuropathy, and encephalopathy	Unknown	Meat, grains, fruits, and vegetables
Copper	Absorbed via specific intestinal transporter Circulates bound to ceruloplasmin Enzyme cofactor (superoxide dismutase, cytochrome oxidase, and enzymes involved in iron metabolism and connective tissue formation)	Microcytic anemia, osteoporosis, neutropenia, neurologic symptoms, depigmentation of hair and skin	Acute: nausea, emesis, abdominal pain, coma, and hepatic necrosis Chronic toxicity (liver and brain injury) occurs in Wilson disease (see Chapter 357.2) and secondary to excess intake (see Chapter 357.3)	Vegetables, grains, nuts, liver, margarine, legumes, corn oil
Fluoride	Incorporated into bone	Dental caries (see Chapter 312)	Chronic: dental fluorosis (see Chapter 307)	Toothpaste, fluoridated water
Iodine	Component of thyroid hormone (see Chapter 564)	Hypothyroidism (see Chapters 566 and 568)	Hypothyroidism and goiter (see Chapters 566 and 568); maternal excess can cause congenital hypothyroidism and goiter (see Chapter 568.1)	Saltwater fish, iodized salt
Iron	Component of hemoglobin, myoglobin, cytochromes, and other enzymes	Anemia (see Chapter 456), decreased alertness, impaired learning	Acute (see Chapter 63): nausea, vomiting, diarrhea, abdominal pain, and hypotension Chronic excess usually secondary to hereditary disorders (see Chapters 463.9 and 357.4); causes organ dysfunction	Meat, fortified foods Deficiency can also result from blood loss (hookworm infestation, menorrhagia)
Manganese	Enzyme cofactor	Hypercholesterolemia, weight loss, decreased clotting proteins*	Neurologic manifestations, cholestatic jaundice	Nuts, meat, grains, tea
Molybdenum	Enzyme cofactor (xanthine oxidase and others)	Tachycardia, tachypnea, night blindness, irritability, coma*	Hyperuricemia and increased risk of gout	Legumes, grains, liver
Selenium	Enzyme cofactor (prevents oxidative damage)	Cardiomyopathy (Keshan disease), myopathy	Nausea, diarrhea, neurologic manifestations, nail and hair changes, garlic odor	Meat, seafood, whole grains, garlic
Zinc	Enzyme cofactor Constituent of zinc-finger proteins, which regulate gene transcription	Decreased growth, dermatitis of extremities and around orifices, impaired immunity, poor wound healing, hypogonadism, diarrhea Supplements beneficial in diarrhea and improve neurodevelopmental outcomes	Abdominal pain, diarrhea, vomiting Can worsen copper deficiency	Meat, shellfish, whole grains, legumes, cheese

*These deficiency states have been reported only in case reports associated with parenteral nutrition or highly unusual diets.

unusual diets or prolonged total parenteral nutrition without adequate delivery of a specific trace element. They can also occur in children with short bowel or malabsorption. Excess intake of trace elements (see Table 54-1) is uncommon, but it can result from environmental exposure or overuse of supplements.

For a number of reasons, children are especially susceptible to trace element deficiency. First, growth creates an increased demand for most trace elements. Second, some organs are more likely to sustain permanent damage because of trace element deficiency during childhood. The developing brain is particularly vulnerable to the consequences of certain deficiency states (iron, iodide). Similarly, adequate fluoride is most critical for dental health during childhood. Third, children, especially in the developing world, are more prone to gastrointestinal disorders that can cause trace element deficiencies because of malabsorption.

A normal diet provides adequate intake of most trace elements. However, the intake of certain trace elements varies significantly in different geographic locations. Iodide-containing food is plentiful near the ocean, but inland areas often have inadequate sources, leading to goiter and **hypothyroidism.** Iodine deficiency is not a problem in the United States because of the widespread use of iodized salt; however, symptomatic iodine deficiency (goiter and hypothyroidism) is common in many developing countries. Selenium content of the soil and consequently of food is also quite variable. Dietary selenium deficiency (associated with cardiomyopathy) occurs in certain locations, such as some parts of China.

The consequences of severe isolated trace mineral deficiency are illustrated in certain genetic disorders. The manifestations of **Menkes disease** (see Chapters 357.5 and 599) are caused by a mutation in the gene coding for a protein that facilitates intestinal copper absorption. This mutation results in severe copper deficiency; subcutaneous copper is an effective treatment. The recessive disorder **acrodermatitis enteropathica** (see Chapter 671) is secondary to malabsorption of zinc. These patients respond dramatically to zinc supplementation.

Children can have apparently asymptomatic deficiencies of certain trace elements but still benefit from supplementation. As an example, zinc is highly effective in treating children before or during diarrheal illnesses in the developing world.

Zinc deficiency is quite common in the developing world and is often associated with malnutrition or other micronutrient deficiencies (iron). Chronic zinc deficiency is associated with dwarfism, hypogonadism, dermatitis, and T-cell immunodeficiency. Diets rich in phytates bind zinc, impairing its absorption. Zinc supplementation in at-risk children reduces the incidence and severity of diarrhea, pneumonia, and possibly malaria. In developing countries, children who have diarrhea may benefit from zinc supplementation, especially if there is underlying malnutrition.

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Fluid and Electrolyte Disorders

PART VII

Chapter 55

Electrolyte and Acid-Base Disorders

55.1 Composition of Body Fluids

Larry A. Greenbaum

TOTAL BODY WATER

Total body water (TBW) as a percentage of body weight varies with age (Fig. 55-1). The fetus has very high TBW, which gradually decreases to approximately 75% of birthweight for a term infant. Premature infants have higher TBW than term infants. During the 1st yr of life, TBW decreases to approximately 60% of body weight and basically remains at this level until puberty. At puberty, the fat content of females increases more than that in males, who acquire more muscle mass than females. Because fat has very low water content and muscle has high water content, by the end of puberty TBW in males remains at 60%, but TBW in females decreases to approximately 50% of body weight. The high fat content in overweight children causes a decrease in TBW as a percentage of body weight. During dehydration, TBW decreases and, thus, is a smaller percentage of body weight.

FLUID COMPARTMENTS

TBW is divided between 2 main compartments: intracellular fluid (ICF) and extracellular fluid (ECF). In the fetus and newborn, the ECF volume is larger than the ICF volume (see Fig. 55-1). The normal postnatal diuresis causes an immediate decrease in the ECF volume. This is followed by continued expansion of the ICF volume, which results from cellular growth. By 1 yr of age, the ratio of the ICF volume to the ECF volume approaches adult levels. The ECF volume is approximately 20-25% of body weight, and the ICF volume is approximately 30-40% of body weight, close to twice the ECF volume (Fig. 55-2). With puberty, the increased muscle mass of males causes them to have a higher ICF volume than females. There is no significant difference in the ECF volume between postpubertal females and males.

The ECF is further divided into the plasma water and the interstitial fluid (see Fig. 55-2). The plasma water is 5% of body weight. The blood volume, given a hematocrit of 40%, is usually 8% of body weight, although it is higher in newborns and young infants; in premature newborns, it is approximately 10% of body weight. The volume of plasma water can be altered by pathologic conditions, including dehydration, anemia, polycythemia, heart failure, abnormal plasma osmolality, and hypoalbuminemia. The interstitial fluid, normally 15% of body weight, can increase dramatically in diseases associated with edema, such as heart failure, protein-losing enteropathy, liver failure, nephrotic syndrome, and sepsis. An increase in interstitial fluid also occurs in patients with ascites or pleural effusions.

There is a delicate equilibrium between the intravascular fluid and the interstitial fluid. The balance between hydrostatic and oncotic forces regulates the intravascular volume, which is critical for proper tissue perfusion. The intravascular fluid has a higher concentration of albumin than the interstitial fluid, and the consequent oncotic force draws water into the intravascular space. The maintenance of this gradient depends on the limited permeability of albumin across the capillaries. The hydrostatic pressure of the intravascular space, which is due to the pumping action of the heart, drives fluid out of the intravascular space. These forces favor movement into the interstitial space at the arterial ends of the capillaries. The decreased hydrostatic forces and increased oncotic forces, which result from the dilutional increase in albumin concentration, cause movement of fluid into the venous ends of the capillaries. Overall, there is usually a net movement of fluid out of the intravascular space to the interstitial space, but this fluid is returned to the circulation via the **lymphatics.** An imbalance in these forces may cause expansion of the interstitial volume at the expense of the intravascular volume. In children with hypoalbuminemia, the decreased oncotic pressure of the intravascular fluid contributes to the development of **edema.** Loss of fluid from the intravascular space may compromise the intravascular volume, placing the child at risk for inadequate blood flow to vital organs. This is especially likely in diseases in which capillary leak occurs because the loss of albumin from the intravascular space is associated with an increase in the albumin concentration in the interstitial space, further compromising the oncotic forces that normally maintain intravascular volume. In contrast, with **heart failure,** there is an increase in venous hydrostatic pressure from expansion of the intravascular volume, which is caused by impaired pumping by the heart, and the increase in venous pressure causes fluid to move from the intravascular space to the interstitial space. Expansion of the intravascular volume and increased intravascular pressure also cause the edema that occurs with acute glomerulonephritis.

ELECTROLYTE COMPOSITION

The composition of the solutes in the ICF and ECF are very different (Fig. 55-3). Sodium and chloride are the dominant cation and anion, respectively, in the ECF. The sodium and chloride concentrations in the ICF are much lower. Potassium is the most abundant cation in the ICF, and its concentration within the cells is approximately 30 times higher than in the ECF. Proteins, organic anions, and phosphate are the most plentiful anions in the ICF. The dissimilarity between the anions in the ICF and the ECF is largely determined by the presence of intracellular molecules that do not cross the cell membrane, the barrier separating the ECF and the ICF. In contrast, the difference in the distribution of cations—sodium and potassium—is a result of the activity of the Na^+,K^+-adenosine triphosphatase (ATPase) pump, which uses cellular energy to actively extrude sodium from cells and move potassium into cells. The chemical gradient between the intracellular potassium concentration and the extracellular potassium concentration creates the electrical gradient across the cell membrane. The concentration-dependent movement of potassium out of the cell makes the intracellular space negative relative to the extracellular space.

The difference in the electrolyte compositions of the ECF and the ICF has important ramifications in the evaluation and treatment of electrolyte disorders. The serum concentration of an electrolyte, which is measured clinically, does not always reflect the body content. This is because of the larger volume of the ICF compared with the ECF and the variation in electrolyte concentrations between these 2 compartments. The intracellular potassium concentration is much higher than the serum concentration. A shift of potassium from the intracellular space can maintain a normal or even an elevated serum potassium concentration, despite massive losses of potassium from the intracellular space. This is dramatically seen in diabetic ketoacidosis, in which a state of significant potassium depletion is often masked because of a transmembrane shift of potassium from the ICF to the ECF. For potassium and phosphorus, electrolytes with a high intracellular concentration, the serum level may not reflect total body content. Similarly, the serum calcium concentration does not predict the body content of calcium, which is largely in bone.

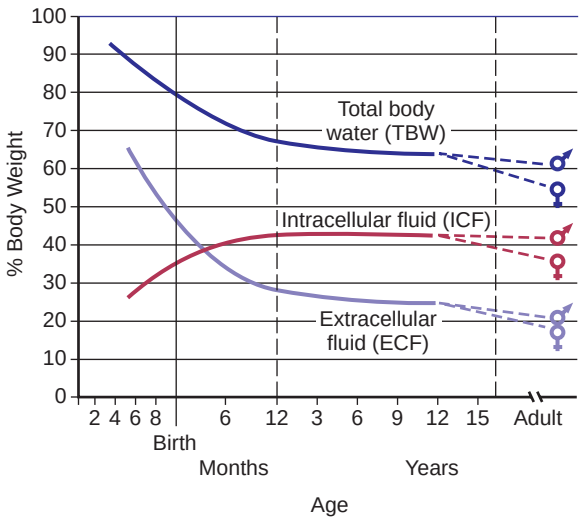

Figure 55-1 Total body water, intracellular fluid, and extracellular fluid as a percentage of body weight and a function of age. *(From Winters RW: Water and electrolyte regulation. In Winters RW, editor:* The body fluids in pediatrics, *Boston, 1973, Little, Brown.)*

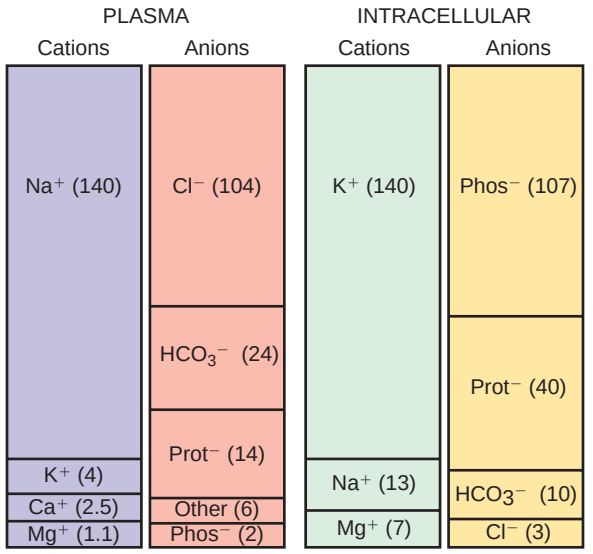

Figure 55-3 The concentrations of the major cations and anions in the intracellular space and the plasma, expressed in mEq/L.

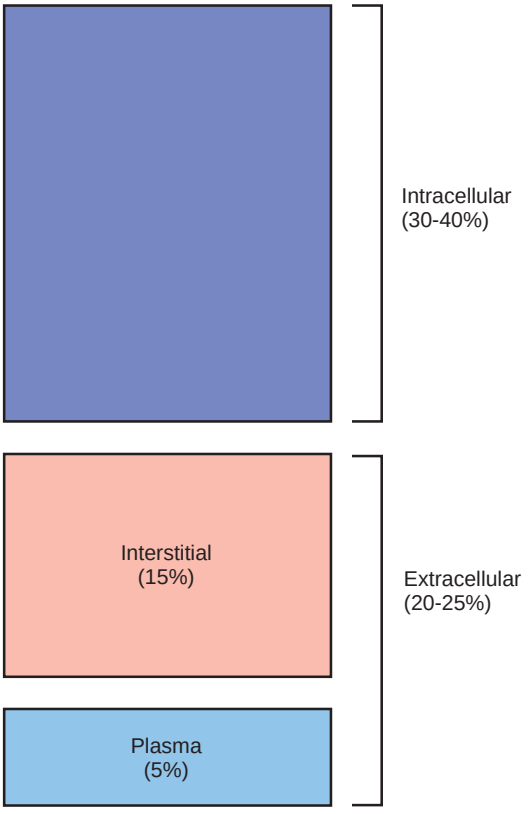

Figure 55-2 Compartments of total body water, expressed as percentages of body weight, in an older child or adult.

OSMOLALITY

The ICF and the ECF are in **osmotic equilibrium** because the cell membrane is permeable to water. If the osmolality in 1 compartment changes, then water movement leads to a rapid equalization of osmolality. This can lead to significant shifts of water between the intracellular space and the extracellular space. Clinically, the primary process is usually a change in the osmolality of the ECF, with a resultant shift of water into the ICF if the ECF osmolality decreases or a shift of water out of the ICF if the ECF osmolality increases. *The osmolality of the ECF can be determined, and it usually equals the ICF osmolality*. The plasma osmolality is normally 285-295 mOsm/kg, and it is measured by the degree of freezing point depression. The plasma osmolality can also be *estimated* by a calculation based on the following formula:

$$\text{Osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18 + [\text{BUN}]/2.8$$

Glucose and blood urea nitrogen (BUN) are measured in mg/dL. Division of these values by 18 and 2.8, respectively, as shown, converts the units into mmol/L. Multiplication of the sodium value by 2 accounts for its accompanying anions, principally chloride and bicarbonate. The calculated osmolality is usually slightly lower than the measured osmolality.

Glucose and urea normally contribute little to the plasma osmolality; multiplication of the sodium value by 2 provides an approximation of the osmolality. Urea is not confined to the extracellular space because it readily crosses the cell membrane and its intracellular concentration approximately equals its extracellular concentration. Whereas an elevated sodium concentration causes a shift of water from the intracellular space, with uremia, there is no osmolar gradient between the 2 compartments and, consequently, no movement of water. The only exception is during **hemodialysis,** when the decrease in extracellular urea is so rapid that the intracellular urea does not have time to equilibrate. This may lead to the **disequilibrium syndrome,** in which water shifts into brain cells, potentially causing severe symptoms. Ethanol, because it freely crosses cell membranes, is another ineffective osmole. The effective osmolality can be calculated as follows:

$$\text{Effective osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18$$

The effective osmolality (also called the tonicity) determines the osmotic force that is mediating the shift of water between the ECF and the ICF.

Hyperglycemia causes an increase in the plasma osmolality because it is not in equilibrium with the intracellular space. During hyperglycemia there is a shift of water from the intracellular space to the extracellular space. This is clinically important in children with hyperglycemia during diabetic ketoacidosis. The shift of water causes dilution of the sodium in the extracellular space, causing hyponatremia despite an elevated plasma osmolality. The magnitude of this effect can be calculated as follows:

$$[\text{Na}]_{\text{corrected}} = [\text{Na}]_{\text{measured}} + 1.6 \times ([\text{glucose}] - 100\ \text{mg/dL})/100$$

where $[Na]_{measured}$ = sodium concentration measured by the clinical laboratory and $[Na]_{corrected}$ = corrected sodium concentration (the

sodium concentration if the glucose concentration were normal and its accompanying water moved back into the cells). The $[Na]_{corrected}$ is the more reliable indicator of the patient's true ratio of total body sodium to TBW, the normal determinant of the sodium concentration.

Normally, the measured osmolality and the calculated osmolality are within 10 mOsm/kg. However, there are some clinical situations in which this does not occur. The presence of **unmeasured osmoles** causes the measured osmolality to be significantly elevated in comparison with the calculated osmolality. This difference is the **osmolal gap,** which is present when the measured osmolality exceeds the calculated osmolality by >10 mOsm/kg. Examples of unmeasured osmoles include ethanol, ethylene glycol, methanol, sucrose, sorbitol, and mannitol. These substances increase the measured osmolality but are not part of the equation for calculating osmolality. The presence of an osmolal gap is a clinical clue to the presence of unmeasured osmoles and may be diagnostically useful when there is clinical suspicion of poisoning with methanol or ethylene glycol.

Pseudohyponatremia is a second situation in which there is discordance between the measured osmolality and the calculated osmolality. Lipids and proteins are the solids of the serum. In patients with elevated serum lipids or proteins, the water content of the serum decreases because water is displaced by the larger amount of solids. Some instruments measure sodium concentration by determining the amount of sodium per liter of serum, including the solid component. When the solid component increases, there is a decrease in the sodium concentration per liter of serum, despite a normal concentration of sodium when based on the amount of sodium per liter of serum water. *It is the concentration of sodium in serum water that is physiologically relevant.* A similar problem occurs when using instruments that require dilution of the sample prior to measurement of sodium (indirect potentiometry). In both situations, the plasma osmolality is normal despite the presence of pseudohyponatremia, because the method for measuring osmolality is not appreciably influenced by the percentage of serum that is composed of lipids and proteins. Pseudohyponatremia is diagnosed by the finding of a normal measured plasma osmolality despite hyponatremia. This laboratory artifact does not occur if the sodium concentration in water is measured directly with an ion-specific electrode, such as occurs with the instruments used for measuring arterial blood gases. **Pseudohypernatremia** may occur in patients with very low levels of serum proteins via a similar mechanism.

When there are no unmeasured osmoles and pseudohyponatremia is not a concern, the calculated osmolality provides an accurate estimate of the plasma osmolality. Measurement of plasma osmolality is useful for detecting or monitoring unmeasured osmoles and confirming the presence of true hyponatremia. Whereas many children with high plasma osmolality are dehydrated—as seen with hypernatremic dehydration or diabetic ketoacidosis—high osmolality does not always equate with dehydration. A child with **salt poisoning** or **uremia** has an elevated plasma osmolality but may be volume overloaded. In many situations, it is best to focus on the components of the plasma osmolality and to analyze them individually to reach a correct clinical conclusion.

Bibliography is available at Expert Consult.

55.2 Regulation of Osmolality and Volume

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The regulation of plasma *osmolality* and the intravascular *volume* is controlled by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Maintenance of normal osmolality depends on control of water balance. Control of volume status depends on regulation of sodium balance. When volume depletion is present, it takes precedence over regulation of osmolality, and retention of water contributes to the maintenance of intravascular volume.

REGULATION OF OSMOLALITY

The plasma osmolality is tightly regulated and maintained at 285-295 mOsm/kg. Modification of water intake and excretion maintains normal plasma osmolality. In the steady state, the combination of water intake and water produced by the body from oxidation balances water losses from the skin, lungs, urine, and gastrointestinal tract. Only water intake and urinary losses can be regulated.

Osmoreceptors in the hypothalamus sense the plasma osmolality (see Chapter 556). An elevated effective osmolality leads to secretion of antidiuretic hormone (ADH) by neurons in the supraoptic and paraventricular nuclei in the hypothalamus. The axons of these neurons terminate in the posterior pituitary. Circulating ADH binds to its V_2 receptors in the collecting duct cells of the kidney, and, via the generation of cyclic adenosine monophosphate, causes insertion of water channels (aquaporin-2) into the renal collecting ducts. This produces increased permeability to water, permitting resorption of water into the hypertonic renal medulla. The end result is that the urine concentration increases and water excretion decreases. Urinary water losses cannot be completely eliminated because there is obligatory excretion of urinary solutes, such as urea and sodium. The regulation of ADH secretion is tightly linked to plasma osmolality, responses being detectable with a 1% change in the osmolality. ADH secretion virtually disappears when the plasma osmolality is low, allowing excretion of maximally dilute urine. The consequent loss of **free water** (water without sodium) corrects the plasma osmolality. ADH secretion is not an all-or-nothing response; there is a graded adjustment as the osmolality changes.

Production of concentrated urine under the control of ADH requires a hypertonic renal medulla. The countercurrent multiplier, produced by the loop of Henle and the vasa recta, generates this hypertonicity. ADH stimulates sodium transport in the loop of Henle, helping to maintain this gradient when water retention is necessary.

Water intake is regulated by hypothalamic osmoreceptors, although these are different from the osmoreceptors that determine ADH secretion. These hypothalamic osmoreceptors, by linking to the cerebral cortex, stimulate thirst when the serum osmolality increases. Thirst occurs with a small increase in the serum osmolality.

Control of osmolality is subordinate to maintenance of an adequate intravascular volume. When volume depletion is present, both ADH secretion and thirst are stimulated, regardless of the plasma osmolality. The sensation of thirst requires moderate volume depletion but only a 1-2% change in the plasma osmolality. Although all of the mechanisms are not clear, angiotensin II, which is increased during volume depletion, is known to stimulate thirst. Baroreceptors, when sensing volume depletion, may also stimulate thirst.

A number of conditions can limit the kidney's ability to excrete adequate water to correct low plasma osmolality. In the **syndrome of inappropriate antidiuretic hormone (SIADH),** ADH continues to be produced despite a low plasma osmolality. In the presence of ADH, urinary dilution does not occur, and sufficient water is not excreted (see Chapters 55.3 and 559).

The glomerular filtration rate (GFR) affects the kidney's ability to eliminate water. With a decrease in the GFR, less water is delivered to the collecting duct, limiting the amount of water that can be excreted. The impairment in the GFR must be quite significant to limit the kidney's ability to respond to an excess of water.

The **minimum urine osmolality** is approximately 30-50 mOsm/kg. This places an upper limit on the kidney's ability to excrete water; sufficient solute must be present to permit water loss. Massive water intoxication may exceed this limit, whereas a lesser amount of water is necessary in the child with a diet that has very little solute. This is occasionally seen and can produce severe hyponatremia in children who receive little salt and have little urea production as a result of inadequate protein intake. Volume depletion is an extremely important cause of decreased water loss by the kidney despite a low plasma osmolality. This "appropriate" secretion of ADH occurs because volume depletion takes precedence over the osmolality in the regulation of ADH.

The normal response to increased plasma osmolality is conservation of water by the kidney. In **central diabetes insipidus,** this does not

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occur because of an absence of ADH secretion (see Chapters 55.3 and 558). Patients with **nephrogenic diabetes insipidus** have an inability to respond to ADH and produce dilute urine despite an increase in plasma osmolality (see Chapters 55.3 and 530).

The **maximum urine osmolality** is approximately 1,200 mOsm/kg. The obligatory solute losses dictate the minimum volume of urine that must be produced, even when maximally concentrated. Obligatory water losses increase in patients with high salt intake or high urea losses, as may occur after relief of a urinary obstruction or during recovery from acute tubular necrosis. An increase in urinary solute and, consequently, water losses occurs with an **osmotic diuresis,** which occurs classically from glycosuria in diabetes mellitus as well as iatrogenically after mannitol administration. There are developmental changes in the kidney's ability to concentrate the urine. The maximum urine osmolality in a newborn, especially a premature newborn, is less than that in an older infant or child. This limits the ability to conserve water and makes such a patient more vulnerable to hypernatremic dehydration. Very high fluid intake, as seen with **psychogenic polydipsia,** can dilute the high osmolality in the renal medulla, which is necessary for maximal urinary concentration. If fluid intake is restricted in patients with this condition, there may be some impairment in the kidney's ability to concentrate the urine, although this defect corrects after a few days without polydipsia. This may also occur during the initial treatment of central diabetes insipidus with desmopressin acetate; the renal medulla takes time to achieve its normal maximum osmolality. Loop diuretics, such as furosemide, by inhibiting sodium resorption in the ascending limb of the loop of Henle, decrease medullary hypertonicity, preventing excretion of maximally concentrated urine.

REGULATION OF VOLUME

An appropriate intravascular volume is critical for survival; both volume depletion and volume overload may cause significant morbidity and mortality. Because sodium is the principal extracellular cation and it is restricted to the ECF, adequate body sodium is necessary for maintenance of intravascular volume. The principal extracellular anion, chloride, is also necessary, but for simplicity, sodium balance is considered the main regulator of volume status because body content of sodium and that of chloride usually change proportionally, given the need for equal numbers of cations and anions. In some situations, chloride depletion is considered the dominant derangement causing volume depletion (metabolic alkalosis with volume depletion). In other situations, such as volume depletion with metabolic acidosis, sodium depletion may exceed chloride depletion.

The kidney determines sodium balance because there is little homeostatic control of sodium intake, even though salt craving does occasionally occur, typically in children with chronic renal salt loss. The kidney regulates sodium balance by altering the percentage of filtered sodium that is resorbed along the nephron. Normally, the kidney excretes <1% of the sodium filtered at the glomerulus. In the absence of disease, extrarenal losses and urinary output match intake, with the kidney having the capacity to adapt to large variations in sodium intake. When necessary, urinary sodium excretion can be reduced to virtually undetectable levels or increased dramatically.

Urinary sodium excretion is regulated by both intrarenal and extrarenal mechanisms. The most important determinant of renal sodium excretion is the volume status of the child; it is the effective intravascular volume that influences urinary sodium excretion. The effective intravascular volume is the volume status that is sensed by the body's regulatory mechanisms. Heart failure is a state of volume overload, but the effective intravascular volume is low because poor cardiac function prevents adequate perfusion of the kidneys and other organs. This fact explains the avid renal sodium retention that is often present in patients with heart failure.

Sodium resorption occurs throughout the nephron. Whereas the majority of filtered sodium is resorbed in the proximal tubule and the loop of Henle, the distal tubule and the collecting duct are the main sites for precise regulation of sodium balance. Approximately 65% of the filtered sodium is reclaimed in the proximal tubule, which is the major site for resorption of bicarbonate, glucose, phosphate, amino acids, and other substances that are filtered by the glomerulus. The transport of all these substances is linked to sodium resorption by cotransporters, or a sodium-hydrogen exchanger in the case of bicarbonate. This link is clinically important for bicarbonate and phosphate because their resorption parallels sodium resorption. In patients with **metabolic alkalosis and volume depletion**, correction of the metabolic alkalosis requires urinary loss of bicarbonate, but the volume depletion stimulates sodium and bicarbonate retention, preventing correction of the alkalosis. Volume expansion causes increased urinary losses of phosphate, even when there is phosphate depletion. Resorption of uric acid and urea occurs in the proximal tubule and increases when sodium retention increases. This arrangement accounts for the elevated uric acid and BUN measurements that often accompany dehydration, which is a stimulus for sodium retention in the proximal tubule. The cells of the proximal tubule are permeable to water; thus, water resorption in this segment parallels sodium resorption.

The loop of Henle is, in terms of absolute amount, the second most important site of sodium resorption along the nephron. The Na^+,K^+,$2Cl^-$ cotransporter on the luminal side of the membrane reclaims filtered sodium and chloride, whereas most of the potassium is recycled back into the lumen. This is the transporter that is inhibited by furosemide and other loop diuretics, which are highly effective at increasing sodium excretion. The ascending limb of the loop of Henle is not permeable to water, permitting sodium retention without water. ADH stimulates sodium retention in this segment; this arrangement helps create a more hypertonic medulla, which maximizes water conservation when ADH acts in the medullary collecting duct. Because loop diuretics inhibit sodium retention in this segment, their use causes a less hypertonic medulla, preventing excretion of maximally concentrated urine in the presence of ADH.

Sodium retention in the distal tubule is mediated by the thiazide-sensitive Na^+,Cl^- cotransporter. This segment of the nephron is relatively impermeable to water, and along with sodium and chloride retention, the distal tubule is important for delivery of fluid with a low sodium concentration to the collecting duct. This allows for excretion of water without sodium in patients who stop secreting ADH because of low plasma osmolality. Thiazide diuretics, by inhibiting sodium and chloride retention in this segment, prevent the excretion of water without electrolytes—partially explaining the severe hyponatremia that occasionally develops in patients receiving chronic thiazide diuretics.

The collecting duct, the final segment of the nephron, is important for the regulation of excretion of water, potassium, acid, and sodium. Even though the amount of sodium resorbed in this segment is less than in any other segment, this is the critical site for the regulation of sodium balance. Sodium resorption occurs via a sodium channel that is regulated by aldosterone. When these channels are open under the influence of aldosterone, almost all of the sodium can be resorbed. The uptake of sodium creates a negative charge in the lumen of the collecting duct, which facilitates the secretion of potassium and hydrogen ions. The potassium-sparing diuretics amiloride and triamterene block these sodium channels, and the inhibition of sodium uptake decreases potassium excretion. The potassium-sparing diuretic spironolactone blocks the binding of aldosterone to its receptor; thus, it indirectly decreases the activity of the sodium channels. The collecting duct is important for the regulation of water balance because it responds to ADH by inserting water channels that increase the permeability to water, and the hypertonicity of the renal medulla allows for maximal concentration of the urine.

The amount of sodium filtered at the glomerulus is directly proportional to the GFR. If sodium resorption in the nephron were constant, complete resorption of sodium with a small decrease in the GFR and significant renal sodium wasting with a small increase would result. This does not occur, however, because sodium resorption in the nephron is proportional to sodium delivery, a principle called **glomerular tubular balance.**

The **renin–angiotensin system** is an important regulator of renal sodium excretion. The juxtaglomerular apparatus produces renin in

response to decreased effective intravascular volume. Specific stimuli for renin release are decreased perfusion pressure in the afferent arteriole of the glomerulus, decreased delivery of sodium to the distal nephron, and β_1-adrenergic agonists, which increase in response to intravascular volume depletion. Renin, a proteolytic enzyme, cleaves angiotensinogen, producing angiotensin I. Angiotensin-converting enzyme converts angiotensin I into angiotensin II. The actions of angiotensin II include direct stimulation of the proximal tubule to increase sodium resorption and stimulation of the adrenal gland to increase aldosterone secretion. Through its actions in the distal nephron—specifically, the late distal convoluted tubule and the collecting duct—aldosterone increases sodium resorption. Aldosterone also stimulates potassium excretion, increasing urinary losses. Along with decreasing urinary loss of sodium, angiotensin II acts as a vasoconstrictor, which helps maintain adequate blood pressure in the presence of volume depletion.

Volume expansion stimulates the synthesis of atrial natriuretic peptide, which is produced by the atria in response to atrial wall distention. Along with increasing the GFR, atrial natriuretic peptide inhibits sodium resorption in the medullary portion of the collecting duct, facilitating an increase in urinary sodium excretion.

Volume overload occurs when sodium intake exceeds output. In children with kidney failure, there is an impaired ability to excrete sodium. This impairment tends to be proportional to the decrease in the GFR, although in some kidney diseases, such as renal dysplasia and juvenile nephronophthisis, damaged tubules cause significant sodium loss until the GFR is quite low. In general, as the GFR decreases, restriction of sodium intake becomes increasingly necessary. The GFR is low at birth, limiting a newborn's ability to excrete a sodium load. In other situations, there is a loss of the appropriate regulation of renal sodium excretion. This loss occurs in patients with excessive aldosterone, as is seen in primary hyperaldosteronism or renal artery stenosis, wherein excess renin production leads to high aldosterone levels. In acute glomerulonephritis, even without significantly reduced GFR, the normal intrarenal mechanisms that regulate sodium excretion malfunction, causing excessive renal retention of sodium and volume overload.

Renal retention of sodium occurs during volume depletion, but this appropriate response causes the severe excess in total body sodium that is present in heart failure, liver failure, nephrotic syndrome, and other causes of hypoalbuminemia. In these diseases, the effective intravascular volume is decreased, causing the kidney and the various regulatory systems to respond, leading to renal sodium retention and edema formation.

Volume depletion usually occurs when sodium losses exceed intake. The most common etiology in children is gastroenteritis. Excessive losses of sodium may also occur from the skin in children with burns, in sweat from patients with cystic fibrosis, or after vigorous exercise. Inadequate intake of sodium is uncommon except in neglect, in famine, or with an inappropriate choice of liquid diet in a child who cannot take solids. Urinary sodium wasting may occur in a range of renal diseases, from renal dysplasia to tubular disorders, such as Bartter syndrome. The neonate, especially if premature, has a mild impairment in the ability to conserve sodium. Iatrogenic renal sodium wasting takes place during diuretic therapy. Renal sodium loss occurs as a result of derangement in the normal regulatory systems. An absence of aldosterone, seen most commonly in children with **congenital adrenal hyperplasia** caused by 21-hydroxylase deficiency, causes sodium wasting (see Chapter 576).

Isolated disorders of water balance can affect volume status and sodium balance. Because the cell membrane is permeable to water, changes in TBW influence both the extracellular volume and the intracellular volume. In isolated water loss, as occurs in diabetes insipidus, the impact is greater on the intracellular space because of its higher volume compared with the extracellular space. This is why, in comparison with other types of dehydration, hypernatremic dehydration has less impact on plasma volume; most of the fluid loss comes from the intracellular space. Yet, significant water loss eventually affects intravascular volume and will stimulate renal sodium retention, even if total body sodium content is normal. Similarly, with acute water intoxication or SIADH, there is an excess of TBW, but most is in the intracellular space. However, there is some effect on the intravascular volume, which causes renal excretion of sodium. Children with SIADH or water intoxication have high urine sodium concentrations, despite hyponatremia. This finding reinforces the concept that there are independent control systems for water and sodium, yet the 2 systems interact when pathophysiologic processes dictate, and control of effective intravascular volume always takes precedence over control of osmolality.

Bibliography is available at Expert Consult.

55.3 Sodium

Larry A. Greenbaum

SODIUM METABOLISM

Body Content and Physiologic Function

Sodium is the dominant cation of the ECF (see Fig. 55-3), and it is the principal determinant of extracellular osmolality. Sodium is therefore necessary for the maintenance of intravascular volume. Less than 3% of sodium is intracellular. More than 40% of total body sodium is in bone; the remainder is in the interstitial and intravascular spaces. The low intracellular sodium concentration, approximately 10 mEq/L, is maintained by Na^+,K^+-ATPase, which exchanges intracellular sodium for extracellular potassium.

Intake

A child's diet determines the amount of sodium ingested—a predominantly cultural determination in older children. An occasional child has salt craving because of an underlying salt-wasting renal disease or adrenal insufficiency. Children in the United States tend to have very high sodium intakes because their diets include a large amount of "junk" food or fast food. Infants receive sodium from breast milk (≈7 mEq/L) and formula (7-13 mEq/L, for 20 calorie/oz formula).

Sodium is readily absorbed throughout the gastrointestinal tract. Mineralocorticoids increase sodium transport into the body, although this effect has limited clinical significance. The presence of glucose enhances sodium absorption owing to the presence of a cotransport system. This is the rationale for including sodium and glucose in oral rehydration solutions (see Chapter 340).

Excretion

Sodium excretion occurs in stool and sweat, but the kidney regulates sodium balance and is the principal site of sodium excretion. There is some sodium loss in stool, but it is minimal unless diarrhea is present. Normally, sweat has 5-40 mEq/L of sodium. Sweat sodium concentration is increased in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism. The higher sweat losses in these conditions may cause or contribute to sodium depletion.

Sodium is unique among electrolytes because water balance, not sodium balance, usually determines its concentration. When the sodium concentration increases, the resultant higher plasma osmolality causes increased thirst and increased secretion of ADH, which leads to renal conservation of water. Both of these mechanisms increase the water content of the body, and the sodium concentration returns to normal. During hyponatremia, the decrease in plasma osmolality stops ADH secretion, and consequent renal water excretion leads to an increase in the sodium concentration. Even though water balance is usually regulated by osmolality, volume depletion does stimulate thirst, ADH secretion, and renal conservation of water. Volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.

The excretion of sodium by the kidney is not regulated by the plasma osmolality. The patient's effective plasma volume determines the amount of sodium in the urine. This is mediated by a variety of regulatory systems, including the renin–angiotensin–aldosterone system and

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intrarenal mechanisms. In hyponatremia or hypernatremia, the underlying pathophysiology determines the amount of urinary sodium, not the serum sodium concentration.

HYPERNATREMIA

Hypernatremia is a sodium concentration >145 mEq/L, although it is sometimes defined as >150 mEq/L. Mild hypernatremia is fairly common in children, especially among infants with gastroenteritis. Hypernatremia in hospitalized patients may be iatrogenic—caused by inadequate water administration or, less often, by excessive sodium administration. Moderate or severe hypernatremia has significant morbidity, including the result of underlying disease, the effects of hypernatremia on the brain, and the risks of overly rapid correction.

Etiology and Pathophysiology

There are 3 basic mechanisms of hypernatremia (Table 55-1). Sodium intoxication is frequently iatrogenic in a hospital setting as a result of correction of metabolic acidosis with sodium bicarbonate. Baking soda, a putative home remedy for upset stomach, is another source of sodium bicarbonate; the hypernatremia is accompanied by a profound metabolic alkalosis. In hyperaldosteronism, there is renal retention of sodium and resultant hypertension; hypernatremia may not be present or is usually mild.

Table 55-1 Causes of Hypernatremia

EXCESSIVE SODIUM
Improperly mixed formula
Excess sodium bicarbonate
Ingestion of seawater or sodium chloride
Intentional salt poisoning (child abuse or Munchausen syndrome by proxy)
Intravenous hypertonic saline
Hyperaldosteronism
WATER DEFICIT
Nephrogenic diabetes insipidus
Acquired
X-linked (OMIM 304800)
Autosomal recessive (OMIM 222000)
Autosomal dominant (OMIM 125800)
Central diabetes insipidus
Acquired
Autosomal recessive (OMIM 125700)
Autosomal dominant (OMIM 125700)
Wolfram syndrome (OMIM 222300/598500)
Increased insensible losses
Premature infants
Radiant warmers
Phototherapy
Inadequate intake:
Ineffective breastfeeding
Child neglect or abuse
Adipsia (lack of thirst)
WATER AND SODIUM DEFICITS
Gastrointestinal losses
Diarrhea
Emesis/nasogastric suction
Osmotic cathartics (lactulose)
Cutaneous losses
Burns
Excessive sweating
Renal losses
Osmotic diuretics (mannitol)
Diabetes mellitus
Chronic kidney disease (dysplasia and obstructive uropathy)
Polyuric phase of acute tubular necrosis
Postobstructive diuresis

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

The classic causes of hypernatremia from a water deficit are **nephrogenic** and **central diabetes insipidus** (see Chapters 530 and 558). Hypernatremia develops in diabetes insipidus only if the patient does not have access to water or cannot drink adequately because of immaturity, neurologic impairment, emesis, or anorexia. Infants are at high risk because of their inability to control their own water intake. Central diabetes insipidus and the genetic forms of nephrogenic diabetes insipidus typically cause massive urinary water losses and very dilute urine. The water losses are less dramatic, and the urine often has the same osmolality as plasma when nephrogenic diabetes insipidus is secondary to intrinsic renal disease (obstructive uropathy, renal dysplasia, sickle cell disease).

The other causes of a water deficit are also secondary to an imbalance between losses and intake. Newborns, especially if premature, have high insensible water losses. Losses are further increased if the infant is placed under a radiant warmer or with the use of phototherapy for hyperbilirubinemia. The renal concentrating mechanisms are not optimal at birth, providing an additional source of water loss. Ineffective breastfeeding, often in a primiparous mother, can cause severe hypernatremic dehydration. Adipsia, the absence of thirst, is usually secondary to damage to the hypothalamus, such as from trauma, tumor, hydrocephalus, or histiocytosis. Primary adipsia is rare.

When hypernatremia occurs in conditions with deficits of sodium and water, the water deficit exceeds the sodium deficit. This occurs only if the patient is unable to ingest adequate water. Diarrhea results in depletion of both sodium and water. Because diarrhea is hypotonic—typical sodium concentration of 35-65 mEq/L—water losses exceed sodium losses, potentially leading to hypernatremia. Most children with gastroenteritis do not have hypernatremia because they drink enough hypotonic fluid to compensate for stool water losses (see Chapter 340). Fluids such as water, juice, and formula are more hypotonic than the stool losses, allowing correction of the water deficit and potentially even causing hyponatremia. Hypernatremia is most likely to occur in the child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia.

Osmotic agents, including mannitol and glucose in diabetes mellitus, cause excessive renal losses of water and sodium. Because the urine is hypotonic (sodium concentration of approximately 50 mEq/L) during an osmotic diuresis, water loss exceeds sodium loss and hypernatremia may occur if water intake is inadequate. Certain chronic kidney diseases, such as renal dysplasia and obstructive uropathy, are associated with tubular dysfunction, leading to excessive losses of water and sodium. Many children with such diseases have disproportionate water loss and are at risk for hypernatremic dehydration, especially if gastroenteritis supervenes. Similar mechanisms occur during the polyuric phase of acute tubular necrosis and after relief of urinary obstruction (postobstructive diuresis). Patients with either condition may have an osmotic diuresis from urinary losses of urea and an inability to conserve water because of tubular dysfunction.

Clinical Manifestations

Most children with hypernatremia are dehydrated and show the typical clinical signs and symptoms (see Chapter 57). Children with hypernatremic dehydration tend to have better preservation of intravascular volume because of the shift of water from the intracellular space to the extracellular space. This shift maintains blood pressure and urine output and allows hypernatremic infants to be less symptomatic initially and potentially to become more dehydrated before medical attention is sought. Breastfed infants with hypernatremia are often profoundly dehydrated, with failure to thrive. Probably because of intracellular water loss, the pinched abdominal skin of a dehydrated, hypernatremic infant has a "doughy" feel.

Hypernatremia, even without dehydration, causes central nervous system (CNS) symptoms that tend to parallel the degree of sodium elevation and the acuity of the increase. Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperpnea. Alert patients are very thirsty, even though nausea may be present. Hypernatremia may cause fever, although many patients have

an underlying process that contributes to the fever. Hypernatremia is associated with hyperglycemia and mild hypocalcemia; the mechanisms are unknown. Beyond the sequelae of dehydration, there is no clear direct effect of hypernatremia on other organs or tissues, except the brain.

Brain hemorrhage is the most devastating consequence of untreated hypernatremia. As the extracellular osmolality increases, water moves out of brain cells, leading to a decrease in brain volume. This decrease can result in tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges. Patients may have subarachnoid, subdural, and parenchymal hemorrhages. Seizures and coma are possible sequelae of the hemorrhage, although seizures are more common during correction of hypernatremia. The cerebrospinal fluid protein is often elevated in infants with significant hypernatremia, probably owing to leakage from damaged blood vessels. Neonates, especially if premature, seem especially vulnerable to hypernatremia and excessive sodium intake. There is an association between rapid or hyperosmolar sodium bicarbonate administration and the development of intraventricular hemorrhages in neonates. Even though central pontine myelinolysis (CPM) is classically associated with overly rapid correction of hyponatremia, both CPM and extrapontine myelinolysis can occur in children with hypernatremia. Thrombotic complications occur in severe hypernatremic dehydration; they include stroke, dural sinus thrombosis, peripheral thrombosis, and renal vein thrombosis. This is secondary to dehydration and possibly hypercoagulability associated with hypernatremia.

Diagnosis

The etiology of hypernatremia is usually apparent from the history. Hypernatremia resulting from water loss occurs only if the patient does not have access to water or is unable to drink. In the absence of dehydration, it is important to ask about sodium intake. Children with excess sodium intake do not have signs of dehydration, unless another process is present. Severe sodium intoxication causes signs of volume overload, such as pulmonary edema and weight gain. **Salt poisoning** is associated with an elevated fractional excretion of sodium, whereas hypernatremic dehydration causes a low fractional excretion of sodium. In hyperaldosteronism, hypernatremia is usually mild or absent and is associated with edema, hypertension, hypokalemia, and metabolic alkalosis.

When there is isolated water loss, the signs of volume depletion are usually less severe initially because much of the loss is from the intracellular space. When pure water loss causes signs of dehydration, the hypernatremia and water deficit are usually severe. In the child with renal water loss, either central or nephrogenic diabetes insipidus, the urine is inappropriately dilute and urine volume is not low. The urine is maximally concentrated and urine volume is low if the losses are extrarenal or due to inadequate intake. With extrarenal causes of loss of water, the urine osmolality should be >1,000 mOsm/kg. When diabetes insipidus is suspected, the evaluation may include measurement of ADH and a water deprivation test, including a trial of desmopressin acetate (synthetic ADH analog) to differentiate between nephrogenic diabetes insipidus and central diabetes insipidus (see Chapters 530 and 558). A water-deprivation test is unnecessary if the patient has simultaneous documentation of hypernatremia and poorly concentrated urine (osmolality lower than that of plasma). In children with central diabetes insipidus, administration of desmopressin acetate increases the urine osmolality above the plasma osmolality, although maximum osmolality does not occur immediately because of the decreased osmolality of the renal medulla as a result of the chronic lack of ADH. In children with nephrogenic diabetes insipidus, there is no response to desmopressin acetate.

With combined sodium and water deficits, analysis of the urine differentiates between renal and nonrenal etiologies. When the losses are extrarenal, the kidney responds to volume depletion with low urine volume, concentrated urine, and sodium retention (urine sodium <20 mEq/L, fractional excretion of sodium <1%). With renal causes, the urine volume is not appropriately low, the urine is not maximally concentrated, and the urine sodium may be inappropriately elevated.

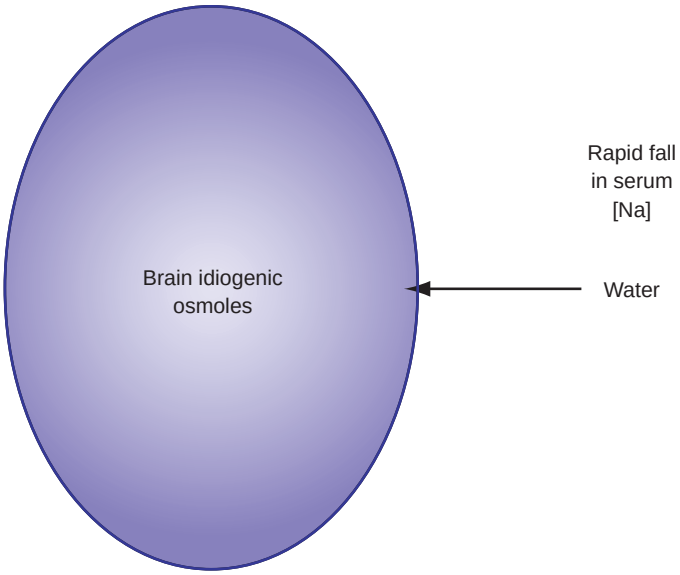

Figure 55-4 Mechanism of brain edema during correction of hypernatremia. A rapid decrease of the serum concentration during treatment of hypernatremia causes movement of water into brain cells, leading to cerebral edema. The presence of idiogenic osmoles in brain cells is responsible for the osmotic gradient.

Treatment

As hypernatremia develops, the brain generates **idiogenic osmoles** to increase the intracellular osmolality and prevent the loss of brain water. This mechanism is not instantaneous and is most prominent when hypernatremia has developed gradually. If the serum sodium concentration is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the 2 compartments (Fig. 55-4). The resultant brain swelling manifests as seizures or coma.

Because of the associated dangers, hypernatremia should not be corrected rapidly. The goal is to decrease the serum sodium by <12 mEq/L every 24 hr, a rate of 0.5 mEq/L/hr. The most important component of correcting moderate or severe hypernatremia is frequent monitoring of the serum sodium value so that fluid therapy can be adjusted to provide adequate correction, neither too slow nor too fast. If a child has seizures as a result of brain edema secondary to rapid correction, administration of hypotonic fluid should be stopped. An infusion of 3% saline can acutely increase the serum sodium, reversing the cerebral edema.

In the child with hypernatremic dehydration, as in any child with dehydration, the **first priority is restoration of intravascular volume** with isotonic fluid (see Chapter 57). Normal saline is preferable to lactated Ringer solution because the lower sodium concentration of the latter can cause the serum sodium to decrease too rapidly, especially if multiple fluid boluses are given. Repeated boluses of normal saline (10-20 mL/kg) may be required to treat hypotension, tachycardia, and signs of poor perfusion (peripheral pulses, capillary refill time) (see Chapters 57 and 70).

The sodium concentration of the deficit replacement fluid, the rate of fluid administration, and the presence of continued water losses determine the rate of decrease of the sodium concentration. The following formula is often cited for calculating the water deficit:

$$\text{Water deficit} = \text{Body weight} \times 0.6(1\text{-}145)/[\text{current sodium}])$$

This calculation is equivalent to 3-4 mL of water per kg for each 1 mEq that the current sodium level exceeds 145 mEq. The utility of such formulas has never been proven in clinical practice. Most patients with hypernatremic dehydration do well with a fluid sodium concentration of approximately half-normal saline, but with a fluid rate that is only 20-30% greater than maintenance fluid. Use of this

concentration prevents excessive delivery of free water and too rapid a decrease in the serum sodium level. Patients with pure water loss may require a more hypotonic fluid (0.2 normal saline). Excessive water and sodium losses may also need to be replaced. If signs or symptoms of volume depletion develop, the patient receives additional boluses of isotonic saline. Monitoring of the rate of decrease of the serum sodium concentration permits adjustment in the rate and sodium concentration of the fluid that the patient is receiving, avoiding overly rapid correction of the hypernatremia (see Chapter 57 for additional details). Many patients with mild to moderate hypernatremic dehydration as a result of gastroenteritis can be managed with oral rehydration (see Chapter 340).

Acute, severe hypernatremia, usually secondary to sodium administration, can be corrected more rapidly because idiogenic osmoles have not had time to accumulate. This fact balances the high morbidity and mortality rates associated with hypernatremia with the dangers of overly rapid correction. When hypernatremia is severe and is caused by sodium intoxication, it may be impossible to administer enough water to correct the hypernatremia rapidly without worsening the volume overload. In this situation, dialysis allows for removal of the excess sodium, with the precise strategy dependent on the mode of dialysis. In less-severe cases, the addition of a loop diuretic increases the removal of excess sodium and water, decreasing the risk of volume overload. With sodium overload, hypernatremia is corrected with sodium-free intravenous fluid (5% dextrose in water).

Hyperglycemia from hypernatremia is not usually a problem and is not treated with insulin because the acute decrease in glucose may precipitate cerebral edema by lowering plasma osmolality. Rarely, the glucose concentration of intravenous fluids must be reduced (from 5% dextrose in water to 2.5% dextrose in water). The secondary hypocalcemia is treated as needed.

It is important to address the underlying cause of the hypernatremia, if possible. The child with central diabetes insipidus should receive desmopressin acetate. Because this treatment reduces renal excretion of water, excessive intake of water must consequently be avoided to prevent both overly rapid correction of the hypernatremia and the development of hyponatremia. Over the long-term, reduced sodium intake and the use of medications can somewhat ameliorate the water losses in nephrogenic diabetes insipidus (see Chapter 530). The daily water intake of a child who is receiving tube feeding may need to be increased to compensate for high losses. The patient with significant ongoing losses, such as through diarrhea, may need supplemental water and electrolytes (see Chapter 56). Sodium intake is reduced if it contributed to the hypernatremia.

HYPONATREMIA

Hyponatremia, a very common electrolyte abnormality in hospitalized patients, is a serum sodium level <135 mEq/L. Both total body sodium and TBW determine the serum sodium concentration. Hyponatremia exists when the ratio of water to sodium is increased. This condition can occur with low, normal, or high levels of body sodium. Similarly, body water can be low, normal, or high.

Etiology and Pathophysiology

Table 55-2 lists the causes of hyponatremia. Pseudohyponatremia is a laboratory artifact that is present when the plasma contains very high concentrations of protein (multiple myeloma, intravenous immunoglobulin infusion) or lipid (hypertriglyceridemia, hypercholesterolemia). It does not occur when a direct ion-selective electrode determines the sodium concentration in undiluted plasma, a technique that is used by arterial blood gas analyzers or point-of-care instruments. In true hyponatremia, the measured osmolality is low, whereas it is normal in pseudohyponatremia. Hyperosmolality, as may occur with hyperglycemia, causes a low serum sodium concentration because water moves down its osmotic gradient from the intracellular space into the extracellular space, diluting the sodium concentration. However, because the manifestations of hyponatremia are a result of the low plasma osmolality, patients with hyponatremia resulting from hyperosmolality do not have symptoms of hyponatremia. When the etiology of the hyperosmolality resolves, such as hyperglycemia in diabetes mellitus, water moves back into the cells and the sodium concentration rises to its "true" value. Mannitol or sucrose, a component of intravenous immunoglobulin preparations, may cause hyponatremia because of hyperosmolality.

Classification of hyponatremia is based on the patient's volume status. In **hypovolemic hyponatremia,** the child has lost sodium from the body. The water balance may be positive or negative, but sodium loss has been higher than water loss. The pathogenesis of the

Table 55-2 Causes of Hyponatremia

PSEUDOHYPONATREMIA
Hyperlipidemia
Hyperproteinemia
HYPEROSMOLALITY
Hyperglycemia
Iatrogenic (mannitol, sucrose, glycine)
HYPOVOLEMIC HYPONATREMIA
EXTRARENAL LOSSES
Gastrointestinal (emesis, diarrhea)
Skin (sweating or burns)
Third space losses (bowel obstruction, peritonitis, sepsis)
RENAL LOSSES
Thiazide or loop diuretics
Osmotic diuresis
Postobstructive diuresis
Polyuric phase of acute tubular necrosis
Juvenile nephronophthisis (OMIM 256100/606966/602088/604387/611498)
Autosomal recessive polycystic kidney disease (OMIM 263200)
Tubulointerstitial nephritis
Obstructive uropathy
Cerebral salt wasting
Proximal (type II) renal tubular acidosis (OMIM 604278)*
Lack of aldosterone effect (high serum potassium):
Absence of aldosterone (e.g., 21-hydroxylase deficiency [OMIM 201910])
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Urinary tract obstruction and/or infection
EUVOLEMIC HYPONATREMIA
Syndrome of inappropriate antidiuretic hormone secretion
Nephrogenic syndrome of inappropriate antidiuresis (OMIM 304800)
Desmopressin acetate
Glucocorticoid deficiency
Hypothyroidism
Water intoxication:
Iatrogenic (excess hypotonic intravenous fluids)
Feeding infants excessive water products
Swimming lessons
Tap water enema
Child abuse
Psychogenic polydipsia
Diluted formula
Beer potomania
Exercise-induced hyponatremia
HYPERVOLEMIC HYPONATREMIA
Heart failure
Cirrhosis
Nephrotic syndrome
Acute, chronic kidney injury
Capillary leak caused by sepsis
Hypoalbuminemia caused by gastrointestinal disease (protein-losing enteropathy)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

hyponatremia is usually a combination of sodium loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and this fluid contains sodium. Most fluid that is lost has a lower sodium concentration than that of plasma. Viral diarrhea fluid has, on average, a sodium concentration of 50 mEq/L. Replacing diarrhea fluid, which has a sodium concentration of 50 mEq/L, with formula, which has only approximately 10 mEq/L of sodium, reduces the sodium concentration. Intravascular volume depletion interferes with renal water excretion, the body's usual mechanism for preventing hyponatremia. The volume depletion stimulates ADH synthesis, resulting in renal water retention. Volume depletion also decreases the GFR and enhances water resorption in the proximal tubule, thereby reducing water delivery to the collecting duct.

Diarrhea as a result of gastroenteritis is the most common cause of **hypovolemic hyponatremia** in children. Emesis causes hyponatremia if the patient takes in hypotonic fluid, either intravenously or enterally, despite the emesis. Most patients with emesis have either a normal sodium concentration or hypernatremia. Burns may cause massive losses of isotonic fluid and resultant volume depletion. Hyponatremia develops if the patient receives hypotonic fluid. Losses of sodium from sweat are especially high in children with cystic fibrosis, aldosterone deficiency, or pseudohypoaldosteronism, although high losses can occur simply in a hot climate. Third-space losses are isotonic and can cause significant volume depletion, leading to ADH production and water retention, which can cause hyponatremia if the patient receives hypotonic fluid. In diseases that cause volume depletion through extrarenal sodium loss, the urine sodium level should be low (<10 mEq/L) as part of the renal response to maintain the intravascular volume. The only exceptions are diseases that cause both extrarenal and renal sodium losses: adrenal insufficiency and pseudohypoaldosteronism.

Renal sodium loss may occur in a variety of situations. In some situations, the urine sodium concentration is >140 mEq/L; thus, hyponatremia may occur without any fluid intake. In many cases, the urine sodium level is less than the serum concentration; thus, the intake of hypotonic fluid is necessary for hyponatremia to develop. In diseases associated with urinary sodium loss, the urine sodium level is >20 mEq/L despite volume depletion. This may not be true if the urinary sodium loss is no longer occurring, as is frequently the case if diuretics are discontinued. Because loop diuretics prevent generation of a maximally hypertonic renal medulla, the patient can neither maximally dilute nor concentrate the urine. The inability to maximally retain water provides some protection against severe hyponatremia. The patient receiving thiazide diuretics can concentrate the urine and is at higher risk for severe hyponatremia. Osmotic agents, such as glucose during diabetic ketoacidosis, cause loss of both water and sodium. Urea accumulates during renal failure and then acts as an osmotic diuretic after relief of urinary tract obstruction and during the polyuric phase of acute tubular necrosis. Transient tubular damage in these conditions further impairs sodium conservation. The serum sodium concentration in these conditions depends on the sodium concentration of the fluid used to replace the losses. Hyponatremia develops when the fluid is hypotonic relative to the urinary losses.

Renal salt wasting occurs in hereditary kidney diseases, such as juvenile nephronophthisis and autosomal recessive polycystic kidney disease. Obstructive uropathy, most commonly a consequence of posterior urethral valves, produces salt wasting, but patients with the disease may also have hypernatremia as a result of impaired ability to concentrate urine and high water loss. Acquired tubulointerstitial nephritis, usually secondary to either medications or infections, may cause salt wasting, along with other evidence of tubular dysfunction. CNS injury may produce cerebral salt wasting, which is theoretically caused by the production of a natriuretic peptide that causes renal salt wasting. In type II renal tubular acidosis (RTA), usually associated with Fanconi syndrome (see Chapter 529.1), there is increased excretion of sodium and bicarbonate in the urine. Patients with Fanconi syndrome also have glycosuria, aminoaciduria, and hypophosphatemia because of renal phosphate wasting.

Aldosterone is necessary for renal sodium retention and for the excretion of potassium and acid. In congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, the block of aldosterone production results in hyponatremia, hyperkalemia, and metabolic acidosis. In pseudohypoaldosteronism, aldosterone levels are elevated, but there is no response because of either a defective sodium channel or a deficiency of aldosterone receptors. A lack of tubular response to aldosterone may occur in children with urinary tract obstruction, especially during an acute urinary tract infection.

In **hypervolemic hyponatremia,** there is an excess of TBW and sodium, although the increase in water is greater than the increase in sodium. In most of the conditions that cause hypervolemic hyponatremia, there is a decrease in the effective blood volume, resulting from third space fluid loss, vasodilation, or poor cardiac output. The regulatory systems sense a decrease in effective blood volume and attempt to retain water and sodium to correct the problem. ADH causes renal water retention, and the kidney, under the influence of aldosterone and other intrarenal mechanisms, retains sodium. The patient's sodium concentration decreases because water intake exceeds sodium intake and ADH prevents the normal loss of excess water.

In these disorders, there is a low urine sodium concentration (<10 mEq/L) and an excess of both TBW and sodium. The only exception is in patients with renal failure and hyponatremia. These patients have an expanded intravascular volume, and hyponatremia can therefore appropriately suppress ADH production. Water cannot be excreted because very little urine is being made. Serum sodium is diluted through ingestion of water. Because of renal dysfunction, the urine sodium concentration may be elevated, but urine volume is so low that urine sodium excretion has not kept up with sodium intake, leading to sodium overload. The urine sodium concentration in renal failure varies. In patients with acute glomerulonephritis, because it does not affect the tubules, the urine sodium level is usually low, whereas in patients with acute tubular necrosis, it is elevated because of tubular dysfunction.

Patients with hyponatremia and no evidence of volume overload or volume depletion have **euvolemic hyponatremia.** These patients typically have an excess of TBW and a slight decrease in total body sodium. Some of these patients have an increase in weight, implying that they are volume-overloaded. Nevertheless, from a clinical standpoint, they usually appear normal or have subtle signs of fluid overload.

In SIADH, the secretion of ADH is not inhibited by either low serum osmolality or expanded intravascular volume (see Chapter 559). The result is that the child with SIADH is unable to excrete water. This results in dilution of the serum sodium and hyponatremia. The expansion of the extracellular volume as a result of the retained water causes a mild increase in intravascular volume. The kidney increases sodium excretion in an effort to decrease intravascular volume to normal; thus, the patient has a mild decrease in body sodium. SIADH most commonly occurs with disorders of the CNS (infection, hemorrhage, trauma, tumor, thrombosis), but lung disease (infection, asthma, positive pressure ventilation) and malignant tumors (producing ADH) are other potential causes. A variety of medications may cause SIADH, including recreational use of 3,4-methylenedioxymethylamphetamine (MDMA, or "Ecstasy"), opiates, antiepileptic drugs (carbamazepine, oxcarbazepine, valproate), tricyclic antidepressants, vincristine, Cytoxan, and selective serotonin reuptake inhibitors. The diagnosis of SIADH is one of exclusion, because other causes of hyponatremia must be eliminated (Table 55-3). Because SIADH is a state of intravascular volume expansion, low serum uric acid and BUN levels are supportive of the diagnosis.

A rare gain-of-function mutation in the renal ADH receptor causes **nephrogenic syndrome of inappropriate antidiuresis.** Patients with this X-linked disorder appear to have SIADH but have undetectable levels of ADH.

Hyponatremia in hospitalized patients is frequently caused by inappropriate production of ADH and administration of hypotonic intravenous fluids. Causes of inappropriate ADH production include stress, medications such as narcotics or anesthetics, nausea, and respiratory illness. The synthetic analog of ADH, desmopressin acetate, causes

Table 55-3 Diagnostic Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion

Absence of:
Renal, adrenal, or thyroid insufficiency
Heart failure, nephrotic syndrome, or cirrhosis
Diuretic ingestion
Dehydration
Urine osmolality >100 mOsm/kg (usually > plasma)
Serum osmolality <280 mOsm/kg and serum sodium <135 mEq/L
Urine sodium >30 mEq/L
Reversal of "sodium wasting" and correction of hyponatremia with water restriction

water retention and may cause hyponatremia if fluid intake is not appropriately limited. The main uses of desmopressin acetate in children are for the management of central diabetes insipidus and of nocturnal enuresis.

Excess water ingestion can produce hyponatremia. In these cases, the sodium concentration decreases as a result of dilution. This decrease suppresses ADH secretion, and there is a marked water diuresis by the kidney. Hyponatremia develops only because the intake of water exceeds the kidney's ability to eliminate water. This condition is more likely to occur in infants because their lower GFR limits their ability to excrete water.

Hyponatremia may develop in infants <6 mo of age when caregivers offer water to their infant as a supplement, during hot weather, or when they run out of formula. Hyponatremia may result in transient seizures, hypothermia, and poor tone. With cessation of water intake, the hyponatremia rapidly corrects. Infants <6 mo of age should not be given water to drink; infants between 6 and 12 mo of age should not receive more than 1-2 ounces. If the infant appears thirsty, the parent should offer formula or breastfeed the child.

In some situations, the water intoxication causes acute hyponatremia and is a consequence of a massive acute water load. Examples of causes of this water load include infant swimming lessons, inappropriate use of hypotonic intravenous fluids, water enemas, and forced water intake as a form of child abuse. Chronic hyponatremia occurs in children who receive water, but limited sodium and protein. The minimum urine osmolality is approximately 50 mOsm/kg, the kidney can excrete 1 L of water only if there is enough solute ingested to produce 50 mOsm for urinary excretion. Because sodium and urea (a breakdown product of protein) are the principal urinary solutes, a lack of intake of sodium and protein prevents adequate water excretion. This occurs with the use of diluted formula or other inappropriate diets. Subsistence on beer, a poor source of sodium and protein, causes hyponatremia because of the inability to excrete the high water load ("beer potomania"). **Exercise-induced hyponatremia**, reported commonly during marathons, is caused by excessive water intake, salt losses from sweat, and secretion of ADH.

The pathogenesis of the hyponatremia in glucocorticoid deficiency is multifactorial, and includes increased ADH secretion. In hypothyroidism, there is an inappropriate retention of water by the kidney, but the precise mechanisms are not clearly elucidated.

Clinical Manifestations

Hyponatremia causes a decrease in the osmolality of the extracellular space. Because the intracellular space then has a higher osmolality, water moves from the extracellular space to the intracellular space to maintain osmotic equilibrium. The increase in intracellular water causes cells to swell. Although cell swelling is not problematic in most tissues, it is dangerous for the brain, which is confined by the skull. As brain cells swell, there is an increase in intracranial pressure, which impairs cerebral blood flow. Acute, severe hyponatremia can cause brainstem herniation and apnea; respiratory support is often necessary. Brain cell swelling is responsible for most of the symptoms of hyponatremia. Neurologic symptoms of hyponatremia include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. Patients may have hypothermia and Cheyne-Stokes respirations. Hyponatremia can cause muscle cramps and weakness; rhabdomyolysis can occur with water intoxication.

The symptoms of hyponatremia are mostly a result of the decrease in extracellular osmolality and the resulting movement of water down its osmotic gradient into the intracellular space. Brain swelling can be significantly obviated if the hyponatremia develops gradually, because brain cells adapt to the decreased extracellular osmolality by reducing intracellular osmolality. This reduction is achieved by extrusion of the main intracellular ions (potassium and chloride) and a variety of small organic molecules. This process explains why the range of symptoms in hyponatremia is related to both the serum sodium level and its rate of decrease. A patient with chronic hyponatremia may have only subtle neurologic abnormalities with a serum sodium level of 110 mEq/L, but another patient may have seizures because of an acute decline in serum sodium level from 140 to 125 mEq/L.

Diagnosis

The history usually points to a likely etiology of the hyponatremia. Most patients with hyponatremia have a history of volume depletion. Diarrhea and diuretic use are very common causes of hyponatremia in children. A history of polyuria, perhaps with enuresis, and/or salt craving is present in children with primary kidney diseases or absence of aldosterone effect. Children may have signs or symptoms suggesting a diagnosis of hypothyroidism or adrenal insufficiency (see Chapters 565 and 575). Brain injury raises the possibility of SIADH or cerebral salt wasting, with the caveat that SIADH is much more likely. Liver disease, nephrotic syndrome, renal failure, or congestive heart failure may be acute or chronic. The history should include a review of the patient's intake, both intravenous and enteral, with careful attention to the amounts of water, sodium, and protein.

The traditional first step in the diagnostic process is determination of the plasma osmolality. This is done because some patients with a low serum sodium value do not have low osmolality. The clinical effects of hyponatremia are secondary to the associated low osmolality. Without a low osmolality, there is no movement of water into the intracellular space.

A patient with hyponatremia can have a low, normal, or high osmolality. A normal osmolality in combination with hyponatremia occurs in pseudohyponatremia. Children with elevation of serum glucose concentration or of another effective osmole (mannitol) have a high plasma osmolality and hyponatremia. The presence of a low osmolality indicates "true" hyponatremia. Patients with low osmolality are at risk for neurologic symptoms and require further evaluation to determine the etiology of the hyponatremia.

In some situations, true hyponatremia is present despite a normal or elevated plasma osmolality. The presence of an ineffective osmole, most commonly urea, increases the plasma osmolality, but because the osmole has the same concentration in the intracellular space, it does not cause fluid to move into the extracellular space. There is no dilution of the serum sodium by water, and the sodium concentration remains unchanged if the ineffective osmole is eliminated. Most importantly, the ineffective osmole does not protect the brain from edema caused by hyponatremia. Hence, a patient may have symptoms of hyponatremia despite having a normal or increased osmolality because of uremia.

In patients with true hyponatremia, the next step in the diagnostic process is to clinically evaluate the volume status. Patients with hyponatremia can be hypovolemic, hypervolemic, or euvolemic. The diagnosis of volume depletion relies on the usual findings with dehydration (see Chapter 57), although subtle volume depletion may not be clinically apparent. In a patient with subtle volume depletion, a fluid bolus results in a decrease in the urine osmolality and an increase in the serum sodium concentration. Children with hypervolemia are **edematous** on physical examination. They may have ascites, pulmonary edema, pleural effusion, or hypertension.

Hypovolemic hyponatremia can have renal or nonrenal causes. The urine sodium concentration is very useful in differentiating between renal and nonrenal causes. When the losses are nonrenal and the kidney is working properly, there is renal retention of sodium, a normal homeostatic response to volume depletion. Thus, the urinary sodium concentration is low, typically <10 mEq/L, although sodium conservation in neonates is less avid. When the kidney is the cause of the sodium loss, the urine sodium concentration is >20 mEq/L, reflecting the defect in renal sodium retention. The interpretation of the urine sodium level is challenging with diuretic therapy because it is high when diuretics are being used but low after the diuretic effect is gone. This becomes an issue only when diuretic use is surreptitious. The urine sodium concentration is not useful if a metabolic alkalosis is present; the urine chloride concentration must be used instead (see Chapter 55.7).

Differentiating among the nonrenal causes of hypovolemic hyponatremia is usually facilitated by the history. Although the renal causes are more challenging to distinguish, a high serum potassium concentration is associated with disorders in which the sodium wasting is caused by absence of or ineffectiveness of aldosterone.

In the patient with hypervolemic hyponatremia, the urine sodium concentration is a helpful parameter. It is usually <10 mEq/L, except in the patient with renal failure.

Treatment

The management of hyponatremia is based on the pathophysiology of the specific etiology. The management of all causes requires judicious monitoring and avoidance of an overly quick normalization of the serum sodium concentration. A patient with severe symptoms (seizures), no matter the etiology, should be given a bolus of hypertonic saline to produce a small, rapid increase in serum sodium. Hypoxia worsens cerebral edema, and hyponatremia may cause hypoxia. Hence, pulse oximetry should be monitored, and hypoxia aggressively corrected.

With all causes of hyponatremia, it is important to avoid "overly rapid" correction. The reason is that rapid correction of hyponatremia may cause CPM. This syndrome, which occurs within several days of rapid correction of hyponatremia, produces neurologic symptoms, including confusion, agitation, flaccid or spastic quadriparesis, and death. There are usually characteristic pathologic and radiologic changes in the brain, especially in the pons, but extrapontine lesions are quite common and may cause additional symptoms. Despite severe symptoms, full recovery does occur in some patients.

CPM is more common in patients who are treated for chronic hyponatremia than in those treated for acute hyponatremia. Presumably, this difference is based on the adaptation of brain cells to the hyponatremia. The reduced intracellular osmolality that is an adaptive mechanism for chronic hyponatremia makes brain cells susceptible to dehydration during rapid correction of the hyponatremia, and this may be the mechanism of CPM. Even though CPM is rare in pediatric patients, it is advisable to avoid correcting the serum sodium concentration by >12 mEq/L/24 hr or >18 mEq/L/48 hr. Desmopressin is a potential option if the serum sodium level is increasing too rapidly. This guideline does not apply to acute hyponatremia, as may occur with water intoxication, because the hyponatremia is more often symptomatic and there has not been time for the adaptive decrease in brain osmolality to occur. The consequences of brain edema in acute hyponatremia exceed the small risk of CPM.

Patients with hyponatremia can have severe neurologic symptoms, such as seizures and coma. The seizures associated with hyponatremia generally are poorly responsive to anticonvulsants. The child with hyponatremia and severe symptoms needs to receive treatment that will quickly reduce cerebral edema. This goal is best accomplished by increasing the extracellular osmolality so that water moves down its osmolar gradient from the intracellular space to the extracellular space.

Intravenous hypertonic saline rapidly increases serum sodium, and the effect on serum osmolality leads to a decrease in brain edema. Each mL/kg of 3% sodium chloride increases the serum sodium by approximately 1 mEq/L. A child with active symptoms often improves after receiving 4-6 mL/kg of 3% sodium chloride.

The child with **hypovolemic hyponatremia** has a deficiency in sodium and may have a deficiency in water. The cornerstone of therapy is to replace the sodium deficit and any water deficit that is present. The first step in treating any dehydrated patient is to restore the intravascular volume with isotonic saline. Ultimately, complete restoration of intravascular volume suppresses ADH production, thereby permitting excretion of the excess water. Chapter 57 discusses the management of hyponatremic dehydration.

The management of **hypervolemic hyponatremia** is difficult. Patients with this disorder have an excess of both water and sodium. Administration of sodium leads to worsening volume overload and edema. In addition, the patients are retaining water and sodium because of their ineffective intravascular volume or renal insufficiency. The cornerstone of therapy is water and sodium restriction, because the patients have volume overload. Diuretics may help by causing excretion of both sodium and water. Vasopressin antagonists, by blocking the action of ADH and causing a water diuresis, are effective in correcting the hypervolemic hyponatremia caused by heart failure or cirrhosis.

Some patients with low albumin resulting from nephrotic syndrome have a better response to diuretics after an infusion of 25% albumin; the sodium concentration often normalizes as a result of expansion of the intravascular volume. A child with heart failure may have an increase in renal water and sodium excretion if there is an improvement in cardiac output. This improvement will "turn off" the regulatory hormones that are causing renal water (ADH) and sodium (aldosterone) retention. The patient with renal failure cannot respond to any of these therapies except fluid restriction. Insensible fluid losses eventually result in an increase in the sodium concentration as long as insensible and urinary losses are greater than intake. A more definitive approach in children with renal failure is to perform dialysis, which removes water and sodium.

In isovolumic hyponatremia, there is usually an excess of water and a mild sodium deficit. Therapy is directed at eliminating the excess water. The child with acute excessive water intake loses water in the urine because ADH production is turned off as a result of the low plasma osmolality. Children may correct their hyponatremia spontaneously over 3-6 hr. For acute, symptomatic hyponatremia as a result of water intoxication, hypertonic saline may be needed to reverse cerebral edema. For chronic hyponatremia from poor solute intake, the child needs to receive an appropriate formula, and excess water intake should be eliminated.

Children with iatrogenic hyponatremia caused by the administration of hypotonic intravenous fluids should receive 3% saline if they are symptomatic. Subsequent management is dictated by the patient's volume status. The hypovolemic child should receive isotonic intravenous fluids. The child with nonphysiologic stimuli for ADH production should undergo fluid restriction. Prevention of this iatrogenic complication requires judicious use of intravenous fluids (see Chapter 56).

Specific hormone replacement is the cornerstone of therapy for the hyponatremia of hypothyroidism or cortisol deficiency. Correction of the underlying defect permits appropriate elimination of the excess water.

SIADH is a condition of excess water, with limited ability of the kidney to excrete water. The mainstay of its therapy is fluid restriction. Furosemide is effective in the patient with SIADH and severe hyponatremia. Even in a patient with SIADH, furosemide causes an increase in water and sodium excretion. The loss of sodium is somewhat counterproductive, but this sodium can be replaced with hypertonic saline. Because the patient has a net loss of water and the urinary losses of sodium have been replaced, there is an increase in the sodium concentration, but no significant increase in blood pressure. Vasopressin antagonists (conivaptan, lixivaptan, tolvaptan), which block the action of ADH and cause a water diuresis, are effective at correcting euvolemic hyponatremia, but overly rapid correction is a potential complication.

Treatment of chronic SIADH is challenging. Fluid restriction in children is difficult for nutritional and behavioral reasons. Other

options are long-term furosemide therapy with sodium supplementation, an oral vasopressin antagonist (tolvaptan), or oral urea.

Bibliography is available at Expert Consult.

55.4 Potassium

Larry A. Greenbaum

POTASSIUM METABOLISM

Body Content and Physiologic Function

The intracellular concentration of potassium, approximately 150 mEq/L, is much higher than the plasma concentration (see Fig. 55-3). The majority of body potassium is contained in muscle. As muscle mass increases, there is an increase in body potassium. There is thus an increase in body potassium during puberty, and it is more significant in males. The majority of extracellular potassium is in bone; <1% of total body potassium is in plasma.

Because most potassium is intracellular, the plasma concentration does not always reflect the total body potassium content. A variety of conditions alter the distribution of potassium between the intracellular and extracellular compartments. The Na^+,K^+-ATPase maintains the high intracellular potassium concentration by pumping sodium out of the cell and potassium into the cell. This activity balances the normal leak of potassium out of cells via potassium channels that is driven by the favorable chemical gradient. Insulin increases potassium movement into cells by activating the Na^+,K^+-ATPase. Hyperkalemia stimulates insulin secretion, which helps mitigate the hyperkalemia. Acid–base status affects potassium distribution, probably via potassium channels and the Na^+,K^+-ATPase. A decrease in pH drives potassium extracellularly; an increase in pH has the opposite effect. β-Adrenergic agonists stimulate the Na^+,K^+-ATPase, increasing cellular uptake of potassium. This increase is protective, in that hyperkalemia stimulates adrenal release of catecholamines. α-Adrenergic agonists and exercise cause a net movement of potassium out of the intracellular space. An increase in plasma osmolality, as with mannitol infusion, leads to water movement out of the cells, and potassium follows as a result of solvent drag. The serum potassium concentration increases by approximately 0.6 mEq/L with each 10-mOsm rise in plasma osmolality.

The high intracellular concentration of potassium, the principal intracellular cation, is maintained via the Na^+,K^+-ATPase. The resulting chemical gradient is used to produce the resting membrane potential of cells. Potassium is necessary for the electrical responsiveness of nerve and muscle cells and for the contractility of cardiac, skeletal, and smooth muscle. The changes in membrane polarization that occur during muscle contraction or nerve conduction make these cells susceptible to changes in serum potassium levels. The ratio of intracellular to extracellular potassium determines the threshold for a cell to generate an action potential and the rate of cellular repolarization. The intracellular potassium concentration affects cellular enzymes. Potassium is necessary for maintaining cell volume because of its important contribution to intracellular osmolality.

Intake

Potassium is plentiful in food. Dietary consumption varies considerably, even though 1-2 mEq/kg is the recommended intake. The intestines normally absorb approximately 90% of ingested potassium. Most absorption occurs in the small intestine, whereas the colon exchanges body potassium for luminal sodium. Regulation of intestinal losses normally has a minimal role in maintaining potassium homeostasis, although renal failure, aldosterone, and glucocorticoids increase colonic secretion of potassium. The increase in intestinal losses in the setting of renal failure and hyperkalemia, which stimulates aldosterone production, is clinically significant, helping to protect against hyperkalemia.

Excretion

There is some loss of potassium in sweat, but it is normally minimal. The colon has the ability to eliminate some potassium. In addition, after an acute potassium load, much of the potassium, >40%, moves intracellularly, through the actions of epinephrine and insulin, which are produced in response to hyperkalemia. This process provides transient protection from hyperkalemia, but most ingested potassium is eventually excreted in the urine. The kidneys principally regulate long-term potassium balance, and they alter excretion in response to a variety of signals. Potassium is freely filtered at the glomerulus, but 90% is resorbed before the distal tubule and collecting duct, the principal sites of potassium regulation. The distal tubule and the collecting duct have the ability to absorb and secrete potassium. It is the amount of tubular secretion that regulates the amount of potassium that appears in the urine. The plasma potassium concentration directly influences secretion in the distal nephron. As the potassium concentration increases, secretion increases.

The principal hormone regulating potassium secretion is aldosterone, which is released by the adrenal cortex in response to increased plasma potassium. Its main site of action is the cortical collecting duct, where aldosterone stimulates sodium movement from the tubule into the cells. This movement creates a negative charge in the tubular lumen, facilitating potassium excretion. In addition, the increased intracellular sodium stimulates the basolateral Na^+,K^+-ATPase, causing more potassium to move into the cells lining the cortical collecting duct. Glucocorticoids, ADH, a high urinary flow rate, and high sodium delivery to the distal nephron also increase urinary potassium excretion. Potassium excretion is decreased by insulin, catecholamines, and urinary ammonia. Whereas ADH increases potassium secretion, it also causes water resorption, decreasing urinary flow. The net effect is that ADH has little overall impact on potassium balance. Alkalosis causes potassium to move into cells, including the cells lining the collecting duct. This movement increases potassium secretion, and because acidosis has the opposite effect, it decreases potassium secretion.

The kidney can dramatically vary potassium excretion in response to changes in intake. Normally, approximately 10-15% of the filtered load is excreted. In an adult, excretion of potassium can vary from 5-1,000 mEq/day.

HYPERKALEMIA

Hyperkalemia—because of the potential for lethal arrhythmias—is one of the most alarming electrolyte abnormalities.

Etiology and Pathophysiology

Three basic mechanisms cause hyperkalemia (Table 55-4). In the individual patient, the etiology is sometimes multifactorial.

Spurious hyperkalemia or pseudohyperkalemia is very common in children because of the difficulties in obtaining blood specimens. This laboratory result is usually caused by hemolysis during a heelstick or phlebotomy, but it can be the result of prolonged tourniquet application or fist clenching, either of which causes local potassium release from muscle.

The serum potassium level is normally 0.4 mEq/L higher than the plasma value, secondary to potassium release from cells during clot formation. This phenomenon is exaggerated with thrombocytosis because of potassium release from platelets. For every 100,000/m^3 increase in the platelet count, the serum potassium level rises by approximately 0.15 mEq/L. This phenomenon also occurs with the marked white blood cell count elevations sometimes seen with leukemia. Elevated white blood cell counts, typically >200,000/m^3, can cause a dramatic elevation in the serum potassium concentration. Analysis of a plasma sample usually provides an accurate result. It is important to analyze the sample promptly to avoid potassium release from cells, which occurs if the sample is stored in the cold, or cellular uptake of potassium and spurious hypokalemia, which occurs with storage of the sample at room temperature. Occasionally, heparin causes lysis of leukemic cells and a false elevation of the plasma sample; a blood gas syringe has less heparin and may provide a more accurate reading than a standard tube. There are rare genetic disorders causing leakage of potassium from red cells that may causes familial pseudohyperkalemia.

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Table 55-4 Causes of Hyperkalemia

SPURIOUS LABORATORY VALUE
Hemolysis
Tissue ischemia during blood drawing
Thrombocytosis
Leukocytosis
Familial pseudohyperkalemia (OMIM 609153/611184/612126)
INCREASED INTAKE
Intravenous or oral
Blood transfusions
TRANSCELLULAR SHIFTS
Acidosis
Rhabdomyolysis
Tumor lysis syndrome
Tissue necrosis
Hemolysis/hematomas/gastrointestinal bleeding
Succinylcholine
Digitalis intoxication
Fluoride intoxication
β-Adrenergic blockers
Exercise
Hyperosmolality
Insulin deficiency
Malignant hyperthermia (OMIM 145600/601887)
Hyperkalemic periodic paralysis (OMIM 170500)
DECREASED EXCRETION
Renal failure
Primary adrenal disease:
Acquired Addison disease
21-Hydroxylase deficiency (OMIM 201910)
3β-Hydroxysteroid dehydrogenase deficiency (OMIM 201810)
Lipoid congenital adrenal hyperplasia (OMIM 201710)
Adrenal hypoplasia congenita (OMIM 300200)
Aldosterone synthase deficiency (OMIM 203400/610600)
Adrenoleukodystrophy (OMIM 300100)
Hyporeninemic hypoaldosteronism:
Urinary tract obstruction
Sickle cell disease (OMIM 603903)
Kidney transplant
Lupus nephritis
Renal tubular disease:
Pseudohypoaldosteronism type I (OMIM 264350/177735)
Pseudohypoaldosteronism type II (OMIM 145260)
Bartter syndrome, type 2 (OMIM 241200)
Urinary tract obstruction
Kidney transplant
Medications:
Angiotensin-converting enzyme inhibitors
Angiotensin II blockers
Potassium-sparing diuretics
Calcineurin inhibitors
Nonsteroidal antiinflammatory drugs
Trimethoprim
Heparin
Drospirenone (in some oral contraceptives)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Because of the kidney's ability to excrete potassium, it is unusual for excessive intake, by itself, to cause hyperkalemia. This condition can occur in a patient who is receiving large quantities of intravenous or oral potassium for excessive losses that are no longer present. Frequent or rapid blood transfusions can acutely increase the potassium level because of the potassium content of blood, which is variably elevated. Increased intake may precipitate hyperkalemia if there is an underlying defect in potassium excretion.

The intracellular space has a very high potassium concentration, so a shift of potassium from the intracellular space to the extracellular space can have a significant effect on the plasma potassium level. This shift occurs with metabolic acidosis, but the effect is minimal with an organic acid (lactic acidosis, ketoacidosis). A respiratory acidosis has less impact than a metabolic acidosis. Cell destruction, as seen with rhabdomyolysis, tumor lysis syndrome, tissue necrosis, or hemolysis, releases potassium into the extracellular milieu. The potassium released from red blood cells in internal bleeding, such as hematomas, is resorbed and enters the extracellular space.

Normal doses of succinylcholine or β-blockers and fluoride or digitalis intoxication all cause a shift of potassium out of the intracellular compartment. Succinylcholine should not be used during anesthesia in patients at risk for hyperkalemia. β-Blockers prevent the normal cellular uptake of potassium mediated by binding of β-agonists to the β_2-adrenergic receptors. Potassium release from muscle cells occurs during exercise, and levels can increase by 1-2 mEq/L with high activity. With an increased plasma osmolality, water moves from the intracellular space and potassium follows. This process occurs with hyperglycemia, although in nondiabetic patients, the resultant increase in insulin causes potassium to move intracellularly. In diabetic ketoacidosis, the absence of insulin causes potassium to leave the intracellular space, and the problem is compounded by the hyperosmolality. The effect of hyperosmolality causes a transcellular shift of potassium into the extracellular space after mannitol or hypertonic saline infusions. **Malignant hyperthermia,** which is triggered by some inhaled anesthetics, causes muscle release of potassium (see Chapter 611.2). **Hyperkalemic periodic paralysis** is an autosomal dominant disorder caused by a mutated sodium channel. It results in episodic cellular release of potassium and attacks of paralysis (see Chapter 611.1).

The kidneys excrete most of the daily potassium intake, so a decrease in kidney function can cause hyperkalemia. Newborn infants in general, and especially premature infants, have decreased kidney function at birth and thus are at increased risk for hyperkalemia despite an absence of intrinsic renal disease. Neonates also have decreased expression of potassium channels, further limiting potassium excretion.

A wide range of primary **adrenal disorders,** both hereditary and acquired, can cause decreased production of aldosterone, with secondary hyperkalemia (see Chapters 575 and 576). Patients with these disorders typically have metabolic acidosis and salt wasting with hyponatremia. Children with more subtle adrenal insufficiency may have electrolyte problems only during acute illnesses. The most common form of **congenital adrenal hyperplasia,** 21-hydroxylase deficiency, typically manifests in male infants as hyperkalemia, metabolic acidosis, hyponatremia, and volume depletion. Females with this disorder usually are diagnosed as newborns because of their ambiguous genitalia; treatment prevents the development of electrolyte problems.

Renin, via angiotensin II, stimulates aldosterone production. A deficiency in renin, a result of kidney damage, can lead to decreased aldosterone production. Hyporeninemia occurs in many kidney diseases, with some of the more common pediatric causes listed in Table 55-4. These patients typically have hyperkalemia and a metabolic acidosis, without hyponatremia. Some of these patients have impaired renal function, partially accounting for the hyperkalemia, but the impairment in potassium excretion is more extreme than expected for the degree of renal insufficiency.

A variety of **renal tubular disorders** impair renal excretion of potassium. Children with **pseudohypoaldosteronism type 1** have hyperkalemia, metabolic acidosis, and salt wasting leading to hyponatremia and volume depletion; aldosterone values are elevated. In the autosomal recessive variant, there is a defect in the renal sodium channel that is normally activated by aldosterone. Patients with this variant have severe symptoms, beginning in infancy. Patients with the autosomal dominant form have a defect in the aldosterone receptor, and the disease is milder, often remitting in adulthood. **Pseudohypoaldosteronism type 2 (familial hyperkalemic hypertension),** also called **Gordon syndrome,** is an autosomal dominant disorder characterized by hypertension caused by salt retention and impaired excretion of potassium and acid, leading to hyperkalemia and metabolic acidosis. Activating mutations in either WNK1 or WNK4, both serine-threonine kinases located in the distal nephron, cause Gordon syndrome. In the **Bartter syndrome** caused by

mutations in the potassium channel ROMK (type 2 Bartter syndrome), there can be transient hyperkalemia in neonates, but hypokalemia subsequently develops (see Chapter 531).

Acquired renal tubular dysfunction, with an impaired ability to excrete potassium, occurs in a number of conditions. These disorders, all characterized by tubulointerstitial disease, are often associated with impaired acid secretion and a secondary metabolic acidosis. In some affected children, the metabolic acidosis is the dominant feature, although a high potassium intake may unmask the defect in potassium handling. The tubular dysfunction can cause renal salt wasting, potentially leading to hyponatremia. Because of the tubulointerstitial damage, these conditions may also cause hyperkalemia as a result of hyporeninemic hypoaldosteronism.

The risk of hyperkalemia resulting from medications is greatest in patients with underlying renal insufficiency. The predominant mechanism of medication-induced hyperkalemia is impaired renal excretion, although angiotensin-converting enzyme inhibitors may worsen hyperkalemia in anuric patients, probably by inhibiting gastrointestinal potassium loss, which is normally upregulated in renal insufficiency. The hyperkalemia caused by trimethoprim generally occurs only at the very high doses used to treat *Pneumocystis jiroveci* pneumonia in patients with AIDS. Potassium-sparing diuretics may easily cause hyperkalemia, especially because they are often used in patients who are receiving oral potassium supplements. Oral contraceptives containing drospirenone, which blocks the action of aldosterone, may cause hyperkalemia and should not be used in patients with decreased renal function.

Clinical Manifestations

The most important effects of hyperkalemia are a result of the role of potassium in membrane polarization. The cardiac conduction system is usually the dominant concern. Changes in the electrocardiogram (ECG) begin with peaking of the T waves. This is followed, as the potassium level increases, by ST-segment depression, an increased PR interval, flattening of the P wave, and widening of the QRS complex. This process can eventually progress to ventricular fibrillation. Asystole may also occur. Some patients have paresthesias, fasciculations, weakness, and even an ascending paralysis, but cardiac toxicity usually precedes these clinical symptoms, emphasizing the danger of assuming that an absence of symptoms implies an absence of danger. Chronic hyperkalemia is generally better tolerated than acute hyperkalemia.

DIAGNOSIS

The etiology of hyperkalemia is often readily apparent. Spurious hyperkalemia is very common in children, so obtaining a second potassium measurement is often appropriate. If there is a significant elevation of the white blood cell or platelet count, the second measurement should be performed on a plasma sample that is evaluated promptly. The history should initially focus on potassium intake, risk factors for transcellular shifts of potassium, medications that cause hyperkalemia, and the presence of signs of renal insufficiency, such as oliguria and edema. Initial **laboratory evaluation** should include creatinine, BUN, and assessment of the acid–base status. Many etiologies of hyperkalemia cause a metabolic acidosis; a metabolic acidosis worsens hyperkalemia through the transcellular shift of potassium out of cells. Renal insufficiency is a common cause of the combination of metabolic acidosis and hyperkalemia. This association is also seen in diseases associated with aldosterone insufficiency or aldosterone resistance. Children with absence of or ineffective aldosterone often have hyponatremia and volume depletion because of salt wasting. Genetic diseases, such as congenital adrenal hyperplasia and pseudohypoaldosteronism, usually manifest in infancy and should be strongly considered in the infant with hyperkalemia and metabolic acidosis, especially if hyponatremia is present. It is important to consider the various etiologies of a transcellular shift of potassium. In some of these disorders, the potassium level continues to increase, despite the elimination of all potassium intake, especially when there is concurrent renal insufficiency. This increase is potentially seen in tumor lysis syndrome, hemolysis, rhabdomyolysis, and other causes of cell death. All of these entities can cause concomitant hyperphosphatemia and hyperuricemia. Rhabdomyolysis produces an elevated creatinine phosphokinase (CPK) value and hypocalcemia, whereas children with hemolysis have hemoglobinuria and a decreasing hematocrit. For the child with diabetes, an elevated blood glucose value suggests a transcellular shift of potassium.

Treatment

The plasma potassium level, the ECG, and the risk of the problem worsening determine the aggressiveness of the therapeutic approach. High serum potassium levels and the presence of ECG changes require vigorous treatment. An additional source of concern is the patient in whom plasma potassium levels are rising despite minimal intake. This situation can happen if there is cellular release of potassium (tumor lysis syndrome), especially in the setting of diminished excretion (renal failure).

The first action in a child with a concerning elevation of plasma potassium is to stop all sources of additional potassium (oral, intravenous). Washed red blood cells can be used for patients who require blood transfusions. If the potassium level is >6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation. Peak T waves are the first sign of hyperkalemia followed by a prolonged PR interval and, when most severe, a prolonged QRS complex. Life-threatening ventricular arrhythmias may also develop. The treatment of hyperkalemia has 2 basic goals: (a) to stabilize the heart to prevent life-threatening arrhythmias and (b) to remove potassium from the body. The treatments that acutely prevent arrhythmias all have the advantage of working quickly (within minutes) but do not remove potassium from the body. *Calcium stabilizes the cell membrane of heart cells, preventing arrhythmias.* It is given intravenously over a few minutes, and its action is almost immediate. Calcium should be given over 30 min in a patient who is receiving digitalis, because otherwise the calcium may cause arrhythmias. Bicarbonate causes potassium to move intracellularly, lowering the plasma potassium level. It is most efficacious in a patient with a metabolic acidosis. Insulin causes potassium to move intracellularly but must be given with glucose to avoid hypoglycemia. The combination of insulin and glucose works within 30 min. Nebulized albuterol, by stimulation of β_1-receptors, leads to rapid intracellular movement of potassium. This has the advantage of not requiring an intravenous route of administration, allowing it to be given concurrently with the other measures.

It is critical to begin measures that remove potassium from the body. In patients who are not anuric, a loop diuretic increases renal excretion of potassium. A high dose may be required in a patient with significant renal insufficiency. Sodium polystyrene sulfonate (Kayexalate) is an exchange resin that is given either rectally or orally. Sodium in the resin is exchanged for body potassium, and the potassium-containing resin is then excreted from the body. Some patients require dialysis for acute potassium removal. Dialysis is often necessary if the patient has either severe renal failure or an especially high rate of endogenous potassium release, as is sometimes present with tumor lysis syndrome or rhabdomyolysis. Hemodialysis rapidly lowers plasma potassium levels. Peritoneal dialysis is not nearly as quick or reliable, but it is usually adequate as long as the acute problem can be managed with medications and the endogenous release of potassium is not high.

Long-term management of hyperkalemia includes reducing intake via dietary changes and eliminating or reducing medications that cause hyperkalemia (see Chapter 535). Some patients require medications to increase potassium excretion, such as sodium polystyrene sulfonate and loop or thiazide diuretics. Some infants with chronic renal failure may need to start dialysis to allow adequate caloric intake without hyperkalemia. It is unusual for an older child to require dialysis principally to control chronic hyperkalemia. The disorders that are caused by a deficiency in aldosterone respond to replacement therapy with fludrocortisone.

HYPOKALEMIA

Hypokalemia is common in children, with most cases related to gastroenteritis.

Etiology and Pathophysiology

There are 4 basic mechanisms of hypokalemia (Table 55-5). Spurious hypokalemia occurs in patients with leukemia and very elevated white blood cell counts if plasma for analysis is left at room temperature, permitting the white blood cells to take up potassium from the plasma. With a transcellular shift, there is no change in total body potassium, although there may be concomitant potassium depletion resulting from other factors. Decreased intake, extrarenal losses, and renal losses are all associated with total body potassium depletion.

Table 55-5 Causes of Hypokalemia

SPURIOUS
High white blood cell count
TRANSCELLULAR SHIFTS
Alkalemia
Insulin
α-Adrenergic agonists
Drugs/toxins (theophylline, barium, toluene, cesium chloride, hydroxychloroquine)
Hypokalemic periodic paralysis (OMIM 170400)
Thyrotoxic period paralysis
Refeeding syndrome
DECREASED INTAKE
Anorexia nervosa
EXTRARENAL LOSSES
Diarrhea
Laxative abuse
Sweating
Sodium polystyrene sulfonate (Kayexalate) or clay ingestion
RENAL LOSSES
With metabolic acidosis
Distal rental tubular acidosis (OMIM 179800/602722/267300)
Proximal renal tubular acidosis (OMIM 604278)*
Ureterosigmoidostomy
Diabetic ketoacidosis
Without specific acid–base disturbance
Tubular toxins: amphotericin, cisplatin, aminoglycosides
Interstitial nephritis
Diuretic phase of acute tubular necrosis
Postobstructive diuresis
Hypomagnesemia
High urine anions (e.g., penicillin or penicillin derivatives)
With metabolic alkalosis
Low urine chloride
Emesis or nasogastric suction
Chloride-losing diarrhea (OMIM 214700)
Cystic fibrosis (OMIM 219700)
Low-chloride formula
Posthypercapnia
Previous loop or thiazide diuretic use
High urine chloride and normal blood pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/602522/241200/601678)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Loop and thiazide diuretics
High urine chloride and high blood pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17β-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)

*Most cases of proximal renal tubular acidosis are not caused by this primary genetic disorder. Proximal renal tubular acidosis is usually part of Fanconi syndrome, which has multiple etiologies.

EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

Because the intracellular potassium concentration is much higher than the plasma level, a significant amount of potassium can move into cells without markedly changing the intracellular potassium concentration. Alkalemia is one of the more common causes of a transcellular shift. The effect is much greater with a metabolic alkalosis than with a respiratory alkalosis. The impact of exogenous insulin on potassium movement into the cells is substantial in patients with diabetic ketoacidosis. Endogenous insulin may be the cause when a patient is given a bolus of glucose. Both endogenous (epinephrine in stress) and exogenous (albuterol) β-adrenergic agonists stimulate cellular uptake of potassium. Theophylline overdose, barium intoxication, administration of cesium chloride (a homeopathic cancer remedy), and toluene intoxication from paint or glue sniffing can cause a transcellular shift hypokalemia, often with severe clinical manifestations. Children with **hypokalemic periodic paralysis,** a rare autosomal dominant disorder, have acute cellular uptake of potassium (see Chapter 611). **Thyrotoxic periodic paralysis,** which is more common in Asians, is an unusual initial manifestation of hyperthyroidism. Affected patients have dramatic hypokalemia as a result of a transcellular shift of potassium. Hypokalemia can occur during refeeding syndrome (see Chapter 338.8).

Inadequate potassium intake occurs in **anorexia nervosa;** accompanying bulimia and laxative or diuretic abuse exacerbates the potassium deficiency. Sweat losses of potassium can be significant during vigorous exercise in a hot climate. Associated volume depletion and hyperaldosteronism increase renal losses of potassium (discussed later). Diarrheal fluid has a high concentration of potassium, and hypokalemia as a result of diarrhea is usually associated with a metabolic acidosis resulting from stool losses of bicarbonate. In contrast, a normal acid–base balance or a mild metabolic alkalosis is seen with laxative abuse. Intake of sodium polystyrene sulfonate or ingestion of clay because of pica increases stool losses of potassium.

Urinary potassium wasting may be accompanied by a metabolic acidosis (proximal or distal RTA). In diabetic ketoacidosis, although it is often associated with normal plasma potassium caused by transcellular shifts, there is significant total body potassium depletion from urinary losses because of the osmotic diuresis, and the potassium level may decrease dramatically with insulin therapy (see Chapter 589). Both the polyuric phase of acute tubular necrosis and postobstructive diuresis cause transient, highly variable potassium wasting and may be associated with a metabolic acidosis. Tubular damage, which occurs either directly from medications or secondary to interstitial nephritis, is often accompanied by other tubular losses of nutrients, including magnesium, sodium, and water. Such tubular damage may cause a secondary RTA with a metabolic acidosis. Isolated magnesium deficiency causes renal potassium wasting. Penicillin is an anion that is excreted in the urine, resulting in increased potassium excretion because the penicillin anion must be accompanied by a cation. Hypokalemia from penicillin therapy occurs only with the sodium salt of penicillin, not with the potassium salt.

Urinary potassium wasting is often accompanied by a metabolic alkalosis. This condition is usually associated with increased aldosterone, which increases urinary potassium and acid losses, contributing to the hypokalemia and the metabolic alkalosis. Other mechanisms often contribute to both the potassium losses and the metabolic alkalosis. With emesis or nasogastric suction, there is gastric loss of potassium, but this is fairly minimal, given the low potassium content of gastric fluid (≈10 mEq/L). More important is the gastric loss of hydrochloric acid (HCl), leading to a metabolic alkalosis and a state of volume depletion. The kidney compensates for the metabolic alkalosis by excreting bicarbonate in the urine, but there is obligate loss of potassium and sodium with the bicarbonate. The volume depletion raises aldosterone levels, further increasing urinary potassium losses and preventing correction of the metabolic alkalosis and hypokalemia until the volume depletion is corrected. Urinary chloride is low as a response to the volume depletion. Because the volume depletion is secondary to chloride loss, this is a state of chloride deficiency. There

were cases of chloride deficiency resulting from infant formula deficient in chloride, which caused a metabolic alkalosis with hypokalemia and low urine chloride levels. Current infant formula is not deficient in chloride. A similar mechanism occurs in cystic fibrosis because of chloride loss in sweat. In **congenital chloride-losing diarrhea**, an autosomal recessive disorder, there is high stool loss of chloride, leading to metabolic alkalosis, an unusual sequela of diarrhea. Because of stool potassium losses, chloride deficiency, and metabolic alkalosis, patients with this disorder have hypokalemia. During respiratory acidosis, there is renal compensation, with retention of bicarbonate and excretion of chloride. After the respiratory acidosis is corrected, the patients have chloride deficiency and posthypercapnic alkalosis with secondary hypokalemia. Patients with chloride deficiency, metabolic alkalosis, and hypokalemia have a urinary chloride level of <10 mEq/L. Loop and thiazide diuretics lead to hypokalemia, metabolic alkalosis, and chloride deficiency. During treatment, these patients have high urine chloride levels resulting from the effect of the diuretic. However, after the diuretics are discontinued, there is residual chloride deficiency, the urinary chloride level is appropriately low, and neither the hypokalemia nor the alkalosis resolves until the chloride deficiency is corrected.

The combination of metabolic alkalosis, hypokalemia, a high urine chloride level, and normal blood pressure is characteristic of **Bartter syndrome, Gitelman syndrome,** and **current diuretic use.** Patients with any of these conditions have high urinary losses of potassium and chloride, despite a state of relative volume depletion with secondary hyperaldosteronism. Bartter and Gitelman syndromes are autosomal recessive disorders caused by defects in tubular transporters (see Chapter 531). Bartter syndrome is usually associated with hypercalciuria, and often with nephrocalcinosis, whereas children with Gitelman syndrome have low urinary calcium losses but hypomagnesemia as a consequence of urinary magnesium losses. Some patients with Bartter syndrome have hypomagnesemia.

Some patients with hypoparathyroidism and hypocalcemia caused by an activating mutation of the calcium-sensing receptor (autosomal dominant hypoparathyroidism) have hypokalemia, hypomagnesemia, and metabolic alkalosis. The reason is that activation of the calcium-sensing receptor in the loop of Henle impairs tubular resorption of sodium and chloride, causing volume depletion and secondary hyperaldosteronism. **EAST syndrome,** an autosomal recessive disorder caused by mutations in the gene for a potassium channel present in the kidney, inner ear, and brain, consists of epilepsy, ataxia, sensorineural hearing loss, and tubulopathy (hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria).

In the presence of high aldosterone levels, there is urinary loss of potassium, hypokalemia, metabolic alkalosis, and an elevated urinary chloride level. Also, renal retention of sodium leads to hypertension. Primary hyperaldosteronism caused by adenoma or hyperplasia is much less common in children than in adults (see Chapter 578). Glucocorticoid-remediable aldosteronism, an autosomal dominant disorder that leads to high levels of aldosterone, is often diagnosed in childhood, although hypokalemia is not always present.

Increased aldosterone levels may be secondary to increased renin production. Renal artery stenosis leads to hypertension from increased renin and secondary hyperaldosteronism. The increased aldosterone can cause hypokalemia and metabolic alkalosis, although most patients have normal electrolyte levels. Renin-producing tumors, which are extremely rare, can cause hypokalemia.

A variety of disorders cause hypertension and hypokalemia without increased aldosterone levels. Some are a result of increased levels of mineralocorticoids other than aldosterone. Such increases occur in 2 forms of **congenital adrenal hyperplasia** (see Chapter 576). In 11β-hydroxylase deficiency, which is associated with virilization, the value of 11-deoxycorticosterone is elevated, causing variable hypertension and hypokalemia. A similar mechanism, increased 11-deoxycorticosterone, occurs in 17α-hydroxylase deficiency, but patients with this disorder are more uniformly hypertensive and hypokalemic, and they have a defect in sex hormone production. Cushing syndrome, frequently associated with hypertension, less commonly causes metabolic alkalosis and hypokalemia. This is secondary to the mineralocorticoid activity of cortisol. In 11β-hydroxysteroid dehydrogenase deficiency, an autosomal recessive disorder, the enzymatic defect prevents the conversion of cortisol to cortisone in the kidney. Because cortisol binds to and activates the aldosterone receptor, children with this deficiency have all the features of excessive mineralocorticoids, including hypertension, hypokalemia, and metabolic alkalosis. Patients with this disorder, which is also called apparent mineralocorticoid excess, respond to spironolactone therapy, which blocks the mineralocorticoid receptor. An acquired form of 11β-hydroxysteroid dehydrogenase deficiency occurs from the ingestion of substances that inhibit this enzyme. A classic example is glycyrrhizic acid, which is found in natural licorice. **Liddle syndrome** is an autosomal dominant disorder that results from an activating mutation of the distal nephron sodium channel that is normally upregulated by aldosterone. Patients have the characteristics of hyperaldosteronism—hypertension, hypokalemia, and alkalosis—but low serum aldosterone levels. These patients respond to the potassium-sparing diuretics (triamterene and amiloride) that inhibit this sodium channel (see Chapter 531.3).

Clinical Manifestations

The heart and skeletal muscle are especially vulnerable to hypokalemia. ECG changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and the P wave. Ventricular fibrillation and torsades de pointes may occur, although usually only in the context of underlying heart disease. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias, such as supraventricular tachycardia, ventricular tachycardia, and heart block (see Chapter 435).

The clinical consequences of hypokalemia in skeletal muscle include muscle weakness and cramps. Paralysis is a possible complication, generally only at potassium levels <2.5 mEq/L. It usually starts in the legs and moves to the arms. Respiratory paralysis may require mechanical ventilation. Some patients have rhabdomyolysis; the risk increases with exercise. Hypokalemia slows gastrointestinal motility. This effect manifests as constipation; with potassium levels <2.5 mEq/L, an ileus may occur. Hypokalemia impairs bladder function, potentially leading to urinary retention.

Hypokalemia causes **polyuria** and **polydipsia** by impairing urinary concentrating ability, which produces nephrogenic diabetes insipidus. Hypokalemia stimulates renal ammonia production, an effect that is clinically significant if hepatic failure is present, because the liver cannot metabolize the ammonia. Consequently, hypokalemia may worsen hepatic encephalopathy. Chronic hypokalemia may cause kidney damage, including interstitial nephritis and renal cysts.

Diagnosis

Most causes of hypokalemia are readily apparent from the history. It is important to review the child's diet, gastrointestinal losses, and medications. Both emesis and diuretic use can be surreptitious. The presence of hypertension suggests excess mineralocorticoids. Concomitant electrolyte abnormalities are useful clues. The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea and of distal and proximal RTA. A concurrent metabolic alkalosis is characteristic of emesis or nasogastric losses, aldosterone excess, use of diuretics, and Bartter and Gitelman syndromes. Figure 55-5 shows an approach to persistent hypokalemia.

If a clear etiology is not apparent, the measurement of urinary potassium distinguishes between renal and extrarenal losses. The kidneys should conserve potassium in the presence of extrarenal losses. Urinary potassium losses can be assessed with a 24 hr urine collection, a spot potassium : creatinine ratio, a fractional excretion of potassium, or calculation of the transtubular potassium gradient (TTKG), which is the most widely used approach in children:

$$\text{TTKG} = [\text{K}]_{\text{urine}}/[\text{K}]_{\text{plasma}} \times (\text{plasma osmolality/urine osmolality})$$

where $[K]_{urine}$ = urine potassium concentration and $[K]_{plasma}$ = plasma potassium concentration.

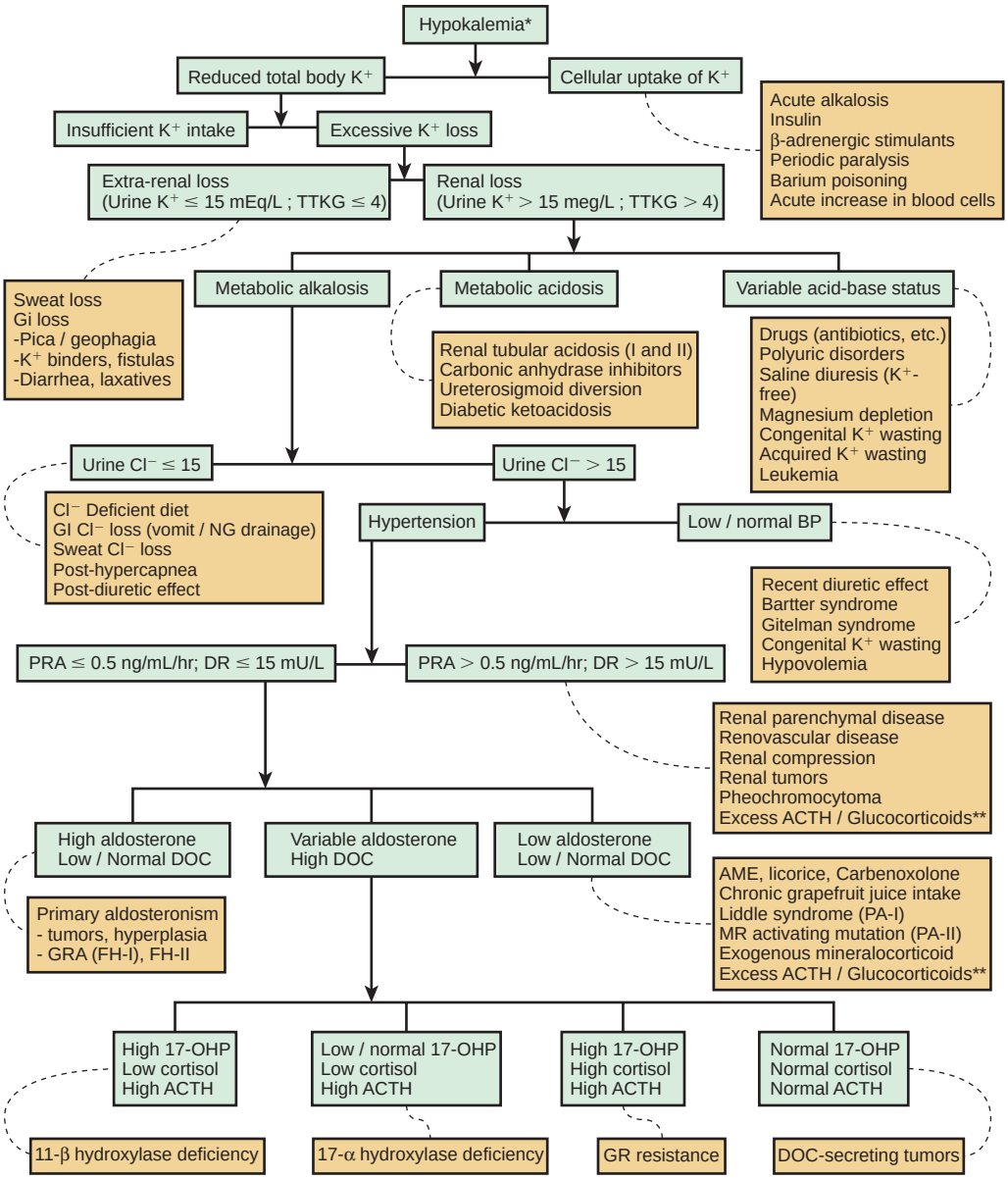

Figure 55-5 Diagnostic algorithm to evaluate persistent hypokalemia. *Spurious hypokalemia must be excluded. **Hypokalemia is uncommon in uncomplicated edematous disorders and in conditions associated with excessive glucocorticosteroids. Conditions associated with high circulating levels of glucocorticosteroids often have normal renin activity. 17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone; AME, apparent mineralocorticoid excess; BP, blood pressure; Cl^-, chloride; DOC, 11-deoxycorticosterone; DR, direct renin assay; GI, gastrointestinal; FH-II, familial hyperaldosteronism type II; GR, glucocorticoid receptor; GRA (FH-I), glucocorticoid remediable aldosteronism (familial hyperaldosteronism type I); K^+, potassium; MR, mineralocorticoid receptor; PA-I, pseudoaldosteronism type I; PA-II, pseudoaldosteronism type II; PRA, plasma renin activity; TTKG, transtubular potassium gradient. *(From Shoemaker LR, Eaton BV, Buchino JJ: A three-year-old with persistent hypokalemia, J Pediatr 151:696–699, 2007.)*

The urine osmolality must be greater than the serum osmolality for the result of this calculation to be valid. A TTKG >4 in the presence of hypokalemia suggests excessive urinary losses of potassium. The urinary potassium excretion value can be misleading if the stimulus for renal loss, such as a diuretic, is no longer present.

Treatment

Factors that influence the treatment of hypokalemia include the potassium level, clinical symptoms, renal function, the presence of transcellular shifts of potassium, ongoing losses, and the patient's ability to tolerate oral potassium. Severe, symptomatic hypokalemia requires aggressive treatment. Supplementation is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive potassium. The plasma potassium level does not always provide an accurate estimation of the total body potassium deficit because there may be shifts of potassium from the intracellular space to the plasma. Clinically, such shifts occur most commonly with metabolic acidosis and the insulin deficiency of diabetic ketoacidosis; the plasma potassium measurement underestimates the degree of total body potassium depletion. When these problems are corrected, potassium moves into the intracellular space, so more potassium supplementation is required to correct the hypokalemia. Likewise, the presence of a transcellular shift of potassium into the cells indicates that the total body potassium depletion is less severe. In an isolated transcellular shift, as occurs in hypokalemic periodic paralysis, potassium supplementation should be used cautiously,

given the risk of hyperkalemia when the transcellular shift resolves. This caution is especially required in thyrotoxic periodic paralysis, which responds dramatically to propranolol, with correction of weakness and hypokalemia. Patients who have ongoing losses of potassium need correction of the deficit and replacement of the ongoing losses.

Because of the risk of hyperkalemia, intravenous potassium should be used very cautiously. Oral potassium is safer, albeit not as rapid in urgent situations. Liquid preparations are bitter tasting; microencapsulated or wax matrix formulations are less irritating than tablets to the gastric mucosa (oral dose: 2-4 mEq/kg/day with a maximum of 120-240 mEq/day in divided doses). The dose of intravenous potassium is 0.5-1.0 mEq/kg, usually given over 1 hr. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred. Potassium chloride is the usual choice for supplementation, although the presence of concurrent electrolyte abnormalities may dictate other options. Patients with acidosis and hypokalemia can receive potassium acetate or potassium citrate. If hypophosphatemia is present, then some of the potassium deficit can be replaced with potassium phosphate. It is sometimes possible to decrease ongoing losses of potassium. For patients with excessive urinary losses, potassium-sparing diuretics are effective, but they need to be used cautiously in patients with renal insufficiency. If hypokalemia, metabolic alkalosis, and volume depletion are present (with gastric losses), then restoration of intravascular volume with adequate sodium chloride will decrease urinary potassium losses. Correction of concurrent hypomagnesemia is important because hypomagnesemia may cause hypokalemia. Disease-specific therapy is effective in many of the genetic tubular disorders.

Bibliography is available at Expert Consult.

55.5 Magnesium

Larry A. Greenbaum

MAGNESIUM METABOLISM

Body Content and Physiologic Function

Magnesium is the fourth most common cation in the body and the third most common intracellular cation (see Fig. 55-3). Between 50% and 60% of body magnesium is in bone, where it serves as a reservoir because 30% is exchangeable, allowing movement to the extracellular space. Most intracellular magnesium is bound to proteins; only approximately 25% is exchangeable. Because cells with higher metabolic rates have higher magnesium concentrations, most intracellular magnesium is present in muscle and liver.

The normal plasma magnesium concentration is 1.5-2.3 mg/dL (1.2-1.9 mEq/L; 0.62-0.94 mmol/L), with some variation among clinical laboratories. Infants have slightly higher plasma magnesium concentrations than older children and adults. Only 1% of body magnesium is extracellular (60% ionized; 15% complexed; 25% protein bound). In the United States, serum magnesium is reported as mg/dL (Table 55-6).

Table 55-6 Conversion Factors for Calcium, Magnesium, and Phosphorus

	UNIT	CONVERSION FACTOR	UNIT
Calcium	mg/dL	0.25	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.5	mEq/L
Magnesium	mg/dL	0.411	mmol/L
	mEq/L	0.5	mmol/L
	mg/dL	0.822	mEq/L
Phosphorus	mg/dL	0.32	mmol/L

Values in the left-column unit are converted into the right-column unit via multiplying by the conversion factor (e.g., calcium of 10 mg/dL × 0.25 = 2.5 mmol/L). Division of the right-column unit by the conversion factor converts to the units of the left-column unit.

Magnesium is a necessary cofactor for hundreds of enzymes. It is important for membrane stabilization and nerve conduction. Adenosine triphosphate (ATP) and guanosine triphosphate need associated magnesium when they are used by adenosine triphosphatases, cyclases, and kinases.

Intake

Between 30% and 50% of dietary magnesium is absorbed. Good dietary sources include green vegetables, cereals, nuts, meats, and hard water, although many foods contain magnesium. Human milk contains approximately 35 mg/L of magnesium; formula contains 40-70 mg/L. The small intestine is the major site of magnesium absorption, but the regulation of magnesium absorption is poorly understood. There is passive absorption, which permits high absorption in the presence of excessive intake. It probably occurs via a paracellular mechanism. Absorption is diminished in the presence of substances that complex with magnesium (free fatty acids, fiber, phytate, phosphate, oxalate); increased intestinal motility and calcium also decrease magnesium absorption. Vitamin D and parathyroid hormone (PTH) may enhance absorption, although this effect is limited. Intestinal absorption does increase when intake is decreased, possibly via a saturable active transport system. If there is no oral intake of magnesium, obligatory secretory losses prevent the complete elimination of intestinal losses.

Excretion

Renal excretion is the principal regulator of magnesium balance. There is no defined hormonal regulatory system, although PTH may increase tubular resorption. Approximately 15% of resorption occurs in the proximal tubule, and 70% in the thick ascending limb (TAL) of the loop of Henle. Proximal resorption may be higher in neonates. High serum magnesium levels inhibit resorption in the TAL, suggesting that active transport is involved. Approximately 5-10% of filtered magnesium is resorbed in the distal tubule. Hypomagnesemia increases absorption in the TAL and the distal tubule.

HYPOMAGNESEMIA

Hypomagnesemia is relatively common in hospitalized patients, although most cases are asymptomatic. Detection requires a high index of suspicion because magnesium is not measured in most basic metabolic panels.

Etiology and Pathophysiology

Gastrointestinal and renal losses are the major causes of hypomagnesemia (Table 55-7). Diarrheal fluid contains up to 200 mg/L of magnesium; gastric contents have only approximately 15 mg/L, but high losses can cause depletion. Steatorrhea causes magnesium loss as a result of the formation of magnesium-lipid salts; restriction of dietary fat can decrease losses.

Hypomagnesemia with secondary hypocalcemia, a rare autosomal recessive disorder, is caused by decreased intestinal absorption of magnesium and renal magnesium wasting. Patients with this disorder have mutations in a gene (*TRPM6*) that is expressed in intestine and kidney. TRPM6 codes for a transient receptor potential cation channel. The patients have seizures, tetany, tremor, or restlessness at 2-8 wk of life as a result of severe hypomagnesemia (0.2-0.8 mg/dL) and secondary hypocalcemia.

Renal losses may occur because of medications that are direct tubular toxins. Amphotericin frequently causes significant magnesium wasting and is typically associated with other tubular defects (especially potassium wasting). Cisplatin produces dramatic renal magnesium losses. Diuretics affect tubular handling of magnesium. Loop diuretics cause a mild increase in magnesium excretion, and thiazide diuretics have even less effect. Chronic use of proton pump inhibitors may cause hypomagnesemia. Potassium-sparing diuretics reduce magnesium losses. Osmotic agents, such as mannitol, glucose in diabetes

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Table 55-7 Causes of Hypomagnesemia

GASTROINTESTINAL DISORDERS
Diarrhea
Nasogastric suction or emesis
Inflammatory bowel disease
Celiac disease
Cystic fibrosis
Intestinal lymphangiectasia
Small bowel resection or bypass
Pancreatitis
Protein-calorie malnutrition
Hypomagnesemia with secondary hypocalcemia (OMIM 602014)*
RENAL DISORDERS
Medications
Amphotericin
Cisplatin
Cyclosporin
Loop diuretics
Mannitol
Pentamidine
Proton pump inhibitors
Aminoglycosides
Thiazide diuretics
Epidermal growth factor receptor inhibitors
Diabetes
Acute tubular necrosis (recovery phase)
Postobstructive nephropathy
Chronic kidney diseases
Interstitial nephritis
Glomerulonephritis
Post–renal transplantation
Hypercalcemia
Intravenous fluids
Primary aldosteronism
Genetic diseases
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/601678)
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (OMIM 248250)
Familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement (OMIM 248190)
Autosomal recessive renal magnesium wasting with normocalciuria (OMIM 611718)
Renal cysts and diabetes syndrome (OMIM 137920)
Autosomal dominant hypomagnesemia (OMIM 160120/613882/154020)
EAST syndrome (OMIM 612780)
Autosomal dominant hypoparathyroidism (OMIM 146200)
Mitochondrial disorders (OMIM 500005)
MISCELLANEOUS CAUSES
Poor intake
Hungry bone syndrome
Insulin administration
Pancreatitis
Intrauterine growth retardation
Infants of diabetic mothers
Exchange transfusion

*This disorder is also associated with renal magnesium wasting.
EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

mellitus, and urea in the recovery phase of acute tubular necrosis, increase urinary magnesium losses. Epidermal growth factor receptor inhibitors cause renal magnesium wasting. Intravenous fluid, by expanding the intravascular volume, decreases renal resorption of sodium and water, thereby impairing magnesium resorption. Hypercalcemia inhibits magnesium resorption in the loop of Henle, although this inhibition does not occur in hypercalcemia caused by familial hypercalcemic hypocalciuria or lithium.

A number of rare genetic diseases cause renal magnesium loss. **Gitelman and Bartter syndromes,** both autosomal recessive disorders, are the most common entities (see Chapter 531). Gitelman syndrome, which is caused by a defect in the thiazide-sensitive Na^+-Cl^- cotransporter in the distal tubule, is usually associated with hypomagnesemia. Hypomagnesemia occurs in a minority of patients with Bartter syndrome, which can be caused by mutations in multiple genes that are necessary for sodium and chloride reabsorption in the loop of Henle. In both disorders, there is hypokalemic metabolic alkalosis. Typically, hypomagnesemia is not severe and is asymptomatic, although tetany as a result of hypomagnesemia occasionally occurs.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (Michelis-Castrillo syndrome), an autosomal recessive disorder, is caused by mutations in the gene for claudin 16 (paracellin-1), which is located in the tight junctions of the TAL of the loop of Henle. Patients with the disease have severe renal wasting of magnesium and calcium with secondary hypomagnesemia and nephrocalcinosis; serum calcium levels are normal. Chronic renal failure frequently occurs during childhood. Other features include kidney stones, urinary tract infections, hematuria, increased PTH levels, tetany, seizures, incomplete distal RTA, hyperuricemia, polyuria, and polydipsia. Patients with **familial hypomagnesemia with hypercalciuria, nephrocalcinosis, and severe ocular involvement** have mutations in the gene for claudin 19.

Autosomal recessive renal magnesium wasting with normocalciuria is caused by mutations in the epidermal growth factor gene. Clinical manifestations include seizures, mild to moderate psychomotor retardation, and brisk tendon reflexes.

Autosomal dominant renal magnesium wasting is caused by mutations in a number of different genes. A dominant-negative mutation in the gene encoding the Na^+,K^+-adenosine triphosphatase γ subunit is associated with hypomagnesemia, increased urinary magnesium losses, hypocalciuria, and normocalcemia. Patients may present with seizures; most are asymptomatic, despite serum magnesium levels of 0.8-1.5 mg/dL. Mutations in *CNNM2*, which encodes a protein that mediates magnesium-sensitive sodium currents, cause isolated hypomagnesemia. A mutation in *KCNA1*, a gene that encodes a potassium channel, also causes an autosomal dominant form of hypomagnesemia; symptoms may be severe.

Renal cysts and diabetes syndrome, which is caused by mutations in the gene for hepatocyte nuclear factor-1β, is associated with hypomagnesemia, despite the frequent presence of renal insufficiency. The hypomagnesemia is usually mild but may cause symptomatic hypocalcemia. **EAST syndrome** is caused by mutations in a potassium channel, and patients with this autosomal recessive disorder have hypokalemia, metabolic alkalosis, and hypomagnesemia. **Autosomal dominant hypoparathyroidism** is caused by an activating mutation in the calcium-sensing receptor, which also senses magnesium levels in the kidney (see Chapter 571). The mutated receptor inappropriately perceives that magnesium and calcium levels are elevated, leading to urinary wasting of both cations. Hypomagnesemia, if present, is usually mild. A mutation in a mitochondrially encoded transfer RNA is associated with hypomagnesemia, hypertension, and hypercholesterolemia. Hypomagnesemia is occasionally present in children with other mitochondrial disorders.

Poor intake is an unusual cause of hypomagnesemia, although it can be seen in children who are hospitalized and receive only intravenous fluids without magnesium. In **hungry bone syndrome,** which most frequently occurs after parathyroidectomy in patients with hyperparathyroidism, magnesium moves into bone as a result of accelerated bone formation. These patients usually have hypocalcemia and hypophosphatemia via the same mechanism. A similar mechanism can occur during the **refeeding phase of protein-calorie malnutrition** in children, with high magnesium use during cell growth depleting the patient's limited reserves. Insulin therapy stimulates uptake of magnesium by cells, and in diabetic ketoacidosis, in which total body magnesium is low because of osmotic losses, hypomagnesemia frequently occurs. In **pancreatitis,** there is saponification of magnesium and calcium in necrotic fat, causing both hypomagnesemia and hypocalcemia.

Transient hypomagnesemia in newborns, which is sometimes idiopathic, is more commonly seen in infants of diabetic mothers, presumably as a result of maternal depletion from osmotic losses. Other maternal diseases that cause magnesium losses predispose infants to hypomagnesemia. Hypomagnesemia is more common in infants with intrauterine growth restriction. Hypomagnesemia may develop in newborn infants who require exchange transfusions because of magnesium removal by the citrate in banked blood.

Clinical Manifestations

Hypomagnesemia causes secondary hypocalcemia by impairing the release of PTH by the parathyroid gland and through blunting of the tissue response to PTH. Thus, hypomagnesemia is part of the differential diagnosis of hypocalcemia (see Chapter 571). It usually occurs only at magnesium levels <0.7 mg/dL. The dominant manifestations of hypomagnesemia are caused by hypocalcemia: tetany, presence of Chvostek and Trousseau signs, and seizures. However, with severe hypomagnesemia, these same signs and symptoms may be present despite normocalcemia. Persistent hypocalcemia caused by hypomagnesemia is a rare cause of rickets.

Many causes of hypomagnesemia also result in hypokalemia. Hypomagnesemia may produce renal potassium wasting and hypokalemia that corrects only with magnesium therapy. ECG changes with hypomagnesemia include flattening of the T wave and lengthening of the ST segment. Arrhythmias may occur, almost always in the setting of underlying heart disease.

Diagnosis

The etiology of hypomagnesemia is often readily apparent from the clinical situation. The child should be assessed for gastrointestinal disease, adequate intake, and kidney disease, with close attention paid to medications that may cause renal magnesium wasting. When the diagnosis is uncertain, an evaluation of urinary magnesium losses distinguishes between renal and nonrenal causes. The fractional excretion of magnesium (FE_{Mg}) is calculated via the following formula:

$$FE_{Mg} = (U_{Mg} \times P_{Cr})/([0.7 \times P_{Mg}] \times U_{Cr}) \times 100$$

where U_{Mg} is urinary magnesium concentration, P_{Cr} is plasma creatinine concentration, P_{Mg} is plasma magnesium concentration, and U_{Cr} is urinary magnesium concentration. The plasma magnesium concentration is multiplied by 0.7 because approximately 30% is bound to albumin and not filtered at the glomerulus.

The FE_{Mg} does not vary with age, but it does change according to the serum magnesium concentration. The FE_{Mg} ranges from 1-8% in children with normal magnesium levels. In the presence of hypomagnesemia as a result of extrarenal causes, it should be low because of renal conservation, typically <2%. The FE_{Mg} is inappropriately elevated in the setting of renal magnesium wasting; values are usually >4% and frequently are >10%. The measurement should not be made during a magnesium infusion, because the acute increase in serum magnesium increases urinary magnesium. Other approaches for evaluating urinary magnesium losses include calculation of 24 hr urinary magnesium losses and of the ratio of urine magnesium : urine creatinine, both of which vary with age.

The genetic causes of renal magnesium loss are distinguished on the basis of the measurement of other serum and urinary electrolytes. Children with Gitelman and Bartter syndromes have hypokalemia and metabolic alkalosis.

Treatment

Severe hypomagnesemia is treated with parenteral magnesium. Magnesium sulfate is given at a dose of 25-50 mg/kg (0.05-0.1 mL/kg of a 50% solution; 2.5-5.0 mg/kg of elemental magnesium). It is administered as a slow intravenous infusion, although it may be given intramuscularly in neonates. The rate of intravenous infusion should be slowed if a patient experiences diaphoresis, flushing, or a warm sensation. The dose is often repeated every 6 hr (every 8-12 hr in neonates), for a total of 2-3 doses, before the plasma magnesium concentration is rechecked. Lower doses are used in children with renal insufficiency.

Long-term therapy is usually given orally. Preparations include magnesium gluconate (5.4 mg elemental magnesium/100 mg), magnesium oxide (60 mg elemental magnesium/100 mg), and magnesium sulfate (10 mg elemental magnesium/100 mg). There are sustained-released preparations, such as Slow-Mag (60 mg elemental magnesium/tablet) and Mag-Tab SR (84 mg elemental magnesium/tablet). Oral magnesium dosing should be divided to decrease cathartic side effects. Alternatives to oral magnesium are intramuscular injections and nighttime nasogastric infusion, both designed to minimize diarrhea. Magnesium supplementation must be used cautiously in the context of renal insufficiency.

HYPERMAGNESEMIA

Clinically significant hypermagnesemia is almost always secondary to excessive intake. It is unusual, except in neonates born to mothers who are receiving intravenous magnesium for preeclampsia or eclampsia (see Chapter 106).

Etiology and Pathophysiology

There is no feedback mechanism to prevent magnesium absorption from the gastrointestinal tract. Magnesium is present in high amounts in certain laxatives, enemas, cathartics used to treat drug overdoses, and antacids. It is also usually present in total parenteral nutrition, and neonates may receive high amounts transplacentally if maternal levels are elevated. Usually the kidneys excrete excessive magnesium, but this ability is diminished in patients with chronic renal failure. In addition, neonates and young infants are vulnerable to excessive magnesium ingestion because of their reduced GFR. Most pediatric cases not related to maternal hypermagnesemia occur in infants as a result of excessive use of antacids or laxatives. Mild hypermagnesemia may occur in chronic renal failure, familial hypocalciuric hypercalcemia, diabetic ketoacidosis, lithium ingestion, milk-alkali syndrome, and tumor lysis syndrome. The hypermagnesemia in diabetic ketoacidosis occurs despite significant intracellular magnesium depletion as a result of urinary losses; hypomagnesemia often occurs after insulin treatment.

Clinical Manifestations

Symptoms usually do not appear until the plasma magnesium level is >4.5 mg/dL. Hypermagnesemia inhibits acetylcholine release at the neuromuscular junction, producing hypotonia, hyporeflexia, and weakness; paralysis occurs at high concentrations. The neuromuscular effects may be exacerbated by aminoglycoside antibiotics. Direct CNS depression causes lethargy and sleepiness; infants have a poor suck. Elevated magnesium values are associated with hypotension because of vascular dilation, which also causes flushing. Hypotension can be profound at higher concentrations from a direct effect on cardiac function. ECG changes include prolonged PR, QRS, and QT intervals. Severe hypermagnesemia (>15 mg/dL) causes complete heart block and cardiac arrest. Other manifestations of hypermagnesemia include nausea, vomiting, and hypocalcemia.

Diagnosis

Except for the case of the neonate with transplacental exposure, a high index of suspicion and a good history are necessary to make the diagnosis of hypermagnesemia. Prevention is essential; magnesium-containing compounds should be used judiciously in children with renal insufficiency.

Treatment

Most patients with normal renal function rapidly clear excess magnesium. Intravenous hydration and loop diuretics can accelerate this process. In severe cases, especially in patients with underlying renal insufficiency, dialysis may be necessary. Hemodialysis works faster than peritoneal dialysis. Exchange transfusion is another option in newborn infants. Supportive care includes monitoring of cardiorespiratory status, provision of fluids, monitoring of electrolyte levels, and

the use of pressors for hypotension. In acute emergencies, especially in the context of severe neurologic or cardiac manifestations, 100 mg/kg of intravenous calcium gluconate is transiently effective.

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55.6 Phosphorus

Larry A. Greenbaum

Approximately 65% of plasma phosphorus is in phospholipids, but these compounds are insoluble in acid and are not measured by clinical laboratories. It is the phosphorus content of plasma phosphate that is determined. The result is reported as either phosphate or phosphorus, although even when the term phosphate is used, it is actually the phosphorus concentration that is measured and reported. The result is that the terms phosphate and phosphorus are often used interchangeably. The term *phosphorus* is preferred when one is referring to the plasma concentration. Conversion from the units used in the United States (mg/dL) to mmol/L is straightforward (see Table 55-6).

PHOSPHORUS METABOLISM

Body Content and Physiologic Function

Most phosphorus is in bone or is intracellular, with <1% in plasma. At a physiologic pH, there are monovalent and divalent forms of phosphate because the pK of these forms is 6.8. Approximately 80% is divalent, and the remainder is monovalent at a pH of 7.4. A small percentage of plasma phosphate, approximately 15%, is protein bound. The remainder can be filtered by the glomerulus, with most existing as free phosphate and a small percentage complexed with calcium, magnesium, or sodium. Phosphate is the most plentiful intracellular anion, although the majority is part of a larger compound (ATP).

More than that of any other electrolyte, the phosphorus concentration varies with age (Table 55-8). The teleologic explanation for the high concentration during childhood is the need for phosphorus to facilitate growth. There is diurnal variation in the plasma phosphorus concentration, with the peak during sleep.

Phosphorus, as a component of ATP and other trinucleotides, is critical for cellular energy metabolism. It is necessary for cell signaling and nucleic acid synthesis, and it is a component of cell membranes and other structures. Along with calcium, phosphorus is necessary for skeletal mineralization. There is a significant need for a net positive phosphorus balance during growth, with the growing skeleton especially vulnerable to deficiency.

Intake

Phosphorus is readily available in food. Milk and milk products are the best sources of phosphorus; high concentrations are present in meat and fish. Vegetables have more phosphorus than fruits and grains. Gastrointestinal absorption of phosphorus is fairly proportional to intake, with approximately 65% of intake being absorbed, including a small amount that is secreted. Absorption, almost exclusively in the small intestine, occurs via a paracellular diffusive process and a vitamin D–regulated transcellular pathway. However, the impact of the change in phosphorus absorption caused by vitamin D is relatively small compared with the effect of variations in phosphorus intake.

Table 55-8 Serum Phosphorus Levels During Childhood

AGE	PHOSPHORUS LEVEL (mg/dL)
0-5 day	4.8-8.2
1-3 yr	3.8-6.5
4-11 yr	3.7-5.6
12-15 yr	2.9-5.4
16-19 yr	2.7-4.7

Excretion

Despite the wide variation in phosphorus absorption dictated by oral intake, excretion matches intake, except for the needs for growth. The kidney regulates phosphorus balance, which is determined by intrarenal mechanisms and hormonal actions on the nephron.

Approximately 90% of plasma phosphate is filtered at the glomerulus, although there is some variation based on plasma phosphate and calcium concentrations. There is no significant secretion of phosphate along the nephron. Resorption of phosphate occurs mostly in the proximal tubule, although a small amount can be resorbed in the distal tubule. Normally, approximately 85% of the filtered load is resorbed. A sodium-phosphate cotransporter mediates the uptake of phosphate into the cells of the proximal tubule.

The dietary phosphorus determines the amount of phosphate resorbed by the nephron. There are both acute and chronic changes in phosphate resorption that are based on intake. Many of these changes appear to be mediated by intrarenal mechanisms that are independent of regulatory hormones. Fibroblast growth factor-23 (FGF-23) inhibits renal resorption of phosphorus in the proximal tubule, and its level increases in the setting of hyperphosphatemia. FGF-23 also inhibits synthesis of calcitriol in the kidney by decreasing 1α-hydroxylase activity.

PTH, which is secreted in response to a low plasma calcium level, decreases resorption of phosphate, increasing the urinary phosphate level. This process appears to have a minimal effect during normal physiologic variation in PTH levels. However, it does have an impact in the setting of pathologic changes in PTH synthesis.

Low plasma phosphorus stimulates the 1α-hydroxylase in the kidney that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol). Calcitriol increases intestinal absorption of phosphorus and is necessary for maximal renal resorption of phosphate. The effect of a change in calcitriol on urinary phosphate is significant only when the level of calcitriol was initially low, arguing against a role for calcitriol in nonpathologic conditions.

HYPOPHOSPHATEMIA

Because of the wide variation in normal plasma phosphorus levels, the definition of hypophosphatemia is age-dependent (see Table 55-8). The normal range reported by a laboratory may be based on adult normal values and, therefore, may be misleading in children. A serum phosphorus level of 3 mg/dL, a normal value in an adult, indicates clinically significant hypophosphatemia in an infant.

The plasma phosphorus level does not always reflect the total body stores because only 1% of phosphorus is extracellular. Thus, a child may have significant phosphorus deficiency despite a normal plasma phosphorus concentration. This situation is especially common in conditions in which there is a shift of phosphorus from the intracellular space.

Etiology and Pathophysiology

A variety of mechanisms cause hypophosphatemia (Table 55-9). A transcellular shift of phosphorus into cells occurs with processes that stimulate cellular usage of phosphorus (glycolysis). Usually, this shift causes only a minor, transient decrease in plasma phosphorus, but if intracellular phosphorus deficiency is present, the plasma phosphorus level can decrease significantly, producing symptoms of acute hypophosphatemia. Glucose infusion stimulates insulin release, leading to entry of glucose and phosphorus into the cells. Phosphorus is then used during glycolysis and other metabolic processes. A similar phenomenon can occur during the treatment of diabetic ketoacidosis, and patients with this disorder are typically phosphorus-depleted owing to urinary phosphorus losses. **Refeeding** of patients with protein-calorie malnutrition causes anabolism, which leads to significant cellular demand for phosphorus. The increased phosphorus uptake for incorporation into newly synthesized compounds containing phosphorus leads to hypophosphatemia, which can be severe and symptomatic. Refeeding hypophosphatemia occurs frequently during treatment of severe anorexia nervosa. It can occur during treatment of children with malnutrition from any cause, such as cystic fibrosis, Crohn

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Table 55-9 Causes of Hypophosphatemia

TRANSCELLULAR SHIFTS
Glucose infusion
Insulin
Refeeding
Total parenteral nutrition
Respiratory alkalosis
Tumor growth
Bone marrow transplantation
Hungry bone syndrome
DECREASED INTAKE
Nutritional
Premature infants
Low phosphorus formula
Antacids and other phosphate binders
RENAL LOSSES
Hyperparathyroidism
Parathyroid hormone–related peptide
X-linked hypophosphatemic rickets (OMIM 307800)
Overproduction of fibroblast growth factor-23
Tumor-induced rickets
McCune-Albright syndrome
Epidermal nevus syndrome
Neurofibromatosis
Autosomal dominant hypophosphatemic rickets (OMIM 193100)
Autosomal recessive hypophosphatemic rickets (OMIM 241520)
Fanconi syndrome
Dent disease (OMIM 300009/300555)
Hypophosphatemic rickets with hypercalciuria (OMIM 241530)
Hypophosphatemic nephrolithiasis/osteoporosis type 1 (OMIM 612286)
Hypophosphatemic nephrolithiasis/osteoporosis type 2 (OMIM 612287)
Volume expansion and intravenous fluids
Metabolic acidosis
Diuretics
Glycosuria
Glucocorticoids
Kidney transplantation
MULTIFACTORIAL
Vitamin D deficiency
Vitamin D–dependent rickets type 1 (OMIM 264700)
Vitamin D–dependent rickets type 2 (OMIM 277440)
Alcoholism
Sepsis
Dialysis

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

disease, burns, neglect, chronic infection, or famine. Hypophosphatemia usually occurs within the 1st 5 days of refeeding and is prevented by a gradual increase in nutrition with appropriate phosphorus supplementation. Total parenteral nutrition without adequate phosphorus can cause hypophosphatemia.

Phosphorus moves into the intracellular space during a respiratory alkalosis and during recovery from a respiratory acidosis. An acute decrease in the carbon dioxide concentration, by raising the intracellular pH, stimulates glycolysis, leading to intracellular use of phosphorus and hypophosphatemia. Because a metabolic alkalosis has less effect on the intracellular pH (carbon dioxide diffuses across cell membranes much faster than bicarbonate), there is minimal transcellular phosphorus movement with a metabolic alkalosis.

Tumors that grow rapidly, such as those associated with leukemia and lymphoma, may use large amounts of phosphorus, leading to hypophosphatemia. A similar phenomenon may occur during the hematopoietic reconstitution that follows bone marrow transplantation. In **hungry bone syndrome,** there is avid bone uptake of phosphorus, along with calcium and magnesium, which can produce plasma deficiency of all 3 ions. Hungry bone syndrome is most common after parathyroidectomy for hyperparathyroidism because the stimulus for bone dissolution is acutely removed, but bone synthesis continues.

Nutritional phosphorus deficiency is unusual because most foods contain phosphorus. However, infants are especially susceptible because of their high demand for phosphorus to support growth, especially of the skeleton. Very-low-birthweight infants have particularly rapid skeletal growth, and phosphorus deficiency and rickets may develop if they are fed human milk or formula for term infants. There is also a relative deficiency of calcium. The provision of additional calcium and phosphorus, using breast milk fortifier or special premature infant formula, prevents this complication. Phosphorus deficiency, sometimes with concomitant calcium and vitamin D deficiencies, occurs in infants who are not given enough milk or who receive a milk substitute that is nutritionally inadequate.

Antacids containing aluminum hydroxide, such as Maalox and Mylanta, bind dietary phosphorus and secreted phosphorus, preventing absorption. This process can cause phosphorus deficiency and rickets in growing children. A similar mechanism causes hypophosphatemia in patients who are overtreated for hyperphosphatemia with phosphorus binders. In children with kidney failure, the addition of dialysis to phosphorus binders increases the risk of iatrogenic hypophosphatemia in these normally hyperphosphatemic patients. This complication, which is more common in infants, can worsen renal osteodystrophy.

Excessive renal losses of phosphorus occur in a variety of inherited and acquired disorders. Because PTH inhibits the resorption of phosphorus in the proximal tubule, **hyperparathyroidism** causes hypophosphatemia (see Chapter 573). The dominant clinical manifestation, however, is hypercalcemia, and the hypophosphatemia is usually asymptomatic. The phosphorus level in hyperparathyroidism is not extremely low, and there is no continued loss of phosphorus because a new steady state is achieved at the lower plasma phosphorus level. Renal excretion, therefore, does not exceed intake over the long-term. There are occasional malignancies that produce PTH-related peptide, which has the same actions as PTH and causes hypophosphatemia and hypercalcemia.

A variety of diseases cause renal phosphate wasting, hypophosphatemia, and rickets resulting from excess FGF-23 (see Chapter 51). These disorders include **X-linked hypophosphatemic rickets, tumor-induced osteomalacia**, **autosomal dominant hypophosphatemic rickets,** and **autosomal recessive hypophosphatemic rickets**. Heterozygous mutations in a phosphate transporter or a regulator of proximal tubule phosphate transport cause hypophosphatemia, osteoporosis, and nephrolithiasis (**hypophosphatemic nephrolithiasis/osteoporosis type 1 or 2**).

Fanconi syndrome is a generalized defect in the proximal tubule leading to urinary wasting of bicarbonate, phosphorus, amino acids, uric acid, and glucose (see Chapter 529). The clinical sequelae are a result of the metabolic acidosis and hypophosphatemia. In children, an underlying genetic disease, most commonly cystinosis, often causes Fanconi syndrome, but it can be secondary to a variety of toxins and acquired diseases. Some patients have incomplete Fanconi syndrome, and phosphorus wasting may be one of the manifestations.

Dent disease, an X-linked disorder, can cause renal phosphorus wasting and hypophosphatemia, although the latter is not present in most cases. Other possible manifestations of Dent disease include tubular proteinuria, hypercalciuria, nephrolithiasis, rickets, and chronic renal failure. Dent disease may be secondary to mutations in a gene that encodes a chloride channel or the OCRL1 gene, which may also cause Lowe syndrome (see Chapter 529.1). **Hypophosphatemic rickets with hypercalciuria** is a rare disorder, principally described in kindreds from the Middle East. Mutations in a sodium-phosphate cotransporter cause hypophosphatemia in this disorder, and complications may include nephrolithiasis and osteoporosis; the disorder is autosomal dominant.

Metabolic acidosis inhibits resorption of phosphorus in the proximal tubule. In addition, metabolic acidosis causes a transcellular shift of phosphorus out of cells because of intracellular catabolism. This

released phosphorus is subsequently lost in the urine, leading to significant phosphorus depletion, even though the plasma phosphorus level may be normal. This classically occurs in diabetic ketoacidosis in which renal phosphorus loss is further increased by the osmotic diuresis. With correction of the metabolic acidosis and the administration of insulin, both of which cause a transcellular movement of phosphorus into the cells, there is a marked decrease in the plasma phosphorus level.

Volume expansion from any cause, such as hyperaldosteronism or SIADH, inhibits resorption of phosphorus in the proximal tubule. This effect also occurs with high rates of intravenous fluids. Thiazide and loop diuretics can increase renal phosphorus excretion, but the increase is seldom clinically significant. Glycosuria and glucocorticoids inhibit renal conservation of phosphorus. Hypophosphatemia is common after kidney transplantation as a result of urinary phosphorus losses. Possible explanations include preexisting secondary hyperparathyroidism from chronic renal failure, glucocorticoid therapy, and upregulation of FGF-23 before transplantation. The hypophosphatemia usually resolves in a few months.

Both acquired and genetic causes of **vitamin D deficiency** are associated with hypophosphatemia (see Chapter 51). The pathogenesis is multifactorial. Vitamin D deficiency, by impairing intestinal calcium absorption, causes secondary hyperparathyroidism that leads to increased urinary phosphorus wasting. An absence of vitamin D decreases intestinal absorption of phosphorus and directly decreases renal resorption of phosphorus. The dominant clinical manifestation is rickets, although some patients have muscle weakness that may be related to phosphorus deficiency.

Alcoholism is the most common cause of severe hypophosphatemia in adults. Fortunately, many of the risk factors that predispose adult alcoholics to hypophosphatemia are not usually present in adolescents (malnutrition, antacid abuse, recurrent episodes of diabetic ketoacidosis). Hypophosphatemia often occurs in sepsis, but the mechanism is not clear. Aggressive, protracted hemodialysis, as might be used for the treatment of methanol or ethylene glycol ingestion, can cause hypophosphatemia.

Clinical Manifestations

There are acute and chronic manifestations of hypophosphatemia. Rickets occurs in children with long-term phosphorus deficiency. The clinical features of rickets are described in Chapter 51.

Severe hypophosphatemia, typically at levels <1.0-1.5 mg/dL, may affect every organ in the body because phosphorus has a critical role in maintaining adequate cellular energy. Phosphorus is a component of ATP and is necessary for glycolysis. With inadequate phosphorus, red blood cell 2,3-diphosphoglycerate levels decrease, impairing release of oxygen to the tissues. Severe hypophosphatemia can cause hemolysis and dysfunction of white blood cells. Chronic hypophosphatemia causes proximal muscle weakness and atrophy. In the intensive care unit, phosphorus deficiency may slow weaning from mechanical ventilation or cause acute respiratory failure. **Rhabdomyolysis** is the most common complication of acute hypophosphatemia, usually in the setting of an acute transcellular shift of phosphorus into cells in a child with chronic phosphorus depletion (anorexia nervosa). The rhabdomyolysis is actually somewhat protective, in that there is cellular release of phosphorus. Other manifestations of severe hypophosphatemia include cardiac dysfunction and neurologic symptoms, such as tremor, paresthesia, ataxia, seizures, delirium, and coma.

Diagnosis

The history and basic laboratory evaluation often suggest the etiology of hypophosphatemia. The history should investigate nutrition, medications, and familial disease. Hypophosphatemia and rickets in an otherwise healthy young child suggests a genetic defect in renal phosphorus conservation, Fanconi syndrome, inappropriate use of antacids, poor nutrition, vitamin D deficiency, or a genetic defect in vitamin D metabolism. The patient with Fanconi syndrome usually has metabolic acidosis, glycosuria, aminoaciduria, and a low plasma uric acid level. Measurement of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, calcium, and PTH differentiates among the various vitamin D deficiency disorders and primary renal phosphate wasting (see Chapter 51). Hyperparathyroidism is easily distinguished by the presence of elevated plasma PTH and calcium values.

Treatment

The plasma phosphorus level, the presence of symptoms, the likelihood of chronic depletion, and the presence of ongoing losses dictate the approach to therapy. Mild hypophosphatemia does not require treatment unless the clinical situation suggests that chronic phosphorus depletion is present or that losses are ongoing. Oral phosphorus can cause diarrhea, so the doses should be divided. Intravenous therapy is effective in patients who have severe deficiency or who cannot tolerate oral medications. Intravenous phosphorus is available as either sodium phosphate or potassium phosphate, with the choice usually based on the patient's plasma potassium level. Starting doses are 0.08-0.16 mmol/kg over 6 hr. The oral preparations of phosphorus are available with various ratios of sodium and potassium. This is an important consideration because some patients may not tolerate the potassium load, whereas supplemental potassium may be helpful in some diseases, such as Fanconi syndrome and malnutrition. Oral maintenance dosages are 2-3 mmol/kg/day in divided doses.

Increasing dietary phosphorus is the only intervention needed in infants with inadequate intake. Other patients may also benefit from increased dietary phosphorus, usually from dairy products. Phosphorus-binding antacids should be discontinued in patients with hypophosphatemia. Certain diseases require specific therapy (see Chapter 51).

HYPERPHOSPHATEMIA

Etiology and Pathophysiology

Renal insufficiency is the most common cause of hyperphosphatemia, with the severity proportional to the degree of kidney impairment (see Chapter 535). This occurs because gastrointestinal absorption of the large dietary intake of phosphorus is unregulated, and the kidneys normally excrete this phosphorus. As renal function deteriorates, increased excretion of phosphorus is able to compensate. When kidney function is <30% of normal, hyperphosphatemia usually develops, although the time of its development may vary considerably according to dietary phosphorus absorption. Many of the other causes of hyperphosphatemia are more likely to develop in the setting of renal insufficiency (Table 55-10).

Cellular content of phosphorus is high relative to plasma phosphorus, and cell lysis can release substantial phosphorus. This is the etiology of hyperphosphatemia in **tumor lysis syndrome, rhabdomyolysis,** and **acute hemolysis.** These disorders cause concomitant potassium

Table 55-10 Causes of Hyperphosphatemia

TRANSCELLULAR SHIFTS
Tumor lysis syndrome
Rhabdomyolysis
Acute hemolysis
Diabetic ketoacidosis and lactic acidosis
INCREASED INTAKE
Enemas and laxatives
Cow's milk in infants
Treatment of hypophosphatemia
Vitamin D intoxication
DECREASED EXCRETION
Renal failure
Hypoparathyroidism or pseudohypoparathyroidism (OMIM 146200/603233/103580/241410/203330)
Acromegaly
Hyperthyroidism
Tumoral calcinosis with hyperphosphatemia (OMIM 211900)

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

release and the risk of hyperkalemia. Additional features of tumor lysis and rhabdomyolysis are hyperuricemia and hypocalcemia, whereas indirect hyperbilirubinemia and elevated lactate dehydrogenase values are often present with hemolysis. An elevated CPK level is suggestive of rhabdomyolysis. During lactic acidosis or diabetic ketoacidosis, usage of phosphorus by cells decreases, and phosphorus shifts into the extracellular space. This problem reverses when the underlying problem is corrected, and especially with diabetic ketoacidosis, patients subsequently become hypophosphatemic as a result of previous renal phosphorus loss.

Excessive intake of phosphorus is especially dangerous in children with renal insufficiency. Neonates are at risk because renal function is normally reduced during the 1st few months of life. In addition, they may erroneously be given doses of phosphorus that are meant for an older child or adult. In infants fed cow's milk, which has higher phosphorus content than breast milk or formula, hyperphosphatemia may develop. **Fleet Enema** has a high amount of phosphorus that can be absorbed, especially in the patient with an ileus. Infants and children with Hirschsprung disease are especially vulnerable. There is often associated hypernatremia owing to sodium absorption and water loss from diarrhea. Sodium phosphorus laxatives may cause hyperphosphatemia if the dose is excessive or if renal insufficiency is present. Hyperphosphatemia occurs in children who receive overly aggressive treatment for hypophosphatemia. Vitamin D intoxication causes excessive gastrointestinal absorption of both calcium and phosphorus, and the suppression of PTH by hypercalcemia decreases renal phosphorus excretion.

The absence of PTH in **hypoparathyroidism** or PTH responsiveness in **pseudohypoparathyroidism** causes hyperphosphatemia because of increased resorption of phosphorus in the proximal tubule of the kidney (see Chapters 571 and 572). The associated hypocalcemia is responsible for the clinical symptoms. The hyperphosphatemia in hyperthyroidism or acromegaly is usually minor. It is secondary to increased resorption of phosphorus in the proximal tubule from the actions of thyroxine or growth hormone. Excessive thyroxine can also cause bone resorption, which may contribute to the hyperphosphatemia and cause hypercalcemia. Patients with **familial tumoral calcinosis,** a rare autosomal recessive disorder, have hyperphosphatemia as a result of decreased renal phosphate excretion and heterotopic calcifications. The disease may be secondary to mutations in the genes for a glycosyltransferase, the phosphatonin FGF-23, or the gene for Klotho, which encodes the coreceptor for FGF-23.

Clinical Manifestations

The principal clinical consequences of hyperphosphatemia are hypocalcemia and systemic calcification. The hypocalcemia is probably due to tissue deposition of calcium-phosphorus salt, inhibition of 1,25-dihydroxyvitamin D production, and decreased bone resorption. Symptomatic hypocalcemia is most likely to occur when the phosphorus level increases rapidly or when diseases predisposing to hypocalcemia are present (chronic renal failure, rhabdomyolysis). Systemic calcification occurs because the solubility of phosphorus and calcium in the plasma is exceeded. This is believed to happen when plasma calcium × plasma phosphorus, both measured in mg/dL, is >70. Clinically, this condition is often apparent in the conjunctiva, where it manifests as a foreign-body feeling, erythema, and injection. More ominous manifestations are hypoxia from pulmonary calcification and renal failure from nephrocalcinosis.

Diagnosis

Plasma creatinine and BUN levels should be assessed in any patient with hyperphosphatemia. The history should focus on intake of phosphorus and the presence of chronic diseases that may cause hyperphosphatemia. Measurement of potassium, uric acid, calcium, lactate dehydrogenase, bilirubin, hemoglobin, and CPK may be indicated if rhabdomyolysis, tumor lysis, or hemolysis is suspected. With mild hyperphosphatemia and significant hypocalcemia, measurement of the serum PTH level distinguishes between hypoparathyroidism and pseudohypoparathyroidism.

Treatment

The treatment of acute hyperphosphatemia depends on its severity and etiology. Mild hyperphosphatemia in a patient with reasonable renal function spontaneously resolves; the resolution can be accelerated by dietary phosphorus restriction. If kidney function is not impaired, then intravenous fluids can enhance renal phosphorus excretion. For more significant hyperphosphatemia or a situation such as tumor lysis or rhabdomyolysis, in which endogenous phosphorus generation is likely to continue, addition of an oral phosphorus binder prevents absorption of dietary phosphorus and can remove phosphorus from the body by binding what is normally secreted and absorbed by the gastrointestinal tract. Phosphorus binders are most effective when given with food. Binders containing aluminum hydroxide are especially efficient, but calcium carbonate is an effective alternative and may be preferred if there is a need to treat concomitant hypocalcemia. Preservation of renal function, for example with high urine flow in rhabdomyolysis or tumor lysis, is an important adjunct because it will permit continued excretion of phosphorus. If the hyperphosphatemia is not responding to conservative management, especially if renal insufficiency is supervening, then dialysis may be necessary to increase phosphorus removal.

Dietary phosphorus restriction is necessary for diseases causing chronic hyperphosphatemia. However, such diets are often difficult to follow, given the abundance of phosphorus in a variety of foods. Dietary restriction is often sufficient in conditions such as hypoparathyroidism and mild renal insufficiency. For more problematic hyperphosphatemia, such as with moderate renal insufficiency and end-stage renal disease, phosphorus binders are usually necessary. They include calcium carbonate, calcium acetate, sevelamer, and lanthanum. Aluminum-containing phosphorus binders are no longer used in chronic renal insufficiency because of the risk of aluminum toxicity. Dialysis directly removes phosphorus from the blood in patients with end-stage renal disease, but it is only an adjunct to dietary restriction and phosphorus binders, in that elimination of phosphorus by dialysis is not efficient enough to keep up with normal dietary intake.

Bibliography is available at Expert Consult.

55.7 Acid–Base Balance

Larry A. Greenbaum

ACID–BASE PHYSIOLOGY

Introduction and Terminology

Chronic, mild derangements in acid–base status may interfere with normal growth and development, whereas acute, severe changes in pH can be fatal. Control of acid–base balance depends on the kidneys, the lungs, and intracellular and extracellular buffers.

A normal pH is 7.35-7.45. There is an inverse relationship between the pH and the hydrogen ion concentration. At a pH of 7.40, the hydrogen ion concentration is 40 nmol/L. A normal serum sodium concentration, 140 mEq/L, is 1 million times higher. Maintaining a normal pH is necessary because hydrogen ions are highly reactive and are especially likely to combine with proteins, altering their function.

An **acid** is a substance that releases ("donates") a hydrogen ion (H^+). A base is a substance that accepts a hydrogen ion. An acid (HA) can dissociate into a hydrogen ion and a conjugate base (A^-), as follows:

$$HA \leftrightarrow H^+ + A^-$$

A strong acid is highly dissociated, so in this reaction, there is little HA. A weak acid is poorly dissociated; not all of the hydrogen ions are released from HA. A^- acts as a base when the reaction moves to the left. These reactions are in equilibrium. When HA is added to the system, there is dissociation of some HA until the concentrations of H^+ and A^- increase enough that a new equilibrium is reached. Addition of hydrogen ions causes a decrease in A^- and an increase in HA. Addition of A^- causes a decrease in hydrogen ions and an increase in HA.

Buffers are substances that attenuate the change in pH that occurs when acids or bases are added to the body. Given the extremely low

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concentration of hydrogen ions in the body at physiologic pH, without buffers a small amount of hydrogen ions could cause a dramatic decline in the pH. Buffers prevent the decrease in pH by binding the added hydrogen ions, as follows:

$$A^- + H^+ \rightarrow HA$$

The increase in hydrogen ion concentration drives this reaction to the right. Similarly, when base is added to the body, buffers prevent the pH from increasing by releasing hydrogen ions, as follows:

$$HA \rightarrow A^- + H^+$$

The best buffers are weak acids and bases. This is because a buffer works best when it is 50% dissociated (half HA and half A^-). The pH at which a buffer is 50% dissociated is its pK (ionization constant of acid). The best physiologic buffers have a pK close to 7.40. The concentration of a buffer and its pK determine the buffer's effectiveness (buffering capacity). When the pH is lower than the pK of a buffer, there is more HA than A^-. When the pH is higher than the pK, there is more A^- than HA.

Physiologic Buffers

The bicarbonate and nonbicarbonate buffers protect the body against major changes in pH. The **bicarbonate buffer system** is routinely monitored clinically. The bicarbonate buffer system is based on the relationship between carbon dioxide (CO_2) and bicarbonate (HCO_3^-):

$$CO_2 + H_2O \leftrightarrow H^+ + HCO_3^-$$

Carbon dioxide acts as an acid in that, after combining with water, it releases a hydrogen ion; bicarbonate acts as its conjugate base in that it accepts a hydrogen ion. The pK of this reaction is 6.1. The Henderson-Hasselbalch equation expresses the relationship among pH, pK, and the concentrations of an acid and its conjugate base. This relationship is valid for any buffer. The Henderson-Hasselbalch equation for bicarbonate and carbon dioxide is as follows:

$$pH = 6.1 + \log[HCO_3^-]/[CO_2]$$

The Henderson-Hasselbalch equation for the bicarbonate buffer system has 3 variables: pH, $[HCO_3^-]$, and $[CO_2]$. Thus, if any 2 of these variables are known, it is possible to calculate the third. When one is using the Henderson-Hasselbalch equation, it is important that carbon dioxide and bicarbonate have the same units. Carbon dioxide is reported clinically as mm Hg and must be multiplied by its solubility constant, 0.03 mmol/L/mm Hg, before the Henderson-Hasselbalch equation can be used. Mathematical manipulation of the Henderson-Hasselbalch equation produces the following relationship:

$$[H^+] = 24 \times P_{CO_2}/(HCO_3^-)$$

At a normal hydrogen ion concentration of 40 nmol (pH 7.40), the partial pressure of carbon dioxide (P_{CO_2}), which is expressed as mm Hg in this equation, is 40 when the bicarbonate concentration is 24 mEq/L. This equation emphasizes that the hydrogen ion concentration, and hence pH, can be determined by the ratio of P_{CO_2} and the bicarbonate concentration.

The bicarbonate buffer system is very effective as a result of the high concentration of bicarbonate in the body (24 mEq/L) and the fact that it is an open system. The remaining body buffers are in a closed system. The bicarbonate buffer system is an open system because the lungs increase carbon dioxide excretion when the blood carbon dioxide concentration increases. When acid is added to the body, the following reaction occurs:

$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

In a closed system, the CO_2 would increase. The higher CO_2 concentration would lead to an increase in the reverse reaction:

$$CO_2 + H_2O \rightarrow H^+ + HCO_3^-$$

This would increase the concentration of hydrogen ions, limiting the buffering capacity of bicarbonate. However, because the lungs excrete the excess carbon dioxide, the reverse reaction does not increase; this fact enhances the buffering capacity of bicarbonate. The same principle holds with the addition of base, because the lungs decrease carbon dioxide excretion and prevent the level of carbon dioxide from falling. The lack of change in carbon dioxide concentration dramatically increases the buffering capacity of bicarbonate.

The **nonbicarbonate buffers** include proteins, phosphate, and bone. Protein buffers consist of extracellular proteins, mostly albumin and intracellular proteins, including hemoglobin. Proteins are effective buffers, largely because of the presence of the amino acid histidine, which has a side chain that can bind or release hydrogen ions. The pK of histidine varies slightly, depending on its position in the protein molecule, but its average pK is approximately 6.5. This is close enough to a normal pH (7.4) to make histidine an effective buffer. Hemoglobin and albumin have 34 and 16 histidine molecules, respectively.

Phosphate can bind up to 3 hydrogen molecules, so it can exist as PO_4^{3-}, HPO_4^{2-}, $H_2PO_4^{1-}$, or H_3PO_4. However, at a physiologic pH, most phosphate exists as either HPO_4^{2-} or $H_2PO_4^{1-}$. $H_2PO_4^{1-}$ is an acid, and HPO_4^{2-} is its conjugate base:

$$H_2PO_4^{1-} \leftrightarrow H^+ + HPO_4^{2-}$$

The pK of this reaction is 6.8, making phosphate an effective buffer. The concentration of phosphate in the extracellular space is relatively low, limiting the overall buffering capacity of phosphate; it is less important than albumin. However, phosphate is found at a much higher concentration in the urine, where it is an important buffer. In the intracellular space, most phosphate is covalently bound to organic molecules (ATP), but it still serves as an effective buffer.

Bone is an important buffer. Bone is basic—it is composed of compounds such as sodium bicarbonate and calcium carbonate—and thus, dissolution of bone releases base. This release can buffer an acid load, although at the expense of bone density, if it occurs over an extended period. In contrast, bone formation, by consuming base, helps buffer excess base.

Clinically, we measure the extracellular pH, but it is the intracellular pH that affects cell function. Measurement of the intracellular pH is unnecessary because changes in the intracellular pH parallel the changes in the extracellular pH. However, the change in the intracellular pH tends to be less than the change in the extracellular pH because of the greater buffering capacity in the intracellular space.

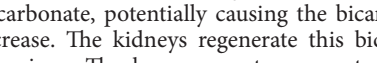
NORMAL ACID–BASE BALANCE

The lungs and kidneys maintain a normal acid–base balance. Carbon dioxide generated during normal metabolism is a weak acid. The lungs prevent an increase in the P_{CO_2} in the blood by excreting the CO_2 that the body produces. CO_2 production varies according to the body's metabolic needs, increasing with physical activity. The rapid pulmonary response to changes in the CO_2 concentration occurs via central sensing of the P_{CO_2} and a subsequent increase or decrease in ventilation to maintain a normal P_{CO_2} (35-45 mm Hg). An increase in ventilation decreases the P_{CO_2}, and a decrease in ventilation increases the P_{CO_2}.

The kidneys excrete endogenous acid. An adult normally produces approximately 1-2 mEq/kg/24 hr of hydrogen ions. Children normally produce 2-3 mEq/kg/24 hr of hydrogen ions. The 3 principal sources of hydrogen ions are dietary protein metabolism, incomplete metabolism of carbohydrates and fat, and stool losses of bicarbonate. Because metabolism of protein generates hydrogen ions, endogenous acid production varies with protein intake. The complete oxidation of carbohydrates or fats to carbon dioxide and water does not generate hydrogen ions; the lungs remove the carbon dioxide. However, incomplete metabolism of carbohydrates or fats produces hydrogen ions. Incomplete glucose metabolism can produce lactic acid, and incomplete triglyceride metabolism can produce keto acids, such as β-hydroxybutyric acid and acetoacetic acid. There is always some baseline incomplete metabolism that contributes to endogenous acid production. This factor increases in pathologic conditions, such as lactic acidosis and diabetic ketoacidosis. Stool loss of bicarbonate is the third major source of endogenous acid production. The stomach secretes hydrogen ions,

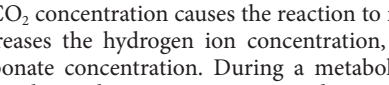
but most of the remainder of the gastrointestinal tract secretes bicarbonate, and the net effect is a loss of bicarbonate from the body. To secrete bicarbonate, the cells of the intestine produce hydrogen ions that are released into the bloodstream. For each bicarbonate molecule lost in the stool, the body gains 1 hydrogen ion. This source of endogenous acid production is normally minimal but may increase dramatically in a patient with diarrhea.

The hydrogen ions formed from endogenous acid production are neutralized by bicarbonate, potentially causing the bicarbonate concentration to decrease. The kidneys regenerate this bicarbonate by secreting hydrogen ions. The lungs cannot regenerate bicarbonate, even though loss of carbon dioxide lowers the hydrogen ion concentration, as shown in the following reaction:



$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

A decrease in CO_2 concentration causes the reaction to move to the right, which decreases the hydrogen ion concentration, but it also lowers the bicarbonate concentration. During a metabolic acidosis, hyperventilation can lower the CO_2 concentration, decrease the hydrogen ion concentration, and thus increase the pH. The underlying metabolic acidosis is still present. Similarly, the kidneys cannot correct an abnormally high CO_2 concentration, as shown in the following reaction:



$$H^+ + HCO_3^- \rightarrow CO_2 + H_2O$$

An increase in the bicarbonate concentration also causes the reaction to move to the right, which increases the CO_2 concentration while simultaneously decreasing the hydrogen ion concentration. During a respiratory acidosis, increased renal generation of bicarbonate can decrease the hydrogen ion concentration and increase the pH, but cannot repair the respiratory acidosis. Both the lungs and the kidneys can affect the hydrogen ion concentration and hence the pH. However, only the lungs can regulate the CO_2 concentration, and only the kidneys can regulate the bicarbonate concentration.

Renal Mechanisms

The kidneys regulate the serum bicarbonate concentration by modifying acid excretion in the urine. This requires a 2-step process. First, the renal tubules resorb the bicarbonate that is filtered at the glomerulus. Second, there is tubular secretion of hydrogen ions. The urinary excretion of hydrogen ions generates bicarbonate that neutralizes endogenous acid production. The tubular actions necessary for renal acid excretion occur throughout the nephron (Fig. 55-6).

The resorption of filtered bicarbonate is a necessary first step in renal regulation of the acid–base balance. A normal adult has a GFR of approximately 180 L/24 hr. This fluid enters the Bowman space with a bicarbonate concentration that is essentially identical to the plasma concentration, normally 24 mEq/L. Multiplying 180 L by 24 mEq/L indicates that >4,000 mEq of bicarbonate enters the Bowman space each day. This bicarbonate, if not reclaimed along the nephron, would be lost in the urine and would cause a profound metabolic acidosis.

The proximal tubule reclaims approximately 85% of the filtered bicarbonate (Fig. 55-7). The final 15% is reclaimed beyond the proximal tubule, mostly in the ascending limb of the loop of Henle. Bicarbonate molecules are not transported from the tubular fluid into the cells of the proximal tubule. Rather, hydrogen ions are secreted into the tubular fluid, leading to conversion of filtered bicarbonate into CO_2 and water. The secretion of hydrogen ions by the cells of the proximal tubule is coupled to generation of intracellular bicarbonate, which is transported across the basolateral membrane of the proximal tubule cell and enters the capillaries. The bicarbonate produced in the cell replaces the bicarbonate filtered at the glomerulus.

Increased bicarbonate resorption by the cells of the proximal tubule—the result of increased hydrogen ion secretion—occurs in a variety of clinical situations. Volume depletion increases bicarbonate resorption. This is partially mediated by activation of the renin–angiotensin system; angiotensin II increases bicarbonate resorption. Increased bicarbonate resorption in the proximal tubule is one of the mechanisms that accounts for the metabolic alkalosis that may occur in some patients with volume depletion. Other stimuli that increase bicarbonate resorption include hypokalemia and an increased P_{CO_2}. This partially explains the observations that hypokalemia causes a metabolic alkalosis and that a respiratory acidosis leads to a compensatory increase in serum bicarbonate concentration.

Stimuli that decrease bicarbonate resorption in the proximal tubule may cause a decrease in the serum bicarbonate concentration. A decrease in the P_{CO_2} (respiratory alkalosis) decreases proximal tubule bicarbonate resorption, partially mediating the decrease in serum bicarbonate concentration that compensates for a respiratory alkalosis.

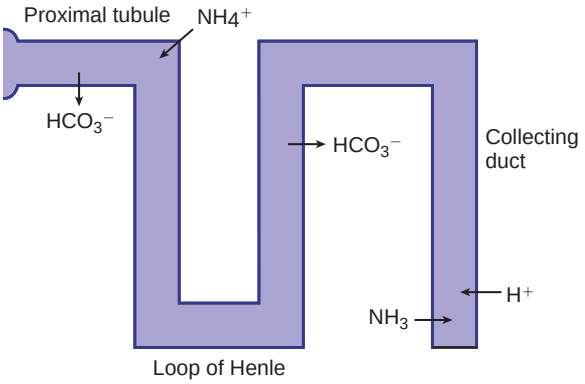


Figure 55-6 Tubular sites involved in acid–base balance. The proximal tubule is the site where most filtered bicarbonate is reclaimed, even though other sites along the nephron, especially the thick ascending limb of the loop of Henle, resorb some of the filtered bicarbonate. The collecting duct is the principal location for the hydrogen ion secretion that acidifies the urine. The proximal tubule generates the ammonia that serves as a urinary buffer in the collecting duct.

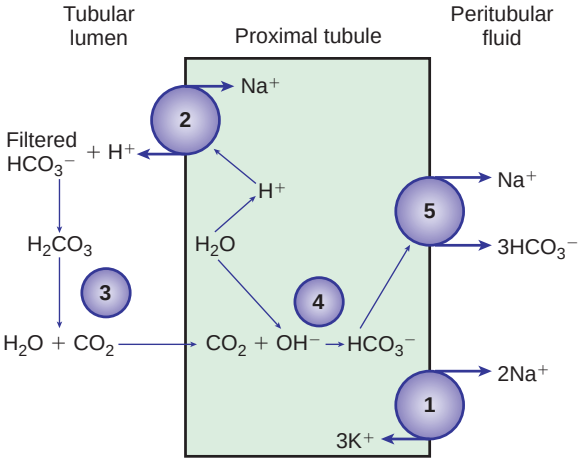


Figure 55-7 Resorption of filtered bicarbonate in the proximal tubule. The Na^+,K^+-ATPase *(1)* excretes sodium across the basolateral cell membrane, maintaining a low intracellular sodium concentration. The low intracellular sodium concentration provides the energy for the Na^+,H^+ antiporter *(2)*, which exchanges sodium from the tubular lumen for intracellular hydrogen ions. The hydrogen ions that are secreted into the tubular lumen then combine with filtered bicarbonate to generate carbonic acid. CO_2 and water are produced from carbonic acid (H_2CO_3). This reaction is catalyzed by luminal carbonic anhydrase *(3)*. CO_2 diffuses into the cell and combines with OH^- ions to generate bicarbonate. This reaction is catalyzed by an intracellular carbonic anhydrase *(4)*. The dissociation of water generates an OH^- ion and an H^+ ion. The Na^+,H^+ antiporter *(2)* secretes the hydrogen ions. Bicarbonate ions cross the basolateral membrane and enter the blood via the $3HCO_3^-/1Na^+$ cotransporter *(5)*. The energy for the $3HCO_3^-/1Na^+$ cotransporter comes from the negatively charged cell interior, which makes it electrically favorable to transport a net negative charge (i.e., 3 bicarbonates and only 1 sodium) out of the cell.

PTH decreases proximal tubule bicarbonate resorption; hyperparathyroidism may cause a mild metabolic acidosis. A variety of medications and diseases cause a metabolic acidosis by impairing bicarbonate resorption in the proximal tubule. Examples are the medication acetazolamide, which directly inhibits carbonic anhydrase, and the many disorders that cause proximal RTA (see Chapter 329).

After reclaiming filtered bicarbonate, the kidneys perform the second step in renal acid–base handling, the excretion of the acid created by endogenous acid production. Excretion of acid occurs mostly in the collecting duct, with a small role for the distal tubule.

Along with secretion of hydrogen ions by the tubular cells lining the collecting duct, adequate excretion of endogenous acid requires the presence of urinary buffers. The hydrogen pumps in the collecting duct cannot lower the urine pH below 4.5. The hydrogen ion concentration at pH 4.5 is <0.04 mEq/L; it would require >25 L of water with a pH of 4.5 to excrete 1 mEq of hydrogen ions. A 10-kg child, with an endogenous acid production of 20 mEq of hydrogen ions each day, would need to have a daily urinary output of >500 L without the presence of urinary buffers. As in the blood, buffers in the urine attenuate the decrease in pH that occurs with the addition of hydrogen ions. The 2 principal urinary buffers are phosphate and ammonia.

Urinary phosphate is proportional to dietary intake. Whereas most of the phosphate filtered at the glomerulus is resorbed in the proximal tubule, the urinary phosphate concentration is usually much greater than the serum phosphate concentration. This arrangement allows phosphate to serve as an effective buffer via the following reaction:

$$H^+ + HPO_4^{2-} \rightarrow H_2PO_4^{1-}$$

The pK of this reaction is 6.8, making phosphate an effective buffer as the urinary pH decreases from 7.0 to 5.0 within the collecting duct. Although phosphate is an effective buffer, its buffering capacity is limited by its concentration; there is no mechanism for increasing urinary phosphate excretion in response to changes in acid–base status.

In contrast, ammonia production can be modified, allowing for regulation of acid excretion. The buffering capacity of ammonia is based on the reaction of ammonia with hydrogen ions to form ammonium:

$$NH_3 + H^+ \rightarrow NH_4^+$$

The cells of the proximal tubule are the source of the excreted ammonia, mostly through metabolism of glutamine via the following reactions:

$$\text{Glutamine} \rightarrow NH_4^+ + \text{glutamate}^-$$

$$\text{Glutamine}^- \rightarrow NH_4^+ + \alpha\text{-ketoglutarate}^{2-}$$

The metabolism of glutamine generates 2 ammonium ions. In addition, the metabolism of α-ketoglutarate generates 2 bicarbonate molecules. The ammonium ions are secreted into the lumen of the proximal tubule, whereas the bicarbonate molecules exit the proximal tubule cells via the basolateral $Na^+,3HCO_3^-$ cotransporter (see Fig. 55-6). This arrangement would seem to accomplish the goal of excreting hydrogen ions (as NH_4^+) and regenerating bicarbonate molecules. However, the ammonium ions secreted in the proximal tubule do not remain within the tubular lumen. Cells of the TAL of the loop of Henle resorb the ammonium ions. The result is that there is a high medullary interstitial concentration of ammonia, but the tubular fluid entering the collecting duct does not have significant amounts of ammonium ions. Moreover, the hydrogen ions that were secreted with ammonia, as ammonium ions, in the proximal tubule enter the bloodstream, canceling the effect of the bicarbonate generated in the proximal tubule. The excretion of ammonium ions, and hence of hydrogen ions, depends on the cells of the collecting duct.

The cells of the collecting duct secrete hydrogen ions and regenerate bicarbonate, which is returned to the bloodstream (Fig. 55-8). This bicarbonate neutralizes endogenous acid production. Phosphate and ammonia buffer the hydrogen ions secreted by the collecting duct. Ammonia is an effective buffer because of the high concentrations in the medullary interstitium and because the cells of the collecting duct are permeable to ammonia but not to ammonium. As ammonia

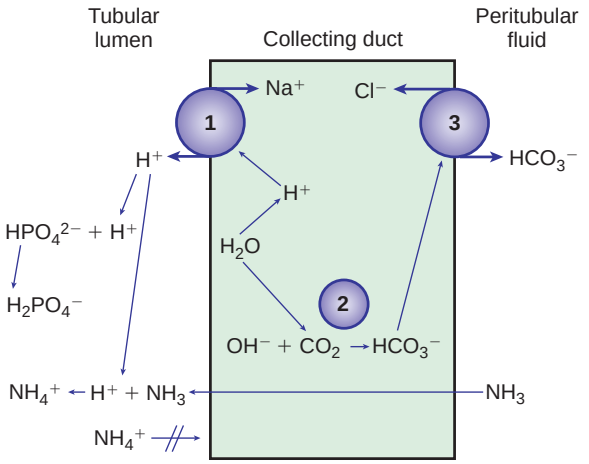


Figure 55-8 **Secretion of hydrogen ions in the collecting duct.** The dissociation of water generates an OH^- ion and an H^+ ion. The H^+-ATPase *(1)* secretes hydrogen ions into the tubular lumen. Bicarbonate is formed when an OH^- ion combines with CO_2 in a reaction mediated by carbonic anhydrase *(2)*. Bicarbonate ions cross the basolateral membrane and enter the blood via the HCO_3^-/Cl^- exchanger *(3)*. The hydrogen ions in the tubular lumen are buffered by phosphate and ammonia (NH_3). NH_3 can diffuse from the peritubular fluid into the tubular lumen, but ammonium (NH_4^+) cannot pass through the cells of the collecting duct.

diffuses into the lumen of the collecting duct, the low urine pH causes almost all of the ammonia to be converted into ammonium. This process maintains a low luminal ammonia concentration. Because the luminal pH is lower than the pH in the medullary interstitium, there is a higher concentration of ammonia within the medullary interstitium than in the tubular lumen, favoring movement of ammonia into the tubular lumen. Even though the concentration of ammonium in the tubular lumen is higher than in the interstitium, the cells of the collecting duct are impermeable to ammonium, preventing back-diffusion of ammonium out of the tubular lumen and permitting ammonia to be an effective buffer. The kidneys adjust hydrogen ion excretion according to physiologic needs. There is variation in endogenous acid production, largely a result of diet and pathophysiologic stresses, such as diarrheal losses of bicarbonate, which increase the need for acid excretion. Hydrogen excretion is increased by upregulation of hydrogen ion secretion in the collecting duct, causing the pH of the urine to decrease. This response is fairly prompt, occurring within hours of an acid load, but it is limited by the buffering capacity of the urine; the hydrogen pumps in the collecting duct cannot lower the pH to <4.5. A more significant increase in acid excretion requires upregulation of ammonia production by the proximal tubule so that more ammonia is available to serve as a buffer in the tubular lumen of the collecting duct. This response to a low serum pH reaches its maximum within 5-6 days; ammonia excretion can increase approximately 10-fold over the baseline value.

Acid excretion by the collecting duct increases in a number of different clinical situations. The extracellular pH is the most important regulator of renal acid excretion. A decrease in the extracellular pH from either a respiratory or a metabolic acidosis causes an increase in renal acid excretion. Aldosterone stimulates hydrogen ion excretion in the collecting duct, causing an increase in the serum bicarbonate concentration. This explains the metabolic alkalosis that occurs with primary hyperaldosteronism or secondary hyperaldosteronism caused by volume depletion. Hypokalemia increases acid secretion, by both stimulating ammonia production in the proximal tubule and increasing hydrogen ion secretion in the collecting duct. Hypokalemia therefore tends to produce a metabolic alkalosis. Hyperkalemia has the opposite effects, which may cause a metabolic acidosis.

In patients with an increased pH, the kidney has 2 principal mechanisms for correcting the problem. First, less bicarbonate is resorbed in the proximal tubule, leading to an increase in urinary bicarbonate

losses. Second, in a limited number of specialized cells, the process for secretion of hydrogen ions by the collecting duct (see Fig. 55-8) can be reversed, leading to secretion of bicarbonate into the tubular lumen and secretion of hydrogen ions into the peritubular fluid, where they enter the bloodstream.

CLINICAL ASSESSMENT OF ACID–BASE DISORDERS

The following equation, a rearrangement of the Henderson-Hasselbalch equation, emphasizes the relationship among the P_{CO_2}, the bicarbonate concentration, and the hydrogen ion concentration:

$$[H^+] = 24 \times P_{CO_2}/[HCO_3^-]$$

An increase in the P_{CO_2} or a decrease in the bicarbonate concentration increases the hydrogen ion concentration; the pH decreases. A decrease in the P_{CO_2} or an increase in the bicarbonate concentration decreases the hydrogen ion concentration; the pH increases.

Terminology

Acidemia is a pH below normal (<7.35), and **alkalemia** is a pH above normal (>7.45). An acidosis is a pathologic process that causes an increase in the hydrogen ion concentration, and an alkalosis is a pathologic process that causes a decrease in the hydrogen ion concentration. Whereas acidemia is always accompanied by an acidosis, a patient can have an acidosis and a low, normal, or high pH. For example, a patient may have a mild metabolic acidosis but a simultaneous, severe respiratory alkalosis; the net result may be alkalemia. Acidemia and alkalemia indicate the pH abnormality; acidosis and alkalosis indicate the pathologic process that is taking place.

A **simple acid–base disorder** is a single primary disturbance. During a simple metabolic disorder, there is respiratory compensation. With a metabolic acidosis, the decrease in the pH increases the ventilatory drive, causing a decrease in the P_{CO_2}. The decrease in the CO_2 concentration leads to an increase in the pH. This appropriate respiratory compensation is expected with a primary metabolic acidosis. Despite the decrease in the CO_2 concentration, appropriate respiratory compensation is not a respiratory alkalosis, even though it is sometimes erroneously called a compensatory respiratory alkalosis. A low P_{CO_2} can be either the result of a primary respiratory alkalosis or of an appropriate respiratory compensation for a metabolic acidosis. Appropriate respiratory compensation also occurs with a primary metabolic alkalosis, although in this case the CO_2 concentration increases to attenuate the increase in the pH. The respiratory compensation for a metabolic process happens quickly and is complete within 12-24 hr; it cannot overcompensate for or normalize the pH.

During a primary respiratory process, there is metabolic compensation, mediated by the kidneys. The kidneys respond to a respiratory acidosis by increasing hydrogen ion excretion, thereby increasing bicarbonate generation and raising the serum bicarbonate concentration. The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; the serum bicarbonate concentration decreases. Unlike respiratory compensation, which occurs rapidly, it takes 3-4 days for the kidneys to complete appropriate metabolic compensation. There is, however, a small and rapid compensatory change in the bicarbonate concentration during a primary respiratory process. The expected appropriate metabolic compensation for a respiratory disorder depends on whether the process is acute or chronic.

A **mixed acid–base disorder** is present when there is more than 1 primary acid–base disturbance. An infant with bronchopulmonary dysplasia may have a respiratory acidosis from chronic lung disease and a metabolic alkalosis from the furosemide used to treat the chronic lung disease. More dramatically, a child with pneumonia and sepsis may have severe acidemia as a result of a combined metabolic acidosis caused by lactic acid and respiratory acidosis caused by ventilatory failure.

There are formulas for calculating the appropriate metabolic or respiratory compensation for the 6 primary simple acid–base disorders (Table 55-11). The appropriate compensation is expected in a simple disorder; it is not optional. If a patient does not have the appropriate compensation, then a mixed acid–base disorder is present. A patient has a primary metabolic acidosis with a serum bicarbonate concentration of 10 mEq/L. The expected respiratory compensation is a CO_2 concentration of 23 mm Hg ± 2 ($1.5 \times 10 + 8 \pm 2 = 23 \pm 2$; Table 55-11). If the patient's CO_2 concentration is >25 mm Hg, a concurrent respiratory acidosis is present; the CO_2 concentration is higher than expected. A patient may have a respiratory acidosis despite a CO_2 level below the "normal" value of 35-45 mm Hg. In this example, a CO_2 concentration <21 mm Hg indicates a concurrent respiratory alkalosis; the CO_2 concentration is lower than expected.

Table 55-11 Appropriate Compensation During Simple Acid–Base Disorders

DISORDER	EXPECTED COMPENSATION
Metabolic acidosis	$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$
Metabolic alkalosis	P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in serum $[HCO_3^-]$
RESPIRATORY ACIDOSIS	
Acute	$[HCO_3^-]$ increases by 1 for each 10 mm Hg increase in P_{CO_2}
Chronic	$[HCO_3^-]$ increases by 3.5 for each 10 mm Hg increase in P_{CO_2}
RESPIRATORY ALKALOSIS	
Acute	$[HCO_3^-]$ falls by 2 for each 10 mm Hg decrease in P_{CO_2}
Chronic	$[HCO_3^-]$ falls by 4 for each 10 mm Hg decrease in P_{CO_2}

Table 55-12 Normal Values of Arterial Blood Gases

pH	7.35-7.45
$[HCO_3^-]$	20-28 mEq/L
P_{CO_2}	35-45 mm Hg

Diagnosis

A systematic evaluation of an arterial blood gas sample, combined with the clinical history, can usually explain the patient's acid–base disturbance. Assessment of an arterial blood gas sample requires knowledge of normal values (Table 55-12). In most cases, this is accomplished via a 3-step process (Fig. 55-9):

- Determine whether acidemia or alkalemia is present.
- Determine a cause of the acidemia or alkalemia.
- Determine whether a mixed disorder is present.

Most patients with an acid–base disturbance have an abnormal pH, although there are 2 exceptions. The first exception is in the patient with a mixed disorder, wherein the 2 processes have opposite effects on pH (a metabolic acidosis and a respiratory alkalosis) and cause changes in the hydrogen ion concentration that are comparable in magnitude, albeit opposite. The second exception is in the patient with a simple chronic respiratory alkalosis; in some instances, the appropriate metabolic compensation is enough to normalize the pH. In both of these situations, the presence of an acid–base disturbance is deduced because of the abnormal CO_2 and/or bicarbonate levels. Determining the acid–base disturbance in these situations requires proceeding to the third step of this process.

The second step requires inspection of the serum bicarbonate and CO_2 concentrations to determine a cause of the abnormal pH (see Fig. 55-9). In most cases, there is only 1 obvious explanation for the abnormal pH. In some mixed disorders, however, there may be 2 possibilities (a high P_{CO_2} and a low $[HCO_3^-]$ in a patient with acidemia). In such cases, the patient has 2 causes for abnormal pH (a metabolic acidosis and a respiratory acidosis, in this instance), and it is unnecessary to proceed to the third step.

The third step requires determining whether the patient's compensation is appropriate. It is assumed that the primary disorder

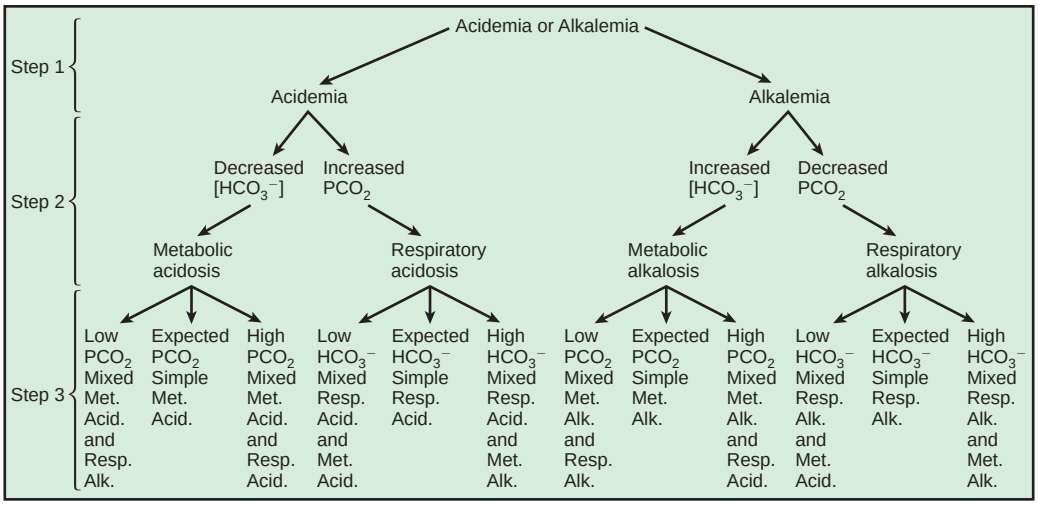


Figure 55-9 Three-step process for interpreting acid–base disturbances. In step 1, determine whether the pH is low (acidemia) or high (alkalemia). In step 2, establish an explanation for the acidemia or alkalemia. In step 3, calculate the expected compensation (see Table 55-11) and determine whether a mixed disturbance is present. Met. Acid., metabolic acidosis; Met. Alk., metabolic alkalosis; Resp. Acid., respiratory acidosis; Resp. Alk., respiratory alkalosis.

was diagnosed in the second step, and the expected compensation is calculated (see Table 55-11). If the compensation is appropriate, then a simple acid–base disorder is present. If the compensation is not appropriate, then a mixed disorder is present. The identity of the second disorder is determined by deciding whether the compensation is too little or too much compared with what was expected (see Fig. 55-9).

The history is always useful in evaluating and diagnosing patients with acid–base disturbances. It is especially helpful in a respiratory process. The expected metabolic compensation for a respiratory process changes according to whether the process is acute or chronic, which can be deduced only from the history. The metabolic compensation for an acute respiratory acidosis is less than that for a chronic respiratory acidosis. In a patient with a respiratory acidosis, a small increase in the bicarbonate concentration would be consistent with a simple acute respiratory acidosis or a mixed disorder (a chronic respiratory acidosis and a metabolic acidosis). Only the history can differentiate among the possibilities. Knowledge of the length of the respiratory process and the presence or absence of a risk factor for a metabolic acidosis (diarrhea) allows the correct conclusion to be reached.

METABOLIC ACIDOSIS

Metabolic acidosis occurs frequently in hospitalized children; diarrhea is the most common etiology. For a patient with an unknown medical problem, the presence of a metabolic acidosis is often helpful diagnostically, because it suggests a relatively narrow differential diagnosis.

Patients with a metabolic acidosis have a low serum bicarbonate concentration, although not every patient with a low serum bicarbonate concentration has a metabolic acidosis. The exception is the patient with a respiratory alkalosis, which causes a decrease in the serum bicarbonate concentration as part of appropriate renal compensation. In a patient with an isolated metabolic acidosis, there is a predictable decrease in the blood CO_2 concentration, as follows:

$$P_{CO_2} = 1.5 \times [HCO_3^-] + 8 \pm 2$$

A mixed acid–base disturbance is present if the respiratory compensation is not appropriate. If the P_{CO_2} is greater than predicted, then the patient has a concurrent respiratory acidosis. A lower P_{CO_2} than predicted indicates a concurrent respiratory alkalosis or, less commonly, an isolated respiratory alkalosis. Because the appropriate respiratory compensation for a metabolic acidosis **never normalizes** the patient's pH, the presence of a normal pH and a low bicarbonate concentration occurs only if some degree of respiratory alkalosis is present. In this situation, distinguishing an isolated chronic respiratory alkalosis from a mixed metabolic acidosis and acute respiratory alkalosis may be possible only clinically. In contrast, the combination of a low serum pH and a low bicarbonate concentration occurs only if a metabolic acidosis is present.

Etiology and Pathophysiology

There are many causes of a metabolic acidosis (Table 55-13), which occur via 3 basic mechanisms:

- Loss of bicarbonate from the body
- Impaired ability to excrete acid by the kidney
- Addition of acid to the body (exogenous or endogenous)

Diarrhea, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body. The amount of bicarbonate lost in the stool depends on the volume of diarrhea and the bicarbonate concentration of the stool, which tends to increase with more severe diarrhea. The kidneys attempt to balance the losses by increasing acid secretion, but metabolic acidosis occurs when this compensation is inadequate. Diarrhea often causes volume depletion as a result of losses of sodium and water, potentially exacerbating the acidosis by causing shock and a lactic acidosis. In addition, diarrheal losses of potassium lead to hypokalemia. Moreover, the volume depletion causes increased production of aldosterone. This increase stimulates renal retention of sodium, helping to maintain intravascular volume, but also leads to increased urinary losses of potassium, exacerbating the hypokalemia.

There are 3 forms of RTA: distal (type I), proximal (type II), and hyperkalemic (type IV) (see Chapter 529). In distal RTA, children may have accompanying hypokalemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis. Failure to thrive because of chronic metabolic acidosis is the most common presenting complaint. Patients with distal RTA cannot acidify their urine and, thus, have a urine pH >5.5 despite a metabolic acidosis.

Proximal RTA is rarely present in isolation. In most patients, proximal RTA is part of Fanconi syndrome, a generalized dysfunction of the proximal tubule. The dysfunction leads to glycosuria, aminoaciduria, and excessive urinary losses of phosphate and uric acid. The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically. Chronic hypophosphatemia leads to rickets in children (see Chapter 51). Rickets and/or failure to thrive may be the presenting complaint. The ability to acidify the urine is intact in proximal RTA; thus, untreated patients have a urine pH <5.5. However, bicarbonate therapy increases bicarbonate losses in the urine, and the urine pH increases.

In hyperkalemic RTA, renal excretion of acid and potassium is impaired. Hyperkalemic RTA is the result of either an absence of

Table 55-13 Causes of Metabolic Acidosis

NORMAL ANION GAP
Diarrhea
Renal tubular acidosis (RTA):
Distal (type I) RTA (OMIM 179800/602722/267300)*
Proximal (type II) RTA (OMIM 604278)†
Hyperkalemic (type IV) RTA (OMIM 201910/264350/177735/145260)‡
Urinary tract diversions
Posthypocapnia
Ammonium chloride intake
INCREASED ANION GAP
Lactic acidosis
Tissue hypoxia
Shock
Hypoxemia
Severe anemia
Liver failure
Malignancy
Intestinal bacterial overgrowth
Inborn errors of metabolism
Medications
Nucleoside reverse transcriptase inhibitors
Metformin
Propofol
Ketoacidosis
Diabetic ketoacidosis
Starvation ketoacidosis
Alcoholic ketoacidosis
Kidney failure
Poisoning
Ethylene glycol
Methanol
Salicylate
Toluene
Paraldehyde

*Along with these genetic disorders, distal RTA may be secondary to renal disease or medications.

†Most cases of proximal RTA are not caused by this primary genetic disorder. Proximal RTA is usually part of Fanconi syndrome, which has multiple etiologies.

‡Hyperkalemic RTA can be secondary to a genetic disorder (some of the more common are listed) or other etiologies.

OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

aldosterone or an inability of the kidney to respond to aldosterone. In severe aldosterone deficiency, as occurs with congenital adrenal hyperplasia because of 21α-hydroxylase deficiency, the hyperkalemia and metabolic acidosis are accompanied by hyponatremia and volume depletion from renal salt wasting. Incomplete aldosterone deficiency causes less-severe electrolyte disturbances; children may have isolated hyperkalemic RTA, hyperkalemia without acidosis, or isolated hyponatremia. Patients may have aldosterone deficiency caused by decreased renin production by the kidney; renin normally stimulates aldosterone synthesis. Children with hyporeninemic hypoaldosteronism usually have either isolated hyperkalemia or hyperkalemic RTA. The manifestations of aldosterone resistance depend on the severity of the resistance. In the autosomal recessive form of pseudohypoaldosteronism type I, which is the result of an absence of the sodium channel that normally responds to aldosterone, there is often severe salt wasting and hyponatremia. In contrast, the aldosterone resistance in kidney transplant recipients usually produces either isolated hyperkalemia or hyperkalemic RTA; hyponatremia is unusual. Similarly, the medications that cause hyperkalemic RTA do not cause hyponatremia. Pseudohypoaldosteronism type II, an autosomal recessive disorder also known as **Gordon syndrome,** is a unique cause of hyperkalemic RTA because the genetic defect causes volume expansion and hypertension.

Children with **abnormal urinary tracts,** usually secondary to congenital malformations, may require diversion of urine through intestinal segments. Ureterosigmoidostomy, anastomosis of a ureter to the sigmoid colon, almost always produces a metabolic acidosis and hypokalemia. Consequently, ileal conduits are now the more commonly used procedure, although there is still a risk of a metabolic acidosis.

The **appropriate metabolic compensation for a chronic respiratory alkalosis** is a decrease in renal acid excretion. The resultant decrease in the serum bicarbonate concentration lessens the alkalemia caused by the respiratory alkalosis. If the respiratory alkalosis resolves quickly, the patient continues to have a decreased serum bicarbonate concentration, causing acidemia as the result of a metabolic acidosis. This resolves over 1-2 days via increased acid excretion by the kidneys.

Lactic acidosis most commonly occurs when inadequate oxygen delivery to the tissues leads to anaerobic metabolism and excess production of lactic acid. Lactic acidosis may be secondary to shock, severe anemia, or hypoxemia. When the underlying cause of the lactic acidosis is alleviated, the liver is able to metabolize the accumulated lactate into bicarbonate, correcting the metabolic acidosis. There is normally some tissue production of lactate that is metabolized by the liver. In children with severe liver dysfunction, impairment of lactate metabolism may produce a lactic acidosis. Rarely, a metabolically active malignancy grows so fast that its blood supply becomes inadequate, with resultant anaerobic metabolism and lactic acidosis. Patients who have short bowel syndrome resulting from small bowel resection can have bacterial overgrowth. In these patients, excessive bacterial metabolism of glucose into D-lactic acid can cause a lactic acidosis. Lactic acidosis occurs in a variety of inborn errors of metabolism, especially those affecting mitochondrial oxidation (see Chapter 87.4). Finally, medications can cause lactic acidosis. Nucleoside reverse transcriptase inhibitors that are used to treat HIV infection inhibit mitochondrial replication; lactic acidosis is a rare complication, although elevated serum lactate concentrations without acidosis are quite common. Metformin, commonly used for treating type 2 diabetes mellitus, is most likely to cause a lactic acidosis in patients with renal insufficiency. High dosages and prolonged use of propofol can cause lactic acidosis. Propylene glycol is a diluent in a variety of oral and intravenous medications; excessive intake causes a lactic acidosis, principally from accumulation of D-lactic acid.

In **insulin-dependent diabetes mellitus,** inadequate insulin leads to hyperglycemia and diabetic ketoacidosis (see Chapter 589). Production of acetoacetic acid and β-hydroxybutyric acid causes the metabolic acidosis. Administration of insulin corrects the underlying metabolic problem and permits conversion of acetoacetate and β-hydroxybutyrate into bicarbonate, which helps correct the metabolic acidosis. However, in some patients, urinary losses of acetoacetate and β-hydroxybutyrate may be substantial, preventing rapid regeneration of bicarbonate. In these patients, full correction of the metabolic acidosis requires renal regeneration of bicarbonate, a slower process. The hyperglycemia causes an osmotic diuresis, usually producing volume depletion, along with substantial losses of potassium, sodium, and phosphate.

In **starvation ketoacidosis,** the lack of glucose leads to keto acid production, which, in turn, can produce a metabolic acidosis, although it is usually mild as a result of increased acid secretion by the kidney. In alcoholic ketoacidosis, which is much less common in children than in adults, the acidosis usually follows a combination of an alcoholic binge with vomiting and poor intake of food. The acidosis is potentially more severe than with isolated starvation, and the blood glucose level may be low, normal, or high. Hypoglycemia and acidosis also suggest an inborn error of metabolism.

Renal failure causes a metabolic acidosis because of the need for the kidneys to excrete the acid produced by normal metabolism. With mild or moderate renal insufficiency, the remaining nephrons are usually able to compensate by increasing acid excretion. When the GFR is <20-30% of normal, the compensation is inadequate and a metabolic acidosis develops. In some children, especially those with chronic renal failure because of tubular damage, the acidosis develops at a higher GFR because of a concurrent defect in acid secretion by the distal tubule (distal RTA).

A variety of **toxic ingestions** (see Chapter 63) can cause a metabolic acidosis. **Salicylate** intoxication is now much less common because aspirin is no longer recommended for fever control in children. Acute

salicylate intoxication occurs after a large overdose. Chronic salicylate intoxication is possible with gradual buildup of the drug. Especially in adults, respiratory alkalosis may be the dominant acid–base disturbance. In children, the metabolic acidosis is usually the more significant finding. Other symptoms of salicylate intoxication are fever, seizures, lethargy, and coma. Hyperventilation may be particularly marked. Tinnitus, vertigo, and hearing impairment are more likely with chronic salicylate intoxication.

Ethylene glycol, a component of antifreeze, is converted in the liver to glyoxylic and oxalic acids, causing a severe metabolic acidosis. Excessive oxalate excretion causes calcium oxalate crystals to appear in the urine, and calcium oxalate precipitation in the kidney tubules can cause renal failure. The toxicity of methanol ingestion also depends on liver metabolism; formic acid is the toxic end product that causes the metabolic acidosis and other sequelae, which include damage to the optic nerve and CNS. Symptoms may include nausea, emesis, visual impairment, and altered mental status. Toluene inhalation and paraldehyde ingestion are other potential causes of a metabolic acidosis.

Many **inborn errors of metabolism** cause a metabolic acidosis (see Chapters 84-87). The metabolic acidosis may be the result of excessive production of keto acids, lactic acid, and/or other organic anions. Some patients have accompanying hypoglycemia or hyperammonemia. In most patients, the acidosis occurs episodically, only during acute decompensations, which may be precipitated by ingestion of specific dietary substrates, the stress of a mild illness, or poor compliance with dietary or medical therapy. In a few inborn errors of metabolism, patients have a chronic metabolic acidosis.

Clinical Manifestations

The underlying disorder usually produces most of the signs and symptoms in children with a mild or moderate metabolic acidosis. The clinical manifestations of the acidosis are related to the degree of acidemia; patients with appropriate respiratory compensation and less severe acidemia have fewer manifestations than those with a concomitant respiratory acidosis. At a serum pH <7.2, there may be impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present. With acidemia, there may be a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in children with volume depletion or shock. Acidemia causes vasoconstriction of the pulmonary vasculature, which is especially problematic in newborn infants with persistent pulmonary hypertension (see Chapter 101.7).

The normal respiratory response to metabolic acidosis—compensatory hyperventilation—may be subtle with mild metabolic acidosis, but it causes discernible increased respiratory effort with worsening acidemia. The acute metabolic effects of acidemia include insulin resistance, increased protein degradation, and reduced ATP synthesis. Chronic metabolic acidosis causes failure to thrive in children. Acidemia causes potassium to move from the intracellular space to the extracellular space, thereby increasing the serum potassium concentration. Severe acidemia impairs brain metabolism, eventually resulting in lethargy and coma.

Diagnosis

The etiology of a metabolic acidosis is often apparent from the history and physical examination. Acutely, diarrhea and shock are common causes of a metabolic acidosis. Shock, which causes a lactic acidosis, is usually apparent on physical examination and can be secondary to dehydration, acute blood loss, sepsis, or heart disease. Failure to thrive suggests a chronic metabolic acidosis, as happens with renal insufficiency or RTA. New onset of polyuria occurs in children with undiagnosed diabetes mellitus and diabetic ketoacidosis. Metabolic acidosis with seizures and/or a depressed sensorium, especially in an infant, warrants consideration of an inborn error of metabolism. Meningitis and sepsis with lactic acidosis are more common explanations for metabolic acidosis with neurologic signs and symptoms. Identification of a toxic ingestion such as of ethylene glycol or methanol is especially important because of the potentially excellent response to specific therapy. A variety of medications can cause a metabolic acidosis; they may be prescribed or accidentally ingested. Hepatomegaly and metabolic acidosis may occur in children with sepsis, congenital or acquired heart disease, hepatic failure, or inborn errors of metabolism.

Basic laboratory tests in a child with a metabolic acidosis should include measurements of BUN, serum creatinine, serum glucose, urinalysis, and serum electrolytes. Elevated BUN and creatinine values are present in renal insufficiency, whereas an elevated BUN : creatinine ratio (>20 : 1) supports a diagnosis of prerenal azotemia and the possibility of poor perfusion with lactic acidosis. Metabolic acidosis, hyperglycemia, glycosuria, and ketonuria support a diagnosis of diabetic ketoacidosis. Starvation causes ketosis, but the metabolic acidosis, if present, is usually mild (HCO_3^- >18). In most children with ketosis from poor intake and metabolic acidosis there is a concomitant disorder, such as gastroenteritis with diarrhea, that explains the metabolic acidosis. Alternatively, metabolic acidosis with or without ketosis occurs in inborn errors of metabolism; patients with these disorders may have hyperglycemia, normoglycemia, or hypoglycemia. Adrenal insufficiency may cause metabolic acidosis and hypoglycemia. Metabolic acidosis with hypoglycemia also occurs with liver failure. Metabolic acidosis, normoglycemia, and glycosuria occur in children when type II RTA is part of Fanconi syndrome; the defect in resorption of glucose by the proximal tubule of the kidney causes the glycosuria.

The serum potassium level is often abnormal in children with a metabolic acidosis. Even though a metabolic acidosis causes potassium to move from the intracellular space to the extracellular space, many patients with a metabolic acidosis have a low serum potassium level owing to excessive body losses of potassium. With diarrhea, there are high stool losses of potassium and often secondary renal losses of potassium, whereas in type I or type II RTA, there are increased urinary losses of potassium. In diabetic ketoacidosis, urinary losses of potassium are high, but the shift of potassium out of cells because of a lack of insulin and metabolic acidosis is especially significant. Consequently, the initial serum potassium level can be low, normal, or high, even though total body potassium is almost always decreased. The serum potassium level is usually increased in patients with acidosis due to renal insufficiency; urinary potassium excretion is impaired. The combination of metabolic acidosis, hyperkalemia, and hyponatremia occurs in patients with severe aldosterone deficiency (adrenogenital syndrome) or aldosterone resistance. Patients with less severe, type IV RTA often have only hyperkalemia and metabolic acidosis. Very ill children with metabolic acidosis may have an elevated serum potassium value as a result of a combination of renal insufficiency, tissue breakdown, and a shift of potassium from the intracellular space to the extracellular space secondary to the metabolic acidosis.

The **plasma anion gap** is useful for evaluating patients with a metabolic acidosis. It divides patients into 2 diagnostic groups, those with normal anion gap and those with increased anion gap. The following formula determines the anion gap:

$$\text{Anion gap} = [Na^+] - [Cl^-] - [HCO_3^-]$$

A normal anion gap is 4-11, although there is variation among laboratories. The number of serum anions must equal the number of serum cations to maintain electrical neutrality (Fig. 55-10). The anion gap is the difference between the measured cation (sodium) and the measured anions (chloride + bicarbonate). The anion gap is also the difference between the unmeasured cations (potassium, magnesium, calcium) and the unmeasured anions (albumin, phosphate, urate, sulfate). An increased anion gap occurs when there is an increase in unmeasured anions. With a lactic acidosis, there is endogenous production of lactic acid, which is composed of positively charged hydrogen ions and negatively charged lactate anions. The hydrogen ions are largely buffered by serum bicarbonate, resulting in a decrease in the bicarbonate concentration. The hydrogen ions that are not buffered by bicarbonate cause the serum pH to decrease. The lactate anions remain, causing the increase in the anion gap.

An increase in unmeasured anions, along with hydrogen ion generation, is present in all causes of an increased gap metabolic acidosis (see Table 55-13). In diabetic ketoacidosis, the keto acids β-hydroxybutyrate

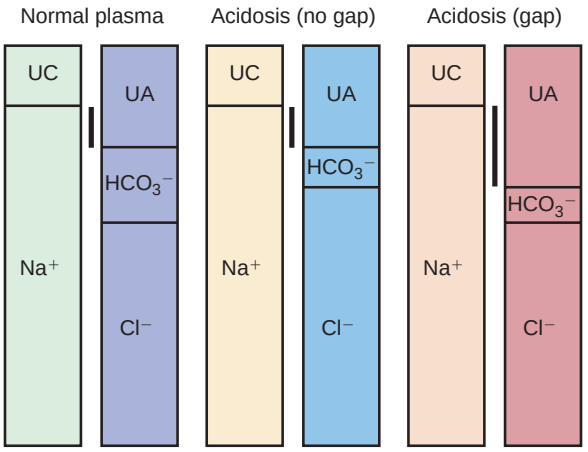


Figure 55-10 The anion gap, which is the difference between the sodium concentration and the combined concentrations of chloride and bicarbonate *(vertical lines)*. In both a gap and a nongap metabolic acidosis, there is a decrease in the bicarbonate concentration. There is an increase in unmeasured anions (UA) in patients with a gap metabolic acidosis. In a nongap metabolic acidosis, there is an increase in the serum chloride concentration. UC, unmeasured cations.

and acetoacetate are the unmeasured anions. In renal failure, there is retention of unmeasured anions, including phosphate, urate, and sulfate. The increase in unmeasured anions in renal failure is usually less than the decrease in the bicarbonate concentration. Renal failure is thus a mix of an increased gap and a normal gap metabolic acidosis. The normal gap metabolic acidosis is especially prominent in children with renal failure as a result of tubular damage, as occurs with renal dysplasia or obstructive uropathy, because these patients have a concurrent RTA. The unmeasured anions in toxic ingestions vary: formate in methanol intoxication, glycolate in ethylene glycol intoxication, and lactate and keto acids in salicylate intoxication. In inborn errors of metabolism, the unmeasured anions depend on the specific etiology and may include keto acids, lactate, and other organic anions. In a few inborn errors of metabolism, the acidosis occurs without generation of unmeasured anions; thus, the anion gap is normal.

A **normal anion gap** metabolic acidosis occurs when there is a decrease in the bicarbonate concentration without an increase in the unmeasured anions. With diarrhea, there is a loss of bicarbonate in the stool, causing a decrease in the serum pH and bicarbonate concentration; the serum chloride concentration increases to maintain electrical neutrality (see Fig. 55-10). Hyperchloremic metabolic acidosis is an alternative term for a normal anion gap metabolic acidosis. Calculation of the anion gap is more precise than using the chloride concentration to differentiate between a normal and an increased gap metabolic acidosis, in that the anion gap directly determines the presence of unmeasured anions. Electrical neutrality dictates that the chloride concentration increases or decreases according to the serum sodium concentration, making the chloride concentration a less reliable predictor of unmeasured anions than the more direct measure, calculation of the anion gap.

Approximately 11 mEq of the anion gap is normally secondary to albumin. A 1 g/dL decrease in the albumin concentration decreases the anion gap by roughly 2.5 mEq/L. Similarly, an increase in unmeasured cations, such as calcium, potassium, and magnesium, decreases the anion gap. Conversely, a decrease in unmeasured cations is a very unusual cause of an increased anion gap. Because of these variables, the broad range of a normal anion gap, and other variables, the presence of a normal or an increased anion gap is not always reliable in differentiating among the causes of a metabolic acidosis, especially when the metabolic acidosis is mild. In some patients there is more than 1 explanation for the metabolic acidosis, such as the child with diarrhea and lactic acidosis as a result of poor perfusion. The anion gap should not be interpreted in dogmatic isolation; consideration of other laboratory abnormalities and the clinical history improves its diagnostic utility.

Treatment

The most effective therapeutic approach for patients with a metabolic acidosis is repair of the underlying disorder, if possible. The administration of insulin in diabetic ketoacidosis and the restoration of adequate perfusion with intravenous fluids in lactic acidosis because of hypovolemia or shock eventually result in normalization of the acid–base balance. In other diseases, the use of bicarbonate therapy is indicated because the underlying disorder is irreparable. Children with metabolic acidosis caused by RTA or chronic renal failure require long-term base therapy. Patients with acute renal failure and metabolic acidosis need base therapy until their kidneys' ability to excrete hydrogen normalizes. In other disorders, the cause of the metabolic acidosis eventually resolves, but base therapy is necessary during the acute illness. In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings (ethylene glycol, methanol) and inborn errors of metabolism (pyruvate carboxylase deficiency, propionic acidemia). Some inborn errors of metabolism require long-term base therapy.

The use of base therapy in diabetic ketoacidosis and lactic acidosis is controversial; there is little evidence that it improves patient outcome, and it has a variety of potential side effects. The risks of giving sodium bicarbonate include the possibility of causing hypernatremia or volume overload. Furthermore, the patient may have overcorrection of the metabolic acidosis once the underlying disorder resolves, because metabolism of lactate or keto acids generates bicarbonate. The rapid change from acidemia to alkalemia can cause a variety of problems, including hypokalemia and hypophosphatemia. Bicarbonate therapy increases the generation of CO_2, which can accumulate in patients with respiratory failure. Because CO_2 readily diffuses into cells, the administration of bicarbonate can lower the intracellular pH, potentially worsening cell function. Base therapy is usually reserved for children with severe acute lactic acidosis and severe diabetic ketoacidosis.

Oral base therapy is given to children with chronic metabolic acidosis. Sodium bicarbonate tablets are available for older children. Younger children generally take citrate solutions; the liver generates bicarbonate from citrate. Citrate solutions are available as sodium citrate, potassium citrate, and a 1:1 mix of sodium citrate and potassium citrate. The patient's potassium needs dictate the choice. Children with type I or type II RTA may have hypokalemia and may benefit from potassium supplements, whereas most children with chronic renal failure cannot tolerate additional potassium.

Oral or intravenous base can be used in acute metabolic acidosis; intravenous therapy is generally used when a rapid response is necessary. Sodium bicarbonate may be given as a bolus, usually at a dose of 1 mEq/kg, in an emergency situation. Another approach is to add sodium bicarbonate or sodium acetate to the patient's intravenous fluids, remembering to remove an equal amount of sodium chloride from the solution to avoid giving an excessive sodium load. Careful monitoring is mandatory so that the dose of base can be titrated appropriately. Tris-hydroxymethyl aminomethane (THAM) is an option in patients with a metabolic acidosis and a respiratory acidosis, because it neutralizes acids without releasing CO_2. THAM also diffuses into cells and therefore provides intracellular buffering.

Hemodialysis is another option for correcting a metabolic acidosis, and it is an appropriate choice in patients with renal insufficiency, especially if significant uremia or hyperkalemia is also present. Hemodialysis is advantageous for correcting the metabolic acidosis caused by methanol or ethylene glycol intoxication, because hemodialysis removes the offending toxin. In addition, these patients often have a severe metabolic acidosis that does not respond easily to intravenous bicarbonate therapy. Peritoneal dialysis is another option for correcting the metabolic acidosis due to renal insufficiency, although, because it relies on lactate as the source of base, it may not correct the metabolic acidosis in patients with concomitant renal failure and lactic acidosis.

Many causes of metabolic acidosis require specific therapy. Administration of a glucocorticoid and a mineralocorticoid is necessary in patients with adrenal insufficiency. Patients with diabetic ketoacidosis require insulin therapy, whereas patients with lactic acidosis respond to measures that alleviate tissue hypoxia. Along with correction of acidosis, patients with methanol or ethylene glycol ingestion should receive an agent that prevents the breakdown of the toxic substance to its toxic metabolites. Fomepizole has supplanted ethanol as the treatment of choice. These agents work by inhibiting alcohol dehydrogenase, the enzyme that performs the first step in the metabolism of ethylene glycol or methanol. There are a variety of disease-specific therapies for patients with a metabolic acidosis resulting from an inborn error of metabolism.

METABOLIC ALKALOSIS

Metabolic alkalosis in children is most commonly secondary to emesis or diuretic use. The serum bicarbonate concentration is increased with a metabolic alkalosis, although a respiratory acidosis also leads to a compensatory elevation of the serum bicarbonate concentration. With a simple metabolic alkalosis, however, the pH is elevated; alkalemia is present. Patients with a respiratory acidosis are acidemic. A metabolic alkalosis, by decreasing ventilation, causes appropriate respiratory compensation. P_{CO_2} increases by 7 mm Hg for each 10 mEq/L increase in the serum bicarbonate concentration. Appropriate respiratory compensation never exceeds a P_{CO_2} of 55-60 mm Hg. The patient has a concurrent respiratory alkalosis if the P_{CO_2} is lower than the expected compensation. A greater-than-expected P_{CO_2} occurs with a concurrent respiratory acidosis.

Etiology and Pathophysiology

The kidneys normally respond promptly to a metabolic alkalosis by increasing base excretion. Two processes are therefore usually present to produce a metabolic alkalosis. The first process is the generation of the metabolic alkalosis, which requires the addition of base to the body. The second process is the maintenance of the metabolic alkalosis, which requires impairment in the kidney's ability to excrete base.

The etiologies of a metabolic alkalosis are divided into 2 categories on the basis of urinary chloride level (Table 55-14). The alkalosis in patients with a **low urinary chloride** level is maintained by **volume depletion;** thus, volume repletion is necessary for correction of the alkalosis. The volume depletion in these patients is caused by losses of sodium and potassium, but the loss of chloride is usually greater than the losses of sodium and potassium combined. Because chloride losses are the dominant cause of the volume depletion, these patients require chloride to correct the volume depletion and metabolic alkalosis; they are said to have **chloride-responsive metabolic alkalosis.** In contrast, the alkalosis in a patient with an elevated urinary chloride concentration does not respond to volume repletion and so is termed **chloride-resistant metabolic alkalosis.**

Emesis or nasogastric suction results in **loss of gastric fluid,** which has a high content of HCl. Generation of hydrogen ions by the gastric mucosa causes simultaneous release of bicarbonate into the bloodstream. Normally, the hydrogen ions in gastric fluid are reclaimed in the small intestine (by neutralizing secreted bicarbonate). Thus, there is no net loss of acid. With loss of gastric fluid, this does not occur, and a metabolic alkalosis develops. This period is the generation phase of the metabolic alkalosis.

The maintenance phase of the metabolic alkalosis from gastric losses is due to the volume depletion ("chloride depletion" from gastric loss of HCl). Volume depletion interferes with urinary loss of bicarbonate, the normal renal response to a metabolic alkalosis. During volume depletion, several mechanisms prevent renal bicarbonate loss. First, there is a reduction in the GFR, so less bicarbonate is filtered. Second, volume depletion increases resorption of sodium and bicarbonate in the proximal tubule, limiting the amount of bicarbonate that can be excreted in the urine. This effect is mediated by angiotensin II and by adrenergic stimulation of the kidney, which are both increased in response to volume depletion. Third, the increase in aldosterone during volume depletion increases bicarbonate resorption and hydrogen ion secretion in the collecting duct.

Table 55-14 Causes of Metabolic Alkalosis

CHLORIDE-RESPONSIVE (URINARY CHLORIDE <15 MEQ/L)
Gastric losses
Emesis
Nasogastric suction
Diuretics (loop or thiazide)
Chloride-losing diarrhea (OMIM 214700)
Chloride-deficient formula
Cystic fibrosis (OMIM 219700)
Post-hypercapnia
CHLORIDE-RESISTANT (URINARY CHLORIDE >20 MEQ/L)
High blood pressure
Adrenal adenoma or hyperplasia
Glucocorticoid-remediable aldosteronism (OMIM 103900)
Renovascular disease
Renin-secreting tumor
17β-Hydroxylase deficiency (OMIM 202110)
11β-Hydroxylase deficiency (OMIM 202010)
Cushing syndrome
11β-Hydroxysteroid dehydrogenase deficiency (OMIM 218030)
Licorice ingestion
Liddle syndrome (OMIM 177200)
Normal blood pressure
Gitelman syndrome (OMIM 263800)
Bartter syndrome (OMIM 607364/602522/241200/601678)
Autosomal dominant hypoparathyroidism (OMIM 146200)
EAST syndrome (OMIM 612780)
Base administration

EAST, epilepsy, ataxia, sensorineural hearing loss, and tubulopathy; OMIM, database number from the Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim).

In addition to volume depletion, gastric losses are usually associated with hypokalemia as a result of both gastric loss of potassium and, most importantly, increased urinary potassium losses. The increased urinary losses of potassium are mediated by aldosterone, through volume depletion, and by the increase in intracellular potassium secondary to the metabolic alkalosis, which causes potassium to move into the cells of the kidney, causing increased potassium excretion. Hypokalemia contributes to the maintenance of the metabolic alkalosis by decreasing bicarbonate loss. Hypokalemia increases hydrogen ion secretion in the distal nephron and stimulates ammonia production in the proximal tubule. Ammonia production enhances renal excretion of hydrogen ions.

A metabolic alkalosis can develop in patients receiving **loop** or **thiazide diuretics.** Diuretic use leads to volume depletion, which increases angiotensin II, aldosterone, and adrenergic stimulation of the kidney. Diuretics increase the delivery of sodium to the distal nephron, further enhancing acid excretion. Moreover, these diuretics cause hypokalemia, which increases acid excretion by the kidney. The increase in renal acid excretion generates the metabolic alkalosis, and the decrease in bicarbonate loss maintains it. In addition, patients who are receiving diuretics have a "contraction alkalosis." Diuretic use causes fluid loss without bicarbonate; thus, the remaining body bicarbonate is contained in a smaller total body fluid compartment. The bicarbonate concentration increases, helping to generate the metabolic alkalosis.

Diuretics are often used in patients with edema, such as those with nephrotic syndrome, heart failure, or liver failure. In many of these patients, metabolic alkalosis resulting from diuretic use develops despite the continued presence of edema. This is because the effective intravascular volume is low, and it is the effective intravascular volume that stimulates the compensatory mechanisms that cause and maintain a metabolic alkalosis. Many of these patients have a decreased effective intravascular volume before they begin diuretic therapy, increasing the likelihood of diuretic-induced metabolic alkalosis.

Diuretic use increases chloride excretion in the urine. Consequently, while a patient is receiving diuretics, the urine chloride level is typically

high (>20 mEq/L). After the diuretic effect has worn off, the urinary chloride level is low (<15 mEq/L) owing to appropriate renal chloride retention in response to volume depletion. Thus, categorization of diuretics on the basis of urinary chloride level depends on the timing of the measurement. However, the metabolic alkalosis from diuretics is clearly chloride responsive; it is corrected after adequate volume repletion. This is the rationale for including this process among the chloride-responsive causes of a metabolic alkalosis.

Most patients with diarrhea have a metabolic acidosis as a result of stool losses of bicarbonate. In **chloride-losing diarrhea,** an autosomal recessive disorder, there is a defect in the normal intestinal exchange of bicarbonate for chloride, causing excessive stool losses of chloride (see Chapter 338). In addition, stool losses of hydrogen ions and potassium cause metabolic alkalosis and hypokalemia, both of which are exacerbated by increased renal hydrogen and potassium losses from volume depletion. Treatment is with oral supplements of potassium and sodium chloride. Use of a gastric proton pump inhibitor, by decreasing gastric HCl production, reduces both the volume of diarrhea and the need for electrolyte supplementation.

An infant formula with extremely low chloride content has led to chloride deficiency and volume depletion. The infants fed this formula, which is no longer available, had a metabolic alkalosis and hypokalemia. **Cystic fibrosis** can rarely cause metabolic alkalosis, hypokalemia, and hyponatremia because of excessive losses of sodium chloride in sweat (see Chapter 403). The volume depletion causes the metabolic alkalosis and hypokalemia through increased urinary losses, whereas the hyponatremia, a less-common finding, is secondary to sodium loss combined with renal water conservation in an effort to protect the intravascular volume ("appropriate" ADH production).

A **posthypercapnic metabolic alkalosis** occurs after the correction of a chronic respiratory acidosis. This is typically seen in patients with chronic lung disease who are started on mechanical ventilation. During chronic respiratory acidosis, appropriate renal compensation leads to an increase in the serum bicarbonate concentration. This elevated bicarbonate concentration, because it is still present after acute correction of the respiratory acidosis, causes a metabolic alkalosis. The metabolic alkalosis persists because the patient with a chronic respiratory acidosis is intravascularly depleted because of the chloride loss that occurred during the initial metabolic compensation for the primary respiratory acidosis. In addition, many children with a chronic respiratory acidosis receive diuretics, which further decrease the intravascular volume. The metabolic alkalosis responds to correction of the intravascular volume deficit.

The **chloride-resistant** causes of metabolic alkalosis can be subdivided according to blood pressure status. Patients with **hypertension** either have increased aldosterone levels or act as if they do. Aldosterone levels are elevated in children with adrenal adenomas or hyperplasia. Aldosterone causes renal retention of sodium, with resultant hypertension. Metabolic alkalosis and hypokalemia result from aldosterone-mediated renal excretion of hydrogen ions and potassium. The urinary chloride level is not low because these patients are volume-overloaded, not volume-depleted. The volume expansion and hypertension allow normal excretion of sodium and chloride despite the presence of aldosterone. This is known as the mineralocorticoid escape phenomenon.

In **glucocorticoid-remediable aldosteronism,** an autosomal dominant disorder, there is excess production of aldosterone owing to the presence of an aldosterone synthase gene that is regulated by adrenocorticotropic hormone (ACTH) (see Chapter 576.8). Glucocorticoids effectively treat this disorder by inhibiting ACTH production by the pituitary, downregulating the inappropriate aldosterone production. Renovascular disease and renin-secreting tumors both cause excessive renin, leading to an increase in aldosterone, although hypokalemia and metabolic alkalosis are less-common findings than hypertension. In 2 forms of **congenital adrenal hyperplasia,** 11β-hydroxylase deficiency and 17α-hydroxylase deficiency, there is excessive production of the mineralocorticoid 11-deoxycorticosterone (see Chapters 576.2 and 576.4). Hypertension, hypokalemia, and metabolic alkalosis are more likely in 17α-hydroxylase deficiency than in 11β-hydroxylase deficiency. These disorders respond to glucocorticoids because the excess production of 11-deoxycorticosterone is under the control of ACTH.

Cushing syndrome frequently causes hypertension. Cortisol has some mineralocorticoid activity, and high levels can produce hypokalemia and metabolic alkalosis in patients with Cushing syndrome.

Cortisol can bind to the mineralocorticoid receptors in the kidney and function as a mineralocorticoid. This binding normally does not occur because 11β-hydroxysteroid dehydrogenase in the kidney converts cortisol to cortisone, which does not bind to the mineralocorticoid receptor. In 11β-hydroxysteroid dehydrogenase deficiency, also called **apparent mineralocorticoid excess,** cortisol is not converted in the kidney to cortisone. Cortisol is therefore available to bind to the mineralocorticoid receptor in the kidney and act as a mineralocorticoid. Patients with this deficiency, despite low levels of aldosterone, are hypertensive and hypokalemic, and they have a metabolic alkalosis. The same phenomenon can occur with excessive intake of natural licorice, a component of which, glycyrrhizic acid, inhibits 11β-hydroxysteroid dehydrogenase. The autosomal dominant disorder **Liddle syndrome** is secondary to an activating mutation of the sodium channel in the distal nephron (see Chapter 531.3). Upregulation of this sodium channel is one of the principal actions of aldosterone. Because this sodium channel is continuously open, children with Liddle syndrome have the features of hyperaldosteronism, including hypertension, hypokalemia, and metabolic alkalosis, but low serum levels of aldosterone.

Bartter syndrome and **Gitelman syndrome** are autosomal recessive disorders associated with **normal blood pressure,** elevations of urinary chloride, metabolic alkalosis, and hypokalemia (see Chapter 531). In Bartter syndrome, patients have a defect in sodium and chloride resorption in the loop of Henle. This leads to excessive urinary losses of sodium and chloride, and as in patients receiving loop diuretics, volume depletion and secondary hyperaldosteronism occur, causing hypokalemia and metabolic alkalosis. Gitelman syndrome is usually milder than Bartter syndrome. Patients have renal sodium and chloride wasting with volume depletion due mutations in the gene encoding the thiazide-sensitive sodium-chloride transporter in the distal tubule. As in patients receiving a thiazide diuretic, affected patients have volume depletion and secondary hyperaldosteronism with hypokalemia and metabolic alkalosis. Children with Gitelman syndrome have hypocalciuria and hypomagnesemia. Some patients with autosomal dominant hypoparathyroidism have hypokalemia and metabolic alkalosis due to impaired sodium and chloride resorption in the loop of Henle. **EAST syndrome** causes hypokalemia, metabolic alkalosis and hypomagnesemia.

Excessive base intake can cause a metabolic alkalosis. Affected patients do not have a low urine chloride level, unless there is associated volume depletion. In the absence of volume depletion, excess base is rapidly corrected via renal excretion of bicarbonate. Rarely, massive base intake can cause a metabolic alkalosis by overwhelming the kidney's ability to excrete bicarbonate. This may occur in infants who are given baking soda as a "home remedy" for colic or stomach upset. Each teaspoon of baking soda has 42 mEq of sodium bicarbonate. Infants have increased vulnerability because of a lower GFR, limiting the rate of compensatory renal bicarbonate excretion. A metabolic alkalosis may also occur in patients who receive a large amount of sodium bicarbonate during cardiopulmonary resuscitation. Blood products are anticoagulated with citrate, which is converted into bicarbonate by the liver. Patients who receive large amounts of blood products may have a metabolic alkalosis. Iatrogenic metabolic alkalosis can occur as a result of acetate in total parenteral nutrition. Aggressive use of bicarbonate therapy in a child with a lactic acidosis or diabetic ketoacidosis may cause a metabolic alkalosis. This event is especially likely in a patient in whom the underlying cause of the lactic acidosis is successfully corrected (restoration of intravascular volume in a patient with severe dehydration). Once the cause of the lactic acidosis resolves, lactate can be converted by the liver into bicarbonate, which when combined with infused bicarbonate can create a metabolic alkalosis. A similar phenomenon can occur in a child with diabetic ketoacidosis

because the administration of insulin allows keto acids to be metabolized, producing bicarbonate. However, this phenomenon rarely occurs because of judicious use of bicarbonate therapy in diabetic ketoacidosis and because there are usually significant pretreatment losses of keto acids in the urine, preventing massive regeneration of bicarbonate. Base administration is most likely to cause a metabolic alkalosis in patients who have an impaired ability to excrete bicarbonate in the urine. This impairment occurs in patients with concurrent volume depletion or renal insufficiency.

Clinical Manifestations

The symptoms in patients with a metabolic alkalosis are often related to the underlying disease and associated electrolyte disturbances. Children with chloride-responsive causes of metabolic alkalosis often have symptoms related to volume depletion, such as thirst and lethargy. In contrast, children with chloride-unresponsive causes may have symptoms related to hypertension.

Alkalemia causes potassium to shift into the intracellular space, producing a decrease in the extracellular potassium concentration. Alkalemia leads to increased urinary losses of potassium. Increased potassium losses are present in many of the conditions that cause a metabolic alkalosis. Therefore, most patients with a metabolic alkalosis have hypokalemia, and their symptoms may be related to the hypokalemia (see Chapter 55.4).

The symptoms of a metabolic alkalosis are caused by the associated alkalemia. The magnitude of the alkalemia is related to the severity of the metabolic alkalosis and the presence of concurrent respiratory acid–base disturbances. During alkalemia, the ionized calcium concentration decreases as a result of increased binding of calcium to albumin. The decrease in the ionized calcium concentration may cause symptoms of **tetany** (carpopedal spasm).

Arrhythmias are a potential complication of a metabolic alkalosis, and the risk for arrhythmia increases if there is concomitant hypokalemia. Alkalemia increases the risk of digoxin toxicity, and antiarrhythmic medications are less effective in the presence of alkalemia. In addition, alkalemia may decrease cardiac output. A metabolic alkalosis causes a compensatory increase in the P_{CO_2} by decreasing ventilation. In patients with underlying lung disease, the decrease in ventilatory drive can cause hypoxia. In patients with normal lungs, the hypoventilation seen in severe metabolic alkalosis can cause hypoxia.

Diagnosis

Measurement of the urinary chloride concentration is the most helpful test in differentiating among the causes of a metabolic alkalosis. The urine chloride level is low in patients with a metabolic alkalosis resulting from volume depletion, unless there is a defect in renal handling of chloride. The urine chloride level is superior to the urine sodium level in assessment of volume status in patients with a metabolic alkalosis, because the normal renal response to a metabolic alkalosis is to excrete bicarbonate. Because bicarbonate is negatively charged, it can be excreted only with a cation, usually sodium and potassium. Hence, a patient with a metabolic alkalosis may excrete sodium in the urine despite the presence of volume depletion, which normally causes avid sodium retention. *The urine chloride level is usually a good indicator of volume status, and it differentiates among the chloride-resistant and chloride-responsive causes of a metabolic alkalosis.*

Diuretics and gastric losses are the most common causes of metabolic alkalosis and are usually readily apparent from the patient history. Occasionally, metabolic alkalosis, usually with hypokalemia, may be a clue to the presence of bulimia or surreptitious diuretic use (see Chapter 28). Patients with bulimia have a low urine chloride level, indicating that they have volume depletion as a result of an extrarenal etiology, but there is no alternative explanation for their volume depletion. Surreptitious diuretic use may be diagnosed by obtaining a urine toxicology screen for diuretics. The urine chloride level is increased while a patient is using diuretics but is low when the patient stops taking them. Rarely, children with mild Bartter syndrome or Gitelman syndrome are misdiagnosed as having bulimia or abusing diuretics. The urine chloride value is always elevated in Bartter syndrome and Gitelman syndrome, and the urine toxicology screen for diuretics has a negative result. Metabolic alkalosis with hypokalemia is occasionally the initial manifestation of cystic fibrosis. An elevated sweat chloride finding is diagnostic.

Patients with a metabolic alkalosis and a high urinary chloride level are subdivided according to blood pressure status. Children with normal blood pressure may have Bartter syndrome or Gitelman syndrome. Excess base administration is another diagnostic possibility, but it is usually apparent from the history. In patients with sodium bicarbonate ingestion (baking soda), which may be unreported by the parent, the metabolic alkalosis usually occurs with significant hypernatremia. In addition, unless volume depletion is superimposed, the metabolic alkalosis from base ingestion resolves itself once the source of base is eliminated.

Measuring serum concentrations of renin and aldosterone differentiates children with a metabolic alkalosis, a high urinary chloride level, and elevated blood pressure. Both renin and aldosterone are elevated in children with either renovascular disease or a renin-secreting tumor. Aldosterone is high and renin is low in patients with adrenal adenomas or hyperplasia and glucocorticoid-remediable aldosteronism. Renin and aldosterone are low in children with Cushing syndrome, Liddle syndrome, licorice ingestion, 17α-hydroxylase deficiency, 11β-hydroxylase deficiency, and 11β-hydroxysteroid dehydrogenase deficiency. An elevated 24 hr urine cortisol value is diagnostic of Cushing syndrome, which is suspected from the presence of the other classic features of this disease (see Chapter 577). Elevations of 11-deoxycorticosterone values are seen in 17α-hydroxylase deficiency and 11β-hydroxylase deficiency.

Treatment

The approach to treatment of metabolic alkalosis depends on the severity of the alkalosis and the underlying etiology. In children with a mild metabolic alkalosis ($[HCO_3^-] < 32$), intervention is often unnecessary, although this depends on the specific circumstances. In a child with congenital heart disease who is receiving a stable dose of a loop diuretic, a mild alkalosis does not require treatment. In contrast, intervention may be appropriate in a child with a worsening mild metabolic alkalosis because of nasogastric suction. The presence of a concurrent respiratory acid–base disturbance also influences therapeutic decision making. A patient with a concurrent respiratory acidosis should have some increase in bicarbonate owing to metabolic compensation; thus, the severity of the pH elevation is more important than the bicarbonate concentration. In contrast, a patient with a respiratory alkalosis and a metabolic alkalosis is at risk for severe alkalemia; treatment may be indicated, even if the increase in bicarbonate value is only mild.

Intervention is usually necessary in children with moderate or severe metabolic alkalosis. The most effective approach is to address the underlying etiology. In some children, nasogastric suction may be decreased or discontinued. Alternatively, the addition of a gastric proton pump inhibitor reduces gastric secretion and losses of HCl. Diuretics are an important cause of metabolic alkalosis, and if a change is tolerated, they should be eliminated or the dose reduced. Adequate potassium supplementation or the addition of a potassium-sparing diuretic is also helpful in a child with a metabolic alkalosis from diuretics. Potassium-sparing diuretics not only decrease renal potassium losses but, by blocking the action of aldosterone, also decrease hydrogen ion secretion in the distal nephron, increasing urinary bicarbonate excretion. Many children cannot tolerate discontinuation of diuretic therapy; thus, potassium supplementation and potassium-sparing diuretics are the principal therapeutic approach. Arginine HCl may also be used to treat chloride-responsive metabolic acidosis if sodium or potassium salts are not appropriate. Arginine HCl may raise the serum potassium levels during administration. Rarely, in cases of severe metabolic alkalosis, acetazolamide is an option. A carbonic anhydrase inhibitor, acetazolamide decreases resorption of bicarbonate in the proximal tubule, causing significant bicarbonate loss in the urine. The patient receiving this drug must be monitored closely,

because acetazolamide produces major losses of potassium in the urine and increases fluid losses, potentially necessitating a reduction in dosage of other diuretics.

Most children with a metabolic alkalosis have one of the chloride-responsive etiologies. In these situations, administration of sufficient sodium chloride and potassium chloride to correct the volume deficit and the potassium deficit is necessary to correct the metabolic alkalosis. This approach may not be an option in the child who has volume depletion due to diuretics, because volume repletion may be contraindicated. Adequate replacement of gastric losses of sodium and potassium in a child with a nasogastric tube can minimize or prevent the development of the metabolic alkalosis. With adequate intravascular volume and a normal serum potassium concentration, the kidney is able to excrete the excess bicarbonate within a couple of days.

In children with the chloride-resistant causes of a metabolic alkalosis that are associated with hypertension, volume repletion is contraindicated because it would exacerbate the hypertension and would not repair the metabolic alkalosis. Ideally, treatment focuses on eliminating the excess aldosterone effect. Adrenal adenomas can be resected, licorice intake can be eliminated, and renovascular disease can be repaired. Glucocorticoid-remediable aldosteronism, 17α-hydroxylase deficiency, and 11β-hydroxylase deficiency respond to the administration of glucocorticoids. The mineralocorticoid effect of cortisol in 11β-hydroxysteroid dehydrogenase deficiency can be decreased with the use of spironolactone, which blocks the mineralocorticoid receptor. In contrast, the metabolic alkalosis in children with Liddle syndrome does not respond to spironolactone; however, either triamterene or amiloride is effective therapy because both agents block the sodium channel that is constitutively active in Liddle syndrome.

In children with Bartter syndrome and Gitelman syndrome, therapy includes oral potassium supplementation and potassium-sparing diuretics. Children with Gitelman syndrome often require magnesium supplementation, whereas children with severe Bartter syndrome often benefit from indomethacin.

RESPIRATORY ACIDOSIS

A respiratory acidosis is an inappropriate increase in blood CO_2 (P_{CO_2}). Carbon dioxide is a byproduct of metabolism, and it is removed from the body by the lungs. During a respiratory acidosis, there is a decrease in the effectiveness of CO_2 removal by the lungs. A respiratory acidosis is secondary to either pulmonary disease, such as severe bronchiolitis, or nonpulmonary disease, such as a narcotic overdose. Even though body production of CO_2 can vary, normal lungs are able to accommodate this variation; excess production of CO_2 is not an isolated cause of a respiratory acidosis. With impairment of alveolar ventilation, the rate of body production of CO_2 may affect the severity of the respiratory acidosis, but this is usually not a significant factor.

A respiratory acidosis causes a decrease in the blood pH, but there is normally a metabolic response that partially compensates, minimizing the severity of the acidemia. The acute metabolic response to a respiratory alkalosis occurs within minutes. The metabolic compensation for an acute respiratory acidosis is secondary to titration of acid by nonbicarbonate buffers. This buffering of hydrogen ions causes a predictable increase in the serum bicarbonate concentration: Plasma bicarbonate increases by 1 for each 10 mm Hg increase in the P_{CO_2} (acute compensation).

With a chronic respiratory acidosis, there is more significant metabolic compensation and, thus, less severe acidemia than in an acute respiratory acidosis with the same increase in P_{CO_2}. During a chronic respiratory acidosis, the kidneys increase acid excretion. This response occurs over 3-4 days and causes a predictable increase in the serum bicarbonate concentration: Plasma bicarbonate increases by 3.5 for each 10 mm Hg increase in the P_{CO_2} (chronic compensation).

The increase of serum bicarbonate concentration during a chronic respiratory acidosis is associated with a decrease in body chloride. After acute correction of a chronic respiratory acidosis, the plasma bicarbonate continues to be increased, and the patient has a metabolic alkalosis. Because of the chloride deficit, this is a chloride-responsive metabolic alkalosis; it corrects once the patient's chloride deficit is replaced.

A mixed disorder is present if the metabolic compensation is inappropriate. A higher-than-expected bicarbonate value occurs in the setting of a concurrent metabolic alkalosis, and a lower-than-expected bicarbonate value occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory acidosis requires clinical knowledge of the acuity of the process, because the expected compensation is different, depending on whether the process is acute or chronic.

The P_{CO_2} cannot be interpreted in isolation to determine whether a patient has a respiratory acidosis. A respiratory acidosis is always present if a patient has acidemia and an elevated P_{CO_2}. However, an elevated P_{CO_2} also occurs as appropriate respiratory compensation for a simple metabolic alkalosis. The patient is alkalemic; this is not a respiratory acidosis. During a mixed disturbance, a patient can have a respiratory acidosis and a normal or even low P_{CO_2}. This condition may occur in a patient with a metabolic acidosis; a respiratory acidosis is present if the patient does not have appropriate respiratory compensation (the P_{CO_2} is higher than expected from the severity of the metabolic acidosis).

Etiology and Pathophysiology

The causes of a respiratory acidosis are either pulmonary or nonpulmonary (Table 55-15). CNS disorders can decrease the activity of the central respiratory center, reducing ventilatory drive. A variety of medications and illicit drugs suppress the respiratory center. The signals from the respiratory center need to be transmitted to the respiratory muscles via the nervous system. Respiratory muscle failure can be secondary to disruption of the signal from the CNS in the spinal cord, the phrenic nerve, or the neuromuscular junction. Disorders directly affecting the muscles of respiration can prevent adequate ventilation, causing a respiratory acidosis.

Mild or moderate lung disease often causes a respiratory alkalosis as a result of hyperventilation secondary to hypoxia or stimulation of lung mechanoreceptors or chemoreceptors. Only more severe lung disease causes a respiratory acidosis. Upper airway diseases, by impairing air entry into the lungs, may decrease ventilation, producing a respiratory acidosis.

Increased production of CO_2 is never the sole cause of a respiratory acidosis, but it can increase the severity of the disease in a patient with decreased ventilation of CO_2. Increased production of CO_2 occurs in patients with fever, hyperthyroidism, excess caloric intake, and high levels of physical activity. Increased respiratory muscle work also increases CO_2 production.

Clinical Manifestations

Patients with a respiratory acidosis are often tachypneic in an effort to correct the inadequate ventilation. Exceptions include patients with a respiratory acidosis resulting from CNS depression and patients who are on the verge of complete respiratory failure secondary to fatigue of the respiratory muscles.

The symptoms of respiratory acidosis are related to the severity of the hypercarbia. Acute respiratory acidosis is usually more symptomatic than chronic respiratory acidosis. Symptoms are also increased by concurrent hypoxia or metabolic acidosis. In a patient breathing room air, hypoxia is always present if a respiratory acidosis is present. The potential CNS manifestations of respiratory acidosis include anxiety, dizziness, headache, confusion, asterixis, myoclonic jerks, hallucinations, psychosis, coma, and seizures.

Acidemia, no matter the etiology, affects the cardiovascular system. An arterial pH <7.2 impairs cardiac contractility and the normal response to catecholamines, in both the heart and the peripheral vasculature. Hypercapnia causes vasodilation, most dramatically in the cerebral vasculature, but hypercapnia produces vasoconstriction of the pulmonary circulation. Respiratory acidosis increases the risk of cardiac arrhythmias, especially in a child with underlying cardiac disease.

Table 55-15 Causes of Respiratory Acidosis

CENTRAL NERVOUS SYSTEM DEPRESSION
Encephalitis
Head trauma
Brain tumor
Central sleep apnea
Primary pulmonary hypoventilation (Ondine curse)
Stroke
Hypoxic brain damage
Obesity-hypoventilation (Pickwickian syndrome)
Increased intracranial pressure
Medications
Narcotics
Barbiturates
Anesthesia
Benzodiazepines
Propofol
Alcohols
DISORDERS OF THE SPINAL CORD, PERIPHERAL NERVES, OR NEUROMUSCULAR JUNCTION
Diaphragmatic paralysis
Guillain-Barré syndrome
Poliomyelitis
Spinal muscular atrophies
Tick paralysis
Botulism
Myasthenia
Multiple sclerosis
Spinal cord injury
Medications
Vecuronium
Aminoglycosides
Organophosphates (pesticides)
RESPIRATORY MUSCLE WEAKNESS
Muscular dystrophy
Hypothyroidism
Malnutrition
Hypokalemia
Hypophosphatemia
Medications
Succinylcholine
Corticosteroids
PULMONARY DISEASE
Pneumonia
Pneumothorax
Asthma
Bronchiolitis
Pulmonary edema
Pulmonary hemorrhage
Acute respiratory distress syndrome
Neonatal respiratory distress syndrome
Cystic fibrosis
Bronchopulmonary dysplasia
Hypoplastic lungs
Meconium aspiration
Pulmonary thromboembolus
Interstitial fibrosis
UPPER AIRWAY DISEASE
Aspiration
Laryngospasm
Angioedema
Obstructive sleep apnea
Tonsillar hypertrophy
Vocal cord paralysis
Extrinsic tumor
Extrinsic or intrinsic hemangioma
MISCELLANEOUS
Flail chest
Cardiac arrest
Kyphoscoliosis
Decreased diaphragmatic movement due to ascites or peritoneal dialysis

Diagnosis

The history and physical findings often point to a clear etiology. For the obtunded patient with poor respiratory effort, evaluation of the CNS is often indicated. This may include imaging studies (CT or MRI) and, potentially, a lumbar puncture for cerebrospinal fluid analysis. A toxicology screen for illicit drugs may also be appropriate. A response to naloxone is both diagnostic and therapeutic. In many of the diseases affecting the respiratory muscles, there is evidence of weakness in other muscles. Stridor is a clue that the child may have upper airway disease. Along with a physical examination, a chest radiograph is often helpful in diagnosing pulmonary disease.

In many patients, respiratory acidosis may be multifactorial. A child with bronchopulmonary dysplasia, an intrinsic lung disease, may worsen because of respiratory muscle dysfunction caused by severe hypokalemia resulting from long-term diuretic therapy. Conversely, a child with muscular dystrophy, a muscle disease, may worsen because of aspiration pneumonia.

For a patient with respiratory acidosis, calculation of the gradient between the alveolar oxygen concentration and the arterial oxygen concentration, the A-a O_2 gradient, is useful for distinguishing between poor respiratory effort and intrinsic lung disease. The A-a O_2 gradient is increased if the hypoxemia is caused by intrinsic lung disease (see Chapter 373).

Treatment

Respiratory acidosis is best managed by treatment of the underlying etiology. In some instances, the response is very rapid, such as after the administration of naloxone to a patient with a narcotic overdose. In contrast, in the child with pneumonia, a number of days of antibiotic therapy may be required before the respiratory status improves. In many children with a chronic respiratory acidosis, there is no curative therapy, although an acute respiratory illness superimposed on a chronic respiratory condition is usually reversible.

All patients with an acute respiratory acidosis are hypoxic, and therefore need to receive supplemental oxygen. Mechanical ventilation is necessary in some children with a respiratory acidosis. Children with a significant respiratory acidosis caused by a CNS disease usually require mechanical ventilation because such a disorder is unlikely to respond quickly to therapy. In addition, hypercarbia causes cerebral vasodilation, and the increase in intracranial pressure can be dangerous in a child with an underlying CNS disease. Readily reversible CNS depression, such as from a narcotic overdose, may not require mechanical ventilation. Decisions on mechanical ventilation for other patients depend on a number of factors. Patients with severe hypercarbia—P_{CO_2} >75 mm Hg—usually require mechanical ventilation (see Chapter 71). The threshold for intubation is lower if there is concomitant metabolic acidosis, a slowly responsive underlying disease, or hypoxia that responds poorly to oxygen, or if the patient appears to be tiring and respiratory arrest seems likely.

In patients with a chronic respiratory acidosis, the respiratory drive is often less responsive to hypercarbia and more responsive to hypoxia. Hence, with chronic respiratory acidosis, excessive use of oxygen can blunt the respiratory drive and therefore increase the P_{CO_2}. In these patients, oxygen must be used cautiously.

When possible, it is best to avoid mechanical ventilation in a patient with a chronic respiratory acidosis because extubation is often difficult. However, an acute illness may necessitate mechanical ventilation in a child with a chronic respiratory acidosis. When intubation is necessary, the P_{CO_2} should be lowered only to the patient's normal baseline, and this should be done gradually. These patients normally have an elevated serum bicarbonate concentration as a result of metabolic compensation for their respiratory acidosis. A rapid lowering of the P_{CO_2} can cause a severe metabolic alkalosis, potentially leading to complications, including cardiac arrhythmias, decreased cardiac output, and decreased cerebral blood flow. In addition, prolonged mechanical ventilation at a normal P_{CO_2} causes the metabolic compensation to resolve. When the patient is subsequently extubated, the patient will no longer benefit from metabolic compensation, causing a more severe acidemia because of the respiratory acidosis.

RESPIRATORY ALKALOSIS

A respiratory alkalosis is an inappropriate reduction in the blood CO_2 concentration. This is usually secondary to hyperventilation, initially causing removal of CO_2 to surpass production. Eventually, a new steady state is achieved, with removal equaling production, albeit at a lower CO_2 tension (P_{CO_2}). A respiratory alkalosis that is not the result of hyperventilation may occur in children receiving extracorporeal membrane oxygenation or hemodialysis, with CO_2 lost directly from the blood in the extracorporeal circuit.

With a simple respiratory alkalosis, the pH increases but there is a normal metabolic response that attenuates some of the change in the blood pH. A metabolic response to an acute respiratory alkalosis occurs within minutes, mediated by hydrogen ion release from nonbicarbonate buffers. The metabolic response to an acute respiratory alkalosis is predictable: Plasma bicarbonate falls by 2 for each 10 mm Hg decrease in the P_{CO_2} (acute compensation).

A chronic respiratory alkalosis leads to more significant metabolic compensation because of the actions of the kidneys, which decrease acid secretion, producing a decrease in the serum bicarbonate concentration. Both the proximal and distal tubules decrease acid secretion. Metabolic compensation for a respiratory alkalosis develops gradually and takes 2-3 days to produce the full effect: Plasma bicarbonate falls by 4 for each 10 mm Hg decrease in the P_{CO_2} (chronic compensation).

A chronic respiratory alkalosis is the only acid–base disturbance wherein appropriate compensation may normalize the pH, albeit >7.4.

A mixed disorder is present if the metabolic compensation is inappropriate. A higher than expected bicarbonate level occurs in the setting of a concurrent metabolic alkalosis, and a lower than expected bicarbonate level occurs in the setting of a concurrent metabolic acidosis. Evaluating whether compensation is appropriate during a respiratory alkalosis requires clinical knowledge of the acuity of the process, because the expected compensation differs according to whether the process is acute or chronic.

A low P_{CO_2} value does not always indicate a respiratory alkalosis. The P_{CO_2} also decreases as part of the appropriate respiratory compensation for a metabolic acidosis; this is not a respiratory alkalosis. A metabolic acidosis is the dominant acid–base disturbance in a patient with acidemia and a low P_{CO_2}, even though there could still be a concurrent respiratory alkalosis. In contrast, a respiratory alkalosis is always present in a patient with alkalemia and a low P_{CO_2}. Even a normal P_{CO_2} value may be consistent with a respiratory alkalosis in a patient with a metabolic alkalosis because an elevated P_{CO_2} is expected as part of appropriate respiratory compensation for the metabolic alkalosis.

Table 55-16 | Causes of Respiratory Alkalosis

HYPOXEMIA OR TISSUE HYPOXIA
Pneumonia
Pulmonary edema
Cyanotic heart disease
Congestive heart failure
Asthma
Severe anemia
High altitude
Laryngospasm
Aspiration
Carbon monoxide poisoning
Pulmonary embolism
Interstitial lung disease
Hypotension
LUNG RECEPTOR STIMULATION
Pneumonia
Pulmonary edema
Asthma
Pulmonary embolism
Hemothorax
Pneumothorax
Respiratory distress syndrome (adult or infant)
CENTRAL STIMULATION
Central nervous system disease
Subarachnoid hemorrhage
Encephalitis or meningitis
Trauma
Brain tumor
Stroke
Fever
Pain
Anxiety (panic attack)
Psychogenic hyperventilation or anxiety
Liver failure
Sepsis
Pregnancy
Mechanical ventilation
Hyperammonemia
Extracorporeal membrane oxygenation or hemodialysis
Medications
Salicylate intoxication
Theophylline
Progesterone
Exogenous catecholamines
Caffeine

Etiology and Pathophysiology

A variety of stimuli can increase the ventilatory drive and cause a respiratory alkalosis (Table 55-16). Arterial hypoxemia or tissue hypoxia stimulates peripheral chemoreceptors to signal the central respiratory center in the medulla to increase ventilation. The resultant greater respiratory effort increases the oxygen content of the blood but depresses the P_{CO_2}. The effect of hypoxemia on ventilation begins when the oxygen saturation decreases to approximately 90% (P_{O_2} = 60 mm Hg), and hyperventilation increases as hypoxemia worsens. Acute hypoxia is a more potent stimulus for hyperventilation than chronic hypoxia; thus, chronic hypoxia, as occurs in cyanotic heart disease, causes a much-less-severe respiratory alkalosis than an equivalent degree of acute hypoxia. There are many causes of hypoxemia or tissue hypoxia, including primary lung disease, severe anemia, and carbon monoxide poisoning.

The lungs contain chemoreceptors and mechanoreceptors that respond to irritants and stretching and send signals to the respiratory center to increase ventilation. Aspiration or pneumonia may stimulate the chemoreceptors, whereas pulmonary edema may stimulate the mechanoreceptors. Most of the diseases that activate these receptors may also cause hypoxemia and can, therefore, potentially lead to hyperventilation via 2 mechanisms. Patients with primary lung disease may initially have a respiratory alkalosis, but worsening of the disease, combined with respiratory muscle fatigue, often causes respiratory failure and the development of a respiratory acidosis.

Hyperventilation in the absence of lung disease occurs with direct stimulation of the central respiratory center. This occurs with CNS diseases, such as meningitis, hemorrhage, and trauma. Central hyperventilation due to lesions, such as infarcts or tumors near the central respiratory center in the midbrain, increases the rate and depth of the respiratory effort. This respiratory pattern portends a poor prognosis because these midbrain lesions are frequently fatal. Systemic processes may cause centrally mediated hyperventilation. Although the exact mechanisms are not clear, liver disease causes a respiratory alkalosis that is usually proportional to the degree of liver failure. Pregnancy causes a chronic respiratory alkalosis, probably mediated by progesterone acting on the respiratory centers. Salicylates, although often causing a concurrent metabolic acidosis, directly stimulate the respiratory center to produce a respiratory alkalosis. The respiratory alkalosis during sepsis is probably due to cytokine release.

Hyperventilation may be secondary to an underlying disease that causes pain, stress, or anxiety. In psychogenic hyperventilation or in panic attacks, there is no disease process accounting for the hyperventilation. This disorder may occur in a child who has had an emotionally stressful experience. Alternatively, it may be part of a panic disorder,

especially if there are repeated episodes of hyperventilation. In such a patient, the symptoms of acute alkalemia increase anxiety, potentially perpetuating the hyperventilation.

A respiratory alkalosis is quite common in children receiving mechanical ventilation because the respiratory center is not controlling ventilation. In addition, these children may have a decreased metabolic rate and hence less CO_2 production because of sedation and paralytic medications. Normally, decreased CO_2 production and the resultant hypocapnia decrease ventilation, but this physiologic response cannot occur in a child who cannot reduce ventilatory effort.

Clinical Manifestations

The disease process that is causing the respiratory alkalosis is usually more concerning than the clinical manifestations of the respiratory alkalosis. Chronic respiratory alkalosis is usually asymptomatic because metabolic compensation decreases the magnitude of the alkalemia.

Acute respiratory alkalosis may cause chest tightness, palpitations, lightheadedness, circumoral numbness, and paresthesias of the extremities. Less-common manifestations include tetany, seizures, muscle cramps, and syncope. The lightheadedness and syncope are probably a result of the reduction in cerebral blood flow that is caused by hypocapnia. The reduction in cerebral blood flow is the rationale for using hyperventilation to treat children with increased intracranial pressure. The paresthesias, tetany, and seizures may be partially related to the reduction in ionized calcium that occurs because alkalemia causes more calcium to bind to albumin. A respiratory alkalosis also causes a mild reduction in the serum potassium level. Patients with psychogenic hyperventilation tend to be most symptomatic as a result of the respiratory alkalosis, and these symptoms, along with a sensation of breathlessness, exacerbate the hyperventilation.

Diagnosis

In many patients, hyperventilation producing a respiratory alkalosis is not clinically detectable, even with careful observation of the patient's respiratory effort. Metabolic compensation for a respiratory alkalosis causes a low serum bicarbonate concentration. When hyperventilation is not appreciated and only serum electrolytes are evaluated, there is often a presumptive diagnosis of a metabolic acidosis. If a respiratory alkalosis is suspected, only a blood gas determination can make the diagnosis.

Hyperventilation does not always indicate a primary respiratory disorder. In some patients, the hyperventilation is appropriate respiratory compensation for a metabolic acidosis. With a primary metabolic acidosis, acidemia is present and the serum bicarbonate level is usually quite low if there is clinically detectable hyperventilation. In contrast, the serum bicarbonate level never goes below 17 mEq/L as part of the metabolic compensation for acute respiratory alkalosis, and simple acute respiratory alkalosis causes alkalemia.

The etiology of a respiratory alkalosis is often apparent from the physical examination or history, and it may consist of lung disease, neurologic disease, or cyanotic heart disease. Hypoxemia is a common cause of hyperventilation, and it is important to diagnose because it suggests a significant underlying disease that requires expeditious treatment. Hypoxemia may be detected on physical examination (cyanosis) or by pulse oximetry. However, normal pulse oximetry values do not completely eliminate hypoxemia as the etiology of the hyperventilation. There are 2 reasons why pulse oximetry is not adequate for eliminating hypoxemia as a cause of a respiratory alkalosis. First, pulse oximetry is not very sensitive at detecting a mildly low arterial partial pressure of oxygen (pO_2). Second, the hyperventilation during a respiratory alkalosis causes the pO_2 to increase, possibly to a level that is not identified as abnormal by pulse oximetry. Only an arterial blood gas measurement can completely eliminate hypoxia as an explanation for a respiratory alkalosis. Along with hypoxemia, it is important to consider processes that cause **tissue hypoxia without necessarily causing hypoxemia**. Examples are carbon monoxide poisoning, severe anemia, and heart failure.

Lung disease without hypoxemia may cause hyperventilation. Although lung disease is often apparent by history or physical examination, a chest radiograph may detect more subtle disease. The patient with a pulmonary embolism may have benign chest radiograph findings, normal pO_2, and isolated respiratory alkalosis, although hypoxia may eventually occur. Diagnosis of a pulmonary embolism requires a high index of suspicion and should be considered in children without another explanation for respiratory alkalosis, especially if risk factors are present, such as prolonged bed rest and a hypercoagulable state (e.g., nephrotic syndrome or lupus anticoagulant).

Treatment

There is seldom a need for specific treatment of respiratory alkalosis. Rather, treatment focuses on the underlying disease. Mechanical ventilator settings are adjusted to correct iatrogenic respiratory alkalosis, unless the hyperventilation has a therapeutic purpose (e.g., treatment of increased intracranial pressure).

For the patient with hyperventilation secondary to anxiety, efforts should be undertaken to reassure the child, usually enlisting the parents. Along with reassurance, patients with psychogenic hyperventilation may benefit from benzodiazepines. During an acute episode of psychogenic hyperventilation, rebreathing into a paper bag increases the patient's P_{CO_2}. Using a paper bag, instead of a plastic bag, allows adequate oxygenation but permits the CO_2 concentration in the bag to increase. The resultant increase in the patient's P_{CO_2} decreases the symptoms of the respiratory alkalosis that tend to perpetuate the hyperventilation. Rebreathing should be performed only once other causes of hyperventilation have been eliminated; pulse oximetry during the rebreathing is prudent.

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Chapter 56

Maintenance and Replacement Therapy

Larry A. Greenbaum

Maintenance intravenous fluids are used in a child who cannot be fed enterally. Along with maintenance fluids, children may require concurrent **replacement fluids** if they have continued excessive losses, such as may occur with drainage from a nasogastric (NG) tube or with high urine output because of nephrogenic diabetes insipidus. If dehydration is present, the patient also needs to receive **deficit** replacement (see Chapter 57). A child awaiting surgery may need only maintenance fluids, whereas a child with diarrheal dehydration needs maintenance and deficit therapy and also may require replacement fluids if significant diarrhea continues.

MAINTENANCE THERAPY

Children normally have large variations in their daily intake of water and electrolytes. The only exceptions are patients who receive fixed dietary regimens orally, via a gastric tube, or as intravenous total parenteral nutrition (TPN). Healthy children can tolerate significant variations in intake because of the many homeostatic mechanisms that can adjust absorption and excretion of water and electrolytes (see Chapter 55). The calculated water and electrolyte needs that form the basis of maintenance therapy are not absolute requirements. Rather, these calculations provide reasonable guidelines for a starting point to estimate intravenous therapy. Children do not need to be started on intravenous fluids simply because their intake is being monitored in a hospital and they are not taking "maintenance fluids" orally, unless there is a pathologic process present that necessitates high fluid intake.

Table 56-1 Goals of Maintenance Fluids

Prevent dehydration
Prevent electrolyte disorders
Prevent ketoacidosis
Prevent protein degradation

Maintenance fluids are most commonly necessary in preoperative and postoperative surgical patients; many nonsurgical patients also require maintenance fluids. It is important to recognize when it is necessary to begin maintenance fluids. A normal teenager who is given nothing by mouth (NPO) overnight for a morning procedure does not require maintenance fluids because a healthy adolescent can easily tolerate 12 or 18 hr without oral intake. In contrast, a 6 mo old child waiting for surgery should begin receiving intravenous fluids within 8 hr of the last feeding. Infants become dehydrated more quickly than older patients. A child with obligatory high urine output from nephrogenic diabetes insipidus should begin receiving intravenous fluids soon after being classified as NPO.

Maintenance fluids are composed of a solution of water, glucose, sodium, and potassium. This solution has the advantages of simplicity, long shelf life, low cost, and compatibility with peripheral intravenous administration. Such a solution accomplishes the major objectives of maintenance fluids (Table 56-1). Patients lose water, sodium, and potassium in their urine and stool; water is also lost from the skin and lungs. Maintenance fluids replace these losses, thereby avoiding the development of dehydration and deficiency of sodium or potassium.

The glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient, prevents the development of starvation ketoacidosis, and diminishes the protein degradation that would occur if the patient received no calories. Glucose also provides added osmoles, thus avoiding the administration of hypotonic fluids that may cause hemolysis.

Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins. This fact is typically not problematic for a patient receiving intravenous fluids for a few days. A patient receiving maintenance intravenous fluids is receiving inadequate calories and will lose 0.5-1% of weight each day. It is imperative that patients not remain on maintenance therapy indefinitely; TPN should be used for children who cannot be fed enterally for more than a few days, especially patients with underlying malnutrition.

Prototypical maintenance fluid therapy does not provide electrolytes such as calcium, phosphorus, magnesium, and bicarbonate. For most patients, this lack is not problematic for a few days, although there are patients who will not tolerate this omission, usually because of excessive losses. A child with renal tubular acidosis wastes bicarbonate in urine. Such a patient will rapidly become acidemic unless bicarbonate (or acetate) is added to the maintenance fluids. It is important to remember the limitations of maintenance fluid therapy.

MAINTENANCE WATER

Water is a crucial component of maintenance fluid therapy because of the obligatory daily water losses. These losses are both measurable (urine, stool) and not measurable (insensible losses from the skin and lungs). Failure to replace these losses leads to a child who is thirsty, uncomfortable, and, ultimately, dehydrated.

The goal of maintenance water is to provide enough water to replace these losses. Although urinary losses are approximately 60% of the total, the normal kidney has the ability to markedly modify water losses, with daily urine volume potentially varying by more than a factor of 20. Maintenance water is designed to provide enough water so that the kidney does not need to significantly dilute or concentrate the urine. It also provides a margin of safety, so that normal homeostatic mechanisms can adjust urinary water losses to prevent overhydration and dehydration. This adaptability obviates the need for absolute precision in determining water requirements. This fact is important, given the absence of absolute accuracy in the formulas for calculation of water needs. Table 56-2 provides a system for calculating maintenance water on the basis of the patient's weight and emphasizes the high water needs of smaller, less-mature patients. This approach is reliable, although calculations based on weight do overestimate the water needs of an overweight child, in whom it is better to base the calculations on the lean body weight, which can be estimated by using the 50th percentile of body weight for the child's height. It is also important to remember that there is an upper limit of 2.4 L/24 hr in adult-sized patients. Intravenous fluids are written as an hourly rate. The formulas in Table 56-3 enable rapid calculation of the rate of maintenance fluids.

Table 56-2 Body Weight Method for Calculating Daily Maintenance Fluid Volume

BODY WEIGHT	FLUID PER DAY
0-10 kg	100 mL/kg
11-20 kg	1,000 mL + 50 mL/kg for each kg >10 kg
>20 kg	1,500 mL + 20 mL/kg for each kg >20 kg*

*The maximum total fluid per day is normally 2,400 mL.

Table 56-3 Hourly Maintenance Water Rate

For body weight of 0-10 kg: 4 mL/kg/hr
For body weight of 10-20 kg: 40 mL/hr + 2 mL/kg/hr × (wt – 10 kg)
For body weight of >20 kg: 60 mL/hr + 1 mL/kg/hr × (wt – 20 kg)*

*The maximum fluid rate is normally 100 mL/hr.

Table 56-4 Composition of Intravenous Solutions

FLUID	[Na]	[Cl^-]	[K^+]	[Ca^{2+}]	[LACTATE–]
Normal saline (0.9% NaCl)	154	154	—	—	—
Half-normal saline (0.45% NaCl)	77	77	—	—	—
0.2 normal saline (0.2% NaCl)	34	34	—	—	—
Ringer lactate	130	109	4	3	28

INTRAVENOUS SOLUTIONS

The components of the commonly available solutions are shown in Table 56-4. Normal saline (NS) and Ringer lactate (LR) are isotonic solutions; they have approximately the same tonicity as plasma. Isotonic fluids without glucose are used for the acute correction of intravascular volume depletion (see Chapter 57). *The usual choices for maintenance fluid therapy in children are half-normal saline (1/2 NS) and NS.* These solutions are available with 5% dextrose (D5) or without dextrose. In addition, they are available with 20 mEq/L of potassium chloride, 10 mEq/L of potassium chloride, or no potassium. A hospital pharmacy can also prepare custom-made solutions with different concentrations of sodium or potassium. In addition, other electrolytes, such as calcium, magnesium, phosphate, acetate, and bicarbonate, can be added to intravenous solutions. Custom-made solutions take time to prepare and are much more expensive than commercial solutions. The use of custom-made solutions is necessary only for patients who have underlying disorders that cause significant electrolyte imbalances. The use of commercial solutions saves time and expense.

A normal plasma osmolality is 285-295 mOsm/kg. Infusing an intravenous solution peripherally with a much lower osmolality can cause water to move into red blood cells, leading to hemolysis. Thus, intravenous fluids are generally designed to have an osmolality that is either close to 285 or greater (fluids with moderately higher osmolality do not cause problems). Thus, 0.2NS (osmolality = 68) should not be

administered peripherally, but D5 0.2NS (osmolality = 346) or D5 ½ NS + 20 mEq/L KCl (osmolality = 472) can be administered.

There is controversy about the appropriate sodium content of maintenance fluids, considering the observation that hypotonic fluids may cause hyponatremia, which may have serious sequelae. Hypotonic fluids seem more physiologic given the low sodium content of breast milk and formula. However, hospitalized children often have impaired water excretion, either as a result of volume depletion or of nonosmotic stimuli for antidiuretic hormone (ADH) production (respiratory disease, central nervous system disease, stress, pain, nausea, medications such as narcotics). Hypotonic fluids increase the risk of hyponatremia; *0.2NS is no longer recommended as a standard maintenance fluid and its use is restricted at many hospitals.*

GLUCOSE

Maintenance fluids usually contain D5, which provides 17 calories/100 mL and nearly 20% of the daily caloric needs. This level is enough to prevent ketone production and helps minimize protein degradation, but the child will lose weight on this regimen. The weight loss is the principal reason why a patient needs to be started on TPN after a few days of maintenance fluids if enteral feedings are still not possible. Maintenance fluids are also lacking in such crucial nutrients as protein, fat, vitamins, and minerals.

SELECTION OF MAINTENANCE FLUIDS

D5 ½NS + 20 mEq/L KCl is recommended in the child who is NPO and does not have volume depletion or risk factors for nonosmotic ADH production. Children with volume depletion, baseline hyponatremia, or at risk for nonosmotic ADH production (lung infections such as bronchiolitis or pneumonia; central nervous system infection) should receive D5 NS + 20 mEq/L KCl. Surgical patients typically receive isotonic fluids (NS, LR) during surgery and in the recovery room for 6-8 hr postoperatively; the rate is typically approximately two-thirds of the calculated maintenance rate, with dextrose added if clinically indicated. Subsequent maintenance fluids should be D5 NS or LR, with addition of 10-20 mEq/L of KCl based on the serum potassium and the clinical setting. Electrolytes should be measured at least daily in all children receiving more than 50% of maintenance fluids intravenously unless the child is receiving prolonged intravenous fluids (TPN).

These guidelines assume that there is no disease process present that would require an adjustment in either the volume or the electrolyte composition of maintenance fluids. Neonates, and especially premature infants, are outside of the scope of these guidelines given their unique physiology. Children with renal insufficiency may be hyperkalemic or unable to excrete potassium and may not tolerate 10 or 20 mEq/L of potassium. Patients with persistent ADH production because of an underlying disease process (syndrome of inappropriate ADH secretion, congestive heart failure, nephrotic syndrome, liver disease) should receive less than maintenance fluids. Children with meningitis are fluid restricted unless intravascular volume depletion is present (see Chapter 603.1). Treatment is individualized, and careful monitoring is critical.

In children with complicated pathophysiologic derangements, it may be necessary to empirically adjust the electrolyte composition and rate of maintenance fluids on the basis of electrolyte measurements and assessment of fluid balance. **In all children, it is critical to carefully monitor weight, urine output, and electrolytes to identify overhydration or underhydration, hyponatremia, and other electrolyte disturbances, and to then adjust the rate or composition of the intravenous solution accordingly.**

VARIATIONS IN MAINTENANCE WATER AND ELECTROLYTES

The calculation of maintenance water is based on standard assumptions regarding water losses. There are patients, however, in whom these assumptions are incorrect. To identify such situations, it is helpful to understand the source and magnitude of normal water losses. Table 56-5 lists the 3 sources of normal water loss.

Table 56-5 Sources of Water Loss

Urine: 60%
Insensible losses: ≈35% (skin and lungs)
Stool: 5%

Table 56-6 Adjustments in Maintenance Water

SOURCE	CAUSES OF INCREASED WATER NEEDS	CAUSES OF DECREASED WATER NEEDS
Skin	Radiant warmer Phototherapy Fever Sweat Burns	Incubator (premature infant)
Lungs	Tachypnea Tracheostomy	Humidified ventilator
Gastrointestinal tract	Diarrhea Emesis Nasogastric suction	—
Renal	Polyuria	Oliguria/anuria
Miscellaneous	Surgical drain Third spacing	Hypothyroidism

Urine is the most important contributor to normal water loss. Insensible losses represent approximately one-third of total maintenance water (40% in infants and closer to 25% in adolescents and adults). Insensible losses are composed of evaporative losses from the skin and lungs that cannot be quantitated. The evaporative losses from the skin do not include sweat, which would be considered an additional (sensible) source of water loss. Stool normally represents a minor source of water loss.

Maintenance water and electrolyte needs may be increased or decreased, depending on the clinical situation. This may be obvious, in the case of the infant with profuse diarrhea, or subtle, in the case of the patient who has decreased insensible losses while receiving mechanical ventilation. It is helpful to consider the sources of normal water and electrolyte losses and to determine whether any of these sources is being modified in a specific patient. It is then necessary to adjust maintenance water and electrolyte calculations.

Table 56-6 lists a variety of clinical situations that modify normal water and electrolyte losses. The skin can be a source of very significant water loss, particularly in neonates, especially premature infants, who are under radiant warmers or are receiving phototherapy. Very-low-birthweight infants can have insensible losses of 100-200 mL/kg/24 hr. Burns can result in massive losses of water and electrolytes, and there are specific guidelines for fluid management in children with burns (see Chapter 75). Sweat losses of water and electrolytes, especially in a warm climate, can also be significant. Children with cystic fibrosis have increased sodium losses from the skin. Some children with pseudohypoaldosteronism also have increased cutaneous salt losses.

Fever increases evaporative losses from the skin. These losses are somewhat predictable, leading to a 10-15% increase in maintenance water needs for each 1°C (1.8°F) increase in temperature above 38°C (100.4°F). These guidelines are for a patient with a persistent fever; a 1 hr fever spike does not cause an appreciable increase in water needs.

Tachypnea or a tracheostomy increases evaporative losses from the lungs. A humidified ventilator causes a decrease in insensible losses from the lungs and can even lead to water absorption via the lungs; a ventilated patient has a decrease in maintenance water requirements. It may be difficult to quantify the changes that take place in the individual patient in these situations.

REPLACEMENT FLUIDS

The gastrointestinal (GI) tract is potentially a source of considerable water loss. GI water losses are accompanied by electrolytes and thus may cause disturbances in intravascular volume and electrolyte concentrations. GI losses are often associated with loss of potassium, leading to hypokalemia. Because of the high bicarbonate concentration in stool, children with diarrhea usually have a metabolic acidosis, which may be accentuated if volume depletion causes hypoperfusion and a concurrent lactic acidosis. Emesis or losses from an NG tube can cause a metabolic alkalosis (see Chapter 55).

In the absence of vomiting, diarrhea, or NG drainage, GI losses of water and electrolytes are usually quite small. All GI losses are considered excessive, and the increase in the water requirement is equal to the volume of fluid losses. Because GI water and electrolyte losses can be precisely measured, it is possible to use an appropriate replacement solution.

It is impossible to predict the losses for the next 24 hr; it is better to replace excessive GI losses as they occur. The child should receive an appropriate maintenance fluid that does not consider the GI losses. The losses should then be replaced after they occur, with use of a solution with a similar electrolyte concentration as the GI fluid. The losses are usually replaced every 1-6 hr, depending on the rate of loss, with very rapid losses being replaced more frequently.

Diarrhea is a common cause of fluid loss in children. It can cause dehydration and electrolyte disorders. In the unusual patient with significant diarrhea and a limited ability to take oral fluid, it is important to have a plan for replacing excessive stool losses. The volume of stool should be measured, and an equal volume of replacement solution should be given. Data are available on the average electrolyte composition of diarrhea in children (Table 56-7). With use of this information, it is possible to design an appropriate replacement solution. The solution shown in Table 56-7 replaces stool losses of sodium, potassium, chloride, and bicarbonate. Each 1 mL of stool should be replaced by 1 mL of this solution. The average electrolyte composition of diarrhea is just an average, and there may be considerable variation. It is therefore advisable to consider measuring the electrolyte composition of a patient's diarrhea if the amount is especially excessive or if the patient's serum electrolyte levels are problematic.

Loss of gastric fluid, via either emesis or NG suction, is also likely to cause dehydration, in that most patients with either condition have impaired oral intake of fluids. Electrolyte disturbances, particularly hypokalemia and metabolic alkalosis, are also common. These complications can be avoided by judicious use of a replacement solution. The composition of gastric fluid shown in Table 56-8 is the basis for designing a replacement solution.

Table 56-7	Replacement Fluid for Diarrhea
AVERAGE COMPOSITION OF DIARRHEA	
Sodium: 55 mEq/L	
Potassium: 25 mEq/L	
Bicarbonate: 15 mEq/L	
APPROACH TO REPLACEMENT OF ONGOING LOSSES	
Solution: D5 ½NS + 30 mEq/L sodium bicarbonate + 20 mEq/L KCl	
Replace stool mL/mL every 1-6 hr	

Table 56-8	Replacement Fluid for Emesis or Nasogastric Losses
AVERAGE COMPOSITION OF GASTRIC FLUID	
Sodium: 60 mEq/L	
Potassium: 10 mEq/L	
Chloride: 90 mEq/L	
APPROACH TO REPLACEMENT OF ONGOING LOSSES	
Solution: normal saline + 10 mEq/L KCl	
Replace output mL/mL every 1-6 hr	

Patients with gastric losses frequently have hypokalemia, although the potassium concentration of gastric fluid is relatively low. The associated urinary loss of potassium is an important cause of hypokalemia in this situation (see Chapter 55). These patients may need additional potassium either in their maintenance fluids or in their replacement fluids to compensate for prior or ongoing urinary losses. Restoration of the patient's intravascular volume, by decreasing aldosterone synthesis, lessens the urinary potassium losses.

Urine output is normally the largest cause of water loss. Diseases such as renal failure and syndrome of inappropriate ADH secretion can lead to a decrease in urine volume. The patient with oliguria or anuria has a decreased need for water and electrolytes; continuation of maintenance fluids produces fluid overload. In contrast, postobstructive diuresis, the polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetes insipidus increase urine production. To prevent dehydration, the patient must receive more than standard maintenance fluids when urine output is excessive. The electrolyte losses in patients with polyuria are variable. In diabetes insipidus, the urine electrolyte concentration is usually low, whereas children with diseases such as juvenile nephronophthisis and obstructive uropathy usually have increased losses of both water and sodium.

The approach to decreased or increased urine output is similar (Table 56-9). The patient receives fluids at a rate to replace insensible losses. This is accomplished by a rate of fluid administration that is 25-40% of the normal maintenance rate, depending on the patient's age. Replacing insensible losses in the anuric child will theoretically maintain an even fluid balance, with the caveat that 25-40% of the normal maintenance rate is only an estimate of insensible losses. In the individual patient, this rate is adjusted on the basis of monitoring of the patient's weight and volume status. Most children with renal insufficiency receive little or no potassium because the kidney is the principal site of potassium excretion.

For the oliguric child, it is important to add a urine replacement solution to prevent dehydration. This issue is especially important in the patient with acute renal failure, in whom output may increase slowly, potentially leading to volume depletion and worsening of renal failure if the patient remains on only insensible fluids. A replacement solution of D5 ½NS is usually appropriate initially, although its composition may have to be adjusted if urine output increases significantly.

Most children with polyuria (except in diabetes mellitus; (see Chapter 589) should be started on replacement of insensible fluid plus urine losses. This approach avoids the need to attempt to calculate the volume of urine output that is "normal" so that the patient can be given replacement fluid for the excess. In these patients, urine output is, by definition, excessive, and it is important to measure the sodium and potassium concentrations of the urine to help in formulating the urine replacement solution.

Surgical drains and chest tubes can produce measurable fluid output. These fluid losses should be replaced when they are significant. They can be measured and replaced with an appropriate replacement solution. Third space losses, which manifest as edema and ascites, are due to a shift of fluid from the intravascular space into the interstitial space. Although these losses cannot be quantitated easily, third space losses can be large and may lead to intravascular volume depletion, despite

Table 56-9	Adjusting Fluid Therapy for Altered Renal Output
OLIGURIA/ANURIA	
Replacement of insensible fluid losses (25-40% of maintenance) with D5 ½NS	
Replace urine output mL/mL with D5 ½NS ± KCl	
POLYURIA	
Replacement of insensible fluid losses (25-40% of maintenance) with D5 ½NS ± KCl	
Measure urine electrolytes	
Replace urine output mL/mL with solution based on measured urine electrolytes	

the patient's weight gain. Replacement of third space fluid is empirical but should be anticipated in patients who are at risk, such as children who have burns or abdominal surgery. Third space losses and chest tube output are isotonic; thus, they usually require replacement with an isotonic fluid, such as NS or LR. Adjustments in the amount of replacement fluid for third space losses are based on continuing assessment of the patient's intravascular volume status. Protein losses from chest tube drainage can be significant, occasionally necessitating that 5% albumin be used as a replacement solution.

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Chapter 57

Deficit Therapy

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Dehydration, most often caused by gastroenteritis, is a common problem in children. Most cases can be managed with oral rehydration (see Chapter 340). **Even children with mild to moderate hyponatremic or hypernatremic dehydration can be managed with oral rehydration.**

CLINICAL MANIFESTATIONS

The first step in caring for the child with dehydration is to assess the degree of dehydration (Table 57-1), which dictates both the urgency of the situation and the volume of fluid needed for rehydration. The infant with mild dehydration (3-5% of body weight dehydrated) has few clinical signs or symptoms. The infant may be thirsty; the alert parent may notice a decline in urine output. The history is most helpful. The infant with moderate dehydration has clear physical signs and symptoms. Intravascular space depletion is evident from an increased heart rate and reduced urine output. This patient needs fairly prompt intervention. The infant with severe dehydration is gravely ill. The decrease in blood pressure indicates that vital organs may be receiving inadequate perfusion. Immediate and aggressive intervention is necessary. If possible, the child with severe dehydration should initially receive intravenous therapy. For older children and adults, mild, moderate, or severe dehydration represents a lower percentage of body weight lost. This difference occurs because water accounts for a higher percentage of body weight in infants (see Chapter 55).

Clinical assessment of dehydration is only an estimate; thus, the patient must be continually reevaluated during therapy. The degree of dehydration is underestimated in hypernatremic dehydration because the movement of water from the intracellular space to the extracellular space helps preserve the intravascular volume.

Table 57-1 Clinical Evaluation of Dehydration

Mild dehydration (<5% in an infant; <3% in an older child or adult): Normal or increased pulse; decreased urine output; thirsty; normal physical findings
Moderate dehydration (5-10% in an infant; 3-6% in an older child or adult): Tachycardia; little or no urine output; irritable/lethargic; sunken eyes and fontanel; decreased tears; dry mucous membranes; mild delay in elasticity (skin turgor); delayed capillary refill (>1.5 sec); cool and pale
Severe dehydration (>10% in an infant; >6% in an older child or adult): Peripheral pulses either rapid and weak or absent; decreased blood pressure; no urine output; very sunken eyes and fontanel; no tears; parched mucous membranes; delayed elasticity (poor skin turgor); very delayed capillary refill (>3 sec); cold and mottled; limp, depressed consciousness

The history usually suggests the etiology of the dehydration and may predict whether the patient will have a normal sodium concentration (isotonic dehydration), hyponatremic dehydration, or hypernatremic dehydration. The neonate with dehydration due to poor intake of breast milk often has hypernatremic dehydration. Hypernatremic dehydration is likely in any child with losses of hypotonic fluid and poor water intake, such as may occur with diarrhea, and poor oral intake because of anorexia or emesis. Hyponatremic dehydration occurs in the child with diarrhea who is taking in large quantities of low-salt fluid, such as water or formula.

Some children with dehydration are appropriately thirsty, but in others the lack of intake is part of the pathophysiology of the dehydration. Even though decreased urine output is present in most children with dehydration, good urine output may be deceptively present if a child has an underlying renal defect, such as diabetes insipidus or a salt-wasting nephropathy, or in infants with hypernatremic dehydration.

Physical examination findings are usually proportional to the degree of dehydration. Parents may be helpful in assessment of the child for the presence of sunken eyes, because this finding may be subtle. Pinching and gently twisting the skin of the abdominal or thoracic wall detects tenting of the skin (turgor, elasticity). Tented skin remains in a pinched position rather than springing quickly back to normal. It is difficult to properly assess tenting of the skin in premature infants or severely malnourished children. Activation of the sympathetic nervous system causes tachycardia in children with intravascular volume depletion; diaphoresis may also be present. Postural changes in blood pressure are often helpful for evaluating and assessing the response to therapy in children with dehydration. Tachypnea in children with dehydration may be present secondary to a metabolic acidosis from stool losses of bicarbonate or due to lactic acidosis from shock (see Chapter 70).

LABORATORY FINDINGS

Several laboratory findings are useful for evaluating the child with dehydration. The serum sodium concentration determines the type of dehydration. Metabolic acidosis may be a result of stool bicarbonate losses in children with diarrhea, secondary renal insufficiency, or lactic acidosis from shock. The anion gap is useful for differentiating among the various causes of a metabolic acidosis (see Chapter 55). Emesis or nasogastric losses usually cause a metabolic alkalosis. The serum potassium concentration may be low as a result of diarrheal losses. In children with dehydration as a result of emesis, gastric potassium losses, metabolic alkalosis, and urinary potassium losses all contribute to hypokalemia. Metabolic acidosis, which causes a shift of potassium out of cells, and renal insufficiency may lead to hyperkalemia. A combination of mechanisms may be present; thus, it may be difficult to predict the child's acid–base status or serum potassium level from the history alone.

The blood urea nitrogen (BUN) value and serum creatinine concentration are useful in assessing the child with dehydration. Volume depletion without parenchymal renal injury may cause a disproportionate increase in the BUN with little or no change in the creatinine concentration. This condition is secondary to increased passive resorption of urea in the proximal tubule as a result of appropriate renal conservation of sodium and water. The increase in the BUN with moderate or severe dehydration may be absent or blunted in the child with poor protein intake, because urea production depends on protein degradation. The BUN may be disproportionately increased in the child with increased urea production, as occurs with a gastrointestinal bleed or with the use of glucocorticoids, which increase catabolism. A significant elevation of the creatinine concentration suggests renal insufficiency, although a small, transient increase can occur with dehydration. **Acute tubular necrosis** (acute kidney injury) (see Chapter 535) because of volume depletion is the most common etiology of renal insufficiency in a child with volume depletion, but occasionally the child may have previously undetected chronic renal insufficiency or an alternative explanation for the acute renal failure. Renal vein thrombosis is a well-described sequela of severe dehydration in infants;

possible findings include thrombocytopenia and hematuria (see Chapter 519.7).

Hemoconcentration from dehydration causes increases in hematocrit, hemoglobin, and serum proteins. These values normalize with rehydration. A normal hemoglobin concentration during acute dehydration may mask an underlying anemia. A decreased albumin level in a dehydrated patient suggests a chronic disease, such as malnutrition, nephrotic syndrome, or liver disease, or an acute process, such as capillary leak. An acute or chronic protein-losing enteropathy may also cause a low serum albumin concentration.

CALCULATION OF THE FLUID DEFICIT

Determining the fluid deficit necessitates clinical determination of the percentage of dehydration and multiplication of this percentage by the patient's weight; a child who weighs 10 kg and is 10% dehydrated has a fluid deficit of 1 L.

APPROACH TO SEVERE DEHYDRATION

The child with dehydration needs acute intervention to ensure that there is adequate tissue perfusion. This resuscitation phase requires rapid restoration of the circulating intravascular volume and treatment of shock with an isotonic solution, such as normal saline (NS) or Ringer lactate (LR) (see Chapter 70). The child is given a fluid bolus, usually 20 mL/kg of the isotonic fluid, over approximately 20 min. The child with severe dehydration may require multiple fluid boluses and may need to receive the boluses as fast as possible. In a child with a known or probable metabolic alkalosis (the child with isolated vomiting), LR should not be used because the lactate would worsen the alkalosis.

Colloids, such as blood, 5% albumin, and plasma, are rarely needed for fluid boluses. A crystalloid solution (NS or LR) is satisfactory, with both less infectious risk and lower cost. Blood is obviously indicated in the child with significant anemia or acute blood loss. Plasma is useful for children with a coagulopathy. The child with hypoalbuminemia may benefit from 5% albumin, although there is evidence that albumin infusions increase mortality in adults. The volume and the infusion rate for colloids are generally modified compared with crystalloids (see Chapters 473).

The initial resuscitation and rehydration phase is complete when the child has an adequate intravascular volume. Typically, the child shows clinical improvement, including a lower heart rate, normalization of blood pressure, improved perfusion, better urine output, and a more alert affect.

With adequate intravascular volume, it is appropriate to plan the fluid therapy for the next 24 hr. A general approach is outlined in Table 57-2, with the caveat that there are many different approaches to correcting dehydration. In isonatremic or hyponatremic dehydration, the entire fluid deficit is corrected over 24 hr; a slower approach is used for hypernatremic dehydration (discussed later). The volume of isotonic fluids that the patient has received is subtracted from this total. The remaining fluid volume is then administered over 24 hr. The potassium concentration may need to be decreased or, less commonly, increased, depending on the clinical situation. Potassium is not usually included in the intravenous fluids until the patient voids and normal renal function is documented via measurement of BUN and creatinine. Children with significant ongoing losses need to receive an appropriate replacement solution (see Chapter 56).

Table 57-2 Fluid Management of Dehydration

Restore intravascular volume:
Normal saline: 20 mL/kg over 20 min
Repeat as needed
Calculate 24-hr fluid needs: maintenance + deficit volume
Subtract isotonic fluid already administered from 24 hr fluid needs
Administer remaining volume over 24 hr using 5% dextrose NS + 20 mEq/L KCl
Replace ongoing losses as they occur

MONITORING AND ADJUSTING THERAPY

The formulation of a plan for correcting a child's dehydration is only the beginning of management. **All calculations in fluid therapy are only approximations.** This statement is especially true for the assessment of percentage dehydration. It is equally important to monitor the patient during treatment and to modify therapy on the basis of the clinical situation. Table 57-3 lists the cornerstones of patient monitoring. The patient's vital signs are useful indicators of intravascular volume status. The child with decreased blood pressure and an increased heart rate will probably benefit from a fluid bolus. Central venous pressure is an excellent indicator of fluid status in the critically ill child with shock.

The patient's intake and output are critically important in the dehydrated child. The child who, after 8 hr of therapy, has more output than input because of continuing diarrhea needs to be started on a replacement solution. See the guidelines in Chapter 56 for selecting an appropriate replacement solution. Urine output is useful for evaluating the success of therapy. Good urine output indicates that rehydration has been successful.

Signs of dehydration on physical examination suggest the need for continued rehydration. Signs of fluid overload, such as edema and pulmonary congestion, are present in the child who is overhydrated. An accurate daily weight measurement is critical for the management of the dehydrated child. There should be a gain in weight during successful therapy.

Measurement of serum electrolyte levels at least daily is appropriate for any child who is receiving intravenous rehydration. Such a child is at risk for sodium, potassium, and acid–base disorders. It is always important to look at trends. For instance, a sodium value of 144 mEq/L is normal; but if the sodium concentration was 136 mEq/L 12 hr earlier, then there is a distinct risk that the child will be hypernatremic in 12 or 24 hr. It is advisable to be proactive in adjusting fluid therapy.

Both hypokalemia and hyperkalemia are potentially serious (see Chapter 55). Because dehydration can be associated with acute renal failure and hyperkalemia, potassium is withheld from intravenous fluids until the patient has voided. The potassium concentration in the patient's intravenous fluids is not rigidly prescribed. Rather, the patient's serum potassium level and underlying renal function are used to modify potassium delivery. The patient with an elevated creatinine value and a potassium level of 5 mEq/L does not receive any potassium until the serum potassium level decreases. Conversely, the patient with a potassium level of 2.5 mEq/L may require additional potassium.

Metabolic acidosis can be quite severe in dehydrated children. Although normal kidneys eventually correct this problem, a child with renal dysfunction may be unable to correct a metabolic acidosis, and a portion of the patient's intravenous sodium chloride may have to be replaced with sodium bicarbonate or sodium acetate.

The serum potassium level is modified by the patient's acid–base status. Acidosis increases serum potassium by causing intracellular potassium to move into the extracellular space. Thus, as acidosis is corrected, the potassium concentration decreases. Again, it is best to anticipate this problem and to monitor the serum potassium concentration and adjust potassium administration appropriately.

Table 57-3 Monitoring Therapy

Vital signs:
Pulse
Blood pressure
Intake and output:
Fluid balance
Urine output
Physical examination:
Weight
Clinical signs of depletion or overload
Electrolytes

HYPONATREMIC DEHYDRATION

The pathogenesis of hyponatremic dehydration usually involves a combination of sodium and water loss and water retention to compensate for the volume depletion. The patient has a pathologic increase in fluid loss, and the lost fluid contains sodium. Most fluid that is lost has a lower sodium concentration, so patients with only fluid loss would have hypernatremia. Diarrhea has, on average, a sodium concentration of 50 mEq/L. Replacing diarrheal fluid with water, which has almost no sodium, causes a reduction in the serum sodium concentration. The volume depletion stimulates synthesis of antidiuretic hormone, resulting in reduced renal water excretion. Hence, the body's usual mechanism for preventing hyponatremia, renal water excretion, is blocked. The risk of hyponatremia is further increased if the volume depletion is a result of loss of fluid with a higher sodium concentration, as may occur with renal salt wasting, third space losses, or diarrhea with high sodium content (cholera).

The initial goal in treating hyponatremia is correction of intravascular volume depletion with isotonic fluid (NS or LR). An overly rapid (>12 mEq/L over the first 24 hr) or overcorrection in the serum sodium concentration (>135 mEq/L) is associated with an increased risk of **central pontine myelinolysis** (see Chapter 55). Most patients with hyponatremic dehydration do well with the same basic strategy that is outlined in Table 57-2. Again, potassium delivery is adjusted according to the initial serum potassium level and the patient's renal function. Potassium is not given until the patient voids.

The patient's sodium concentration is monitored closely to ensure appropriate correction, and the sodium concentration of the fluid is adjusted accordingly. Patients with ongoing losses require an appropriate replacement solution (see Chapter 56). Patients with neurologic symptoms (seizures) as a result of hyponatremia need to receive an acute infusion of hypertonic (3%) saline to increase the serum sodium concentration rapidly (see Chapter 55).

HYPERNATREMIC DEHYDRATION

Hypernatremic dehydration is the most dangerous form of dehydration because of complications of hypernatremia and of therapy. Hypernatremia can cause serious neurologic damage, including central nervous system hemorrhages and thrombosis. This damage appears to be secondary to the movement of water from the brain cells into the hypertonic extracellular fluid, causing brain cell shrinkage and tearing blood vessels within the brain (see Chapter 55).

The movement of water from the intracellular space to the extracellular space during hypernatremic dehydration partially protects the intravascular volume. Unfortunately, because the initial manifestations are milder, children with hypernatremic dehydration are often brought for medical attention with more profound dehydration.

Children with hypernatremic dehydration are often lethargic, and they may be irritable when touched. Hypernatremia may cause fever, hypertonicity, and hyperreflexia. More severe neurologic symptoms may develop if cerebral bleeding or thrombosis occurs.

Overly rapid treatment of hypernatremic dehydration may cause significant morbidity and mortality. Idiogenic osmoles are generated within the brain during the development of hypernatremia. These idiogenic osmoles increase the osmolality within the cells of the brain, providing protection against brain cell shrinkage caused by movement of water out of the cells and into the hypertonic extracellular fluid. They dissipate slowly during the correction of hypernatremia. With overly rapid lowering of the extracellular osmolality during the correction of hypernatremia, an osmotic gradient may be created that causes water movement from the extracellular space into the cells of the brain, producing cerebral edema. Symptoms of the resultant cerebral edema can range from seizures to brain herniation and death.

To minimize the risk of cerebral edema during the correction of hypernatremic dehydration, the serum sodium concentration should not decrease by >12 mEq/L every 24 hr. The deficits in severe hypernatremic dehydration may need to be corrected over 2-4 days (Table 57-4).

The initial resuscitation of hypernatremic dehydration requires restoration of the intravascular volume with NS. *LR should not be used because it is more hypotonic than NS and may cause too rapid a decrease in the serum sodium concentration, especially if multiple fluid boluses are necessary.*

Table 57-4 Treatment of Hypernatremic Dehydration

- Restore intravascular volume:
  - Normal saline: 20 mL/kg over 20 min (repeat until intravascular volume restored)
  - Determine time for correction on basis of initial sodium concentration:
    - [Na] 145-157 mEq/L: 24 hr
    - [Na] 158-170 mEq/L: 48 hr
    - [Na] 171-183 mEq/L: 72 hr
    - [Na] 184-196 mEq/L: 84 hr
- Administer fluid at constant rate over time for correction:
  - Typical fluid: 5% dextrose + half-normal saline (with 20 mEq/L KCl unless contraindicated)
  - Typical rate: 1.25-1.5 times maintenance
- Follow serum sodium concentration
- Adjust fluid on basis of clinical status and serum sodium concentration:
  - Signs of volume depletion: administer normal saline (20 mL/kg)
  - Sodium decreases too rapidly; either:
    - Increase sodium concentration of intravenous fluid
    - Decrease rate of intravenous fluid
  - Sodium decreases too slowly; either:
    - Decrease sodium concentration of intravenous fluid
    - Increase rate of intravenous fluid
- Replace ongoing losses as they occur

To avoid cerebral edema during correction of hypernatremic dehydration, the fluid deficit is corrected slowly. The rate of correction depends on the initial sodium concentration (see Table 57-4). There is no general agreement on the choice or the rate of fluid for correcting hypernatremic dehydration. The choice and the rate of fluid administration are not nearly as important as vigilant monitoring of the serum sodium concentration and adjustment of the therapy according to the result (see Table 57-4). The rate of decrease of the serum sodium concentration is roughly related to the "free water" delivery, although there is considerable variation between patients. Free water is water without sodium. NS contains no free water, half-NS (½NS) is 50% free water, and water is 100% free water. Smaller patients, to achieve the same decrease in the sodium concentration, tend to need higher amounts of free water delivery per kilogram because of higher insensible fluid losses. Five percent dextrose (D5) with ½NS is usually an appropriate starting solution for a patient with hypernatremic dehydration. Some patients, especially infants with ongoing **high insensible water losses**, may need to receive D5 0.2NS, which should be used with great caution and constant monitoring. Others require D5 NS. A child with dehydration as a result of pure free water loss, as usually occurs with diabetes insipidus, usually needs a more hypotonic fluid than a child with depletion of both sodium and water due to diarrhea.

Adjustment in the sodium concentration of the intravenous fluid is the most common approach to modifying the rate of decrease in the serum concentration (see Table 57-4). For difficult-to-manage patients with severe hypernatremia, having 2 intravenous solutions (e.g., D5 ½ NS and D5 NS, both with the same concentration of potassium) at the bedside can facilitate this approach by allowing for rapid adjustments of the rates of the 2 fluids. If the serum sodium concentration decreases too rapidly, the rate of D5 NS can be increased and the rate of D5 ½ NS can be decreased by the same amount. Adjustment in the total rate of fluid delivery is another approach to modifying free water delivery. For example, if the serum sodium concentration is decreasing too slowly, the rate of the intravenous fluid can be increased, thereby increasing the delivery of free water. There is limited flexibility in modifying the rate of the intravenous fluid because patients generally should receive 1.25-1.5 times the normal maintenance fluid rate. Nevertheless, in some situations, it can be a helpful adjustment.

Because increasing the rate of the intravenous fluid increases the rate of decline of the sodium concentration, signs of volume depletion are

treated with additional isotonic fluid boluses. The serum potassium concentration and the level of renal function dictate the potassium concentration of the intravenous fluid; potassium is withheld until the patient voids. Patients with hypernatremic dehydration need an appropriate replacement solution if they have ongoing, excessive losses (see Chapter 56).

Seizures are the most common manifestation of **cerebral edema** from an overly rapid decrease of the serum sodium concentration during correction of hypernatremic dehydration. Signs of increased intracranial pressure or impending herniation may develop quite rapidly (see Chapter 68). Acutely, increasing the serum concentration via an infusion of 3% sodium chloride can reverse the cerebral edema. Each 1 mL/kg of 3% sodium chloride increases the serum sodium concentration by approximately 1 mEq/L. An infusion of 4 mL/kg often results in resolution of the symptoms. This strategy is similar to that used for treating symptomatic hyponatremia (see Chapter 55).

In patients with severe hypernatremia, oral fluids must be used cautiously. Infant formula, because of its low sodium concentration, has a high free water content, and especially if added to intravenous therapy, it may contribute to a rapid decrease in the serum sodium concentration. Less hypotonic fluid, such as an oral rehydration solution, may be more appropriate initially (see Chapter 340). If oral intake is allowed, its contribution to free water delivery must be taken into account, and adjustment in the intravenous fluid is usually appropriate. Judicious monitoring of the serum sodium concentration is critical.

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Chapter 58

Fluid and Electrolyte Treatment of Specific Disorders

ACUTE DIARRHEA

See Chapter 340.

PYLORIC STENOSIS

See Chapter 329.1.

PERIOPERATIVE FLUIDS

See Chapter 61.

Pediatric Drug Therapy

PART VIII

Chapter 59

Pediatric Pharmacogenetics, Pharmacogenomics, and Pharmacoproteomics

Kathleen A. Neville and J. Steven Leeder

The role of genetic factors in drug disposition and response, **pharmacogenetics**, has resulted in many examples of how variations in human genes can lead to interindividual differences in pharmacokinetics and drug response at the level of individual patients. Pharmacogenetic variability contributes to the broad range of drug responses observed in children at any given age or developmental stage; it is expected that children will benefit from the promise of **personalized medicine**—identifying the right drug for the right patient at the right time (Fig. 59-1). Numerous maturational processes occur from birth through adolescence such that utilization of information resulting from the Human Gene Project and related initiatives must take into account the changing patterns of gene expression that occur over development to improve pharmacotherapeutics in children.

PHARMACOGENETICS, PHARMACOGENOMICS, AND THE CONCEPT OF PERSONALIZED MEDICINE

The terms *pharmacogenomics* and *pharmacogenetics* tend to be used interchangeably, and precise, consensus definitions are often difficult to determine. **Pharmacogenetics** classically is defined as the study or clinical testing of genetic variations that give rise to interindividual differences in the response to drugs. The earliest examples of pharmacogenetic traits include specific adverse drug reactions, such as unusually prolonged respiratory muscle paralysis caused by succinylcholine, hemolysis associated with antimalarial therapy, and isoniazid-induced neurotoxicity, all of which are a consequence of inherited variations in enzyme activity. The importance of pharmacogenetic differences has become better understood and is exemplified by the fact that the half-lives of several drugs are more similar in monozygotic twins than in dizygotic twins. However, it is important to note that in addition to pharmacogenetic differences, environmental factors (diet, smoking status, concomitant drug or toxicant exposure), physiologic variables (age, sex, disease, pregnancy), and patient compliance all contribute to variations in drug metabolism and response. Likewise, ethnicity is another potential genetic determinant of drug variability. For example, Chinese patients who are HLA-B*1502–positive and white patients who are positive for HLA-A*3101 have an increased risk of carbamazepine-induced Stevens-Johnson syndrome; white patients who are HLA-B*5701–positive have an increased risk of hypersensitivity to abacavir (Table 59-1).

Pharmacogenomics represents the marriage of pharmacology and genomics, and can be defined as the broader application of genome-wide technologies and strategies to identify both disease processes that represent new targets for drug development and factors predictive of efficacy and risk of adverse drug reactions.

Pharmacokinetics describes temporal aspects of what the body does to a drug. It is often studied in conjunction with **pharmacodynamics**, which explores what a drug does to the body (see Chapter 60). The **pharmacokinetic** properties of a drug are determined by the genes that control the drug's disposition in the body (absorption, distribution, metabolism, excretion). Drug metabolizing enzymes and drug transporters play a particularly important role in this process (Table 59-2), and the functional consequences of genetic variations in many drug metabolizing enzymes have been described between subjects of both similar and different ethnic groups. The most common clinical manifestation of pharmacogenetic variability in drug biotransformation is an increased risk of concentration-dependent toxicity as a result of reduced clearance and consequent drug accumulation. On the other hand, rapid metabolism can lead to accumulation of a toxic metabolite, as has been reported for the hepatic conversion of codeine to morphine in 4 children ages 2-5 yr who received codeine for pain after tonsillectomy and adenoidectomy. This variant pharmacokinetics resulted in 3 deaths and 1 near-death from respiratory depression. As a result of these concerns, physicians are reminded to prescribe any drug at the lowest effective dose, for the shortest time, and only on an as-needed basis.

An equally important manifestation of this variability is lack of efficacy resulting from variations in metabolism of prodrugs. The pharmacogenetics of drug receptors and other target proteins involved in signal transduction or disease pathogenesis can also be expected to contribute significantly to interindividual variability in drug disposition and response.

Therapeutic drug monitoring programs recognize that all patients are unique and that the serum concentration-time data for an individual patient theoretically can be used to optimize pharmacotherapy. These programs have been the earliest application of personalized medicine; however, routine therapeutic drug monitoring does not necessarily translate to improved patient outcome in all situations.

The concept of **personalized medicine** is based on the premise that the wealth of information accompanying the application of genomic technologies to patient-related problems will allow for (1) stratification of patient populations according to their response to a particular medication (e.g., lack of drug efficacy or excessive toxicity), and (2) stratification of diseases into specific subtypes that are categorized according to genomic criteria and by response to particular treatments.

DEFINITION OF PHARMACOGENETIC TERMS

Genetic polymorphisms (variations) result when copies of a specific gene present within a population do not have identical nucleotide sequences. The term **allele** refers to one of a series of alternative DNA sequences for a particular gene. In humans, there are 2 copies of every gene. An individual's genotype for a given gene is determined by the set of alleles that the individual possesses. The most common form of genetic variation involves a single base change at a given location, referred to as a **single-nucleotide polymorphism (SNP)** (see Chapter 81). At the other end of the spectrum are **copy number variations,** which refer to the deletion or duplication of identical or near identical DNA sequences that may be thousands to millions of bases in size. Copy number variations occur less frequently than SNPs, but may constitute 0.5-1% of an individual's genome, and thereby contribute significantly to phenotypic variation. **Haplotypes** are collections of SNPs and other allelic variations that are located close to each other and when inherited together these create a catalog of haplotypes, or **HapMap.** When the alleles at a particular gene locus on both chromosomes are identical, a **homozygous** state exists, whereas the term **heterozygous** refers to the situation in which different alleles are present at the same gene locus. The term **genotype** refers to an individual's

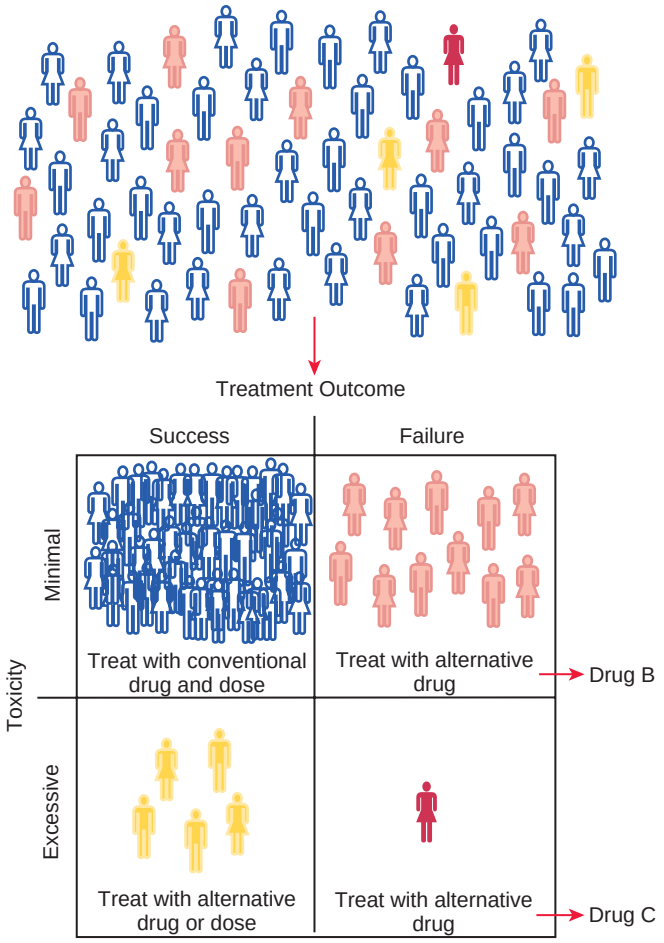


Figure 59-1 **The promise of genomic medicine to human health and disease.** The goal of personalized medicine will be achieved by identifying subgroups of patients who will respond favorably to a given drug with a minimum of side effects, as well as those who will not respond or who will show excessive toxicity with standard doses. A further benefit of pharmacogenomics will be the ability to select the most appropriate alternative drug for patients who cannot be treated successfully with conventional drugs and doses. *(Adapted from Yaffe SJ, Aranda JV:* Neonatal and pediatric pharmacology, *ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins.)*

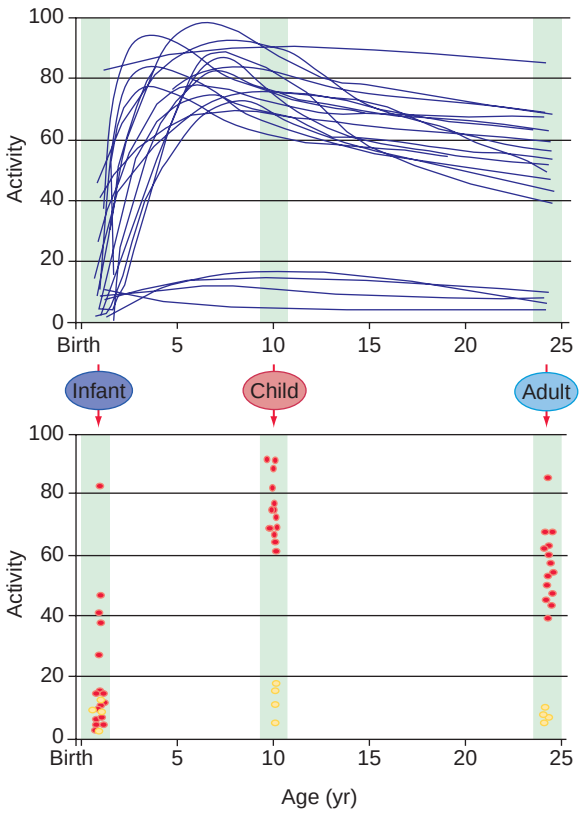


Figure 59-2 **Developmental phenotypes.** Variability in developmental changes in gene expression and functional enzyme activity are superimposed on pharmacogenetic determinants. The *top panel* shows the developmental profile of a theoretical drug-metabolizing enzyme over a 25 yr span in 20 subjects. At maturity (adults), allelic variation within the coding region of the gene gives rise to 2 distinct phenotypes, high activity in 92% of the population ("extensive metabolizers"; *red circles*) and low activity in 8% of the population ("poor metabolizers"; *yellow circles*). However, there is also interindividual variability in the rate at which functional activity is acquired after birth. For example, the 2 phenotypes may not be readily distinguishable in newborn infants immediately after birth. Furthermore, there may be discrete periods during childhood in which the genotype-phenotype relationship may differ from that observed in adults (e.g., developmental stages at which enzyme activity appears to be greater in children than in adults). *(Adapted from Leeder JS: Translating pharmacogenetics and pharmacogenomics into drug development for clinical pediatric and beyond.* Drug Discov Today *9:567–573, 2004.)*

genetic constitution, whereas the observable characteristics or physical manifestations constitute the **phenotype,** which is the net consequence of genetic and environmental effects (see Chapters 77-80). Pharmacogenetics focuses on the phenotypic consequences of allelic variation in single genes. **Pharmacogenetic polymorphisms** are monogenic traits that are functionally relevant to drug disposition and action and are caused by the presence (within 1 population) of more than 1 allele (at the same gene locus) and more than 1 phenotype with regard to drug interaction with the organism. The key elements of pharmacogenetic polymorphisms are heritability, the involvement of a single gene locus, functional relevance, and the fact that distinct phenotypes are observed within the population only after drug challenge.

DEVELOPMENTAL OR PEDIATRIC PHARMACOGENETICS AND PHARMACOGENOMICS

Our current understanding of pharmacogenetic principles involves enzymes responsible for drug **biotransformation.** Individuals are classified as being "fast," "rapid," or "extensive" metabolizers at one end of the spectrum, and "slow" or "poor" metabolizers at the other end of the continuum. This may or may not also include an "intermediate" metabolizer group, depending on the particular enzyme. With regard to biotransformation, children are more complex than adults as fetuses and newborns may be phenotypically "slow" or "poor" metabolizers for certain drug-metabolizing pathways because of their stage of development, and may acquire a phenotype consistent with their genotype at some point later in the developmental process as they mature. Examples of drug-metabolizing pathways that are significantly affected by ontogeny include glucuronidation and some of the cytochrome P450 (CYP) activities (see Chapters 60, 96, and 97). It is also apparent that not all infants acquire drug metabolism activity at the same rate. This is attributable to interactions between genetics and environmental factors. Interindividual variability in the trajectory (i.e., rate and extent) of acquired drug biotransformation capacity may be considered a **developmental phenotype** (Fig. 59-2), and it helps to explain the considerable variability in some CYP activities observed immediately after birth.

Pharmacogenetic, Pharmacogenomic, and Pharmacoproteomic and Metabolomic Tools

Several genotyping platforms are approved by the Food and Drug Administration and are beginning to enter the clinical arena. The Roche AmpliChip CYP450 Test was the first such device to receive FDA

Table 59-1 Examples of Effects of Gene Polymorphisms on Drug Response

GENE	ENZYME/TARGET	DRUG	CLINICAL RESPONSE
BCHE	Butyrylcholinesterase	Succinylcholine	Prolonged paralysis
CYP2C9	Cytochrome P450 2C9	Warfarin	Individuals having one or more reduced function alleles require lower doses of warfarin for optimal anticoagulation, especially initial anticoagulant control
CYP2C19	Cytochrome P450 2C19	Clopidogrel	Individuals having one or more loss-of-function alleles have reduced capacity to form the pharmacologically active metabolite of clopidogrel and reduced antiplatelet effect
CYP2D6	Cytochrome P450 2D6	Codeine	Poor metabolizers—individuals with 2 loss-of-function alleles—do not metabolize codeine to morphine and thus experience no analgesic effect; ultrarapid metabolizers (3 or more functional alleles) may experience morphine toxicity
G6PD	Glucose-6-phosphate dehydrogenase	Primaquine (others)	Hemolysis
*HLA-A*3101*	Human leukocyte antigen A31	Carbamazepine	Carriers of the *HLA-A*3101* allele have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis from carbamazepine
*HLA-B*1502*	Human leukocyte antigen B15	Allopurinol	Han Chinese carriers of the *HLA-B*1502* allele have an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis from carbamazepine
*HLA-B*5701*	Human leukocyte antigen B57	Abacavir Flucloxacillin	Carriers of the *HLA-B*5701* allele have an increased risk of hypersensitivity reactions to abacavir and abacavir- and flucloxacillin-induced liver injury
*HLA-B*5801*	Human leukocyte antigen B58	Allopurinol	Carriers of the *HLA-B*5801* allele have an increased risk of severe cutaneous adverse reactions to allopurinol, including hypersensitivity reactions, Stevens-Johnson syndrome, and toxic epidermal necrolysis
NAT2	*N*-acetyltransferase 2	Isoniazid, hydralazine	Individuals homozygous for "slow acetylation" polymorphisms are more susceptible to isoniazid toxicity, or hydralazine-induced systemic lupus erythematosus
SLCO1B1	Organic anion transporting protein (OATP) 1B1	Simvastatin	Carriers of the *SLCO1B1*5* allele are at increased risk for musculoskeletal side effects from simvastatin
TPMT	Thiopurine *S*-methyltransferase	Azathioprine 6-Mercaptopurine	Individuals homozygous for an inactivating mutation have severe toxicity if treated with standard doses of azathioprine or 6-mercaptopurine; rapid metabolism causes undertreatment
UGT1A1	Uridine diphospho-glucuronosyltransferase 1A1	Irinotecan	The *UGT1A1*28* allele is associated with decreased glucuronidation of SN-38, the active metabolite of irinotecan, and increased risk of neutropenia
VKORC1	Vitamin K oxidoreductase complex 1	Warfarin	Individuals with a haplotype associated with reduced expression of the VKORC1 protein, the therapeutic target of warfarin, require lower doses of the drug for stable anticoagulation

approval, and many additional products have become available (https://www.pharmgkb.org/views/viewGeneticTests.action). In general, applications are limited to 1 or 2 genes, such as *CYP2C9* and *VKORC1* genotyping to guide warfarin therapy or genotyping of *UGT1A1* to reduce the risk of irinotecan toxicity. A more comprehensive chip that covers >90% of the absorption, distribution, metabolism, and excretion markers as defined by the PharmaADME group (http://pharmaadme.org) is available for drug development and research purposes, and the National Institute of General Medical Sciences–sponsored Pharmacogenomics Research Network has developed a list of high-priority genes of interest (http://pgrn.org/download/attachments/131165/PGRN-seq%20Gene%20List%2010-15-12%20Scherer%20Genes.pdf?version=1&modificationDate=1350681059000&api=v2).

In contrast to pharmacogenetic studies that typically target single genes, pharmacogenomic analyses are considerably broader in scope and focus on complex and highly variable drug-related phenotypes with targeting of many genes. Genomewide genotyping technologies have progressed beyond "SNP chips" to evaluate genetic variation at more than 1 million sites throughout an individual genome for SNP and copy number variation analyses to include massively parallel "next-generation sequencing" technologies. Genomewide association studies have been conducted in several pediatric settings, acute lymphoblastic leukemia, and pediatric inflammatory bowel disease. One goal of this type of study is to identify novel genes involved in disease pathogenesis that can lead to new therapeutic targets. Genomewide association studies are also being applied to identify genetic associations with response to drugs, such as warfarin and clopidogrel, and risk for drug-induced toxicity, including statin-induced myopathy and flucloxacillin hepatotoxicity. The "Manhattan plot," a form of data presentation for genomewide association studies, is common in many medical journals (Fig. 59-3*A*). Next-generation sequencing is being applied to rapidly diagnose mendelian disorders and pathologies thought to have a genetic origin when all other diagnostic approaches have been exhausted.

Investigating differential gene expression before and after drug exposure has the potential to correlate gene expression with variable drug responses and possibly uncover the mechanisms of tissue-specific drug toxicities. These types of studies use **microarray technology** or RNA-Seq (based on next-generation sequencing technologies) to monitor global changes in expression of thousands of genes (the **transcriptome**) simultaneously. The underlying hypothesis of these global

Table 59-2 Some Important Relationships Between Drugs and Cytochrome P450 (CYP) Enzymes* and P-Glycoprotein (P-gp) Transporter

ENZYME	DRUG SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	Caffeine, clomipramine (*Anafranil*†), clozapine (*Clozaril*†), theophylline	Cimetidine (*Tagamet*†) Fluvoxamine (*Luvox*†) Ciprofloxacin (*Cipro*)	Omeprazole (*Prilosec*†) Tobacco
CYP2C9	Diclofenac (*Voltaren*†), ibuprofen (*Motrin*†), piroxicam (*Feldene*†), losartan (*Cozaar*), irbesartan (*Avapro*), celecoxib (*Celebrex*), tolbutamide (*Orinase*†), warfarin (*Coumadin*†), phenytoin (*Dilantin*)	Fluconazole (*Diflucan*) Fluvastatin (*Lescol*) Amiodarone (*Cordarone*) Zafirlukast (*Accolate*)	Rifampin (*Rifadin*†)
CYP2C19	Omeprazole, Lansoprazole (*Prevacid*), pantoprazole (*Protonix*), (*S*)-mephenytoin, (*S*)-citalopram (*Lexapro*); nelfinavir (*Viracept*), diazepam (*Valium*†), voriconazole (*Vfend*)	Cimetidine Fluvoxamine	Rifampin
CYP2D6	**CNS-active agents:** Atomoxetine (*Strattera*), amitriptyline (*Elavil*†), desipramine (*Norpramin*†), imipramine (*Tofranil*†), paroxetine (*Paxil*), haloperidol (*Haldol*†), risperidone (*Risperdal*), thioridazine (*Mellaril*†) **Antiarrhythmic agents:** Mexiletine (*Mexitil*), propafenone (*Rythmol*) **β Blockers:** Propranolol (*Inderal*†), metoprolol (*Lopressor*†), timolol (*Blocadren*†) **Narcotics:** Codeine, dextromethorphan, hydrocodone (*Vicodin*†) **Others:** Tamoxifen (*Nolvadex*)	Fluoxetine (*Prozac*†) Paroxetine (*Paxil*) Amiodarone (*Cordarone*†) Quinidine (*Quinidex*†) Terbinafine Cimetidine Ritonavir	
CYP3A4	**Calcium channel blockers:** Diltiazem (*Cardizem*†), felodipine (*Plendil*), nimodipine (*Nimotop*), nifedipine (*Adalat*†), nisoldipine (*Sular*), nitrendipine, verapamil (*Calan*†) **Immunosuppressive agents:** Cyclosporine (*Sandimmune*, *Neoral*†), tacrolimus (*Prograf*) **Steroids:** Budesonide (*Pulmicort*), cortisol, 17β-estradiol, progesterone, testosterone **Macrolide antibiotics:** Clarithromycin (*Biaxin*), erythromycin (*Erythrocin*†), troleandomycin (*TAO*) **Anticancer agents:** Cyclophosphamide (*Cytoxan*†), gefitinib (*Iressa*), ifosfamide (*Ifex*), tamoxifen, vincristine (*Oncovin*†), vinblastine (*Velban*†) **Benzodiazepines:** Alprazolam (*Xanax*†), midazolam *Versed*†), triazolam (*Halcion*†) **Opioids:** Alfentanil (*Alfenta*†), fentanyl (*Sublimaze*†), sufentanil (*Sufenta*†) **HMG-CoA reductase inhibitors:** Lovastatin (*Mevacor*†, simvastatin (*Zocor*), atorvastatin (*Lipitor*) **HIV protease inhibitors:** Indinavir (*Crixivan*), nelfinavir, ritonavir (*Norvir*), saquinavir (*Invirase*, *Fortovase*), amprenavir (*Agenerase*) **Others:** Quinidine (*Quinidex*†), sildenafil (*Viagra*), eletriptan (*Relpax*), ziprasidone (*Geodon*)	Amiodarone Fluconazole Ketoconazole (*Nizoral*†) Itraconazole (*Sporanox*) Clarithromycin Erythromycin Troleandomycin Imatinib Ritonavir‡ Indinavir Grapefruit juice Nefazodone (*Serzone*)	Barbiturates Carbamazepine (*Tegretol*†) Phenytoin (*Dilantin*†) Efavirenz (*Sustiva*) Nevirapine (*Viramune*) Rifampin Ritonavir‡ St. John's wort
P-gp	Aldosterone, amprenavir, atorvastatin, cyclosporine, dexamethasone (*Decadron*†), digoxin (*Lanoxin*†), diltiazem, domperidone (*Motilium*), doxorubicin (*Adriamycin*†), erythromycin, etoposide (*VePesid*), fexofenadine (*Allegra*), hydrocortisone, indinavir, ivermectin (*Stromectol*), lovastatin loperamide (*Imodium*†), nelfinavir, ondansetron (*Zofran*), paclitaxel (*Taxol*), quinidine, saquinavir, simvastatin, verapamil, vinblastine, vincristine	Amiodarone Carvedilol (*Coreg*) Clarithromycin Cyclosporine Erythromycin Itraconazole Ketoconazole Quinidine Ritonavir‡ Tamoxifen Verapamil	Amprenavir Clotrimazole (*Mycelex*†) Phenothiazine Rifampin Ritonavir‡ St. John's wort

*http://www.drug-interactions.com.
†Also available generically.
‡Can be both an inhibitor and an inducer.
CNS, central nervous system; HMG-CoA, β-hydroxy-β-methylglutaryl–coenzyme A.
From Drug interactions. Med Lett *2003;45(1158):47.*

gene profiling studies is that the measured signal intensity for each gene transcript represents its relative expression level; RNA-Seq allows absolute quantitation of gene expression, as well as detection of alternative splicing events. Gene expression profiling data are used to improve disease classification and risk stratification, and are utilized commonly in oncology. This approach was used to address treatment resistance in acute lymphoblastic leukemia, and has provided clinically relevant insights into the mechanistic basis of drug resistance and the genomic basis of interindividual variability in drug response. Subsets of transcripts, or gene expression "signatures," are being investigated as potential prognostic indicators for identifying patients at risk for treatment failure (Fig. 59-3*B*).

Proteomic studies use many different techniques to detect, quantify, and identify proteins in a sample **(expression proteomics),** and to

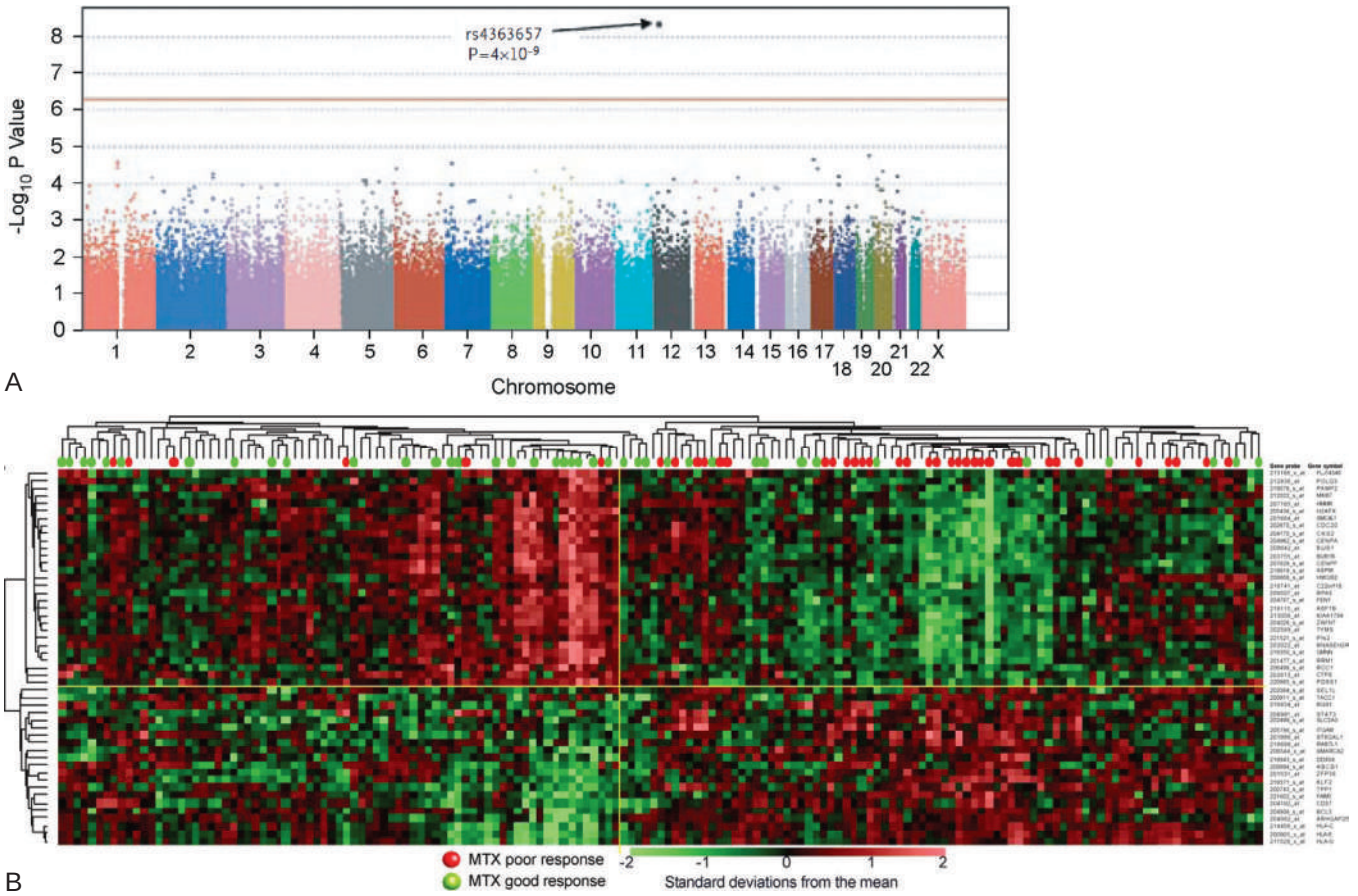


Figure 59-3 Presentations of pharmacogenomic data. **A,** Manhattan Plot from a genomewide association study. The Manhattan plot derives its name from the similarity of such a plot to the Manhattan skyline, and presents the genomewide significance of several hundred thousand SNPs distributed throughout the genome with the trait or phenotype of interest. In this example, each SNP included on the "chip" is plotted along the *x*-axis according to its chromosomal coordinate, with each color representing an individual chromosome from chromosome 1 to the X chromosome. The *y*-axis represents the inverse $\log_{10}$ of the *p* value for the association—the higher the value on the *y*-axis, the smaller the *p* value. A value of "15" corresponds to a *p* value of 10^{-15}. SNPs exceeding a particular threshold are subject to further verification and validation. **B,** "Heat map" constructed from gene expression data. In a heat map, the level of expression of many genes as obtained from microarray analysis is presented as a 2-dimensional matrix of values. Each column represents an individual patient and each row is an individual RNA transcript designated by the gene name. The level of gene expression is indicated by the color of each rectangle on a continuum from high expression *(red)* to low expression *(green)*. In this example, ALL patients are clustered by their response to methotrexate, with patients responding to the drug having markedly different patterns of gene expression compared to nonresponders. One goal of personalized medicine is to use genomic information, like microarray data, to identify signatures of drug response (or risk of drug toxicity), to select the most appropriate drug among available options for each patient. (***A*** *reprinted with permission from Search Collaborative Group. SLCO1B1 variants and statin-induced myopathy—a genome-wide study.* N Engl J Med *359:789–799, 2008;* ***B*** *from Sorich MJ, Pottier N, Pei D, Yang W, Kager L, et al. In vivo response to methotrexate forecasts outcome of acute lymphoblastic leukemia and has a distinct gene expression profile.* PLoS Med *5(4): e83, 2008.)*

characterize protein function in terms of activity and protein–protein or protein–nucleic acid interactions **(functional proteomics)**. Two-dimensional electrophoresis coupled with mass spectral detection is the mainstay of expression proteomics. Protein "spots" of interest are "picked," digested with a proteolytic enzyme such as trypsin, and identified by mass spectrometry. The data generated are compared with theoretically derived peptide mass databases for protein identification.

Metabolomics and metabonomics utilize sophisticated analytical platforms, such as nuclear magnetic resonance spectroscopy and liquid or gas chromatography coupled with mass spectral detection, to measure the concentrations of all small molecules present in a sample. **Metabolomics** refers to the study of the complete set of low-molecular-weight molecules (metabolites) present in a living system (cell, tissue, organ or organism) at a particular developmental or pathological state. **Metabonomics** is defined as the study of how the metabolic profile of biological systems changes in response to alterations because of pathophysiologic stimuli, toxic exposures, dietary changes, etc. **Pharmacometabonomics** has been defined as "the prediction of the outcome, efficacy or toxicity, of a drug or xenobiotic intervention in an individual based on a mathematical model of preintervention metabolite signatures." In the future, integrating metabolomics with pharmacogenomics and transcriptomics will result in a more "systems-based" understanding of cellular processes, especially in the context of drug efficacy and toxicity.

DEVELOPMENTAL PHARMACOGENETICS OF DRUG BIOTRANSFORMATION: APPLICATIONS TO PEDIATRIC DRUG THERAPY PRACTICE

The major consequence of pharmacogenetic polymorphisms in drug metabolizing enzymes is concentration-dependent toxicity caused by impaired drug clearance. In certain cases, reduced conversion of prodrug to therapeutically active compounds is also of clinical importance (see Table 59-2). Chemical modification of drugs via biotransformation reactions generally results in termination of biologic activity through decreased affinity for receptors or other cellular targets as well as more rapid elimination from the body. The process of drug biotransformation can be very complex, but is characterized by 3 important features. First is the concept of broad **substrate specificity**—a single

isozyme may metabolize a large variety of chemically diverse compounds. Second, many different enzymes may be involved in the biotransformation of a single drug (**enzyme multiplicity**). Finally, a given drug may undergo several different types of reactions. One example of this **product multiplicity** occurs with racemic warfarin, where at least 7 different hydroxylated metabolites are produced by different CYP isoforms.

Drug biotransformation reactions are conveniently classified into 2 main types, phase I and phase II reactions, which occur sequentially and serve to terminate biologic activity and enhance elimination (see Chapter 60). Phase I reactions introduce or reveal (via oxidation, reduction, or hydrolysis) a functional group within the substrate drug molecule that serves as a site for a phase II conjugation reaction. Phase II reactions involve conjugation with endogenous substrates, such as acetate, glucuronic acid, glutathione, glycine, and sulfate. These reactions further increase the polarity of an intermediate metabolite, make the compound more water soluble and thereby enhance its renal excretion. Interindividual variability in drug biotransformation activity (for both phase I and phase II reactions) is a consequence of the complex interplay among genetic (genotype, sex, race or ethnic background) and environmental (diet, disease, concurrent medication, other xenobiotic exposure) factors. The pathway and rate of a given compound's biotransformation is a function of each individual's unique phenotype with respect to the forms and amounts of drug-metabolizing enzymes expressed.

The **CYP** enzymes are quantitatively the most important of the **phase I enzymes**. These heme-containing proteins catalyze the metabolism of many lipophilic endogenous substances (i.e., steroids, fatty acids, fat-soluble vitamins, prostaglandins, leukotrienes, and thromboxanes) as well as exogenous compounds, including a multitude of drugs and environment toxins. CYP nomenclature is based on evolutionary considerations and uses the root symbol *CYP* for *cytochrome P450.* CYP enzymes that share at least 40% homology are grouped into families denoted by an Arabic number after the *CYP* root. Subfamilies, designated by a letter, appear to represent clusters of highly related genes. Members of the human CYP2 family, for example, have >67% amino acid sequence homology. Individual P450s in a subfamily are numbered sequentially (e.g., CYP3A4, CYP3A5). CYP enzymes that have been identified as being important in human drug metabolism are predominantly found in the CYP1, CYP2, and CYP3 gene families. Importantly, enzyme activity may be induced or inhibited by various agents (see Table 59-2).

For most CYP enzymes, genotype–phenotype relationships are influenced by development in that fetal expression is limited (with the exception of CYP3A7) and functional activity is acquired postnatally in isoform-specific patterns.

Phase II enzymes include arylamine *N*-acetyltransferases (NAT1, NAT2), glucuronosyltransferases (UGTs), epoxide hydrolase, glutathione *S*-transferases, sulfotransferases, and methyltransferases (catechol *O*-methyltransferase, thiopurine *S*-methyltransferase, several *N*-methyltransferases). Like the CYPs, UGTs, sulfotransferases, and glutathione *S*-transferases are gene families with multiple individual isoforms, each having its own preferred substrates, mode of regulation, and tissue-specific pattern of expression.

Clearance of some compounds appears to be greater in children relative to adults and the correlation between genotype and phenotype in neonatal life through adolescence may be overridden by these developmental phenomena.

CYP2D6

The *CYP2D6* gene locus is highly polymorphic, with more than 100 allelic variants identified to date (http://www.cypalleles.ki.se/cyp2d6.htm; see Table 59-2). Individual alleles are designated by the gene name *(CYP2D6)* followed by an asterisk, and an Arabic number. By convention, *CYP2D6*1* designates the fully functional wild-type allele. Allelic variants are the consequence of point mutations, single base-pair deletions or additions, gene rearrangements, or deletion of the entire gene, resulting in a reduction or complete loss of activity. Inheritance of 2 recessive loss-of-function alleles results in the **poor-metabolizer phenotype,** which is found in approximately 5-10% of white subjects and approximately 1-2% of Asian subjects. In white subjects, the *3, *4, *5, and *6 alleles are the most common loss-of-function alleles and account for approximately 98% of poor-metabolizer phenotypes. In contrast, CYP2D6 activity on a population basis tends to be lower in Asian and African-American populations because of a lower frequency of nonfunctional alleles (*3, *4, *5, and *6) and a relatively high frequency of population-selective alleles that are associated with decreased activity relative to the wild-type *CYP2D6*1* allele. The *CYP2D6*10* allele occurs at a frequency of approximately 50% in Asians, whereas *CYP2D6*17* and *CYP2D6*29* occur at relatively high frequencies in subjects of black African origin.

CYP2D6 is involved in the biotransformation of more than 40 therapeutic entities, including several β-receptor antagonists, antiarrhythmics, antidepressants, antipsychotics, and morphine derivatives (for an updated list, see http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2). CYP2D6 substrates commonly encountered in pediatrics include selective serotonin inhibitors (SSRIs; fluoxetine, paroxetine, sertraline), risperidone, atomoxetine, promethazine, tramadol, and codeine. Furthermore, nonprescription cold remedies such as dextromethorphan, diphenhydramine and chlorpheniramine are also CYP2D6 substrates. An analysis of CYP2D6 ontogeny in vitro that utilized a relatively large number of samples revealed that CYP2D6 protein and activity remain relatively constant after 1 wk of age up to 18 yr. Similarly, results from an in vivo longitudinal phenotyping study involving more than 100 infants over the 1st year of life demonstrated considerable interindividual variability in CYP2D6 activity, but no relationship between CYP2D6 activity and postnatal age between 2 wk and 12 mo of age. Furthermore, a cross-sectional study involving 586 children reported that the distribution of CYP2D6 phenotypes in children was comparable to that observed in adults by at least 10 yr of age. Thus, both available in vitro and in vivo data, albeit based on phenotype data rather than information on drug clearance from pharmacokinetic studies, imply that genetic variation is more important than developmental factors as a determinant of CYP2D6 variability in children.

One consequence of CYP2D6 developmental pharmacogenetics may be the syndrome of irritability, tachypnea, tremors, jitteriness, increased muscle tone, and temperature instability in neonates born to mothers receiving SSRIs during pregnancy. Controversy currently exists as to whether these symptoms reflect a neonatal withdrawal (hyposerotonergic) state or represent manifestations of serotonin toxicity analogous to the hyperserotonergic state associated with the SSRI-induced serotonin syndrome in adults (see Chapter 106.1). Delayed expression of CYP2D6 (and CYP3A4) in the 1st few wk of life is consistent with a hyperserotonergic state caused by delayed clearance of paroxetine and fluoxetine (CYP2D6) or sertraline (CYP3A4) in neonates exposed to these compounds during pregnancy. Furthermore, decreases in plasma SSRI concentrations and resolution of symptoms would be expected with increasing postnatal age and maturation of these pathways. Given that treatment of a "withdrawal" reaction may include administration of an SSRI, there is considerable potential for increased toxicity in affected neonates. Resolution of the question whether symptoms are caused by withdrawal vs a hyperserotonergic state is essential for appropriate management of SSRI-induced neonatal adaptation syndromes. Until further data are available, it is prudent to consider newborns and infants younger than 28 days of age as CYP2D6 genotypic poor metabolizers.

In older children, drug accumulation and resultant concentration-dependent toxicities in CYP2D6 genotypic poor metabolizers should be anticipated in the same way that they are in adults because of the risk of significant morbidity and mortality. Although a fluoxetine-related death has been reported in a 9 yr old child with a CYP2D6 poor metabolizer genotype, experience with paroxetine indicates that the risk of drug accumulation may also occur, under certain conditions, in individuals at the opposite end of the activity spectrum. The pharmacokinetics of paroxetine and nefazodone, both CYP2D6 substrates, correlate with the CYP2D6 phenotype in children and adolescents

7-17 yr of age. However, chronic dosing of paroxetine may lead to greater-than-anticipated drug accumulation in children classified as CYP2D6 extensive metabolizers. In depressed children and adolescents, as well as in adults, there is a disproportionate increase in peak concentrations and area under the serum concentration–time curves at higher dose levels. However, nonlinearity is more prominent in patients who are CYP2D6 extensive metabolizers, especially those with gene duplications and 3 or more functional alleles. The largest decreases in paroxetine clearance observed with ascending doses are seen in patients who have the greatest clearance at the initial dose level (10 mg/day) and are predicted to have the greatest CYP2D6 activity based on CYP2D6 genotype. This seemingly paradoxical effect is best explained in the context of data from in vitro studies. One proposed mechanism involves oxidation of paroxetine within the CYP2D6 active site to form a reactive intermediate that is associated with irreversible modification of the CYP2D6 protein in or near the active site. In theory, the greater the initial CYP2D6 activity, the greater the burden of reactive metabolite burden that is formed and thereby an increased loss of CYP2D6 catalytic activity. As a consequence, as the paroxetine dose is increased in patients with higher initial drug clearance, the risk of excessive drug accumulation increases disproportionately.

Theoretically, younger children may experience decreased efficacy or therapeutic failure with drugs such as codeine and tramadol that are dependent on functional CYP2D6 activity for conversion to the pharmacologically active species. CYP2D6 catalyzes the *O*-demethylation of inactive codeine to active morphine. Infants and children appear capable of converting codeine to morphine and achieving morphine : codeine ratios comparable to those of adults. However, in one study, morphine and its metabolites were not detected in 36% of children receiving codeine, making the level of analgesia from codeine unreliable in the studied pediatric population. Interestingly, in this study levels of morphine and its metabolites were not related to CYP2D6 phenotype. Finally, ultrarapid CYP2D6 metabolism of codeine may result in opiate intoxication, including maternal ultrarapid metabolism of codeine, which can result in high serum and breast milk concentrations of morphine and may have adverse effects in the breastfed neonate.

CYP2C9

Although several clinically useful compounds are substrates for CYP2C9 (http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2), the effects of allelic variation are most profound for drugs with a narrow therapeutic index, such as phenytoin, warfarin, and tolbutamide. In vitro studies show a progressive increase in CYP2C9 expression from 1-2% of mature levels in the 1st trimester to approximately 30% at term. Considerable variability (approximately 35-fold) in expression is apparent over the 1st 5 mo of life, with approximately one-half of the samples studied exhibiting values equivalent to those observed in adults. One interpretation of these data is that there is broad interindividual variability in the rate at which CYP2C9 expression is acquired after birth, and in general, the ontogeny of CYP2C9 activity in vivo, as inferred from pharmacokinetic studies of phenytoin in newborns, is consistent with the in vitro results. The apparent half-life of phenytoin is prolonged (approximately 75 hr) in preterm infants, but decreases to approximately 20 hr in term newborns. By 2 wk of age, the half-life has further declined to 8 hr. Concentration-dependent (saturable) metabolism of phenytoin, reflecting the functional acquisition of CYP2C9 activity, does not appear until approximately 10 days of age. The maximal velocity of phenytoin metabolism is reported to decrease from an average of 14 mg/kg/day in infants to 8 mg/kg/day in adolescents, which may reflect changes in the ratio of liver mass to total body mass observed over this period of development, as has been observed for warfarin.

At least 56 allelic variants of *CYP2C9* have been reported, but not all have been evaluated for their functional consequences. The *CYP2C9*2* allele is associated with approximately 5.5-fold decreased intrinsic clearance for *S*-warfarin relative to the wild-type enzyme. Allelic variations resulting in amino acid changes within the enzyme active site, such as the *CYP2C9*3, CYP2C9*4,* and *CYP2C9*5* alleles, are associated with activities that are approximately 5% of the wild-type protein. Approximately one-third of the white population carries a variant *CYP2C9* allele (*2 and *3 alleles, most commonly), whereas the *2 and *3 alleles are virtually nonexistent in African-American, Chinese, Japanese, and Korean populations. In contrast, the *5 allele has been detected in African-Americans, but not in white subjects. The risk of bleeding complications in patients treated with warfarin and with concentration-dependent toxicity in patients treated with phenytoin is most pronounced for individuals with a *CYP2C9*3/*3* genotype.

Compared to adults, the pharmacogenetics of warfarin dosing has not been studied as extensively in children. In adults, genetic variation in CYP2C9 and the warfarin target,VKORC1, as well as patient age, sex and weight, can account for 50-60% of the variation in warfarin dose requirements. A large fraction of the source of variation is still unknown, but it may be at least partially attributed to interactions with other drugs and foods. Studies in children demonstrate that the contribution of *VCKORC1* and *CYP2C9* genotypes to variability in warfarin dose to achieve a stable international normalized ratio is quite variable, ranging from <5% to approximately 30%, and in each study the contribution of age, or a developmental variable that correlates with age (e.g., height or weight) accounts for the largest amount of variability. The factors contributing to differences between children and adults, and especially among the published pediatric studies, are not clear at this time.

CYP2C19

In vitro, CYP2C19 protein and catalytic activity can be detected at levels representing 12-15% of mature values by 8 wk of gestation and remain essentially unchanged throughout gestation and at birth. Over the 1st 5 mo of postnatal age, CYP2C19 activity increases linearly. Adult levels are achieved by 10 yr of age, although variability in expression is estimated to be approximately 21-fold between 5 mo and 10 yr of age. The major source of this variability is likely pharmacogenetic in nature. The CYP2C19 poor-metabolizer phenotype (also known as *mephenytoin hydroxylase deficiency*) is present in 3-5% of the white population and 20-25% of Asians. Although 25 variant alleles have been reported to date, the 2 most common variant alleles, *CYP2C19*2* and *CYP2C19*3,* result from single base substitutions that introduce premature stop codons and, consequently, truncated polypeptide chains that possess no functional activity. Despite consistent increases in CYP2C19 activity observed in vitro over the 1st 5 mo of life, the results of an in vivo phenotyping study with omeprazole in Mexican children revealed a broad range of activity and implied that 17% of infants younger than 4 mo of age could be classified as poor metabolizers (no poor metabolizers were detected beyond that point). In contrast, 20% of children 3-9 mo old were classified as ultrarapid metabolizers compared with 6% of infants 1-3 mo of age. Similarly, a series of studies investigating pantoprazole pharmacokinetics in newborns, children and adolescents has revealed that the apparent oral clearance of pantoprazole is independent of *CYP2C19* genotype in the 1st 2-3 mo after birth, but poor metabolizers can be distinguished from extensive metabolizers after 4-6 mo of age. The pharmacokinetic parameters of omeprazole are comparable to those observed in adults are achieved by 2 yr of age.

CYP2C19 also plays an important role in the metabolism of lansoprazole. In Japanese adults treated with lansoprazole, amoxicillin, and clarithromycin for *Helicobacter pylori* infection, the eradication rate for CYP2C19 poor metabolizers (97.8%) and heterozygous extensive metabolizers (1 functional *CYP2C19* allele; 92.1%) was significantly greater than that observed in homozygous extensive metabolizers (72.7%). Of the 35 patients in whom initial treatment did not eradicate *H. pylori,* 34 had at least 1 functional *CYP2C19* allele and eradication could be achieved with higher lansoprazole doses in almost all cases. Given that the frequency of the functional *CYP2C19*1* allele is considerably greater in white subjects (approximately 0.84 [84%]) compared with Japanese subjects (approximately 0.55 [55%]), eradication failure can be expected to occur more frequently in whites. Because

proton pump inhibitors are widely used in children, pharmacogenetic as well as developmental considerations should guide pediatric dosing strategies.

CYP3A4, CYP3A5, and CYP3A7

The CYP3A subfamily consists of 4 members in humans (CYPs 3A4, 3A5, 3A7, and 3A43) and is quantitatively the most important group of CYP enzymes in terms of human hepatic drug biotransformation. These isoforms catalyze the oxidation of many different therapeutic entities, several of which are of potential importance to pediatric practice (for an updated list, see http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf; see Table 59-2). CYP3A7 is the predominant CYP isoform in fetal liver and can be detected in embryonic liver as early as 50-60 days' gestation. CYP3A4, the major CYP3A isoform in adults, is essentially absent in fetal liver, but increases gradually throughout childhood. Over the 1st 6 mo of life, CYP3A7 expression exceeds that of CYP3A4, although its catalytic activity toward most CYP3A substrates is rather limited compared with that of CYP3A4. CYP3A4 is also abundantly expressed in intestine, where it contributes significantly to the first-pass metabolism of orally administered drugs which are substrates (i.e., midazolam). CYP3A5 is polymorphically expressed and is present in approximately 25% of adult liver samples studied in vitro.

Several methods have been proposed to measure CYP3A activity. Using these various phenotyping probes, CYP3A4 activity has been reported to vary widely (up to 50-fold) among individuals, but the population distributions of activity are essentially unimodal and evidence for polymorphic activity has been elusive. Although 24 allelic variants have been identified to date (http://www.cypalleles.ki.se/cyp3a4.htm), most occur relatively infrequently and do not appear to be of clinical importance. Of interest to pediatrics is the *CYP3A4*1B* allele present in the *CYP3A4* promoter region. The clinical significance of this allelic variant appears limited with respect to drug biotransformation activity, despite being associated with 2-fold increased activity over the wild-type *CYP3A4*1* allele in in vitro assays. Although there does not appear to be an association between the *CYP3A4*1B* allele and age of menarche, a significant relationship does exist between the number of *CYP3A4*1B* alleles and the age at onset of puberty, as defined by Tanner breast score. In one study, 90% of 9 yr old girls with a *CYP3A4*1B/*1B* genotype had a Tanner breast score of ≥2 compared with 56% of *CYP3A4*1A/*1B* heterozygotes and 40% of girls homozygous for the *CYP3A4*1A* allele. Because CYP3A4 plays an important role in testosterone catabolism, the authors of the latter study proposed that the estradiol : testosterone ratio may be shifted toward higher values in the presence of the *CYP3A4*1B* allele and trigger the hormonal cascade that accompanies puberty. Intestinal CYP3A4 activity is inhibited by grapefruit juice and may result in higher levels of the many drugs metabolized by this enzyme; very large quantities of grapefruit juice may also inhibit the hepatic CYP3A4.

The *CYP3A4*22* allele has received attention due to its association with reduced clearance of statins in adults as well as immunosuppressants, such as cyclosporine and tacrolimus, in children and adults. Improved response to inhaled fluticasone has also been reported in asthmatic children who are carriers of the *CYP3A4*22* allele.

Polymorphic *CYP3A5* expression is largely the result of a SNP in intron 3 that creates a cryptic splice site and gives rise to messenger RNA splice variants that retain part of intron 3 with a premature stop codon. The truncated messenger RNA transcripts associated with this allele, *CYP3A5*3,* cannot be translated into a functional protein. Individuals with at least 1 wild-type *CYP3A5*1* allele express functional CYP3A5 protein, whereas those homozygous for *CYP3A5*3 (CYP3A5*3/*3)* do not express appreciable amounts of functional protein. Approximately 60% of African-Americans show functional hepatic CYP3A5 activity compared with only 33% of European Americans. Clinically important consequences of *CYP3A5* allelic variation have been reported in children. In pediatric heart transplant patients with a *CYP3A5*1/*3* genotype, tacrolimus concentrations were approximately 50% of those observed in patients with *CYP3A5*3/*3* genotypes, when corrected for dose, 3 mo, 6 mo, and 12 mo after transplant. Thus, larger doses of tacrolimus are required in patients with functional CYP3A5 protein to achieve comparable blood levels and to minimize the risk of rejection.

Glucuronosyltransferases

The UGT gene superfamily catalyzes the conjugation (with glucuronic acid) of several drugs used clinically in pediatrics, including morphine, acetaminophen, nonsteroidal antiinflammatory drugs, and benzodiazepines. The effect of development on glucuronidation capacity has been well described and is illustrated by hyperbilirubinemia, **gray baby syndrome** (the cardiovascular collapse associated with high doses of chloramphenicol in newborns), and the 3.5-fold increase in morphine clearance observed in premature neonates at 24-39 wk postconceptional age. As with the CYPs, there are multiple UGT isoforms, and the acquisition of functional UGT activity appears to be isoform- and substrate-specific.

UGT1A1 is the major UGT gene product responsible for bilirubin glucuronidation, and more than 100 genetic alterations have been reported (Table 59-3), most of which are rare and are more properly considered mutations rather than gene polymorphisms (see Chapters 102 and 357.1). Inheritance of 2 defective alleles is associated with reduced bilirubin-conjugating activity and gives rise to clinical conditions, such as Crigler-Najjar syndrome and Gilbert syndrome. More frequently occurring polymorphisms involve a dinucleotide (TA) repeat in the atypical TATA box of the *UGT1A1* promoter. The wild-type *UGT1A1*1* allele has 6 repeats (TA_6), and the TA_5 *(UGT1A1*33),* TA_7 *(UGT1A1*28),* and TA_8 *(UGT1A1*34)* variants are all associated with reduced activity. *UGT1A1*28,* the most frequent variant, is a contributory factor to prolonged neonatal jaundice. This variant is also associated with impaired glucuronidation and thus toxicity of the active metabolite, SN-38, of the chemotherapeutic agent irinotecan. Allelic variations in *UGT1A7* and *UGT1A9* are also associated with irinotecan toxicity in adults with colorectal cancer.

The consequences of allelic variation in the *UGT2B* family are less certain. The predominant routes of morphine elimination include biotransformation to the pharmacologically active 6-glucuronide and the inactive 3-glucuronide. 6-Glucuronide formation is almost exclusively catalyzed by UGT2B7, whereas several UGTs in the UGT1A subfamily and UGT2B7 both contribute to 3-glucuronide formation. Increased 6-glucuronide : morphine ratios have been reported in individuals homozygous for the SNPs constituting the *UGT2B7*2* allele. Although individuals genotyped as *UGT2B7*2/*2* may produce higher than anticipated concentrations of pharmacologically active morphine and its metabolites, prospective pharmacogenetic studies addressing phenotype-genotype correlations and the consequences of morphine analgesia have had conflicting results.

Arylamine *N*-Acetyltransferases

One of the earliest discovered and most widely recognized genetic polymorphisms is the NAT2 polymorphism. Approximately 50% of whites and African-Americans in North America are phenotypically slow metabolizers, placing a substantial number of individuals at increased risk for the development of adverse drug effects, such as sulfasalazine-induced hemolysis, hydrazine or arylamine-induced peripheral neuropathy, procainamide- or isoniazid-induced systemic lupus erythematosus, and Stevens-Johnson syndrome or toxic epidermal necrolysis associated with sulfonamide administration. NAT2 function is inherited in an autosomal dominant fashion, with the inheritance of 2 "slow" alleles required for expression of the slow-metabolizer phenotype. The relative proportion of rapid and slow metabolizers varies considerably with ethnic or geographic origin. The percentage of slow acetylators among Canadian Eskimos is 5%, but it approaches 90% in some Mediterranean populations.

In vivo, with the use of caffeine as a phenotyping probe, all infants 0-55 days of age appear to be phenotypically slow acetylators, whereas 50% and 62% of infants 122-224 and 225-342 days of age, respectively, can be characterized as fast acetylators. Several independent studies indicate that maturation of the NAT2 phenotype occurs during the 1st 4 yr of life. Phenotype-genotype discordance is likely to be most

Table 59-3 Internet Resources for Pharmacogenetics and Pharmacogenomics*

INTRODUCTION TO PHARMACOGENOMICS	
http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/current-topics/pharmacogenomics.shtml	
http://ghr.nlm.nih.gov/handbook/genomicresearch/pharmacogenomics	
http://learn.genetics.utah.edu/content/pharma/	
http://pgrn.org/display/pgrnwebsite/PGRN+Home	
http://www.pharmgkb.org/	
PHARMACOGENETICS: ALLELIC VARIANTS OF DRUG METABOLIZING ENZYMES	
CYP2C9	http://www.cypalleles.ki.se/cyp2c9.htm
CYP2C19	http://www.cypalleles.ki.se/cyp2c19.htm
CYP2D6	http://www.cypalleles.ki.se/cyp2d6.htm
CYP3A4	http://www.cypalleles.ki.se/cyp3a4.htm
CyP3A5	http://www.cypalleles.ki.se/cyp3a5.htm
UGTs	http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/
NAT1 and NAT2	http://nat.mbg.duth.gr/
PHARMACOGENETICS: SUBSTRATES OF DRUG METABOLIZING ENZYMES	
http://static.medicine.iupui.edu/divisions/clinpharm/content/p450_Table_Oct_11_2009.pdf	
PHARMACOGENETICS-BASED DOSING GUIDELINES	
Dosing guidelines incorporating pharmacogenetic data developed by the Clinical Pharmacogenetics Implementation Consortium are available on the National Guidelines Clearinghouse website a publicly accessible resource for evidence-based clinical guidelines sponsored by the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health Services:	
CYP2D6, CYP2C19, and tricyclic antidepressants	http://www.guideline.gov/content.aspx?id=43954
CYP2D6 and codeine	http://www.guideline.gov/content.aspx?id=39534
TPMT and thiopurines	http://www.guideline.gov/content.aspx?id=43955
HLA-B and allopurinol	http://www.guideline.gov/content.aspx?id=39536
HLA-B and abacavir	http://www.guideline.gov/content.aspx?id=39535
SLCO1B1 and simvastatin	http://www.guideline.gov/content.aspx?id=39537

*All sites were accessible on November 30, 2014.
HLA, human leukocyte antigen; TMPT, thiopurine methyltransferase.

apparent in the 1st 2-4 mo of life, and drugs that are highly dependent on NAT2 function for their elimination should be used with caution.

Thiopurine *S*-Methyltransferase

Thiopurine *S*-methyltransferase (TPMT) is a cytosolic enzyme that catalyses the *S*-methylation of aromatic and heterocyclic sulfur-containing compounds, such as 6-mercaptopurine (6MP), azathioprine, and 6-thioguanine, used in the treatment of acute lymphoblastic leukemia (ALL), inflammatory bowel disease, juvenile arthritis, and for the prevention of renal allograft rejection. To exert its cytotoxic effects, 6MP requires metabolism to thioguanine nucleotides by a multistep process that is initiated by hypoxanthine guanine phosphoribosyl transferase. TPMT prevents thioguanine nucleotide production by methylating 6MP (Fig. 59-4*A*). TPMT activity is usually measured in erythrocytes, with activity in erythrocytes reflecting that which is found in other tissues, including liver and leukemic blasts. Although approximately 89% of whites and African-Americans have high TPMT activity and 11% have intermediate activity, 1 in 300 individuals inherit TPMT deficiency as an autosomal recessive trait (Fig. 59-4*B*). In newborn infants, peripheral blood TPMT activity is reported to be 50% greater than in race-matched adults and shows a distribution of activity that is consistent with the polymorphism characterized in adults. There are no data currently to indicate how long this higher activity is maintained, although TPMT activities were comparable to previously reported adult values in a population of Korean schoolchildren age 7-9 yr. In patients with intermediate or low activity, more drug is shunted toward production of cytotoxic thioguanine nucleotides. TPMT can also methylate 6-thioinosine 5′-monophosphate to generate a methylated metabolite that is capable of inhibiting de novo purine synthesis (Fig. 59-4*C*). Three mutations have been identified in the TPMT gene (*2, *3A, *3C), which account for 98% of white subjects with low activity. These mutations encode proteins that undergo rapid proteolysis resulting in low enzyme activity.

*TPMT***3A* is the most common mutant allele and is characterized by 2 nucleotide transition mutations, G460A and A719G, that lead to 2 amino acid substitutions, Ala154Thr and Tyr240Cys (see Fig. 59-4*D*). Although the *3A allele only has a frequency of 0.03% in the general population, it represents 55% of all mutant alleles. Either mutation alone results in loss of functional activity through the production of unstable proteins that are subject to accelerated proteolytic degradation. Less-frequent allelic variants involve SNPs that produce amino acid substitutions in the coding region and defective intron–exon splicing. A polymorphic locus has been identified in the promoter region of the *TPMT* gene involving 4-8 repeats of a specific nucleotide sequence in tandem. Although these repeats appear to modulate TPMT activity when expressed in vitro, their role in regulating activity in vivo has not been clearly established.

The relatively few patients with low to absent TPMT activity (0.3%) are at increased risk for **severe myelosuppression** if treated with routine doses of thiopurines; thus, they require a 10-15–fold reduction in dose to minimize this risk. Furthermore, if not dosed properly, patients may be at increased risk for relapse as a result of inadequate or absent treatment with thiopurines. Given the expanding use of 6MP and azathioprine in pediatrics to treat inflammatory bowel disease and juvenile arthritis and to prevent renal allograft rejection, TPMT pharmacogenetics is not a trivial matter.

Introduction of the TPMT phenotype or genotype determination into pediatric practice will lead to safer, more efficacious treatment in pediatric patient groups. Although the majority of research has been conducted in patients with acute lymphoblastic leukemia, the observation that patients classified as having intermediate TPMT activity are more likely to be intolerant of 6MP or azathioprine and likely will require more frequent dosage reductions in response to drug-induced myelosuppression is equally applicable to other pediatric patient groups (i.e., patients with Crohn disease) treated with this family of drugs.

PHARMACOGENETICS OF DRUG TRANSPORTERS

There are several major types of membrane transporters, including organic anion transporter (OAT), organic anion transporting polypeptides (OATPs), organic cation transporting proteins (OCTs), and the adenosine triphosphate–binding cassette (ABC) transporters, such as P-glycoprotein and the multidrug-resistant proteins (MRPs).

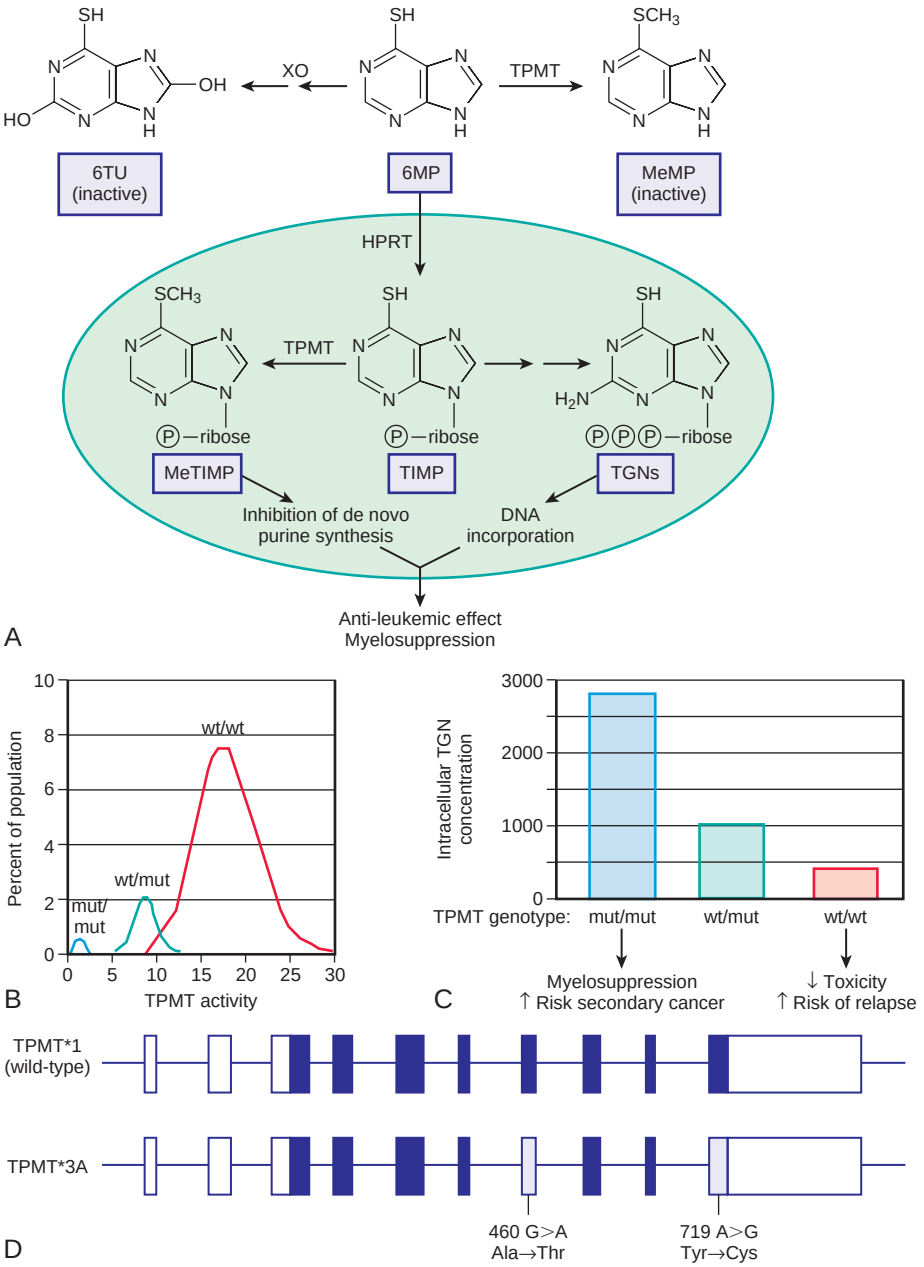


Figure 59-4 Thiopurine *S*-methyltransferase (TPMT) polymorphism. **A,** 6-Mercaptopurine (6MP) undergoes metabolism to thioguanine nucleotides (TGNs) to exert its cytotoxic effects. TPMT and xanthine oxidase reduce the amount of 6MP available for the bioactivation pathway to TGNs. TPMT can also methylate 6-thioinosine 5′-monophosphate (TIMP) to generate a methylated compound capable of inhibiting de novo purine synthesis. **B,** Distribution of TPMT activity in humans. Of the population, 89% has high activity, whereas 11% has intermediate activity. Approximately 1 in 300 individuals homozygous for 2 loss-of-function alleles has very low activity. **C,** Correlation between the TPMT genotype and intracellular TGN concentrations. In TPMT poor metabolizers, more 6MP is available to go down the bioactivation pathway to form TGNs; this situation is associated with an increased risk of myelosuppression. **D,** The most common variant TPMT allele is the result of 2 mutations that give rise to an unstable protein product that undergoes proteolytic degradation. *HPRT,* 6-thiomethylinosine 5-monophosphate; *MeMP,* 6-methylmercaptopurine; *MeTIMP,* hypoxanthine-guanine phosphoribosyl transferase; *mut,* mutant; *6TU,* 6-thiouric acid; *wt,* wild type. *(Modified with permission from Relling MV, Dervieux T: Pharmacogenetics and cancer therapy.* Nat Rev Cancer *11:99–108, 2001; copyright 2001, Macmillan Magazines Ltd.)*

Membrane transporters are heavily involved in drug disposition and actively transport substrate drugs between organs and tissues. Drug transporters are expressed at numerous epithelial barriers, such as intestinal epithelial cells, hepatocytes, renal tubular cells, and at the blood–brain barrier (Fig. 59-5). Transporters often are also determinants of drug resistance, and many drugs work by affecting the function of transporters. As such, polymorphisms in the genes encoding these proteins may have a significant effect on the absorption, distribution, metabolism, and excretion as well as the pharmacodynamic effect of a wide variety of compounds.

The Adenosine Triphosphate–Binding Cassette Superfamily

The ABC transporters belong to the largest known transporter gene family and translocate a variety of substrates, including chemotherapy agents. ABC multidrug transporter expression is implicated in tumor cell resistance to anticancer therapy, altered disposition of chemotherapy drugs, and toxic side effects associated with chemotherapy. More recently, the genetic heterogeneity of a number of the ABC transporter genes has been described. Apart from having at least 1 adenosine triphosphate (ATP)-binding domain, these transporters are

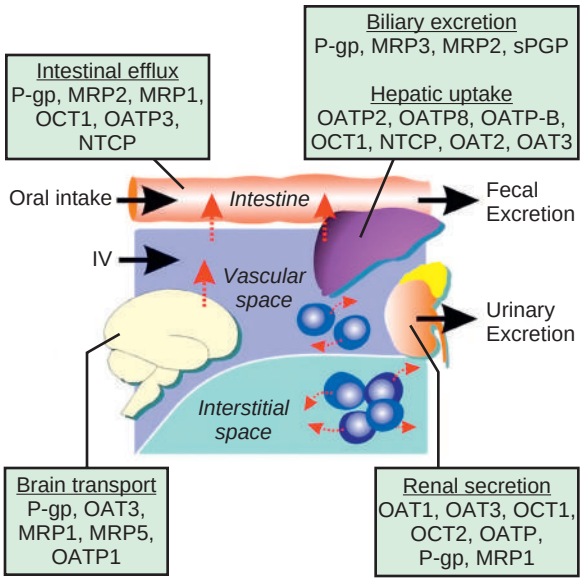


Figure 59-5 Schematic of important transport proteins and their known locations in humans. Spheres correspond to drug molecules. *(Reprinted with permission from American Pharmacists Association. Ritschel WA, Kearns GL, editors.* Handbook of basic pharmacokinetics including clinical applications, *ed 7, Washington, DC, 2009, American Pharmacists Association, p. 45.)*

characterized by a signature sequence of amino acid residues within the ATP-binding domain. In humans, the ABC transporters function as efflux pumps, which, together with detoxification enzymes, constitute a complex integrated "chemoimmunologic defense" system against drugs and other foreign chemicals. A variety of epithelial barriers, including the kidney, liver, and blood–brain barrier, have abundant expression of ABC transporters, such as P-glycoprotein (P-gp; also known as *MDR1*), and MRPs 1, 2, and 3. Powered by ATP, these transporters actively extrude substrates from the respective cell and organ.

Studies conducted in children need to also consider the ontogeny of P-gp expression. Based on studies utilizing human lymphocytes, it appears that P-gp activity is high at birth, decreases between the ages of 0 and 6 mo, and stabilizes between 6 mo and 2 yr of age. In contrast, P-gp can be detected in human neural stem/progenitor cells and decreases with differentiation. Furthermore, P-gp has been proposed as an endothelial marker for development of the blood–brain barrier, and expression increases with postnatal age as the blood–brain barrier matures. Thus, the developmental patterns of P-gp expression likely are tissue-specific, but data are very limited in this regard. Nevertheless, it is likely that expression of P-gp at a young age in gut and liver represents a protective mechanism in which both endogenous and exogenous toxins are efficiently excreted from the body. However, developmental patterns of expression in tissues of drug response, such as lymphocytes and tumors, may also affect the efficacy of intracellular drugs. For example, polymorphisms in the gene have been shown to be predictive of the ability to wean steroids after heart transplantation, as well as the susceptibility to and clinical outcome of treatment for pediatric ALL. On the other hand, immaturity of P-gp expression in the developing blood–brain barrier may contribute to discrete periods of increased susceptibility to drug toxicity in the central nervous system. However, for most other drugs, including immunosuppressants and protease inhibitors, studies investigating the effect of *ABCB1* polymorphisms in drug disposition and response have yielded conflicting results. In one study investigating the relationship between *ABCB1* genotype and cyclosporine pharmacokinetics, an effect of genotype on oral availability was only apparent in children older than 8 yr of age.

Organic Anion Transporting Polypeptides

OATPs in the solute carrier OAT (SLCO) represent a family of glycoprotein transporters with 12 transmembrane spanning domains, and are expressed in various epithelial cells. There are 11 OATPs in humans, some of which are ubiquitously expressed and others whose expression is restricted to specific tissues. Typical substrates include bile salts, hormones and their conjugates, toxins, and various drugs. The solute carrier, human OATP1A2 (OATP-A, OATP1, and OATP), is highly expressed in the intestine, kidney, cholangiocytes and the blood–brain barrier and may be important in the absorption, distribution, and excretion of a broad array of clinically important drugs. Several nonsynonymous polymorphisms have been identified in the gene encoding OATP1A2, SLCO1A2 (SLC21A3), with some of these variants demonstrating functional changes in the transport of OATP1A2 substrates.

OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) are liver-specific transporters and promote the cellular uptake of endogenous substrates, such as bilirubin, bile acids, dehydroepiandrosterone-sulfate and leukotriene C_4, as well as various drugs, including several statins, methotrexate, and enalapril. Allelic variation in OATP1B1 (specifically, the *SLCO1B1*5* allele) results in reduced clearance and increased systemic exposure of several statin drugs (atorvastatin, pravastatin, and simvastatin), and is associated with an increased risk of musculoskeletal side effects from simvastatin. The ontogeny of OATP1B1 has not been extensively studied in children, but the results of a small pharmacogenetic study conducted in children with familial hypercholesterolemia and pediatric cardiac transplant patients revealed an association between *SLCO1B1*5* and pravastatin concentrations that was the opposite to that observed in adults. Several studies confirm that the 2 SNPs determining the most common *SLCO1B1* haplotypes (**1a, *1b, *5,* and **15*), rs4149056 and rs2306283, are associated with decreased clearance of high-dose methotrexate in children with ALL. Genotyping for *SLCO1B1* may be helpful in identifying patients at increased risk of toxicity due to reduced clearance/increased accumulation of methotrexate, but prospective studies have not yet been conducted.

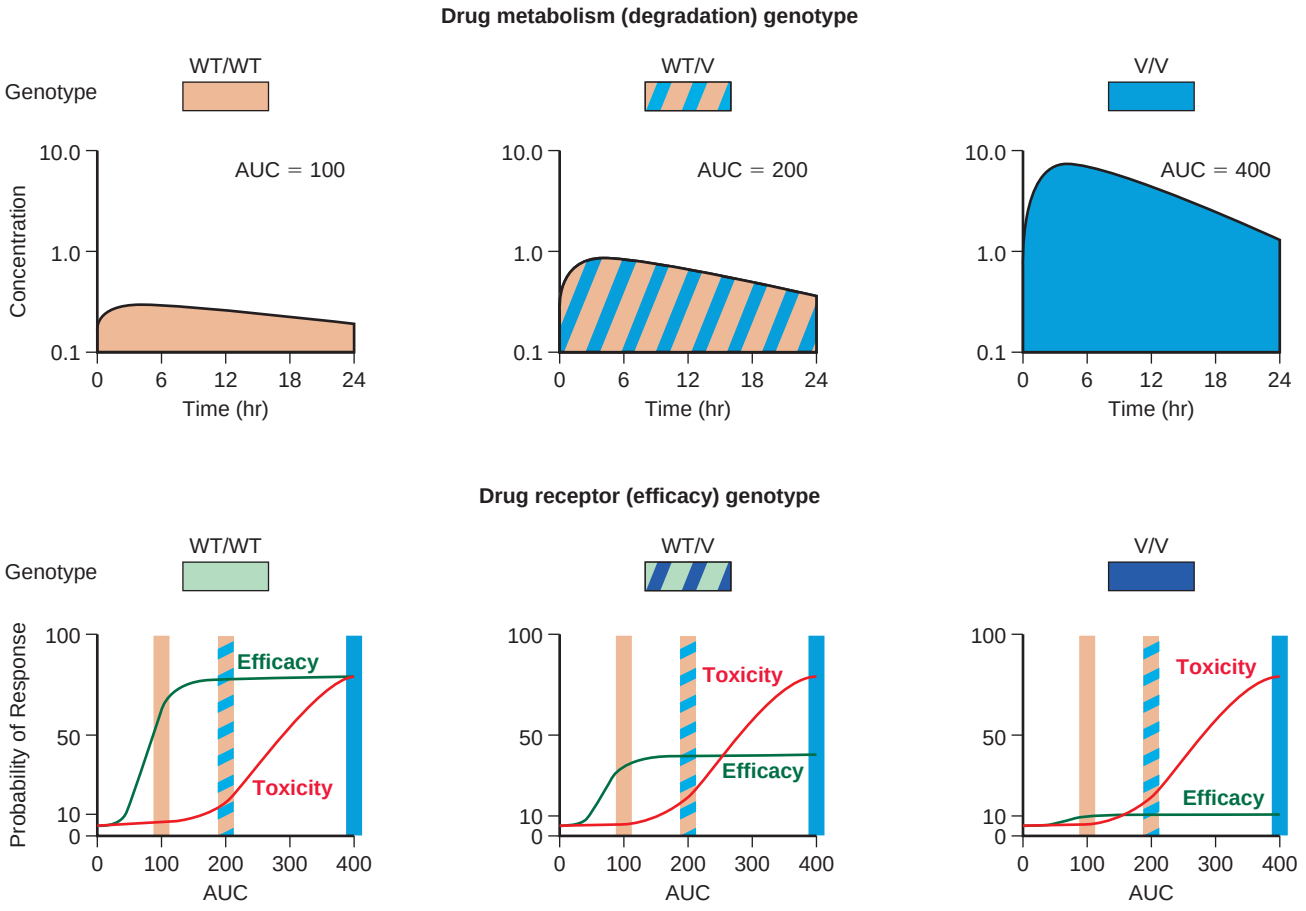
Organic Cation Transporters

OCTs in the SCL22A subfamily are primarily expressed on the basolateral membrane of polarized epithelia, and mediate the renal secretion of small organic cations. Originally, OCT1 (also known as SLC22A1) was thought to be primarily expressed in liver, but recent studies localized its expression to the apical side of proximal and distal renal tubules. OCT2 (SLC22A2) is predominantly expressed on the basolateral surface of proximal renal tubules. In adults, allelic variation in OCT1 and OCT2 is associated with increased renal clearance of metformin. The role of genetic variation of OCT1 and OCT2 has not been studied in children, but developmental factors appear to be operative. For example, neonates possess very limited ability to eliminate organic cations, but this function increases rapidly during the 1st few mo of life, and when standardized for body weight or surface area, it tends to exceed adult levels during the toddler stage.

PHARMACOGENETICS OF DRUG RESPONSE: POLYMORPHISMS IN DRUG RECEPTORS, ION CHANNELS, AND OTHER DRUG TARGETS DURING GROWTH AND DEVELOPMENT

Receptors are the targets for drugs and endogenous transmitters because of their inherent molecular recognition sites. Drugs and transmitters bind to the receptor to produce a pharmacologic effect. Variability in the receptor protein or the ion channel may determine the magnitude of the pharmacologic response. For example, polymorphisms of the β_2-adrenergic receptor gene *(ADRB2)* are associated with variable responses to bronchodilator drugs.

Drug responses are seldom monogenic events because multiple genes are involved in both drug binding to the pharmacologic target and the subsequent downstream signal transduction events that ultimately collectively manifest as a therapeutic effect. Although genotypes at a particular locus may show a statistically significant effect on the outcome of interest, they may account for only a relatively small amount of the overall population variability for that outcome. For example, a particular group of SNPs in the corticotropin-releasing hormone receptor 1 *(CRHR1)* gene is associated with a statistically



Polygenic drug response

Metabolism genotype		Receptor genotype	Probability of Response: Efficacy	Probability of Response: Toxicity	Therapeutic Index	Individual risk : benefit assessment: Benefit	vs	risk
	+		65%	5%	13.0	Benefit	>>>>	Risk
	+		32%	5%	6.0	Benefit	>>>	Risk
	+		10%	5%	2.0	Benefit	>	Risk
	+		75%	15%	5.0	Benefit	>>	Risk
	+		40%	15%	2.7	Benefit	>	Risk
	+		10%	15%	0.7	Risk	>	Benefit
	+		80%	80%	1.0	Benefit	≈	Risk
	+		40%	80%	0.5	Risk	>>	Benefit
	+		10%	80%	0.1	Risk	>>>>	Benefit

Figure 59-6 Polygenic determinants of drug response. The potential effects of 2 genetic polymorphisms are illustrated. In each panel, there is a profile for subjects who have 2 wild-type alleles (WT/WT), those who are heterozygous for 1 wild-type and 1 variant (V) allele (WT/V), and those who have 2 variant alleles (V/V) for the depicted gene. The *top panel* illustrates a potential polymorphism involving a drug-metabolizing enzyme where variant alleles result in decreased drug metabolism and greater exposure (as shown by the increasing area under the concentration-time curve [AUC]). The *second panel* illustrates a potential polymorphism involving a drug receptor and depicts variant alleles which result in decreased receptor sensitivity. Note that for each receptor type, there are 3 possibilities for drug exposure. At the bottom is a table that shows the 9 resulting combinations of drug-metabolism and drug-receptor genotypes and the corresponding drug-response phenotypes calculated from data shown in the second panel. These phenotypes allow for calculation of a therapeutic index (i.e., efficacy : toxicity, in this example these range from 13 [65%:5%] to 0.1 [10%:80%]), which results in the ability to perform an individualized risk : benefit assessment. *(Adapted from Evans WE, McLeod HL: Pharmacogenomics—drug disposition, drug targets, and side effects.* N Engl J Med *348:538–549, 2003.)*

significant improvement in forced expiratory volume in 1 sec, but accounts for only 6% of the overall variability in response to inhaled corticosteroids (see Chapter 144). A series of subsequent studies has determined that allelic variation in several genes in the steroid pathway contributes to overall response to this form of therapy.

The listing and classification of receptors is a major initiative of the International Union of Pharmacology. The list of receptors and voltage-gated ion channels is available on the International Union of Pharmacology website (http://www.guidetopharmacology.org/).

CURRENT AND FUTURE APPLICATIONS FOR PHARMACOGENETICS AND PHARMACOGENOMICS IN PEDIATRICS

Progress being made in the treatment of ALL provides an outstanding example of how the application of pharmacogenomic principles can improve pediatric drug therapy (see Chapter 495). Despite improved understanding of the genetic determinants of drug response, however, many complexities remain to be resolved. Patients with ALL who have 1 wild-type allele and intermediate TPMT activity tend to have a better response to 6MP therapy than patients with 2 wild-type alleles and full activity. Reduced TPMT activity also places patients at risk for irradiation-induced secondary brain tumors and etoposide-induced acute myeloid leukemias. Pharmacogenetic polymorphisms of several additional genes also have the potential to influence successful treatment of ALL. Multiple genetic and treatment-related factors interact to create patient subgroups with varying degrees of risk, and these represent an opportunity for pharmacogenomic approaches to identify subgroups of patients who will benefit from specific treatment regimens and those who will be at risk for short- and long-term toxicities (Fig. 59-6).

The 20% of patients with ALL who do not respond to chemotherapy represent an additional challenge for pharmacogenomic research. Gene expression (microarray) studies in ALL blasts are able to discriminate among phenotypic subtypes and identify some individuals who are at risk for treatment failure. An analysis of acute treatment-induced changes in the gene response of ALL blasts obtained 1 day after the initiation of 6MP and methotrexate as single agents or in combinations of high-dose or low-dose methotrexate and 6MP showed several important insights into the cellular response to these treatments. Changes in gene expression were treatment-specific and could accurately discriminate among the 4 treatments. ALL cells of different molecular subtypes shared common cellular responses to treatment, suggesting that it may be possible to personalize treatment strategies in ALL.

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Chapter 60

Principles of Drug Therapy

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The clinical pharmacology of a given drug reflects a multifaceted set of properties that pertain to its disposition and action, and the response (e.g., adverse effects, therapeutic effects, and therapeutic outcome) to their administration/use. The 3 most important facets of the clinical pharmacology of a drug are its pharmacokinetics, pharmacodynamics, and the role of genetic variability as it may impact drug disposition or action (i.e., pharmacogenomics) (see Chapter 59).

Pharmacokinetics describes the movement of a drug throughout the body and the concentrations (or amounts) of a drug that reach a given body space and/or tissue and its residence time therein. Pharmacokinetics of a drug are conceptualized by considering those characteristics which collectively, are the determinants of the dose–concentration–effect relationship; namely, absorption, distribution, metabolism and excretion. **Pharmacodynamics** describes the relationship between drug dose or drug concentration and response. The response may be desirable *(effectiveness)* or untoward *(toxicity)*. Although in clinical practice the response to drugs in different patient populations is often described by a standard dosing or concentration range, response is best conceptualized along a continuum where the relationship between dose and response(s) are not linear. **Pharmacogenetics** is the study of how variant forms of human genes contribute to interindividual variability in either drug disposition (e.g., variant alleles of gene controlling the expression of a drug transporter) and/or response (e.g., variant alleles altering the drug–receptor interaction). The finding that drug responses can be influenced by the patient's genetic profile has offered great hope for realizing individualized pharmacotherapy when the relationship between genotype and phenotype (either disease and/or drug response) is predictive of drug response (see Chapter 59). In the developing child, it is apparent ontogeny that has the potential of modulating drug response through altering both pharmacokinetics and pharmacodynamics.

GENERAL PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES

Drug effect is produced only when an exposure (both amount and duration) occurs that is sufficient to produce a drug–receptor interaction capable of modulating the cellular milieu and inducing a biologic response. Thus, exposure–response relationships for a given drug represent an interface between pharmacokinetics and pharmacodynamics that can be simply conceptualized by consideration of 2 profiles: (1) plasma concentration vs effect (Fig. 60-1) and (2) plasma concentration vs time (Fig. 60-2).

The relationship between drug concentration and effect for most drugs is not linear (see Fig. 60-1). At a drug concentration of zero, the effect from the drug is generally zero or not perceptible (E_0). Following drug administration and/or with dose escalation, the concentration increases as does the effect; first in an apparent linear fashion (at low drug concentrations) followed by a nonlinear increase in effect to an asymptotic point in the relationship where a maximal effect (E_{max}) is attained that does not perceptibly change with further increases in

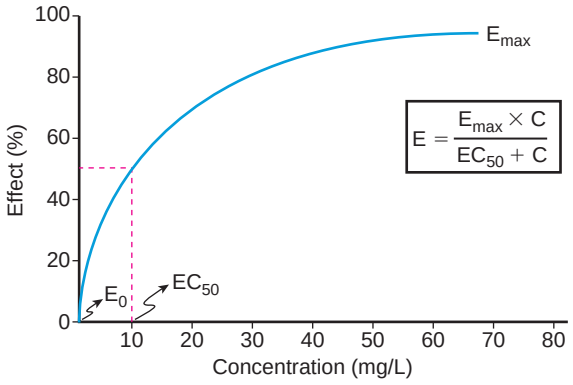

Figure 60-1 Plasma concentration vs effect curve. The percent effect is measured as a function of increasing drug concentration in the plasma. The dose at which no effect is seen in the population is E_0. The dose of a drug required to produce a specified effect in 50% of the population is abbreviated as EC_{50}. The concentration associated with the maximal effect that can be produced by a drug is abbreviated as E_{max}. *(From Abdel-Rahman SM, Kearns GL. The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors,* Textbook of pediatric infectious disease, *ed 6, Philadelphia, 2009, WB Saunders, pp. 3156–3178, reproduced with permission.)*

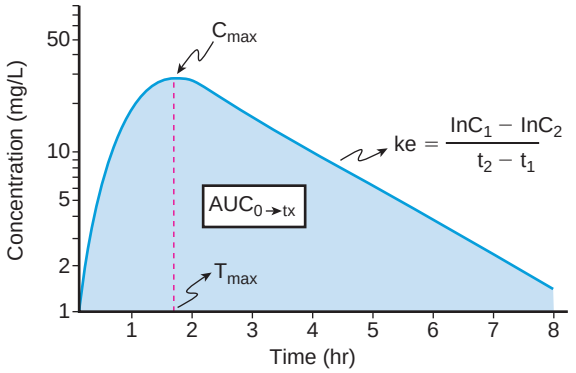

Figure 60-2 **Semilogarithmic plot of the plasma concentration vs time curve for a hypothetical drug following extravascular administration.** The area under the plasma level-time curve (AUC) is a concentration and time-dependent measure of systemic drug exposure. After administration, the drug is absorbed and reaches the maximal concentration (C_{max}) at its peak time (T_{max}). Following completion of drug absorption and distribution, plasma drug concentrations decline in an apparent monoexponential fashion whereby the slope of the apparent elimination phase represents the apparent elimination rate constant (ke). *(From Abdel-Rahman SM, Kearns GL. The pharmacokinetic-pharmacodynamic interface: determinants of anti-infective drug action and efficacy in pediatrics. In Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL, editors,* Textbook of pediatric infectious disease, *ed 6, Philadelphia, 2009, WB Saunders, pp. 3156–3178, reproduced with permission.)*

drug concentration. The point in the concentration–effect relationship where the observed effect represents 50% of the E_{max} is defined as EC_{50}, a common pharmacodynamic term used to compare concentration–effect relationships between patients (or research subjects) and between drugs that may be in a given drug class. In practice, E_{max} can be derived either from visual interpolation of the concentration–effect profile or via mathematical curve fitting of the relationship.

Because it is rarely possible to measure drug concentrations at or near the receptor, it is necessary to utilize a surrogate measurement to assess exposure–response relationships. In most instances, this surrogate is represented by the plasma drug concentration vs time curve. For drugs whose pharmacokinetic properties are best described by 1st-order (as opposed to zero-order or mixed-order) processes, a semilogarithmic plot of plasma drug concentration vs time data for an agent given by an extravascular route of administration (e.g., intramuscular, subcutaneous, intracisternal, peroral, transmucosal, transdermal, rectal) produces a pattern similar to that illustrated by Figure 60-2. The ascending portion of this curve represents a time during which the liberation of a drug from its formulation, dissolution of the drug in a biologic fluid (e.g., gastric or intestinal fluid, interstitial fluid; a prerequisite for absorption) and absorption of a drug are rate-limiting relative to its elimination. After the time (T_{max}) where maximal plasma concentrations (C_{max}) are observed, the plasma concentration decreases as metabolism and elimination become rate limiting; the terminal portion of this segment of the plasma concentration vs time curve being representative of drug elimination from the body. Finally, the area under the plasma concentration vs time curve (AUC), a concentration- and time-dependent parameter reflective of the degree of systemic exposure from a given drug dose, can be determined by integrating the plasma concentration data over time. By being able to characterize the pharmacokinetics of a specific drug, the clinician can use the data to individualize dosing regimens for patients who by virtue of development and/or disease, must have adjustments to either the dose and/or dosing interval so as to enable the production of the degree of systemic exposure associated with desired pharmacologic effects. For drugs where a therapeutic plasma concentration range and/or "target" systemic exposure (i.e., AUC) is known, a priori knowledge of pharmacokinetic parameters for a given population or patient within a population can facilitate the selection of a drug dosing regimen. When linked with information regarding the pharmacodynamic behavior of a drug and the status of the patient (e.g., age, organ function, disease state, concomitant medications), the application of pharmacokinetics affords the practitioner the ability to exercise some real degree of adaptive control over therapeutic decision making by enabling the selection of a drug and dosing regimen that has the greatest likelihood of producing both efficacy and safety.

THE IMPACT OF ONTOGENY ON DRUG DISPOSITION

Development represents a continuum of biologic events that enable adaptation, somatic growth, neurobehavioral maturation and eventually reproduction. The impact of development on the pharmacokinetics of a given drug is determined, to a great degree, by age-related changes in body composition and the acquisition of function in organs and organ systems, which are important in determining drug metabolism and excretion. Even though it is often convenient to classify pediatric patients on the basis of postnatal age for the provision of drug therapy (e.g., neonate 0-1 mo of age; infant 1-24 mo of age; children 2-12 yr of age; and adolescents 12-18 yr of age), it is important to recognize that the changes in physiology are not linearly related to age and may not correspond to these age-defined breakpoints. In fact, the most dramatic changes in drug disposition occur during the 1st 18 mo of life where the acquisition of organ function is most dynamic. Additionally, it is important to note that the pharmacokinetics of a given drug may be altered in pediatric patients consequent to intrinsic (e.g., gender, genotype, ethnicity, inherited diseases) or extrinsic (e.g., acquired disease states, xenobiotic exposure, diet, variability in therapeutic adherence) factors that may occur during the 1st 2 decades of life.

During development, certain stages of life profoundly influence drug response and disposition. Dramatic pharmacokinetic, pharmacodynamic, and psychosocial changes occur as preterm infants mature toward term, as infants mature through the 1st few years of life, and as children reach puberty and adolescence (Fig. 60-3). It is most useful to conceptualize the impact of ontogeny on drug disposition by considering its specific facets, namely, drug absorption, distribution, metabolism, and excretion, as well as ontogeny's impact on drug action (pharmacodynamics).

Drug Absorption

Absorption usually occurs via passive diffusion, but active transport or facilitated diffusion also may be necessary for drug entry into cells. Several physiologic factors affect this process, 1 or more of which may be altered in the face of certain disease states (e.g., inflammatory bowel disease, diarrhea) and, consequently, produce changes in drug bioavailability. The rate and extent of absorption can be significantly affected as a consequence of a child's normal growth and development.

Peroral Absorption

The most important factors that influence drug absorption from the gastrointestinal tract are related to the physiology of the stomach, intestine, and biliary tract (see Fig. 60-3*C* and Table 60-1). The rate and extent of peroral absorption of drugs depends primarily on the pH-dependent passive diffusion and motility of the stomach and intestinal tract as both of these factors will influence transit time of the drug. Gastric pH changes significantly throughout development with the highest (alkaline) values occurring during the neonatal period. In the fully mature neonate, the gastric pH ranges from 6-8 at birth and drops to 2-3 within a few hours of birth. However, after the 1st 24 hr of life, the gastric pH drifts upward because of the immaturity of the parietal cells. As the parietal cells mature, the gastric acid secretory capacity increases (pH decreases) over the 1st few months of life to reach consistent adult levels by 3-7 yr of age. As a result, the peroral bioavailability of acid-labile drugs, such as penicillin or ampicillin, is increased. In contrast, the absorption of weak organic acids (e.g., phenobarbital and phenytoin) is relatively decreased, a condition which may necessitate the administration of larger doses in the very young to achieve therapeutic plasma levels.

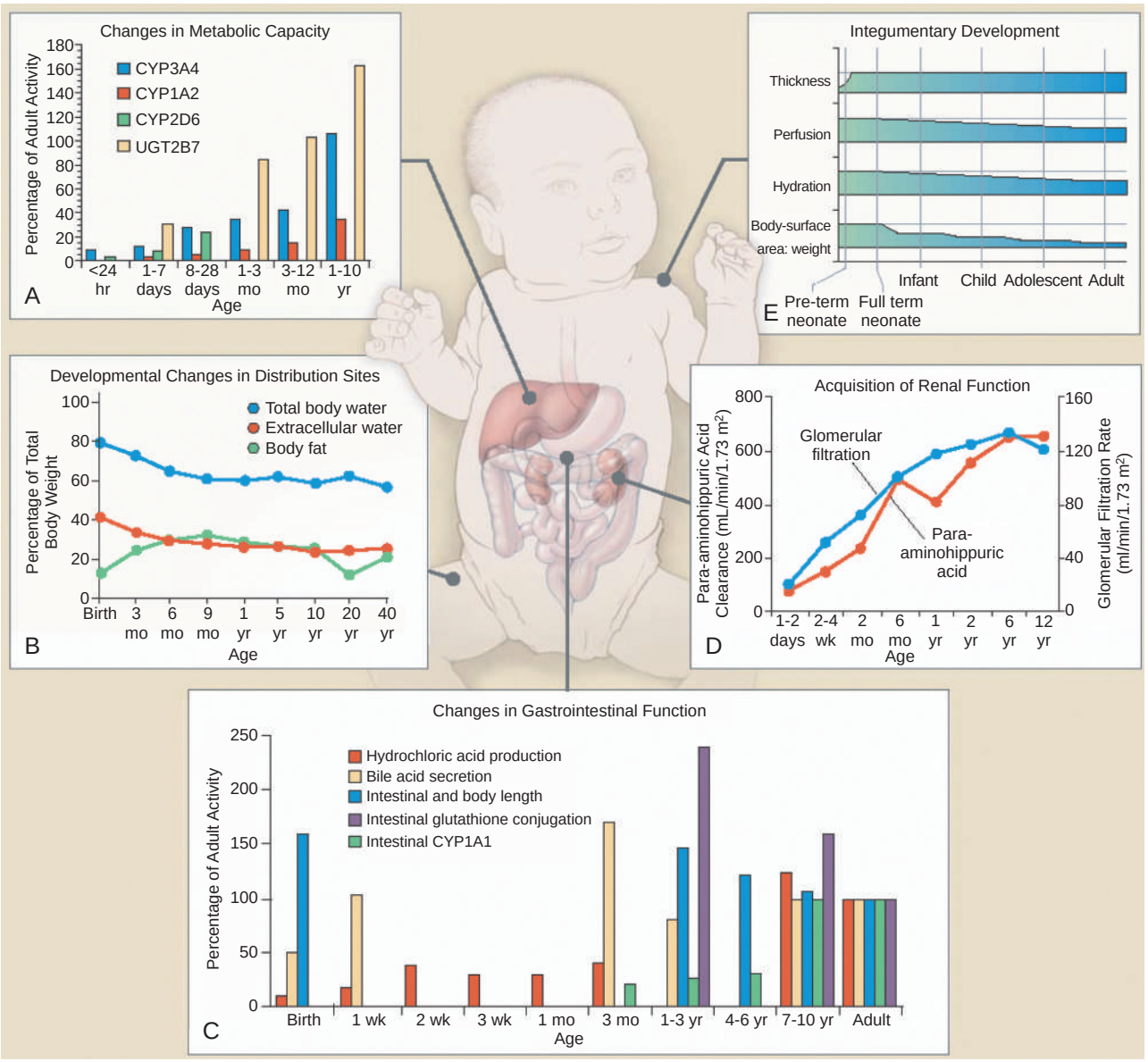

Figure 60-3 Developmental changes in physiologic factors that influence drug disposition in infants, children, and adolescents. Physiologic changes in multiple organ systems during development are responsible for age-related differences in drug disposition. **A**, As this graph shows, the activity of many cytochrome P450 (CYP) isoforms and a single glucuronosyltransferase (UGT) isoform is markedly diminished during the 1st 2 mo of life. In addition, the acquisition of adult activity over time is enzyme- and isoform-specific. **B,** This chart shows age-dependent changes in body composition that influence the apparent volume of distribution of drugs. Infants in the 1st 6 mo of life have markedly expanded total-body water and extracellular water, expressed as a percentage of total-body weight, as compared with older infants and adults. **C,** This graph summarizes the age-dependent changes in both the structure and function of the gastrointestinal tract. As with hepatic drug-metabolizing enzymes **(A)**, the activity of CYP1A1 in the intestine is low during early life. **D,** This chart shows the effect of postnatal development on the processes of active tubular secretion–represented by the clearance of paraaminohippuric acid and the glomerular filtration rate, both of which approximate adult activity by 6-12 mo of age. **E,** This graph shows age dependence in the thickness, extent of perfusion, and extent of hydration of the skin and the relative size of the skin-surface area (reflected by the ratio of body surface area to body weight). Although skin thickness is similar in infants and adults, the extent of perfusion and hydration diminishes from infancy to adulthood. *(From Kearns GL, Abdel-Rahman SM, Alander SW, et al, Developmental pharmacology—drug disposition, action, therapy in infants and children.* N Engl J Med *349:1157–1167, 2003. Reproduced with permission.)*

Gastric emptying time is prolonged throughout infancy and childhood consequent to reduced motility which may retard drug passage into the intestine where the majority of absorption takes place. Gastric emptying rates reach or exceed adult values by 6-8 mo of life. As such, intestinal motility is important for the rate of drug absorption and, like other factors, is dependent on the age of the child. Consequently, the rate of absorption of drugs with limited water solubility (e.g., phenytoin, carbamazepine) can be dramatically altered consequent to changes in gastrointestinal motility. In older infants and young children, more rapid rates of intestinal drug transit can reduce the bioavailability for some drugs (e.g., phenytoin) and/or drug formulations (e.g., sustained-release) by reducing their residency time at the absorption surfaces in the small intestine.

Lastly, neonates, particularly premature neonates, have a reduced bile acid pool and biliary function resulting in a decreased ability to solubilize and absorb lipophilic drugs. Even though biliary function

Table 60-1 Developmental Alteration in Intestinal Drug Absorption

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Gastric pH	>5	4-2	Normal (2-3)
Gastric emptying time	Irregular	Increased	Slightly increased
Intestinal motility	Reduced	Increased	Slightly increased
Intestinal surface area	Reduced	Near adult	Adult pattern
Microbial colonization	Reduced	Near adult	Adult pattern
Biliary function	Immature	Near adult	Adult pattern

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

Table 60-2 Influence of Ontogeny on Drug Absorption

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Oral absorption	Erratic	Increased	Near adult
Intramuscular absorption	Variable	Increased	Near adult
Percutaneous absorption	Increased	Increased	Near adult
Rectal absorption	Very efficient	Efficient	Near adult

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

develops in the 1st few months of life, it may be difficult for the neonate and young infant to absorb fat-soluble vitamins as low concentrations of bile acids are necessary for their absorption.

Extravascular Drug Absorption

With a bioavailability of 100%, intravenous drug administration is assumed to be the most dependable and accurate route for drug delivery. Absorption of drugs from tissues and organs (e.g., intramuscular, transdermal, and rectal) can also be affected by development (Table 60-2). Intramuscular blood flow changes with age, which can result in variable and unpredictable absorption. Reduced muscular blood flow in the 1st few days of life, the relative inefficiency of muscular contractions (useful in dispersing an IM drug dose), and an increased percentage of water per unit of muscle mass may delay the rate and/or extent of drugs given intramuscularly to the neonate. Muscular blood flow increases into infancy and, consequently, the bioavailability of drugs given by the IM route is comparable to that seen in children and adolescents.

In contrast, mucosal permeability (rectal and buccal) in the neonate is increased and thus, may result in enhanced absorption by this route. Transdermal drug absorption in the neonate and very young infant is increased as the result of a more hydrated stratum corneum (see Fig. 60-3*E*). In addition, the ratio of body surface area to body weight is greater in infants and children compared to adults. Collectively, these developmental differences may predispose the child to increased exposure and risk for toxicity for drugs/chemicals placed on the skin (e.g., silver sulfadiazine, topical corticosteroids, benzocaine, diphenhydramine) with higher likelihood of occurrence during the 1st 12 mo of life.

Normal developmental differences in drug absorption from most all extravascular routes of administration can influence the dose-plasma concentration relationship in a manner sufficient to alter pharmacodynamics. It should be recognized that the presence of disease states which influence a physiologic barrier for drug absorption and/or the time that a drug spends at a given site of absorption can further influence drug bioavailability and effect.

Drug Distribution

Drug distribution is influenced by a variety of drug-specific physiochemical factors (e.g., molecular size and weight, apparent partition coefficient, pK_a), the presence of drug transporters, blood/tissue protein binding, blood and tissue pH and perfusion. However, age-related changes to drug distribution are primarily related to developmental changes in body composition and the quantity of plasma proteins capable of drug binding. Age-dependent changes in the relative sizes of body water (total body water [TBW], extracellular water) and fat compartments may alter the apparent volume of distribution (VD) for a given drug. The absolute amounts and distribution of body water and fat depend on a child's age and nutritional status. As well, certain disease states (e.g., ascites, dehydration, burn injuries, disruption of the integument involving large surface area) can influence body water compartment sizes and thereby, further impact the VD for certain drugs.

Newborns have a much higher proportion of body mass in the form of water (~75% TBW) than older infants and children (see Fig. 60-3*B*). As well, the percent of extracellular water changes (decreases) from the newborn stage (approximately 45%) into adulthood (approximately 20-30%). In fact, the increase of TBW in the neonate is attributable to extracellular water. The reduction in TBW is rapid in the 1st year of life with adult values (approximately 55%) achieved by approximately 12 yr of age. In contrast, the percentage of intracellular water as a function of body mass remains stable from the 1st months of life through adulthood. The impact of developmental changes in body water spaces are exemplified by drugs such as the aminoglycoside antibiotics; compounds that distribute predominantly throughout the extracellular fluid space and have a higher VD (0.4-0.7 L/kg) in neonates and infants as compared to adults (0.2-0.3 L/kg).

Body fat percentage and composition increase during normal development. The body fat percentage in a neonate is approximately 16% (57% water and 35% lipid). Despite the relatively low body fat content in the neonate, it is important to note that the lipid content in the developing central nervous system (CNS) is high, which has implications for the distribution of lipophilic drugs and their CNS effects (e.g., propranolol) during this time period. The body fat percentage tends to increase up to approximately 10 yr of age and then changes composition with respect to puberty and sex to approach adult body fat composition (26% water and 71% lipid). In addition, a sex difference exists as the child ages into adolescence. The total body fat in males is reduced by 50% between 10 and 20 yr of life as compared to females in whom the reduction is approximately 25%.

Albumin, total proteins, and total globulins (e.g., α_1-acid glycoprotein) are the most important circulating proteins responsible for drug binding in plasma. The absolute concentration of these proteins is influenced by age, nutrition, and disease (Table 60-3). The concentrations of most all circulating plasma proteins are reduced in the neonate and young infant (approximately 80% of adult) and reach adult values by 1 year of age. A similar pattern of maturation is observed with α_1-acid glycoprotein (an acute-phase reactant capable of binding basic drugs) where neonatal plasma concentrations are approximately 3 times lower than in maternal plasma and attain adult values by approximately 1 year of age.

The extent of drug binding to proteins in the plasma may influence distribution characteristics. Only free, unbound drug can be distributed from the vascular space into other body fluids and, ultimately, to tissues where drug–receptor interaction occurs. Drug protein binding depends on a number of age-related variables, which can include the absolute amount of proteins and their available binding sites; the conformational structure of the binding protein (e.g., reduced binding of

Table 60-3 Factors Influencing Drug Binding in Pediatrics

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Plasma albumin	Reduced	Near adult	Near adult
Fetal albumin	Present	Absent	Absent
Total proteins	Reduced	Decreased	Near adult
Total globulins	Reduced	Decreased	Near adult
Serum bilirubin	Increased	Normal	Adult pattern
Serum free fatty acids	Increased	Normal	Adult pattern

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

Table 60-4 Impact of Development on Drug Metabolism

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Cytochrome P450 activity	Reduced	Increased	Slightly increased
Phase II enzyme activity	Reduced	Increased	Near adult
Blood esterase activity	Reduced	Normal (by 1 yr)	Adult pattern
Presystemic enzyme activity	Reduced	Increased	Near adult

Direction of alteration given relative to expected normal adult pattern.
Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

acidic drugs to glycated albumin in patients with poorly controlled diabetes mellitus); the affinity constant of the drug for the protein; the influence of pathophysiologic conditions that either reduce circulating protein concentrations (e.g., ascites, major burn injury, chronic malnutrition, hepatic failure) or alter their structure (e.g., diabetes, uremia); and the presence of either endogenous or exogenous substances, which may compete for protein binding.

Developmentally associated changes in drug binding can occur as a consequence of altered protein concentrations and/or binding affinity. For example, circulating fetal albumin in the neonate has significantly reduced binding affinity for acid drugs such as phenytoin, which is extensively (94-98%) bound to albumin in adults as compared to 80-85% in the neonate. The resultant 6-8–fold difference in the free fraction can result in CNS adverse effects in the neonate when total plasma phenytoin concentrations are within the generally accepted "therapeutic range" (10-20 mg/L). The importance of reduced drug-binding capacity of albumin in the neonate is exemplified by interactions between endogenous ligands (e.g., bilirubin, free fatty acids) and drugs with greater binding affinity (e.g., the ability of sulfonamides to produce kernicterus).

Drug transporters, such as P-glycoprotein, MDR1, and MDR2 (multidrug resistance 1 or 2), can influence drug distribution. These drug transporters can markedly influence the extent to which drugs cross membranes in the body and whether drugs can penetrate or are secreted from the target sites (inside cancer cells or microorganisms, or crossing the blood–brain barrier). Thus, drug resistance to cancer chemotherapy, antibiotics, or epilepsy may be conferred by these drug transport proteins and their effect on drug distribution. While there are limited data on the ontogeny of drug transport proteins, available information demonstrates their presence as early as 22 wk gestation and low levels in the neonatal period which appear to rapidly increase to adult values by 1-2 yr of age.

Drug Metabolism

Metabolism reflects the biotransformation of an endogenous or exogenous molecule by 1 or more enzymes to moieties that are more hydrophilic and thus, can be more easily eliminated by excretion, secretion or exhalation. Although metabolism of a drug generally reduces its ability to produce a pharmacologic action, it can result in metabolites that have significant potency, thereby contributing to the overall pharmacodynamic profile of a drug (e.g., biotransformation of the tricyclic antidepressant amitriptyline to nortriptyline; cefotaxime to desacetylcefotaxime; theophylline to caffeine) or in some instances, can produce significant toxicity (e.g., biotransformation of codeine to morphine). In the case of prodrugs (e.g., zidovudine, enalapril, fosphenytoin) or some drug salts/esters (e.g., cefuroxime axetil, clindamycin phosphate), biotransformation is required to produce a pharmacologically active moiety. Finally, for some drugs, cellular injury and associated adverse reactions are the result of drug metabolism (e.g., acetaminophen hepatotoxicity, Stevens-Johnson syndrome associated with sulfamethoxazole).

The primary organ responsible for drug metabolism is the liver, although the kidney, small intestine, lung, adrenals, blood (phosphatases, esterases) and skin can also biotransform certain compounds. Drug metabolism occurs primarily in the endoplasmic reticula of cells via 2 general classes of enzymatic processes: **phase I,** or nonsynthetic, and **phase II,** or synthetic, reactions. Phase I reactions include oxidation, reduction, hydrolysis, and hydroxylation reactions, whereas phase II reactions primarily involve conjugation with an endogenous ligand (e.g., glycine, glucuronide, glutathione or sulfate). As illustrated by Figure 60-3*A*, many drug metabolizing enzymes demonstrate an ontogenic profile with generally low activity present at birth and maturation over a period of months to years (Table 60-4).

Even though there are many enzymes that are capable of catalyzing the biotransformation of drugs and xenobiotics, the quantitatively most important are represented by the cytochromes P450 (CYPs), a supergene family with at least 16 primary enzymes. The specific CYP isoforms responsible for the majority of human drug metabolism are represented by CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. These enzymes represent the products of genes that in some instances, are polymorphically expressed with allelic variants producing enzymes generally resulting in either no or reduced catalytic activity (a notable exception being the *17 allele of CYP2C19 which conveys increased activity) (see Chapter 59). At birth, the concentration of drug-oxidizing enzymes in fetal liver (corrected for liver weight) appears similar to that in adult liver. However, the activity of these oxidizing enzyme systems is reduced, which results in slow clearance (and prolonged elimination) of many drugs that are substrates for them (e.g., phenytoin, caffeine, diazepam, and many others). Postnatally, the hepatic CYPs appear to mature at different rates. Within hours after birth, CYP2E1 activity increases rapidly with CYP2D6 being detectable soon thereafter. CYP2C (CYP2C9 and CYP2C19) and CYP3A4 are present within the 1st mo of life, and a few months later, CYP1A2. CYP3A4 activity in young infants may exceed that observed in adults as reflected by the clearance of drugs that are substrates for this enzyme (e.g., cyclosporine, tacrolimus).

Compared to phase I drug-metabolizing enzymes, the impact of development on the activity of phase II enzymes (acetylation, glucuronidation, sulfation) is not characterized as well. Generally speaking, phase II enzyme activity is decreased in the newborn and increases into childhood. For example, conjugation of compounds metabolized by isoforms of glucuronosyltransferase (UGT; e.g., morphine, bilirubin, and chloramphenicol) is reduced at birth but can exceed adult values by 3-4 yr of age. Also, the ontogeny of UGT expression is isoform specific. Newborns and infants primarily metabolize the commonly used analgesic acetaminophen by sulfate conjugation whereas the UGT isoforms responsible for its glucuronidation (UGT1A1 and UGT1A9) have markedly reduced activity. As children age, the

glucuronide conjugate becomes predominant in the metabolism of therapeutic doses of acetaminophen. In contrast, the glucuronidation of morphine (a UGT2B7 substrate) can be detected as early as 24 wk gestation.

The activity of certain hydrolytic enzymes, including blood esterases, is also reduced during the neonatal period. The reduced activity of these plasma esterases in the newborn may account for the delayed metabolism (prolonged effect) of local anesthetics in the neonate. In addition, this may account for the prolonged effect that cocaine has on the fetus with prenatal exposures. Adult esterase activity is achieved by 10-12 mo of age.

The development of presystemic clearance or "1st-pass" metabolism is unclear given the involvement of multiple enzymes and transporters in the small intestine, many of which have patterns of developmental expression that may be more or less concordant. However, given that the activity of almost all drug metabolizing enzymes is markedly reduced in the neonate, the bioavailability of drugs given by the peroral route that may be subjected to significant presystemic clearance in older children and adults would appear to be markedly increased during the 1st days to weeks of life. It is important for the clinician to recognize that estimates of bioavailability for a host of drugs available in reference texts and therapeutic compendia are most often derived from studies conducted in young adults. Consequently, this information may not be predictive of the rate and/or extent of peroral drug absorption in a neonate or infant.

Finally, with regard to the impact of development on drug metabolism, it must be recognized that most therapeutic drugs are polyfunctional substrates for a host of enzymes and/or transporters. It is the isoform specific ontogenic profile (see Fig. 60-3) that must be considered in the context of deducing how development per se can affect the metabolic portion of drug clearance. True developmental dependence of drug clearance (CL) must also consider the role of pharmacogenetic constitution on the activity of enzymes/transporters (see Chapter 59) and the impact of ontogeny on the nonmetabolic routes (e.g., renal drug excretion, salivary and biliary drug excretion, pulmonary drug excretion) that contribute to the overall drug clearance (i.e., Total CL = $CL_{hepatic} + CL_{renal} + CL_{nonrenal}$).

Renal Drug Elimination

The kidney is the primary organ responsible for the excretion of drugs and their metabolites. The development of renal function begins during early fetal development and is complete by early childhood (see Fig. 60-3*D*; Table 60-5). Total renal drug clearance *(CL_{renal})* can be conceptualized by considering the following equation:

$$CL_{renal} = (GFR + ATS) - ATR$$

where glomerular filtration rate *(GFR)*, active tubular secretion *(ATS)*, and active tubular reabsorption *(ATR)* of drugs can contribute to overall clearance. As is true for hepatic drug metabolism, only free (unbound) drug and/or metabolite can be filtered by a normal glomerulus and/or either secreted or reabsorbed via a renal tubular transport proteins.

Renal clearance is limited in the newborn by both anatomical and functional immaturity of the nephron unit. In both the term and preterm neonate, GFR averages 2-4 mL/min/1.73 m^2 at birth. During the 1st few days of life, a drop in renal vascular resistance occurs which results in a net increase in renal blood flow and a re-distribution of intrarenal blood flow from a predominantly medullary to a cortical distribution. All of these changes are associated with a commensurate increase in GFR. In term neonates, GFR increases rapidly over the 1st few months of life and approaches adult values by 10-12 mo of life (see Fig. 60-3*D*). The rate of GFR acquisition is blunted in preterm neonates consequent to continued nephrogenesis, which occurs in the early postnatal period. In young children between 2 and 5 yr of age, GFR may exceed adult values, especially during periods of increased metabolic demand (e.g., during a fever).

In addition, there is a relative glomerular/tubular imbalance because of a more advanced maturation of glomerular function. Such an imbalance may persist up to 6 mo of age and may account for the observed decrease in the ATS of drugs commonly used in neonates and young infants (e.g., β-lactam antibiotics). Finally, there is some evidence that ATR is reduced in neonates and that it appears to mature at a slower rate than the GFR.

Altered renal drug clearance in the newborn and infants result in the different dosing recommendations commonly seen in pediatrics. The aminoglycoside antibiotic gentamicin provides an illustrative example. In adolescents and young adults with normal values for GFR (85-130 mL/min/1.73 m^2), the recommended dosing interval for the drug is 8 hr. In young children who may have a GFR >130 mL/min/1.73 m^2, a gentamicin dosing interval of every 6 hr may be necessary in selected patients who have serious infections that require maintaining steady-state peak and trough plasma concentrations near the upper boundary of the recommended therapeutic range. In contrast, to maintain "therapeutic" gentamicin plasma concentrations in neonates during the 1st few weeks of life, a dosing interval of 18-24 hr is required.

The impact of developmental differences in GFR on the elimination characteristics of a given drug can be assessed by estimating the apparent elimination rate constant (Kel) for a drug by using the following equation:

$$\text{Kel (in reduced renal function)} = \text{Kel}_{normal} \cdot \{[(\text{GFR}_{observed}/\text{GFR}_{normal}) - 1] \cdot \text{Fel}\} + 1$$

where the *Fel* represents the fraction of the drug excreted unchanged in an adult with normal renal function, $GFR_{observed}$ is the value calculated (from creatinine clearance or an age-appropriate estimation equation) for the patient (in mL/min/1.73 m^2), GFR_{normal} is the average value considered for a healthy adult (i.e., 120 mL/min/1.73 m^2) and Kel_{normal} is estimated from the average elimination $T_{½}$ (terminal half-life) for a drug taken from the medical literature using the following equation:

$$\text{Kel}_{normal}\ [\text{hr}^{-1}] = 0.693/T_{½normal}\ [\text{hr}]$$

Table 60-5 Impact of Development on Renal Drug Elimination

PHYSIOLOGIC ALTERATION	NEONATE	INFANTS	CHILDREN
Glomerular filtration	Reduced	Normal (by 1 year)	Adult pattern
Active tubular secretion	Reduced	Near normal	Adult pattern
Active tubular reabsorption	Reduced	Near normal	Adult pattern
Active drug excretion	Reduced	Near normal	Adult pattern
Passive drug excretion	Reduced	Increased	Adult pattern
Excretion of basic drugs	Increased	Increased	Near normal

Direction of alteration given relative to expected normal adult pattern.

Data from Morselli PL. Development of physiological variables important for drug kinetics. In: Morselli PL, Pippenger CE, Penry JK, editors. Antiepileptic drug therapy in pediatrics. *New York, 1983, Raven Press, pp. 1–12.*

Likewise, the elimination $T_{½}$ for a drug in patients with reduced renal function can be estimated as follows:

$$T_{½} \text{ (in reduced renal function)} = 0.693/\text{Kel (in reduced function)}$$

An estimate of the drug elimination $T_{½}$ in patients with reduced renal function with knowledge of the desired interdose excursion in steady-state plasma concentrations can provide an ability to determine the desired drug dosing interval.

Impact of Ontogeny on Pharmacodynamics

Although, it is generally accepted that developmental differences in drug action exist, there is little evidence of true age-related pharmacodynamic variation among children of differing age groups and adults. Drug action is typically mediated by interaction of a small molecule with 1 or more receptors, which may be located either on or in a cell. Drug effect is mediated at the receptor by 4 main biochemical mechanisms involved in cell signaling. Binding of the receptors on the cell surface or within the cell activate downstream pathways that mediate a specific cellular action. Some receptors act as enzymes whereby, upon ligand binding, the enzyme phosphorylates downstream effector proteins, thereby activating or inhibiting a cellular signal. Guanosine triphosphate–binding regulatory protein, also known as G-protein–coupled receptors, are known targets for many drugs. Upon ligand binding, guanosine triphosphate binds to and activates the G-protein, in turn allowing it to activate second messenger regulatory proteins in the cell, again mediating cellular signaling. Other receptors mediate their actions through ion channels whereby, upon ligand binding, the cell's membrane potential or ionic composition is altered allowing cellular activation or inhibition. Lastly, some receptors act as transcription factors that, when bound by a ligand, transcription of specific genes within the cell are activated. Drug action is concentration dependent with onset and offset generally associated with appearance and disappearance, respectively, of the drug at the receptor(s) in an amount that is sufficient to initiate the cascade of biologic effects that terminate in drug action (see Fig. 60-1). The minimum effective concentration of a drug is that observed with the immediate onset of effect, whereas the duration of action is predicated upon the maintenance of drug concentrations at the receptor within a range that is associated with the desirable pharmacologic action(s). Receptor binding by a drug may have varying consequences. Drugs that are **agonists** bind to and activate the receptor, directly or indirectly achieving the desired effect. An agonist binding to a receptor results in the same biologic effect as binding of the endogenous ligand. **Partial agonist** binding results in activation of the receptor but maximal effect is not achieved even in the presence of receptor saturation. **Antagonists** bind to a receptor preventing binding of other molecules thereby preventing activation of the receptor.

Age-related pharmacokinetic variation resulting in altered drug disposition may result in less or more drug being available at the receptor(s) consequent to whether drug clearance is decreased or increased relative to values in adults. The resultant alteration in the dose–concentration profile may result in an attenuated (ineffective) or exaggerated (toxicity) response in children, which is especially relevant for drugs with a narrow therapeutic index (Fig. 60-4). Thus, in some circumstances, apparent developmental differences in drug response/effect may be simply explained on pharmacokinetic basis.

There is evidence supporting developmental differences in receptor number, density, distribution, function, and ligand affinity for some drugs. As there are limited data from humans, much of what is known has been derived from animal studies. In the CNS, unique developmental aspects of drug–receptor interaction affect therapeutic efficacy of both analgesic and sedative drugs in neonates. For example, the number of γ-aminobutyric acid receptors, which mediates inhibitory signal transduction in the CNS, is reduced in newborns compared to adults. Functional differences have also been observed between neonatal and adult brain upon γ-aminobutyric acid receptor activation. These changes may explain observed differences in dosing of drugs such as midazolam in infants, and in part may explain seizures experienced by infants upon benzodiazepine exposure. Another example

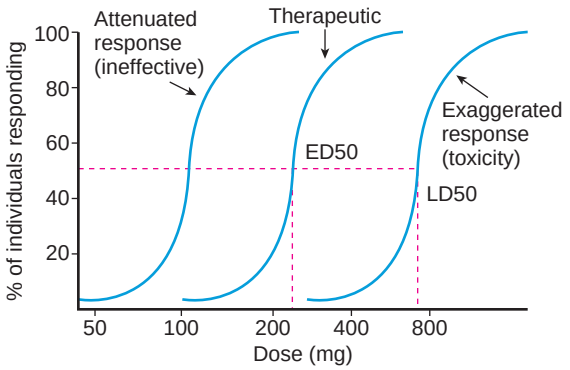

Figure 60-4 Quantal dose–effect curve. Age-related pharmacokinetic variation may result in alterations in drug concentration at the receptor resulting in ineffective, therapeutic, or toxic results. LD_{50} represents the dose at which 50% of the population is lethal. The ratio of the LD_{50} to the ED_{50} is an indication of the therapeutic index, which is a reflection of drug potency relative to its concentration.

in the CNS is illustrated by the μ-opioid receptor whereby receptor number is reduced in newborns and receptor distribution also differs between newborns and adults.

For the clinician, the consideration of age-dependent differences in pharmacodynamics is particularly relevant when they are associated with adverse drug reactions (e.g., higher incidence of valproic acid-associated hepatotoxicity in young infants; greater frequency of paradoxical CNS reactions to diphenhydramine in infants; weight gain associated with use of atypical antipsychotic drugs in adolescents) or when drugs have a narrow therapeutic index. This latter situation is exemplified by the immunomodulatory agent cyclosporine and the anticoagulant warfarin. In children younger than 1 yr old, the mean concentration of cyclosporine required to inhibit monocyte proliferation and the expression of the inflammatory cytokine interleukin-2 is less than required in older children. The age-associated pharmacodynamics of warfarin observed in children with congenital heart disease is, to a great degree, associated with developmental differences in serum concentrations of vitamin-K dependent coagulation factors (II, VII, IX, X) between children and adults. Developmental differences in drug action have also been observed between prepubertal children and adults with regard to warfarin action. Prepubertal children compared to adults exhibit a more profound response, demonstrated by lower protein C concentration, prothrombin fragments 1 and 2, and greater rise in international normalized ratio, to comparable doses of warfarin. Thus, when age-dependent pharmacodynamics of a given drug are evident, the use of simple allometric approaches for "scaling" the pediatric dose from the usual adult dose may not produce the desired pharmacologic effects.

Surrogate End Points

The assessment of pharmacodynamics in human infants and children has been hampered historically by a relative inability to use invasive methods for the direct assessment of drug effect. As a result, surrogate end points and biomarkers have been explored and, in some cases, have been successfully used to evaluate the impact of ontogeny on pharmacodynamics.

Biomarkers and surrogate end points (markers) are ideally simple, reliable, inexpensive, and easily obtainable measures of a biologic response or disease phenotype that can be used to facilitate either clinical research or patient care. **Biomarkers** have been defined by the U.S. National Institutes of Health as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." A **surrogate end point** is defined "as a biomarker that is intended to substitute for a specific clinical end point. A surrogate end point is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or

other scientific evidence." Reliable surrogate end points predict a specific physiologic event(s) (e.g., intraesophageal pH to assess gastroesophageal reflux), which may be utilized diagnostically, prognostically, or in predicting a specific drug response (therapeutic, subtherapeutic, or adverse) or potentially, the impact of ontogeny on pharmacodynamics. Specific examples of surrogate end points used in pediatric pharmacology include measurement of esophageal pH to assess the action of prokinetic or acid-modifying drugs, use of gastric scintigraphy and stable isotope-labeled compounds (e.g., ^{13}C-acetate, ^{13}C-octanoic acid) to assess gastric emptying rate, and pulmonary function tests (e.g., forced expiratory volume at 1 sec) to evaluate the effect(s) of drugs on pulmonary function in patients with conditions such as asthma and cystic fibrosis. Examples of biomarkers that have been used in pediatric studies to assess drug disposition or effect include hemoglobin A_{1C} plasma concentration (to assess efficacy of peroral hypoglycemic agents); urinary leukotriene concentrations (to assess effects of nonsteroidal antiinflammatory drugs); minimal inhibitory and minimal bacteriocidal concentrations of drugs to selected antiinfective agents; and the use of selective genotyping tests (e.g., projection of therapeutic warfarin dose requirement by use of *CYP2C9* [gene controlling expression of the enzyme primarily responsible for warfarin metabolism] and *VKORC1* [gene controlling expression of enzyme primarily involved in regulating warfarin effects on vitamin K dependent clotting factors] genotyping.

Additional Considerations in Pediatric Therapeutics

The use of adult-dose modification for pediatric dose prediction is based on the association between body size/composition and the physiologic determinants of drug disposition across the spectrum of age. Although these approaches may have some potential clinical utility in children older than 8 yr of age and in adolescents whose organ function and body composition approximates that of young adults, their utility is severely limited in neonates, infants, and children younger than 2 yr of age in whom ontogeny produces dramatic differences in drug disposition. This is especially problematic for therapeutic drugs whose doses cannot be easily individualized using patient-specific pharmacokinetic data obtained from therapeutic drug monitoring.

More than 20 different approaches for initial selection of a drug dose for pediatric patients have been described. The majority of these utilize either total body weight (BW) or body surface area (BSA) as surrogates, which reflect the developmental changes of either body composition or organ function that collectively are the major determinants of drug disposition. Dose selection based on BW or BSA will generally produce similar relationships between drug dose and resultant plasma concentration, except for those drugs whose apparent VD corresponds to the extracellular fluid pool (i.e., VD < 0.3 L/kg) for which a BSA-based approach is preferable. In contrast, for drugs whose apparent VD exceeds the extracellular fluid space (i.e., VD ≥ 0.3 L/kg), a BW-based approach for dose selection is preferable, which is the most frequently used method in pediatrics. When the pediatric dose for a given drug is not known, these principles can be used to best approximate a proper dose for the initiation of treatment as is illustrated by the following equations:

$$\text{Child dose (if VD} < 0.3\ \text{L/kg)} = (\text{child BSA in m}^2/1.73\ \text{m}^2) * \text{adult dose}$$

$$\text{Infant dose (if VD} \geq 0.3\ \text{L/kg)} = (\text{infant BW in kg}/70\ \text{kg}) * \text{adult dose}$$

It should be noted that this approach assumes that the child's weight, height, and body composition are age appropriate and normal, and that the "reference" normal adult has a BW and BSA of 70 kg and 1.73 m^2, respectively. It is useful only for selection of dose size and does not offer information regarding dosing interval because the equations contain no specific variable that describes potential age-associated differences in drug clearance.

In neonates and young infants with developmental immaturity in either GFR and/or ATS, it is often necessary to adjust the "normal" dosing interval (i.e., that used for older infants and children who have attained developmental competence of renal function) for drugs with significant (i.e., >50%) renal elimination so as to prevent excessive drug accumulation (and possible associated toxicity) with administration of multiple doses. To accomplish this therapeutic goal, it is necessary to estimate the apparent $T_{½}$ of the drug.

Drug-Level Monitoring

Drug response (either therapeutic or toxic) occurs only as a consequence of drug exposure. Clinically, systemic drug exposure is most commonly evaluated through assessing the plasma drug concentration; a surrogate measurement for a drug reaching its pharmacologic receptor(s).

In the patient, drug-level monitoring can be used to facilitate 2 approaches for evaluating the dose–concentration–effect relationship; therapeutic drug monitoring and pharmacokinetic-based dose individualization (clinical pharmacokinetics). **Therapeutic drug monitoring** largely entails a retrospective, reactive approach whereby drug concentrations in plasma (primarily) or other biologic fluids are measured at some point during either a constant rate intravenous infusion or during a dosing interval for drugs given by intermittent dosing schedules. These levels are then compared with those that are "desired" for a given drug based on published information and used to adjust the dose/dosing regimen in a quasi-empiric fashion. In using a therapeutic drug-monitoring approach, it should be recognized that for many drugs that are therapeutically monitored in the clinical setting (e.g., aminoglycoside antibiotics, vancomycin, phenytoin, phenobarbital, cyclosporine, tacrolimus, mycophenolate mofetil, selected antiretroviral drugs, acyclovir), "desired" plasma concentrations are generally determined from studies in adult patients in whom drug disposition and disease states may be quite different from those in infants and children.

In contrast to therapeutic drug monitoring, **clinical pharmacokinetics** represents a prospective, proactive approach where plasma drug concentrations are used to estimate pharmacokinetic parameters (e.g., apparent Kel, elimination $T_{½}$, apparent VD, total plasma clearance, AUC) which are then used to calculate a dosing regimen required to attain a desired level of systemic exposure (e.g., AUC, steady-state peak and/or trough plasma drug concentrations) that would portend a desired pharmacologic response. Of these 2 approaches, the use of drug-level data for performing clinical pharmacokinetics provides the most optimal approach for individualizing dose/dosing regimen and maintaining some adaptive control over the dose-concentration- effect relationship. This approach is particularly useful for patients who by virtue of their age and/or disease states, may have "abnormal" pharmacokinetics. Approaches used to enable the performance of clinical pharmacokinetics include the manual use of established formulas for calculating pharmacokinetic parameters (generally using a simple 1 compartment open model consequent to the few number of plasma drug-level observations obtained in the context of clinical patient care) or computer-based algorithms (e.g., Bayesian estimation, population-based pharmacokinetic approaches).

Common to both of the aforementioned approaches is the need to accurately assess plasma drug concentrations in a given patient. Figure 60-5 represents a hypothetical general steady-state plasma concentration vs time profile for a drug given by an extravascular route. It is provided to illustrate the following general principles that should be recognized and/or followed when plasma drug-level monitoring is used in patients as a "tool" to individualize drug treatment:

- When a drug reaches a pharmacokinetic steady state (a period corresponding to 5 times the apparent elimination $T_{½}$ for a given drug), both the excursion between the peak (C_{max}) and trough (C_{min}) plasma concentration and the AUC are identical between dose intervals provided that (1) the dose is not changed; (2) an exact dose-to-dose interval is maintained for drug administration; and (3) the route or rate of drug administration between dosing intervals has not changed.
- Steady-state plasma drug concentrations provide the best surrogate for assessing exposure–response relationships for a given drug. When used to support clinical pharmacokinetic approaches for dose regimen design, they provide the most accurate estimation of patient-specific pharmacokinetic parameters. Plasma

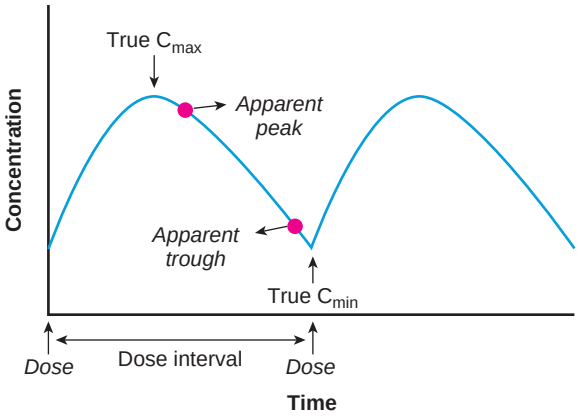

Figure 60-5 **Plasma concentration vs time profile for a hypothetical drug at steady state.** When dose size, route of administration, time of administration, and dosing interval remain constant, the resultant true peak (C_{max}) and trough (C_{min}) plasma concentrations and AUC from dose to dose are identical. Apparent values for C_{max} and C_{min} are denoted to illustrate the potential difference from true values that can result when the actual times for obtaining samples for either therapeutic drug monitoring or clinical pharmacokinetic applications are not realized.

concentrations assessed before the attainment of steady state can be useful for evaluating exaggerated drug response or predicting eventual steady-state drug levels/exposure.

To reliably interpret any drug plasma concentration, it is imperative that the clinician know and consider (1) the expected pharmacokinetic profile for a given drug (e.g., time after dosing required for completion of drug absorption (for extravascularly administered drugs) and distribution); (2) the exact time that the drug was administered; (3) for drugs given by intravenous infusion, the total duration of infusion (including time required to flush the dose from the intravenous tubing); (4) pertinent limitations of the analytical method used to measure the plasma drug level (e.g., range of linearity, potential for analytical interference from concomitant drugs); (5) the method used to obtain the blood specimen(s) used for plasma level determination (e.g., venous puncture vs cutaneous puncture; use of a vascular catheter that was different from the catheter used for drug administration); (6) whether the blood specimen was adequate for accurate drug level measurement (e.g., sufficient volume, presence or absence of hemolysis or lipemia); and (7) the *exact* time that the blood specimens were obtained in relationship to the time of drug administration and the drug dosing interval. This last point is illustrated by Figure 60-5, which denotes the "true" peak (C_{max}) and trough (C_{min}) plasma concentrations in relationship to apparent values; a situation that frequently occurs when "peak" and "trough" blood levels are ordered and nursing/phlebotomy procedures allow some period of leeway as to when they can be obtained. When such a discrepancy is realized and the exact timing of the samples relative to dose administration is known, corrections can be made to insure that pharmacokinetic parameters estimated from the data are accurate. If such a discrepancy is not realized, errant parameter estimation and dose regimen calculation/determination may result, thereby compromising either the safety or efficacy of drug treatment.

Drug Formulation and Administration

One of the more unique challenges in pediatric therapeutics is the **drug formulation** itself. Despite the increasing sensitivity for the need to study drugs in children before they are used in children and to have available "pediatric-friendly" formulations, many drug products that are formulated only for use in adults are routinely given to pediatric patients. Their use can result in inaccurate dosing (e.g., administration of a fixed dose to children with widely varying body weights), loss of desired performance characteristics of the formulation (e.g., crushing a sustained-release tablet or cutting a transdermal patch) and the exposure of infants and children to excipients (e.g., binding agents, preservatives) in amounts capable of producing adverse effects.

Peroral Drug Administration

One of the principal determinants of peroral drug administration in children is the ability to actually get the drug into the body. Peroral formulations are often expelled by children because of poor taste and texture. This is a significant issue, especially when considering that taste sensation differs as a consequence of development and on an interindividual basis. Solid formulations, such as tablets and capsules, are not easily administered to the majority of infants and children owing to their inability to easily and safely swallow them. For example, incomplete development of swallowing coordination may result in choking or aspiration when solid formulations are given to infants and small children. Finally, solid peroral formulations limit the ability for dose titration and dosing flexibility. Drug developers in the United States and abroad are working to address this limitation by the development of new techniques suitable for both oral and peroral drug administration that encompass both products (e.g., dispersible peroral tablets, oral films, titratable granules, oral melts) and drug administration devices (e.g., dosing straws, graduated cylinders for peroral granules).

With regard to dosing accuracy with peroral formulations, liquids (e.g., drops, solutions, syrups, suspensions, elixirs) are preferred for infants and young children. The utility of these formulations is often limited by palatability when taste-masking of the active ingredient(s) cannot be effectively achieved. In the case of suspension formulations, improper reconstitution and/or resuspension prior to dose administration can introduce problems related to accuracy of dosing. Other potential limitations of peroral liquid drug formulations (including those that may be extemporaneously compounded by the pharmacist from drug powder or from solid peroral dosage forms of a given drug) include potential problems related to drug stability, contamination (chemical or bacterial), portability and for some products, the need for them to be refrigerated so as to insure drug stability.

Administration of liquid medications can be associated with risk if the device for administering the medication is not appropriate (e.g., use of a kitchen teaspoon as opposed to a 5.0 mL dosing spoon) or used improperly when measuring a dose that is appropriate for the patient's age or weight. The low cost and convenience of hypodermic syringes has prompted many physicians and pharmacists to dispense them with liquid medications in order to improve accuracy. Although this approach is seemingly associated with greater accuracy in dosing, parents/caregivers can have difficulty in reading the graduations on a syringe and, also, the plastic caps on the plungers of syringes can produce a choking hazard for infants and young children. All of these problems can be obviated by education of parents/caregivers on how to reliably use special syringes for peroral dosing that pharmacists should dispense with every liquid drug formulation.

Parenteral Drug Administration

In contrast to adults where vascular access is relatively easy to obtain, difficulties are often present in the infant and young child. These are often produced by the smaller diameter of peripheral vessels (relative to the size of the intravenous cannula), developmentally associated differences in body composition (e.g., body fat distribution) and the use of topical anesthetic agents, some of which can produce venous constriction. The small peripheral blood vessels in infants and young children can also limit the volume and rate of intravenous drug administration because of issues of capacity and, in the instance of drugs capable of producing venous irritation, infusion-related discomfort.

An underappreciated issue that can complicate parenteral drug administration to infants occurs when the concentration of a given drug formulation does not enable accurate measurement of dose. Errors consequent to improper dilution of adult formulations necessary to ensure appropriate osmolarity and volume for IV administration (the most common resulting in a 10-fold overdose) are not uncommon. For example, morphine, a drug commonly used in neonates, infants, and children, is commonly available in a 2 mg/mL

concentration. A usual 0.1 mg/kg morphine dose for a 1 kg infant using this formulation would require a nurse or pharmacist to accurately withdraw 0.05 mL and administer it into a length of IV tubing with a dead space volume that may exceed that of the dose by approximately 100-fold. In this situation, accuracy of dose and infusion time can be significantly compromised. Although underdosing is often a serious problem when attempting to administer very small volumes, overdoses also occur, owing to inaccurate extemporaneous dilutions. Moreover, attempts to compensate for the volumes present within the IV tubing further predispose the patient to receive an incorrect, possibly unsafe, dose. Whenever such concentrated drug formulations are the only source for use, appropriate alteration of the stock parenteral solution should be performed and manufactured by the pharmacy department. As well, many errors can be avoided by the use of standard dilutions that all practitioners are aware of and using standardized approaches for IV drug administration that minimize complications associated with unrealized drug dilution and errant infusion times (e.g., pediatric syringe pumps attached to low-volume tubing).

Although used rather infrequently, IM drug administration offers a route of administration for many drugs in those instances where venous access is not immediately available or when a therapeutic drug regimen involves use of a single or limited number of doses. Although appealing with respect to immediacy, this route of administration can be associated with problems (e.g., muscle and/or nerve damage, sterile abscess formation, variable rate of drug absorption consequent to developmental differences in vascular perfusion of muscle beds), especially in the neonate and small infant. Finally, the decision to utilize the IM route must take into consideration the physicochemical properties (e.g., pH, osmolarity, solubility) of the drug formulation and/or any diluent used to prepare it.

Other Routes for Drug Administration

Neonates, infants, children, and adolescents with certain pulmonary conditions (e.g., reactive airway disease, viral-induced bronchiolitis, asthma, cystic fibrosis) frequently receive drugs (e.g., corticosteroids, β-adrenergic agonists, antimicrobial agents, mucolytic drugs) via inhalation. The pulmonary surface area in pediatric patients of all ages is a very effective, easily traversable barrier for drug absorption. Rate-limiting factors for pulmonary drug absorption include physicochemical factors associated with the drug and delivery system (e.g., particle size, diffusion coefficient, chemical stability of drug molecule in the lung) and physical factors that influence intrapulmonary drug deposition (e.g., active vs passive drug delivery to the tracheobronchial tree, respiratory minute volume, internal airway diameter); many of which are developmentally determined. For drugs formulated for delivery using a metered-dose inhaler (either drug powder or suspended particles using a carrier gas), developmental factors (e.g., incoordination of device actuation with inhalation, inability to follow instructions for clearing of airway, and passive inhalation with actuation of delivery device) either prevent their use (such as in infants and small children) or limit the bioavailability of the drug to be administered. In these instances, specific devices (e.g., masks, spacer chambers) and/or methods of delivery (e.g., continuous aerosolization via mask) can be used to improve the efficiency of drug delivery and, thereby, drug efficacy.

In pediatric patients, percutaneous drug administration is generally reserved for agents intended to produce a local effect within the dermis. Development has an impact on the barrier of the skin that, if not recognized and controlled for, can produce situations in which systemic toxicity can result (see "Drug Absorption" above). Similar therapeutic challenges occur when transmucosal routes (e.g., buccal, sublingual, rectal) are used for drug administration. Specifically, unpredictable systemic bioavailability may complicate treatment consequent to variability in the rate and/or extent of drug absorption. Finally, direct intraosseous drug administration via puncture of the tibia is occasionally used in infants and small children for administration of drugs and crystalloid fluids given acutely during resuscitation efforts. It is particularly useful when vascular access sufficient for drug administration cannot be immediately accomplished as the onset of action by this route is comparable with that seen after IV administration.

Adherence and Compliance

Beyond proper individualization of drug dose based on developmental considerations, the influence of concomitant disease/treatment and the selection of the proper drug formulation, the success of drug treatment in a pediatric patient is inextricably linked to the successful administration of the drug. Physical and cognitive immaturity makes the infant and the child a dependent creature in almost all respects, including those related to therapeutic drug administration. Until a child reaches an age at which they can physically self-administer a drug in an accurate, proficient fashion and can mentally assume responsibility for this task (generally from 7-14 yr of age, depending on the individual child), compliance with a drug regimen becomes the responsibility of an adult. In a hospital environment, compliance is ensured through the actions of physicians, nurses, and pharmacists who, collectively through an integrated system of medical care, assume this responsibility. Upon discharge, the responsibility is transferred to parents/guardians or other adult caregivers in an environment that is generally nonmedical. At this juncture, therapeutic compliance morphs into adherence as defined by the potential for conflicting demands (e.g., multiple adult caregivers; different external environments such as home, daycare, school; parents tending to the needs of multiple children) to introduce variability (anticipated and unpredictable) in drug administration. Whether treatment is for a self-limiting (e.g., antibiotic administration) or chronic (e.g., asthma, diabetes) condition, challenges to therapeutic adherence have the potential to serve as primary determinants of drug safety and efficacy in infants and young children.

In contrast to the period encompassing infancy and childhood, adolescence poses its own unique challenges to therapeutic adherence. During this period, psychosocial maturation almost always lags behind physical maturation. Development of cognitive and physical skills in most adolescents enables them to self-administer a prescribed medication in a proper manner with little to no supervision. However, psychodynamic issues experienced by a substantial number of adolescents (e.g., complete understanding of the ramifications of undertreatment, disease progression, and/or roles of disease prevention, and/or health maintenance; perceptions of immortality and the associated lack of need for treatment; disorganized patterns of thinking capable of confounding treatment schedules; defiant/oppositional behavior toward authority figures) can often precipitate therapeutic failure, through either undertreatment or overtreatment, the latter occasionally leading to drug toxicity. Unfortunately, the only maneuver that can be used to facilitate therapeutic compliance and adherence in the pediatric patient is the combination of vigilance (on behalf of all caregivers) and repetitive education coupled with positive reinforcement (e.g., the use of motivational interviewing techniques). When children reach the age of assent (i.e., generally by 7 yr of age in children who have normal neurobehavioral development), they have the beginning level of cognitive ability sufficient to engender understanding about their medical condition(s) and how effective treatment can be used to improve their life. Through diligent efforts placed toward patient education and reeducation, older children and adolescents can assume a level of responsibility for active partnership in their overall medical management, one that will mature as educational efforts, driven by a shared desire for an optimal outcome, are regularly made. The pediatrician's role in fostering this is paramount given their understanding of development and the regular patient–parent interactions that occur from birth through adolescence.

Drug–Drug Interactions

Pharmacokinetic and/or pharmacodynamic properties of drugs may be altered when 2 or more drugs are coadministered to a patient (refer to Table 60-6). Even though many interactions occur at the level of drug metabolism, they may also occur at the level of drug absorption (e.g., inhibition of intestinal CYP3A4 activity by grapefruit juice or St. John's wort and consequent reduction in presystemic clearance of

Table 60-6 Mechanism-Based Drug Interaction Table

	EXAMPLE DRUG COMBINATION	RESULT
PHARMACODYNAMIC		
Additive	a. Fentanyl and midazolam b. Class 1A antiarrhythmic with erythromycin c. Vancomycin plus aminoglycoside	Use of multiple medications with similar side effect profiles can lead to additive effects such as increased sedation (a), increased QT prolongation (b), and increased potential for nephrotoxicity (c)
Synergy	Penicillin plus aminoglycoside	Improved bactericidal efficacy against some Gram-positive organisms. Use of penicillin inhibits bacterial cell wall synthesis which for some Gram-positive organisms can improve the intracellular penetration of the aminoglycoside, which inhibits bacterial cell protein synthesis by binding to 30S and 50S ribosomal subunits
Antagonism	Opiate plus naloxone	Competitive receptor antagonism: Decreased efficacy of opiate medications, improvement in respiratory effort
PHARMACOKINETIC		
Absorption	*Inhibition of MDR1:* Amiodarone and digoxin	Increased digoxin concentration, digoxin toxicity (↓ digoxin 50%)
	Complex formation: Quinolone and tetracycline antibiotics with divalent/trivalent cations (e.g.; Ca^{2+}, Mg^{2+}, Fe^{3+}, Al^{3+})	Decreased antibiotic absorption
	Mycophenolate mofetil plus antacids	Decreased absorption of mycophenolate mofetil
	Pharmaceutical preparations: Ceftriaxone with IV fluids containing calcium	Crystalline deposits in lungs/kidneys of neonates
Distribution	Ceftriaxone + endogenous bilirubin	Displacement of bilirubin from albumin binding site, increased risk kernicterus in neonates
	NSAID plus warfarin	Displacement of warfarin from albumin binding site with consequent exaggerated anticoagulant response
Metabolism	*Induction:* Rifampin plus antiretrovirals	Decreased serum concentration of antiretroviral because of induced CYP metabolism
	Inhibition: Azole antifungals plus CYP3A4 substrates	↑ Drug levels because of inhibition of CYP3A4-mediated metabolism resulting in drug toxicity
Elimination	Penicillin plus probenecid	Decreased tubular secretion of penicillin resulting in increased serum concentrations
	Methotrexate plus aspirin	Inhibition of renal tubular secretion of methotrexate resulting increased methotrexate concentration

This table is not meant to be an all-inclusive list of drug–drug interactions. Care should be taken when prescribing all medications, and the potential of interactions should be considered. The practitioner is encouraged to assess the possibility of all interactions when prescribing medications.

NSAID, nonsteroidal antiinflammatory drug.

Modified from Rizack M, Hillman C: The Medical Letter handbook of adverse drug interactions. *New Rochelle, NY, 1989, The Medical Letter.*

CYP3A4 substrates), distribution (e.g., displacement of warfarin plasma protein binding by ibuprofen with consequent increased hemorrhagic risk), or elimination (e.g., inhibition of ATS of β-lactam antibiotics by probenecid). Drug–drug interactions may also occur at the level of the receptor (via competitive antagonism), many of which are intentional and produce therapeutic benefit in pediatric patients (e.g., antihistamine reversal of histamine effects, naloxone reversal of opiate adverse effects).

Drug–drug interactions that occur at the level of drug metabolism can be somewhat predictable based on a priori knowledge of a given drug's biotransformation profile. Although such information can be derived from the primary literature, it may not be immediately translated into a useful clinical context consequent to limitations associated with in vitro to in vivo extrapolation, which can include (1) use of animal models for characterizing metabolism; (2) extrapolating enzyme kinetics derived from pooled human liver microsomes or recombinant human drug-metabolizing enzymes to estimates of in vivo drug clearance; (3) extrapolating in vitro data obtained from fully competent (i.e., adult activity) hepatic microsomes to estimates of clearance in patients who may have developmental and/or disease-associated compromise in enzyme activity; (4) inaccurate accounting for pharmacogenetic variation in drug-metabolizing activity (i.e., constitutive activity); (5) the contribution of multiple different drug-metabolizing enzymes in the overall biotransformation of a given drug (i.e., a polyfunctional drug substrate); and (6) the potential role of enzyme induction or inhibition in vivo that is not reflected from conditions used for in vitro metabolism studies.

Despite these limitations, information pertaining to drug–substrate interaction can be useful in ascertaining the direction (e.g., enzyme inhibition → reduced clearance → higher plasma drug concentration → enhanced effect as compared to enzyme induction → increased clearance → reduced plasma drug concentration → diminished effect) of a drug–drug interaction. Although multiple sources describing specific drug–drug interactions exist (e.g., primary and secondary literature, drug product labeling), the information may not be complete or updated. In examining multiple information sources pertaining to this topic, the authors found a data compilation from Indiana University (http://medicine.iupui.edu/clinpharm/ddis/) to be the most complete and clinically useful. Utilizing primary literature should be assessed when information is not available in online sources.

Drug interactions may also occur at a pharmaceutical level as a result of a physicochemical incompatibility of two medications when combined. Such interactions generally alter the chemical structure of 1 or both constituents, thereby rendering them inactive and potentially dangerous (e.g., intravenous infusion of a crystalline precipitate or unstable suspension). For example, ceftriaxone should be avoided in infants younger than 28 days of age if they are receiving or are expected to receive intravenous calcium-containing products because of reports of neonatal deaths resulting from crystalline deposits in the lungs and kidneys. Alternatively, 2 drugs simultaneously administered perorally may form a complex that can inhibit drug absorption (e.g., coadministration of doxycycline with a food or drugs containing divalent cations).

Nonprescription preparations, herbal supplements, and certain foods also have the potential to produce interactions with drugs. These are often quite challenging for the clinician, especially for alternative therapies, in that their composition (or potency) may not be completely discernable from the product labels and because the disposition of many natural products has not been studied in either children or adults. Many patients and their parents also do not consider alternative

therapies (including nutraceuticals) to be "medicines" (and, consequently, will not disclose their use during a routine medication history) but to be safe "nutritional supplements" despite absent regulation for their testing. Consequently, a patient visit should begin with a thorough medication history that includes discussions of which nonprescription medications and herbal products are being used and their regularity of use. This allows the clinician to identify the primary ingredients contained in these products and query their potential for producing clinically significant drug–drug interactions. This can be efficiently accomplished through available web-based search engines (e.g., Natural Medicines Comprehensive Database, http://naturaldatabase.therapeuticresearch.com/home.aspx).

One of the most daunting challenges for the clinician is not to determine whether a drug–drug or drug–food interaction may be present, but if it will be of sufficient magnitude so as to be clinically significant. Extensive databases of reported and/or potential (e.g., theoretical mechanism- or metabolism-based) drug interactions exist and are widely available via the Internet (e.g., http://www.medscape.com/druginfo/druginterchecker; http://www.drugs.com/; http://www.umm.edu/adam/drug_checker.htm), some of which provide some assessment as to their potential significance. Many computer-based proprietary information systems used by hospital and community pharmacies are routinely used to screen a patient's medication profile (generally restricted to prescribed drugs) against new prescriptions to evaluate the potential for drug–drug interactions.

The provision of individualized, optimal drug therapy requires that the clinician make an assessment of potential drug–drug interactions and their significance. This requires knowledge of the interaction, the patient's condition, concomitant treatments (prescriptions, nonprescription drugs, alternative medicines), the impact of development on the dose– concentration–response relationship and a consideration of the risk-vs-benefit profile of the drug being prescribed. The clinician must be cognizant that if the clinician treats a potential drug–drug interaction as an absolute contraindication to drug use, it is possible that an alternative drug choice could produce a treatment associated with either less benefit or greater risk. Although many drugs have the potential to cause drug interactions, not all those documented may be clinically relevant for a given patient. *For patients with complex histories who require treatment with multiple medications, consultation with a clinical pharmacologist or pharmacist can help provide guidance on drug–drug interactions and their potential to impact therapy.*

Adverse Drug Reactions

Adverse drug reactions (ADRs) have been defined by the World Health Organization as "a response to a drug that is noxious and unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function." There are 2 traditional pharmacologic classifications of ADRs: type A and type B. Type A reactions are dose dependent, predictable, and account for 85-90% of all ADRs. These are often considered as "side effects" to medications. Type B reactions are not dose dependent, are unpredictable and account for approximately 10-15% of all adverse reactions. These are generally considered to represent hypersensitivity (i.e., allergic) reactions whereas some can have a nonimmune basis. Historically, such standardized definitions describing adverse events have not been routinely utilized. Furthermore, patients sometimes misinterpret some side effects as allergies (e.g., diarrhea with amoxicillin/clavulanate) and this may be perpetuated through the patient's medical record, thus potentially restricting a useful and necessary medication.

In the pediatric population, ADRs are common occurrences that produce a major burden to patients and the healthcare system. Studies concerning ADRs in pediatric patients suggest the following: (1) approximately 9% of all pediatric patients admitted to the hospital experience an ADR during their treatment; (2) the apparent incidence of ADRs in children in outpatient clinics is approximately 1.5%; (3) ADRs have been reported as being responsible for >2% of pediatric admissions to children's hospitals; and (4) approximately 40% of ADRs occurring in hospitalized children are potentially life-threatening. In considering these "statistics" it should be recognized that the true incidence of ADRs in children is not known as a consequence of generalized underreporting by healthcare providers (physicians, nurses, pharmacists), parents/caregivers, and patients (who may not recognize signs/symptoms and/or be unable to report them), and in many countries (including the United States), the lack of a standardized surveillance and real-time reporting system. As a consequence, estimation of their incidence relies upon spontaneous, volunteer reporting systems that lack uniformity and critical evaluation and do not provide both numerator and denominator data necessary to determine true incidence of a specific ADR in a specific subpopulation of patients.

Despite the limitations associated with determining the incidence of ADRs in children, it is estimated that their occurrence in patients 0-4 yr of age (3.8%) is more than double that seen at any other time throughout childhood and adolescence. The reasons for this are not currently known but may involve developmental differences in pharmacokinetics and/or pharmacodynamics (i.e., altered dose–concentration–effect relationship), age-associated differences in physiologic "systems" that modulate drug and/or metabolite-mediated cellular injury (e.g., the immune system) and/or the therapeutic use of drugs known to have a relatively high incidence of producing ADRs (e.g., delayed hypersensitivity reactions associated with β-lactam antibiotics). Also, it is important to recognize that infants can experience ADRs from drugs that are not administered to them therapeutically, but from incidental drug exposure (e.g., transplacental drug passage, breastfeeding). Examples include neonatal abstinence syndrome associated with maternal opiate use, production of a hyperserotonergic state in neonates born to mothers who received selective serotonin reuptake inhibitors during and through pregnancy, and opiate toxicity in breastfed infants whose mothers were taking codeine for pain management. In these instances, drug accumulation occurring because of reduced activity of drug-metabolizing enzymes associated with development, and, potentially, pharmacogenetically determined phenotypic changes that, in concert, can produce a level of systemic drug exposure sufficient to produce exaggerated drug response or frank toxicity.

There are also specific ADRs that occur at a much greater frequency in infants and children as compared to adults. Examples include aspirin-associated Reye syndrome, cefaclor-associated serum sickness-like reactions, lamotrigine-induced cutaneous toxicity, and in infants younger than 2 yr of age, valproic acid–induced hepatotoxicity. It is not clear whether the age predilection for these specific ADRs is associated with developmental differences in drug biotransformation related to both metabolite formation and detoxification or, alternatively, has a pharmacogenetic basis. Finally, it should be recognized that children, like adults, do experience hypersensitivity reactions to drugs. Examples include reactions to anticonvulsant drugs (e.g., phenytoin, carbamazepine, phenobarbital), sulfonamides (e.g., sulfamethoxazole, sulfasalazine), minocycline, cefaclor, and abacavir. These specific ADRs are not characteristic of type I (i.e., immediate) hypersensitivity reactions (e.g., true penicillin allergy) or anaphylactoid reactions; rather, they represent delayed hypersensitivity reactions that are classified as idiosyncratic with respect to their origin. A relatively common constellation of symptoms (fever, rash, and lymphadenopathy) suggests that abnormal activation/regulation of the immune system is a predominant component of their pathogenesis. Data from in vitro studies of sulfamethoxazole hypersensitivity also support this assertion. A requisite role for metabolic bioactivation (for anticonvulsants, sulfamethoxazole, and cefaclor) and, possibly, genetic factors, such as allelic variants in HLA-B (e.g., HLA-B*5701 and HLA-B*1502 associated with hypersensitivity reactions to abacavir and carbamazepine) appear also to be involved in their etiology.

PERSONALIZED MEDICINE

See also Chapter 59.

The general concept of personalized medicine involves the application of genomic information to predicting a disease, disease severity, and therapeutic response. This "new vision of medicine" has been described as the 3 Ps: predictive, personalized, and preventive. However, in children, ontogeny should also be considering when

discussing personalizing therapeutic treatments. Thus, the aim of pediatric personalized medicine is to uniquely combine genetic variation with developmental stage to provide a tailored approach to either drug avoidance (in the case of predicted, significant risk of an ADR) or treatment.

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Chapter 61

Anesthesia, Perioperative Care, and Sedation

Randall C. Wetzel

The primary purpose of general anesthesia is to suppress the conscious perception of, and physiologic response to, noxious stimuli and to render the patient unconscious. Potent drugs are used to blunt physiologic responses to what would otherwise be life-threatening trauma (surgery). Intraoperatively, the anesthesiologist is responsible for providing analgesia as well as physiologic and metabolic stability (Table 61-1). This responsibility is facilitated by obtaining an adequate preanesthesia history (Table 61-2). Although anesthetic risk has greatly decreased, the increased risk of morbidity and mortality in the perioperative period demands the utmost vigilance. The risk is even higher in certain disease states (Table 61-3).

GENERAL ANESTHESIA

Analgesia

Providing analgesia for procedures both in and out of the operating room is a major responsibility and functions within a spectrum of care (Table 61-4). Techniques exist to provide profound pain relief during operative procedures for all patients, including the most critically ill infants. Blunting the physiologic responses to painful stimuli inhibits the stress response and its multiple deleterious physiologic and metabolic consequences. The response to painful and stressful stimuli is a potent stimulus of the **systemic inflammatory response syndrome,** which leads to increased catabolism, physiologic instability, and increased mortality (see Chapter 70). Appropriate use of medication, such as fentanyl anesthesia in neonates, reduces the incidence of postoperative bradycardia, hypotension, acidosis, interventricular hemorrhage, coagulation abnormalities, hypoglycemia, and death.

Hypnosis and Amnesia

The blunting of both consciousness **(hypnosis)** and conscious recall **(amnesia)** is a crucial feature of pediatric anesthesia care. Awareness of painful, anxiety-provoking, and stressful conditions for children is

Table 61-1 Goals of Anesthesia

Analgesia
Amnesia and a decreased level of consciousness
Akinesia–absence of movement in response to painful stimuli
Physiologic support and homeostatic management throughout the perioperative process
Vigilance

Table 61-2 The Preanesthetic History

Child's previous anesthetic and surgical procedures:
- Review the anesthetic record for information about the mask and endotracheal tube size; the type and size of laryngoscope used; difficulties with mask ventilation or intubation; prolonged emergence (awakening) from anesthesia; postoperative vomiting, postoperative agitation and disordered postoperative behavior in the days following anesthesia/surgery. In addition, a history of hyperthermia or acidosis in the child or family member should be sought.

Perinatal problems (especially for infants):
- Need for prolonged hospitalization
- Need for supplemental oxygen or intubation and ventilation
- History of apnea and bradycardia
- History of cardiovascular compromise

Other major illnesses and hospitalizations
Family history of anesthetic complications, malignant hyperthermia, or pseudocholinesterase deficiency
Respiratory problems:
- Long-term exposure to environmental tobacco smoke
- Obstructive apnea, breathing irregularities, or cyanosis (especially in infants younger than 6 mo of age)
- History of snoring or an obstructive breathing pattern
- Recent upper respiratory tract infection
- Recurrent respiratory infections
- Previous laryngotracheitis (croup) or laryngomalacia
- Asthma or wheezing during respiratory infections
- Airway abnormalities, facial anomalies, mucopolysaccharidosis

Cardiac problems:
- Murmur or history of congenital heart disease—ask for details
- Dysrhythmia
- Exercise intolerance
- Syncope
- Cyanosis

Gastrointestinal problems:
- Reflux and vomiting
- Feeding difficulties
- Failure to thrive
- Liver disease

Exposure to exanthems or potentially infectious pathogens
Neurologic problems:
- Seizures
- Developmental delay
- Neuromuscular diseases
- Increased intracranial pressure

Hematologic problems:
- Anemia
- Bleeding diathesis
- Tumor
- Immunocompromise
- Prior blood transfusions and reactions

Renal problems:
- Renal insufficiency, oliguria, anuria
- Fluid and electrolyte abnormalities

Psychosocial considerations:
- Posttraumatic stress
- Drug abuse, use of cigarettes or alcohol
- Physical or sexual abuse
- Family dysfunction
- Previous traumatic medical or surgical experience
- Psychosis, anxiety, depression

Gynecologic considerations:
- Sexual history (sexually transmitted infections)
- Possibility of pregnancy

Current medications:
- Prior administration of corticosteroids

Allergies:
- Drugs
- Iodine
- Latex products
- Surgical tape
- Food (especially soya and egg albumin)

Dental condition (loose or cracked teeth)
When and what the child last ate (especially in emergency procedures)

Table 61-3 Specific Pediatric Diseases and Their Anesthetic Implications

DISEASE	IMPLICATIONS
RESPIRATORY SYSTEM	
Asthma	Intraoperative bronchospasm that may be severe and even fatal Preoperative control is essential Pneumothorax or atelectasis Optimal preoperative medical management is essential; preoperative steroids may be required
Difficult airway	Special equipment and personnel may be required Should be anticipated in children with dysmorphic features or acute airway obstruction, as in epiglottitis or laryngotracheobronchitis or with an airway foreign body Patients with Down syndrome may require evaluation of the atlantooccipital joint Patients with storage diseases may be at high risk
Bronchopulmonary dysplasia	Barotrauma with positive pressure ventilation Oxygen toxicity, pneumothorax a risk
Cystic fibrosis	Airway reactivity, bronchorrhea, increased intraoperative pulmonary shunt and hypoxia Risk of pneumothorax, pulmonary hemorrhage Atelectasis, risk of prolonged postoperative ventilation Patient should be assessed for cor pulmonale
Sleep apnea	Pulmonary hypertension and cor pulmonale must be excluded Careful postoperative observation for obstruction required
CARDIAC	
	Need for antibiotic prophylaxis for bacterial endocarditis Use of air filters; careful purging of air from the intravenous equipment Physician must understand the effects of various anesthetics on the hemodynamics of specific lesions Preload optimization and avoidance of hyperviscous states in cyanotic patients Possible need for preoperative evaluation of myocardial function and pulmonary vascular resistance Provide information about pacemaker function and ventricular device function
HEMATOLOGIC	
Sickle cell disease	Possible need for simple or exchange transfusion based on preoperative hemoglobin concentration and percentage of hemoglobin S Importance of avoiding acidosis, hypoxemia, hypothermia, dehydration, and hyperviscosity states
Oncology	Pulmonary evaluation of patients who have received bleomycin, *bis*-chloroethyl-nitrosourea, chloroethyl-cyclohexyl-nitrosourea, methotrexate, or radiation to the chest Avoidance of high oxygen concentration Cardiac evaluation of patients who have received anthracyclines; risk of severe myocardial depression with volatile agents Potential for coagulopathy
RHEUMATOLOGIC	
	Limited mobility of the temporomandibular joint, cervical spine, arytenoid cartilages Careful preoperative evaluation required Possible difficult airway
GASTROINTESTINAL	
Esophageal, gastric	Potential for reflux and aspiration
Liver	High overall morbidity and mortality in patients with hepatic dysfunction Altered metabolism of many anesthetic drugs Potential for coagulopathy and uncontrollable intraoperative bleeding
RENAL	
	Altered electrolyte and acid–base status Altered clearance of many anesthetic drugs Need for preoperative dialysis in selected cases Succinylcholine to be used with extreme caution and only when the serum potassium level has recently been shown to be normal
NEUROLOGIC	
Seizure disorder	Avoidance of anesthetics that may lower the seizure threshold Optimal control ascertained preoperatively Preoperative serum anticonvulsant measurements
Increased intracranial pressure	Avoidance of agents that increase cerebral blood flow Avoidance of hypercarbia
Neuromuscular disease	Avoidance of depolarizing relaxants; at risk for hyperkalemia Patient may be at risk for malignant hyperthermia
Developmental delay	Patient may be uncooperative during induction and emergence
Psychiatric	Monoamine oxidase inhibitor (or cocaine) may interact with meperidine, resulting in hyperthermia and seizures Selective serotonin reuptake inhibitors may induce or inhibit various hepatic enzymes that may alter anesthetic drug clearance Illicit drugs may have adverse effects on cardiorespiratory homeostasis and may potentiate the action of anesthetics
ENDOCRINE	
Diabetes	Greatest risk is unrecognized intraoperative hypoglycemia; if insulin is administered, intraoperative blood glucose level monitoring needed; glucose and insulin must be provided, with adjustment for fasting condition and surgical stress
SKIN	
Burns	Difficult airway Risk of rhabdomyolysis and hyperkalemia from succinylcholine following burns for many months Fluid shifts Bleeding Coagulopathy
IMMUNOLOGIC	
	Retroviral drugs may inhibit benzodiazepine clearance Immunodeficiency requires careful infection control practices Cytomegalovirus-negative blood products, irradiation, or leukofiltration may be required
METABOLIC	
	Careful assessment of glucose homeostasis in infants

Table 61-4 Definitions of Anesthesia Care

MONITORED ANESTHESIA CARE A specific anesthesia service in which an anesthesiologist has been requested to participate in the care of a patient undergoing a diagnostic or therapeutic procedure. Monitored anesthesia care includes all aspects of anesthesia care: a preprocedure assessment, intraprocedure care, and postprocedure anesthesia management. During monitored anesthesia care, the anesthesiologist or a member of the anesthesia care team provides a number of specific services, which may include some or all of, but are not limited to, the following: • Discussing anesthesia care with the family and child, obtaining consent, allaying anxiety and answering questions—family centered anesthesia care. • Monitoring of vital signs, maintenance of the patient's airway, and continual evaluation of vital functions. • Diagnosing and treating clinical problems that occur during the procedure. • Administering sedatives, analgesics, hypnotics, anesthetic agents, or other medications as necessary to ensure patient safety and comfort. • Providing other medical services as needed to accomplish the safe completion of the procedure. Anesthesia care often includes the administration of medications for which the loss of normal protective reflexes or loss of consciousness is likely. *Monitored anesthesia care* refers to those clinical situations in which the patient remains able to protect the airway for the majority of the procedure. If the patient is rendered unconscious and/or loses normal protective reflexes for an extended period, this is considered a general anesthetic.
LIGHT SEDATION Administration of anxiolysis and/or analgesia that obtunds consciousness but does not obtund normal protective reflexes (cough, gag, swallow, hemodynamic reflexes), or spontaneous ventilation.
DEEP SEDATION Sedation that obtunds consciousness and normal protective reflexes or possesses a significant risk of blunting normal protective reflexes (cough, gag, swallow, hemodynamic reflexes), hemodynamic and respiratory insufficiency may occur.
GENERAL ANESTHESIA Administration of hypnosis, sedation, and analgesia that results in the loss of normal protective reflexes.
REGIONAL ANESTHESIA Induction of neural blockade (either central, neuraxial, epidural, or spinal; or peripheral nerve block, e.g., digital nerve block, brachial plexus block), which provides analgesia and is associated with regional motor blockade. Consciousness is not obtunded. Special expertise is required. Frequently, in children, anxiolysis and sedation are also necessary for this technique to be successful. Regional anesthesia (e.g., caudal epidural blockade) is used to supplement general anesthesia and provide postoperative analgesia.
LOCAL ANESTHESIA Provision of analgesia by local infiltration of an appropriate anesthetic agent. Does not require the presence or involvement of an anesthesiologist, although an anesthesiologist may provide local anesthesia services.
NO ANESTHESIOLOGIST An anesthesiologist will not be involved in the care of the child in any way.

just as deleterious, physically and psychologically, as the painful procedures themselves. Management is aimed at blunting the fear and emotional response during surgery, painful procedures (bone marrow aspiration, lumbar punctures), or nonpainful but anxiety-provoking procedures (MRI, CT). Many drugs provide anxiolysis, blunting of recall, and amnesia for such events (Table 61-5). Obtundation of consciousness may accompany the provision of analgesia. Hypnotic and sedative agents can induce altered consciousness without producing any analgesia; *analgesia* and *obtunded consciousness* are not synonymous. It is also possible to provide analgesia (local, spinal, or epidural analgesia) without obtunding consciousness.

Sedation describes a medically induced state that is on a continuum between the fully alert, awake state and general anesthesia (see Table 61-4). In addition to inducing unconsciousness and amnesia, general anesthesia obtunds or ablates critical physiologic reflexes; the most important are **airway-protective reflexes:** coughing, gagging, and swallowing. Cardiorespiratory reflexes are also obtunded with general anesthesia; respiratory depression and hemodynamic compromise may occur and may be profound. As sedation deepens toward general anesthesia, loss of airway patency, loss of airway-protective reflexes, and loss of cardiovascular stability occur. *Light (minimal) sedation* is anxiolysis without loss of these reflexes or airway patency. *Deep sedation* occurs when these reflexes are obtunded or lost (see Table 61-4). **Adequate sedation in children may be accompanied by the actual or potential loss of vital reflexes**. It is mandatory that those providing sedation for a child be able to detect the transition into deep sedation and general anesthesia and be prepared to manage the child's airway and circulation, and provide CPR if required.

Akinesia (Immobility or Muscular Relaxation)

Akinesia is the absence of movement. It is necessary to ensure safe and adequate operative conditions and to provide ideal conditions for advanced and meticulous surgery. Akinesia is often produced with muscle relaxants (see Table 61-5). These agents facilitate respiratory management in the perioperative period and in critically ill patients. The absence of movement is neither the absence of pain nor the presence of amnesia. **Whenever neuromuscular blocking agents are used, analgesia and sedation must be provided.**

Physiologic Support

The need for anesthesia increases the need to monitor and support physiologic integrity and homeostasis. Sedation and anesthesia have significant and potentially life-threatening physiologic consequences (see Tables 61-4 and 61-5). Maintenance of adequate cardiorespiratory function, fluid management, electrolyte control, thermoregulation, and concern for all aspects of the child's health are critical during anesthesia.

Vigilance

Constant, critical attention by physicians who understand the demands of the surgical procedure, as well as the changes in physiologic status and their implications, is mandatory to provide safe perioperative care

Table 61-5 Selected Drugs Used in Anesthesia

DRUG	USES AND IMPLICATIONS
MUSCLE RELAXANTS	
Succinylcholine	Used to facilitate endotracheal intubation and maintain muscle relaxation in emergency situations; now virtually never given routinely A depolarizing neuromuscular blocking agent with rapid onset and offset properties Associated with the development of malignant hyperthermia in susceptible patients Degraded by plasma cholinesterase, which may be deficient in some individuals; such a deficiency may result in prolonged effect Fasciculations may be associated with immediate increases in intracranial and intraocular pressures as well as postoperative muscle pain
Vecuronium, rocuronium, mivacurium, *cis*-atracurium, all aminosteroids	Nondepolarizing neuromuscular blockers Have less-rapid onset than succinylcholine but are longer-acting Prolonged ICU use may lead to profound muscle weakness Vecuronium and rocuronium are metabolized by the liver and excreted in bile; they are the most commonly used neuromuscular blocking agents *cis*-Atracurium is metabolized by plasma cholinesterase and therefore may be of benefit in patients with hepatic or renal disease
HYPNOTICS	
Propofol	Rapidly acting hypnotic; amnestic, but not analgesic, a general anesthetic agent Like pentothal, may cause hypotension Causes respiratory depression May increase the seizure threshold Great utility in titrated doses for sedation and with local anesthetic and short-acting opioid for outpatient procedures May suppress nausea Associated with the often fatal propofol infusion syndrome when used in prolonged intravenous infusion (>24 hr) and therefore not used for ICU sedation in children
Etomidate	Cardiovascular stability on induction with no increase in intracranial pressure Inhibits corticosteroid synthesis and increases ICU mortality Associated with myoclonus, potential difficulty with assisted ventilation, and pain on injection
Ketamine	Hypnotic analgesic and amnestic Causes sialorrhea and should be coadministered with an antisialagogue, such as atropine or glycopyrrolate May be associated with laryngospasm Causes endogenous catecholamine release, tachycardia, and bronchodilation Increases intracranial and intraocular pressures Decreases the seizure threshold
SEDATIVE–ANXIOLYTICS	
Benzodiazepines	Produce sedation, anxiolysis, or hypnosis, depending on the dose May produce antegrade, but not retrograde, amnesia All agents raise the seizure threshold, are metabolized by the liver, and depress respiration, especially when administered with opioids Frequently administered as premedications Diazepam may be painful on injection and has active metabolites Midazolam can be administered by various routes and has a short half-life Lorazepam has no active metabolites Sedation effected by all benzodiazepines may be reversed by flumazenil, but respiratory depression may not be reliably reversed
Dexmedetomidine	Produces anxiolysis, sedation, sympatholysis, by α_2-receptor stimulation centrally; has mild analgesic properties Side effects include hypotension and bradycardia Commonly used for procedural and ICU sedation Continuous infusion for ICU sedation; currently limited to 24 hr
ANALGESIC–SEDATIVES	
Opioids	Gold standard for providing analgesia All cause respiratory depression Morphine and, to a lesser extent, hydromorphone may cause histamine release The synthetic opioids fentanyl, sufentanil, and short-acting alfentanil may have a greater propensity to cause chest wall rigidity when administered rapidly or in high doses and are also associated with the rapid development of tolerance; these 3 drugs have particular utility in cardiac surgery because of the hemodynamic stability associated with their use Remifentanil is an ultra–short-acting synthetic opioid that is metabolized by plasma cholinesterase; it may have particular utility when deep sedation and analgesia are required along with the ability to assess neurologic status intermittently
INHALATIONAL AGENTS	
Nitrous oxide	Causes amnesia and mild analgesia at low concentrations Danger of hypoxic mixture if the oxygen concentration is not monitored and preventive safety mechanisms are not in place
Potent vapors, sevoflurane, desflurane, isoflurane	"Complete anesthetics"—they induce a state of hypnosis, analgesia, and amnesia All are myocardial depressants, and some are vasodilators May trigger malignant hyperthermia in susceptible individuals Sevoflurane is almost universally used for inhalation induction of anesthesia in children All are bronchodilators at equipotent concentrations Isoflurane, and especially desflurane are associated with a higher incidence of laryngospasm, when used for anesthetic induction, than sevoflurane

for all children. Careful attention to a child's preoperative condition is mandatory for minimizing the risk during perioperative care (see Tables 61-3 and 61-4).

INDUCTION OF GENERAL ANESTHESIA

The goal of induction of general anesthesia is to rapidly achieve surgical anesthesia by using IV or, more commonly in children, inhalational induction agents. In children who are too young to tolerate the establishment of vascular access before the induction of anesthesia, it is routine to induce anesthesia by mask inhalation of volatile anesthetics. In the operating room, a child is often accompanied by the parents (parental presence during induction [PPI]) and placed on the operating room table. Before the induction of anesthesia, monitors are usually applied to the child. These include a pulse oximeter, electrocardiogram electrodes, and a blood pressure cuff. The child is then cautiously introduced to the face mask, which contains a high gas flow (5-7 L/min of oxygen), frequently mixed with nitrous oxide. Inhalation of nitrous oxide and oxygen for 60-90 sec induces a state of euphoria. The airway responses to inhalational anesthetics are now blunted, and sevoflurane can be introduced into the inhaled gas mixture. This leads to unconsciousness within 30-60 sec while the child continues to breathe spontaneously.

The child is now "asleep," and the parents can be asked to leave. An IV line is then started, and comprehensive intraoperative monitoring initiated. Surgical anesthesia can be maintained by spontaneous ventilation with a mask; this is safe only when the airway is secure and patent, the stomach is empty, and the child is older than 6 mo of age. Procedures longer than 1 hr are not usually performed with mask inhalational anesthesia. If these conditions are not met, if the surgeon needs to approach the airway, or if muscular paralysis is required, then the airway must be secured with endotracheal intubation. Although endotracheal intubation can be performed under deep inhalational anesthesia with respiratory depression and obtunded cough and gag reflexes, the depth of anesthesia required to ablate airway reflexes is very close to the level that induces hemodynamic instability. Therefore, muscle relaxation with IV, nondepolarizing muscle relaxants is induced to facilitate endotracheal intubation. *Succinylcholine is rarely, if ever, used*. After paralysis is induced, direct laryngoscopy and airway intubation can be performed. Correct endotracheal tube placement is confirmed by direct laryngoscopy, end-tidal CO_2 measurement, endotracheal tube fogging, and the finding of bilaterally equal breath sounds during positive-pressure ventilation. If necessary, fiberoptic airway endoscopy and chest radiograph, in addition to these measures, can be used to confirm correct endotracheal tube placement.

After endotracheal intubation, spontaneous ventilation may be permitted, if muscle relaxants are not used or have worn off; it is routine to provide controlled mechanical ventilation. When the child is completely anesthetized, positioned for surgery, and hemodynamically stable, and maintenance anesthesia is achieved, the surgery can begin.

Inhalational Anesthetics

General anesthesia may be induced and maintained by either inhalation or the IV route. The inhalational anesthetics used in children include sevoflurane, isoflurane, and desflurane. Although halothane is the prototypical pediatric inhalational anesthetic agent, it has been replaced by sevoflurane and is no longer used in the United States.

The *minimal alveolar concentration* (MAC) of an inhalational anesthetic is the alveolar concentration (expressed as percent at 1 atmosphere) that provides sufficient depth of anesthesia for surgery in 50% of patients. For potent inhalational agents, the alveolar concentration of an anesthetic reflects the arterial concentration of anesthetic in the blood perfusing the brain. Thus, the MAC is an indication of anesthetic potency and is analogous to the ED_{50} (effective dose in 50% of recipients) of a drug. MAC is age-dependent, is lower in premature infants than in full-term infants, and decreases from term through infancy to preadolescence. In adolescence, MAC again increases, falling thereafter. Inhalational anesthetic agents are poorly soluble in blood but rapidly equilibrate between alveolar gas and blood.

Respiratory Effects

The advantages of inhalational anesthesia are rapid onset, rapid offset, convenient route of delivery and excretion (respiratory), and the ability to provide profound analgesia and amnesia. Inhalational anesthetics are all airway irritants and, in low doses, can cause laryngospasm. All inhalational anesthetics depress ventilation in a dose-dependent manner. Thus, expired CO_2 and Pa_{CO_2} (arterial partial pressure of carbon dioxide) increase in spontaneously breathing children. In addition, anesthesia also decreases end-expiratory lung volume. Small lung volumes result in a decrease in lung compliance, increases in total pulmonary resistance, work of breathing, and intrapulmonary arteriovenous shunting, and a restrictive lung defect. Inhalational anesthetics also shift the CO_2 response curve to the right, thus decreasing, but not ablating, the increase in minute ventilation with increasing Pa_{CO_2}.

Inhalational anesthetics, which may induce apnea and hypoxia in premature infants and newborns, are less frequently used in premature infants and children. In neonates and young infants, general anesthesia always necessitates endotracheal intubation and controlled mechanical ventilation. In older children, spontaneous breathing through a mask or a laryngeal mask airway without controlled ventilation is possible for shorter operations. The decreased end-expiratory lung volume and increased work of breathing always necessitate higher inspired oxygen tension.

Cardiovascular Effects

Cardiovascular effects of inhalational anesthesia include depressed cardiac output and peripheral vasodilation; hypotension is frequent. *This is accentuated in hypovolemic patients*. This hypotensive effect is more pronounced in neonates than in older children and adults. Inhalational anesthetics also decrease baroreceptor and heart rate responses. Inhalational anesthesia blunts the hypoxic pulmonary vasomotor response in the pulmonary circulation, an effect that may contribute to hypoxemia.

The net effect of inhalational anesthesia is decreased oxygen delivery. Perioperatively, catabolism is enhanced and oxygen demand is increased; there may be a profound imbalance between oxygen demand and oxygen delivery. Development of a metabolic acidosis intraoperatively may reflect this imbalance. Because the cardiovascular depressant effects of inhalational anesthesia are greater in premature and newborn infants, these agents are of limited use in such patients.

All inhalational anesthetic agents cause *cerebrovasodilation*. Sevoflurane is a more potent cerebrovasodilator than isoflurane. Thus, in children with elevated intracranial pressure, impaired cerebral perfusion, or head trauma, and in premature neonates at risk for intraventricular hemorrhage, inhalational anesthetics should be used with extreme caution. Although inhalational anesthetics decrease cerebral oxygen consumption, they may disproportionately decrease blood flow, thus worsening oxygen delivery.

Specific Anesthetics

Sevoflurane

Sevoflurane is the most commonly used inhalational anesthetic in children for both induction and maintenance of general anesthesia. It is not a significant airway irritant and leads to smoother induction than isoflurane. Emergence from sevoflurane anesthesia is quite rapid; there is a significant amount of **emergence delirium**, especially if pain has been inadequately controlled or induction was stormy and preoperative anxiety high. This effect can be blunted by pretreatment with midazolam and adequate use of opioids, although the latter delay recovery from anesthesia. Metabolism of sevoflurane yields free fluoride, which may cause renal damage; consequently, the FDA has restricted the use of sevoflurane to <2 MAC hr, preferably with fresh gas flow rates >2 L/min.

Isoflurane

Isoflurane maintains cardiac output and cerebral perfusion more effectively than sevoflurane. Isoflurane is pungent and a significant airway irritant, with an unacceptably high incidence of complications, such as laryngospasm during induction. Emergence from anesthesia with

isoflurane is quite smooth, but slower than for sevoflurane. Cerebral blood flow is only minimally affected, and cerebral oxygen delivery is maintained. Because isoflurane is not a suitable induction agent, induction with sevoflurane or with an intravenous agent, and maintenance with isoflurane is a common pediatric anesthesia practice.

Desflurane

A potent airway irritant, desflurane causes coughing, breath holding, and laryngospasm during induction and therefore is unsuitable for induction. It is frequently used for maintenance of anesthesia, and emergence from desflurane anesthesia is rapid.

Nitrous Oxide

Nitrous oxide is a tasteless, colorless, odorless gas with potent analgesic properties. It induces a state of euphoria (hence its nickname, "laughing gas"). The MAC of nitrous oxide is >100; consequently, it is not suitable as a sole agent to maintain anesthesia. Nevertheless, nitrous oxide has few complications and produces little or no hemodynamic or respiratory depression. Commonly, during maintenance of general anesthesia, the inhalational gas mixture is 70% nitrous oxide and 30% oxygen, with the addition of an inhalational anesthetic or potentiation of analgesia with an opioid or a hypnotic agent. The deleterious effects of nitrous oxide are increased postoperative nausea and vomiting and, with long-term use (days), bone marrow suppression. Although there is no evidence of harmful sequelae of the use of nitrous oxide for routine anesthesia, its use has decreased because of the greater incidence of nausea and vomiting associated with it. Nitrous oxide is a potent analgesic that is safely used in a mixture of 50% nitrous oxide and oxygen (Entonox) in obstetrics and in emergency departments to provide analgesia. Although this combination appears to be safe, it potentiates the respiratory depressive effects of opioids, and its use, in combination with any other sedative, hypnotic, or opioid agent, requires very close monitoring because it may produce general anesthesia.

Intravenous Anesthetic Agents

Anesthesia can be both induced and maintained with either intermittent boluses or continuous infusions of IV anesthetic agents. Intravenous anesthetics include barbiturates, opioids, benzodiazepines, and miscellaneous drugs, such as propofol and ketamine. Intravenous anesthetic agents can induce anesthesia more rapidly than inhalational anesthetics, with fewer complications. Vascular access is required, so unless IV access has already been obtained, inhalation induction is the preferred route. For children arriving in the operating room with vascular access, IV induction should be routine, because it rapidly takes the child from the awake state to the anesthetized state with less psychologic and cardiorespiratory compromise than occurs with inhalational induction. All IV agents affect cardiorespiratory function. The 1 exception to this may be ketamine, which, in lower doses, releases catecholamines, which maintain cardiac function and blood pressure.

Propofol

Propofol is the most commonly used IV induction agent in pediatric anesthesiology and has a rapid onset. In doses of 2-3 mg/kg, propofol induces both respiratory depression and hypotension. Propofol can sometimes burn and itch on injection. It is formulated in 10% soy emulsion with egg emulsifiers, so is contraindicated in patients with soy or egg allergy. After induction of anesthesia, propofol is also a useful agent for maintaining hypnosis and amnesia, and can be used as a sole anesthetic agent for nonpainful procedures, such as radiation therapy, MRI, and CT studies. Combined with opioids, it provides excellent, brief anesthesia for painful procedures, such as lumbar puncture and bone marrow aspiration. Propofol is a general anesthetic agent that obtunds airway reflexes, respiration, and hemodynamic function; it should not be considered a "sedation agent." Although hemodynamic stability, and even spontaneous respirations, can be maintained with cautious propofol sedation, its use for prolonged sedation over several hours to days in children younger than 12 yr is associated with hemodynamic collapse, bradycardia, metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidemia, profound shock, and death (**propofol infusion syndrome**). Its use for prolonged sedation (>12 hr) in the critical care setting in children is contraindicated.

Barbiturates

The most commonly used barbiturate for IV induction is sodium thiopental, although it is now rarely used. Although loss of consciousness is rapid, barbiturates do not provide analgesia. Thiopental depresses respiration, induces apnea, and can cause hypotension in the hypovolemic patient. Induction with 3-5 mg/kg of thiopental usually produces 5-10 min of unconsciousness within seconds. After IV induction with sodium thiopental, maintenance anesthesia can be established using benzodiazepines, IV opioids, or inhalational anesthetics.

Pentobarbital is commonly used for sedation in children. It is an IV drug that induces loss of consciousness. It is also a potent respiratory depressant, particularly when used in conjunction with opioids and benzodiazepines. Pentobarbital has a very prolonged effect. It is not an analgesic agent, and painful procedures cannot be performed with pentobarbital sedation without supplemental analgesia. Pentobarbital sedation that is deep enough for anxiolysis and nonpainful procedures generally results in prolonged sleep. Its potency and long duration of action make it difficult to titrate. It is not an ideal drug for sedation for short or painful procedures.

Sodium methohexital (Brevital) is another IV induction agent. It is similar to sodium thiopental and has a similar spectrum of respiratory depression.

Etomidate

Etomidate is an imidazole derivative used for the induction of anesthesia, frequently in emergency situations. Its action is not as rapid as that of propofol. The lack of cardiovascular depression has led to the use of etomidate in patients with hemodynamic compromise, cardiac disease, and septic shock. Unfortunately, by inhibition of 11β-hydroxylase, this agent depresses synthesis of both mineralocorticoids and glucocorticoids for up to 72 hr following a single induction dose. Etomidate increases mortality when used as a sedative in ICUs (for which it is now contraindicated) and when used in patients who receive merely an induction dose. Adrenal suppression by etomidate further complicates the management of the very patients with hemodynamic compromise in whom the agent has been indicated. The decision to continue use of this agent must weigh the serious risks against the short-term benefit of hemodynamic stability during anesthesia induction and sedation.

Ketamine

Ketamine rapidly induces general anesthesia that lasts for 15-30 min when given at 1-3 mg/kg IV. It has few side effects and can maintain adequate blood pressure and cardiac output. Ketamine is also effective when given intramuscularly, subcutaneously, nasally, or orally; the dose must be increased for these alternative routes. Ketamine dissociates the connections between the cortex and limbic system *(dissociative anesthesia)* by its inhibition of *N*-methyl-D-aspartate receptors, producing a unique anesthetic state. Ketamine is not only a hypnotic agent, providing obtundation and loss of consciousness, but also an analgesic agent, and can act as a sole IV agent to provide general anesthesia. With low doses of this agent, airway reflexes and spontaneous ventilation may be maintained; at higher doses, loss of airway reflexes, apnea, and respiratory depression occur. It is unwise to rely on ketamine to prevent aspiration of gastric contents during deep sedation. Intravenous ketamine is a useful general anesthetic agent for short procedures.

Ketamine produces disturbing postanesthetic dreams and hallucinations. These can occur at the time of emergence from anesthesia and for several weeks. In adults, the incidence of this effect is 30-50%; in prepubertal children, it may be 5-10%. Premedication with a benzodiazepine, such as midazolam, greatly reduces these sequelae; a benzodiazepine is routinely given to children receiving ketamine anesthesia. The other side effect of ketamine is that it is a potent secretagogue, enhancing oral and bronchial secretions. A drying agent, such as atropine or glycopyrrolate, is administered before the administration of ketamine.

A bronchial smooth muscle relaxant (bronchodilator), ketamine is a useful agent for sedating asthmatic patients and others in the ICU. Ketamine has been reported to increase intracranial pressure and therefore is not indicated in patients at risk for elevated intracranial pressure. Ketamine can increase myocardial oxygen demand and should be used cautiously in patients with impaired myocardial oxygen delivery or cardiac outflow tract obstruction.

Opioids

Opioids are superb analgesic agents, providing analgesia for painful procedures and postprocedural pain (see Chapter 62). Large doses of morphine (0.5-2 mg/kg), combined with nitrous oxide, provide adequate analgesia for painful procedures and surgery. Opioids suppress the CO_2 response, can induce apnea, and are respiratory depressants. Morphine is often associated with hypotension and bronchospasm from histamine release; it is used with caution in children with asthma. Morphine is a long-acting agent, and an equivalent dose per kilogram gives much higher blood levels in neonates than in older children, with plasma concentrations approximating 3 times those in adults. This reason for this difference is the longer elimination half-life (14 hr) in children than in adults (2 hr). Because of the prolonged activity and hemodynamic instability induced by morphine, the fentanyl class of synthetic opioids has replaced it.

Fentanyl is an effective agent to provide pain relief, analgesia, and sedation for painful procedures, with a shorter duration of action and a more stable hemodynamic profile than morphine. In equal analgesic doses, all opioids are equally potent respiratory depressants. Other anesthetic agents potentiate this respiratory depression, whether they are inhalational anesthetics or IV barbiturates or benzodiazepines.

Fentanyl use at 30-50 μg/kg obtunds the hemodynamic response to surgery and provides stable operating conditions. Effective analgesia and anesthesia can be provided with IV fentanyl in a 2-3 μg/kg bolus followed by a 1-3 μg/kg/hr continuous infusion. Hemodynamic effects can be blunted and recall totally obtunded with use of a nitrous-narcotic anesthetic technique, although muscle tone may remain high and spontaneous movements can occur. Nitrous-narcotic anesthetics usually are supplemented with a nondepolarizing muscle relaxant during maintenance anesthesia. If the patient will be extubated and resume spontaneous ventilation, reversal of the muscle relaxant is necessary.

Other synthetic opioids (sufentanil, alfentanil, remifentanil) are available, but fentanyl is the most commonly used opioid. Both sufentanil and alfentanil have been used for cardiac anesthesia; their potency is different from that of fentanyl. Alfentanil appears to cause an increased incidence of muscle rigidity, convulsions, and prolonged respiratory depression compared with fentanyl, and is not used in children.

Remifentanil has very rapid onset and offset of action. In doses of 0.25 μg/kg/min, surgical anesthesia can be maintained with this agent. Its short half-life and rapid offset are advantageous for rapid emergence from anesthesia. Unfortunately, its rapid offset of action also leads to postprocedural and postoperative pain and requires analgesic supplementation, frequently with an opioid, which removes the advantage of anesthesia with a short-acting opioid. Remifentanil may have a role in providing rapidly deepening anesthesia for particularly painful events or rapidly inducing analgesia. It is also used intraoperatively by continuous infusion to maintain anesthesia. It is a potent respiratory depressant and provides no postprocedural analgesia, features that limit its use.

Benzodiazepines

Benzodiazepines induce hypnosis, anxiolysis, sedation, and amnesia, and have anticonvulsant activity. In larger doses, they cause respiratory depression and apnea; they are synergistic with opioids and barbiturates in their respiratory depressant effects. Benzodiazepines are γ-aminobutyric acid agonists.

The most commonly used benzodiazepine in pediatric anesthesia is midazolam. Short acting and water soluble, it can be injected intravenously without pain. It is a potent hypnotic–anxiolytic–anticonvulsant and is approximately 4 times more potent than diazepam. In anxiolytic doses, midazolam (0.15 mg/kg) has no effect on respiratory rate, heart rate, or blood pressure, and provides excellent preoperative sedation that is frequently accompanied by amnesia. It can be administered orally, nasally, rectally, intravenously, or intramuscularly. Use of oral midazolam at a dose of 0.5-1.0 mg/kg, mixed in sweet, flavored syrup, induces anxiolysis in approximately 90% of children. This agent has no hemodynamic, oxygenation, or respiratory depressant effects at this dose level, but when midazolam is used as a sole agent, children may frequently lose their balance and head control, may have blurred vision, and, rarely, may become dysphoric. A child sedated with midazolam should not be left unattended and is not safe walking. Most children rapidly accept an inhalational anesthetic mask after oral midazolam premedication. The widespread use of preoperative oral midazolam has decreased the practice of PPI to calm younger children.

Dexmedetomidine

Dexmedetomidine is an IV agent that obtunds consciousness through central α_2-receptor stimulation, much like clonidine. It appears to cause no respiratory depression and produces anxiolysis, sedation, and mild analgesia. It is a sympatholytic, and its side effects include hypotension and bradycardia. Dexmedetomidine is commonly used for sedation in ICU patients as well as for procedures; it is being explored as an adjuvant for general anesthesia, especially in cardiac patients.

Complications During Induction of Anesthesia

The period between full wakefulness, with the child in control of airway reflexes, and general anesthesia, with total loss of control, is fraught with difficulty. During induction, laryngospasm, bronchospasm, vomiting, pulmonary aspiration of gastric contents, and subsequent aspiration pneumonitis pose a constant threat although they rarely occur. Concern about vomiting and aspiration dictates the use of preanesthetic fasting (NPO [nothing by mouth]) guidelines and indicates rapid sequence anesthetic induction.

Laryngospasm is the most common complication. During induction of anesthesia, especially with inhalational anesthetics, a period of excitement may occur. This period is associated with heightened airway reflexes, which can lead to coughing, gagging, laryngospasm, and bronchospasm. Laryngospasm is reflex closure of the larynx, which makes it impossible for the child to breathe or for assisted ventilation to be used. The child may make violent inspiratory efforts against a closed glottis, generating significantly negative intrathoracic pressure. This may affect cardiovascular function and cause postobstructive pulmonary edema. Laryngospasm can be prolonged, and hypoxia may ensue. Laryngospasm occurs in up to 2% of all anesthetic inductions in children younger than 9 yr and is half as common in older patients. Laryngospasm occurs twice as frequently in children with active or recent upper respiratory tract infection (URI). A history of passive smoking from environmental (parental) tobacco smoke increases the likelihood of laryngospasm 10-fold, and even more if the smoker is the child's mother.

Laryngospasm can be relieved during induction of anesthesia by increasing the anesthetic dosage, either intravenously or through inhalation (although with the glottis closed, further administration of inhalational anesthesia is not possible). Muscle relaxation relieves laryngospasm, and in an acute situation, this situation may be an indication for succinylcholine. Constant positive airway pressure administered by someone skilled in airway management to ensure patency of the soft tissues of the oropharynx may be beneficial in alleviating laryngospasm. Laryngospasm may also occur during emergence from anesthesia, because a state of excitement is again traversed between deep anesthesia and wakefulness.

Bronchospasm can occur during induction, either in response to histamine release as a result of many of the anesthetic agents or as part of a hyperexcitable stage. Endotracheal intubation may also induce bronchospasm during induction. Bronchospasm during induction is particularly common in children with asthma. Bronchospasm secondary to intubation in a patient with reactive airway disease can be severe, may be associated with life-threatening hypoxemia, and may make it

impossible to ventilate the child. The use of histamine-releasing anesthetic agents has been associated with total airway obstruction, respiratory failure, and cardiac arrest. Environmental tobacco smoke is a risk factor.

Other pulmonary problems with induction of anesthesia include massive atelectasis with hypoxemia, impaired ventilation and perfusion, blunted hypoxic pulmonary vasoconstriction, and increased airway secretions with decreased bronchociliary function. **Hypersecretion** is prevented by the routine use of antisialagogues, such as atropine. The newer inhalation agents are less-potent secretagogues, and the use of atropine premedication is much less common, but is probably indicated if ketamine is used.

Hemodynamic complications upon anesthesia induction include **hypotension,** which can be profound in hypovolemic patients; decreased myocardial function, which can be severe in patients with compromised cardiac function; and tachycardia and cardiac dysrhythmias. Inhalational anesthetics sensitize the myocardium to circulating catecholamines, and induction and excitement are associated with a hypercatecholaminergic state.

Parental Presence During Induction of Anesthesia

Parents may expect to be with their child during the induction of anesthesia. Removing a terrified child from the comforting arms of a parent is stressful for the child, the parent, and the caregivers. If this parental separation cannot be achieved comfortably with preoperative psychoprophylaxis and behavioral modification, including education and desensitization to the operative environment, or with pharmacologic aids, such as preoperative medications including benzodiazepine and barbiturates, then there may be a need to defer parent–child separation until general anesthesia is induced. Preoperative medication with oral benzodiazepine more frequently provides calm, smooth induction conditions than PPI without pharmacologic preparation. Although the use of PPI in the hands of a confident, competent anesthesia practitioner can replace the need for preoperative medication, it does not reliably predict smooth induction. PPI appears to decrease neither emergence phenomena nor the incidence of postoperative behavioral changes, and it does not appear to add an advantage for the child over that provided by preoperative sedative medication, such as with oral midazolam.

MAINTENANCE OF ANESTHESIA

Maintenance of anesthesia is the period between induction and emergence. The child should be asleep, unaware of pain, unresponsive with either motion or hemodynamic responses to painful stimuli, and homeostatically supported. The child is comatose, without airway-protective reflexes and with suppression or absence of respiration, and has received drugs that suppress hemodynamic adaptive responses. The child is also exposed to surgical trauma, and there may be blood loss and significant fluid shifts (third spacing), decreased intravascular volume, and hypothermia.

Anesthesia is usually maintained with or without nitrous oxide, an inhalational anesthetic such as isoflurane or sevoflurane, and an opioid for intraoperative analgesia, potentiation and deepening of anesthesia, and postoperative analgesia. A benzodiazepine is added either during premedication or intraoperatively to supplement hypnosis and amnesia. A nondepolarizing muscle relaxant (vecuronium or rocuronium) completes the pharmacologic maintenance of anesthesia. Agents can be given by continuous inhalational anesthesia or by continuous or bolus IV infusion.

During maintenance, the child may breathe spontaneously through an anesthetic mask or endotracheal tube or may be mechanically ventilated. All general anesthetic agents decrease end-expiratory lung volume, which is generally lower than functional residual capacity, with increases in pulmonary closing capacity and intrapulmonary shunt. Hypoxia would occur without supplemental oxygenation. These effects are compounded by respiratory depressant effects and the depressed CO_2 response curve. Therefore, it is generally considered that use of anesthetics for longer than 1 hr requires endotracheal intubation and positive-pressure ventilation. For long procedures, spontaneous breathing through a mask is possible; in smaller children, in whom the surgical field and the airway may be close together, the need to maintain a patent airway necessitates endotracheal intubation.

Muscle relaxation to facilitate endotracheal intubation was once accomplished with succinylcholine. This agent has a high-risk profile, however, and is associated with postoperative pain (muscle spasms); hyperkalemia; elevated intracranial, intraocular, and intragastric pressures; malignant hyperthermia; and myoglobinuria and renal damage. Succinylcholine is now rarely used, except to provide rapid relief of laryngospasm. Intubation of the airway is facilitated with a nondepolarizing, short-acting muscle relaxant. Rocuronium is the drug most commonly used for intubation. For procedures that last longer than 40 min, vecuronium and alcuronium are suitable to induce muscle relaxation for intubation. After intubation of the airway, the decision must be made whether to maintain muscle relaxation to facilitate surgery or to allow the child to resume spontaneous respiration. Prolonged use of a nondepolarizing muscle relaxant is common practice but may contribute to postoperative respiratory compromise if it is not fully reversed with appropriate agents.

Reversal of neuromuscular blockade is standard anesthetic practice. Effects of nondepolarizing muscle relaxants are reversed by increasing the concentration of acetylcholine with neostigmine (acetylcholine esterase inhibitor) and either atropine or glycopyrrolate to prevent the vagal effects. With the virtual abandonment of succinylcholine, only nondepolarizing muscle relaxants are routinely used for intubation. The termination of their action depends on metabolism and elution away from the neuromuscular junction. This process, even for the shortest-acting muscle relaxants (rocuronium), can take several minutes. An intubating dose of rocuronium to rapidly induce paralysis in emergency situations may not spontaneously reverse for 20 min or longer (compared with ≈3 min for succinylcholine). If the airway cannot be secured, disaster may follow in the child who is unable to breathe spontaneously and in whom blockade cannot be reversed.

Thermoregulation is critical during anesthesia. The absence of movement and the inhibition of shivering lead to difficulty in thermogenesis. All the contributors to heat loss—convection, radiation, evaporation, and conduction—occur during anesthesia. Humidification and warming of inspired air are required. Additional warming devices are commonly used, such as rewarming blankets. General anesthetic agents increase the interthreshold range (the minimal temperature change that will lead to sympathetic response, generally 0.3°C [0.5°F]). Although temperature sensing may remain normal, an autonomic response to hypothermia is not triggered. Anesthetic agents cause vasoparesis, which further impairs thermoregulation and increases heat loss. In newborns, inhalational anesthetics inhibit nonshivering thermogenesis from brown fat, putting them at higher risk for hypothermia.

Fluid Maintenance During Surgery and Anesthesia

Patients who are unconscious and immobile have lost venous pump mechanisms and have peripheral venous pooling. Anesthetic agents cause vasodilation, and anesthetized patients have relative hypovolemia. Intravascular volume expansion is frequently required after the induction of anesthesia to maintain adequate perfusion, tissue oxygenation, urine output, and blood pressure. Volume expansion is most commonly provided by isotonic salt-containing solutions (normal saline, lactated Ringer solution). Autonomic responses may be increased as part of the surgical stress response, with vasoconstriction and intravascular volume contraction caused by diuresis, intravascular volume loss from hemorrhage, evaporation (insensible loss, increased during surgery), and third space (interstitial space) fluid losses resulting from the inflammatory response. Abnormalities in the distribution of renal blood flow and secretion of antidiuretic hormone further complicate the regulation of intravascular volume.

The concern about **hypoglycemia** as a result of preoperative fasting led to the recommendation that infants and small children receive

Table 61-6	Intraoperative Pediatric Fluid Replacement
4 mL/kg/hr	1-10 kg
2 mL/kg/hr	10-20 kg
1 mL/kg/hr	per kg >20 kg
Example: a 22-kg child requires: (4 × 10) + (2 × 10) + (1 × 2) = 62 mL/hr	

isotonic solutions with 5% glucose. The occurrence of hyperglycemia and potential neurologic injury during cardiopulmonary bypass, or during neurosurgery and other situations in which central nervous system injury can occur, however, along with the recognition that hypoglycemia is rare in nonneonates, has called into question the routine use of glucose-containing solutions. In neonates, glucose monitoring during and after anesthesia is indicated. In older children with normal nutritional status, isotonic salt solutions without additional glucose are adequate. In children who are receiving parenteral alimentation with a solution containing a high glucose concentration (>10%), continuation of the glucose concentration should be ensured to avoid rebound hypoglycemia, which would occur if the high-glucose solution was stopped.

Intraoperative fluid maintenance includes (1) current maintenance fluids and replacement of usual deficits during the NPO period; (2) replacement of third space losses; and (3) replacement of extraordinary losses (hemorrhage). Infants should receive glucose-containing isotonic fluids, such as 5% dextrose in water with either 0.25 normal saline or isotonic crystalloid solutions. Table 61-6 is a guideline for determining fluid deficits and maintenance requirements in the operating room. Fluid deficits should be replaced over the 1st 2 or 3 hr of intraoperative management. Deficits are generally calculated as the number of hours of NPO status multiplied by the hourly maintenance rate for the child. Half of this deficit is replaced during the 1st hr and half during each of the subsequent 2 hr. If hypotension or tachycardia occurs or persists in the early stages of anesthesia, more rapid replacement of the fluid deficit is indicated. The deficit is replaced with isotonic crystalloid solutions.

Third space losses are replaced with isotonic salt solutions. For large operations, such as abdominal or thoracic procedures, during which there may be a large amount of evaporative loss as well as a significant amount of third space loss, 8-10 mL/kg per hr of surgery is generally given as IV fluid replacement. For smaller operations, such as herniorrhaphy, pyloromyotomy, and minor procedures, fluid replacement at 3-5 mL/kg/hr is indicated for third space losses. Even when surgery involves the extremities and third space losses are minor, it is wise to give an additional 1-2 mL/kg/hr to replace them.

A crystalloid solution is indicated for blood loss, at 3 mL per mL of blood lost. This formula could be reduced somewhat if blood is replaced on an mL-per-mL basis with packed red blood cells or whole blood equivalent. The use of albumin or other suitable colloid, such as fresh-frozen plasma in neonatal surgery, also decreases the amount of crystalloid replacement needed for blood loss. During maintenance anesthesia, if large-volume transfusions are required, warming the blood and crystalloid solutions avoids hypothermia. With major surgery and the resultant systemic inflammatory response syndrome, capillary integrity is lost and third space losses are common. Failure to replace this third space loss and restore intravascular volume leads to hypotension, shock, acidemia, and renal failure, and further stimulates the systemic inflammatory response syndrome.

RECOVERY FROM ANESTHESIA

Recovery from anesthesia includes emergence and postoperative recovery from surgery and anesthetics. **Emergence** describes the time and the physiologic response to decreasing depth of anesthesia during return to consciousness. During emergence, patients experience decreased anesthetic effect, increased stress responses, physiologic and psychologic responses to painful stimuli, excitement, and anxiety. Conscious realization of pain may lead to physiologic responses during emergence. Normal physiologic functions, such as spontaneous ventilation, resume and hemodynamic function improves. After routine elective procedures, the child should be fully conscious before leaving the operating room, with intact airway reflexes, the ability to follow simple commands, the effects of muscle relaxants reversed, and airway patency maintained. If the child is going to the ICU, or if for surgical reasons the decision is made to leave the child intubated, analgesia and sedation should be maintained, along with mechanical ventilation, in the postoperative period. Ideally, emergence should be as brief as possible, with maintenance of analgesia and anxiolysis and restoration of cardiorespiratory function. Inhalational anesthetic agents leave the system rapidly during ventilation, and muscle relaxants can be reversed; however, the effects of opioids, benzodiazepines, and IV hypnotic agents may be prolonged.

During emergence, the decision must be made whether to reverse the effects of muscle relaxants. The effects of long-acting, nondepolarizing muscle relaxants (vecuronium and pancuronium) are invariably reversed. If the child appears to be weak or to have respiratory depression in the postoperative phase, prolonged neuromuscular blockade should be considered.

POSTANESTHESIA CARE UNIT

In the postanesthesia care unit (PACU), the child is observed until there is adequate recovery from anesthesia and sedation. Parents should be permitted to comfort their children in the PACU. Achievement of spontaneous breathing, adequate arterial saturation (>95%), and hemodynamic stability are key recovery end points. The child should be arousable, responsive, and oriented before discharge from the PACU. The amount of time spent in the PACU depends on whether the child is being discharged to an inpatient nursing unit, to an ICU, to a postrecovery area, or directly home. Discharge from the PACU depends on the child's overall functional status—not merely the physiologic end points, but also the behavioral end points as well as the adequate provision of analgesia and control of postoperative nausea and vomiting. There are several scoring systems (Table 61-7) for determining whether a child is ready to be discharged from the PACU.

Complications in the Postanesthesia Care Unit

Respiratory Depression

Prolonged emergence from anesthesia and respiratory depression can be caused by opioids or inadequate antagonism of neuromuscular blocking agents. Pain can cause significant hypoventilation, especially after thoracic or abdominal surgery. Delayed emergence from anesthesia can occur as a result of retention of inhaled anesthetic agents worsened by hypoventilation. Hypothermia, especially in neonates, delays metabolism and excretion of anesthetics and also aggravates neuromuscular blockade. If respiratory depression is profound, then maintenance of the airway may require an oral airway. If the depression is severe, endotracheal intubation and mechanical ventilation are indicated.

Only in rare cases, in which **opioid suppression** is suspected, is reversal of the effects of opioid with naloxone indicated. Opioid reversal with naloxone reverses not only the respiratory depression but also the analgesia. A somnolent child with respiratory depression may become excited, agitated in severe pain, uncontrollable, and/or hypertensive after naloxone. Opioid reversal necessitates bedside attention by the physician to monitor the child's behavioral, hemodynamic, and respiratory status. *Naloxone is shorter-acting than most opioid analgesics.*

Atelectasis is another respiratory complication occurring in the 1st 48 hr after anesthesia. Although atelectasis suggests an inhaled foreign body, it is most likely caused by secretions and decreased respiratory effort secondary to pain. Microatelectasis may lead to postoperative infections. Aspiration pneumonia is another postoperative complication.

Postoperative stridor occurs in up to 2% of all pediatric patients. The use of uncuffed, atraumatic, nonirritant endotracheal tubes has decreased the incidence of airway trauma. The use of appropriately sized endotracheal tubes and assurance of an air leak <30 cm H_2O

Table 61-7 Recovery Scores

ALDRETE RECOVERY SCORE	>9 REQUIRED FOR DISCHARGE
ACTIVITY—VOLUNTARILY OR ON COMMAND	
Moves 4 extremities	2
Moves 2 extremities	1
No motion	0
BREATHING	
Deep breath, cough, cry	2
Dyspnea or shallow breathing	1
Apnea	0
BLOOD PRESSURE	
Within 20% of preanesthetic value	2
Within 20–50% of preanesthetic value	1
>50% outside preanesthetic value	0
COLOR	
Pink	2
Pale, blotchy, dusky	1
Cyanotic	0
CONSCIOUSNESS	
Fully aware, responds	2
Arouses to stimulus	1
Unresponsive	0
STEWARD RECOVERY SCORE	**6 REQUIRED FOR DISCHARGE**
ACTIVITY	
Moves limbs purposefully	2
Nonpurposeful movement	1
Still	0
CONSCIOUSNESS	
Awake	2
Responsive	1
Unresponsive	0
AIRWAY	
Coughing on command or crying	2
Maintaining patent airway	1
Requires airway maintenance	0

pressure further decreases the risk of airway trauma. A history of stridor increases the likelihood of postoperative complications. Stridor may be severe enough after extubation to require reintubation. Retractions and respiratory distress in the postoperative period should suggest this complication, and stridor or wheezing should confirm the diagnosis. Racemic epinephrine aerosols are effective therapy; their use requires prolonged observation because of the potential for recurrence of the airway obstruction. Stridor in infants suggests the need for overnight observation.

Hemodynamic instability is much less common in the PACU. Volume expansion may be required to maintain adequate blood pressure, peripheral perfusion, and urine output. Requirement for excessive volume replacement (>30 mL/kg) to maintain blood pressure, perfusion, and urine output in the postoperative period is an indication of shock and occult bleeding, and it necessitates surgical consultation.

Emergence delirium is noted in <3% of children and is more common in those 3-9 yr old. In the immediate hour after surgery, children may become extremely restless, combative, and disoriented, and may be screaming, inconsolably crying, or poorly communicative. These children pose a danger to themselves. This phenomenon is more common when barbiturates are used as part of premedication or induction and inhalational anesthetics or ketamine forms part of the maintenance anesthetic. Although disorientation is common in the postanesthetic stage, erratic, delirious behavior requires attention, with gentle restraint, a quiet environment, and comforting. Potential postoperative complications, such as hypoglycemia and hypoxemia, should be ruled out. Occasionally, it is necessary to sedate the child with benzodiazepines, although these agents prolong postanesthesia recovery time and when they wear off, emergence delirium may recur.

Awareness During Anesthesia

A primary goal of anesthesiology is obtunding consciousness to ablate awareness during procedures and recall afterward. In adults, certain anesthetic techniques are associated with an unacceptably high incidence of recall during anesthesia. Awareness and recall of events during a surgical procedure can be unpleasant and terrifying; the long-term sequelae of such recall in children are unknown. Continuous monitoring of cerebral electroencephalographic function by monitoring of the bispectral index has been recommended. Unfortunately, data in children do not confirm the efficacy of bispectral index monitoring as a means of determining anesthetic depth, and this fact, combined with the absence of meaningful data on intraoperative awareness and recall in infants and children, does not currently support the routine use of bispectral index monitoring.

Postoperative Nausea and Vomiting

After general anesthesia, 40-50% of children may experience nausea and vomiting. More than 80% of all high-risk children receiving inhalational anesthesia experience postoperative nausea and vomiting (PONV). It may occur in the immediate postoperative period, within the 1st 1-2 hr, or several hours after surgery and anesthesia. The etiology may be related to the stress and trauma of surgery combined with the emetic effects of anesthetic agents. Pain is an important cause of nausea and vomiting. Opioid analgesics also induce nausea and vomiting. Preoperative fasting does not decrease the incidence of nausea and vomiting. Indeed, hydration and glucose supplementation appear to be important factors in decreasing PONV. The use of analgesic agents other than opioids (acetaminophen, ketorolac) and regional or local anesthesia is associated with decreased PONV.

This complication prolongs recovery room times, requires significant nursing attention, and increases the use of potent antiemetic agents (ondansetron, other serotonin antagonists). Ondansetron is very efficacious as a prophylactic and in the treatment of PONV. Ondansetron and other serotonin antagonists are recommended for high-risk patients (strabismus surgery) or for actual treatment of PONV. They are contraindicated in children taking serotonin reuptake inhibitors for migraine headaches. Metoclopramide is useful prophylactically. Droperidol (which has an FDA-required black box label warning) must be used with caution because of the rare occurrence of prolonged QT interval and ventricular arrhythmias associated with its use.

Thermoregulation and Malignant Hyperthermia

For patients in the PACU, thermoregulation remains abnormal for several hours. Shivering is common in the postoperative state, and a feeling of extreme cold is common. Warm blankets are very comforting and seem to decrease shivering. **Hypothermia,** especially in neonates, leads to hypotension, bradycardia, acidosis, apnea, and prolongation of the effect of opioids and neuromuscular blocking agents. Although hypothermia has deleterious effects, rewarming must be done cautiously to avoid burning and cutaneous hyperthermia. **Hyperthermia,** with temperatures in excess of 39°C (102.2°F), is of concern in the postoperative period. If it occurs within hours of the use of an inhalational anesthetic, especially if succinylcholine was used, malignant hyperthermia must be suspected.

Malignant hyperthermia is an acute hypermetabolic syndrome that is triggered by inhalational anesthetic agents and succinylcholine. It resembles neuroleptic malignant syndrome. The onset of malignant hyperthermia may be acute, and its course may be fulminant and rapidly fatal. This condition, albeit rare (approximately 1 in 60,000 pediatric patients given anesthesia) is a constant concern. The disease is familial, and a family history of death or a febrile reaction during anesthesia should alert the anesthesiologist to its potential. Its clinical course is characterized by rapid onset of fever, acidosis, hypercarbia, and increased expired CO_2. High fever (38.5-46.0°C [101.3-114.8°F],

rising 1°C [1.8°F] every 5 min), muscle rigidity, metabolic acidosis, and hemodynamic collapse can occur. Death ensues from shock and cardiac dysrhythmias with ventricular fibrillation that is unresponsive to treatment. The mortality rate for malignant hyperthermia was once >70%. Aggressive therapy, including discontinuation of all inhalational anesthetic administration, correction of the metabolic acidosis, and treatment with the muscle relaxant sodium dantrolene, has reduced the mortality rate to <5%. Dantrolene and a kit containing supplies necessary to treat malignant hyperthermia should be present at every site where pediatric anesthesia is provided.

Malignant hyperthermia is probably genetically heterogeneous, with more than 10 genes contributing to susceptibility. Genetic mutations in the ryanodine receptor (the calcium channel of the sarcoplasmic reticulum) have been reported in 20-40% of humans with malignant hyperthermia. **Certain myopathies** are associated with the risk of malignant hyperthermia; these include Duchenne muscular dystrophy, Noonan phenotype, and, in children with a history of ptosis, squint, scoliosis, and muscle cramping. It is wise to avoid the use of succinylcholine in children with myopathies.

Malignant hyperthermia appears to occur from a massive triggering of excitation contraction coupling, sarcolemmal calcium release, and propagation of contraction by a complex biochemical process. The prolonged ischemic contraction leads to myolysis, with release of myoglobin, very high serum creatine phosphokinase levels, and renal failure secondary to myoglobinuria. Malignant hyperthermia generally occurs within the 1st 2 hr of anesthesia, but (rarely) can occur up to 24 hr later.

Certain phenomena are clues to the risk of malignant hyperthermia. The occurrence of masseter spasm during induction, with rigid clenching of the masseter muscles and an inability to open the mouth, may presage full-blown disease. Acute myoglobinuria associated with a malignant hyperthermia triggering agent is another clue. The child may not be hypermetabolic or febrile, but may have dark urine and high serum creatine phosphokinase levels, with the risk of myoglobin-induced renal tubular damage. The finding of dark urine after administration of an anesthetic requires investigation for malignant hyperthermia. An elevated creatine phosphokinase value and heme-positive urine in the absence of red blood cells in the urine indicate a need for renal protection with mannitol and alkaline diuresis.

Rapid therapy is essential. All known triggering agents must be stopped. Intravenous administration of dantrolene sodium (2.5 mg/kg IV as an initial dose) is begun as soon as possible. The need for repeated doses is indicated by the persistence of muscle rigidity, acidosis, and tachycardia, up to a maximum dose of 10 mg/kg. Once the symptoms are controlled, the patient should be observed for at least 24 hr after the laboratory values have returned to normal, because relapse can occur.

Prevention of malignant hyperthermia in susceptible patients requires the avoidance of triggering agents, which include inhalational anesthetics. Most anesthesiology departments are capable of delivering general anesthetics using anesthesia machines from which all traces of anesthetic vapors have been removed. Intravenous anesthesia and a nitrous-opioid technique are safe. Dantrolene prophylaxis is not recommended because the disease is rapidly treatable and because the drug causes respiratory depression and muscle weakness. For a child in whom malignant hyperthermia is suspected, the malignant hyperthermia hotline, 1-800-MHHYPER (1-800-644-9737), should be used to notify the Malignant Hyperthermia Association of the United States (MHAUS). The Malignant Hyperthermia Association registers susceptible patients and provides diagnostic and therapeutic information. Preanesthesia susceptibility testing includes genetic analysis of the ryanodine receptor gene, muscle biopsies, in vitro contraction studies, and, possibly, measurement of muscle CO_2 production in response to intramuscular caffeine.

Postoperative Apnea

Apnea within the 1st 48 hr after surgery and anesthesia in premature infants is common; both central apnea and obstructive apnea (mixed apnea) may occur. The use of respiratory depressants may impair respiratory control in neonates. Apnea is also a recognized stress response in neonates, and inadequate anesthesia is associated with increased apnea and respiratory complications.

The risk of postoperative apnea in premature neonates is inversely proportional to postconceptual age at the time of surgery. This risk is minimal by the time premature infants have reached the postconceptual age of 60 wk. Apnea is most common within the 1st 12 hr after surgery; postanesthetic apnea has been reported in premature infants up to 48 hr later. The incidence of apnea in full-term infants is debatable and has not been clearly demonstrated. It is generally agreed that general anesthesia should be avoided, except for emergency surgery, in full-term children younger than 44 wk postconceptual age. If surgery is required within the 1st mo of life, overnight observation and monitoring are indicated. Theophyllines decrease the incidence of postoperative apnea; they do not ablate it and therefore are not routinely used. The safest course is to monitor premature infants younger than 60 wk postconceptual age and full-term infants younger than 1 mo for at least 24 hr after anesthesia.

PREANESTHETIC EVALUATION

Most previously healthy children require minimal preoperative assessment. The American Society of Anesthesiologists (ASA) classification system for anesthetic care is the American Society of Anesthesiologists Physical Status classification (Table 61-8).

For American Society of Anesthesiologists Physical Status 1 patients, a brief history, notation of medical allergies, and a physical examination focusing on the airway, lungs, and cardiac function are sufficient. For all children who are being assessed for anesthesia risk, a family history should be obtained, for reactions to anesthetics, for drug allergies, and for sudden intraoperative death or hyperthermia after surgery, which may indicate a risk of malignant hyperthermia. In previously anesthetized children, questions should be asked regarding intraoperative anesthetic complications. The history should focus on determining whether the child is at risk for anesthetic or surgical stress as well as cardiorespiratory disease and airway compromise.

Recent URIs should be noted. A URI is an upper respiratory illness associated with fever, mucopurulent green or yellow nasal discharge, productive cough, injected sclerae, and increased mucous secretions. Clear rhinorrhea is generally not a concern. URIs can increase airway reactivity for up to 6 wk in both normal children and children with a history of reactive airway disease. URIs can also increase the risk of laryngospasm and bronchospasm, reduce mucociliary clearance, and raise the risk of intraoperative atelectasis and hypoxemia. It is generally recommended to avoid general anesthesia for elective procedures for 4-6 wk after a URI. In patients with chronic sinusitis and nasal polyps, infection should be thoroughly treated before elective anesthesia.

Acute, fatal bronchospasm can occur during induction of anesthesia and endotracheal intubation for routine, minor surgery in children with asthma. Those children at particular risk for anesthetic complications with asthma are those who were (1) admitted to the hospital within the previous year for their asthma, (2) seen in an emergency department in the last 6 mo, (3) admitted to an ICU, or (4) treated with

Table 61-8 American Society of Anesthesiology Physical Status Classification

Class 1: Healthy patient, no systemic disease
Class 2: Mild systemic disease with no functional limitations (mild chronic renal failure, iron deficiency anemia, mild asthma)
Class 3: Severe systemic disease with functional limitations (hypertension, poorly controlled asthma or diabetes, congenital heart disease, cystic fibrosis)
Class 4: Severe systemic disease that is a constant threat to life (critically and/or acutely ill patients with major systemic disease)
Class 5: Moribund patients not expected to survive 24 hr, with or without surgery
Additional classification: "E"—emergency surgery

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parenteral systemic steroids. The child should be free of wheezing for at least several days before surgery, even if this necessitates an increase in β-agonist dosage and the addition of steroids. Preoperative steroids are indicated for all children with asthma who are receiving asthma therapy or who have received such therapy within the last year. Prednisone, 1 mg/kg given 24 and 12 hr before surgery, significantly decreases airway reactivity perioperatively. Active wheezing is an indication for canceling elective surgery. If wheezing cannot be controlled on an outpatient basis with β-agonists, steroids, and other asthma therapy, then hospital admission of the child for more aggressive therapy before surgery is indicated.

Bronchopulmonary dysplasia also poses significant intraoperative risks. The same applies to cystic fibrosis and other chronic lung diseases. Every effort should be made to ensure that children with such disorders achieve the best possible respiratory status before surgery. Infections should be treated and reactive airways optimally treated without evidence of wheezing.

Airway Evaluation

Because the induction of anesthesia is associated with loss of spontaneous ventilation and airway reflexes, predicting the inability to bag-and-mask ventilate or endotracheally intubate a child before anesthesia is critical. The anesthesiologist must be told if the child has congenital anomalies that affect the airway (Table 61-9). Such anomalies include micrognathia syndromes, macroglossia syndromes, and some thoracic anomalies. Congenital anomalies associated with airway compromise should be diagnosed preoperatively. Conditions that impair mouth opening (temporomandibular joint disease) should be noted. A history of wheezing or stridor may indicate postoperative airway complications and difficult intraoperative airway management.

Mediastinal Masses

Children with anterior mediastinal masses, such as lymphomas and primary mediastinal tumors, are at serious risk for airway compromise, cardiac tamponade, and vascular obstruction. Induction of general anesthesia and even mild sedation can lead rapidly to total loss of the airway, with inability to ventilate the child and cardiovascular collapse. These patients often present in a semiemergency fashion, with the need for both a tissue diagnosis of the mass before treatment is initiated and a surgically placed central venous line.

Significant compression of vital structures can occur with seemingly mild symptoms. Tachypnea, orthopnea, wheezing, and sleep disturbances or avoidance of prone or supine positions are significant indications of serious risk. Pericardial tamponade or superior vena cava syndromes are more concerning findings. A CT scan showing >50% compression of the airway at the carina is an indication to prohibit general anesthesia and provide only mild sedation. Echocardiographic or CT evidence of pericardial tamponade, right ventricular compression, or compression of the pulmonary artery suggests severe risk. Biopsy with the child under local anesthesia may be indicated. If anesthesia is required, cardiopulmonary bypass should be considered, in case it becomes impossible to ventilate the child during surgery. In high-risk children, consideration should be given to initiating treatment with steroids, radiation therapy, and chemotherapy before obtaining a tissue diagnosis.

Table 61-9 Difficult Airway Syndromes

Achondroplasia
Airway tumors, hemangiomas
Apert syndrome
Beckwith-Wiedemann syndrome
Choanal atresia
Cornelia de Lange syndrome
Cystic hygroma/teratoma
DiGeorge syndrome
Fractured mandible
Goldenhar syndrome
Juvenile rheumatoid arthritis
Mucopolysaccharidosis
Pierre Robin syndrome
Smith-Lemli-Opitz syndrome
Treacher-Collins syndrome
Trisomy 21
Turner syndrome

Down Syndrome

Children with Down syndrome are occasionally behaviorally difficult and are especially fearful of medical caregivers (see Chapter 81). Their cardiac anomalies, macroglossia, and upper airway obstruction can be challenging. Children with Down syndrome have atlantoaxial instability due to odontoid hypoplasia and joint laxity (see Chapter 680.3). In younger children, extension of the neck, routinely used to maintain and intubate the airway, may lead to cervical dislocation and spinal cord trauma. Some anesthesiologists recommend extension and flexion lateral neck films to detect instability before anesthesia. In children with Down syndrome, it is wise to exercise caution in stabilizing the cervical spine and also to avoid cervical flexion and extension.

Cardiovascular System

Because of the depressant effects of anesthetics and the increased metabolic demands of surgery, any compromise of myocardial function should be clearly delineated preoperatively. A preoperative electrocardiogram, an echocardiogram, and a cardiology consultation are indicated for children with a history of heart disease. An intracardiac shunt will affect oxygenation status intraoperatively. Because of the significant effect on the oxygen supply-and-demand relationship caused by general anesthesia and surgical stress, obstructive lesions, such as a valvular stenosis, must also be clearly defined. A history of cardiac dysrhythmias should be clearly understood, because inhalational anesthetics are dysrhythmogenic.

In neonates, ductus arteriosus, myocardial compromise, pulmonary edema, or congenital heart disease can significantly complicate oxygen delivery during anesthesia. Accurate diagnosis of cardiac murmurs in neonates is essential. Any preoperative cardiovascular compromise will be worsened intraoperatively and can catastrophically complicate the perioperative course.

Anemia should be diagnosed and corrected preoperatively if possible. A hematocrit value >30% is generally acceptable for routine elective anesthesia. If there are reasons to expect significant blood loss or prolonged convalescence, anemia should be corrected preoperatively. In the emergency setting, transfusion may be required. Although lower hematocrit values can be tolerated in unstressed children, the significant threat to oxygen delivery posed by anesthesia and surgery, especially if blood loss is expected, requires maintenance of an adequate hemoglobin concentration perioperatively.

Evidence of coagulopathy should be sought. Easy bruising, the use of aspirin, and familial bleeding disorders should be discussed. Intraoperative hemorrhagic bleeding can be difficult to control; massive perioperative blood transfusions have significant risk of morbidity and mortality. Preoperative correction of coagulopathic disorders is indicated. In neonates, assurance of vitamin K prophylaxis and adequate coagulation status is critical before any significant surgery. In neonates and critically ill children, adequacy of platelet count and, where indicated, coagulation factors, prothrombin time, and partial thromboplastin time should be assured.

Neurobehavioral Considerations

Seizures, significant neurologic impairment, altered level of consciousness, respiratory airway compromise secondary to neurologic disease, and neuromuscular disease should be sought and evaluated. Anticonvulsant drug metabolism is often altered perioperatively, and this change may affect anticonvulsant drug levels. Anticonvulsants may also complicate anesthetic management. Maintenance of appropriate anticonvulsant therapy postoperatively is important to avoid new seizures. Cerebrospinal fluid secretion is increased during surgery and general anesthesia. This fact is significant in patients in whom elevated intracranial pressure is suspected and in children with ventriculoperitoneal

shunts. In infants or older children with ventriculoperitoneal shunts, shunt patency and function should be assured before surgery.

Illness and the need for surgery or painful medical procedures are psychologically traumatic events for children and their families. Children are also remarkably adept at sensing stressful signals from their parents and caregivers. Many children who require anesthesia may have significant levels of fear and anxiety. Most children undergoing surgery have new-onset negative behavioral changes in the postoperative period, such as maladaptive behavioral responses that include generalized anxiety, enuresis, enhanced separation anxiety, temper tantrums, nighttime crying, and fear of strangers, doctors, and hospitals. Approximately 20% show these negative behavioral adaptations for 6 mo after surgery. Sleep quality is also altered postoperatively, resulting in further behavioral compromise.

The risk factors for postoperative behavioral changes include preoperative or induction anxiety and behaviors indicating extreme stress, as well as emergence excitation. The type of surgery may be important, with tonsillectomy and genitourinary surgery having a high incidence of postoperative behavioral changes, whereas simple procedures (tympanostomy tubes) seem to be associated with fewer changes. Another risk factor is recurrent procedures, such as anesthesia for laser surgery, strabismus surgery, or repeated eye examinations, which lead to difficult behavioral changes and have a significant effect on family dynamics.

Preoperative psychologic preparation programs decrease the incidence of postoperative behavioral changes, which last for up to 1 mo. PPI does not improve postoperative behavior. Oral midazolam (0.5 mg/kg) may decrease negative behavioral changes after surgery. Midazolam has the benefit of providing not only rapid-onset anxiolysis in 10-20 min but also very effective and rapid (10 min) amnesia.

Preoperative Preparation

The child should be in the best possible nutritional state, and nutritional supplementation, even hyperalimentation in chronically ill children, may be worthwhile.

Preoperative Fasting

Aspiration of gastric contents is a perioperative disaster and, if superimposed on lung disease, may be rapidly fatal. Aspiration may lead to laryngospasm and bronchospasm, with hypoxemia and hypoxic ischemic encephalopathy. It may also produce intraoperative atelectasis and postoperative pneumonia. It is vital to ensure that the stomach is as empty as possible before the induction of anesthesia. Acid aspiration is less likely with an empty stomach. Table 61-10 lists preoperative fasting (NPO status) guidelines.

Clear, sweet liquids (Pedialyte, 5% dextrose in water) facilitate gastric emptying, help avoid hypoglycemia, and can be given up to 2 hr before anesthesia in any child. For older infants and children, a fasting period of 4 hr for liquids provides optimal safety and minimal discomfort. Solids must be avoided for at least 8 hr before surgery. Because surgery is frequently scheduled in the morning, and for ease and clarity of understanding, the general guideline is no consumption of solids after midnight. Many conditions delay gastric emptying, and prolonged periods of fasting may be required in the presence of stress, anxiety, illness, trauma, gross obesity, or biliary atresia, or in children with delayed gastric emptying for other reasons.

Table 61-10 Guidelines for Preoperative Fasting ("2-4-6-8 Rule")*

TIME BEFORE SURGERY (hr)	ORAL INTAKE
2	Clear, sweet liquids
4	Breast milk
6	Infant formula, fruit juices, gelatin
8	Solid food

*These are general guidelines and may differ among hospitals.

The Full Stomach

Because of the serious complications of aspiration of gastric contents, it is desirable to secure the airway as rapidly as possible after obtundation in patients at risk for having a full stomach. Gastric emptying may be delayed for up to 96 hr after an acute episode of trauma or surgical illness. Under these circumstances, induction of general anesthesia and endotracheal intubation are performed in a rapid sequence (**rapid sequence induction**; see Chapter 67).

The risks of rapid sequence induction include the possibility that if the airway cannot be intubated, the child is paralyzed without a protected airway and ventilation may be hazardous or impossible. Rapid sequence induction should be performed by those who can definitely achieve endotracheal intubation quickly. It should be avoided in patients with a history of failed oral endotracheal intubation or with any of the many syndromes (micrognathia) associated with difficult intubation. Under these circumstances, bronchoscopic awake intubation may be indicated.

Before rapid sequence anesthesia induction, the child should be preoxygenated by breathing 100% oxygen for 2 min to give an extra margin of safety if intubation is difficult. The child should not receive assisted ventilation either before or after the administration of drugs because this may lead to increased gastric air and actually increase the likelihood of vomiting, regurgitation, and aspiration.

One common regimen for rapid sequence induction includes the administration of 1.5-3 mg/kg of propofol concurrently with either 0.9-1.2 mg/kg of rocuronium or 1.5 mg/kg of vecuronium. Immediately after the administration of sedation and muscle relaxants, the Sellick maneuver (cricoid pressure) should be performed by applying firm pressure in a posterior direction against the cricoid cartilage. This displaces the cricoid cartilage into the esophagus, forming an artificial sphincter to prevent reflux of the gastroesophageal contents. Cricoid pressure should be maintained until correct placement of the endotracheal tube is verified by direct visualization, fogging of the tube, and, in all circumstances, positive end-tidal CO_2.

POSTOPERATIVE PAIN MANAGEMENT

Continuation of analgesia and anxiolysis should follow surgery or painful procedures (see Chapter 62). Complete freedom from pain is not possible. Preoperative education about the surgery and a pain management plan, development of skills designed to decrease anticipatory anxiety, and active participation in treatment planning can be helpful for some children and families. Adjunctive therapy, such as virtual reality, hypnosis, pet therapy, and play therapy, also can decrease the need for potent analgesics postoperatively.

The combination of opioid and nonopioid analgesic agents and an understanding of the benefits and risks provide the foundation of pain management. A judicious combination of nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, intravenous acetaminophen, opioids, and regional analgesia has a role in postoperative pain management. Repeated evaluation is as important as the modality of pain management. Continuous and repetitive small doses of analgesia around the clock are more effective at reducing pain than occasional prn dosing intervals.

Patient-controlled analgesia (PCA), nurse-controlled analgesia, and parent-controlled analgesia are all used postoperatively (see Chapter 62). PCA provides continuous pain treatment and self-medication (vs intermittent or prn pain control) as well as control and comfort in an otherwise personally uncontrolled circumstance. PCA provides both a background low-dose infusion rate of a continuous opioid and the opportunity to supplement analgesia with bolus doses as needed. The practitioner can determine the continuous infusion rate, the bolus dose, the lockout interval, and the number of boluses per unit time that the patient may receive. PCA relies on the theory that patients cannot or will not overdose themselves because somnolence will decrease repeated self-administration. In young children, the use of the *pain button* (for pain relief) may be more difficult to ensure; children as young as 5 yr old have been able to use PCA successfully. In older children and adolescents, PCA should be a standard modality of postoperative pain management.

Regional Anesthesia

Regional anesthesia is the use of anesthetics to block the conduction of afferent neural impulses to the central nervous system. These can be local analgesic techniques, peripheral nerve blocks, nerve plexus blocks, or epidural and subarachnoid (spinal) nerve blocks. They may be administered either through a single injection (single shot) or through continuous infusion, as is common with epidural and occasionally subarachnoid blocks. They may be used for intraoperative anesthesia and postoperative analgesia, and they have the potential to decrease intraoperative analgesia and anesthetic use, as well as to provide postoperative pain management. Increased use of regional indwelling catheters to deliver continuous analgesia has shortened recovery times and hospital stays in children.

Analgesia at the site of need, without central cardiorespiratory depressant effects, can be valuable. Local anesthesia, with injection of lidocaine or bupivacaine into the affected area, can provide procedural analgesia that lasts for several hours. Infiltration of the wound site and the edges of an incision decreases postoperative pain in the initial hours after surgery. This can be performed by the surgeon at the conclusion of surgery and may supplement postoperative analgesia.

Epidural analgesia is common in pediatric practice. The epidural space lies between the dura and the pia and arachnoid membranes, an area through which all nerve roots pass. Bathing these nerve roots in local anesthetics inhibits conduction of pain impulses centrally. A single dose of epidural anesthetic may provide hours of pain relief, and a continuous infusion may provide effective pain relief for hours to days. The epidural injection of opioids can provide analgesia for 12-24 hr and is a potential supplement to postoperative analgesia.

A lumbar epidural injection is placed in the lumbar area to provide analgesia for labor and for surgery below the thorax. Caudal epidural analgesia is placed through the sacral hiatus, inferior to the distal end of the spinal cord. This is the site most commonly used for regional anesthesia and analgesia in children and is efficacious for the provision of pelvic and lower limb anesthesia as well as beneficial in orthopedic and urologic surgery. A continuous infusion of bupivacaine is the most common means of providing postoperative epidural pain relief; it may be mixed with an opioid (fentanyl or preservative-free morphine). It is also possible to provide epidural PCA with a continuous infusion pump and the ability of the patient to self-medicate with bolus prn dosing. Epidural analgesia can also provide pain relief in patients with chronic pain or pain caused by advanced malignant conditions.

The most serious complications of neuraxial anesthesia include cephalad spread of blockade with respiratory depression, paralysis of respiratory muscles, and, in extreme cases, brainstem analgesia and depression. The most common complications of neuraxial analgesia include mild discomfort; a paresthesia-like feeling of numbness and tingling; pruritus, which, if opioids are used, can be quite distressing; and occasional nausea and vomiting. Infection and epidural hematoma are extremely rare. Neuraxial opioids, especially when administered intrathecally, can cause respiratory depression; their use requires postoperative monitoring. The use of neuraxial opioids often requires treatment with antipruritic as well as antiemetic drugs.

Bibliography is available at Expert Consult.

61.1 Sedation and Procedural Pain

Randall C. Wetzel

The same drugs that induce general anesthesia are often used to provide sedation (see Table 61-5). Sedation care requires a presedation evaluation, intraprocedural monitoring, and postsedation recovery, analogous to the provision of anesthesia. Sedation is on the continuum between wakefulness and general anesthesia (see Table 61-4). The term **conscious sedation** refers to a condition in which a patient is sleepy, comfortable, and cooperative but maintains airway-protective and ventilatory reflexes. Unfortunately, for most children, this level of sedation provides little or no analgesia, and both psychologic and physiologic responses to painful stimuli persist. Sedation that is sufficient to obtund painful responses is most likely deep sedation. **Deep sedation** is a state of unarousability to voice and is accompanied by suppression of reflex responses. Management of sedated children requires vigilance and knowledge to ensure their safety and is governed by the same guidelines as anesthesia care (Table 61-11). A dose of sedative medication that causes minimal sedation in one subject may produce complete unconsciousness and apnea in another. Careful attention to guidelines for appropriate monitoring and management of sedation in children is imperative. For threatening and nonpainful procedures, anxiolysis or light sedation is frequently sufficient. For painful procedures (e.g., bone marrow aspiration, insertion of percutaneous IV catheter lines, lumbar punctures), the combination of sedation with analgesia that is required in children produces deep sedation.

Table 61-11 Systematic Approach to Sedation in Children

Thorough medical history, anticipating underlying medical problems that predispose the patient to sedation problems
Careful physical examination focused on the cardiorespiratory system and airway
Appropriate fasting
Informed consent
Pediatric drug dosing (mg/kg)
Appropriately sized equipment
A separate, dedicated observer to monitor sedated patients who may have airway compromise (induced or preexisting)
Documentation of vital signs and condition on a time-based record
Emergency backup system, "code" team, and "crash cart"
Fully equipped and staffed recovery area
Discharge criteria documenting recovery from sedation

Many specialists provide sedation and anesthesia care for children. The use of anesthetic agents is not limited to anesthesiologists, but a hospital's department of anesthesiology provides expertise in developing and managing systems of anesthesia care, including sedation. With the widespread use of the deceptively safe general anesthetic agent propofol to provide sedation, hospitals, pediatricians, and other care providers must ensure that credentialing, oversight, quality assurance, and protocols for administration of anesthetic agents provide safe care. Involvement of anesthesiologists in organizing services, training other practitioners, overseeing safety, systems, and quality, and remaining involved in the delivery of such care is sound practice. The elements of a safe system to provide procedural sedation for children are as follows:

- Defining the required knowledge set
- Defining the required skill set
- Determining the appropriate requisite training
- Ensuring adequate understanding of the drugs and their effects (desired and undesired) and interactions
- Credentialing providers
- Ensuring ongoing maintenance of skills
- Reviewing the practice
- Ensuring that the sites where anesthesia care is provided meet recognized standards
- Last but not least, overseeing a process of continuous quality improvement

Sedation with chloral hydrate (not approved by the FDA in the United States or the European Medicines Agency in the European Union), pentobarbital, or benzodiazepines is often adequate for nonpainful procedures. Nevertheless, there can be a high failure rate as well as complications by using this method, such as prolonged sedation (hours to overnight), ataxia, nausea and vomiting, desaturation, and the occasional need for rapid intervention. The temptation to add opioids and deepen sedation increases the risk of complications. The use of dexmedetomidine for procedural sedation is safe; recovery time can be prolonged, and success can be variable. The quickest way to ensure safely reversible sedation is with potent anesthetic agents.

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The ultra–short-acting anesthetics (propofol, methohexital, remifentanil) provide effective procedural sedation, but their use carries a higher likelihood of inadvertent oversedation and induction of general anesthesia. These anesthetics offer efficient and rapidly reversible procedural sedation. However, their use requires the presence of an anesthesiologist and/or specially trained, experienced, and qualified physicians.

Bibliography is available at Expert Consult.

61.2 Anesthetic Neurotoxicity

Randall C. Wetzel

There is compelling experimental evidence that anesthesia-induced neurodegeneration with developmental impairment occurs in neonatal animals. Pediatric anesthesiologists have become deeply concerned by the demonstration of anesthetic-induced apoptotic neuronal cell death, central nervous system neurodegenerative changes, and their effects on the developing brain. These studies demonstrate both histopathologic changes and developmental defects from both inhalational and IV anesthetics, including isoflurane, ketamine, benzodiazepines, and propofol given to newborn animals. Combinations of drugs may cause more injury. Existing nonclinical data implicate both *N*-methyl-D-aspartate and γ-aminobutyric acid pathways in apoptosis and cell death in neonates.

The studies reporting these results were performed in animals (largely rodents), and great controversy exists concerning dose, duration of treatment, species differences, and experimental design. Although there is cause for concern and further study, alternatives to general anesthesia for many procedures in infants do not exist. Perhaps regional anesthetic techniques and narcotic-based anesthetics will be increasingly used. Interestingly, dexmedetomidine appears to block the neurotoxic effects of other anesthetics. There is insufficient current data for suggesting the safety of one anesthetic approach over another. The potential for this neurotoxicity must be balanced against the necessity of providing adequate anesthesia for neonates.

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Chapter 62

Pediatric Pain Management

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Pain is both a sensory and an emotional experience that, when unrecognized and undertreated, extracts a significant physiologic, biochemical, and psychologic toll. Many disease processes and most interventional procedures in pediatrics are associated with pain.

DEFINITION AND CATEGORIES OF PAIN

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." The important elements of this definition to be emphasized are (1) pain encompasses both peripheral physiologic and central cognitive/emotional components and (2) pain may or may not be associated with ongoing tissue damage—pain may exist in the absence of demonstrable somatic pathology, and may rather be the acquired or genetic consequence of abnormalities of peripheral neural signaling, central modulation, or brain processing of peripheral sensations or nociception.

Table 62-1 specifies important pain categories commonly treated (somatic, visceral, and neuropathic) and defines the elements and characteristics of nociception, the peripheral physiologic aspect of pain perception (Fig. 62-1). *Nociception* refers to how specialized fibers (largely, but not exclusively, the small unmyelinated A-delta and C fibers) in the peripheral nervous system transmit nerve impulses (usually transmitting signals originating from peripheral mechano- and chemoreceptors) through synapses in the spinal cord's dorsal horn through (but not exclusively through) the spinothalamic tracts to the brain's higher centers, where nociception is converted to pain, with all of its cognitive and emotional ramifications.

THE ASSESSMENT AND MEASUREMENT OF PAIN IN CHILDREN

Whenever feasible, the physician should ask the patient about the character, location, quality, duration, frequency, and intensity of the pain. Some children may not report pain because of fears (often well-founded) of talking to strangers, disappointing or bothering others, receiving an injection if they report pain, returning to the hospital if they admit to pain, and other negative possible reactions. For infants and nonverbal children, their parents, pediatricians, nurses, and other caregivers are constantly challenged to interpret whether the children's distressed behaviors represent pain, fear, hunger, or a range of other perceptions or emotions. Therapeutic trials of comfort measures (cuddling, feeding) and analgesic medications may be helpful in clarifying the triggers of the behaviors.

Behavior and physiologic signs are useful, but they can be misleading. A toddler may scream and grimace during an ear examination because of fear rather than pain. Conversely, children with inadequately relieved persistent pain from cancer, sickle cell disease, trauma, or surgery may withdraw from their surroundings and appear very quiet, leading observers to conclude falsely that they are comfortable or sedated. In these situations, increased dosing of analgesics may make the child become more, not less, interactive and alert. Similarly, neonates and young infants may close their eyes, furrow their brows, and clench their fists in response to pain. Adequate analgesia is often associated with eye opening and increased involvement in the surroundings. A child who is experiencing significant chronic pain may play normally as a way to distract attention away from pain. This coping behavior is sometimes misinterpreted as evidence of the child's "faking" or exaggerating pain at other times.

Age-Specific and Developmentally Specific Measures

Because infants, young children, and nonverbal children cannot express the quantity of pain they experience, several pain scales have been devised in an attempt to quantify pain in these populations (Fig. 62-2; Table 62-2).

The Newborn and Infant

There are several behavioral distress scales for the infant and young child, mostly emphasizing the patient's facial expressions, crying, and body movement. Facial expression measures appear most useful and specific in neonates. Autonomic and vital signs can indicate pain, but because they are nonspecific, they may reflect other processes, including fever, hypoxemia, and cardiac or renal dysfunction.

The Older Child

Children ages 3-7 yr become increasingly articulate in describing the intensity, location, and quality of pain. Pain is occasionally referred to adjacent areas; referral of hip pain to the leg or knee is common in this age range. Self-report measures for children this age include using drawings, pictures of faces, or graded color intensities. Children age 8 yr and older can usually use verbal numerical rating scales or visual analog pain scales accurately (see Fig. 62-2). Verbal numerical ratings are preferred and considered the gold standard; valid and reliable ratings can be obtained from children 8 yr and older. The Numerical

Rating Scale consists of numbers from 0-10, in which 0 represents no pain and 10 represents very severe pain. There is debate about the label for the highest pain rating, but the current agreement is *not* to use the term "worst pain possible," because children can always imagine a greater pain. In the United States, regularly documented pain assessments are required for hospitalized children and children attending outpatient hospital clinics and emergency departments. Pain scores do not always correlate with changes in heart rate or blood pressure.

The Cognitively Impaired Child

Measuring pain in cognitively impaired children remains a challenge. Understanding pain expression and experience in this population is important, because behaviors may be misinterpreted as indicating that cognitively impaired children are more insensitive to pain than cognitively competent children. Children with trisomy 21 may express pain less precisely and more slowly than the general population. Pain in children with autism spectrum disorders may be difficult to assess because these children may be both *hyposensitive* and *hypersensitive* to many different types of sensory stimuli, and they may have limited communication abilities. Although self-reports of pain can be elicited from some children who are cognitively impaired, observational measures have better validation among these children. The Noncommunicating Child's Pain Checklist—Postoperative Version is recommended for children up to 18 yr. Maladaptive behaviors and reduction in functions may also indicate pain. Children with severe cognitive impairments frequently experience pain.

A CONCEPTUAL FRAMEWORK FOR THE TREATMENT OF PEDIATRIC PAIN

A number of models have been developed to understand the various factors that influence children's pain. Many of these theories focus on factors that explain the interindividual variability in pain perception, and the chronicity and impairment experienced with pain. Central to these models are interrelationships among biologic, cognitive, affective, and social factors that influence children's pain and disability, commonly referred to as biopsychosocial models of pain. Biologic factors include the child's physical health, central nervous system factors (pain processing), sex, pubertal status, and genetic factors.

Table 62-1 Pain Categories and Characteristics

PAIN CATEGORY	DEFINITION AND EXAMPLES	CHARACTERISTICS
Somatic	Pain resulting from injury to or inflammation of tissues (skin, muscle, tendons, bone, joints, fascia, vasculature, etc.) *Examples:* burns, lacerations, fractures, infections, inflammatory conditions	*In skin and superficial structures:* sharp; pulsatile; well-localized *In deep somatic structures:* dull; aching; pulsatile; not well-localized
Visceral	Pain resulting from injury to or inflammation of viscera *Examples:* angina, hepatitic distention, bowel distention or hypermobility, pancreatitis	Aching and cramping; nonpulsatile; poorly localized (e.g., appendiceal pain perceived around umbilicus) or referred to distant locations (e.g., angina perceived in shoulder)
Neuropathic	Pain resulting from injury to, inflammation of, or dysfunction of the peripheral or central nervous systems. *Examples:* complex regional pain syndrome, phantom limb pain, Guillain-Barré syndrome, sciatica	Spontaneous; burning; lancinating or shooting; dysesthesias (pins and needles, electrical sensations); hyperalgesia (amplification of noxious stimuli); hyperpathia (widespread pain in response to a discrete noxious stimulus); allodynia (pain in response to nonpainful stimulation); pain may be perceived distal or proximal to site of injury, usually corresponding to innervation pathways (e.g., sciatica)

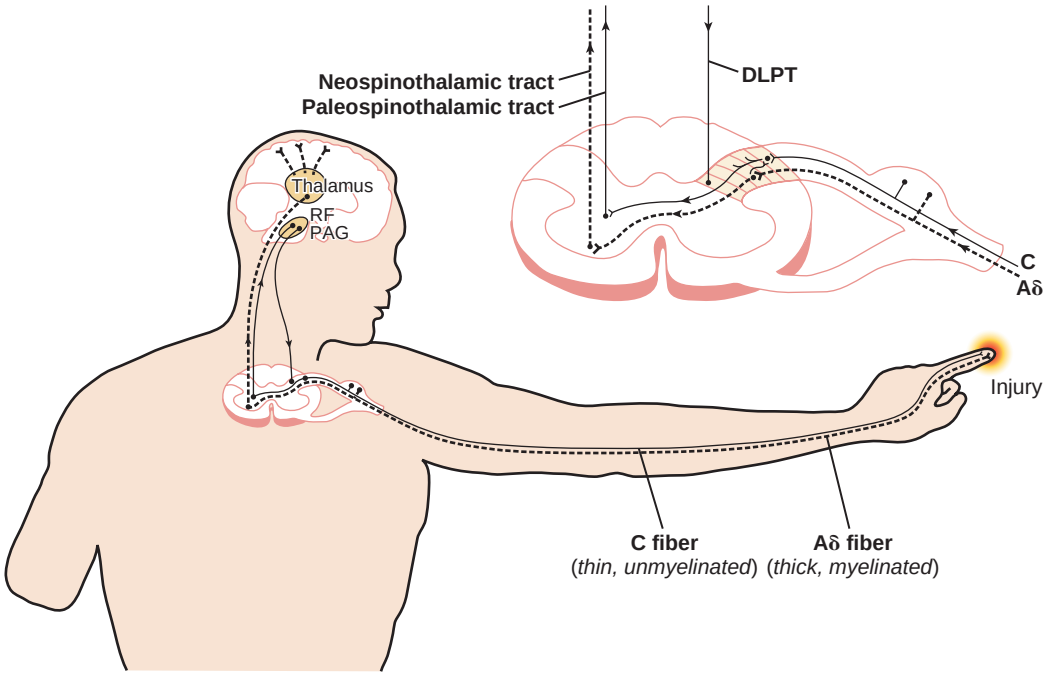


Figure 62-1 The typical neural pathways of nociception, also showing higher projection of nociception to the cortex, where the sensation of nociception is translated to the conscious and emotional phenomenon of pain. *DLPT,* dorsolateral pontine tegmentum; *PAG,* periaqueductal gray; *RF,* reticular formation.

Behavioral Indicators

Facial grimacing: The Neonatal Facial Coding System* uses several facial actions that may be indicators of pain. Pain is characterized by a bulging brow with tight creases in between; tightly closed eyelids; a deeply furrowed nasolabial groove; a horizontal, wide opened mouth; and a taut tongue that may be quivering along with the chin.

Crying: May be an indicator of pain.

Activity: Withdrawal or immobilization of a limb may be an indicator of pain.

Response to comfort measures: Feeding, swaddling, holding, and ensuring that the infant is neither wet nor cold may help to discriminate between pain and other conditions.

Physiologic indicators: Alterations in heart rate, blood pressure, SpO_2, respiratory rate, or alterations in pattern of respiration may be nonspecific indicators of pain.

Multidimensional Instrument

FLACC† *Scoring System:* May be used in preverbal, mechanically ventilated, or cognitively impaired patients; it is an acronym that includes five indicators, each scored as a 0, 1, or 2 that forms a ten-point composite scale with a range from "0" (no pain) to "10" (worst pain).

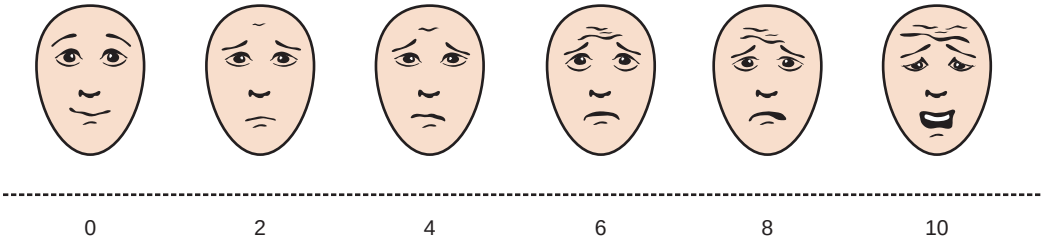
FLACC: Score each category between 0 and 2. The total score may be any number from 0 to 10.

Score:	0	1	2
Face	No expression	Occational action	Frequent action
Legs	Normal	Restless or tense	Kicking, legs withdrawn
Activity	Quiet	Shifting or tense	Rigid, arched, jerking
Cry	None	Moan, whimper	Steady crying, screaming, sobbing, or frequent complaints
Consolability	Content	Consolable	Inconsolable

Self-Report of Pain

Categorical description: Toddlers or young children are asked to say if they are having "a little bit," a "middle amount," or "a lot" of pain.

Faces Scales‡: Children who do not have an appreciation of ordinal numbering are asked to rate their pain based upon cartoons depicting facial indicators of distress.



NRS§: Older children and teenagers are asked to rate their pain on a scale of "0" (no pain) to "10" (worst pain).

VAS§: Children or teenagers are asked to move an indicator along a mechanical slide to depict the level of pain; the clinician reads a number along a 10-cm indicator on the back to determine the numeric score.

Figure 62-2 Clinically useful pain assessment tools. *(Adapted from Burg FD, Ingelfinger JR, Polin RA, et al, editors:* Current pediatric therapy, *ed 18, Philadelphia, 2006, WB Saunders, p. 16; and Hicks CL, von Baeyer CL, Spafford P, et al: The Faces Pain Scale—revised: toward a common metric in pediatric pain measurement,* Pain *93:173–183, 2001.)*

Individual child cognitive and affective factors related to perception of pain are anxiety, fear, negative affect, pain behaviors, and functional disability, whereas social factors include such areas as culture, socioeconomic status, school environment, social and peer interactions, and parental and family factors.

A framework that considers the interplay of biologic, psychologic, and social factors is useful for understanding pediatric pain and to guide pain assessment and the delivery of both pharmacologic and nonpharmacologic interventions for pain management. Many simple interventions designed to promote relaxation and patient control can be expected to work synergistically with pain medications for optimal relief of pain and related distress. Moreover, psychologic interventions are often coupled with physical therapy interventions to assist in the management of disabling chronic pain.

Pharmacologic Treatment of Pain

Developmental Pharmacology

The pharmacokinetics and pharmacodynamics of analgesics vary with age; drug responses in infants and young children differ from those in older children and adults. The elimination half-life of most analgesics is prolonged in neonates and young infants because of their immature hepatic enzyme systems and glomerular filtration. Clearance of

Table 62-2 Pain Measurement Tools

NAME	FEATURES	AGE RANGE	ADVANTAGES	VALIDATION AND USES	LIMITATIONS
Visual Analog Scale (VAS)	Horizontal 10-cm line; subject marks a spot on the line between anchors of "no pain" (or neutral face) and "most pain imaginable" (or sad face)	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Cannot be used in younger children or in those with cognitive limitations Requires language skills and numerical processing; upper anchor of "most pain" requires an experiential reference point that is lacking in many children
Likert Scale	Integers from 0-10, inclusive, corresponding to a range from no pain to most pain	6-8 yr and older	Good psychometric properties; validated for research purposes	Acute pain Surgical pain Chronic pain	Same as for VAS
Faces Scales (e.g., FACES-R, Wong-Baker, Oucher, Bieri, McGrath scales)	Subjects rate their pain by identifying with line drawings of faces or photos of children	4 yr and older	Can be used at younger ages than VAS and Likert	Acute pain Surgical pain	Choice of "no pain" face affects responses (neutral vs smiling); not culturally universal
Behavioral or combined behavioral-physiologic scales (e.g., FLACC, N-PASS, CHEOPS, OPS, FACS, NIPS)	Scoring of observed behaviors (e.g., facial expression, limb movement) ± heart rate and blood pressure	Some work for any ages; some work for specific age groups, including preterm infants	May be used in both infants and nonverbal children	FLACC, N-PASS: Acute pain Surgical pain	Nonspecific; overrates pain in toddlers and preschool children; underrates persistent pain; some measures are convenient, but others require videotaping and complex processing; vital sign changes unrelated to pain can occur and may affect total score
Autonomic measures (e.g., heart rate, blood pressure, heart rate spectral analyses)	Scores changes in heart rate, blood pressure, or measures of heart rate variability (e.g., "vagal tone")	All ages	Can be used at all ages; useful for patients receiving mechanical ventilation		Nonspecific; vital sign changes unrelated to pain may occur, and may artifactually increase or decrease score
Hormonal-metabolic measures	Plasma or salivary sampling of "stress" hormones (e.g., cortisol, epinephrine)	All ages	Can be used at all ages		Nonspecific; changes unrelated to pain can occur; inconvenient; cannot provide "real-time" information; standard normal values not available for every age bracket

analgesics may also be variable in young infants and children. Renal blood flow, glomerular filtration, and tubular secretion increase dramatically in the 1st few weeks, approaching adult values by 3-5 mo of age. Renal clearance of analgesics is often greater in toddlers and preschool-age children than in adults, whereas in premature infants clearance is reduced. Age-related differences in body composition and protein binding also exist. Total-body water as a fraction of body weight is greater in neonates than in children or adults. Tissues with high perfusion, such as the brain and heart, account for a larger proportion of body mass in neonates than do other tissues, such as muscle and fat. Because of decreased serum concentrations of albumin and α_1-acid glycoprotein, neonates have reduced protein binding of some drugs, resulting in higher amounts of free, unbound, pharmacologically active drug.

Acetaminophen, Aspirin, Nonsteroidal Antiinflammatory, and Coxib Drugs

Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) have replaced aspirin as the most commonly used antipyretics and oral, nonopioid analgesics (Table 62-3).

Acetaminophen, a generally safe, nonopioid analgesic and antipyretic, has the advantage of intravenous, rectal, and oral routes of administration. Acetaminophen is not associated with the gastrointestinal or antiplatelet effects of aspirin and NSAIDs, making it a particularly useful drug in patients with cancer. Unlike aspirin and NSAIDs, acetaminophen has only mild antiinflammatory action.

Acetaminophen toxicity can result from either a large single dose or cumulative, excessive dosing over days or weeks (see Chapters 63 and 363). A single, massive overdose overwhelms the normal glucuronidation and sulfation metabolic pathways in the liver, whereas long-term overdosing exhausts supplies of the sulfhydryl donor glutathione, leading to alternative cytochrome P450–catalyzed oxidative metabolism and the production of the hepatotoxic metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). Toxicity manifests as fulminant hepatic necrosis and failure in infants, children, and adults. Drug biotransformation processes are immature in neonates, very active in young children, and somewhat less active in adults. Young children are more resistant to acetaminophen-induced hepatotoxicity than are adults as a result of metabolism differences: Sulfation predominates over glucuronidation in young children, leading to a reduction in *N*-acetyl-*p*-benzoquinone imine production.

Aspirin is indicated for certain rheumatologic conditions and for inhibition of platelet adhesiveness, as in the treatment of Kawasaki disease. Concerns about Reye syndrome have resulted in a substantial decline in pediatric aspirin use (see Chapter 357).

The **NSAIDs** are used widely to treat pain and fever in children. NSAIDs are nonselective cyclooxygenase (COX) inhibitors (coxibs), that is, drugs that nonselectively block the activity of both COX-1

Table 62-3 Commonly Used Nonopioid Medications

MEDICATION	DOSAGE	COMMENT(S)
Acetaminophen	10-15 mg/kg PO q4h 10 mg/kg IV q4h 15 mg/kg IV q6h 10 mg/kg IV q6h (<2 yr) 20-30 mg/kg/PR q4h 40 mg/kg/PR q6-8h Maximum daily dosing: 90 mg/kg/24 hr (children) 60 mg/kg/24 hr (<2 yr) 30-45 mg/kg/24 hr (neonates)	Little antiinflammatory action; no antiplatelet or adverse gastric effects; overdosing can produce fulminant hepatic failure
Aspirin	10-15 mg/kg PO q4h Maximum daily dosing: 120 mg/kg/24 hr (children)	Antiinflammatory; prolonged antiplatelet effects; may cause gastritis; associated with Reye syndrome
Ibuprofen	8-10 mg/kg PO q6h	Antiinflammatory; transient antiplatelet effects; may cause gastritis; extensive pediatric safety experience
Naprosyn	5-7 mg/kg PO q8-12h	Antiinflammatory; transient antiplatelet effects; may cause gastritis; more prolonged duration than that of ibuprofen
Ketorolac	Loading dose 0.5 mg/kg, then 0.25-0.3 mg/kg IV q6h to a maximum of 5 days; maximum dose 30 mg loading with maximum dosing of 15 mg q6h	Antiinflammatory; reversible antiplatelet effects; may cause gastritis; useful for short-term situations in which oral dosing is not feasible
Celecoxib	3-6 mg/kg PO q12-24h	Antiinflammatory; no antiplatelet or gastric effects; cross-reactivity with sulfa allergies
Choline magnesium salicylate	10-20 mg/kg PO q8-12h	Weak antiinflammatory; lower risk of bleeding and gastritis than with conventional NSAIDs
Nortriptyline, amitriptyline, desipramine	0.1-0.5 mg/kg PO qhs	For neuropathic pain; facilitates sleep; may enhance opioid effect; may be useful in sickle cell pain; risk of dysrhythmia in prolonged QTc syndrome; may cause fatal dysrhythmia in overdose; FDA says agents may enhance suicidal ideation
Gabapentin	100 mg bid or tid titrated to up to 3,600 mg/24 hr	For neuropathic pain; associated with sedation, dizziness, ataxia, headache, and behavioral changes
Quetiapine, risperidone, chlorpromazine, haloperidol	Quetiapine: 6.25 or 12.5 mg PO qd (hs); may use q6h prn acute agitation with pain. Escalate dose to 25 mg/dose if needed. Risperidone: useful for PDD spectrum or tic disorder and chronic pain; 0.25-1 mg (in 0.25-mg increments) qd or bid; see PDR for other dosing.	Useful when arousal is amplifying pain; often used when patient first starting SSRI and then weaned after at least 2 wk; check for normal QTc before initiating; side effects include extrapyramidal reactions (diphenhydramine may be used to treat) and sedation; in high doses, can lower the seizure threshold
Fluoxetine	10-20 mg PO qd (usually in morning)	SSRI for children with anxiety disorders in which arousal amplifies sensory signaling; useful in PDD spectrum disorders in very low doses; best to use in conjunction with psychiatric evaluation
Sucrose solution via pacifier or gloved finger	*Preterm infants (gestational age):* 28 wk: 0.2 mL swabbed into mouth 28-32 wk: 0.2-2 mL, depending on suck/swallow >32 wk: 2 mL *Term infants:* 1.5-2 mL PO over 2 min	Allow 2 min before starting procedure; analgesia may last up to 8 min; the dose may be repeated once

FDA, U.S. Food and Drug Administration; IV, intravenous(ly): NSAIDs, nonsteroidal antiinflammatory drugs; PDD, pervasive developmental disorder; PDR, *Physicians' Desk Reference;* PR, per rectum; QTc, corrected QT interval on an electrocardiogram; SSRI, selective serotonin reuptake inhibitor.

(found in gastric mucosa and platelets) and COX-2 (active in inflammatory pathways and cortical renal blood flow regulation) enzymes that synthesize prostaglandins. In children with juvenile idiopathic arthritis, ibuprofen and aspirin are equally effective, but ibuprofen is associated with fewer side effects and better drug adherence. NSAIDs and coxibs used adjunctively in surgical patients reduce opioid requirements (and, therefore, opioid side effects) by as much as 35-40%. Although NSAIDs can be useful postoperatively, they should be used as an adjunct to, not as a substitute for, opioids in patients with moderate to severe pain.

Ketorolac, an IV or intranasal NSAID, is useful in treating moderate to severe acute pain in patients who are unable or unwilling to swallow oral NSAIDs. Intravenous ibuprofen is approved in the United States for the management of pain and fever for 5 days or fewer, although there is no pediatric indication in the package labeling. In Europe, IV ibuprofen is used to treat pediatric pain.

Adverse effects of NSAIDs are uncommon, but they may be serious when they occur. They include inhibition of bone growth and healing; gastritis with pain and bleeding; decreased renal blood flow that may reduce glomerular filtration and enhance sodium reabsorption, in some cases leading to tubular necrosis; hepatic dysfunction and liver failure; inhibition of platelet function; and an increased incidence of cardiovascular events in patients predisposed to stroke and myocardial infarction. Although the overall incidence of bleeding is very low, gastric bleeding is the most common cause of mortality related to this class of analgesics.

NSAIDs should not be used in the child with a bleeding diathesis or at risk for bleeding or when surgical hemostasis is a concern, such as after tonsillectomy. The drug class is usually avoided in the setting of bone healing, except perhaps in the 1st few days following surgery.

Renal injury from short-term use of ibuprofen in euvolemic children is quite rare; the risk is increased by hypovolemia or cardiac

dysfunction. The safety of both ibuprofen and acetaminophen for short-term use is well established (see Table 62-3).

Coxib drugs available in the United States are limited to oral celecoxib, whereas in Europe and elsewhere parenteral parecoxib and oral rofecoxib are available (parecoxib was not approved for use in the United States, while rofecoxib was approved and withdrawn from the market because of concern of enhancement of the risk of heart attacks and stroke, which was subsequently found to be associated with all the coxibs and NSAID drugs as well). The coxib drugs are selective COX-2 enzyme inhibitors; therefore they are effective antiinflammatory and analgesic molecules that generally do not result in platelet inhibition and bleeding or in gastric inflammation or ulceration, findings that may be seen with the nonselective COX inhibitors in the NSAID class. However, coxib drugs do inhibit regulation of cortical renal blood flow, and therefore carry the same risk of renal dysfunction and acute tubular necrosis. Celecoxib is therefore an appropriate primary or adjunctive analgesic to use in children following surgery, children with gastric mucosal pathology, or oncology patients in whom concern for hemostasis contraindicates conventional NSAIDs.

Opioids

Opioids are analgesic substances either derived from the opium poppy (opiates) or synthesized to have a similar chemical structure and mechanism of action (opioids). The older, pejorative term narcotics should not be used for these agents, because it connotes criminality and lacks pharmacologic descriptive specificity. Opioids are administered for moderate and severe pain, such as acute postoperative pain, sickle cell crisis pain, and cancer pain. Opioids can be administered by the oral, rectal, oral transmucosal, transdermal, intranasal, IV, epidural, intrathecal, subcutaneous, or intramuscular route. Historically, infants and young children have been underdosed with opioids for fear of significant respiratory side effects. In contrast, the use of opioids for moderate-to-severe noncancer pain does not have the evidence base that their use in cancer-associated pain does. There is concern for the potential for unwarranted use of opioids to increase the incidence of side effects. With proper understanding of the pharmacokinetic and pharmacodynamics of opioids, children can receive effective relief of pain and suffering with a good margin of safety (Tables 62-4 to 62-7).

Opioids act by mimicking the actions of endogenous opioid peptides, binding to receptors in the brain, brainstem, spinal cord, and peripheral nervous system, and thus leading to inhibition of nociception. Opioids have dose-dependent respiratory depressant effects, and they blunt ventilatory responses to hypoxia and hypercarbia. These respiratory depressant effects can be increased with coadministration of other sedating drugs, such as benzodiazepines or barbiturates. What was once thought to represent infants' particular sensitivity to the opioids' respiratory depressant effects we now understand to be a result of infants' lower metabolic clearance of opioids and higher blood levels with frequent dosing.

Optimal use of opioids requires proactive and anticipatory management of side effects (see Table 62-6). Common side effects include constipation, nausea, vomiting, urinary retention, and pruritus. The most common, troubling, but treatable side effect is constipation. Stool softeners and stimulant laxatives should be administered to most patients receiving opioids for more than a few days. Constipation also remains a problem with long-term opioid administration. A peripherally acting opiate μ-receptor antagonist, methylnaltrexone, promptly and effectively reverses opioid-induced constipation in patients with chronic pain who are receiving opioids daily. In addition lubiprostone, an epithelial chloride channel agent, has been approved for the treatment of opioid-induced constipation in adults with chronic noncancer pain. The side effect of nausea typically subsides with long-term dosing, but it may require treatment with antiemetics, such as a phenothiazine, butyrophenones, antihistamines, or a serotonin receptor antagonist such as ondansetron or granisetron. Pruritus and other complications during patient-controlled analgesia (PCA) with opioids may be effectively managed by low-dose IV naloxone (see Table 62-6).

One of the potent barriers to effective management of pain with opioids is the unrealistic fear of addiction held by many prescribing pediatricians and parents. Pediatricians should understand the phenomena of tolerance, dependence, withdrawal, and addiction (see Table 62-5) and should know that the rational short- or long-term use of opioids in children does not lead to a predilection or risk of addiction in a child not otherwise at risk by virtue of genetic background and social milieu. It is important for pediatricians to realize that even patients with recognized substance-abuse diagnoses are entitled to effective analgesic management, which often includes the use of opioids. When there are legitimate concerns about addiction in a patient, then safe, effective opioid pain management is often best managed by specialists in pain management and/or addiction medicine.

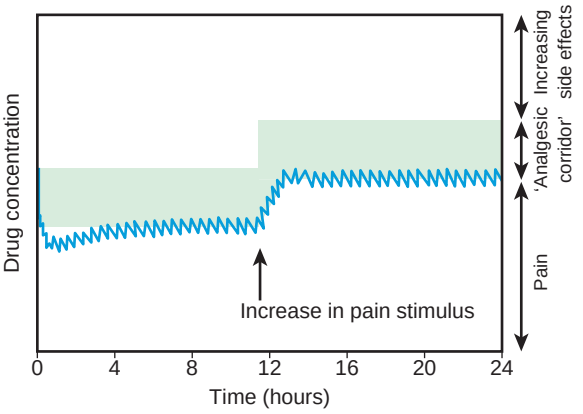


Figure 62-3 Patient-controlled analgesia is more likely to keep blood concentrations of opioid within the "analgesic corridor" and allows rapid titration if there is an increase in pain stimulus requiring higher blood levels of opioid to maintain the analgesia. *(From Burg FD, Ingelfinger JR, Polin RA, et al, editors:* Current pediatric therapy, *ed 18. Philadelphia, 2006, WB Saunders, p. 16.)*

There is no longer a reason to administer opioids by intramuscular injection. Continuous IV infusion of opioids is an effective option that permits more constant plasma concentrations and clinical effects than intermittent IV bolus dosing, without the pain associated with intramuscular injection. The most common approach in pediatric centers is to administer a low-dose basal opioid infusion, while permitting patients to use a patient-controlled analgesia (PCA) device to titrate the dosage above the infusion (see Chapter 61; Fig. 62-3). Compared with children given intermittent intramuscular morphine, children using PCA reported better pain scores. PCA has several other advantages: (1) dosing can be adjusted to account for individual pharmacokinetic and pharmacodynamic variation and for changing pain intensity during the day; (2) psychologically, the patient is more in control, actively coping with the pain; (3) overall opioid consumption is lower; (4) fewer side effects occur; and (5) patient satisfaction is generally much higher. Children as young as 5-6 yr can effectively use PCA. The device can be activated by parents or nurses—the latter practice known as PCA-by-proxy; PCA-by-proxy produces analgesia in a safe, effective manner for children who cannot activate the PCA demand button themselves because they are too young or intellectually or physically impaired. PCA overdoses occur when well-meaning, inadequately instructed parents pushed the PCA button in medically complicated situations with or without the use of PCA-by-proxy, highlighting the need for patient and family education, the use of protocols, and adequate nursing supervision.

Local Anesthetics

Local anesthetics are widely used in children for topical application, cutaneous infiltration, peripheral nerve block, epidural neuraxial blocks, intrathecal infusions, and IV infusions (see Chapter 61; Table 62-8). Local anesthetics can be used with excellent safety and effectiveness. Local anesthetics interfere with neural transmission by blocking sodium channels. Excessive systemic dosing can cause seizures, central nervous system (CNS) depression, and by cardiac and arteriolar sodium channel blockade hypotension, arrhythmias, cardiac

Table 62-4 Pediatric Dosage Guidelines for Opioid Analgesics

DRUG	EQUIANALGESIC DOSES		PARENTERAL DOSING (WEIGHT)		IV:PO DOSE RATIO	ORAL DOSING (WEIGHT)		COMMENTS
	IV	ORAL	<50 kg	>50 kg		<50 kg	>50 kg	
Fentanyl	10 µg	100 µg	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	0.5-1 µg/kg q1-2h 0.5-1.5 µg/kg/hr	Oral transmucosal: 1:10 Transdermal: 1:1	Oral transmucosal: 10 µg/kg Transdermal: 12.5-50 µg/hr	Transdermal patches available; patch reaches steady state at 24 hr and should be changed q72h	70-100 times as potent as morphine with rapid onset and shorter duration With high doses and rapid administration, can cause chest-wall rigidity Useful for short procedures; transdermal form should be used only in opioid-tolerant patients with chronic pain
Hydrocodone	N/A	1.5 mg	N/A	N/A	N/A	0.15 mg/kg	10 mg	Weak opioid; only available in form with acetaminophen
Hydromorphone	0.2 mg	0.6 mg	0.01 mg q2-4h 0.002 mg/kg/hr	0.01 mg q2-4h 0.002 mg/kg/hr	1:3	0.04-0.08 mg/kg q3-4h	2-4 mg q3-4h	5× the potency of morphine; no histamine release and fewer adverse events than morphine
Meperidine	10 mg	30 mg	0.5 mg/kg q2-4h	0.5 mg/kg q2-4h	1:4	2-3 mg/kg q3-4h	100-150 mg q3-4h	Primary use in low doses is for treatment of rigors and shivering after anesthesia or with amphotericin or blood products Not appropriate for repeated dosing
Methadone	1 mg	2 mg	0.1 mg/kg q8-24h	0.1 mg/kg q8-24h	1:2	0.2 mg/kg q8-12h PO; available as liquid or tablet	2.5 mg tid	Duration 12-24 hr; useful in certain types of chronic pain; requires additional vigilance, because it will accumulate over 72 hr and produce delayed sedation When patients who are tolerant to opioids are switched to methadone, they show incomplete cross-tolerance and improved efficacy; because it is associated with prolonged QTc, monitoring is needed for children on high and extended dosing
Morphine	1 mg	3 mg	0.05 mg/kg q2-4h 0.01-0.03 mg/kg/hr	*Bolus:* 5-8 mg q2-4h	1:3	Immediate release: 0.3 mg/kg q3-4h Sustained release: 20-35 kg: 10-15 mg q8-12h 35-50 kg: 15-30 mg q8-12h	Immediate release: 15-20 mg q3-4h Sustained release: 30-90 mg q8-12h	Potent opioid for moderate/severe pain; may cause histamine release Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose
Oxycodone	N/A	3 mg	N/A	N/A	N/A	0.1-0.2 mg q3-4h; available in liquid (1 mg/mL)	Immediate release: 5-10 mg q4h Sustained release: 10-120 mg q8-12h	Strong opioid only available as an oral agent in North America; more potent than and preferable to hydrocodone Sustained-release form must be swallowed whole; if crushed, becomes immediate-acting, leading to acute overdose

N/A, not available.

Table 62-5 Practical Aspects of Prescribing Opioids

- Morphine, hydromorphone, or fentanyl is regarded as first choice for severe pain.
- Dosing should be titrated and individualized. There is no "right" dose for everyone.
- The right dose is the dose that relieves pain with a good margin of safety.
- Dosing should be more cautious in infants, in patients with coexisting diseases that increase risk or impair drug clearance, and with concomitant administration of sedatives.
- Anticipate and treat peripheral side effects, including constipation, nausea, and itching.
- Give doses at sufficient frequency to prevent the return of severe pain before the next dose.
- Use a drug delivery method, such as patient-controlled anesthesia or continuous infusions that avoid the need for "prn" decision making.
- With opioid dosing for more than 1 wk, taper gradually to avoid abstinence syndrome.
- When converting between parenteral and oral opioid doses, use appropriate potency ratios (see Table 62-4).
- *Tolerance* refers to decreasing drug effect with continued administration of a drug. Over time a patient will need higher dosing to achieve the same clinical effect; however, tolerance to sedation and respiratory depression develop more rapidly than tolerance to analgesia. Thus, with higher doses, patients do not experience oversedation or respiratory depression.
- *Dependence* refers to the need for continued drug dosing to prevent abstinence syndrome when a drug is abruptly discontinued or its dose reduced. Abstinence syndrome is characterized by irritability, agitation, autonomic arousal, nasal congestion, piloerection, diarrhea and/or jitteriness, and yawning; it is produced by administration of potent opioids for >5-7 days.
- *Addiction,* a psychiatric pathology, refers to psychologic craving, compulsive drug-seeking behavior, and drug use despite medical harm. Addiction has strong genetic determinants. Opioid therapy does not lead to addiction in nonsusceptible individuals, nor does opioid underdosing prevent addiction; it may in fact increase drug-seeking behavior for relief of pain (such as watching the clock), referred to as "pseudoaddiction."

Table 62-6 Management of Opioid-Induced Adverse Effects

Respiratory depression	*Naloxone:* 0.01-0.02 mg/kg up to a full reversal dose of 0.1 mg/kg. May be given IV, IM, subcutaneously (SC), or via endotracheal tube (ET). The full reversal dose should initially be used for apnea in opioid-naïve patients. In opioid-tolerant patients, a reduced dose should be given and titrated up slowly to treat symptoms but prevent acute withdrawal. Ventilation may need to be supported during this process. Dose may be repeated every 2 min to a total of 10 mg. Adult maximum dose is 2 mg/dose. Give with caution to patients who are receiving long-term opioid therapy, as it may precipitate acute withdrawal. Duration of effect is 1-4 hr; therefore, close observation for renarcotization is essential.
Excessive sedation without evidence of respiratory depression	*Methylphenidate**: 0.3 mg/kg per dose PO (typically 10-20 mg/dose to a teenager) before breakfast and lunch. Do not administer to patients receiving clonidine, because dysrhythmias may develop. *Dextroamphetamine*: 2.5-10 mg on awakening and at noon. Not for use in young children or in patients with cardiovascular disease or hypertension. *Modafinil:* Pediatric dose not established. May be useful in selected patients. Typical adult dose: 50-200 mg/day. Change opioid or decrease the dose.
Nausea and vomiting	*Metoclopramide*†: 0.15 mg/kg IV up to 10 mg/dose q6-12h for 24 hr. *Trimethobenzamide:* PO or rectally (PR) if weight <15 kg, 100 mg q6h; if >15 kg, 200 mg q6h. (Note: Suppository contains benzocaine 2%.) Not for use in newborn infants or premature infants. 5-HT_3 blockers: *Ondansetron:* 0.15 mg/kg up to 8 mg IV q6-8h not to exceed 32 mg/day (also available as a sublingual tablet). *Granisetron:* 10-20 μg/kg IV q12-24h. *Prochlorperazine** (Compazine): >2 yr or >20 kg, 0.1 mg/kg per dose q8h IM or PO up to 10 mg/dose. Change opioid.
Pruritus	*Hydroxyzine*: 0.5 mg/kg PO q6h. *Nalbuphine:* 0.1 mg/kg IV q6h for pruritus caused by intraaxial opioids, especially fentanyl. Administer slowly over 15-20 min. May cause acute reversal of systemic μ-receptor effects and leave κ-agonism intact. *Naloxone:* 0.003-0.1 mg/kg/hr IV infusion (titrate up to decrease pruritus and reduce infusion if pain increases). *Ondansetron:* 0.05-0.1 mg/kg IV or PO q8h. *Cyproheptadine*†: 0.1-0.2 mg/kg PO q8-12h. Maximum dose 12 mg. Change opioid.
Constipation	Encourage water consumption, high-fiber diet, and vegetable roughage. *Bulk laxatives:* Metamucil, Maltsupex. *Lubricants:* Mineral oil 15-30 mL PO qd as needed (not for use in infants because of aspiration risk). *Surfactants:* Sodium docusate (Colace): <3 yr: 10 mg PO q8h 3-6 yr: 15 mg PO q8h 6-12 yr: 50 mg PO q8h >12 yr: 100 mg PO q8h *Stimulants:* Bisacodyl suppository (Dulcolax): <2 yr: 5 mg PR qhs >2 yr: 10 mg PR qhs *Senna syrup* (218 mg/5 mL): >3 yr, 5 mL qhs. *Enema:* Fleet's hypertonic phosphate enema (older children; risk of hyperphosphatemia). *Electrolytic/osmotic:* Milk of magnesia; for severe impaction: polyethylene glycol (GoLYTELY, MiraLAX).
Urinary retention	Straight catheterization, indwelling catheter.

*Avoid in patients taking monoamine oxidase inhibitors.
†May be associated with extrapyramidal side effects, which may be more commonly seen in children than in adults.
Modified from Burg FD, Ingelfinger JR, Polin RA, et al, editors: Current pediatric therapy, *ed 18, Philadelphia, 2006, WB Saunders, p. 16.*

Table 62-7 Equianalgesic Doses and Half-Lives ($T_{1/2\beta}$) of Some Commonly Used Opioids

OPIOID	IM/IV DOSE (mg)	ORAL DOSE (mg)	$T_{1/2\beta}$ (hr)
Morphine	10	30	2-3
Meperidine	100	400	3-4
Oxycodone	15	20-30	2-3
Fentanyl	0.15-0.2	—	3-5
Alfentanil	0.75-1.5	—	1-2
Sufentanil	0.02	—	2-3
Diamorphine	5	60	0.5*
Methadone	10	10-15	15-40
Hydromorphone	1.5	7.5	3-4
Tramadol†	100	100	5-7
Buprenorphine	0.4	0.8 (sublingual)	3-5
Pentazocine	60	150	3-5
Nalbuphine	10-20	—	2-4
Butorphanol	2	—	2-3

NOTES:
- Published reports vary in the suggested doses considered to be equianalgesic to morphine. Therefore, titration to clinical response in each patient is necessary.
- Suggested doses are the results of single-dose studies only. Therefore, use of the data to calculate total daily dose requirements and repeated or continuous doses may not be appropriate.
- There may be incomplete cross-tolerance between these drugs. In patients who have been receiving 1 opioid for a prolonged period, it is usually necessary to use a dose lower than the expected equianalgesic dose when changing to another opioid, and to titrate to effect.

*Rapidly hydrolyzed to morphine.
†Only part of its analgesic action results from action on μ opioid receptors.
Modified from Macintyre PE, Ready LB: Acute pain management: a practical guide, *ed 2, Philadelphia, 2001, WB Saunders, p. 19.*

Table 62-8 Classes of Local Anesthetic Drugs

Amides are metabolized in the liver and the elimination half-lives vary from about 1.5-3.5 hr	Lidocaine (lignocaine) Bupivacaine Prilocaine Dibucaine (cinchocaine) Mepivacaine Etidocaine Ropivacaine
Esters are metabolized in plasma (and to a lesser extent the liver) by pseudocholinesterases; thus their half-lives in the circulation are shorter than those of amides	Procaine Chloroprocaine Cocaine Tetracaine (amethocaine) Benzocaine

Modified from Macintyre PE, Ready LB: Acute pain management: a practical guide, *ed 2, Philadelphia, 2001, WB Saunders, p. 19.*

depression, and cardiovascular collapse. Unlike opioids, local anesthetics therefore require a strict maximum dosing schedule. Pediatricians should be aware of the need to calculate these doses and adhere to guidelines.

Topical local anesthetic preparations do not generally result in measurable systemic blood levels, and can reduce pain in diverse circumstances: suturing of lacerations, placement of peripheral IV catheters, lumbar punctures, and accessing of indwelling central venous ports. The application of tetracaine, epinephrine, and cocaine (TAC) results in good anesthesia for suturing wounds, but TAC should not be used on mucous membranes. Combinations of tetracaine with phenylephrine and lidocaine-epinephrine-tetracaine are equally as effective as TAC, eliminating the need to use a controlled substance (cocaine). EMLA, a topical eutectic mixture of lidocaine and prilocaine used to anesthetize intact skin, is commonly applied for venipuncture, lumbar puncture, and other needle procedures. EMLA is generally safe for use in neonates, but it is associated with prilocaine-induced methemoglobinemia. In circumcision, EMLA is more effective than placebo in providing analgesia, but probably less effective than ring block of the penis. EMLA should be used cautiously for circumcision, because its use may cause redness and blistering on the penis. A small area should be tested for hypersensitivity before EMLA is more widely applied. Lidocaine cream, 5%, has replaced EMLA in many pediatric centers. Lidocaine is the most commonly used local anesthetic for cutaneous infiltration. Maximum safe doses of lidocaine are 5 mg/kg without epinephrine and 7 mg/kg with epinephrine. Although concentrated solutions (2%) are commonly available from hospital pharmacies, more dilute solutions such as 0.25% and 0.5% are as equally as effective as 1-2% solutions. The diluted solutions cause less burning discomfort on injection and permit use of larger volumes without achieving toxic doses. In the surgical setting, cutaneous infiltration is more often performed with bupivacaine 0.25% or ropivacaine 0.2% because of the much longer duration of effect. The maximum dose of these long-acting amide anesthetics is 2-3 mg/kg.

Table 62-9 Examples of Neuropathic Pain Syndromes

PERIPHERAL NERVOUS SYSTEM FOCAL AND MULTIFOCAL LESIONS Postherpetic neuralgia Cranial neuralgias (such as trigeminal neuralgia, glossopharyngeal neuralgia) Diabetic mononeuropathy Nerve entrapment syndromes Plexopathy from malignancy or irradiation Phantom limb pain Posttraumatic neuralgia (such as nerve root compression or after thoracotomy) Ischemic neuropathy
PERIPHERAL NERVOUS SYSTEM GENERALIZED POLYNEUROPATHIES *Metabolic/nutritional:* Diabetes mellitus, pellagra, beriberi, multiple nutritional deficiency, hypothyroidism *Toxic:* Alcohol-, platinum-, or taxane-based chemotherapy, isoniazid, antiretroviral drugs *Infective/autoimmune:* HIV, acute inflammatory polyneuropathy (Guillain-Barré syndrome), neuroborreliosis (Bannwarth syndrome) *Hereditary:* Fabry disease *Malignancy:* Carcinomatosis *Others:* Idiopathic small fiber neuropathy
CENTRAL NERVOUS SYSTEM LESIONS Spinal cord injury Prolapsed disc Stroke (brain infarction, spinal infarction) Multiple sclerosis Surgical lesions (such as rhizotomy, cordotomy) Complex neuropathic disorders Complex regional pain syndrome types I and II

Modified from Freynhagen R, Bennett MI: Diagnosis and management of neuropathic pain, BMJ *339:b3002, 2009.*

Neuropathic pain may respond well to the local application of a lidocaine topical patch (Lidoderm) for 12 hr per day (Table 62-9). *Peripheral neuropathic* pain also may respond to IV lidocaine infusions, which may be used in hospital settings for refractory pain, complex regional pain syndromes, and pain associated with malignancies or the therapy of malignancies, such as oral mucositis following bone marrow transplantation. In these instances, 1-2 mg/kg/hr should be administered, and the infusion titrated to achieve a blood lidocaine level in the 2-5 μg/mL range, with use of twice-daily therapeutic blood monitoring. Table 62-10 lists approaches to *central neuropathic pain*.

Table 62-10 Treatment Recommendations for Central Neuropathic Pain Adapted from Current Evidence-Based Literature

MEDICATION CLASS/DRUG	RECOMMENDED STAGE OF TREATMENT
ANTIDEPRESSANTS	
Tricyclics (amitriptyline, nortriptyline)	1st or 2nd
Serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine)	1st or 2nd
ANTICONVULSANTS	
Pregabalin	1st or 2nd
Gabapentin	1st or 2nd
Lamotrigine	2nd or 3rd (in pain after stroke)
Valproate	3rd
OPIOIDS*	
Levorphanol	
MISCELLANEOUS	
Cannabinoids	2nd (in multiple sclerosis)
Mexiletine	3rd

*2nd or 3rd (no specification).

From Freynhagen R, Bennett MI: Diagnosis and management of neuropathic pain, BMJ 339:b3002, 2009.

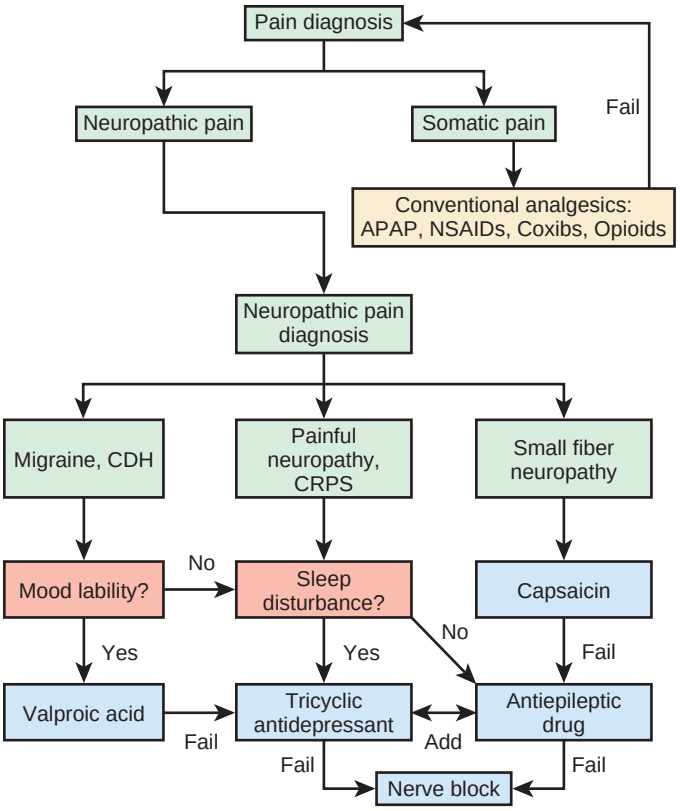


Figure 62-4 A decision tree for the selection of conventional and nonconventional analgesics. *APAP*, acetaminophen; *CDH*, chronic daily headaches; *CRPS*, complex regional pain syndromes; *NSAIDs*, nonsteroidal antiinflammatory drugs.

UNCONVENTIONAL MEDICATIONS IN PEDIATRIC PAIN

Unconventional analgesic medication refers to a wide number of drugs that were developed for other indications but that have been found to have analgesic properties. These drugs include some antidepressants, antiepileptic drugs (AEDs), and neurotropic drugs.

The unconventional analgesics are generally used to manage neuropathic pain conditions, migraine disorders, fibromyalgia syndrome, and some forms of functional chronic abdominal pain syndromes, but they are generally not used to manage surgical, somatic, or musculoskeletal pain. Figure 62-4 presents a decision-making tree that will help the physician select the appropriate analgesic category for various types of pain. The AED gabapentin confers analgesia as well as opioid-sparing benefits following major surgery in adults and in one well-conducted clinical trial in adolescents following spine surgery.

Although several unconventional analgesics have been approved by the FDA for analgesic uses, none has been specifically approved for use in youth with chronic pain. Thus, these drugs should be used with caution, with a focus on mitigating pain to allow a child to participate effectively in therapies and return to normal activity as soon as possible. The use of psychotropic medications should be guided by the principles applied to pharmacologic treatment of any symptom or disease. Target symptoms should be identified, and medication side effects monitored. To determine dosing regimens, the physician should consider the child's weight and the effects that medical condition and other medications, such as psychotropic drugs, may have on the child's metabolism. When available, therapeutic blood-level monitoring should be performed. Side effects should be addressed in detail with both parent and child, and specific instructions given for responding to possible adverse events. It may be necessary to directly address concerns about addiction, dependence, and tolerance in order to decrease treatment-related anxiety and improve medication adherence.

Antidepressant Medications

Antidepressant medications are useful in adults with chronic pain, including neuropathic pain, headaches, and rheumatoid arthritis, independent of their effects on depressive disorders. Antidepressants' analgesic properties inhibit norepinephrine reuptake in the CNS. In children, because clinical trials have been limited, the practitioner should use antidepressants cautiously to treat chronic pain or associated depressive or anxiety symptoms. The FDA issued a "black box warning," its strongest warning, to inform the public of a small but significant increase in suicidal thoughts and attempts in children and adolescents receiving antidepressants. A meta-analysis of studies involving children and adolescents receiving antidepressants indicated that no suicides had been completed. The pediatrician should address this issue with parents of patients being treated with antidepressants and should develop monitoring plans consistent with current FDA recommendations.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs), which have been studied most in children with chronic pain, are effective in pain relief for symptoms including neuropathic pain, functional abdominal pain, and migraine. The efficacy of TCAs may be based on inhibition of the neurochemical pathways involved in norepinephrine and serotonin reuptake and their interference with other neurochemicals involved in the perception or neural conduction of pain. Because sedation is the most common side effect of TCAs, these medications are also effective in treating the sleep disorders that frequently accompany pediatric pain. Biotransformation of TCAs is extensive in healthy children, so the child should be started on a bedtime dose, which may be able to then be titrated to a daily divided dose, with the larger dose given at bedtime. However, TCAs typically are administered only at bedtime. Pain symptoms usually remit at lower doses than those recommended or required for the treatment of mood disorders. Most children and adolescents do not require more than 0.25-0.5 mg/kg of amitriptyline or nortriptyline once a day at bedtime.

Attention should also be paid to hepatic microsomal enzyme metabolism, because CYP2D6 inhibitors, such as cimetidine and quinidine, can increase levels of TCAs. Anticholinergic side effects, which are remarkably uncommon in children in comparison with adults, often remit over time. Constipation, orthostatic hypotension, and

dental caries from dry mouth should be addressed by emphasizing the importance of hydration and oral hygiene. Other side effects include weight gain, mild bone marrow suppression, and liver dysfunction. Some practitioners recommend monitoring complete blood count and liver function values at baseline and periodically during therapy. TCA blood levels can be obtained as well, but pursuit of therapeutic blood monitoring generally should be decided on an individual basis, particularly if adherence, overdose, or sudden changes in mental status are an issue.

All TCAs inhibit cardiac conduction pathways and prolong the QT interval. Sudden cardiac death is reported in children taking TCAs, principally desipramine, probably related to QTc prolongation. There is no general agreement for monitoring the electrophysiologic effects of these drugs, but it is prudent to obtain a careful personal and family history focusing on cardiac arrhythmias, heart disease, and syncope before the initiation of treatment. If personal or family history is positive for any of these conditions, a baseline electrocardiogram should be obtained, with care taken to ensure that the QTc is <445 msec. We recommend that if the dose of amitriptyline or nortriptyline is increased beyond 0.25-0.5 mg/kg/day, an electrocardiogram should be performed for each dosing increase. With TCAs as with other antidepressants, physical dependence and a known discontinuation syndrome can occur. The discontinuation syndrome includes agitation, sleep disturbances, appetite changes, and gastrointestinal symptoms. These medications should be tapered slowly to assist in distinguishing among symptoms that indicate rebound, withdrawal, or the need for continuing the medication.

Serotonin and Serotonin-Norepinephrine Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have minimal efficacy in the treatment of a variety of pain syndromes in adults. SSRIs are very useful when symptoms of depression or anxiety disorders are present and cannot be addressed adequately by nonpharmacologic means. Although many SSRIs are used in practice with children, only fluoxetine has been approved by the FDA for use in children and adolescents. SSRIs have a significantly milder side-effect profile than do TCAs (most side effects of both are transient), and they have no anticholinergic side effects. Chief side effects include gastrointestinal symptoms, headaches, agitation, insomnia, sexual dysfunction, and anxiety. Rarely, hyponatremia, or the syndrome of inappropriate antidiuretic hormone secretion, may occur. Interactions with other medications that have serotonergic effects (tramadol, trazodone, tryptophan, and triptan migraine medication) may also occur. When these medications are used in combination, there is increased likelihood that a life-threatening **serotonergic syndrome** may occur, with associated symptoms of myoclonus, hyperreflexia, autonomic instability, muscle rigidity, and delirium. There is also a **discontinuation syndrome** associated with shorter-acting SSRIs (paroxetine), which includes dizziness, lethargy, paresthesias, irritability, and vivid dreams. Dosages of medications should be tapered slowly over several weeks.

The selective serotonin-norepinephrine reuptake inhibitors duloxetine and venlafaxine demonstrate significant efficacy with chronic neuropathic and other pain syndromes because they inhibit both serotonin and norepinephrine reuptake, and they may directly block associated pain receptors as well. Venlafaxine has no pain indication labeling, but duloxetine is FDA approved for managing neuropathic pain (diabetic neuropathy) and fibromyalgia syndrome.

Because both SSRIs and selective serotonin-norepinephrine reuptake inhibitors have fewer anticholinergic side effects than TCAs, adherence to them is better than in psychiatric populations taking TCAs. Side effects of both types of drugs include gastrointestinal symptoms, hyperhidrosis, dizziness, and agitation, but these effects generally wane over time. Hypertension and orthostatic hypotension may occur; in addition, the patient's blood pressure should be closely followed, and appropriate hydration should be stressed. Note that whereas appetite stimulation and weight gain are associated with all TCAs, duloxetine is often associated with weight loss, frequently a desirable side effect, especially in weight-conscious adolescent females.

Antiepileptic Drugs

Traditional anticonvulsants, such as carbamazepine and valproic acid, are believed to relieve chronic pain by blocking sodium (valproate and the gabapentinoids) or calcium channels (carbamazepine and oxcarbazepine) at the cellular neuronal level, thereby suppressing spontaneous electrical activity and restoring the normal threshold to depolarization of hypersensitive nociceptive neurons, without affecting normal nerve conduction. These medications are particularly useful in patients with mood disorders and neuropathic pain. In adults, the FDA has approved carbamazepine for trigeminal neuralgia and valproate for migraine prophylaxis, and pregabalin is approved in adults for neuropathic pain complicating diabetes, zoster, and for management of fibromyalgia. Anticonvulsant medications generally have gastrointestinal side effects in addition to sedation, anemia, ataxia, rash, and hepatotoxicity. Carbamazepine and oxcarbazepine are associated with an increased incidence of Stevens-Johnson syndrome. Liver function values and a complete blood count should be obtained at start of therapy (baseline) and monitored with use of both these agents. These medications have narrow therapeutic windows and may have extreme variability in therapeutic blood medication levels, as well as multiple drug–drug interactions; also, they may produce liver disease and renal impairment. Drug levels should be measured with each dose increase and periodically thereafter. Carbamazepine, in particular, causes autoinduction of hepatic microsomal enzymes, which can further complicate obtaining a therapeutic medication level. Frequent pregnancy tests are useful in menstruating female adolescents taking valproate, because severe neural tube defects are associated with this medication.

Less-toxic AEDs have supplanted the use of valproate and carbamazepine in patients with pain. These agents have their own, sometimes troubling side effect profiles, but they are far less toxic than their predecessors and they do not require monitoring of liver function, bone marrow function, or therapeutic blood levels. They are also far less lethal in accidental or deliberate overdose.

Gabapentin, the most widely prescribed AED for the management of pain disorders, demonstrates efficacy in treating children with chronic pain, particularly neuropathic pain, and is playing an increasing role in the management of routine surgical pain. Gabapentin has proven effective in treating chronic headache disorders, and many neuropathic pain syndromes including complex regional pain syndromes, chemotherapy induced neuropathy, postherpetic neuralgia, and diabetic neuropathy in both children and adults. This agent has a relatively benign side-effect profile and few drug interactions. Side effects include somnolence, dizziness, and ataxia. Children occasionally demonstrate side effects not reported in adults—severe impulsive or oppositional behavior, agitation, and, occasionally, depression. These side effects do not seem to be dose related.

A molecularly similar AED, **pregabalin**, works by mechanisms similar to those of gabapentin but appears to have a better side-effect profile. Because it undergoes virtually no hepatic metabolism, pregabalin has no significant drug–drug interactions, a concern in patients with chronic pain, who frequently take multiple medications—for both the pain and the underlying medical condition associated with the pain.

Topiramate also demonstrates greater success than traditional anticonvulsants in treating trigeminal neuralgia in adults and in migraine prophylaxis. Topiramate therapy results more frequently in cognitive dysfunction and short-term memory loss compared with gabapentin or pregabalin, and these neurocognitive effects are particularly problematic for school-age children. The pediatrician should also be aware that in female adolescents, topiramate is associated with weight loss, whereas other anticonvulsants are typically associated with significant weight gain.

Benzodiazepines

Children and adolescents with chronic pain may have comorbid psychologic conditions such as depressed mood, sleep disturbances, or anxiety disorders, including generalized anxiety disorder, separation anxiety, posttraumatic stress disorder, and panic attacks. Pervasive developmental disorders are also common in this population.

Psychologic factors can affect a youth's ability to cope with a pain disorder; a conditioned response to pain may be to feel out of control and to lead to increases in anxiety and pain. Conversely, the feeling of helplessness can sensitize the child to increasing amounts of pain, leading the child to perseverate on the pain, think catastrophically, and feel hopeless. Changes in children's normal routines, with a negative impact on participation in valued activities, may further promote hopelessness, resulting in increased pain experiences and development of a depressive disorder.

Benzodiazepines are anxiolytic medications that also have muscle relaxant effects. They are particularly appropriate in acute situations as valuable adjuncts to the management of pain in the hospital setting, because they inhibit painful muscle spasms in surgical patients, but more importantly because they suppress the anxiety that virtually every hospitalized child experiences, anxiety that interferes with restorative sleep and amplifies the child's perception of pain. Benzodiazepines are useful to calm children with anxiety and anticipatory anxiety about planned, painful procedures.

Because dependence, tolerance, and withdrawal may occur with prolonged use, benzodiazepines are generally not recommended for the routine management of *chronic pain*. In concert with psychotherapy, they help control anxiety symptoms that amplify the perception of pain. Infrequently, benzodiazepines may cause behavioral disinhibition, psychosis-like behaviors, or, in large doses, respiratory depression. When dosing these medications, the pediatrician should consider that many benzodiazepines are metabolized by the cytochrome P450 microsomal enzyme system. This issue may be less significant with lorazepam and oxazepam, which undergo 1st-pass hepatic conjugation. Side effects common to benzodiazepines include sedation, ataxia, anemia, increased bronchial secretions, and depressed mood. If a benzodiazepine is administered for more than several consecutive days, the dosage should be slowly tapered over 2 or more weeks; if therapy is abruptly discontinued, autonomic instability, delirium, seizures, and profound insomnia may occur. There are data that suggest that the use of benzodiazepines during hospitalization for serious disease, such as organ transplantation, might increase the risk of development of posttraumatic stress disorder.

Antipsychotics and Major Sedatives

Low doses of antipsychotic medications are often used to address more-severe anxiety and agitation sometimes associated with chronic pain. The use of these medications is controversial because the associated adverse events may be severe. Typical antipsychotics, including thioridazine (Mellaril), haloperidol (Haldol), and chlorpromazine (Thorazine), are associated with a decrease in seizure threshold, agranulocytosis, weight gain, cardiac conduction disturbances, tardive dyskinesia, orthostatic hypotension, hepatic dysfunction, and life-threatening laryngeal dystonia. These side effects are generally less severe with atypical antipsychotics. Because they may still occur, the pediatrician should obtain a baseline electrocardiogram, liver function values, and complete blood count. If the pediatrician is using typical antipsychotics, an inventory of movement disturbances, such as the Abnormal Involuntary Movement Scale test, should be performed at baseline and at every follow-up visit, because movement disorders can worsen with abrupt withdrawal of medications or can become irreversible.

Atypical antipsychotics are generally associated with less-severe side–effect profiles, particularly with regard to side effects such as dyskinesias and dystonias. Use of olanzapine (Zyprexa), which is particularly helpful with insomnia and severe anxiety, requires assessing and monitoring blood levels of glucose, cholesterol, and triglyceride; olanzapine's side effects may include diabetes, hypercholesterolemia, or significant weight gain. The anticholinergic side effects associated with quetiapine (Seroquel) warrant frequent monitoring of blood pressure. Risperidone at doses >6 mg may cause side effects similar to those of typical antipsychotics. Clozapine (Clozaril), which causes increased incidence of life-threatening agranulocytosis, should generally be avoided as a treatment for children and adolescents with chronic pain. Aripiprazole (Abilify) has been used for severe anxiety and/or for treatment-resistant depression. All antipsychotics are associated with the rare, but potentially lethal **neuroleptic malignant syndrome**, which includes severe autonomic instability, muscular rigidity, hyperthermia, catatonia, and altered mental status.

Nonpharmacologic Treatment of Pain

Numerous psychologic and physical treatments for relieving pain, fear, and anxiety as well as enhancing functioning have been a mainstay of pediatric pain treatment and have excellent safety profiles and proven effectiveness. In the area of acute and procedural pain, nonpharmacologic strategies have long been used to help reduce distress in children undergoing medical procedures and surgery. Many of the behavioral methods aim to help children shift attention from pain and alter pain perception (e.g., distraction, hypnosis, imagery). In the treatment of chronic pain, cognitive-behavioral therapies (CBTs) are the most implemented nonpharmacologic treatment. CBT was developed with the goal of modifying social/environmental and behavioral factors that may exacerbate the child's experience of pain and pain-related disability. There are now several decades of research available on CBTs for pediatric chronic pain. Meta-analyses of randomized controlled trials of CBT interventions have found large positive effects of psychologic intervention on pain reduction in children with headache, abdominal pain, and fibromyalgia. Effective strategies include cognitive-behavioral skills training, parent training, relaxation therapy, and biofeedback. The relative or comparative effectiveness of different interventions has been examined in studies of headache and abdominal pain in children. Biofeedback and relaxation therapies have been found to have superior effects to pharmacologic treatments in reducing headache pain in children and adolescents. Similarly, for recurrent abdominal pain, positive effects for CBT were found relative to pharmaceutical, botanical, and dietary interventions (which had very weak evidence).

Nonpharmacologic treatments of pain may be generalized to other treatment needs. A child with cancer who learns self-hypnosis to reduce distress from lumbar punctures may successfully apply this skill to other stressful medical and nonmedical situations. When deciding how to incorporate nonpharmacologic techniques to treat pain, the practitioner should: (1) pay attention to the patient's environment, optimal positioning, and physical comfort; (2) seek to integrate nonpharmacologic techniques with appropriate analgesics; (3) give children (and family members) developmentally and situationally appropriate information as to what to expect, given the child's medical condition, procedures, and treatments; (4) include patients and their families in decision making to ensure an appropriate treatment choice and to optimize adherence to treatment protocols; and (5) above all, develop a **communication plan** among the different therapists, typically with the pediatrician as the case manager, so that the messages to the child and parent are consistent and the modes of therapy are organized into an **integrative team approach**.

Cognitive-behavioral strategies refer to techniques that teach children how to manage pain by learning new ways to think about the pain and to change behaviors associated with the pain. This includes strategies aimed at enhancing children's confidence and self-efficacy, decreasing fear of pain, and promoting exposure to previously avoided activities. In addition, pain coping skills may shift the child's attentional focus away from pain and painful stimuli. Behavioral strategies focused on modifying contingencies in the child's environment (such as parental responses to pain behaviors) may influence pain expression, leading to changes in how children behave or respond to pain. Strategies may also be aimed specifically at modifying individual and family coping (e.g., difficulties in social relationships, psychosocial distress).

Parent and family education and/or psychotherapy, particularly cognitive-behavioral family approaches, have been shown to be effective for treating chronic pain. Parents can learn to cope with their own distress and to understand pain mechanisms and appropriate treatment of pain. Key strategies include teaching parents to alter family patterns that may inadvertently exacerbate pain through developing behavior plans. Parents are taught to create plans for the child to manage the child's own symptoms and increase independent functioning. Often, all adult caregivers (e.g., parents and teachers) need

guidance on developing a behavioral incentive plan to help the child return to school, gradually increase attendance, and receive tutoring, after a prolonged, pain-related absence.

Other Psychologic or Psychiatric Treatment

In addition to pain, there may be other psychologic disorders (e.g., anxiety disorders, major depression) that should be identified and addressed either as part of or separate from the pain management plan. Individual psychotherapy or psychiatric intervention may be warranted to adequately treat a comorbid disorder.

Relaxation techniques promote muscle relaxation and reduction of anxiety, which often accompanies and increases pain. Controlled breathing and progressive muscle relaxation are commonly used relaxation techniques for preschool-age and older children. Asking the child to focus on the breath and pretend to be blowing up a big balloon, while pursing the lips and exhaling slowly may help induce controlled breathing.

Distraction helps a child of any age shift attention away from pain and onto other activities. Common attention sustainers in the environment include bubbles, music, video games, television, the telephone, conversation, school, and play. Asking children to tell stories, or asking parents to read to the child, and even mutual story-telling can be helpful distracters. Being involved with social, school, physical, or other activities helps the child in chronic pain to regain function.

Hypnotherapy helps a child focus on an imaginative experience that is comforting, safe, fun, or intriguing. Hypnotherapy captures the child's attention, alters his sensory experiences, reduces distress, reframes pain experiences, creates time distortions, helps the child dissociate from the pain, and enhances feelings of mastery and self-control. Children with chronic pain can use metaphor, for example, imagining they have overcome something feared because of pain in real life. As the child increases mastery of imagined experiences, the enhanced sense of control can be used during actual pain rehabilitation. Hypnotherapy is best for children of school age or older.

Biofeedback involves controlled breathing, relaxation, or hypnotic techniques with a mechanical device that provides visual or auditory feedback to the child when the desired action is approximated. Common targets of actions include muscle tension, peripheral skin temperature through peripheral vasodilation, and anal control through rectal muscle contraction and relaxation. Biofeedback also enhances the child's sense of mastery and control, especially for the child who needs more "proof" of change than that generated through hypnotherapy alone.

Iyengar yoga was developed to achieve balance in mind, body, and spirit. This form of therapeutic yoga is especially effective for treating chronic pain; improving mood, energy, and sleep; and reducing anxiety. Iyengar yoga involves a series of asanas (body poses) oriented to the specific medical condition or symptoms. It uses props, such as blankets, bolsters, blocks, and belts, to support the body while the patient assumes more healing poses. Yoga promotes a sense of energy, relaxation, strength, balance, and flexibility and, over time, enhances a sense of mastery and control. In more advanced yoga, the child may learn certain types of breathing (pranayama) for added benefit. Mostly, through this form of yoga, the child learns mindfulness or being present and in the moment. By focusing on body and breath, the child can develop strategies to avoid ruminating about the past or worrying about the future.

Massage therapy involves the therapist's touching and applying varied degrees of pressure on the child's muscles. This massage is very useful for children with chronic pain and especially helpful for those with myofascial pain. There are several types of massage, including craniosacral therapy. For young children, it can be helpful to have parents learn and perform brief massage on their children before bedtime.

Physical therapy can be especially useful for children with chronic, musculoskeletal pain and for those deconditioned from inactivity. Exercise appears to specifically benefit muscle functioning, circulation, and posture, also improving body image, body mechanics, sleep, and mood. The physical therapist and the child can develop a graded exercise plan for enhancing the child's overall function.

Acupuncture involves the placement of needles at specific acupuncture points along a meridian, or energy field, after a diagnosis of excess or deficienct energy in that meridian as the primary cause of the pain is made by the acupuncturist. Acupuncture is a feasible, popular part of a pain management plan for children with chronic pain. Acupuncture alleviates chronic nausea, fatigue, and several chronic pain states, including migraine and chronic daily headaches, abdominal pain, and myofascial pain. Acupuncture also has efficacy in adults with myofascial pain, primary dysmenorrhea, sickle cell crisis pain, and sore throat pain. The acupuncturist must relate well to children so that the experience is not traumatic, because added stress would undo the benefits gained.

Transcutaneous electrical nerve stimulation (TENS) is the use of a battery-operated tool worn on the body to send electrical impulses into the body at certain frequencies set by the machine. TENS is believed to be quite safe and can be tried for many forms of localized pain. Children often find TENS helpful and effective.

Music and art therapy can be especially helpful for young and nonverbal children who would otherwise have trouble with traditional talk psychotherapies. Also, many creative children can more easily express fears and negative emotions through creative expression and, with the therapist's help, learn about themselves in the process.

Dance, movement, pet therapies, and aromatherapy have also been used and may be very helpful but have not been well studied in children for pain control.

Invasive Interventions in Treating Pain

Interventional neuraxial and peripheral nerve blocks provide intraoperative anesthesia, postoperative analgesia (see Chapter 61), treatment of acute pain (e.g., long bone fracture and the pain of acute pancreatitis), and contribute to the management of chronic pain (e.g., headaches, abdominal pain, complex regional pain syndromes [CRPS], and cancer pain). Even though interventional procedures are typically rarely used in nonmalignant chronic pain in children, they are described here so that the pediatrician will understand the different types of procedures that are more commonly carried out in adults and rarely described in pediatric texts.

Regional anesthesia provides several benefits: (1) it is an alternative to or augmentation of opioid-based pain control, thereby minimizing the opioid side effects of nausea, vomiting, somnolence, respiratory depression, pruritus, constipation, and physical dependence; (2) it generally provides better quality pain relief because it interrupts nociceptive pathways and more profoundly inhibits endocrine stress responses; (3) it results in earlier ambulation in recovering surgical patients; (4) it helps prevent atelectasis in the setting of severe chest pain; and (5) it usually results in earlier discharge from the hospital. Theoretically, the interruption of nociceptive pathways in the periphery by regional anesthetics will prevent, or reverse the process of amplification of pain signals induced by nociception (CNS wind-up, glial cell activation, etc.). For postoperative pain, effective regional anesthesia and good analgesia reduce the risks of acute pain transitioning into chronic pain.

Regional anesthesia is considered safe and effective if performed by trained staff with the proper equipment. Most nerve blocks are performed by an anesthesiologist or pain management physician; a few are easily performed by a nonanesthesiologist with appropriate training.

Head and Neck Blocks

Primary pain syndromes of the head, such as trigeminal neuralgia, are distinctly unusual in the pediatric population, and few surgical procedures in the head and neck are amenable to regional anesthesia. Pain following tonsillectomies is not amenable to nerve blockade, and neurosurgical incisional pain is usually mitigated by local infiltration of local anesthetic into the wound margins by the surgeon. Headache disorders, very common in the pediatric age group, often respond well to block of the greater and lesser occipital nerves, which provide sensation to much of the cranial structures, from the anterior hairline to the cervical region. The greater occipital nerve can be blocked adjacent to the occipital artery, which can usually be identified at the occipital

ridge midway between the occipital prominence and the mastoid process by palpation, Doppler sound amplification, or visually by ultrasound. The lesser occipital nerves emerge from deeper layers midway between the greater occipital nerve and the mastoid process, where subcutaneous infiltration is effective.

Upper-Extremity Blocks

The brachial plexus block controls pain during surgical procedures or other lesions of the upper extremities. This block also protects the extremity from movement, reduces arterial spasm, and blocks sympathetic outflow to the upper extremity. The brachial plexus, responsible for cutaneous and motor innervation of the upper extremity, is an arrangement of nerve fibers originating from spinal nerves C5 through C8 and T1, extending from the neck into the axilla, arm, and hand. The brachial plexus innervates the entire upper limb, except for the trapezius muscle and an area of skin near the axilla. If pain is located proximal to the elbow, the brachial plexus may be blocked above the clavicle (roots and trunks); if the pain is located distal to the elbow, the brachial plexus may be blocked below it (cords and nerves). The block may be given as a single injection with a long-acting anesthetic (bupivacaine or ropivacaine, sometimes augmented with clonidine or dexamethasone to prolong block duration and intensity) to provide up to 12 hr of analgesia, or given via a catheter (to infuse local anesthetic) attached to a pump that can provide continuous analgesia over days or even weeks.

Anesthesiologists frequently use an IV regional block (or Bier block) with a local anesthetic in combination with a vasodilator such as phentolamine and an NSAID (typically ketorolac) to manage the pain of CRPS. The technique requires placement of an IV cannula into the distal part of the affected extremity, exsanguination of the extremity by elevating and wrapping it in an elastic (Esmarch) bandage, and application of a double pneumatic tourniquet, which is then inflated. Local anesthetic with additives as indicated is then injected into the IV cannula, filling the exsanguinated vasculature. The tourniquet must remain inflated for at least 30 min to allow fixation of local anesthetic to tissues, which reduces peak blood concentration and toxicity upon tourniquet deflation. Although the anesthetic effect is limited to the time of tourniquet inflation, analgesia for pain disorders usually persists for days, weeks, or months after the block.

Trunk and Abdominal Visceral Blocks

Trunk blocks provide somatic and visceral analgesia and anesthesia for pain or surgery of the thorax and abdominal area. Sympathetic, motor, and sensory blockade may be obtained. These blocks are often used in combination to provide optimal relief. Intercostal and paravertebral blocks may be beneficial in those patients for whom an epidural injection or catheter is contraindicated, for example, in the patient with a coagulopathy. Respiratory function is maintained, and the side effects of opioid therapy are eliminated.

The intercostal, paravertebral, rectus sheath, and transverse abdominal plane blocks are the most useful ones for pediatric chest and abdominal pain. The celiac plexus block is most useful for visceral pain caused by malignant cancer or pancreatitis. A pediatrician may perform an intercostal block, but the other blocks are best performed by an experienced anesthesiologist or pain physician.

The intercostal block is used to block the intercostal nerves, the anterior rami of the thoracic nerves from T1 to T11. These nerves lie inferior and posterior to each rib, and between the inner and innermost intercostal muscles, with their corresponding vein and artery, where they can be blocked, generally posterior to the posterior axillary line. Ultrasound imaging of the intercostal nerves helps avoid injury to intercostal vessels or insertion of the needle through the pleura, which results in pneumothorax.

The paravertebral block, an alternative to intercostal nerve block or epidural analgesia, is useful for pain associated with thoracotomy or with unilateral abdominal surgery, such as nephrectomy or splenectomy. Essentially this block results in multiple intercostal blocks with a single injection. The thoracic paravertebral space, lateral to the vertebral column, contains the sympathetic chain, rami communicantes, and dorsal and ventral roots of the spinal nerves. Because it is a continuous space, local anesthetic injection will provide sensory, motor, and sympathetic blockade to several dermatomes. The paravertebral block may be performed as a single injection, or, for a very prolonged effect, as a continuous infusion over several days or weeks via a catheter inserted in the paravertebral space. This block is best performed by an anesthesiologist or interventional pain physician.

Ilioinguinal and iliohypogastric nerve blocks are indicated for surgery for inguinal hernia repair, hydrocele, or orchiopexy repair as well as for chronic pain subsequent to these procedures. The first lumbar nerve divides into the iliohypogastric and ilioinguinal nerves, which emerge from the lateral border of the psoas major muscle. The iliohypogastric nerve supplies the suprapubic area as it pierces the transversus abdominis muscle and runs deep to the internal oblique muscle. The ilioinguinal nerve supplies the upper medial thigh and superior inguinal region as it also pierces the transversus abdominis muscle and runs across the inguinal canal. Ultrasound guidance has made this nerve block nearly always successful.

The **celiac plexus block** is indicated for surgery or pain of the pancreas and upper abdominal viscera. The celiac plexus, located on each side of the L1 vertebral body, contains 1-5 ganglia. The aorta lies posterior, the pancreas anterior, and the inferior vena cava lateral to these nerves. The celiac plexus receives sympathetic fibers from the greater, lesser, and least splanchnic nerves, as well as from parasympathetic fibers from the vagus nerve. Autonomic fibers from the liver, gallbladder, pancreas, stomach, spleen, kidneys, intestines, and adrenal glands originate from the celiac plexus. This block requires CT guidance or fluoroscopy to provide direct visualization of the appropriate landmarks and to confirm correct needle placement. The close proximity of structures such as the aorta and vena cava make this a technical procedure best performed by an anesthesiologist, interventional pain physician, or radiologist.

Lower-Extremity Blocks

Lumbar plexus and sciatic nerve blocks provide pain control for painful conditions or surgical procedures of the lower extremities, with the benefit of providing analgesia to only 1 extremity while preserving motor and sensory function of the other. Unlike with some caudal or lumbar epidural blocks, the patient may still bear weight on the affected leg. The lumbosacral plexus is an arrangement of nerve fibers originating from spinal nerves L2-L4, and S1-S3. The lumbar plexus arises from L2-L4 and divides into the lateral femoral cutaneous, femoral, and obturator nerves. These nerves supply the muscles and sensation of the upper leg, with a sensory branch of the femoral nerve extending below the knee to innervate the medial aspect of the foreleg, ankle, and foot (saphenous nerve). The sacral plexus arises from L4-S3 and divides into the major branches of the sciatic, tibial, and common peroneal nerves. These nerves, in turn, supply the posterior thigh, lower leg, and foot. Unlike brachial plexus blocks, whose targets are accessible, blockade of the entire lower extremity requires more than 1 injection because the lumbosacral sheath is not accessible. Separate injections are necessary for the posterior (sciatic) and anterior (lumbar plexus) branches; the injections can be performed at any of several levels during the course of the nerve, as is clinically expedient. The lumbar plexus can be blocked in the back, resulting in analgesia of the femoral, lateral femoral cutaneous, and obturator nerves. Alternatively, any of these 3 nerves can be individually anesthetized, depending on the location of the pain. Similarly, the sciatic nerve can be anesthetized proximally as it emerges from the pelvis or more distally in the posterior thigh, or its major branches (the tibial and peroneal nerves) can be individually anesthetized. These nerve blocks are generally best performed by an anesthesiologist, interventional pain physician, or radiologist.

Sympathetic Blocks

Sympathetic blocks were once thought to be useful in the diagnosis and treatment of sympathetically mediated pain, CRPS, and other neuropathic pain conditions, but more recently large meta-analyses have shown their utility to be small. The peripheral sympathetic trunk is formed by the branches of the thoracic and lumbar spinal segments,

and it extends from the base of the skull to the coccyx. The sympathetic chain, which consists of separate ganglia containing nerves and autonomic fibers with separate plexuses, can be differentially blocked. These separate plexuses include the stellate ganglion in the lower neck and upper thorax, the celiac plexus in the abdomen, the second lumbar plexus for the lower extremities, and the ganglion impar for the pelvis. When blocks of these plexuses are performed, sympathectomy is obtained without attendant motor or sensory anesthesia.

The **stellate ganglion block** is indicated for pain in the face or upper extremity as well as for CRPS, phantom limb pain, amputation stump pain, or circulatory insufficiency of the upper extremities. The stellate ganglion arises from spinal nerves C7-T1 and lies anterior to the 1st rib. It contains ganglionic fibers to the head and upper extremities. Structures in close proximity include the subclavian and vertebral arteries anteriorly, the recurrent laryngeal nerve, and the phrenic nerve. The Chassaignac tubercle, the transverse process of the C6 vertebral body superior to the stellate ganglion, is a useful and easily palpable landmark for the block, but radiographic or ultrasound imaging is more typically used than surface anatomy and palpation.

The lumbar sympathetic block addresses pain in the lower extremity, CRPS, phantom limb pain, amputation stump pain, and pain from circulatory insufficiency. The lumbar sympathetic chain contains ganglionic fibers to the pelvis and lower extremities. It lies along the anterolateral surface of the lumbar vertebral bodies and is most often injected between the L2 and L4 vertebral bodies.

The analgesia produced by peripheral sympathetic blocks usually outlives the duration of the local anesthetic, often persisting for weeks or indefinitely. If analgesia is transient, the blocks may be performed with catheter insertion for continuous local anesthesia of the sympathetic chain over a period of days or weeks. Because precise radiographically guided placement of the needle and/or catheter is required for safety and success, sympathetic blocks are generally best performed by an anesthesiologist, interventional pain physician, or interventional radiologist.

Epidural Anesthesia (Thoracic, Lumbar, and Caudal)

Epidural anesthesia and analgesia are indicated for pain below the clavicles, management of CRPS, cancer pain unresponsive to systemic opioids, and pain limited by opioid side effects.

The 3 layers of the spinal meninges—the dura mater (outer), the arachnoid mater (middle), and the pia mater (inner)—envelop the spinal neural tissue. The subarachnoid space contains cerebrospinal fluid between the arachnoid mater and pia mater. The epidural space extends from the foramen magnum to the sacral hiatus. The epidural space, which contains fat, lymphatics, blood vessels, and the spinal nerves as they leave the spinal cord, separates the dura mater from the periosteum of the surrounding vertebral bodies. In children, the fat in the epidural space is not as dense as in adults, predisposing to greater spread of the local anesthetic from the site of injection.

Epidural local anesthetics block both sensory and sympathetic fibers, and if the local anesthetic is of sufficient concentration, they also block motor fibers. Mild hypotension may occur, although it is unusual in children younger than 8 yr. Epidural local anesthetics high in the thoracic spine may also anesthetize the sympathetic nerves to the heart (the cardiac accelerator fibers), producing bradycardia. In addition to using local anesthetics, it is routine to use opioids and α-agonists in the epidural space. These agents have their primary site of action in the spinal cord, to which they diffuse from their epidural depot. Side effects of epidural opioid administration include delayed respiratory depression, particularly when hydrophilic opioids such as morphine are used. The risk of this effect requires that children receiving epidural opioids by intermittent injection or continuous infusion be monitored by continuous pulse oximetry and nursing observation, particularly during the 1st 24 hr of therapy or after significant dose escalations. Respiratory depression occurring after the 1st 24 hr of epidural opioid administration is distinctly unusual.

Epidural clonidine, an α_2-agonist with μ-opioid analgesic properties, is associated with minimal risk and side effects. Although product labeling indicates use only in children with severe cancer pain, it is commonly used for routine postoperative pain as well as pain syndromes such as CRPS. Mild sedation is the most common side effect of epidural clonidine, and it is not associated with respiratory depression.

Because performing epidural blockade is technical and may result in spinal cord injury, it is best done by an anesthesiologist or pain physician skilled in the technique.

INTRATHECAL ANALGESIA

Intrathecal catheters infused with opioids, clonidine, ziconotide, and local anesthetics are occasionally applicable in pediatric patients suffering from intractable pain from cancer or other conditions. Typically, intrathecal catheters are attached to an implanted electronic pump containing a drug reservoir sufficient for several months of dosing. The technique is technical and best performed by an experienced pain management physician.

NERVE ABLATION AND DESTRUCTION

In infrequent pediatric cases, pain remains refractory in spite of maximal reliance upon oral and IV medications and nerve blockade. In these instances, temporary (ablation) or permanent (lytic) destruction of 1 or more nerves may be performed. These situations are rather extraordinary in children, and the techniques should be carefully weighed against the consideration of inducing permanent nerve destruction in a growing child with decades of life ahead. On the other hand, when pain is severe in life-limiting disease processes, the long-term considerations are less concerning, and these techniques should be discussed with a pain management specialist skilled in their performance.

CONSIDERATIONS FOR SPECIAL PEDIATRIC POPULATIONS

Pain Perception and Effects of Pain on Newborns and Infants

There are a number of sources of pain in the newborn period. These include acute pain (diagnostic and therapeutic procedures, minor surgery, monitoring), continuous pain (pain from thermal/chemical burns, postsurgical and inflammatory pain), and chronic or disease-related pain (repeated heelsticks, indwelling catheters, necrotizing enterocolitis, nerve injury, chronic conditions, thrombophlebitis). The most common sources of pain in healthy infants are acute procedures, such as heel lances, operations, and, in boys, circumcision.

In premature infants in the neonatal intensive care unit (NICU), there are many procedures performed. In the 1st wk of life, approximately 94% of preterm infants younger than 28 wk of gestational age are ventilated. Other procedures are heelsticks (the most commonly performed) and airway suctioning. Only a few of these procedures are preceded by any type of analgesia. Repeated handling and acute pain episodes sensitize the neonate to increased reactivity and stress responses to subsequent procedures they undergo as neonates or children. Typical stress responses include increases in heart rate, respiratory rate, blood pressure, and intracranial pressure. Cardiac vagal tone, transcutaneous oxygen saturation, carbon dioxide levels, and peripheral blood flow are decreased. Autonomic signs include changes in skin color, vomiting, gagging, hiccupping, diaphoresis, dilated pupils, and palmar and forehead sweating.

To assess pain in the newborn, it is critical to observe the infant for facial expression, body movements, crying, and any other atypical functional behaviors. The observer must consider the context in which the behavior is experienced. The infant's state (agitated, alert, asleep) and gestational and post-gestational ages also affect behavioral stress responses.

Untreated pain in the newborn has serious short-term and longer-term consequences. There has been a shift in most NICUs to more liberal use of opioids. Nonetheless, morphine, the traditional gold standard of analgesia for acute pain, may not be very effective and may have adverse long-term consequences. No differences have been found in the incidence of severe intraventricular hemorrhage or in the mortality rate when infants receiving morphine are compared with the

placebo group, and there are no changes in assessed pain from tracheal suctioning in ventilated infants receiving morphine compared with those receiving a placebo infusion. Morphine may not alleviate acute pain in ventilated preterm neonates, although there are few data on the effects of morphine and fentanyl in nonventilated newborns. The lack of opioid effects for acute pain in neonates may be due to an immaturity of opioid receptors; acute pain may cause the uncoupling of μ opioid receptors in the forebrain. Repetitive acute pain may create central neural changes in the newborn that may have long-term consequences for later pain vulnerability, cognitive effects, and opioid tolerance. There are both anatomic and behavioral manifestations of the adverse effects of neonatal stress, including pain, on brain development. Most neonatologists use opioids in painful situations. Sucrose and pacifiers are also being used in the NICU. The effects of sucrose (sweet taste) are believed to be opioid-mediated because they are reversed with naloxone; stress and pain relief are integrated through the endogenous opioid system. Sucrose, with or without a pacifier, may be effective for acute pain and stress control. Other nonpharmacologic strategies for stress and pain control include infant care by an individual primary nurse, tactile-kinesthetic stimuli (massage), "kangaroo care," and soothing sensorial saturation.

Children with Cancer Pain

The World Health Organization proposed an analgesic therapy model for cancer pain known as the *analgesic ladder* (Table 62-11). Designed to guide therapy in the Third World, this ladder consists of a hierarchy of oral pharmacologic interventions intended to treat pain of increasing magnitude. The hierarchy ignores modalities such as the use of nonconventional analgesics and interventional pain procedures, which are within the capability of physicians to prescribe in developed countries. Nevertheless, because oral medications are simple and efficacious, especially for home use, the ladder presents a framework for rationally using them before applying other drugs and techniques of drug administration.

Oral medications are the 1st line of analgesic treatment. Because NSAIDs affect platelet adhesiveness, they are typically not used. Opioid therapy is the preferred approach for moderate or severe pain. Nonopioid analgesics are used for mild pain, a weak opioid is added for moderate pain, and strong opioids are administered for more severe pain. Adjuvant analgesics can be added, and side effects and comorbid symptoms are actively managed. Determining the type and sources of the pain will help develop an effective analgesic plan. Certain treatments, such as the chemotherapeutic agent vincristine, are associated with neuropathic pain. Such pain might require anticonvulsants or TCAs. Organ-stretching pain from tumor growth within an organ might require strong opioids and/or radiation therapy if the tumor is radiosensitive. Organ obstruction, such as intestinal obstruction, should be diagnosed to relieve or bypass the obstruction.

It is important to consider both pharmacologic and nonpharmacologic strategies (e.g., cognitive-behavioral treatment, family and parent support) to treat pain in children with cancer.

Table 62-11 World Health Organization Analgesic Ladder for Cancer Pain

STEP 1 Patients who present with mild to moderate pain should be treated with a nonopioid.
STEP 2 Patients who present with moderate to severe pain or for whom the step 1 regimen fails should be treated with an oral opioid for moderate pain combined with a nonopioid analgesic.
STEP 3 Patients who present with very severe pain or for whom the step 2 regimen fails should be treated with an opioid used for severe pain, with or without a nonopioid analgesic.

Children with Pain Associated with Advanced Disease

Patients with advanced diseases, including cancer, AIDS, neurodegenerative disorders, and cystic fibrosis, need palliative care approaches that focus on optimal quality of life. Nonpharmacologic and pharmacologic means of management of pain and other distressing symptoms are palliative care's key components. It should be highlighted here that "palliative care" should be offered to all children with serious diseases, whether or not the diseases are potentially curable and whether or not long life expectancy is predicted. Examples include young children diagnosed with acute lymphoblastic leukemia (>90% posttreatment life expectancy) and children undergoing organ transplantation. Palliative care in pediatrics is meant to connote treatment that focuses on symptom reduction, quality of life, and good family and clinical team communication. It is not just reserved for patients in hospice care or those at the end of life. Differences among these conditions that relate to the progression of underlying illness, associated distressing symptoms, and common emotional responses should shape individual treatment plans (see Chapter 43). For end-of-life care, more than 90% of children and adolescents with cancer can be made comfortable by standard escalation of opioids according to the World Health Organization protocol. A small subgroup (5%) has enormous opioid dose escalation to >100 times the standard morphine or other opiate infusion rate. In most of these cases, there is spread of solid tumors to the spinal cord, roots, or plexus, and signs of neuropathic pain are evident. Methadone given orally is often used in palliative care, not just end of life care, because of its long half-life and its targeting of both opioid and *N*-methyl-D-aspartate receptors. The type of pain experienced by the patient (neuropathic, myofascial) should determine the need for adjunctive agents. Complementary measures, such as massage, hypnotherapy, and/or spiritual care, should also be considered in palliative care. Although the oral route of opioid administration should be encouraged, especially to facilitate care at home if possible, some children are unable to take oral opioids. Transdermal and sublingual routes, as well an intravenous infusion with a PCA, are likely next choices. Small, portable infusion pumps are convenient for home use. If venous access is limited, a useful alternative is to administer opioids (especially morphine or hydromorphone, but not methadone or meperidine) through continuous subcutaneous infusion, with or without a bolus option. A small (e.g., 22-gauge) cannula is placed under the skin and secured on the thorax, abdomen, or thigh. Sites may be changed every 3-7 days, as needed. As noted, alternative routes for opioids include the transdermal and oral transmucosal routes. These latter routes are preferred over IV and subcutaneous drug delivery when the patient is being treated at home.

Examples of Chronic and Recurrent Pain Syndromes

Chronic pain is defined as recurrent or persistent pain lasting longer than the normal tissue healing time, approximately 3-6 mo. Children may experience pain related to injury (e.g., burns) or a chronic or underlying disease process (e.g., cancer, arthritis); pain can also be the chronic condition itself (e.g., CRPS, fibromyalgia, functional abdominal pain). During childhood, abdominal, musculoskeletal, and headache pain are the most frequently occurring conditions. However, definitions of chronic pain do not take into account standard criteria for assessing particular pain symptoms or for evaluating the intensity or impact of pain, and therefore include individuals with varying symptoms and experiences. Consequently, in epidemiologic surveys, prevalence estimates vary widely. Overall prevalence rates for different childhood pains range from 4-88%. For example, an average of 13.5-31.8% of adolescents in a community sample reported having weekly abdominal, headache, or musculoskeletal pains. Most epidemiologic studies report prevalence and do not report the severity or impact of the pain. Research indicates that only a subset of children and adolescents with chronic pain (approximately 5%) experience moderate-severe disability, and this likely better represents the estimated population for whom help is needed to treat pain and associated problems.

COMPLEX REGIONAL PAIN SYNDROMES

Neuropathic pain is caused by abnormal excitability in the peripheral or CNS that may persist after an injury heals or inflammation subsides. The pain, which can be acute or chronic, is described as burning or stabbing and may be associated with cutaneous hypersensitivity (allodynia), distortion of sensation (dysesthesia), and amplification of noxious sensations (hyperalgesia and hyperpathia). Neuropathic pain conditions may be responsible for >35% of referrals to chronic pain clinics, conditions that commonly include posttraumatic and postsurgical peripheral nerve injuries, phantom pain after amputation, pain after spinal cord injury, and pain caused by metabolic neuropathies. Neuropathic pain typically responds poorly to opioids. In adults, evidence suggests the efficacy of TCAs (nortriptyline, amitriptyline) and anticonvulsants (gabapentin, pregabalin) for treatment of neuropathic pain (see Tables 62-9 and 62-10).

CRPS type 1, formerly known as reflex sympathetic dystrophy, is well-described in the pediatric population. CRPS type 1 is a syndrome of neuropathic pain that typically follows an antecedent and usually minor injury to an extremity without identifiable nerve injury. The syndrome of CRPS type 1 includes severe spontaneous neuropathic pain, hyperpathia, hyperalgesia, severe cutaneous allodynia to touch and cold, changes in blood flow (typically extremity cyanosis), and sweating. In more advanced cases, symptoms include dystrophic changes of the hair, nails, and skin, immobility of the extremity (dystonia), and muscle atrophy. In the most advanced cases, symptoms include ankylosis of the joints of the extremity. Specific causal factors in CRPS type 1 in both children and adults remain elusive, although coincidental events may be noted. **CRPS type 2**, formerly referred to as causalgia, is less common.

The syndromes of CRPS type 2 and CRPS type 1 are virtually identical, except that the former is associated with a well-defined peripheral nerve injury. Treatment of CRPS in children has been extrapolated from that in adults, with some low-level evidence for efficacy of physical therapy, cognitive-behavioral therapy, nerve blocks, TCAs, gabapentin, and some other related drugs. All experts in pediatric pain management agree on the value of aggressive physical therapy. Some centers provide aggressive therapy without the use of pharmacologic agents or interventional nerve blocks; unfortunately, recurrent episodes may be seen in up to 50% of patients. Physical therapy can be extraordinarily painful for children to endure; it is tolerated only by the most stoic and motivated patients. If children have difficulty enduring the pain, there is a well-established role for using pharmacologic agents with or without peripheral or central neuraxial nerve blocks to render the affected limb sufficiently analgesic so that physical therapy can be tolerated. Pharmacologic interventions include the use of AEDs such as gabapentin and/or TCAs such as amitriptyline (see Fig. 62-4). Although there is clear evidence of a peripheral inflammatory component of CRPS, with release of cytokines and other inflammatory mediators from the peripheral nervous system in the affected limb, the use of antiinflammatory agents has been disappointing. Commonly used nerve block techniques include sympathetic nerve blocks, IV regional anesthetics, epidural analgesia, and peripheral nerve blocks. In extreme and refractory cases, more invasive strategies have been reported, including surgical sympathectomy and spinal cord stimulation. Although an array of treatments have some benefit, the mainstay of treatment remains physical therapy emphasizing desensitization, strengthening, and functional improvement. Additionally, pharmacologic agents and psychologic and complementary therapies are important components of a treatment plan. Invasive techniques, although not curative, are valuable if they permit the performance of frequent and aggressive physical therapy that cannot be carried out otherwise. Some children with CRPS become so easily sensitized that persistent and bothersome pain may develop at the site of the invasive procedure. A good biopsychosocial evaluation will help determine the orientation of the treatment components. At this time, there are insufficient data to indicate the superior value of interventional blocks, such as epidural anesthesia delivery, in children with CRPS type I, over physical and psychologic interventions, with or without pharmacological support.

MYOFASCIAL PAIN DISORDERS AND FIBROMYALGIA

Myofascial pain disorders are associated with tender points in the affected muscles as well as with muscle spasms (tight muscles). Treatment is targeted at relaxing the affected muscles through physical therapy, Iyengar yoga, massage, and/or acupuncture. Rarely are pharmacologic muscle relaxants helpful other than for creating tiredness at night for sleep. Dry needling or injections of local anesthetic into the tender points has been advocated, but the data do not support this as a standard treatment. Similarly, although botulinum toxin injections may be used, no data support this practice in children. Often poor body postures, repetitive use of a part of the body not used to that movement, or carrying heavy backpacks initiates pain. When it becomes widespread with multiple tender points, the diagnosis may be made of juvenile fibromyalgia, which may or may not continue to subsequently become adult fibromyalgia. Likely there are different subtypes of widespread pain syndromes, and physical therapy is a key component of treatment. Psychologic interventions may play an important role to assist the child in resuming normal activities and to manage any psychologic comorbidities. Any pain rehabilitation plan should enhance return to full function. Because there is a high incidence of chronic pain in parents of children presenting with a chronic pain condition, especially fibromyalgia, attention to parent and family factors is important. Parent training may entail teaching the parent to model more appropriate pain coping behaviors and to recognize the child's independent attempts to manage pain and function adaptively. Parents may also need referrals to obtain appropriate pain management for their own pain condition.

The drugs pregabalin and duloxetine have both been approved for management of fibromyalgia in adults in the United States, but there are no clinical studies confirming their effectiveness in children and adolescents.

ERYTHROMELALGIA

Erythromelalgia in children is generally primary, whereas in adults it may be either primary or secondary to malignancy or other hematologic disorders such as polycythemia vera. Patients with this disorder exhibit red, warm, hyperperfused distal limbs. The disorder is usually bilateral, and it may involve either or both the hands and feet. Patients perceive burning pain and typically seek relief by immersing the affected extremities in ice water, sometimes so often and for so long so that skin pathology results. Primary erythromelalgia has recently been shown to be caused by a genetic mutation in the gene for the NaV1.7 neuronal sodium channel on peripheral C nociceptive fibers, resulting in their spontaneous depolarization, and thus continuous burning pain. The most common mutation identified is in the *SCN9A* gene, although there are several mutations that affect the NaV1.7 channel. Interestingly, another mutation in the NaV1.7 channel results in a rare but devastating genetic condition, the congenital indifference to pain.

It is easy to distinguish erythromelalgia (or related syndromes) from CRPS. The limb afflicted with CRPS is typically cold and cyanotic, the disease is typically unilateral, and children with CRPS have cold allodynia, making immersion in cold water exquisitely painful; in erythromelalgia, ice water immersion is analgesic, the condition is bilateral and symmetrical, and associated with hyperperfusion of the distal extremity. The evaluation of hyperperfused limbs with burning pain should include genetic testing for Fabry disease and screening for hematologic malignancies, with diagnosis of primary erythromelalgia being one of exclusion. There are presently few clinical laboratories that are certified to perform the DNA analysis required to identify the common NaV1.7 mutations.

The definitive treatment of Fabry disease includes enzyme replacement as disease-modifying treatment and administration of neuropathic pain medications, such as gabapentin, although the success of antineuropathic pain drugs in small-fiber neuropathies has not been impressive. The treatment of erythromelalgia is far more problematic. Antineuropathic pain medications, such as AEDs and TCAs are typically prescribed but rarely helpful (see Fig. 62-4). Although one might predict that sodium channel–blocking AEDs might be effective in this

sodium channelopathy, oxcarbazepine has not proven to be a particularly effective modality. The pain responds well to regional anesthetic nerve blocks, but it returns immediately when the effects of the nerve block resolve. In contrast, in other neuropathic syndromes, the analgesia usually (and inexplicably) persists well after the resolution of the pharmacologic nerve block. Aspirin and even nitroprusside infusions are reported to be of benefit with secondary erythromelalgia, but they are not reported to be helpful in children with primary erythromelalgia. There are case reports in adults and clinical experience in children suggesting that periodic treatment with high-dose capsaicin cream is effective in alleviating the burning pain and disability of erythromelalgia. Capsaicin (essence of chili pepper) cream is a vanilloid receptor (TRPV1) agonist that depletes small-fiber peripheral nerve endings of the neurotransmitter substance P, which is an important neurotransmitter in the generation and transmission of nociceptive impulses. Once depleted, these nerve endings are no longer capable of generating spontaneous pain until the receptors regenerate, a process that takes many months.

OTHER CHRONIC PAIN CONDITIONS IN CHILDREN

It should be noted that there are a variety of genetic and other medical/surgical conditions that are often associated with chronic pain. Examples include Fabry disease, Chiari/syringomyelia, juvenile idiopathic arthritis, mitochondrial disorders, degenerative neurologic diseases, cerebral palsy, autism spectrum disorders, intestinal pseudoobstruction, inflammatory bowel disease, chronic migraine and chronic daily headaches, irritable bowel disease, and others. In many cases, treating the underlying disease, such as enzyme replacement in Fabry disease and in other lysosomal disorders, will reduce what otherwise might be progression of symptoms, but may not totally reduce pain and suffering, and other modalities will be needed. Finally, pain that persists and is not well treated can lead to central sensitization and widespread pain, such as seen in children with one pain source who develop fibromyalgia.

MANAGING COMPLEX CHRONIC PAIN PROBLEMS

Some patients with chronic pain have a prolonged course of evaluation in attempts to find what is expected as the singular "cause" of the pain, and thus also undergo many failed treatments. Parents worry that the doctors have not yet discovered the cause that may be serious and life-threatening, and children often feel not believed, that they are faking their pain, or are "crazy." There may be no identifiable or diagnosable condition and families may seek opinions from multiple treatment facilities in an attempt to find help for their suffering child. In fact, in many cases what may have begun as an acute injury or infectious event may result for some children into a chronic pain syndrome, with changes in the neurobiology of the pain signaling system.

In the context of disabling chronic pain, it is very important for the pediatrician to (1) avoid overmedication because this can exacerbate associated disability, (2) maintain an open mind and reassess the diagnosis if the clinical presentation changes, and (3) understand and communicate to the family that pain has a biologic basis (likely related to neural signaling and neurotransmitter dysregulation), and the pain is naturally distressing to the child and family. All patients and families should receive a simple explanation of pain physiology that helps them understand the importance of (1) functional rehabilitation to normalize pain signaling, (2) the low risk of causing further injury with systematic increases in normal functioning, and (3) the likely failure of treatment if pain is managed as if it were acute. Because it is counterintuitive for most people to move a part of the body that hurts, many patients with chronic pain have atrophy or contractures of a painful extremity from disuse. Additionally, associated increases in worry and anxiety may exacerbate pain and leave the body even more vulnerable to further illness, injury, and disability. Pain can have a significant impact on many areas of normal functioning and routine for children, and school absenteeism and related consequences of missed schooling are often significant problems. Appropriate assessment and evaluation of the child with chronic pain and the child's family is the critical first step necessary in developing a treatment plan.

Interdisciplinary pediatric pain programs have become the standard of care for treating complex chronic pain problems in youth. In recognition of the severity and complexity of pain and disability for some children, different settings and treatment delivery models for providing pain care have been explored. One option is inpatient and day hospital treatment programs. They often address barriers to access to outpatient treatment and coordination of care. In addition, they provide an intensive treatment option for children who do not make adequate progress in outpatient treatment or who are severely disabled by pain. Early programs developed in the 1990s focused on treatment of CRPS through intensive inpatient rehabilitation and exercise-based treatment programs. Later developing programs expanded to other clinical populations and expanded the treatment focus to incorporate a range of rehabilitation and psychologic therapies delivered both individually and in groups. The typical length of inpatient admissions for children with chronic pain in such programs is 3-4 wk and there is emerging evidence to suggest benefit from these programs.

Another intervention delivery option is remote management, referring to pain interventions utilized outside of the clinic/hospital setting to reach children in their homes or communities. Interventions are typically delivered using some form of technology, such as the Internet, or may rely on other media such as telephone counseling or use of written self-help materials. Most typically, remote management of pain includes monitoring, counseling, and/or delivery of behavioral and CBT interventions. Internet interventions have received the most research attention to date with published examples for several different pediatric chronic pain conditions with promising findings for pain reduction. Telemedicine, while in widespread use clinically for many pediatric health conditions, has not yet been formally evaluated in pediatric pain. Within any community, the pediatrician will need to locate appropriate referral sources for patients with complex chronic pain.

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Chapter 63

Poisoning

Mark A. Kostic

Poisoning is now the number 1 cause of injury death in the United States, even surpassing that from motor vehicle collisions. The majority of these deaths are unintentional (i.e., not suicide). In adolescents, poisoning is the third leading cause of injury-related death. Of the more than 2 million human poisoning exposures reported annually to the National Poison Data Systems of the American Association of Poison Control Centers, approximately 50% occur in children younger than 6 yr old. Almost all of these exposures are unintentional and reflect the propensity for young children to put virtually anything in their mouths. Fortunately, children younger than 6 yr account for <2% of all poisoning fatalities reported to National Poison Data Systems.

More than 90% of toxic exposures in children occur in the home, and most involve only a single substance. Ingestion accounts for the vast majority of exposures, with a minority occurring via the dermal, inhalational, and ophthalmic routes. Approximately 50% of cases involve nondrug substances, such as cosmetics, personal care items, cleaning solutions, plants, and foreign bodies. Pharmaceutical preparations account for the remainder of exposures, and analgesics, topical preparations, cough and cold products, and vitamins are the most commonly reported categories.

The majority of poisoning exposures in children younger than 6 yr can be managed without direct medical intervention (beyond a call to

Table 63-1 Common Agents Potentially Toxic to Young Children (<6 yr) in Small Doses*

SUBSTANCE	TOXICITY
Aliphatic hydrocarbons (e.g., gasoline, kerosene, lamp oil)	Acute lung injury
Antimalarials (chloroquine, quinine)	Seizures, dysrhythmias
Benzocaine	Methemoglobinemia
β Blockers (lipid-soluble β blockers [e.g., propranolol] are more toxic than water-soluble β blockers [e.g., atenolol])	Bradycardia, hypotension
Calcium channel blockers	Bradycardia, hypotension, hyperglycemia
Camphor	Seizures
Caustics (pH <2 or >12)	Airway, esophageal and gastric burns
Clonidine	Lethargy, bradycardia, hypotension
Diphenoxylate and atropine (Lomotil)	CNS depression, respiratory depression
Hypoglycemics, oral (sulfonylureas and meglitinides)	Hypoglycemia, seizures
Laundry detergent packets (pods)	Airway issues, respiratory distress, altered mental status
Lindane	Seizures
Monoamine oxidase inhibitors	Hypertension followed by delayed cardiovascular collapse
Methyl salicylate	Tachypnea, metabolic acidosis, seizures
Opioids (especially methadone, buprenorphine)	CNS depression, respiratory depression
Organophosphate pesticides	Cholinergic crisis
Phenothiazines (especially chlorpromazine, thioridazine)	Seizures, dysrhythmias
Theophylline	Seizures, dysrhythmias
Tricyclic antidepressants	CNS depression, seizures, dysrhythmias, hypotension

*"Small dose" typically implies 1 or 2 pills or 5 mL.
CNS, central nervous system.

the regional poison control center), either because the product involved is not inherently toxic or the quantity of the material involved is not sufficient to produce clinically relevant toxic effects. However, a number of substances are potentially highly toxic to toddlers in small doses (Table 63-1). In 2012, carbon monoxide and analgesics (acetaminophen and salicylate) were the leading causes of poison-related fatalities in young children (<6 yr). In addition, prescription opioids, antidepressants, cardiovascular drugs, and aliphatic hydrocarbons were significant causes of mortality.

Poison prevention education should be an integral part of all well-child visits, starting at the 6 mo visit. Counseling parents and other caregivers about potential poisoning risks, how to poison-proof a child's environment, and what to do if an ingestion or exposure occurs diminishes the likelihood of serious morbidity or mortality. Poison prevention education materials are available from the American Academy of Pediatrics and regional poison control centers. A network of poison control centers exists in the United States, and anyone at any time can contact a regional poison center by calling this toll-free number: **1-800-222-1222**. Parents should be encouraged to share this number with grandparents, relatives, babysitters, and any other caregivers.

Product safety measures, poison prevention education, early recognition of exposures, and around-the-clock access to regionally based poison control centers all contribute to the favorable outcomes in young children. Poisoning exposures in children 6-12 yr old are much less common, involving only approximately 6% of all reported pediatric exposures. A second peak in pediatric exposures occurs in adolescence. Exposures in the adolescent age group are primarily intentional (suicide or abuse or misuse of substances) and thus often result in more severe toxicity (see Chapter 114). Families should be informed and given anticipatory guidance that nonprescription and prescription medications, and even household products (e.g., inhalants), are common sources of adolescent exposures. Adolescents (ages 13-19 yr) accounted for 45 of the 73 poison-related pediatric deaths in 2012 reported to National Poison Data System (4% of all fatalities called in to poison centers). Pediatricians should be aware of the signs of drug abuse or suicidal ideation in this population and should aggressively intervene (see Chapter 114).

PREVENTION

Deaths caused by unintentional poisoning among younger children have decreased dramatically over the past 2 decades, particularly among children younger than 5 yr of age. In 1970, when the Poison Packaging Prevention Act was passed, 226 poisoning deaths of children younger than age 5 yr occurred compared with only 21 in 2012. Poisoning prevention demonstrates the effectiveness of passive strategies, including the use of child-resistant packaging and limited doses per container. Difficulty using child-resistant containers by adults is an important cause of poisoning in young children today; in 18.5% of households in which poisoning occurred in children younger than 5 yr of age, the child-resistant closure was replaced, and 65% of the packaging used did not work properly. Nearly 20% of ingestions occur from drugs owned by grandparents, a group that has difficulty using traditional child-resistant containers.

Even though there has been success in preventing poisoning in young children, there has been a remarkable rise in poison-related death over the past 20 yr in the adolescent population. This has mirrored the ever-increasing rate of opioid prescriptions written by healthcare providers.

APPROACH TO THE POISONED PATIENT

The initial approach to the patient with a witnessed or suspected poisoning should be no different than that in any other sick child, starting with stabilization and rapid assessment of the airway, breathing, circulation, and mental status (see Chapter 67). In any patient with altered mental status, a serum dextrose concentration should be obtained early and naloxone administration should be considered. A targeted history and physical examination serves as the foundation for a thoughtful differential diagnosis, which can then be further refined through laboratory testing and other diagnostic studies.

INITIAL EVALUATION

History

Obtaining an accurate problem-oriented history is of paramount importance. Intentional poisonings (suicide attempts; abuse or misuse) are typically more severe than unintentional, exploratory ingestions. In patients without a witnessed exposure, historical features such as age of the child (toddler or adolescent), acute onset of symptoms without prodrome, sudden alteration of mental status, multiple system organ dysfunction, or high levels of household stress should suggest a possible diagnosis of poisoning.

Description of the Exposure

For household and workplace products, names (brand, generic, chemical) and specific ingredients, along with their concentrations, can often

be obtained from the labels. Poison control center specialists can also help to identify possible ingredients and review the potential toxicities of each component. In cases of suspected ingestion, poison center specialists can help identify pills based on markings, shape, and color. If referred to the hospital for evaluation, parents should be instructed to bring the products, pills, and/or containers with them to assist with identifying and quantifying the exposure. If a child is found with an unknown pill in the child's mouth, the history must include a list of all medications in the child's environment (including medications that grandparents, parents, siblings, caregivers, or other visitors might have brought into the house). In the case of an unknown exposure, clarifying where the child was found (e.g., garage, kitchen, laundry room, bathroom, backyard, workplace) can help to generate a list of potential toxins.

Next, it is important to clarify the timing of the ingestion and to obtain some estimate of how much of the substance was ingested. It is better to overestimate the amount ingested to prepare for the worst-case scenario. Counting pills or measuring the remaining volume of a liquid ingested can sometimes be useful in generating estimates. For inhalational, ocular, or dermal exposures, the concentration of the agent and the length of contact time with the material should be determined if possible.

Symptoms

Obtaining a description of symptoms experienced after ingestion, including their timing of onset relative to the time of ingestion and their progression, can generate a list of potential toxins and to predict the severity of the ingestion. Coupled with physical exam findings, reported symptoms assist practitioners in identifying *toxidromes* or recognized poisoning syndromes suggestive of poisoning from specific substances or classes of substances (Tables 63-2, 63-3, and 63-4).

Past Medical History

Underlying diseases can make a child more susceptible to the effects of a toxin. Concurrent drug therapy can also increase susceptibility because certain drugs may interact with the toxin. Pregnancy is a common precipitating factor in adolescents' suicide attempts and can influence both evaluation of the patient and subsequent treatment. A history of psychiatric illness can make patients more prone to substance abuse, misuse, intentional ingestions, and polypharmacy complications. A developmental history is important to ensure that the history provided is appropriate for the child's developmental stage (e.g., a report of a 6 mo old picking up a large container of laundry detergent and drinking it should raise a red flag).

Social History

Understanding the child's social environment helps to identify potential sources of exposures (caregivers, visitors, grandparents, recent parties or social gatherings) and environmental stressors (new baby, parent's illness, financial stress) that might have contributed to the ingestion. Unfortunately, some poisonings occur in the setting of serious neglect or intentional abuse.

Physical Examination

A targeted physical exam is important to identifying the potential toxin and assessing the severity of the exposure. Initial efforts should be directed toward assessing and stabilizing the airway, breathing, circulation, and mental status. Once one has ensured that the airway is secure and the patient is stable from a cardiopulmonary standpoint, a more extensive physical exam can help to identify characteristics of specific toxins or classes of toxins.

In the poisoned patient, the key features of the physical exam are the vital signs, mental status, pupils (size, reactivity) nystagmus, skin, bowel sounds, and odors. These findings might suggest a toxidrome that can guide the differential diagnosis and initial management.

Laboratory Evaluation

For select intoxications (e.g., salicylates, some anticonvulsants, acetaminophen, iron, digoxin, methanol, lithium, ethylene glycol, carbon monoxide, lead), quantitative blood concentrations are integral to confirming the diagnosis and formulating a treatment plan. For most exposures, quantitative measurement is not readily available and is not likely to alter management. All intoxicant levels must be interpreted in conjunction with the history. For instance, a methanol level of 20 mg/dL 1 hr after ingestion may well be nontoxic, whereas a similar level 24 hr after ingestion implies a patient with significant poisoning. In general, patients with multiple or chronic exposures to a drug or other chemical will be more symptomatic at lower drug levels than those with a single exposure.

Both urine drug-of-abuse screens and the more comprehensive drug screens vary widely in their ability to detect toxins and generally add little information to the clinical assessment, particularly if the agent is known and the patient's symptoms are consistent with that agent. If a drug screen is ordered, it is important to know that the components screened for, and the lower limits of detection, vary from laboratory to laboratory. In addition, the interpretation of most drug screens is hampered by false-positive and false-negative results; standard urine opiate screens will not be positive after exposure to a synthetic opioid (e.g., methadone, buprenorphine, fentanyl). The urine drug-of-abuse screen is typically of limited utility when it comes to medical clearance, but does serve a useful function for psychiatrists in their evaluation of the adolescent patient. Apart from its psychiatric usefulness, urine drug-of-abuse screens are potentially helpful in patients with altered mental status of unknown etiology, persistent, unexplained tachycardia, acute myocardial ischemia or stroke at a young age, and in the assessment of a neglected or abused child. Consultation with a medical toxicologist can be helpful in interpreting drug screens and ordering specific drug levels or metabolites that can aid in patient management.

In the case of a neglected or allegedly abused child, a positive toxicology screen can add substantial weight to a claim of abuse or neglect. In these cases and any case with medicolegal implications, any positive screen *mus*t be confirmed with gas chromatography/mass spectroscopy, which is considered the gold standard measurement for legal purposes.

Acetaminophen is a widely available medication and a commonly detected coingestant with the potential for severe toxicity. There is an effective antidote to acetaminophen poisoning that is time-dependent. Given that patients might initially be asymptomatic and might not report acetaminophen as a coingestant, an acetaminophen level should be checked in all patients who present after an intentional exposure or ingestion. A basic chemistry panel (electrolytes, renal function, glucose) is necessary for all poisoned or potentially poisoned patients. Any patient with acidosis (a low serum bicarbonate level on the serum chemistry panel), must have an anion gap calculated because of the more specific differential diagnoses associated with an elevated anion gap metabolic acidosis. Patients with a known overdose of acetaminophen should have their liver transaminases assessed, as well as an INR (international normalized ratio). A serum creatine kinase level is indicated on any patient with a prolonged "down time" as rhabdomyolysis can result from laying supine on a hard surface without movement for just a few hours. Serum osmolality is only helpful as a surrogate marker for a toxic alcohol exposure if a serum concentration of the alcohol cannot be obtained in a reasonable time frame. A urine pregnancy test is, of course, mandatory for all adolescent female patients. Based on the clinical presentation and the presumed poison, additional lab tests may also be helpful (Table 63-5).

Additional Diagnostic Testing

An electrocardiogram (ECG) is a quick and noninvasive bedside test that can yield important clues to diagnosis and prognosis. Toxicologists pay particular attention to the ECG intervals (Table 63-6). A widened QRS interval, putting the patient at risk for monomorphic ventricular tachycardia, suggests blockade of fast sodium channels, and may be seen after ingestion of tricyclic antidepressants, diphenhydramine, and cocaine, among others. A widened QTc interval suggests effects at the potassium rectifier channels and portends a risk of torsades de pointes (polymorphic ventricular tachycardia).

Table 63-2 Selected Historical and Physical Findings in Poisoning

SIGN	TOXIN
ODOR	
Bitter almonds	Cyanide
Acetone	Isopropyl alcohol, methanol, paraldehyde, salicylates
Alcohol	Ethanol
Wintergreen	Methyl salicylate
Garlic	Arsenic, thallium, organophosphates, selenium
OCULAR SIGNS	
Miosis	Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates and other cholinergics, clonidine, phenothiazines, sedative–hypnotics, olanzapine
Mydriasis	Anticholinergics (e.g., antihistamines, TCAs, atropine), sympathomimetics (cocaine, amphetamines, PCP) postanoxic encephalopathy, opiate withdrawal
Nystagmus	Anticonvulsants, sedative–hypnotics, alcohols, PCP, ketamine, dextromethorphan
Lacrimation	Organophosphates, irritant gas or vapors
Retinal hyperemia	Methanol
CUTANEOUS SIGNS	
Diaphoresis	Cholinergics (organophosphates), sympathomimetics, withdrawal syndromes
Alopecia	Thallium, arsenic
Erythema	Boric acid, elemental mercury, cyanide, carbon monoxide, disulfiram, scombroid, anticholinergics, vancomycin
Cyanosis (unresponsive to oxygen)	Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver
ORAL SIGNS	
Salivation	Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine
Oral burns	Corrosives, oxalate-containing plants
Gum lines	Lead, mercury, arsenic, bismuth
GASTROINTESTINAL SIGNS	
Diarrhea	Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, opioid withdrawal
Hematemesis	Arsenic, iron, caustics, NSAIDs, salicylates
Constipation	Lead
CARDIAC SIGNS	
Tachycardia	Sympathomimetics, anticholinergics, antidepressants, antipsychotics, methylxanthines (theophylline, caffeine), salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal (ethanol, sedatives, clonidine, opioids), serotonin syndrome, neuroleptic malignant syndrome
Bradycardia	β Blockers, calcium channel blockers, digoxin, clonidine, organophosphates, opioids, sedative–hypnotics
Hypertension	Sympathomimetics, anticholinergics, monoamine oxidase inhibitors, serotonin syndrome, neuroleptic malignant syndrome, clonidine withdrawal
Hypotension	β Blockers, calcium channel blockers, cyclic antidepressants, iron, antipsychotics, barbiturates, clonidine, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation
RESPIRATORY SIGNS	
Depressed respirations	Opioids, sedative-hypnotics, alcohol, clonidine, barbiturates
Tachypnea	Salicylates, sympathomimetics, caffeine, metabolic acidosis, carbon monoxide, hydrocarbon aspiration
CENTRAL NERVOUS SYSTEM SIGNS	
Ataxia	Alcohols, anticonvulsants, sedative–hypnotics, lithium, dextromethorphan, carbon monoxide, inhalants
Coma	Opioids, sedative–hypnotics, anticonvulsants, antidepressants, antipsychotics, ethanol, anticholinergics, clonidine, GHB, alcohols, salicylates, barbiturates
Seizures	Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), cholinergics (organophosphates), isoniazid, camphor, lindane, salicylates, lead, nicotine, tramadol, water hemlock, withdrawal
Delirium/psychosis	Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal
Peripheral neuropathy	Lead, arsenic, mercury, organophosphates

GHB, γ-hydroxybutyrate; LSD, lysergic acid diethylamide; NSAID, nonsteroidal antiinflammatory drug; PCP, phencyclidine; TCA, tricyclic antidepressant.

Chest x-ray may reveal signs of pneumonitis (e.g., hydrocarbon aspiration), noncardiogenic pulmonary edema (e.g., salicylate toxicity), or a foreign body. Abdominal x-ray is most helpful in screening for the presence of lead paint chips or other foreign bodies. It may detect a bezoar, demonstrate radiopaque tablets, or reveal drug packets in a body packer. Upper endoscopy may be useful for prognosis after significant caustic ingestions. Further diagnostic testing is based on the differential diagnosis and pattern of presentation.

PRINCIPLES OF MANAGEMENT

The principles of management of the poisoned patient are supportive care, antidotes, decontamination, and enhanced elimination. Few patients meet criteria for all of these interventions, though clinicians should consider each option in every poisoned patient so as not to miss a potentially lifesaving therapy. Antidotes are available for relatively few poisons (Table 63-7), thus emphasizing the importance of meticulous supportive care and close clinical monitoring.

Poison control center staff are specifically trained to provide expertise in the management of poisoning exposures. Parents should be instructed to call the poison control center (**1-800-222-1222**) for any concerning exposure. Poison specialists can assist parents in assessing the potential toxicity and severity of the exposure; they can further determine which children can be safely monitored at home and which children should be referred to the emergency department for further

Table 63-3 Recognizable Poison Syndromes ("Toxidromes")

TOXIDROME	SIGNS						POSSIBLE TOXINS
	VITAL SIGNS	MENTAL STATUS	PUPILS	SKIN	BOWEL SOUNDS	OTHER	
Sympathomimetic	Hypertension, tachycardia, hyperthermia	Agitation, psychosis, delirium, violence	Dilated	Diaphoretic	Normal to increased		Amphetamines, cocaine, PCP, bath salts (cathinones), ADHD medication
Anticholinergic	Hypertension, tachycardia, hyperthermia	Agitated, delirium, coma, seizures	Dilated	Dry, hot	Diminished	Ileus urinary retention	Antihistamines, tricyclic antidepressants, atropine, jimson weed
Cholinergic	Bradycardia BP and temp typically normal	Confusion, coma, fasciculations	Small	Diaphoretic	Hyperactive	Diarrhea, urination, bronchorrhea, bronchospasm, emesis, lacrimation, salivation	Organophosphates (insecticides, nerve agents), carbamates (physostigmine, neostigmine, pyridostigmine) Alzheimer medications, myasthenia treatments
Opioids	Respiratory depression bradycardia, hypotension, hypothermia	Depression, coma, euphoria	Pinpoint	Normal	Normal to decreased		Methadone, buprenorphine, morphine, oxycodone, heroin, etc.
Sedative–hypnotics	Respiratory depression, HR normal to decreased, BP normal to decreased, temp normal to decreased	Somnolence, coma	Small or normal	Normal	Normal		Barbiturates, benzodiazepines, ethanol
Serotonin syndrome (similar findings with neuroleptic malignant syndrome)	Hyperthermia, tachycardia, hypertension or hypotension (autonomic instability)	Agitation, confusion, coma	Dilated	Diaphoretic	Increased	Neuromuscular hyperexcitability: clonus, hyperreflexia (lower extremities > upper extremities)	SSRIs, lithium, MAOIs, linezolid, tramadol, meperidine, dextromethorphan
Salicylates	Tachypnea, hyperpnea, tachycardia, hyperthermia	Agitation, confusion, coma	Normal	Diaphoretic	Normal	Nausea, vomiting, tinnitus, ABG with primary respiratory alkalosis and primary metabolic acidosis; tinnitus or difficulty hearing	Aspirin and aspirin-containing products, methyl-salicylate
Withdrawal (sedative–hypnotic)	Tachycardia, tachypnea, hyperthermia	Agitation, tremor, seizure, hallucinosis, delirium tremens	Dilated	Diaphoretic	Increased		Lack of access to ethanol, benzodiazepines, barbiturates, GHB, or excessive use of flumazenil
Withdrawal (opioid)	Tachycardia	Restlessness, anxiety	Dilated	diaphoretic	Hyperactive	Nausea, vomiting, diarrhea	Lack of access to opioids or excessive use of naloxone

ABG, arterial blood gas; ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; GHB, γ-hydroxybutyrate; HR, heart rate; MAOI, monoamine oxidase inhibitor; PCP, phencyclidine; SSRI, selective serotonin reuptake inhibitor; temp, temperature.

Table 63-4 Mini-Toxidromes

TOXIDROMES	SYMPTOMS AND SIGNS	EXAMPLES
α_1 Antagonists	CNS depression, tachycardia, miosis	Chlorpromazine, quetiapine, clozapine, olanzapine, risperidone
α_2 Agonist	CNS depression, bradycardia, hypertension (early), hypotension (late), miosis	Clonidine, oxymetazoline, tetrahydrozoline, tizanidine
Clonus/myoclonus	CNS depression, myoclonic jerks, clonus, hyperreflexia	Carisoprodol, lithium, serotonergic agents, bismuth, organic lead, organic mercury
Sodium channel blockers	CNS toxicity, wide QRS	Cyclic antidepressants and structurally related agents, propoxyphene, quinidine/quinine, amantadine, antihistamines, bupropion, cocaine
Potassium channel blockers	CNS toxicity, long QT	Butyrophenones, methadone, phenothiazines, ziprasidone

CNS, central nervous system.
From Ruha AM, Levine M: Central nervous system toxicity. Emerg Med Clin North Am *32(1):205–221, 2014, Table 2, p. 208.*

Table 63-5 Screening Laboratory Clues in Toxicologic Diagnosis

ANION GAP METABOLIC ACIDOSIS (MNEMONIC = MUDPILES CAT) **M**ethanol, metformin **U**remia **D**iabetic ketoacidosis **P**ropylene glycol **I**soniazid, iron, massive ibuprofen **L**actic acidosis **E**thylene glycol **S**alicylates **C**ellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide) **A**lcoholic ketoacidosis **T**ylenol
ELEVATED OSMOLAR GAP Alcohols: ethanol, isopropyl, methanol, ethylene glycol
HYPOGLYCEMIA (MNEMONIC = HOBBIES) **H**ypoglycemics, oral: sulfonylureas, meglitinides **O**ther: quinine, unripe ackee fruit **B**eta **B**lockers **I**nsulin **E**thanol **S**alicylates (late)
HYPERGLYCEMIA Salicylates (early) Calcium channel blockers Caffeine
HYPOCALCEMIA Ethylene glycol Fluoride
RHABDOMYOLYSIS Neuroleptic malignant syndrome, serotonin syndrome Statins Mushrooms (*Tricholoma equestre*) Any toxin causing prolonged immobilization (e.g., opioids, antipsychotics) or excessive muscle activity or seizures (e.g., sympathomimetics)
RADIOPAQUE SUBSTANCE ON KUB (MNEMONIC = CHIPPED) **C**hloral hydrate, calcium carbonate **H**eavy metals (lead, zinc, barium, arsenic, lithium, bismuth) **I**ron **P**henothiazines **P**lay-Doh, potassium chloride **E**nteric-coated pills **D**ental amalgam, drug packets

KUB, kidney-ureter-bladder radiograph.

Table 63-6 Electrocardiographic Findings in Poisoning

PR INTERVAL PROLONGATION Digoxin Lithium
QRS PROLONGATION Tricyclic antidepressants Diphenhydramine Carbamazepine Cardiac glycosides Chloroquine, hydroxychloroquine Cocaine Lamotrigine Quinidine, quinine, procainamide, disopyramide Phenothiazines Propoxyphene Propranolol Bupropion, venlafaxine (rare)
QTc PROLONGATION* Amiodarone Antipsychotics (typical and atypical) Arsenic Cisapride Citalopram and other SSRIs Clarithromycin, erythromycin Disopyramide, dofetilide, ibutilide Fluconazole, ketoconazole, itraconazole Methadone Pentamidine Phenothiazines Sotalol

*This is a select list of important toxins, other medications are also associated with QTc prolongation.
SSRI, selective serotonin reuptake inhibitor.

evaluation and care. Ninety percent of all exposures in children younger than 6 yr of age called into poison centers are managed at home. The American Academy of Clinical Toxicology has generated consensus statements for out-of-hospital management of common ingestions (e.g., acetaminophen, iron, calcium channel blockers) that serve to guide poison center recommendations regarding whom to refer to an emergency department. Up to a third of calls to poison centers involve hospitalized patients.

SUPPORTIVE CARE

Careful attention is paid first to the "ABCs" of airway, breathing and circulation; there should be a low threshold to aggressively manage the airway of a poisoned patient because of the patient's propensity to

Table 63-7 Common Antidotes for Poisoning

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Acetaminophen	*N*-Acetylcysteine (Mucomyst)	140 mg/kg loading, followed by 70 mg/kg q4h	PO	Vomiting (patient-tailored regimens are the norm)
	N-Acetylcysteine (Acetadote)	150 mg/kg over 1 hr, followed by 50 mg/kg over 4 hr, followed by 100 mg/kg over 16 hr	IV	Anaphylactoid reactions (most commonly seen with loading dose) (Higher doses of the infusion are often recommended depending upon the acetaminophen level and the degree of injury)
Anticholinergics	Physostigmine	0.02 mg/kg over 5 min; may repeat q5-10min to 2 mg max	IV/IM	Bradycardia, seizures, bronchospasm *Note:* Do not use if conduction delays on ECG
Benzodiazepines	Flumazenil	0.2 mg over 30 sec; if response is inadequate, repeat q1min to 1 mg max	IV	Agitation, seizures; **do not use for unknown ingestions**
β Blockers	Glucagon	0.15 mg/kg bolus followed by infusion of 0.05-0.15 mg/kg/hr	IV	Hyperglycemia, vomiting
Calcium channel blockers	Insulin	1 unit/kg bolus followed by infusion of 0.5-1 unit/kg/hr	IV	Hypoglycemia Follow serum potassium and glucose closely
	Calcium salts	Dose depends on the specific calcium salt	IV	
Carbon monoxide	Oxygen	100% FIO_2 via non–rebreather mask (or ET if intubated)	Inhalational	Some patients may benefit from hyperbaric oxygen (see text)
Cyanide	Cyanide kit:			
	Amyl nitrate	1 crushable ampule; inhale 30 sec of each min	Inhalation	Methemoglobinemia
	Sodium nitrate	0.33 mL/kg of 3% solution if hemoglobin level is not known; otherwise, based on tables with product	IV	Methemoglobinemia Hypotension
	Sodium thiosulfate	1.6 mL/kg of 25% solution; may be repeated q30-60min to max of 50 mL	IV	If inducing methemoglobinemia is contraindicated; consider only using the thiosulfate component of the kit
	Hydroxocobalamin (Cyanokit)	70 mg/kg (adults: 5 g) given over 15 min	IV	Flushing/erythema, nausea, rash, chromaturia, hypertension, headache
Digitalis	Digoxin-specific Fab antibodies (Digibind; DigiFab)	1 vial binds 0.6 mg of digitalis glycoside; #vials = digitalis level × weight in kg/100	IV	Allergic reactions (rare), return of condition being treated with digitalis glycoside
Ethylene glycol, methanol	Fomepizole	15 mg/kg load; 10 mg/kg q12h × 4 doses; 15 mg/kg q12h until EG level is <20 mg/dL	IV	Infuse slowly over 30 min; If fomepizole is not available, can treat with oral ethanol (80 proof)
Iron	Deferoxamine	Infusion of 5-15 mg/kg/hr (max: 6 g/24 hr)	IV	Hypotension (minimized by avoiding rapid infusion rates)
Isoniazid (INH)	Pyridoxine	Empirical dosing: 70 mg/kg (max dose = 5 g) If ingested dose is known: 1 g per gram of INH	IV	May also be used for *Gyromitra* mushroom ingestions
Lead and other heavy metals (e.g., arsenic, inorganic mercury)	BAL (dimercaprol)	3-5 mg/kg/dose q4hr, for the 1st day; subsequent dosing depends on the toxin	Deep IM	Local injection site pain and sterile abscess, vomiting, fever, salivation, nephrotoxicity *Caution:* prepared in peanut oil; contraindicated in patients with peanut allergy
	Calcium disodium EDTA	35-50 mg/kg/day × 5 days; may be given as a continuous infusion or 2 divided doses/day	IV	Vomiting, fever, hypertension, arthralgias, allergic reactions, local inflammation, nephrotoxicity (maintain adequate hydration, follow UA and renal function)
	Dimercaptosuccinic acid (succimer, DMSA, Chemet)	10 mg/kg/dose q8h × 5 days, then 10 mg/kg q12h × 14 days	PO	Vomiting, hepatic transaminase elevation, rash

Continued

Table 63-7 Common Antidotes for Poisoning—cont'd

POISON	ANTIDOTE	DOSAGE	ROUTE	ADVERSE EFFECTS, WARNINGS, COMMENTS
Methemoglobinemia	Methylene blue, 1% solution	0.1-0.2 mL/kg (1-2 mg/kg) over 5-10 min; may be repeated q30-60min	IV	Vomiting, headache, dizziness, blue discoloration of urine
Opioids	Naloxone	0.01-0.1 mg/kg; adolescents/adults: 0.04-2 mg, repeated as needed; may give continuous infusion	IV	Acute withdrawal symptoms if given to addicted patients May also be useful for clonidine ingestions (inconsistent response)
Organophosphates	Atropine	0.05-0.1 mg/kg repeated q5-10min as needed	IV/ET	Tachycardia, dry mouth, blurred vision, urinary retention
	Pralidoxime (2-PAM)	25-50 mg/kg over 5-10 min (max: 200 mg/min); can be repeated after 1-2 hr, then q10-12hr as needed	IV/IM	Nausea, dizziness, headache, tachycardia, muscle rigidity, bronchospasm (rapid administration)
Salicylates	Sodium bicarbonate	Bolus 1-2 mEq/kg followed by a continuous infusion	IV	Follow potassium closely and replete as necessary Goal urine pH 7.5-8.0
Sulfonylureas	Octreotide and dextrose	1-2 μg/kg/dose (adults 50-100 μg) q6-8hr	IV/SC	
Tricyclic antidepressants	Sodium bicarbonate	Bolus 1-2 mEq/kg; repeated bolus dosing as needed to keep QRS <110 msec	IV	Indications: QRS widening (≥110 ms), hemodynamic instability; follow potassium

BAL, British antilewisite; DMSA, dimercaptosuccinic acid; ECG, electrocardiogram; FIO2, fraction of inspired oxygen; EDTA, ethylenediaminetetraacetic acid; EG, ethylene glycol; ET, endotracheal tube; max, maximum; UA, urinalysis.

quickly become comatose. In fact, endotracheal intubation is often the only significant intervention needed in many poisoned patients, especially those poisoned with neuroleptics. An important caveat is with the tachypneic patient with a clear lung exam and normal oxygen saturation. This should alert the clinician to the likelihood that the patient is compensating for an acidemia. Paralyzing such a patient and underventilating them might prove fatal. If intubation is absolutely necessary for airway protection or a tiring patient, a good rule of thumb is to match the ventilatory settings to the patient's preintubation minute ventilation.

In the hypotensive patient, it should be remembered that these patients often are not hypovolemic, but are poisoned; aggressive fluid resuscitation may lead to fluid overload. If hypotension persists after 1 or 2 standard boluses of crystalloid, infusion of a direct-acting vasopressor, such as norepinephrine or epinephrine, is preferred. Dysrhythmias are managed in the standard fashion apart from those caused by agents that block the fast sodium channels of the heart for which sodium bicarbonate therapy is utilized.

Seizures are primarily managed with agents that potentiate the γ-aminobutyric acid complex, such as benzodiazepines or barbiturates. Creatinine kinase levels should be drawn on any patient found unconscious. The goal of supportive therapy is to support the patient's vital functions until the patient can eliminate the toxin.

Table 63-8 Additional Antidotes

ANTIDOTES	TOXIN OR POISON
Latrodectus antivenin	Black widow spider
Botulinum antitoxin	Botulinum toxin
Insulin and glucose	Calcium channel antagonists
Diphenhydramine and/or benztropine	Dystonic reactions
Calcium salts	Fluoride, calcium channel blockers
Protamine	Heparin
Folinic acid	Methotrexate, trimethoprim, pyrimethamine
Crotalidae-specific Fab antibodies	Rattlesnake envenomation
Sodium bicarbonate	Sodium channel blockade (tricyclic antidepressants, type 1 antiarrhythmics)

Antidotes

Antidotes are available for relatively few toxins (see Tables 63-7 and 63-8), but early and appropriate use of an antidote is a key element in managing the poisoned patient.

Decontamination

The majority of poisonings in children are from ingestion, although exposures can also occur via inhalational, dermal, and ocular routes. The goal of decontamination is to minimize absorption of the toxic substance. The specific method employed depends on the properties of the toxin itself and the route of exposure. Regardless of the decontamination method used, the efficacy of the intervention decreases with increasing time since exposure. *Decontamination should not be routinely employed for every poisoned patient.* Instead, careful decisions regarding the utility of decontamination should be made for each patient and should include consideration of the toxicity and pharmacologic properties of the exposure, the route of the exposure, the time since the exposure, and the risks vs the benefits of the decontamination method.

Dermal and ocular decontamination begin with removal of any contaminated clothing and particulate matter, followed by flushing of the affected area with tepid water or normal saline. Treating clinicians should wear proper protective gear when performing irrigation. Flushing for a minimum of 10-20 minutes is recommended for most exposures, although some chemicals (e.g., alkaline corrosives) require much longer periods of flushing. Dermal decontamination, especially after exposure to adherent or lipophilic (e.g., organophosphates) agents, should include thorough cleansing with soap and water. Water should *not* be used for decontamination after exposure to highly reactive agents, such as elemental sodium, phosphorus, calcium oxide, and titanium tetrachloride. After an inhalational

exposure, decontamination involves moving the patient to fresh air and administering supplemental oxygen if indicated.

Gastrointestinal (GI) decontamination is a controversial topic among medical toxicologists. *GI decontamination strategies are most likely to be effective in the 1st hour after an acute ingestion*. GI absorption may be delayed after ingestion of agents that slow GI motility (anticholinergic medications, opioids), massive pill ingestions, sustained-release preparations, and ingestions of agents that can form pharmacologic bezoars (e.g., enteric-coated salicylates). GI decontamination at more than 1 hr after ingestion may be considered in patients who ingest toxic substances with these properties. Even rapid institution of GI decontamination with activated charcoal will, at best, bind only approximately 30% of the ingested substance. GI decontamination should never supplant excellent supportive care and should not be employed in an unstable or persistently vomiting patient. Described methods of GI decontamination include induced emesis with ipecac, gastric lavage, cathartics, activated charcoal, and whole-bowel irrigation (WBI). Of these, only activated charcoal and WBI are likely to be of clinical benefit.

Syrup of Ipecac

Syrup of ipecac contains 2 emetic alkaloids that work in both the central nervous system (CNS) and locally in the GI tract to produce vomiting. In the 1960s, the American Academy of Pediatrics lobbied for nonprescription availability of ipecac and in the 1980s recommended that ipecac be given to parents at the 6 mo well-child check, coupled with a discussion about poison prevention strategies. Since then, studies have failed to document a significant clinical impact from the use of ipecac and have documented multiple adverse events from its use. After a review of the evidence and assessment of the risks and benefits of ipecac use, the American Academy of Pediatrics, the American Academy of Clinical Toxicology, and the American Association of Poison Control Centers have all published statements in favor of **abandoning the use of ipecac.**

Gastric Lavage

Gastric lavage involves placing a tube into the stomach to aspirate contents, followed by flushing with aliquots of fluid, usually water or normal saline. Although gastric lavage was used routinely for many years, objective data do not document or support clinically relevant efficacy. This is particularly true in children, in whom only small-bore tubes can be used. Lavage is time-consuming and painful, and can induce bradycardia via a vagal response to tube placement. It can delay administration of more definitive treatment (activated charcoal), and under the best circumstances only removes a fraction of gastric contents. *Thus, in most clinical scenarios, the use of gastric lavage is no longer recommended.*

Single-Dose Activated Charcoal

Activated charcoal is thought to be a potentially useful method of GI decontamination, although clinical data to support this claim is limited. Charcoal is "activated" via heating to extreme temperatures, creating an extensive network of pores that provides a very large adsorptive surface area. Many, but not all, toxins are adsorbed onto its surface, thus preventing absorption from the GI tract. *Charcoal is most likely to be effective when given within 1 hr of ingestion.* Charged molecules (i.e., heavy metals, lithium, iron) and liquids do not bind well to activated charcoal (Table 63-9). Charcoal administration should also be avoided after ingestion of a caustic substance, because the presence of charcoal can impede subsequent endoscopic evaluation. A repeat dose of activated charcoal may be warranted in the cases of ingestion of an extended release product or, more commonly, with a significant salicylate poisoning as a result of its delayed and erratic absorption pattern.

The dose of activated charcoal is 1 g/kg in children or 50-100 g in adolescents and adults. Before administering charcoal, one *must* ensure that the patient's airway is intact or protected and that the patient has a benign abdominal exam. In the awake, uncooperative adolescent or child who refuses to drink the activated charcoal, there is relatively little utility and potential morbidity associated with forcing activated charcoal down a nasogastric tube, and such practice should be avoided. Approximately 20% of children vomit after receiving a dose of charcoal, emphasizing the importance of an intact airway and avoiding administration of charcoal after ingestion of substances that are particularly toxic when aspirated (e.g., hydrocarbons). If charcoal is given through a gastric tube in an intubated patient, placement of the tube should be carefully confirmed before activated charcoal is given because instillation of charcoal directly into the lungs can have disastrous effects. Constipation is another common side effect of activated charcoal, and in rare cases, bowel perforation has been reported.

Table 63-9	Substances Poorly Adsorbed By Activated Charcoal
Alcohols	
Caustics: alkalis and acids	
Cyanide	
Heavy metals (e.g., lead)	
Hydrocarbons	
Iron	
Lithium	

In young children, practitioners may attempt to improve palatability by adding flavorings (chocolate or cherry syrup) or giving the mixture over ice cream. Cathartics (sorbitol, magnesium sulfate, magnesium citrate) have been used in conjunction with activated charcoal to prevent constipation and accelerate evacuation of the charcoal–toxin complex. There are no data demonstrating their value and there are numerous reports of adverse effects from cathartics. Cathartics should be used with care in young children and should never be used in multiple doses because of the risk of dehydration and electrolyte imbalance.

Whole-Bowel Irrigation

WBI involves instilling large volumes (35 mL/kg/hr in children or 1-2 L/hr in adolescents) of a polyethylene glycol electrolyte solution (e.g., GoLYTELY) to "wash out" the entire GI tract. This technique may have some success after the ingestion of slowly absorbed substances (sustained-release preparations), substances not well adsorbed by charcoal (e.g., lithium, iron), transdermal patches, and drug packets. WBI can be combined with the use of activated charcoal, if appropriate (cocaine or heroin body packers). In children, WBI is of greatest utility in decontaminating the gut of a child whose abdominal X-ray demonstrates multiple lead paint chips. Careful attention should be paid to assessment of the airway and abdominal exam before initiating WBI, which should never be given to a patient without bowel sounds or with signs of obstruction or ileus, or without a protected airway. Given the rate of administration and volume needed to flush the system, WBI is typically administered via a nasogastric tube. WBI is continued until the rectal effluent is clear. Complications of WBI include vomiting, abdominal pain, and abdominal distention. Bezoar formation might respond to WBI but may also require endoscopy or surgery.

Enhanced Elimination

Enhancing excretion is only useful for a few toxins; in these cases, enhancing elimination is a potentially lifesaving intervention that results in improved clearance of a poison that has already been absorbed.

Urinary Alkalinization

A charged molecule, being polar and hydrophilic, does not easily cross a fat membrane. Such is the mechanism by which alkalinizing the urine enhances the elimination of some drugs that are weak acids by forming charged particles that are "trapped" within the renal tubules and thus excreted. Urinary alkalinization is accomplished via a continuous infusion of sodium bicarbonate–containing intravenous fluids, with a goal urine pH of 7.5-8. Alkalinization of the urine is most useful in managing salicylate and methotrexate toxicity.

Serum pH should be closely monitored because a serum pH of >7.55 is potentially dangerous to cellular functions. Other complications of

urinary alkalinization include electrolyte derangements, such as hypokalemia and hypocalcemia. This method of enhanced elimination is contraindicated in patients who are unable to tolerate the large volumes of fluid needed to achieve alkalinization, including patients with heart failure, kidney failure, pulmonary edema, or cerebral edema.

Hemodialysis

Few drugs or toxins are removed by dialysis in amounts sufficient to justify the risks and difficulty of dialysis. Toxins that are amenable to dialysis have the following properties: low volume of distribution (<1 L/kg), low molecular weight, low degree of protein binding, and high degree of water solubility. Examples of toxins for which dialysis may be useful include methanol, ethylene glycol, salicylates, theophylline, bromide, lithium, and, potentially, valproic acid. In addition to enhancing the elimination of the toxin itself, hemodialysis can also be useful to correct severe electrolyte disturbances and acid–base derangements resulting from the ingestion (e.g., metformin-associated lactic acidosis).

Multiple-Dose Activated Charcoal

Whereas single-dose activated charcoal is used as a method of decontamination, multiple doses of activated charcoal (MDACs) can help to enhance the elimination of some toxins. MDAC is typically given as 0.5 g/kg every 4-6 hr (for ≤24 hr) and continued until there is significant clinical improvement, including satisfactory decline of serum drug concentrations. MDACs enhance elimination via 2 proposed mechanisms: interruption of enterohepatic recirculation and "GI dialysis," which uses the intestinal mucosa as the dialysis membrane and pulls toxins from the bloodstream back into the intraluminal space, where they are adsorbed to the charcoal. The American Academy of Clinical Toxicology/European Association of Poisons Centres and Clinical Toxicologists position statement recommends MDAC in managing significant ingestions of carbamazepine, dapsone, phenobarbital, quinine, and theophylline. As with single-dose activated charcoal, contraindications to use of MDAC include an unprotected airway and a concerning abdominal exam (e.g., ileus, distention, peritoneal signs); thus the airway and abdominal exam *should be assessed before each dose.* A cathartic (e.g., sorbitol) may be given with the first dose, but it should not be used with subsequent doses owing to the risk of dehydration and electrolyte derangements. Although MDAC reduces the serum level of an intoxicant quicker than without MDAC, it has not been shown to have a significant impact on outcome.

Intralipid Emulsion Therapy

A potentially life-saving intervention of infusing Intralipid emulsions is a means of sequestering fat-soluble drugs and decreasing their impact at target organs. Initial experience regarding this intervention has been developed by anesthesiologists as a reversal agent for asystole resulting from inadvertent intravenous injection of bupivacaine. There are dozens of case reports published demonstrating the dramatic and rapid recovery of premorbid poisoned patients given a dose of Intralipid. Using the same 20% Intralipid used for total parenteral nutrition, a bolus dose of 1.5 mL/kg is given over 3 min, followed by an infusion of 0.25 mL/kg/min until recovery or a total of 10 mL/kg has been infused. Lipophilic drugs (LogP >2) are potentially bound by Intralipid emulsions, including calcium channel blockers (verapamil and diltiazem) and tricyclic antidepressants.

SELECTED COMPOUNDS COMMONLY INVOLVED IN PEDIATRIC POISONINGS

Herbal medicines (see Chapter 64), drugs of abuse (see Chapter 114), and environmental health hazards (see Chapters 718-725) are covered elsewhere.

Pharmaceuticals

Analgesics

Acetaminophen. Acetaminophen (APAP) is the most widely used analgesic and antipyretic in pediatrics, available in multiple formulations, strengths, and combinations. Consequently, APAP is commonly available in the home, where it can be unintentionally ingested by young children, taken in an intentional overdose by adolescents and adults, or inappropriately dosed in all ages. APAP toxicity remains the most common cause of acute liver failure in the United States, and is the number 1 cause of intentional poisoning death in the United States.

Pathophysiology. APAP toxicity results from the formation of a highly reactive intermediate metabolite, *N*-acetyl-*p*-benzoquinone imine. In therapeutic use, only a small percentage of a dose (approximately 5%) is metabolized by the hepatic cytochrome P450 enzyme CYP2E1 to *N*-acetyl-*p*-benzoquinone imine, which is then immediately conjugated with glutathione to form a nontoxic mercapturic acid conjugate. In overdose, glutathione stores are overwhelmed, and free *N*-acetyl-*p*-benzoquinone imine is able to combine with hepatic macromolecules to produce hepatocellular necrosis. The single acute toxic dose of APAP is generally considered to be >200 mg/kg in children and >7.5-10 g in adolescents and adults. Repeated administration of APAP at supratherapeutic doses (>90 mg/kg/day for consecutive days) can lead to hepatic injury or failure in some children, especially in the setting of fever, dehydration, poor nutrition, and other conditions that serve to reduce glutathione stores.

Any child with a history of acute ingestion of >200 mg/kg (unusual in children younger than 6 yr old) or with an acute intentional ingestion of any amount should be referred to a healthcare facility for clinical assessment and measurement of a serum APAP level.

Clinical and Laboratory Manifestations. Classically, 4 general stages of APAP toxicity have been described (Table 63-10). The initial signs are nonspecific (i.e., nausea and vomiting) and may not be present. Thus, the diagnosis of APAP toxicity cannot be based on clinical symptoms alone, but instead requires consideration of the combination of the patient's history, symptoms, and laboratory findings.

If a toxic ingestion is suspected, a serum APAP level should be measured 4 hr after the reported time of ingestion. For patients who present to medical care more than 4 hr after ingestion, a stat APAP level should be obtained. *APAP levels obtained <4 hr after ingestion, unless "nondetectable," are difficult to interpret and cannot be used to estimate the potential for toxicity.* Other important baseline labs include hepatic transaminases, renal function tests, and coagulation parameters.

Treatment. When considering the treatment of a patient poisoned or potentially poisoned with APAP, and after assessment of the ABCs, it is helpful to place the patient into one of the following 4 categories.

1. ***Prophylactic:*** By definition, these patients have a normal aspartate aminotransferase (AST). If the APAP level is known and the ingestion is within 24 hr of the level being drawn, then treatment

Table 63-10 Classic Stages in the Clinical Course of Acetaminophen Toxicity

STAGE	TIME AFTER INGESTION	CHARACTERISTICS
I	0.5-24 hr	Anorexia, vomiting, malaise Labs typically normal, except for acetaminophen level
II	24-48 hr	Resolution of earlier symptoms; right upper quadrant abdominal pain and tenderness; elevated hepatic transaminases (aspartate aminotransferase > alanine aminotransferase), INR
III	3-5 days	Peak transaminase elevations; development of liver failure, multi organ-system failure, death *or* recovery begins
IV	4 days-2 wk	Resolution of liver function abnormalities Clinical recovery precedes histologic recovery

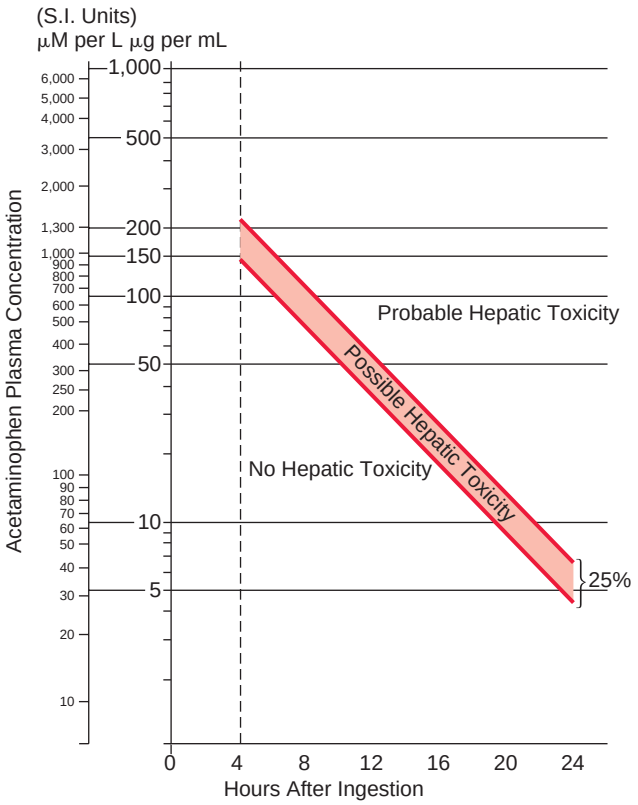

Figure 63-1 Rumack-Matthew nomogram for acetaminophen poisoning, a semilogarithmic plot of plasma acetaminophen concentrations vs time. Cautions for the use of this chart: The time coordinates refer to time after ingestion, serum concentrations obtained before 4 hr are not interpretable, and the graph should be used only in relation to a single acute ingestion with a known time of ingestion. This nomogram is not useful for chronic exposures or unknown time of ingestion and should be used with caution in the setting of coingestants that that slow gastrointestinal motility. The *lower solid line* is typically used in the United States to define toxicity and direct treatment, whereas the *upper line* is generally used in Europe. *(From Rumack BH, Hess AJ, editors:* Poisindex, *Denver, 1995, Micromedix. Adapted from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity,* Pediatrics *55:871–876, 1975.)*

decisions are based on where the level falls on the Rumack-Matthew nomogram (Fig. 63-1). Any patient with a serum APAP level in the possible or probable hepatotoxicity range per the nomogram should be treated with *N*-acetylcysteine (NAC). This nomogram is only intended for use in patients who present within 24 hr of a single *acute* APAP ingestion with a known time of ingestion. If treatment is recommended, they should receive either oral Mucomyst or IV Acetadote for 24 or 21 hr, respectively. Repeat AST and APAP concentration drawn toward the end of that interval should be obtained. If the AST is normal and the APAP becomes nondetectable, then treatment may be discontinued. If the AST becomes elevated, then the patient moves into the next category of treatment (injury). If APAP is still present, treatment should be continued until the level is nondetectable. In the case of a patient with a documented APAP level, normal AST, and an unknown time of ingestion, treatment should ensue until the level is nondetectable, with normal transaminases.

The importance of instituting therapy with either IV or oral NAC no later than 8 hr from the time of ingestion cannot be overemphasized. No patient, no matter the size of the ingestion, who receives NAC within 8 hr of overdose should die from liver failure. The further out from the 8 hr mark the initiation of therapy is delayed, the greater the risk of acute liver failure. Any patient presenting close to that 8 hr mark or beyond it after an APAP overdose should be empirically started on NAC pending lab results.

2. ***Hepatic Injury:*** These patients are exhibiting evidence of hepatocellular necrosis, manifested first as elevated liver transaminases (AST rises first, then the alanine aminotransferase), followed by a rise in the INR. Any patient in this category requires therapy with NAC (IV or oral). When to discontinue therapy in the clinically well patient remains controversial, but in general, the transaminases and INR have peaked and fallen significantly "toward" normal (they do not need to be normal). Most patients' liver enzymes will peak 3 or 4 days after their ingestion.
3. ***Acute Liver Failure:*** The King's College criteria are used to determine which patients should be referred for consideration of liver transplant. These criteria include acidemia (serum pH <7.3) after adequate fluid resuscitation, coagulopathy (INR >6), renal dysfunction (creatinine >3.4 mg/dL), and grade III or IV hepatic encephalopathy (see Chapter 364). A serum lactic acid >3 mmol/L (after IV fluids) adds to both the sensitivity and specificity of the criteria to predict death without liver transplant. The degree of transaminase elevation does not factor in to this decision making process.
4. ***Repeated Supratherapeutic Ingestion:*** APAP is particularly prone to unintentional overdose through the ingestion of multiple medications containing the drug or simply because people assume it to be safe at any dose. Ingestion of amounts significantly greater than the recommended daily dose for several days or more puts one at risk for liver injury. Because the Rumack-Matthew nomogram is not helpful in this scenario, a conservative approach is in order. In the asymptomatic patient, if the AST is normal and the APAP is <10 μg/mL, then no therapy is indicated. A normal AST and an elevated APAP warrants NAC dosing for at least long enough for the drug to metabolize while the AST remains normal. An elevated AST puts the patient in the "hepatic injury" category described above. A patient presenting with symptoms (i.e., right upper quadrant pain, vomiting, jaundice) should be empirically started on NAC pending lab results.

NAC is available in oral and intravenous forms, and both are equally efficacious (see Table 63-7 for the dosing regimens of the oral vs IV form). The intravenous form is used in patients with intractable vomiting, those with evidence of hepatic failure, and pregnant patients. Oral NAC has an unpleasant taste and smell, and can be mixed in soft drink or fruit juice or given via nasogastric tube to improve tolerability of the oral regimen. Administration of IV NAC (as a standard 3% solution to avoid administering excess free water, typically in 5% dextrose), especially the initial loading dose, is associated in some patients with the development of anaphylactoid reactions (non–immunoglobulin E mediated). These reactions are typically managed by stopping the infusion; treating with diphenhydramine, albuterol, and/or epinephrine as indicated; and restarting the infusion at a slower rate once symptoms have resolved. IV NAC is also associated with mild elevation in measured INR (range: 1.2-1.5). IV dosing does, however, deliver less drug to the liver compared with the oral regimen. As a result, many toxicologists now recommend higher doses of the IV formulation in patients with large overdoses.

Transaminases, synthetic function, and renal function should be followed daily while the patient is being treated with NAC. Patients with worsening hepatic function or clinical status might benefit from more frequent lab monitoring. A patient-tailored approach is the norm for when to stop NAC therapy, for deciding whom to refer for transplantation evaluation, and often for the dose of IV NAC in patients with either very high APAP levels or signs of significant injury. Consultation with the regional poison center and medical toxicologist can help streamline the care of these patients, ultimately shortening their length of stay with potentially improved outcomes.

Salicylates. The incidence of salicylate poisoning in young children has declined dramatically since APAP and ibuprofen replaced aspirin as the most commonly used analgesics and antipyretics in

pediatrics. However, salicylates remain widely available, not only in aspirin-containing products but also in antidiarrheal medications, topical agents (e.g., keratolytics, sports creams), oil of wintergreen, and some herbal products. Oil of wintergreen contains 5 g of salicylate in 1 teaspoon (5 mL), meaning ingestion of very small volumes of this product has the potential to cause severe toxicity.

Pathophysiology. Salicylates lead to toxicity by interacting with a wide array of physiologic processes, including direct stimulation of the respiratory center, uncoupling of oxidative phosphorylation, inhibition of the tricarboxylic acid cycle, and stimulation of glycolysis and gluconeogenesis. The acute toxic dose of salicylates is generally considered to be >150 mg/kg. More significant toxicity is seen after ingestions of >300 mg/kg, and severe, potentially fatal, toxicity is described after ingestions of >500 mg/kg.

Clinical and Laboratory Manifestations. Salicylate ingestions are classified as acute or chronic, and acute toxicity is far more common in pediatric patients. Early signs of acute salicylism include nausea, vomiting, diaphoresis, and tinnitus. Moderate salicylate toxicity can manifest as tachypnea and hyperpnea, tachycardia, and altered mental status. The tachycardia results in large part from marked insensible losses from vomiting, tachypnea, diaphoresis, and uncoupling of oxidative phosphorylation. Thus, careful attention should be paid to volume status and early volume resuscitation in the significantly poisoned patient. Signs of severe salicylate toxicity include hyperthermia, coma, and seizures. Chronic salicylism can have a more insidious presentation, and patients can show marked toxicity at significantly lower salicylate levels than in acute toxicity.

Classically, lab values from a patient poisoned with salicylates reveal a primary respiratory alkalosis and a primary, elevated anion gap, metabolic acidosis. Early in the course of acute salicylism, respiratory alkalosis dominates. As the respiratory stimulation diminishes, the patient will move toward the metabolic acidosis. Hyperglycemia (early) and hypoglycemia (late) have been described. Abnormal coagulation studies and acute kidney injury may be seen but are not common.

Serial serum salicylate levels should be closely monitored (every 2-3 hr initially) until they are consistently down trending. Salicylate absorption in overdose is often unpredictable and erratic, especially with an enteric coated product, and levels can rapidly increase into the highly toxic range, even many hours after the ingestion. The Done nomogram is of poor value and should not be used. Serum and urine pH and electrolytes should be followed closely. An APAP level should be checked in any patient who intentionally overdoses on salicylates, because APAP is a common coingestant and because people often confuse or combine their nonprescription analgesic medications. Salicylate toxicity can cause a noncardiogenic pulmonary edema, especially in chronic overdose; consequently, a chest x-ray is recommended in any patient in respiratory distress.

Treatment. For the patient who presents soon after an acute ingestion, initial treatment should include gastric decontamination with activated charcoal. Salicylate pills occasionally form concretions called bezoars, which should be suspected if serum salicylate concentrations continue to rise many hours after ingestion or are persistently elevated in spite of appropriate management. Gastric decontamination is typically not useful after chronic exposure.

Initial therapy focuses on aggressive volume resuscitation and prompt initiation of sodium bicarbonate therapy in the symptomatic patient, even before obtaining serum salicylate levels. Therapeutic salicylate levels are 10-20 mg/dL, and levels >30 mg/dL warrant treatment.

The primary mode of therapy for salicylate toxicity is **urinary alkalinization**. Urinary alkalinization enhances the elimination of salicylates by converting salicylate to its ionized form, "trapping" it in the renal tubules, and thus enhancing elimination. In addition, maintaining an alkalemic serum pH decreases CNS penetration of salicylates because charged particles are less able to cross the blood–brain barrier. Alkalinization is achieved by administration of a sodium bicarbonate infusion at approximately 2 times maintenance fluid rates. *The goals of therapy include a urine pH of 7.5-8, a serum pH of 7.45-7.55, and decreasing serum salicylate levels.* In general, in the presence of an acidosis, an aspirin-poisoned patient's status can be directly related to the patient's serum pH. The lower the pH, the greater the relative amount of salicylate in the uncharged/nonpolar form and the greater the penetration of the blood–brain barrier by the drug. Careful attention should also be paid to serial potassium levels, because hypokalemia impairs alkalinization of the urine; potassium is often added to the bicarbonate drip. Repeat doses of charcoal may be beneficial because of the often delayed and erratic absorption of aspirin. Parenteral glucose should be provided to any salicylate poisoned patients with altered mental status as they may have CNS hypoglycemia not noted in a peripheral serum glucose test.

In cases of severe toxicity, hemodialysis may be required. Indications for dialysis include severe acid–base abnormalities (specifically severe acidosis and acidemia), a rising salicylate level despite adequate decontamination and properly alkalinized urine, pulmonary edema, cerebral edema, seizures, and renal failure. Serum salicylate concentrations should always be interpreted along with the clinical status of the patient; on their own they are not a clear indicator of the need for dialysis.

Ibuprofen and Other Nonsteroidal Antiinflammatory Drugs. Ibuprofen and other nonsteroidal antiinflammatory drugs (NSAIDs) are often involved in unintentional and intentional overdoses owing to their widespread availability and common use as analgesics and antipyretics. Fortunately, serious effects after NSAID overdose are rare owing to their wide therapeutic index.

Pathophysiology. NSAIDs inhibit prostaglandin synthesis by reversibly inhibiting the activity of cyclooxygenase (COX), the primary enzyme responsible for the biosynthesis of prostaglandins. In therapeutic use, side effects include GI irritation, reduced renal blood flow, and platelet dysfunction. In an attempt to minimize these side effects, NSAID analogs have been developed that are more specific for the inducible form of COX (the COX-2 isoform) than the constitutive form, COX-1. However, overdose of the more selective COX-2 inhibitors (e.g., celecoxib [Celebrex]) is treated the same as overdose of nonspecific COX inhibitors (e.g., ibuprofen) because at higher doses, COX-2–selective agents lose their COX inhibitory selectivity.

Ibuprofen, the primary NSAID used in pediatrics, is well tolerated, even in overdose. In children, acute doses of <200 mg/kg rarely cause toxicity, but ingestions of >400 mg/kg can produce more serious effects, including altered mental status and metabolic acidosis.

Clinical and Laboratory Manifestations. Symptoms usually develop within 4-6 hr of ingestion and resolve within 24 hr. If toxicity does develop, it is typically manifested as nausea, vomiting, and abdominal pain. Although GI bleeding and ulcers have been described with chronic use, they are rare in the setting of acute ingestion. After massive ingestions, patients can develop marked CNS depression, anion gap metabolic acidosis, renal insufficiency, and (rarely) respiratory depression. Seizures have also been described, especially after overdose of mefenamic acid. Specific drug levels are not readily available nor do they inform management decisions. Renal function studies, acid–base balance, complete blood count, and coagulation parameters should be monitored after very large ingestions. Coingestants, especially APAP, should be ruled out after any intentional ingestion.

Treatment. Supportive care, including use of antiemetics and acid blockade as indicated, is the primary therapy for NSAID toxicity. Decontamination with activated charcoal should be considered if a patient presents within 1-2 hr of a potentially toxic ingestion. There is no specific antidote for this class of drugs. Given the high degree of protein binding and excretion pattern of NSAIDs, none of the modalities used to enhance elimination are particularly useful in managing these overdoses. Unlike in patients with salicylate toxicity, urinary alkalinization is not helpful for NSAID toxicity. Patients who develop significant clinical signs of toxicity should be admitted to the hospital for ongoing supportive care and monitoring. Patients who remain asymptomatic for 4-6 hr after ingestion may be considered medically cleared.

Oral Opioids. Opioids are a commonly abused class of medications (see Chapter 114), both in their IV and oral forms. Two specific

oral opioids, buprenorphine and methadone, merit particular mention because of potential life-threatening toxicity in toddlers with ingestion of even 1 pill. Both agents are used in managing opioid dependence, although buprenorphine is the drug of choice. Methadone is also widely used in the treatment of chronic pain, meaning multiday prescriptions can be filled. Both drugs are readily available for illicit purchase and potential abuse. Both drugs are of great potential toxicity to a toddler, especially buprenorphine, owing to its long half-life and high potency.

Pathophysiology. Methadone is a lipophilic synthetic opioid with potent agonist effects at μ-opioid receptors, leading to both its desired analgesic effects and undesired side effects, including sedation, respiratory depression, and impaired GI motility. Methadone is thought to cause QTc interval prolongation via interactions with the human ether-a-go-go–related gene (hERG)-encoded potassium rectifier channel. Methadone has an average half-life of >25 hr, which may be extended to >50 hr in overdose.

Suboxone is a combination of buprenorphine, a potent opioid with partial agonism at μ-opioid receptors and weak antagonism at κ-opioid receptors, and naloxone. Naloxone has poor oral bioavailability but is included in the formulation to discourage diversion for intravenous use, during which it can precipitate withdrawal. Suboxone is formulated for buccal or sublingual administration; consequently, toddlers can absorb significant amounts of drug even by sucking on a tablet. Buprenorphine has an average half-life of 37 hr.

Clinical and Laboratory Manifestations. In children, methadone and buprenorphine ingestions can manifest with the classic opioid toxidrome of respiratory depression, sedation, and miosis. Signs of more-severe toxicity can include bradycardia, hypotension, and hypothermia. Even in therapeutic use, methadone is associated with a prolonged QTc interval and risk of torsades de pointes. Accordingly, an ECG should be part of the initial evaluation after ingestion of methadone or any unknown opioid. Neither drug is detected on routine urine opiate screens, although some centers have added a separate urine methadone screen. Levels of both drugs can be measured, although this is rarely done clinically and is seldom helpful in the acute setting. An exception may be in the cases involving concerns about neglect or abuse, at which point urine for gas chromatography/mass spectroscopy, the legal gold standard, should be sent to confirm and document the presence of the drug.

Treatment. Patients with significant respiratory depression or CNS depression should be treated with the opioid antidote, naloxone (see Table 63-7). In pediatric patients who are not chronically on opioids, the full reversal dose of 0.1 mg/kg (max: 2 mg/dose) should be used. In contrast, opioid-dependent patients should be treated with smaller initial doses (0.01 mg/kg), which can then be repeated as needed to achieve the desired clinical response, hopefully avoiding abrupt induction of withdrawal. Because the half-lives of methadone and buprenorphine are far longer than that of naloxone, patients can require multiple doses of naloxone. These patients may benefit from a continuous infusion of naloxone, typically started at two-thirds of the reversal dose/hr and titrated to maintain an adequate respiratory rate and level of consciousness. Patients who have ingested methadone should be placed on a cardiac monitor and have serial ECGs to monitor for the development of a prolonged QTc interval. If a patient does develop a prolonged QTc, management includes close cardiac monitoring, repletion of electrolytes (potassium, calcium, and magnesium), and having magnesium and a defibrillator readily available should the patient develop torsades de pointes.

Given the potential for clinically significant and prolonged toxicity, any toddler who has ingested methadone, even if asymptomatic, should be admitted to the hospital for at least 24 hr of monitoring. Some experts advocate a similar approach to management of buprenorphine ingestions, even in the asymptomatic patient. As we gain more experience with pediatric buprenorphine exposures, some patients who remain absolutely asymptomatic for 6-8 hr after ingestion and *have a stable social setting* may be candidates for earlier discharge. In the meantime, these cases should be discussed with a poison control center or medical toxicologist before determining disposition.

Cardiovascular Medications

β-Adrenergic Receptor Blockers. β Blockers competitively inhibit the action of catecholamines at the β receptor. Therapeutically, β blockers are used for a variety of conditions, including hypertension, coronary artery disease, tachydysrhythmias, anxiety disorders, migraines, essential tremor, and hyperthyroidism. Because of its lipophilicity and blockade of fast sodium channels, propranolol is considered to be the most toxic member of the β-blocker class. Overdoses of water-soluble β blockers (e.g., atenolol) are associated with milder symptoms.

Pathophysiology. In overdose, β blockers decrease chronotropy and inotropy in addition to slowing conduction through atrioventricular nodal tissue. Clinically, these effects are manifested as bradycardia, hypotension, and heart block. Patients with reactive airways disease can experience bronchospasm as a result of blockade of β_2-mediated bronchodilation. β_2 Blockers interfere with glycogenolysis and gluconeogenesis, which can sometimes lead to hypoglycemia, especially in patients with poor glycogen stores (e.g., toddlers).

Clinical and Laboratory Manifestations. Toxicity typically develops within 6 hr of ingestion, although it may be delayed after ingestion of sotalol or sustained-release preparations. The most common features of severe poisoning are bradycardia and hypotension. Lipophilic agents, including propranolol, can enter the CNS and cause altered mental status, coma, and seizures. Overdose of β blockers with membrane-stabilizing properties (e.g., propranolol) can cause QRS interval widening and ventricular dysrhythmias.

Evaluation after β-blocker overdose should include an ECG, frequent reassessments of hemodynamic status, and blood glucose. Serum levels of β blockers are not readily available for routine clinical use and are not useful in management of the poisoned patient.

Treatment. In addition to supportive care and GI decontamination as indicated, glucagon is the antidote of choice for β-blocker toxicity (see Table 63-7). Glucagon stimulates adenyl cyclase and increases levels of cyclic adenosine monophosphate independent of the β receptor. Glucagon is typically given as a bolus and, if this is effective, followed by a continuous infusion. In practice, however, glucagon is often only marginally effective, limited by its proemetic effects, especially at the doses typically required. Other potentially useful interventions include calcium, vasopressors, and high-dose insulin. Seizures are managed with benzodiazepines, and QRS widening should be treated with sodium bicarbonate. Children who ingest 1 or 2 water-soluble β blockers are unlikely to develop toxicity and can typically be discharged to home if they remain asymptomatic over a 6-hr observation period. Children who ingest sustained-release products, highly lipid-soluble agents, and sotalol can require longer periods of observation before safe discharge. Any symptomatic child should be admitted for ongoing monitoring and directed therapy.

Calcium Channel Blockers. Calcium channel blockers (CCBs) are used for a variety of therapeutic indications and have the potential to cause severe toxicity, even after exploratory ingestions. Specific agents include verapamil, diltiazem, and the dihydropyridines (e.g., amlodipine, nifedipine). Of these, diltiazem and verapamil are the most dangerous in overdose.

Pathophysiology. CCBs antagonize L-type calcium channels, inhibiting calcium influx into myocardial and vascular smooth muscle cells. Verapamil works primarily by slowing inotropy and chronotropy, and has no effect on systemic vascular resistance (SVR). Diltiazem has effects both on the heart and the peripheral vasculature. The dihydropyridines exclusively diminish SVR. Verapamil and diltiazem can significantly diminish myocardial contractility and conduction, with diltiazem also lowering SVR. By contrast, dihydropyridines will drop the SVR, leading to vasodilation and reflex tachycardia (though this receptor selectivity may be lost after a large overdose). Because the same L-type calcium channels blocked by CCBs are also on the pancreatic islet cells, it is the norm for any patient significantly poisoned with a CCB to be hyperglycemic.

Clinical and Laboratory Manifestations. The onset of symptoms typically is soon after ingestion, although it may be delayed with ingestions of sustained-release products. Overdoses of CCBs lead

to hypotension, accompanied by bradycardia, normal heart rate, or even tachycardia, depending on the agent. One unique characteristic of CCB overdose is that patients can exhibit profound hypotension with preserved consciousness.

Initial evaluation should include an ECG, continuous and careful hemodynamic monitoring, and rapid measurement of serum glucose levels. Both the absolute degree of hyperglycemia and the percentage increase in serum glucose have been correlated with the severity of CCB toxicity in adults. The development of hyperglycemia can even precede the development of hemodynamic instability. Blood levels of CCBs are not readily available and are not useful in guiding therapy.

Treatment. Once initial supportive care has been instituted, GI decontamination should begin with activated charcoal as appropriate. WBI may be beneficial in a stable patient after ingestion of a sustained-release product. Calcium channel blockade in the smooth muscles of the GI tract can lead to greatly diminished motility; thus, any form of GI decontamination should be undertaken with careful attention to serial abdominal exams.

Calcium salts, administered either through a peripheral IV as calcium gluconate, or via a central line as calcium chloride, help to overcome blocked calcium channels. *High-dose insulin euglycemia therapy is considered the antidote of choice for CCB toxicity.* An initial bolus of 1 unit/kg of regular insulin is followed by an infusion at 0.5-1 unit/kg/hr (see Table 63-6). The main mechanism of high-dose insulin euglycemia is to improve the metabolic efficiency of a poisoned heart that is in need of carbohydrates for energy (instead of the usual free fatty acids), but has minimal circulating insulin. Blood glucose levels should be closely monitored, and supplemental glucose may be given to maintain euglycemia, although this is rarely necessary in the severely poisoned patient. Additional therapies include judicious IV fluid boluses and vasopressors (often in very high doses). Cardiac pacing is rarely of value. Lipid emulsion therapy (discussed earlier), is a potentially life-saving intervention especially for patients poisoned with the more lipid soluble CCBs, verapamil and diltiazem. In extreme cases, an intraaortic balloon pump or extracorporeal membrane oxygenation are potential rescue devices. Given the potential for profound and sometimes delayed toxicity in toddlers after ingestion of 1 or 2 CCB tablets, hospital admission and 24 hr of monitoring for all of these patients is strongly recommended.

Clonidine. Although originally intended for use as an antihypertensive, clonidine prescriptions in the pediatric population have increased markedly, owing to its reported efficacy in the management of attention-deficit/hyperactivity disorder, tic disorders, and other behavioral disorders. With this increased use has come a significant increase in pediatric ingestions and therapeutic misadventures. Clonidine is available in pill and transdermal patch forms.

Pathophysiology. Clonidine, along with the closely related agent guanfacine, is a centrally acting α_2-agonist with a very narrow therapeutic index. Agonism at central α_2 receptors decreases sympathetic outflow, producing lethargy, bradycardia, hypotension, and apnea. Toxicity can develop after ingestion of as little as 1 pill or after sucking on or swallowing a discarded transdermal patch. Even a "used" transdermal patch might contain as much as one-third to one-half of the original amount of drug.

Clinical and Laboratory Manifestations. The most common clinical manifestations of clonidine toxicity include lethargy, miosis, and bradycardia. Hypotension, respiratory depression, and apnea may be seen in severe cases. Very early after ingestion, patients may be hypertensive in the setting of agonism at peripheral α receptors and resulting vasoconstriction. Symptoms develop relatively soon after ingestion and typically resolve within 24 hr. Serum clonidine concentrations are not readily available and are of no clinical value in the acute setting. Though signs of clinical toxicity are common after clonidine overdose, death from clonidine alone is extremely unusual.

Treatment. Given the potential for significant toxicity, most young children warrant referral to a healthcare facility for evaluation after unintentional ingestions of clonidine. Gastric decontamination is usually of little value, owing to the small quantities ingested and the rapid onset of serious symptoms. Aggressive supportive care is imperative and is the cornerstone of management. Naloxone, often in high doses, has shown variable efficacy in treating clonidine toxicity. Other potentially useful therapies include atropine, IV fluid boluses, and vasopressors. Symptomatic children should be admitted to the hospital for close cardiovascular and neurologic monitoring. It should also be noted, that in a patient chronically on clonidine or guanfacine, rapid discontinuation of the drug, or even missing 1 or 2 doses, could lead to potentially dangerous elevations in blood pressure.

Digoxin. Digoxin is a cardiac glycoside extracted from the leaves of *Digitalis lanata*. Other natural sources of cardiac glycosides include *Digitalis purpura* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (lily of the valley), Siberian ginseng, and the *Bufo marinus* toad. Therapeutically, digoxin is used in the management of heart failure and some supraventricular tachydysrhythmias. Acute overdose can occur in the setting of dosing errors (especially in younger children), unintentional or intentional medication ingestion, or exposure to plant material containing digitalis glycosides. Regarding exposure to such plants, toxicity is unusual unless the poison is concentrated in the form of a tea. Chronic toxicity can result from alteration of the digoxin dose, alteration in digoxin clearance as a result of renal impairment, or drug interactions.

Pathophysiology. Digoxin blocks the Na^+, K^+-ATPase (adenosine triphosphatase) pump, leading to intracellular loss of K^+ and gain of Na^+ and Ca^{2+}. This resulting rise in Ca^{2+} available to the contractile myocardium improves inotropy. An increase in myocardial automaticity leads to subsequent atrial, nodal, and ventricular ectopy. Digoxin also affects nodal conduction, leading to a prolonged refractory period, decreased sinus node firing, and slowed conduction through the atrioventricular node. Impaired Na-K exchange results in dangerously high levels of serum potassium. Overall, digoxin overdose manifests as a combination of slowed or blocked conduction and increased ectopy.

Clinical and Laboratory Manifestations. Nausea and vomiting are common initial symptoms of acute digoxin toxicity, manifesting within 6 hr of overdose. Cardiovascular manifestations include bradycardia, heart block, and a wide variety of dysrhythmias. CNS manifestations consist of lethargy, confusion, and weakness. Chronic toxicity is more insidious and manifests with GI symptoms, altered mental status, and visual disturbances.

Initial assessment should include an ECG, serum digoxin level, serum potassium, and kidney function tests. The serum digoxin level should be assessed at least 6 hr after ingestion and carefully interpreted in the setting of clinical symptoms because the digoxin level alone does not entirely reflect the severity of intoxication. In acute ingestions, serum potassium is an independent marker of morbidity and mortality, with levels >5.5 mEq/L predicting poor outcomes. In chronic toxicity, serum potassium is less useful as a prognostic marker and may be altered due to concomitant use of diuretics.

Digoxin has a very narrow therapeutic index. Therapeutic plasma digoxin concentrations are 0.5-2.0 ng/mL; a level >2 ng/mL is considered toxic and a level >6 ng/mL is considered potentially fatal (in chronic poisonings). Numerous drug interactions affect plasma digoxin concentrations. Medications known to increase serum digoxin concentrations include the macrolides, erythromycin and clarithromycin, spironolactone, verapamil, amiodarone, and itraconazole.

Treatment. Initial treatment includes good general supportive care and gastric decontamination with activated charcoal if the ingestion was recent. An antidote for digoxin, digoxin-specific Fab antibody fragments (Digibind or DigiFab) is available (see Table 63-7). Fab fragments bind free digoxin in both the intravascular and the interstitial spaces to form a pharmacologically inactive complex that is subsequently renally eliminated. Indications for Fab fragments include life-threatening dysrhythmias, K^+ value >5-5.5 mEq/L, serum digoxin level >15 ng/mL at any time or >10 ng/mL 6 hr after ingestion, ingestion >4 mg in children or >10 mg in adults, clinically significant hypotension or other cardiovascular instability, altered mental status, and renal failure. Atropine is potentially useful in managing symptomatic bradycardia. Although dogma states that patients on digoxin with severe hyperkalemia and QRS widening on the ECG should not receive calcium salts, this has not been supported in the literature. Once

stabilized, consultation with a cardiologist is recommended in the management of patients chronically on digoxin, because administration of Fab fragments can lead to recurrence of the patient's underlying dysrhythmias or dysfunction.

Iron. Historically, iron was a common cause of childhood poisoning deaths. However, preventive measures such as childproof packaging have significantly decreased the rates of serious iron toxicity in young children. Iron-containing products remain widely available, with the most potentially toxic being adult iron preparations and prenatal vitamins. The severity of an exposure is related to the amount of *elemental iron* ingested. Ferrous sulfate contains 20% elemental iron, ferrous gluconate 12%, and ferrous fumarate 33%. Multivitamin preparations and children's vitamins rarely contain enough elemental iron to cause significant toxicity.

Pathophysiology. Iron is directly corrosive to the GI mucosa, leading to hematemesis, melena, ulceration, infarction, and potential perforation. Early iron-induced hypotension is caused by massive volume losses, increased permeability of capillary membranes, and venodilation mediated by free iron. Iron accumulates in tissues, including the Kupffer cells of the liver and myocardial cells, leading to hepatotoxicity, coagulopathy, and cardiac dysfunction. Metabolic acidosis develops in the setting of hypotension, hypovolemia, and iron's direct interference with oxidative phosphorylation and the Krebs cycle. Pediatric patients who ingest >40 mg/kg of elemental iron should be referred to medical care for evaluation, although moderate to severe toxicity is typically seen with ingestions of >60 mg/kg.

Clinical and Laboratory Manifestations. Iron toxicity is classically described in 4, often overlapping, stages. The initial stage, 30 min to 6 hr after ingestion, consists of profuse vomiting and diarrhea (often bloody), abdominal pain, and significant volume losses leading to potential hypovolemic shock. Patients who do not develop GI symptoms within 6 hr of ingestion are unlikely to develop serious toxicity. The 2nd stage, 6-24 hr after ingestion, is often referred to as the "quiescent phase," as GI symptoms typically have resolved. However, careful clinical exam can reveal subtle signs of hypoperfusion, including tachycardia, pallor, and fatigue. During the 3rd stage, occurring 12-36 hr after ingestion, patients develop multisystem organ failure, shock, hepatic and cardiac dysfunction, acute lung injury or acute respiratory distress syndrome (ARDS), and profound metabolic acidosis. Death occurs most commonly during this stage. In patients who survive, the 4th stage (4-6 wk after ingestion) is marked by formation of strictures and signs of GI obstruction.

Symptomatic patients and patients with a large exposure by history should have serum iron levels drawn 4-6 hr after ingestion. Serum iron concentrations of <500 μg/dL 4-8 hr after ingestion suggest a low risk of significant toxicity, whereas concentrations of >500 μg/dL indicate that significant toxicity is likely. Additional lab evaluation in the ill patient should include arterial blood gas, complete blood count, serum glucose level, liver function tests, and coagulation parameters. Careful attention should be paid to ongoing monitoring of the patient's hemodynamic status. An abdominal x-ray might reveal the presence of iron tablets, though not all formulations of iron are radiopaque.

Treatment. Close clinical monitoring, combined with aggressive supportive and symptomatic care, is essential to the management of iron poisoning. Activated charcoal does not adsorb iron, and WBI remains the decontamination strategy of choice. Deferoxamine, a specific chelator of iron, is the antidote for moderate to severe iron intoxication (see Table 63-7). Indications for deferoxamine treatment include a serum iron concentration of >500 μg/dL or moderate to severe symptoms of toxicity, regardless of serum iron concentration. Deferoxamine is preferably given via continuous IV infusion at a rate of 15 mg/kg/hr. Hypotension is a common side effect of deferoxamine infusion and is managed by slowing the rate of the infusion and administering fluids and/or vasopressors as needed. Prolonged deferoxamine infusion (>24 hr) has been associated with pulmonary toxicity (ARDS) and *Yersinia* sepsis. The deferoxamine–iron complex can color the urine reddish ("vin rosé"), although this is an unreliable indicator of iron excretion. Clear end points for deferoxamine chelation are not well defined, but therapy is typically continued until clinical symptoms resolve. Consultation with a poison control center or medical toxicologist can yield guidelines for discontinuing deferoxamine.

Oral Hypoglycemics

Oral medications used in the management of type 2 diabetes include sulfonylureas, biguanides (e.g., metformin), thiazolidinediones, and meglitinides. Of these, only the sulfonylureas and meglitinides have the potential to cause profound hypoglycemia in both diabetic and nondiabetic patients. These classes of medications are widely prescribed and thus readily available for both unintentional and intentional exposures. In toddlers, ingestion of a single sulfonylurea tablet can lead to significant toxicity.

Pathophysiology. Sulfonylureas work primarily by enhancing endogenous insulin secretion. In binding to the sulfonylurea receptor, these drugs induce closure of potassium channels, leading to membrane depolarization, opening of calcium channels, and stimulation of calcium-mediated insulin release. Even in therapeutic use, the duration of hypoglycemic action can last up to 24 hr.

Clinical and Laboratory Manifestations. Hypoglycemia and symptoms associated with hypoglycemia are the primary clinical manifestations of sulfonylurea toxicity. These signs and symptoms can include diaphoresis, tachycardia, lethargy, irritability, coma, seizures, and even focal neurologic findings. As with other hyperinsulinemic states, sulfonylurea overdoses are associated with a nonketotic hypoglycemia. In the majority of cases, hypoglycemia develops within 6 hr of ingestion but can be delayed up to 16-18 hr after ingestion. Toddlers are particularly susceptible to hypoglycemia during an overnight fast.

Treatment. Patients with symptomatic hypoglycemia should be promptly treated with dextrose. In patients with mild symptoms, oral dextrose may be sufficient. However, patients with severe symptoms or profound hypoglycemia should be treated with a bolus of IV dextrose. Continuous dextrose infusions and repeated IV dextrose boluses should be avoided if possible, because this can stimulate further insulin release and lead to recurrent and prolonged hypoglycemia. Instead, the preferred antidote for symptomatic sulfonylurea toxicity is octreotide (see Table 63-7). Octreotide is a somatostatin analog that works via inhibiting insulin release. Octreotide is given IV or SC, typically in doses of 1-2 μg/kg (50-100 μg in adults) every 6-8 hr.

Given the potential for significant hypoglycemia, toddlers with witnessed or suspected sulfonylurea ingestions should be admitted to the hospital for monitoring and serial glucose measurements, at least for 12 hr, including an overnight fast. Patients of any age who develop hypoglycemia are also candidates for admission given the prolonged duration of hypoglycemic activity. Prophylactic IV dextrose infusions are not recommended because they can mask the symptoms of toxicity and stimulate further insulin secretion. Patients who require IV dextrose and/or octreotide should be monitored until they can demonstrate euglycemia for at least 8 hr off of all therapy.

With the increasing numbers of adolescents with type 2 diabetes, pediatricians should be familiar with the toxic effects of metformin as well. Although this agent does not cause hypoglycemia, its association with lactic acidosis is well documented (Metformin Associated Lactic Acidosis–MALA). This state typically arises after a large overdose in which the agent interferes with the liver's ability to clear lactic acid. Dangerously high serum lactate levels can result, leading to hemodynamic instability. Hemodialysis is usually the best option for patients with severe metformin-associated lactic acidosis.

Psychiatric Medications: Antidepressants

Selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, sertraline, paroxetine, citalopram) are the most commonly prescribed class of antidepressants. This trend results in large part from their wide therapeutic index and more favorable side-effect profile when compared to older agents such as tricyclic antidepressants (TCAs; amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, imipramine) and monoamine oxidase inhibitors. Newer agents include the serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine) and other atypical antidepressants (e.g., bupropion).

Tricyclic Antidepressants. Although TCAs are now prescribed less commonly for depression, they remain in use for a variety of other conditions, including chronic pain syndromes, enuresis, attention-deficit/hyperactivity disorder, and obsessive compulsive disorder. TCAs can cause significant toxicity in children, even with ingestion of 1 or 2 pills (10-20 mg/kg).

Pathophysiology. TCAs achieve their desired antidepressant effects primarily via blockade of norepinephrine and serotonin reuptake. TCAs have complex interactions with other receptor types. Antagonism at muscarinic acetylcholine receptors leads to clinical features of the anticholinergic toxidrome. Antagonism at peripheral α-receptors leads to hypotension and syncope. Key to the toxicity of TCAs is their ability to block fast sodium channels, leading to impaired cardiac conduction and arrhythmias.

Clinical and Laboratory Manifestations. Cardiovascular and CNS symptoms dominate the clinical presentation of TCA toxicity. Symptoms typically develop within 1-2 hr of ingestion, and serious toxicity usually manifests within 6 hr of ingestion. Patients can have an extremely rapid progression from mild symptoms to life-threatening dysrhythmias. Patients often develop features of the anticholinergic toxidrome, including delirium, mydriasis, dry mucous membranes, tachycardia, hyperthermia, urinary retention, and slow GI motility. CNS toxicity can include lethargy, coma, myoclonic jerks, and seizures. Sinus tachycardia is the most common cardiovascular manifestation of toxicity; however, patients can develop widening of the QRS complex, premature ventricular contractions, and ventricular arrhythmias. Refractory hypotension is a poor prognostic indicator and is the most common cause of death in TCA overdose.

An ECG is a readily available bedside test that can help determine the diagnosis and prognosis of the TCA-poisoned patient (Fig. 63-2). A QRS duration of >100 msec identifies patients who are at risk for seizures and cardiac arrhythmias. An R wave in lead aVR of ≥3 mm is also an independent predictor of toxicity. Both of these ECG parameters are superior to measured serum TCA concentrations in identifying patients at risk for serious toxicity, and obtaining levels is rarely helpful in management of the acutely ill patient.

Treatment. Initial attention should be directed to supporting vital functions, including airway and ventilation support as needed. Gastric decontamination can be accomplished with activated charcoal in appropriate patients. Treating clinicians should obtain an ECG as soon as possible and follow serial ECGs to monitor for progression of toxicity.

Four primary effects seen at the bedside, along with their treatment recommendations, are listed here:

1. ***Altered mental status:*** TCA-poisoned patients can become deeply comatose relatively quickly, so careful and prompt attention to the airway and placement of an endotracheal tube is of paramount importance. The airway should be secured prior to any GI decontamination efforts.
2. ***Widened QRS on the ECG:*** TCAs (along with other agents such as diphenhydramine, cocaine, etc) will block the fast sodium channels on the myocardial cells, slowing the upstroke of the QRS complex. Because the effect on sodium channels is greatest within the 1st 6 hr, frequent ECGs (i.e., every 20-30 min) during this time frame are important. As the QRS approaches 160 msec, the chance of the patient developing monomorphic ventricular tachycardia rises to 30%. Sodium, usually in the form of sodium bicarbonate, is the antidote of choice. *Indications for sodium bicarbonate include a QRS duration ≥110 msec, ventricular dysrhythmias, and hypotension*. Multiple bolus doses of sodium bicarbonate, 1-2 mEq/kg each, may be needed to narrow the QRS to <110 msec. Some authors prefer to then place the patient on an infusion of sodium bicarbonate, but this may not be necessary if careful attention is paid to the QRS after the initial doses and repeat bolus dosing is provided as needed during those 1st 6-12 hr. Hypertonic (3%) saline and/or lipid emulsion therapy may be beneficial in refractory cases.
3. ***Hypotension:*** A direct acting vasopressor, such as norepinephrine or epinephrine, is the agent of choice. Boluses of intravenous crystalloid fluids should be used with caution to prevent fluid overload.
4. ***Seizures:*** Likely a result of the anticholinergic effects of TCAs, seizures are relatively common, typically brief, and should be treated with agents the work on the γ-aminobutyric acid receptor complex in the brain. Benzodiazepines are the agent of choice.

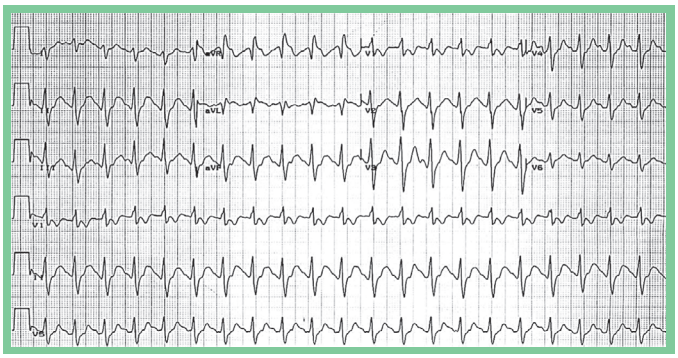

Figure 63-2 Electrocardiographic findings in tricyclic antidepressant toxicity. Note the tachycardia, widened QRS interval (144 msec), and prominent R wave in lead aVR. These findings are consistent with blockade of fast sodium channels.

Asymptomatic children should receive appropriate decontamination and be observed with continuous cardiac monitoring and serial ECGs for at least 6 hr. If any manifestations of toxicity develop, the child should be admitted to a monitored setting. Children who remain completely asymptomatic with normal serial ECGs may be candidates for discharge after 6 hr of close observation.

Selective Serotonin Reuptake Inhibitors. In overdose, SSRIs are considerably less toxic than TCAs. SSRIs are unlikely to cause significant toxicity in exploratory ingestions. Some data suggest that initiating SSRI therapy is associated with an increased risk of suicidal ideation and behavior (see Chapter 21).

Pathophysiology. SSRIs selectively block the reuptake of serotonin in the CNS. In contrast to TCAs and atypical antidepressants, SSRIs do not directly interact with other receptor types.

Clinical and Laboratory Manifestations. In overdose, the principal manifestations of toxicity are sedation and tachycardia. Cardiac conduction abnormalities (primarily QTc prolongation) and seizures have been described in significant overdoses, especially after ingestions of citalopram. An ECG should be part of the initial assessment after SSRI ingestion. Serum creatine kinase levels are almost always elevated in a patient with clinically significant serotonin syndrome.

Although development of the **serotonin syndrome** is seen more often after therapeutic use or overdose of several serotonergic agents in combination, it has also been described in ingestions of SSRIs alone (Table 63-11). Clinically, serotonin syndrome describes a spectrum of altered mental status, autonomic instability, fever, and neuromuscular hyperactivity (hyperreflexia, tremors, clonus in the lower extremities more than the upper extremities). One or all of these signs may be present to varying degrees.

Treatment. Initial management includes a careful assessment for signs and symptoms of serotonin syndrome and an ECG. Most patients simply require supportive care and observation until their mental status improves and tachycardia, if present, resolves. Management of serotonin syndrome is directed by the severity of symptoms; possible therapeutic interventions include benzodiazepines in mild cases and intubation, sedation, and paralysis in patients with severe manifestations (e.g., significant hyperthermia). Because agonism at the 5-HT_{2A} serotonin receptor is thought to be primarily responsible for the development of serotonin syndrome, use of the $5HT_{2A}$ receptor antagonist cyproheptadine is also beneficial. Cyproheptadine is only available in an oral form.

Atypical Antidepressants. The class known as atypical antidepressants includes agents such as venlafaxine and duloxetine (serotonin and norepinephrine reuptake inhibitors), bupropion (dopamine, norepinephrine, and some serotonin reuptake blockade), and

Table 63-11 Drugs Associated with the Serotonin Syndrome

DRUG TYPE	DRUGS
Selective serotonin reuptake inhibitors	Sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram
Antidepressant drugs	Trazodone, nefazodone, buspirone, clomipramine, venlafaxine
Monoamine oxidase inhibitors	Phenelzine, moclobemide, clorgyline, isocarboxazid
Anticonvulsants	Valproate
Analgesics	Meperidine, fentanyl, tramadol, pentazocine
Antiemetic agents	Ondansetron, granisetron, metoclopramide
Antimigraine drugs	Sumatriptan
Bariatric medications	Sibutramine
Antibiotics	Linezolid (a monoamine oxidase inhibitor), ritonavir (through inhibition of cytochrome P450 enzyme isoform 3A4)
Nonprescription cough and cold remedies	Dextromethorphan
Drugs of abuse	Methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products	Tryptophan, *Hypericum perforatum* (St. John's wort), *Panax ginseng* (ginseng)
Other	Lithium

From Boyer EW, Shannon M: The serotonin syndrome, N Engl J Med *352:1112–1120, 2005.*

trazodone (serotonin reuptake blockade and peripheral α-receptor antagonism). The variable receptor affinities of these agents lead to some distinctions in their clinical manifestations and management.

Clinical and Laboratory Manifestations. In overdose, venlafaxine and other serotonin and norepinephrine reuptake inhibitors are associated with cardiac conduction defects, including QRS and QTc prolongation, and seizures. Bupropion is one of the most common etiologies of toxicant-induced seizures in the United States. After ingestion of sustained or extended-release preparations, seizures can occur as late as 18-20 hr after ingestion. In addition, bupropion can cause tachycardia, agitation, and QRS and QTc prolongation. The structure of bupropion contains an amphetamine moiety, which can cause a false-positive result on the urine amphetamine screen. In addition to sedation and signs of serotonin excess, trazodone overdose may be associated with hypotension from blockade of peripheral α-receptors.

Treatment. Management is directed to clinical signs and symptoms. QRS interval prolongation may be treated with IV sodium bicarbonate as described in detail earlier. Seizures are often brief and self-limited, but they can be treated with benzodiazepines if necessary. Trazodone-associated hypotension typically responds to fluids, though it can require vasopressors in extreme cases. Because of the potential for delayed seizures, patients who ingest a sustained-release preparation of bupropion should be admitted to a monitored setting for at least 20-24 hr of observation.

Monoamine Oxidase Inhibitors. Monoamine oxidase inhibitors are now rarely used therapeutically; however, they remain important agents to know about given their potential for serious and delayed toxicity. Ingestions of as little as 1 or 2 pills (6 mg/kg) are associated with toxicity in children. Clinical manifestations initially include hypertension, hyperthermia, tachycardia, muscle rigidity, and seizures followed up to 24 hr later by hemodynamic instability and cardiovascular collapse. *Any child who ingests a monoamine oxidase inhibitor should be admitted to a monitored setting for at least 24 hr, regardless of symptoms.* Management includes blood pressure control, cooling and benzodiazepines for hyperthermia, serial monitoring of creatine kinase and renal function, and fluid and vasopressor therapy for hemodynamic instability.

Psychiatric Medications: Antipsychotics

Clinicians are increasingly prescribing antipsychotic medications in the pediatric population. Antipsychotic medications are commonly classified as either typical or atypical. In general, typical agents are associated with more side effects and toxicity than the atypical agents.

Pathophysiology. Typical or traditional antipsychotics (i.e., haloperidol, droperidol, thioridazine, chlorpromazine, and fluphenazine) are characterized by their antagonism at D_2 dopamine receptors. In therapeutic use, these agents are associated with extrapyramidal symptoms, tardive dyskinesia, and development of the neuroleptic malignant syndrome (NMS). The atypical agents (i.e., aripiprazole, clozapine, quetiapine, risperidone, ziprasidone) were developed with less dopamine (D_2-receptor) antagonism in efforts to avoid these side effects and improve their efficacy in managing the "negative" symptoms of schizophrenia. Instead, these agents have complex and varied interactions with multiple receptor types, including α-receptors, serotonin receptors, muscarinic acetylcholine receptors, and histamine receptors.

Clinical and Laboratory Manifestations. Typical antipsychotic toxicity commonly includes sedation, tachycardia, and prolongation of the QTc interval. Patients can present with acute dystonia, akathisia, and NMS, although these are seen less commonly in acute overdoses than in therapeutic use. The phenothiazines (e.g., thioridazine) can cause widening of the QRS interval owing to blockade of fast sodium channels. Clinically, NMS can be difficult to distinguish from serotonin syndrome.

Although the presentation of atypical antipsychotic toxicity can vary based on the receptor affinities of the specific agent, sedation, tachycardia, and QTc prolongation are common. Peripheral α-receptor blockade (e.g., with quetiapine) is associated with hypotension. In therapeutic use, clozapine is associated with agranulocytosis.

Diagnostic testing should include an ECG. Patients with hyperthermia or muscle rigidity should have a serum creatine kinase level sent to monitor for possible rhabdomyolysis. Antipsychotic levels are not readily available and are not helpful in managing acute poisoning.

Management. Initial management involves assessing and supporting vital functions. In some patients, CNS depression may be so profound as to require intubation for airway control. Acute dystonia is treated with diphenhydramine, benztropine, and sometimes benzodiazepines. Management of NMS includes conscientious supportive care, IV fluids, cooling, benzodiazepines, and bromocriptine or dantrolene in severe cases. QTc prolongation is managed with repletion of electrolytes (especially calcium, magnesium, and potassium), continuous cardiac monitoring, overdrive pacing, IV magnesium sulfate and/or defibrillation if the patient develops torsades de pointes. Seizures typically are well controlled with benzodiazepines. Hypotension usually responds to boluses of IV fluids, though vasopressor therapy is necessary in some cases.

Household Products

Caustics

Caustics include acids and alkalis as well as a few common oxidizing agents (see Chapter 327). Strong acids and alkalis can produce severe injury even in small-volume ingestions.

Pathophysiology. Alkalis produce a liquefaction necrosis, allowing further tissue penetration of the toxin and setting the stage for possible perforation. Acids produce a coagulative necrosis, which limits further tissue penetration, though perforation can still occur. The severity of the corrosive injury depends on the pH and

concentration of the product as well as the length of contact time with the product. Agents with a pH of <2 or >12 are most likely to produce significant injury.

Clinical Manifestations. Ingestion of caustic materials can produce injury to the oral mucosa, esophagus, and stomach. Patients can have significant esophageal injury even in the absence of visible oral burns. Symptoms include pain, drooling, vomiting, abdominal pain, and difficulty swallowing or refusal to swallow. Laryngeal injury can manifest as stridor and respiratory distress, necessitating intubation. In the most severe cases, patients can present in shock after perforation of a hollow viscus. Circumferential burns of the esophagus are likely to cause strictures when they heal, which can require repeated dilation or surgical correction and long-term follow-up for neoplastic changes in adulthood (see Chapter 327.2). Caustics on the skin or in the eye can cause significant tissue damage.

Treatment. Initial treatment of caustic exposures includes thorough removal of the product from the skin or eye by flushing with water. Emesis and lavage are contraindicated. Activated charcoal should not be used because it does not bind these agents and can predispose the patient to vomiting and subsequent aspiration. Stridor or other signs of respiratory distress should alert the provider to the need for a thorough evaluation of the airway for potential intubation or surgical airway management. Endoscopy can be performed within 12-24 hr of ingestion for prognostic and diagnostic purposes in symptomatic patients or those in whom injury is suspected on the basis of history and known characteristics of the ingested product. Endoscopy is contraindicated in any patient with signs of peritonitis. The use of corticosteroids or prophylactic antibiotics is not beneficial.

Cholinesterase-Inhibiting Insecticides

The most commonly used insecticides are organophosphates and carbamates; both are inhibitors of cholinesterase enzymes (acetylcholinesterase, pseudocholinesterase, and erythrocyte acetylcholinesterase). Most pediatric poisonings occur as the result of unintentional exposure to insecticides in and around the home or farm. The class of chemical warfare weapons known as "nerve agents" are also organophosphate compounds with a similar mechanism of action, but much greater potency.

Pathophysiology. Organophosphates and carbamates produce toxicity by binding to and inhibiting acetylcholinesterase, preventing the degradation of acetylcholine and resulting in its accumulation at nerve synapses. If left untreated, organophosphates form an irreversible bond to acetylcholinesterase, permanently inactivating the enzyme. This process, called *aging*, occurs over a variable time period depending on the characteristics of the specific organophosphate. Afterwards, a period of weeks to months is required to regenerate inactivated enzymes. In contrast, carbamates form a temporary bond to the enzymes, typically allowing reactivation of acetylcholinesterase within 24 hr.

Clinical and Laboratory Manifestations. Clinical manifestations of organophosphate and carbamate toxicity relate to the accumulation of acetylcholine at peripheral nicotinic and muscarinic synapses and in the CNS. Symptoms of carbamate toxicity are usually less severe than those seen with organophosphates. A commonly used mnemonic for the symptoms of cholinergic excess at muscarinic receptors is ***DUMBBELS***, which stands for *d*iarrhea/defecation, *u*rination, *m*iosis, *b*ronchorrhea/*b*ronchospasm, *b*radycardia, *e*mesis, *l*acrimation, and *s*alivation. Nicotinic signs and symptoms include muscle weakness, fasciculation, tremors, hypoventilation (diaphragm weakness), hypertension, tachycardia, and dysrhythmias. Severe manifestations include coma, seizures, shock, arrhythmias, and respiratory failure.

Diagnosis of poisoning is based primarily on history and physical exam findings. Red blood cell cholinesterase and pseudocholinesterase activity levels can be measured in the laboratory. These are only helpful when compared to the patient's known baseline. As such, these assessments are typically limited to farm workers undergoing ongoing occupational surveillance.

Treatment. Basic decontamination should be performed, including washing all exposed skin with soap and water and immediately removing all exposed clothing. Activated charcoal is unlikely to be of benefit as these are liquids that are rapidly absorbed. Basic supportive care should be provided, including fluid and electrolyte replacement and intubation and ventilation if necessary. The use of succinylcholine for rapid sequence intubation should be avoided as this paralytic is metabolized by the same cholinesterase enzymes now poisoned, leading to prolonged paralysis.

Two antidotes are useful in treating cholinesterase inhibitor poisoning: atropine and pralidoxime (see Table 63-7). Atropine, which antagonizes the muscarinic acetylcholine receptor, is useful for both organophosphate and carbamate intoxication. Often, large doses of atropine must be administered by intermittent bolus or via continuous infusion to control symptoms. Atropine dosing is primarily targeted to drying the respiratory secretions. Pralidoxime breaks the bond between the organophosphate and the enzyme, reactivating acetylcholinesterase. Pralidoxime is only effective if it is used before the bond ages and becomes permanent. Pralidoxime is not necessary for carbamate poisonings because the bond between the insecticide and the enzyme degrades spontaneously.

Without treatment, symptoms of organophosphate poisoning can persist for weeks, requiring continuous supportive care. Even with treatment, some patients develop a delayed polyneuropathy and a range of chronic neuropsychiatric symptoms.

Hydrocarbons

Hydrocarbons include a wide array of chemical substances found in thousands of commercial products. Specific characteristics of each product determine whether exposure will produce systemic toxicity, local toxicity, both, or neither. Nevertheless, aspiration of even small amounts of certain hydrocarbons can lead to serious, potentially life-threatening toxicity.

Pathophysiology. The most important manifestation of hydrocarbon toxicity is aspiration pneumonitis via inactivation of the type II pneumocytes and resulting surfactant deficiency (see Chapter 397). Aspiration usually occurs during coughing and gagging at the time of ingestion or vomiting after the attempted ingestion of an aliphatic hydrocarbon. The propensity of a hydrocarbon to cause aspiration pneumonitis is inversely proportional to its viscosity, and directly proportional to its volatility. Compounds with low viscosity and high volatility, such as mineral spirits, naphtha, kerosene, gasoline, and lamp oil, spread rapidly across surfaces and cover large areas of the lungs when aspirated. Only small quantities (<1 mL) of such chemicals need be aspirated to produce significant injury. Pneumonitis does not result from dermal absorption of hydrocarbons or from ingestion in the absence of aspiration. Gasoline and kerosene are poorly absorbed, but they often cause considerable irritation of the GI mucosa as they pass through the intestines.

Certain hydrocarbons have unique toxicities and can cause symptoms after ingestion, inhalation, or dermal exposures. Several chlorinated solvents, most notably carbon tetrachloride, can produce hepatic toxicity. Methylene chloride, found in some paint removers, is metabolized to carbon monoxide. Benzene is known to cause cancer, most commonly acute myelogenous leukemia, after long-term exposure. Nitrobenzene, aniline, and related compounds can produce methemoglobinemia. A number of volatile hydrocarbons, including toluene, propellants, refrigerants, and volatile nitrites, are commonly abused by inhalation. Some of these substances, principally the halogenated hydrocarbons (which contain a chlorine, bromine, or fluorine), can sensitize the myocardium to the effects of endogenous catecholamines. This can result in dysrhythmias and "sudden sniffing death." Chronic abuse of these agents can lead to cerebral atrophy, neuropsychologic changes, peripheral neuropathy, and kidney disease (see Chapter 114).

Clinical and Laboratory Manifestations. Transient, mild CNS depression is common after hydrocarbon ingestion or inhalation. Aspiration is characterized by coughing, which usually is the first clinical finding. Chest radiographs may initially be normal, but they often show abnormalities within 6 hr of exposure in patients who have aspirated. Respiratory symptoms can remain mild or progress rapidly to ARDS and respiratory failure. Fever and leukocytosis are common accompanying signs in patients with pneumonitis and don't necessarily

imply bacterial superinfection. Chest radiographs can remain abnormal long after the patient is clinically normal. Pneumatoceles can appear on the chest radiograph 2-3 wk after exposure.

After inhalational exposures to halogenated hydrocarbons, patients can present with ventricular dysrhythmias, often refractory to conventional management. Recurrent inhalation of the aromatic hydrocarbon toluene can lead to a type IV renal tubular acidosis.

Treatment. Emesis and lavage are contraindicated given the risk of aspiration. Activated charcoal is not useful because it does not bind the common hydrocarbons and can also induce vomiting. If hydrocarbon-induced pneumonitis develops, respiratory treatment is supportive (see Chapter 397). Neither corticosteroids nor prophylactic antibiotics have shown any clear benefit. Standard mechanical ventilation, high-frequency ventilation, and extracorporeal membrane oxygenation have all been used to manage the respiratory failure and ARDS associated with severe hydrocarbon-induced pneumonitis.

Patients with dysrhythmias in the setting of halogenated hydrocarbon inhalation should be treated with β blockers (usually esmolol) to block the effects of endogenous catecholamines on the sensitized myocardium.

Toxic Alcohols

Methanol is commonly found in windshield washer fluids, deicers, paint removers, fuel additives, liquid fuel canisters, and industrial solvents. *Ethylene glycol* is commonly found in antifreeze. Unintentional ingestion is the most common exposure in children, and small-volume ingestions of concentrated products can theoretically cause toxicity. The pathophysiology, acid–base derangements, and treatment of both chemicals are similar, although they differ in their primary end-organ toxicity. In both cases, the metabolites of the parent compounds are responsible for the serious clinical effects that can follow exposure.

Isopropyl alcohol (rubbing alcohol, hand sanitizers) causes intoxication similar to that associated with ethanol but can also cause a hemorrhagic gastritis and myocardial depression in massive ingestions. Unlike ethylene glycol and methanol, isopropyl alcohol is metabolized to a ketone and does not cause a metabolic acidosis. Management is similar to that of ethanol ingestions (see Chapter 114) and is not further discussed here.

Methanol.

Pathophysiology. Methanol is oxidized in the liver by alcohol dehydrogenase to formaldehyde, which is further oxidized to formic acid by aldehyde dehydrogenase. Toxicity is caused primarily by formic acid, which inhibits mitochondrial respiration.

Clinical and Laboratory Manifestations. Drowsiness, mild inebriation, nausea, and vomiting develop early after ingestion. The onset of serious effects, including profound metabolic acidosis and visual disturbances, is often delayed for up to 12-24 hr as the parent methanol is undergoing metabolism to its toxic metabolites. This metabolism is further slowed if ethanol has also been ingested, since the liver will preferentially metabolize ethanol. Visual disturbances include blurred or cloudy vision, constricted visual fields, decreased acuity, and the "feeling of being in a snowstorm" appear only after acidosis is well established. These visual defects may be reversible if treated early, but untreated they can lead to permanent blindness. On exam, dilated pupils, retinal edema, and optic disc hyperemia may be noted. Initially, patients have an elevated osmolar gap and then develop an anion gap metabolic acidosis as the parent compound is metabolized to formic acid.

In young children, determining if a significant exposure has occurred is usually difficult based on history. Methanol blood levels are available at some laboratories and should be sent after a concerning exposure. If methanol blood levels are not readily available, estimation of an osmolar gap may be used as a surrogate marker, but a normal osmolar gap does not rule out ingestion of any alcohol. Serum osmolality is measured by the freezing point depression method and compared with a calculated serum osmolarity.

Treatment. Treatment is as discussed for ethylene glycol toxicity.

Ethylene Glycol.

Pathophysiology. Ethylene glycol is oxidized by alcohol dehydrogenase in the liver to glycoaldehyde, which is further converted to glycolic acid by aldehyde dehydrogenase. Glycolic acid is responsible for the metabolic acidosis, and is further metabolized to glyoxylic and then to oxalic acid. Oxalic acid combines with serum and tissue calcium, forming calcium oxalate crystals that deposit throughout the body, especially in the renal parenchyma, leading to acute tubular necrosis.

Clinical and Laboratory Manifestations. Early symptoms include nausea, vomiting, CNS depression, and inebriation. Delayed manifestations include an anion gap metabolic acidosis, hypocalcemia, and acute kidney injury. Even later, patients can develop cranial nerve palsies.

Both ethylene glycol and methanol are capable of producing profound, life threatening metabolic acidosis and acidemia, with measured serum bicarbonates that may even be nondetectable. The onset of the acidosis is delayed up to 4-12 hr after ethylene glycol ingestion, and may be delayed further with any concomitant ingestion of ethanol. Ethylene glycol blood concentrations are technically difficult to perform and are available only at some larger reference laboratories. In the absence of readily available ethylene glycol concentrations, calculation of the osmolar gap may be helpful as a surrogate marker.

Examination of the urine with a Wood lamp is neither sensitive nor specific for ethylene glycol ingestion. The earliest sign on a urinalysis of ethylene glycol poisoning is usually hematuria. Calcium oxalate crystals can be seen on urine microscopy but might not be evident early after exposure. Electrolytes (including calcium), acid–base status, kidney function, and ECG should be closely monitored in poisoned patients.

Treatment. Because methanol and ethylene glycol are rapidly absorbed, gastric decontamination is generally not of value. The classic antidote for methanol and ethylene glycol poisoning was ethanol, a preferential substrate for alcohol dehydrogenase, thus preventing the metabolism of parent compounds to toxic metabolites. *Fomepizole* (see Table 63-7), a potent competitive inhibitor of alcohol dehydrogenase, has almost entirely replaced the use of ethanol owing to its ease of administration, lack of CNS and metabolic effects, and overall excellent patient tolerability profile. As with all poisons, a serum concentration must be interpreted along with the time removed from exposure. A patient with a methanol level of 20 mg/dL 24 hr after exposure had a much larger dose than a patient with the same level only 1 hr after ingestion. Indications for fomepizole include ethylene glycol or methanol level >20 mg/dL, history of potentially toxic ingestion (e.g., any intentional overdose), or history of ingestion with evidence of acidosis. There are few disadvantages to giving the initial dose of fomepizole to patients with a concerning history of ingestion or lab findings, and given the dosing schedule of fomepizole (every 12 hr), this strategy buys the clinician time to confirm or exclude the diagnosis before giving a second dose. Adjunctive therapy includes folate (methanol toxicity), pyridoxine (ethylene glycol toxicity) and sodium bicarbonate infusions for both (if acidemic). If a child has had an unintentional exposure and a level of the alcohol cannot be obtained, a reasonable approach is to follow serum chemistries every 4 hr until the child is 12 hr removed from the exposure. If the bicarbonate level on the chemistry panel does not fall in that time frame, then a toxic exposure is unlikely (assuming no ethanol is present).

Hemodialysis effectively removes ethylene glycol, methanol, and their metabolites (except calcium oxalate) and corrects acid–base and electrolyte disturbances. Fomepizole should be given both before and immediately after dialysis. Indications for dialysis include a methanol level of >50 mg/dL, acidosis, severe electrolyte disturbances, and renal failure. However, in the absence of acidosis and kidney failure, even massive ethylene glycol ingestions have been managed without dialysis. Methanol is another story, because its elimination in the setting of alcohol dehydrogenase inhibition is very prolonged, thus often warranting dialysis to remove the parent compound. Therapy (fomepizole and/or dialysis) should be continued until ethylene glycol and methanol levels are <20 mg/dL. While the visual effects from

methanol poisoning are usually permanent, the kidney injury from ethylene glycol injury is not. Patients requiring hemodialysis after ethylene glycol poisoning will almost always recover complete renal function within 2-6 wk. Consultation with a poison control center, medical toxicologist, and nephrologist may be helpful in managing toxic alcohol ingestions.

Plants

Exposure to plants, both inside the home and outside in backyards and fields, is one of the most common causes of unintentional poisoning in children. Fortunately, the majority of ingestions of plant parts (leaves, seeds, flowers) result in either no toxicity or mild, self-limiting effects. However, ingestion of certain plants (Table 63-12 outlines some of the most toxic plants) can lead to serious toxicity.

The potential toxicity of a particular plant is highly variable, depending on the part of the plant involved (flowers are generally less toxic than the root or seed), the time of year, growing conditions, and the route of exposure. Assessment of the potential severity after an exposure is also complicated by the difficulty in properly identifying the plant. Many plants are known by several common names, which can vary among communities. Poison control centers have access to professionals who can assist in properly identifying plants. They also are well versed in the common poisonous plants in their service area and the seasons when they are more abundant. For these reasons, consultation with the local poison control center may be very helpful in the management of these ingestions.

For potentially toxic plant ingestions, consider decontamination with activated charcoal in patients who present within 1-2 hr of ingestion; otherwise, treatment is primarily supportive and based on symptoms. The most common manifestation of toxicity after plant ingestion is GI upset, which can be managed with antiemetics and fluid and electrolyte support. Table 63-12 outlines management strategies for a few specific toxicities.

Toxic Gases

Carbon Monoxide

Although many industrial and naturally occurring gases pose a health risk by inhalation, the most common gas involved in pediatric exposures is carbon monoxide (CO). CO is a colorless, odorless gas produced during the combustion of any carbon-containing fuel. The less efficient the combustion, the greater the amount of CO produced. Wood-burning stoves, kerosene heaters, old furnaces or hot water heaters and automobiles are a few of the potential sources of CO, as is any closed space fire.

Pathophysiology. CO binds to hemoglobin with an affinity >200 times that of oxygen, forming carboxyhemoglobin (HbCO). In doing so, CO displaces oxygen and creates a conformational change in hemoglobin that impairs the delivery of oxygen to the tissues, leading to tissue hypoxia. HbCO levels are not well correlated with clinical signs of toxicity, likely because CO interacts with multiple proteins in addition to hemoglobin. CO binds to cytochrome oxidase, disrupting cellular respiration. CO displaces nitric oxide (NO) from proteins, allowing NO to bind with free radicals to form the toxic metabolite peroxynitrite. NO is also a potent vasodilator, in part responsible for clinical symptoms including headache, syncope, and hypotension.

Clinical and Laboratory Manifestations. Early symptoms are nonspecific and include headache, malaise, nausea, and vomiting. These symptoms are often misdiagnosed as indicating flu or food poisoning. At higher exposure levels, patients can develop mental status changes, confusion, ataxia, syncope, tachycardia, and tachypnea. Severe poisoning is manifested by coma, seizures, myocardial ischemia, acidosis, cardiovascular collapse, and potentially death. On exam, patients might have cherry-red skin. Emergency department evaluation should include an arterial or venous blood gas with HbCO determined by co-oximetry, and creatine kinase in severely poisoned patients, and an ECG in any patient with cardiac symptoms.

Treatment. In addition to general supportive care, treatment requires the administration of 100% oxygen to enhance elimination of CO. In ambient air, the average half-life of HbCO is 4-6 hr. This is dramatically reduced to 60-90 min by providing 100% oxygen at normal atmospheric pressures via a non-rebreather facemask. Severely poisoned patients might benefit from *hyperbaric oxygen (HBO),* which decreases the half-life of HbCO to 20-30 minutes. Though the clinical benefits and referral guidelines for HBO therapy remain controversial, commonly cited indications include syncope, coma, seizure, altered mental status, acute coronary syndrome, HbCO level >25%, abnormal cerebellar examination, and pregnancy. Consultation with a poison control center, medical toxicologist, or HBO facility can assist clinicians in determining which patients could benefit from HBO therapy. Sequelae of CO poisoning include persistent and delayed cognitive and cerebellar effects. HBO advocates believe that the risk of such sequelae is minimized through the delivery of 100% oxygen at 3 atmospheres of pressure. Patients are typically treated with oxygen, via either non-rebreather or a hyperbaric chamber, for between 6 and 24 hr. Prevention of CO poisoning should involve educational initiatives and the use of home CO detectors.

Hydrogen Cyanide

Pathophysiology. Cyanide inhibits cytochrome oxidase, part of the electron transport chain, interrupting cellular respiration and leading to profound tissue hypoxia. Patients may be exposed to hydrogen cyanide gas in the workplace (manufacturing of synthetic fibers, nitriles, and plastics) or via smoke inhalation in a fire.

Clinical and Laboratory Manifestations. Onset of symptoms is rapid after a significant exposure. Clinical manifestations of toxicity include headache, agitation and confusion, sudden loss of consciousness, tachycardia, cardiac dysrhythmias, and metabolic acidosis. Cyanide levels can be measured in whole blood, but they are not readily available at most institutions. A severe lactic acidosis (lactate >10 mmol/L) in fire victims suggests cyanide toxicity. Impaired oxygen extraction by tissues is implied by elevated mixed venous oxygen saturation, another laboratory finding suggesting cyanide toxicity.

Treatment. Treatment includes removal from the source of exposure, rapid administration of high concentrations of oxygen, and antidotal therapy. The cyanide antidote kit includes nitrites (amyl nitrite and sodium nitrite) used to produce methemoglobin, which then reacts with cyanide to form cyanomethemoglobin (see Table 63-7). The third part of the kit is sodium thiosulfate, given to hasten the metabolism of cyanomethemoglobin to hemoglobin and the less-toxic thiocyanate. In patients for whom induction of methemoglobinemia could produce more risk than benefit, the sodium thiosulfate component of the kit may be given alone. The FDA has approved *hydroxocobalamin* (a form of vitamin B_{12}) for use in known or suspected cyanide poisoning. This antidote reacts with cyanide to form the nontoxic cyanocobalamin, which is then excreted in urine. Side effects of hydroxocobalamin include red discoloration of the skin and urine, transient hypertension, and interference with colorimetric lab assays. *Overall, the safety profile of hydroxocobalamin appears superior to that of the cyanide antidote kit; thus this is now the preferred antidote for cyanide poisoning.*

Some Miscellaneous Toxic Agents Found in the Home

Single-Use Detergent Sacs

Commonly known as laundry "pods" for clothing, these products look like candy to many children. When bitten into, a relatively large dose of concentrated detergent is expelled under pressure onto the child's posterior pharynx and vocal cords. This can lead to stridor and other signs of respiratory distress. Occasionally, and for unknown reasons, these children may also develop altered mental status. Supportive care with attention to any airway and breathing issues is warranted. Admission to the hospital is often indicated. It should be noted, that these are not considered caustic ingestions. The pH of these products is in the neutral zone. As such, upper GI endoscopy is rarely indicated. Curiously, laundry detergent drank from a bottle is rarely of significant concern.

Table 63-12 Commonly Ingested Plants with Significant Toxic Potential

PLANT	SYMPTOMS	MANAGEMENT
Autumn crocus (*Colchicum autumnale*)	Vomiting Diarrhea Initial leukocytosis followed by bone marrow failure Multisystem organ failure	Activated charcoal decontamination Aggressive fluid resuscitation and supportive care
Belladonna alkaloids: jimson weed (*Datura stramonium*) Belladonna ("deadly nightshade"; *Atropa belladonna*)	Anticholinergic toxidrome Seizures	Supportive care, benzodiazepines Consider physostigmine if patient is a threat to self or others; only use if no conduction delays on ECG
Cardiac glycoside–containing plants (foxglove, lily of the valley, oleander, yellow oleander, etc)	Nausea Vomiting Bradycardia Dysrhythmias (AV block, ventricular ectopy) Hyperkalemia	Digoxin-specific Fab fragments
Jequirity bean and other abrin-containing species (e.g., rosary pea, precatory bean)	Oral pain Vomiting Diarrhea Shock Hemolysis Renal failure	Supportive care, including aggressive volume resuscitation and correction of electrolyte abnormalities
Monkshood (*Aconitum* species)	Numbness and tingling of lips/tongue Vomiting Bradycardia	Atropine for bradycardia Supportive care
Oxalate-containing plants: *Philodendron, Dieffenbachia, Colocasia* ("elephant ear")	Local tissue injury Oral pain Vomiting	Supportive care, pain control
Poison hemlock *(Conium maculatum)*	Vomiting Agitation followed by CNS depression Paralysis Respiratory failure	Supportive care
Pokeweed	Hemorrhagic gastroenteritis Burning of mouth and throat	Supportive care
Rhododendron	Vomiting Diarrhea Bradycardia	Atropine for symptomatic bradycardia Supportive care
Tobacco	Vomiting Agitation Diaphoresis Fasciculations Seizures	Supportive care
Water hemlock (*Cicuta* species)	Abdominal pain Vomiting Delirium Seizures	Supportive care, including benzodiazepines for seizures
Yew (*Taxus* species)	GI symptoms QRS widening Hypotension CV collapse	Supportive care Atropine for bradycardia Sodium bicarbonate does not appear to be effective

AV, atrioventricular; CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; Fab, fragment, antigen binding; GI, gastrointestinal.

Electric Dishwasher Detergent

Especially when in the form of crystals, these products are highly alkaline (pH >13) and exposure via ingestion can lead to significant burns to the vocal cords and GI tract. Admission for upper GI endoscopy is usually indicated.

Magnets

Most foreign body ingestions are allowed to pass through the GI tract once they are known to have passed into the stomach. However, ingestion of 2 or more magnets (unless they are very weak refrigerator style magnets) cause concern for bowel obstruction and/or perforation. Admission for attempted retrieval via endoscopy or clearance via WBI is to be considered.

Batteries

Any disk or button style battery lodged in the esophagus or airway should be considered a true emergency warranting immediate referral to an endoscopist for removal. These batteries can cause necrosis of the tissues to which they are lodged via continued electrical discharge and/or leaking of their contents (the former is likely the primary method of injury). Mucosal contact for even 2 hr might induce necrosis. Once past the lower esophageal sphincter, button or even larger batteries (e.g., AA, AAA size) can usually be allowed to pass through the GI tract with close follow up.

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Chapter 64

Complementary Therapies and Integrative Medicine

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Integrative medicine focuses on promoting physical, mental, emotional, spiritual, social, educational, and occupational well-being in the context of a medical home in a healthy family and community. The foundations of integrative medicine are health-promoting practices including optimal nutrition and dietary supplements to avoid deficiencies; avoiding intake of addictive substances such as nicotine and illicit drugs; physical activity, adequate sleep, a healthy environment, and supportive social relationships. Evidence-based complementary therapies such as herbal remedies and other dietary supplements, massage, chiropractic, and other forms of bodywork, yoga, tai chi, meditation practices, hypnosis, guided imagery, biofeedback, and acupuncture may also be used. Although prayer and healing rituals are sometimes included under the rubric of complementary and integrative therapies, they are not covered in this chapter.

Not including multivitamins and mineral supplements (such as iron and calcium), the estimated prevalence of complementary and alternative medicine use in the United States by youth younger than 18 yr of age in 2007 was 8.7 million; the most common therapies included natural products, chiropractic, and deep breathing. Use of complementary therapies is most common among youth with chronic, incurable, or recurrent conditions such as asthma, autism, cancer, depression, and pain. For example, complementary therapies were used by 42-71% of pediatric patients in a 2013 study of specialty outpatient clinics in Canada; the therapies most commonly used by these patients were dietary supplements. Side effects were uncommon and most were minor.

Table 64-1 Most Commonly Used Dietary Supplements in Pediatrics

PRODUCT	USES
VITAMINS	
B_2 (riboflavin)	Migraine headache prophylaxis
B_6 (pyridoxine)	Pyridoxine-dependent epilepsy; neuropathy; nausea associated with pregnancy
B_9 (folate)	Prevention of neural tube defects
D	Prevention of rickets; treatment of deficiencies
Multivitamins	General health promotion, ADHD
MINERALS	
Iodine (salt)	Prevent goiter and mental retardation
Iron	Prevent and treat iron deficiency
Magnesium	Constipation, asthma, migraine prevention
Zinc	Diarrhea in nutrient-poor populations
HERBS	
Aloe vera	Mild burns
Chamomile	Mild sedative, dyspepsia
Echinacea	Prevention of upper respiratory infections
Ginger	Nausea
Lavender (aromatherapy)	Mild sedative
Peppermint	Irritable bowel syndrome
Tea tree oil	Anti-bacterial (acne remedies), pediculicide (lice)
OTHER	
Melatonin	Insomnia
Omega-3 fatty acids (fish oil)	ADHD, allergies, inflammation, anxiety and mood disorders
Probiotics	Antibiotic-associated diarrhea; *Clostridium difficile*–associated diarrhea; constipation; irritable bowel syndrome; pouchitis; inflammatory bowel disorders

ADHD, attention-deficit/hyperactivity disorder.

DIETARY SUPPLEMENTS

Under the 1994 Dietary Supplement Health and Education Act, a dietary supplement is a product taken by mouth that contains a *dietary ingredient* intended to supplement the diet. These may include vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements are the most commonly used complementary therapies for children and adolescents (Table 64-1). Some uses are common and recommended, such as vitamin D supplements for breastfed infants and probiotics to prevent *Clostridium difficile*–associated diarrhea, whereas other uses are more controversial, such as using herbal products to treat otitis media.

In the United States, dietary supplements do not undergo the same stringent evaluation and postmarketing surveillance as prescription medications. Although they may not claim to prevent or treat specific medical conditions, product labels may make *structure–function* claims. For example, a label may claim that a product *promotes a healthy immune system*, but it may not claim to cure the common cold.

According to the 2007 National Health Interview Survey, 37% of children in the United States used dietary supplements, with the majority using multivitamin and mineral products (31%) exclusively. Use of dietary supplements is most common among children whose families have higher income and education and whose parents use them; among older children; and among those suffering from chronic conditions.

Despite this widespread use, many patients and their parents who use dietary supplements do not talk with their physician about their use. Several guidelines have called for more complete dietary supplement history taking by healthcare professionals. The Joint Commission recommends that clinicians routinely ask patients about their use of dietary supplements and include this information as part of the medication reconciliation process.

DIETARY SUPPLEMENT SAFETY

Dietary supplements may have safety issues in children, though toxicity is much less common with nonprescription dietary supplements than with prescription medications. Toxicity depends on dose, use of cotherapies, and the underlying medical condition of the child. Modern use of a dietary supplement (e.g., ephedra for weight loss) may not reflect its traditional use (e.g., ephedra as a component of a traditional Chinese medicine tea in small doses to improve allergic or respiratory symptoms). Moreover, herbs that are apparently safe for most adults may be more hazardous in specific conditions (e.g., newborns, patients with impaired renal or hepatic function), under special circumstances (e.g., after organ transplantation or other surgery), or when combined with prescription medications. Some natural products are toxic in and of themselves (Table 64-2). Acute hepatic toxicity and death can result from ingestion of even small amounts of *Amanita* mushrooms. Even when a product is safe when used correctly, it can cause mild or severe toxicity when used incorrectly. Although peppermint is a commonly used and usually benign gastrointestinal spasmolytic included in after-dinner mints, it can exacerbate gastroesophageal reflux. Probiotics are generally safe when taken orally, but in an immune-compromised patient in an ICU setting, they may (rarely) cause sepsis.

Table 64-2 Potentially Toxic Herbs

HERB	TOXIC CONSTITUENTS	TYPICAL USES	POTENTIAL ACUTE ADVERSE EFFECTS	HOW TO TREAT OVERDOSE
Aconitum (monkshood, wolfsbane)	**Diester alkaloids:** Hypaconitine and aconitine (aconitine increases permeability for sodium ions and slows down repolarization, leading to paralysis of the nerve)	Facial neuralgia and sciatica Headache and migraines Rheumatic pain, arthritis, gout Pericarditis sicca	Nausea, vomiting, hypersalivation **CNS:** Paresthesias, muscular weakness, dizziness, ataxia, seizures, coma **Cardiac:** Bradycardia, hypotension, rhythm disorders	Supportive care Dioxin-specific antibodies, unless history excludes cardiac glycosides Do not give ipecac Activated charcoal and gastric emptying might help Avoid type 1 antiarrhythmics
Artemisia absinthium (wormwood)	**Thujone and isothujone:** Neurotoxins	Anorexia Dyspeptic conditions Liver and gallbladder disorders	**Mental status changes:** Restlessness, vertigo, tremors, agitation, seizures, headache Vomiting; stomach and intestinal cramps Rhabdomyolysis and renal failure	Supportive care Benzodiazepines
Atropa belladonna (deadly nightshade) of atropine)	**Alkaloids:** Hyoscyamine (the L-isomer)	Gastrointestinal symptoms Cardiac insufficiency and arrhythmia Asthma	**Anticholinergic reaction:** Tachycardia, hyperthermia, mydriasis, urine and feces retention, restlessness Nervous system and respiratory depression	Gastric lavage Physostigmine given in consultation with a poison specialist External cooling if temperature is >38.9°C (102°F) Benzodiazepines Hydration
Ayurvedic herbal remedies	Contaminated with lead, mercury, or arsenic	Traditional medicine from India; many purposes	Acute or chronic heavy metal toxicity	Depends on heavy metal
Digitalis purpurea (foxglove)	**Cardioactive glycosides:** Purpurea glycoside, digitoxin	Ulcers, boils, headaches, abscesses, paralysis, cardiac insufficiency	Nausea and vomiting, headache, loss of appetite Cardiac rhythm disorders **CNS:** Stupor, confusion, visual disorders, depression, psychosis, hallucinations	Supportive care Gastric lavage Activated charcoal Treatment of symptoms
Ephedra sinica (ma huang) Common names: Miner's tea, Mexican tea, Desert herb	**Alkaloids:** Ephedrine, pseudoephedrine (stimulates sympathomimetic receptors and the CNS)	Decongestant for upper respiratory infection Asthma Weight loss Stimulant	**Cardiac:** Hypertension, cardiomyopathy, myocardial infarction, arrhythmias **CNS:** Dizziness, restlessness, headaches, anxiety, hallucinations, tremors, seizures, psychosis, strokes Nausea and vomiting Contraindicated in diabetes or hypertension, angle-closure glaucoma, anxiety, prostate adenoma, thyroid disease, pheochromocytoma	Activated charcoal Benzodiazepine for seizures and sedation Vasodilators for hypertension Lidocaine and β blockers for arrhythmias External cooling if temperature is >38.9°C (102°F) Hydration therapy
Illicium anisatum (Japanese star anise tea)	Anisatins; block γ-aminobutyric acid	Colic in Latino and Caribbean populations	Seizures, tonic postures, myoclonus, hyperexcitability, irritability	Recovery with supportive care within 48 hr
Lobelia inflata (lobelia)	**Piperidine alkaloid:** L-Lobeline (stimulates nicotinic receptors)	Expectorant Asthma Spasmolytic Emetic To induce mental clarity and a feeling of well-being	**Gastrointestinal:** Nausea and vomiting, abdominal pain, diarrhea **CNS:** Anxiety, headache, dizziness, tremors, seizures, paresthesias, euphoria **Cardiac:** Arrhythmias, bradycardia, transient increase in blood pressure, decreased respiratory rate In overdose, lobeline can cause hypotension. Diaphoresis, muscle fasciculations and weakness, tremors, respiratory depression Dermatitis	Supportive care Gastric emptying Activated charcoal Benzodiazepines

Continued

Table 64-2 Potentially Toxic Herbs—cont'd

HERB	TOXIC CONSTITUENTS	TYPICAL USES	POTENTIAL ACUTE ADVERSE EFFECTS	HOW TO TREAT OVERDOSE
Longdan xieganwan	Aristolochic acid	Enhance health	Renal interstitial fibrosis End-stage renal failure Renal cell carcinoma	Supportive care
Mentha pulegium (pennyroyal)	Pennyroyal oil has a hepatotoxic effect Acute poisoning is not found with proper administration of the designated therapeutic use of pennyroyal leaf; however, the drug is not recommended owing to hepatotoxicity	Insect repellent Respiratory illness Digestive disorders Emmenagogue Abortifacient Wound treatment Gout	Uterine contractions **Gastrointestinal:** Nausea, vomiting, abdominal pain, hepatitis **Neurotoxin:** Delirium, dizziness, convulsions, seizures, paralysis, encephalopathy, coma Renal failure and hypertension Shock and disseminated intravascular coagulation Contraindicated in pregnancy	Supportive care *N*-Acetylcysteine
Pausinystalia yohimbe (yohimbe)	Indole alkaloids **Yohimbe:** α_2-Adrenoreceptor antagonist	Sexual disorders Exhaustion Improve muscle function	**Adverse reactions:** Dizziness, headache, anxiety, hypertension, indigestion, rash, insomnia, tachycardia, tremor, vomiting, hallucinations, nervousness, paresthesias, hypothermia, salivation, mydriasis, diarrhea, palpations, tachycardia Contraindicated in kidney and liver disease	Gastric emptying Activated charcoal Antiarrhythmics Hydration
Phytolacca americana (pokeweed, American nightshade)	Triterpene saponins (irritate mucous membranes) Lectins (toxic)	Antiinflammatory Arthritis Cancer Emetic and cathartic Rheumatism	Dizziness, somnolence, nausea, vomiting, diarrhea, tachycardia, hemorrhagic gastritis, hypotension, lymphocytosis, headache, respiratory depression, seizures	Hydration therapy, electrolyte correction, gastric emptying Activated charcoal Electrolyte replacement Emesis should not be induced if patient is experiencing symptoms of overdose
Stramonium folium (jimsonweed)	**Alkaloids:** Hyoscyamine (the L-isomer of atropine)	Asthma and cough Diseases of the autonomic nervous system	In high doses, leads to restlessness, mania, hallucinations, delirium **Overdose:** Tachycardia, mydriasis, flushing, dry mouth, decreased sweating, miction, constipation	Supportive care Gastric lavage Decreasing temperature Physostigmine Benzodiazepines
Viscum album (mistletoe)	Alkaloids Viscotoxins *(Viscum album)* cause hypotension, bradycardia, and arterial vasoconstriction Lectins	Antineoplastic adjuvant Antihypertensive Nervous disorders: calmative agent Rheumatism Antispasmodic	Fever, headaches, nausea, vomiting, diarrhea, bradycardia, angina, change in blood pressure, seizures, confusion, hallucination, allergic reactions, miosis, mydriasis, chills, coma 2 reported deaths in the last 35 yr; most ingestions lead to mild reactions	Supportive therapy Data inconclusive for inducing emesis Activated charcoal

CNS, central nervous system.

Although there are good manufacturing practices for dietary supplements in the United States, dietary supplement labels might not accurately reflect the contents or concentrations of ingredients. Because of natural variability, variations of 10-1,000–fold have been reported for several popular herbs, even across lots produced by the same manufacturer. Herbal products may be unintentionally contaminated with pesticides, microbial agents or products, or the wrong herb that was misidentified during harvesting. Products from developing countries (e.g., Ayurvedic products from South Asia) might contain toxic levels of mercury, cadmium, arsenic, or lead, either from unintentional contamination during manufacturing or from intentional additions by producers who believe that these metals have therapeutic value. Approximately 30-40% of Asian patent medicines include potent pharmaceuticals, such as analgesics, antibiotics, hypoglycemic agents, or corticosteroids; typically, the labels for these products are not written in English and do not note the inclusion of pharmaceutical agents. Even conventional mineral supplements, such as calcium, have been contaminated with lead or had significant problems with product variability.

Many families use supplements concurrently with medications, posing hazards of interactions (Table 64-3). St. John's wort induces CYP3A4 activity of the P450 enzyme system and thus can enhance elimination of most drugs, including digoxin, cyclosporine, protease inhibitors, oral contraceptives, and numerous antibiotics, leading to

Table 64-3 The HDS–Drug Interactions with Major Severity* (Other Than St. John's Wort)

HDS	DRUGS	POTENTIAL CONSEQUENCES/ REACTIONS†
5-Hydroxytryptophan	Fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine	↑Risk of serotonin syndrome
Acacia	Amoxicillin	↓Absorption of amoxicillin
Alfalfa	Warfarin	↓The effect of warfarin
Aloe vera	Digoxin	↑Digoxin toxicity
American ginseng	Warfarin	↓The effect of warfarin
Arginine	Enalapril, nitroglycerin	↑Hypotensive effects
	Spironolactone	↑Risk of hyperkalemia
Bitter orange	Phenelzine	↑Risk of hypertensive crisis
Cowhage	Methyldopa	↑Hypotensive effects
Danshen	Aspirin, ticlopidine, warfarin	↑Risk of bleeding
	Digoxin	↑Digoxin toxicity
Digitalis	Bendroflumethiazide, chlorothiazide, chlorthalidone, hydrochlorothiazide, hydroflumethiazide, indapamide, methyclothiazide, metolazone, polythiazide, trichlormethiazide	↑Digoxin toxicity
	Digoxin	↑Digoxin toxicity
Dong quai	Aspirin, heparin, ticlopidine, warfarin	↑Risk of bleeding
Evening primrose	Warfarin	↑Risk of bleeding
Garlic	Ritonavir	↓The effect of ritonavir
	Saquinavir	↓The effect of saquinavir
	Warfarin	↑Risk of bleeding
Ginkgo	Aspirin, cilostazol, clopidogrel, dipyridamole, heparin, ibuprofen, naproxen, ticlopidine, warfarin	↑Risk of bleeding
	Risperidone	↑Risk of risperidone adverse effects
	Trazodone	Excessive sedation and potential coma
Glucosamine	Warfarin	↑Risk of bleeding
Green tea	Ephedrine	↑Risk of stimulatory adverse effects
Guarana	Ephedrine	↑Risk of stimulatory adverse effects
Hawthorn	Digoxin	↑Digoxin toxicity
Henbane	Chlorpheniramine, clemastine, dimenhydrinate, diphenhydramine, doxylamine, promethazine	↑Risk of anticholinergic side effects
Kava	Alprazolam, chlordiazepoxide, clonazepam, diazepam, estazolam, flurazepam, lorazepam, midazolam, morphine, oxazepam, phenobarbital, quazepam, temazepam, triazolam	↑Central nervous system depression
	Droperidol	↑Central nervous system depression
Licorice	Warfarin	↑Risk of bleeding
L-Tryptophan	Citalopram, duloxetine, fluoxetine, fluvoxamine, isocarboxazid, paroxetine, phenelzine, selegiline, sertraline, sibutramine, tranylcypromine, venlafaxine	↑Risk of serotonin syndrome
	Zolpidem	↑Zolpidem-induced side effect
Melatonin	Zolpidem	↑Sedative effects
N-Acetylcysteine	Nitroglycerin	Severe hypotension, intolerable headaches
Niacin	Atorvastatin, cerivastatin, lovastatin, rosuvastatin, simvastatin	↑Risk of myopathy or rhabdomyolysis
PABA	Dapsone, Sulfamethoxazole	↓Antibacterial effect
Pleurisy root	Digoxin	↑Digoxin toxicity
Potassium	Amiloride, benazepril, captopril, enalapril, fosinopril, indomethacin, lisinopril, moexipril, quinapril, ramipril, spironolactone, trandolapril, triamterene	↑Risk of hyperkalemia
Red yeast rice	Cyclosporine	↑Creatine phosphokinase values
S-Adenosylmethionine	Clomipramine	↑Risk of serotonin syndrome
Scotch broom	Haloperidol	↑The potential toxicity
	Phenelzine	↑Risk of hypertensive crisis
Valerian	Alprazolam, phenobarbital	↑Central nervous system depression

Continued

Table 64-3 The HDS–Drug Interactions with Major Severity* (Other Than St. John's Wort—cont'd

HDS	DRUGS	POTENTIAL CONSEQUENCES/ REACTIONS†
Vitamin A	Acitretin, bexarotene, etretinate, isotretinoin, tretinoin	↑Risk of vitamin A toxicity
Vitamin B_6	Altretamine	↓Response to altretamine
Vitamin E	Dicumarol	↑Risk of bleeding
Vitamin K	Warfarin	↓Effect of warfarin
Willow	Diclofenac, ibuprofen, naproxen, ticlopidine, warfarin	↑Risk of bleeding

*Any HDS–drug interactions with severity rated as contraindicated or major in either database of MicroMedex or NMCD were included in this table.
†Potential consequences or reactions were documented according to either aforementioned database with severity rating as major or contraindicated.
↓, Decreasing; ↑, increasing; HDS, herb and dietary supplements; PABA, para-aminobenzoic acid.
Adapted from Tsai HH, Lin HW, Pickard AS, et al: Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. Int J Clin Pract *66:1056–1078, 2012, Table 4, p. 1065.*

Table 64-4 Common Folk Medicines By Cultural Origin

NAME	CONTENTS	POTENTIAL TOXICITY
HISPANIC		
Siete jarabes	Almond, castor oil, tolu, wild cherry licorice, cocillana, honey	GI upset, catharsis, electrolyte disturbances
Agua maravilla	Witch hazel, ethanol	Ethanol toxicity
Jarabe maguey	Maguey (Agave spp)	GI upset
Alcanfor	Camphor	Camphor toxicity
Azarcon	Lead	Lead intoxication
Greta	Lead	Lead intoxication
Azogue	Elemental mercury	Mercury intoxication
Ipecacuanha	Ipecac	Vomiting, myopathy
SOUTHEAST ASIAN		
Paylooah	Lead	Lead intoxication
INDIAN AND AYURVEDIC		
Surma	Lead	Lead intoxication
Deshi Dawa	Lead	Lead intoxication

GI, gastrointestinal.
From Kingston RL, Foley C. Herbal, traditional, and alternative medicines. In Shannon MW, Borron SW, Burns MJ, editors. Haddad and Winchester's clinical management of poisoning and drug overdose, *ed 4, Philadelphia, 2007, WB Saunders, Table 68-3.*

subtherapeutic serum levels. In contrast, St. John's wort may *enhance* the risk of the serotonin syndrome in patients on selective serotonin reuptake inhibitor agents, increase the sedation of opioids, increase the photosensitivity reactions of certain drugs, and increase the toxicity of propofol and sevoflurane.

Many folk medicine are named based on their natural language (Tables 64-4 and 64-5), which must be taken into consideration when treating specific ethnic populations.

DIETARY SUPPLEMENT EFFICACY

Evidence about the effectiveness of dietary supplements to prevent or treat pediatric problems is mixed, depending on the product used and condition treated. Some herbal products may be helpful adjunctive treatments for common childhood problems; some herbs have proved helpful for colic (fennel and the combination of chamomile, fennel, vervain, licorice, and balm mint), nausea (ginger), irritable bowel syndrome (peppermint), and diarrhea (probiotics).

MASSAGE AND CHIROPRACTIC

Massage is commonly provided at home by parents and by professional massage therapists, physical therapists, and nurses in clinical settings. Infant massage is routinely provided in many neonatal intensive care units to promote growth and development in preterm infants. Massage also has been demonstrated to be beneficial for pediatric patients suffering from asthma, insomnia, colic, cystic fibrosis, and juvenile ideopathic arthritis. Massage therapy is generally safe. Professional massage practice is regulated by state governments; more than 40 states license massage therapists, and 3 offer statewide independent certification.

More than 50,000 chiropractors are licensed in the United States, including licensure in all 50 states. Chiropractic care is covered by most major insurers. Up to 14% of all chiropractic visits are for pediatric patients, not including care provided by chiropractors working for athletic departments or professional teams. While chiropractic care may be useful for treating minor musculoskeletal injuries, parents need to be cautioned not to rely on chiropractic as the primary treatment for serious conditions, such as neurologic deficits, cancer or autism; data suggest that severe complications are possible.

MIND–BODY THERAPIES

Mind–body therapies such as slow, deep breathing, meditation, guided imagery, biofeedback, hypnosis, tai chi, and yoga, are the second most commonly used group of complementary therapies in pediatrics. These practices can be learned informally through books, YouTube videos, CDs, DVDs, smart phone applications, or classes, or in therapeutic sessions with health professionals, such as psychologists and social workers (Table 64-6). Substantial research suggests that such practices can aid in reducing anxiety, insomnia, and stress-related conditions including migraine headaches and functional abdominal pain. They can also help patients struggling with chronic pain.

Table 64-5 Spanish-English Botanical Name Translation Chart

SPANISH NAME	ENGLISH NAME	BOTANICAL NAME
Ajo	Garlic	*Allium sativum*
Cebolla	Onion	*Allium cepa*
Cenela	Cinnamon	*Cinnamomum aromaticum*
Clavo	Cloves	*Eugenia aromatica*
Comino	Cumin	*Cuminum cyminum*
Epasote or herba Sancti Mariae	Wormseed	*Chenopodium anthelminticum*
Estafiate	Wormwood	*Artemisia absinthium*
Eucalipto	Eucalyptus	*Eucalyptus globulus*
Granada	Pomegranate	*Punica granatum*
Jengibre	Ginger	*Zingiber officinale*
Limon	Lemon	*Citrus limon*
Manzanilla	Chamomile	*Anthemis nobilis* or *Chamomilla recutita* or *Matricaria chamomilla*
Oregano	Oregano	*Origanum vulgare*
Pelos de elote	Corn silk	*Zea mays*
Savila	Aloe vera	*Aloe vera*
Tomillo	Thyme	*Thymus vulgaris*
Una de gato	Cat's claw	*Uncaria tomentosa*
Valeriana	Valerian	*Valeriana officinalis*
Yerba buena	Spearmint	*Mentha spicata*

Table 64-6 Commonly Used Mind–Body Practices in Pediatrics

PRACTICE	USES
Biofeedback	Preventing migraine headaches; reducing stress and anxiety; encopresis/constipation treatment; treatment of stress incontinence; neurofeedback is experimental for ADHD
Deep breathing	Relaxation; stress management
Guided imagery	Stress management, anxiety, pain relief
Hypnosis	Correcting habit disorders; preventing headaches; managing pain
Meditation	Stress management, improving concentration
Tai chi	Improved balance, coordination, concentration, discipline
Yoga	Improved balance, coordination, concentration

ACUPUNCTURE

Modern acupuncture incorporates treatment traditions from China, Japan, Korea, France, and other countries. In the United States, acupuncturists are licensed to practice in 43 states, and acupuncture services are offered by more than 30% of North American academic pediatric pain treatment programs. The technique that has undergone most scientific study involves penetrating the skin with thin, solid, metallic needles manipulated by hand or by electrical stimulation. Variants include rubbing (shiatsu), heat (moxibustion), lasers, magnets, pressure (acupressure), or electrical currents.

Although most pediatric patients are averse to needles, patients who suffer from severe chronic pain or nausea may be amenable to trying acupuncture and often report that it is helpful. Acupuncture can offer significant benefits in the treatment of recurrent headache, anxiety, back and other types of pain, depression, and nausea. As with any therapy involving needles, infections and bleeding can occur, but more serious complications, such as pneumothorax, occur in <1 in 30,000 treatments.

Bibliography is available at Expert Consult.

Internet Resources

American Academy of Pediatrics Section on Integrative Medicine: http://www2.aap.org/sections/chim/default.cfm

Consortium of Academic Health Centers for Integrative Medicine: http://www.imconsortium.org/

National Institutes of Health's National Center for Complementary and Integrative Medicine: http://nccam.nih.gov

Natural Medicines Comprehensive Database (requires subscription): http://www.naturaldatabase.com

Natural Standard (requires subscription): http://www.naturalstandard.com

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The Acutely Ill Child

PART IX

Chapter 65

Evaluation of the Sick Child in the Office and Clinic

Patrick C. Drayna and Marc H. Gorelick

Acutely ill children pose a challenge to a busy pediatrician's office. Illnesses can span the spectrum from simple viral infections to life-threatening emergencies. Pediatricians need to distinguish between patients who can be managed with close outpatient follow-up and those that need to be stabilized and transported to a higher level of care. Although patients of all ages can present with similar symptoms, the etiology of the illness can be age-dependent. The initial approach must focus on the general evaluation and stabilization of the acutely ill infant and child.

HISTORY

A thorough history is paramount to arriving at the correct diagnosis. Obtaining an accurate history from young patients is challenging, and parents often provide the most important information. On the basis of the chief complaint(s), the pediatrician must ask open-ended questions that help distinguish between common and potentially life-threatening entities. Common complaints leading to acute care visits for potential emergencies include **fever**, **altered mental status**, **vomiting**, **respiratory distress**, and **abdominal pain**.

Fever is the most common reason for a sick child visit. Most fevers are the result of self-limited viral infections. However, pediatricians need to be aware of the age-dependent potential for serious bacterial infections (e.g., urinary tract infections, sepsis, meningitis, pneumonia, dysentery, osteoarticular infection). During the first 2-3 mo of life, the neonate is at risk for sepsis caused by pathogens that are uncommon in older children. These organisms include group B streptococcus, *Escherichia coli, Listeria monocytogenes,* and herpes simplex virus. In neonates, the history must include maternal obstetric information and the patient's birth history. Risk factors for sepsis include maternal group B streptococcus colonization, prematurity, chorioamnionitis, and prolonged rupture of membranes. If there is a maternal history of sexually transmitted infections during the pregnancy, the differential diagnosis must be expanded to include those pathogens. Septic infants can present with lethargy, poor feeding, grunting respirations, and cool or mottled extremities, in addition to fever (or hypothermia). Infants with fever, irritability, and a bulging fontanel should be evaluated for meningitis. As the infant matures beyond 3 mo of age, the bacterial pathogens that usually cause bacteremia, sepsis, and meningitis are *Streptococcus pneumoniae, Haemophilus influenzae* type b, and *Neisseria meningitidis.* Urosepsis secondary to an *E. coli* urinary tract infection also needs to be considered. Immunization against some serotypes of *S. pneumoniae* has markedly reduced the occurrence of occult bacteremia and serious infections caused by that organism, as has immunization against *H. influenzae* type b. These remain potential concerns in those children not fully immunized against these pathogens. Other ailments that manifest with fever include septic arthritis and osteomyelitis, juvenile idiopathic arthritis, and Kawasaki disease. Children with a septic joint generally present with only 1 joint that is painful and often have pseudoparalysis of that joint. In contrast, patients with juvenile rheumatoid arthritis may present with pain, stiffness, swelling, and warmth of several joints. The diagnosis of Kawasaki disease should be considered if the patient meets the diagnostic criteria for this illness although some patients may have an atypical or incomplete presentation (see Chapter 166).

For patients presenting with **altered mental status**, the pediatrician should inquire about the presence of other symptoms, such as fever or headache. Screening questions should be asked regarding feeding changes, medications in the household, or the possibility of trauma. Parents will often describe a febrile child as "lethargic," but further questioning will reveal a tired-appearing child who interacts appropriately when the child has defervesced. Febrile patients need to be differentiated from the lethargic patient who presents with sepsis or meningitis. Infants with meningitis or sepsis may have a history of irritability, inconsolability, poor feeding, grunting respirations, seizures, decreased urine output, and/or color changes such as pallor, mottling, or cyanosis. Patients with poisonings or inborn errors of metabolism can also present with lethargy, poor feeding, unusual odors, seizures, and/or vomiting. Nonaccidental trauma should always be considered in a lethargic infant. Older children may present with altered mental status as a result of meningitis/encephalitis, trauma, or ingestions. Children with meningitis may have a history of fever and complaints of neck pain; other associated symptoms can include rash, headache, photophobia and/or vomiting. Children with ingestions can present with other abnormal neurologic symptoms such as ataxia, slurred speech, seizures, or characteristic constellations of vital sign changes and other physical findings (toxidromes).

Vomiting is a very common complaint of intestinal, other abdominal (e.g., pancreas, liver) or nongastrointestinal (e.g., hyperammonemia, increased intracranial pressure, poisoning) origin and may be a nonspecific sign of systemic illness. Questions to ask include about the presence of bilious or bloody emesis, abdominal distention, weight changes, presence of diarrhea, obstipation or hematochezia, history of trauma, and presence of headache. Although common causes of vomiting are gastroesophageal reflux and viral gastroenteritis, the pediatrician needs to be aware of other serious causes. In the infant, bilious emesis and abdominal distention and/or pain are worrisome for obstruction, as may be seen with malrotation with midgut volvulus or Hirschsprung disease. It is important to consider extraabdominal causes of vomiting in the neonate, including hydrocephalus, incarcerated hernia, inborn errors of metabolism, and nonaccidental trauma. Markedly increasing head circumference or a bulging fontanel can be the result of congenital hydrocephalus or can signal the presence of subdural hematomas from nonaccidental trauma. An infant who appears immediately hungry after projectile vomiting suggests a differential diagnosis of pyloric stenosis. In an older child, the differential diagnosis includes intussusception, incarcerated hernia, diabetic ketoacidosis, appendicitis, poisonings, and trauma. Patients with intussusception may present with vomiting and colicky abdominal pain. A history of increased urination in the presence of vomiting may herald the diagnosis of diabetes mellitus. Patients with headache and vomiting raise a concern for increased intracranial pressure and should be questioned about neurologic changes, meningismus, and fever.

Parents can interpret different symptoms as **respiratory distress**. Tachypnea secondary to fever is often a source of parental anxiety. Parents of newborn infants are sometimes alarmed by the presence of periodic breathing. Normal variations in respiratory patterns must be distinguished from true respiratory distress. Parents need to be questioned regarding associated symptoms such as fever, limitation of neck movement, drooling, choking, and the presence of stridor or wheezing.

A history of apnea or cyanosis warrants further investigation. Although wheezing is often secondary to bronchospasm, it can also be caused by cardiac disease or congenital anomalies such as vascular rings. Infants with congenital heart defects may be tachypneic but may lack any signs of respiratory distress as a compensatory mechanism for shock or metabolic acidosis. Parents often confuse and interpret stridor as wheezing, and care should be taken to differentiate the two. Stridor is most commonly caused by croup. However, anatomic abnormalities such as laryngeal webs, laryngomalacia, subglottic stenosis, and paralyzed vocal cords also cause stridor. Toddlers who present with wheezing or stridor after a coughing or choking episode should be evaluated for a foreign body aspiration. In toxic-appearing children with stridor, the pediatrician should consider epiglottitis, bacterial tracheitis, or a rapidly expanding retropharyngeal abscess. The incidence of epiglottitis has markedly declined with the advent of the *H. influenzae* type b (Hib) vaccine, but remains a possibility in the unimmunized or partially immunized patient. Children with retropharyngeal abscesses may also present with drooling and limitation of neck movement (especially hyperextension) after a recent upper respiratory infection or penetrating mouth injury.

Abdominal pain is another frequent complaint. Often this symptom is caused by a minor illness such as constipation, functional abdominal pain, urinary tract infection, or gastroenteritis. Parents should be questioned about associated symptoms including stooling patterns, abdominal distention, fever, urinary symptoms, and vomiting. In neonates, a tender abdomen is concerning for the presence of a small bowel obstruction; these infants tend to appear ill. There may be a history of vomiting and decreased or no stooling. Pediatricians should be wary of neonates with abdominal tenderness and bloody stools, as 10% of cases of necrotizing enterocolitis occur in term infants. Infants with milk protein intolerance can also present with bloody stools, but these infants are well-appearing and do not have abdominal tenderness. In older patients, the differential diagnosis for a potential emergency with abdominal pain expands to include intussusception and appendicitis. Patients with intussusception can present in a variety of ways, ranging from having episodes of colicky abdominal pain, but otherwise well in between episodes, to being lethargic or in shock. The diagnosis of appendicitis in the child younger than 3 yr is extremely difficult because children in this age group do not localize their pain well. Often the diagnosis is made after the appendix has ruptured.

The child's **past medical history** also needs to be obtained. It is important to be aware of any underlying chronic problems that might predispose the child to recurring infections or a serious acute illness. The child with sickle cell anemia is at increased risk for bacteremia, as well as painful vasoocclusive crisis. A careful review of systems can help in identifying the nature of the acute illness, as well as any complications needing intervention, such as dehydration accompanying an otherwise minor viral illness.

PHYSICAL EXAM

Observation is important in the evaluation of the acutely ill child. Most observational data that the pediatrician gathers during an acute illness should focus on assessing the child's response to stimuli. Do they awaken easily with a stimulus? Do they smile and interact with the examiner? Can the crying child be consoled by the parents' comforting? Assessing responses to stimuli requires knowledge of normal responses for different age groups, the manner in which those normal responses are elicited, and to what degree a response might be impaired. Thus, the pediatrician must be both clinically and developmentally oriented.

During the **physical examination**, the pediatrician seeks evidence of illness. The portions of the physical examination that require the child to be most cooperative are completed first. Initially, it is best to seat the child on the parent's lap; the older child may be seated on the examination table. It is also important to assess the child's willingness to move and ease of movement. It is reassuring to see the child moving about on the parent's lap with ease and without discomfort. Vital signs are often overlooked but are invaluable in assessing ill children. The degree of fever, the presence of tachycardia out of proportion to the fever, and the presence of tachypnea and hypotension all suggest a serious infection. The respiratory evaluation includes determining respiratory rate, the presence or absence of hypoxia by pulse oximetry, and noting any evidence of inspiratory stridor, expiratory wheezing, grunting, coughing, or increased work of breathing (e.g., retractions, nasal flaring, belly breathing). Because acute infections in children are most often caused by viral infections, the presence of nasal discharge may be noted. It is possible at this time to assess the skin for rashes. Frequently, viral infections cause an exanthem and many of these eruptions are diagnostic (e.g., the reticulated rash and "slapped-cheek" appearance of parvovirus infections or the typical appearance of hand-foot-and-mouth disease caused by coxsackieviruses). The skin examination may also yield evidence of more serious infections (bacterial cellulitis or petechiae and purpura associated with bacteremia). Cutaneous perfusion should be assessed by warmth and capillary refill time. When the child is seated and is least perturbed, an assessment of the fontanel can be completed; the examiner can determine whether the fontanel is depressed, flat, or bulging.

During this initial portion of the physical examination, when the child is most comfortable, the heart and lungs are auscultated. In the acutely febrile child, because of the relatively frequent occurrence of respiratory illnesses, it is important to assess adequacy of air entry into the lungs, equality of breath sounds, and evidence of adventitial breath sounds, especially wheezes, rales, and rhonchi. The coarse sound of air moving through a congested nasal passage is frequently transmitted to the lungs. The examiner can become attuned to these coarse sounds by placing the stethoscope near the child's nose and then compensating for this sound as the chest is auscultated. The cardiac examination is next; findings such as pericardial friction rub, loud murmurs, and distant heart sounds may indicate an infectious process involving the heart. The eyes are examined to identify features that might indicate an infectious process. Often, viral infections result in a watery discharge or redness of the bulbar conjunctivae. Bacterial infection, if superficial, results in purulent drainage; if the infection is more deep-seated, tenderness, swelling, and redness of the tissues surrounding the eye are present, as well as proptosis, reduced visual acuity, and altered extraocular movement. The extremities may then be evaluated not only for ease of movement but also for the possibility of swelling, heat, or tenderness; such abnormalities may indicate focal infections.

The components of the physical examination that are more bothersome to the child are completed last. This is best done with the patient on the examination table. Initially, the neck is examined to assess for areas of swelling, redness, or tenderness, as may be seen in cervical adenitis. Resistance to neck movement should prompt evaluation for signs of meningeal irritation (i.e., Kernig and Brudzinski signs) or a retropharyngeal abscess. During examination of the abdomen, the diaper is removed. The abdomen is inspected for distention. Auscultation is performed to assess adequacy of bowel sounds, followed by palpation. The child often fusses as the abdomen is auscultated and palpated. Every attempt should be made to quiet the child; if this is not possible, increased fussing as the abdomen is palpated may indicate tenderness, especially if this finding is reproducible. In addition to focal tenderness, palpation may elicit involuntary guarding or rebound tenderness (including tenderness to percussion); these findings indicate peritoneal irritation, as is seen in appendicitis. The inguinal area and genitals are then sequentially examined. The child is then placed in the prone position, and abnormalities of the back are sought. The spine and costovertebral angle areas are percussed to elicit any tenderness; such a finding may be indicative of vertebral osteomyelitis or diskitis and pyelonephritis, respectively.

Examining the ears and throat completes the physical examination. These are usually the most bothersome parts of the examination for the child, and parents frequently can be helpful in minimizing head movement. During the oropharyngeal examination, it is important to document the presence of enanthemas; these may be seen in many infectious processes, such as hand-foot-and-mouth disease caused by coxsackievirus. This portion of the examination is also important in documenting inflammation or exudates on the tonsils, which may be viral or bacterial.

Repeating portions of the assessment may be indicated. If the child cried continuously during the initial clinical evaluation, the examiner may not be certain whether the crying was caused by the high fever, stranger anxiety, or pain, or is indicative of a serious or localizing illness. Constant crying also makes portions of the physical examination, such as auscultation of the chest, more difficult. Before a repeat assessment is performed, efforts to make the child as comfortable as possible are indicated.

Febrile children can appear very ill, initially appearing listless, tachycardic, and tachypneic. These patients should receive antipyretic medications and be reassessed once they have defervesced. In the majority of children with uncomplicated viral illnesses, the vital signs normalize. Persistence of abnormal vital signs should prompt the clinician to further investigate the source of fever. Continued tachycardia and poor perfusion may be secondary to myocarditis. Tachypnea may be the sole symptom in patients with pneumonia, especially in children whose chief complaint is abdominal pain due to lower lobe pneumonia. Persistent irritability suggests meningitis/encephalitis.

RISK FACTORS

The sensitivity of the carefully performed clinical assessment, observation, history, and physical examination for the presence of serious illness is approximately 90%. If a serious illness is suspected, other data should be sought to improve this sensitivity level. Important supplemental data are age, body temperature, and the results of screening laboratory tests as indicated. Febrile children in the first 3 mo of life have yet to achieve immunologic maturity and therefore are more susceptible to severe infections. Thus, the febrile infant is at greater risk for serious bacterial infection than the child beyond 3 mo of age and warrants careful evaluation. Data from the era before widespread immunization for *H. influenzae* type b and pneumococcus suggest the risk of bacteremia in infants increases as the magnitude of fever increases; it is unclear how this applies today.

Screening laboratory tests may be helpful in identifying the febrile child at increased risk for selected serious illnesses. Practice guidelines from the prevaccine era suggested that white blood cell count might be useful in establishing a higher risk of bacteremia. Because the incidence of occult pneumococcal bacteremia in febrile children has declined significantly as a result of the introduction of conjugated pneumococcal vaccine, the utility of white blood cell count in otherwise healthy febrile young children older than 2-3 mo of age is questionable. Urinalysis and urine culture must always be considered when the source of fever is not apparent, especially in the highest-risk groups: females and uncircumcised males younger than 2 yr of age and all boys younger than 1 yr of age. The presence of leukocyte esterase, >5 white blood cells/high-power field on a spun urine specimen, or bacteria detected by Gram stain on an unspun urine specimen suggests urinary tract infection, but the sensitivity of these indicators is, on average, only 75-85%; urine culture is the definitive test. Procalcitonin, C-reactive protein, and interleukin-6 are being investigated as potential biomarkers of differentiating serious bacterial illness from benign viral disease in children.

MANAGEMENT

Most patients who present to the pediatrician's office with an acute illness will not require resuscitation. However, the pediatrician needs to be prepared to evaluate and begin resuscitation for the seriously ill or unstable child. The pediatrician's office should be stocked with appropriate equipment necessary to stabilize an acutely ill child. Maintenance of that equipment and ongoing training of the office staff in use of the equipment and procedures is required (see Chapter 66). The evaluation must begin with assessment of the ABCs—airway, breathing, and circulation. When assessing the airway, chest rise should be evaluated, and evidence of increased work of breathing sought. The examiner should ensure that the trachea is midline. If the airway is patent and no signs of airway obstruction are present, the patient is allowed to assume a position of comfort. If the child shows signs of airway obstruction, repositioning of the head with the chin-lift maneuver may alleviate the obstruction. An oral or nasal airway may be necessary in patients in whom airway patency cannot be maintained. These devices are not well-tolerated in conscious patients and may induce gagging or vomiting, and instead are most often utilized to facilitate effective bag-valve-mask ventilation. Once airway patency has been established, the adequacy of breathing should be evaluated. Slow respiratory rates or cyanosis may signal respiratory failure. If the airway is patent but the child's respiratory effort is inadequate, positive pressure ventilation via bag-valve-mask should be initiated. Oxygen should be administered to all seriously ill or hypoxic children via nasal cannula or face mask. Auscultation of the lung fields should assess for air entry, symmetry of breath sounds, and presence of adventitious breath sounds such as crackles or wheezes. Bronchodilator therapy can be initiated to alleviate bronchospasm. Racemic epinephrine is indicated for stridor at rest in a patient with croup. Once airway and breathing have been addressed, circulation must be evaluated. This involves assessment of cardiac output. Symptoms of shock include tachycardia, cool extremities, delayed capillary refill time, mottled or pale skin, and effortless tachypnea. *Hypotension is a late finding in shock and indicates significant decompensation has already taken place.* Vascular access is necessary for volume resuscitation in patients with impaired circulation, and an intraosseous line should be considered early on if there is any difficulty in vascular access for a patient requiring resuscitation. Once an intervention is performed, the clinician must reassess the patient.

If the febrile child is older than 3 mo and appears well, if the history or physical examination does not suggest a serious illness, the child may be followed expectantly. This profile applies to most children with acute febrile illnesses. If, on the other hand, the child appears ill, or the history or physical examination suggests a serious infection, definitive laboratory tests appropriate for those findings are indicated (chest x-ray for a child with grunting). If advanced imaging is required (ultrasound or CT scan for suspected appendicitis), it may be prudent to defer such testing to pediatric specialty care if the decision has already been made to transport the child to a higher level of care. The area of greatest controversy is whether laboratory studies are needed in a febrile child who appears well and has no abnormalities on history and physical examination, but who is younger than 3 mo or whose temperature is high. Many would agree that a sepsis work-up is indicated in the febrile child younger than 1 mo and possibly in the febrile child who is as old as 3 mo.

DISPOSITION

The majority of children evaluated in the office for an acute illness can be managed on an outpatient basis. These patients should have reassuring physical examinations, stable vital signs, and adequate follow-up. A mildly dehydrated patient can be discharged to home for a trial of oral rehydration. Patients with a respiratory illness who are exhibiting signs of mild respiratory distress may be monitored at home with a repeat examination scheduled for the next day. Depending on the child's status, the comfort of the parents, and the relationship of the family with the physician, telephone follow-up may be all that is necessary.

If the physician feels comfortable in following as an outpatient the child in whom no specific diagnosis has been established, a follow-up examination may yield the diagnosis. During the initial visit, or from one visit to the next during the acute illness, the change in symptoms or in the findings on physical examination over time may provide important diagnostic clues. For the child in whom a diagnosis has already been established and who does not require hospitalization, follow-up by telephone or an office visit should be used to monitor the course of the illness and to further educate and support the parents.

However, if it is deemed that the child needs a higher level of care, it is the pediatrician's responsibility to decide what method of transfer is appropriate. Physicians may be reluctant to call for help because of a misperception that 911 services should be activated only for full-blown resuscitations. Emergency Medical Services (EMS) transport should be initiated for any child who is physiologically unstable (e.g., with severe respiratory distress, hypoxia, signs of shock, or altered mental status). If the family's ability to comply promptly with

recommendation for emergency department evaluation is in question, that patient should also be transported by EMS. Some physicians and families may defer calling EMS because of the perception that a parent can get to the hospital faster by private car. Although rapidity of transport should be considered, the need for further interventions during transport and the risk of clinical decompensation are other important factors in the decision to activate EMS. Ultimately, the legal responsibility for choosing an appropriate level of transport for a patient lies with the referring physician, until responsibility of care is officially transferred to another medical provider.

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Chapter 66

Emergency Medical Services for Children

Joseph L. Wright and Steven E. Krug

The overwhelming majority of the 30 million children who present annually for emergency care in the United States are seen at community hospital emergency departments (EDs). Visits to children's hospital EDs account for just 11% of initial emergency care encounters. This distribution suggests that the greatest opportunity to optimize care for acutely ill or injured pediatric patients, on a population basis, occurs broadly as part of a systems-based approach to emergency services, an approach that incorporates the unique needs of children at every level. Conceptually, emergency medical services for children are characterized by an integrated, continuum of care model (Fig. 66-1). The model is designed such that patient care flows seamlessly from the primary care medical home through transport and on to hospital-based definitive care. It includes the following 5 principal domains of activity:

1. Prevention, primary and secondary
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: ED and inpatient
4. Interfacility transport, as necessary, for definitive or subspecialty care (see Chapter 66.1)
5. Rehabilitation.

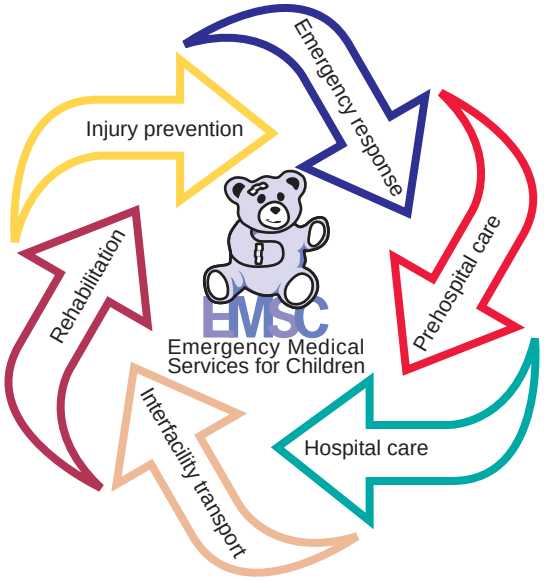

Figure 66-1 The emergency medical services for children (EMSC) continuum of care. Seriously ill and injured children interface with a large number of healthcare personnel as they move through the EMSC system.

The federal Emergency Medical Services for Children (EMSC) program of the Health Resources and Services Administration's Maternal and Child Health Bureau has stewarded improvements in the care of children in the context of the continuum of care model. The programmatic mission of the EMSC program is as follows:

- To ensure state-of-the-art emergency medical care for the ill or injured child and adolescent.
- To ensure that pediatric services are well integrated into an emergency medical services system and backed by optimal resources.
- To ensure that the entire spectrum of emergency services—including primary prevention of illness and injury, acute care, and rehabilitation—is provided to infants, children, adolescents, and young adults.

EMSC funding to states and U.S. territories has created a national framework upon which necessary advances in education, advocacy, and research are taking place. EMSC grantees, constituents, and stakeholders as well as professional organizations such as the American Academy of Pediatrics are collaboratively engaged in implementation activities and projects that address the pediatric-specific recommendations stemming from the Institute of Medicine (IOM) report *The Future of Emergency Care in the United States Health System*.

THE PRIMARY CARE PHYSICIAN AND OFFICE PREPAREDNESS

The primary care physician (PCP) has multiple important roles in the emergency medical services system. Through anticipatory guidance, the PCP can help shape the attitudes, knowledge, and behaviors of parent and child, with the primary goal of preventing acute medical events, such as injury and status asthmaticus. The point of care initiation for many acute problems is often the PCP office. From the standpoint of personnel, equipment, training, and protocols, the PCP office setting must be adequately prepared to initially manage acute and emergency exacerbations of common pediatric conditions, such as respiratory distress and seizures. Furthermore, on rare occasion, the PCP office environment may be confronted with a child in clinical extremis who requires resuscitative intervention and stabilization. It is, therefore, incumbent upon the PCP not only to ensure access to emergency medical services (EMS), that is, 911 system activation, but also to ensure that there is adequate, onsite psychomotor skill preparation to deal with such an emergency. Office preparedness requires training and continuing education for staff members, protocols for emergency intervention, ready availability of appropriate resuscitation drugs and equipment, and knowledge of local EMS resources and ED capabilities.

Staff Training and Continuing Education

It is a reasonable expectation that all office staff, including receptionists and medical assistants, be trained in cardiopulmonary resuscitation (CPR) and that their certification be maintained on an annual basis. Nurses and physicians should also have training in a systematic approach to pediatric resuscitation. Core knowledge may be obtained through standardized courses in advanced life support (ALS) offered by national medical associations and professional organizations. Frequent recertification is important for knowledge retention and skill maintenance. Examples are the Pediatric Advanced Life Support (PALS) and Pediatric Emergency Assessment, Recognition and Stabilization (PEARS) courses sponsored by the American Heart Association, the Advanced Pediatric Life Support (APLS) course sponsored by the American Academy of Pediatrics (AAP) and the American

College of Emergency Physicians (ACEP), and the Emergency Nurses Pediatric Course (ENPC) sponsored by the Emergency Nurses Association (ENA).

Protocols

Standardized protocols for telephone triage of seriously ill or injured children are essential. When a child's status is in question and prehospital care is available, ambulance transport in the care of trained personnel is always preferable to transport by privately owned vehicle. This obviates the potentially serious medical consequences of relying on unskilled and distraught parents without the ability to provide even basic life support (BLS) measures to an unstable child during transport to an ED. Practitioners can work with their local pediatric emergency care resource center (e.g., children's hospital or academic department of pediatrics) to develop and maintain written protocols for office-based management of a range of conditions, including anaphylaxis, cardiopulmonary arrest, head trauma, ingestions, shock, status asthmaticus, status epilepticus, and upper airway obstruction. Regular practice using mock code scenarios improves office-based practitioner confidence and self-efficacy in managing these problems.

Resuscitation Equipment

Availability of necessary equipment is a vital part of an emergency response. Every physician's office should have essential resuscitation equipment and medications packaged in a pediatric resuscitation cart or kit (Table 66-1). This cart or kit should be checked on a regular basis and kept in an accessible location known to all office staff. Outdated medications, a laryngoscope with a failed light source, or an empty oxygen tank represents a potential catastrophe in a resuscitation scenario. Such an incident can be easily avoided if an equipment checklist and maintenance schedule are implemented. A pediatric kit that includes posters, laminated cards, or a color-coded length-based resuscitation tape specifying emergency drug doses and equipment size is invaluable in avoiding critical therapeutic errors during resuscitation.

To facilitate emergency response when a child needs rapid intervention in the office, all personnel should have designated roles. Organizing a "code team" within the office ensures that necessary equipment is made available to the physician in charge, that an appropriate medical record detailing all interventions and the child's response is generated, and that the 911 call for EMS response or a transport team is made in a timely fashion.

Transport

Once the child has been stabilized, a decision must be made on how to transport a child to a facility capable of providing definitive care. If a child has required airway or cardiovascular support, has altered mental status or unstable vital signs, or has significant potential to deteriorate en route, it is not appropriate to send the child via privately owned vehicle, regardless of proximity to a hospital. Even when an ambulance is called, it is the PCP's responsibility to initiate essential life support measures and to attempt to stabilize the child before transport.

In metropolitan centers with numerous public and private ambulance agencies, the PCP must be knowledgeable about the level of service that is provided by each. The availability of BLS versus ALS services, the configuration of the transport team, and pediatric expertise vary markedly among agencies and across jurisdictions. BLS services provide basic support of airway, breathing, and circulation, whereas ALS units are capable of providing resuscitation drugs and procedural interventions as well. Some communities may have only BLS services available, whereas others may have a 2-tiered system, providing both BLS and ALS. It may be appropriate to consider medical air transport when definitive or specialized care is not available within an immediate community or when ground transport times are prolonged. In that case, initial transport via ground to an appropriate helicopter landing zone or a local hospital for interval stabilization may be undertaken, pending arrival of the air transport team. Independent of whether a child is to be transported by air or ground, copies of the pertinent medical records and any radiologic studies or laboratory results should be sent with the patient, and a call made to the physicians at the receiving facility to alert them to the referral and any treatments administered. Such notification is not merely a courtesy; direct physician-to-physician communication is essential to ensure adequate transmission of patient care information, to allow

Table 66-1 Recommended Drugs and Equipment for Pediatric Office Emergencies

	PRIORITY
DRUGS	
Oxygen	E
Albuterol for inhalation	E
Epinephrine (1 : 1,000)	E
Activated charcoal	S
Antibiotics	S
Anticonvulsants (diazepam/lorazepam)	S
Corticosteroids (parenteral/oral)	S
Dextrose (25%)	S
Diphenhydramine (parenteral, 50 mg/mL)	S
Epinephrine (1 : 10,000)	S
Atropine sulfate (0.1 mg/mL)	S
Naloxone (0.4 mg/mL)	S
Sodium bicarbonate (4.2%)	S
INTRAVENOUS FLUIDS	
Normal saline (NS) or lactated Ringer solution (500-mL bags)	S
5% dextrose, 0.45 NS (500-mL bags)	S
EQUIPMENT FOR AIRWAY MANAGEMENT	
Oxygen and delivery system	E
Bag-valve-mask (450-mL and 1,000-mL)	E
Clear oxygen masks, breather and non-rebreather, with reservoirs (infant, child, adult)	E
Suction device, tonsil tip, bulb syringe	E
Nebulizer (or metered-dose inhaler with spacer/mask)	E
Oropharyngeal airways (sizes 00-5)	E
Pulse oximeter	E
Nasopharyngeal airways (sizes 12-30F)	S
Magill forceps (pediatric, adult)	S
Suction catheters (sizes 5-16F and Yankauer suction tip)	S
Nasogastric tubes (sizes 6-14F)	S
Laryngoscope handle (pediatric, adult) with extra batteries, bulbs	S
Laryngoscope blades (straight 0-2; curved 2-3)	S
Endotracheal tubes (uncuffed 2.5-5.5; cuffed 6.0-8.0)	S
Stylets (pediatric, adult)	S
Esophageal intubation detector or end-tidal carbon dioxide detector	S
EQUIPMENT FOR VASCULAR ACCESS AND FLUID MANAGEMENT	
Butterfly needles (19-25 gauge)	S
Catheter-over-needle device (14-24 gauge)	S
Arm boards, tape, tourniquet	S
Intraosseous needles (16-, 18-gauge)	S
Intravenous tubing, micro-drip	S
MISCELLANEOUS EQUIPMENT AND SUPPLIES	
Color-coded tape or preprinted drug doses	E
Cardiac arrest board/backboard	E
Sphygmomanometer (infant, child, adult, thigh cuffs)	E
Splints, sterile dressings	E
Automated external defibrillator with pediatric capabilities	S
Spot glucose test	S
Stiff neck collars (small/large)	S
Heating source (overhead warmer/infrared lamp)	S

E, essential; S, strongly suggested.

From American Academy of Pediatrics, Committee on Pediatric Emergency Medicine; Frush K: Policy statement-preparation for emergencies in the offices of pediatricians and pediatric primary care providers, Pediatrics *120:200-212, 2007. Reaffirmed* Pediatrics *128:e748, 2011.*

mobilization of necessary resources in the ED, and to redirect the transport if the emergency physician believes that the child would be more optimally treated at a facility with specialized services.

PEDIATRIC PREHOSPITAL CARE

Prehospital care refers to emergency assistance rendered by trained emergency medical personnel before a child reaches a treating medical facility. The goals of prehospital care are to further minimize systemic insult or injury through a series of well-defined and appropriate interventions and to embrace principles that ensure patient safety. Most communities in the United States have a formalized EMS system; the organizational structure and nature of emergency medical response depend greatly on local demographics and population base. EMS may be provided by volunteers or career professionals working in a fire-based or independent "third service" response system. Key points to recognize in negotiation of the juncture between the community physician and the local EMS system include access to the system, provider capability, and destination determination.

Access to the EMS System

Virtually all Americans have access to the 911 telephone service that provides direct access to a dispatcher who coordinates police, fire, and EMS responses. Some communities have an enhanced 911 system, in which the location of the caller is automatically provided to the dispatcher, permitting emergency response even if the caller, such as a young child, cannot give an address. The extent of medical training for these dispatchers varies among communities, as do the protocols by which they assign an emergency response level (BLS vs ALS). In some smaller communities, no coordinated dispatch exists, and emergency medical calls are handled by the local law enforcement agency.

When activating the 911 system, the physician must make clear to the dispatcher the nature of the medical emergency and the condition of the child. In many communities, emergency medical dispatchers are trained to ask a series of questions per protocol that determines the appropriate level of provider to be sent.

Provider Capability

There are many levels of training for prehospital EMS providers, ranging from individuals capable of providing only first aid to those trained and licensed to provide ALS. All EMS personnel, whether basic emergency medical technicians (EMTs) or paramedics, receive training in pediatric emergencies; however, pediatric cases actually constitute roughly 10% of all EMS transports.

First responders may be law enforcement officers or firefighters, who are dispatched to provide emergency medical assistance, or bystanders. Public safety personnel have a minimum of 40 hr of training in first aid and CPR. Their role is to provide rapid response and stabilization pending the arrival of more highly trained personnel. In some smaller communities, this may be the only prehospital emergency medical response available.

In the United States, the bulk of emergency medical response is provided by EMTs, who may be volunteers or paid professionals. Basic EMTs may staff an ambulance after undergoing a training program of approximately 100 hr. They are licensed to provide BLS services but may receive further training in some jurisdictions to expand their scope of practice to include intravenous catheter placement and fluid administration, management of airway adjuncts, and the use of an automated external defibrillator.

Paramedics, or EMT-Ps, represent the highest level of EMT response, with medical training and supervised field experience of approximately 1,000 hr. Paramedic skills include advanced airway management, including endotracheal intubation; placement of peripheral, central, or intraosseous lines; intravenous administration of drugs; administration of nebulized aerosols; needle thoracostomy; and cardioversion and defibrillation. These professionals provide ALS services, functioning out of an ambulance equipped as a mobile intensive care unit. In a joint policy statement entitled *Equipment for Ground Ambulances*, the AAP, the ACEP, the American College of Surgeons Committee on Trauma, EMSC, the ENA, the National Association of EMS Physicians, and the National Association of EMS Officials have published guideline standards for essential ambulance equipment, medications, and supplies necessary to provide BLS and ALS care across the age spectrum. This essential equipment list represents one of the reference standards that the federal EMSC program has adopted as a performance measure for state-level operational readiness to care for children in an EMS system.

Both basic EMTs and paramedics function under the delegated licensing authority of a supervisory EMS medical director. This physician oversight of prehospital practice is broadly characterized under the umbrella term *medical control.* **Direct, or online, medical control** refers to medical direction either at the scene or in real time via voice or video transmission. **Indirect, or offline, medical control** refers to the administering of medical direction prior to and after the provision of care. Offline activities, such as provider education and training, protocol development, and medical leadership of quality assurance/quality improvement programs, represent areas in need of greater pediatric input. As a measure of the degree to which EMSC permanence is being established in state EMS systems, the federal EMSC program has required demonstration of participation in online and offline medical direction activities for pediatric patients and the seating of an EMSC advisory committee at the state level. These advisory bodies are well positioned to support EMS agencies in their pediatric readiness as well as provide a forum for the active engagement of pediatric care experts at a system level.

Destination Determination

The destination to which a pediatric patient is transported may be defined by parental preference, provider preference, or jurisdictional protocol, which is typically predicated on field assessment of anatomic and physiologic criteria and, in the case of trauma, mechanism of injury. In communities served by an organized trauma or regionalized EMS system that incorporates pediatric designation based on objectively verified hospital capabilities, seriously ill or injured children may be triaged by protocol to the highest-level center reachable within a reasonable amount of time. The mantra is to deliver the child to the **"right care in the right time,"** even if it requires bypassing closer hospitals. An exception is the child in full arrest, for whom expeditious transport to the nearest facility is always warranted. In 2012, modification of the Centers for Disease Control and Prevention's national field trauma triage guidelines included a refinement of age-specific vital sign assessment criteria to more accurately reflect the unique physiologic response to injury in children. The Centers for Disease Control and Prevention guidelines are a valuable resource for pediatricians involved in EMS medical direction and are accessible as a multipurpose toolkit, including an educational webinar and downloadable mobile application, at http://www.cdc.gov/fieldtriage.

Regionalization in the context of EMS is defined as a geographically organized system of services that ensures access to care at a level appropriate to patient needs while maintaining efficient use of available resources. This system concept is especially germane in the care of children, given the relative scarcity of facilities capable of managing the full range and scope of pediatric conditions (Fig. 66-2). Regionalized systems of care coordinated with emergency medical dispatch, field triage, and EMS transport have demonstrated efficacy in improving outcomes for pediatric trauma patients, especially for younger children and for children with isolated head injury. Emerging evidence also suggests a similar benefit conferred to children in shock identified in the field who are preferentially transported to hospital EDs with documented pediatric ALS capability. The existence of statewide or regional standardized systems that formally recognize hospitals able to stabilize and/or manage pediatric medical emergencies is another federal EMSC performance measure against which operational capacity to provide optimal pediatric emergency care in this country is currently being judged.

In communities that do not have a hospital with the equipment and personnel resources to provide definitive pediatric inpatient care, interfacility transport of a child to a regional center should be undertaken after initial stabilization (see Chapter 66.1). When interfacility

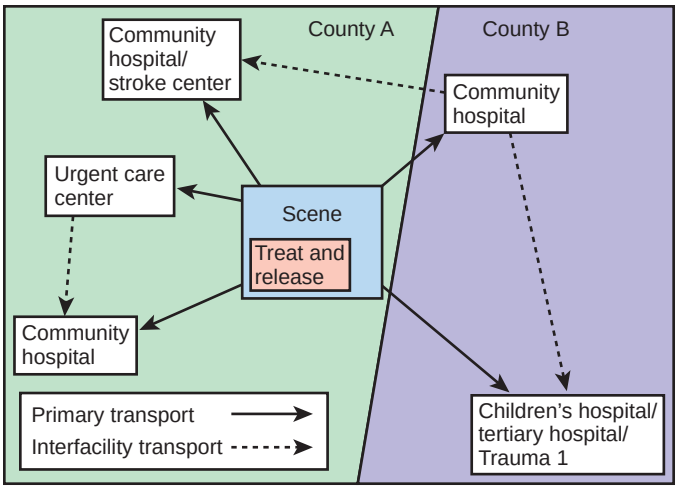

Figure 66-2 **Transport options within a coordinated, regionalized emergency medical services system model.** The objective is to ensure access to definitive care at a level appropriate to meet patient needs. *Solid arrows,* primary transport; *dotted arrows,* interfacility transport. *(Adapted from Institute of Medicine, Committee on the Future of Emergency Care in the U.S. Health System:* Hospital-based emergency care: at the breaking point, *Washington, DC, 2006, National Academies Press.)*

transport is to be undertaken, indications for transfer, parental consent for transfer, and acceptance of the patient by the receiving physician must all be clearly documented in the medical record.

THE EMERGENCY DEPARTMENT

The ability of hospital EDs to respond to the emergency care of children varies and depends on a number of factors in addition to availability of equipment and supplies. Training, awareness, and experience of the staff as well as access to pediatricians and medical and surgical subspecialists also play a key role. The majority of children who require emergency care are evaluated in community hospitals by physicians, nurses, and other healthcare providers with variable degrees of pediatric training and experience. Although children account for 25-30% of all ED visits, only a fraction of these encounters represent true emergencies. Because the volume of critical pediatric cases is low, emergency physicians and nurses working in community hospitals often have limited opportunity to reinforce their knowledge and skills in the assessment of ill or injured children and in pediatric resuscitation. General pediatricians from the community may be consulted when a seriously ill or injured child presents to the ED, and they should have a structured approach to the initial evaluation and treatment of an unstable child of any age, regardless of the underlying diagnosis. Early recognition of life-threatening abnormalities in oxygenation, ventilation, perfusion, and central nervous system function and rapid intervention to correct those abnormalities are key to successful resuscitation and stabilization of the pediatric patient.

In its report *The Future of Emergency Care in the U.S. Health System*, the IOM strongly recommended that hospitals and EMS systems appoint qualified coordinators for pediatric emergency care, a recommendation consistent with pediatric emergency readiness guidelines advocated by the AAP and ACEP. Only 18% of EDs in the United States currently appoint a physician coordinator, and 12% appoint a nursing coordinator for pediatric emergency care. EDs that do appoint these positions tend to be more prepared as measured by compliance with nationally published guidelines on the care of children in the ED.

Minimum standards must be met by community EDs to ensure that children receive the best emergency care possible. Updated guidelines for the care of children in the ED have been published, reaffirmed and are endorsed by the AAP, the ACEP, and the ENA. These guidelines provide current information on policies, procedures, protocols, quality assurance methods, and equipment and supplies considered essential for managing pediatric emergencies. Specific recommendations on equipment, supplies, and medications for the ED are listed and updates are available on the AAP website. Table 66-2 lists sample policies, procedures, and protocols specifically addressing the needs of children in the ED.

The way in which the family supports the child during a crisis and, consequently, how the family is supported in the ED when caring for the child are critical to patient recovery, family satisfaction, and

Table 66-2 Guidelines for Pediatric-Specific Policies, Procedures, and Protocols for the Emergency Department

Illness and injury triage
Pediatric patient assessment and reassessment
Documentation of pediatric vital signs, abnormal vital signs, and actions to be taken for abnormal vital signs
Immunization assessment and management of the underimmunized patient
Sedation and analgesia for procedures, including medical imaging
Consent (including situations in which a parent is not immediately available)
Social and mental health issues
Physical or chemical restraint of patients
Child maltreatment (physical and sexual abuse, sexual assault, and neglect) mandated reporting criteria, requirements, and processes
Death of the child in the emergency department
Do-not-resuscitate orders
Family-centered care, including: 1. Involving families in patient care decision-making and in medication safety processes. 2. Family presence during all aspects of emergency care, including resuscitation. 3. Education of the patient, family, and regular caregivers. 4. Discharge planning and instruction. 5. Bereavement counseling.
Communication with patient's medical home or primary healthcare provider
Medical imaging policies that address age- or weight-appropriate dosing for children receiving studies that impart ionizing radiation, consistent with ALARA (as low as reasonably achievable) principles
All-hazard disaster preparedness plan that addresses the following pediatric issues: a. Availability of medications, vaccines, equipment, and appropriately trained providers for children in disasters. b. Pediatric surge capacity for both injured and noninjured children. c. Decontamination, isolation, and quarantine of families and children of all ages. d. A plan that minimizes parent-child separation and includes system tracking of pediatric patients, allowing for the timely reunification of separated children with their families. e. Access to specific medical and mental health therapies, as well as social services, for children in the event of a disaster. f. Disaster drills, which should include a pediatric mass casualty incident at least every 2 yr. g. Care of children with special healthcare needs. h. A plan that includes evacuation of pediatric units and pediatric specialty units.

Data from American Academy of Pediatrics Committee on Pediatric Emergency Medicine; American College of Emergency Physicians Pediatric Committee; Emergency Nurses Association Pediatric Committee: Joint policy statement—guidelines for care of children in the emergency department, Pediatrics *124:1233-1243, 2009. Reaffirmed* Pediatrics *132:e281, 2013.*

the mitigation of posttraumatic stress. Commitment to patient- and family-centered care in the ED ensures that the patient and family experience guides the practice of culturally sensitive care and promotes patient dignity, comfort, and autonomy. In the ED setting, particular issues, such as family presence, deserve specific attention. Surveys of parents have indicated that most want to be with their child during invasive procedures and even during resuscitation. Allowing their presence has been shown to reduce parental and patient anxiety and does not interfere with procedure performance. Patient- and family-centered care is also associated with improved care quality and patient safety.

EMERGING ISSUES IN EMSC

Of the pediatric-specific recommendations promulgated by the IOM in its widely publicized 2006 report on the future of emergency care, 3 have emerged as especially important for EMSC. The first deals directly with increased federal funding for the EMSC program, which supports more than 80 grantees with an established presence in 49 states, 5 U.S. territories, the District of Columbia, and the freely associated states of Micronesia, Palau, and the Marshall Islands. The grant awards cover 5 distinct funding categories ranging from basic science and clinical investigation to public sector capacity-building programs to national technical assistance centers to multicenter trials conducted within a large research network. Through the diversity of activity generated within the program, and in collaboration with stakeholders, the EMSC program affords synergistic opportunity to further the progress realized in the program's first 30 yr of existence. A tumultuous appropriations history not-with-standing, including several years of budget elimination, Congressional reauthorization, due in 2014, and will ensure stability for the EMSC program at least in the near term.

In addition to EMSC resource support, the IOM also recommended that (a) federal agencies in partnership with state and regional planning bodies and emergency care provider organizations convene a panel with multidisciplinary expertise to develop strategies for addressing pediatric needs in the event of a disaster, and (b) the U.S. Department of Health and Human Services conduct a study to examine the gaps and opportunities in emergency care research, including pediatric emergency care, and recommend a strategy for the optimal organization and funding of the research effort. Both of these recommendations have generated activity of significant import to the emergency care community, EMSC specifically, and warrant mention.

Disaster Preparedness

Children constitute approximately 30% of the population; in a catastrophic event, natural or human-made, several unique factors place children at disproportionate, increased risk. During the day large groups of children are typically cohorted, separate from their families, in schools and daycare centers where mass casualties can easily occur and reunification is challenging. Furthermore, in the event of a biologic or chemical attack, unique anatomic, developmental, and physiologic features make children especially vulnerable to absorption and/or inhalation of toxic agents. Following the broad pediatric impact of the devastating Gulf Coast hurricanes Katrina and Rita in the mid-2000s, Congress established the National Commission on Children and Disasters. The Commission's mandate was to conduct a comprehensive study to examine and assess the needs of children as they relate to preparation for, mitigation of, response to, and recovery from all hazards, including major disasters and emergencies. The findings and recommendations of the Commission's 2010 report to the President and to Congress have established a broad framework for ongoing preparedness efforts related not only to child physical health, but also, importantly, to behavioral and emotional well-being. In addition, pertinent resources related to pediatric-focused areas of concerns such as evacuation, separation-reunification, sheltering, countermeasures, surge capacity and triage are being monitored and chronicled under the PEDPrepared Disaster Clearinghouse at the EMSC National Resource Center website, http://www.emscnrc.org/pedprepared.

Bibliography is available at Expert Consult.

66.1 Interfacility Transport of the Seriously Ill or Injured Pediatric Patient

*Elizabeth A. Edgerton and Bruce L. Klein**

Patients often seek treatment at facilities that lack sufficient expertise to treat their conditions, necessitating transfer to more appropriate specialty centers. This is especially pronounced in pediatrics. EMS providers or parents usually take children to local EDs first, where their conditions and physiologic stabilities are assessed. Although bringing a child directly to the local ED may be proper logistically, local EDs can be less than ideal for pediatric emergencies. Children account for 27% of all ED visits but only 6% of EDs have all the necessary supplies for pediatric emergencies. Also, general EDs are less likely to have pediatric expertise or policies in place for the care of children. Outcomes for critically ill children treated in pediatric intensive care units (PICUs) are better than for those treated in adult ICUs. When pediatric critical care is required, transport to a regional PICU is indicated. In addition, often the type of subspecialty care needed (e.g., pediatric orthopedics) is available only at the pediatric center.

Pediatric transport medicine consists of the interfacility transfer of infants, children, and adolescents from community facilities to pediatric centers that can provide the needed level of expertise. Transport is performed by professionals proficient in pediatric transport on specially age-equipped ground, rotorcraft, or fixed-wing ambulances. Pediatric transport medicine is a multidisciplinary field comprising pediatric critical care and pediatric emergency medicine physicians (and, sometimes for very young infants, neonatologists); nurses, respiratory therapists, and paramedics with advanced training for pediatric transport; and communications specialists. The goal is to deliver quality pediatric care to the region's children, while optimizing the use of regional resources. For the individual child, the aim is to stabilize and, when appropriate, begin treating as soon as possible—that is, at the local ED and during transport, well before arrival at the referral center.

The AAP Section on Transport Medicine, the Association of Air Medical Services, the Federal Aviation Administration (FAA), and others have published recommendations regarding transport programs. Models for pediatric transport services vary depending on the needs and available resources in a geographic region, but all should have certain basic components: a network of community hospitals and regional pediatric centers; an established communications and dispatch system that easily facilitates transfer to the pediatric center; ground and/or air ambulances; medical and nursing leadership from pediatric critical care or pediatric emergency medicine (or neonatology); experienced pediatric medical control physicians (MCPs); a multidisciplinary team of pediatric transport professionals specially trained to provide the appropriate level of care required during transport; operational and clinical policies and procedures that guarantee safe, state-of-the-art, and timely pediatric critical care transport; and a database for quality and performance assessment.

COMMUNICATIONS AND DISPATCH CENTER

Communications are one of the most vital components of a regional transport system. Treating a critically ill or injured child is an uncommon event for most community physicians. Therefore, they need to know *whom*, *how*, and *when* to call for assistance in the stabilization and transfer of a pediatric patient. The communications and dispatch center provides a single telephone number for such calls.

The communications and dispatch center coordinates communications among the outlying facility, receiving unit, MCP, transport team, and others. This center may be part of a hospital unit (e.g., ED, PICU), self-contained in a single institution (e.g., Emergency Communications and Information Center), or based offsite as a freestanding center coordinating communications and dispatch for multiple transport programs.

Staffing varies depending on the type of center. On-duty nurses or physicians may receive calls at unit-based models with low volumes.

*Adapted initially from Dr. Lorry R. Frankel's chapter in the 18th edition of this book.

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In contrast, dedicated communications specialists usually staff self-contained or freestanding centers, which tend to be busier. The communications specialist has numerous responsibilities, including answering the referring physician's call promptly; documenting essential patient demographic information; arranging for immediate consultation with the MCP; dispatching the transport team to the referring facility expeditiously; updating the referring facility with any changes in the arrival time; and coordinating medical control and other necessary transport-related calls. The transport team must be equipped with a cellular telephone or radio for immediate contact with the receiving and referring facilities.

MEDICAL CONTROL PHYSICIAN

The MCP is involved in the clinical care and safe transport of the patient from the time of referral through arrival at the receiving hospital unit. The MCP's oversight increases once the transport team arrives at the referring facility. The MCP should have expertise in pediatric critical care or pediatric emergency medicine (or sometimes neonatology). Besides having the knowledge required to stabilize a critically ill or injured child, the MCP must be familiar with the transport environment; the transport team members' capabilities; the program's policies and procedures; and the region's geography, medical resources, and regulations regarding interhospital transport. The MCP must possess good interpersonal and communication skills and must be able to maintain collegiality with the referring hospital's staff during a potentially difficult and stressful situation.

Once a transport call is received, the MCP must be immediately available to confer with the referring physician. Although the MCP may have other responsibilities, these transport responsibilities take priority in order to avoid undue delays when transferring a critically ill child. Often the MCP recommends further testing or therapeutic interventions that can be delivered by the referring hospital before the transport team arrives. The MCP may seek additional guidance from other specialists, as necessary. Because the child's condition may change rapidly, the MCP must remain ready to give additional advice. All conversations and recommendations regarding the care of the patient should be documented. Some centers record these conversations.

After discussion with the referring physician—and, when warranted, with the transport staff—the MCP determines the best team composition and vehicle for transport. The MCP usually does not accompany the team but remains available, by phone or radio, to supervise care.

TRANSPORT TEAM

Transport team composition varies among programs—and sometimes within an individual program. The team's composition is based on a variety of factors, including the severity of the child's illness or injury; the distance to the referring facility; the team members' advanced practice abilities; the referrer's (reasonable or unreasonable) insistence that a physician be present; the program's historical professional makeup; and the region's staffing regulations. The team should be composed of physicians, nurses, respiratory therapists, and/or paramedics who have expertise in pediatric critical care or pediatric emergency medicine (or neonatology in some cases), as well as advanced education and training in those cognitive and procedural areas important for pediatric critical care transport. There is a lower incidence of transport-related morbidity for critically ill and injured children transported by pediatric specialty teams than for those transported by generalist teams.

Various scoring systems have been developed to predict the need for a physician during transport. It seems that a team member's training, experience, and skill in treating critically ill patients are more important considerations than that team member's professional degree. Team members must understand basic pediatric pathophysiology and collectively must be able to assess and monitor a critically ill or injured child; manage the airway and provide respiratory support; obtain vascular access; perform point-of-care testing; and administer those medications commonly used in pediatric critical care transport. They must be familiar with the physiologic alterations as well as practical difficulties of the transport environment and, importantly, must be comfortable working in an out-of-hospital setting. Physicians are less often deployed on transport teams in part because of the advanced training that other healthcare professionals on the transport team receive.

The transport team should have a designated team leader who, in addition to the team leader's many other responsibilities, interacts with the MCP during the transport. Once the team arrives at the referring facility, the team should reassess the child's condition, review all of the pertinent diagnostic studies and therapies, and discuss the situation with the referring staff and parents. If the patient's condition has changed significantly, the team leader may need to contact the MCP for additional advice. Otherwise, the team leader should generally notify the MCP before starting to bring the child to the receiving facility. Any care delivered by the team during transport should be documented, and copies of all medical records—including laboratory data, radiographs, and scans—should accompany the child to the pediatric center. The receiving unit must be updated prior to arrival so it can finalize preparations for the patient.

GROUND VERSUS AIR AMBULANCE

Transport options include ground, rotorcraft, and fixed-wing ambulances. Vehicle selection depends on the child's emergency needs; transport team's capabilities; any out-of-ordinary staffing or equipment requirements (e.g., for extracorporeal membrane oxygenation, inhaled nitric oxide or heliox); referring facility's abilities; distance; terrain; traffic patterns; ground or air ambulance availability; helicopter landing pad or airport access; weather conditions; and expense.

The transport vehicle must be equipped with electrical power, oxygen, and suction and must have sufficient space for the equipment and supplies that the team brings along—stretcher or isolette, monitor, ventilator, oxygen tank(s), medication pack(s), infusion pumps, and more. Compared with helicopters, ambulances are more spacious and able to carry more weight, so they can accommodate larger teams and more equipment. Another advantage of ground ambulance transport is the ability to stop en route if the patient's condition deteriorates; this feature greatly facilitates the performance of certain interventions, such as intubation.

An airplane may be able to fly to an area when distance (>150 miles), altitude, or weather precludes helicopter use. However, the use of an airplane necessitates several ambulance transfers, with their attendant delays and potential complications. There also are delays when the plane must fly from a remote base to the program's jurisdiction.

TRANSPORT PHYSIOLOGY

When possible, the transport team tries to provide the same care during transport as the patient would receive in the specialty center. This can be difficult, though, because of limitations in personnel, equipment, and space, as well as other environmental challenges.

The team and child are subjected to variable intensities of background noise and vibration while traveling in the vehicle cabin. Noise can impair the team's ability to auscultate breath sounds, heart sounds, and blood pressure, another reason for monitoring vital signs mechanically and relying on other assessment modalities, such as the level of mentation, skin color, and capillary refill. To mitigate noise, the helicopter crew and patient should wear helmets or headphones (or another wearable noise attenuator such as MiniMuffs [Natus Medical Incorporated, San Carlos, CA]). Motion and vibration can lead to increased metabolic rate, shortness of breath, and fatigue in the patient, as well as motion sickness in the patient and staff.

On fixed- or certain rotary-wing transports, the patient may suffer adverse physiologic effects from altitude. With increasing altitude, the barometric (atmospheric) pressure decreases and gases expand. As the barometric pressure drops and gas expands, the partial pressures of ambient oxygen (P_{O_2}) and, consequently, arterial oxygen (P_{AO_2}) decrease. For example, at 8,000 feet—an elevation at which unpressurized airplanes may fly, as well as the effective cabin altitude for many pressurized airplanes flying at 35,000 to 40,000 feet—the barometric pressure, P_{O_2}, P_{AO_2}, and arterial oxygen saturation fall to 565 mm Hg, 118 mm Hg, 61 mm Hg, and 93%, respectively. (In comparison, the barometric pressure, P_{O_2}, P_{AO_2}, and arterial oxygen saturation are

760 mm Hg, 159 mm Hg, 95 mm Hg, and 100% at sea level.) Although healthy individuals usually tolerate these changes well, patients with respiratory insufficiency, significant blood loss, or shock may decompensate and should receive supplemental oxygen.

Gases expand 10-15% at the few thousand feet at which helicopters typically fly, and approximately 30% at 8,000 feet. Gases within the body itself also expand as the altitude increases. Gas expansion must be appreciated during transport via air of a patient with a pneumocephalus, pneumothorax, bowel obstruction, or another condition involving entrapped gas. Prior to transport, a pneumothorax should be decompressed, and a nasogastric tube inserted for ileus.

SAFETY

Safety is of paramount importance and mandates constant vigilance by everyone involved. Accident rates for pediatric air and ground transport are estimated at approximately 1/1,000 transports. The team should routinely attend pilot briefs, as well as perform safety inspections of the vehicles and equipment, aided by checklists. When in doubt, the MCP should solicit input from the staff about whether to transport via air or ground ambulance or to employ lights and sirens, decisions that cannot be taken lightly. The pilot's or driver's judgment as to the safety of proceeding during inclement weather or with a mechanical problem must not be overruled.

Organizations, such as the FAA and the National Transportation Safety Board, play a role in ensuring safe interfacility transport. The Commission on Accreditation of Medical Transport Systems (CAMTS) is an independent, peer review organization that was established in 1990 in response to the number of air medical accidents in the 1980s. CAMTS, through voluntary participation, audits and accredits fixed-wing, rotary-wing, and ground interfacility medical transport services.

FAMILY-CENTERED CARE

Family-centered care represents a philosophy that respects the important role that family members play in a child's care. It recognizes family members and healthcare providers as partners in caring for the child. Family presence during transport is beneficial because it provides support to children in stressful situations and assists healthcare providers in delivering care to patients with complex and/or chronic medical problems.

As care is transitioned from the referring hospital, it is the transport team's responsibility to maintain family-centered care. The team meets with family members to explain the transport process, obtain consent, and discuss anticipated management. When possible, the transport team should attempt to accommodate a family member's presence onboard. However, the family member and child may need to be separated when the child is critically ill and rapid transport is essential, or if there is space or weight limitations in the air or ground ambulance. In these situations, it is important that family members have a clear understanding of how the child will be cared for during the separation.

REFERRING HOSPITAL RESPONSIBILITIES

Transfer of a patient to another facility requires written documentation by the referring physician of the need and reasons for transfer, including a statement that the risks and benefits, as well as any alternatives, have been discussed with the parents. The parent's informed consent to the transfer should be obtained.

Federal law under the Emergency Medical Treatment and Active Labor Act (EMTALA), part of the Consolidated Omnibus Budget Reconciliation Act (COBRA), imposes specific requirements that a patient presenting to an ED be given a medical screening examination without regard to ability to pay. If upon examination an emergency medical condition is found, the hospital is required to stabilize the patient or to transfer the patient to another facility if unable to stabilize the patient or if requested by the patient. The primary requirement is that the referring physician must certify that the medical risks of transfer are outweighed by its potential benefits. The receiving hospital must agree to accept the patient and have the space and staff to provide the necessary treatment. The transferring hospital is responsible for arranging for the transfer and ensuring that it is performed by qualified medical personnel with appropriate equipment. It must send copies of the patient's medical records and test results, even those that become available after the transfer is complete.

Some referring hospitals have entered into transfer agreements with specialty centers in the interests of facilitating the smooth and safe transfer of the pediatric patient. Having prepared forms for all of the above purposes also aids in the transfer process.

Each hospital needs to review its facility's guidelines, and if established guidelines do not exist the EMSC, in partnership with the Emergency Nurses Association and the Society of Trauma Nurses, has developed the "Inter Facility Transfer Tool Kit for the Pediatric Patient" (available at www.pediatricreadiness.org). This tool kit includes the essentials for comprehensively and safely transferring the pediatric patient to the most appropriate level of care in a timely manner.

EDUCATIONAL OUTREACH

Besides safe and rapid transport, regional pediatric transport programs (and their specialty centers) have an obligation to provide educational opportunities to community healthcare providers so that these providers can acquire the necessary skills to evaluate and stabilize a critically ill or injured child until the transport team arrives. These learning activities may include transport case reviews; lectures on pediatric acute care topics; resuscitation programs such as the PALS course, APLS course, and S.T.A.B.L.E. (sugar and safe care, temperature, airway, blood pressure, lab work, emotional support) program; and rotations through the specialty center's pediatric ED and PICU. These activities also help cement relationships with the referring facility's staff.

Bibliography is available at Expert Consult.

66.2 Outcomes and Risk Adjustment

Evaline A. Alessandrini

Health services research has documented wide variation in the likelihood that patients receive quality, evidence-based healthcare, and this can negatively impact the health of children and youth. The complexities of delivering high-quality healthcare are magnified in the ED. Patients are in crisis, EDs are often overcrowded, patient–physician relationships are based on brief interactions, and the variety of complaints and diagnoses is immense.

OUTCOME MEASURES IN EMERGENCY MEDICAL SERVICES FOR CHILDREN

Emergency Care for Children: Growing Pains, one report of the 2007 IOM series on the future of emergency care, recommends that pediatric emergency medical systems specifically support the development of national standards for emergency care performance measurement. The Donabedian structure–process–outcome model has set the framework for most contemporary quality measurement and improvement activities. Structural elements provide indirect quality-of-care measures related to a physical setting and resources. Process indicators provide a measure of the quality of care and services by evaluating the method or process by which care is delivered, including both technical and interpersonal components. Outcome elements describe valued results related to lengthening life, relieving pain, reducing disabilities, and satisfying the consumer.

Defining relevant outcomes for pediatric emergency care is difficult. A true "outcome-based" approach describes observable measures such as mortality, risk of organ system failure, and disability. An alternative approach is a "resource-based" outcome measure definition related to the level of care required. Children who are more ill, in general, require more resources. Thus, resource use across groups of patients reflects relative severity of illness in the groups. Examples of resource-based outcomes include need for hospital admission (ED disposition), ED

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Table 66-3 Stakeholder-Endorsed Outcome Measures for Pediatric Emergency Care

- Overall patient satisfaction with ED visit—nurses
- Overall patient satisfaction with ED visit—physicians
- Parent/caregiver understanding of ED discharge instructions
- ED length of stay for patients <18 yr of age
- Percentage of patients <18 yr of age left without being seen (LWBS)
- Effective pediatric procedural sedation
- Acute fracture patients with documented reduction in pain within 90 min of ED arrival
- Improvement in asthma severity score for patients with acute exacerbations
- ED revisit within 48 hr resulting in admission
- Medication error rates
- Global sentinel never events
- Unplanned return visit within 72 hr for the same/related asthma exacerbation
- Failure to achieve seizure control within 30 min of ED arrival
- Return visits within 48 hr resulting in admission for all urgent and emergency patients

Table 66-4 Elements of the PRISA II Score

- Age <90 days
- Minor injury
- Abdominal pain in an adolescent
- Immunodeficiency
- Indwelling medical device
- Controller asthma medication
- Referral status
- Temperature
- Decreased mental status
- Low systolic blood pressure (<70 neonates and infants; <83 children; <100 adolescents)
- High diastolic blood pressure (>59 neonates and infants; >70 children; >90 adolescents)
- Low serum bicarbonate value (<20 mEq/L)
- High potassium value (>4.9 mEq/L)
- High blood urea nitrogen value (>80 mg/dL)
- High white blood cell count (>20,000/mm^3)
- Oxygen therapy other than during inhaled bronchodilator treatments
- Low bicarbonate and high potassium values

length of stay, costs, and diagnostic and therapeutic interventions performed in the ED. Table 66-3 provides a list of outcome measures for pediatric emergency care developed by EMSC stakeholders during 2 separate consensus meetings.

RISK ADJUSTMENT

Measuring outcomes offers opportunities for EDs and other components of the healthcare system to make effective improvements over time, benchmark, and compare their end results with those of other institutions. Meaningful comparisons between EDs or within an ED over time generally require risk adjustment, which accounts for patient-related attributes such as age, or for preexisting conditions associated with the outcome of interest. Risk-adjustment "levels the playing field," so that comparison of outcomes is as fair and meaningful as possible. Because children present to EDs with illnesses of varying acuity, ranging from rashes and colds to cardiac arrest, there is an inextricable linkage of severity to outcomes. Severity typifies the concept of "risk"—the higher the severity, the higher the risk of a given outcome. Without risk adjustment, EDs with sicker patients may appear to have worse outcomes.

A large number of instruments have been developed to adjust for severity or risk in clinical research and quality improvement activities. The commonly used PRISM (Pediatric Risk of Mortality) score is not well-suited for EMSC, given the extremely low rate of mortality. Several disease-specific acuity scoring systems are available for use in EMSC. The majority of these are intended for use in trauma patients, including the Injury Severity Score, Trauma Score, and Pediatric Trauma Score.

RISK ADJUSTMENT TOOLS IN EMSC

The choice of a risk-adjustment tool depends on several factors, including the population under study, the setting, and the outcomes of interest. Two risk-adjustment tools have been developed specifically for pediatric emergency medicine, the second-generation Pediatric Risk of Admission (PRISA II) score and the Revised Pediatric Emergency Assessment Tool (RePEAT).

Pediatric Risk of Admission II

PRISA II uses components of acute and chronic medical history and physiology to determine the probability of hospitalization. The outcome measure of interest is mandatory hospital admission (admissions utilizing therapies best delivered on an inpatient basis). Table 66-4 lists the patient-related attributes contributing to the PRISA II risk-adjustment score. Analytic models including the PRISA II score have good calibration (how well the probabilities predicted from the model correlated with the observed outcomes in the population) and discrimination (the ability to categorize subjects correctly into the categories of interest) with respect to mandatory hospital admission. Construct validity of the PRISA score was demonstrated by measuring the rates of the secondary outcomes: mandatory admission, PICU admission, and mortality. As the probability of hospital admission rose, the proportion of patients with these increasing care requirements also increased. This finding strongly supports the use of the PRISA II score as a valid measure of severity of illness. In addition, PRISA II was used to demonstrate racial/ethnic differences in severity-adjusted hospitalization rates, and also demonstrated that teaching hospitals had higher than expected severity-adjusted admission rates in comparison with nonteaching hospitals.

Table 66-5 Elements of the RePEAT Score

- Age
- Chief complaint
- Triage category
- Current use of prescription medications
- Arrival via EMS (ground/air)
- Heart rate
- Respiratory rate
- Temperature

Revised Pediatric Emergency Assessment Tool

The RePEAT uses a limited set of data collected at the time of triage to model severity of illness as reflected by the level of care provided in the ED. This tool was developed to predict the level of care provided—routine assessment (clinical examination only ± nonprescription medicine), specific ED care (ED diagnostics and/or therapeutics), or hospital admission—with the implicit assumption that patients with a higher level of care have a higher severity of illness. Table 66-5 lists the patient-related attributes contributing to the RePEAT risk-adjustment score. As with the PRISA II score, analytic models including the RePEAT score have good calibration and discrimination with respect to predicting ED care and hospital admission. Furthermore, analytic models that compare costs and ED length of stay between EDs are improved by adjustment for severity of illness using the RePEAT score. These results demonstrate that RePEAT is a reasonable marker of severity of illness and that inclusion of this severity index substantially improves the ability to compare outcomes between EDs.

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66.3 Principles Applicable to the Developing World

Jennifer I. Chapman and David M. Walker

International pediatric emergency medicine is an emerging academic field whose practitioners are committed to international collaboration aimed at improving the quality of care for children outside their national borders (Table 66-6).

Many models currently exist for the delivery of emergency care. The **triage officer** model is one in which a practitioner who works in an ED briefly provides intake for all patients and calls specialists to provide definitive care depending on the nature of the presenting complaint. The **multiple physician** model describes a scenario in which patients are divided by their chief complaints into medical, surgical, and pediatric groups. The field of emergency medicine provides a specialist skilled in the recognition, stabilization, and definitive treatment of a wide variety of acute illnesses and injuries. This approach to managing an emergency center is more efficient, relies less heavily on specialist availability, and requires fewer highly trained practitioners to operate. Children and adolescents constitute a subpopulation of emergency patients that deserves special attention because of pediatric-specific conditions, unique anatomy and physiology, developmental staging, and parental interactions.

The maturity of pediatric emergency medicine (PEM) in any given area depends on the healthcare priorities and resources of that geographic or physical setting. The places in which emergency care takes place range from the community (for those with no access to organized medical care) to state-of-the-art pediatric EDs in populated centers. The scope ranges from care of the individual patient to the management of populations of children involved in large-scale disasters. Barriers to quality care are different in each situation and in each part of the world, with the implication for the astute international PEM practitioner that solutions must be targeted to the local context of healthcare within a given environment.

Table 66-6 Pediatric Emergency Medicine (PEM) Professional Organizations

Pediatric Emergency Medicine Society of Australia and New Zealand (PEMS) Website: www.pems-aunz.org	Australia, New Zealand
PEM Section, Canadian Association of Emergency Physicians (CAEP)	Canada
PEM Section, Canadian Paediatric Society (CPS) Website: www.cps.ca/en/sections/section/emergency-medicine	Canada
Groupe Francophone de Réanimation et Urgences Pédiatriques (GFRUP) Website: www.gfrup.com	France
Society for Trauma and Emergency Pediatrics (STEP) Website: stepindia.org.in	India
Pediatric Emergency Medicine Israel (PEMI) Website: www.pemi.org.il	Israel
La Società Italiana di Medicina Emergenza ed Urgenza Pediatrica (SIMEUP) Website: www.simeup.com	Italy
La Asociación Nacional Mexicana de Urgencias/Emergencias Pediátricas (ANMUEP) Website: www.anmuep.org	Mexico
Sociedad Española de Urgencias de Pediatria (SEUP) Website: www.seup.org	Spain
Pediatric Emergency Medicine Switzerland (PEMS) Website: www.pems.ch	Switzerland
Çocuk Acil Tıp ve Yoğun Bakım Derneği (Society of Pediatric Emergency and Intensive Care Medicine) Website: www.cayd.org.tr	Turkey
PEM Section, European Society for Emergency Medicine (EuSEM) Website: www.eusem.org/sectionpaediatric/	Europe
Association of Paediatric Emergency Medicine (APEM) Website: www.apem.me.uk	UK
PEM Interest Group, Society for Academic Emergency Medicine (SAEM) Website: http://community.saem.org/saem/communities/viewcommunities/groupdetails?CommunityKey=3dc973c2-35fd-42c2-9dcf-99e69a20d206	USA
Section on Emergency Medicine, American Academy of Pediatrics (AAP) Website: www.aap.org/sections/pem	USA
PEM Section, American College of Emergency Physicians (ACEP) Website: www.acep.org/pediatricsection	USA

EMSC AND THE CONTINUUM OF CARE MODEL

EMSC is a U.S. federal initiative designed to reduce child and youth disability and death as a result of severe illness or injury. The EMSC program has developed an operational framework for conceptualizing a systems approach to emergency care for children, known as the *continuum of care model*. The model specifically refers to the seamless care of ill and injured children from the community and medical home through to definitive care and return to the community. It has the following 5 principal components:

1. Prevention
2. Out-of-hospital care, both emergency response and prehospital transport
3. Hospital-based care: emergency center and inpatient unit
4. Interfacility transport, as necessary, for definitive or subspecialty care (see Chapter 66.1)
5. Rehabilitation

This framework can also be applied to discussion of emergency care for children on an global level. With medical infrastructures that may not be consistent or well-organized, or that have been weakened by civil strife, natural disasters, and economic loss, the focus of child health in the developing world has been on prevention and acute care.

APPLYING THE CONTINUUM OF CARE MODEL TO THE DEVELOPING WORLD

Prevention

Infectious Diseases

International child health has focused mainly on reducing preventable childhood illnesses, primarily through immunizations. Enormous advances have been realized in measles, neonatal tetanus, and polio reduction; wild-type smallpox was eradicated in 1978. Although there are advocates for providing primary care interventions (e.g., vaccinations) in the ED, the role of the PEM practitioner in this area of prevention has been limited.

Injuries

Injuries are a leading cause of childhood morbidity and mortality. Unintentional injuries constitute 90% of injury mortality to children ages 5-19 yr and are the cause of 9% of the world's mortality. Intentional injuries, an underrecognized and underreported phenomenon primarily for cultural reasons, make a smaller but significant contribution. Unintentional injuries cause more than 2,000 childhood deaths daily or 950,000 annually worldwide. The burden of these deaths is borne disproportionately by children in middle- and lower-income

countries, where more than 95% of all injury deaths occur. For each of these deaths, many more children are permanently disabled and an even larger number are treated and released without permanent sequelae.

The World Health Organization (WHO) and United Nations Children's Fund (UNICEF) have outlined several proven injury prevention strategies of which child health practitioners in the global community must be aware. The top 3 causes of injury mortality are traffic-related injuries, burns, and drowning. There are 7 specific effective strategies for reducing **road traffic injuries:** a minimum drinking age, appropriate child restraints and seatbelts, helmets for motorcycle and bicycle riders, reduced vehicle speeds around schools and residential areas, running lights on motorcycles, graduated licensing for drivers, and separation of different types of road users. There is insufficient evidence to demonstrate that school-based programs on drunk driving, increased pedestrian visibility, or designated driver programs are effective. Although these strategies have been proven effective, the data are based on research from the United States and may not be generalizable to other countries. It may be difficult to reduce vehicle speeds around schools when there is insufficient infrastructure for street signs. Alternatively, lack of separation of car and bus traffic from bicyclists and pedestrians contributes to unsafe and dangerous road conditions. This is more of a problem in lower- and middle-income countries, where bicycles and motorized 2-wheel vehicles are used to carry children as well as goods, while the drivers negotiate among rapidly moving vehicles. With rising income, these countries have seen increases in both the number of cars and the number of 2-wheeled vehicles, with a corresponding increase in the number of related injuries.

For reducing **drowning deaths**, strategies that have proven effective focus on creating barriers between children and water hazards, such as covering wells, buckets, and other standing sources of water, and placing high fences around pools (see Chapter 74). **Burns** have been addressed by advocating for installation of smoke detectors and lowering the temperature of water from water heaters (see Chapter 75).

For the PEM practitioner, involvement in prevention depends largely on the local epidemiology of injuries and the factors contributing to those injuries. Involvement can include parental and patient education or activism to change local practices through laws and new community standards. Additionally, work can be done with groups of practitioners or healthcare centers to increase capacity to care for injured children. One can also work on a larger scale on projects initiated by a group such as the WHO, UNICEF, or Safe Kids Worldwide, to develop and evaluate intervention strategies that target specific preventable injuries.

Out-of-Hospital Care

Out-of-hospital care comprises access to emergency services, prehospital care, and interfacility transport of patients. Morbidity and mortality arise from delayed or limited access to emergency care, lack of prehospital care, transport without proper monitoring or trained personnel, or delayed transport to a higher level of care. Safe transport of seriously ill children is a neglected global health issue. An emergency response system must address the following links in the patient's care: a communication system with prompt activation of EMS, the correct assessment and initial treatment of the patient, and the rapid transport to definitive care.

Access to Care

When a child is injured or ill, a parent or caretaker must be able to access help and activate EMS. Many countries around the world have dedicated emergency numbers to rapidly dispatch medical, police, or fire services. The simple "112" emergency number has been adopted and is being phased in throughout the European Union member states, to be used to access medical, fire and police services in addition to secondary regional emergency access numbers. The universal U.S. emergency number system 911 today covers the large majority of the country (98%) and has enhanced features of automatically linking the phone number to an address. However, there remain limitations to universal access resulting from absence of phones in some households, unclear addresses in rural areas, and insufficient reach of the emergency system. In low- and middle-income countries, no such universal emergency numbers have been established, requiring access by direct dialing to an ambulance, if such private services exist. In most low- and middle-income countries, the family must bring the ill or injured child to the health facility for stabilization and treatment. For this to occur, families must overcome financial and geographic barriers, which can result in delayed presentation for care. This delay predictably increases the acuity of the illness or injury and associated complications, and decreases the likelihood of full recovery and survival.

Prehospital Care

In regions with maturing EMS systems, there must be adequately trained personnel to stabilize and transport the child to a medical facility. The quality and level of training of such prehospital personnel vary tremendously among countries and within regions of the same country. In urban areas, there is a greater concentration of medical care and therefore a greater opportunity to have strong prehospital training. In most of Asia and sub-Saharan Africa, trained personnel are used primarily to transfer patients between health facilities, and not from the initial site of illness or injury. In most high-income countries, EMS are dispatched to the patient.

A different approach to prehospital work is exemplified by the French EMS, called Service d'Aide Médicale Urgente (SAMU). In this system, a physician is integral to the prehospital team. A physician, typically an emergency medicine specialist in larger areas, will review every call for acuity and can dispatch a physician-led team by ambulance to go to the patient's home to assess, stabilize, and initiate treatment. This Franco-German system is used in other countries, including many in Latin America and Europe. There are no clear data on the cost-effectiveness and patient outcomes associated with delivery of patients to the nearest facility versus bringing hospital resources to the patient. Some research suggests, however, that it is difficult for ambulance-based physicians to maintain their field skills given the relatively low frequency of high-acuity or high-complexity cases.

Around the world, the effort to establish standardized approaches to prehospital care exists primarily in the form of courses to educate EMS and hospital personnel in the emergency management of patients. For trauma care, the WHO manuals *Prehospital Trauma Care Systems* and *Guidelines for Essential Trauma Care* both focus on guidelines for prehospital and trauma care systems that are affordable and sustainable. The AAP course Pediatric Education for Prehospital Professionals is a dynamic, modularized teaching tool designed to provide specific pediatric prehospital education that can be adapted to any EMS system. Table 66-7 lists additional prehospital resources.

Although most middle- and high-income countries have a system of trained EMS workers, low-income countries lack this advanced tier of emergency care. In these countries, commercial drivers, volunteers, and willing bystanders provide the first line of care. Training a cadre of first responders can rely on existing networks of aid or can be drawn from specific populations, such as students, soldiers, or public servants. Training needs to emphasize basic lifesaving and limb-saving interventions, including how to stop bleeding and support breathing, access advanced care, and splint broken limbs. In Ghana, for example, 335 taxi drivers participated in a first-aid course that relied heavily on demonstration and practice rather than knowledge transfer through didactic sessions. Taxi drivers were selected because they already provided much of the transport for injured patients, either voluntarily or for pay by the family. Two years after the course, external evaluators favorably rated the quality of their care in comparison with that of a group of untrained drivers. In rural areas, such first responders become vital in providing emergency interventions when more definitive care is distant. Thus, a system of trained first responders forms the foundation of an effective prehospital system.

Methods of Transport

In many low-income countries, there is no means of transport other than the family's motorized or other type of transport. Health centers may only have 1 vehicle for transport to a higher-level facility. This

Table 66-7	Pediatric Emergency Medicine (PEM) Resources
Prehospital	Advanced Medical Life Support (AMLS) Newest course developed by the National Association of Emergency Medical Technicians (NAEMT) to provide more clinical teaching and reasoning around emergent medical problems. Course is open to physicians, nurses EMTs and paramedics. Website: www.naemt.org/education/amls/amls.aspx
	Prehospital Trauma Life Support Available in 33 countries, PHTLS is the leading continuing education program for prehospital emergency trauma care. Website: www.phtls.org
	International Trauma Life Support Training course for prehospital trauma care. Website: www.itrauma.org
	The Sphere Project Downloadable modules on disaster preparedness. Website: www.sphereproject.org
	Pediatric Education for Prehospital Professionals (PEPP) Curriculum designed specifically to teach prehospital professionals how to assess and manage ill or injured children. Website: www.peppsite.org
	Pocket Book of Hospital Care for Children A publication of WHO providing guidelines for the management of common illnesses with limited resources. Incorporates both the Emergency Triage Assessment and Treatment (ETAT) and Integrated Management of Childhood Illness (IMCI) guidelines. Website: www.who.int/maternal_child_adolescent/documents/9241546700/en/index.html
Hospital care	Where There Is No Doctor: A Village Health Handbook Healthcare manual for health workers, clinicians, and others involved in primary healthcare delivery and health promotion programs around the world. Available for purchase or as a free download. Website: www.hesperian.org
	CHILDisaster Network Registry for those with education and experience in humanitarian emergencies to volunteer their time when needed in time of a disaster. Website: www.aap.org/disaster
Humanitarian emergencies	Management of Complex Humanitarian Emergencies: Focus on Children and Families Training course offered by the Children in Disasters Project, sponsored by the Rainbow Center for Global Child Health (RCGCH) in Cleveland, OH. Held in early June annually.
	Manual for the Health Care of Children in Humanitarian Emergencies Publication of WHO that provides comprehensive guidance on child care in emergencies; includes information on care of traumatic injuries and mental health emergencies. Website: www.who.int/child_adolescent_health/documents/9789241596879/en/index.html
	PEMdatabase.org A website devoted to pediatric emergency medicine. Contains links to conferences, evidence-based medicine reviews, research networks, and professional organizations. Website: www.pemdatatbase.org
Access to academic publications relevant to PEM	HINARI Access to Research Initiative Program established by WHO and others to enable developing countries to gain access to one of the world's largest collections of biomedical and health literature. Website: www.who.int/hinari/en
	ACEP Ambassador Program Provides the names of U.S.-boarded emergency medicine physicians who can provide advice and information on issues pertaining to the progress and status of emergency medicine in their assigned countries. Website: www.acep.org/content.aspx?id=25138
Involvement	International emergency medicine section, American College of Emergency Physicians This group maintains a list of international organizations and clinical opportunities, many of which involve emergency care of children. Website: http://www.acep.org/_InternationalSection/International-Emergency-Medicine-Related-Resources/
	Section of International Child Health, American Academy of Pediatrics Lists of non-U.S. clinical opportunities, many of which involve emergency care. Website: http://www2.aap.org/sections/ich/working_overseas.htm
	U.S. Agency for International Development (USAID) Government agency providing U.S. economic and humanitarian assistance worldwide. Website: www.usaid.gov
	WHO Publication catalog, media resources, health articles, and current health news. Website: www.who.int/topics/child_health/en
Health organizations involved in international PEM activities	UNICEF Organization dedicated to providing lifesaving assistance to children affected by disasters and to protecting their rights in any circumstances. Website: www.unicef.org
	Safe Kids Worldwide The first and only international nonprofit organization dedicated solely to preventing unintentional childhood injury. Website: www.safekids.org

vehicle may also be used for outreach primary care services, such as offering immunizations and collecting drugs and equipment from a central supply location, and, sometimes, improperly for personal reasons by local officials or politicians. In large cities, taxis and auto rickshaws are frequently used because they are rapidly available and well disseminated within cities. Where there are organized prehospital systems, different types of vehicles are adapted for emergency transportation, from fully equipped ambulances to basic transport with trained personnel. The WHO recommends identifying transport vehicles in advance, choosing vehicles that can be repaired and maintained locally, and equipping the vehicles according to recognized standards. Therefore the provision of available and appropriately staffed and equipped transport vehicles is crucial to the realization of recommended emergency care plans.

Hospital-Based Care

Once a child has reached a medical facility for the care of an injury or illness, adequate emergency services must be available. In many countries, the ED serves only as a triage area where patients are distinguished by their likely disease process and directed for admission to the corresponding unit within the hospital. Strengthening emergency services includes seeing the ED as a unit where definitive treatment can be provided to the ill and injured child. Critically ill children must receive not only prompt care but also correct care. Such expedience and accuracy are ensured by implementation of an effective triage system, moving the sickest patients to immediate care and standardizing the initial care of emergency conditions.

Triage

Children requiring emergency care frequently are not promptly recognized. Too often, children presenting to EDs are treated on a first-come first-served basis, in an approach that creates long waiting times for critically ill children, a contributor to unnecessary mortality. Medical facilities need to adopt an efficient and effective triage system in order to rapidly respond to the needs of patients and to assign the appropriate amount of resources. To this end, WHO has developed a course entitled Emergency Triage Assessment and Treatment (ETAT). This course teaches health practitioners to triage patients on arrival as having emergency, priority, or nonurgent signs and to provide emergency treatment for life-threatening conditions. ETAT emphasizes the evaluation of a patient's ABCD status to identify emergency situations—the patency of the airway (A), the quality of breathing (B), the quality of circulation and presence of coma or convulsions (C), and the presence of severe dehydration (D).

One of the benefits of the ETAT guidelines is that they can be adapted to centers with limited resources and are applicable to areas with high morbidity and mortality from meningitis, dehydration, malaria, respiratory illness, and malnutrition. Another benefit is that the care algorithms are based on limited diagnostic studies, that is, hemoglobin measurement, blood smear for malaria, and bedside blood glucose testing. Widely accepted triage assessment guidelines are teachable to emergency care staff, and their adoption can provide better organization within a healthcare center. At the Queen Elizabeth Central Hospital in Blantyre, Malawi, for example, the institution of triage and rapid treatment in its emergency care center led to a 50% decrease in the mortality of children within 24 hr of presentation to the hospital, with a further 50% decrease as implementation and practice of triaging patients have continued.

Beyond triage, education on overall emergency center organization is a low-resource intervention that can obviate some of the obstacles to quality care delivery. Additionally, the arrangement of short-stay areas (hydration and infusion rooms) can lessen the burden on inpatient units.

Pediatric-Specific Emergency Centers

Descriptions on the development of pediatric-specific emergency centers are insufficient. Anecdotally, most countries have developed at least 1 pediatric-capable center, usually as part of an academic medical center. The emergency services in these centers are variable, but certainly can be a starting point from which to build overall improvement in pediatric emergency care.

Practitioners

Throughout the world, nurses, paramedics, and nonspecialist physicians provide most of the care to acutely ill or injured children. The majority of sick children attend local clinics or district or central hospitals, where financial and human resources are not always matched to the potential acuity of presenting patient complaints. Nominal supervision is provided to staff attending these patients. Pediatric EDs located in tertiary hospitals are often staffed by training physicians with little or no supervision from faculty, who themselves may have limited exposure to or training in PEM. General hospitals lack dedicated pediatric staff; guidelines as to which patients should be moved to a higher level of care are often not standardized and depend on local influences and/or cultural beliefs about health and illness.

Clinical Guidelines

The Integrated Management of Childhood Illnesses (IMCI) guidelines were developed by the WHO and UNICEF to provide assistance in the initial triage and management of the presenting signs and symptoms of the major killers of the under–5 yr population in first-level health facilities (e.g., clinics, health centers, and outpatient departments of hospitals). The flow charts within each chapter of the IMCI manuals allow easy accessibility to materials that can enhance education and outreach to less experienced health workers.

Evaluations in various countries of the implementation of IMCI guidelines have shown improvements in health worker performance and quality of care as well as decreases in delay in treatment and mortality of under–5 yr children. These guidelines also dramatically reduce the cost of healthcare. The WHO website provides all the necessary implementation tools, including course manuals and evaluation tools.

Trauma

Morbidity and mortality from trauma is one of the most prevalent problems for children worldwide. Trauma care presents the challenge of sequential, often simple, interventions that must be performed in a timely manner to limit the severity of the outcome. However, with lack of specific training, signs and symptoms of pediatric trauma may go unrecognized or may be underappreciated. Trauma courses such as Advanced Trauma Life Support are educational tools that can be disseminated to improve the quality of care at emergency centers worldwide. For low-resource settings, the WHO has developed the Integrated Management for Emergency and Essential Surgical Care toolkit, which provides clear directions and reasoning for the initial care of injured patients. Not expressly addressed in the Advanced Trauma Life Support course is specific concern about child abuse as the cause of trauma. This is an area of pediatric care that many countries do not yet address in their medical training, their law enforcement, or their judicial systems. The epidemiologic need for reliable trauma registries is great, as is the need to identify personnel with trauma management skill sets and dedicated trauma centers to serve as higher-level referral sites.

Equipment

Pediatric emergency textbooks, pediatric and emergency medicine professional organizations, WHO, and nongovernmental and governmental health organizations have all published pediatric emergency equipment guidelines, for a variety of settings in which acutely ill and injured children would present. Although these equipment guidelines may represent minimum supplies to treat the widest variety of pediatric emergencies, the roles of substitution and improvisation often provide for equivalent function of recommended supplies.

Inpatient Services

After the initial stabilization, children requiring ongoing care are admitted to the hospital. The quality of inpatient services varies greatly depending on institutional and provider experience, comfort with pediatric conditions, and the resources available to treat them. The WHO has produced the *Pocket Book of Hospital Care for Children,*

which is based on IMCI guidelines and focuses on inpatient management of high-morbidity/high-mortality illnesses common in developing countries.

HUMANITARIAN DISASTERS

Children are a vulnerable population who experience disproportionate suffering during humanitarian emergencies, either natural (earthquakes, tsunamis, hurricanes, floods, and droughts) or manmade (armed conflicts, terrorist attacks). The under–5 yr population is especially susceptible to infectious diseases, malnutrition, and trauma following disasters. The Rainbow Center for Global Child Health at the Case Western Reserve University School of Medicine offers a training course, Management of Humanitarian Emergencies: Focus on Children and Families, that concentrates on the needs of children in disasters. The intent of the Center is to educate and train health professionals, relief workers, and policymakers to recognize and address the unique needs of children affected by manmade and natural disasters worldwide. The AAP also maintains a CHILDisaster Network, which acts as an electronic database of child health professionals with education and experience in humanitarian emergencies. Nongovernmental organizations can access the database to solicit practitioners to aid in disaster response.

The WHO's *Manual for the Health Care of Children in Humanitarian Emergencies* is based on IMCI guidelines and addresses the emergency care of children in disaster situations in which hospital facilities and resources are not immediately available. It goes beyond the IMCI guidelines by discussing initial assessment and management of trauma, burns, and poisonings. Preexisting IMCI guidelines assumed a functioning health system that facilitated the referral of children, which may not be available in all emergency situations. This manual also includes the initial management of severe conditions, such as injuries, burns, neonatal illness, and psychosocial problems, which are considered high priority in acute care settings.

Exchange and Dissemination of Information

The WHO established the HINARI (Health InterNetwork Access to Research Initiative) program to allow free or reduced-cost access to more than 6,200 journal publications. This Internet access is made available to the 108 countries with gross national income per capita less than $3,500. For middle-income countries not meeting the financial eligibility, Internet access continues to be a barrier, and resources may be limited to out-of-date textbooks and journals.

Another valuable tool is the website Pemdatabase.org. This nonproprietary site was started as an online resource for PEM practitioners. It contains links to PEM abstracts and articles, evidence-based reviews, pediatric resuscitation websites, relevant journals, as well as PEM conferences and professional organizations.

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Chapter 67

Pediatric Emergencies and Resuscitation

Mary E. Hartman and Ira M. Cheifetz

Injuries are the leading cause of death in American children and young adults and are responsible for more childhood deaths than all other causes combined (see Chapter 5.1). Children are particularly vulnerable to injury for a number of reasons, including their small size, relative physical uncoordination, and limited ability to predict or understand danger. In addition, the immaturity of their developing bones, ligaments, and muscles; their thin body walls; and their relatively large heads, compared with total body surface area, make young children susceptible to serious or fatal injury from falls and collisions.

Most injuries in childhood are unintentional, and many are preventable. Motor vehicle–related injuries are the most common cause of unintentional injury and death for U.S. children, many of which are related to speeding, aggressive driving, failure to use proper passenger restraints, and/or alcohol. Consistent use of bicycle helmets could reduce the severity of head injuries, the leading cause of death when a bicyclist is struck by a car, by more than 80%. Four-sided fencing around swimming pools and use of flotation devices for every passenger in a boat could greatly reduce the risk of drowning, the second leading cause of accidental death in children younger than 5 yr and the third major cause of death in adolescents. Serious injuries can become fatal when appropriate medical care is delayed.

Rapid, effective bystander cardiopulmonary resuscitation (CPR) for children is associated with survival rates as high as 70%, with good neurologic outcome. However, bystander CPR is still provided for less than 50% of children who experience cardiac arrest outside medical settings. This has led to long-term survival rates of <40%, with many survivors suffering a poor neurologic outcome.

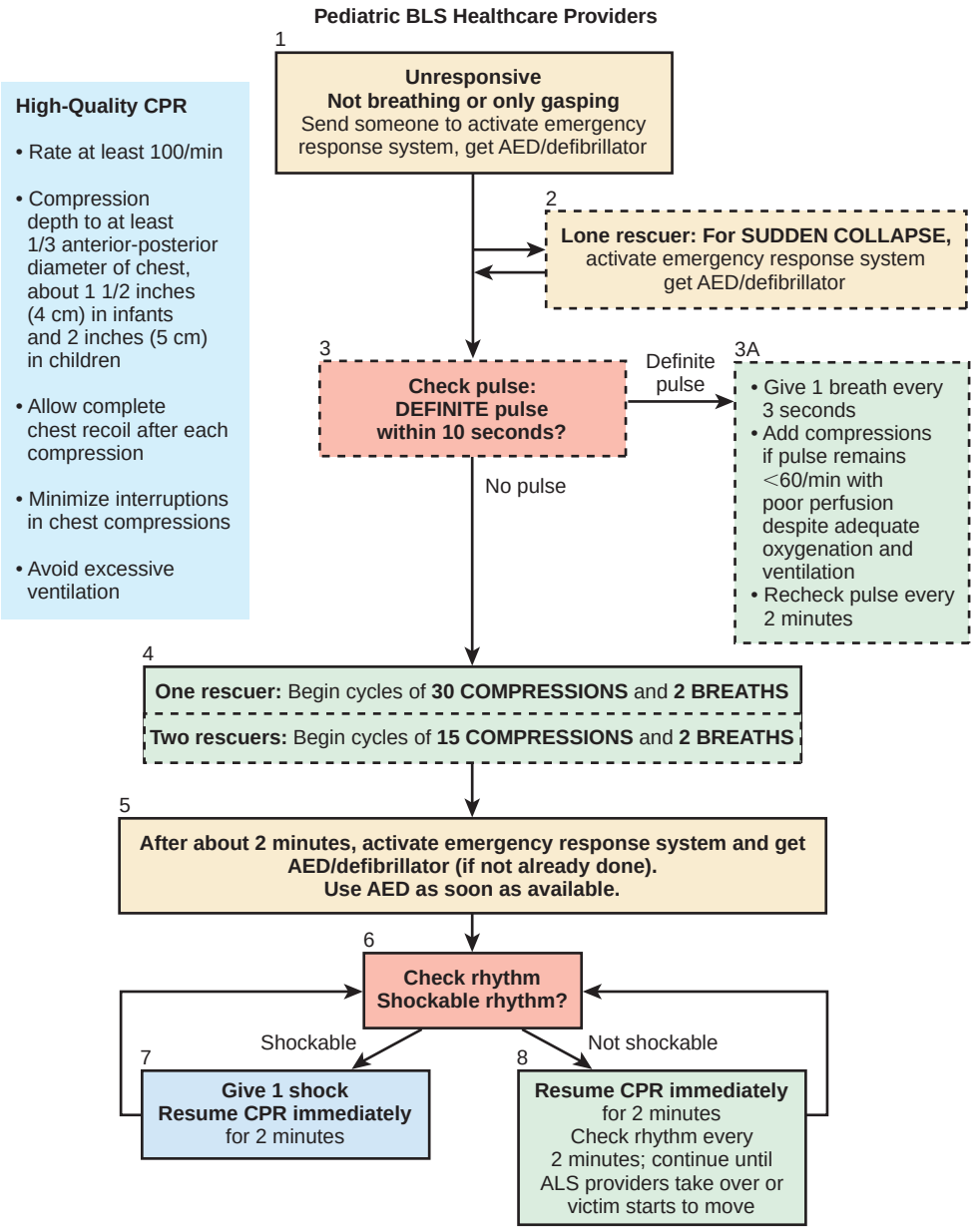
APPROACH TO THE EMERGENCY EVALUATION OF A CHILD

The first response to a pediatric emergency of any cause is a systematic, rapid **general assessment** of the scene and the child to identify immediate threats to the child, care providers, or others. If an emergency is identified, the emergency response system (emergency medical services [EMS]) should be activated immediately. Care providers should then proceed through **primary**, **secondary**, and **tertiary assessments** as allowed by the child's condition, safety of the scene, and resources available. This standardized approach provides organization to what might otherwise be a confusing or chaotic situation and reinforces an organized thought process for care providers. If, at any point in these assessments, the caregiver identifies a life-threatening problem, the assessment is halted and lifesaving interventions are begun. Further assessment and intervention should be delayed until other caregivers arrive or the condition is successfully treated.

General Assessment

Upon arrival at the scene of a compromised child, a caregiver's first task is a quick survey of the scene itself. Is the rescuer or child in imminent danger because of circumstances at the scene (fire, high-voltage electricity)? If so, can the child be safely extricated to a safe location for assessment and treatment? Can the child be safely moved with the appropriate precautions (i.e., cervical spine protection), if indicated? A rescuer is expected to proceed only if these safety conditions have been met.

Once the caregiver and patient's safety has been ensured, the caregiver performs **a rapid visual survey** of the child, assessing the child's **general appearance and cardiopulmonary function**. This action should be very quick (only a few seconds) and should include assessment of (1) general appearance (determining color, tone, alertness, and responsiveness); (2) adequacy of breathing (distinguishing between normal, comfortable respirations and respiratory distress or apnea); and (3) adequacy of circulation (identifying cyanosis, pallor, or mottling). A child found unresponsive from an *unwitnessed* collapse should be approached with a gentle touch and the verbal question, "Are you OK?" If there is no response, the caregiver should immediately shout for help and send someone to both activate the emergency response system (EMS) and locate an automated external defibrillator (AED) (Fig. 67-1). The provider should then determine whether the child is breathing and, if not, provide 2 rescue breaths as described later under "Recognition and Treatment of Respiratory Distress and Failure." If the child is adequately breathing, then the circulation is quickly assessed. Any child with a heart rate below 60 beats/min or without a pulse requires immediate CPR, as described under



Note: The boxes bordered with dashed lines are performed by healthcare providers and not by rescuers

Figure 67-1 Pediatric basic life support algorithm. AED, automated external defibrillator; ALS, advanced life support; CPR, cardiopulmonary resuscitation. *(From Berg MD, Schexnayder SM, Chameides L, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 13,* Circulation *122[Suppl 3]:S862–S875, 2010, Fig. 3, p. S866.)*

"Recognition and Management of Cardiac Arrest." If the caregiver *witnesses* the sudden collapse of a child, the caregiver should have a higher suspicion for a sudden cardiac event. In this case, rapid deployment of an AED is of paramount importance. The provider should very briefly delay care of the child to activate EMS and locate the nearest AED.

Primary Assessment

Once the emergency response system has been activated and the child is determined not to need CPR, the caregiver should proceed with a primary assessment that includes a **brief, hands-on assessment of cardiopulmonary and neurologic function and stability**. This assessment includes a limited physical exam, evaluation of vital signs, and measurement of pulse oximetry if possible. Again, a standardized approach is best. The American Heart Association, in its Pediatric Advanced Life Support (PALS) curriculum, supports the structured format of **Airway, Breathing, Circulation, Disability, Exposure (ABCDE)**. The goal of the primary assessment is to obtain a focused, systems-based assessment of the child's injuries or abnormalities, so that resuscitative efforts can be directed to these areas; if the caregiver identifies a life-threatening abnormality, further evaluation is postponed until appropriate corrective action has been taken.

The exam and vital sign data can be interpreted only if the caregiver has a thorough understanding of normal values. In pediatrics, normal respiratory rate, heart rate, and blood pressure have age-specific norms (Table 67-1). These ranges can be difficult to remember, especially if used infrequently. However, several standard principals apply: (1) no child's respiratory rate should be >60 breaths/min for a sustained period; (2) normal heart rate is roughly 2-3 times normal respiratory rate for age; and (3) a simple guide for pediatric blood pressure is that

Table 67-1 Normal Vital Signs According to Age

AGE	HEART RATE (beats/min)	BLOOD PRESSURE (mm Hg)	RESPIRATORY RATE (breaths/min)
Premature	120-170*	55-75/35-45†	40-70‡
0-3 mo	100-150*	65-85/45-55	35-55
3-6 mo	90-120	70-90/50-65	30-45
6-12 mo	80-120	80-100/55-65	25-40
1-3 yr	70-110	90-105/55-70	20-30
3-6 yr	65-110	95-110/60-75	20-25
6-12 yr	60-95	100-120/60-75	14-22
12+ yr	55-85	110-135/65-85	12-18

*In sleep, infant heart rates may drop significantly lower, but if perfusion is maintained, no intervention is required.
†A blood pressure cuff should cover approximately two-thirds of the arm; too small a cuff yields spuriously high pressure readings, and too large a cuff yields spuriously low pressure readings.
‡Many premature infants require mechanical ventilatory support, making their spontaneous respiratory rate less relevant.

Table 67-2 AVPU Neurologic Assessment

A	The child is awake, alert, and interactive with parents and care providers
V	The child responds only if the care provider or parents call the child's name or speak loudly
P	The child responds only to painful stimuli, such as pinching the nail bed of a toe or finger
U	The child is unresponsive to all stimuli

From Ralston M, Hazinski MF, Zaritsky AL, et al, editors: Pediatric advanced life support course guide and PALS provider manual: provider manual, *Dallas, 2007, American Heart Association.*

Table 67-3 Glasgow Coma Scale

EYE OPENING (TOTAL POSSIBLE POINTS 4)			
Spontaneous	4		
To voice	3		
To pain	2		
None	1		
VERBAL RESPONSE (TOTAL POSSIBLE POINTS 5)			
OLDER CHILDREN		**INFANTS AND YOUNG CHILDREN**	
Oriented	5	Appropriate words; smiles, fixes, and follows	5
Confused	4	Consolable crying	4
Inappropriate	3	Persistently irritable	3
Incomprehensible	2	Restless, agitated	2
None	1	None	1
MOTOR RESPONSE (TOTAL POSSIBLE POINTS 6)			
Obeys	6		
Localizes pain	5		
Withdraws	4		
Flexion	3		
Extension	2		
None	1		

Adapted and modified from Teasdale G, Jennett B: Assessment of coma and impaired consciousness: a practical scale, Lancet *2:81–84, 1974.*

the lower limit of systolic blood pressure should be ≥60 mm Hg for neonates; ≥70 mm Hg for 1 mo-1 yr olds; ≥70 mm Hg + (2 × age) for 1-10 yr olds; and ≥90 mm Hg for any child older than 10 yr.

Airway and Breathing

The most common precipitating event for cardiac instability in infants and children is respiratory insufficiency. Therefore, rapid assessment of respiratory failure and immediate restoration of adequate ventilation and oxygenation remain the first priority in the resuscitation of a child. Using a systematic approach, the caregiver should first assess whether the child's airway is patent and maintainable. A healthy, patent airway is open and unobstructed, allowing normal respiration without noise or effort. A maintainable airway is one that is either already patent or can be made patent with a simple maneuver. To assess airway patency, the provider should look for breathing movements in the child's chest and abdomen, listen for breath sounds, and feel the movement of air at the child's mouth and nose. Abnormal breathing sounds (i.e., snoring or stridor), increased work of breathing, and apnea are all findings potentially consistent with airway obstruction. If there is evidence of airway obstruction, then maneuvers to relieve the obstruction should be instituted before the caregiver proceeds to evaluate the child's breathing (see under "Recognition and Treatment of Respiratory Distress and Failure").

Assessment of breathing includes evaluation of the child's respiratory rate, respiratory effort, abnormal sounds, and pulse oximetry. Normal breathing appears comfortable, is quiet, and occurs at an age-appropriate rate. Abnormal respiratory rates include apnea and rates that are either too slow (bradypnea) or too fast (tachypnea). **Bradypnea and irregular respiratory patterns require urgent attention, as they are often signs of impending respiratory failure and apnea.** Signs of increased respiratory effort include nasal flaring, grunting, chest or neck muscle retractions, head bobbing, and "seesaw" respirations. Hemoglobin oxygen desaturation, as measured by pulse oximetry, often accompanies parenchymal lung disease apnea or airway obstruction. However, providers should keep in mind that adequate perfusion is required to produce a reliable oxygen saturation measurement. A child with low oxygen saturation is a child in distress. Central cyanosis is a sign of severe hypoxia and indicates an emergent need for oxygen supplementation and respiratory support.

Circulation

Cardiovascular function is assessed by evaluation of skin color and temperature, heart rate, heart rhythm, pulses, capillary refill time, and blood pressure. In nonhospital settings, much of the important information can be obtained without measuring the blood pressure; lack of blood pressure data should not prevent the provider for determining adequacy of circulation or implementing a lifesaving response. Mottling, pallor, delayed capillary refill, cyanosis, poor pulses, and cool extremities are all signs of diminished perfusion and compromised cardiac output. Tachycardia is the earliest and most reliable sign of shock, but is itself fairly nonspecific and should be correlated with other components of the exam, such as weakness, threadiness, and absence of pulses. An age-specific approach to pulse assessment will yield best results.

Disability

In the setting of a pediatric emergency, *disability* refers to a child's neurologic function in terms of the level of consciousness and cortical function. Standard evaluation of a child's neurologic condition can be done quickly with an assessment of pupillary response to light (if one is available) and use of either of the standard scores used in pediatrics: the Alert, Verbal, Pain, Unresponsive (AVPU) Pediatric Response Scale and the Glasgow Coma Scale (GCS) (Tables 67-2, 67-3, and 68-1). The causes of decreased level of consciousness in children are numerous and include conditions as diverse as respiratory failure with hypoxia or hypercarbia, hypoglycemia, poisonings or drug overdose, trauma, seizures, infection, and shock. **Most commonly, an ill or injured child has an altered level of consciousness because of respiratory compromise, circulatory compromise, or both**. Any child with a depressed

level of consciousness should be immediately assessed for abnormalities in cardiorespiratory status.

The Alert, Verbal, Pain, Unresponsive Pediatric Response Scale. The AVPU scoring system is used to determine both a child's level of consciousness and cerebral cortex function. Unlike the GCS (see later), the AVPU scale is not developmentally dependent—a child does not have to understand spoken language or follow commands, merely respond to a stimulus. The child is scored according to the amount of stimulus required to get a response, from alert (no stimulus, the child is already awake and interactive) to unresponsive (child does not respond to any stimulus) (see Table 67-2).

The Glasgow Coma Scale. Although the GCS has not been validated as a prognostic scoring system for infants and young children as it has been in adults, it is commonly used in the assessment of pediatric patients with an altered level of consciousness. The GCS is the most widely used method of evaluating a child's neurologic function and has 3 components. Individual scores for eye opening, verbal response, and motor response are added together, with a maximum of 15 points (see Table 67-3). Patients with a GCS score ≤8 require aggressive management, including stabilization of the airway and breathing with endotracheal intubation and mechanical ventilation, respectively, and, if indicated, placement of an intracranial pressure monitoring device. The Full Outline of Unresponsiveness (FOUR) score is another useful assessment and monitoring tool (see Table 68-1).

Exposure

Exposure is the final component of the pediatric primary assessment. This component of the exam is reached only after the child's airway, breathing, and circulation have been assessed and determined to be stable or have been stabilized through simple interventions. In this setting, *exposure* stands for the dual responsibility of the provider to both expose the child to assess for previously unidentified injures and consider prolonged exposure in a cold environment as a possible cause of hypothermia and cardiopulmonary instability. The provider should undress the child (as is feasible and reasonable) to perform a focused physical exam, assessing for burns, bruising, bleeding, joint laxity, and fractures. If possible, the provider should assess the child's temperature. All maneuvers should be performed with careful maintenance of cervical spine precautions.

Secondary Assessment

For care providers in community or outpatient settings, transfer of care of a child to emergency or hospital personnel may occur before a full secondary assessment is possible. However, before the child is removed from the scene and separated from witnesses or family, a brief history should be obtained for medical providers at the accepting facility. **The components of a secondary assessment include a focused history and focused physical exam.**

The history should be targeted to information that could explain cardiorespiratory or neurologic dysfunction and should take the form of a **SAMPLE history (Signs/symptoms, Allergies, Medications, Past medical history, timing of Last meal, and Events leading to this situation)**. Medical personnel not engaged in resuscitative efforts can be dispatched to elicit history from witnesses or relatives. The physical exam during the secondary assessment is a thorough head-to-toe exam, although the severity of the child's illness or injury could necessitate curtailing portions of the exam or postponing nonessential elements until a later time.

Tertiary Assessment

The tertiary assessment occurs in a hospital setting, where ancillary laboratory and radiographic assessments contribute to a thorough understanding of the child's condition. A basic blood chemistry profile, complete blood count, liver function tests, coagulation studies, and arterial blood gas analyses give fairly broad (but somewhat nonspecific) estimates of renal function, acid–base balance, cardiorespiratory function, and presence or absence of shock. Chest radiographs can be useful to evaluate both the heart and lungs, although more detailed estimates of heart function and cardiac output can be made with echocardiography. Arterial and central venous catheters can be placed to monitor arterial and central venous pressure (see under "Vascular Access").

RECOGNITION AND TREATMENT OF RESPIRATORY DISTRESS AND FAILURE

The goals of initial management of respiratory distress or failure are to rapidly stabilize the child's airway and breathing and to identify the cause of the problem so that further therapeutic efforts can be appropriately directed.

Airway Obstruction

Children <5 yr old are particularly susceptible to foreign-body aspiration and choking. Liquids are the most common cause of choking in infants, whereas small objects and food (e.g., grapes, nuts, hot dogs, candies) are the most common source of foreign bodies in the airways of toddlers and older children. A history consistent with foreign-body aspiration is considered diagnostic. Any child in the proper setting with the sudden onset of choking, stridor, or wheezing has foreign-body aspiration until proven otherwise.

Airway obstruction is treated with a sequential approach, starting with the head-tilt/chin-lift maneuver to open and support the airway, followed by inspection for a foreign body, and finger-sweep clearance or suctioning if one is visualized (Fig. 67-2). Blind suctioning or finger sweeps of the mouth **are not recommended**. A nasopharyngeal airway or oropharyngeal airway can be inserted for airway support, if indicated. A conscious child suspected of having a partial foreign-body obstruction should be permitted to cough spontaneously until coughing is no longer effective, respiratory distress and stridor increase, or the child becomes unconscious.

If the child becomes unconscious, the child should be gently placed on the ground, supine. The provider should then open the airway with the head-tilt/chin-lift maneuver and attempt mouth-to-mouth ventilation (Figs. 67-3 and 67-4). If ventilation is unsuccessful, the airway is repositioned, and ventilation attempted again. If there is still no chest rise, attempts to remove a foreign body are indicated. In an infant <1 yr old, a combination of 5 back blows and 5 chest thrusts is administered

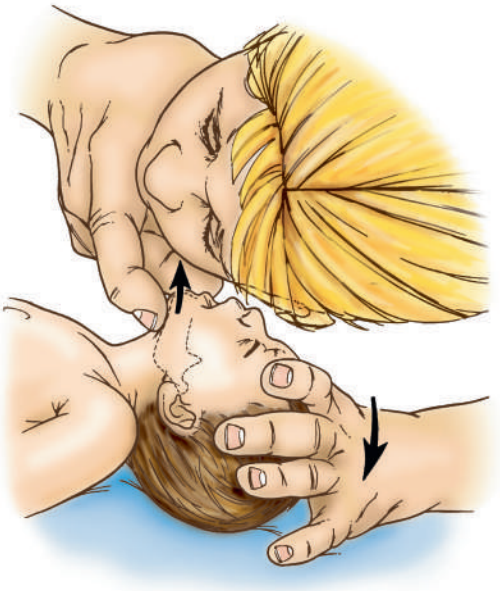


Figure 67-2 Opening the airway with the head-tilt/chin-lift maneuver. One hand is used to tilt the head, extending the neck. The index finger of the rescuer's other hand lifts the mandible outward by lifting the chin. Head-tilt should not be performed if a cervical spine injury is suspected. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

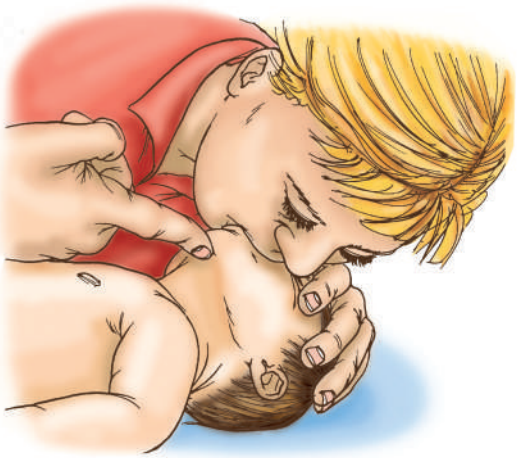


Figure 67-3 Rescue breathing in an infant. The rescuer's mouth covers the infant's nose and mouth, creating a seal. One hand performs the head-tilt while the other hand lifts the infant's jaw. Avoid head-tilt if the infant has sustained head or neck trauma. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Figure 67-4 Rescue breathing in a child. The rescuer's mouth covers the child's mouth, creating a mouth-to-mouth seal. One hand maintains the head-tilt; the thumb and forefinger of the same hand are used to pinch the child's nose. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

(Fig. 67-5). After each cycle of back blows and chest thrusts, the child's mouth should be visually inspected for the presence of the foreign body. If identified within finger's reach, it should be removed with a gentle finger sweep. If no foreign body is visual, ventilation is again attempted. If this is unsuccessful, the head is repositioned, and ventilation attempted again. If there is no chest rise, the series of back blows and chest thrusts is repeated.

For a conscious child >1 yr old, providers should give a series of 5 abdominal thrusts (Heimlich maneuver) with the child standing or sitting (Fig. 67-6); this should occur with the child lying down if unconscious (Fig. 67-7). After the abdominal thrusts, the airway is examined for a foreign body, which should be removed if visualized. If no foreign body is seen, the head is repositioned, and ventilation attempted. If it is unsuccessful, the head is repositioned and ventilation is attempted again. If these efforts are unsuccessful, the Heimlich sequence is repeated.

Figure 67-5 Back blows *(top)* and chest thrusts *(bottom)* to relieve foreign-body airway obstruction in the infant. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Figure 67-6 Abdominal thrusts with the victim standing or sitting (conscious). *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Figure 67-7 Abdominal thrusts with victim lying (conscious or unconscious). *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Airway Narrowing

Airway obstruction can also be caused by airway narrowing, in both the upper and lower airways. *Upper airway obstruction* refers to narrowing of the extrathoracic portion of the airway, including the oropharynx, larynx, and trachea. In the upper airways, narrowing is most often caused by airway edema (croup or anaphylaxis). Lower airway disease affects all intrathoracic airways, notably the bronchi and bronchioles. In the lower airways, bronchiolitis and acute asthma exacerbations are the major contributors to intrathoracic airway obstruction in children, causing airway narrowing through a combination of airway swelling, mucus production, and circumferential smooth muscle constriction of smaller airways.

Airway support for these processes is dictated by both the underlying condition and the clinical severity of the problem. In cases of mild upper airway obstruction, the child has minimally elevated work of breathing (evidenced by tachypnea and few to mild retractions). Stridor, if present at all, should be audible with only coughing or activity. Children with these findings can be supported with nebulized cool mist and supplemental oxygen as needed. In cases with moderate obstruction, in which the child has a higher work of breathing and more pronounced stridor, nebulized racemic epinephrine and oral or intravenous (IV) dexamethasone can be added. Children with severe upper airway obstruction have marked retractions, prominent stridor, and decreased air entry on auscultation of the lung fields. Most children with significant airway obstruction are also hypoxic, and many appear dyspneic and agitated. A child in severe distress needs to be closely observed, as the signs of impending respiratory failure may be initially confused with improvement. Stridor becomes quieter and retractions less prominent when a child's respiratory effort begins to diminish. The child in respiratory failure can be distinguished from one who is improving by evidence of poor air movement on auscultation and lethargy or decreased level of consciousness from hypercarbia, hypoxia, or both. When anaphylaxis is suspected as the cause for upper airway edema, providers should administer an intramuscular or IV dose of epinephrine as needed (see Chapter 149). No matter the cause, any child in impending respiratory failure should be prepared for endotracheal intubation and respiratory support.

In cases of lower airway obstruction, therapies are targeted to both relieving the obstruction and reducing the child's work of breathing. Inhaled bronchodilators, such as albuterol, augmented by oral or IV corticosteroids, remain the mainstay of therapy in settings of mild to moderate acute distress caused by lower airway obstruction. Children with more significant obstruction appear dyspneic, with tachypnea, retractions, and easily audible wheezing. In these cases, the addition of an anticholinergic agent, such as nebulized ipratropium bromide, or a smooth muscle relaxant, such as magnesium sulfate, may provide further relief, although the evidence for these measures remains controversial (see Chapter 144). Supplemental oxygen and IV fluid hydration can also be useful adjuncts. As in cases of upper airway obstruction, impending respiratory failure in children with lower airway obstruction can be insidious. When diagnosed early in a school-age child who is cooperative, respiratory failure can be averted through judicious use of noninvasive support, with continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or heliox (combined helium-oxygen therapy). Endotracheal intubation should be performed only by skilled providers, preferably in a hospital setting, because there is a high risk of respiratory and circulatory compromise in patients with lower airway obstruction during the procedure.

Parenchymal Lung Disease

Parenchymal lung disease includes a heterogeneous list of conditions, such as pneumonia, acute respiratory distress syndrome, pneumonitis, bronchiolitis, bronchopulmonary dysplasia, cystic fibrosis, and pulmonary edema. The commonalities of these conditions are their effects on the small airways and alveoli, including inflammation and exudation leading to consolidation of lung tissue, decreased gas exchange, and increased work of breathing. Clinical management of these conditions includes specific treatment as indicated (i.e., antibiotics for bacterial pneumonia) and supportive care in the form of supplemental oxygen, noninvasive respiratory support (with CPAP or BiPAP), or invasive mechanical ventilation.

Advanced Airway Management Techniques

Bag-Valve-Mask Positive Pressure Ventilation

Rescue breathing with a bag-valve-mask apparatus can be as effective as endotracheal intubation and safer when the provider is inexperienced with intubation. Bag-valve-mask ventilation itself requires training to ensure that the provider is competent to select the correct mask size, open the child's airway, form a tight seal between the mask and the child's face, deliver effective ventilation, and assess the effectiveness of the ventilation. An appropriately sized mask is one that fits over the child's mouth and nose but does not extend below the chin or over the eyes (Fig. 67-8). An adequate seal is best achieved via a combination "C–E" grip on the mask, in which the thumb and index finger form the letter "C" on top of the mask, pressing the mask downward onto the child's face, and the remaining 3 fingers form an "E" grip under the child's mandible, holding the jaw forward and extending the head up toward the mask. Using this method, the care provider can secure the mask to the child's face with 1 hand and use the other hand to compress the ventilation bag (Fig. 67-9).

The provider may have to move the head and neck through a range of positions to find the one that best maintains airway patency and allows maximal ventilation. In infants and young children, optimal ventilation is often provided when the child's head is in the neutral "sniffing" position without hyperextension of the head (Fig. 67-10). Poor chest rise and persistently low oxygen saturation values indicate inadequate ventilation. In this setting, the care provider should recheck the mask's seal on the child's face, reposition the child's head, and consider suctioning the airway if indicated. If these maneuvers do not restore ventilation, then the provider should consider endotracheal intubation.

Endotracheal Intubation

A child requires intubation when at least 1 of these conditions exists: (1) the child is unable to maintain airway patency or protect the airway against aspiration (as occurs in settings of neurologic compromise); (2) the child is failing to maintain adequate oxygenation; (3) the child is failing to control blood carbon dioxide levels and maintain safe

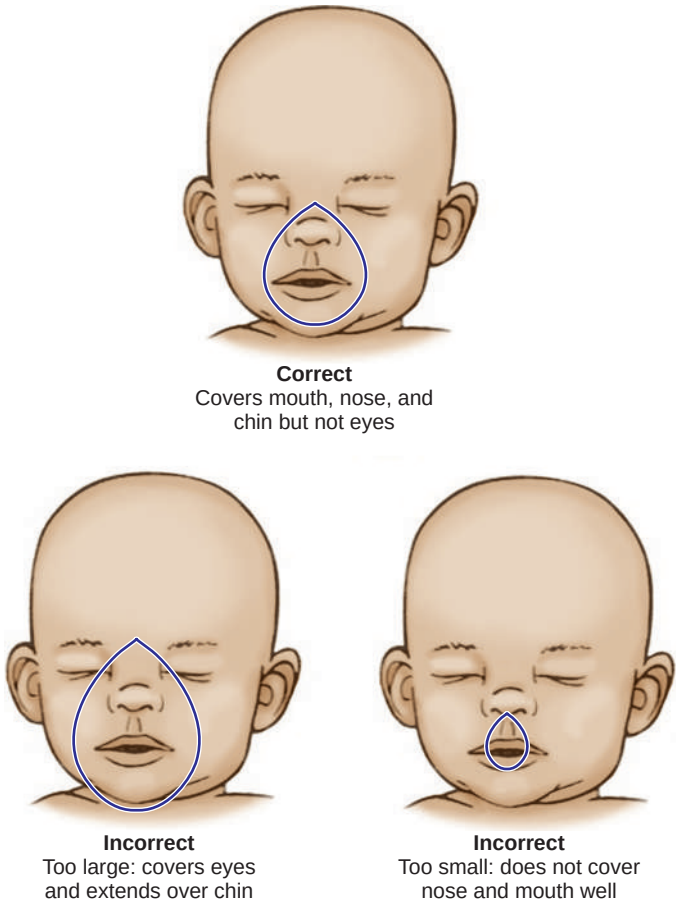


Figure 67-8 Appropriate sizing technique for pediatric bag-valve-mask apparatus. *(From American Academy of Pediatrics and the American Heart Association; Kattwinkel J (ed):* Textbook of Neonatal Resuscitation, *ed 6. Elk Grove, IL: American Academy of Pediatrics, 2011. Fig 3-17.)*

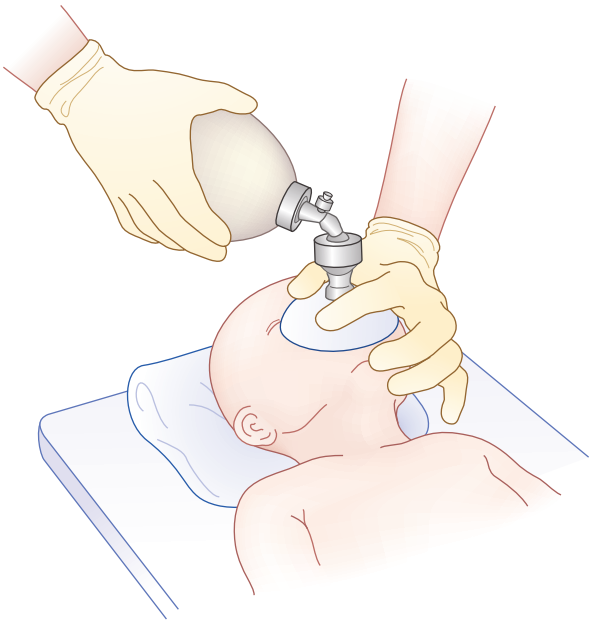


Figure 67-9 "C–E" grip to secure bag-valve-mask to a child's face with appropriate seal.

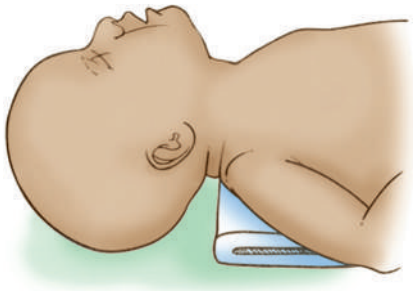


Figure 67-10 Appropriate head position for bag-valve-mask ventilation. *(From American Academy of Pediatrics and the American Heart Association; Kattwinkel J (ed):* Textbook of Neonatal Resuscitation, *ed 6. Elk Grove, IL: American Academy of Pediatrics, 2011. Fig 3-19.)*

acid–base balance; (4) sedation and/or paralysis is required for a procedure; and (5) care providers anticipate a deteriorating course that will eventually lead to any of the first 4 conditions. There are few *absolute contraindications* to tracheal intubation, but experts generally agree that in settings of known complete airway obstruction, endotracheal intubation should be avoided, and emergency cricothyroidotomy performed instead. Another important consideration is to ensure that caregivers provide appropriate cervical spine protection during the intubation procedure when neck or spinal cord injury is suspected.

The most important phase of the intubation procedure is the preprocedure preparation, when the provider ensures all the equipment and staff needed for safe intubation are present and functioning. An easy pneumonic for this is **SOAP MM**: suction (Yankauer suction catheter attached to wall suction); oxygen (both preoxygenation of the patient and devices needed to deliver oxygen, such as a bag-valve-mask device); airway (appropriately sized endotracheal tube and laryngoscope); people (all those needed during and immediately after the procedure, such as respiratory therapists and nurses); monitor (to monitor the child's oxygen saturation, heart rate, and blood pressure); and medications (to sedate the child and allow the provider to control the airway). A simple formula for selecting the appropriately sized endotracheal tube (ET) is as follows:

$$\text{Uncuffed ET size (in mm)} = \left(\frac{\text{age in years}}{4}\right) + 4$$

Analgesia is recommended to reduce metabolic stress, discomfort, and anxiety during intubation. Pretreatment with a sedative, an analgesic, and possibly a muscle relaxant is recommended unless the situation is an emergency (i.e., apnea, asystole, unresponsiveness) and the administration of drugs would cause an unacceptable delay.

Because many intubations in critically ill children are emergency procedures, caregivers should be prepared for rapid sequence intubation (RSI) (Fig. 67-11; Table 67-4). The goals of RSI are to induce anesthesia and paralysis and to complete intubation quickly. This approach minimizes elevations of intracranial pressure and blood pressure that may accompany intubation in awake or lightly sedated patients. Because the stomach generally cannot be emptied before RSI, the Sellick maneuver (downward pressure on the cricoid cartilage to compress the esophagus against the vertebral column) should be used to prevent aspiration of gastric contents.

Once the patient is intubated, proper ET placement should be assessed by auscultation of breath sounds, evidence of symmetric chest rise, and analysis of exhaled carbon dioxide (CO_2) by a colorimetric device placed within the respiratory tubing near the ET or a device that directly measures carbon dioxide elimination (i.e., capnogram or capnograph). Chest radiography is necessary to confirm appropriate tube position.

RECOGNITION AND MANAGEMENT OF SHOCK

In simple terms, shock occurs when oxygen and nutrient delivery to the tissues is inadequate to meet metabolic demands (see Chapter 70).

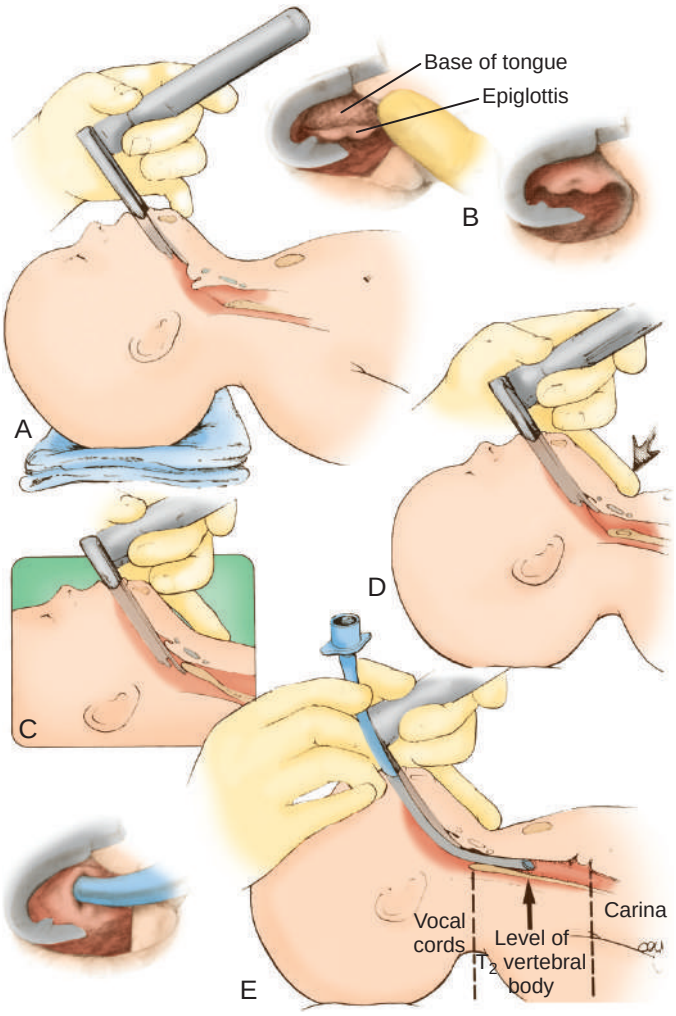


Figure 67-11 *A-E,* Intubation technique. *(From Fleisher G, Ludwig S:* Textbook of pediatric emergency medicine, *Baltimore, 1983, Williams & Wilkins, p. 1250.)*

The definition of shock does not include hypotension, and it is important for care providers to understand that **shock does not begin when blood pressure drops; it merely worsens and becomes more difficult to treat once blood pressure is abnormal.**

Early *compensated* shock, whereby oxygen delivery is mostly preserved through compensatory mechanisms, is defined by the presence of normal blood pressure. When compensatory mechanisms fail, the shock progresses to *decompensated* shock, which is defined by hypotension and organ dysfunction. In *irreversible* shock, organ failure progresses and death ensues.

Shock is also often described according to the underlying pathophysiology, which dictates the appropriate therapeutic response. *Hypovolemic shock* is the most common type of shock in children worldwide, usually related to fluid losses from severe diarrhea. Hemorrhage is a cause of hypovolemic shock after trauma or intestinal hemorrhage. When hypovolemia occurs as a result of third spacing of intravascular fluids into the extravascular compartment, the shock is described as *distributive shock*. The most common causes of distributive shock are sepsis and burn injuries, in which release of inflammatory cytokines causes massive capillary leak of fluid and proteins, leading to low oncotic pressure and intravascular volume. In settings of profound myocardial dysfunction, a child has tissue hypoperfusion from *cardiogenic shock*. The most common causes of cardiogenic shock are congenital heart disease, myocarditis, and cardiomyopathies. *Obstructive shock* occurs when cardiac output is lowered by obstruction of blood flow to the body, as occurs when a ductus arteriosus closes in a child with ductus-dependent systemic blood flow in pericardial tamponade, tension pneumothorax, or massive pulmonary embolism.

The evaluation of a child in shock should proceed as described in the preceding sections on primary, secondary, and tertiary assessments. If the child presents in a hospital setting, providers should obtain central venous and arterial access to permit a more thorough laboratory assessment of all organ systems, including studies of renal and liver function, acid–base balance and presence of lactic acidosis, hypoxemia and/or hypercapnia, and evidence of coagulopathy or disseminated intravascular coagulation. Chest radiography and more sophisticated assessments, such as echocardiography, may also be useful. Respiratory and cardiovascular support should be provided as indicated.

The treatment of shock focuses on the modifiable determinants of oxygen delivery while reducing the imbalance between oxygen demand and supply. A multipronged approach is recommended; it consists of optimizing the oxygen content of the blood, improving the volume and distribution of cardiac output, correcting metabolic derangements, and reducing oxygen demand. Blood oxygen content is maximized when hemoglobin values are normal and 100% of available hemoglobin is saturated with oxygen. Transfusion should be considered in the presence of hemorrhagic or distributive shock, in which crystalloid volume resuscitation has led to hemodilution and anemia. High oxygen saturations may be achieved by simple maneuvers such as oxygen administration via nasal cannula or face mask, but supportive measures that provide positive pressure, such as CPAP, BiPAP, or even mechanical ventilation, may be necessary. Therapies to increase cardiac output should be selected on the basis of underlying pathophysiology. For hypovolemic and distributive shock, aggressive volume resuscitation, guided by arterial and central venous pressures, is the mainstay of therapy. In obstructive shock, relief of the obstruction is critical. The ductus arteriosus can often be reopened with prostaglandin administration, and tamponade physiology can be relieved with appropriate drain placement, as described under "Nonvascular Emergency Procedures."

RECOGNITION OF BRADYARRHYTHMIAS AND TACHYARRHYTHMIAS

In the advanced life support setting, arrhythmias are most usefully classified according to the observed heart rate (slow or fast) and its effect on perfusion (adequate or poor). If, in the primary survey, a caregiver finds a child with an abnormal heart rate plus poor perfusion and/or altered mental status, then the rhythm is inadequate no matter its rate. In those settings, the child is diagnosed with shock, and further evaluation is halted until appropriate resuscitation has been initiated.

Bradyarrhythmias

By definition, a child is *bradycardic* when the heart rate is slower than the normal range for age (see Table 67-1). Sinus bradycardia can be a harmless incidental finding in an otherwise healthy person and is not commonly associated with cardiac compromise. A relative bradycardia occurs when the heart rate is too slow for a child's activity level or metabolic needs. A clinically significant bradycardia occurs when the heart rate is slow and there are signs of systemic hypoperfusion (i.e., pallor, altered mental status, hypotension, acidosis). Symptomatic bradycardia occurs most often in the setting of hypoxia but can also be caused by hypoglycemia, hypocalcemia, other electrolyte abnormalities, and intracranial hypertension. Bradyarrhythmias are often the most common prearrest rhythms in young children.

Initial management of symptomatic bradycardia includes support or opening of the airway and confirming or establishing adequate oxygenation and ventilation (Fig. 67-12). After the child's breathing has been secured, the child should be reassessed for continued bradycardia and poor perfusion. If cardiac compromise was solely the result of respiratory insufficiency, support of the child's airway and breathing may have been sufficient to restore normal hemodynamics. If respiratory support does not correct the perfusion abnormalities, then further care is based on the quality of perfusion and the degree of

Table 67-4 Rapid Sequence Intubation

STEP	PROCEDURE	COMMENT/EXPLANATION
1	Obtain a brief history and perform an assessment	Rule out drug allergies; examine the airway anatomy (e.g., micrognathia, cleft palate)
2	Assemble equipment, medications, etc.	See lists below
3	Preoxygenate the patient	With bag/mask, nasal cannula, hood or blow-by
4	Premedicate the patient with lidocaine, atropine	Lidocaine minimizes the ICP rise with intubation and can be applied topically to the airway mucosa for local anesthesia Atropine helps blunt the bradycardia associated with upper airway manipulation and reduces airway secretions
5	Induce sedation and analgesia	Sedatives: *Thiopental* (2-5 mg/kg): Very rapid onset; can cause hypotension *Diazepam* (0.1 mg/kg): Onset 2-5 min; elimination in 30-60 min or more *Ketamine* (2 mg/kg): Onset 1-2 min; elimination in 30-40 min. May cause hallucinations if used alone; causes higher ICP, mucous secretions, increased vital signs, and bronchodilation Analgesics: *Fentanyl* (3-10 μg/kg, may repeat 3-4×): Rapid administration risks "tight chest" response, with no effective ventilation. Effects wear off in 20-30 min *Morphine* (0.05-0.1 mg/kg dose): May last 30-60 min; may lead to hypotension in hypovolemic patients
6	Pretreat with nondepolarizing paralytic agent	Small dose of a nondepolarizing paralytic agent (see below), with intent of diminishing the depolarizing effect of succinylcholine, which is administered next
7	Administer muscle relaxants	Succinylcholine dose is 1-2 mg/kg; causes initial contraction of muscles, then relaxation. This depolarization can, however, raise ICP and blood pressure. Onset of paralysis in 30-40 sec; duration is 5-10 min Increased use of pretreatment with a nondepolarizing muscle relaxant, especially rocuronium (1 mg/kg), which has a very rapid onset and short duration. Other nondepolarizing agents include vecuronium and pancuronium, both dosed at 0.1 mg/kg
8	Perform a Sellick maneuver	Pressure on the cricoid cartilage, to occlude the esophagus and prevent regurgitation or aspiration
9	Perform endotracheal intubation	ET: Select the proper size for the age and weight of the child Laryngoscope blades: A variety of Miller and the Macintosh blades Patient supine; the neck is extended moderately to the "sniffing" position
10	Secure the tube and verify the position with a roentgenogram	ET secured with tape to the cheeks and upper lip or to an adhesive patch applied to the skin near the mouth
11	Begin mechanical ventilation	Verify tube placement before ventilating with positive pressure; if an ET tube is in one bronchus, barotraumas may occur

ET, endotracheal tube; ICP, intracranial pressure.

bradycardia. **A heart rate less than 60 beats/min with poor perfusion is an indication to begin chest compressions.** If the bradycardia persists, vascular access should be obtained; resuscitative epinephrine should be administered, and it should be repeated every 3-5 min for persistent symptomatic bradycardia. If increased vagal tone (e.g., in the setting of head injury with raised intracranial pressure) or primary atrioventricular block is suspected, atropine can also be given. For cases of refractory bradycardia, cardiac pacing should be considered. During the resuscitation of a child with bradycardia, providers should assess and treat factors known to cause bradycardia, referred to collectively as the **6 Hs** (hypoxia, hypovolemia, hydrogen ions [acidosis], hypokalemia or hyperkalemia, hypoglycemia, hypothermia), and **5 Ts** (toxins, tamponade, tension pneumothorax, thrombosis [in either the pulmonary or cardiac circulations], and trauma [causing hypovolemia, intracranial hypertension, cardiac compromise or tamponade]) (Table 67-5).

Tachyarrhythmias

Tachyarrhythmias represent a variety of rhythm disturbances of both atrial and ventricular origin (see Chapter 435). Sinus tachycardia is a normal physiologic response to the body's need for increased cardiac output or oxygen delivery, as occurs with fever, exercise, or stress. It can also occur in more pathologic states, such as hypovolemia, anemia, pain, anxiety, and metabolic stress. Tachyarrhythmias that do not originate in the sinus node are often categorized as narrow complex rhythms (those originating in the atrium, such as atrial flutter or supraventricular tachycardia [SVT]) and wide complex rhythms (those rhythms of ventricular origin, such as ventricular tachycardia).

The initial management of tachycardia includes confirmation that the child has an adequate airway and life-sustaining breathing and circulation (Fig. 67-13). For children with persistent symptoms, further treatment is based on whether the QRS complex of the electrocardiogram (ECG) is narrow (≤0.09 sec) or wide (>0.09 sec). For narrow complex tachycardia, providers must distinguish between sinus tachycardia and SVT. In sinus tachycardia, (a) the history and onset are consistent with a known cause of tachycardia, such as fever or dehydration and (b) P waves are consistently present, are of normal morphology, and occur at a rate that varies somewhat. In SVT, (a) onset is often abrupt without prodrome and (b) P waves are absent or polymorphic, and when present, their rate is often fairly steady at or above 220 beats/min. For children with SVT and good perfusion, vagal maneuvers can be attempted. In cases in which SVT is associated with poor perfusion, providers should rapidly move to convert the child's heart rhythm back to sinus rhythm. If the child already has IV access, then adenosine can be given via IV with rapid "push." Adenosine has an extremely short half-life, so a proximal IV is best, and the adenosine should be set up with a 3-way stopcock so it can be given and immediately flushed into the circulation. If the child does not have IV access, or adenosine does

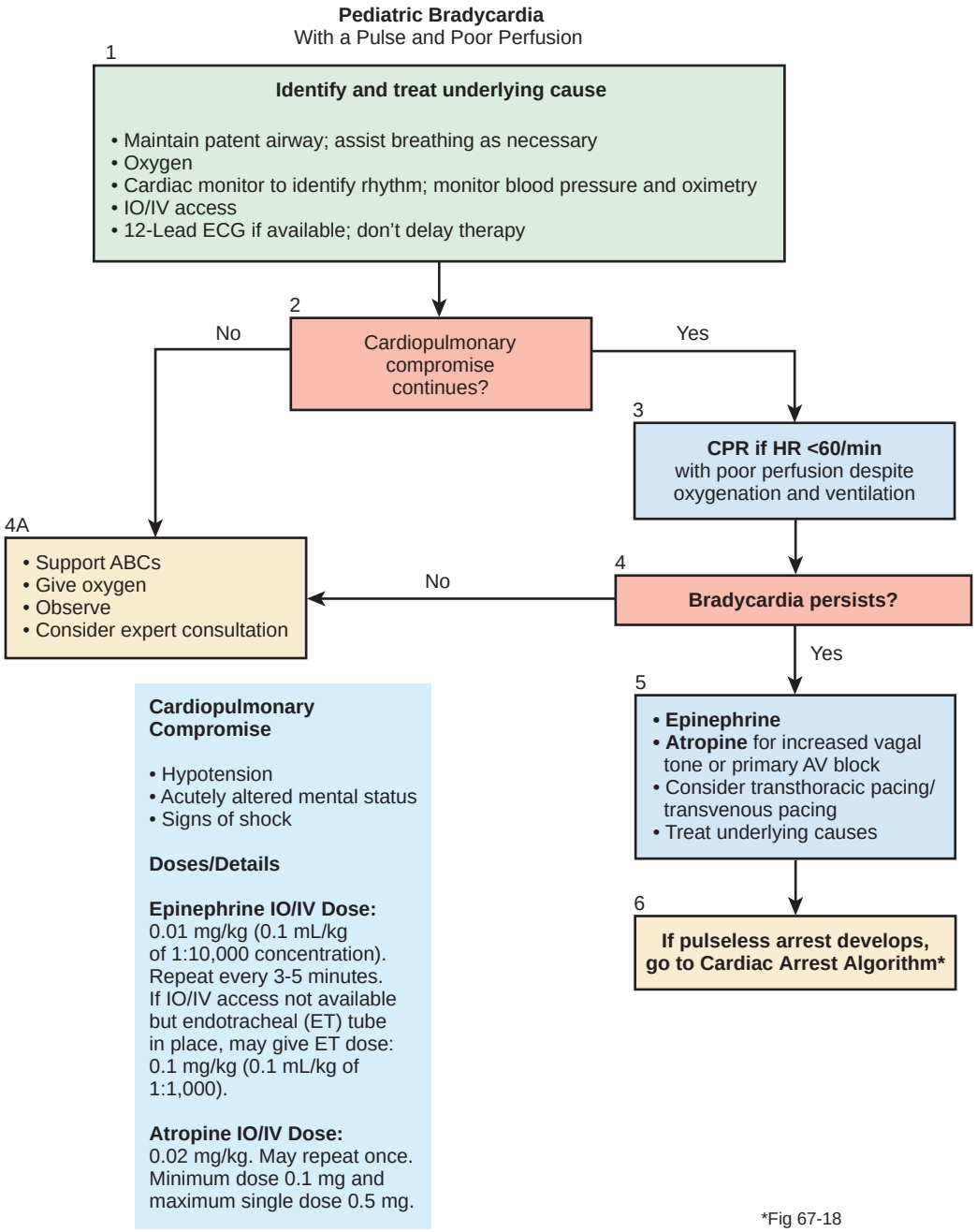


Figure 67-12 Pediatric advanced life support bradycardia algorithm. ABCs, airway, breathing, and circulation; AV, atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14,* Circulation *122[Suppl 3]:S876–S908, 2010, Fig. 2, p. S887.)*

not successfully convert the heart rhythm back to sinus rhythm, then **synchronized cardioversion**, using 0.5-1.0 joule/kg, should be performed. In cases of wide complex tachycardia, providers should move immediately to cardioversion and increase the dose to 2 joules/kg if 1 joule/kg is not effective. As with cases of bradycardia, providers should review the 6 Hs and 5 Ts to identify factors that might be contributing to the tachycardia (see Table 67-5).

RECOGNITION AND MANAGEMENT OF CARDIAC ARREST

Cardiac arrest occurs when the heart fails as an effective pump and blood flow ceases. Outwardly, the patient in cardiac arrest presents as unresponsive and apneic with no palpable pulse. Internally, the cessation of nutrient flow causes progressive tissue ischemia and organ dysfunction. If not rapidly reversed, cardiac arrest leads to progressive deterioration in brain and heart function such that resuscitation and recovery are no longer possible.

Pediatric cardiac arrest is rarely caused by a sudden coronary event or arrhythmia. Instead, cardiac arrest in children is most often the end result of progressive asphyxia, caused by tissue hypoxia, acidosis, and nutrient depletion at the end stages of respiratory deterioration, shock, or heart failure. Therefore, **the most important treatment of cardiac arrest is anticipation and preventive: Intervening when a child manifests respiratory distress or early stages of shock can prevent deterioration to full-blown arrest**. When sudden cardiac arrest does occur, it is most often associated with an arrhythmia, specifically ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). In sudden events such as these, the key to successful resuscitation is early

Table 67-5 Potentially Treatable Conditions Associated with Cardiac Arrest

CONDITION	COMMON CLINICAL SETTINGS	CORRECTIVE ACTIONS
Acidosis	Preexisting acidosis, diabetes, diarrhea, drugs and toxins, prolonged resuscitation, renal disease, and shock	Reassess the adequacy of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement Hyperventilate Consider intravenous bicarbonate if pH <7.2 after above actions have been taken
Cardiac tamponade	Hemorrhagic diathesis, cancer, pericarditis, trauma, after cardiac surgery, and after myocardial infarction	Administer fluids; obtain bedside echocardiogram, if available Perform pericardiocentesis; immediate surgical intervention is appropriate if pericardiocentesis is unhelpful but cardiac tamponade is known or highly suspected
Hypothermia	Alcohol abuse, burns, central nervous system disease, debilitated patient, drowning, drugs and toxins, endocrine disease, history of exposure, homelessness, extensive skin disease, spinal cord disease, and trauma	If hypothermia is severe (temperature <30°C [86°F]), limit initial shocks for ventricular fibrillation or pulseless ventricular tachycardia to 3; initiate active internal rewarming and cardiopulmonary support If hypothermia is moderate (temperature 30-34°C [86-93.2°F]), proceed with resuscitation (space medications at longer intervals than usual), passively rewarm child, and actively rewarm truncal body areas
Hypovolemia, hemorrhage, anemia	Major burns, diabetes, gastrointestinal losses, hemorrhage, hemorrhagic diathesis, cancer, pregnancy, shock, and trauma	Administer fluids Transfuse packed red blood cells if hemorrhage or profound anemia is present Thoracotomy is appropriate when a patient has cardiac arrest from penetrating trauma and a cardiac rhythm and the duration of cardiopulmonary resuscitation before thoracotomy is <10 min
Hypoxia	Consider in all patients with cardiac arrest	Reassess the technical quality of cardiopulmonary resuscitation, oxygenation, and ventilation; reconfirm endotracheal tube placement
Hypomagnesemia	Alcohol abuse, burns, diabetic ketoacidosis, severe diarrhea, diuretics, and drugs (e.g., cisplatin, cyclosporine, pentamidine)	Administer 1-2 g magnesium sulfate IV over 2 min
Poisoning	Alcohol abuse, bizarre or puzzling behavioral or metabolic presentation, classic toxicologic syndrome, occupational or industrial exposure, and psychiatric disease	Consult a toxicologist for emergency advice on resuscitation and definitive care, including an appropriate antidote Prolonged resuscitation efforts may be appropriate; immediate cardiopulmonary bypass should be considered, if available
Hyperkalemia	Metabolic acidosis, excessive administration of potassium, drugs and toxins, vigorous exercise, hemolysis, renal disease, rhabdomyolysis, tumor lysis syndrome, and clinically significant tissue injury	If hyperkalemia is identified or strongly suspected, treat* with all of the following: 10% calcium chloride (5-10 mL by slow IV push; do not use if hyperkalemia is secondary to digitalis poisoning), glucose and insulin (50 mL of 50% dextrose in water and 10 units of regular insulin IV), sodium bicarbonate (50 mmol IV; most effective if concomitant metabolic acidosis is present), and albuterol (15-20 mg nebulized or 0.5 mg by IV infusion)
Hypokalemia	Alcohol abuse, diabetes, use of diuretics, drugs and toxins, profound gastrointestinal losses, hypomagnesemia	If profound hypokalemia (<2.0-2.5 mmol of potassium) is accompanied by cardiac arrest, initiate urgent IV replacement (2 mmol/min IV for 10-15 mmol)*; then reassess
Pulmonary embolism	Hospitalized patient, recent surgical procedure, peripartum, known risk factors for venous thromboembolism, history of venous thromboembolism, or prearrest presentation consistent with a diagnosis of acute pulmonary embolism	Administer fluids; augment with vasopressors as necessary Confirm the diagnosis, if possible; consider immediate cardiopulmonary bypass to maintain patient's viability Consider definitive care (e.g., thrombolytic therapy, embolectomy by interventional radiology or surgery)
Tension pneumothorax	Placement of a central catheter, mechanical ventilation, pulmonary disease (including asthma, chronic obstructive pulmonary disease, and necrotizing pneumonia), thoracentesis, and trauma	Needle decompression, followed by chest tube insertion

*Adult dose. Adjust for size of child. See Table 67-6.

From Eisenbery MS, Mengert TJ: Cardiac resuscitation, N Engl J Med *344:1304–1313, 2001.*

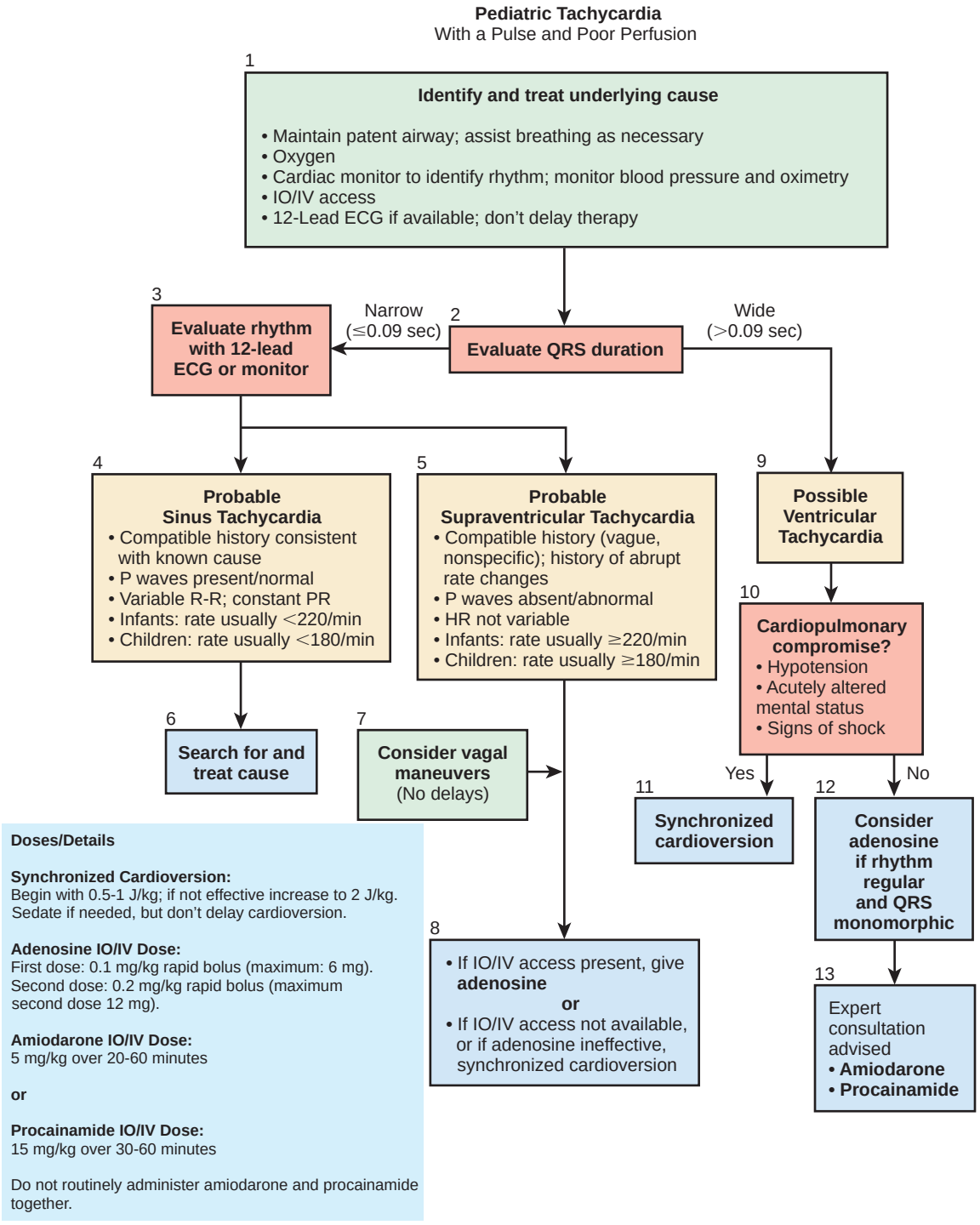


Figure 67-13 Pediatric advanced life support tachycardia algorithm. AV, atrioventricular (conductor); ECG, electrocardiogram; HR, heart rate. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14,* Circulation *122[Suppl 3]:S876–S908, 2010, Fig. 3, p. S888.)*

recognition of the arrhythmia and prompt treatment with high-quality CPR and defibrillation.

The principle behind high-quality CPR is that adequate chest compressions—those that circulate blood around the body with a good pulse pressure—are the most important component of CPR. The caregiver providing chest compressions should ***push hard, push fast, allow for complete chest recoil, and minimize interruptions.*** Ideally, chest compressions should be interrupted only for ventilation, a rhythm check, or delivery of a defibrillating shock.

Cardiac arrest is recognized from general and primary survey findings consistent with a pale or cyanotic child who is unresponsive, apneic, and pulseless. Even experienced providers have a relatively high error rate when asked to determine presence or absence of pulse in a child. Therefore, any child found unresponsive and apneic can be presumed to be in cardiac arrest, and a rescuer should respond accordingly. **A lone rescuer for an *unwitnessed* pediatric cardiac arrest in an outpatient setting should treat the arrest as asphyxial in nature and should immediately initiate CPR.** The rescuer should perform

Figure 67-14 Combined jaw-thrust/spine stabilization maneuver for the pediatric trauma victim. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

Figure 67-15 Cardiac compressions. *Top,* The infant is supine on the palm of the rescuer's hand. *Bottom,* Performing CPR while carrying an infant or small child. Note that the head is kept level with the torso. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

initial rescue breaths and 2 min of chest compressions and ventilations before leaving the child to activate the emergency response system. For an in-hospital arrest, the provider should call for help and send someone else to activate the emergency response system while beginning CPR. **A lone rescuer in an outpatient setting who *witnesses* a child's sudden collapse should treat the arrest as a primary arrhythmia, should immediately activate the EMS system, and should obtain an AED.** Upon returning to the child, the rescuer should confirm pulselessness, turn on the AED, place the leads on the child's chest, and follow the defibrillator's voice commands.

The initial step in CPR for a child of any age is to restore ventilation and oxygenation as quickly as possible. Upon confirmation of unresponsiveness, apnea, and pulselessness, the provider should open the airway with a head-tilt/chin-lift maneuver (or jaw-thrust if cervical spine trauma is suspected) and provide 2 initial rescue breaths (Fig. 67-14). These breaths are deep and slow, lasting approximately 1 sec per breath. The breaths are adequate if they cause the chest to rise and fall and improve the child's color. If the breaths appear inadequate, the child should be repositioned, and the breaths delivered again. If the breaths remain ineffective, the provider should assess the child for foreign body aspiration. After 2 effective rescue breaths, the child's pulse should be assessed. If the child has a pulse but remains apneic (or with ineffective breathing), then the rescuer should continue to provide assisted ventilation at an age-appropriate rate. Infants and children ≤8 yr old should receive rescue breathing at a rate of roughly 15-20 breaths/min, or roughly 1 breath every 3-5 sec. Children >8 yr old should receive 10-12 breaths/min, or 1 breath every 5-6 sec.

If the child remains pulseless, chest compressions should be initiated. Chest compressions in infants <1 yr old may be performed by placing 2 thumbs on the midsternum with the hands encircling the thorax or by placing 2 fingers over the midsternum and compressing (Figs. 67-15 and 67-16). For children >1 yr old, the care provider should perform chest compressions over the lower half of the sternum with the heel of 1 hand, or with 2 hands as used for adult resuscitation (Fig. 67-17). In all cases, care should be taken to avoid compression of the xiphoid and the ribs. When feasible, a cardiac resuscitation board should be placed under the child's back to maximize the efficiency of compressions. When a lone rescuer provides CPR, the universal ratio of 30 compressions to 2 ventilations is used. Pediatric patients in cardiac arrest are thought to have the best chance of survival if more frequent ventilation is offered. Therefore, the ratio should be lowered to 15 compressions to 2 ventilations for children ≤8 yr old as soon as a second care provider is available. In the outpatient setting, resuscitation effort should pause periodically to allow the provider to make an assessment of the possible return of spontaneous heart rate, pulse, and respirations. The goal of CPR is to reestablish spontaneous circulation at a level that is compatible with survival. If resuscitative efforts do not succeed in reestablishing life-sustaining breathing and circulation, the medical team must decide whether continued efforts are warranted or whether the resuscitation should be stopped. If EMS care is en route, bringing the potential for further escalation in care such as endotracheal intubation, vascular access, and medications, CPR should be continued as long as possible or deemed reasonable by the rescuers.

In the in-hospital setting, the ECG should dictate further resuscitative efforts. For children without a pulse and in asystole or electromechanical dissociation (pulseless electrical activity), providers should continue rescue breathing and CPR, obtain vascular access, and give emergency IV epinephrine (Fig. 67-18). For continued asystole or pulseless electrical activity, epinephrine can be repeated every 3-5 min. Patient history, physical exam findings, and laboratory evaluation should be used to elicit correctable causes of arrest (such as the 6 Hs and 5 Ts) (see Table 67-5). CPR should be continued after epinephrine administration, to circulate the drug through the body. After 5 cycles of CPR, providers should reassess the child for the presence of a pulse or a change in the ECG rhythm that would necessitate a different response.

For those children with pulseless VT or VF, emergency defibrillation is indicated (see Fig. 67-18). Providers should apply the pads to the child's bare chest and back and follow the verbal instructions given by the AED. For younger children, a defibrillator (if available) set to the dose of 2 joules/kg should be used. Ideally, the AED used in a child

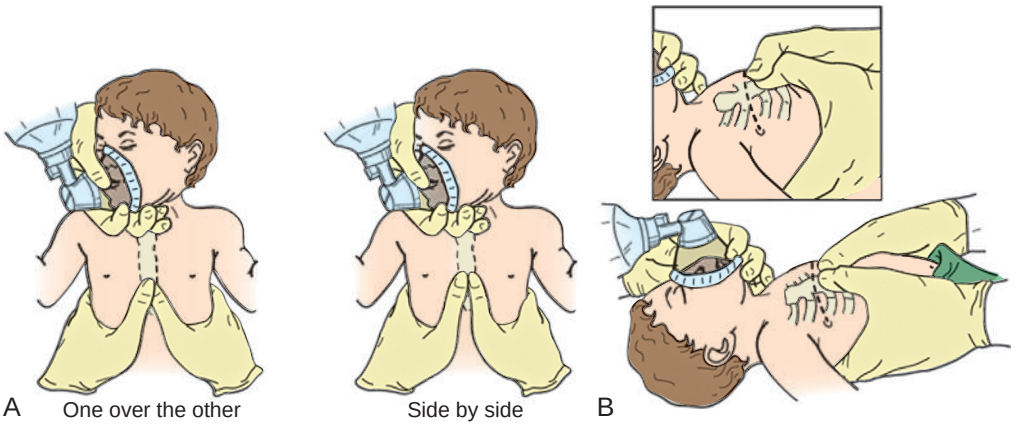


Figure 67-16 Thumb method of chest compressions. *A*, Infant receiving chest compressions with thumb 1 fingerbreadth below the nipple line and hands encircling chest. *B*, Hand position for chest encirclement technique for external chest compressions in neonates. Thumbs are side by side over the lower third of the sternum. In the small newborn, thumbs may need to be superimposed *(inset)*. Gloves should be worn during resuscitation. *(From Fleisher GR, Ludwig S, editors:* Textbook of pediatric emergency medicine, *Philadelphia, 2010, Wolters Kluwer/Lippincott Williams & Wilkins Health, Fig. 2.2.)*

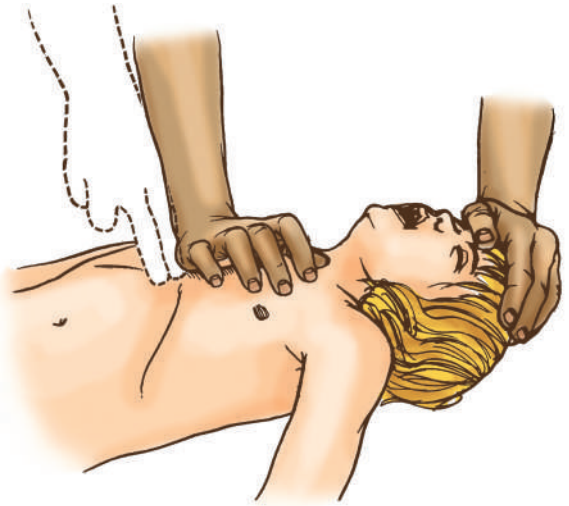


Figure 67-17 Locating the hand position for chest compression in a child. Note that the rescuer's other hand is used to maintain the head position to facilitate ventilation. *(From Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part V. Pediatric basic life support,* JAMA *268:2251–2261, 1992.)*

≤8 yr of age should be equipped with an attenuated adult dose or should be designed for children; if neither device is available, a standard adult AED should be used. CPR should be immediately restarted after defibrillation. Emergency dose epinephrine can also be administered with another 5 cycles of CPR to ensure its circulation throughout the child's body. If the ECG rhythm continues to show VF or VT, defibrillation can be alternated with epinephrine. For refractory VF or VT, an IV antiarrhythmic, such as amiodarone or lidocaine, can be given (Tables 67-6 and 67-7).

New approaches to CPR in adults have highlighted the potential value of bystander chest compression alone in the initial resuscitation in a community setting. In addition, the combination of vasopressin, methylprednisolone, and epinephrine during an in-hospital cardiac arrest followed by hydrocortisone during the postresuscitation shock period has resulted in a better outcome than patients treated with epinephrine alone. Whether these observations are applicable to young children, who often have different etiologies for cardiopulmonary arrest, has not been determined.

Traditionally, continuing CPR >20 min in children with in-hospital cardiac arrest has been considered futile. With current practice for CPR, survival for in-hospital cardiac arrest is approximately 40% for CPR duration <15 min compared with approximately 12% for CPR lasting >35 min. Survivors had a favorable neurologic outcome in 70% with a CPR duration <15 min compared with 60% for those requiring resuscitation for >35 min.

VASCULAR ACCESS

Venous Access

Veins suitable for cannulation are numerous, but there is considerable anatomic variation from patient to patient. In the upper extremities, the median antecubital vein, located in the antecubital fossa, is often the largest and easiest to access (Fig. 67-19). Many veins on the dorsum of the hand are also suitable for cannulation because they are often large and easily located on the flat surface of the dorsum of the hand, and their cannulation is well tolerated. The cephalic vein is usually cannulated at the wrist, along the forearm, or at the elbow. The median vein of the forearm is also suitable because it lies along a flat surface of the forearm. In the lower extremity, the great saphenous vein, located just anterior to the medial malleolus, is accessible in most patients. The dorsum of the foot usually has a large vein in the midline, passing across the ankle joint, but catheters are difficult to maintain in this vein because dorsiflexion tends to dislodge them. A second large vein on the lateral side of the foot, running in the horizontal plane, usually 1-2 cm dorsal to the lower margin of the foot, is preferable (Fig. 67-20). The most notable scalp veins are the superficial temporal (just anterior to the ear) and posterior auricular (just behind the ear).

Deeper and larger central veins can provide more reliable, larger-bore access for medications, nutritive solutions, and blood sampling than peripheral venous lines. They may be reached by percutaneous cannulation or surgical exposure. In infants and young children, the femoral vein is often the easiest to access and cannulate, but the internal jugular and subclavian veins may also be used (Figs. 67-21 and 67-22). Because of its proximity to the median nerve, the brachial vein is not often recommended for cannulation.

Intraosseous Access

Intraosseous (IO) needles (for intramedullary venous plexus access) are special rigid, large-bore needles that resemble those used for bone marrow aspiration. IO cannulation is recommended for patients for whom IV access proves difficult or unattainable, even in older children. If venous access is not available within 1 min in a child with cardiopulmonary arrest, an IO needle should be placed in the anterior proximal tibia (with care taken to avoid traversing the epiphyseal plate). The needle should penetrate the anterior layer of compact bone, and its tip

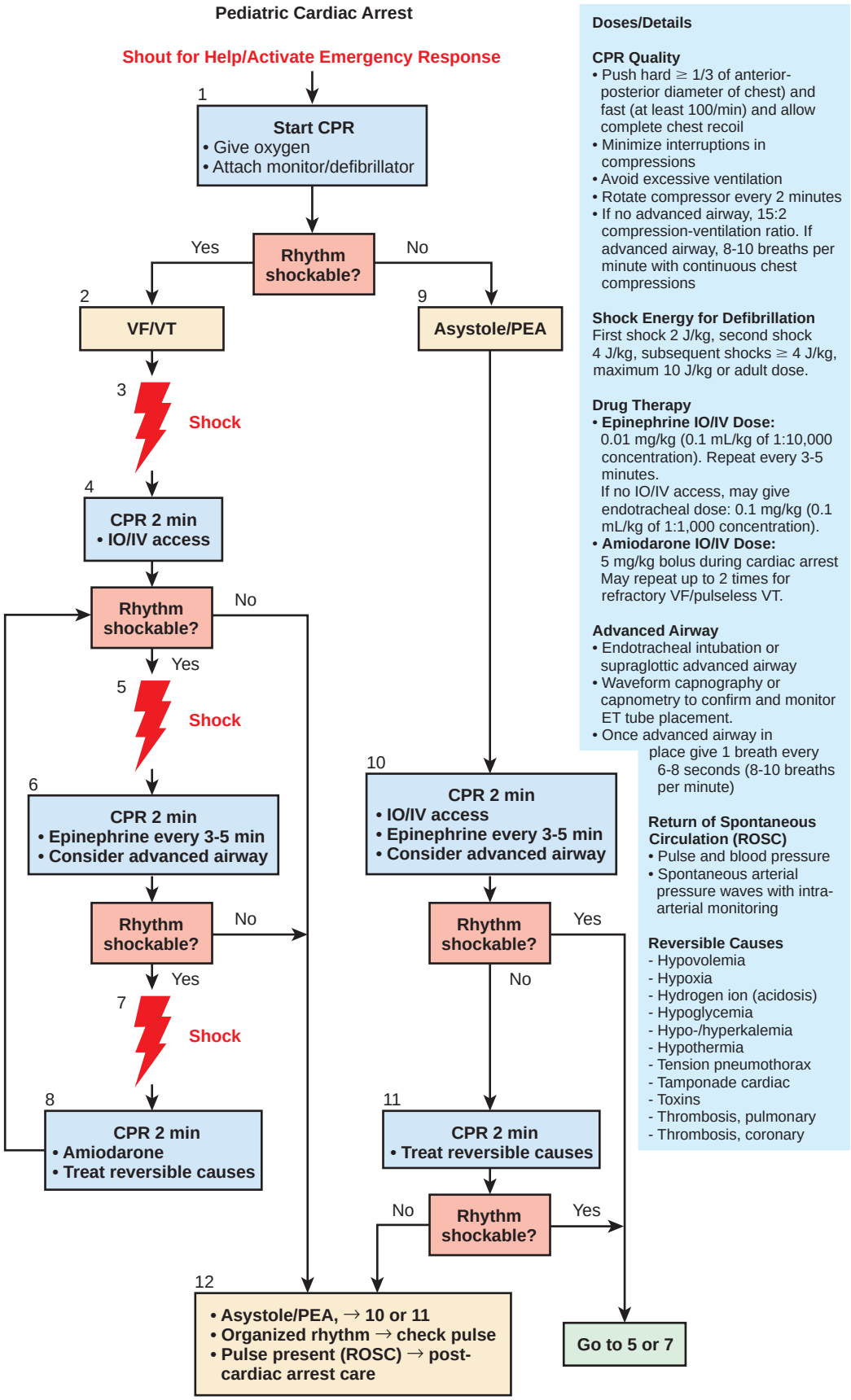


Figure 67-18 Pediatric advanced life support pulseless arrest algorithm. *(From Kleinman ME, Chameides L, Schexnayder SM, et al: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, part 14,* Circulation *122[Suppl 3]: S876–S908, 2010, Fig. 1, p. S885.)*

Table 67-6 Medications for Pediatric Resuscitation and Arrhythmias

MEDICATION	DOSE	REMARKS
Adenosine	0.1 mg/kg (maximum 6 mg) Repeat: 0.2 mg/kg (maximum 12 mg)	Monitor ECG Rapid IV/IO bolus
Amiodarone	5 mg/kg IV/IO; repeat up to 15 mg/kg Maximum: 300 mg	Monitor ECG and blood pressure Adjust administration rate to urgency (give more slowly when perfusing rhythm is present) Use caution when administering with other drugs that prolong QT interval (consider expert consultation)
Atropine	0.02 mg/kg IV/IO 0.03 mg/kg ET* Repeat once if needed Minimum dose: 0.1 mg Minimum single dose: Child, 0.5 mg Adolescent, 1 mg	Higher doses may be used with organophosphate poisoning
Calcium chloride (10%)	20 mg/kg IV/IO (0.2 mL/kg)	Slowly Adult dose: 5-10 mL
Epinephrine	0.01 mg/kg (0.1 mL/kg 1:10,000) IV/IO 0.1 mg/kg (0.1 mL/kg 1:1,000) ET* Maximum dose: 1 mg IV/IO; 10 mg ET	May repeat q 3-5 min
Glucose	0.5-1 g/kg IV/IO	D10W: 5-10 mL/kg D25W: 2-4 mL/kg D50W: 1-2 mL/kg
Lidocaine	Bolus: 1 mg/kg IV/IO Maximum dose: 100 mg Infusion: 20-50 μg/kg/min ET*: 2-3 mg	
Magnesium sulfate	25-50 mg/kg IV/IO over 10-20 min; faster in torsades de pointes Maximum dose: 2g	
Naloxone	<5 yr or ≤20 kg: 0.1 mg/kg IV/IO/ET* ≥5 yr or >20 kg: 2 mg IV/IO/ET*	Use lower doses to reverse respiratory depression associated with therapeutic opioid use (1-15 μg/kg)
Procainamide	15 mg/kg IV/IO over 30-60 min Adult dose: 20 mg/min IV infusion up to total maximum dose of 17 mg/kg	Monitor EGG and blood pressure Use caution when administering with other drugs that prolong QT interval (consider expert consultation)
Sodium bicarbonate	1 mEq/kg/dose IV/IO slowly	After adequate ventilation

*Flush with 5 mL of normal saline and follow with 5 ventilations.
ECG, electrocardiogram; ET, endotracheal tube; IO, intraosseous; IV, intravenous.
From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation *112:IV1–203, 2005.*

Table 67-7 Medications to Maintain Cardiac Output and for Postresuscitation Stabilization*

MEDICATION	DOSE RANGE	COMMENT
Inamrinone	0.75-1 mg/kg IV/IO over 5 min; may repeat 2×; then: 2-20 μg/kg/min	Inodilator
Dobutamine	2-20 μg/kg/min IV/IO	Inotrope; vasodilator
Dopamine	2-20 μg/kg/min IV/IO in low doses; pressor in higher doses	Inotrope; chronotrope; renal and splanchnic vasodilator
Epinephrine	0.1-1 μg/kg/min IV/IO	Inotrope; chronotrope; vasodilator in low doses; vasopressor in higher doses
Milrinone	50-75 μg/kg IV/IO over 10-60 min then 0.5-0.75 μg/kg/min	Inodilator
Norepinephrine	0.1-2 μg/kg/min	Inotrope; vasopressor
Sodium nitroprusside	1-8 μg/kg/min	Vasodilator; prepare only in D5W

*Alternative formula for calculating an infusion: Infusion rate (mL/hr) = [weight (kg) × dose (μg/kg/min) × 60 (min/hr)]/concentration μg/mL).
D5W, 5% dextrose in water; IO, intraosseous; IV, intravenous.
From ECC Committee, Subcommittees and Task Forces of the American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation *112:IV1–IV203, 2005.*

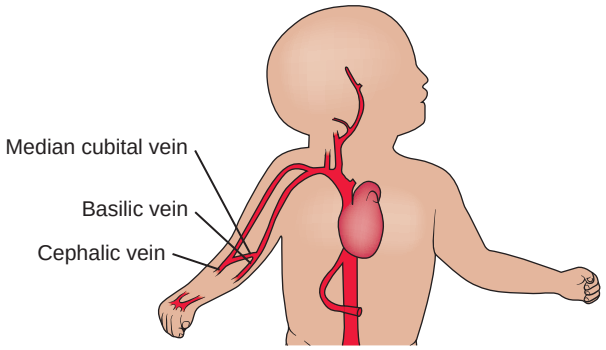


Figure 67-19 Veins of the upper extremity. *(From Roberts JR, Hedges JR, editors:* Clinical procedures in emergency medicine, *ed 4, Philadelphia, 2004, Saunders.)*

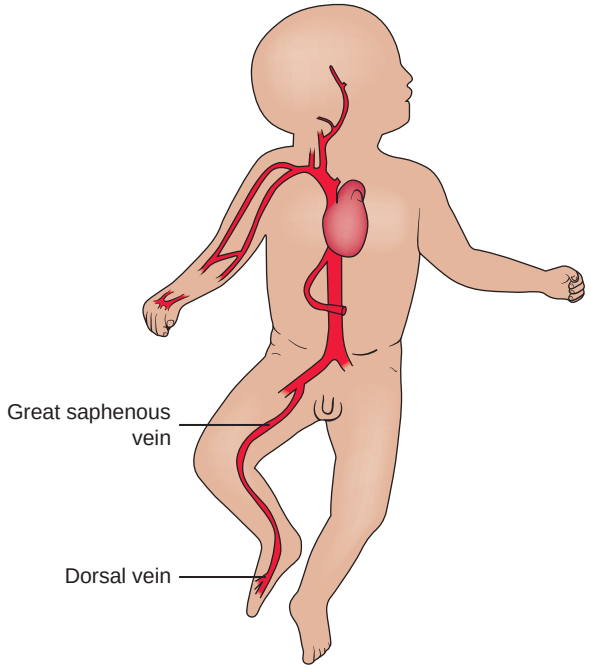


Figure 67-20 Veins of the lower extremity. *(From Roberts JR, Hedges JR, editors:* Clinical procedures in emergency medicine, *ed 4, Philadelphia, 2004, Saunders.)*

advanced into the spongy interior of the bone (Fig. 67-23). Commercially available IO kits frequently include drills that obviate the complications of needle placement associated with manual placement. Any and all medications, blood products, and fluids may be administered through the IO route, including all medications required for emergency resuscitation. Complications are uncommon, but may include osteomyelitis with prolonged infusions and tibial fracture.

Arterial Access

Arterial access is indicated when care providers need frequent blood sampling, particularly to assess adequacy of oxygenation, ventilation, or acid–base balance, and/or continuous blood pressure monitoring. The radial artery, the most commonly cannulated artery, lies on the lateral side of the anterior wrist, just medial to the styloid process of the radius (Fig. 67-24). The ulnar artery, just lateral to the tendon of the flexor carpi ulnaris, is used less often because of its proximity to the ulnar nerve. Useful sites in the lower extremity, particularly in neonates and infants, are the dorsalis pedis artery, on the dorsum of the foot between the tendons of the tibialis anterior and the extensor hallucis longus, and the posterior tibial artery, posterior to the medial

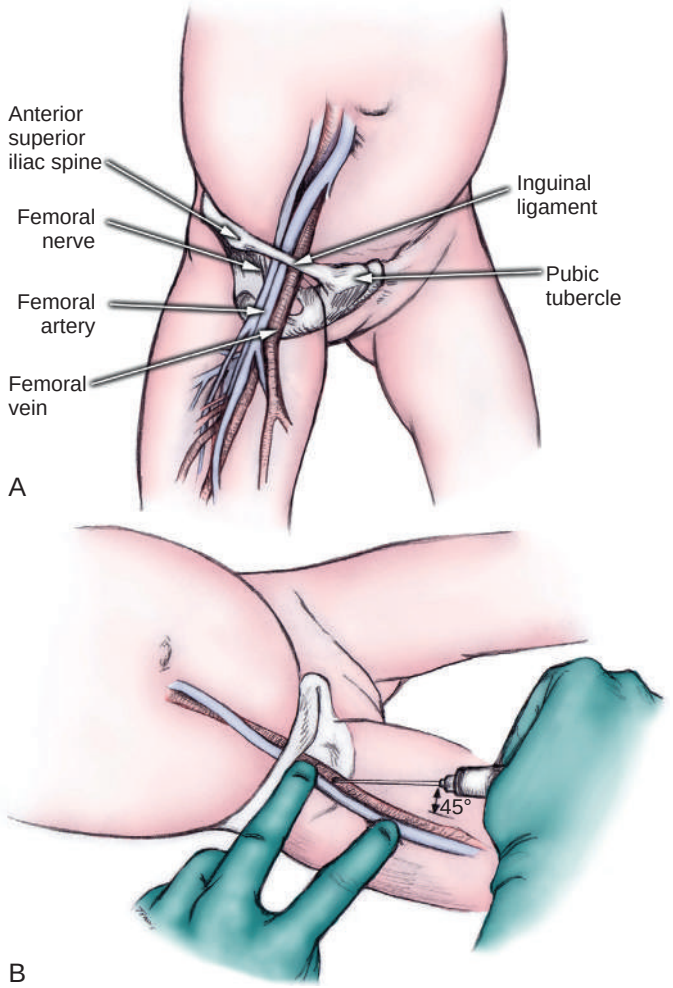


Figure 67-21 Femoral vein approach. Remember the mnemonic NAVEL for nerve, artery, vein, empty space, and lymphatics. *(From Putigna F, Solenberger R:* Central venous access. http://emedicine.medscape.com/article/940865-overview.*)*

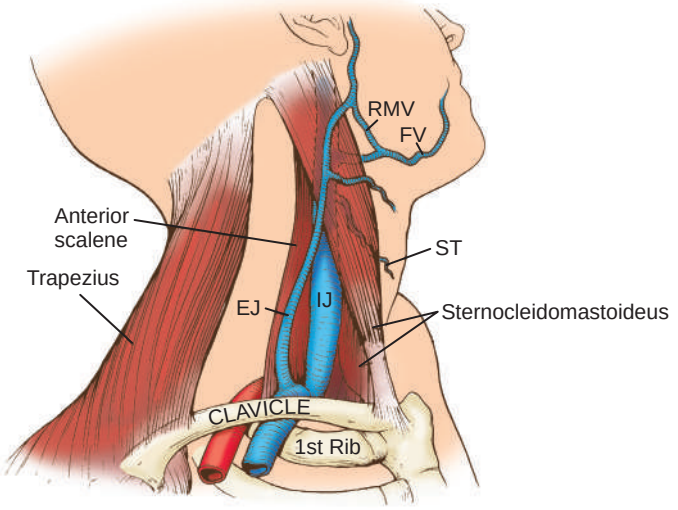


Figure 67-22 Internal and external jugular veins. EJ, external jugular vein; FV, facial vein; IJ, internal jugular vein; RMV, retromandibular vein; ST, superior thyroid vein. The 2 heads of the sternocleidomastoideus are indicated by the *lines. (From Mathers LW, Smith DW, Frankel L: Anatomic considerations in placement of central venous catheters,* Clin Anat *5:89, 1992. Reprinted by permission of Wiley-Liss.)*

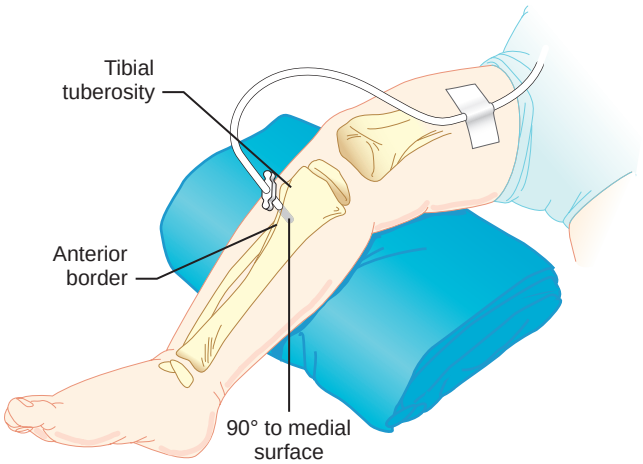


Figure 67-23 Intraosseous cannulation technique. *(From Zwass MS, Gregory GA: Pediatric and neonatal intensive care. In Miller RD, Eriksson LI, Fleisher LA, et al, editors:* Miller's anesthesia, *ed 7, Philadelphia, 2009, Churchill Livingstone, Fig. 84-1.)*

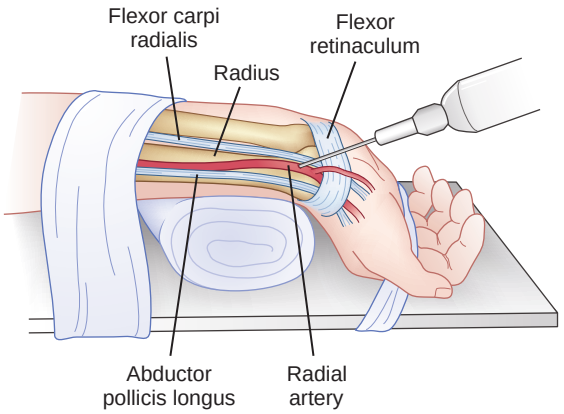


Figure 67-24 Radial artery anatomy and cannulation.

malleolus. Arterial catheters require special care for insertion and subsequent management because the blood flow to tissue can be compromised and considerable hemorrhage can occur if an arterial catheter is dislodged.

NONVASCULAR EMERGENCY PROCEDURES

Thoracentesis and Chest Tube Placement

Thoracentesis is the placement of a needle or catheter into the pleural space to evacuate fluid, blood, or air. Most insertions are performed in one of the intercostal spaces between the 4th and 9th ribs in the plane of the midaxillary line. After appropriate systemic and local anesthesia/sedation is performed as clinically indicated, a skin incision is made, and dissection through the chest wall is accomplished in layers with use of blunt dissection techniques. The needle (and later, the chest tube) that enters the pleural space should penetrate the intercostal space by passing over the superior edge of the lower rib, because there are larger vessels along the inferior edge of the rib. Ideally, the chest tube should lie anterior in the pleural space for air accumulation, and posterior for fluid accumulation. A radiograph must be obtained to verify chest tube placement and evacuation of the pleural space.

Pericardiocentesis

When fluid, blood, or gas accumulates in the pericardial sac, a danger is that the heart will be compressed and will not be able to fill and empty with normal volumes of blood, leading to diminished cardiac output. The cardinal signs of such a restrictive pericardial effusion are tachycardia, hypotension, and decreasing oxygen saturation. Pericardiocentesis includes needle aspiration of the pericardial sac, often followed by the placement of a catheter for continuous drainage. As for thoracentesis, chest radiography should be done to confirm catheter location as well as to evaluate for presence of any complications, such as pneumothorax or hemothorax.

POSTRESUSCITATION CARE

After successful resuscitation, close observation in an intensive care unit, where the child can receive ongoing multiorgan system assessments and support, is critical. Optimal postresuscitation care includes ongoing support of cardiovascular and respiratory system function as needed and the identification and treatment of other organ system dysfunction that may have contributed to (or resulted from) the child's cardiopulmonary instability. Good postresuscitation intensive care also includes supportive services for the child's parents, siblings, family, and friends.

Induced hypothermia (32-34°C [89.6-91.4°F] for ≈48 hr) may improve survival and neurologic function in adult and pediatric survivors of CPR. This is a controversial treatment that has inconsistently proven beneficial in comatose adult survivors of cardiac arrest. Randomized clinical trials in children are in progress. *Furthermore, hyperthermia must be avoided.* Hypoxic-ischemic encephalopathy with subsequent development of seizures, intellectual impairment, and spasticity, is a serious and common complication of cardiac arrest. *In addition hyperglycemia and hypoglycemia should be avoided.*

Postresuscitation management generally has 2 phases, similar to earlier, emergency resuscitative care. First, the providers must assess the child's airway and breathing and must support oxygenation and ventilation as indicated. If the child has ongoing respiratory failure and has been supported with bag-valve-mask ventilation until this time, the providers should now move forward with intubation. Once the child is intubated, mechanical ventilation must be established, and respiratory assessments performed, such as chest radiography and arterial blood gas sampling and analysis. The child's circulatory system must also be assessed and supported as needed. Continuous arterial blood pressure monitoring can help the provider determine the need for, and response to, inotropic and chronotropic medications (see Table 67-7). Once the ABCs have been managed, providers can move on to full organ system assessments. A systematic approach that employs a full physical exam and laboratory evaluation to reveal the child's respiratory, cardiovascular, neurologic, gastrointestinal, renal, and hematologic system function should be used.

Communication with the family is an essential element of postresuscitation care. The family should be thoroughly briefed on the elements of the resuscitation performed, the child's condition, and ongoing medical concerns, uncertainties, or issues by the *most senior provider available*. This provider should be available to answer the family's questions, clarify information, and provide comfort. Other support staff, such as social workers and chaplains, should be contacted, as the family wishes, to provide additional support and comfort. For situations in which the resuscitation is ongoing and the child is not expected to survive, the American Academy of Pediatrics recommends that the provider make every effort possible to have the family present at the bedside if they wish. Family presence during CPR or other emergency resuscitative efforts, even if the child dies, is associated with a more positive medical experience than if they are excluded. In cases in which the child is critically ill but stable, the family should be brought to the bedside as soon as the healthcare team deems it safe and appropriate.

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Chapter 68

Neurologic Emergencies and Stabilization

Patrick M. Kochanek and Michael J. Bell

NEUROCRITICAL CARE PRINCIPLES

The brain has high metabolic demands, which are further increased during growth and development. Preservation of nutrient supply to the brain is the mainstay of care for children with evolving brain injuries. *Intracranial dynamics* describes the physics of the interactions of the contents—brain parenchyma, blood (arterial, venous, capillary) and cerebrospinal fluid (CSF)—within the cranium. Normally, brain parenchyma accounts for up to 85% of the contents of the cranial vault, and the remaining portion is divided between CSF and blood. The brain resides in a relatively rigid cranial vault, and cranial compliance decreases with age as the skull ossification centers gradually replace cartilage with bone. The **intracranial pressure (ICP)** is derived from the volume of its components and the bony compliance. The **perfusion pressure** of the brain (cerebral perfusion pressure [CPP]) is equal to the pressure of blood entering the cranium (mean arterial pressure) minus the ICP, in most cases.

Increases in intracranial volume can result from swelling, masses, or increases in blood and CSF volumes. As these volumes increase, compensatory mechanisms decrease ICP by (a) decreasing CSF volume (CSF is displaced into the spinal canal or absorbed by arachnoid villi), (b) decreasing cerebral blood volume (venous blood return to the thorax is augmented), and/or (c) increasing cranial volume (sutures pathologically expand or bone is remodeled). Once compensatory mechanisms are exhausted (the increase in cranial volume is too large), small increases in volume lead to large increases in ICP or intracranial hypertension (Fig. 68-1). As ICP continues to increase, brain ischemia can occur as CPP falls. Further increases in ICP can ultimately displace the brain downward into the foramen magnum—a process called **cerebral herniation,** which can become irreversible in minutes and may lead to severe disability or death; Figure 68-2 notes other sites of brain herniation.

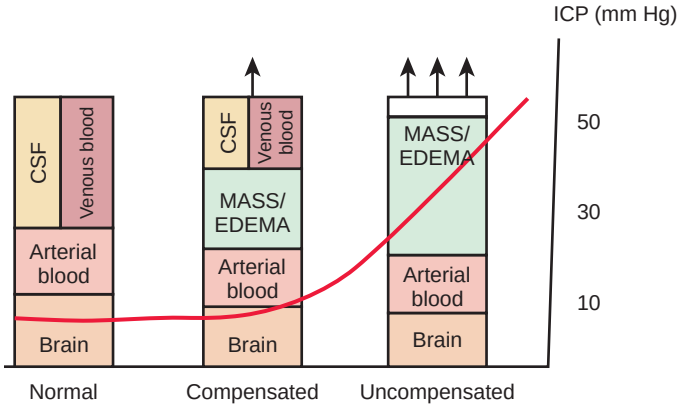

Figure 68-1 **The Munro-Kellie doctrine describes intracranial dynamics in the setting of an expanding mass lesion (i.e., hemorrhage, tumor) or brain edema.** In the normal state, the brain parenchyma, arterial blood, CSF, and venous blood occupy the cranial vault at a low pressure, generally <10 mm Hg. With an expanding mass lesion or brain edema, initially there is a compensated state as a result of reduced CSF and venous blood volumes, and ICP remains low. Further expansion of the lesion, however, leads to an uncompensated state when compensatory mechanisms are exhausted and intracranial hypertension results. See text for details.

Oxygen and glucose are required by brain cells for normal functioning, and these nutrients must be constantly supplied by cerebral blood flow (CBF). Normally, CBF is constant over a wide range of blood pressures (blood pressure autoregulation of CBF) via actions mainly within the cerebral arterioles. Cerebral arterioles are maximally dilated at lower blood pressures and maximally constricted at higher pressures so that CBF does not vary during normal fluctuations (Fig. 68-3). Acid–base balance of the CSF (often reflected by acute changes in arterial partial pressure of carbon dioxide [$Paco_2$]), body/brain temperature, glucose utilization, and other vasoactive mediators (i.e., adenosine, nitric oxide) can also affect the cerebral vasculature.

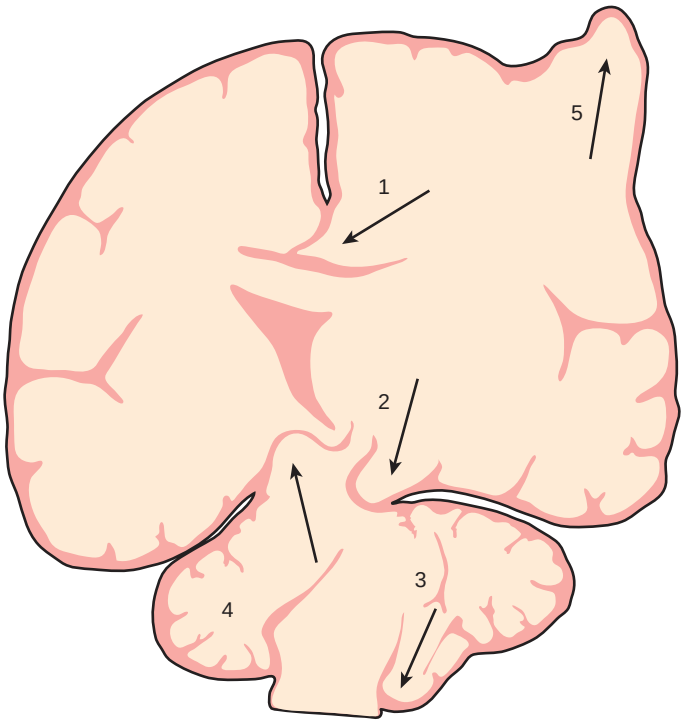

Figure 68-2 **Different forms of brain herniation.** *1,* Cingulate. *2,* Uncal. *3,* Cerebellar tonsillar. *4,* Upward cerebellar. *5,* Transcalvarial. *(From Fishman RA:* Cerebrospinal fluid in diseases of the nervous system, *Philadelphia, 1980, Saunders.)*

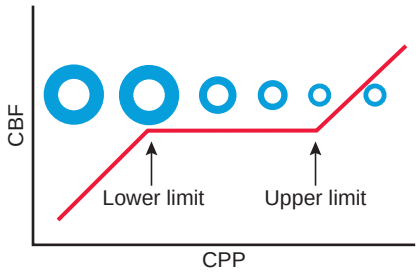

Figure 68-3 **Schematic of the relationship between CBF and CPP.** The diameter of a representative cerebral arteriole is also shown across the center of the *y* axis to facilitate understanding of the vascular response across CPP that underlies blood pressure autoregulation of CBF. CPP is generally defined as the mean arterial pressure (MAP) minus the ICP. At normal values for ICP, this generally represents MAP. Thus, normally, CBF is kept constant between the lower limit and upper limit of autoregulation; in normal adults, these values are ≈50 mm Hg and 150 mm Hg, respectively. In children, the upper limit of autoregulation is likely proportionally lower than the adult value relative to normal MAP for age. However, according to the work of Vavilala et al. (2003), lower limit values are surprisingly similar in infants and older children. Thus, infants and young children may have less reserve for adequate CPP. See text for details.

Knowledge of these concepts is instrumental to preventing secondary brain injury. Increases in CSF pH that occur because of inadvertent hyperventilation (decreased Pa_{CO_2}) can produce cerebral ischemia. Hyperthermia-mediated increases in cerebral metabolic demands may damage vulnerable brain regions after injury. Hypoglycemia can produce neuronal death when CBF fails to compensate. Prolonged seizures can lead to permanent injuries if hypoxemia occurs from loss of airway control.

Attention to detail and constant reassessment are paramount in managing children with critical neurologic insults. Among the most valuable tools for serial, objective assessments of neurologic condition is the Glasgow Coma Scale (GCS) (see Table 67-3 in Chapter 67). Originally developed to assess level of consciousness after traumatic brain injury (TBI) in adults, the GCS is also valuable in pediatrics. Modifications to the GCS have been made for nonverbal children and are available for infants and toddlers (see Table 67-3 in Chapter 67). Serial assessments of the GCS score along with a focused neurologic examination are invaluable to detection of injuries before permanent damage occurs in the vulnerable brain.

The FOUR (full outline of unresponsiveness) score (Table 68-1) is a modification of the GCS, which eliminates the verbal response but adds two functional assessments of the brain stem (pupil, corneal, cough reflexes, and respiratory patterns).

The most-studied monitoring device in clinical practice is the **ICP monitor**. Monitoring is accomplished by a catheter inserted either into the cerebral ventricle (externalized ventricular drain) or into brain parenchyma (parenchymal transducer). ICP-directed therapies are standard of care in TBI and are used in other conditions, such as intracranial hemorrhage, Reye syndrome, and some cases of encephalopathy, meningitis, and encephalitis. Other devices being used include catheters that measure brain tissue oxygen concentration, external probes that noninvasively assess brain oxygenation by absorbance of near-infrared light (near-infrared spectroscopy), monitors of brain electrical activity (continuous electroencephalography [EEG] or somatosensory, visual, or auditory evoked potentials), and CBF monitors (transcranial Doppler, xenon CT, perfusion MRI, or tissue probes). In the current severe TBI guidelines, brain tissue oxygen concentration monitoring received level III support and thus, may be considered.

TRAUMATIC BRAIN INJURY

Etiology

Mechanisms of TBI include motor vehicle crashes, falls, assaults, and abusive head trauma. Most TBIs in children are from closed-head injuries.

Epidemiology

TBI is an important pediatric public health problem, with approximately 37,000 cases resulting in the death of more than 7,000 children annually in the United States.

Pathology

Epidural, subdural, and parenchymal intracranial hemorrhages can result. Injury to gray or white matter is also commonly seen and includes focal cerebral contusions, diffuse cerebral swelling, axonal injury, and injury to the cerebellum or brainstem. Patients with severe TBI often have multiple findings; diffuse and potentially delayed cerebral swelling is common.

Pathogenesis

TBI results in primary and secondary injury. Primary injury from the impact produces irreversible tissue disruption. In contrast, 2 types of secondary injury are targets of neurointensive care. First, some of the ultimate damage seen in the injured brain evolves over hours or days, and the underlying mechanisms involved (edema, apoptosis, and secondary axotomy) are therapeutic targets. Second, the injured brain is vulnerable to additional insults because injury disrupts normal autoregulatory defense mechanisms; disruption of autoregulation of CBF can lead to ischemia from hypotension that would otherwise be tolerated by the uninjured brain.

Table 68-1 Commonly Used Coma Scores

GLASGOW COMA SCALE	FULL OUTLINE OF UNRESPONSIVENESS (FOUR) SCORE
Eye Opening 1 = does not open eyes 2 = opens eyes in response to noxious stimuli 3 = opens eyes in response to voice 4 = opens eyes spontaneously	*Eye Response* 4 = eyelids open or opened, tracking, or blinking to command 3 = eyelids open but not tracking 2 = eyelids closed but open to loud voice 1 = eyelids closed but open to pain 0 = eyelids remain closed with pain
Verbal Output 1 = makes no sounds 2 = makes incomprehensible sounds 3 = utters inappropriate words 4 = confused and disoriented 5 = speaks normally and oriented	*Motor Response* 4 = thumbs-up, fist, or peace sign 3 = localizing to pain 2 = flexion response to pain 1 = extension response to pain 0 = no response to pain or generalized myoclonus status
Motor Response (Best) 1 = makes no movements 2 = extension to painful stimuli 3 = abnormal flexion to painful stimuli 4 = flexion/withdrawal to painful stimuli 5 = localized to painful stimuli 6 = obeys commands	*Brainstem Reflexes* 4 = pupil and corneal reflexes present 3 = one pupil wide and fixed 2 = pupil or corneal reflexes absent 1 = pupil and corneal reflexes absent 0 = absent pupil, corneal, and cough reflex
	Respiration 4 = not intubated, regular breathing pattern 3 = not intubated, Cheyne-Stokes breathing pattern 2 = not intubated, irregular breathing 1 = breathes above ventilatory rate 0 = breathes at ventilator rate or apnea

From Edlow JA, Rabinstein A, Traub SJ, Wijdicks EFM: Diagnosis of reversible causes of coma. Lancet 384:2064-2076, 2014.

Clinical Manifestations

The hallmark of **severe TBI** is coma (**GCS score 3-8**). Often, coma is seen immediately after the injury and is sustained. In some cases, such as with an epidural hematoma, a child may be alert on presentation but may deteriorate after a period of hours. A similar picture can be seen in children with diffuse swelling, in whom a *talk-and-die* scenario has been described. Clinicians should also not be lulled into underappreciating the potential for deterioration of a child with **moderate TBI** (**GCS score 9-12**) with a significant contusion, because progressive swelling can potentially lead to devastating complications. In the comatose child with severe TBI, the second key clinical manifestation is the development of intracranial hypertension. The development of increased ICP with impending herniation may be heralded by new-onset or worsening headache, depressed level of consciousness, vital sign changes (hypertension, bradycardia, irregular respirations), and signs of 6th (lateral rectus palsy) or 3rd (anisocoria [dilated pupil], ptosis, down-and-out position of globe as a result of rectus muscle palsies) cranial nerve compression. Increased ICP is managed with continuous ICP monitoring, as well as monitoring for clinical signs of increased ICP or impending herniation. The development of brain swelling is progressive. Significantly raised ICP (>20 mm Hg) can occur early after severe TBI, but peak ICP generally is seen at 48-72 hr.

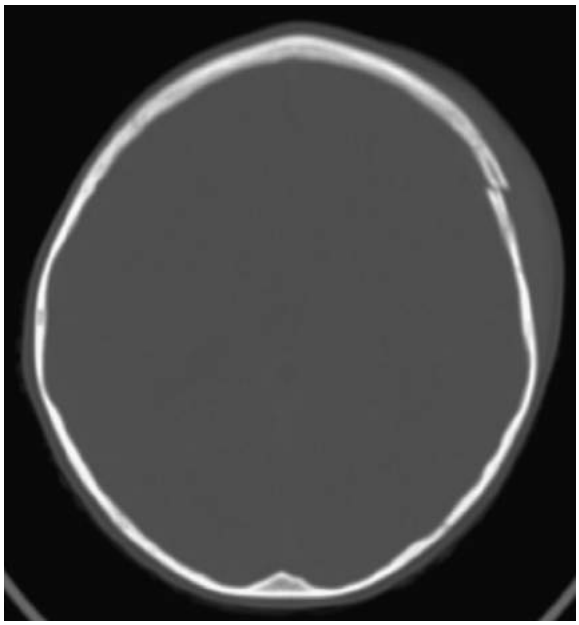

Figure 68-4 Mildly displaced skull fracture seen on CT imaging (bone window view) in a 4 yr old who fell and hit her head on a curb.

Figure 68-5 Left frontal epidural hematoma observed on CT imaging in a 12 yr old child who fell off his bike onto concrete surface.

Need for ICP-directed therapy may persist for longer than a week. A few children have coma without increased ICP, resulting from axonal injury or brainstem injury. *In addition to head trauma, it is critical to identify potential cervical spine injury.*

Laboratory Findings

Cranial CT should be obtained immediately after resuscitation and cardiopulmonary stabilization (Figs. 68-4 to 68-10). In some cases, magnetic resonance imaging can be diagnostic (Fig. 68-11). Generally, other laboratory findings are normal in isolated TBI, although occasionally coagulopathy or the development of the syndrome of inappropriate antidiuretic hormone secretion or, rarely, cerebral salt wasting is seen. In the setting of TBI with polytrauma, other injuries can result in laboratory abnormalities, and a full trauma survey is important in all patients with severe TBI (see Chapter 72).

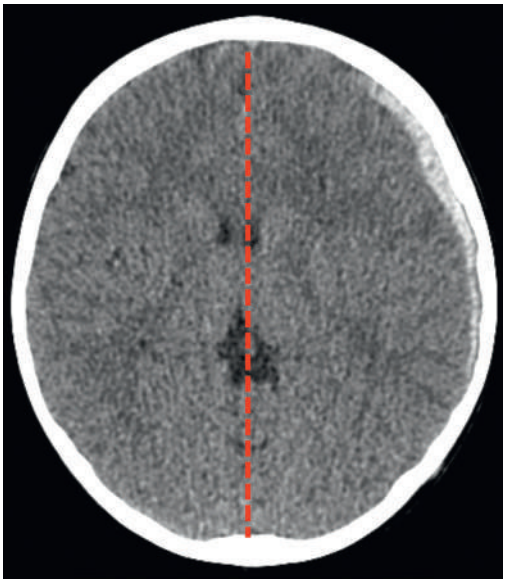

Figure 68-6 Left subdural hematoma observed on CT imaging in a 10 yr old child after a motor vehicle accident. Note, there is effacement of the left lateral ventricle and midline shift noted (see *dotted line* for midline reference).

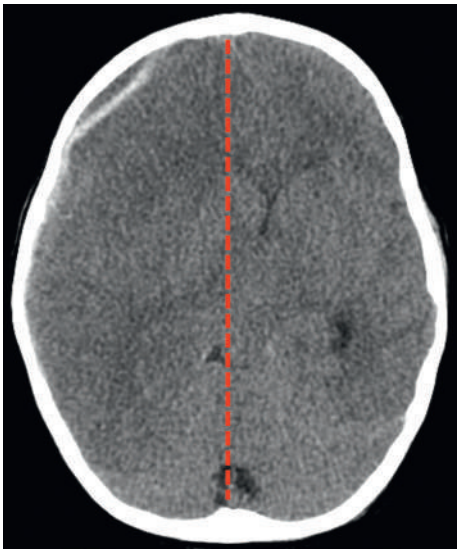

Figure 68-7 Hyperacute right frontal subdural hematoma observed on CT imaging in a 5 yr old after a motor vehicle accident. Note that the hyperacute aspect of the subdural hematoma is dark on CT imaging in the early stage after injury. Also, note that there is marked midline shift of intracranial contents, as both lateral ventricles are displaced into the left side of the skull.

Diagnosis and Differential Diagnosis

In severe TBI, the diagnosis is generally obvious from the history and clinical presentation. Occasionally, TBI severity can be overestimated because of concurrent alcohol or drug intoxication. The diagnosis of TBI can be problematic in cases of abusive head trauma or following an anoxic event such as drowning or smoke inhalation.

Treatment

Infants and children with severe or moderate TBI (GCS score 3-8 or 9-12, respectively) receive intensive care unit (ICU) monitoring. Evidence-based guidelines for management of severe TBI have been published (Fig. 68-12). This approach to ICP-directed therapy is also reasonable for other conditions in which ICP is monitored. Care involves a multidisciplinary team comprising pediatric caregivers from

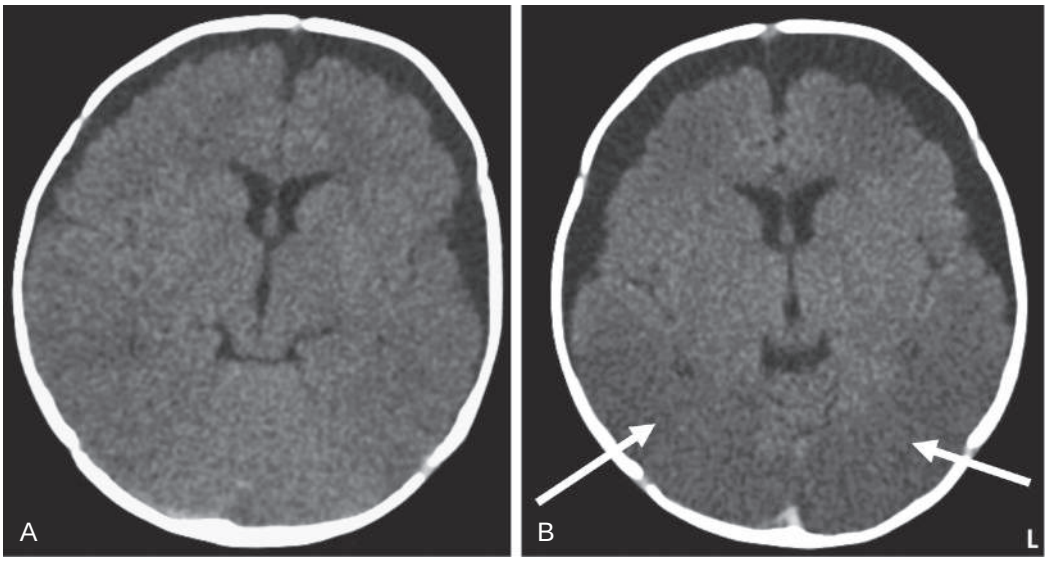

Figure 68-8 In a 3 mo old child who suffered from abusive head trauma, initial CT imaging *(A)* demonstrates chronic subdural hematoma bilaterally. Three days after hospitalization *(B)*, the subdural hematomas are slightly larger but infarctions are noted in the posterior areas of brain parenchyma (see *arrows*).

Figure 68-9 In a 16 yr old who fell off of his dirt bike, CT imaging demonstrates intraparenchymal hemorrhage and significant surrounding edema (*arrow*).

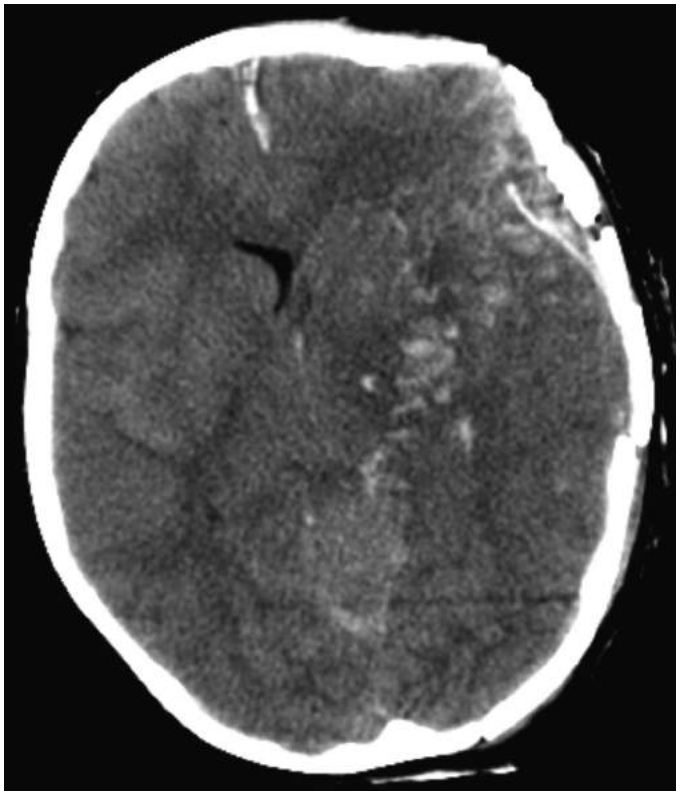

Figure 68-10 An 11 yr old child was hit in the head by a horse, and CT imaging demonstrates multiple, comminuted skull fractures with fragments of bone within the brain parenchyma, multifocal areas of intraparenchymal hemorrhage, and obliteration of the left lateral ventricle.

neurologic surgery, critical care medicine, surgery, and rehabilitation, and is directed at preventing secondary insults and managing raised ICP. Initial stabilization of infants and children with severe TBI includes rapid sequence tracheal intubation with spine precautions along with maintenance of normal extracerebral hemodynamics, including blood gas values (partial pressure arterial oxygen, Pa_{CO_2}), mean arterial pressure, and temperature. Intravenous fluid boluses may be required to treat hypotension. Euvolemia is the target, and hypotonic fluids should be rigorously avoided; normal saline is the fluid of choice. Pressors may be needed as guided by monitoring of central venous pressure, with avoidance of both fluid overload and exacerbation of brain edema. A trauma survey should be performed. Once stabilized, the patient should be taken for CT scanning to rule out the need for emergency neurosurgical intervention. If surgery is not

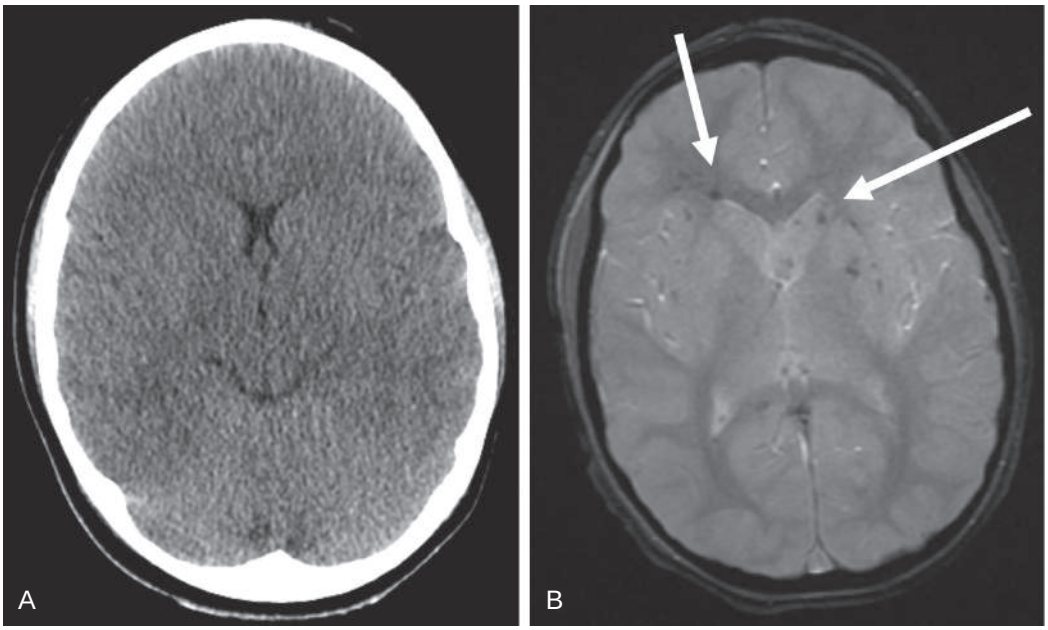

Figure 68-11 In a 6 yr old child who was hit by a car while riding his bike, initial CT imaging demonstrates no obvious abnormality (*A*). However, immediate MRI demonstrates multiple areas of punctate hemorrhages (lucencies) consistent with diffuse axonal injury (*B, arrows*).

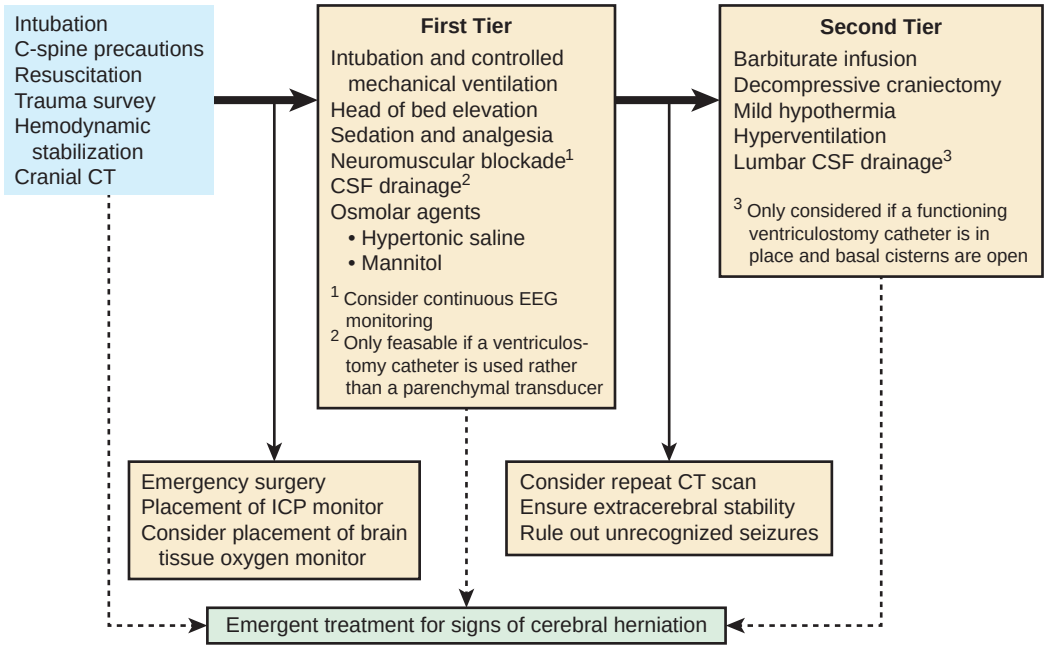

Figure 68-12 Schematic outlining the approach to management of a child with severe TBI. It is based on the 2012 guidelines for the management of severe TBI, along with minor modifications from later literature. The ICP and CPP targets are discussed in the text. This schematic is specifically presented for severe TBI, for which the experience with ICP-directed therapy is greatest. Nevertheless, the general approach provided here is relevant to the management of intracranial hypertension in other conditions for which evidence-based data on ICP monitoring and ICP-directed therapy are lacking. Please see text for details.

required, an ICP monitor should be inserted to guide the treatment of intracranial hypertension. Serial assessment of brain edema on CT scan can also help guide management.

During stabilization or at any time during the treatment course, patients can present with signs and symptoms of cerebral **herniation** (pupillary dilation, systemic hypertension, bradycardia, extensor posturing). Because herniation and its devastating consequences can sometimes be reversed if promptly addressed, it should be treated as a medical emergency, with use of hyperventilation with a fraction of inspired oxygen of 1.0, and intubating doses of either thiopental or pentobarbital and either mannitol (0.25-1.0 g/kg IV) or hypertonic saline (3% solution, 5-10 mL/kg IV).

ICP should be maintained <20 mm Hg; age-dependent CPP targets are ≈50 mm Hg for children 2-6 yr of age; 55 mm Hg for those 7-10 yr of age; and 65 mm Hg for those 11-16 yr of age. First-tier therapy includes elevation of the head of the bed, ensuring midline positioning of the head, controlled mechanical ventilation, and sedation and analgesia (i.e., benzodiazepines and narcotics). If neuromuscular blockade is needed, it may be desirable to monitor EEG continuously because *status epilepticus* can occur; this complication will not be recognized

in a paralyzed patient and is associated with raised ICP and unfavorable outcome. If a ventricular rather than parenchymal catheter is used to monitor ICP, therapeutic CSF drainage is available and can be provided either continuously (often targeting an ICP >5 mm Hg) or intermittently in response to ICP spikes, generally 20 mm Hg. Other first-tier therapies include the osmolar agents mannitol (0.25-1.0 g/kg IV over 20 min), given in response to ICP spikes >20 mm Hg or with a fixed (q4-6h) dosing interval, and hypertonic saline (often given as a continuous infusion of 3% saline at 0.1-1.0 mL/kg/hr). Choice of osmolar agent depends on the preference of the treating center. These 2 agents can be used concurrently. It is recommended to avoid serum osmolality >320 mOsm/L. A Foley urinary catheter should be placed to monitor urine output.

If ICP remains refractory to treatment, careful reassessment of the patient is needed to rule out unrecognized hypercarbia, hypoxemia, fever, hypotension, hypoglycemia, pain, and seizures. Repeat imaging should be considered to rule out a surgical lesion. Guidelines-based second-tier therapies for refractory raised ICP are available, but evidence favoring a given second-tier therapy is limited. In some centers, decompressive craniectomy is used. Others use a pentobarbital infusion, with a loading dose of 5-10 mg/kg over 30 min followed by 5 mg/kg every hour for 3 doses and then maintenance with an infusion of 1 mg/kg/hr. Careful blood pressure monitoring is required because of the possibility of drug-induced hypotension and the frequent need for support with fluids and/or pressors. Mild hypothermia (32-34°C [89.6-93.2°F]) to control refractory ICP can be induced and maintained by means of surface cooling. Sedation and neuromuscular blockade are used to prevent shivering, and rewarming should be slow, no faster than 1°C (1.8°F) every 4-6 hr. Hypotension should be prevented during rewarming. Refractory raised ICP can also be treated with hyperventilation (Pa_{CO_2} = 25-30 mm Hg). Other second-tier therapies (e.g., lumbar CSF drainage) are options.

Supportive Care

Euvolemia should be maintained, and isotonic fluids are recommended until resolution of intracranial hypertension. The syndrome of inappropriate antidiuretic hormone secretion and salt wasting can develop and are important to differentiate, because management of the former is fluid restriction and that of the latter is sodium replacement. Severe hyperglycemia (blood glucose level >200 mg/dL) should be avoided and treated. The blood glucose level should be monitored frequently. Early nutrition with enteral feedings is advocated. Corticosteroids should generally not be used unless adrenal insufficiency is documented. Tracheal suctioning can exacerbate raised ICP. Timing of the use of sedation around suctioning events and/or use of tracheal or IV lidocaine can be helpful. Seizures are common after severe acute TBI. Early posttraumatic seizures (within 1 wk) will complicate management of TBI and are often difficult to treat. Anticonvulsant prophylaxis with fosphenytoin, carbamazepine, or levetiracetam is a common treatment option. Late posttraumatic seizures (≥7 days after TBI) and, if recurrent, late posttraumatic epilepsy are not prevented by prophylactic anticonvulsants, whereas early posttraumatic seizures are prevented by initiating anticonvulsants soon after TBI. Antifibrinolytic agents (tranexamic acid) reduce hemorrhage size as well as the development of new focal ischemic cerebral lesions, and improve survival in adults with severe traumatic brain injury.

Prognosis

Mortality rates for children with severe TBI who reach the pediatric ICU range between 10% and 30%. Ability to control ICP is related to patient survival, and the extent of cranial and systemic injuries correlates with quality of life. Motor and cognitive sequelae resulting from severe TBI generally benefit from rehabilitation to minimize long-term disabilities. Recovery from TBI may take months to achieve. Physical therapy, and in some centers methylphenidate, helps with motor and behavioral recovery. Pituitary insufficiency may be an uncommon but significant complication of severe TBI.

Bibliography is available at Expert Consult.

68.1 Brain Death

K. Jane Lee

Brain death is the irreversible cessation of all functions of the entire brain, including the brainstem. It is also known as the determination of death using neurologic criteria. Although brain death is legally accepted in the United States as the equivalent of death from the irreversible cessation of circulatory and respiratory functions, it can be difficult to understand and is not universally accepted.

EPIDEMIOLOGY

In children, brain death most commonly develops following TBI (including brain injury from nonaccidental trauma) or asphyxial injury. Pathogenesis is multifactorial, with the end result being irreversible loss of brain and brainstem function.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Guidelines for the determination of brain death in children were first published in 1987 by a Special Task Force to the American Academy of Pediatrics. These were revised for the first time in 2011 by a combined group from the Society of Critical Care Medicine, the American Academy of Pediatrics, and the Child Neurology Society.

Brain death is primarily a clinical diagnosis. Although ancillary tests such as EEG and CBF studies are sometimes used to assist in making the diagnosis, repeated clinical examination is the standard for diagnosis. The 3 key components of clinical brain death diagnosis are demonstrations of coexisting **irreversible coma with a known cause**, **absence of brainstem reflexes**, and **apnea**.

Before a determination of brain death may be made, it is of utmost importance that the cause of the coma be determined through the use of historical, radiologic, and laboratory data to rule out a reversible condition. Potentially reversible causes of coma include metabolic disorders; toxins; sedative drugs; paralytic agents; hypothermia; hypoxia; hypotension/shock; recent cardiopulmonary resuscitation; hypoglycemia/hyperglycemia; hyponatremia/hypernatremia; hypercalcemia; hypermagnesemia; nonconvulsive status epilepticus; hypothyroidism; hypocortisolism; hypercarbia; liver or renal failure; sepsis; meningitis; encephalitis; subarachnoid hemorrhage; and surgically remediable brainstem lesions. Confounding factors must be corrected prior to initiation of brain death assessment.

Coma

The state of **coma** requires that the patient be unresponsive, even to noxious stimuli. Any purposeful motor response, such as localization, does not constitute coma. Likewise, any posturing (decerebrate or decorticate) is not consistent with coma, and therefore not consistent with brain death. The presence of spinal cord reflexes—even complex reflexes—does not preclude the diagnosis of brain death.

Brainstem Reflexes

Brainstem reflexes must be absent. Table 68-2 lists the brainstem reflexes to be tested, the brainstem location of each reflex, and the result of each test that is consistent with a diagnosis of brain death.

Apnea

Apnea is the absence of respiratory effort in response to an adequate stimulus. A partial pressure of carbon dioxide (pCO_2) value ≥60 mm Hg *and* >20 mm Hg above baseline is considered sufficient. Apnea is clinically confirmed through the apnea test. Because the apnea test has the potential to destabilize the patient, this test is performed only if the first 2 criteria for brain death (irreversible coma and absence of brainstem reflexes) are already confirmed.

The **apnea test** assesses the function of the medulla in driving ventilation. It is performed by first ensuring appropriate hemodynamics and temperature and the absence of apnea-producing drug effects or significant metabolic derangements. The patient is then preoxygenated with 100% oxygen for approximately 10 minutes and ventilation is adjusted to achieve a pCO_2 of approximately 40 mm Hg. A baseline

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Table 68-2 Brainstem Reflex Testing to Determine Brain Death

BRAINSTEM REFLEX	AREA TESTED	HOW TO PERFORM THE EXAM	EXPLANATION OF RESULTS
Pupillary light reflex	CN II and III, midbrain	Shine a light into the eyes while closely observing pupillary size	Midposition (4-6 mm) or fully dilated pupils that are not reactive to light are consistent with brain death. Pinpoint pupils, even if nonreactive, suggest intact function of the Edinger-Westphal nucleus in the midbrain and are therefore not consistent with brain death.
Oculocephalic reflex (doll's-eyes reflex)	CN III, VI, and VIII, midbrain, pons	Manually rotate the patient's head side to side and closely watch the position of the eyes. Should not be performed in a patient with a cervical spine injury.	In an intact patient, the eyes remain fixed on a distant spot, as if maintaining eye contact with that spot. In an exam consistent with brain death, the eyes move in concert with the patient's head movement.
Corneal reflex	CN III, V, and VII, pons	Touch the patient's cornea with a cotton swab.	In the intact patient, the touch results in eyelid closure, and the eye may rotate upward. In an exam consistent with brain death, there is no response.
Oculovestibular reflex	CN III, IV, VI, and VIII, pons, midbrain	Irrigate the tympanic membrane with iced water or saline and look for eye movement.	Absence of eye movement is consistent with brain death.
Gag and cough reflex	CN IX and X, medulla	Touch the posterior pharynx with a tongue depressor or a cotton-tipped swab to stimulate a gag. Advance a suction catheter through the endotracheal tube to the carina to stimulate a cough.	Absence of both a cough and a gag is consistent with brain death.

CN, cranial nerve.

blood gas result documents the starting values. During the test, oxygenation can be maintained with 100% oxygen via a T-piece attached to the endotracheal tube or via a resuscitation bag such as a Mapleson device. Throughout the test, the child's hemodynamics and oxygen saturation are monitored while the physician observes for respiratory efforts. A blood gas sample is obtained approximately 10 min into the test and every 5 min thereafter until the target pCO_2 is surpassed; ventilatory support is resumed at that time. If at any point during the test the patient becomes hypoxic or hypotensive, the test is aborted and ventilatory support is resumed. Absence of respiratory efforts with a pCO_2 ≥60 mm Hg and >20 mm Hg above baseline is consistent with brain death.

OBSERVATION PERIODS

To establish the diagnosis of brain death, the findings must remain consistent for 2 examinations separated by an observation period. Recommended observation periods are 24 hr for neonates from 37 wk gestation to term infants 30 days old, and 12 hr for infants and children older than 30 days. An observation period of 24-48 hr prior to initiation of brain death assessment is recommended following CPR or severe acute brain injury.

ANCILLARY STUDIES

Ancillary studies are not required for the diagnosis of brain death unless the clinical examination including the apnea test cannot be safely or reliably completed. Examples include cervical spinal cord injury, presence of high-therapeutic or supratherapeutic levels of sedative medications, or hemodynamic instability or desaturation during an apnea test. Ancillary studies may also be used to shorten the recommended observation period. In this case, 2 complete clinical examinations, including apnea test, should be completed and documented along with the ancillary study.

The 2 most commonly used ancillary tests are EEG and radionuclide CBF studies. A valid **EEG** to support suspected brain death must be performed according to accepted technical requirements, under conditions of normothermia and appropriate hemodynamics, and in the absence of drug levels sufficient to suppress the EEG response. An EEG that demonstrates **electrocerebral silence** over a 30 min recording time under these conditions supports the diagnosis of brain death. Advantages of this study are its wide availability and low risk. Disadvantages include potential confounders, such as artifact in the tracing and the presence of suppressing levels of drugs such as barbiturates.

A **radionuclide CBF study** consists of intravenous injection of a radiopharmaceutical agent followed by imaging of the brain to look for cerebral uptake. Like EEG, nuclear medicine scans are widely available and low risk. Unlike EEG, these studies are not affected by drug levels. A study that shows absence of uptake in the brain demonstrates absence of CBF and is supportive of brain death. Four-vessel intracranial contrast angiography was previously used as the definitive ancillary test, but practical technical difficulties and risks have led to the use of nuclear medicine scans instead.

Interpretation of both EEG and radionuclide CBF studies should be done by appropriately trained and qualified individuals. If the studies show electrical activity or presence of CBF, brain death cannot be declared. A 24 hr waiting period is recommended prior to repeating the clinical examination or ancillary study.

DOCUMENTATION

Documentation is an important aspect of diagnosing brain death. Complete documentation should include statements of the following:

1. Etiology and irreversibility of the coma.
2. Absence of confounding factors: hypothermia, hypotension, hypoxia, significant metabolic derangement, significant drug levels.
3. Absence of motor response to noxious stimulation.
4. Absence of brainstem reflexes: pupillary light reflex, oculocephalic/oculovestibular reflex, corneal reflex, cough and gag reflex.
5. Absence of respiratory effort in response to an adequate stimulus; blood gas values should be documented at the beginning and end of the apnea test.

SUPPORTIVE CARE

Following a diagnosis of brain death, supportive care may continue for hours to days as the family makes decisions about potential organ donation and comes to terms with the diagnosis. A diagnosis of brain death may not be accepted by the family for personal, religious, or

cultural reasons. It is important for care providers to be patient and supportive of the family dealing with this difficult situation.

OBJECTIONS TO THE IDEA OF BRAIN DEATH

Although the concept of brain death is widely accepted and very useful in facilitating organ transplantation, it is not accepted by all. Several countries do not recognize brain death, and some individuals, both medical personnel and laypeople, object to the idea of brain death.

It has been pointed out that some patients who meet brain death criteria continue to show evidence of integrative functioning, such as control over free-water homeostasis (absence of diabetes insipidus), control of temperature regulation, capacity for growth and wound healing, and variability of heart rate and blood pressure in response to stimulus. Along with scientific arguments, there are also philosophical arguments about what constitutes death and whether a person who lacks function of the brain, but not of the body, is truly dead.

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Chapter 69

Syncope

George F. Van Hare

Syncope is defined as a sudden transient loss of consciousness with inability to maintain postural tone. The most common cause of syncope in the normal pediatric population is **neurocardiogenic syncope**, also known as vasovagal syncope (Table 69-1). Although this type of syncope is very common in adolescence and has an excellent prognosis, other causes for loss of consciousness are more dangerous, thus syncope may be the first sign of more serious conditions (Table 69-2). Indeed, the occurrence of syncope may well be the pediatrician's best opportunity to diagnose a life-threatening condition before the patient subsequently succumbs. The task of the clinician, therefore, is not only to counsel the family and the patient concerning the common form, but also to rule out a number of important life-threatening cardiac problems.

EPIDEMIOLOGY

Most syncope presents during adolescence, typically between 11 and 13 yr of age. The incidence is somewhat higher in girls than in boys. Approximately 25% of all young adults will have experienced at least 1 episode of neurocardiogenic syncope.

MECHANISMS

Syncope by whatever mechanism is caused by a lack of adequate cerebral blood flow with loss of consciousness and inability to see remain upright. The mechanisms underlying neurocardiogenic syncope are not completely understood but seem to involve some trigger event that leads to vasodilation, venous pooling in the lower part of the body exacerbated by prolonged standing, decreased cardiac filling with compensatory sinus tachycardia and sympathetic nervous system activity, and, finally, activation of cardiac C fibers leading to reflex bradycardia. The typical event is triggered by a variety of factors, such as disgust, the site of blood, other emotional reactions, particular smells, or simply prolonged standing (see Table 69-1). Most patients display a mixed picture with both blood pressure and heart rate changes. Prior to syncope, the blood pressure declines and the heart rate increases, and with loss of consciousness there is often significant bradycardia. Other patients display a principally vasopressor response with a drop in blood pressure as the most important feature. Still others primarily have a cardioinhibitory response in which sudden profound bradycardia or asystole occurs with little or no change in blood pressure prior to the event. Making the distinction between these various patterns leading

Table 69-1 Noncardiac Causes of Syncope

Reflex vasodepressor syncope
Neurocardiogenic (vasovagal)
Emotion (seeing blood)
Pain (needle phobia)
Miscellaneous situational reflex
Tussive
Sneeze
Exercise/post exercise
Swallowing
Stretching
Defecation
Micturition
Valsalva (increased intrathoracic pressure)
Breath holding spells
Systemic illness
Hypoglycemia
Anemia
Infection
Hypovolemia, dehydration
Adrenal insufficiency
Narcolepsy/cataplexy
Pulmonary embolism
Ruptured ectopic pregnancy
Central nervous system
Seizure (atonic, absence, myoclonic-astatic)
Stroke/transient ischemic attack
Subarachnoid hemorrhage
Dysautonomia
Basilar artery migraine
Drug effects
β-Blocking agents
Vasodilating agents
Opiates
Sedatives
Drugs prolonging QT interval
Diuretics
Anticonvulsant agents
Antihistamines
Antidepressant agents
Anxiolytic agents
Drugs of abuse
Insulin, oral hypoglycemic agents
Carbon monoxide
Other etiologies
Carotid sinus sensitivity
Subclavian steal
Panic attack/anxiety
Conversion disorder

Table 69-2 Life-Threatening Cardiac Causes of Syncope

Long QT syndromes (congenital and drug induced)
Cardiomyopathies
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Arrhythmogenic right ventricular dysplasia
Brugada syndrome
Catecholminergic polymorphic ventricular tachycardia
Myocarditis
Wolff-Parkinson-White syndrome
Coronary artery anomalies
Late postoperative arrhythmias
Congenital or acquired complete atrioventricular block
Aortic, mitral, or pulmonic valve stenosis
Primary pulmonary hypertension
Eisenmenger syndrome
Dissecting aortic aneurysm (Marfan syndrome)
Cardiac tumor

to syncope is important for treatment considerations. In any case, with loss of consciousness and the assumption of supine posture, venous return and atrial filling dramatically increases and adequate blood pressure returns quickly.

Primary cardiac causes of syncope (see Table 69-2) include arrhythmias (see Chapter 435) such as **long QT syndrome**, **Wolff-Parkinson-White syndrome** (particularly with atrial fibrillation), ventricular tachycardia, and occasionally supraventricular tachycardia. Ventricular tachycardia may be associated with **hypertrophic cardiomyopathy**, repaired **congenital heart disease**, or a genetic cause such as **catecholaminergic polymorphous ventricular tachycardia**. Other arrhythmias that may lead to syncope are bradyarrhythmias such as **sinus node dysfunction** and high-grade 2nd or 3rd degree atrioventricular (AV) block. Patients with **congenital complete AV** block may present with syncope. Syncope may also be caused by cardiac obstructive lesions, such as **critical aortic stenosis,** or coronary artery anomalies, such as an **aberrant left coronary artery arising from the right sinus of Valsalva**. Finally, patients with **primary pulmonary hypertension** or **Eisenmenger syndrome** may experience syncope. In all of the obstructive forms of syncope, exercise increases the likelihood of an episode as the obstruction interferes with the ability of the heart to increased cardiac output in response to exercise.

Noncardiac causes of loss of consciousness include epilepsy, but may also include basilar artery migraine, hysterical syncope, and pseudoseizures (see Table 69-1). Occasionally patients with narcolepsy may present as syncope. Hypoglycemia and hyperventilation may also present with syncope.

EVALUATION

The most important goal in the evaluation of the new patient with syncope is to diagnose life-threatening causes of syncope so that these causes can be managed. Many patients presenting with sudden cardiac arrest caused by conditions such as long QT syndrome will have previously experienced an episode of syncope, and so the presentation with syncope is an opportunity to prevent sudden death.

The most important tool in evaluation is a careful history. The patient with neurocardiogenic syncope will be able to describe the circumstances of the event and specific prodromal symptoms. Typically, the patient will have been standing for a period of time, often on a hot day, or has gotten up suddenly from sleep or resting in a supine position. Occurrence in the shower is common, presumably caused by standing and vasodilation caused by hot water. For boys, the occurrence while urinating while standing is sometimes reported. The occurrence of syncope in girls while sitting or standing and having their hair brushed is common. Typical prodromal symptoms prior to syncope include lightheadedness, dizziness, nausea, sweating, and feeling hot or cold. Patients may report visual field changes and "rushing" in their ears. Witnesses will usually note extreme pallor or a gray color change. Injury to the patient as a result of the episode of syncope is unusual in common syncope, as the patient usually has adequate prodromal symptoms to avoid injury. Loss of consciousness is generally transient once the patient becomes supine; the loss of consciousness resolves rapidly (seconds to minutes), and there is no clear postevent state of sleepiness. Often, patients will describe other episodes with similar prodromal symptoms which did not lead to complete loss of consciousness but were aborted, often because the patient was able to assume recumbent posture. Some patients have a few tonic–clonic movements while unconscious, which resolve within seconds, and do not signify a seizure disorder.

The characteristics of cardiac syncope not due to neurocardiogenic mechanisms are generally quite different. A number of "red flags" can be identified that should lead the clinician to be suspicious that the mechanism is a life-threatening cardiac cause rather than simple fainting (Table 69-3). The occurrence during exercise suggests an arrhythmia or coronary obstruction. Injury as a result of an episode of syncope suggests sudden occurrence with a lack of adequate prodromal symptoms, and suggests an arrhythmia. The occurrence of syncope while recumbent would be quite unusual in a patient with neurocardiogenic syncope and therefore raises the possibility of a cardiac or neurologic cause. Occasionally, a patient with syncope caused by a tachyarrhythmia will report the sensation of a racing heart prior to the event, but this is actually unusual.

Table 69-3 "Red Flags" in the Evaluation of Patients with Syncope

Syncope with activity or exercise or supine
Syncope not associated with prolonged standing
Syncope precipitated by loud noise or extreme emotion
Absence of presyncope or lightheadedness
Family history of syncope, drowning, sudden death, familial ventricular arrhythmia syndromes*, cardiomyopathy
Syncope requiring CPR
Injury with syncope
Anemia
Other cardiac symptoms
Chest pain
Dyspnea
Palpitations
History of cardiac surgery
History of Kawasaki disease
Implanted pacemaker
Abnormal physical examination
Murmur
Gallop rhythm
Loud and single second heart sound
Systolic click
Increased apical impulse (tachycardia)
Irregular rhythm
Hypo- or hypertension
Clubbing
Cyanosis

*Long Qt syndrome, Brugada syndrome, catecholamine polymorphic ventricular tachycardia, arrhythmogenic right ventricular dysplasia.

A careful family history is essential in evaluation of syncope. Specifically, if there are first-degree relatives with inherited syndromes, such as a long QT syndrome or hypertrophic cardiomyopathy, this should lead to more specific evaluation of the patient. Also, if there are relatives who have died suddenly in young age without a clear and convincing cause, inherited cardiac arrhythmias or cardiomyopathies should also be suspected.

Patients with a history of heart disease, especially cardiac repair, may have causes that are specific to their repair. Sinus node dysfunction is common after the Senning or Mustard procedure for transposition of the great vessels. Ventricular tachycardia may be seen following repair of tetralogy of Fallot. A patient with a history of septal defect repair should be evaluated for the late occurrence of AV block, and patients with an implanted pacemaker should be evaluated for pacemaker lead failure.

The physical examination may also offer clues (see Table 69-3). Patients with hypertrophic cardiomyopathy may have a prominent cardiac impulse and/or an ejection murmur, as will patients with aortic stenosis. The patient with primary pulmonary hypertension will have a loud and single second heart sound and may also have an ejection click and the murmur of pulmonary insufficiency. Scars from prior cardiac surgery and pacemaker implantation would be evident.

All patients presenting with a first episode of syncope should have an electrocardiogram obtained, looking primarily for QT interval prolongation, preexcitation, ventricular hypertrophy, T-wave abnormalities, and conduction abnormalities. Other tests that may be needed depending on the results of the initial evaluation may include echocardiography, cardiac MRI, or 24-hr Holter monitoring. In patients for whom there is a strong suspicion of a paroxysmal arrhythmia, an implantable loop recorder may be the most effective means of diagnosis.

Tilt-table testing was originally developed by the military and was applied to the general population of otherwise normal individuals who have experienced syncope. While patients with neurocardiogenic syncope often will experience an episode during the tilt-table test, the test is poorly reproducible and neither particularly sensitive nor

specific. The use of tilt-table testing for the otherwise normal adolescent with simple fainting is discouraged. Some pediatric cardiologists still employ the test in severely affected individuals who are not responding to standard therapy, as a way of planning more aggressive therapy.

Additional tests to look for anemia, hypoglycemia, drugs of abuse, and other etiologies noted in Table 69-1 will be determined by the history and physical exam.

TREATMENT

Most patients with neurocardiogenic syncope will experience eventual resolution by adulthood; many even get better spontaneously within a few months or years. Many therapies have been employed for this condition, but it is difficult to determine which ones are truly effective because of the lack of randomized prospective studies. Nonetheless, initial salt and water supplementation is commonly recommended, particularly in those who have a low-salt diet or who have limited their fluid intake. A reasonable second step is treatment with fludrocortisone, a mineralocorticoid that promotes sodium and water retention with potassium loss. In patients who have a prominent low-blood-pressure response, the α-agonist midodrine may be useful. Both midodrine and fludrocortisone should be managed with careful monitoring of the supine blood pressure, as they may lead to supine hypertension. Some have advocated the use of β blockers such as, pindolol, which offers some advantages because of its intrinsic sympathomimetic activity; randomized prospective trials have not supported the effectiveness of beta blockers. Occasionally, the use of selective serotonin reuptake inhibitors is effective in certain patients. Occasional patients who present with profound bradycardia or asystole can be helped by implantation of a dual-chamber transvenous pacemaker with programmed hysteresis (rapid pacing in response to a sudden drop in heart rate).

The most important therapeutic step is educational. Once the young patient is aware of the importance of the prodromal symptoms, they can take appropriate steps to change position and not attempt to remain standing. In many, this is all that is necessary to adequately manage their symptoms.

Bibliography is available at Expert Consult.

69.1 Disorders of Orthostatic Intolerance

George F. Van Hare

Postural orthostatic tachycardia syndrome (POTS) is a female-predominant condition in which the patient experiences an impressive and symptomatic elevation in heart rate on standing. This orthostatic intolerance disorder manifests with presyncopal symptoms, lightheadedness, dizziness, palpitations, leg weakness and tremulousness on standing. An orthostatic heart rate of >120 beats/min and a rise in heart rate of ≥30 beats/min with 5 min of standing suggest the diagnosis. *This should not be confused with neurocardiogenic syncope*. Patients with POTS often also complain of other symptoms, such as fatigue, chest pain, headaches, abdominal pain, bloating, nausea, emesis, sleep disturbances, and fatigue. There is an overlap with patients with POTS and chronic fatigue syndrome or functional gastrointestinal disorders. Many patients are evaluated in dysautonomia programs and may have evidence of a **small fiber polyneuropathy**. Treatment of POTS is symptomatic and often not particularly successful. The use of β blockers may be effective; some physicians have advised increase physical activity through cardiac rehabilitation.

Juvenile-onset widespread pain syndromes associated with a small fiber polyneuropathy (dysautonomia) have associated gastrointestinal, cardiovascular, fatigue, headache symptoms as well as erythromelalgia. Steroids or intravenous immunoglobulin has been used to treat this disorder.

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Chapter 70

Shock

David A. Turner and Ira M. Cheifetz

Shock is an acute process characterized by the body's inability to deliver adequate oxygen to meet the metabolic demands of vital organs and tissues. Insufficient oxygen at the tissue level is unable to support normal aerobic cellular metabolism, resulting in a shift to less-efficient anaerobic metabolism. As shock progresses, increases in tissue oxygen extraction are unable to compensate for this deficiency in oxygen delivery, leading to progressive clinical deterioration and lactic acidosis. If inadequate tissue perfusion persists, adverse vascular, inflammatory, metabolic, cellular, endocrine, and systemic responses worsen physiologic instability.

Compensation for inadequate oxygen delivery involves a complex set of responses that attempt to preserve oxygenation of the vital organs (i.e., brain, heart, kidneys, liver) at the expense of other organs (i.e., skin, gastrointestinal tract, muscles). Of importance, the brain is especially sensitive to periods of poor oxygen supply, given its lack of capacity for anaerobic metabolism. Initially, shock is often well compensated, but it may rapidly progress to an uncompensated state requiring more aggressive therapies to achieve clinical recovery or improvement. The combination of a continued presence of an inciting trigger and the body's exaggerated and potentially harmful neurohumoral, inflammatory, and cellular responses leads to the progression of shock. Irrespective of the underlying cause of shock, the specific pattern of response, pathophysiology, clinical manifestations, and treatments may vary significantly, depending on the specific etiology (which may be unknown), the clinical circumstances, and an individual patient's biologic response to the shock state. Untreated shock causes irreversible tissue and organ injury (i.e., irreversible shock) and, ultimately, death.

EPIDEMIOLOGY

Shock occurs in approximately 2% of all hospitalized infants, children, and adults in developed countries, and the mortality rate varies substantially depending on the etiology and clinical circumstances. Most patients who do not survive, do not die in the acute hypotensive phase of shock, but rather as a result of associated complications and **multiple organ dysfunction syndrome (MODS).** MODS is defined as any alteration of organ function that requires medical support for maintenance, and the presence of MODS in patients with shock substantially increases the probability of death. In pediatrics, educational efforts and the utilization of standardized management guidelines that emphasize early recognition and intervention along with the rapid transfer of critically ill patients to a pediatric intensive care unit have led to decreases in the mortality rate for shock (Fig. 70-1).

DEFINITION

Shock classification systems generally define 5 major types of shock: hypovolemic, cardiogenic, distributive, obstructive, and septic (Table 70-1). **Hypovolemic shock,** the most common cause of shock in children worldwide, is most frequently caused by diarrhea, vomiting, or hemorrhage. **Cardiogenic shock** is seen in patients with either congenital heart disease (before or after surgery, including heart transplantation) or with congenital or acquired cardiomyopathies, including acute myocarditis. **Obstructive shock** stems from any lesion that creates a mechanical barrier that impedes adequate cardiac output, which include pericardial tamponade, tension pneumothorax, pulmonary embolism, and ductus-dependent congenital heart lesions. **Distributive shock** is caused by inadequate vasomotor tone, which leads to capillary leak and maldistribution of fluid into the interstitium. **Septic shock** is often discussed synonymously with distributive shock, but the septic process usually involves a more complex interaction of distributive, hypovolemic, and cardiogenic shock.

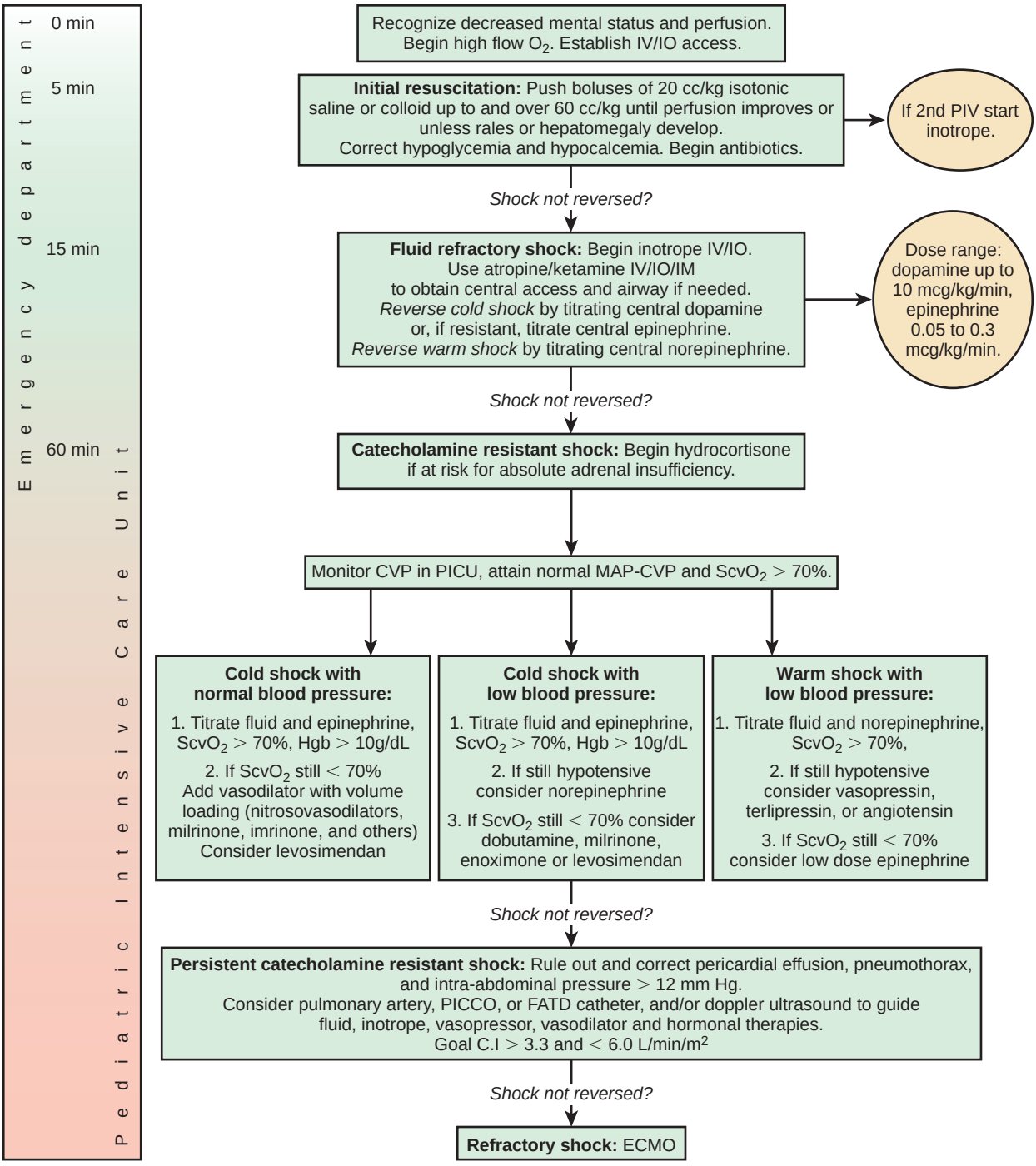

Figure 70-1 Algorithm for time-sensitive, goal-directed, stepwise management of hemodynamic support in infants and children. CI, cardiac index; CRRT, continuous renal replacement therapy; CVP, central venous pressure; ECMO, extracorporeal membrane oxygenation; FATD, femoral arterial thermodilution; Hgb, hemoglobin; IM, intramuscular; IO, intraosseous; IV, intravenous; MAP, mean arterial pressure; PICCO, pulse contour cardiac output. *(From Brierly J, Carcillo JA, Choong K, et al: Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine,* Crit Care Med *37:666-688, 2009. Copyright 2009, Society of Critical Care Medicine and Lippincott Williams & Wilkins.)*

PATHOPHYSIOLOGY

An initial insult triggers shock, leading to inadequate oxygen delivery to organs and tissues. Compensatory mechanisms attempt to maintain blood pressure by increasing cardiac output and systemic vascular resistance (SVR). The body also attempts to optimize oxygen delivery to the tissues by increasing oxygen extraction and redistributing blood flow to the brain, heart, and kidneys at the expense of the skin and gastrointestinal tract. These responses lead to an initial state of **compensated shock,** in which blood pressure is maintained. If treatment is not initiated or is inadequate during this period, **decompensated shock** develops, with hypotension and tissue damage that may lead to **multisystem organ dysfunction** and ultimately death (Fig. 70-2, Tables 70-2 and 70-3).

In the early phases of shock, multiple compensatory physiologic mechanisms act to maintain blood pressure and preserve tissue perfusion and oxygen delivery. Cardiovascular effects include increases in heart rate, stroke volume, and vascular smooth muscle tone, which are regulated through sympathetic nervous system activation and

Table 70-1 Types of Shock

HYPOVOLEMIC	CARDIOGENIC	DISTRIBUTIVE	SEPTIC	OBSTRUCTIVE
Decreased preload secondary to internal or external losses	Cardiac pump failure secondary to poor myocardial function	Abnormalities of vasomotor tone from loss of venous and arterial capacitance	Encompasses multiple forms of shock Hypovolemic: third spacing of fluids into the extracellular, interstitial space Distributive: early shock with decreased afterload Cardiogenic: depression of myocardial function by endotoxins	Decreased cardiac output secondary to direct impediment to right- or left-heart outflow or restriction of all cardiac chambers
POTENTIAL ETIOLOGIES Blood loss: hemorrhage; Plasma loss: burns, nephrotic syndrome; Water/electrolyte loss: vomiting, diarrhea	Congenital heart disease Cardiomyopathies: infectious or acquired, dilated or restrictive Ischemia Arrhythmias	Anaphylaxis Neurologic: loss of sympathetic vascular tone secondary to spinal cord or brainstem injury Drugs	Bacterial Viral Fungal (immunocompromised patients are at increased risk)	Tension pneumothorax Pericardial tamponade Pulmonary embolism Anterior mediastinal masses Critical coarctation of the aorta

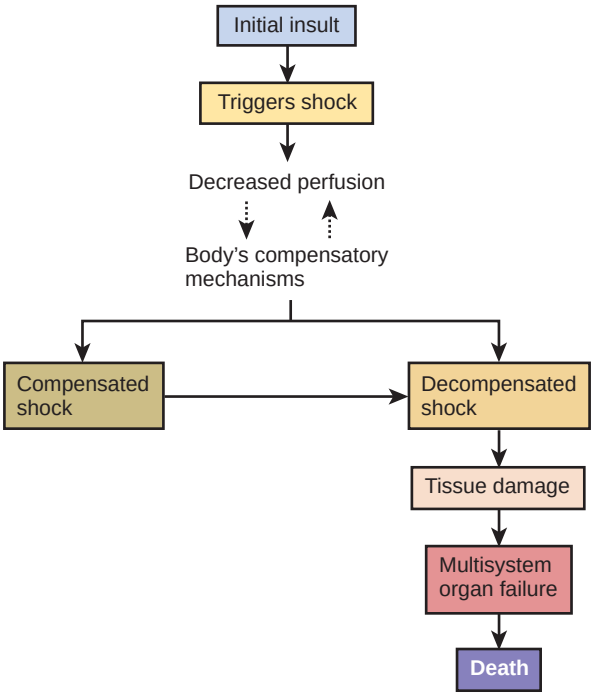

Figure 70-2 Algorithm for decompensated shock.

neurohormonal responses. Respiratory compensation involves greater CO_2 elimination in response to the metabolic acidosis and increased CO_2 production from poor tissue perfusion. Renal excretion of hydrogen ions and retention of bicarbonate also increase in an effort to maintain normal body pH (see Chapter 55.7). Maintenance of intravascular volume is facilitated via sodium regulation through the renin–angiotensin–aldosterone and atrial natriuretic factor axes, cortisol and catecholamine synthesis and release, and antidiuretic hormone secretion. Despite these compensatory mechanisms, the underlying shock and host response lead to vascular endothelial cell injury and significant leakage of intravascular fluids into the interstitial extracellular space.

Another important aspect of the initial pathophysiology of shock is the impact on cardiac output. All forms of shock affect cardiac output via several mechanisms, with changes in heart rate, preload, afterload, and myocardial contractility occurring separately or in combination (Table 70-4). **Hypovolemic shock** is characterized primarily by fluid loss and decreased preload. Tachycardia and an increase in SVR are the initial compensatory responses to maintain cardiac output and systemic blood pressure. Without adequate volume replacement, hypotension develops, followed by tissue ischemia and further clinical deterioration. When there is preexisting low plasma oncotic pressure (caused by nephrotic syndrome, malnutrition, hepatic dysfunction, acute severe burns, etc.), even further volume loss and exacerbation of shock may occur because of endothelial breakdown and worsening capillary leak.

In contrast, the underlying pathophysiologic mechanism leading to **distributive shock** is a state of abnormal vasodilation and decreased SVR. Sepsis, hypoxia, poisonings, anaphylaxis, spinal cord injury, or mitochondrial dysfunction can cause vasodilatory shock (Fig. 70-3). The lowering of SVR is accompanied initially by a maldistribution of blood flow away from vital organs and a compensatory increase in cardiac output. This process leads to significant decreases in both preload and afterload. Therapies for distributive shock must address both of these problems simultaneously.

Cardiogenic shock may be seen in patients with myocarditis, cardiomyopathy, congenital heart disease, or arrhythmias, or following cardiac surgery (see Chapter 434). In these instances, myocardial contractility is affected, leading to systolic and/or diastolic dysfunction. The later phases of all forms of shock frequently have a negative impact on the myocardium, leading to development of a cardiogenic component to the shock state.

Septic shock is often a unique combination of distributive, hypovolemic, and cardiogenic shock. Hypovolemia from intravascular fluid losses occurs through capillary leak. Cardiogenic shock results from the myocardial-depressant effects of sepsis, and distributive shock is the result of decreased SVR. The degree to which a patient exhibits each of these responses varies, but there are frequently alterations in preload, afterload, and myocardial contractility.

In septic shock, it is important to distinguish between the inciting infection and the host inflammatory response. Normally, host immunity prevents the development of sepsis via activation of the reticular endothelial system along with the cellular and humoral immune systems. This host immune response produces an inflammatory cascade of toxic mediators, including hormones, cytokines, and enzymes. If this inflammatory cascade is uncontrolled, derangement of the microcirculatory system leads to subsequent organ and cellular dysfunction.

The **systemic inflammatory response syndrome** (**SIRS**) is an inflammatory cascade that is initiated by the host response to an

Table 70-2 Criteria for Organ Dysfunction

ORGAN SYSTEM	CRITERIA FOR DYSFUNCTION
Cardiovascular	Despite administration of isotonic intravenous fluid bolus ≥60 mL/kg in 1 hr: decrease in BP (hypotension) systolic BP <90 mm Hg, mean arterial pressure <70 mm Hg, <5th percentile for age, or systolic BP <2 SD below normal for age *or* Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose) *or* Two of the following: Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate: >1 mmol/Liter or >2× upper limit of normal Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 sec Core to peripheral temperature gap >3°C (5.4°F)
Respiratory	PaO_2/FIO_2 ratio <300 in absence of cyanotic heart disease or preexisting lung disease *or* $PaCO_2$ >65 torr or 20 mm Hg over baseline $PaCO_2$ *or* Need for >50% FIO_2 to maintain saturation ≥92% *or* Need for nonelective invasive or noninvasive mechanical ventilation
Neurologic	GCS score ≤11 *or* Acute change in mental status with a decrease in GCS score ≥3 points from abnormal baseline
Hematologic	Platelet count <100,000/mm^3 or a decline of 50% in the platelet count from the highest value recorded over the last 3 days (for patients with chronic hematologic or oncologic disorders) *or* INR >1.5 *or* Activated prothrombin time >60 sec
Renal	Serum creatinine >0.5 mg/dL, ≥2× upper limit of normal for age, or 2-fold increase in baseline creatinine value
Hepatic	Total bilirubin ≥4 mg/dL (not applicable for newborn) Alanine transaminase level 2× upper limit of normal for age

BP, blood pressure; FIO_2, fraction of inspired oxygen; GCS, Glasgow Coma Scale; INR, international normalized ratio; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, partial pressure arterial oxygen.

infectious or noninfectious trigger (Table 70-5). This inflammatory cascade is triggered when the host defense system does not adequately recognize and/or clear the triggering event. The inflammatory cascade initiated by shock can lead to hypovolemia, cardiac and vascular failure, acute respiratory distress syndrome (ARDS), insulin resistance, decreased cytochrome P450 activity (decreased steroid synthesis), coagulopathy, and unresolved or secondary infection. Tumor necrosis factor (TNF) and other inflammatory mediators increase vascular permeability, causing diffuse capillary leak, decreased vascular tone, and an imbalance between perfusion and metabolic demands of the tissues. TNF and interleukin (IL)-1 stimulate the release of proinflammatory and antiinflammatory mediators, causing fever and vasodilation. Proinflammatory mediators include IL-6, IL-12, interferon-γ, and macrophage migration inhibitory factor; antiinflammatory cytokines include IL-10, transforming growth factor-β, and IL-4. Arachidonic acid metabolites lead to the development of fever, tachypnea, ventilation–perfusion abnormalities, and lactic acidosis. Nitric oxide, released from the endothelium or inflammatory cells, is a major contributor to hypotension. Myocardial depression is caused directly by myocardial-depressant factors, TNF, and some interleukins, and further depressed via depleted catecholamines, increased β-endorphin, and production of myocardial nitric oxide.

The inflammatory cascade (Fig. 70-4) is initiated by toxins or superantigens via macrophage binding or lymphocyte activation. The vascular endothelium is both a target of tissue injury and a source

Table 70-4 Pathophysiology of Shock

EXTRACORPOREAL FLUID LOSS Hypovolemic shock may be a result of direct blood loss through hemorrhage or abnormal loss of body fluids (diarrhea, vomiting, burns, diabetes mellitus or insipidus, nephrosis)
LOWERING PLASMA ONCOTIC FORCES Hypovolemic shock may also result from hypoproteinemia (liver injury, or as a progressive complication of increased capillary permeability)
ABNORMAL VASODILATION Distributive shock (neurogenic, anaphylaxis, or septic shock) occurs when there is loss of vascular tone—venous, arterial, or both (sympathetic blockade, local substances affecting permeability, acidosis, drug effects, spinal cord transection)
INCREASED VASCULAR PERMEABILITY Sepsis may change the capillary permeability in the absence of any change in capillary hydrostatic pressure (endotoxins from sepsis, excess histamine release in anaphylaxis)
CARDIAC DYSFUNCTION Peripheral hypoperfusion may result from any condition that affects the heart's ability to pump blood efficiently (ischemia, acidosis, drugs, constrictive pericarditis, pancreatitis, sepsis)

Table 70-3 Signs of Decreased Perfusion

ORGAN SYSTEM	↓ PERFUSION	↓↓ PERFUSION	↓↓↓ PERFUSION
Central nervous system	—	Restless, apathetic, anxious	Agitated/confused, stuporous, coma
Respiration	—	↑ Ventilation	↑↑ Ventilation
Metabolism	—	Compensated metabolic acidemia	Uncompensated metabolic acidemia
Gut	—	↓ Motility	Ileus
Kidney	↓ Urine volume ↑ Urinary specific gravity	Oliguria (<0.5 mL/kg/hr)	Oliguria/anuria
Skin	Delayed capillary refill	Cool extremities	Mottled, cyanotic, cold extremities
Cardiovascular system	↑ Heart rate	↑↑ Heart rate ↓ Peripheral pulses	↑↑ Heart rate ↓ Blood pressure, central pulses only

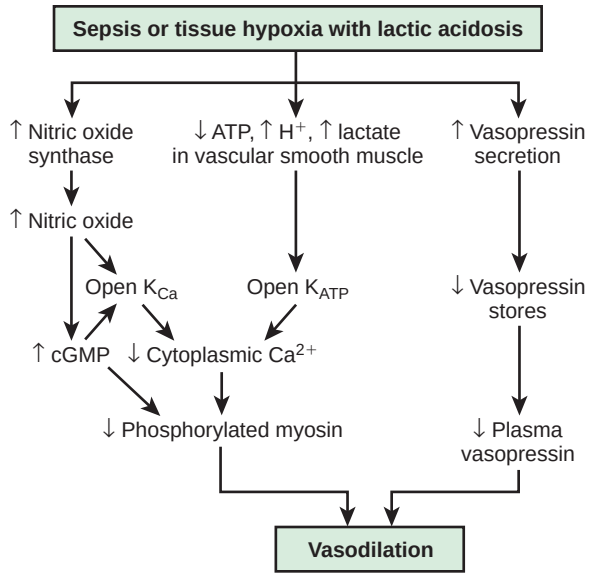

Figure 70-3 Mechanisms of vasodilatory shock. Septic shock and states of prolonged shock causing tissue hypoxia with lactic acidosis increase nitric oxide synthesis, activate the adenosine triphosphate (ATP)–sensitive and calcium-regulated potassium channels (K_{ATP} and K_{Ca}, respectively) in vascular smooth muscle, and lead to depletion of vasopressin. cGMP, cyclic guanosine monophosphate. *(From Landry DW, Oliver JA: The pathogenesis of vasodilatory shock,* N Engl J Med *345:588-595, 2001.)*

of mediators that may cause further injury. Biochemical responses include the production of arachidonic acid metabolites, release of myocardial depressant factors, release of endogenous opiates, activation of the complement system, as well as the production and release of many other mediators, which may be either proinflammatory or antiinflammatory. The balance between these mediator groups for an individual patient contributes to the progression of disease and affects the chance for survival.

CLINICAL MANIFESTATIONS

Table 70-1 shows a classification system for shock. Categorization is important, but there may be significant overlap among these groups, especially in septic shock. The clinical presentation of shock depends in part on the underlying etiology, but if unrecognized and untreated, all forms of shock follow a common and untoward progression of clinical signs and pathophysiologic changes that may ultimately lead to irreversible organ injury and death (see Fig. 70-2).

Shock may initially manifest as only tachycardia, with or without tachypnea. Progression leads to decreased urine output, poor peripheral perfusion, respiratory distress or failure, alteration of mental status, and low blood pressure (see Table 70-3). A significant misconception is that shock occurs only with low blood pressure; hypotension is often a late finding and is not a criterion for the diagnosis of shock because of a complex set of compensatory mechanisms attempting to preserve blood pressure. Hypotension reflects an advanced state of decompensated shock and is associated with increased morbidity and mortality.

Hypovolemic shock often manifests initially as orthostatic hypotension and is associated with dry mucous membranes, dry axillae, poor skin turgor, and decreased urine output. Depending on the degree of dehydration, the patient with hypovolemic shock may present with either normal or slightly cool distal extremities, and pulses may be normal, decreased, or absent depending on disease severity. The presenting signs of **cardiogenic shock** are tachypnea, cool extremities, delayed capillary filling time, poor peripheral and/or central pulses, declining mental status, and decreased urine output, caused by the combination of decreased cardiac output and compensatory peripheral

Table 70-5 Differential Diagnosis of Systemic Inflammatory Response Syndrome

INFECTION
Bacteremia or meningitis (*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis,* group A streptococcus, *Staphylococcus aureus*)
Viral illness (influenza, enteroviruses, hemorrhagic fever group, herpes simplex virus, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus)
Encephalitis (arboviruses, enteroviruses, herpes simplex virus)
Rickettsiae (Rocky Mountain spotted fever, *Ehrlichia,* Q fever)
Syphilis
Vaccine reaction (pertussis, influenza, measles)
Toxin-mediated reaction (toxic shock, staphylococcal scalded skin syndrome)
CARDIOPULMONARY
Pneumonia (bacteria, virus, mycobacteria, fungi, allergic reaction)
Pulmonary emboli
Heart failure
Arrhythmia
Pericarditis
Myocarditis
METABOLIC-ENDOCRINE
Adrenal insufficiency (adrenogenital syndrome, Addison disease, corticosteroid withdrawal)
Electrolyte disturbances (hyponatremia or hypernatremia; hypocalcemia or hypercalcemia)
Diabetes insipidus
Diabetes mellitus
Inborn errors of metabolism (organic acidosis, urea cycle, carnitine deficiency, mitochondrial disorders)
Hypoglycemia
Reye syndrome
GASTROINTESTINAL
Gastroenteritis with dehydration
Volvulus
Intussusception
Appendicitis
Peritonitis (spontaneous, associated with perforation or peritoneal dialysis)
Necrotizing enterocolitis
Hepatitis
Hemorrhage
Pancreatitis
HEMATOLOGIC
Anemia (sickle cell disease, blood loss, nutritional)
Methemoglobinemia
Splenic sequestration crisis
Leukemia or lymphoma
Hemophagocytic syndromes
NEUROLOGIC
Intoxication (drugs, carbon monoxide, intentional or accidental overdose)
Intracranial hemorrhage
Infant botulism
Trauma (child abuse, accidental)
Guillain-Barré syndrome
Myasthenia gravis
OTHER
Anaphylaxis (food, drug, insect sting)
Hemolytic-uremic syndrome
Kawasaki disease
Erythema multiforme
Hemorrhagic shock–encephalopathy syndrome
Poisoning
Toxic envenomation
Macrophage activation syndrome

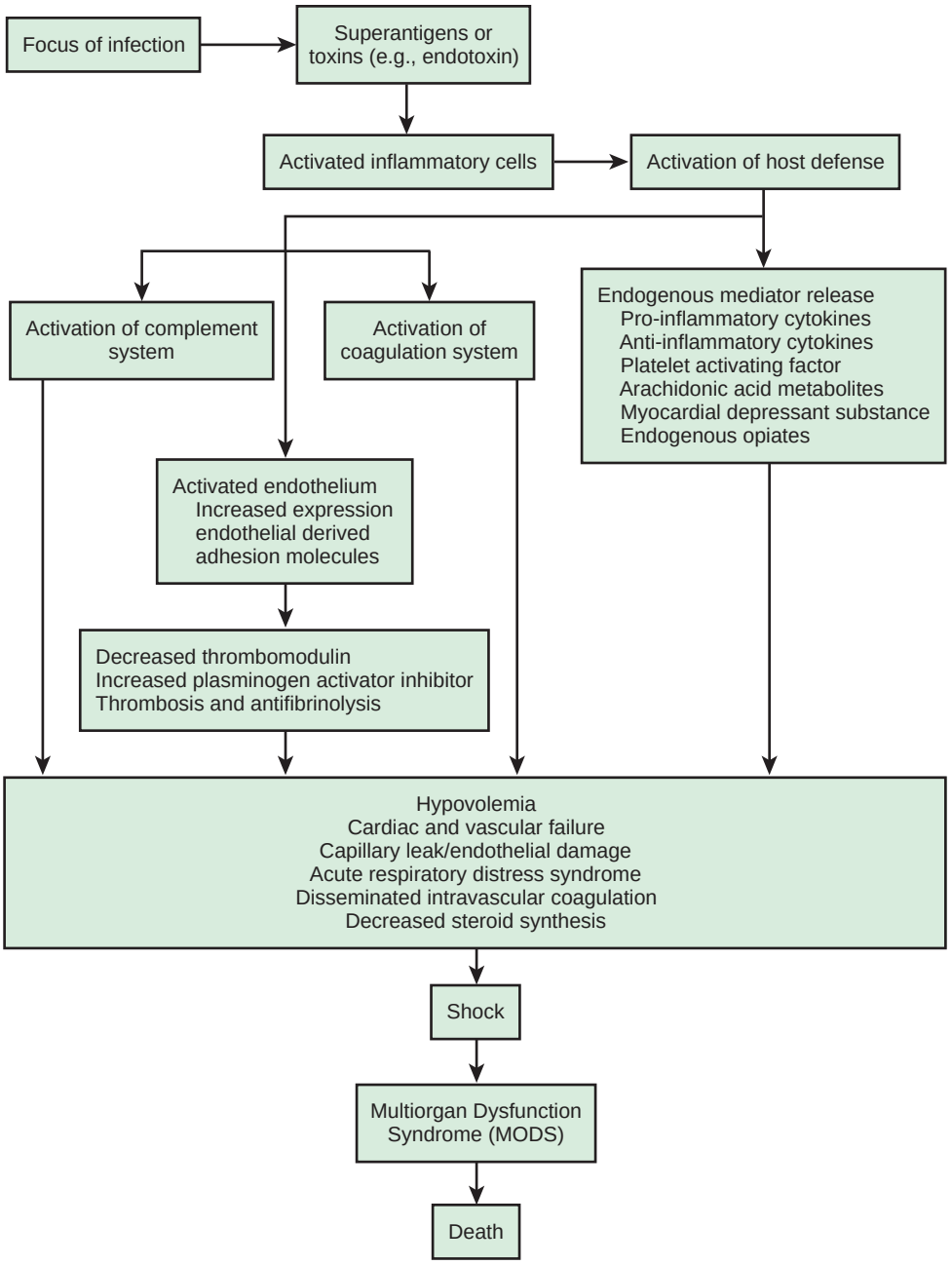

Figure 70-4 Hypothetical pathophysiology of the septic process.

vasoconstriction (see Chapter 442.1). **Obstructive shock** often also manifests as inadequate cardiac output because of a physical restriction of forward blood flow, and the acute presentation may quickly progress to cardiac arrest. **Distributive shock** manifests initially as peripheral vasodilation and increased but inadequate cardiac output.

Regardless of etiology, uncompensated shock, with hypotension, high SVR, decreased cardiac output, respiratory failure, obtundation, and oliguria, occurs late in the progression of disease. Table 70-6 lists the hemodynamic findings in various shock states. Additional clinical findings in shock include cutaneous lesions such as petechiae, diffuse erythema, ecchymoses, ecthyma gangrenosum, and peripheral gangrene. Jaundice can be present either as a sign of infection or as a result of **MODS**.

Sepsis is defined as **SIRS** resulting from a suspected or proven infectious etiology. The clinical spectrum of sepsis begins when a systemic (e.g., bacteremia, rickettsial disease, fungemia, viremia) or localized (e.g., meningitis, pneumonia, pyelonephritis) infection progresses from sepsis to **severe sepsis** (the presence of sepsis combined with organ dysfunction). Further deterioration leads to **septic shock** (severe sepsis plus the persistence of hypoperfusion or hypotension despite adequate fluid resuscitation or a requirement for vasoactive agents), **MODS**, and possibly death (Table 70-7). This is a complex spectrum of clinical problems that is a leading cause of mortality in children worldwide. This mortality can be mitigated and outcomes improved with early recognition and treatment.

Although **septic shock** is primarily distributive in nature, multiple other elements of pathophysiology are represented in this disease process. The initial signs and symptoms of sepsis include alterations in temperature regulation (hyperthermia or hypothermia), tachycardia, and tachypnea. In the early stages (hyperdynamic phase, low SVR, or "warm" shock), cardiac output increases in an attempt to maintain adequate oxygen delivery and meet the greater metabolic demands of the organs and tissues. As septic shock progresses, cardiac output falls in response to the effects of numerous inflammatory mediators, leading to a compensatory elevation in SVR and the development of "cold" shock.

Table 70-6 Hemodynamic Variables in Different Shock States

TYPE OF SHOCK	CARDIAC OUTPUT	SYSTEMIC VASCULAR RESISTANCE	MEAN ARTERIAL PRESSURE	CAPILLARY WEDGE PRESSURE	CENTRAL VENOUS PRESSURE
Hypovolemic	↓	↑	↔ or ↓	↓↓↓	↓↓↓
Cardiogenic*					
Systolic	↓↓	↑↑↑	↔ or ↓	↑↑	↑↑
Diastolic	↔	↑↑	↔	↑↑	↑
Obstructive	↓	↑	↔ or ↓	↑↑†	↑↑†
Distributive	↑↑	↓↓↓	↔ or ↓	↔ or ↓	↔ or ↓
Septic					
Early	↑↑↑	↓↓↓	↔ or ↓‡	↓	↓
Late	↓↓	↓↓	↓↓	↑	↑ or ↔

*Systolic or diastolic dysfunction.
†Wedge pressure, central venous pressure, and pulmonary artery diastolic pressures are equal.
‡Wide pulse pressure.

Table 70-7 International Consensus Definitions for Pediatric Sepsis

Infection	Suspected or proven infection or a clinical syndrome associated with high probability of infection
SIRS	Two of 4 criteria, 1 of which must be abnormal temperature or abnormal leukocyte count: 1. Core temperature >38.5°C (101.3°F) or <36°C (96.8°F) (rectal, bladder, oral, or central catheter) 2. Tachycardia: Mean heart rate >2 SD above normal for age in absence of external stimuli, chronic drugs or painful stimuli *or* Unexplained persistent elevation over 0.5-4 hr *or* In children <1 yr old, persistent bradycardia over 0.5 hr (mean heart rate <10th percentile for age in absence of vagal stimuli, β-blocker drugs, or congenital heart disease) 3. Respiratory rate >2 SD above normal for age or acute need for mechanical ventilation not related to neuromuscular disease or general anesthesia 4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy) or >10% immature neutrophils
Sepsis	SIRS plus a suspected or proven infection
Severe sepsis	Sepsis plus 1 of the following: 1. Cardiovascular organ dysfunction, defined as: • Despite >40 mL/kg of isotonic intravenous fluid in 1 hr: • Hypotension <5th percentile for age or systolic blood pressure <2 SD below normal for age *or* • Need for vasoactive drug to maintain blood pressure *or* • 2 of the following: • Unexplained metabolic acidosis: base deficit >5 mEq/L • Increased arterial lactate: >2 times upper limit of normal • Oliguria: urine output <0.5 mL/kg/hr • Prolonged capillary refill: >5 sec • Core to peripheral temperature gap >3°C (5.4°F) 2. ARDS as defined by the presence of a PaO_2/FIO_2 ratio ≤300 mm Hg, bilateral infiltrates on chest radiograph, and no evidence of left heart failure or Sepsis plus 2 or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic)
Septic shock	Sepsis plus cardiovascular organ dysfunction as defined above
MODS	Presence of altered organ function such that homeostasis cannot be maintained without medical intervention

FIO_2, fraction of inspired oxygen; PaO_2, partial pressure arterial oxygen.

DIAGNOSIS

Shock is a clinical diagnosis based on a thorough history and physical examination (see Tables 70-2 and 70-3). Of note, septic shock has a specific consensus conference definition (see Table 70-7). In cases of suspected septic shock, an infectious etiology should be sought through culture of clinically appropriate specimens and prompt initiation of empiric antimicrobial therapy based on patient age, underlying disease, and geographic location, recognizing that time is necessary for incubation of cultures, and results often are not positive. Additional evidence for identifying an infectious etiology as the cause of SIRS includes physical examination findings, imaging, presence of white blood cells in normally sterile body fluids, and suggestive rashes such as petechiae and purpura. Affected children should be admitted to an intensive care unit or other highly monitored environment, as indicated by clinical status and the resources of the medical facility. These patients necessitate continuous monitoring, with a combination of

noninvasive (pulse oximetry, capnography, near infra-red spectroscopy) and invasive (central venous pressure, arterial blood pressure) techniques as clinically indicated.

LABORATORY FINDINGS

Laboratory findings often include evidence of hematologic abnormalities and electrolyte disturbances. Hematologic abnormalities may include thrombocytopenia, prolonged prothrombin and partial thromboplastin times, reduced serum fibrinogen level, elevations of fibrin split products, and anemia. Elevated neutrophil counts and increased immature forms (i.e., bands, myelocytes, promyelocytes), vacuolation of neutrophils, toxic granulations, and Döhle bodies can be seen with infection. Neutropenia or leukopenia may be an ominous sign of overwhelming sepsis.

Glucose dysregulation, a common stress response, may manifest as hyperglycemia or hypoglycemia. Other electrolyte abnormalities are hypocalcemia, hypoalbuminemia, and metabolic acidosis. Renal and/or hepatic function may also be abnormal. Patients with ARDS or pneumonia have impairment of oxygenation (decreased partial pressure arterial oxygen [Pa_{O_2}]) as well as of ventilation (increased arterial partial pressure of carbon dioxide [Pa_{CO_2}]) in the later stages of lung injury (see Chapter 71).

The hallmark of uncompensated shock is an imbalance between oxygen delivery (D_{O_2}) and oxygen consumption (V_{O_2}). Oxygen delivery normally exceeds oxygen consumption threefold. The oxygen extraction ratio is approximately 25%, thus producing a normal **mixed venous oxygen saturation** (SV_{O_2}) of 75-80%. A falling SV_{O_2} value, as measured by cooximetry, reflects an increasing oxygen extraction ratio and documents a decrease in oxygen delivery relative to consumption. This increase in oxygen extraction by the end-organs is an attempt to maintain adequate oxygen delivery at the cellular level. This state is manifested clinically by increased lactic acid production (high anion gap, metabolic acidosis) caused by anaerobic metabolism and the compensatory increase in tissue oxygen extraction. The gold standard measurement of SV_{O_2} is from a pulmonary arterial catheter, but measurements from this location are often not clinically feasible. Sites such as the right ventricle, right atrium, superior vena cava (SV_{CO_2}), or inferior vena cava are often used as for surrogate measures of mixed venous blood to follow the adequacy of oxygen delivery and effectiveness of therapeutic interventions. *Elevated blood lactate levels reflect poor tissue oxygen delivery noted in all forms of shock.*

TREATMENT

Initial Management

Early recognition and prompt intervention are extremely important in the management of all forms of shock (Tables 70-8 to 70-12). **(The vital sign targets and dose recommendations in Tables 70-9 to 70-11 should be adjusted to pediatric-size patients).** Baseline mortality is much lower in pediatric shock than in adult shock, and further improvements in mortality are associated with early interventions (see Fig. 70-1). The initial assessment and treatment of the pediatric shock patient should include stabilization of airway, breathing, and circulation as established by the American Heart Association's pediatric advanced life support and neonatal advanced life support guidelines (see Chapter 67). Depending on the severity of shock, further airway intervention, including intubation and mechanical ventilation, may be necessary to lessen the work of breathing and decrease the body's overall metabolic demands.

Given the predominance of sepsis and hypovolemia as the most common causes of shock in the pediatric population, most therapeutic regimens are based on guidelines established in these settings. Immediately following establishment of intravenous (IV) or intraosseous

Table 70-8 Goal-Directed Therapy of Organ System Dysfunction in Shock

SYSTEM	DISORDERS	GOALS	THERAPIES
Respiratory	Acute respiratory distress syndrome Respiratory muscle fatigue Central apnea	Prevent/treat: hypoxia and respiratory acidosis Prevent barotrauma Decrease work of breathing	Oxygen Noninvasive ventilation Early endotracheal intubation and mechanical ventilation Positive end-expiratory pressure (PEEP) Permissive hypercapnia High-frequency ventilation Extracorporeal membrane oxygenation (ECMO)
Renal	Prerenal failure Renal failure	Prevent/treat: hypovolemia, hypervolemia, hyperkalemia, metabolic acidosis, hypernatremia/hyponatremia, and hypertension Monitor serum electrolytes	Judicious fluid resuscitation Establishment of normal urine output and blood pressure for age Furosemide (Lasix) Dialysis, ultrafiltration, hemofiltration
Hematologic	Coagulopathy (disseminated intravascular coagulation) Thrombosis	Prevent/treat: bleeding Prevent/treat: abnormal clotting	Vitamin K Fresh-frozen plasma Platelets Heparinization
Gastrointestinal	Stress ulcers Ileus Bacterial translocation	Prevent/treat: gastric bleeding Avoid aspiration, abdominal distention Avoid mucosal atrophy	Histamine H_2-receptor–blocking agents or proton pump inhibitors Nasogastric tube Early enteral feedings
Endocrine	Adrenal insufficiency, primary or secondary to chronic steroid therapy	Prevent/treat: adrenal crisis	Stress-dose steroids in patients previously given steroids Physiologic dose for presumed primary insufficiency in sepsis
Metabolic	Metabolic acidosis	Correct etiology Normalize pH	Treatment of hypovolemia (fluids), poor cardiac function (fluids, inotropic agents) Improvement of renal acid excretion Low-dose (0.5-2.0 mEq/kg) sodium bicarbonate if the patient is not showing response, pH <7.1, and ventilation (CO_2 elimination) is adequate

Table 70-9 Recommendations: Initial Resuscitation and Infection Issues—Adults

INITIAL RESUSCITATION
1. Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). Goals during the 1st 6 hr of resuscitation:
   (a) Central venous pressure 8-12 mm Hg
   (b) Mean arterial pressure (MAP) ≥65 mm Hg
   (c) Urine output ≥0.5 mL kg^{-1} hr
   (d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively
2. In patients with elevated lactate levels, targeting resuscitation to normalize lactate as rapidly as possible.

SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT
1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy.
2. Hospital-based performance improvement efforts in severe sepsis.

DIAGNOSIS
1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (>45 min) in the start of antimicrobial(s). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hr) inserted.
2. Use of the 1,3 β-D-glucan assay, mannan and antimannan antibody assays, if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection.

ANTIMICROBIAL THERAPY
1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock and severe sepsis without septic shock as the goal of therapy.
2a. Initial empiric antiinfective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis.
2b. Antimicrobial regimen should be reassessed daily for potential deescalation.
3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection.
4a. Combination empirical therapy for neutropenic patients with severe sepsis and for patients with difficult to treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp.
   For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum β-lactam and either an aminoglycoside or a fluoroquinolone is for *Pseudomonas aeruginosa* bacteremia. A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections.
4b. Empiric combination therapy should not be administered for more than 3-5 days. Deescalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.
5. Duration of therapy typically 7-10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*; some fungal and viral infections or immunologic deficiencies, including neutropenia.
6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin.
7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause.

SOURCE CONTROL
1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the 1st 12 hr after the diagnosis is made, if feasible.
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred.
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established.

INFECTION PREVENTION
1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; this infection control measure can then be instituted in healthcare settings and regions where this methodology is found to be effective.
1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Table 5, p. 589.*

access, aggressive, early goal-directed therapy should be initiated unless there are significant concerns for cardiogenic shock as an underlying pathophysiology. Rapid IV administration of 20 mL/kg isotonic fluid should be initiated in an attempt to reverse the shock state. This bolus should be repeated quickly up to 60-80 mL/kg; it is not unusual for severely affected patients to require this volume within the 1st hr of treatment.

Rapid fluid resuscitation totaling 60-80 mL/kg or more is associated with improved survival without an increased incidence of pulmonary edema. Fluid resuscitation in increments of 20 mL/kg should be titrated to normalize heart rate (according to age-based heart rates), urine output (to 1 mL/kg/hr), capillary refill time (to <2 sec), and mental status. Fluid resuscitation may sometimes require as much as 200 mL/kg or greater. It must be stressed that hypotension is often a late and ominous finding, and normalization of blood pressure alone is not a reliable endpoint for assessing the effectiveness of resuscitation. Although the type of fluid (crystalloid vs. colloid) is an area of ongoing debate, fluid resuscitation (usually crystalloid) in the 1st hr is unquestionably essential to survival in septic shock, regardless of the fluid type administered.

In one study conducted in Kenya and Tanzania, routine bolus fluid resuscitation of severely ill, febrile children with poor perfusion was unexpectedly associated with a higher mortality than children receiving nonbolus intravenous infusions. The children in this study had a

Table 70-10 Surviving Sepsis Campaign Care Bundles

To be completed within 3 hr:
1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

To completed within 6 hr:
5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg
6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   Measure central venous pressure (CVP)*
   Measure central venous oxygen saturation ($ScvO_2$)*
7. Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ of ≥70%, and normalization of lactate.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Fig. 1, p. 591.*

high incidence of malaria, severe anemia, hypoxia, and coma; most were thought to have bacterial infections. There were no children with dengue shock syndrome or hypovolemia secondary to gastroenteritis. The World Health Organization's definition of shock that requires fluid boluses (cold hands, capillary refill >3 sec, fast and weak pulses) was not present in all patients; only 6% had hypotension. This study raises issues about bolus fluid resuscitation in resource poor areas, particularly in children with a high prevalence of malaria and anemia.

If shock remains refractory following 60-80 mL/kg of volume resuscitation, vasopressor therapy (norepinephrine, or epinephrine) should be instituted while additional fluids are administered. Current guidelines recommend administration of these vasoactive agents via peripheral intravenous lines, with very close monitoring of the peripheral intravenous sites while central venous access is being obtained based on data demonstrating that delay in the initiation of inotropes in shock is associated with increased mortality

Additional Early Considerations

In **septic shock** specifically, early administration of broad-spectrum antimicrobial agents is associated with a reduction in mortality. The choice of antimicrobial agents depends on the predisposing risk factors and the clinical situation. Bacterial resistance patterns in the community and/or hospital should be considered in the selection of optimal antimicrobial therapy. Neonates should be treated with ampicillin

Table 70-11 Recommendations: Hemodynamic Support and Adjunctive Therapy—Adults

FLUID THERAPY OF SEVERE SEPSIS
1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock.
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock.
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids.
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients.
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables.

VASOPRESSORS
1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg.
2. Norepinephrine as the first choice vasopressor.
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure.
4. Vasopressin 0.03 units/min can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage.
5. Low-dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/min should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) NE is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low, or (c) as salvage therapy when combined inotrope/vasopressor drugs and low-dose vasopressin have failed to achieve MAP target.
8. Low-dose dopamine should not be used for renal protection.
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available.

INOTROPIC THERAPY
1. A trial of dobutamine infusion up to 20 μg/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.
2. Not using a strategy to increase cardiac index to predetermined supranormal levels.

CORTICOSTEROIDS
1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day.
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone.
3. In treated patients, hydrocortisone tapered when vasopressors are no longer required.
4. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock.
5. When hydrocortisone is given, use continuous flow.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Table 6, p. 596.*

Table 70-12 Recommendations: Special Considerations in Pediatrics

INITIAL RESUSCITATION 1. For respiratory distress and hypoxemia start with face mask oxygen or if needed and available, high flow nasal cannula oxygen or nasopharyngeal CPAP (NP CPAP). For improved circulation, peripheral intravenous access or intraosseous access can be used for fluid resuscitation and inotrope infusion when a central line is not available. If mechanical ventilation is required then cardiovascular instability during intubation is less likely after appropriate cardiovascular resuscitation. 2. Initial therapeutic end points of resuscitation of septic shock: capillary refill of ≤2 sec, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL kg^{-1} hr^{-1}, and normal mental status. $ScvO_2$ saturation ≥70% and cardiac index between 3.3 and 6.0 L/min/m^2 should be targeted thereafter. 3. Follow American College of Critical Care Medicine-Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock. 4. Evaluate for and reverse pneumothorax, pericardial tamponade, or endocrine emergencies in patients with refractory shock.
ANTIBIOTICS AND SOURCE CONTROL 1. Empiric antibiotics should be administered within 1 hr of the identification of severe sepsis. Blood cultures should be obtained before administering antibiotics when possible but this should not delay administration of antibiotics. The empiric drug choice should be changed as epidemic and endemic ecologies dictate (e.g., H1N1, methicillin-resistant *Staphylococcus aureus* [MRSA], chloroquine-resistant malaria, penicillin-resistant pneumococci, recent ICU stay, neutropenia). 2. Clindamycin and antitoxin therapies for toxic shock syndromes with refractory hypotension. 3. Early and aggressive source control. 4. *Clostridium difficile* colitis should be treated with enteral antibiotics if tolerated. Oral vancomycin is preferred for severe disease.
FLUID RESUSCITATION 1. In the industrialized world with access to inotropes and mechanical ventilation, initial resuscitation of hypovolemic shock begins with infusion of isotonic crystalloids or albumin with boluses of up to 20 mL/kg crystalloids (or albumin equivalent) over 5-10 minutes, titrated to reversing hypotension, increasing urine output, and attaining normal capillary refill, peripheral pulses, and level of consciousness without inducing hepatomegaly or rales. If hepatomegaly or rales exist then inotropic support should be implemented, not fluid resuscitation. In nonhypotensive children with severe hemolytic anemia (severe malaria or sickle cell crises), blood transfusion is considered superior to crystalloid or albumin bolus.
INOTROPES/VASOPRESSORS/VASODILATORS 1. Begin peripheral inotropic support until central venous access can be attained in children who are not responsive to fluid resuscitation. 2. Patients with low cardiac output and elevated systemic vascular resistance states with normal blood pressure should be given vasodilator therapies in addition to inotropes.
EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) 1. Consider ECMO for refractory pediatric septic shock and respiratory failure.
CORTICOSTEROIDS 1. Timely hydrocortisone therapy in children with fluid refractory, catecholamine resistant shock and suspected or proven absolute (classic) adrenal insufficiency.
PROTEIN C AND ACTIVATED PROTEIN CONCENTRATE No recommendation as no longer available.
BLOOD PRODUCTS AND PLASMA THERAPIES 1. Similar hemoglobin targets in children as in adults. During resuscitation of low superior vena cava oxygen saturation shock (<70 %), hemoglobin levels of 10 g/dL are targeted. After stabilization and recovery from shock and hypoxemia, a lower target (>7.0 g/dL) can be considered reasonable. 2. Similar platelet transfusion targets in children as in adults. 3. Use plasma therapies in children to correct sepsis-induced thrombotic purpura disorders, including progressive disseminated intravascular coagulation, secondary thrombotic microangiopathy, and thrombotic thrombocytopenic purpura.
MECHANICAL VENTILATION 1. Lung-protective strategies during mechanical ventilation.
SEDATION/ANALGESIA/DRUG TOXICITIES 1. We recommend use of sedation with a sedation goal in critically ill mechanically ventilated patients with sepsis. 2. Monitor drug toxicity labs because drug metabolism is reduced during severe sepsis, putting children at greater risk of adverse drug-related events.
GLYCEMIC CONTROL 1. Control hyperglycemia using a similar target as in adults (≤180 mg/dL). Glucose infusion should accompany insulin therapy in newborns and children because some hyperglycemic children make no insulin whereas others are insulin resistant.
DIURETICS AND RENAL REPLACEMENT THERAPY 1. Use diuretics to reverse fluid overload when shock has resolved, and if unsuccessful then continuous venovenous hemofiltration (CVVH) or intermittent dialysis to prevent >10% total body weight fluid overload.
DEEP VEIN THROMBOSIS (DVT) PROPHYLAXIS No recommendation on the use of DVT prophylaxis in prepubertal children with severe sepsis.
STRESS ULCER (SU) PROPHYLAXIS No recommendation on the use of SU prophylaxis in prepubertal children with severe sepsis
NUTRITION 1. Enteral nutrition given to children who can be fed enterally, and parenteral feeding in those who cannot (grade 2C).

CPAP, continuous positive airway pressure.

Adapted from Dellinger PR, Levy MM, Rhodes A, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med *41(2):580-637, 2013, Table 9, p. 614.*

plus cefotaxime and/or gentamicin. Acyclovir should be added if herpes simplex virus is suspected clinically. In infants and children, community-acquired infections with *Neisseria meningitidis* can initially be treated empirically with a 3rd-generation cephalosporin (ceftriaxone or cefotaxime). *Haemophilus influenzae* infections can be treated empirically with a 3rd-generation cephalosporin (ceftriaxone or cefotaxime). The prevalence of resistant *Streptococcus pneumoniae* requires the addition of vancomycin. Suspicion of community- or hospital-acquired, methicillin-resistant *Staphylococcus aureus* infection warrants coverage with vancomycin, depending on local resistance patterns. If an intraabdominal process is suspected, anaerobic coverage should be included with an agent such as metronidazole, clindamycin, or piperacillin-tazobactam.

Nosocomial sepsis should generally be treated with at least a 3rd- or 4th-generation cephalosporin or a penicillin with an extended Gram-negative spectrum (e.g., piperacillin-tazobactam). An aminoglycoside should be added as the clinical situation warrants. Vancomycin should be added to the regimen if the patient has an indwelling medical device (see Chapter 179), Gram-positive cocci are isolated from the blood, methicillin-resistant *S. aureus* infection is suspected, or as empiric coverage for *S. pneumoniae* in a patient with meningitis. Empirical coverage for fungal infections should be considered for selected immunocompromised patients (see Chapter 178). It should be noted that these are broad, generalized recommendations that must be tailored to the individual clinical scenario and to the local resistance patterns of the community and/or hospital.

Distributive shock that is not secondary to sepsis is caused by a primary abnormality in vascular tone. Cardiac output in affected patients is usually maintained and may initially be supranormal. These patients may benefit temporarily from volume resuscitation, but the early initiation of a vasoconstrictive agent to increase SVR is an important element of clinical care. Patients with spinal cord injury and spinal shock may benefit from either phenylephrine or vasopressin to increase SVR, and epinephrine is the treatment of choice for patients with anaphylaxis (Table 70-13). Epinephrine has peripheral α-adrenergic as well as inotropic effects that may improve the myocardial depression seen with anaphylaxis and its associated inflammatory response (see Chapter 149).

Patients with **cardiogenic shock** have poor cardiac output secondary to systolic and/or diastolic myocardial depression, often with a compensatory elevation in SVR. These patients may show poor response to fluid resuscitation and may decompensate quickly when fluids are administered. Smaller boluses of fluid (5-10 mL/kg) should be given in cardiogenic shock to replace deficits and maintain preload. In any patient with shock whose clinical status deteriorates with fluid resuscitation, a cardiogenic etiology should be considered, and further administration of intravenous fluids should be provided judiciously. Early initiation of myocardial support with epinephrine or dopamine to improve cardiac output is important in this context and early consideration should be given to administration of inodilator, such as milrinone.

Despite adequate cardiac output with the support of inotropic agents, a high SVR with poor peripheral perfusion and acidosis may persist in cardiogenic shock. Therefore, if not already started, milrinone therapy may improve systolic function and decrease SVR without causing a significant increase in heart rate. Furthermore, this agent has the added benefit of enhancing diastolic relaxation. Dobutamine or other vasodilating agents, such as nitroprusside, may also be considered in this setting (Table 70-14). Titration of these agents should target clinical end points, including increased urine output, improved peripheral perfusion, resolution of acidosis, and normalization of mental status. Even though they may be beneficial in other forms of shock, agents that improve blood pressure by increasing SVR, such as norepinephrine and vasopressin, should generally be avoided in patients with cardiogenic shock. These agents may cause further decompensation and potentially precipitate cardiac arrest as a result of the increased afterload and additional work imposed on the myocardium. The combination of inotropic and vasoactive agents must be tailored to the pathophysiology of the individual patient with close and frequent reassessment of the patient's cardiovascular status.

For patients with **obstructive shock**, fluid resuscitation may be briefly temporizing in maintaining cardiac output, but the primary insult must be immediately addressed. Examples of lifesaving therapeutic interventions for such patients are pericardiocentesis for pericardial effusion, pleurocentesis or chest tube placement for pneumothorax, thrombectomy/thrombolysis for pulmonary embolism, and the initiation of a prostaglandin infusion for ductus-dependent cardiac lesions. There is often a "last-drop" phenomenon associated with some obstructive lesions, in that small additional amounts of intravascular volume depletion may lead to a rapid deterioration, including cardiac arrest, if the obstructive lesion is not corrected.

Regardless of the etiology of shock, metabolic status should be meticulously maintained (see Table 70-8). Electrolyte levels should be monitored closely and corrected as needed. Hypoglycemia is common and should be promptly treated. Neonates and infants in particular may have profound glucose dysregulation in association with shock. Glucose levels should be checked routinely and treated appropriately, especially early in the course of illness. Hypocalcemia, which may contribute to myocardial dysfunction, should be treated with a goal of normalizing the ionized calcium concentration. There is no evidence that supranormal calcium levels benefit the myocardium, and hypercalcemia may actually be associated with increased myocardial toxicity.

Adrenal function is another important consideration in shock, and hydrocortisone replacement may be beneficial. Up to 50% of critically ill patients may have absolute or relative adrenal insufficiency. Patients at risk for adrenal insufficiency include those with congenial adrenal hypoplasia, abnormalities of the hypothalamic-pituitary axis, and

Table 70-13 Cardiovascular Drug Treatment of Shock

DRUG	EFFECT(S)	DOSING RANGE	COMMENT(S)
Dopamine	↑ Cardiac contractility Significant peripheral vasoconstriction at >10 μg/kg/min	3-20 μg/kg/min	↑ Risk of arrhythmias at high doses
Epinephrine	↑ Heart rate and ↑ cardiac contractility Potent vasoconstrictor	0.05-3.0 μg/kg/min	May ↓ renal perfusion at high doses ↑ Myocardial O_2 consumption Risk of arrhythmia at high doses
Dobutamine	↑ Cardiac contractility Peripheral vasodilator	1-10 μg/kg/min	—
Norepinephrine	Potent vasoconstriction No significant effect on cardiac contractility	0.05-1.5 μg/kg/min	↑ Blood pressure secondary to ↑ systemic vascular resistance ↑ Left ventricular afterload
Phenylephrine	Potent vasoconstriction	0.5-2.0 μg/kg/min	Can cause sudden hypertension ↑ O_2 consumption

Table 70-14	Vasodilators/Afterload Reducers		
DRUG	**EFFECT(S)**	**DOSING RANGE**	**COMMENT(S)**
Nitroprusside	Vasodilator (mainly arterial)	0.5-4.0 μg/kg/min	Rapid effect Risk of cyanide toxicity with prolonged use (>96 hr)
Nitroglycerin	Vasodilator (mainly venous)	1-20 μg/kg/min	Rapid effect Risk of increased intracranial pressure
Prostaglandin E_1	Vasodilator Maintains an open ductus arteriosus in the newborn with ductal-dependent congenital heart disease	0.01-0.2 μg/kg/min	Can lead to hypotension Risk of apnea
Milrinone	Increased cardiac contractility Improves cardiac diastolic function Peripheral vasodilation	Load 50 μg/kg over 15 min 0.5-1.0 μg/kg/min	Phosphodiesterase inhibitor—slows cyclic adenosine monophosphate breakdown

recent therapy with corticosteroids (including patients with asthma, rheumatic diseases, malignancies, and inflammatory bowel disease). These patients are at high risk for adrenal dysfunction and should receive stress doses of hydrocortisone. Steroids may also be considered in patients with shock that is unresponsive to fluid resuscitation and catecholamines. While there may be a subset of pediatric septic shock patients that benefit from treatment with hydrocortisone, currently available pediatric data do not demonstrate an overall survival benefit in patients with shock treated with hydrocortisone. Determination of baseline cortisol levels prior to steroid administration may be beneficial in guiding therapy, although this idea remains controversial.

Considerations for Continued Therapy

After the 1st hr of therapy and attempts at early reversal of shock, focus on goal-directed endpoints should continue in an intensive care setting (see Fig. 70-1 and Table 70-8). Clinical endpoints serve as global markers for organ perfusion and oxygenation. Laboratory parameters such as SVo_2 (or $ScvO_2$), serum lactate concentration, cardiac index, and hemoglobin serve as adjunctive measures of tissue oxygen delivery. Hemoglobin should be maintained at 10 g/dL, SVo_2 (or $ScvO_2$) >70%, and cardiac index at 3.3-6.0 L/min/m^2 to optimize oxygen delivery in the acute phase of shock. It is important to note that cardiac index is rarely monitored in the clinical setting owing to the limited use of pulmonary artery catheters and the lack of accurate noninvasive cardiac output monitors for infants and children. Blood lactate levels and calculation of base deficit from arterial blood gas values are very useful markers for the adequacy of oxygen delivery. These traditional markers are all indicators of global oxygen utilization and delivery, and there is increasing interest in measures of local tissue oxygenation including near infra-red spectroscopy of the cerebrum, flank, or abdomen.

Respiratory support should be used as clinically appropriate. When shock leads to ARDS requiring mechanical ventilation, lung-protective strategies to keep plateau pressure below 30 cm H_2O and maintain tidal volume at 6 mL/kg have been shown to improve mortality in adult patients (see Chapter 71). These data are extrapolated to pediatric patients because of the lack of definitive pediatric studies in this area. Additionally, after the initial shock state has been reversed, data demonstrate that judicious fluid administration, renal replacement therapy, and fluid removal may also be useful in children with anuria or oliguria and fluid overload (see Chapter 535). Other interventions include correction of coagulopathy with fresh frozen plasma or cryoprecipitate and platelet transfusions as necessary, especially in the presence of active bleeding.

If shock remains refractory despite maximal therapeutic interventions, mechanical support with **extracorporeal membrane oxygenation** or a **ventricular assist device** may be indicated. Extracorporeal membrane oxygenation may be lifesaving in cases of refractory shock regardless of underlying etiology. Similarly, a ventricular assist device may be indicated for refractory cardiogenic shock in the setting of cardiomyopathy or recent cardiac surgery. Systemic anticoagulation, which is required while patients are receiving mechanical support, may be difficult, given the significant coagulopathy often encountered in refractory shock, especially when the underlying etiology is sepsis. Mechanical support in refractory shock poses substantial risks but can improve survival in specific populations of patients.

PROGNOSIS

In septic shock, mortality rates are as low as 3% in previously healthy children and 6-9% in children with chronic illness (compared with 25-30% in adults). With early recognition and therapy, the mortality rate for pediatric shock continues to improve, but shock and MODS remain one of the leading causes of death in infants and children. The risk of death involves a complex interaction of factors, including the underlying etiology, presence of chronic illness, host immune response, and timing of recognition and therapy.

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Chapter 71

Respiratory Distress and Failure

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The term **respiratory distress** is often used to indicate signs and symptoms of abnormal respiratory pattern. A child with nasal flaring, tachypnea, chest wall retractions, stridor, grunting, dyspnea, and wheezing is often judged as having respiratory distress. The magnitude of these findings is used to judge the clinical severity of respiratory distress. Although nasal flaring is a nonspecific sign, the other signs are useful in localizing the site of pathology (see Chapters 373 and 374). Respiratory failure is defined as inability of the lungs to provide sufficient oxygen (hypoxic respiratory failure) or remove carbon dioxide (ventilatory failure) to meet metabolic demands. Whereas respiratory

Table 71-1 Typical Localizing Signs for Pulmonary Pathology

SITE OF PATHOLOGY	RESPIRATORY RATE	RETRACTIONS	AUDIBLE SOUNDS
Extrathoracic airway	↑	↑↑↑↑	Stridor
Intrathoracic extrapulmonary	↑	↑↑	Wheezing
Intrathoracic intrapulmonary	↑↑	↑↑	Wheezing
Alveolar interstitial	↑↑↑	↑↑↑	Grunting

distress is a clinical impression, the diagnosis of **respiratory failure** indicates inadequacy of oxygenation or ventilation, or both. Respiratory distress can occur in patients without respiratory disease, and respiratory failure can occur in patients without respiratory distress.

RESPIRATORY DISTRESS

A careful physical examination must be performed when managing a child in respiratory distress. Nasal flaring is an extremely important sign of distress, especially in infants. It is indicative of discomfort, pain, fatigue, or breathing difficulty. The state of responsiveness is another crucial sign. Lethargy, disinterest in surroundings, and poor cry are suggestive of exhaustion, hypercarbia, and impending respiratory failure. Abnormalities of the rate and depth of respirations can occur with both pulmonary and nonpulmonary causes of respiratory distress. In diseases of decreased lung compliance, such as pneumonia and pulmonary edema, respirations are characteristically rapid and shallow (decreased tidal volume). In obstructive airway diseases, such as asthma and laryngotracheitis, respirations are deep (increased tidal volume) but less rapid. Rapid and deep respirations without other respiratory signs should alert the physician to the possibility of nonrespiratory causes of respiratory distress, such as response to metabolic acidosis (diabetic ketoacidosis, renal tubular acidosis) or stimulation of the respiratory center (encephalitis, ingestion of central nervous system [CNS] stimulants). Chest wall, suprasternal, and subcostal retractions are manifestations of increased inspiratory effort, weak chest wall, or both. Inspiratory stridor indicates airway obstruction above the thoracic inlet, whereas expiratory wheezing results from airway obstruction below the thoracic inlet. Grunting is most commonly heard in diseases with decreased functional residual capacity (e.g., pneumonia, pulmonary edema) and peripheral airway obstruction (e.g., bronchiolitis).

Respiratory Disease Manifesting as Respiratory Distress

Clinical examination is important in localizing the site of pathology (see Chapter 373). Extrathoracic airway obstruction occurs anywhere above the thoracic inlet. Inspiratory stridor, suprasternal, chest wall, and subcostal retractions, and prolongation of inspiration are hallmarks of extrathoracic airway obstruction. By comparison, features of intrathoracic airway obstruction are prolongation of expiration and expiratory wheezing. Typical manifestations of alveolar interstitial pathology are rapid, shallow respirations, chest wall retractions, and grunting. The site of pathology can be localized and the differential diagnosis established on the basis of the clinical signs and symptoms (Tables 71-1 and 71-2).

Respiratory Distress without Respiratory Disease

Although respiratory distress most commonly results from diseases of lungs, airways, and chest wall, pathology in other organ systems can manifest as "respiratory distress" and lead to misdiagnosis and inappropriate management (Table 71-3). Respiratory distress resulting from heart failure or diabetic ketoacidosis may be misdiagnosed as asthma and improperly treated with albuterol, resulting in worsened hemodynamic state or ketoacidosis. Careful history and physical examination provide essential clues in avoiding misdiagnosis.

Table 71-2 Examples of Anatomic Sites of Lesions Causing Respiratory Failure

LUNG	RESPIRATORY PUMP
CENTRAL AIRWAY OBSTRUCTION Choanal atresia Tonsilloadenoidal hypertrophy Retropharyngeal/peritonsillar abscess Laryngomalacia Epiglottitis Vocal cord paralysis Laryngotracheitis Subglottic stenosis Vascular ring/pulmonary sling Mediastinal mass Foreign-body aspiration Obstructive sleep apnea	THORACIC CAGE Kyphoscoliosis Diaphragmatic hernia Flail chest Eventration of diaphragm Asphyxiating thoracic dystrophy Prune-belly syndrome Dermatomyositis Abdominal distention
PERIPHERAL AIRWAY OBSTRUCTION Asthma Bronchiolitis Foreign-body aspiration Aspiration pneumonia Cystic fibrosis α_1-Antitrypsin deficiency	BRAINSTEM Arnold-Chiari malformation Central hypoventilation syndrome CNS depressants Trauma Increased intracranial pressure CNS infections
ALVEOLAR-INTERSTITIAL DISEASE Lobar pneumonia Acute respiratory distress syndrome/hyaline membrane disease Interstitial pneumonia Hydrocarbon pneumonia Pulmonary hemorrhage/hemosiderosis	SPINAL CORD Trauma Transverse myelitis Spinal muscular atrophy Poliomyelitis Tumor/abscess
	NEUROMUSCULAR Phrenic nerve injury Birth trauma Infant botulism Guillain-Barré syndrome Muscular dystrophy Myasthenia gravis Organophosphate poisoning

Cardiovascular Disease Manifesting as Respiratory Distress

A child with cardiovascular pathology may present with respiratory distress caused by 2 mechanisms: (1) decreased lung compliance and (2) cardiogenic shock (Table 71-4). Diseases that result in an increased pulmonary arterial blood flow (e.g., left-to-right shunts) or increased pulmonary venous pressure (e.g., left ventricular dysfunction from hypertension or myocarditis, obstructed total anomalous pulmonary

Table 71-3 Nonpulmonary Causes of Respiratory Distress

	EXAMPLE(S)	MECHANISM(S)
Cardiovascular	Left-to-right shunt Congestive heart failure Cardiogenic shock	↑ Pulmonary blood/water content Metabolic acidosis Baroreceptor stimulation
Central nervous system	Increased intracranial pressure Encephalitis Neurogenic pulmonary edema Toxic encephalopathy	Stimulation of brainstem respiratory centers
Metabolic	Diabetic ketoacidosis Organic acidemia Hyperammonemia	Stimulation of central and peripheral chemoreceptors
Renal	Renal tubular acidosis Hypertension	Stimulation of central and peripheral chemoreceptors Left ventricular dysfunction → increased pulmonary blood/water content
Sepsis	Toxic shock syndrome Meningococcemia	Cytokine stimulation of respiratory centers Baroreceptor stimulation from shock Metabolic acidosis

Table 71-4 Cardiovascular Pathology Manifesting as Respiratory Distress

I. DECREASED LUNG COMPLIANCE
- A. Left-to-Right Shunts
  1. Ventricular septal defect, atrial septal defect, patent ductus arteriosus, atrioventricular canal, truncus arteriosus
  2. Cerebral or hepatic arteriovenous fistula
- B. Ventricular Failure
  1. Left-heart obstructive lesions
     - a) aortic stenosis
     - b) coarctation of the aorta
     - c) mitral stenosis
     - d) interrupted aortic arch
     - e) hypoplastic left heart syndrome
  2. Myocardial infarction
     - a) anomalous left coronary artery arising from the pulmonary artery
  3. Hypertension
     - a) acute glomerulonephritis
  4. Inflammatory/Infectious
     - a) myocarditis
     - b) pericardial effusion
  5. Idiopathic
     - a) dilated cardiomyopathy
     - b) hypertrophic obstructive cardiomyopathy
- C. Pulmonary Venous Obstruction
  1. Total anomalous pulmonary venous return with obstruction
  2. Cor triatriatum

II. SHOCK RESULTING IN METABOLIC ACIDOSIS
- A. Left-Heart Obstructive Lesions
- B. Acute Ventricular Failure
  1. Myocarditis, myocardial infarction

venous return) cause an increase in pulmonary capillary pressure and transudation of fluid into the pulmonary interstitium and alveoli. The increased pulmonary blood and water content leads to decreased lung compliance and results in rapid shallow respirations.

It is important to recognize that interstitial lung edema can not only manifest as alveolar fluid, but as small airway obstruction as well. Wheezing as a sign of congestive cardiac disease is common in infants and young children and should be recognized. Patients with cardiac lesions that result in a low cardiac output state, such as obstructive lesions of left side of the heart and acquired or congenital cardiomyopathy, often present in a state of shock with decreased tissue perfusion and metabolic acidosis. Such children demonstrate respiratory distress because of stimulation of chemoreceptors by metabolic acidosis and stimulation of baroreceptors by decreased blood pressure. The likelihood of a particular cardiovascular illness manifesting as respiratory distress depends on age at presentation (Table 71-5).

Neurologic Disease Manifesting as Respiratory Distress

CNS dysfunction can lead to alterations in respiratory patterns. Increased intracranial pressure (ICP) may manifest as respiratory distress. Early rise in ICP results in stimulation of respiratory centers, leading to increases in the rate (tachypnea) and depth (hyperpnea) of respiration. The resultant decrease in Pa_{CO_2} and elevation of cerebrospinal fluid pH lead to cerebral vasoconstriction and amelioration of intracranial hypertension. Cerebral hemispheric and midbrain lesions often result in hyperpnea as well as tachypnea. In such situations, blood gas measurements typically show respiratory alkalosis without hypoxemia. Pathology affecting the pons and medulla manifests as irregular breathing patterns such as apneustic breathing (prolonged inspiration with brief expiratory periods), Cheyne-Stokes breathing (alternate periods of rapid and slow breathing), and irregular, ineffective breathing or apnea. Level of consciousness is most often impaired when abnormal breathing pattern from a brainstem disorder is present. Along with respiratory changes, other manifestations of CNS dysfunction and increased ICP may be present, such as focal neurologic signs, pupillary changes, hypertension, and bradycardia (see Chapter 63). Occasionally, severe CNS dysfunction can result in **neurogenic pulmonary edema** and respiratory distress, which may be a result of excessive sympathetic discharge resulting in increased pulmonary venous hydrostatic pressure as well as increased pulmonary capillary

Table 71-5 Typical Chronology of Heart Disease Presentation in Children

AGE	MECHANISM	DISEASE
Newborn (1-10 days)	↑ Arteriovenous pressure difference Ductal closure Independent pulmonary and systemic blood flow Pulmonary venous obstruction	Arteriovenous fistula (brain, liver) Single ventricle lesions or severe ventricular outflow obstruction Transposition of the great arteries Total anomalous pulmonary venous return (TAPVR)
Young Infant (1-6 mo)	↓ Pulmonary vascular resistance ↓ Pulmonary artery pressure	Left-to-right shunt Anomalous left coronary artery to the pulmonary artery
Any Age	Rate disturbance Infection Abnormal cardiac myocytes Excess afterload	Tachy- or bradyarrhythmias Myocarditis, pericarditis Cardiomyopathy hypertension

permeability. **Central neurogenic hyperventilation** is characteristically observed in CNS involvement by illnesses such as urea cycle defects and encephalitis. **Bradycardia and apnea** may be caused by CNS-depressant medications, poisoning, prolonged hypoxia, trauma, or infection (see Table 71-2).

Toxic-Metabolic States Manifesting as Respiratory Distress

Direct stimulation of respiratory centers resulting in respiratory alkalosis is encountered in certain intoxications, such as those involving salicylates and theophylline. Similarly, intoxication with general CNS stimulants, such as cocaine and amphetamines may manifest as increased respirations. Presence of endogenous and exogenous toxins, such as organic acidemias, ingestion of methanol and ethylene glycol, and late stages of salicylism, cause metabolic acidosis and compensatory hyperventilation, which can manifest as respiratory distress. Blood gas measurements show decreased pH and compensatory hypocarbia with normal oxygenation. Metabolic disorders causing hyperammonemia, on the other hand, cause respiratory alkalosis (decreased $PaCO_2$ with increased pH) because ammonia is a stimulant of respiratory centers.

Other Nonpulmonary Entities Manifesting as Respiratory Distress

Sepsis and septic shock may manifest as respiratory distress by causing acute respiratory distress syndrome (ARDS), hypovolemic stimulation of baroreceptors, stimulation of respiratory centers by cytokines, and lactic acidosis. Other indirect causes of lung injury include systemic inflammatory conditions, trauma, transfusion-related acute lung injury, and pancreatitis. Similarly, renal disease may manifest as respiratory distress by causing metabolic acidosis (e.g., renal tubular acidosis or renal failure) or hypertensive left ventricular failure and fluid overload.

RESPIRATORY FAILURE

Respiratory failure occurs when oxygenation and ventilation are insufficient to meet the metabolic demands of the body. Respiratory failure may result from an abnormality in (1) lung and airways, (2) chest wall and muscles of respiration, or (3) central and peripheral chemoreceptors. Clinical manifestations depend largely on the site of pathology (Table 71-6). Although respiratory failure is traditionally defined as respiratory dysfunction resulting in Pa_{O_2} <60 torr with breathing of room air and $PaCO_2$ >50 torr resulting in acidosis, the patient's general state, respiratory effort, and potential for impending exhaustion are more important indicators than blood gas values.

Acute lung injury due to pneumonia, sepsis, aspiration, drowning, embolism, trauma, smoke inhalation, or drug overdose may lead to the **ARDS** (Tables 71-7 and 71-8; Fig. 71-1).

Pathophysiology of Respiratory Failure

Respiratory failure can be classified into (1) hypoxic respiratory failure (failure of oxygenation) and (2) hypercarbic respiratory failure (failure of ventilation). Systemic venous (pulmonary arterial) blood is arterialized after equilibration with alveolar gas in the pulmonary capillaries and is carried back to the heart by pulmonary veins. The arterial gas is influenced by the composition of inspired gas, and the effectiveness of alveolar ventilation, pulmonary capillary perfusion, and diffusion capacity of the alveolar capillary membrane. Abnormality at any of these steps can result in respiratory failure. Hypoxic respiratory failure results from intrapulmonary shunting and venous admixture or insufficient diffusion of oxygen from alveoli into pulmonary capillaries. This can be

Table 71-6 Typical Clinical Manifestations of Respiratory Failure

SITE OF PATHOLOGY	SYMPTOM
Lung and Airways	Nasal flaring, retractions, tachypnea, wheezing stridor, grunting
Chest wall and muscles of respiration	Nasal flaring, tachypnea, paradoxical respirations
Respiratory control	Shallow or slow respirations, abnormal respiratory patterns, apnea

Table 71-7 Simplified Consensus Definition of Acute Lung Injury

- Acute onset (<7 days)
- Severe hypoxemia (PaO_2/FIO_2 <300 for acute lung injury, or <200 for acute respiratory distress syndrome)
- Diffuse bilateral pulmonary infiltrates on frontal radiograph consistent with pulmonary edema (these can be patchy and asymmetric, and pleural effusions can be present)
- Absence of left atrial hypertension (pulmonary artery wedge pressure <18 mm Hg if measured)

From Wheeler AP, Bernard GR: Acute lung injury and the acute respiratory distress syndrome: a clinical review, Lancet *369:1553–1564, 2007.*

Table 71-8 New Berlin Definition of ARDS in Infancy and Early Childhood

	BERLIN DEFINITION CRITERIA	SUITABILITY IN INFANTS
Timing	Within 1 wk of a known clinical insult or new or worsening respiratory symptoms	Acute time frame is specified
Chest X-rays or tomography scan	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules. (Illustrative clinical cases and chest X-rays have been provided)	Including illustrative radiographs is important, because ARDS appearance may be different in children and in adults
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema, if no ARDS risk factors are present	Echocardiography widely used, whereas Swan-Ganz catheters are rarely used in early childhood. Including risk factors in the ARDS definition is important, because they may be different in children and in adults
Oxygenation*		
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O†	Noninvasive CPAP is widely used in early childhood. PEEP threshold (5 cm H_2O) is a value commonly used during early childhood
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O	
Severe	PaO_2/FIO_2 < 100 mm Hg with PEEP ≥ 5 cm H_2O	

*If altitude is higher than 1,000 m, the correction factor should be calculated as follows: [PaO_2/FIO_2 × (barometric pressure/760)].
†This may be delivered noninvasively in the mild acute respiratory distress syndrome group.
CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

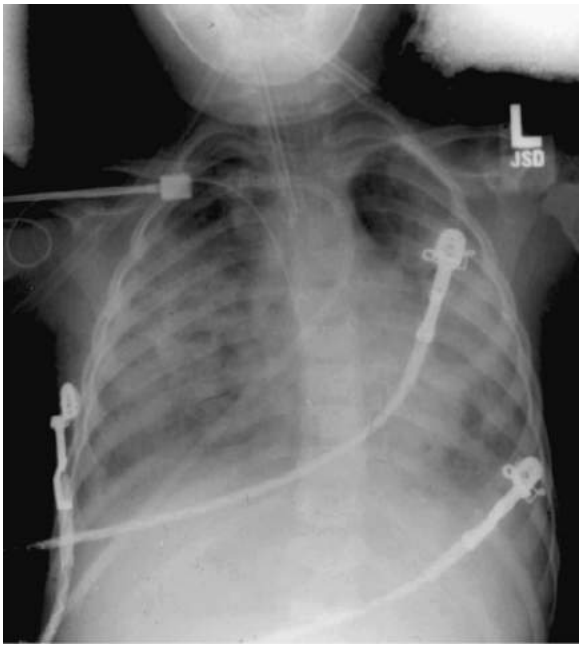

Figure 71-1 Frontal portal chest radiograph showing diffuse bilateral infiltrates consistent with acute lung injury. *(From Wheeler AP, Bernard GR: Acute lung injury and the acute respiratory distress syndrome: a clinical review,* Lancet *369:1553–1564, 2007.)*

caused by conditions such as small airway obstruction, increased barrier to diffusion (such as interstitial edema or fibrosis), or in conditions where alveoli are collapsed or filled with fluid (e.g., ARDS, pneumonia, atelectasis, or pulmonary edema). In most cases, hypoxic respiratory failure is associated with a decreased functional residual capacity, and can be managed by recruitment with positive pressure ventilation. Hypercarbic respiratory failure is caused by decreased minute alveolar ventilation (tidal volume multiplied by respiratory rate). This can occur from centrally-mediated disorders of respiratory drive, increased dead space ventilation, or obstructive airway disease. The two entities may coexist as a combined failure of oxygenation and ventilation.

Ventilation–Perfusion Mismatch, Venous Admixture, Intrapulmonary Shunt

For exchange of O_2 and CO_2 to occur, alveolar gas must be exposed to blood in pulmonary capillaries. Both ventilation and perfusion are lower in nondependent areas of the lung and higher in dependent areas of the lung. The difference in perfusion ($\dot{Q}$) is greater than the difference in ventilation ($\dot{V}$). Perfusion in excess of ventilation results in incomplete "arterialization" of systemic venous (pulmonary arterial) blood and is referred to as *venous admixture*. Perfusion of unventilated areas is referred to as *intrapulmonary shunting* of systemic venous blood to systemic arterial circulation. Conversely, ventilation that is in excess of perfusion is "wasted"; that is, it does not contribute to gas exchange and is referred to as *dead space ventilation*. Dead space ventilation results in return of greater amounts of atmospheric gas which has not participated in gas exchange and has negligible CO_2 to the atmosphere during exhalation. The end result is a decrease in mixed expired P_{CO_2} (P_{ECO_2}) and an increase in the Pa_{CO_2}-P_{ECO_2} gradient. The fraction of tidal volume that occupies dead space (V_D/V_T) is calculated as follows:

$$[(Pa_{CO_2} - P_{ECO_2}) \div Pa_{CO_2}]$$

Normal V_D/V_T is around 0.33. V_D/V_T increases in states that result in decreased pulmonary perfusion, such as pulmonary hypertension, hypovolemia, and decreased cardiac output. Venous admixture and intrapulmonary shunting predominantly affect oxygenation, resulting in a P_{AO_2}-Pa_{O_2} (A-a_{O_2}) gradient without elevation in Pa_{CO_2}. This is caused by the greater ventilation of perfused areas, which is sufficient to normalize Pa_{CO_2} but not Pa_{O_2} because of their respective dissociation curves (see Chapter 365). The relative straight-line relationship of hemoglobin-CO_2 dissociation allows for averaging of P_{CO_2} from hyperventilated and hypoventilated areas. Because the association between oxygen tension and hemoglobin saturation plateaus with increasing Pa_{O_2}, the decreased hemoglobin-O_2 saturation in poorly ventilated areas cannot be compensated for by well-ventilated areas where hemoglobin-O_2 saturation has already reached near-maximum. This results in decreased arterial oxyhemoglobin saturation (Sa_{O_2}) and Pa_{O_2}. Elevation of Pa_{CO_2} in such situations is indicative of coincident alveolar hypoventilation. Examples of diseases leading to venous admixture include asthma and aspiration pneumonia, and those of intrapulmonary shunt include lobar pneumonia and ARDS.

Diffusion

Even if ventilation and perfusion are matched, gas exchange requires diffusion across the interstitial space between alveoli and pulmonary capillaries. Under normal conditions, there is sufficient time for the pulmonary capillary blood to equilibrate with alveolar gas across the interstitial space. When the interstitial space is filled with inflammatory cells or fluid, diffusion is impaired. Because the diffusion capacity of CO_2 is 20 times greater than that of O_2, diffusion defects manifest as hypoxemia rather than hypercarbia. Even with the administration of 100% oxygen, P_{AO_2} increases to around 660 torr from 100 torr at sea level, and the concentration gradient for diffusion of O_2 is increased by only 6.6 times. Therefore, with diffusion defects, lethal hypoxemia will set in before clinically significant CO_2 retention results. In fact, in such situations P_{CO_2} is often decreased because of the hyperventilation that accompanies hypoxemia. Presence of hypercarbia in diseases that impair diffusion is indicative of alveolar hypoventilation from coexisting airway obstruction, exhaustion, or CNS depression. Examples of disease that impair diffusion are interstitial pneumonia, ARDS, scleroderma, and pulmonary lymphangiectasia.

MONITORING A CHILD IN RESPIRATORY DISTRESS AND RESPIRATORY FAILURE

Clinical Examination

It cannot be overemphasized that clinical observation is the most important component of monitoring. The presence and magnitude of abnormal clinical findings, their progression with time, and their temporal relation to therapeutic interventions serve as guides to diagnosis and management (see Chapter 373). As much as possible, the child with respiratory distress or failure should be observed in the position of greatest comfort and in the least threatening environment.

Pulse oximetry is the most commonly utilized technique to monitor oxygenation. Noninvasive and safe, it is the standard of care in bedside monitoring of children during transport, procedural sedation, surgery, and critical illness. It indirectly measures arterial hemoglobin-O_2 saturation by differentiating oxyhemoglobin from deoxygenated hemoglobin using their respective light absorption at wavelengths of 660 nm (red) and 940 nm (infrared). A pulsatile circulation is required to enable detection of oxygenated blood entering the capillary bed. Percentage of oxyhemoglobin is reported as Sa_{O_2}; however, the correct description is oxyhemoglobin saturation as measured by pulse oximetry (Sp_{O_2}). This is because Sp_{O_2} may not reflect Sa_{O_2} in certain situations. It is important to be familiar with the hemoglobin-O_2 dissociation curve (see Chapter 373) in order to estimate Pa_{O_2} at a given oxyhemoglobin saturation. Because of the shape of the hemoglobin-O_2 dissociation curve, changes in Pa_{O_2} above 70 torr are not readily identified by pulse oximetry. Also, at the same Pa_{O_2} level, there may be a significant change in Sp_{O_2} at a different blood pH value. In most situations, an Sp_{O_2} value greater than 95% is a reasonable goal, especially in emergency situations. There are exceptions, such as in patients with single ventricle cardiac lesions, in whom the pulmonary and systemic circulations are receiving blood flow from the same ventricle (e.g., after Norwood procedure for hypoplastic left heart syndrome), or with large left-to-right shunts (e.g., ventricular septal defect and patent ductus arteriosus). In these types of pathophysiologic situations, a lower Sp_{O_2}

is desired to avoid excessive blood flow to the lungs and pulmonary edema from the pulmonary vasodilatory effects of oxygen, and, in the patient with a single ventricle, diverting blood flow away from the systemic circulation. Because most commercially available pulse oximeters recognize all types of hemoglobin as either oxyhemoglobin or deoxygenated hemoglobin, they provide inaccurate information in the presence of carboxyhemoglobin and methemoglobin. In carbon monoxide poisoning, carboxyhemoglobin absorbs light in the same (red) wavelength as oxyhemoglobin, leading to overestimation of oxygen saturation. Methemoglobin absorbs light in both the oxygenated and deoxygenated wavelengths, which can cause either an overestimation or underestimation of oxygen saturation. Data suggests that increasing methemoglobin concentrations tend to drive Spo_2 toward 85%, no matter the actual percent of oxyhemoglobin. At lower methemoglobin levels, the pulse oximetry reading is falsely low, whereas high levels lead to a falsely high pulse oximetry reading. Newer pulse oximeters may have the ability to distinguish dyshemoglobinemias and to prevent false readings, but these are not currently in widespread use. It should be recognized that dangerous levels of hypercarbia may exist in patients with ventilatory failure, who have satisfactory Spo_2 if they are receiving supplemental oxygen. Pulse oximetry should not be the only monitoring method in patients with primary ventilatory failure, such as neuromuscular weakness and CNS depression. It is also unreliable in patients with poor perfusion and poor pulsatile flow to the extremities. Despite these limitations, pulse oximetry is a noninvasive, easily applicable, and effective means of evaluating the percentage of oxyhemoglobin in most patients.

Capnography (end-tidal CO_2 measurement) is helpful in determining the effectiveness of ventilation and pulmonary circulation. This method is especially useful for monitoring the level of ventilation in intubated patients. Diseases resulting in increased dead space or decreased pulmonary blood flow lead to decreases in end-tidal CO_2 and an overestimation of the adequacy of ventilation.

Blood Gas Abnormalities in Respiratory Distress and Respiratory Failure

Arterial blood gas analysis offers valuable assistance in diagnosis, monitoring, and management of a child in respiratory distress and failure. Because of technical difficulties in obtaining an arterial sample in children, a capillary blood gas (CBG) sample is most often obtained in emergency situations. A properly "arterialized" CBG sample obtained by warming the digit and obtaining free flowing blood is acceptable. The blood sample needs to be processed without delay. CBG provides a good estimate of $Paco_2$ and arterial pH, but less so for Pao_2. In patients who mainly require monitoring of their ventilation (especially those whose oxygenation is being monitored with pulse oximetry) a venous blood gas sample provides reliable estimate of arterial pH and Pco_2 values, provided tissue perfusion is reasonably adequate. Venous Pco_2 is approximately 6 torr higher and pH approximately 0.03 lower than the arterial values. Venous Po_2 has a poor correlation with Pao_2. Mixed venous O_2 saturation obtained from a central venous catheter in the right atrium is an excellent marker of the balance between oxygen delivery and oxygen consumption. In patients with a constant arterial O_2 content and O_2 consumption, mixed venous O_2 saturation offers valuable information regarding cardiac output.

Blood gas analysis is important not only for determining the adequacy of oxygenation and ventilation but also for determining site of the respiratory pathology and planning treatment (see Chapter 373). Briefly, in presence of pure alveolar hypoventilation (such as airway obstruction above the carina, decreased CO_2 responsiveness and neuromuscular weakness), the blood gas will show respiratory acidosis with an elevated Pco_2 but a relative sparing of oxygenation. $\dot{V}/\dot{Q}$ mismatch (peripheral airway obstruction, bronchopneumonia) will be reflected in increasing hypoxemia and variable levels of Pco_2 (low, normal, high) depending on severity of disease. Intrapulmonary right to left shunting and diffusion defects (alveolar-interstitial diseases such as pulmonary edema, ARDS) will be associated with a large A-ao_2 gradient and hypoxemia with relative sparing of CO_2 elimination unless there is coincident fatigue or CNS depression.

Acid–Base Abnormalities in a Child with Respiratory Distress and Respiratory Failure

It is crucial to analyze the magnitude and appropriateness of changes in pH, Pco_2 and bicarbonate (HCO_3^-) as they provide useful clues to the underlying pathophysiology and presence of more than one disorder. To do so, it is useful to assume baseline values of pH 7.40, Pco_2 40 torr, and HCO_3^- 24 mEq/L. Newborns have lower renal threshold for bicarbonate and therefore have slightly different baseline values of pH 7.38, Pco_2 35 torr and HCO_3^- 20 mEq/L.

Metabolic Acidosis with Respiratory Compensation

Patients with metabolic acidosis have decreased pH resulting from decreased serum bicarbonate. Chemoreceptor stimulation results in hyperventilation and respiratory compensation which may clinically manifest as respiratory distress. It should be recognized that a normal compensation does not completely correct the pH but rather minimizes a change in pH that would otherwise occur without compensation. The adequacy of respiratory compensation is judged by the extent of the decline in $Paco_2$ in response to the decline in HCO_3^- or pH. A normal compensation for metabolic acidosis results in a fall in Pco_2 by 1.2 torr for every 1 mEq/L fall in HCO_3^- The most commonly used method to analyze the adequacy of respiratory compensation is the Winter's formula: $Paco_2 = (HCO_3^- \times 1.5) + 8 \pm 2$. A quick method is to look at the last 2 digits of pH (provided it is not below 7.10) which should be within 2 torr of Pco_2. For example, pH 7.27, Pco_2 26 torr, and bicarbonate 12 mEq/L represents metabolic acidosis with a normal respiratory compensation response. On the other hand, pH 7.15, Pco_2 30 torr, and HCO_3^- 10 mEq/L constitutes metabolic acidosis with inadequate respiratory compensation. The reasons for inadequate compensation include decreased CO_2 responsiveness (e.g. narcotic poisoning, cerebral edema), abnormalities of lungs and airways, or neuromuscular weakness. A decrease in $Paco_2$ that is greater than what could be expected as a normal compensatory response to metabolic acidosis is indicative of a mixed disorder. For example, a pH 7.20, Pco_2 15 torr, and HCO_3^- 7.5 mEq/L represents metabolic acidosis with a concomitant respiratory alkalosis because the decline in Pco_2 is greater than what can be expected as normal compensation. Combination of metabolic acidosis and respiratory alkalosis is often encountered in serious conditions such as cardiogenic shock (anxiety, stimulation of baroreceptors), sepsis, or toxic-metabolic states (salicylates, organic academia).

Respiratory Acidosis with Metabolic Compensation

Patients with respiratory acidosis have decreased pH as a result of elevated $Paco_2$. An acute increase in Pco_2 of 10 torr results in a decrease in pH by 0.08. Thus, a child with severe status asthmaticus and a $Paco_2$ of 60 torr will have blood pH of around 7.24. Chronically elevated (greater than 3-5 days) $Paco_2$ is accompanied by renal compensation and increase in serum bicarbonate limiting the fall in pH to 0.03 for every 10 torr rise in $Paco_2$. Thus an infant with bronchopulmonary dysplasia who has a basal $Paco_2$ of 60 torr will have blood pH around 7.34. These findings are helpful in distinguishing acute vs. chronic changes in $Paco_2$. Also, for a given level of CO_2 accumulation, a decrease in pH that is greater than expected is indicative of concomitant metabolic acidosis and a decline in pH that is less than expected is due to accompanying metabolic alkalosis.

Assessment of Oxygenation and Ventilation Deficits

For standardizing management, following clinical progress, and determining prognosis for patients with defects in oxygenation or ventilation, various indicators have been proposed. Each one has its strengths and limitations:

A-ao_2 gradient: Calculated by subtracting arterial Po_2 from alveolar Po_2 ($Pao_2 - Pao_2$). For the comparison to be valid, it must be at the same Fio_2.

Pao_2/Fio_2 ratio is calculated by dividing arterial Po_2 by Fio_2. In hypoxic respiratory failure, a Pao_2/Fio_2 value <300 is consistent with acute lung injury, and a value <200 is consistent with ARDS.

Although the intent is to measure $\dot{V}/\dot{Q}$ mismatch, intrapulmonary shunt, and diffusion defect, the status of alveolar hypoventilation could have a significant impact on Pa_{O_2}/F_{IO_2}.

Pa_{O_2}/P_{AO_2} is determined by dividing arterial P_{O_2} by alveolar P_{O_2}. The level of alveolar ventilation is accounted for in the calculation of P_{AO_2}. Therefore, Pa_{O_2}/P_{AO_2} is more indicative of $\dot{V}/\dot{Q}$ mismatch and alveolar capillary integrity.

Oxygenation index (OI) is aimed at standardizing oxygenation to the level of therapeutic interventions such as mean airway pressure (MAP) and F_{IO_2}, which are directed toward improving oxygenation. None of the previously mentioned indicators of oxygenation account for the degree of positive pressure respiratory support. OI is calculated as follows:

$$OI = \left(MAP \times \%\, O_2\ inspired\right) \div Pa_{O_2}$$

The limitation of OI is that level of ventilation is not accounted for in the assessment.

Ventilation index (VI) is aimed at standardizing alveolar ventilation to the level of therapeutic interventions (such as peak inspiratory pressure [PIP] and ventilator rate) directed toward lowering Pa_{CO_2}. VI is calculated as follows:

$$VI = \left[Ventilator\ Rate \times (PIP - PEEP) \times Pa_{CO_2}\right] \div 1000$$

MANAGEMENT

The goal of management for respiratory distress and respiratory failure is to ensure a patent airway and provide necessary support for adequate oxygenation of the blood and removal of CO_2. Compared with hypercapnia, hypoxemia is a life-threatening condition; therefore, initial therapy for respiratory failure should be aimed at ensuring adequate oxygenation.

Oxygen Administration

Supplemental oxygen administration is the least invasive and most easily tolerated therapy for hypoxemic respiratory failure. *Nasal cannula* oxygen provides low levels of oxygen supplementation and is easy to administer. Oxygen is humidified in a bubble humidifier and delivered via nasal prongs inserted in to the nares. In children, a flow rate <5 L/min is most often used because of increasing nasal irritation with higher rates. A common formula for an estimation of the F_{IO_2} during use of a nasal cannula in older children and adults is as follows:

$$F_{IO_2}\%\ O_2\ \text{delivered} = 21\% + \left[\left(\text{nasal cannula flow (L/min)} \times 3\right)\right]$$

The typical F_{IO_2} value using this method is between 23% and 40%, although the F_{IO_2} varies according to the size of the child, the respiratory rate, and the volume of air moved with each breath. In a young child, because typical nasal cannula flows are a greater percentage of total minute ventilation, significantly higher F_{IO_2} may be provided. Alternately, a *simple mask* may be employed, which consists of a mask with open side ports and a valveless oxygen source. Variable amounts of room air are entrained through the ports and around the side of the mask, depending on the fit, size, and minute volume of the child. Oxygen flow rates vary from 5-10 L/min, yielding typical F_{IO_2} values between 0.30 and 0.65. If more precise delivery of oxygen is desired, other mask devices should be used.

A *Venturi mask* delivers preset fractions of oxygen through a mask and reservoir system by entraining precise amounts of room air into the reservoir with high-flow oxygen. The amount of room air entrainment and subsequent F_{IO_2} are determined by the adapter at the end of each mask reservoir. The adapter can be chosen to provide between 30% and 50% oxygen concentrations. Oxygen flow rates of 5-10 L/min are recommended to achieve desired F_{IO_2} and to prevent rebreathing. *Partial rebreather* and *nonrebreather* masks use a reservoir bag attached to a mask to provide higher fractions of oxygen. Partial rebreather masks have 2 open exhalation ports and contain a valveless oxygen reservoir bag. Some exhaled gas can mix with reservoir gas during exhalation, although most exits the mask via the exhalation ports. Through these ports, room air is also entrained during inspiration. A partial rebreather mask can provide up to 0.6 F_{IO_2} as long as oxygen flow is adequate to keep the bag from collapsing (typically 10-15 L/min). As with nasal cannulas, smaller children with smaller tidal volumes entrain less room air, and their F_{IO_2} values will be higher. Nonrebreather masks include 2 one-way valves, 1 between the oxygen reservoir bag and the mask and 1 on 1 of the 2 exhalation ports. This arrangement minimizes mixing of exhaled and fresh gas and entrainment of room air during inspiration. The second exhalation port has no valve, a safeguard to allow some room air to enter the mask in the event of disconnection from the oxygen source. A nonrebreather mask can provide up to 0.95 F_{IO_2}. The use of a nonrebreather mask in conjunction with an oxygen blender allows delivery of fractions of oxygen between 0.50 and 0.95. When supplemental oxygen alone is inadequate to improve oxygenation, or when ventilation problems coexist, additional therapies may be necessary.

Airway Adjuncts

Maintenance of a patent airway is a critical step in maintaining adequate oxygenation and ventilation. Artificial pharyngeal airways may be useful in patients with oropharyngeal or nasopharyngeal airway obstruction and in those with neuromuscular weakness in whom native extrathoracic airway resistance contributes to respiratory compromise. An *oropharyngeal airway* is a stiff plastic spacer with grooves along each side that can be placed in the mouth to run from the teeth along the tongue to its base just above the vallecula. The spacer prevents the tongue from opposing the posterior pharynx and occluding the airway. Because the tip sits at the base of the tongue, it is usually not tolerated by patients who are awake or whose gag reflex is strong. The *nasopharyngeal airway*, or nasal trumpet, is a flexible tube that can be inserted into the nose to run from the nasal opening along the top of the hard and soft palate with the tip ending in the hypopharynx. It is useful in bypassing obstruction from enlarged adenoids or from contact of the soft palate with the posterior nasopharynx. Because it is inserted past the adenoids, a nasopharyngeal airway should be used with caution in patients with bleeding tendencies.

Inhaled Gases

Helium-oxygen mixture (*heliox*) is useful in overcoming airway obstruction and improving ventilation. Helium is much less dense and slightly more viscous than nitrogen. When substituted for nitrogen, helium helps maintain laminar flow across an obstructed airway, decreases airway resistance, and improves ventilation. It is especially helpful in diseases of large airway obstruction in which turbulent airflow is more common, such as acute laryngotracheobronchitis, subglottic stenosis, and vascular ring. It is also used in patients with severe status asthmaticus. To be effective, helium should be administered in concentrations of at least 60%, so associated hypoxemia may limit its use in patients requiring more than 40% oxygen. *Nitric oxide (NO)* is a powerful inhaled pulmonary vasodilator. Its use may improve pulmonary blood flow and $\dot{V}/\dot{Q}$ mismatch in patients with diseases that elevate pulmonary vascular resistance, such as persistent pulmonary hypertension of the newborn, primary pulmonary hypertension, and secondary pulmonary hypertension as a result of chronic excess pulmonary blood flow (e.g., ventriculoseptal defect) or collagen vascular diseases. NO is administered in doses ranging from 5-20 parts per million. Although administration of NO to unintubated patients is possible, it is usually administered to patients receiving mechanical ventilation through endotracheal tubes, because of the need for precision in NO dosing.

Positive-Pressure Respiratory Support

Noninvasive positive-pressure respiratory support is useful in treating both hypoxemic and hypoventilatory respiratory failure. Positive airway pressure helps aerate partially atelectatic or filled alveoli, prevent alveolar collapse at end exhalation, and increase functional residual capacity (FRC). This improves pulmonary compliance and hypoxemia and decreases intrapulmonary shunt. In addition, positive pressure ventilation is useful in preventing collapse of extrathoracic airways by maintaining positive airway pressure during inspiration. Improving compliance and overcoming airway resistance also improves tidal volume and, therefore, ventilation. A **high-flow nasal cannula** delivers

gas flow at 4-16 L/min, providing significant continuous positive airway pressure (CPAP). The amount of CPAP provided is not quantifiable and varies with each patient, depending on the percentage of total inspiratory flow that is delivered from the cannula, airway anatomy, and degree of mouth breathing. In small children, the relative amount of CPAP for a given flow is usually greater than in older children, and may provide significant positive pressure. The FIO_2 can be adjusted by provision of gas flow through an oxygen blender. Another benefit of a high-flow nasal cannula system is the washout of CO_2 from the nasopharynx, which decreases rebreathing of CO_2 and dead space ventilation. For delivery of high-flow air or oxygen, adequate humidification is essential and is achieved with use of a separate heated humidification chamber. CPAP can also be provided through snugly fitting nasal prongs or a tight-fitting facial mask attached to a ventilator or other positive-pressure device. Noninvasive CPAP is most useful in diseases of mildly decreased lung compliance and low FRC, such as atelectasis and pneumonia. Diseases of extrathoracic airway obstruction in which extrathoracic negative airway pressures during inspiration lead to airway narrowing (e.g., laryngotracheitis, obstructive sleep apnea, postextubation airway edema) may also benefit from CPAP. Potential risks include nasal irritation, hyperinflation from excessive CPAP in smaller patients, and abdominal distention from swallowed air.

Bilevel positive airway pressure (BiPAP) machines provide positive airway pressure during exhalation and additional positive pressure during inspiration. A BiPAP device allows one to set an expiratory positive airway pressure and an inspiratory positive airway pressure. The additional positive pressure during inspiration helps augment tidal volume and improve alveolar ventilation in low compliance and obstructive lung disease. The inspiratory and expiratory pressures can be adjusted independently to suit individual needs and comfort. Because of the additional support during inspiration, patients with neuromuscular weakness in particular tend to benefit from BiPAP support. BiPAP may also be helpful in diseases of intrathoracic airway obstruction. During exhalation, expiratory positive airway pressure can decrease the effects of airway closure by raising intraluminal pressure and ameliorating intrathoracic airway collapse. During inspiration, inspiratory positive airway pressure can unload inspiratory muscles, and decrease work of breathing (Fig. 71-2).

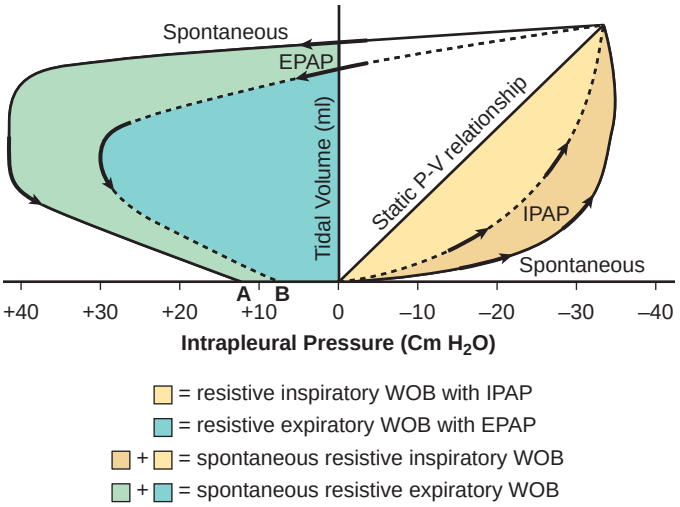

Figure 71-2 **Work of breathing (WOB) in status asthmaticus with and without noninvasive positive pressure ventilation.** In the expiratory limb of the respiratory cycle, the equal pressure point is displaced distally, causing airways to begin to close at a higher lung volume (increased closing capacity), leading to dynamic hyperinflation, and autopositive end-expiratory pressure (auto-PEEP) *(A)*. Application of expiratory positive airway pressure stents the airways, reducing intrathoracic airway collapse, dynamic hyperinflation, auto-PEEP *(B)*, and WOB. In the inspiratory limb, the patient needs to generate less negative pressure to initiate inspiration because of lower autopositive end-expiratory pressure. Inspiratory muscles are further unloaded by inspiratory positive airway pressure (IPAP) throughout inspiration for the given tidal volume. Both expiratory and inspiratory WOB are thus reduced by application of noninvasive positive pressure ventilation. *(From Sarnaik AA, Sarnaik AP: Noninvasive ventilation in pediatric status asthmaticus: Sound physiologic rationale but is it really safe, effective, and cost-efficient?* Pediatr Crit Care Med *13:484–485, 2012.)*

Endotracheal Intubation and Mechanical Ventilation

When hypoxemia or significant hypoventilation persists despite the interventions already described, tracheal intubation and mechanical ventilation are indicated. Additional indications for intubation include maintaining airway patency in patients who have the potential for airway compromise, such as those with actual or potential neurologic deterioration, and in patients with hemodynamic instability.

Proper monitoring is essential to ensuring a safe and successful tracheal intubation. Pulse oximetry, heart rate, and blood pressure monitoring are mandatory and should be forgone only in situations calling for emergency intubation. All necessary equipment, including bag-mask ventilation device, laryngoscope, tracheal tube with stylet, and suction equipment, must be available and working properly prior to initiation of intubation. The proper internal diameter (ID) for the tracheal tube can be estimated using the following formula:

$$ID = (\text{Age}[\text{yr}]/4) + 4$$

Table 71-9 provides average values for age, size, and depth of insertion for tracheal tubes. Preoxygenation of the patient with high fractions of inspired oxygen is essential and will allow maximum procedure time prior to the onset of hypoxemia.

Although intubation can be accomplished without sedation and pharmacologic paralysis in selected patients, the physiologic benefits of these measures to the patient as well as to the facilitation of the intubation usually far outweigh the risks; sedation and paralysis should be considered standard unless contraindicated. Administration of a sedative and analgesic followed by a paralytic agent is a common pharmacologic regimen for facilitating intubation. The particular type and dose of each agent often depends on the underlying disease and clinician preference. Table 71-10 lists commonly used agents. An alternative to this pharmacologic approach, especially when intubation is urgent or the patient is suspected of having a full stomach, increasing the risk of aspiration, is rapid sequence intubation (see Chapter 67).

Once adequate sedation and/or paralysis have been achieved, ventilation should be assisted with a bag-mask device. After optimal

Table 71-9 Average Size and Depth Dimensions for Tracheal Tubes

PATIENT AGE	INTERNAL DIAMETER (mm)	OROTRACHEAL DEPTH (cm)	NASOTRACHEAL DEPTH (cm)
Premature	2.0-3.0	8-9	9-10
Full-term neonate	3.0-3.5	10	11
6 mo	4.0	11	13
12-24 mo	4.5	13-14	16-17
4 yr	5.0	15	17-18
6 yr	5.5	17	19-20
8 yr	6.0	19	21-22
10 yr	6.5	20	22-23
12 yr	7.0	21	23-24
14 yr	7.5	22	24-25
Adult	8.0-9.0	23-25	25-28

Table 71-10 Medications Commonly Used for Intubation

	DRUG	DOSE	ONSET (min)	DURATION (min)	COMMENTS
Sedatives/anesthetics	Midazolam	0.1 mg/kg IV	3-5	60-120	Amnesia Respiratory depression
	Lorazepam	0.1 mg/kg IV	3-5	120-240	Amnesia Respiratory depression
	Ketamine	1-2 mg/kg IV 4-6 mg/kg IM	2-3	10-15	↑ HR, BP, and ICP Bronchodilation
	Propofol	1-3 mg/kg IV	0.5-2	10-15	↓ BP Apnea
	Thiopental	4-7 mg/kg IV	0.5-1	5-10	↓ BP Apnea
Analgesics	Fentanyl	2-5 μg/kg IV	3-5	30-90	Respiratory depression Chest wall rigidity
	Morphine	0.1 mg/kg IV	5-15	120-240	↓ BP Respiratory depression
Neuromuscular blocking agents	Vecuronium	0.1 mg/kg IV	2-3	30-75	↑ HR Renal elimination
	Rocuronium	0.6-1.2 mg/kg IV 1 mg/kg IM	5-15	15-60	↑ HR Renal elimination
	Cisatracurium	0.1 mg/kg IV	2-3	25-30	Histamine release Nonrenal elimination

BP, blood pressure; HR, heart rate; ICP, intracranial pressure; IM, intramuscularly; IV, intravenously.

preoxygenation, intubation can be performed. The clinician uses his/her dominant hand to open the patient's mouth and inserts the laryngoscope blade gently along the tongue to its base. The airway opening can be visualized by applying lift up and away from the clinician, along the axis of the laryngoscope handle. If a straight (Miller) laryngoscope blade is used, the epiglottis is lifted anteriorly by the tip of the blade to visualize the glottis. If a curved (Macintosh) blade is used, the tip should be advanced into the vallecula and then lifted to visualize the glottis. Secretions often obscure visualizations at this step and should be suctioned clear. Once clear visualization of the vocal cords is accomplished, the tube can be placed through the cords. Rapid confirmation of tube placement is essential and should be assessed by as many of the following steps as possible: Auscultation of both lung fields as well as the epigastrium for equal breath sounds and good air movement and evaluation of the abdomen for increasing distention should be performed. Adequate bilateral chest expansion and misting inside the tracheal tube with each breath are suggestive of proper tube placement. An increasing heart rate, if heart rate has decreased during the attempt, and a rising or normal pulse oximetry reading are suggestive of successful tube placement. Preoxygenation may significantly delay a drop in Spo_2 with improper tube placement, leading to a significant delay in its recognition. Confirmation of exhaled CO_2 is mandatory. It can be accomplished with use of a disposable colorimetric CO_2 detector or with capnography. In situations of very low pulmonary perfusion, such as cardiac arrest, exhaled CO_2 may not be detected. A chest radiograph should also be obtained to confirm proper placement of the tracheal tube, which should lie roughly halfway between the glottis and the carina (see Chapter 62).

Transient Manual Ventilation in the Immediate Preintubation and Postintubation Periods

Establishment of ventilation via bag and mask or bag and tracheal tube is required prior to transport of the patient to a setting of continued critical care. The technique of manual ventilation should take into account the underlying pathology. Ventilation of patients with diseases characterized by low FRC (pneumonia, pulmonary edema, ARDS, etc.) should include the application of positive end-expiratory pressure (PEEP) to prevent alveolar derecruitment. This can be accomplished with use of a PEEP valve on a self-inflating ventilation bag or by careful manipulation of exhaust gas using an anesthesia bag. Such diseases are also characterized by a short time constant and therefore are best managed with relatively small tidal volumes and high ventilation rates. Diseases characterized by airway obstruction have prolonged time constants and are therefore best managed with relatively slow rates and high tidal volumes.

Bibliography is available at Expert Consult.

71.1 Mechanical Ventilation

Ashok P. Sarnaik and Christopher Mastropietro

The decision to institute mechanical ventilation is based mainly on the need to assist lung function; supporting left ventricular performance and treating intracranial hypertension are additional indications. Although there are no absolute criteria for derangement of gas exchange, Pa_{O_2} <60 torr while breathing >60% oxygen, Pa_{CO_2} >60 torr, and pH <7.25 are often reasons to initiate mechanical ventilation. Clinical impressions of fatigue and impending exhaustion are also indications for ventilatory support even in the presence of adequate gas exchange. Positive-pressure ventilation is a powerful means of decreasing left ventricular afterload, and it is used for this purpose in patients with cardiogenic shock resulting from left ventricular dysfunction. Mechanical ventilation is also used in patients whose respirations are unreliable (e.g., unconscious patients, those with neuromuscular dysfunction) and when deliberate hyperventilation is desired, such as in patients with intracranial hypertension.

Mechanical ventilation neither is intended to normalize gas exchange nor is a form of cure. The goals are to maintain sufficient oxygenation and ventilation to ensure tissue viability until the disease process has resolved and to minimize the inevitable complications of the therapeutic intervention itself. Pa_{O_2}, Pa_{CO_2}, and pH levels are maintained in ranges that provide a safe environment for the patient while protecting the lungs from damage due to oxygen toxicity, pressure (barotrauma), tidal volume overdistention (volutrauma), atelectrauma, and cytokine release (biotrauma) (Figs. 71-3 and 71-4).

BASIC CONCEPTS OF VENTILATOR MANAGEMENT

Equation of Motion

A pressure gradient is required for air to move from one place to another (Fig. 71-5). During natural spontaneous ventilation, inspiration results from generation of negative intrapleural pressure from

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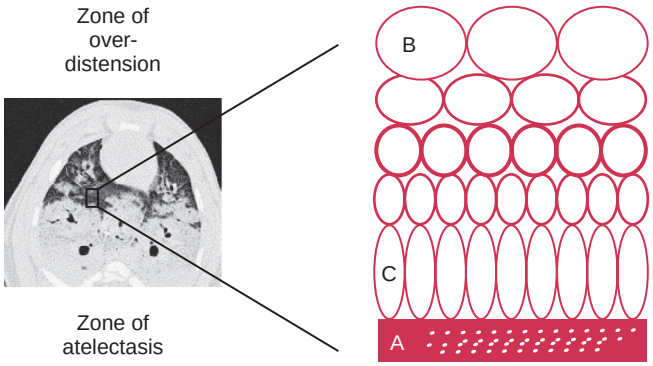

Figure 71-3 Atelectrauma. The interface between collapsed and consolidated lung *(A)* and overdistended lung units *(B)* is heterogeneous and unstable. Depending on ambient conditions, this region is prone to cyclic recruitment and derecruitment and localized asymmetric stretch of lung units *(C)* immediately apposed to regions of collapsed lung. *(From Pinhu L, Whitehead T, Evans T, et al: Ventilator-associated lung injury,* Lancet *361:332–340, 2003.)*

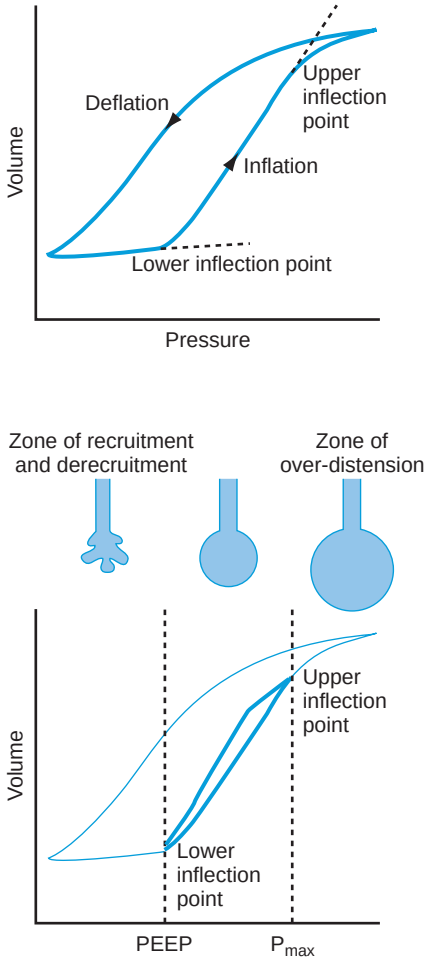

Figure 71-4 Pulmonary pressure-volume relation in a patient with acute lung injury. *Top,* The lower inflection point is typically 12-18 cm H_2O, and the upper inflection point 26-32 cm H_2O. *Bottom,* Specific protective ventilation strategies require that positive end-expiratory pressure is set just above the lower inflection point and the pressure limit (P_{max}) just below the upper inflection point. Hence the lung is ventilated in the safe zone between the zone of recruitment and derecruitment and the zone of overdistention, and both high-volume and low-volume injury are avoided. *(From Pinhu L, Whitehead T, Evans T, et al: Ventilator-associated lung injury,* Lancet *361:332–340, 2003.)*

1. Pressure gradient is required to move air from one place to another
2. Movement of air is opposed by flow-resistive and elastic properties of the system

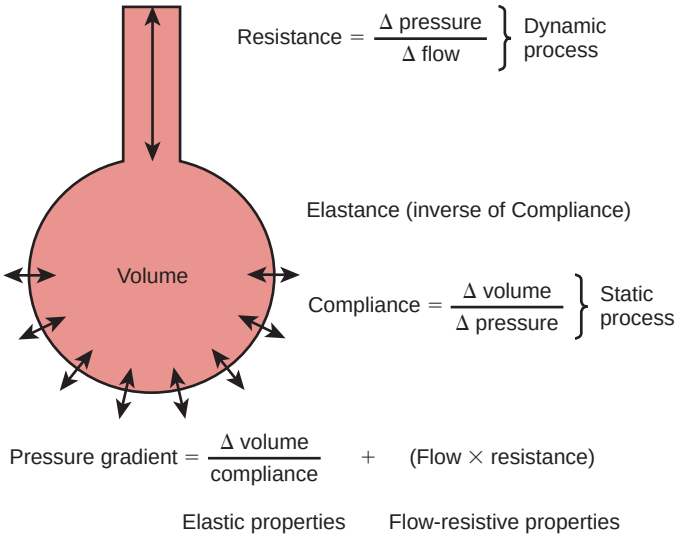

Figure 71-5 Equation of motion. A pressure gradient is required to move air from one place to another. In the lungs, the required pressure gradient must overcome the lung and chest wall elastance (static component) and the flow-resistive properties (dynamic component). The static component is increased in alveolar interstitial diseases and stiff chest wall, whereas the dynamic component is increased with airway obstruction.

contraction of the diaphragm and intercostal muscles, drawing air from the atmosphere across the airways into the alveoli. During mechanical ventilation, inspiration results from positive pressure created by compressed gases through the ventilator, which pushes air across the airways into alveoli. In both spontaneous and mechanical ventilation, exhalation results from alveolar pressure generated by the elastic recoil of the lung and the chest wall. Pressure necessary to move a given amount of air into the lung is determined by 2 factors: lung and chest wall elastance, and airway resistance. Figure 71-5 describes the relationship among pressure gradient, compliance, and resistance. *Elastance*—defined as the change in pressure (ΔP) divided by the change in volume (ΔV)—refers to the property of a substance to oppose deformation. It is opposite of *compliance* ($\Delta V \div \Delta P$), the property of a substance to allow distention or lengthening when subjected to pressure. Compliance (C) is therefore expressed as 1/elastance.

The pressure needed to overcome tissue elastance is measured in conditions in which there is no flow (at end-inspiration and end-expiration) and is therefore a reflection of static conditions in the lung. It is influenced by tidal volume and compliance ($P = \Delta V \div C$). It is increased with high tidal volume and low compliance. This pressure gradient is used to calculate the static compliance of the respiratory system (C_{STAT}).

Resistance (R) refers to the opposition to generation of flow. It is measured as the amount of pressure needed to generate a unit of flow ($\Delta P \div \Delta Flow$). Pressure needed to overcome airway resistance is calculated as flow multiplied by resistance. Because this pressure is needed only when the flow is occurring through the airways, it is referred to as the *dynamic component*. Pressure to overcome flow-resistive properties is measured when there is maximum flow and is therefore under dynamic conditions. It is increased in conditions with greater airway resistance and flow rate. Flow rate depends on the time allowed for inspiration and expiration. At higher respiratory rates, there is less time available for each inspiration and expiration, necessitating higher flows; therefore higher pressure is required to overcome flow-resistive properties. The pressure gradient necessary to move air from one place to another is the sum of pressure needed to overcome the elastic and flow-resistive properties of the lung. This pressure gradient is taken into

account to calculate the dynamic compliance of the respiratory system (C_{DYN}). The difference in change in pressure between static conditions and dynamic conditions is attributable to airway resistance.

Functional Residual Capacity

Also see Chapter 373.

During inspiration, oxygen-enriched gas enters alveoli. During exhalation, oxygen continues to be removed by the pulmonary capillary circulation. *FRC* is the volume of gas left in the alveoli at the end of expiration. It is the only source of gas available for gas exchange during exhalation. In diseases with decreased FRC (e.g., ARDS, pulmonary edema), alveolar oxygen concentration declines sharply throughout expiration, resulting in hypoxemia. Two ventilator strategies commonly employed to improve oxygenation in such situations are the application of PEEP and increasing the inspiratory time (T_I) (Fig. 71-6). PEEP increases FRC, whereas a longer T_I allows longer exposure of pulmonary capillary blood to a higher concentration of O_2 during inspiration.

Time Constant

At the beginning of inspiration, the atmospheric pressure is higher than the pressure in the alveoli, resulting in movement of air into the alveoli. During mechanical ventilation, the ventilator circuit serves as the patient's atmosphere. As alveoli expand with air, the alveolar pressure rises throughout inspiration until it equilibrates with the ventilator pressure, at which time airflow ceases. Expiration starts when the ventilator pressure falls below the alveolar pressure. Alveolar pressure decreases throughout expiration until it reaches the ventilator pressure, at which time no further egress of air from the alveoli occurs. If inspiration or expiration is terminated before pressure equilibration between alveoli and the ventilator is allowed to occur, alveolar expansion during inspiration or alveolar emptying during expiration is incomplete. Incomplete inspiration results in delivery of decreased tidal volume, whereas incomplete expiration is associated with air trapping and the presence of residual PEEP in the alveoli that is greater than the ventilator pressure, referred to as *auto-PEEP*. Some time is required for pressure equilibration to occur between alveoli and the atmosphere, which is reflected in the *time constant* (TC). It takes 3 TCs for 95%, and 5 TCs for 99%, of pressure equilibration to occur. The TC depends on compliance and resistance, and their relationship is depicted in Figure 71-7. TC is calculated as compliance multiplied by resistance ($C \times R$) and is measured in seconds.

Diseases with decreased compliance (increased elastance) are characterized by high elastic recoil pressure, which results in more rapid equilibration of alveolar and ventilator pressures, thereby decreasing TC. Diseases with increased airway resistance are associated with slower flow rates, require longer time for movement of air from one place to another, and therefore have increased TC. Airways expand during inspiration and narrow during expiration (see Chapter 373). Therefore, expiratory time constant (TC_E) is longer than inspiratory time constant (TC_I). In intrathoracic airway obstruction (asthma, bronchiolitis, aspiration syndromes), airway narrowing is much more pronounced during expiration. Therefore, although both TC_E and TC_I are prolonged in such diseases, TC_E is much more prolonged than TC_I. Patients with such diseases therefore are best ventilated with slower rates, higher tidal volume, and longer expiratory time than inspiratory time. In diseases characterized by decreased compliance, both TC_E and TC_I are short; however, the TC_E is closer to TC_I than in normal lungs because of the stiffer alveoli recoil with greater force. Patients with these diseases are best ventilated with small V_T to prevent ventilator-induced lung injury and with a relatively longer inspiratory time in each breath to improve oxygenation.

Critical Opening Pressure

Collapsed or atelectatic alveoli require a considerable amount of pressure to open. Once open, the alveoli require relatively less pressure for continued expansion. The process of opening atelectatic alveoli is called *recruitment*. In a normal lung, alveoli remain open at the end of expiration, and therefore the lung requires relatively less pressure to receive its tidal volume. In a disease process in which the alveoli

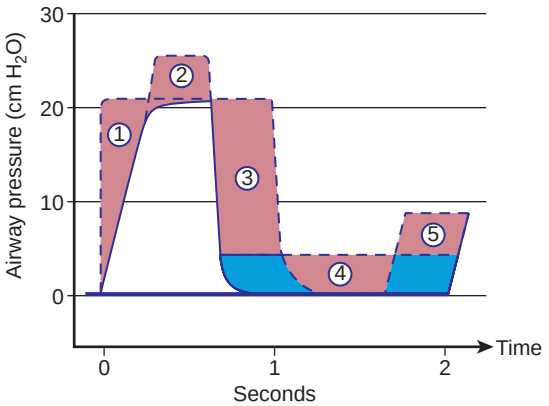

Figure 71-6 Five different ways to increase mean airway pressure: *(1)* Increase the respiratory flow rate, producing a square wave inspiratory pattern; *(2)* increase the peak inspiratory pressure; *(3)* reverse the inspiratory-expiratory ratio or prolong the inspiratory time without changing the rate; *(4)* increase positive end-expiratory pressure; and *(5)* increase the ventilatory rate by reducing the expiratory time without changing the inspiratory time. *(From Harris TR, Wood BR: Physiologic principles. In Goldsmith JP, Karotkin EH, editors:* Assisted ventilation of the neonate, *ed 3. Philadelphia, 1996, WB Saunders.)*

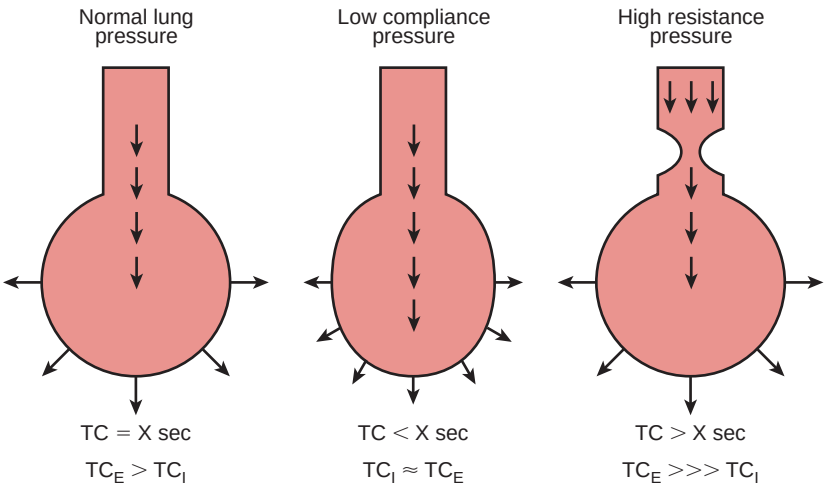

Figure 71-7 Time constant (TC). A certain amount of time is necessary for pressure equilibration (and therefore completion of delivery of gas) to occur between proximal airway and alveoli. TC, a reflection of time required for pressure equilibration, is a product of compliance and resistance. In diseases of decreased lung compliance, less time is needed for pressure equilibration to occur, whereas in diseases of increased airway resistance, more time is required. Expiratory TC is increased much more than inspiratory TC in obstructive airway diseases, because airway narrowing is exaggerated during expiration.

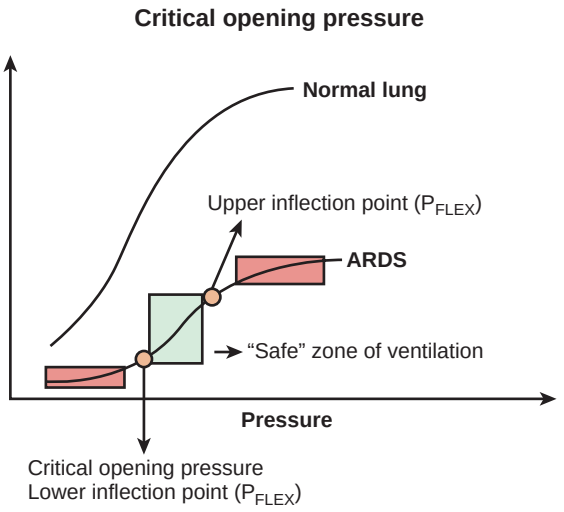

Figure 71-8 Volume-pressure relationship in normal lung and in ARDS. In ARDS, atelectatic alveoli require a considerable amount of pressure to open. Critical opening pressure, also referred to as lower P_{FLEX}, is the airway pressure above which further alveolar expansion occurs with relatively less pressure. Upper P_{FLEX} is the airway pressure above which further increase in pressure results in less alveolar expansion; this is the area of alveolar overdistention. Keeping tidal volume between upper and lower P_{FLEX} values is considered less injurious to the lung.

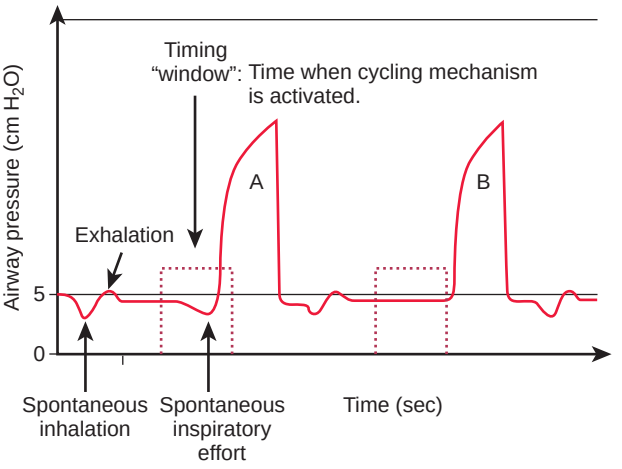

Figure 71-9 Synchronized intermittent mandatory ventilation. At set intervals, the ventilator's timing circuit becomes activated and a timing "window" appears *(dotted line area)*. If the patient initiates a breath in the timing window, the ventilator delivers a mandatory breath. If no spontaneous effort occurs, the ventilator delivers a mandatory breath at a fixed time after the timing window. *(From Banner MJ, Gallagher TJ: Respiratory failure in the adult: ventilatory support. In Kirby RR, Smith RA, Desautels DA, editors:* Mechanical ventilation, *New York, 1985, Churchill Livingstone.)*

collapse at the end of expiration (e.g., ARDS), a substantial amount of pressure is required to open the alveoli during inspiration. This pressure causes ventilator-induced lung injury via 2 mechanisms: (1) barotrauma at the terminal airway–alveolar junction and (2) volutrauma as a result of overdistention of alveoli that are already open (see Figs. 71-3 and 71-4). Although a pulmonary parenchymal disease process is rarely uniform, and each of the millions of alveoli may have its own mechanical characteristics, a composite volume-pressure relationship could be conceptualized for the whole lung (Fig. 71-8).

In these situations, the lower and upper portions of the curve are relatively horizontal, and the middle portion is more vertical. At the beginning of inspiration, atelectatic alveoli are being recruited, requiring high pressure for a relatively small increase in volume. Once they are recruited, further increase in volume requires relatively less pressure. The pressure at which most alveoli are open is called *critical opening pressure*; this point is also referred to as the *lower inflection point* (lower P_{FLEX}). After the lower P_{FLEX}, greater volume can be delivered for relatively less pressure until the upper P_{FLEX} is reached, at which the volume-pressure curve again becomes relatively horizontal. The goal of mechanical ventilation in alveolar interstitial pathology is to deliver a tidal volume between the lower and upper inflection points, the so-called safe zone of ventilation. If V_T is delivered with a change in inflation pressure that includes the lower P_{FLEX}, alveoli are likely to open *and* close during every breath, a process termed *tidal recruitment* that is injurious to the lung, especially at the terminal airway–alveolar junction. If V_T is delivered with a change of pressure that includes the upper P_{FLEX}, overdistention of alveoli is likely to occur, resulting in volutrauma and barotrauma. Keeping tidal ventilation between the upper and lower P_{FLEX} values is accomplished by maintaining a level of PEEP to produce baseline alveolar recruitment and delivering a relatively small (6 mL/kg) V_T. Termed "open lung" strategy, this approach has proved to be beneficial in alveolar interstitial diseases such as ARDS.

PHASES OF MECHANICAL VENTILATION

The planning of a ventilatory strategy must consider the four phases of the respiratory cycle separately, taking into account these patient clinical characteristics: (1) initiation of respiration and a variable that is controlled, often referred to as *mode;* (2) inspiratory phase characteristics, which determine the duration of inspiration and how the pressure or volume is delivered; (3) termination of inspiration, often referred to as *cycle;* and (4) expiratory phase characteristics. Ideally, mechanical ventilation should not completely take over the work of breathing but, rather, should assist the patient's own respiratory effort. In the absence of the patient's effort, respiratory muscle deconditioning may occur, making weaning from mechanical ventilation more difficult.

Initiation of Inspiration and the Control Variable (Mode)

The initiation of inspiration may be set to occur at a predetermined rate and interval regardless of patient effort, or it could be timed in response to patient effort. Once inspiration is initiated, the ventilator breath either is controlled entirely by the ventilator (control mode) or supports the patient's inspiratory effort to a predetermined inspiratory volume or pressure target (support mode). Advances in technology allow for greater patient–ventilator synchrony to occur. The ventilator may be set to be "triggered" by the signal it receives as a result of patient effort. This may be in the form of lowering of either pressure (pressure trigger) or airflow (flow trigger) in the ventilator circuit generated by the patient's inspiratory effort. If no such signal is received because of lack of patient effort, the ventilator delivers a breath at an interval selected by the operator.

Control Modes

Intermittent Mandatory Ventilation Mode

In intermittent mandatory ventilation (IMV), the inspiration is initiated at a set frequency with a timing mechanism independent of patient effort. In between machine-delivered breaths, the patient can breathe spontaneously from a fresh source of gas. IMV allows for adjustment of ventilator support according to the patient's needs, making it useful in the weaning process. Lack of synchrony between machine-delivered breaths and patient efforts may result in ineffective ventilation and patient discomfort, especially when IMV is delivered at a high rate. In such cases, the patient may require sedation and pharmacologic paralysis for efficient delivery of tidal volume. To obviate this problem, *synchronized IMV (SIMV)* is used, whereby the machine-delivered breaths are triggered by the patient's inspiratory efforts (Fig. 71-9). In between the machine-delivered breaths, a fresh source of gas is available for spontaneous patient breaths. In the

absence of patient effort, the patient receives a backup rate much like in IMV mode. Even with SIMV, ventilator–patient asynchrony can occur, because VT, inflation pressure, and inspiratory time are determined by the ventilator alone.

Assist-Control Mode

In assist-control (AC) mode, each and every patient breath is triggered by pressure or flow generated by patient inspiratory effort and "assisted" with either preselected inspiratory pressure or volume. The rate of respirations is therefore determined by the patient's inherent rate. A backup total (patient and ventilator) obligatory rate is set to deliver a minimum number of breaths. On AC mode with a backup rate of 20 breaths/min, all of the breaths of a patient with an inherent respiratory rate of 15 breaths/min will be assisted by the ventilator, and the patient will receive 5 additional breaths/min. On the other hand, a patient with an inherent rate of 25 breaths/min will receive all 25 breaths assisted. Although useful in some patients, the AC mode cannot be used in the weaning process, which involves gradual decrease in ventilator support.

Control Variable

Once initiated, either the tidal volume or the pressure delivered by the machine can be controlled. The machine-delivered breath is thus referred to as either volume-controlled or pressure-controlled (Table 71-11).

With *volume-controlled ventilation* (VCV), machine-delivered volume is the primary control, and the inflation pressure generated depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance are therefore easily detected from changes observed in inflation pressure. In *pressure-controlled ventilation* (PCV), the pressure change above the baseline is the primary control, and the tidal volume delivered to the lungs depends on the respiratory system's compliance and resistance. Changes in respiratory system compliance and resistance do not affect inflation pressure and may therefore go undetected unless the exhaled VT is monitored. VCV and PCV have their own advantages and disadvantages (see Table 71-11). Generally speaking, PCV is more efficient than VCV in terms of amount of tidal volume delivered for a given inflation pressure during ventilation of a lung that has nonuniform time constants, such as asthma. In VCV, relatively less-obstructed airways are likely to receive more of the machine-delivered volume throughout inspiration than relatively more-obstructed airways with longer time constants (Fig. 71-10*A*). This situation would result in uneven ventilation, higher PIP, and a decrease in dynamic compliance. In PCV, because of a constant inflation pressure that is held throughout inspiration, relatively less-obstructed lung units with shorter time constants would achieve pressure equilibration earlier during inspiration than the relatively more-obstructed areas. Thus, units with shorter TCs would attain their final volume earlier in inspiration, and those with longer TCs would continue to receive additional volume later in inspiration (Fig. 71-10*B*). This situation would result in more even distribution of inspired gas, delivery of more VT for the same inflation pressure, and improved dynamic compliance in comparison with VCV.

Pressure-regulated volume control (PRVC) combines the advantages of VCV and PCV. In this mode, the VT and TI are controlled as primary variables but the ventilator determines the amount of pressure needed to deliver the desired VT. Inflation pressure is thus adjusted to deliver the prescribed VT over the TI, depending on the patient's respiratory compliance and resistance.

Support Modes

Pressure-support ventilation (PSV) and *volume-support ventilation* (VSV) are designed to support the patient's spontaneous respirations. With PSV, initiation of inspiration is triggered by the patient's spontaneous breath, which is then "supported" by a rapid rise in ventilator pressure to a preselected level. The inspiration is continued until the inspiratory flow rate falls to a set level (generally 25% of peak flow rate) as the patient's lungs fill up. Thus, TI is controlled by the patient's own efforts. PSV can be combined with SIMV so that any breath above the SIMV rate is supported by PSV. Allowing the patient to control as much of the rate, VT, and inspiratory time as possible is considered a gentler form of mechanical ventilation than SIMV, in which the VT (or inflation pressure) and TI are preset. PSV as the sole source of mechanical ventilator support is often not adequate for patients with severe lung disease; however, it is especially useful in patients in the process of being weaned and in patients who require mechanical ventilation for relatively minor lung disease or for neuromuscular weakness. VSV is similar to PSV, in that all the spontaneous breaths are supported. In VSV, inspiratory pressure to support spontaneous breaths is adjusted to guarantee a preset VT. If there is a change in respiratory mechanics or patient effort, the inspiratory pressure to support the breath initiated by patient effort is automatically adjusted to deliver the set VT.

Inspiratory Phase Characteristics

TI, inspiratory flow waveform, and pressure rise time can be adjusted in the inspiratory phase to suit the patient's respiratory mechanics.

In PCV, the duration of TI is directly set in seconds. In VCV, the inspiratory time can be adjusted by adjusting the inspiratory flow (volume/time). The choice of TI value depends on the respiratory rate, which determines the total duration of each breath, and on the estimation of inspiratory and expiratory time constants. Decreasing the flow rate delivery increases TI, and vice versa. With an increase in TI, the pulmonary capillary blood is exposed to a higher level of alveolar P_{O_2} for a longer time. This is beneficial in diseases with decreased FRC, such as ARDS and pulmonary edema. An increase in TI also increases

Table 71-11 Characteristics of Pressure-Controlled and Volume-Controlled Methods of Ventilation

	PRESSURE-CONTROLLED VENTILATION	VOLUME-CONTROLLED VENTILATION
Control setting(s)	Inflation pressure Inspiratory time Rise time	VT Flow rate Inspiratory flow pattern (constant vs decelerating)
Machine-delivered volume	Depends on respiratory system compliance and resistance	Constant
Inflation pressure	Constant	Depends on respiratory system compliance and resistance
Endotracheal tube leak	Somewhat compensated	Leaked volume part of VT
Distribution of ventilation	More uniform in lungs with varying time constant units	Less uniform in lungs with varying time constant units
Patient comfort	Possibly compromised	Possibly enhanced
Weaning	Inflation pressure adjustment required to deliver desired VT	VT remains constant, inflation pressure automatically weaned

VT, tidal volume.

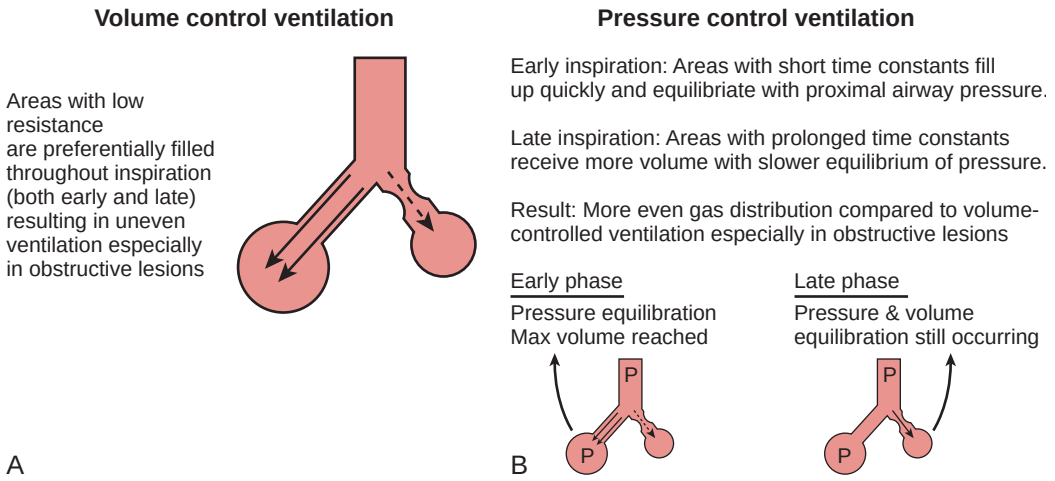

Figure 71-10 *A*, In VCV, VT is delivered to the less-obstructed areas throughout inspiration. Obstructed areas of the lung therefore receive a lower proportion of VT, resulting in uneven ventilation. *B*, In PCV, less-obstructed areas equilibrate with inflation pressure and therefore receive most of their VT early during inspiration. More-obstructed areas, with prolonged time constants, require longer time for pressure equilibration and therefore continue to receive a portion of their VT later during inspiration. The entire VT is more evenly distributed than with volume-cycled ventilation.

VT without increasing inflation pressure in PCV if inspiratory flow is still occurring at the end of expiration. It must be recognized that at a given ventilator rate, an increase in TI decreases expiratory time (TE). Therefore, any strategy that employs an increase in the inspiratory component of the respiratory cycle should ensure that the decreased TE is still sufficient for complete exhalation.

Inspiratory flow waveform can be adjusted in VCV mode as either a constant flow (square waveform) or a decelerating flow (descending ramp waveform). With a square waveform, flow is held constant throughout inspiration. In a descending ramp waveform, the flow is maximum at the start of inspiration and declines throughout its duration. It is debatable which flow pattern is better for a given disease. In PCV and PSV, the prescribed PIP is reached through delivery of airflow. The time required for the ventilator to reach PIP is reflected in the *pressure rise time,* which can be adjusted by control of flow at the beginning of the inspiratory phase. The inspiratory flow rise time is adjusted to provide comfort for a patient who is awake and also to prevent an extremely rapid rise in inspiratory pressure, which might result in barotrauma.

Termination of Inspiration (Cycle)

The two most commonly used inspiratory terminating mechanisms in control modes are time-cycled and volume-cycled. With a time-cycled mechanical breath, inspiration is terminated after a preselected TI has elapsed, whereas with volume-cycled breath, the inspiration ends after a preselected volume has been delivered by the machine into the ventilator circuit. A time-cycled breath is almost always pressure-limited, with the PIP held constant for the duration of inspiration. A volume-cycled breath can be pressure-limited as a safety mechanism to avoid barotrauma. The inspiration-terminating mechanism is set somewhat differently in support modes. In PSV, the inspiration is set to end after the inspiratory flow decreases below a certain percentage (usually 25%) of peak inspiratory flow. This happens when the patient no longer desires to receive additional VT. Such a breath can be termed *flow-cycled*. In volume support mode, inspiration is terminated when the patient has received the desired VT.

Expiratory Phase Maneuvers

The most useful expiratory phase maneuver is the application of PEEP, which is applied to both the control breath and the assisted breath. The most important clinical benefits of PEEP are to recruit atelectatic alveoli and to increase FRC in patients with alveolar–interstitial diseases and thereby improve oxygenation. There is growing recognition that even a brief disconnection from a ventilator, and therefore having zero end-expiratory pressure, can result in significant alveolar derecruitment and decline in oxygenation. In patients with obstructive lesions in which insufficient exhalation results in air trapping and auto-PEEP, extrinsic PEEP (that applied through a mechanical device) can prevent airway closure during expiration and improve ventilation. Other salutary effects of PEEP include redistribution of extravascular lung water away from gas-exchanging areas, improved ventilation–perfusion relationship, and stabilization of the chest wall. The effect of PEEP on lung compliance is variable, depending on the level of PEEP provided and the patient's pulmonary mechanics. By shifting the VT ventilation to a more favorable part of the pressure-volume curve, PEEP may recruit more alveoli, delay airway closure, and improve lung compliance. Excessive PEEP, on the other hand, may lead to overdistention of alveoli and reduced compliance. The effect of PEEP in individual patients can be ascertained by measuring exhaled VT and calculating dynamic compliance. Other deleterious effects of PEEP include decreased venous return, increased pulmonary vascular resistance, and decreased cardiac output.

ADDITIONAL VENTILATORY MODALITIES

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) improves oxygenation in cases of severe hypoxemic respiratory failure resulting from alveolar-interstitial disease. This modality applies a CPAP, designated $CPAP_{HIGH}$, to recruit and maintain FRC with brief intermittent release phases of $CPAP_{LOW}$ to allow alveolar gas to escape. $CPAP_{HIGH}$ is analogous to PIP, and $CPAP_{LOW}$ is similar to setting PEEP. In contrast to the patient receiving conventional mechanical ventilation, a patient receiving APRV spends the majority of time in the $CPAP_{HIGH}$ phase, which may last as long as 3-5 sec with a brief (0.3-0.5 sec) time in the $CPAP_{LOW}$ phase. These atypically long inspiratory times are tolerated because of a floating expiratory valve in the ventilator circuit that permits spontaneous breathing during $CPAP_{HIGH}$ phase. Therefore, even if $CPAP_{HIGH}$ phase can be considered inspiratory and $CPAP_{LOW}$ phase can be considered expiratory as far as the ventilator is concerned, the patient is able to breathe spontaneously during both of these phases. The longer ventilator inspiratory times recruit lung units, and the ability to breathe spontaneously during this phase allows distribution of gas flow to atelectatic lung regions. The outcome benefit of APRV in pediatric hypoxemic respiratory failure has not been proven.

High-Frequency Ventilation

Mechanical ventilation at supraphysiologic rates and low tidal volumes, known as high-frequency ventilation (HFV), improves gas

exchange in a selected group of patients who show no response to traditional ventilatory modalities. The mechanism of alveolar ventilation in HFV is very different from that in conventional ventilation, in that HFV is less dependent on V_T and more dependent on asymmetric velocities and convective dispersion of inspired gas. Patients with severe persistent hypoxic failure are most likely to benefit from HFV. HFV is also helpful in patients with bronchopleural fistula and persistent air leaks. The main tenet of HFV is to recruit lung volume with a high MAP and produce smaller fluctuations in alveolar pressure during inspiration and expiration, thus maintaining a satisfactory FRC and reducing alveolar stretch. The 2 most investigated techniques of HFV are high-frequency oscillation (HFO) and high-frequency jet ventilation (HFJV).

The most commonly used HFV modality is HFO, which employs a mechanism to generate to-and-fro air movement. Additional air is dragged in (entrained) through a parallel circuit via a Venturi effect. Air is pushed in during inspiration and actively sucked out during expiration. The main determinants of oxygenation are F_{IO_2} and MAP, whereas ventilation is determined by changes in pressure (amplitude) from the MAP. Commonly used respiratory frequency varies from 5 Hz (300 breaths/min) in adults and older children, to 6-8 Hz (360-480 breaths/min) in young children, 8-10 Hz (480-600 breaths/min) in infants, and 10-12 Hz (600-720 breaths/min) in newborn and premature babies.

In HFJV, a high-frequency interrupter is interposed between a high-pressure gas source and a small cannula that is incorporated in the endotracheal tube (ET). The cannula propels tiny amounts of gas (jets) at high velocity and high frequency through the ET. An additional amount of gas is entrained from a parallel circuit. Unlike in HFO, expiration occurs passively in HFJV as a result of elastic recoil of the lung and the chest wall. PEEP is set through the parallel circuit by a conventional ventilator in line. Respiratory rate is generally set at 420 breaths/min. Major determinants of oxygenation are F_{IO_2} and PEEP, and the major determinant of ventilation is PIP.

CONVENTIONAL VENTILATOR SETTINGS

F_{IO_2}

The shape of the hemoglobin–oxygen dissociation curve dictates that oxygen content in the blood is not linearly related to P_{aO_2}. A P_{aO_2} value that results in an oxyhemoglobin saturation of 95% is reasonable in most situations, because a higher P_{aO_2} would cause minimal increase in arterial oxygen content, and a modest (≈10 torr) drop in P_{aO_2} would result in minimal decrease in oxyhemoglobin saturation. In most cases, a P_{aO_2} value of 70-75 torr is a reasonable goal. F_{IO_2} values that are higher than those necessary to attain oxyhemoglobin saturations of 95% expose the patient to unnecessary oxygen toxicity. Whenever possible, F_{IO_2} values should be decreased to a level ≤0.4 as long as oxyhemoglobin saturation remains 95% or above.

Mode

The choice of mode of ventilation depends on how much ventilator–patient interaction is desired and the disease entity that is being treated. SIMV or AC is chosen as the control mode, PCV, VCV, or PRVC is chosen as the variable that is to be controlled, and pressure support and volume support are the choices for support modes.

Tidal Volume and Rate

As previously discussed, alveolar ventilation, the chief determinant of P_{aCO_2}, is calculated using V_T, respiratory rate, and dead space volume. A change in V_T results in a corresponding change in V_A without affecting the dead space ventilation. A change in respiratory rate will affect the V_A as well as the dead space ventilation. As mentioned earlier, the choice of V_T and rate depends on the time constant. In a patient with relatively normal lungs, an age-appropriate ventilator rate and a V_T of 7-10 mL/kg would be appropriate initial settings. Diseases associated with decreased time constants (decreased static compliance, e.g., ARDS, pneumonia, pulmonary edema) are best treated with small (6 mL/kg) V_T and relatively rapid rates (25-40 breaths/min). Diseases associated with prolonged TCs (increased airway resistance, e.g., asthma, bronchiolitis) are best treated with relatively slow rates and higher (10-12 mL/kg) V_T. In PCV, the delivered V_T depends on the compliance and resistance of the patient's respiratory system and needs to be monitored to ensure the appropriate amount for a given situation. An inflation pressure of 15-25 cm H_2O is sufficient for most patients, but it may need adjustment, depending on the amount of exhaled V_T observed. It should be emphasized that achieving a "normal" P_{aCO_2} value is not a goal of mechanical ventilation. Mild hypercapnia (permissive hypercapnia) should be acceptable, especially when one is attempting to limit injurious inflation pressures or V_Ts.

Inspiratory Time and Expiratory Time

Inspiratory time and expiratory time are adjusted by setting inspiratory flow rate in VCV and by setting the precise T_I in PCV. Increasing the inspiratory time results in an increase in MAP, improvement in oxygenation in diseases with decreased FRC, and better distribution of V_T in obstructive lung disease. Sufficient expiratory time must be provided to ensure adequate emptying of the alveoli.

Positive End-Expiratory Pressure

The best level of PEEP depends on the disease entity that is being treated, and it may change in the same patient from time to time. Decisions are often based on the P_{aO_2}/F_{IO_2} ratio and the measurement of dynamic compliance.

PATIENT-VENTILATOR ASYNCHRONY

Patient–ventilator asynchrony occurs when the patient's respiratory pattern does not match that of the ventilator. This can occur during all phases of respiration. Adverse effects of patient- ventilator asynchrony include wasted effort, ineffective delivery of desired V_T, excessive generation of intrathoracic pressure resulting in barotrauma and adverse effects on cardiac output, increased work of breathing, and patient discomfort. Although several mechanisms exist to facilitate patient–ventilator asynchrony, a certain amount of asynchrony is inevitable unless the patient is pharmacologically sedated and paralyzed.

Triggering the Ventilator

The patient must be able to trigger the ventilator without excessive effort. Ventilators can be pressure-triggered or flow-triggered. With pressure triggering, the inspiratory valve opens and flow is delivered when a set negative pressure is generated within the patient–ventilator circuit during both inspiration and expiration. The amount of pressure required to trigger an inspiration depends on the pressure trigger sensitivity. In flow triggering, the ventilator provides a base flow of gas through the ventilator–patient circuit. When a flow sensor on the expiratory limb of the patient–ventilator circuit detects a decrease in flow as a result of the patient's inspiratory effort, the inspiratory valve opens and a ventilator breath is delivered. The degree of change in flow required to trigger an inspiration depends on the flow trigger sensitivity. Flow triggering is considered to be more comfortable, primarily because the patient receives some flow prior to triggering the ventilator, in contrast to pressure triggering, in which no flow is provided until the ventilator breath is triggered. Increasing the trigger sensitivity by decreasing the change in either pressure or flow needed to trigger an inspiration decreases the work of breathing. However, reducing the required pressure or flow excessively could result in accidental triggering and unwanted breaths by turbulence caused by condensation in the ventilator circuit, ET leaks, or cardiac oscillations.

Selection of Appropriate Inspiratory Time

The duration of T_I should match the patient's own inspiratory phase. If T_I is too long, the patient's drive to exhale may begin before the ventilator breath has cycled off. When this occurs, exhalation occurs against inspiratory flow and a closed exhalation valve, resulting in increased work of breathing, excessive rise in intrathoracic pressure, and discomfort. If T_I is too short, the patient may be still inhaling without respirator support. In general terms, T_I is usually initiated at 0.5-0.7 sec for neonates, 0.8-1 sec in older children, and 1-1.2 sec for adolescents and adults. Adjustments need to be made through

individual patient observations and according to the type of lung disease present. In patients with severe lung disease (both obstructive and restrictive), unnatural TI and TE values may have to be selected, as discussed earlier. In such situations, adequate analgesia, sedation, and, in extreme cases, neuromuscular blockade may be needed.

Selection of Inspiratory Flow Pattern

In VCV, inappropriate flow may be another source of patient–ventilator dyssynchrony. After initiation of inspiration, if the set amount of flow is inadequate to meet patient demand, a state of "flow starvation" occurs, resulting in excessive work of breathing and discomfort. Such cases may require a decelerating inspiratory flow pattern, in which a higher flow is provided in the beginning of inspiration and less toward the end as the lungs fill up. On the other hand, such a pattern may be uncomfortable for a patient who desires more gradual alveolar filling. The selection of inspiratory flow pattern should be based on the individual patient's respiratory mechanics. In PCV and PSV, the inspiratory rise time determines the manner in which the airway pressure is raised and VT delivered. Considerations for choosing the appropriate rise time in PCV and PSV are similar to those for choosing the inspiratory flow pattern in VCV.

Use of Support Modes

As much as possible, a conscious patient should be allowed to have spontaneous breaths that are supported by either PSV or VSV. This approach minimizes the mandatory breaths generated by the ventilator that are beyond the patient's control to modulate. Therefore, continued assessments should be made to determine whether the patient is able to maintain ventilatory requirements more in support modes and less in control modes.

Use of Sedation and Pharmacologic Paralysis

Having a conscious but comfortable patient is a desirable goal during mechanical ventilation. Spontaneous breaths with good muscle tone and presence of cough are important for adequate clearance of tracheobronchial secretions. The patient's ability to indicate distress is also important in identifying and preventing potential injurious factors. In certain situations, management of patient–ventilator asynchrony assumes far greater importance when the asynchrony is causing unacceptable derangement of gas exchange and ventilator-induced lung injury. Both alveolar interstitial lung pathology and obstructive airway diseases may necessitate unnatural and uncomfortable settings for respiratory rate, TI, and inflation pressures. In such situations, deep sedation is often necessary. Benzodiazepines and opiates are the agents most commonly used for this purpose. In extreme situations, pharmacologic paralysis with a nondepolarizing agent, such as vecuronium, is required to abolish any patient effort and respiratory muscle tone. When pharmacologic paralysis is used, deep sedation must be ensured so that the patient does not sense pain and discomfort. Pharmacologic sedation and paralysis can ensure total control of the patient's ventilation by mechanical means and may result in lifesaving improvement in gas exchange with reduction in inflation pressures. However, long-term use of such agents may be associated with undesirable consequences and higher morbidity. The risk of inadequate tracheobronchial secretions and atelectasis is potentially greater. Long-term use of pharmacologic sedation may be associated with chemical dependency and withdrawal manifestations, and prolonged neuromuscular blockade is associated with neuromyopathy in critically ill patients. The benefits of sedation and pharmacologic paralysis therefore should be carefully balanced with the risks, and periodic assessments should be made to determine the need for their continuation.

Cardiopulmonary Interactions

Mechanical ventilation can have both salutary as well as adverse effects on cardiac performance. By decreasing oxygen consumption necessary for work of breathing, oxygen supply to vital organs is improved. Positive-pressure breathing decreases left ventricular afterload, thus enhancing stroke volume and cardiac output in patients with failing myocardium (e.g., myocarditis). On the other hand, the decreased systemic venous return may further compromise stroke volume in hypovolemic patients. Such patients will require intravascular fluid loading. Also an increase in pulmonary vascular resistance (PVR) as a result of positive intrathoracic pressure may result in further decompensation of a poorly performing right ventricle. PVR is at its lowest value at an optimum FRC. When FRC is too low or too high, PVR (and therefore the right ventricular afterload) is increased. Both desirable and undesirable effects of cardiopulmonary interactions may coexist and require ongoing assessment and necessary interventions.

MONITORING RESPIRATORY MECHANICS

Exhaled Tidal Volume

Exhaled tidal volume (VTE) is measured by a pneumotachometer in the ventilator circuit during exhalation. In VCV, part of the machine-delivered volume may leak out during inspiration and therefore never reach the patient. Measurement of VTE more accurately describes the VT that is contributing to the patient's alveolar ventilation. In PCV, the VTE depends on the patient's respiratory system compliance and resistance, and therefore offers valuable diagnostic clues. A decrease in VTE during PCV is indicative of either decrease in compliance or increase in resistance and is helpful in directing the clinician to appropriate investigation and management. An increase in VTE is indicative of improvement and may require weaning of inflation pressures to adjust the VTE.

Peak Inspiratory Pressure

In VCV and PRVC, the PIP is the secondary variable determined by the patient's respiratory system compliance and resistance. An increase in PIP in these modes is indicative of decreased compliance (e.g., atelectasis, pulmonary edema, pneumothorax) or increased resistance (e.g., bronchospasm, obstructed ET). During VCV and PRVC, decreasing the respiratory rate or prolonging the TI will result in a lower PIP in patients with prolonged time constants because more time will be available for alveoli to fill. In such patients, a decrease in PIP suggests increased compliance or decreased resistance of the respiratory system.

Respiratory System Dynamic Compliance and Static Compliance

The changes in PIP during VCV and PRVC, and in VTE during PCV, are determined by C_{DYN} of the respiratory system (lung and chest wall). Dynamic compliance is calculated as follows:

$$C_{DYN} = V_{TE} \div (PIP - PEEP)$$

It takes into account both the flow-resistive and the elastic properties of the respiratory system. Changes in C_{DYN} can be used to assess effects of different levels of PEEP as tidal ventilation is shifted along the slope of the volume-pressure curve (see Fig. 71-8). An increase in PEEP in alveolar-interstitial diseases (increased elastance), resulting in an increase in C_{DYN} suggests alveolar recruitment, whereas a decrease in C_{DYN} may indicate overdistention. Similarly, in obstructive diseases (increased resistance), adjustment in PEEP levels to ameliorate airway collapse during exhalation can be guided by monitoring C_{DYN}. To assess only the elastic recoil of the lung, measurement of C_{STAT} when there is no airflow is required. This measurement is performed by using an inspiratory hold maneuver with the patient under neuromuscular blockade and observing pressure-time and flow-time waveforms (Fig. 71-11). During this maneuver, inspiratory flow ceases while the expiratory valve continues to remain closed, thus allowing pressure to equilibrate throughout the ventilator circuit and the patient's lungs. This pressure, referred to as the *plateau pressure* (P_{plat}), is reflective of alveolar pressure. C_{STAT} is calculated as follows:

$$C_{STAT} = V_{TE} \div (P_{plat} - PEEP)$$

The difference between C_{DYN} and C_{STAT} is attributable to airway resistance. This difference is minimal in alveolar-interstitial diseases but substantial in airway obstruction.

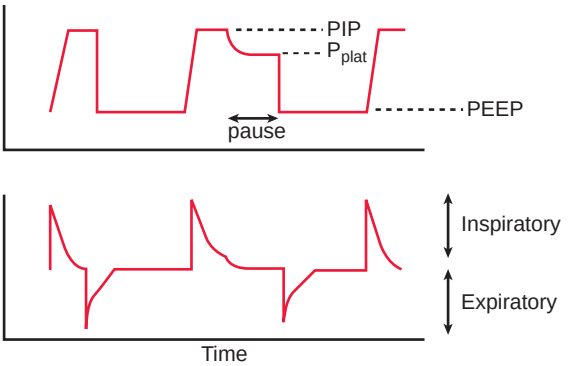

Figure 71-11 Alveolar pressure is best determined by measurement of plateau pressure (P_{plat}). Inspiration is paused for an extended period, and alveolar gas pressure is allowed to equilibrate with the ventilator circuit pressure. Airway pressure at the end of the inspiratory pause is P_{plat}. The difference between peak inspiratory pressure (PIP) and P_{plat} is to overcome flow-resistive properties of the lung, whereas P_{plat} reflects the pressure needed to overcome elastic properties of lung and chest wall.

Assessment of Auto-PEEP

Auto-PEEP is assessed with the use of an expiratory pause maneuver in which inspiration is delayed and alveolar pressure is allowed to equilibrate with the airway. In diseases with airway obstruction, insufficient alveolar emptying may occur if exhalation time is not adequate. The alveolar pressure in excess of the set PEEP at the completion of the expiratory pause is measured as auto-PEEP or intrinsic PEEP. Auto-PEEP can have adverse effects on ventilation and hemodynamic status. It can be managed by decreasing the respiratory rate or inspiratory time and thus allowing greater time for exhalation. Auto-PEEP may also be managed by increasing the set PEEP ("extrinsic" PEEP), thereby delaying airway closure during exhalation and improving alveolar emptying.

Assessment of Dead Space Ventilation

Positive pressure ventilation and application of PEEP may result in a decrease in venous return, cardiac output, and, therefore, also the pulmonary perfusion. Ventilation of poorly perfused alveoli results in dead space ventilation, which does not contribute to gas exchange. The dead space–V_T fraction can be calculated with the following equation:

$$V_D/V_T = (PaCO_2 - PECO_2) \div PaCO_2$$

Normal V_D/V_T is 0.33. Increased V_D/V_T is indicative of poorly perfused alveoli. Patients with increased V_D/V_T may require intravascular volume infusion or other means of augmenting the cardiac output to improve pulmonary perfusion. The V_D/V_T fraction is calculated and displayed by commercially available capnographs, which measure endotracheal P_{CO_2} continuously.

VENTILATOR-INDUCED LUNG INJURY

Like most medical therapies, mechanical ventilation can be harmful if appropriate principles are not followed. Lung volumes that are too high or too low should be avoided. In attempting to recruit and maintain FRC, the clinician must be careful not to overdistend alveoli. Excessive PIP and V_T can lead to unwelcome stress and strain on alveolar walls. This volutrauma and barotrauma can lead to disruption of tight junctions between alveolar epithelial and capillary endothelial cells, causing fluid and protein transudation in the alveoli. Inflammatory mediators and cytokines are released, exacerbating the injury and promoting exudative fluid formation. Decreased production and inactivation of surfactant result in atelectasis and further impairment of gas exchange. Evidence shows that in patients with severe acute hypoxemic respiratory failure, avoidance of V_T ≥10 mL/kg and P_{plat} ≥30 cm H_2O limits diffuse alveolar damage.

Insufficient PEEP is another important mechanism of ventilator-induced lung injury. Alveoli that are recruited during inspiration must remain open during expiration; if they do not, atelectrauma occurs, which is defined as undesirable shear stress on alveolar walls as they are opened and closed repeatedly. Therefore, the ideal PEEP for a patient should maximize the number of open alveoli and minimize the number of overdistended alveoli. Careful adjustments of PEEP may also permit the clinician to wean a patient from a high inspired oxygen concentration, another potential source of lung injury (oxytrauma). Though most patients receive an inspired oxygen concentration of 100% during endotracheal intubation and at the beginning of mechanical ventilation, increasing PEEP to recruit alveoli without overdistention should be quickly instituted to improve oxygenation and permit weaning of the F_{IO_2}. Although an F_{IO_2} value below which there is no risk of oxygen toxicity is unknown, most clinicians aim for a value <0.6.

Ventilator-Associated Pneumonia

The pathophysiology of ventilator-associated pneumonia (VAP) is multifactorial. Aspiration of oral and/or gastric secretions, colonization of ETs, and suppression of cough reflexes with sedation all play a role. New-onset fever and leukocytosis accompanied by demonstration of an infiltrative process by chest radiographs are consistent with a diagnosis of VAP. This complication can lead to worsened gas exchange, increased duration of ventilation, and even death. Elevation of the head of the bed to 30 degrees after initiation of mechanical ventilation and use of a protocol for oral decontamination during mechanical ventilation are two means of reducing the risk for VAP. The most effective strategy to minimize any of the aforementioned complications is regular assessment of extubation readiness and liberation from mechanical ventilation as soon as clinically possible.

Weaning

Weaning from mechanical ventilation should be considered as a patient's respiratory insufficiency begins to improve. Most pediatricians favor gradual weaning from ventilator support. With SIMV, the ventilator rate is slowly reduced, allowing the patient's spontaneous breaths (typically assisted with pressure or volume support) to assume a larger proportion of the minute ventilation. When the ventilator rate is low (<5 breaths/min) such that its contribution to minute ventilation is minimal, assessment of extubation readiness is performed. An alternative method of gradual weaning is transition to a pressure support mode of ventilation. In this mode, no ventilator rate is set, allowing all triggered breaths to be assisted with pressure support. The clinician reduces the pressure support slowly to a low value (<5-10 cm H_2O), at which point assessment of extubation readiness is performed. During either technique, weaning should be halted if tachypnea, increased work of breathing, hypoxemia, hypercapnia, acidosis, diaphoresis, tachycardia, or hypotension occurs.

The most objective means of assessing extubation readiness is a spontaneous breathing trial (SBT). Prior to performance of an SBT, a patient should be awake with intact airway reflexes, capable of handling oropharyngeal secretions, and with stable hemodynamic status. In addition, gas exchange should be adequate, defined as a Pa_{O_2} >60 mm Hg while receiving an F_{IO_2} <0.4 and PEEP ≤5 cm H_2O. If these criteria are present, a patient should be started on CPAP with minimal or no pressure support (≤5 cm H_2O). If this SBT is tolerated with no episodes of respiratory or cardiovascular decompensation, successful extubation is likely. Some neonates and small children cannot be calmed or consoled long enough to complete the SBT. In this situation, extubation readiness must be assessed on a low level of ventilator support. Data suggest that there is a low risk of extubation failure if the patient is comfortable and has stable hemodynamic status with adequate gas exchange and spontaneous V_T >6.5 mL/kg while receiving <20% of total minute ventilation from the ventilator. Certain patient populations are at increased risk for extubation failure, such as young infants, children mechanically ventilated for >7 days, and patients with chronic respiratory or neurologic conditions. These children often benefit from transition to a noninvasive form of positive pressure ventilation (e.g., high-flow nasal cannula, CPAP, or BiPAP)

delivered via nasal prongs or face mask to increase the odds of successful extubation. The likelihood of postextubation upper airway obstruction, the most common cause of extubation failure in children, cannot be predicted on the basis of an SBT result or bedside measurements of physiologic variables. Traumatic endotracheal intubation and subglottic swelling from the ET irritation, especially in patients who exhibit agitation while receiving mechanical ventilation, are common causes of airway narrowing after extubation. Administration of intravenous corticosteroids (dexamethasone 0.5 mg/kg every 6 hr for 4 doses prior to extubation) has been shown to minimize the incidence of postextubation airway obstruction. In patients in whom postextubation airway obstruction develops, the need for re-intubation may be obviated by administration of nebulized racemic epinephrine and heliox.

Bibliography is available at Expert Consult.

71.2 Long-Term Mechanical Ventilation

See Chapter 418.

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Chapter 72

Acute Care of the Victim of Multiple Trauma

Cindy Ganis Roskind, Peter S. Dayan, and Bruce L. Klein

EPIDEMIOLOGY

Injury is a leading cause of death and disability in children throughout the world (see Chapter 5.1). According to the World Health Organization report on child injury prevention, unintentional injuries are one of the leading causes of death in children younger than 20 yr and the leading cause of death in children between 10 and 20 yr of age in the world. Road traffic–related injuries, drowning, fire-related events, and falls rank among the top causes of death and disability in children. In Asia, injury accounts for more than 50% of deaths in children <18 yr, with drowning accounting for approximately half. In the United States, more than 12,000 children die each year secondary to unintentional injury, with motor vehicle–related injuries being the leading cause.

Deaths represent only a small fraction of the total trauma burden. Approximately 9.2 million children are treated in U.S. emergency departments (EDs) each year for injury, most commonly for falls. Many survivors of trauma have permanent or temporary functional limitations. Motor vehicle–related injuries and falls rank among the top 15 causes of disability-adjusted life years in children worldwide.

Trauma is frequently classified according to the number of significantly injured body parts (≥1), the severity of injury (mild, moderate, or severe), and the mechanism of injury (blunt or penetrating). In childhood, blunt trauma predominates, accounting for the majority of injuries. In adolescence, penetrating trauma increases in frequency, accounting for approximately 15% of injuries, and has a higher case fatality rate.

REGIONALIZATION AND TRAUMA TEAMS

Mortality and morbidity rates have decreased in geographic regions with comprehensive, coordinated trauma systems. Treatment at designated trauma centers is associated with decreased mortality. At the scene of injury, paramedics should administer necessary advanced life support and perform triage (Fig. 72-1; Tables 72-1 and 72-2). It is usually preferable to bypass local hospitals and rapidly transport a seriously injured child directly to a pediatric trauma center (or a trauma center with pediatric commitment). Children have lower mortality rates after severe blunt trauma when they are treated in designated pediatric trauma centers or in hospitals with pediatric intensive care units.

Table 72-1 Changes in 2011 Guidelines for Field Triage of Injured Patients Compared with 2006 Guidelines

Step One: Physiologic Criteria
Changed GCS <14 to GCS ≤13
Added "or need for ventilatory support" to respiratory criteria
Step Two: Anatomic Criteria
Changed "all penetrating injuries to head, neck, torso and extremities proximal to elbow and knee" to "all penetrating injuries to head, neck, torso and extremities proximal to elbow or knee"
Changed "flail chest" to "chest wall instability or deformity (e.g., flail chest)"
Changed "crushed, degloved, or mangled extremity" to "crushed, degloved, mangled, or pulseless extremity"
Changed "amputation proximal to wrist and ankle" to "amputation proximal to wrist or ankle"
Step Three: Mechanism-of-Injury Criteria
Added "including roof" to intrusion criterion
Step Four: Special Considerations
Added the following to older adult criteria
SBP <110 might represent shock after age 65 yr
Low-impact mechanisms (e.g., ground-level falls) might result in severe injury
Added "patients with head injury are at high risk for rapid deterioration" to anticoagulation and bleeding disorders criterion
Removed "end-stage renal disease requiring dialysis" and "time-sensitive extremity injury"
Transition Boxes
Changed layout of the figure
Modified specific language of the transition boxes

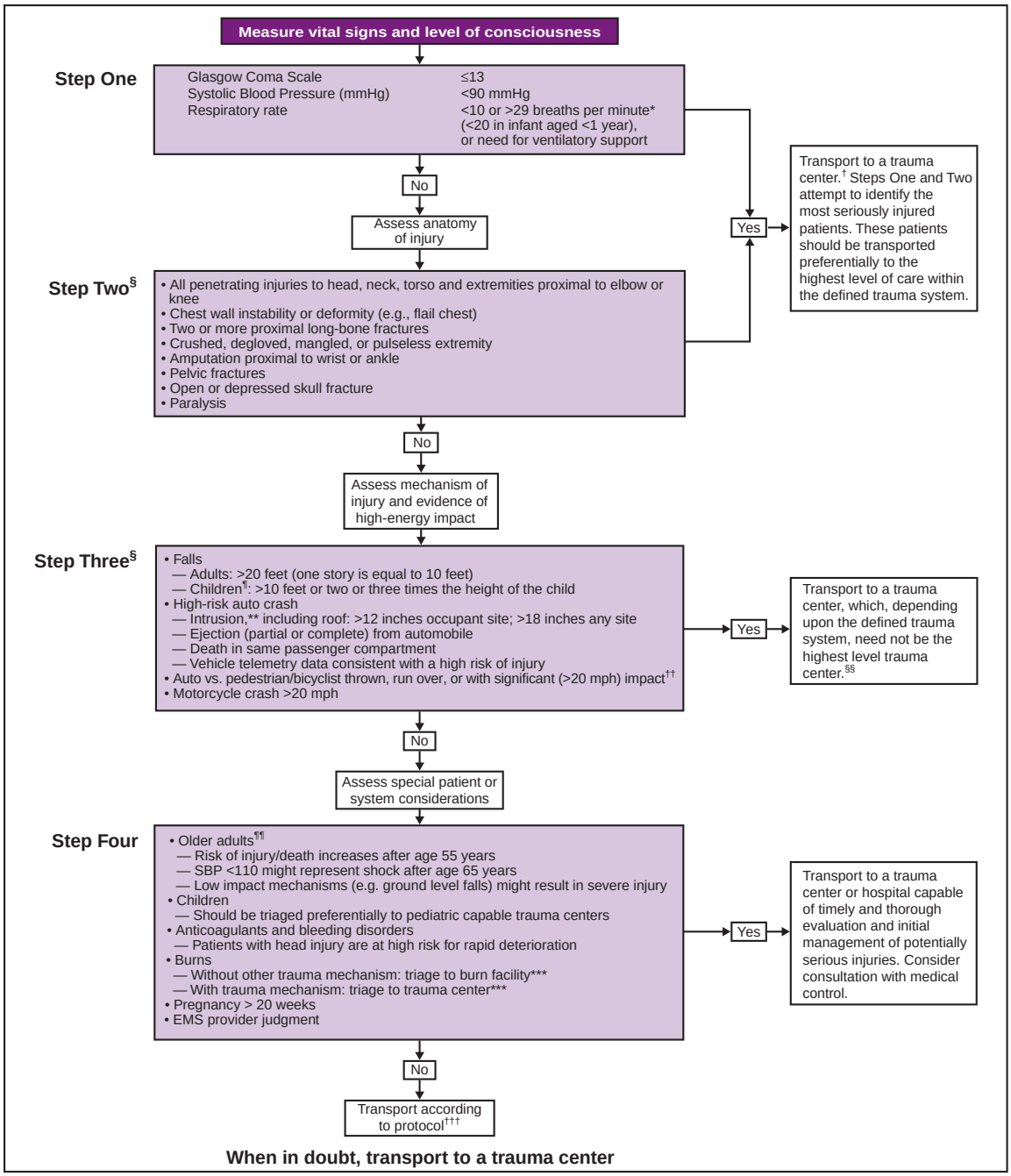
GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

From Sasser SM, Hunt RC, Faul M, et al: Guidelines for field triage of injured patients: Recommendations of the National Expert Panel on Field Triage, 2011. MMWR Recomm Rep *61(RR-1):1-20, 2012 (Box 2, p. 8).*

Table 72-2 Children Requiring Pediatric Trauma Center Care

Patients with serious injury to >1 organ or system
Patients with 1-system injury who require critical care or monitoring in an intensive care unit
Patients with signs of shock who require >1 transfusion
Patients with fracture complicated by suspected neurovascular or compartment injury
Patients with fracture of the axial skeleton
Patients with ≥2 long-bone fractures
Patients with potential replantation of an extremity
Patients with suspected or actual spinal cord or column injury
Patients with head injury with any 1 of the following:
Orbital or facial bone fracture
Cerebrospinal fluid leak
Altered state of consciousness
Changing neurologic signs
Open-head injury
Depressed skull fracture
Requiring intracranial pressure monitoring
Patients suspected of requiring ventilator support

Modified from Krug SE: The acutely ill or injured child. In Behrman RE, Kliegman RM, editors: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 96.*



* The upper limit of respiratory rate in infants is >29 breaths per minute to maintain a higher level of overtriage for infants.

† Trauma centers are designated Level I-IV. A Level I center has the greatest amount of resources and personnel for care of the injured patient and provides regional leadership in education, research, and prevention programs. A Level II facility offers similar resources to a Level I facility, possibly differing only in continuous availability of certain subspecialties or sufficient prevention, education, and research activities for Level I designation; Level II facilities are not required to be resident or fellow education centers. A Level III center is capable of assessment, resuscitation, and emergency surgery, with severely injured patients being transferred to a Level I or II facility. A Level IV trauma center is capable of providing 24-hour physician coverage, resuscitation, and stabilization to injured patients before transfer to a facility that provides a higher level of trauma care.

§ Any injury noted in Step Two or mechanism identified in Step Three triggers a "yes" response.

¶ Age <15 years.

** Intrusion refers to interior compartment intrusion, as opposed to deformation which refers to exterior damage.

†† Includes pedestrians or bicyclists thrown or run over by a motor vehicle or those with estimated impact >20 mph with a motor vehicle.

§§ Local or regional protocols should be used to determine the most appropriate level of trauma center within the defined trauma system; need not be the highest-level trauma center.

¶¶ Age >55 years.

*** Patients with both burns and concomitant trauma for whom the burn injury poses the greatest risk for morbidity and mortality should be transferred to a burn center. If the nonburn trauma presents a greater immediate risk, the patient may be stabilized in a trauma center and then transferred to a burn center.

††† Patients who do not meet any of the triage criteria in Steps One through Four should be transported to the most appropriate medical facility as outlined in local EMS protocols.

Figure 72-1 Guidelines for Field Triage of Injured Patients—United States, 2011. *(From Guidelines for Field Triage of Injured Patients: recommendations of the National Expert Panel on Field Triage. MMWR 61:6, 2012.)*

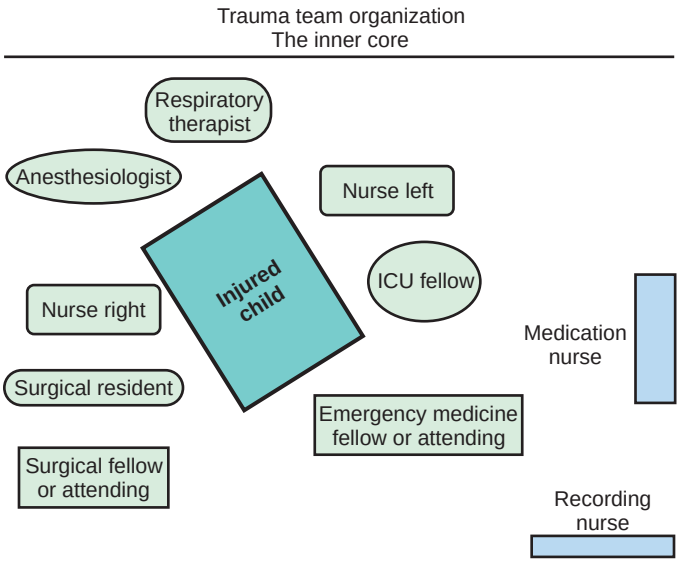


Figure 72-2 Members of the inner core of the trauma team at Children's National Medical Center (Washington, DC). Members of the outer core include a nursing administrator, a social worker, a radiology technician, a transport technician, and a security officer. ICU, intensive care unit.

Table 72-3 Pediatric Trauma Score

	CATEGORY		
Component	+2	+1	−1
Size	≥20 kg	10-12 kg	<10 kg
Airway	Normal	Maintainable	Unmaintainable
Systolic BP	≤90 mm Hg	90-50 mm Hg	<50 mm Hg
CNS	Awake	Obtunded/LOC	Coma/decerebrate
Open wound	None	Minor	Major/penetrating
Skeletal	None	Closed fracture	Open/multiple fractures
Sum total points			

Children with a Pediatric Trauma Score ≤6 are at increased risk of mortality as well as morbidity.

From Tepas JJ, Mollitt DL, Talbert JL, et al: The pediatric trauma score as a predictor of injury severity in the injured child. J Pediatr Surg *22:14–18, 1987, Table 1, p. 15.*

When the receiving ED is notified before the child's arrival, the trauma team should also be mobilized in advance. Each member has defined tasks. A senior surgeon (surgical coordinator) or, sometimes initially, an emergency physician leads the team. Team compositions vary somewhat from hospital to hospital; Figure 72-2 shows the model used at Children's National Medical Center (Washington, DC). Consultants, especially neurosurgeons and orthopedic surgeons, must be promptly available; the operating room staff should be alerted.

Physiologic status, anatomic locations, and/or mechanism of injury are used for field triage as well as to determine whether to activate the trauma team. More importance should be placed on physiologic compromise and less on mechanism of injury. Scoring scales such as the Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), Pediatric Trauma Score (Table 72-3), and Revised Trauma Score use these parameters to predict patient outcome. The AIS and ISS are used together. First, the AIS is used to numerically score injuries—as 1 minor, 2 moderate, 3 serious, 4 severe, 5 critical, or 6 probably lethal—in each of 6 ISS body regions: head/neck, face, thorax, abdomen, extremity, and external. The ISS is the sum of the squares of the highest 3 AIS region scores.

PRIMARY SURVEY

During the primary survey, the physician quickly assesses and treats any life-threatening injuries. The principal causes of death shortly after trauma are airway obstruction, respiratory insufficiency, shock from hemorrhage, and central nervous system injury. The primary survey addresses the ABCDEs: Airway, Breathing, Circulation, neurologic Deficit, and Exposure of the patient and control of the Environment.

Airway/Cervical Spine

Optimizing oxygenation and ventilation, while protecting the cervical spine from potential further injury is of paramount importance. Initially, cervical spine injury should be suspected in any child sustaining multiple, blunt trauma. Children are at risk for such injuries because of their relatively large heads, which augment flexion–extension forces, and weak neck muscles, which predispose them to ligament injuries. To prevent additional spinal injury, the current standard is to immobilize the cervical (and thoracic and lumbar) spine in neutral position with a stiff collar, head blocks, tape or cloth placed across the forehead, torso, and thighs to restrain the child, and a rigid backboard.

Airway obstruction manifests as snoring, gurgling, hoarseness, stridor, and/or diminished breath sounds (even with apparently good respiratory effort). Children are more likely than adults to have airway obstruction because of their smaller oral and nasal cavities, proportionately larger tongues and greater amounts of tonsillar and adenoidal tissue, higher and more anterior glottic openings, and narrower larynxes and tracheas. Obstruction is common in patients with severe head injuries, owing in part to decreased muscle tone, which allows the tongue to fall posteriorly and occlude the airway. With trauma, obstruction can also result from fractures of the mandible or facial bones, secretions such as blood or vomitus, crush injuries of the larynx or trachea, or foreign body aspiration.

If it is necessary to open the airway, a jaw thrust **without head tilt** is recommended. This procedure minimizes cervical spine motion. In an unconscious child, an oropharyngeal airway can be inserted to prevent posterior displacement of the mandibular tissues. A semiconscious child will gag with an oropharyngeal airway but may tolerate a nasopharyngeal airway. *A nasopharyngeal airway is contraindicated when there is a possibility of a cribriform plate fracture*. If these maneuvers plus suctioning do not clear the airway, oral endotracheal intubation is indicated. When endotracheal intubation proves difficult, a laryngeal mask airway can be used as a temporary alternative. A laryngeal mask airway consists of a tube with an inflatable cuff that rests above the larynx and thus does not require placement of the tube into the trachea. Emergency cricothyrotomy is needed in <1% of trauma victims.

Breathing

The physician assesses breathing by counting the respiratory rate; visualizing chest wall motion for symmetry, expansion, and accessory muscle use; and auscultating breath sounds in both axillae. Continuous wave form capnography monitoring may also be used as an adjunct; however it is less reliable in patients with shock. In addition to looking visually for cyanosis, pulse oximetry is standard. If ventilation is inadequate, bag-valve-mask ventilation with 100% oxygen must be initiated immediately, followed by endotracheal intubation. End-expiratory carbon dioxide (CO_2) detectors help verify accurate tube placement.

Head trauma is the most common cause of respiratory insufficiency. An unconscious child with a severe head injury may have a variety of breathing abnormalities, including Cheyne-Stokes respirations, slow irregular breaths, and apnea.

Although less common than a pulmonary contusion, tension pneumothorax and massive hemothorax are immediately life-threatening (Tables 72-4 and 72-5). **Tension pneumothorax** occurs when air accumulates under pressure in the pleural space. The adjacent lung is compacted, the mediastinum is pushed toward the opposite hemithorax, and the heart, great vessels, and contralateral lung are compressed or

Table 72-4 Life-Threatening Chest Injuries

TENSION PNEUMOTHORAX One-way valve leak from the lung parenchyma or tracheobronchial tree Collapse with mediastinal and tracheal shift to the side opposite the leak Compromises venous return and decreases ventilation of the other lung Clinically, manifests as respiratory distress, unilateral absence of breath sounds, tracheal deviation, distended neck veins, tympany to percussion of the involved side, and cyanosis Relieve first with needle aspiration, then with chest tube drainage
OPEN PNEUMOTHORAX (SUCKING CHEST WOUND) Effect on ventilation depends on size
MAJOR FLAIL CHEST Usually caused by blunt injury resulting in multiple rib fractures Loss of bone stability of the thoracic cage Major disruption of synchronous chest wall motion Mechanical ventilation and positive end-expiratory pressure required
MASSIVE HEMOTHORAX Must be drained with a large-bore tube Initiate drainage only with concurrent vascular volume replacement
CARDIAC TAMPONADE Beck Triad: 1. Decreased or muffled heart sounds 2. Distended neck veins from increased venous pressure 3. Hypotension with pulsus paradoxus (decreased pulse pressure during inspiration) Must be drained

Modified from Krug SE: The acutely ill or injured child. In Behrman RE, Kliegman RM, editors: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 97.*

kinked (see Chapter 411). Both ventilation and cardiac output are impaired. Characteristic findings include cyanosis, tachypnea, retractions, asymmetric chest rise, contralateral tracheal deviation, diminished breath sounds on the ipsilateral (more than contralateral) side, and signs of shock. Needle thoracentesis, followed by thoracostomy tube insertion, is diagnostic and lifesaving. **Hemothorax** results from injury to the intercostal vessels, lungs, heart, or great vessels. When ventilation is adequate, fluid resuscitation should begin before evacuation, because a large amount of blood may drain through the chest tube, resulting in shock.

Circulation

The most common type of shock in trauma is hypovolemic shock caused by hemorrhage. Signs of shock include tachycardia; weak pulse; delayed capillary refill; cool, mottled, pale skin; and altered mental status (see Chapter 70). Early in shock, blood pressure remains normal because of compensatory increases in heart rate and peripheral vascular resistance (Table 72-6). Some individuals can lose up to 30% of blood volume before blood pressure declines. *It is important to note that 25% of blood volume equals 20 mL/kg, which is only 200 mL in a 10 kg child.* Losses >40% of blood volume cause severe hypotension that, if prolonged, may become irreversible. Direct pressure should be applied to control external hemorrhage. Blind clamping of bleeding vessels, which risks damaging adjacent structures, is not advisable.

Cannulating a larger vein, such as an antecubital vein, is usually the quickest way to achieve intravenous access. A short, large-bore catheter offers less resistance to flow, allowing for more rapid fluid administration. Ideally, a second catheter should be placed within the first few minutes of resuscitation in a severely injured child. If intravenous access is crucial and not rapidly obtainable, an intraosseous catheter should be inserted; all medications and fluids can be administered intraosseously. Other alternatives are central venous access using the Seldinger technique (e.g., in the femoral vein) and, rarely, surgical

Table 72-5 Differential Diagnosis of Immediately Life-Threatening Cardiopulmonary Injuries

	TENSION PNEUMOTHORAX	MASSIVE HEMOTHORAX	CARDIAC TAMPONADE
Breath sounds	Ipsilaterally decreased more than contralaterally	Ipsilaterally decreased	Normal
Percussion note	Hyperresonant	Dull	Normal
Tracheal location	Contralaterally shifted	Midline or shifted	Midline
Neck veins	Distended	Flat	Distended
Heart tones	Normal	Normal	Muffled

Modified from Cooper A, Foltin GL: Thoracic trauma. In Barkin RM, editor: Pediatric emergency medicine, *ed 2, St. Louis, 1997, Mosby, p. 325.*

Table 72-6 Systemic Responses to Blood Loss in Pediatric Patients

SYSTEM	MILD BLOOD LOSS (<30%)	MODERATE BLOOD LOSS (30-45%)	SEVERE BLOOD LOSS (>45%)
Cardiovascular	Increased heart rate; weak, thready peripheral pulses; normal systolic blood pressure; normal pulse pressure	Markedly increased heart rate; weak, thready central pulses; peripheral pulses absent; low normal systolic blood pressure	Tachycardia followed by bradycardia; central pulses very weak or absent; peripheral pulses absent; hypotension; diastolic blood pressure may be undetectable
Central nervous system	Anxiety; irritability; confusion	Lethargy; dulled response to pain	Coma
Skin	Cool, mottled; capillary refill prolonged	Cyanotic; capillary refill markedly prolonged	Pale and cold
Urine output	Low to very low	Minimal	None

Adapted from American College of Surgeons Committee on Trauma: Advanced trauma life support for doctors: student course manual, *Chicago, 2008, American College of Surgeons, p. 234.*

cutdown (e.g., in the saphenous vein). Ultrasonography can facilitate central venous catheter placement.

Aggressive, intravenous fluid resuscitation is essential early in shock to prevent further deterioration. Isotonic crystalloid solution, such as lactated Ringer injection or normal saline (20 mL/kg), should be infused rapidly. No consensus exists to support the routine use of colloid or hypertonic saline solution for shock (see Chapter 70). When necessary, repeated crystalloid boluses should be given. Most children are stabilized with administration of crystalloid solution alone. However, if the patient remains in shock after boluses totaling 40-60 mL/kg of crystalloid, then 10-15 mL/kg of cross-matched, packed red blood cells should be transfused. Although less desirable, type-specific or O-negative cells can be substituted pending availability of cross-matched blood. When shock persists despite these measures, surgery to stop internal hemorrhage is usually indicated.

Neurologic Deficit

Neurologic status is briefly assessed by determining the level of consciousness and evaluating pupil size and reactivity. The level of consciousness can be classified using the mnemonic AVPU: Alert, responsive to Verbal commands, responsive to Painful stimuli, or Unresponsive.

Head injuries account for at least 75% of pediatric blunt trauma deaths. Primary direct cerebral injury occurs within seconds of the event and is irreversible. Secondary injury is caused by subsequent anoxia or ischemia. The goal is to minimize secondary injury by ensuring adequate oxygenation, ventilation, and perfusion, and maintaining normal intracranial pressure (ICP). A child with severe neurologic impairment—i.e., with a Glasgow Coma Scale (GCS; see Table 67-3 in Chapter 67) score of 8 or less—should be intubated.

Signs of increased ICP, including progressive neurologic deterioration and evidence of transtentorial herniation, must be treated immediately (see Chapter 68). Hyperventilation lowers Pa_{CO_2}, resulting in cerebral vasoconstriction, reduced cerebral blood flow, and decreased ICP. Brief hyperventilation remains an immediate option for patients with acute increases in ICP. Prophylactic hyperventilation or vigorous or prolonged hyperventilation is not recommended, because the consequent vasoconstriction may excessively decrease cerebral perfusion and oxygenation. Mannitol lowers ICP and may improve survival. Because mannitol acts via osmotic diuresis, it can exacerbate hypovolemia and must be used cautiously. Hypertonic saline may be a useful agent for control of increased ICP in patients with severe head injury and may possibly decrease mortality when compared with mannitol. Neurosurgical consultation is mandatory. If signs of increased ICP persist, the neurosurgeon must decide whether to operate emergently.

Exposure and Environmental Control

All clothing should be cut away to reveal any injuries. Cutting is quickest and minimizes unnecessary patient movement.

Children often arrive mildly hypothermic because of their higher body surface area : mass ratios. They can be warmed with use of radiant heat as well as heated blankets and intravenous fluids.

SECONDARY SURVEY

During the secondary survey, the physician completes a detailed, head-to-toe physical examination.

Head Trauma

A GCS or Pediatric GCS score (see Table 67-3 in Chapter 67) should be assigned to every child with significant head trauma. This scale assesses eye opening and motor and verbal responses. In the Pediatric GCS, the verbal score is modified for age. The GCS helps categorize neurologic disability, and serial measurements identify improvement or deterioration over time. Patients with low scores 6-24 hr after injuries have poorer prognoses.

In the ED, CT scanning of the head without a contrast agent has become standard to determine the type of injury in patients with concerning findings. Diffuse cerebral injury with edema is a common and serious finding on CT scan in severely brain-injured children. Focal evacuable hemorrhagic lesions (e.g., epidural hematoma) occur less commonly but may require immediate neurosurgical intervention (Fig. 72-3).

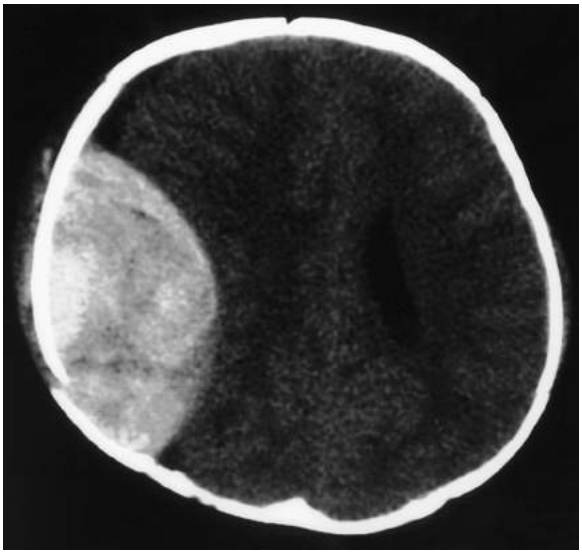


Figure 72-3 According to the history provided, the 7-month-old girl whose head CT scan is shown here did not wake up for her nightly feeding and began vomiting in the morning. The mother's boyfriend reported that the infant had fallen from a chair the previous day. The CT scan shows a large epidural hematoma on the right and marked shift of the midline from right to left. The right lateral ventricle is compressed as a result of the mass effect, and the left lateral ventricle is slightly prominent. The infant underwent emergency surgical evacuation of the epidural hematoma and recovered uneventfully. *(From O'Neill JA Jr:* Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 191.)*

Monitoring of ICP should be strongly considered for children with severe brain injury, particularly for those with a GCS score of 8 or less and abnormal head CT findings (see Chapter 68). An advantage of an intraventricular catheter over an intraparenchymal device is that cerebrospinal fluid can be drained to treat acute increases in ICP. Hypoxia, hypercarbia, hypotension, and hyperthermia must be aggressively managed to prevent secondary brain injury. Cerebral perfusion pressure should be maintained >40 mm Hg at least (although some experts recommend an even higher minimum).

A child with a severe brain injury must be treated aggressively in the ED because it is very difficult to accurately predict long-term neurologic outcome. Compared with adults with similar injuries, children are thought to have better functional outcomes.

Cervical Spine Trauma

Cervical spine injuries occur in <3% of children with blunt trauma—with the risk being substantially higher in those with GCS scores ≤8—but they are associated with significant mortality and morbidity. Bony injuries occur mainly from C1 to C4 in children younger than 8 yr. In older children, they occur equally in the upper and lower cervical spine. The mortality rate is significantly higher in patients with upper cervical spine injuries. *Spinal cord injury without radiographic (vertebral body) abnormalities (SCIWORA) on plain films or CT may be present.* Patients with SCIWORA have neurologic symptoms, and spinal cord abnormalities are nearly always noted on MRI. Approximately 30% of all patients with cervical spine injuries have permanent neurologic deficits.

Evaluation begins with a detailed history and neurologic examination. Identifying the mechanism of injury helps in estimating the likelihood of a cervical spine injury. Both the patient and the paramedic should be asked whether any neurologic symptoms or signs, such as weakness or abnormal sensation, were present before arrival in the

Table 72-7 National Emergency X-Ray Utilization Study (NEXUS) to Rule Out Cervical Spine Injury Following Blunt Trauma

If none of the following are present, the patient is at very low risk for clinically significant cervical spine injury:
- Midline cervical tenderness
- Evidence of intoxication
- Altered level of alertness
- Focal neurologic deficit
- Distracting painful injury

Modified from Hoffman JR, Mower WR, Wolfson AB, et al: Validity of a set of clinical criteria to rule out injury to the cervical spine in patients with blunt trauma, N Engl J Med *343:94-99, 2000, and Viccellio P, Simon H, Pressman BD, et al: A prospective multicenter study of cervical spine injury in children,* Pediatrics *108(2):e20, 2001.*

ED. In a child with neurologic symptoms and normal findings on cervical spine plain radiographs and CT scan, SCIWORA must be considered.

Whenever the history, physical examination, or mechanism of injury suggests a cervical spine injury, radiographs should be obtained after initial resuscitation. The National Emergency X-Radiography Utilization Study (NEXUS) cervical spine rule helps identify low-risk patients who may not require radiographs (Table 72-7). The standard series of plain radiographs includes lateral, anteroposterior, and odontoid views. Some centers use cervical spine CT as the primary diagnostic tool, particularly in patients with abnormal GCS scores and/or significant injury mechanisms, recognizing that CT is more sensitive in detecting bony injury than plain radiographs. CT is also helpful if an odontoid fracture is suspected, because young children typically do not cooperate enough to obtain an "open-mouth" (odontoid) radiographic view. Use of cervical spine CT scan must be balanced with the knowledge that CT exposes thyroid tissue to 90-200 times the amount of radiation from plain films. MRI is indicated in a child with suspected SCIWORA and may also be useful in the evaluation of children who remain obtunded.

Rapid diagnosis of spinal cord injury is essential. Initiating high-dose intravenous methylprednisolone within 8 hr of spinal cord injury has been shown to improve motor outcome and remains standard therapy.

Thoracic Trauma

Pulmonary contusions occur frequently in young children with blunt chest trauma. A child's chest wall is relatively pliable; therefore, less force is absorbed by the rib cage, and more is transmitted to the lungs. Respiratory distress may be noted initially or may develop during the first 24 hr after injury.

Rib fractures result from significant external force. They are noted in patients with more severe injuries and are associated with a higher mortality rate. Flail chest, which is caused by multiple rib fractures, is rare in children. Indications for operative management in thoracic trauma are listed in Table 72-8. Table 72-5 shows the differential diagnosis of immediately life-threatening cardiopulmonary injuries.

Abdominal Trauma

Liver and spleen contusions, hematomas, and lacerations account for the majority of intra-abdominal injuries from blunt trauma. The kidneys, pancreas, and duodenum are relatively spared because of their retroperitoneal location. Pancreatic and duodenal injuries are more common after a bicycle handlebar impact or a direct blow to the abdomen (Table 72-9).

Although a thorough examination for intraabdominal injuries is essential, achieving it often proves difficult. Misleading findings can result from gastric distention after crying or in an uncooperative toddler. Calm reassurance, distraction, and gentle, persistent palpation help with the examination. Important findings include distention, bruises, and tenderness. Specific symptoms and signs give insight into the mechanism of injury and the potential for particular injuries. Pain in the left shoulder may signify splenic trauma. A lap belt mark across the abdomen suggests a bowel or mesentery injury. The presence of certain other injuries, such as lumbar spinal fractures and femur fractures, increases the likelihood of intraabdominal injury.

Table 72-8 Indications for Operation in Thoracic Trauma

THORACOTOMY IMMEDIATELY OR SHORTLY AFTER INJURY
- Massive continuing pneumothorax or large air leak from tracheobronchial injury (cannot expand lung and ventilate)
- Cardiac tamponade
- Open pneumothorax
- Esophageal injury
- Aortic or other vascular injury
- Acute rupture of the diaphragm

DELAYED THORACOTOMY
- Chronic rupture of the diaphragm
- Clotted hemothorax
- Persistent chylothorax
- Traumatic intracardiac defects
- Evacuation of large foreign bodies
- Chronic atelectasis from traumatic bronchial stenosis

Modified from O'Neill JA Jr: Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 157.*

Table 72-9 Frequency of Abdominal Organ Injury by Injury Mechanism

BLUNT		PENETRATING	
Organ	**%**	**Organ**	**%**
Spleen	30	Gastrointestinal tract	70
Liver	28	Liver	27
Kidneys	28	Blood vessels	19
Gastrointestinal tract	14	Kidneys	10
Bladder/urethra/ureters	4	Spleen	9
Pancreas	3	Bladder/urethra/ureters	8
Blood vessels	3	Pancreas	6

Modified from O'Neill JA Jr: Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 159.*

An abdominal CT scan with intravenous contrast medium enhancement rapidly identifies structural and functional abnormalities and is the preferred study in a stable child. It has excellent sensitivity and specificity for splenic (Fig. 72-4), hepatic (Fig. 72-5), and renal injuries, but is not as sensitive for diaphragmatic, pancreatic, or intestinal injuries. Small amounts of free fluid or air or a mesenteric hematoma may be the only sign of an intestinal injury. Administration of an oral contrast agent is not routinely recommended for all abdominal CT scans, but it sometimes aids in identifying an intestinal, especially a duodenal, injury.

Although *focused assessment with sonography in trauma (FAST)* examination helps detect hemoperitoneum, the variably low sensitivity of this test in children suggests that it should not be used to exclude intraabdominal injury in patients with a high pretest probability for injury. Serial FAST exams over time may be used by skilled ultrasonographers to rule out injury in need of intervention. FAST is most useful in patients who have blunt trauma and are hemodynamically unstable or patients who require operative intervention for nonabdominal injuries, because in these cases the performance of a CT scan may not be feasible.

Nonoperative treatment has become standard for hemodynamically stable children with splenic, hepatic, and renal injuries from blunt

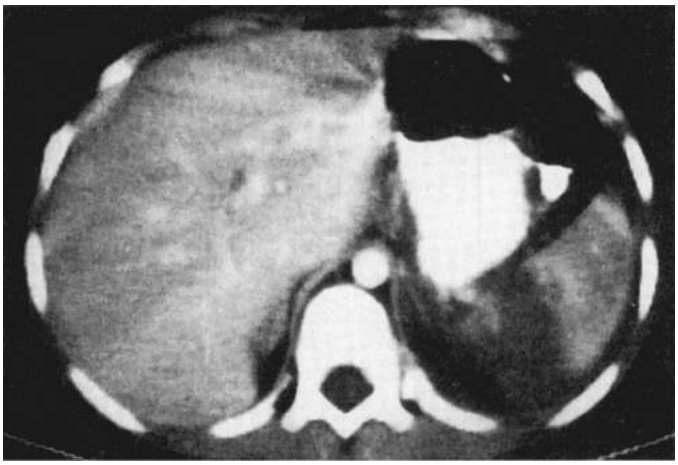


Figure 72-4 CT scan with intravenous and gastrointestinal contrast enhancement shows an isolated splenic rupture that resulted from blunt trauma. This injury responded to nonoperative management, as do most splenic injuries. *(From O'Neill JA Jr:* Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 166.)*

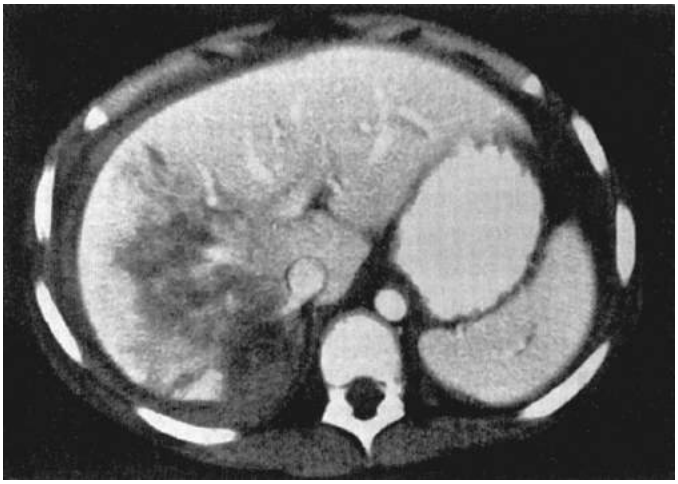


Figure 72-5 CT scan performed after severe blunt injury of the abdomen shows a bursting injury of the liver. The patient was stable, and no operative intervention was required. The decision to perform surgery should be based on the patient's physiologic stability. *(From O'Neill JA Jr:* Principles of pediatric surgery, *ed 2, St. Louis, 2003, Mosby, p. 168.)*

trauma. The majority of such children can be treated nonsurgically. In addition to avoiding perioperative complications, nonoperative treatment decreases the need for blood transfusions and shortens hospital stay. When laparotomy is indicated, splenic repair is preferable to splenectomy.

Pelvic Trauma

Pelvic fractures in children are much less common than in adults, occurring in approximately 4% of children with more severe blunt trauma. Pelvic fractures are typically caused by high forces (e.g., from high-speed motor vehicle crashes or pedestrian impacts) and are often associated with intraabdominal and/or vascular injuries. The pelvis itself forms a ring, and high-force impacts can lead to disruption of this ring. When the ring is disrupted in more than one location, such as the symphysis pubis and the sacroiliac joint, the ring can become unstable and displaced, potentially injuring large pelvic vessels and leading to massive blood loss. Catheter-directed embolization to control bleeding, performed by an interventional radiologist, may be required.

The pelvis should be assessed for stability by means of compression–distraction maneuvers. If instability is noted, immediate external fixation with a pelvis-stabilizing device or a sheet should be applied, and orthopedic consultation sought. A trauma patient with a potential pelvic fracture should receive an anteroposterior pelvic radiograph in the trauma bay, or a CT scan, if highly suspicious. Children without a high-risk clinical finding (i.e., GCS <14; abdominal pain or tenderness, pelvic tenderness, laceration, ecchymosis, or abrasion; positive urinalysis, or femur fracture) or a high-risk mechanism of injury (i.e., unrestrained motor vehicle collision, motor vehicle collision with ejection, motor vehicle collision rollover, auto vs. pedestrian, or auto vs. bicycle) are unlikely to have pelvic fractures, however.

Lower Genitourinary Trauma

The perineum should be inspected, and the stability of the bones of the pelvis assessed. Urethral injuries are more common in males. Findings suggestive of urethral injury include scrotal or labial ecchymoses, blood at the urethral meatus, gross hematuria, and a superiorly positioned prostate on rectal examination (in an adolescent male). Certain pelvic fractures also increase the risk for potential genitourinary injury. Any of these findings is a contraindication to urethral catheter insertion and warrants consultation with a urologist. Retrograde urethrocystogram and CT scan of the pelvis and abdomen are used to determine the extent of injury.

Extremity Trauma

Extremity fractures may initially be missed as clinicians attend to more life-threatening injuries. Thorough examination of the extremities is essential because extremity fractures are among the most frequently overlooked injuries in children with multiple trauma. All limbs should be inspected for deformity, swelling, and bruises; palpated for tenderness; and assessed for active and passive range of motion, sensory function, and perfusion.

Before radiographs are obtained, suspected fractures and dislocations should be immobilized, and an analgesic administered. Splinting a femur fracture helps alleviate pain and may decrease blood loss. An orthopedic surgeon should be consulted immediately to evaluate children with compartment syndrome, neurovascular compromise, open fracture, and most traumatic amputations.

Radiologic and Laboratory Evaluation

Some authorities recommend ordering multiple studies in the ED that include lateral cervical spine, anteroposterior chest, and anteroposterior pelvis radiographs; arterial blood gas analysis; serum lactate determinations; complete blood cell count; electrolyte measurements; blood glucose and blood urea nitrogen measurements; serum creatinine, amylase, and lipase determinations; liver function tests; prothrombin and partial thromboplastin time determinations; blood typing and cross-matching; and urinalysis. One benefit of standardizing the evaluation of patients with major trauma is that fewer decisions need to be made on an individual basis, possibly expediting ED management.

Some of these studies have prognostic importance. A large base deficit is associated with a higher mortality rate, and elevated lactate values correlate with poor prognosis.

There are limitations of standard tests. The lateral cervical spine radiograph can miss clinically significant injuries. Hemoglobin and hematocrit values provide baseline values in the ED, but they may not have yet equilibrated after a hemorrhage. Abnormal liver function test results or elevated serum amylase and lipase values may be noted in patients with significant abdominal trauma, but most patients with significant trauma to the abdomen already have clinical indications for CT scanning or surgery. The majority of previously healthy children have normal coagulation profiles; these may become abnormal after major head trauma. Although routine urinalysis or dipstick urine testing for blood has been recommended for children, other data suggest that this evaluation may be unnecessary in patients without gross hematuria, hypotension, or other associated abdominal injuries.

Table 72-10 Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Brain Injuries After Head Trauma

Children <2 yr are at very low risk of clinically important traumatic brain injury if they have NONE of the following:	*Children 2-18 yr are at very low risk of clinically important traumatic brain injury if they have NONE of the following:*
Severe mechanism of injury	Severe mechanism of injury
History of LOC >5 seconds	History of LOC
GCS ≤14 or other signs of altered mental status	History of vomiting
Not acting normally per parent	GCS ≤14 or other signs of altered mental status
Palpable skull fracture	Severe headache in the ED
Occipital/parietal/temporal scalp hematoma	Signs of basilar skull fracture

Modified from Kuppermann N, Holmes JF, Dayan PS, et al: Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study, Lancet *374:1160–1170, 2009.*

Table 72-11 Prediction Rule for Identification of Children at Very Low Risk of Clinically Important Intraabdominal Injuries After Blunt Trauma

If none of the following are present, the patient is at low risk for clinically significant intraabdominal injury:
GCS <14
Vomiting
Evidence of thoracic wall trauma
Decreased breath sounds
Evidence of abdominal wall trauma or seatbelt sign
Abdominal pain
Abdominal tenderness

Modified from Holmes JF, Lillis K, Monroe D, et al: Identifying children at very low risk of clinically important blunt abdominal injuries, Ann Emerg Med *62(2): 107–116e2, 2013.*

Clinical prediction rules that combine patient history with physical exam findings have been developed to identify those at low risk of injury for whom specific radiographic and laboratory studies may not be necessary. The NEXUS C-spine rule is a sensitive, easily applicable rule that was validated for adults and children, although the younger population was smaller (see Table 72-7). Several clinical prediction rules have been developed to identify children at low risk of traumatic brain injury (Table 72-10). Another clinical prediction rule has been developed to identify children at very low risk of clinically-important intra-abdominal injuries following blunt trauma (Table 72-11). Although this rule has a negative predictive value of 99.9%, it needs to be externally validated before widespread implementation.

Psychological and Social Support

Serious multisystem trauma may result in significant long-term psychological and social difficulties for the child and family, particularly when there is a major head injury. Like adults, children are at risk for depressive symptoms and posttraumatic stress disorder. Caregivers face persistent stress and have been noted to have more psychological symptoms. Psychological and social support, during the resuscitation period and afterwards, is extremely important. Parents often prefer to be offered the choice to be present during resuscitations. A member of the resuscitation team should be made responsible for answering the family's questions and supporting them in the trauma room.

Bibliography is available at Expert Consult.

72.1 Care of Abrasions and Minor Lacerations

Joanna S. Cohen and Bruce L. Klein

LACERATIONS AND CUTS

Lacerations are tears of the skin caused by blunt or shearing forces. A cut (or a stab), in contrast, is an injury inflicted by a sharp object. Although distinguishing between the two can be important for forensic purposes, their evaluation and management are similar. In this chapter, lacerations include cuts and stabs.

Epidemiology

More than half of the 12 million wounds treated annually in U.S. EDs are lacerations. Approximately 30% occur in children younger than 18 yr. Approximately 2% of pediatric office visits are related to wound management.

Evaluation

The history should include the mechanism of injury, the amount of force, and the time the injury occurred. The mechanism helps determine whether there may be foreign material in the wound, which would increase the risk for infection. Particularly in children, it is essential to determine whether the injury was inflicted intentionally. If nonaccidental trauma is suspected, state or local child protective services agency should be notified. The type of force causing the laceration also influences the risk of infection, as a significant crush injury is more likely to become infected than a shearing one. Blunt injury, such as bumping the head, is a common cause of lacerations in children and is less likely to become infected. Theoretically, the amount of bacteria in the wound should increase exponentially with the time from injury to repair; however, the length of time that results in a clinically significant increase in wound infection is unclear. Older wounds may require delayed primary closure or healing by secondary intention. The patient or parent should be asked about any special host factors that may predispose to infection or impede healing, such as diabetes, malnutrition, obesity, and steroid therapy, as well as immunization status, with particular attention to tetanus administration.

On exam, the provider should note the size and depth of the wound, as well as any associated vascular, neurologic, tendon, or other tissue injury. The laceration's location also is important with regard to both the risk for infection and the cosmetic outcome. Compared with lacerations in adults, those in children occur more commonly on the face and scalp and less commonly on the upper extremities. Because the face and scalp are more vascular, wounds located there are less likely to become infected. Lacerations overlying joints are more likely to develop wider scars as a result of tension during healing.

Treatment

The goals of treatment are to establish hemostasis, minimize the risk of infection, restore skin and underlying tissue integrity, and produce the most functionally and cosmetically acceptable result possible. Complications of wounds, including infection, hypertrophic scar formation, and functional limitation occur in 8% of children.

Any significant bleeding must be controlled (with external pressure usually) before a thorough evaluation of the wound can occur. *If there is a skin flap, it should be returned to its original position before application of pressure.* A tourniquet may need to be applied if bleeding cannot be controlled with direct pressure. Clothing over the injury should be removed to minimize wound contamination. Jewelry encircling an injured extremity should be removed to prevent the jewelry from forming a constricting band when the extremity swells.

It is best to administer a local anesthetic early, before exploration and more meticulous cleansing of the wound. This anesthetic can be applied topically (e.g., lidocaine, epinephrine, and tetracaine gel) or infiltrated locally or as a regional nerve block (e.g., lidocaine or bupivacaine), depending on the location of the laceration and the complexity of the repair. Pain from lidocaine infusion can be reduced by buffering the lidocaine with sodium bicarbonate. Sometimes

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nonpharmacologic or additional pharmacologic methods of analgesia and anxiolysis are required for a young, frightened, or uncooperative child. The wound should be examined under proper light to enable identification of foreign bodies or damage to vessels, nerves, or tendons.

Many lacerations, especially heavily contaminated ones, benefit from irrigation, with either water or sterile saline, to reduce the risk of infection. It is important to recognize that many traumatic lacerations treated in the ED or office are only minimally contaminated, containing less than 10^2 bacterial colonies. In fact, in one of the few human studies on irrigation, irrigation did not decrease the infection rate of minimally contaminated scalp or facial lacerations in patients who presented to an ED within 6 hr of injury. Another concern is that higher-pressure irrigation may actually increase tissue damage, making the wound and adjacent tissue more susceptible to infection and delaying healing. These caveats notwithstanding, irrigation has benefits, although which technique to use—that is, which device, what size syringe, what size needle, which solution, how much volume, how much pressure—remains to be determined. These features may vary for different types of lacerations. In heavily contaminated wounds, the benefit of higher-pressure irrigation likely outweighs the harm of tissue damage. For heavily contaminated lacerations, a typical recommendation is to use a 35- to 65-mL syringe attached to a plastic splatter shield, or a 19-gauge needle if a splatter shield is unavailable, and to irrigate with approximately 100 mL of solution per centimeter of wound. Conversely, for relatively clean wounds, lower-pressure irrigation minimizes tissue damage, which may be more important for outcome than any decrease in bacterial clearance that may ensue. Debridement of devitalized tissue with higher-pressure irrigation, scrubbing, or surgical excision can also be necessary in certain cases, such as crush injuries.

Most lacerations seen in the pediatric ED or office should be closed primarily. Contraindications to primary closure (e.g., certain bite wounds) do exist (see Chapter 724). Although it is commonly accepted that the time from injury to repair should be as brief as possible to minimize the risk of infection, there is no universally accepted guideline as to what length of time is too long for primary wound closure. Also, this length of time varies for different types of lacerations. A prudent recommendation is that higher-risk wounds should be closed within 6 hr at most after the injury but that some low-risk wounds (e.g., clean facial lacerations) may be closed as late as 12-24 hr.

Many lacerations can be closed with simple, interrupted, 4-0, 5-0, or 6-0, nonabsorbable sutures. For lacerations under tension, horizontal or vertical mattress sutures, which provide added strength and may evert the wound edges better, can be used instead. For lacerations in cosmetically significant areas, a running intradermal stitch may produce a less conspicuous, more aesthetic scar than simple or mattress skin sutures, which can leave unattractive track marks. Deeper lacerations may need repair with an absorbable dermal and/or fascial layer. Other complex lacerations, such as those involving the ear, eyelid, nose, lip, tongue, genitalia, or fingertip, sometimes require more advanced techniques as well as subspecialty consultation.

Staples, topical skin adhesives, and surgical tape are acceptable alternatives to sutures, depending on the laceration's location and the healthcare provider's preference. Staples are particularly useful for lacerations of the scalp, where the appearance of the scar tends to be less important. Topical skin adhesives (octylcyanoacrylates or butylcyanoacrylates) are ideal for linear, relatively superficial lacerations with easily approximated edges that are not under tension. They are particularly good for lacerations located in areas where suture track marks are especially undesirable, or in situations where resources are constrained.

Maintaining a warm, moist, wound environment following repair accelerates wound healing without increasing the risk of infection. A topical antimicrobial ointment (e.g., bacitracin or a bacitracin, neomycin, and polymyxin B combination) and conventional gauze dressing provide such an environment and reduce the infection rate. Compared with conventional dressings, occlusive dressings (hydrocolloids, hydrogels, polyurethane films) may be better at accelerating healing, reducing infection, and decreasing pain but are more expensive. Occlusive dressings that adhere (hydrocolloids or polyurethane films) are impractical for lacerations with protruding sutures. If the laceration overlies or is near a joint, splinting helps limit mobility and can speed healing and minimize dehiscence.

For most routine lacerations evaluated in the ED or office that are repaired early and meticulously, prophylactic systemic antibiotics are unnecessary because they do not decrease the rate of infection. Antibiotic prophylaxis is or may be indicated for human and many animal bites, for open fractures and joints, and for grossly contaminated wounds, as well as for wounds in patients who are immunosuppressed or have prosthetic devices. Tetanus prophylaxis should be administered, if indicated, according to Centers for Disease Control and Prevention guidelines (see Chapter 211).

ABRASIONS

An *abrasion* is a scrape to the epidermis, and sometimes the dermis, that is usually caused by friction of the skin against a rough surface. "Road rash" is a colloquial term for abrasions that result from friction of the skin against pavement. Motor vehicle collisions with pedestrians and cycling accidents are common causes of road rash in children. Road rash can be extensive, involving multiple areas on the body. These abrasions also can be deep, and they often contain embedded debris. A "rug burn" is an abrasion sustained by sliding across a carpet. Some abrasions display specific patterns and are called *imprint abrasions*. Ligature marks are a type of imprint abrasion caused by a rope or cord that has been tied around a part of the body and has rubbed against the skin. These injuries should alert the clinician to the likelihood of nonaccidental (including self-inflicted) trauma.

Treatment

All abrasions should be cleansed thoroughly, and any debris or foreign material removed. If debris is not removed, abnormal skin pigmentation, known as post-traumatic tattooing, can occur and can be difficult to treat. A nonadherent occlusive dressing or a topical antibiotic and conventional dressing should be applied. Tetanus prophylaxis should be administered, if indicated (see Chapter 211). Large and/or deep abrasions that have not healed in a few weeks require consultation with a plastic surgeon for more advanced care.

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Chapter 73

Altitude-Associated Illness in Children (Acute Mountain Sickness)

Susan Niermeyer and Michael Yaron

High-altitude illness represents a spectrum of clinical entities with neurologic and pulmonary manifestations that overlap in their presentations and share common elements of pathophysiology. **Acute mountain sickness (AMS)** is the relatively benign and self-limited presentation, whereas **high-altitude pulmonary edema (HAPE)** and **high-altitude cerebral edema (HACE)** represent the potentially

life-threatening manifestations. Children are at risk of developing these conditions as they travel to high mountainous locations with their families pursuing outdoor recreation, tourism, or relocation to high-altitude communities.

In 1987, it was estimated that more than 1 million visitors of all ages travelled annually to the remote high mountain ranges of Asia, Africa, and South America, and approximately 35 million visitors travelled annually to high-altitude recreation areas in the western United States; today these numbers are likely to be underestimations. Given the large number of families travelling to high-altitude mountain locations worldwide and the potential for 25% of those travelling to even moderate altitudes to develop altitude-related symptoms, this has become a significant public health issue. Significant morbidity among children travelling with their families to high altitude locations warrants improved education of the populations at risk and the clinicians who care for them.

ETIOLOGY

Definitions

The altitude threshold where clinical illness may begin to occur is 1,500 meters (~4,900 ft). At this altitude a mild impairment in oxygen transport begins, yet altitude illness is relatively rare until higher elevations are reached. Children with underlying medical problems that impair oxygen transport may be predisposed to developing altitude illness at these lower levels. At moderate high altitude, 2,500-3,500 meters (~8,000-11,500 feet) arterial oxygen saturation (Sa_{O_2}) is generally well maintained; however, mild tissue hypoxia may occur as a result of low arterial oxygen partial pressure (Pa_{O_2}) and altitude illness becomes common after rapid ascent over 2,500 m. This is the altitude range that most people visit and the elevation of many popular ski resorts in the United States, thus the most common range to find the greatest number of altitude illness cases. Very high altitude, 3,500-5,500 meters (~11,500-18,000 feet) is associated with the most serious altitude illness, as Sa_{O_2} falls below 90%. Here saturations fall on the steep portion of the oxyhemoglobin dissociation curve, and marked desaturation may occur with relatively small increases in altitude. At these heights severe hypoxemia is seen with sleep, exercise and illness. HAPE and HACE are most common in this environment. *Extreme high altitude,* above 5,500 meters (~18,000 feet) generally results in severe altitude illness during acute ascent without supplemental oxygen. Acclimatization at intermediate altitudes is required to reach extreme altitudes. Complete acclimatization is not possible, and long visits in this range result in progressive deterioration.

Environmental Considerations

The partial pressure of oxygen (pO_2) in the atmosphere decreases logarithmically as geographic altitude rises, but oxygen remains a constant 20.93% of the barometric pressure. The degree of hypoxia is related to the geographic altitude and the local variability of barometric pressure. The shape of the earth is slightly flat at the poles and bulging at the equator. The atmospheric envelope that surrounds the earth has a similar shape; thus the barometric pressure and the relative altitude are lower at higher latitudes than at the equator. The atmospheric envelope also develops seasonal variations in its local thickness, resulting in barometric pressures that are lower and relative altitudes that are higher during the winter season. Local weather can also have a significant effect on barometric pressure from day to day. A strong low-pressure front can reduce the barometric pressure 10-20 mm Hg and result in a significant temporary increase (150-500 m) in relative altitude.

GENERAL EFFECTS OF HYPOBARIC HYPOXIA

Arterial oxygen saturation falls with increasing altitude, eventually triggering central chemoreceptor responses to produce hyperventilation in an attempt to normalize oxygen saturation; relative hypoventilation exacerbates the hypoxemia of high-altitude exposure. During sleep, periodic breathing associated with high-altitude exposure may result in periods of apnea, causing further arterial oxygen desaturation. Fluid homeostasis often shifts at altitude, resulting in a generalized fluid retention and redistribution into intracellular and interstitial spaces manifested by peripheral edema, decreased urinary output, and impaired gas exchange.

Acclimatization

Gradual ascents allowing for acclimatization over several weeks have allowed successful summiting of many of the world's highest peaks without supplemental oxygen. Without this gradual approach, rapid exposure to extreme altitude results in loss of consciousness and asphyxia in a matter of minutes. Children may acclimatize at least as well if not better than adults when comparing heart rate and arterial saturation of children 7-9 yr of age to their parents during a slow ascent.

Some of the responses to hypoxia are mediated at the molecular level by hypoxia inducible factor (HIF). This transcriptional activator orchestrates the expression of hundreds of genes in response to both acute and chronic hypoxic conditions. Acclimatization begins at the altitude that causes the oxygen saturation of arterial blood to fall below sea level values. Most healthy, unacclimatized visitors to high altitude will not experience a significant drop in oxygen saturation ($Sa_{O_2} < 90\%$) until they reach elevations above 8,000 feet. Children with preexisting conditions that reduce oxygen transport may have altitude intolerance and hypoxic stress at lower levels. Of particular importance are both acute and chronic cardiac and respiratory illnesses. An individual's inherent ability to acclimatize is also important. Some acclimatize easily without developing clinical symptoms, others may transiently develop AMS during acclimatization, and a few have marked reactions to altitude exposure, fail to acclimatize, and develop severe altitude illness. Previous successful acclimatization may be predictive of future responses for adults in similar conditions but may not be the case for children.

The most important response to acute hypoxia is an increase in minute ventilation. Peripheral chemoreceptors in the carotid bodies respond to hypoxia by signaling the respiratory control center in the medulla to increase ventilation. This decreases alveolar carbon dioxide partial pressure resulting in a corresponding increase of alveolar oxygen tension and arterial oxygenation. This increased ventilation known as the **hypoxic ventilatory response (HVR)**, varies in magnitude among individuals, may be genetically predetermined, and is related to the ability to acclimatize. A low HVR and relative hypoventilation are implicated in the pathogenesis of both AMS and HAPE, whereas a strong HVR enhances acclimatization. As ventilation increases, a respiratory alkalosis occurs, exerting negative feedback on central respiratory control, limiting further ventilation increase. The kidneys excrete bicarbonate in an effort to compensate for the alkalosis. As the pH normalizes, ventilation rises slowly, reaching a maximum after 4-7 days. *This process is enhanced by acetazolamide, which induces a bicarbonate diuresis.*

Increased sympathetic activity and catecholamine release on ascent result in elevation of heart rate, blood pressure, cardiac output, and venous tone. Except at extreme altitudes, acclimatization results in the resting heart rate gradually returning to near sea level values. *Resting relative tachycardia is evidence of poor acclimatization.*

Hematopoietic acclimatization consists of an increase in hemoglobin and the number of red blood cells and increase in 2,3-diphosphoglycerate. After acute ascent, an early increase of up to 15% occurs in hemoglobin concentration primarily from fluid shifting into the extravascular space. Acclimatization leads to an increase in plasma volume and total blood volume. Erythropoietin is secreted in a HIF-mediated response to hypoxemia within hours of ascent, stimulating the production of new red blood cells, which begin to appear in the circulation in 4 or 5 days. Hypoxemia also increase 2,3-diphosphoglycerate, resulting in a rightward shift of the oxyhemoglobin dissociation curve, favoring release of oxygen from the blood to the tissues. This is counteracted by the leftward shift of the oxyhemoglobin dissociation curve caused by the respiratory alkalosis from hyperventilation. The result is a net null change in the oxyhemoglobin curve and an increase in oxygen-hemoglobin binding in the lung, raising Sa_{O_2}. Climbers at extreme altitude respond with marked hyperventilation, alkalosis and leftward shift; this leftward shift favors oxygen loading in a hypoxic environment and increases Sa_{O_2}. Some

individuals with mutant hemoglobin and high oxygen-hemoglobin affinity have been found to acclimatize more efficiently at moderate altitudes than their normal counterparts.

ACUTE MOUNTAIN SICKNESS

Epidemiology and Risk Factors

The incidence of high-altitude illness depends on several variables including the rate of ascent, previous altitude exposure, and individual genetic susceptibility. Sleeping altitude, final altitude reached, and duration of stay at altitude are also clear risk factors for AMS development. AMS is very common with rapid ascent. Climbers around the world who ascend quickly (1 or 2 days) from sea level to altitudes of 14,000-20,000 feet have a very high incidence of AMS (27-83%). The rapid ascent profile associated with air travel to high altitude locations also results in high AMS attack rates. Trekkers who fly into the Khumbu region to explore the Mt. Everest area have a higher incidence of AMS (47%) compared with those who walk (23%). Skiers who visit resorts in the western United States from sea level generally fly or drive to the region but sleep at relatively moderate altitudes (6,300-9,700 ft). Among this population, AMS occurs in approximately 25%.

Children have the same incidence of AMS as adults. Individual (genetic) susceptibility for the development of AMS plays a significant role in risk assessment. Most individuals with previous histories of AMS after acute ascent are likely to experience similar symptoms with repeated visits to altitude. While anecdotal clinical experience supports this concept in children, limited data exist regarding recurrent AMS in children. Gender does not affect the incidence of AMS.

Pathophysiology

The symptoms of AMS develop several hours after arrival at high altitude, whereas the development of HAPE and HACE generally requires several days of altitude exposure. Because hypoxemia occurs within minutes of arrival, it cannot be the direct cause of high-altitude illness, but rather the initiating factor.

The clinical manifestations of AMS/HACE are primarily the result of central nervous system dysfunction caused by hemodynamic mechanical factors and biochemical mediators of permeability. The central nervous system (CNS) vasodilatory response to hypoxemia causes an increase in cerebral blood flow and volume. Significant elevation of brain volume is observed in moderate to severe AMS and HACE but has not been demonstrated in mild AMS. Hypoxic alteration of CNS vascular autoregulation and hypertension from exercise may increase pressure transmission to the brain's capillary beds resulting in transcapillary leakage and vasogenic edema. HIF-mediated vascular endothelial growth factor, the inducible form of nitric oxide synthase, reactive cytokines, and free radical formation may increase permeability. Both mechanical and biochemical activation of the trigeminovascular system have been proposed as the cause of high-altitude headache, the primary symptom of AMS. While vasogenic edema has been implicated in severe AMS and HACE, magnetic resonance imaging (MRI) reveals signal changes in subjects with and without clinical AMS.

Many of the responses to hypoxia and altitude exposure occur both in individuals who develop symptoms and those who remain free of AMS. To address the discrepancy in symptomatic illness, the "tight fit" hypothesis was proposed. This theory suggests that the development of AMS/HACE is the result of a lack of intracranial space to accommodate increasing volume from brain swelling and edema that develop at altitude. The adequacy of the intracranial and intraspinal space to buffer changes in brain and cerebrospinal fluid (CSF) volume is the central concept. Buffering occurs as the intracranial CSF is displaced via the foramen magnum into the space available in the spinal canal, followed by increased CSF absorption and decreased CSF production. Individuals with less CSF buffering capacity have less compliance and are hypothesized to become more symptomatic (develop AMS).

Diagnosis

In adults, the symptoms of mild AMS are similar to those of a viral syndrome, an ethanol "hangover," or simple physical exhaustion. To diagnose AMS, an adult must be in the setting of a recent gain in altitude, be at the new altitude for at least several hours, and report a headache *plus* at least 1 of the following symptoms: gastrointestinal upset (anorexia, nausea, or vomiting), general weakness or fatigue, dizziness or lightheadedness, or difficulty sleeping. These symptoms comprise the adult Lake Louise criteria for AMS. The headache may vary from mild to severe; anorexia plus nausea, with or without vomiting, are common. Sleep disturbance caused by periodic breathing is common in all visitors to high altitudes but is exacerbated in the setting of AMS. All the symptoms of AMS can range in severity from mild to incapacitating. Symptoms develop within a few hours after ascent and generally reach maximum severity between 24 and 48 hr, followed by gradual resolution. Most adults become symptom free by the 3rd or 4th day. The vague nature of this presentation has resulted in many misdiagnoses and morbidity among adults. In the setting of recent altitude exposure, these symptoms warrant a presumptive diagnosis of AMS and limitation of further ascent. There are no diagnostic physical signs in cases of mild AMS. Any evidence of CNS dysfunction, such as mild ataxia or altered mentation, is early evidence of HACE. Similarly, while dyspnea on exertion is universal at high altitudes, dyspnea at rest is an early indicator of HAPE.

Among infants and older preverbal children (up to 3 yr of age), AMS is diagnosed using nonverbal criteria. In this age range, AMS is manifested by increased fussiness, decreased playfulness, decreased appetite, and sleep disturbance. In most cases of AMS in very young children, all of these symptoms are present. Fussiness is defined as a state of irritability that is not easily explained by a cause, such as tiredness, wet diaper, hunger, teething, or pain from an injury. Fussy behavior may include crying, restlessness or muscular tension. Decreased playfulness may be profound. Alterations of appetite may progress to frank vomiting. Sleep disturbance can manifest with either increased or decreased sleep when compared to normal patterns. Most often decreased sleep and the inability to nap are noted.

The diagnosis of AMS in older children with early language skills (ages 4-11 yr) may be made with cautious use of the adult Lake Louise criteria. The language used in this adult questionnaire may be too complex and may underestimate AMS if not understood by the child. This is particularly true for questions regarding headache (the key symptom of AMS) and gastrointestinal symptoms. An age-appropriate modified Lake Louise Score for 4-11 yr old children has been proposed and used in the research setting (Fig. 73-1). Evaluating for the presence of headache can be accomplished by asking if the "head hurts" or by using a visual "faces" pain scale. Gastrointestinal symptoms are evaluated by asking children if they are "hungry" rather than trying to evaluate their appetite.

Many of the symptoms manifested by AMS in children may also result from the disruption of normal routine with travel. A change in environment, sleeping accommodation, or eating options can result in a fussy child. The threshold scores for AMS diagnostic criteria are modified to account for these baseline variations. Parents can easily learn to recognize AMS in preverbal children using the Children's Lake Louise Score to alert them to the constellation of alterations in fussiness (headache equivalent), appetite, playfulness and sleep in their young child (see Fig. 73-1). Educating parents to recognize the symptoms of AMS in themselves is also important as an ill parent can indirectly compromise a child's safety.

Other acute illnesses can mimic AMS in young children. It must be emphasized that altered mental status, neurologic abnormalities, breathing difficulty or cyanosis are not part of uncomplicated AMS. **Any of these signs warrant immediate medical attention.** If serious bacterial illness, a surgical condition, or another problem meriting specific intervention is suspected in a child, descent to lower altitude is recommended to eliminate the confounding variable of altitude illness.

Periodic Breathing

Periodic breathing at altitude is common at all ages during sleep, resulting in brief repeated episodes of oxyhemoglobin desaturation. Prepubertal children (9-12 yr old) have similar night-time oxygen

AMOUNT OF UNEXPLAINED FUSSINESS

0 1 2 3 4 5 6

No Fussiness — Intermittent Fussiness — Constant Fussiness When Awake

INTENSITY OF FUSSINESS

0 1 2 3 4 5 6

No Fussiness — Moderate Fussiness — Severe Fussiness When Awake

FUSSINESS SCORE (**FS**) = Amount + Intensity

RATE HOW WELL YOUR CHILD HAS **EATEN** TODAY (**E**)

0—Normal
1—Slightly less than normal
2—Much less than normal
3—Vomiting or not eating

RATE HOW **PLAYFUL** YOUR CHILD IS TODAY (**P**)

0—Normal
1—Playing slightly less
2—Playing much less than normal
3—Not playing

RATE ABILITY OF YOUR CHILD TO **SLEEP** TODAY (**S**)

0—Normal
1—Slightly less or more than normal
2—Much less or more than normal
3—Not able to sleep

CLLS = **FS** + **E** + **P** + **S**

The CLLS must be ≥7 with both the FS ≥4 and E+P+S ≥3 to confirm acute mountain sickness.

Figure 73-1 Children's Lake Louise Score. Fussiness is defined as a state of irritability that is not easily explained by a cause, such as tiredness, hunger, teething or pain from an injury. Fussy behavior may include crying, restlessness, or muscular tension. Please rate your child's typical fussy behavior *during the last 24 hr* without the benefit of your intervention.

desaturations as their parents; they have somewhat more stable breathing patterns with less periodicity. While periodic breathing is not a sign of AMS, the exacerbation of hypoxia during sleep plays a role in AMS development. Newborn infants normally have periodicity in their respiratory pattern, and this periodicity is increased by high-altitude exposure and sleep. Oxygen saturations of awake neonates who are born in Colorado at 3,100 m range from 88-91%. During sleep with increased periodic breathing, oxygen saturation may drop to 81% during the 1st wk of life. The amount and magnitude of respiratory periodicity decreases as the child matures and saturation during sleep increases to 86% after 2 mo. A stable mature pattern is usually reached by 6 mo of age. Preterm babies may demonstrate marked periodicity with prolonged desaturation as a result of their immaturity. Acute ascent with a child born preterm is best delayed until maturity, when normal pulmonary function and respiratory drive can be demonstrated. Parents of normal young babies may become distressed as they note marked periodic breathing patterns in their child after ascent to moderate altitude. Clinicians can reassure parents that this is generally not a precursor of true apnea; however, desaturation can occur with periodic breathing in sleep, especially at higher altitudes.

Management

The management of AMS must include strict adherence to the principle that further ascent to a higher sleeping altitude is contraindicated after the symptoms of altitude illness occur. Halting ascent or activity to allow further acclimatization may reverse the symptoms; however; the ascent exacerbates the underlying pathologic processes and may lead to disastrous results. Stopping further ascent and waiting for acclimatization treats most AMS in 1-4 days. Mild cases of AMS may be treated without descent if monitoring by a reliable caregiver is available. In addition to rest, symptomatic therapy includes analgesics and antiemetics. AMS that becomes worse or does not respond to maintenance of altitude, rest, and pharmacologic intervention mandates descent. Descent (500-1,000 m) is effective treatment for all forms of altitude illness and should be tailored to the individual response. *The presence of neurologic abnormalities (ataxia or altered mentation) or evidence of pulmonary edema (dyspnea at rest) mandates descent because these signs indicate a progression of AMS to severe altitude illness.*

Supplemental oxygen administration relieves AMS symptoms, including small amounts (1-2 L/min) given during sleep. In the wilderness, oxygen tanks are impractically heavy and are usually unavailable in adequate amounts; therefore, oxygen therapy is usually reserved for the more serious manifestations of high-altitude illness. In resort settings, oxygen may be readily available for use in the hotel or condominium, but use in children is often difficult. Hyperbaric therapy that simulates descent is also effective.

Treatment of headache and nausea can be beneficial during the course of mild AMS, and in many cases this may be all that is necessary. Ibuprofen and acetaminophen are useful for the treatment of high-altitude headache; evidence supports this conservative approach in children as well. For nausea and vomiting, ondansetron oral dissolving tablets may be used.

Acetazolamide is a carbonic anhydrase inhibitor that induces a renal bicarbonate diuresis, causing a metabolic acidosis that increases ventilation and arterial oxygenation. This respiratory stimulation improves sleep when the hypoxemia caused by periodic breathing is eradicated by acetazolamide. Acetazolamide accelerates acclimatization and, if

Table 73-1 Medications for Treatment of Altitude-Associated Illness in Children (No Studies in Children for High-Altitude Indications)

MEDICATION	CLASSIFICATION	INDICATION	DOSE AND ROUTE	ADVERSE EFFECTS
Acetazolamide	Carbonic anhydrase inhibitor	AMS prevention*	2.5 mg/kg PO every 12 hours; maximum 125 mg/dose	Collateral effects include paresthesias and taste alteration
		AMS treatment	2.5 mg/kg PO every 12 hours; maximum 250 mg/dose	
Dexamethasone	Steroid	AMS prevention†		Risk of adverse effects precludes prophylactic use
		AMS HACE treatment‡	0.15 mg/kg PO/IM/IV every 6 hr; maximum 4 mg/dose	Hypertension, gastrointestinal hemorrhage, pancreatitis, growth inhibition
Nifedipine	Calcium-channel blocker	HAPE treatment (small children)§	0.5 mg/kg PO every 4-8 hr; maximum 20 mg/dose	Hypotension
		HAPE treatment (>60 kg)§	30 mg SR PO every 12 hr or 20 mg SR PO every 8 hours	
		Reentry HAPE prevention	Same dose as HAPE treatment	
Sildenafil	Phosphodiesterase-5 inhibitor	HAPE¶	0.5 mg/kg/dose PO every 4-8 hr; maximum 50 mg/dose every 8 hr	FDA warning against chronic use in children

*AMS prophylaxis is not routinely recommended in children. It is indicated when rapid ascent profile is unavoidable or previous altitude illness in child about to undergo similar ascent profile. Doses as low as 1.25 mg/kg every 12 hr have been successful in some children.

†Use not warranted due to risk of adverse effects. Use slow graded ascent or acetazolamide.

‡Oxygen and descent are the treatment of choice for severe AMS. If acetazolamide is not tolerated dexamethasone may be used. Oxygen, descent, and dexamethasone should be used in HACE.

§In emergency settings where oxygen and descent are not an option, then nifedipine is indicated.

¶In emergency settings where oxygen and descent are not an option, if nifedipine is not well tolerated, then sildenafil may provide an alternative.

given early in the development of AMS, rapidly resolves symptoms. The dose for children is 2.5 mg/kg/dose given twice daily to a maximum of 250 mg/dose (Table 73-1). Treatment for 48 hr is usually adequate for resolution of symptoms.

The most common adverse reactions to acetazolamide in adults include paresthesias, polyuria, and taste alterations. Less common reactions include nausea, drowsiness, tinnitus, transient myopia, and, rarely, rash. Acetazolamide is a nonantibiotic sulfa compound that carries a low risk of cross-reactivity for individuals with an allergy to sulfa antibiotics. A history of anaphylaxis or severe skin reactions to any sulfa-containing medication contraindicates the use of acetazolamide. Acetazolamide should be avoided in breastfeeding mothers and pregnant women.

Dexamethasone is an effective alternative treatment for AMS in adults. Although dexamethasone can resolve the symptoms of AMS, it does not play a role in acclimatization and symptoms may recur when the treatment is withdrawn. Adverse reactions to dexamethasone of concern in the pediatric population are pancreatitis, pseudotumor cerebri, and interference with normal growth. While these reactions are generally seen with prolonged use, dexamethasone should be avoided in children for prophylaxis and used for treatment only in extreme situations where alternatives such as descent or oxygen therapy are unavailable. The dosage of dexamethasone is 0.15 mg/kg/dose orally every 6 hr to a maximum of 4 mg per dose.

Prevention

Individuals who have a known susceptibility to the development of AMS and those for whom slow ascent is impractical may consider prophylactic medication. *Acetazolamide remains the compound of choice for AMS prophylaxis.* Numerous studies have demonstrated its effectiveness in adults, and 125 mg twice daily starting 24 hr before ascent and continuing for the first 2 days at high altitude is recommended. The recommended dosage of acetazolamide for AMS prophylaxis for children is 2.5 mg/kg/dose orally up to 125 mg total given twice daily. Ibuprofen when compared to acetazolamide is equally efficacious in preventing headache in adults. Dexamethasone also prevents AMS. However the potential adverse effects in children preclude its use for prophylaxis in this age group. Recommendations for hyperhydration are frequently given in the lay literature, yet no evidence supports this advice. Drinking excessive amounts of free water may lead to hyponatremia and possibly complicate altitude illness.

HIGH ALTITUDE CEREBRAL EDEMA

Epidemiology and Risk Factors

HACE is rare in children, but it is rapidly fatal if unrecognized. Generally seen in adults with prolonged stays above 3,000 m, HACE is usually associated with concurrent AMS or HAPE, but can occur on its own.

Pathophysiology

HACE is regarded as the extreme expression of the same pathophysiology underlying AMS. In patients with HACE, MRI studies reveal white matter changes consistent with vasogenic edema that correlate with symptoms; evidence of cytotoxic edema has also been described.

Diagnosis

HACE is differentiated from severe AMS by the presence of neurologic signs. Most common are ataxia and altered mental status including confusion, progressive decrease in responsiveness, and eventually coma. Less common are focal cranial nerve palsies, motor and sensory deficits, and seizures. CT imaging is consistent with edema and increased intracranial pressure. MRI shows a high T2 signal in the white matter, specifically in the splenium of the corpus callosum, with diffusion-weighted technique.

Management

Descent remains the most effective treatment for HACE. Supplemental oxygen, if available, is useful especially if descent is not possible or delayed. Portable hyperbaric treatment is beneficial but its use should not delay descent if feasible. Dexamethasone should be administered at a dose of 0.15 mg/kg per dose given orally every 6 hr. The few mild cases of HACE reported in children have recovered with dexamethasone and descent.

HIGH ALTITUDE PULMONARY EDEMA

Epidemiology and Risk Factors

HAPE is a *noncardiogenic pulmonary edema* characterized by extravasation of intravascular fluid into the extravascular space of the lung.

HAPE generally occurs in the setting of recent ascent, most often at altitudes above 2,500 m, but in some cases at altitudes as low as 1,740 m. Among children, HAPE occurs in 2 distinct settings. **Type I HAPE** (or simply HAPE) occurs in a child who resides at low altitude who travels to high altitude. **Type II HAPE** (also termed reentry HAPE or reascent HAPE) affects children who reside at high altitude but become ill on their return home after descent to lower altitudes. HAPE may also occur in children who develop acute respiratory illnesses that exacerbate hypoxia at high altitude. Fatal outcomes of HAPE in children have been reported. Most mild and moderate cases resolve without difficulty, however if unrecognized and untreated, rapid progression to death can occur, especially when infection or cardiac conditions complicate the illness.

The incidence of HAPE is highly variable, as it depends not only on the altitude attained, but also the speed of ascent and prior history of HAPE. HAPE is significantly less common than AMS and its incidence in children resident at low altitude appears to parallel that among low-altitude-resident adults. HAPE affects male and female children more equally than adults, among whom the observed male predominance appears due to strenuous sport activities and military assignments. The occurrence and even the pathophysiology of HAPE may vary by population and genetic background. Individuals of Tibetan ancestry, resident on the Himalayan plateau and having minimal admixture with other populations, represent the extreme of adaptation to high altitude and rarely experience HAPE. Other native populations residing at high altitude, such as Andeans, do not appear to be protected from HAPE, and certain populations may have genetic polymorphisms associated with pulmonary edema. A number of conditions may predispose a child to HAPE (Table 73-2). Preexisting viral respiratory infections have been linked to HAPE, especially in children. Cardiorespiratory conditions associated with pulmonary hypertension, such as atrial and ventricular septal defects, pulmonary vein stenosis, congenital absence of a pulmonary artery, and obstructive sleep apnea also predispose to HAPE. Down syndrome is also a risk factor for HAPE development, as are previously repaired congenital heart defects and the presence of hypoplastic lungs. Undiagnosed structural cardiopulmonary abnormalities may result in severe hypoxia and/or altitude illness once ascent occurs.

Table 73-2 Conditions Associated with Increased Risk of HAPE

Environmental
Ascent above 2,500 m
Rapid rate of ascent (generally >1,000 m per day)
Cold exposure
Cardiac
Anomalies causing increased pulmonary blood flow or increased pulmonary arterial pressure
Ventricular septal defect, atrial septal defect, patent foramen ovale, patent ductus arteriosus
Anomalous pulmonary venous return or pulmonary vein stenosis
Unilateral absent pulmonary artery or isolated pulmonary artery of ductal origin
Coarctation of the aorta
Congestive heart failure
Pulmonary
Chronic lung disease
Bronchopulmonary dysplasia
Pulmonary hypoplasia
Supplemental oxygen requirement at sea level
Pulmonary hypertension
Perinatal respiratory distress
Persistent pulmonary hypertension of the newborn
Perinatal asphyxia or depression
Sleep apnea
Infectious
Upper respiratory tract infection
Bronchitis/bronchiolitis
Pneumonitis
Otitis media
Pharmacologic
Any medication causing central nervous system and respiratory depression
Alcohol
Sympathomimetics
Systemic
Down syndrome (trisomy 21)
History of premature birth or low birthweight

Physiology

Alveolar hypoxia results in vasoconstriction of pulmonary arterioles just proximal to the alveolar capillary bed. Hypoxic pulmonary vasoconstriction is a normal physiologic response to optimize ventilation/perfusion ($\dot{V}/\dot{Q}$) matching by redistributing regional pulmonary blood flow to areas of highest ventilation, thereby optimizing arterial oxygenation. Under conditions that result in widespread alveolar hypoxia, extensive pulmonary vasoconstriction will lead to significant elevations in pulmonary arterial pressure; uneven pulmonary vasoconstriction can result in localized overperfusion, increased capillary pressures, distention, and leakage in the remaining vessels. This explains the patchy and heterogeneous edema that is classically observed in HAPE. The combination of pulmonary hypertension and uneven pulmonary vasoconstriction appears to be necessary in the pathogenesis of HAPE. Children and adolescents acutely exposed to high-altitude hypoxia demonstrated pulmonary hypertension, with increases in pulmonary artery pressure inversely related to age. Once the vascular leak occurs and alveolar fluid accumulates, a defect in transepithelial sodium transport impairs the clearance of alveolar fluid and contributes to HAPE.

Diagnosis

The diagnosis of HAPE is based on clinical findings and their evolution in the context of recent ascent from lower elevation. There is no single diagnostic test or constellation of laboratory findings. Symptoms commonly develop within 24-96 hr, and onset of symptoms often occurs during the first or second night at altitude when hypoxia may be exacerbated during sleep. HAPE generally is not observed beyond 5 days after ascent to altitude (unless additional ascent occurs) because pulmonary vascular remodeling and acclimatization have taken place. The minimum criteria to diagnose HAPE include: recent exposure to altitude, dyspnea at rest, radiographic evidence of alveolar infiltrates, and near-complete resolution of both clinical and radiographic signs within 48 hr after descent or institution of oxygen therapy. Portable ultrasound has been shown useful to diagnose HAPE through the finding of "comet tails," artifacts created by microreflections of the ultrasound beam within interlobular septae thickened by interstitial and/or alveolar edema.

The symptoms of AMS and HAPE show considerable overlap, and AMS may precede the development of HAPE in approximately half of patients. Frequently patients first exhibit general malaise that may progress to more specific signs of dyspnea at rest, then cardiopulmonary distress. Young children may show agitation and general debility. Older children may complain of headache, and children of all ages frequently experience nausea and vomiting. Cough is a common pulmonary sign. Dyspnea at rest, orthopnea, cyanosis, tachycardia, and chest pain herald worsening compromise, which may advance within hours to production of pink-tinged sputum.

Findings on physical exam frequently are less severe than a patient's chest radiograph and the hypoxemia on pulse oximetry would predict. Children often appear pale, with or without visible cyanosis. Low-grade fever (<38.5°C [101.3°F]) is common and respiratory rate is generally increased. Auscultation typically reveals rales, usually greater in the right lung than the left on presentation. The radiographic pattern of pulmonary edema can be highly variable, from patchy and peripheral to more homogeneous in severe cases (Fig. 73-2). Often, the right lung shows more radiographic changes of edema than the left. Cardiomegaly is an uncommon finding, but peribronchial and perivascular cuffing are frequent, as well as enlargement of the pulmonary artery

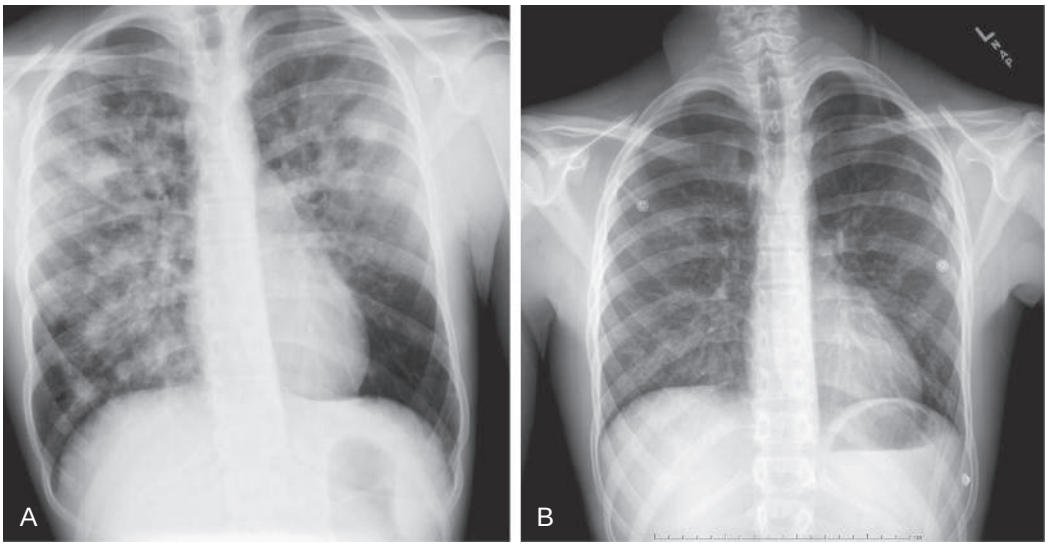

Figure 73-2 AMS and HAPE. A healthy 15 yr old male flew from Buffalo, NY, to Denver, CO, and immediately drove with his school group from the airport to a ski resort at 9,300 feet in the Rocky Mountains. The following day he felt dizzy and complained of headache. Symptoms of headache and dizziness continued along with emesis daily for 2 days. A snowboarding coach brought the patient to the local emergency facility the next day because of dyspnea, cough, headache, emesis, and fatigue. Pulse oximetry showed an arterial saturation of 51%. Chest x-ray showed diffuse pulmonary edema *(A)*. The patient was transported to Denver (5,280 feet) by ambulance with 15 L/min oxygen via a nonrebreathing mask. Saturations improved with descent and were 94% on arrival at the Children's Hospital Colorado emergency department. Breath sounds remained coarse and the patient was tachycardic and tachypneic. Oxygen flow was weaned to 1 L/min shortly after admission. Two days after presentation, lung exam was improved, without crackles. Repeat chest x-ray showed clearing of edema pattern *(B)*. The patient maintained adequate saturations without supplemental oxygen and was discharged. *(Courtesy of the Department of Radiology, Children's Hospital of Colorado.)*

silhouette and dilation of more peripheral pulmonary arteries. Significant arterial oxygen desaturation, as measured by pulse oximetry, is a consistent finding, with saturations frequently below 75%. A complete blood count often reveals a leukocytosis with a left shift of the granulocyte series.

The **differential diagnosis** of HAPE includes pneumonia, bronchitis/bronchiolitis, asthma, and other forms of cardiogenic and noncardiogenic pulmonary edema as well as pulmonary embolism. HAPE is most frequently misdiagnosed as pneumonia or a viral respiratory illness, especially when suspicion of altitude-associated pathology is not appropriately high. The presenting signs of cough, dyspnea, and orthopnea, follow by sputum production can easily be misinterpreted as pneumonia, an impression that is reinforced by the frequent accompaniment of low-grade fever. Respiratory viral infections increase the risk of developing HAPE, which may lead to further confusion in diagnosis.

Complications of HAPE in children often relate to underlying, sometimes undiagnosed, cardiopulmonary pathology or coexisting viral infections which potentiate the severity of pulmonary edema and pulmonary hypertension. Acute altitude exposure in such circumstances may lead to severe presentations that progress rapidly to extreme hypoxemia or cardiac failure and death. Children with trisomy 21, with or without structural cardiac anomalies, show increased susceptibility to HAPE and rapid symptom progression. Neonatal respiratory distress with pulmonary hypertension has been linked to exaggerated hypoxic pulmonary vasoreactivity in early adulthood and thereby a theoretical predisposition to HAPE. Other conditions related to pulmonary overcirculation (atrial and ventricular septal defects, patent foramen ovale, patent ductus arteriosus) small cross-sectional area of the pulmonary vascular bed (unilateral absent pulmonary artery, pulmonary hypoplasia), obstruction to pulmonary venous return (total anomalous pulmonary venous return, pulmonary vein stenosis), or left-sided obstruction (coarctation of the aorta) potentiate HAPE. Inflammatory processes, such as viral infection, predispose to HAPE and may worsen hypoxemia. Infection with respiratory syncytial virus, in particular, may trigger severe pulmonary hypertension.

Management

Descent with supplemental oxygen is the treatment of choice for HAPE in children. When feasible, or in the absence of medical care, rapid descent of at least 500-1,000 m usually results in rapid recovery. As with all altitude illness the magnitude of the descent is tailored to the resolution of symptoms. Oxygen and bed rest without descent can be safe and effective treatment for mild HAPE in children where careful medical observation is available. Mild HAPE in children and young adults at 3,750 m has been treated with bed rest alone, although clinical recovery may be slower compared to treatment with supplemental oxygen.

Supplemental oxygen at altitude is administered at 2-6 L/min by nasal cannula for 48-72 hr to maintain an arterial oxygen saturation of at least 90%. Increasing oxygen saturation above 90% does not result in further reduction in pulmonary artery pressure and does not accelerate edema resolution in adults. Oxygen flow can be weaned with improvement in symptoms and saturations; at flow rates below 2-4 L/min, children may be sufficiently stable and comfortable to continue treatment at home under the monitoring of family. Instructions to avoid physical exertion and exposure to cold should be given to reduce exposure to factors known to elevate pulmonary artery pressure. Most children experience complete resolution of mild HAPE within 24-72 hr of oxygen therapy when treated at altitude of symptom onset.

Pharmacotherapy for pediatric HAPE is rarely needed since oxygen and descent are so effective. In emergency situations without the options of supplemental oxygen or descent, pharmacotherapy is indicated. Nifedipine has been well studied for the treatment of adult HAPE. Extrapolated dosing for children is 0.5 mg/kg/dose given orally every 4-8 hr and titrated to response (maximum 10 mg/dose). Liquid-filled capsules of nifedipine (10 mg/0.34 mL) can be punctured to obtain doses for children less than 20 kg; sustained-release formulations cannot be broken to obtain reliable smaller doses. Patients should be monitored for hypotension during nifedipine administration. Phosphodiesterase type 5 inhibitors have been studied for HAPE prevention in adults. Although sildenafil and tadalafil have shown effectiveness in adults, there is concern around use of this class of agents in young children after the U.S. Food and Drug Administration warning against the use of sildenafil for pediatric pulmonary hypertension

between 1 and 17 yr of age because of an apparent increase in mortality during long-term therapy. Alveolar fluid clearance is upregulated by β-adrenergic agonists and inhaled β-agonists may successfully prevent and treat HAPE.

SPECIAL CONSIDERATIONS

Reentry HAPE

Children residing at high altitude may also experience HAPE of the type termed reentry or reascent HAPE. Reentry HAPE occurs upon reascent to the altitude of residence after a sojourn to low altitude. Although stays at low altitude as short as 24 hr may be sufficient to trigger reentry HAPE, most cases occur after several days at lower altitude. Children between 4 and 18 yr of age are much more likely to develop reentry HAPE than adults.

Reentry HAPE has a significant probability of recurrence and may justify pharmacologic prophylaxis to prevent the accumulated burden of morbidity. Acetazolamide has been used empirically based on its blunting of hypoxic pulmonary vasoconstriction in adults and the potential risk of hypotension and reflex tachycardia with nifedipine. The β_2-adrenergic agonist salmeterol has also been shown effective as prophylaxis in adults. Nifedipine may be a reasonable prophylactic option in older children and adolescents with histories of multiple episodes of HAPE.

Symptomatic High-Altitude Pulmonary Hypertension

Infants and young children resident at high altitude may also experience symptomatic high-altitude pulmonary hypertension, also termed **subacute infantile mountain sickness**. All infants, regardless of altitude of gestation and birth have thickened and muscularized interlobular and intralobular pulmonary arteries and pulmonary artery pressure that are initially near systemic. While muscular regression and fall in pulmonary artery pressure occur rapidly at sea level, infants permanently residing at high altitude demonstrate slowed regression of these characteristics through infancy and even childhood. Certain infants become symptomatic with exaggerated hypoxemia and signs of subacute pulmonary hypertension; these signs correlate with pathologic findings of right ventricular hypertrophy and dilation, increased muscularization of the pulmonary arterial bed and eventual right-sided congestive heart failure. Treatment may require relocation to a lower altitude.

Travel With Young Infants

Newborn infants retain some of the circulatory characteristics of recent fetal life, and these can pose a unique risk for altitude exposure. The fetal circulation has high pulmonary resistance, low pulmonary blood flow and both intra- and extra-cardiac shunts that optimize oxygenation via the placenta instead of the fetal lungs. After birth, a transition begins that closes fetal shunts and establishes normal pulmonary circulation and oxygen transport. **Exposure to marked hypoxia can result in reversion to fetal shunting patterns despite the absence of a placenta.** Normal infants at sea level complete these changes in 4-6 wk, though for infants born at moderate or high altitude, changes may last 3 mo or longer. Travel to high altitude with young infants is generally safe after 4-6 wk when circulatory changes have occurred, breastfeeding is established, and congenital abnormalities may have been detected.

Air travel with young infants frequently raises questions about the effects of exposure to hypobaric hypoxia, as the pressurization of aircraft cabins may vary up to an altitude equivalent of 8,500 feet (approximately 2,600 m). Transoceanic flights are generally not long enough to trigger AMS or HAPE; infants may experience transient desaturation with feedings during flight and likely experience discomfort because of dry air, and stress caused by noise and vibration. Former preterm infants without chronic lung disease who have attained 3 mo corrected gestational age do not appear to experience greater hypoxia during air travel than term infants; infants with more significant lung disease merit hypoxic challenge or provision for supplemental oxygen in flight.

Sickle Trait/Disease

Children with sickle cell disease or sickle trait should avoid travel to altitude, as hypoxemia may trigger sickling and painful crises, including splenic crises. Up to 20% of pediatric patients with sickle cell and sickle-thalassemia disease may experience a vasoocclusive crisis at moderate altitude or in pressurized aircraft. Oxygen is advised for air travelers with known sickle cell disease. Although the majority of children with sickle trait remain asymptomatic, children can experience splenic ischemia or infarction, with severe left upper quadrant pain. Splenic infarction may be more common in nonblack patients (often of Mediterranean origin) with sickle trait.

PREVENTION

A comprehensive approach to travel to high altitude with children should focus on 3 phases: planning the ascent and assessment of risk, recognition and management of altitude-associated illness, and follow-up of any illness relative to future travel or diagnostic testing necessary.

Planning for travel to high altitude with children should consider rate of ascent, formulation of an emergency plan for communication and evacuation, and availability of medical care at the high-altitude destination. Slow ascent with time for acclimatization is the best prevention for all forms of altitude illness. Ideally, the first night should be spent at an altitude no higher than 2,800 m and then 2-3 nights should be spent at 2,500-3,000 m, with a subsequent increase (to a new sleeping altitude) of not more than 500 m each night. One extra night of acclimatization (at the same sleeping altitude) should be taken for every 1,000 m gained. Rapid ascent by air may be avoidable through alternate routes or alternate means of transportation. Difficult descent situations (where further ascent may be necessary before descent is possible) should be avoided with children. The availability of medical care and evacuation from altitude will influence the degree of personal preparation necessary. Widespread coverage by cellular and satellite phone service may give a false sense of security in remote regions where both terrain and weather can limit the arrival of definitive help.

Medical risk assessment encompasses consideration of age, previous altitude-associated illness, and possible predisposing circumstances to altitude illness. Very young infants (younger than 4-6 wk) may not have completed the postnatal circulatory transition and may be more vulnerable to altitude-associated desaturation with periodic breathing, right-to-left shunting across the foramen ovale, and hypoxic pulmonary vasoconstriction. Infants who required supplemental oxygen during the neonatal period, especially for pulmonary hypertension, may be at risk for hypoxemia with prolonged altitude exposure. History and physical exam are useful to identify conditions predisposing to HAPE, including recent viral infections, cardiac malformations, or obstructive sleep apnea. Low-risk children should not need medications for prophylaxis and should use gradual ascent to prevent illness.

Prompt recognition of altitude-associated illness requires awareness of the context in which illness occurs and familiarity with the signs and symptoms. Parents are generally adept at recognizing deviation from baseline behavior of their children. Clinicians should emphasize to parents that breathing difficulty, cyanosis, cough productive of pink-tinged sputum, altered mental status, or neurologic abnormalities are *not* part of uncomplicated AMS, but instead are serious signs of potential HAPE or HACE that deserve immediate medical attention.

Descent is the mainstay of therapy for all forms of altitude-associated illness in children. When descent is not feasible or illness is mild, other therapeutic options may be chosen. Severe altitude illness or death can be avoided in children by adherence to 3 general principles:

1. Recognition of the early signs of altitude illness and willingness by adult caregivers to acknowledge them.
2. No further ascent, especially to sleep at a higher altitude, when experiencing even minor symptoms/signs of altitude illness.
3. Immediate descent if signs/symptoms worsen while resting/receiving treatment at the altitude of onset.

Uncomplicated AMS with full resolution of symptoms upon descent or treatment does not require diagnostic work-up, but may prompt discussion of slower ascent, specific plans for treatment, or even

prophylaxis for future travel. Signs of HAPE or severe hypoxemia in a child disproportionate to the altitude reached should prompt further diagnostic evaluation, including consideration of echocardiography. Underlying cardiac conditions may not be apparent on physical examination at low altitude; cardiac echocardiography or catheterization under conditions of controlled hypoxia or hypoxic exercise may be necessary. Families of HAPE-susceptible children should be advised to avoid travel during or shortly after viral infection.

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Chapter 74

Drowning and Submersion Injury

Derya Caglar and Linda Quan

Drowning is one of the leading causes of childhood morbidity and mortality in the world. Prevention is the most important step to reducing the impact of drowning injury, followed by early initiation of cardiopulmonary resuscitation (CPR) at the scene.

ETIOLOGY

Children are at risk of drowning when they are exposed to a water hazard in their environment. The World Congress of Drowning definition of drowning is: "Drowning is the process of experiencing respiratory impairment from submersion/immersion in liquid." The term *drowning* does not imply the final outcome—death or survival; the outcome should be denoted as fatal or nonfatal drowning. Use of this terminology should improve consistency in reporting and research; the use of confusing descriptive terms such as "near," "wet," "dry," "secondary," "silent," "passive," and "active" should be abandoned. The injury following a drowning event is hypoxia.

EPIDEMIOLOGY

From 2005-2009, an average of 3,880 people per year were victims of fatal drowning and an estimated 5,789 persons were treated in U.S. hospital emergency departments (EDs) for nonfatal drowning. Compared with other types of injuries, drowning has one of the highest case fatality rates. Highest drowning death rates were seen in children ages 1-4 yr and 15-19 yr (2.55 and 1.29/100,000, respectively). In children, drowning is second only to motor vehicle injury as a leading cause of death from unintentional injury in the United States. Pediatric hospitalization rates associated with drowning ranged from 4.7 to 2.4 per 100,000 between 1993 and 2008. Rates of fatal drowning hospitalization declined from 0.5 to 0.3 deaths per 100,000 during the same period. Morbidity following nonfatal drowning is poorly studied.

The risk of drowning and the circumstances leading to it vary by age (Fig. 74-1). Drowning risk also relates to other host factors including male gender, alcohol use, a history of seizures, swimming lessons. Environmental risk factors include exposure to water and varying supervision. These factors are embedded in the context of geography, climate, socioeconomic status, and culture.

Children Younger Than 1 Year of Age

Most (71%) drowning deaths in children younger than 1 yr occur in the bathtub, when an infant is left alone or with an older sibling. Infant tub seats or rings may exacerbate the risk by giving caregivers a false sense of security that the child is safe in the tub. The next major risk to this age group is the large (5-gallon) household bucket, implicated in 16% of infant drowning deaths. These buckets are approximately 30 cm tall and designed to not tip over when half full. The average 9-mo-old child tends to be top-heavy, so can easily fall head first into a half-full bucket, become stuck, and drown within minutes.

Children 1-4 Years of Age

Drowning rates are consistently highest in 1-4 yr old children, likely because of their curious, but unaware, nature, coupled with the rapid progression of their physical capabilities. U.S. rates are highest in the southern regions, in some areas as high as 7.62/100,000, which approaches rates seen in developing countries. A common factor in many of these deaths is a lapse in adult supervision, often <5 min. Most U.S. drownings occur in residential swimming pools. Usually, the child is in the child's own home and the caregiver does not expect the child to be anywhere near the pool.

In rural areas, children in this age group often drown in irrigation ditches or nearby ponds and rivers. The circumstances are similar to those noted previously, in a body of water that is near the house. Drowning is one of the leading causes of farm injury–related deaths in children.

School-age Children

School-age children are at increased risk of drowning in natural bodies of water such as lakes, ponds, rivers, and canals. Although swimming pools account for the majority of nonfatal drownings, open water accounts for a higher death rate from this age group on through adolescence. Unlike for preschool children, swimming or boating activities are important factors in drowning injuries in school-aged children.

Adolescents

The second major peak in drowning death rates occurs in older adolescents, age 15-19 yr. Almost 70% drown in natural freshwater. In this age group particularly, striking disparities in drowning deaths exist in gender and race. Males account for 80% of fatal drownings. The drowning rates for adolescent males are nearly 10 times higher than those for adolescent females. The gender disparity may likely be related to males' greater risk-taking behavior, greater alcohol use, less perception about risks associated with drowning, as well as greater belief in their swimming ability than females. In 2009, as in previous years, drowning rates for black males age 15-19 yr were nearly double those for white males of the same age. Racial differences are only partially explained by socioeconomic status; other cultural factors contribute. Black children are more likely to drown in unguarded public or apartment pools, whereas white children are more likely to drown in private residential pools. Hispanic and foreign-born children have lower rates of drowning than their white counterparts. Differences in exposure to swimming lessons, cultural attitudes, and fears about swimming, as well as experience around water, may contribute to drowning risk.

Underlying Conditions

Several underlying medical conditions are associated with drowning at all ages. A number of studies have found an increased risk, up to 19-fold, in individuals with epilepsy. Drowning risk for children with seizures is greatest in bathtubs and swimming pools. Cardiac etiologies, including arrhythmias, myocarditis, and prolonged QT syndromes have been found in some children who die suddenly in the water (see Chapters 435.5), particularly in those with a family history of syncope, cardiac arrest, prior drowning, or QT prolongation. Some children with long QT syndrome are misdiagnosed as having seizures.

Drowning may also be an intentional injury. A history of the event that changes or is inconsistent with the child's developmental stage is the key to recognition of intentional drowning. Physical examination and other physical injuries rarely provide clues. Child abuse is more often recognized in bathtub-related drownings. Suicide usually occurs in lone swimmers in open water.

Alcohol Use

The use of alcohol and drugs greatly increases the risk of drowning. Of teenagers and adults who die, 30-40% have positive blood alcohol

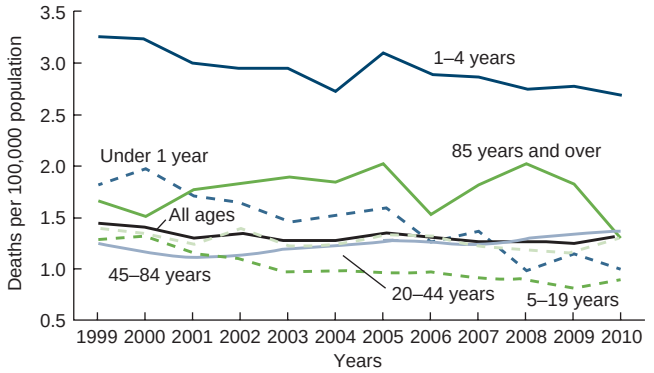

Figure 74-1 Death rates from unintentional drowning, by age group: United States, 1999-2010. A total of 46,419 deaths from unintentional drowning occurred in the United States from 1999 through 2010, an average of 3,868 deaths per year. Source: CDC/NCHS, National Vital Statistics System, Mortality. *(From Xu JQ: Unintentional drowning deaths in the United States, 1999-2010. NCHS Data Brief 149. Hyattsville, MD: National Center for Health Statistics, 2014.)*

levels. Alcohol can impair judgment, leading to riskier behavior, decreased balance and coordination, and blunted ability to self-rescue. Furthermore, an intoxicated adult may provide less-effective supervision of children around water.

Sports and Recreation

Most drowning deaths in the United States occur during recreational activities. Drowning is the leading cause of noncardiac sports-related deaths. Surveys confirm that alcohol use is common during water recreation, as is not using a personal flotation device (PFD) during boating activities. In 2012, the United States Coast Guard reported that almost 90% of those who drowned in boating accidents in the United States were not wearing a PFD.

Global Impact of Drowning

Drowning injury is a significant problem for children worldwide, with the vast majority (96%) of fatalities occurring in low and middle income countries in Asia. Given the relative size of the pediatric population in many of these countries, drowning is one of the leading causes of death globally. A recent UNICEF study estimated that approximately 77,000 children in this region alone died from drowning between 2004 and 2008. This number vastly underestimates the global drowning rate, as many drowning deaths in this region go unreported, with 64-100% of immediate fatalities going unrecognized. In addition, these data exclude any cases of drowning as the result of intentional harm or assault, accidents of watercraft or water transport, and drowning related to forces of nature/cataclysmic storms, which usually claim large numbers of lives per incident; thus true numbers of fatal drownings are likely much higher.

Some patterns of pediatric drowning are similar in all countries. By most accounts, the highest rates are seen in males and in children 1-4 yr old.

Whereas bathtubs and places of recreation (i.e., pools, spas) are significant locations for drowning in U.S. children, these are virtually unreported locations for drownings in developing countries. Instead, the predominant locations are near or around the home, involving bodies of water used for activities of daily living. These include water-collecting systems, ponds, ditches, creeks, and watering holes. In tropical areas, death rates increase during monsoon season, when ditches and holes rapidly fill with rain, and are highest during daylight hours, when caregivers are busy with daily chores.

Drowning during natural disasters such as storms and floods is important in all areas of the world. The largest numbers of reported flood-related deaths occur in developing nations; most are drownings that occur during the storm surge. In the United States and much of Europe, advances in weather monitoring and warning systems have reduced such deaths. U.S. flooding incidents, including hurricanes Katrina and Sandy, showed that drowning caused the most deaths, particularly when people became trapped in their vehicles, were unable or refused to evacuate homes, or attempted to rescue others.

PATHOPHYSIOLOGY

Drowning victims drown silently and do not signal distress or call for help. Vocalization is precluded by efforts to achieve maximal lung volume to keep the head above the water or by aspiration leading to laryngospasm. Young children can struggle for only 10-20 sec and adolescents for 30-60 sec before final submersion. A swimmer in distress is vertical in the water, pumping the arms up and down. This splashing or efforts to breathe are often misconstrued by nearby persons as merely "playing" in the water until the victim sinks.

Anoxic–Ischemic Injury

After experimental submersion, a conscious animal initially panics, trying to surface. During this stage, small amounts of water enter the hypopharynx, triggering laryngospasm. There is a progressive decrease in arterial blood oxygen saturation (Sao_2), and the animal soon loses consciousness from hypoxia. Profound hypoxia and medullary depression lead to terminal apnea. At the same time, the cardiovascular response leads to progressively decreasing cardiac output and oxygen delivery to other organs. By 3-4 min, myocardial hypoxia leads to abrupt circulatory failure. Ineffective cardiac contractions with electrical activity may occur briefly, without effective perfusion (pulseless electrical activity). With early initiation of CPR, spontaneous circulation may initially be successfully restored. The extent of the global hypoxic–ischemic injury determines the final outcome and becomes more evident over subsequent hours.

With modern intensive care, the cardiorespiratory effects of resuscitated drowning victims are usually manageable and are less often the cause of death than irreversible hypoxic–ischemic central nervous system (CNS) injury (see Chapter 68). CNS injury is the most common cause of mortality and long-term morbidity. Although the duration of anoxia before irreversible CNS injury begins is uncertain, it is probably on the order of 3-5 min. Ninety percent of victims with reported submersions of less than 5 min survive and appear normal at hospital discharge.

Several hours after cardiopulmonary arrest, cerebral edema may occur, although the mechanism is not entirely clear. Severe cerebral edema can elevate intracranial pressure (ICP), contributing to further ischemia; intracranial hypertension is an ominous sign of profound CNS damage.

All other organs and tissues may exhibit signs of hypoxic–ischemic injury. In the lung, damage to the pulmonary vascular endothelium can lead to acute respiratory distress syndrome (see Chapter 71). Aspiration may also compound pulmonary injury. Myocardial dysfunction (so-called stunning), arterial hypotension, decreased cardiac output, arrhythmias, and cardiac infarction may also occur. Acute kidney injury, cortical necrosis, and renal failure are common complications of major hypoxic–ischemic events (see Chapter 535.1). Vascular endothelial injury may initiate disseminated intravascular coagulation, hemolysis, and thrombocytopenia. Many factors contribute to gastrointestinal damage; bloody diarrhea with mucosal sloughing may be seen and often portends a fatal injury. Serum levels of hepatic transaminases and pancreatic enzymes are often acutely increased. Violation of normal mucosal protective barriers predisposes the victim to bacteremia and sepsis.

Pulmonary Injury

Pulmonary aspiration (see Chapter 397) occurs in a majority of drowning victims, but the amount of aspirated fluid is usually small. Aspirated water does not obstruct airways and is readily moved into the

pulmonary circulation with positive pressure ventilation. It can wash out surfactant and cause alveolar instability, ventilation-perfusion mismatch, and intrapulmonary shunting. In humans, aspiration of small amounts (1-3 mL/kg) can lead to marked hypoxemia and a 10-40% reduction in lung compliance. The composition of aspirated material can affect the patient's clinical course: Gastric contents, pathogenic organisms, toxic chemicals, and other foreign matter can injure the lung or cause airway obstruction. Clinical management is not significantly different in saltwater and freshwater aspirations, because most victims do not aspirate enough fluid volume to make a clinical difference. A few children may have massive aspiration, increasing the likelihood of severe pulmonary dysfunction.

Cold Water Injury

Drowning should be differentiated from **cold water immersion** injuries, in which the victim remains afloat, keeping the head above water without respiratory impairment in cold waters. The definition of cold water varies from less than 15-20°C (59-68°F).

Heat loss through conduction and convection is more efficient in water than in air. Children are at increased risk for hypothermia because of their relatively high ratio of body surface area to mass, decreased subcutaneous fat, and limited thermogenic capacity. Hypothermia can develop as a result of prolonged surface contact with cold water during immersion, while the airway is above water, or with submersion. Body temperature may also continue to fall as a result of cold air, wet clothes, hypoxia, and hospital transport. Hypothermia in pediatric drowning victims may be observed even after drowning in relatively warm water and in warm climates.

Immersion in cold water has immediate respiratory and cardiovascular effects. Victims experience **cold water shock**, a dynamic series of cardiorespiratory physiologic responses that can cause drowning. In adults, immersion in icy water results in intense involuntary reflex hyperventilation and to a decrease in breath-holding ability to <10 sec, which leads to fluid aspiration. Severe bradycardia, the diving reflex, occurs in adults but is transient and rapidly followed by supraventricular and ectopic tachycardia and hypertension. There is no evidence that the diving reflex has any protective effect.

Even after surviving the chaotic minutes of cold water shock, after an additional 5-10 min of cold water immersion, the victim can become incapacitated. Cooling of large and small muscles disables the victim's ability to grab hold, swim or perform other self-rescue maneuvers. Depending on water and air temperature, insulation, body surface area, thermogenic capacity, physical condition, swimming efforts, or high water flow rates, heat loss with continued immersion can significantly decrease core temperature to hypothermic levels within 30-60 min.

The symptoms and severity of hypothermia are categorized based on body temperature. The victim with mild hypothermia has a temperature of 34-36°C (93.2-96.8°F) with intact thermogenic mechanisms (shivering and nonshivering thermogenesis, vasoconstriction) and active movements. Compensatory mechanisms usually attempt to restore normothermia at body temperatures >32°C (89.6°F). Lower core temperatures lead to impaired cognition, coordination, and muscle strength and with it, less ability to self-rescue. Thermoregulation may fail and spontaneous rewarming will not occur. With moderate hypothermia (30 to <34°C [86 to <93.2°F]), loss of consciousness leads to water aspiration. Progressive bradycardia, impaired myocardial contractility, and loss of vasomotor tone contribute to inadequate perfusion, hypotension, and possible shock. At body temperatures <28°C (82.4°F), extreme bradycardia is usually present with decreases in cardiac output, and the propensity for spontaneous ventricular fibrillation or asystole is high. Central respiratory center depression with moderate to severe hypothermia results in hypoventilation and eventual apnea. A deep coma, with fixed and dilated pupils and absence of reflexes at very low body temperatures (<25-29°C [77-84.2°F]), may give the false appearance of death.

The brain can cool to a neuroprotective level if the cooling process is quick and cardiac output lasts long enough for sufficient heat loss to occur prior to the onset of severe hypoxia. However, if submersion leading to drowning occurs prior to development of a neuroprotective level of hypothermia, severe anoxia devastates tissue organs. The theoretical benefits, implications, and consequences of hypothermia in drowning victims are areas of controversy. Known adverse effects are associated with hypothermia, and these must be balanced against the potential benefits observed in experimental data. One should clearly differentiate among (a) controlled hypothermia, such as that used in the operating room before the onset of hypoxia or ischemia, (b) accidental hypothermia, such as occurs in drowning, which is uncontrolled and variable, with onset during or shortly after hypoxia–ischemia, and (c) therapeutic hypothermia, involving the purposeful and controlled lowering and maintenance of body (or brain) temperature at some time after a hypoxic–ischemic event.

In drowning victims with uncontrolled accidental hypothermia associated with icy water submersion, there are a few case reports of good neurologic recovery after prolonged (10-150 min) cardiopulmonary arrest. Almost all of these rare survivors have been in freezing water (<5°C [41°F]) and had core body temperatures <30°C (86°F), often much lower. Presumably, very rapid and sufficiently deep hypothermia developed in these fortunate survivors before irreversible hypoxic–ischemic injury occurred.

Most often hypothermia is a poor prognostic sign, and a neuroprotective effect has not been demonstrated. In King County, Washington, where the water is cold but rarely icy, 92% of drowning survivors with good neurologic outcomes had initial body temperatures ≥34°C (93.2°F), whereas 61% of those who died or had severe neurologic injury had temperatures <34°C (93.2°F). In another study of comatose drowning patients admitted to pediatric intensive care units (PICUs), 65% of hypothermic patients (body temperature <35°C [95°F]) died, compared with a 27% observed mortality rate in nonhypothermic victims. Similarly, in Finland (where the median water temperature was 16°C [60.9°F]) and in the United States, a beneficial effect of drowning-associated hypothermia was not seen in pediatric submersion victims; submersion duration <10 min was most strongly related to good outcome, not water temperature.

MANAGEMENT

The clinical course and outcome for a submersion victim are primarily determined by the duration of submersion, the speed of the rescue, and the effectiveness of resuscitative efforts. Two groups may be identified on the basis of responsiveness at the scene. The first group consists of children who require minimal resuscitation at the scene and quickly regain spontaneous respiration and consciousness. They have good outcomes and minimal complications. These victims should be transported from the scene to the ED for further evaluation and observation.

The second group comprises children in cardiac arrest who require aggressive or prolonged resuscitation and have a high risk of multiorgan system complications, major neurologic morbidity, or death. Compared with cardiac arrest from other causes, cardiac arrest from drowning has a higher survival rate.

Initial management of drowning victims requires coordinated and experienced prehospital care following the ABCs (airway, breathing, circulation) of emergency resuscitation (see Chapter 67). Cardiopulmonary resuscitation of drowning victims must include providing ventilation. Children with severe hypoxic injury and symptoms often remain comatose and lack brainstem reflexes despite the restoration of oxygenation and circulation. Subsequent ED and PICU care often involve advanced life support strategies and management of multiorgan dysfunction.

Initial Evaluation and Resuscitation

See Chapter 67.

Once a submersion has occurred, immediate institution of CPR efforts at the scene is imperative. The goal is to reverse the anoxia from submersion and limit secondary hypoxic injury after submersion. Every minute that passes without the reestablishment of adequate

breathing and circulation dramatically decreases the possibility of a good outcome. When safe for the victim and the rescuer, institution of in-water resuscitation for nonbreathing victims by trained personnel may improve the likelihood of survival. Victims usually need to be extricated from the water as quickly as possible so that effective CPR can be provided. Common themes in children who have good recovery are a short duration of event and initiation of CPR as soon as possible, prior to arrival of emergency medical services.

Initial resuscitation must focus on rapidly restoring oxygenation, ventilation, and adequate circulation. The airway should be clear of vomitus and foreign material, which may cause obstruction or aspiration. **Abdominal thrusts should not be used** for fluid removal, because many victims have a distended abdomen from swallowed water; abdominal thrusts may increase the risk of regurgitation and aspiration. In cases of suspected airway foreign body, chest compressions or back blows are preferable maneuvers.

The cervical spine should be protected in anyone with potential traumatic neck injury (see Chapters 68 and 72). Cervical spine injury is a rare concomitant injury in drowning; only approximately 0.5% of submersion victims have cervical spine injuries. History of the event and victim age guide suspicion of cervical spine injury. Drowning victims with cervical spine injury are usually preteens or teenagers whose drowning event involved diving, a motorized vehicle crash, a fall from a height, a water sport accident, child abuse, or other clinical signs of serious traumatic injury. In such cases, the neck should be maintained in a neutral position and protected with a well-fitting cervical collar. Patients rescued from unknown circumstances may also warrant cervical spine precautions. In low-impact submersions, spinal injuries are exceedingly rare, and routine spinal immobilization is not warranted.

If the victim has ineffective respiration or apnea, ventilatory support must be initiated immediately (see Chapter 67). Mouth-to-mouth or mouth-to-nose breathing by trained bystanders often restores spontaneous ventilation. As soon as it is available, supplemental oxygen should be administered to all victims. Positive-pressure bag-mask ventilation with 100% inspired oxygen should be instituted in patients with respiratory insufficiency. If apnea, cyanosis, hypoventilation, or labored respiration persists, trained personnel should perform endotracheal tube intubation as soon as possible. Intubation is also indicated to protect the airway in patients with depressed mental status or hemodynamic instability. Hypoxia must be corrected rapidly to optimize the chance of recovery.

Concurrent with securing of airway control, oxygenation, and ventilation, the child's cardiovascular status must be evaluated and treated according to the usual resuscitation guidelines and protocols. Heart rate and rhythm, blood pressure, temperature, and end-organ perfusion require urgent assessment. CPR should be instituted immediately in pulseless, bradycardic, or severely hypotensive victims. Continuous monitoring of the electrocardiogram (ECG) allows appropriate diagnosis and treatment of arrhythmias. Slow capillary refill, cool extremities, and altered mental status are potential indicators of shock (see Chapter 70).

Recognition and treatment of hypothermia are the unique aspects of cardiac resuscitation in the drowning victim (Table 74-1). Core temperature must be evaluated, especially in children, because moderate to severe hypothermia can depress myocardial function and cause arrhythmias. Wet clothing should be removed to prevent ongoing heat losses, however, in the hemodynamically stable patient, rewarming should be initiated in the controlled environment of the receiving ED or PICU. Unstable patients (i.e. arrhythmias) should be warmed to 34°C (93.2°F), taking care not to overheat. Trials are investigating if therapeutic hypothermia might be helpful or if avoiding hyperthermia is actually the key element to long-term neurologic survival.

Often, IV fluids and cardioactive medications are required to improve circulation and perfusion. Vascular access should be established as quickly as possible for the administration of fluids or pressors. Intraosseous catheter placement is a potentially lifesaving vascular access technique that avoids the delay usually associated with multiple attempts to establish IV access in critically ill children. Epinephrine is usually the initial drug of choice in victims with bradyasystolic cardiopulmonary arrest (the IV dose is 0.01 mg/kg of 1 : 10,000 solution given q3-5min as needed). Epinephrine can be given intratracheally (endotracheal tube dose is 0.1-0.2 mg/kg of 1 : 1,000 solution) if no IV access is available. An intravascular bolus of lactated Ringer solution or 0.9% normal saline (10-20 mL/kg) is often used to augment preload; repeated doses may be necessary. Hypotonic or glucose-containing solutions should not be used for intravascular volume administration of drowning victims.

Hospital-Based Evaluation and Treatment

Most pediatric drowning victims should be observed for at least 6-8 hr, even if they are asymptomatic on presentation to the ED. At a minimum, serial monitoring of vital signs (respiratory rate, heart rate, blood pressure, and temperature) and of oxygenation by pulse oximetry, repeated pulmonary examination, and neurologic assessment should be performed in all drowning victims. Other studies may also be warranted, depending on the specific circumstances (possible abuse or neglect, traumatic injuries, or suspected intoxication). Almost half of asymptomatic or minimally symptomatic alert children (those who do not require advanced life support in the prehospital setting or who have an initial ED Glasgow Coma Scale [GCS] score of ≥13) experience some level of respiratory distress or hypoxemia progressing to pulmonary edema, usually during the 1st 4-8 hr after submersion. Most alert children with early respiratory symptoms respond to oxygen and, despite abnormal initial radiographs, become asymptomatic with a return of normal room air Sa_{O_2} and pulmonary examination by 4-6 hr. Subsequent delayed respiratory deterioration is extremely unlikely in such children. Selected low-risk patients who are alert and asymptomatic with normal physical findings and oxygenation levels may be considered for discharge after 6-8 hr of observation, as long as appropriate follow-up can be ensured.

Cardiorespiratory Management

For children who are not in cardiac arrest, the level of respiratory support should be appropriate to the patient's condition and is a continuation of prehospital management. Frequent assessments are required to ensure that adequate oxygenation, ventilation, and airway control are maintained (see Chapter 71). *Hypercapnia should generally be avoided in potentially brain-injured children.* Patients with actual or potential hypoventilation or markedly elevated work of breathing should receive mechanical ventilation to avoid hypercapnia and decrease the energy expenditures of labored respiration.

Measures to stabilize cardiovascular status should also continue. Conditions contributing to myocardial insufficiency include hypoxic–ischemic injury, ongoing hypoxia, hypothermia, acidosis, high airway pressures during mechanical ventilation, alterations of intravascular volume, and electrolyte disorders. Heart failure, shock, arrhythmias, or cardiac arrest may occur. Continuous ECG monitoring is mandatory for recognition and treatment of arrhythmias (see Chapter 435).

The provision of adequate oxygenation and ventilation is a prerequisite to improving myocardial function. Fluid resuscitation and inotropic agents are often necessary to improve heart function and restore tissue perfusion (see Chapter 67). Increasing preload with IV fluids may be beneficial through improvements in stroke volume and cardiac output. Overzealous fluid administration, especially in the presence of poor myocardial function, can worsen pulmonary edema.

For patients with persistent cardiopulmonary arrest on arrival in the ED after *non–icy water* drowning, the decision to withhold or stop resuscitative efforts can be addressed by review of the history and the response to treatment. Because there are reports of good outcome following ongoing CPR in the ED, most drowning victims should be treated aggressively upon presentation. However, for children who do not show ready response to aggressive resuscitative efforts, the need for prolonged ongoing CPR after non–icy water submersion almost invariably predicts death or persistent vegetative state. Consequently, in most cases, discontinuation of CPR in the ED is probably warranted

Table 74-1 Approach to Drowning-Prevention Strategies

	HOME	RECREATION	NEIGHBORHOOD
Water hazards	Swimming pools Ponds Bathtubs Large buckets	Playing in water- swimming, wading Playing near water Being on water—boating	Irrigation ditches Watering holes Water drainage
Common risks	Lapse in supervision Unexpected toddler exposure Delayed discovery of child Reliance on water wings or pool toys Reliance on sibling or bath seat for bathing supervision	Lapse in supervision Change in weather Unfamiliarity with or change(s) in water conditions: • Steep drop-off • Current/tide • Low temperature Alcohol use Peer pressure	Lapse in supervision, particularly when caregiver is socializing Risky behavior when with peers
Prevention strategies	Recognize hazards and risks Provide constant adult supervision around water Install 4-sided, isolation fencing of pools Install rescue equipment and phone at poolside Learn swimming and water survival skills Avoid bath, instead shower, if a child/teen with seizure disorder Learn first aid and CPR	Provide constant adult supervision Swim in lifeguarded areas Know when and how to wear U.S. Coast Guard–approved PFDs Avoid alcohol and other drugs Learn swimming and water survival skills Teach children about water safety Be aware of current weather and water conditions Learn first aid and CPR	Identify hazardous bodies of water Prevent access to water with barriers Provide fenced-in "safe area" for water recreation Provide lifeguarded swim sites Provide access to low cost swim/water survival lessons

for victims of non–icy water submersion who do not respond to resuscitation within 25-30 min. Final decisions regarding whether and when to discontinue resuscitative efforts must be individualized, with the understanding that the possibility of good outcome is generally very low with protracted resuscitation efforts.

Neurologic Management

Drowning victims who present to the hospital awake and alert usually have normal neurologic outcomes. In comatose victims, irreversible CNS injury is highly likely. The most critical and effective neurologic intensive care measures after drowning are rapid restoration and maintenance of adequate oxygenation, ventilation, and perfusion. Core body temperature and glucose management may also be important modulators of neurologic injury after hypoxia–ischemia.

Comatose drowning patients are at risk for intracranial hypertension. There is little evidence that ICP monitoring and therapy to reduce intracranial hypertension improve outcomes for drowning victims. Patients with elevated ICP usually have poor outcomes—either death or persistent vegetative state. Children with normal ICP can also have poor outcomes, although less frequently. Conventional neurologic intensive care therapies, such as fluid restriction, hyperventilation, and administration of muscle relaxants, osmotic agents, diuretics, barbiturates, and steroids, have not been shown to benefit the drowning victim, either individually or in combination. There is some evidence that these therapies may reduce overall mortality but increase the number of survivors with severe neurologic morbidity.

Electroencephalographic monitoring has only limited value in the management of drowning victims and is generally not recommended, except to detect seizures or as an adjunct in the clinical evaluation of brain death (see Chapter 68.1). Seizures should be treated if possible, although they tend to be very refractory. There is no evidence that treatment of seizures after drowning improves outcome. Fosphenytoin or phenytoin (loading dose of 10-20 mg of phenytoin equivalents/kg, followed by maintenance dosing with 5-8 mg of phenytoin equivalents/kg/day in 2-3 divided doses; levels should be monitored) may be considered as an anticonvulsant; it may have some neuroprotective effects and may mitigate neurogenic pulmonary edema. Benzodiazepines, barbiturates, and other anticonvulsants may also have some role in seizure therapy.

With optimal management, many initially comatose children can have impressive neurologic improvement, but usually do so within the 1st 24-72 hr. Unfortunately, almost half of deeply comatose drowning victims admitted to the PICU die of their hypoxic brain injury or survive with severe neurologic damage. Many children become brain dead. Deeply comatose drowning victims who do not show substantial improvement on neurologic examination after 24-72 hr and whose coma cannot be otherwise explained should be seriously considered for limitation or withdrawal of support.

Other Management Issues

A few drowning victims may have traumatic injury (see Chapter 72), especially if their drowning event involved participation in high energy water sports such as personal watercraft, boating, diving, or surfing. A high index of suspicion for such injury is required. Spinal precautions should be maintained in victims with altered mental status and suspected traumatic injury. Significant anemia suggests trauma and internal hemorrhage.

Hypoxic–ischemic injury can have multiple systemic effects, although protracted organ dysfunction is uncommon in the absence of severe CNS injury. Hyperglycemia is associated with a poor outcome in pediatric drowning victims. Its etiology is unclear but it is possibly a stress response.

Manifestations of acute kidney injury may be seen after hypoxic–ischemic injury (see Chapter 535). Diuretics, fluid restriction, and dialysis are occasionally needed to treat fluid overload or electrolyte disturbances; renal function usually normalizes in survivors. Rhabdomyolysis after drowning has been reported.

Profuse bloody diarrhea and mucosal sloughing usually portend a grim prognosis; conservative management includes bowel rest, nasogastric suction, and gastric pH neutralization. Nutritional support for most drowning victims is usually not difficult, because the majority of children either die or recover quickly and resume a normal diet within a few days; enteral tube feeding or parenteral nutrition is occasionally indicated in children who do not recover quickly.

Hyperthermia after drowning or other types of brain injury may increase the risk of mortality and exacerbate hypoxic–ischemic CNS damage. Almost half of drowning victims have a fever during the 1st 48 hr after submersion. Hyperthermia is usually not caused by

infection and resolves without antibiotics in approximately 80% of patients. Generally, prophylactic antibiotics are not recommended. However, there is general consensus that fever or hyperthermia (core body temperature >37.5°C [99.5°F]) in comatose drowning victims resuscitated from cardiac arrest should be prevented at all times in the acute recovery period (at least the 1st 24-48 hr).

Psychiatric and psychosocial sequelae in the family of a pediatric drowning victim are common. Grief, guilt, and anger are common among family members, including siblings. Divorce rates of up to 80% within a few years of the injury have been reported, and parents often report difficulties with employment or substance abuse. Friends and family may blame the parents for the event. Professional counseling, pastoral care, or social work referral should be initiated for drowning victims and their families.

Hypothermia Management

Attention to core body temperature starts in the field and continues during transport and in the hospital. The goal is to prevent or treat moderate or severe hypothermia. Damp clothing should be removed from all drowning victims. Rewarming measures are generally categorized as passive, active external, or active internal (see Chapter 76). Passive rewarming measures can be applied in the prehospital or hospital setting; they include the provision of dry blankets, a warm environment, and protection from further heat loss. They should be instituted as soon as possible for hypothermic drowning victims who have not had a cardiac arrest.

Full CPR with chest compressions is indicated for hypothermic victims if no pulse can be found or if narrow complex QRS activity is absent on ECG (see Chapters 67 and 76). When core body temperature is <30°C (86°F), resuscitative efforts should proceed according to the current American Heart Association guidelines for CPR, but IV medications may be given at a lower frequency in moderate hypothermia because of decreased drug clearance. When ventricular fibrillation is present in severely hypothermic victims (core temperature <30°C [86°F]), defibrillation should be initiated but may not be effective until the core temperature is ≥30°C (86°F), at which time successful defibrillation may be more likely.

Significant controversy surrounds the discontinuation of prolonged resuscitative efforts in hypothermic drowning victims. Body temperature should be taken into account before resuscitative efforts are terminated. Other considerations include whether the victim may have been immersed prior to submerged, whether water was icy or the cooling was very rapid with fast-flowing cold water. Victims with profound hypothermia may appear clinically dead, but full neurologic recovery is possible, although rare. Attempts at lifesaving resuscitation should not be withheld on the basis of initial clinical presentation unless the victim is obviously dead (dependent lividity or rigor mortis). Rewarming efforts should usually be continued until the temperature is 32-34°C (89.6-93.2°F); if the victim continues to have no effective cardiac rhythm and remains unresponsive to aggressive CPR, then resuscitative efforts may be discontinued.

Complete rewarming is not indicated for all arrest victims before resuscitative efforts are abandoned. Discontinuing resuscitation in victims of non–icy water submersion who remain asystolic despite 30 min of CPR is probably warranted. Physicians must use their individual clinical judgment about deciding to stop resuscitative efforts, taking into account the unique circumstances of each incident.

Once a drowning victim has undergone successful CPR after a cardiac arrest, temperature management should be carefully considered, and body temperature should be continuously monitored. In victims in whom resuscitation duration was brief and who are awake soon after resuscitation, attempts to restore and maintain normothermia are warranted. Careful monitoring is necessary to prevent unrecognized worsening hypothermia, which can have untoward consequences.

For drowning victims who remain comatose after successful CPR, more contentious issues include rewarming of hypothermic victims and controlled application of therapeutic hypothermia. Although there is no evidence basis or consensus of opinion, many investigators cautiously recommend that hypothermic drowning victims who remain unresponsive because of hypoxic–ischemic encephalopathy after restoration of adequate spontaneous circulation should not be actively rewarmed to normal body temperatures. Active rewarming should be limited to victims with core body temperatures <32°C (89.6°F), but temperatures 32-37.5°C (89.6-99.5°F) should be allowed without further rewarming efforts.

More controversial is the induction of therapeutic hypothermia in drowning victims who remain comatose because of hypoxic-ischemic encephalopathy after CPR for cardiac arrest. The 2002 World Congress on Drowning recommended that hypothermia (32-34°C [89.6-93.2°F]) be instituted as soon as possible after resuscitation and sustained for 12-24 hr. They recommended that patients be intubated, mechanically ventilated, and treated with sedatives and/or analgesics (with or without neuromuscular blocking agents) as necessary to prevent shivering and maintain hypothermia then gradually rewarmed.

However, a specific recommendation for therapeutic hypothermia, especially in children, is not yet generally accepted. The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (2002) did not recommend therapeutic hypothermia in drowned children resuscitated after cardiopulmonary arrest, citing insufficient evidence and older studies demonstrating a potential deleterious effect in pediatric drowning victims. Several subsequent studies evaluating extracorporeal membrane circulation, rewarming, and therapeutic hypothermia in pediatric and adult drowned patients have shown no significant improvement in neurologic outcome or mortality rates.

PROGNOSIS

The outcomes for drowning victims are remarkably bimodal: The great majority of victims either have a good outcome (intact or mild neurologic sequelae) or a bad outcome (severe neurologic sequelae, persistent vegetative state or death), with very few exhibiting intermediate neurologic injury at hospital discharge. Subsequent evaluation of good outcome survivors may identify significant persistent cognitive deficits. Of hospitalized pediatric drowning victims, 15% die and as many as 20% survive with severe permanent neurologic damage.

Strong predictors of outcome are based on the incident and response to treatment at the scene. Intact survival or mild neurologic impairment has been seen in 91% of children with submersion duration <5 min and in 87% with resuscitation duration <10 min. Children with normal sinus rhythm, reactive pupils, or neurologic responsiveness at the scene virtually always had good outcomes (99%). Poor outcome is highly likely in patients with deep coma, apnea, absence of papillary responses, and hyperglycemia in the ED, with submersion durations >10 min, and with failure of response to CPR given for 25 min. In one comprehensive case series, all children with *resuscitation durations* >25 min either died or had severe neurologic morbidity, and all victims with *submersion durations* >25 min died. Long-term health-related quality of life and school performance in subjects who had received either bystander or emergency medical service personnel initiated CPR was high if their submersion duration was <10 mins. Higher morbidity, mortality, and lower quality of life was reported in those patients with >10 mins submersion durations. In several studies of pediatric drowning, submersion duration was the best predictor of outcome and water temperature was not. However, there are rare case reports of intact recovery following non–icy water drowning with longer submersion or resuscitation duration.

The GCS score has some limited utility in predicting recovery. Children with a score ≥6 on hospital admission generally have a good outcome, whereas those with a score ≤5 have a much higher probability of poor neurologic outcome. Occasionally, children with a GCS score of 3 or 4 in the ED have complete recovery. Improvement in the GCS score during the first several hours of hospitalization may indicate a better prognosis. Overall, early GCS assessments fail to adequately

distinguish children who will survive intact from those with major neurologic injury.

Neurologic examination and progression during the 1st 24-72 hr are the best prognosticators of long-term CNS outcome. Children who regain consciousness within 48-72 hr, even after prolonged resuscitation, are unlikely to have serious neurologic sequelae. In a small series of comatose victims of non–icy water submersion, all survivors with a good outcome had spontaneous purposeful movements and normal brainstem function within 24 hr; good recovery did not occur in any child with abnormal brainstem function or absence of purposeful movements at 24 hr. In another small series of drowning victims who remained unconscious >24 hr and survived for at least 1 yr, 73% remained in a persistent vegetative state and the rest had severe neurologic impairment, had many complications and a high mortality rate: 45% died during the study's 1-yr follow-up period.

In a large retrospective series of 274 pediatric drowning victims, of those with an initial GCS score of 3 in the ED, only 14% survived intact. Almost all, 95%, of victims who demonstrated purposeful neurologic function within 48 hr survived intact and 100% of those whose first purposeful neurologic response occurred within 6 hr survived intact. Laboratory and technologic methods to improve prognostication have not yet proved superior to neurologic examination. Serial neurologic evaluations after CPR should be performed over the ensuing 48-72 hr, with consideration given to limitation or withdrawal of support in patients who do not have significant neurologic recovery, even though this may occur before absolute prognostic certainty is achieved.

PREVENTION

The most effective way to decrease the injury burden of drowning is prevention. Drowning is a multifaceted problem, but several evidence based preventive strategies are effective. The pediatrician has a prime opportunity to identify and inform families at risk of these strategies through anticipatory guidance. In 2010, the American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention revised its policy statement on the prevention of drowning to advocate for more anticipatory guidance regarding the appropriate supervision of children, access to swim lessons, the presence of lifeguards, barriers to swimming pools, and use of PFDs. A family-centered approach to anticipatory guidance for water safety helps explore and identify the water hazards that each family is exposed to in their environment. The practitioner can then discuss the best tools and strategies for prevention that are relevant for the particular family. It is important to identify the risks both in and around the home and in other locations they may frequent, often when vacationing, such as vacation or relatives' homes. For some families the focus may be on bathtubs and bucket safety; for others, home pools or hot tubs may be the major hazards. If the family recreates near or on open water, they also need to learn about safety around boats and open water. In a rural environment, water collection systems and natural bodies of water may pose great risk.

Parents must build layers of water protection around their children. Table 74-1 provides an approach to the hazards and preventive strategies relevant to the most common sources of water involved in childhood drowning. A common preventive strategy for exposure to all water types and all ages is ensuring appropriate supervision. Pediatricians should define for parents what constitutes appropriate supervision at the various developmental levels of childhood. Many parents either underestimate the importance of adequate supervision or are simply unaware of the risks associated with water. Even parents who say that constant supervision is necessary will often admit to brief lapses while their child is alone near water. Parents also overestimate the abilities of older siblings; many bathtub drownings occur when an infant or toddler is left with a child younger than 5 yr.

Supervision of infants and young children means that a responsible adult should be with the child every moment. The caregiver must be alert, must not be consuming alcohol or other drugs or socializing, and must be attentive and focused entirely on watching the child. Even a brief moment of inattention, such as to answer a phone, get a drink, or hold a conversation, can have tragic consequences. If the child does not swim, "touch supervision" is required, meaning that the caregiver should be within arm's reach at all times. Adolescents require active adult supervision and avoidance of alcohol or drug use during water activities. Learning to swim offers another layer of protection. Children may start swim lessons at an early age that are developmentally appropriate and aimed at the individual child's readiness and skill level. Swim lessons are beneficial and to provide some level of protection to young children. A study from Bangladesh, where drowning accounts for 20% of all deaths in children ages 1-4 yr, showed that swim lessons and water safety curricula are cost-effective and led to a decrease in mortality from drowning. As with any other water safety intervention, parents need to know that swimming lessons and acquisition of swim skills cannot be solely relied on to prevent drowning. No child can be "drown-proof." A supervising caretaker should be aware of where and how to get help and know how to safely rescue a child in trouble. Because only those trained in water rescue can safely attempt it, families should be encouraged to swim in designated areas only when and where a lifeguard is on duty.

Children and adolescents should never swim alone regardless of their swimming abilities. Even as they become more independent and participate in recreational activities without their parents, they should be encouraged to seek areas that are watched by lifeguards. Lifeguards rescue more than 100,000 Americans each year from drowning, and probably prevent millions more drownings through verbal warnings and prompt interventions when needed. It is important to emphasize that even if the child is considered a strong swimmer, the ability to swim in a pool does not translate to being safe in open water, where water temperature, currents, and underwater obstacles can present additional and unfamiliar challenges. For swimmers, supervision by lifeguards reduces drowning risk, because lifeguards monitor risk behaviors and are trained in the difficult and potentially dangerous task of rescuing drowning victims.

Two of the preventive strategies listed in Table 74-1 deserve special mention. The most vigorously evaluated and effective drowning intervention applies to swimming pools. Isolation fencing that completely surrounds a pool, with a secure, self-locking gate, reduces the risk of drowning. Guidelines for appropriate fencing, provided by the U.S. Consumer Product Safety Commission, are very specific; they were developed through testing of active toddlers in a gymnastics program on their ability to climb barriers of different materials and heights and recent studies show them to be effective in preventing drowning in young children. In families who have a pool on their property, caregivers often erroneously believe that if a child falls into the water there will be a loud noise or splash to alert them. Sadly, these events are usually silent, delaying timely rescue. This finding highlights the need for a fence that actually separates the pool from the house, not just surrounds the entire property. The use of U.S. Coast Guard–approved lifejackets or PFDs should be advised with all families spending time around open water, not just those who consider themselves boaters. This issue is also particularly important for families who will participate in aquatic activities on a vacation. A PFD should be chosen with respect to the weight of the child and the proposed activity. Young children should wear PFDs that will float their head up. Parents should be urged to wear PFDs, too, as their use is associated with greater use by their children. Toys such as water wings and "floaties" should not be relied upon as drowning prevention measures.

Effective preventive efforts must also consider cultural practices. Different ethnic groups may have certain attitudes, beliefs, dress, or other customs that may affect their water safety. The higher drowning risk of minority children needs to be addressed by community-based prevention programs.

In addition to anticipatory guidance, pediatricians can play an active role in drowning prevention by participating in advocacy efforts to

improve legislation for pool fencing, PFD use, and alcohol consumption in various water activities. Several counties in the United States, Australia, and New Zealand have laws requiring isolation fencing for pools. Their effectiveness has been limited by a lack of enforcement. Similarly, all states have boating-under-the-influence laws but, similarly, rarely enforce them. Furthermore, efforts at the community level may be needed to ensure the availability of swimming lessons for underserved populations and lifeguarded swim areas.

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Chapter 75

Burn Injuries

Alia Y. Antoon and Mary K. Donovan

Burns are a leading cause of unintentional injury in children, second only to motor vehicle crashes. There has been a decline in the incidence of burn injury requiring medical care that has coincided with a stronger focus on burn treatment and prevention, increased fire and burn prevention education, greater availability of regional treatment centers, widespread use of smoke detectors, greater regulation of consumer products and occupational safety, and societal changes such as reductions in smoking and alcohol abuse.

EPIDEMIOLOGY

Approximately 2 million people in the United States require medical care for burn injuries each year. Approximately 50% of these patients are younger than age 5 yr, with an average age of 32 mo. The principal cause of the burn is scald; one of the causes of scald burn is heating liquids in the microwave. The leading cause of burn in children 5-14 yr of age is flame injury. In children ages 5-10 yr, this is usually a result of match play, whereas, for older children, it is usually a result of gasoline ignition. Fires are a major cause of mortality in children, accounting for up to 34% of fatal injuries in those younger than age 16 yr. Scald burns account for 85% of total injuries and are most prevalent in children younger than 4 yr. Although the incidence of hot water scalding has been reduced by legislation requiring new water heaters to be preset at 48.9°C (120°F), scald injury remains the leading cause of hospitalization for burns. Steam inhalation used as a home remedy to treat respiratory infections is another potential cause of burns. Flame burns account for 13%; the remaining are electrical and chemical burns. Clothing ignition events have declined since passage of the Federal Flammable Fabric Act requiring sleepwear to be flame-retardant; however, the U.S. Consumer Product Safety Commission has voted to relax the existing children's sleepwear flammability standard. Polyester is the fabric most resistant to ignition by small flame source. Polyester does burn deeply as it melts, but it self-extinguishes when the flame source is removed. Cotton, on the other hand, continues to burn after the flame source has been removed resulting in large deep burns. Polyester melts downward, sparing the face and respiratory tract; cotton burns upward toward the face. Pellet stove, glass front stoves, and flat top stoves are becoming frequent sources of hand burns in children. Approximately 18% of burns are the result of child abuse (usually scalds), making it important to assess the pattern and site of injury and their consistency with the patient history (see Chapter 40). Friction burns from treadmills are also a problem. Hands are the most commonly injured sites, with deep 2nd-degree friction injury sometimes associated with fractures of the fingers. Anoxia, not the actual burn, is a major cause of morbidity and mortality in house fires.

Review of the history usually shows a common pattern: scald burns to the side of the face, neck, and arm if liquid is pulled from a table or stove; burns in the pant leg area if clothing ignites; burns in a splash pattern from cooking; and burns on the palm of the hand from contact with a hot stove. However, "glove or stocking" burns of the hands and feet, single-area deep burns on the trunk, buttocks, or back, and small, full-thickness burns (cigarette burns) in young children should raise the suspicion of child abuse (see Chapter 40).

Burn care involves a range of activities: prevention, acute care and resuscitation, wound management, pain relief, reconstruction, rehabilitation, and psychosocial adjustment. Children with massive burns require early and appropriate psychological and social support as well as resuscitation. Surgical debridement, wound closure, and rehabilitative efforts should be instituted concurrently to promote optimal rehabilitation. Aggressive surgical removal of devitalized tissue, infection control, and judicious use of antibiotics, as well as early nutrition and cautious use of intubation and mechanical ventilation, are necessary to maximize survival. Children who have sustained burn injuries differ in appearance from their peers, necessitating supportive efforts for reentry to school and social and sporting activities.

PREVENTION

The aim of burn prevention is a continuing reduction in the number of serious burn injuries (Table 75-1). Effective first aid and triage can decrease both the extent (area) and the severity (depth) of injuries. The use of flame-retardant clothing and smoke detectors, control of hot water temperature (thermostat settings) to 48.9°C (120°F) within buildings, and prohibition of cigarette smoking have been partially successful in reducing the incidence of burn injuries. Treatment of children with significant burn injuries in dedicated burn centers facilitates medically effective care, improves survival, and leads to greater cost efficiency. Survival of at least 80% of patients with burns of 90% of the body surface area (BSA) is possible; the overall survival rate of children with burns of all sizes is 99%. Death is more likely in children with irreversible anoxic brain injury sustained at the time of the burn. It is well-known that burns occur in predictable patterns. Seasonal pattern sources include:

Winter
- Glass front fireplaces/pellet stoves and radiators increase hand burns
- Treadmill injuries as more people exercise inside—child imitates adults or young child touches belt

Summer
- Fireworks, sparkler—temperatures reach 537.8°C (1000°F)
- Burn contact with hot grill; hand/feet burn from hot embers
- Lawnmowers

Spring/Fall
- Burning leaves
- Gasoline burns
- Tap water scalds are essentially preventable through a combination of behavioral and environmental changes

Pediatricians can play a major role in preventing the most common burns by educating parents and healthcare providers. Simple, effective, efficient, and cost-effective preventive measures include the use of appropriate clothing and smoke detectors, and the planning of routes for emergency exit from the home. The National Fire Protection Association (NFPA) recommends replacing smoke detector batteries annually and the smoke detector alarm every 10 yr (or earlier, if indicated on the device). Child neglect and abuse must be seriously considered when the history of the injury and the distribution of the burn do not match.

ACUTE CARE, RESUSCITATION, AND ASSESSMENT

Indications for Admission

Burns covering >10% of total BSA, burns associated with smoke inhalation, burns resulting from high-tension (voltage) electrical injuries,

Table 75-1 Burn Prophylaxis
PREVENT FIRES
Install and use smoke detectors
Control the hot water thermostat—in public buildings, the maximum water temperature should be 48.9°C (120°F)
Keep fire, matches, and lighters out of the reach of children
Avoid cigarette smoking, especially in bed
Do not leave lit candles unattended
Use flame retardant–treated clothing
Use caution when cooking, especially with oil
Keep cloth items off heaters
PREVENT INJURY
Roll, but do not run, if clothing catches fire; wrap in a blanket
Practice escape procedures
Crawl beneath smoke if a fire occurs indoors
Use educational materials*

*National Fire Protection Association pamphlets and videos.

Table 75-2 Indications for Hospitalization for Burns
Burns affecting >10% of BSA
Burns >10-20% of BSA in adolescent/adult
3rd-Degree burns
Electrical burns caused by high-tension wires or lightening
Chemical burns
Inhalation injury, regardless of the amount of BSA burned
Inadequate home or social environment
Suspected child abuse or neglect
Burns to the face, hands, feet, perineum, genitals, or major joints
Burns in patients with preexisting medical conditions that may complicate the acute recovery phase
Associated injuries (fractures)
Pregnancy

and burns associated with suspected child abuse or neglect should be treated as emergencies, and the child hospitalized (Table 75-2). Small 1st- and 2nd-degree burns of the hands, feet, face, perineum, and joint surfaces also require admission if close follow-up care is difficult to provide. Children who have been in enclosed-space fires and those who have face and neck burns should be hospitalized for at least 24 hr for observation for signs of central nervous system (CNS) effects of anoxia from carbon monoxide poisoning and pulmonary effects from smoke inhalation.

First Aid Measures

Acute care should include the following measures:

1. Extinguish flames by rolling the child on the ground; cover the child with a blanket, coat, or carpet.
2. After determining that the airway is patent, remove smoldering clothing or clothing saturated with hot liquid. Jewelry, particularly rings and bracelets, should be removed or cut away to prevent constriction and vascular compromise during the edema phase in the 1st 24-72 hr after burn injury.
3. In cases of chemical injury, brush off any remaining chemical, if powdered or solid; then use copious irrigation or wash the affected area with water. Call the local poison control center for the neutralizing agent to treat a chemical ingestion.
4. Cover the burned area with clean, dry sheeting and apply cold (not iced) wet compresses to small injuries. Significant large-burn injury (>15% of BSA) decreases body temperature control and contraindicates the use of cold compresses.
5. If the burn is caused by hot tar, use mineral oil to remove the tar.
6. Administer analgesic medications.

Table 75-3 Acute Treatment of Burns
First aid, including washing of wounds and removal of devitalized tissue
Fluid resuscitation
Provision of energy requirements
Control of pain
Prevention of infection—early excision and grafting
Prevention of excessive metabolic expenditures
Control of bacterial wound flora
Use of biologic and synthetic dressings to close the wound

Emergency Care

Life-support measures are as follows (Table 75-3):

1. Rapidly review the cardiovascular and pulmonary status and document pre-existing or physiologic lesions (asthma, congenital heart disease, renal or hepatic disease).
2. Ensure and maintain an adequate airway and provide humidified oxygen by mask or endotracheal intubation (Fig. 75-1). The latter may be needed in children who have facial burns or a burn sustained in an enclosed space, before facial or laryngeal edema becomes evident. If hypoxia or carbon monoxide poisoning is suspected, 100% oxygen should be used (see Chapters 67 and 71).
3. Children with burns >15% of BSA require intravenous (IV) fluid resuscitation to maintain adequate perfusion. In an emergency situation if IV access is unattainable, an intraosseous line should be placed. When inserting central lines to provide high-volume fluid, special attention should be paid to use a very-small-caliber catheter in small children to avoid injury to the vascular lining, which may predispose to formation of clots. All inhalation injuries, regardless of the extent of BSA burn, require venous access to control fluid intake. All high-tension and electrical injuries require venous access to ensure forced alkaline diuresis in case of muscle injury to avoid myoglobinuric renal damage. Lactated Ringer solution, 10-20 mL/kg/hr (normal saline may be used if lactated Ringer solution is not available), is initially infused until proper fluid replacement can be calculated. Consultation with a specialized burn unit should be made to coordinate fluid therapy, the type of fluid, the preferred formula for calculation, and preferences for the use of colloid agents, particularly if transfer to a burn center is anticipated.
4. Evaluate the child for associated injuries, which are common in patients with a history of high-tension electrical burn, especially if there has also been a fall from a height. Injuries to the spine, bones, and thoracic or intraabdominal organs may occur (see Chapter 72). Cervical spine precautions should be observed until this injury is ruled out. There is a very high risk of cardiac abnormalities, including ventricular tachycardia and ventricular fibrillation, resulting from conductivity of the high electric voltage. Cardiopulmonary resuscitation should be instituted promptly at the scene, and cardiac monitoring should be started upon the patient's arrival at the emergency department (see Chapter 67).
5. Children with burns of >15% of BSA should not receive oral fluids (initially), because gastric distention may develop. These children require insertion of a nasogastric tube in the emergency department to prevent aspiration.
6. A Foley catheter should be inserted to monitor urine output in all children who require IV fluid resuscitation.
7. All wounds should be wrapped with sterile dressings until a decision is made about whether to treat the patient on an outpatient basis or refer the patient to an appropriate facility for treatment.
8. A carbon monoxide measurement (carboxyhemoglobin [HbCO]) should be obtained for fire victims, and 100% oxygen administered until the result is known.

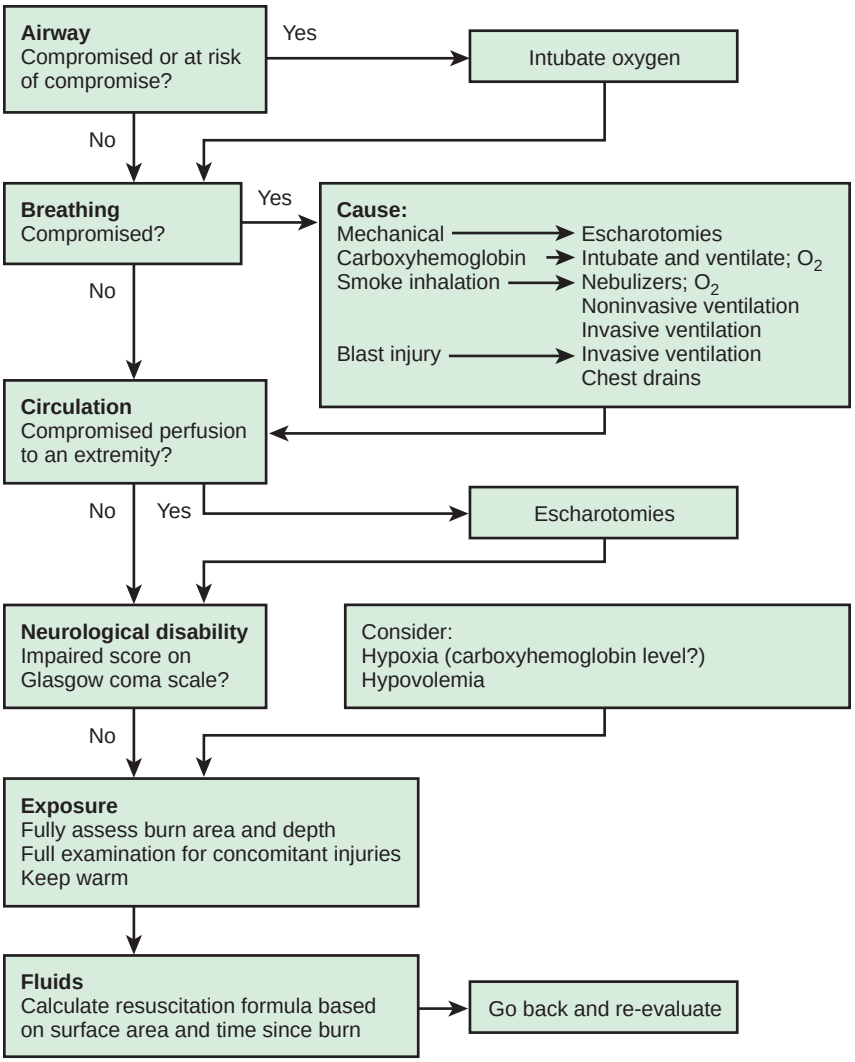

Figure 75-1 Algorithm for the primary survey of a major burn injury. O_2, oxygen. *(From Hettiaratchy S, Papini R: Initial management of a major burn I: overview.* BMJ *328:1555-1557, 2004.)*

9. Review child immunization, burns under 10% BSA do not require tetanus prevention, burns over 10% need tetanus immunization; use diphtheria, tetanus toxoids and acellular pertussis (DTaP) for tetanus prophylaxis for ages <11 yr, and tetanus, diphtheria and pertussis (TdaP) for ages >11 yr (see Chapter 211).

Classification of Burns

Proper triage and treatment of burn injury require assessment of the extent and depth of the injury (Table 75-4 and Fig. 75-2). **First-degree burns** involve only the epidermis and are characterized by swelling, erythema, and pain (similar to mild sunburn). Tissue damage is usually minimal, and there is no blistering. Pain resolves in 48-72 hr; in a small percentage of patients, the damaged epithelium peels off, leaving no residual scars.

A **2nd-degree burn** involves injury to the entire epidermis and a variable portion of the dermal layer (vesicle and blister formation are characteristic). A **superficial** 2nd-degree burn is extremely painful because a large number of remaining viable nerve endings are exposed. Superficial 2nd-degree burns heal in 7-14 days as the epithelium regenerates in the absence of infection. Midlevel to deep 2nd-degree burns also heal spontaneously if wounds are kept clean and infection-free. Pain is less than in more superficial burns because fewer nerve endings remain viable. Fluid losses and metabolic effects of deep dermal (2nd-degree) burns are essentially the same as those of 3rd-degree burns.

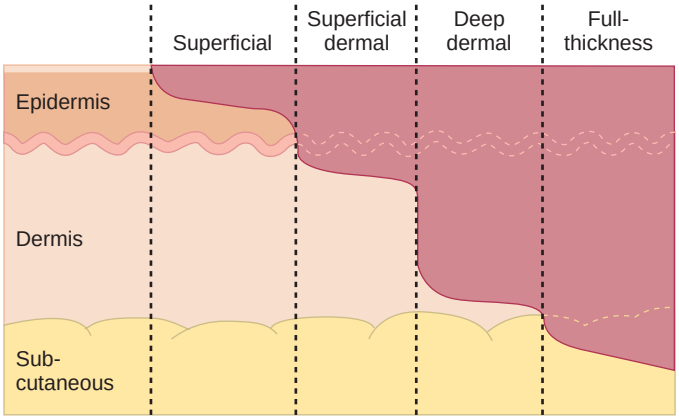

Figure 75-2 Diagram of the different burn depths. *(From Hettiaratchy S, Papini R: Initial management of a major burn II: assessment and resuscitation,* BMJ *329:101-103, 2004.)*

Full-thickness, or 3rd-degree, burns involve destruction of the entire epidermis and dermis, leaving no residual epidermal cells to repopulate the damaged area. The wound cannot epithelialize and can heal only by wound contraction or skin grafting. The absence of painful sensation and capillary filling demonstrates the loss of nerve

Table 75-4 Categories of Burn Depth

	1ST-DEGREE BURN	2ND-DEGREE, OR PARTIAL-THICKNESS, BURN	3RD-DEGREE, OR FULL-THICKNESS, BURN
Surface appearance	Dry, no blisters Minimal or no edema Erythematous Blanches, bleeds	Moist blebs, blisters Underlying tissue is mottled pink and white, with fair capillary refill Bleeds	Dry, leathery eschar Mixed white, waxy, khaki, mahogany, soot-stained No blanching or bleeding
Pain	Very painful	Very painful	Insensate
Histologic depth	Epidermal layers only	Epidermis, papillary, and reticular layers of dermis May include domes of subcutaneous layers	Down to and may include fat, subcutaneous tissue, fascia, muscle, and bone
Healing time	2-5 days with no scarring	Superficial: 5-21 days with no grafting Deep partial: 21-35 days with no infection; if infected, converts to full-thickness burn	Large areas require grafting, but small areas may heal from the edges after wks

and capillary elements. The use of Doppler scanner has become a valuable adjunct tool in burn depth assessment and burn healing potential.

Estimation of Body Surface Area for a Burn

Appropriate burn charts for different childhood age groups should be used to accurately estimate the extent of BSA burned. The volume of fluid needed in resuscitation is calculated from the estimation of the extent and depth of burn surface. Mortality and morbidity also depend on the extent and depth of the burn. The variable growth rate of the head and extremities throughout childhood makes it necessary to use BSA charts, such as that modified by Lund and Brower or the chart used at the Shriners Hospital for Children in Boston (Fig. 75-3). The **rule of nines** used in adults may be used only in children older than 14 yr or as a very rough estimate to institute therapy before transfer to a burn center. In small burns, <10% of BSA, the **rule of palm** may be used, especially in outpatient settings: The area from the wrist crease to the finger crease (the palm) in the child equals 1% of the child's BSA.

TREATMENT

Outpatient Management of Minor Burns

A patient with 1st- and 2nd-degree burns of <10% of BSA may be treated on an outpatient basis unless family support is judged inadequate or there are issues of child neglect or abuse. These outpatients do not require a tetanus booster (unless not fully immunized) or prophylactic penicillin therapy. Blisters should be left intact and dressed with bacitracin or silver sulfadiazine cream (Silvadene). Dressings should be changed once daily, after the wound is washed with lukewarm water to remove any cream left from the previous application. Very small wounds, especially those on the face, may be treated with bacitracin ointment and left open. Debridement of the devitalized skin is indicated when the blisters rupture. A variety of wound dressings/wound membranes are available (e.g., AQUACEL Ag dressing [ConvaTec USA, Skillman, NJ] in a soft felt-like material impregnated with silver ion) may be applied to 2nd-degree burns and wrapped with a dry sterile dressing; similar wound membranes provide pain control, prevention of wound desiccation, and reduction in wound colonization (Table 75-5). These dressings are usually kept on for 7-10 days but are checked twice a week.

Burns to the palm with large blisters usually heal beneath the blisters; they should receive close follow-up on an outpatient basis. The great majority of superficial burns heal in 10-20 days. Deep 2nd-degree burns take longer to heal and may benefit from enzymatic debridement ointment application (collagenase ointment) applied daily on the wound, which aids in the removal of the dead tissue. These ointments should not be applied to the face to avoid the risk of getting them into the eyes.

The depth of scald injuries is difficult to assess early; conservative treatment is appropriate initially, with the depth of the area involved

Table 75-5 Partial Listing of Some Commonly Used Wound Membranes—Selected Characteristics

MEMBRANE	CHARACTERISTIC(S)
Porcine xenograft	Adheres to coagulum Excellent pain control
Biobrane	Bilaminate Fibrovascular in growth into inner layer
Acticoat	Nonadherent dressing that delivers silver
AQUACEL-Ag	Absorptive hydrofiber that delivers silver
Various semipermeable membranes	Provide vapor and bacterial barrier
Various hydrocolloid dressings	Provide vapor and bacterial barrier Absorb exudates
Various impregnated gauzes	Provide barrier while allowing drainage

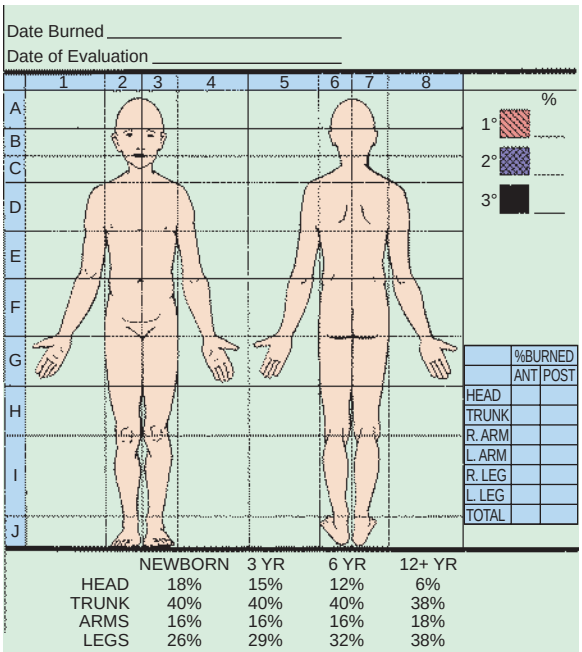

Figure 75-3 Chart to determine the developmentally related percentage of BSA affected by a burn injury. ANT, anterior; POST, posterior; R., right; L., left. *(Courtesy of Shriners Hospital for Crippled Children, Burn Institute, Boston Unit.)*

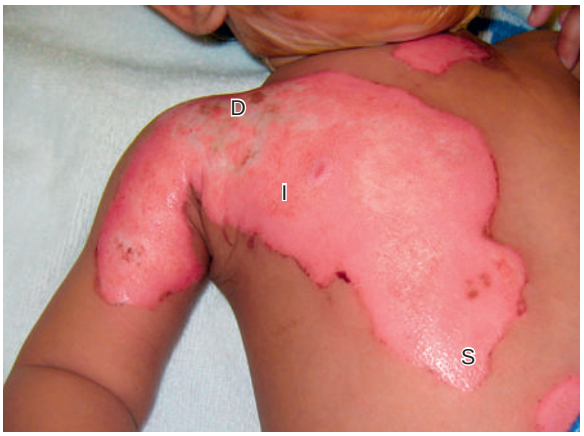

Figure 75-4 Tea scald over the chest and shoulder of a child showing heterogeneity of burn depth. D, deep; I, intermediate; S, superficial. *(From Enoch S, Roshan A, Shah M: Emergency and early management of burns and scalds,* BMJ *338:937-941, 2009.)*

determined before grafting is attempted (Fig. 75-4). This approach obviates the risk of anesthesia and unnecessary grafting.

Fluid Resuscitation

Fluid resuscitation should begin soon after the injury has occurred, in the emergency department before transferring to a burn center. For most children, the Parkland formula is an appropriate starting guideline for fluid resuscitation (4 mL lactated Ringer solution/kg/% BSA burned). Half of the fluid is given over the 1st 8 hr, calculated from the time of onset of injury; the remaining fluid is given at an even rate over the next 16 hr. The rate of infusion is adjusted according to the patient's response to therapy. Pulse and blood pressure should return to normal, and an adequate urine output (>1 mL/kg/hr in children; 0.5-1.0 mL/kg/hr in adolescents) should be accomplished by varying the IV infusion rate. Vital signs, acid–base balance, and mental status reflect the adequacy of resuscitation. Because of interstitial edema and sequestration of fluid in muscle cells, patients may gain up to 20% over baseline (preburn) body weight. Patients with burns of 30% of BSA require a large venous access (central venous line) to deliver the fluid required over the critical 1st 24 hr. Patients with burns of >60% of BSA may require a multilumen central venous catheter; these patients are best cared for in a specialized burn unit. In addition to fluid resuscitation, children should receive standard maintenance fluids (see Chapter 56).

During the 2nd 24 hr after the burn, patients begin to reabsorb edema fluid and to experience diuresis. Half of the 1st day's fluid requirement is infused as lactated Ringer solution in 5% dextrose. Children younger than 5 yr may require the addition of 5% dextrose in the 1st 24 hr of resuscitation. Controversy exists as to whether colloid should be provided in the early period of burn resuscitation. One preference is to use colloid replacement concurrently if the burn is >85% of total BSA. Colloid is usually instituted 8-24 hr after the burn injury. In children younger than 12 mo, sodium tolerance is limited; the volume and sodium concentration of the resuscitation solution should be decreased if the urinary sodium level is rising. The adequacy of resuscitation should be constantly assessed by means of vital signs as well as urine output, blood gas, hematocrit, and serum protein measurements. Some patients require arterial and central venous lines, particularly those undergoing multiple excision and grafting procedures, as needed, for monitoring and replacement purposes. Central venous pressure monitoring may be indicated to assess circulation in patients with hemodynamic or cardiopulmonary instability. Femoral vein cannulation is a safe access for fluid resuscitation, especially in infants and children. Burn patients who require frequent blood gas monitoring benefit from radial or femoral arterial catheterization.

Oral supplementation may start as early as 48 hr after burn. Milk formula, artificial feedings, homogenized milk, or soy-based products can be given by bolus or constant infusion through a nasogastric or small bowel feeding tube. As oral fluids are tolerated, IV fluids are decreased proportionately in an effort to keep the total fluid intake constant, particularly if pulmonary dysfunction is present.

A 5% albumin infusion may be used to maintain the serum albumin levels at a desired 2 g/dL. The following rates are effective: for burns of 30-50% of total BSA, 0.3 mL of 5% albumin/kg/% BSA burn is infused over 24 hr; for burns of 50-70% of total BSA, 0.4 mL/kg/% BSA burn is infused over 24 hr; and for burns of 70-100% of total BSA, 0.5 mL/kg/% BSA burn is infused over 24 hr. Infusion of packed red blood cells is recommended if the hematocrit falls to <24% (hemoglobin = 8 g/dL). Some authorities recommend treatment for hematocrit <30% or hemoglobin <10 g/dL in patients with systemic infection, hemoglobinopathy, cardiopulmonary disease, anticipated (or ongoing) blood loss, and if repeated excision and grafting of full-thickness burns are needed. Fresh-frozen plasma is indicated if clinical and laboratory assessment shows a deficiency of clotting factors, a prothrombin level >1.5 times control, or a partial thromboplastin time >1.2 times control in children who are bleeding or are scheduled for an invasive procedure or a grafting procedure that could result in an estimated blood loss of more than half of blood volume. Fresh-frozen plasma may be used for volume resuscitation within 72 hr of injury in patients younger than 2 yr with burns over 20% of BSA and associated inhalation injury.

Sodium supplementation may be required for children with burns of >20% of BSA if 0.5% silver nitrate solution is used as the topical antibacterial burn dressing. Sodium losses with silver nitrate therapy are regularly as high as 350 mmol/m^2 burn surface area. Oral sodium chloride supplement of 4 g/m^2 burn area/24 hr is usually well tolerated, divided into 4-6 equal doses to avoid osmotic diarrhea. The aim is to maintain serum sodium levels >130 mEq/L and urinary sodium concentration >30 mEq/L. Young children under 5 yr of age are especially susceptible to hyponatremic and cerebral edema. IV potassium supplementation is supplied to maintain a serum potassium level >3 mEq/dL. Potassium losses may be significantly increased when 0.5% silver nitrate solution is used as the topical antibacterial agent or when aminoglycoside, diuretic, or amphotericin therapy is required.

Prevention of Infection and Surgical Management of the Burn Wound

Controversy exists over the prophylactic use of penicillin for all patients hospitalized with acute burn injury and the periodic replacement of central venous catheters to prevent infection. In some units, a 5-day course of penicillin therapy is used for all patients with acute burns; standard-dose crystalline penicillin is given orally or intravenously in 4 divided doses. Erythromycin may be used as an alternative in penicillin-allergic children. Other units have discontinued prophylactic use of penicillin therapy without an increase in the infection rate. Similarly, there is conflicting evidence as to whether relocation of the IV catheter every 48-72 hr decreases or increases the incidence of catheter-related sepsis. Some recommend that the central venous catheter be replaced and relocated every 5-7 days, even if the site is not inflamed and there is no suspicion of catheter-related sepsis.

Mortality related to burn injury is associated not with the toxic effect of thermally injured skin, but with the metabolic and bacterial consequences of a large open wound, reduction of the patient's host resistance, and malnutrition. These abnormalities set the stage for life-threatening bacterial infection originating from the burn wound. Wound treatment and prevention of wound infection also promote early healing and improve aesthetic and functional outcomes. Topical treatment of the burn wound with 0.5% silver nitrate solution, silver sulfadiazine cream, or mafenide acetate (Sulfamylon) cream or topical solution at a concentration of 2.5-5% to be used for wounds with multidrug–resistant bacteria aims at prevention of infection (Table 75-6). These 3 agents have tissue-penetrating capacity. Regardless of the choice of topical antimicrobial agent, it is essential that all 3rd-degree burn tissue be fully excised before bacterial colonization occurs and that the area is grafted as early as possible to prevent deep wound sepsis. Children with a burn of >30% of BSA should be housed in a bacteria-controlled nursing unit to prevent cross-contamination

Table 75-6 Topical Agents Used for Burns

AGENT	EFFECTIVENESS	EASE OF USE
Silvadene cream (silver sulfadiazine)	Good penetration	Changed once daily Residue *must* be washed off with each dressing change
Mafenide acetate cream* (Sulfamylon cream)	Broad spectrum, including *Pseudomonas* Rapid and deep wound penetration	Closed dressings Changed twice daily Residue *must* be washed off with each dressing changed
0.5% Silver nitrate solution	Bacteriostatic Broad spectrum, including some fungi Superficial penetration	Closed bulky dressing soaked every 2 hr and changed once daily
AQUACEL Ag	Dressing impregnated with silver	Applied directly to 2nd-degree burn; occlusive dressing kept for 10 days

*Mafenide acetate solution at concentrations of 2.5% or 5% for use on heavily colonized multidrug–resistant organisms to be used for 5 days only.

and to provide a temperature- and humidity-controlled environment to minimize hypermetabolism.

Deep 2nd-degree burns of >10% of BSA benefit from early excision and grafting. To improve outcome, sequential excision and grafting of 3rd-degree and deep 2nd-degree burns is required in children with large burns. Prompt excision with immediate wound closure is achieved with autografts, which are often meshed to increase the efficiency of coverings. Alternatives for wound closure, such as allografts, xenografts, and Integra (Integra LifeSciences, York, PA) and other synthetic skin coverings (bilaminate membrane composed of a porous lattice of crosslinked chondroitin-6-sulfate engineered to induce neovascularization as it is biodegraded), may be important for wound coverage in patients with extensive injury to limit fluid, electrolyte, and protein losses and to reduce pain and minimize temperature loss. Epidermal cultured cells (autologous keratinocytes) are a costly alternative and are not always successful. An experienced burn team can safely perform early-stage or total excision while burn fluid resuscitation continues. Important keys to success are: (1) accurate preoperative and intraoperative determination of burn depth, (2) the choice of excision area and appropriate timing, (3) control of intraoperative blood loss, (4) specific instrumentation,(5) the choice and use of perioperative antibiotics, and (6) the type of wound coverage chosen. This process can accomplish early wound coverage without the use of recombinant human growth hormone.

Nutritional Support

Supporting the increased energy requirements of a patient with a burn is a high priority. The burn injury produces a hypermetabolic response characterized by both protein and fat catabolism. Depending on the time lapse since the burn, children with a burn of 40% of total BSA require basal energy expenditure (oxygen consumption) approximately 50-100% higher than predicted for their age. Early excision and grafting can decrease the energy requirement. Pain, anxiety, and immobilization increase the physiologic demands. Additional energy expenditure is caused by cold stress if environmental humidity and temperature are not controlled; this is especially true in young infants, in whom the large surface area : mass ratio allows proportionately greater heat loss than in adolescents and adults. Providing environmental temperatures of 28-33°C (82.4-91.4°F), adequate covering during transport and liberal use of analgesics and anxiolytics can decrease caloric demands. Special units to control ambient temperature and humidity may be necessary for children with large surface area burns. Appropriate sleep intervals are necessary and should be part of the regimen. Sepsis increases metabolic rates, and early enteral nutrition, initially with high-carbohydrate, high-protein caloric support (1,800 cal/m^2/24 hr maintenance plus 2,200 cal/m^2 of burn/24 hr) reduces metabolic stress.

The objective of caloric supplementation programs is to maintain body weight and minimize weight loss by meeting metabolic demands. This reduces the loss of lean body mass. Calories are provided at approximately 1.5 times the basal metabolic rate, with 3-4 g/kg of protein/day. The focus of nutritional therapy is to support and compensate for the metabolic needs. Multivitamins, particularly the B vitamin group, vitamin C, vitamin A, and zinc, are also necessary.

Alimentation should be started as soon as is practical, both enterally and parenterally, to meet all of the caloric needs and keep the gastrointestinal tract active and intact after the resuscitative phase. Patients with burns of >40% of total BSA need a flexible nasogastric or small bowel feeding tube to facilitate continuous delivery of calories without the risk of aspiration. To decrease the risk of infectious complications, parenteral nutrition is discontinued as soon as is practical, after delivery of sufficient enteral calories are established. Continuous gastrointestinal feeding is essential, even if feeding is interrupted, causing frequent visits to the operating room, until full grafting takes place. The use of anabolic agents (growth hormone, oxandrolone, low-dose insulin) or anticatabolic agents (propranolol) remains controversial, although β-blocking agents may reduce metabolic stress. Burn centers caring for large burns (>50% BSA, 3rd-degree) in patients who might be malnourished have used the anabolic steroid oxandrolone, at a dose of 0.1-0.2 mg/kg/day given orally, to promote better protein synthesis while the nutritional support by nasogastric feeding and IV hyperalimentation continues.

Topical Therapy

Topical therapy is widely used and is effective against most burn wound pathogens (see Table 75-6). A number of topical agents are used: 0.5% silver nitrate solution, sulfacetamide acetate cream or solution, silver sulfadiazine cream, and Accuzyme ointment or AQUACEL Ag$^+$. Accuzyme is an enzymatic debridement agent and may cause a stinging feeling for 15 min after application. Preferences vary among burn units. Each topical agent has advantages and disadvantages in application, comfort, and bacteriostatic spectrum. Mafenide acetate is a very effective broad-spectrum agent with the ability to diffuse through the burn eschar; it is the treatment of choice for injury to cartilaginous surface, such as the ear; mafenide acetate solution at a concentration of 5% is useful for the treatment of burn wounds that are heavily colonized with multidrug–resistant bacteria (use should be limited to 5 days). The carbonic anhydrase inhibition activity of mafenide acetate may cause acid–base imbalance if large surface areas are treated, and adverse reactions to the sulfur-containing agents may produce transient leukopenia. This latter reaction is mostly noted with the use of silver sulfadiazine cream when applied over large surface areas in children younger than 5 yr of age. This phenomenon is transient, self-limiting, and reversible. No sulfa-containing agent should be used if the child has a history of sulfa allergies.

Inhalational Injury

Inhalational injury is serious in the infant and child, particularly if preexisting pulmonary conditions are present (see Chapter 71). Inhalation injury should be suspected in a patient confined to a closed space (building), with a history of an explosion or a decreased level of consciousness, or with evidence of carbon deposits in the oropharynx or nose, singed facial hair and carbonaceous sputum. Mortality estimates vary, depending on the criteria for diagnosis, but are 45-60% in adults; exact figures are not available in children. Evaluation aims at early identification of inhalation airway injuries. These may occur from (1) direct heat (greater problems with steam burns), (2) acute asphyxia, (3) carbon monoxide poisoning, and (4) toxic fumes, including cyanides from combustible plastics. Sulfur and nitrogen oxides and alkalis

formed during the combustion of synthetic fabrics produce corrosive chemicals that may erode mucosa and cause significant tissue sloughing. Exposure to smoke may cause degradation of surfactant and decrease its production, resulting in atelectasis. Inhalation injury and burn injury are synergistic, and the combined effect can increase morbidity and mortality.

The pulmonary complications of burns and inhalation can be divided into 3 syndromes that have distinct clinical manifestations and temporal patterns:

1. Early complications include carbon monoxide poisoning, airway obstruction, and pulmonary edema.
2. The acute respiratory distress syndrome usually becomes clinically evident later, at 24-48 hr, although it can occur even later (see Chapter 71).
3. Late complications (days to weeks) include pneumonia and pulmonary emboli.

Inhalation injury should be assessed from the evidence of obvious injury (swelling or carbonaceous material in the nasal passages), wheezing, crackles or poor air entry, and laboratory determinations of (HbCO) and arterial blood gases.

Treatment is initially focused on establishing and maintaining a patent airway through prompt and early nasotracheal or orotracheal intubation and adequate ventilation and oxygenation. Wheezing is common, and β-agonist aerosols or inhaled corticosteroids are useful. Aggressive pulmonary toilet and chest physiotherapy are necessary in patients with prolonged nasotracheal intubation or in the rare patient with a tracheotomy. An endotracheal tube can be maintained for months without the need for tracheostomy. If tracheotomy must be performed, it should be delayed until burns at and near the site have healed, and then it should be performed electively, with the child under anesthesia and the use of optimal tracheal positioning and hemostasis. In children with inhalation injury or burns of the face and neck, upper airway obstruction can develop rapidly; endotracheal intubation becomes a lifesaving intervention. Extubation should be delayed until the patient meets the accepted criteria for maintaining the airway.

Signs of CNS injury from hypoxemia caused by asphyxia or carbon monoxide poisoning vary from irritability to depression. Carbon monoxide poisoning may be mild (<20% HbCO), with slight dyspnea, headache, nausea, and decreased visual acuity and higher cerebral functions; moderate (20-40% HbCO), with irritability, agitation, nausea, dimness of vision, impaired judgment, and rapid fatigue; or severe (40-60% HbCO), producing confusion, hallucination, ataxia, collapse, acidosis, and coma. Measurement of HbCO is important for diagnosis and treatment. The Pa_{O_2} value may be normal and the HbCO saturation values misleading because HbCO is not detected by the usual tests of oxygen saturation. Carbon monoxide poisoning is assumed until the tests are performed, and it is treated with 100% oxygen. Significant carbon monoxide poisoning requires hyperbaric oxygen therapy (see Chapter 63).

Patients with severe inhalation injury or with other causes of respiratory deterioration that lead to acute respiratory distress syndrome who do not improve with conventional pressure-controlled ventilation (progressive oxygenation failure, as manifested by oxygen saturation <90% while receiving F_{IO_2} of 0.9-1.0 and positive end-expiratory pressure of at least 12.5 cm H_2O) may benefit from high-frequency ventilation or nitric oxide inhalation treatment. Nitric oxide usually is administered through the ventilator at 5 parts per million (ppm) and increased to 30 ppm. This method of therapy reduces the need for extracorporeal membrane oxygenation.

Pain Relief and Psychologic Adjustment

See Chapter 62.

It is important to provide adequate analgesia, anxiolytics, and psychologic support to reduce early metabolic stress, decrease the potential for posttraumatic stress syndrome, and allow future stabilization as well as physical and psychologic rehabilitation. Patients and family members require team support to work through the grieving process and accept long-term changes in appearance.

Children with burn injury show frequent and wide fluctuations in pain intensity. Appreciation of pain depends on the depth of the burn; the stage of healing; the patient's age and stage of emotional development and cognition; the experience and efficiency of the treating team; the use of analgesics and other drugs; the patient's pain threshold; and interpersonal and cultural factors. From the onset of treatment, **preemptive pain control** during dressing changes is of paramount importance. The use of a variety of nonpharmacologic interventions as well as pharmacologic agents must be reviewed throughout the treatment period. Opiate analgesia, prescribed in an adequate dose and timed to cover dressing changes, is essential to comfort management. A supportive person who is consistently present and "knows" the patient profile can integrate and encourage patient participation in burn care. The problem of undermedication is most prevalent in adolescents, in whom fear of drug dependence may inappropriately influence treatment. A related problem is that the child's specific pain experience may be misinterpreted; for anxious patients, those who are confused and alone, or those with preexisting emotional disorders, even small wounds may illicit intense pain. Anxiolytic medication added to the analgesic is usually helpful and has more than a synergistic effect. Equal attention is necessary to decrease stress in the intubated patient. Other modalities of pain and anxiety relief (relaxation techniques) can decrease the physiologic stress response. Oral morphine sulfate (immediate release) is recommended at a consistent schedule at a dose of 0.3-0.6 mg/kg every 4-6 hr initially and until wound cover is accomplished. Morphine sulfate IV bolus at a dose of 0.05-0.1 mg/kg maximum of 2-5 mg every 2 hr is administered. Morphine sulfate rectal suppositories may be useful at a dose of 0.3-0.6 mg/kg every 4 hr when oral administration is not possible. The use of codeine preparation should be limited to children older than age 6 yr because of the "ultrarapid metabolizers" of codeine into morphine. For anxiety, lorazepam is given on a consistent schedule, 0.05-0.1 mg/kg/dose every 6-8 hr. To control pain during a procedure (dressing change or debridement), oral morphine at a dose of 0.3-0.6 mg/kg is given 1-2 hr before the procedure and this is supplemented by a morphine IV bolus at a dose of 0.05-0.1 mg/kg given immediately before the procedure. Lorazepam at a dose of 0.04 mg/kg is given orally or intravenously, if necessary, for anxiety before the procedure. Midazolam (Versed) is also very useful for conscious sedation given at a dose of 0.01-0.02 mg/kg for nonintubated patients and 0.05-0.1 mg/kg for intubated patients, as an intravenous infusion or bolus, and may be repeated in 10 min. During the process of weaning from analgesics, the dose of oral opiates is reduced by 25% over 1-3 days, sometimes with the addition of acetaminophen as opiates are tapered. Antianxiety medications are tapered by reducing the dose of benzodiazepines at 25-50% per dose daily over 1-3 days.

For ventilated patients, pain control is accomplished by using morphine sulfate intermittently as an IV bolus at a dose of 0.05-0.1 mg/kg every 2 hr. Doses may need to be increased gradually, and some children may need continuous infusion; a starting dose of 0.05 mg/kg/hr given as an infusion is increased gradually as the need of the child changes. Naloxone is rarely needed but should be immediately available to reverse the effect of morphine, if necessary; if needed for an airway crisis, it should be given in a dose of 0.1 mg/kg up to a total of 2 mg, either intramuscularly or intravenously. For patients undergoing assisted respiration who require treatment of anxiety, midazolam is used as an intermittent IV bolus (0.04 mg/kg given by slow push every 4-6 hr) or as a continuous infusion. For intubated patients, opiates do not need to be discontinued during the process of weaning from the ventilator. Benzodiazepine should be reduced to approximately half the dose over 24-72 hr before extubation; too-rapid weaning from a benzodiazepine can lead to seizures.

There is a growing use of psychotropic medication in the care of children with burns, including prescription of selective serotonin reuptake inhibitors as antidepressants, the use of haloperidol as a neuroleptic in the critical care setting, and the treatment of posttraumatic stress disorder with benzodiazepines. Conscious sedation utilizing ketamine or propofol may be used for major dressing changes.

Reconstruction and Rehabilitation

To ensure maximum cosmetic and functional outcome, occupational and physical therapy must begin on the day of admission, continue throughout hospitalization, and, for some patients, continue after discharge. Physical rehabilitation involves body and limb positioning, splinting, exercises (active and passive movement), assistance with activities of daily living, and gradual ambulation. These measures maintain adequate joint and muscle activity with as normal a range of movement as possible after healing or reconstruction. Pressure therapy is necessary to reduce hypertrophic scar formation; a variety of prefabricated and custom-made garments are available for use in different body areas for prevention of hypertrophic scarring. These custom-made garments deliver consistent pressure on scarred areas; they shorten the time of scar maturation and decrease the thickness of the scar, the redness, and the associated itching. Continued adjustments to scarred areas (scar release, grafting, rearrangement) and multiple minor cosmetic surgical procedures are necessary to optimize long-term function and improve appearance. Replacement of areas of alopecia and scarring has been achieved with the use of tissue expander techniques. The use of ultrapulse laser for reduction of scarring is an adjunct in scar management.

School Reentry and Long-Term Outcome

It is best for the child to return to school immediately after discharge. Occasionally, a child may need to attend a few half-days (because of rehabilitation needs). It is important for the child to return to the child's normal routine of attending school and being with peers. Planning for a return to home and school often requires a *school reentry program* that is individualized to each child's needs. For a school-age child, planning for the return to school occurs simultaneously with planning for discharge. The hospital schoolteacher contacts the local school and plans the program with the school faculty, nurses, social workers, recreational/child-life therapists, and rehabilitation therapists. This team should work with students and staff to ease anxiety, answer questions, and provide information. Burns and scars evoke fears in those who are not familiar with this type of injury and can result in a tendency to withdraw from or reject the burned child. A school reentry program should be appropriate to a child's development and changing educational needs.

Major advances have made it possible to save the lives of children with massive burns; whereas some children have had lingering physical difficulties, most have a satisfactory quality of life. The comprehensive burn care that includes experienced multidisciplinary aftercare plays an important role in recovery. Table 75-7 lists the long-term complications of burns.

Table 75-7 Common Long-Term Disabilities in Patients with Burn Injuries

DISABILITIES AFFECTING THE SKIN AND SOFT TISSUE
Hypertrophic scars
Susceptibility to minor trauma
Dry skin
Contractures
Itching and neuropathic pain
Alopecia
Chronic open wounds
Skin cancers
ORTHOPEDIC DISABILITIES
Amputations
Contractures
Heterotopic ossification
Temporary reduction in bone density
METABOLIC DISABILITIES
Heat sensitivity
Obesity
PSYCHIATRIC AND NEUROLOGIC DISABILITIES
Sleep disorders
Adjustment disorders
Posttraumatic stress syndrome
Depression
Body image issues
Neuropathy and neuropathic pain
Long-term neurologic effects of carbon monoxide poisoning
Anoxic brain injury
LONG-TERM COMPLICATIONS OF CRITICAL CARE
Deep-vein thrombosis, venous insufficiency, or varicose veins
Tracheal stenosis, vocal cord disorders, or swallowing disorders
Renal or adrenal dysfunction
Hepatobiliary or pancreatic disease
Cardiovascular disease
Reactive airway disease or bronchial polyposis
PREEXISTING DISABILITIES THAT CONTRIBUTED TO THE INJURIES
Risk-taking behavior
Untreated or poorly treated psychiatric disorder

Modified from Sheridan RL, Schultz JT, Ryan CM, et al: Case records of the Massachusetts General Hospital: weekly clinicopathological exercises: case 6-2004: a 35-year-old woman with extensive, deep burns from a nightclub fire, N Engl J Med *350:810-821, 2004.*

SPECIAL SITUATIONS

Electrical Burns

There are 3 types of electrical burns. **Minor electrical burns** usually occur as a result of biting on an extension cord. These injuries produce localized burns to the mouth, which usually involve the portions of the upper and lower lips that come in contact with the extension cord. The injury may involve or spare the corners of the mouth. Because these are nonconductive injuries (do not extend beyond the site of injury), hospital admission is not necessary and care is focused on the area of the injury visible in the mouth, it is low voltage, does not cause entry or exit wounds, or cardiac issues. Treatment with topical antibiotic creams is sufficient until the patient is seen in a burn unit outpatient department or by a plastic surgeon.

A more serious category of electrical burn is the **high-tension electrical wire burn**, for which children must be admitted for observation, regardless of the extent of the surface area burn. Deep muscle injury is typical and cannot be readily assessed initially. These injuries result from high voltage (>1,000 V) and occur particularly at high-voltage installations, such as electric power stations or railroads; children climb an electric pole and touch an electric box out of curiosity or accidentally touch a high-tension electric wire. Such injuries have a mortality rate of 3-15% for children who arrive at the hospital for treatment. Survivors have a high rate of morbidity, including major limb amputations. Points of entry of current through the skin and the exit site show characteristic features consistent with current density and heat. The majority of entrance wounds involve the upper extremity, with small exit wounds in the lower extremity. The electrical path, from entrance to exit, takes the shortest distance between the 2 points and may produce injury in any organ or tissue in the path of the current. Multiple exit wounds in some patients attest to the possibility of several electrical pathways in the body, placing virtually any structure in the body at risk (Table 75-8). Damage to the abdominal viscera, thoracic structures, and the nervous system (confusion, coma, paralysis) in areas remote from obvious extremity injury occurs and must be sought, particularly in injuries with multiple current pathways or those in which the victim falls from a high pole. Sometimes an **ignition** occurs and results in concurrent flame burn and clothing fire. Cardiac abnormalities, manifested as ventricular fibrillation or cardiac arrest, are common; patients with high-tension electrical injury need an initial electrocardiogram and cardiac monitoring until they are stable and have been fully assessed. Higher-risk patients have abnormal electrocardiographic findings and a history of loss of consciousness. Renal damage from deep muscle necrosis and subsequent myoglobinuria is another complication; such patients need forced alkaline diuresis to minimize renal damage. Soft-tissue (muscle) injury of an extremity may produce a compartment syndrome. Aggressive removal of all dead

Table 75-8 Electrical Injury: Clinical Considerations

	CLINICAL MANIFESTATIONS	MANAGEMENT
General	—	Extricate the patient; perform ABCs of resuscitation; immobilize the spine History: voltage, type of current Complete blood count with platelets, electrolytes, blood urea nitrogen (BUN), creatinine, glucose
Cardiac	Dysrhythmias: asystole, ventricular fibrillation, sinus tachycardia, sinus bradycardia, premature atrial contractions, premature ventricular contractions, conduction defects, atrial fibrillation, ST-T wave changes	Treat dysrhythmias Cardiac monitor, electrocardiogram, and radiographs with suspected thoracic injury Creatinine phosphokinase with isoenzyme measurements if indicated
Pulmonary	Respiratory arrest, acute respiratory distress, aspiration syndrome	Protect and maintain the airway Mechanical ventilation if indicated, chest radiograph, arterial blood gas levels
Renal	Acute renal failure, myoglobinuria	Provide aggressive fluid management unless a central nervous system injury is present Maintain adequate urine output, >1 mL/kg/hr Consider central venous or pulmonary artery pressure monitoring Measure urine myoglobin; perform urinalysis; measure BUN, creatinine
Neurologic	Immediate: loss of consciousness, motor paralysis, visual disturbances, amnesia, agitation; intracranial hematoma Secondary: pain, paraplegia, brachial plexus injury, syndrome of inappropriate antidiuretic hormone secretion, autonomic disturbances, cerebral edema Delayed: paralysis, seizures, headache, peripheral neuropathy	Treat seizures Provide fluid restriction if indicated Consider spine radiographs, especially cervical CT scan of the brain if indicated
Cutaneous/oral	Oral commissure burns, tongue and dental injuries; skin burns resulting from ignition of clothes, entrance and exit burns, and arc burns Electrical burns to the mouth could include oral commissures and lips, low voltage electrical burns secondary to high conductivity of saliva	Search for the entrance/exit wound Treat cutaneous burns; determine the tetanus status Obtain a plastic surgery of ear, nose, and throat consultation if needed No entry or exit wounds, no cardiac involvement. All injuries are localized management is observation till eschar slough off and granulation tissue fills in. Obtain plastic surgeon evaluation after first healing had occurred usually with scar formation.
Abdominal	Viscus perforation and solid organ damage; ileus; abdominal injury rare without visible abdominal burns	Place a nasogastric tube if the patient has airway compromise or ileus Obtain serum glutamate oxaloacetate transaminase or aspartate aminotransferase, serum glutamate-pyruvic transaminase, alanine aminotransferase, amylase, BUN, and creatinine measurements and, CT scans as indicated
Musculoskeletal	Compartment syndrome from subcutaneous necrosis limb edema and deep burns Long bone fractures, spine injuries	Monitor the patient for possible compartment syndrome Obtain radiographs and orthopedic/general surgery consultations as indicated
Ocular	Visual changes, optic neuritis, cataracts, extraocular muscle paresis	Obtain an ophthalmology consultation as indicated

Modified from Hall ML, Sills RM: Electrical and lightning injuries. In Barkin RM, editor: Pediatric emergency medicine, *St. Louis, 1997, Mosby, p. 484.*

and devitalized tissue, even with the risk of functional loss, remains the key to effective management of the electrically damaged extremity. Early debridement facilitates early closure of the wound. Damaged major vessels must be isolated and buried in a viable muscle to prevent exposure. Survival depends on immediate intensive care, whereas a functional result depends on long-term care and delayed reconstructive surgery.

Lightning burns occur when a high-voltage current directly strikes a person (most dangerous) or when the current strikes the ground or an adjacent (in-contact) object. A step voltage burn is observed when lightning strikes the ground and travels up one leg and down the other (the path of least resistance). Lightning burns depend on the current path, the type of clothing worn, the presence of metal, and cutaneous moisture. Entry, exit, and path lesions are possible; the prognosis is poorest for lesions of the head or legs. Internal organ injury along the path is common and does not relate to the severity of the cutaneous burn. Linear burns, usually 1st- or 2nd-degree, are in the locations where sweat is present. Feathering or an arborescent pattern is characteristic of lightning injury. Lightning may ignite clothing or produce serious cutaneous burns from heated metal in the clothing. Internal complications of lightning burns include cardiac arrest caused by asystole, transient hypertension, premature ventricular contractions, ventricular fibrillation, and myocardial ischemia. Most severe cardiac complications resolve if the patient is supported with cardiopulmonary resuscitation (see Chapter 67). CNS complications include cerebral edema, hemorrhage, seizures, mood changes, depression, and paralysis of the lower extremities. Rhabdomyolysis and myoglobinuria (with possible renal failure) also occur. Ocular manifestations include vitreous hemorrhage, iridocyclitis, retinal tearing or retinal detachment.

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Useful Links

www.ameriburn.org.
www.cpsc.gov.
www.safekids.org.

Chapter 76

Cold Injuries

Alia Y. Antoon and Mary K. Donovan

The involvement of children and youth in snowmobiling, mountain climbing, winter hiking, and skiing places them at risk for cold injury. Cold injury may produce either local tissue damage, with the injury pattern depending on exposure to damp cold (frostnip, immersion foot, or trench foot), dry cold (which leads to local frostbite), or generalized systemic effects (hypothermia).

PATHOPHYSIOLOGY

Ice crystals may form between or within cells, interfering with the sodium pump, and may lead to rupture of cell membranes. Further damage may result from clumping of red blood cells or platelets, causing microembolism or thrombosis. Blood may be shunted away from an affected area by secondary neurovascular responses to the cold injury; this shunting often further damages an injured part while improving perfusion of other tissues. The spectrum of injury ranges from mild to severe and reflects the result of structural and functional disturbance in small blood vessels, nerves, and skin.

ETIOLOGY

Body heat may be lost by conduction (wet clothing, contact with metal or other solid conducting objects), convection (wind chill), evaporation, or radiation. Susceptibility to cold injury may be increased by dehydration, alcohol or drug use, impaired consciousness, exhaustion, hunger, anemia, impaired circulation as a consequence of cardiovascular disease, and sepsis; it is also greater in very young or older persons. Certain medications may contribute to hypothermia, while others may display reduced metabolism or clearance during hypothermia (Table 76-1).

Hypothermia occurs when the body can no longer sustain normal core temperature by physiologic mechanisms, such as vasoconstriction, shivering, muscle contraction, and nonshivering thermogenesis. When shivering ceases, the body is unable to maintain its core temperature; when the body core temperature falls to <35°C (95°F), the syndrome of hypothermia occurs. Wind chill, wet or inadequate clothing, and other factors increase local injury and may cause dangerous hypothermia, even in the presence of an ambient temperature that is not <17-20°C (50-60°F).

CLINICAL MANIFESTATIONS

Frostnip

Frostnip results in the presence of firm, cold, white areas on the face, ears, or extremities. Blistering and peeling may occur over the next 24-72 hr, occasionally leaving mildly increased hypersensitivity to cold for some days or weeks. Treatment consists of warming the area with an unaffected hand or a warm object before the lesion reaches a stage of stinging or aching and before numbness supervenes. Rewarming in a water bath (40-42.2°C [104-108°F]) is effective.

Table 76-1 Drugs Displaying Reduced Metabolism or Clearance in Hypothermia

Atropine	Procaine
Digoxin	Propranolol
Fentanyl	Sulfanilamide (AVC cream)
Gentamicin	Succinylcholine
Lidocaine	D-Tubocurarine
Phenobarbital	

Modified from Bope ET, Kellerman RD, editors, Conn's current therapy 2014, *Philadelphia, 2014, Elsevier/Saunders, Box 3, p. 1135.*

Immersion Foot (Trench Foot)

Immersion foot occurs in cold weather when the feet remain in damp or wet, poorly ventilated boots. The feet become cold, numb, pale, edematous, and clammy. Tissue maceration and infection are likely, and prolonged autonomic disturbance is common. This autonomic disturbance leads to increased sweating, pain, and hypersensitivity to temperature changes, which may persist for years. Treatment includes drying the foot, gentle rewarming and nonsteroidal antiinflammatory drugs for pain. Prevention consists of using well-fitting, insulated, waterproof, nonconstricting footwear. Once damage has occurred, patients must choose clothing and footwear that are more appropriate, dry, and well-fitting. The disturbance in skin integrity is managed by keeping the affected area dry and well-ventilated and by preventing or treating infection. Only supportive measures are possible for control of autonomic symptoms.

Frostbite

With frostbite, initial stinging or aching of the skin progresses to cold, hard, white anesthetic and numb areas. Clear or hemorrhagic vesicles may develop over the exposed areas. On rewarming, the area becomes blotchy, itchy, and often red, swollen, and painful. The injury spectrum ranges from complete normality to extensive tissue damage, even gangrene, if early relief is not obtained.

Treatment consists of warming the damaged area. It is important not to cause further damage by attempting to rub the area with ice or snow. The area may be warmed against an unaffected hand, the abdomen, or an axilla during transfer of the patient to a facility where more rapid warming with a warm (not hot) water bath is possible. If the skin becomes painful and swelling occurs, antiinflammatory agents are helpful and an analgesic agent is necessary. Freeze and rethaw cycles are most likely to cause permanent tissue injury, and it may be necessary to delay definitive warming and apply only mild measures if the patient is required to walk on the damaged feet en route to definitive treatment. In the hospital, the affected area should be immersed in warm water (approximately 42°C [107.6°F]), with care taken not to burn the anesthetized skin. Broken vesicles may be debrided, but intact vesicles should be left alone. Vasodilating agents, such as prazosin and phenoxybenzamine, may be helpful. Use of anticoagulants (heparin, dextran) has had equivocal results; results of chemical and surgical sympathectomy have also been equivocal. Oxygen is of help only at high altitudes. Meticulous local care, prevention of infection, and keeping the rewarmed area dry, open, and sterile provide optimal results. Recovery can be complete, and prolonged observation with conservative therapy is justified before any excision or amputation of tissue is considered. Analgesia and maintenance of good nutrition are necessary throughout the prolonged waiting period.

Hypothermia

Hypothermia may occur in winter sports when injury, equipment failure, or exhaustion decreases the level of exertion, particularly if sufficient attention is not paid to wind chill. Immersion in frozen bodies of water and wet wind chill rapidly produce hypothermia. As the core temperature of the body falls, insidious onset of extreme lethargy, fatigue, incoordination, and apathy occurs, followed by mental confusion, clumsiness, irritability, hallucinations, and finally, bradycardia. A number of medical conditions, such as cardiac disease, diabetes mellitus, hypoglycemia, sepsis, β-blocking agent overdose, and substance abuse, may need to be considered in a differential diagnosis. The decrease in rectal temperature to <34°C (93°F) is the most helpful diagnostic feature. Hypothermia associated with drowning is discussed in Chapter 74.

Prevention is a high priority. Of extreme importance for those who participate in winter sports is wearing layers of warm clothing, gloves, socks within insulated boots that do not impede circulation, and a warm head covering, as well as application of adequate waterproofing and protection against the wind. Thirty percent of heat loss for infants occurs from the head. Ample food and fluid must be provided during exercise. Those who participate in sports should be alert to the presence of cold or numbing of body parts, particularly the nose, ears, and

extremities, and they should review methods to produce local warming and know to seek shelter if they detect symptoms of local cold injury. Application of petrolatum (Vaseline) to the nose and ears gives certain protection against frostbite.

Treatment at the scene aims at prevention of further heat loss and early transport to adequate shelter (Table 76-2). Dry clothing should be provided as soon as practical, and transport should be undertaken if the victim has a pulse. If no pulse is detected at the initial review, cardiopulmonary resuscitation is indicated (see Chapter 67; Fig. 76-1). During transfer, jarring and sudden motion should be avoided because these occurrences may cause ventricular arrhythmia. It is often difficult to attain a normal sinus rhythm during hypothermia.

If the patient is conscious, mild muscle activity should be encouraged, and a warm drink offered. If the patient is unconscious, external warming should be undertaken initially with use of blankets and a sleeping bag; wrapping the patient in blankets or sleeping bag with a warm companion may increase the efficiency of warming. On arrival at a treatment center while a warming bath of 45-48°C (113-118°F) water is prepared, the patient should be warmed through inhalation of warm, moist air or oxygen or with heating pads or thermal blankets. Monitoring of serum chemistry values and an electrocardiogram are

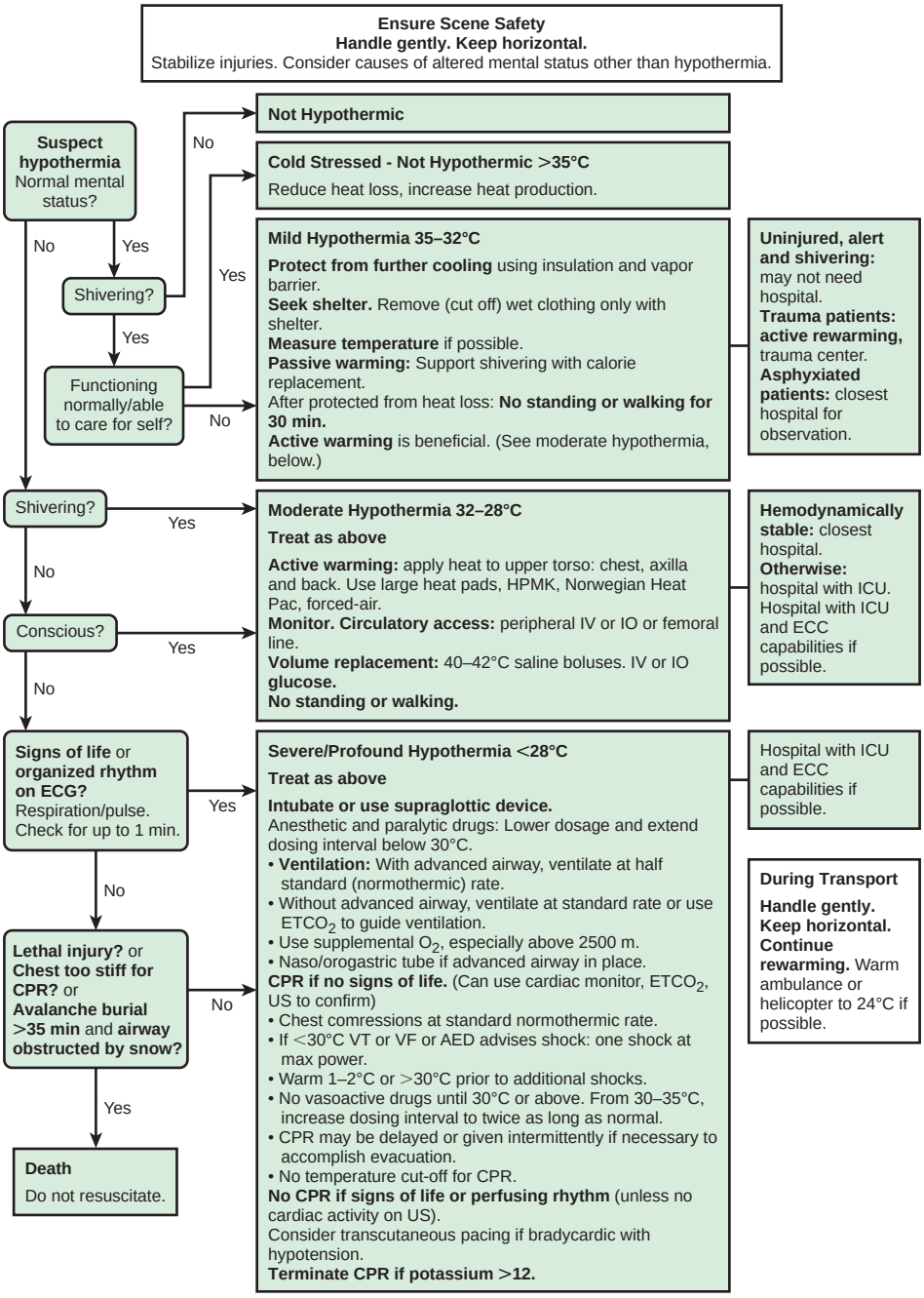

Figure 76-1 Recommendations for out-of-hospital evaluation and treatment of accidental hypothermia. ECG, electrocardiogram; CPR, cardiopulmonary resuscitation; HPMK, Hypothermia Prevention Management Kit; IV, intravenous; IO, intraosseous; ETCO2, end-tidal carbon dioxide; VT, ventricular tachycardia; VF, ventricular fibrillation; AED, automatic external defibrillator; US, ultrasound; ICU, intensive care unit; ECC, extracorporeal circulation. *(From Zafren K, Giesbrecht GG, Danzl DF, et al: Wilderness Medical Society Practice Guidelines for the Out-of-Hospital Evaluation and Treatment of Accidental Hypothermia: 2014 Update,* Wilderness Environ Med *25:S66–S85, 2014. Fig 2.)*

Table 76-2 Management of Hypothermia

HISTORY AND PHYSICAL
Gentle handling of the patient to prevent arrhythmias
ABCDE: cardiopulmonary resuscitation for ventricular fibrillation and asystole
Underlying disease diagnosis and treatment
Vital signs, pulse oximetry, electrocardiogram
Wet or cold clothing removed and patient placed in warm environment
LABORATORY TESTS
Arterial blood gas analysis corrected for temperature
Electrolytes, BUN creatinine, Ca, Mg, P
CBC with differential, PT/PTT, fibrinogen
Glucose, amylase/lipase
LFT
Additional labs, if appropriate, such as toxicology screen
PASSIVE REWARMING
≥32°C (89.6°F) in patients who are capable of spontaneous thermogenesis
ACTIVE REWARMING
<32°C (89.6°F), cardiovascular instability, patients at risk for developing hypothermia
Close monitoring for core-temperature afterdrop
Acute: external and/or core rewarming
Chronic (<32°C [89.6°F] for longer than 24 hr): core rewarming
Extracorporeal membrane oxygenation
Availability of rapid deployment

ABCDE, *a*irway and possibly antibiotics, *b*reathing, *c*irculation, *d*isability or neurologic and possible *d*extrose, *e*xtracorporeal support if all else fails; BUN, blood urea nitrogen; Ca, calcium; CDC, complete blood count; LFT liver function test; Mg, magnesium; P, phosphorus; PT, prothrombin time; PTT, partial thromboplastin time.

From Burg FD, Ingelfinger JR, Polin RA, Gershon AA (eds): Current pediatric therapy, *ed 18, Philadelphia, 2006, Saunders/Elsevier, Table 4, p. 174.*

necessary until the core temperature rises to >35°C (95°F) and can be stabilized. Control of fluid balance, pH, blood pressure, and oxygen concentration is necessary in the early phases of the warming period and resuscitation. In severe hypothermia, there may be a combined respiratory and metabolic acidosis. Hypothermia may falsely elevate pH; nonetheless, most authorities recommend warming the arterial blood gas specimen to 37°C (98.6°F) before analysis and regarding the result as one from a normothermic patient. In patients with marked abnormalities, warming measures, such as gastric or colonic irrigation with warm saline or peritoneal dialysis, may be considered, but the effectiveness of these measures in treating hypothermia is unknown. In accidental deep hypothermia (core temperature 28°C [82.4°F]) with circulatory arrest, rewarming with cardiopulmonary bypass may be lifesaving for previously healthy young individuals. If rewarming is not successful despite appropriate measures, one should suspect infection, drug overdose, endocrine disorders, or a futile resuscitation.

Chilblain (Pernio)

Chilblain (pernio) is a form of cold injury in which erythematous, vesicular, or ulcerative lesions occur. The lesions are presumed to be of vascular or vasoconstrictive origin. They are often itchy, may be painful, and result in swelling and scabbing. The lesions are most often found on the ears, the tips of the fingers and toes, and exposed areas of the legs. The lesions last for 1-2 wk but may persist for longer. Treatment consists of prophylaxis: avoiding prolonged chilling and protecting potentially susceptible areas with a cap, gloves, and stockings. Prazosin and phenoxybenzamine may be helpful in improving circulation if this is a recurrent problem. For significant itching, local corticosteroid preparations may be helpful.

COLD-INDUCED FAT NECROSIS (PANNICULITIS)

A common, usually benign injury, cold-induced fat necrosis occurs upon exposure to cold air, snow, or ice and manifests in exposed (or, less often, covered) surfaces as red (or, less often, purple to blue) macular, papular, or nodular lesions. Treatment is with nonsteroidal antiinflammatory agents. The lesions may last 10 days to 3 wk (see Chapter 660) but may persist for longer. There is a possibility of severe coagulopathy associated with poor outcome in some of the severe cold injuries, thus meriting anticoagulation therapy.

Bibliography is available at Expert Consult.

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Human Genetics

PART X

Chapter 77

Integration of Genetics Into Pediatric Practice

Brendan Lee

Genetic testing involves analyzing genetic material to obtain information related to a person's health status using chromosomal (cytogenetic) analysis (see Chapter 81) or DNA-based testing.

DIAGNOSTIC TESTING

Diagnostic genetic testing helps explain a set of signs and/or symptoms of a disease. The list of disorders for which specific genetic tests is available is extensive. The website http://www.ncbi.nlm.nih.gov/gtr/ provides a database of available tests that is provider driven and so claims are not validated by the site's host, the National Institutes of Health.

Single-gene disorders can be tested by at least 3 different approaches: linkage analysis, array comparative genomic hybridization (aCGH), and direct mutation (DNA sequence-based) analysis, usually by DNA sequencing (Table 77-1). Linkage analysis is used if the responsible gene is mapped but not yet identified, or if it is impractical to find specific mutations, usually because of the large size and larger number of different mutations in some genes. aCGH can be used to detect large multigene deletions or duplications (**copy number variations**). In addition, with increasing resolution, single gene or smaller intragenic deletions or duplications can be detected by aCGH. *Direct DNA mutation analysis is preferred and is possible with the availability of the complete human genome sequence.* An emerging feature is the increasing recognition of oligogenic disease where more than 1 disease gene contributes to a complex phenotype. The ability to sequence hundreds to thousands of genes at once has provided insight into this added layer of complexity in disease pathogenesis.

Linkage testing involves tracking a genetic trait through a family using closely linked polymorphic markers as a surrogate for the trait (Fig. 77-1). It requires testing an extended family and is vulnerable to several pitfalls, such as genetic recombination, genetic heterogeneity, and incorrect diagnosis in the proband. **Genetic recombination** occurs between any pair of loci, the frequency being proportional to the distance between them. This problem can be ameliorated by using very closely linked markers and, if possible, using markers that flank the specific gene. **Genetic heterogeneity** can be problematic for a linkage-based test if there are multiple distinct genomic loci that can cause the same phenotype, resulting in the risk that the locus tested for is not the one responsible for disease in the family. **Incorrect diagnosis** in the proband also leads to tracking the wrong gene. Linkage testing remains useful for several genetic conditions, though it is increasingly being superseded by the availability of direct DNA sequencing. It is critically important that genetic counseling be provided to the family to explain the complexities of interpretation of test results.

aCGH (see Chapter 81) can detect copy number variation in a patient's DNA by comparing it to a standard control DNA. In so doing, it provides a level of genetic resolution between what is available with DNA sequencing and what is available with chromosome analysis. Whereas earlier technologies could only identify large deletions or duplications that might encompass multiple genes, aCGH can resolve deletions or duplications of several kilobases within 1 gene. In theory, this approach can detect deletion and duplication mutations that would be missed by either chromosome analysis or direct mutation testing by DNA sequencing. However, because the specific resolution and coverage of different aCGH platforms can vary tremendously for different gene regions, the sensitivity for detecting deletions and duplications can vary for different diseases and laboratories.

Direct DNA-based mutation testing avoids the pitfalls of linkage testing by detecting the specific gene mutation (i.e., sequence change). The specific approach used is customized to the biology of the gene being tested. In some disorders, 1 or a few distinct mutations occur in all affected individuals. This is the case in sickle cell anemia, in which the same single base substitution occurs in everyone with the disorder. In other conditions, there may be many possible mutations that account for the disorder in different individuals. Cystic fibrosis is an example: more than 1,000 distinct mutations have been found in the *CFTR* gene. Mutation analysis is challenging because no single technique can detect all possible mutations. However, with the completion of the human genome sequence and high-throughput DNA sequencing technology, the approach of choice is to directly sequence DNA that is generated by **polymerase chain reaction** amplification of DNA isolated from peripheral blood white blood cells. The limitation of this approach is that only DNA that is amplified is sequenced, and usually this is restricted to the *coding* or *exonic* regions of a gene. Because mutations sometimes occur in the *noncoding intronic* regions, failure to detect a mutation does not exclude the diagnosis. In addition, genes in a deleted region will not be deleted. Although DNA sequencing can be highly specific, it is not completely sensitive because of practical limitations of what is commercially available. This is, however, rapidly changing because of technologic advances.

The most useful development in clinical DNA diagnosis is application of **next-generation sequencing** technology to testing panels of genes that target disease symptoms (e.g., low bone mass, ataxia) or the **whole exome (whole exome sequencing [WES])**. Here, advances in sequencing methodology have allowed for massively parallel sequencing of hundreds of genes of all of the gene coding sequences (approximately 20,000 genes) from single sample. The challenge is not so much the generation of DNA sequence, but the interpretation of enormous genetic variation within a single sample. Direct sequencing of tens to hundreds of genes in next generation sequencing panels offer a potentially higher sensitivity as the "depth" of read is higher without complicating high discovery rate of **variants of unknown sequences (VUS)**. WES also offers the potential for identifying new disease-gene associations as well as phenotypes caused by more than one disease gene (i.e., oligogenic phenotypes). An important ethical consideration is the reporting of incidental findings, whether medically or nonmedically actionable in a patient; WES may identify mutations that cause aminoglycoside sensitive hearing loss. This would be medically actionable. At the same time, the discovery of apolipoprotein E variants in a child that increase Alzheimer disease risk susceptibility may not. Hence, counseling for patients undergoing WES is important so that only wanted results are reported back to the patient. Guidelines are currently evolving for reporting of incidental findings for WES by the American College of Medical Genetics (www.acmg.net). Practice varies among institutions and recommendations vary among international genetic organizations about the approach for revealing incidental findings to patients. Many leave the choice up to the patient/family about revealing incidental findings from WES/whole genome sequencing. Most require revealing to the patient/family significant diseases

Table 77-1 Approaches for Genetic Testing

TYPE OF MUTATION TESTING	RESOLUTION	ADVANTAGES	DISADVANTAGES	SAMPLE REQUIREMENTS
Linkage	Depends on location of polymorphic markers near putative disease gene	Possible when specific disease-causing genetic mutation is not identifiable or found	Can give only diagnostic probability based on likelihood of genetic recombination between presumed DNA mutation and polymorphic markers	Requires multiple family members with documented mendelian pattern of inheritance within family
aCGH	Several kilobases to several hundreds of kilobases	Able to detect small deletion or duplications within 1 or more genes	Can miss small deletions or insertions depending on resolution of the array used	Single patient sample sufficient, though having sample from biological parents can help with interpretation
Direct DNA-based testing (e.g., DNA sequencing)	Single base-pair changes	High specificity if previously described deleterious mutation is found	Can miss deletion or duplication of a segment of gene	Single patient sample sufficient, though having sample from biological parents can help with interpretation

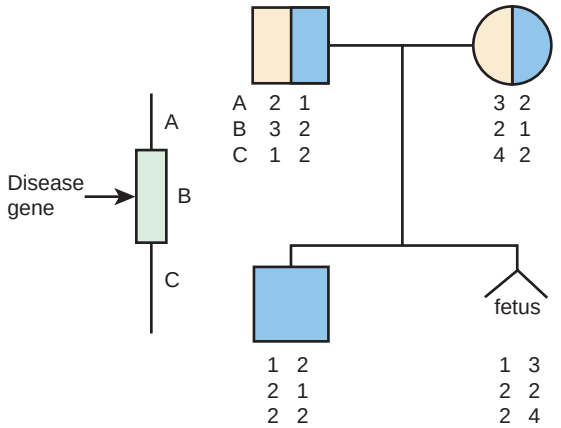

Figure 77-1 Use of linkage analysis in prenatal diagnosis of an autosomal recessive disorder. Both parents are carriers, and they have 1 affected son. The numbers below the symbols indicate alleles at 3 polymorphic loci: A, B, and C. Locus B resides within the disease gene. The affected son inherited the 1-2-2 chromosome from his father and the 2-1-2 chromosome from his mother. The fetus has inherited the same chromosome from the father, but the 3-2-4 chromosome from the mother and therefore is most likely to be a carrier.

Table 77-2 Variants That Are Incidental Findings Are Assigned to 1 of 4 Categories

Childhood onset	Medically actionable*
Childhood onset	Not medically actionable†
Adult onset	Medically actionable*
Adult onset	Not medically actionable†

*"Medically actionable" refers to a variant in a gene in which knowledge of the particular variant will affect medical decision making such as initiation of a treatment, family planning, etc.

†"Not medically actionable" refers to variants that increase the individual's risk for a disease in which no treatment is proven to significantly change medical decision making.

From Bick D, Dimmock D: Whole exome and whole genome sequencing. Curr Opin Pediatr *23:594–600, 2011, Table 2, p. 597.*

(actionable) with a specific and successful treatment/prevention strategy (Table 77-2).

Genetic testing is interpreted in light of 3 factors: analytical validity, clinical validity, and clinical utility. **Analytical validity** is test accuracy: Does the test correctly detect the presence or absence of mutation? Most genetic tests have a very high analytical validity, assuming that human error, such as sample mix-up, has not occurred. Such errors are possible, and unlike most medical tests, a genetic test is unlikely to be repeated, because it is assumed that the result will not change over time. Therefore, human errors can go undetected for long periods of time.

Clinical validity is the degree to which the test correctly predicts presence or absence of disease. False-positive and false-negative test results can occur. **False-positive results** are more likely for predictive tests than for diagnostic tests. An important contributing factor is **nonpenetrance:** An individual with an at-risk genotype might not clinically express the condition. Another factor is the finding of a genetic variant of unknown significance. Detection of a base sequence variation in an affected patient does not prove that it is the cause of the patient's disorder. In exomic sequencing, there may be more than 30,000 VUS; in whole genome sequencing there may be more than 3,000,000 VUS. Various lines of evidence are used to establish pathogenicity. These include finding the variant only in affected individuals, inferring that the variant alters the function of the gene product, determining whether the amino acid altered by the mutation is conserved in evolution, and determining whether the mutation segregates with disease in the family. In some cases, it is possible to be sure whether the variant is pathogenic or incidental. In spite of all of these approaches, it might still be impossible to definitively assign causality with 100% confidence.

False-negative results reflect an inability to detect a mutation in an affected patient. This occurs principally in disorders where genetic heterogeneity—**allelic** (different mutations occur in one causative gene) heterogeneity or **locus** (more than one gene can cause a disease) heterogeneity—is the rule. It is difficult to detect all possible mutations within a gene, because mutations can be varied in location within the gene and in the type of mutation. Direct sequencing may miss gene deletions or rearrangements, and mutations may be found within noncoding sequences such as introns or the promoter; a negative DNA test does not necessarily exclude a diagnosis.

Clinical utility is the degree to which the results of a test guide clinical management. For genetic testing, clinical utility includes establishing a diagnosis that obviates the need for additional workup or guiding surveillance or treatment. Test results may also be used as a basis for genetic counseling. For some disorders, genetic testing is possible but the test results do not add to the clinical assessment. If the diagnosis and genetic implications are already clear, it might not be necessary to pursue genetic testing.

PREDICTIVE TESTING

Predictive genetic testing involves performing a test in a person who is at risk for developing a genetic disorder **(presymptomatic),** usually on the basis of family history, yet who does not manifest signs or

symptoms. This is usually done for disorders that display age-dependent penetrance; the likelihood of manifesting signs and symptoms increases with age, as in cancer or Huntington disease.

A major caution with predictive testing is that the presence of a gene mutation does not necessarily mean that the disease will develop. Many of the disorders with age-dependent penetrance display *incomplete penetrance*. A person who inherits a mutation might never develop signs of the disorder. There is concern that a positive DNA test could result in stigmatization of the person and might not provide information that will guide medical management. Stigmatization might include psychological stress, but it could also include discrimination, including denial of health, life, or disability insurance, or employment (see Chapter 78).

It is generally agreed that predictive genetic tests should be performed for children if the results of the test will benefit the medical management of the child. Otherwise, the test should be deferred until the child has an understanding of the risks and benefits of testing and can provide informed consent. Individual states offer varying degrees of protection from discrimination on the basis of genetic testing. A major milestone in the prevention of genetic discrimination was the passage of the Genetic Information Nondiscrimination Act (GINA) in 2008, which is a federal law that prohibits discrimination in health coverage or employment based on genetic information; it does not protect against refusal of life insurance.

PREDISPOSITIONAL TESTING

It is expected that genetic tests will become available that will predict risk of disease. Common disorders are multifactorial in etiology; there may be many different genes that contribute to risk of any specific condition (see Chapter 82). Most of the genetic variants that have been found to correlate with risk of a common disease add small increments of relative risk, probably in most cases too little to guide management. It is possible that further discovery of genes that contribute to common disorders will reveal examples of variants that convey more significant levels of risk. It is also possible that testing several genes together will provide more information about risk than any individual gene variant would confer. The rationale for predispositional testing is that the results would lead to strategies aimed at risk reduction as part of a *personalized approach* to healthcare maintenance. This might include avoidance of environmental exposures that would increase risk of disease (cigarette smoking and α_1-antitrypsin deficiency), medical surveillance (familial breast cancer and mammography), or, in some cases, pharmacologic (statins and hypercholesteremia) treatment. The value of predispositional testing will need to be critically appraised through outcomes studies as these tests are developed.

PHARMACOGENETIC TESTING

Polymorphisms in drug metabolism genes can result in distinctive patterns of drug absorption, metabolism, excretion, or effectiveness (see Chapters 59 and 82). Knowledge of individual genotypes will guide pharmacologic therapy, allowing customization of choice of drug and dosage to avoid toxicity and provide a therapeutic response. An example of this is testing for polymorphisms within the methylenetetrahydrofolate reductase (*MTHFR*) gene for susceptibility of potentially increased toxicity to methotrexate antimetabolite therapy for treatment of acute lymphoblastic leukemia.

77.1 Genetic Counseling

Brendan Lee

Genetic counseling is a communication process in which the genetic contribution to health is explained, along with specific risks of transmission of a trait and options to manage the condition and its inheritance (Table 77-3). The counselor is expected to present information in a neutral, nondirective manner and to provide support to the individual and family to cope with decisions that are made.

Table 77-3 Indications for Genetic Counseling

Advanced parental age
• Maternal age ≥35 yr
• Paternal age ≥50 yr
Previous child with or family history of
• Congenital abnormality
• Dysmorphology
• Intellectual disability
• Isolated birth defect
• Metabolic disorder
• Chromosome abnormality
• Single-gene disorder
Adult-onset genetic disease (presymptomatic testing)
• Cancer
• Huntington disease
Consanguinity
Teratogen exposure (occupational, abuse)
Repeated pregnancy loss or infertility
Pregnancy screening abnormality
• Maternal serum α-fetoprotein
• Maternal triple or quad screen or variant of this test
• Fetal ultrasonography
• Fetal karyotype
Heterozygote screening based on ethnic risk
• Sickle cell anemia
• Tay-Sachs, Canavan, and Gaucher diseases
• Thalassemias
Follow-up to abnormal neonatal genetic testing
Prior to whole genome or exome sequencing
Prior to preimplantation genetic testing

Genetic counseling has evolved from a model of care that was developed in the context of prenatal diagnosis and pediatrics (see Table 77-3). For prenatal diagnosis, the task is to assess risk of a couple having a child with a genetic condition and to advise the couple about options to manage that risk, including reproductive options such as artificial insemination and prenatal or preimplantation genetic diagnosis. In pediatrics, the task is to establish a diagnosis in a child, provide longitudinal care for the child, and advise the parents about risk of recurrence as well as options to deal with that risk.

The genetic counseling role has expanded, particularly with advances in understanding the genetics of adult-onset or common disorders. Genetic counseling has a major role in risk assessment for cancer, especially breast and ovarian cancer or colon cancer, for which well-defined genetic tests are available to assess risk to an individual.

TALKING TO FAMILIES

The type of information provided to a family depends on the urgency of the situation, the need to make decisions, and the need to collect additional information. There are 4 situations in which genetic counseling is particularly important.

The first is the **prenatal diagnosis** of a congenital anomaly or genetic disease. The need for information is urgent because a family must often decide whether to continue or to terminate a pregnancy. Risks to the mother must also be considered. The second type of situation occurs when a child is born with a life-threatening congenital anomaly or genetic disease. Decisions must be made immediately with regard to how much support should be provided for the child and whether certain types of therapy should be attempted. The third situation arises later in life when a diagnosis with a genetic implication is made; a couple is planning a family and there is a family history of a genetic problem, including whether one member of a couple carries a translocation or is a carrier of an abnormal gene for an autosomal recessive or X-linked disorder; an adolescent or young adult has a family history of an adult-onset genetic disorder (Huntington disease, breast cancer); unusual features are present and a diagnosis is wanting or not possible; and there is suspected exposure to a toxic substance or teratogen. It is often necessary to have several meetings with a family in this third situation. Urgency is not as much of an issue as being sure that they have

as much information and as many options as are available. The fourth situation is counselling prior to genome sequencing where the family is given options of what they want reported back to them (actionable, nonactionable incidental findings vs. a specific diagnosis).

GENETIC COUNSELING

Providing accurate information to families requires:

- Taking a careful family history and constructing a pedigree that lists the patient's relatives (including abortions, stillbirths, deceased persons) with their sex, age, and state of health, up to and including 3rd-degree relatives.
- Gathering information from hospital records about the affected individual and, in some cases, about other family members.
- Documenting prenatal, pregnancy, and delivery histories.
- Reviewing the latest available medical, laboratory, and genetic information concerning the disorder.
- Performing a careful physical examination of the affected individual (photographs, measurements) and of apparently unaffected individuals in the family.
- Establishing or confirming the diagnosis by the diagnostic tests available.
- Giving the family information about support groups.
- Providing new information to the family as it becomes available (a mechanism for updating needs to be established).

Counseling sessions must include the specific condition, knowledge of the diagnosis of the particular condition, the natural history of the condition, the genetic aspects of the condition and the risk of recurrence, prenatal diagnosis and prevention, therapies and referral, support groups, and nondirective counseling.

Specific Condition or Conditions

If a specific diagnosis is made and confirmed, that should be discussed with the family and information should be provided in writing. However, often the disorder fits into a spectrum (e.g., one of many types of arthrogryposis) or the diagnosis is clinical rather than laboratory based. In those situations, the family needs to understand the limits of present knowledge and that additional research will probably lead to better information in the future.

Knowledge of the Diagnosis of the Particular Condition

Although it is not always possible to make an exact diagnosis, having a diagnosis as accurate as possible is important. Estimates of recurrence risk for various family members depend on an accurate diagnosis. When a specific diagnosis cannot be made (as in many cases of multiple congenital anomalies), the various possibilities in the differential diagnosis should be discussed with the family and empirical information should be provided. If specific diagnostic tests are available, they should be discussed. Often, empirical recurrence risks can be given even without a specific laboratory-based diagnosis. At the same time, even negative laboratory testing can further modify this risk.

Natural History of the Condition

It is very important to discuss the natural history of the specific genetic disorder in the family. Affected persons and their families have questions regarding the prognosis and potential therapy that can be answered only with knowledge of the natural history. If there are other possible diagnoses, their natural history may also be discussed. If the disorder is associated with a spectrum of clinical outcomes or complications, the worst and best scenarios, as well as treatment and referral to the appropriate specialist, should be addressed.

Genetic Aspects of the Condition and Recurrence Risk

The genetic aspects and risk of recurrence are important because all family members need to be aware of their reproductive choices. The genetics of the disorder can be explained with visual aids (e.g., diagrams of chromosomes). It is important to provide accurate occurrence and recurrence risks for various members of the family, including unaffected individuals. If a definite diagnosis cannot be made, it is necessary to use empirical recurrence risks. Counseling should give patients the necessary information to understand the various options and let the patients make their own informed decisions regarding pregnancy, adoption, artificial insemination, prenatal diagnosis, screening, carrier detection, and termination of pregnancy. It may be necessary to have more than 1 counseling session.

Prenatal Diagnosis and Prevention

Many different methods of prenatal diagnosis are available, depending on the specific genetic disorder (see Chapter 96). The use of ultrasonography allows prenatal diagnosis of anatomic abnormalities such as congenital heart defects. Amniocentesis and chorionic villus sampling are used to obtain fetal tissue for analysis of chromosomal abnormalities, biochemical disorders, and DNA studies. Maternal blood or serum sampling is used for some types of screening. Fetal cells can be retrieved from the umbilical cord or from maternal blood (free fetal DNA) for testing, although mothers might harbor cells from all previous pregnancies.

Therapies and Referral

A number of genetic disorders require the care of a specialist. Girls with Turner syndrome usually need to be evaluated by an endocrinologist. Prevention of known complications is a priority. The psychological adjustment of the family might require specific intervention. When to discuss the diagnosis of a chronic disease with the patient is always a difficult decision. The decision to do so should always involve the parents and an assessment of the maturity and capacity of the child or adolescent.

Alternative medicines or nontraditional therapies are often brought to attention by parents after exhaustive Internet searches. Such treatments should not necessarily be dismissed out of hand because the physician and counselor should serve as an important resource for helping parents navigate the maze of nonstandard treatments. Instead, the relative merits of treatments should be framed in the context of cost and benefit, scientific rationale, evidence from controlled and/or observational studies, the placebo effect, safety of the treatment, and the gaps in our own scientific knowledge base.

Support Groups

A large number of community lay support groups have been formed to provide information and to fund research on specific genetic and nongenetic conditions. An important part of genetic counseling is to give information about these groups to patients and to suggest a contact person for the families. Many groups have established websites with very helpful information; it is important to stress to families that their individual disease course will be unique.

Follow-up

Families should be encouraged to continue to ask questions and keep up with new information about the specific disorder. New developments often influence the diagnosis and therapy of specific genetic disorders. Lay support groups are a good source of new information.

Nondirective Counseling

Genetic counseling is usually nondirective; choices about reproduction are left to the family to decide what is right for them. The role of the counselor (physician, genetic counselor, nurse, medical geneticist) is to provide information in understandable terms and outline the range of options available.

77.2 Management and Treatment of Genetic Disorders

Brendan Lee

Genetic conditions are often chronic disorders; few are amenable to curative therapies. Nevertheless, many management options are

available. All patients and families should be provided information about the disorder, genetic counseling, anticipatory guidance, and appropriate medical surveillance. Surgical management is available for many conditions that are associated with congenital anomalies or predisposition to tumors.

Resources for patients include the National Organization of Rare Disorders (www.rarediseases.org), the Genetic Alliance (www.geneticalliance.org), the National Library of Medicine (www.nlm.nih.gov/medlineplus/geneticdisorders.html), and a large number of disease-specific websites. A current listing of federally and privately funded clinical trials, including many for genetic diseases, is available at www.*ClinicalTrials.gov*.

Specific medical therapies for genetic disorders can be classified into physiologic and replacement therapies. Much effort is currently focused in developing gene and cell therapies.

PHYSIOLOGIC THERAPIES

Physiologic therapies attempt to ameliorate the phenotype of a genetic disorder by modifying the physiology of the affected individual. The underlying defect itself is not altered by treatment. Physiologic therapies are used in the treatment of **inborn errors of metabolism** (see Chapter 84). These include dietary manipulation, such as avoiding phenylalanine by persons with phenylketonuria; coenzyme supplementation for some patients with methylmalonic acidemia and mitochondrial diseases; stimulation of alternative pathways to excrete ammonia for those with urea cycle disorders; bisphosphonate treatment for those with osteogenesis imperfecta to reduce bone fractures; and avoiding cigarette smoking by persons with α_1-antitrypsin deficiency. Physiologic treatments can be highly effective, but they usually need to be maintained for a lifetime because they do not affect the underlying genetic disorder. Many of these treatments are most effective when begun early in life before irreversible damage has occurred. This is the rationale for comprehensive newborn screening for inborn errors of metabolism.

Many physiologic therapies use small-molecule pharmaceuticals (e.g., to remove ammonia in those with urea cycle disorders). Pharmacologic treatments directly target a defective cellular pathway that is altered by an abnormal or a missing gene product. However, there are relatively few such therapies. One example is the development of imatinib, a small molecule tyrosine kinase inhibitor developed specifically to target the biologic pathway altered in chronic myelogenous leukemia (CML). CML is usually associated with a chromosome 9;22 translocation (the Philadelphia chromosome) that creates a fusion of the BCR protein and the *Abl* oncogene. Imatinib is a small molecule that blocks the adenosine triphosphate binding in the fusion protein; it is highly effective in treatment of CML and several other malignancies. Other examples include large-molecule biologics such as "humanized" monoclonal antibodies.

REPLACEMENT THERAPIES

Replacement therapies include replacement of a missing metabolite, an enzyme, an organ, or even a specific gene.

Enzyme Replacement

Enzyme replacement therapy is a component of the treatment of cystic fibrosis to manage intestinal malabsorption. Pancreatic enzymes are easily administered orally, because they must be delivered to the gastrointestinal tract.

Enzyme replacement strategies are effective for some lysosomal storage disorders. Enzymes are targeted for the lysosome by modification with mannose-6-phosphate, which binds to a specific receptor. This receptor is also present on the cell surface, so lysosomal enzymes with exposed mannose-6-phosphate residues can be infused into the blood and are taken into cells and transported to lysosomes. Enzyme replacement therapies are available for Gaucher disease and Fabry disease, some mucopolysaccharidoses (I, II, VI), Niemann-Pick disease type C, and Pompe disease.

One complication of enzyme replacement therapy is antibody response to the enzyme. The magnitude of this response is not always predictable and varies depending on the enzyme preparation and the disease. In most cases, the patient's antibody response does not affect the treatment's efficacy (e.g., in Gaucher disease), but in other situations it may be a significant hurdle (e.g., in Pompe disease).

Transplantation

Cell and organ transplantation are potentially effective approaches to replacement of a defective gene. Aside from transplantation to replace damaged tissues, transplantation of stem cells, liver, or bone marrow is also used for several diseases, mainly inborn errors of metabolism, and hematologic or immunologic disorders. A successful transplant is essentially curative, though there may be significant risks and side effects (see Chapters 135-139). Cell and tissue transplantation are effective in many clinical scenarios, but there is always short-term morbidity, often associated with either surgical (liver) or preparative (bone marrow) regimens, and long-term morbidity related to chronic immunosuppression and graft failure. Bone marrow transplantation is the best example of stem cell therapy, but much effort is focused on identifying, characterizing, expanding, and using other tissue stem cells for regenerative therapies.

Alternatively, research has focused on replacing a defective gene (gene therapy). In theory, if we can target the specific tissue that has a deficiency in the gene or gene product, this can offer a less invasive means of achieving a cure of a genetic disorder. Ultimately, gene therapy depends on the unique interaction of the disease pathophysiology, which is specific to the patient, and the gene delivery vehicle.

Gene-transfer vehicles include viral and nonviral approaches. Most human clinical trials have used viral vectors because of their efficiency of tissue transduction. In some diseases, such as X-linked and adenosine deaminase-deficient severe combined immunodeficiency, clinical gene therapy is a viable and effective option (see Chapter 126.1). Preliminary results suggest that gene therapy (intraocular delivery) may be effective for Leber congenital amaurosis.

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Chapter 78

The Genetic Approach in Pediatric Medicine

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Since the completion of the Human Genome Project, we have seen an unprecedented expansion in our understanding of how human health is impacted by variations in genomic sequence and epigenetic, non-sequence-based, changes that affect gene expression. This period has also seen the development and implementation of new clinical tests that have made it easier for physicians to detect such changes. In addition, this period has seen a dramatic increase in the availability of information about the genetic aspects of pediatric diseases, particularly on the Internet (Table 78-1).

THE BURDEN OF GENETIC DISORDERS IN CHILDHOOD

Medical problems associated with genetic disorders can appear at any age with the most obvious and serious problems typically manifesting in childhood. It has been estimated that 53/1,000 children and young adults can be expected to have diseases with an important genetic component. If congenital anomalies are included, the rate increases to 79/1,000. In 1978, it was estimated that just over half of admissions to

Table 78-1 Useful Internet Genetic Reference Sites

RESOURCE	WEB ADDRESS
National Center for Biotechnology Information. A general reference maintained by the National Library of Medicine.	www.ncbi.nlm.nih.gov
Online Mendelian Inheritance in Man. A useful resource for clinicians containing information on all known mendelian disorders and more than 12,000 genes. Information focuses on the relationship between phenotype and genotype.	www.ncbi.nlm.nih.gov/omim
Genetic Testing Registry. A resource that provides information on individual genes, genetic tests, clinical laboratories, and medical conditions. This resource also provides access to GeneReviews, a collection of expert-authored reviews on a variety of genetic disorders.	www.ncbi.nlm.nih.gov/gtr/
Genetics Home Reference. A resource that provides consumer-friendly information about the effects of genetic variations on human health.	www.ghr.nlm.nih.gov
National Human Genome Research Institute. A resource for information about human genetics and ethical issues.	www.genome.gov
Human Gene Mutation Database. A searchable index of all described mutations in human genes with phenotypes and references.	www.hgmd.cf.ac.uk
DECIPHER. A database designed to aid physicians in determining the potential consequences of chromosomal deletions and duplications.	http://decipher.sanger.ac.uk
Database of Genomic Variants. A database of chromosomal alterations seen in normal controls.	http://dgv.tcag.ca/dgv/app/home
Gene Letter. An online magazine of genetics.	www.geneletter.com
American Society of Human Genetics	www.ashg.org
American College of Medical Genetics	www.acmg.net

pediatric hospitals were for a genetically determined condition. By 1996, owing to changes in healthcare delivery and a greater understanding of the genetic basis of many disorders, that percentage rose to 71% in 1 large pediatric hospital in the United States, and 96% of chronic disorders leading to admission had an obvious genetic component or were influenced by genetic susceptibility. Major categories of genetic disorders include single-gene, genomic, chromosomal, and multifactorial conditions.

Individually, **single-gene disorders** are rare, but collectively they represent an important contribution to childhood disease. The hallmark of a single-gene disorder is that the phenotype is overwhelmingly determined by changes that affect an individual gene. The phenotypes associated with single-gene disorders can vary from one patient to another based on the severity of the change affecting the gene and additional modifications caused by genetic, environmental, and/or stochastic factors. This feature of genetic disease is termed **variable expressivity**. Common single-gene disorders include sickle cell anemia and cystic fibrosis.

Single-gene disorders tend to occur when changes in a gene have a profound effect on the quantity of the gene product produced—either too much or too little—or the function of the gene product—either a loss of function or a harmful gain of function. Single-gene disorders can be caused by de novo changes that are not found in the unaffected parents of the affected individual or they may be caused by inherited changes. When a single-gene disorder is known to be caused by changes in only 1 gene or a small number of individual genes, searching for deleterious changes is most often performed by directly sequencing that gene and, in some cases, looking for small deletions and/or duplications. When multiple genes can potentially cause a particular disorder, it is sometimes more efficient and cost effective to screen large numbers of disease causing genes using a disease-specific panel that takes advantage of next generation sequencing technology than to screen genes individually. When such panels are not available, or when the diagnosis is in question, physicians may consider screening the protein coding regions of all genes by **whole exome sequencing** on a clinical basis. Indeed in many circumstances, whole exome sequencing is less expensive than sequencing multiple individual genes. In the future, whole genome sequencing—in which an individual's entire genome is sequenced—may become a valid clinical option as the cost of such tests fall and our ability to interpret the clinical consequences of thousands of changes that are identified in such tests improves.

The risk of having a child with a particular single gene disorder can vary from one population to another. In some cases this is the result of a **founder effect,** in which a specific change affecting a disease-causing gene becomes relatively common in a population derived from a small number of founders. This high frequency is maintained when there is relatively little interbreeding with persons outside of that population because of social, religious, or physical barriers. This is the case for Tay-Sachs disease in Ashkenazi Jews and French Canadians. Other changes may be subject to positive selection when found in the heterozygous carrier state. In this case, carriers of a genetic change (heterozygotes) have a survival advantage over noncarriers. This can occur even when individuals who inherit 2 copies of the change (homozygotes) have severe medical problems. This type of positive selection is evident among individuals in sub-Saharan Africa who carry a hemoglobin mutation that confers relative resistance to malaria but causes sickle cell anemia in homozygotes.

Genomic disorders are a group of diseases caused by alterations in the genome, including deletions (copy number loss), duplications (copy number gain), inversions (altered orientation of a genomic region) and chromosomal rearrangements (altered location of a genomic region). **Contiguous gene disorders** are caused by changes that affect two or more genes that contribute to the clinical phenotype and are located near each other on a chromosome. DiGeorge syndrome, which is caused by deletions of genes located on chromosome 22q11, is a common example. Some genomic disorders are associated with distinctive phenotypes whose pattern can be recognized clinically. Other genomic disorders do not have a distinctive pattern of anomalies, but can cause developmental delay, cognitive impairment, structural birth defects, abnormal growth patterns and changes in physical appearance. Fluorescent in situ hybridization (FISH) can provide information about the copy number and location of a specific genomic region. Array-based copy number detection assays can be used to screen for chromosomal deletions (large and small) and duplication across the genome but do not provide information about the orientation or location of genomic regions. A chromosome analyses (karyotyping) can detect relatively large chromosomal deletions and duplications and can also be useful in identifying inversions and chromosomal rearrangements even when they are copy-number neutral

changes that do not result in a deletion or duplication of genomic material.

Deletions, duplications, and chromosomal rearrangements that affect whole chromosomes, or large portions of a chromosome, are commonly referred to as **chromosomal disorders.** One of the most common chromosomal disorders is Down syndrome, which is most commonly associated with the presence of an extra copy, or **trisomy,** of an entire chromosome 21. When all or a part of a chromosome is missing, the disorder is referred to as **monosomy**. Translocations are a type of chromosomal rearrangement in which a genomic region from 1 chromosome is transferred to a different location on the same chromosome or on a nonhomologous chromosome. Translocations can be balanced, meaning that no genetic material has been lost or gained, or they can be unbalanced, in which case some genetic material has been deleted or duplicated. Chromosomal disorders can often be identified on a chromosome analysis (karyotype) or by FISH. Evidence of a chromosomal disorder may also be revealed by an array-based copy number detection assays if genetic material has been gained or lost.

In some cases, only a portion of cells that make up a person's body are affected by the single gene defect, the genomic disorder or the chromosomal defect. This is referred to as **mosaicism** and indicates that the individual's body is made up of 2 or more distinct cell populations.

Polygenic disorders are caused by the cumulative effects of changes or variations in more than 1 gene. Multifactorial disorders are caused by the cumulative effects of changes or variations in multiple genes and/or the combined effects of both genetic and environmental factors. Spina bifida and isolated cleft lip or palate are common birth defects that display multifactorial inheritance patterns. Multifactorial inheritance is seen in many common pediatric disorders, such as asthma and diabetes mellitus. These traits can cluster in families but do not have a mendelian pattern of inheritance (see Chapter 80). In most cases, the genetic changes or variations that are contributing to a particular case are unknown and genetic counseling is based on empirical data.

THE CHANGING PARADIGM OF GENETICS IN MEDICINE

Genetic testing is increasingly available for a wide variety of both rare and relatively common genetic disorders. Genetic testing is commonly used in pediatric medicine to resolve uncertainty regarding the underlying etiology of a child's medical problems and provides a basis for improved genetic counseling and possibly specific therapy. Even in cases where a specific treatment is not available, identifying a genetic cause can aid physicians in providing individuals and family with accurate prognostic and recurrence risk information and usually helps to relieve unfounded feelings of guilt and/or stem the tide of misdirected blame.

Genetic tests will ultimately come to underlie a high proportion of medical decisions and will be seamlessly incorporated into routine medical care. Although most genetic testing is presently aimed at identifying or confirming a diagnosis, in the future, genetic testing may find wider application as a means of determining if an individual is predisposed to develop a particular disease. Another area in which genetic testing could make a significant impact is on individualized drug treatment. It has long been known that genetic variation in the enzymes involved in drug metabolism underlies differences in the therapeutic effect and toxicity of some drugs. As the genetic changes that underlie these variations are identified, new genetic tests may be developed that will allow physicians to tailor treatments based on individual variations in drug metabolism, responsiveness, and susceptibility to toxicity (see Chapter 59). It is likely that the expansion of such testing will depend, at least in part, on the extent to which such testing can be linked to strategies to prevent disease or improve outcome (see Chapter 77). If such links can be made, it could usher in a new era of personalized medical treatment.

Long-standing and highly successful carrier screening programs have existed for disorders such as Tay-Sachs disease and many other rare single-gene disorders that are prevalent in specific populations. Couples are commonly offered screening for a variety of conditions, in part based on ancestry (Tay-Sachs disease, hemoglobinopathies, cystic fibrosis). Couples found to be at increased risk for such disorders can be offered prepregnancy or prenatal testing aimed at detecting specific disease causing mutations.

Prenatal screening is routinely offered for chromosomal disorders such as trisomy 13, trisomy 18, and Down syndrome. An increasing number of pregnancies affected by these and other genetic disorders are being recognized by noninvasive screening tests of maternal serum in the first and second trimesters and by fetal ultrasound. When genetic disorders are suspected, chorionic villus sampling at 10-12 wk of gestation or by amniocentesis at 16-18 wk of gestation can provide material for genetic testing. Approaches to noninvasive prenatal diagnosis by sampling of cell-free fetal DNA or fetal cells in maternal blood are also becoming available. When a couple is at risk for a specific genetic defect, **preimplantation genetic diagnosis** can sometimes be used to select unaffected early embryos, which are then implanted as part of an in vitro fertilization procedure.

Although prenatally obtained genetic material can be used to identify single-gene disorders, genomic disorders, and chromosomal anomalies, the information obtained on any pregnancy depends on the tests that are ordered. It is important that physicians select the most appropriate prenatal tests and that couples understand both the limitations of these tests and that no amount of genetic testing can guarantee the birth of a healthy child.

Specific treatments are not available for the majority of genetic disorders. However, there are some important exceptions. Inborn errors of metabolism were the first genetic disorders to be recognized, and many are amenable to treatment by dietary manipulation (see Chapter 84). These conditions result from genetically determined deficiency of specific enzymes, leading to the buildup of toxic substrates and/or deficiency of critical end products.

Individual metabolic disorders tend to be very rare, but their combined impact on the pediatric population is significant. Tandem mass spectrometry has made it relatively inexpensive to screen for a large number of these disorders in the newborn period. Use of this technology not only dramatically increases the number of metabolic disorders identified within a population but also allows treatment to be initiated at a much earlier stage in development (see Chapters 77 and 84).

Another area where progress has been made regarding genetic therapies has been in the treatment of lysosomal storage disorders. These are a group of metabolic diseases caused by defects in lysosomal function. Lysosomes are cellular organelles that contain specific digestive enzymes. Some of these disorders that were lethal or associated with intractable chronic illness can now be treated using specially modified enzymes that are administered by intravenous infusion. These enzymes are then taken up by cells and incorporated into lysosomes. Conditions such as Gaucher disease and Fabry disease are routinely treated using **enzyme replacement,** and similar therapies are being developed for other lysosomal disorders.

Therapeutic advances are also being made in the treatment of nonmetabolic genetic disorders. Improvements in surgical techniques and intensive care medicine are extending the survival of children with life-threatening birth defects like congenital diaphragmatic hernia and severe cardiac defects. In many cases, the life expectancy of children with debilitating genetic disorders is also increasing. A good example is the increasing life expectancy of individuals with cystic fibrosis, largely owing to improvements in antibiotic therapy as well as the management of chronic pulmonary disease and malabsorption. A major consequence of these advances is that an increasing percentage of affected patients is surviving into adulthood, creating a need to transition care from pediatric to adult providers.

Gene-replacement therapies have long been anticipated. However, it has proved difficult to develop safe and effective approaches for inserting genes into diseased tissues in a way that allows physiologically meaningful levels of gene expression to be maintained over long periods. Stem cell-based therapies have also been touted as a potential treatment for a number of intractable disorders, but clear evidence that such therapies are effective has yet to materialize.

ETHICS ISSUES

Like all medical care, genetic testing, diagnosis, and treatment should be performed confidentially. Nothing is as personal as one's genetic information, and all efforts should be made to avoid any stigma for the patient. Many people fear that results of genetic testing will put them, or their child, at risk for genetic discrimination. Genetic discrimination occurs when people are treated unfairly because of a difference in their DNA that suggests that they have a genetic disorder or are at an increased risk of developing a certain disease. In the United States, the Genetic Information Nondiscrimination Act of 2008 protects individuals from genetic discrimination at the hands of health insurers and employers, but does not extend protection against discrimination from providers of life, disability, or long-term care insurance.

Like all medical decision-making, the decisions about genetic testing should be based on a careful evaluation of the potential benefits and risks. In the pediatric setting, these decisions may be more difficult because physicians and parents are often called on to make decisions for a child who cannot directly participate in discussions about the testing. Molecular diagnostic tests are often used to diagnose malformation syndromes, cognitive delay, or other disabilities wherein there is a clear benefit to the child. In other cases, such as genetic testing for susceptibility to adult-onset diseases, it is appropriate to wait until the child or adolescent is mature enough to weigh the pros and cons and make his or her own decisions about genetic testing.

Policies regarding genetic testing of children have been developed collaboratively by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics and Genomics (ACMG; *Pediatrics* 131[3]:620-622, 2013). These recommendations are outlined here:

1. Decisions about whether to offer genetic testing and screening should be driven by the best interest of the child.
2. Genetic testing is best offered in the context of genetic counseling. Genetic counseling can be performed by clinical geneticists, genetic counselors, or any other health care provider with appropriate training and expertise. The AAP and ACMG support the expansion of educational opportunities in human genomics and genetics for medical students, residents, and practicing pediatric primary care providers.

Diagnostic Testing

3. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally, and when appropriate, the assent of the child should be obtained.
4. When performed for therapeutic purposes, pharmacogenetic testing of children is acceptable, with permission of parents or guardians and, when appropriate, the child's assent. If a pharmacogenetic test result carries implications beyond drug targeting or dose-responsiveness, the broader implications should be discussed before testing.

Newborn Screening

5. The AAP and ACMG support the mandatory offering of newborn screening for all children. After education and counseling about the substantial benefits of newborn screening, its remote risks, and the next steps in the event of a positive screening result, parents should have the option of refusing the procedure, and an informed refusal should be respected.

Carrier Testing

6. The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. The AAP and ACMG advise against school-based testing or screening programs, because the school environment is unlikely to be conducive to voluntary participation, thoughtful consent, privacy, confidentiality, or appropriate counseling about test results.
7. For pregnant adolescents or for adolescents considering reproduction, genetic testing and screening should be offered as clinically indicated, and the risks and benefits should be explained clearly.

Predictive Genetic Testing

8. Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.
9. Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.
10. For ethical and legal reasons, healthcare providers should be cautious about providing predictive genetic testing to minors without the involvement of their parents or guardians, even if a minor is mature. Results of such tests may have significant medical, psychological, and social implications, not only for the minor but also for other family members.

Histocompatibility Testing

11. Tissue compatibility testing of minors of all ages is permissible to benefit immediate family members but should be conducted only after thorough exploration of the psychosocial, emotional, and physical implications of the minor serving as a potential stem cell donor. A donor advocate or similar mechanism should be in place from the outset to avert coercion and safeguard the interests of the child.

Adoption

12. The rationale for genetic testing of children in biological families should apply for adopted children and children awaiting placement for adoption. If a child has a known genetic risk, prospective adoptive parents must be made aware of this possibility. In rare cases, it may be in a child's best interest to undergo predictive genetic testing for a known risk before adoption to ensure the child's placement with a family capable of and willing to accept the child's potential medical and developmental challenges. In the absence of such indications, genetic testing should not be performed as a condition of adoption.

Disclosure

13. At the time of genetic testing, parents or guardians should be encouraged to inform their child of the test results at an appropriate age. Parents or guardians should be advised that, under most circumstances, a request by a mature adolescent for test results should be honored.
14. Results from genetic testing of a child may have implications for the parents and other family members. Healthcare providers have an obligation to inform parents and the child, when appropriate, about these potential implications. healthcare providers should encourage patients and families to share this information and offer to help explain the results to the extended family or refer them for genetic counseling.
15. Misattributed paternity, use of donor gametes, adoption, or other questions about family relationships may be uncovered "incidentally" whenever genetic testing is performed, particularly when testing multiple family members. This risk should be discussed, and a plan about disclosure or nondisclosure should be in place before testing.

Direct-to-Consumer Testing

16. The AAP and ACMG strongly discourage the use of direct-to-consumer and home-kit genetic testing of children because of the lack of oversight on test content, accuracy, and interpretation.

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Chapter 79

The Human Genome

Daryl A. Scott and Brendan Lee

The Human Genome Project, culminated in the sequencing of the human genome and greatly expanded our ability to study human genes and to explore the roles of genes in both rare and common disorders. Over time, it has also become apparent that the genome includes far more than a coded store of information to produce proteins.

The human genome has approximately 25,000 genes that encode the wide variety of proteins found in the human body. Reproductive or germline cells contain 1 copy (N) of this genetic complement and are **haploid,** whereas somatic (nongermline) cells contain 2 complete copies (2N) and are **diploid.** Genes are organized into long segments of DNA, which, during cell division, are compacted into intricate structures together with proteins to form chromosomes. Each somatic cell has 46 chromosomes: 22 pairs of autosomes, or nonsex chromosomes, and 1 pair of sex chromosomes (XY in a male, XX in a female). Germ cells (ova or sperm) contain 22 autosomes and 1 sex chromosome, for a total of 23. At fertilization, the full diploid chromosome complement of 46 is again realized in the embryo.

Most of the genetic material is contained in the cell's nucleus. The mitochondria (the cell's energy-producing organelles) contain their own unique genome. The **mitochondrial chromosome** consists of a double-stranded circular piece of DNA, which contains 16,568 base pairs (bp) of DNA and is present in multiple copies per cell. The proteins that occupy the mitochondria are produced either in the mitochondria, using information contained in the mitochondrial genome, or are produced outside of the mitochondria, using information contained in the nuclear genome and transported into the organelle. Sperm do not usually contribute mitochondria to the developing embryo, so all mitochondria are maternally derived and a child's mitochondrial genetic makeup derives exclusively from the child's biological mother.

FUNDAMENTALS OF MOLECULAR GENETICS

The central tenet of molecular genetics is that information encoded in DNA, predominantly located in the cell nucleus, is transcribed into messenger RNA (mRNA), which is then transported to the cytoplasm, where it is translated into protein. A gene is a unit that includes a regulatory region and a coding region that stores information corresponding to the sequence of amino acids in a specific protein.

DNA consists of a pair of chains of a sugar-phosphate backbone linked by pyrimidine and purine bases to form a **double helix** (Fig. 79-1). The sugar in DNA is deoxyribose. The pyrimidines are cytosine (C) and thymine (T); the purines are guanine (G) and adenine (A). The bases are linked by hydrogen bonds such that A always pairs with T and G with C. Each strand of the double helix has polarity, with a free phosphate at one end (5′) and an unbonded hydroxyl on the sugar at the other end (3′). The 2 strands are oriented in opposite polarity in the double helix.

The replication of DNA follows the pairing of bases in the parent DNA strand. The original 2 strands unwind by breaking the hydrogen bonds between base pairs. Free nucleotides, consisting of a base attached to a sugar-phosphate, form new hydrogen bonds with their complementary bases on the parent strand; new phosphodiester bonds are created by the enzyme **DNA polymerase.** Replication of chromosomes begins simultaneously at multiple sites, forming replication bubbles that expand bidirectionally until the entire DNA molecule (chromosome) is replicated. Errors in DNA replication, or mutations induced by environmental mutagens such as irradiation or chemicals, are detected and potentially corrected by DNA repair systems.

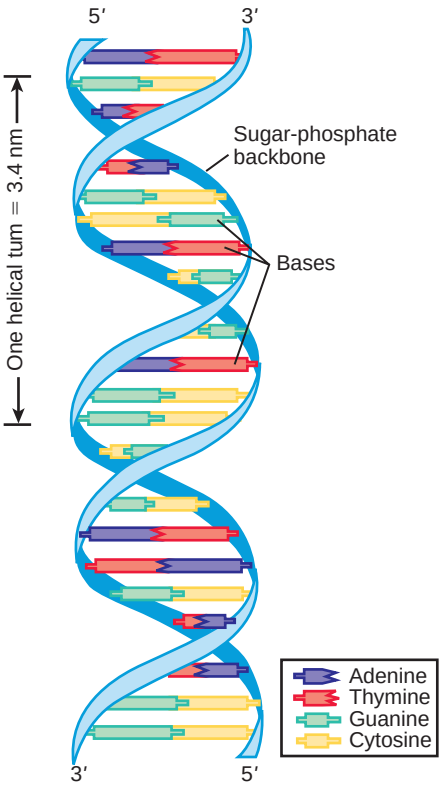

Figure 79-1 DNA double helix, with sugar-phosphate backbone and nitrogenous bases. *(From Jorde LB, Carey JC, Bamshad MJ, et al, editors:* Medical genetics, *ed 2, St. Louis, 1999, Mosby, p. 8.)*

A prototypical gene consists of a regulatory region, segments called **exons** that encode the amino acid sequence of a protein, and intervening segments called **introns** (Fig. 79-2). **Transcription** starts at the promoter region and continues through the entire length of the gene to form mRNA. The introns are removed and the exons spliced together to form a mature message, which is exported to the cytoplasm. There the mRNA is bound to ribosomes and translated into protein.

Transcription is initiated by attachment of RNA polymerase to the promoter site upstream of the beginning of the coding sequence. Specific proteins bind to the region to either repress or activate transcription by opening up the chromatin, which is a complex of DNA and histone proteins. It is the action of these regulatory proteins **(transcription factors)** that determines, in large part, when a gene is turned on or off. Some genes are also turned on and off by methylation of cytosine bases that are adjacent to guanines (CpG [cytosine-phosphate-guanine] bases). Methylation is an example of an **epigenetic** change, meaning a change that can affect gene expression, and possibly the characteristics of a cell or organism, but that does not involve a change in the underlying genetic sequence. Gene regulation is flexible and responsive, with genes being turned on or off during development and in response to internal and external environmental conditions and stimuli.

Transcription proceeds through the full length of the gene, synthesizing mRNA in a 5′ to 3′ direction. RNA, like DNA, is a sugar-phosphate chain with pyrimidines and purines. In RNA, the sugar is ribose and uracil replaces the thymine found in DNA. The RNA reads off 1 strand of DNA to copy a complementary RNA sequence. A "cap" consisting of 7-methylguanosine is added to the 5′ end of the RNA in a 5′-5′ bond and, for most transcripts, several hundred adenine bases are enzymatically added to the 3′ end after transcription.

mRNA **processing** occurs in the nucleus and consists of excision of the introns and splicing together of the exons. Specific sequences at the start and end of introns mark the sites where the splicing machinery will act on the transcript. In some cases, there may be tissue-specific

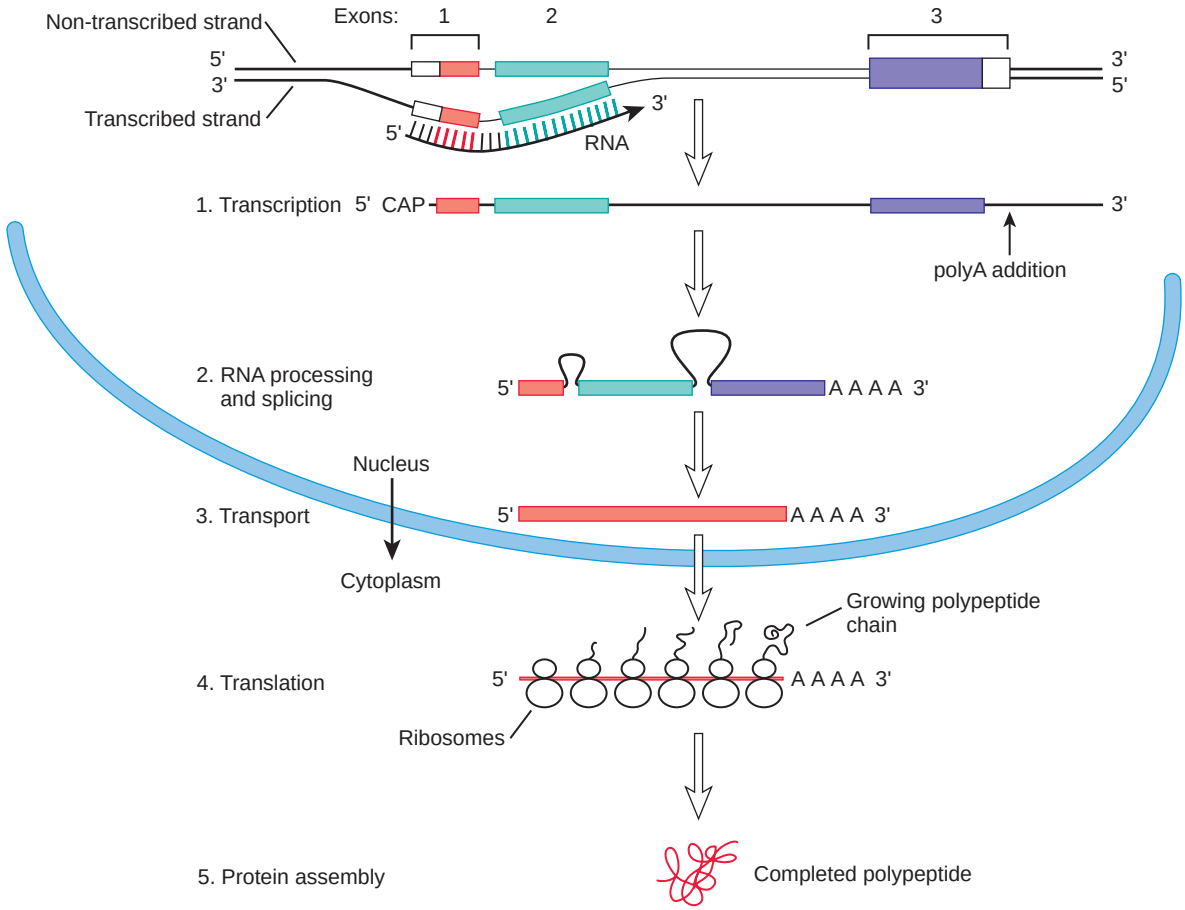

Figure 79-2 Flow of information from DNA to RNA to protein for a hypothetical gene with three exons and two introns. Within the exons, blue indicates the coding sequences. Steps include transcription, RNA processing and splicing, RNA transport from the nucleus to the cytoplasm, and translation. *(From Nussbaum RL, McInnis RR, Willard HF, Hamosh A, editors:* Thompson & Thompson genetics in medicine, *ed 7, Philadelphia, 2007, Saunders/Elsevier,* Fig 3.5, *p. 31.)*

patterns to splicing, so that the same primary transcript can produce multiple distinct proteins.

The processed transcript is next exported to the cytoplasm, where it binds to ribosomes, which are complexes of protein and RNA. The genetic code is then read in triplets of bases, each triplet corresponding with a specific amino acid or providing a signal that terminates **translation.** The triplet codons are recognized by transfer RNAs that include complementary anticodons and bind the corresponding amino acid, delivering it to the growing peptide. A new amino acid is enzymatically attached to the peptide; each time an amino acid is added, the ribosome moves one triplet codon step along the mRNA. Eventually a stop codon is reached, at which point translation ends and the peptide is released. In some proteins, there are **posttranslational modifications,** such as attachment of sugars (glycosylation); the protein is then delivered to its destination within or outside the cell by trafficking mechanisms that recognize portions of the peptide.

An emerging layer of complexity and genetic regulation is that of noncoding RNAs. This refers to RNAs that are transcribed from DNA but are not translated into proteins. Noncoding RNAs function in mediating splicing and the processing of coding RNAs in the nucleus and the translation of coding RNAs in ribosomes. The roles of large noncoding RNAs (>200 bp) and short noncoding RNAs (<200 bp) extend beyond these processes to impact a diverse set of biologic functions including regulation of gene expression. For example, microRNAs (miRNAs) are a class of small RNAs that control gene expression in the cell by directly targeting specific sets of coding RNAs by direct RNA–RNA binding. This RNA–RNA interaction can lead to degradation of the target coding RNA or inhibition of translation of the protein specified by that coding RNA. miRNAs, in general, target and regulate several hundred mRNAs.

GENETIC VARIATION

The process of producing protein from a gene is subject to disruption at multiple levels owing to alterations in the coding sequence (Fig. 79-3). Changes in the regulatory region can lead to altered gene expression, including increased or decreased rates of transcription, failure of gene activation, or activation of the gene at inappropriate times or in inappropriate cells. Changes in the coding sequence can lead to **substitution** of one amino acid for another **(missense mutation** or **nonsynonymous)** or creation of a stop codon in the place of an amino acid codon. Overall, missense or nonsense mutations are the most common (~56% of mutations); small deletions or insertions represent approximately 24% of mutations (Table 79-1). Some single-base changes do not affect the amino acid (silent or wobble mutation or synonymous), because there may be several triplet codons that correspond with a single amino acid. Amino acid substitutions can have a profound effect on protein function if the chemical properties of the substituted amino acid are markedly different from the usual one. Other substitutions can have a subtle or no effect on protein function, particularly if the substituted amino acid is chemically similar to the original one.

Genetic changes can also include **insertions** or **deletions.** Insertions or deletions of a nonintegral multiple of 3 bases into the coding sequence leads to a **frameshift,** altering the grouping of bases into triplets. This leads to translation of an incorrect amino acid sequence and often a premature stop to translation. Insertion or deletion of an

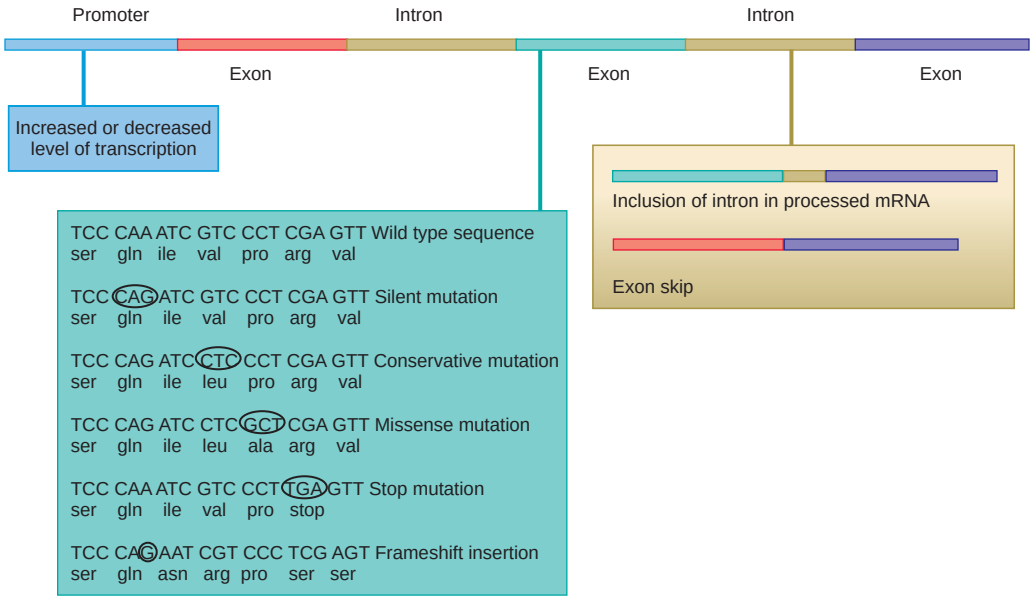

Figure 79-3 Various types of intragenic mutations. Promoter mutations alter rate of transcription or disrupt gene regulation. Base changes within exons can have various effects, as shown. Mutations within introns can lead to inclusion of some intronic sequence in the final processed mRNA, or it can lead to exon skipping.

Table 79-1 Main Classes, Groups, and Types of Mutation and Effects on Protein Product

CLASS	GROUP	TYPE	EFFECT ON PROTEIN PRODUCT
Substitution	Synonymous	Silent*	Same amino acid
	Nonsynonymous	Missense*	Altered amino acid—may affect protein function or stability
		Nonsense*	Stop codon—loss of function or expression from degradation of mRNA
		Splice site	Aberrant splicing—exon skipping or intron retention
		Promoter	Altered gene expression
Deletion	Multiple of 3 (codon)		In-frame deletion of 1 or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of function or expression
	Large deletion	Partial gene deletion	May result in premature termination with loss of function or expression
		Whole gene deletion	Loss of expression
Insertion	Multiple of 3 (codon)		In-frame insertion of 1 or more amino acid(s)—may affect protein function or stability
	Not multiple of 3	Frameshift	Likely to result in premature termination with loss of function or expression
	Large insertion	Partial gene duplication	May result in premature termination with loss of function or expression
		Whole gene duplication	May have an effect because of increased gene dosage
	Expansion of trinucleotide repeat	Dynamic mutation	Altered gene expression or altered protein stability or function

*Some have been shown to cause aberrant splicing.
From Turnpenny P, Ellard S (Editors): Emery's elements of medical genetics, *ed 14, Philadelphia, 2012, Elsevier/Churchill Livingstone, Table 2.2, p. 23.*

integral multiple of 3 bases into the coding sequence will insert or delete a corresponding number of amino acids from the protein leading to in-frame alterations that maintain the amino acid sequence outside of the deleted or duplicated amino acids. Larger-scale insertions or deletions can disrupt a coding sequence or result in complete deletion of an entire gene or group of genes.

Mutations usually can be classified as causing a loss of function or a gain of function. **Loss-of-function mutations** cause a reduction in the level of protein function as a result of decreased expression or production of a protein that does not work as efficiently. In some cases, loss of protein function from one gene is sufficient to cause disease. **Haploinsufficiency** describes the situation in which maintenance of a normal phenotype requires the proteins produced by both copies of a gene, and a 50% decrease in gene function results in an abnormal phenotype. Hence, haploinsufficient phenotypes are, by definition, dominantly inherited. Loss-of-function mutations can also have a dominant negative effect when the abnormal protein product actively interferes with the function of the normal protein product. Both of these situations lead to diseases inherited in a dominant fashion (see Chapter 80). In other cases, loss-of-function mutation must be present in both copies of a gene before an abnormal phenotype results. This situation typically results in diseases inherited in a recessive fashion (see Chapter 80).

Gain-of-function mutations typically cause dominantly inherited diseases. These mutations can result in production of a protein molecule with an increased ability to perform a normal function or they

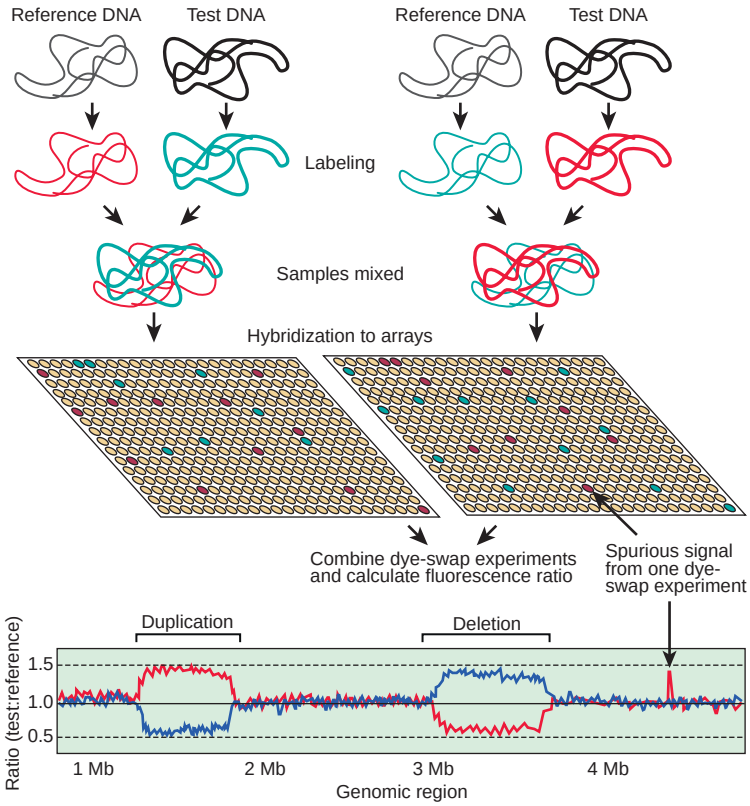

Figure 79-4 Array comparative genomic hybridization. Test and reference DNA samples are differentially labeled, mixed, and passed over a target array of probes (e.g., bacterial artificial chromosome clones or oligonucleotides) containing DNA fragments from across the whole human genome. The experiment is often repeated with reversal of the test and reference dyes to detect dye effects or identify spurious signals. DNA samples hybridize with their corresponding probe, and the ratio of fluorescence from each probe (test:reference) is used to detect regions that vary in copy number between the test and the reference sample (*red line:* original hybridization; *blue line:* dye-swapped hybridization). Equal copy number for both the test and reference DNA is identified by equal binding, resulting in a ratio of 1:1. Duplication in a genomic region of the test sample is identified by an increased ratio, and a deletion is identified by a decreased ratio, but a deletion in the test sample is indistinguishable from a duplication in the reference sample. These ratios are usually converted to log2 scale for further analysis. *(Adapted from Feuk L, Carson AR, Scherer SW: Structural variation in the human genome,* Nat Rev Genet *7:85–97, 2006, with permission from* Nature Reviews Genetics.*)*

can confer a novel property on the protein. The gain-of-function mutation in **achondroplasia,** the most common of the disproportionate, short-limbed short stature disorders, exemplifies the enhanced function of a normal protein. Achondroplasia results from a mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*), which leads to activation of the receptor, even in the absence of fibroblast growth factor. In **sickle cell disease,** an amino acid is substituted into the hemoglobin molecule that has little effect on the ability of the protein to transport oxygen. However, sickle hemoglobin chains have a novel property. Unlike normal hemoglobin, sickle hemoglobin chains aggregate under conditions of deoxygenation, forming fibers that deform the red cells.

Other gain-of-function mutations result in overexpression or inappropriate expression of a gene product. Many cancer-causing genes **(oncogenes)** are normal regulators of cellular proliferation during development. However, expression of these genes in adult life and/or in cells in which they usually are not expressed can result in neoplasia.

In some cases, changes in gene expression are caused by changes in the number of copies of a gene that are present in the genome (Fig. 79-4). Although some **copy number variations** are common and do not appear to cause or predispose to disease, others are clearly disease causing. Charcot-Marie-Tooth disease type 1A, the most common inherited form of chronic peripheral neuropathy of childhood, is caused by duplications of the gene for peripheral myelin protein 22, resulting in overexpression as a consequence of the existence of 3 active copies of this gene. Deletions of this same gene leaving only 1 active copy are responsible for a different disorder, hereditary neuropathy with liability to pressure palsies.

Deletions and duplications can vary in their extent and can involve several genes, even when they are not visible on a traditional chromosome analysis. Such changes are commonly called **microdeletions** and **microduplications.** When deletion or duplication of 2 or more genes in the same chromosomal region each play a role in the resulting clinical features, the condition can also be referred to as a **contiguous gene disorder**.

In some cases the recognition of a specific constellation of features leads the clinician to suspect a specific microdeletion or microduplication syndrome. Examples of such disorders include Smith-Magenis, DiGeorge, and Williams syndromes. In other cases, the clinician may be alerted to this possibility by an unusually diverse array of clinical features in one patient or the presence of unusual features in a person with a known condition. Owing to the close physical proximity of a series of genes, different deletions involving the short arm of the X chromosome can produce individuals with various combinations of ichthyosis, Kallmann syndrome, ocular albinism, intellectual disability, chondrodysplasia punctata, and short stature.

DNA rearrangements can also take place in somatic cells-meaning cells that do not go on to produce ova or sperm. Rearrangements that occur in lymphoid cells are required for the formation of functional immunoglobulin in B cells and antigen-recognizing receptors on T cells. Large segments of DNA, which code for the variable and the constant regions of either immunoglobulin or the T-cell receptor, are physically joined at a specific stage in the development of an immunocompetent lymphocyte. These rearrangements take place during development of the lymphoid cell lineage in humans and result in the extensive diversity of immunoglobulin and T-cell receptor molecules. It is as a result of this postgermline DNA rearrangement that no 2 individuals, not even identical twins, are really identical, because mature lymphocytes from each will have undergone random DNA rearrangements at these loci.

Studies of the human genome sequence reveal that any 2 individuals differ in about 1 base in 1,000. Some of these differences are silent; some result in changes that explain phenotypic differences (hair or eye color, physical appearance); some have medical significance, causing single-gene disorders such as sickle cell anemia or explaining susceptibility to common pediatric disorders such as asthma. Genetic variants in a single gene that occur at a frequency of >1% in a population are often referred to as **polymorphisms.** These variations may be silent or subtle or have significant phenotypic effects.

GENOTYPE-PHENOTYPE CORRELATIONS IN GENETIC DISEASE

The term **genotype** is used to signify the internally coded, heritable information of an individual and can also be used to refer to which particular alternative version **(allele)** of a gene is present at a specific location **(locus)** on a chromosome. A **phenotype** is the observed structural, biochemical, and physiologic characteristics of an individual, determined by the genotype, and can also refer to the observed structural and functional effects of a mutant allele at a specific locus. Many mutations result in predictable phenotypes. In these cases, physicians can predict clinical outcomes and plan appropriate treatment strategies based on a patient's genotype.

The **long QT syndrome** exemplifies a disorder with predictable associations between a patient's genotype and his or her phenotype (see Chapter 435.5). Long QT syndrome is genetically heterogeneous, meaning that mutations in several different genes can cause the same disorder. The risk for cardiac events (syncope, aborted cardiac arrest, or sudden death) is higher with long QT syndrome mutations involving the *KCNQ1* gene (63%) or the *KCNH2* gene (46%) than among subjects with mutations in the *SCN5A* gene (18%). In addition, those with mutations involving *KCNQ1* experience most of their episodes during exercise and rarely during rest or sleep. In contrast, individuals with mutations in *KCNH2* and *SCN5A* are more likely to have episodes during sleep or rest, and rarely during exercise. Therefore, mutations in specific genes (genotype) are correlated with specific manifestations (phenotype) of long QT syndrome. These types of relationships are commonly referred to as *genotype–phenotype correlations.*

Mutations in the fibrillin-1 gene associated with **Marfan syndrome** represent another example of predictable genotype–phenotype correlations (see Chapter 702). Marfan syndrome is characterized by the combination of skeletal, ocular, and aortic manifestations, with the most devastating outcome being aortic root dissection and sudden death. Sixty-five exons make up the fibrillin-1 gene, and mutations have been found in almost all of these exons. The location of the mutation within the gene (genotype) might play a significant role in determining the severity of the condition (phenotype). Neonatal Marfan syndrome is caused by mutations in exons 24-27 and in exons 31 and 32, whereas milder forms are caused by mutations in exons 59-65 and in exons 37 and 41.

Genotype–phenotype correlations have also been observed in some complications of **cystic fibrosis** (CF; see Chapter 403). Although pulmonary disease is the major cause of morbidity and mortality, CF is a multisystem disorder that affects not only the epithelia of the respiratory tract but also the exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands. CF is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene. More than 1,600 different mutations have been identified. The most common is a deletion of 3 nucleotides that removes the amino acid phenylalanine (F) at the 508th position on the protein (ΔF508 mutation), which accounts for approximately 70% of all CF mutations and is associated with severe disease. The best genotype–phenotype correlations in CF are seen in the context of pancreatic function, with most common mutations being classified as either pancreatic sufficient or pancreatic insufficient. Persons with pancreatic sufficiency usually have either 1 or 2 pancreatic-sufficient alleles, indicating that pancreatic-sufficient alleles are dominant. In contrast, the genotype–phenotype correlation in pulmonary disease is much weaker, and persons with identical genotypes have wide variations in the severity of their pulmonary disease. This finding may be accounted for in part by genetic modifiers or environmental factors.

There are many disorders in which the effects of mutations on phenotype can be modified by changes in the other allele of the same gene, by changes in specific **modifier genes,** and/or variations in a number of unspecified genes **(genetic background).** When sickle cell anemia is coinherited with the gene for hereditary persistence of fetal hemoglobin, the sickle cell phenotypic expression is less severe. Modifier genes in CF can influence the development of congenital meconium ileus, or colonization with *Pseudomonas aeruginosa.* Modifier genes can also affect the manifestations of Hirschsprung disease, neurofibromatosis type 2, craniosynostosis, and congenital adrenal hyperplasia. The combination of genetic mutations producing glucose-6-phosphate dehydrogenase deficiency and longer versions of the TATAA element in the uridine diphosphate–glucuronosyltransferase gene promoter exacerbates neonatal physiologic hyperbilirubinemia.

HUMAN GENOME PROJECT

A rudimentary genetic map can be made using genetic linkage, which is based on the principle that alleles at 2 genetic loci that are located near each other segregate together in a family unless they are separated by genetic **recombination.** The frequency of recombination between the loci can be used to estimate the physical distance between points. Some of the first maps of the human genome were linkage maps based on a set of polymorphic genetic loci located along the entire human genome. Linkage analysis is still used to map the location of genetic changes responsible for phenotypic traits and genetic disorders that are inherited in a mendelian fashion.

In contrast to linkage maps, which are based on recombination frequencies, physical maps rely on overlapping DNA fragments to determine the location of loci with respect to one another. Several strategies can be used to create physical maps of a chromosomal region. In one strategy, segments of the region of interest with lengths from hundreds or thousands to a few million base pairs are isolated and placed in microorganisms such as bacteria or yeast. Common regions contained in different organism can then be identified and this information can be used to piece together a map composed of overlapping DNA pieces, each contained in a different microorganism. The pieces contained in each organism can then be sequenced to obtain the DNA sequence of the entire region. An alternative strategy involves breaking the entire genome into random fragments, sequencing the fragments, and then using a computer to order the fragments based on overlapping segments. This whole genome approach in combination with new next-generation sequencing technologies has resulted in a dramatic reduction in the cost of sequencing an individual's entire genome.

Analysis of the human genome has produced some surprising results. The number of genes is still not known precisely but appears to be around 25,000. This is fewer than had been expected and in the same range as many simpler organisms. The number of protein products encoded by the genome is greater than the number of genes. This is a result of the presence of alternative promoter regions, alternative splicing, and posttranslational modifications, which can allow a single gene to encode a number of protein products.

It is also apparent that most of the human genome does not encode protein, with <5% being transcribed and translated, though a much larger percentage may be transcribed without translation. Many transcribed sequences are not translated but represent genes that encode RNAs that serve a regulatory role. A large fraction of the genome consists of repeated sequences that are interspersed among the genes. Some of these are transposable genetic elements that can move from place to place in the genome. Others are static elements that were expanded and dispersed in the past during human evolution. Other repeated sequences might play a structural role. There are also regions of genomic duplications. Such duplications are substrate for evolution, allowing genetic motifs to be copied and modified to serve new roles in the cell. Duplications can also play a role in chromosomal rearrangement, permitting nonhomologous chromosome segments to pair during meiosis and exchange material. This is another source of evolutionary change and a potential source of chromosomal instability leading to congenital anomalies or cancer. Low copy repeats also play an important role in causing genomic disorders. When low copy repeats flank unique genomic segments, these regions can be duplicated or deleted through a process known as *nonallelic homologous recombination.*

Availability of the entire human genomic sequence permits the study of large groups of genes, looking for patterns of gene expression or genome alteration. Microarrays permit the expression of thousands of genes to be analyzed on a small glass chip. Increasingly, studies of gene expression are being performed using next generation sequencing

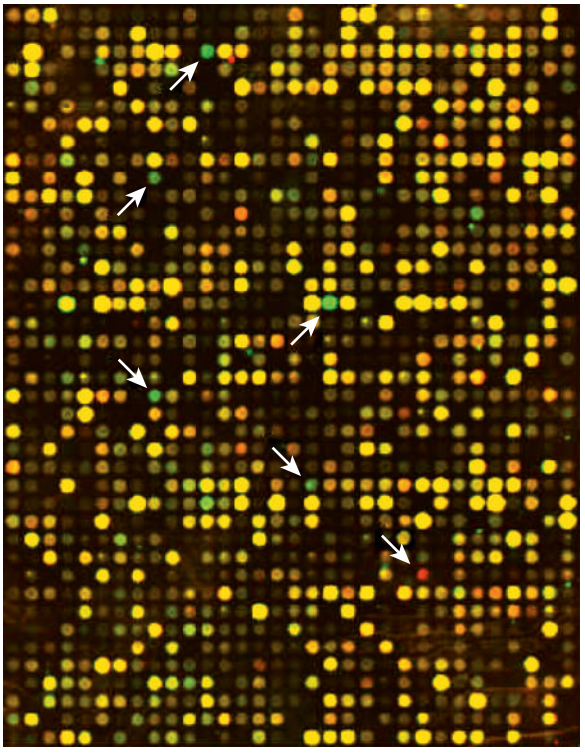

Figure 79-5 **Microarray containing 36,000 oligonucleotides.** The microarray was exposed to RNA from normal fibroblasts (labeled in *red*; see *arrows*) and fibroblasts from a patient with Niemann-Pick disease, type C (labeled *green*). Arrows point to regions in which there was a strong hybridization signal with either normal or disease RNA. This microarray was used to search for genes that are highly expressed in the fibroblasts of patients. *(From Jorde LB, Carey JC, Bamshad MJ, et al, editors:* Medical genetics, *ed 3, St. Louis, 2006, Mosby, p. 116.)*

techniques to obtain information about all of the RNA transcripts in a tissue sample. In some cases the patterns of gene expression provide signatures for particular disease states, such as cancer, or change in response to therapy (Fig. 79-5).

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Chapter 80

Patterns of Genetic Transmission

Daryl A. Scott and Brendan Lee

FAMILY HISTORY AND PEDIGREE NOTATION

The family history remains the most important screening tool for pediatricians in identifying a patient's risk for developing a wide range of diseases, from multifactorial conditions, such as diabetes and attention-deficit disorder, to single-gene disorders such as sickle cell anemia and cystic fibrosis. Through a detailed family history the physician can often ascertain the mode of genetic transmission and the risks to family members. Because not all familial clustering of disease is caused by genetic factors, a family history can also identify common environmental and behavioral factors that influence the occurrence of disease. The main goal of the family history is to identify genetic susceptibility, and the cornerstone of the family history is a systematic and standardized pedigree.

A **pedigree** provides a graphic depiction of a family's structure and medical history. It is important when taking a pedigree to be systematic and use standard symbols and configurations (Figs. 80-1 to 80-4) so that anyone can read and understand the information. In the pediatric setting, the **proband** is typically the child or adolescent who is being evaluated. The proband is designated in the pedigree by an arrow.

A 3 to 4–generation pedigree should be obtained for every new patient as an initial screen for genetic disorders segregating within the family. The pedigree can provide clues to the inheritance pattern of these disorders and can aid the clinician in determining the risk to the proband and other family members. The closer the relationship of the proband to the person in the family with the genetic disorder, the greater is the shared genetic complement. **First-degree** relatives, such as a parent, full sibling, or child, share ½ their genetic information on average; first cousins share ⅛. Sometimes the person providing the family history may mention a distant relative who is affected with a genetic disorder. In such cases a more extensive pedigree may be needed to identify the risk to other family members. For example, a history of a distant maternally related cousin with mental retardation caused by fragile X syndrome can still place a male proband at an elevated risk for this disorder.

MENDELIAN INHERITANCE

There are 3 classic forms of genetic inheritance: **autosomal dominant, autosomal recessive,** and **X-linked.** These are referred to as *mendelian inheritance forms,* after Gregor Mendel, the 19th-century monk whose experiments led to the laws of **segregation of characteristics, dominance,** and **independent assortment.** These remain the foundation of single-gene inheritance.

Autosomal Dominant Inheritance

Autosomal dominant inheritance is determined by the presence of 1 abnormal gene on 1 of the autosomes (chromosomes 1-22). Autosomal genes exist in pairs, with each parent contributing 1 copy. In an autosomal dominant trait, a change in 1 of the paired genes has an effect on the phenotype; this can refer to physical manifestations, behavioral characteristics, or differences detectable only through laboratory tests, even though the other copy of the gene is functioning correctly.

The pedigree for an autosomal dominant disorder (Fig. 80-5) demonstrates certain characteristics. The disorder is transmitted in a vertical (parent-to-child) pattern and can appear in multiple generations. This is illustrated by individual I.1 (see Fig. 80-5) passing on the changed gene to II.2 and II.5. An affected individual has a 50% (1 in 2) chance of passing on the deleterious gene in *each* pregnancy and, therefore, of having a child affected by the disorder. This is referred to as the **recurrence risk** for the disorder. Unaffected individuals (family members who do not manifest the trait) do not pass the disorder to their children. Males and females are equally affected. Although not a characteristic per se, the finding of male-to-male transmission essentially confirms autosomal dominant inheritance. Vertical transmission can also be seen with X-linked traits. However, because a father passes on his Y chromosome to a son, male-to-male transmission cannot be seen with an X-linked trait. Therefore, male-to-male transmission eliminates X-linked inheritance as a possible explanation. Although male-to-male transmission can occur with Y-linked genes as well, there are very few Y-linked disorders compared with thousands having the autosomal dominant inheritance pattern.

Although parent-to-child transmission is a characteristic of autosomal dominant inheritance, for many patients with an autosomal dominant disorder there is no history of an affected family member. There are several possible reasons: First, the patient may represent a **new mutation** that occurred in the DNA of the egg or sperm that came together to form that individual. Second, many autosomal dominant conditions demonstrate **incomplete penetrance,** meaning that not all individuals who carry the mutation have phenotypic manifestations. In a pedigree this can appear as a **skipped generation,** in which an

Instructions:
—Key should contain all information relevant to interpretation of pedigree (e.g., define fill/shading)
—For clinical (non-published) pedigrees include:
a) name of proband/consultand
b) family names/initials of relatives for identification, as appropriate
c) name and title of person recording pedigree
d) historian (person relaying family history information)
e) date of intake/update
f) reason for taking pedigree (e.g., abnormal ultrasound, familial cancer, developmental delay, etc.)
g) ancestry of both sides of family
—Recommended order of information placed below symbol (or to lower right)
a) age; can note year of birth (e.g., b.1978) and/or death (e.g., d. 2007)
b) evaluation (see Figure 75-4)
c) pedigree number (e.g., I-1, I-2, I-3)
—Limit identifying information to maintain confidentiality and privacy

	Male	Female	Gender not specified	Comments
1. Individual	b.1925	30 y	4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.). Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
			With ≥2 conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.	
3. Multiple individuals, number known	5	5	5	Number of siblings written inside symbol. (Affected individuals should not be grouped.)
4. Multiple individuals, number unknown or unstated	n	n	n	"n" used in place of "?".
5. Deceased individual	d. 35	d. 4 mo	d. 60's	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/testing.
7. Proband	P	P		An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	SB 28 wk	SB 30 wk	SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	P LMP: 7/1/2007 47,XY,+21	P 20 wk 46, XX	P	Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

Pregnancies not carried to term	Affected	Unaffected	
10. Spontaneous abortion (SAB)	17 wks female cyctic hygroma	<10 wks	If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)	18 wks 47, XY,+18		Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)	ECT		Write ECT below symbol.

Figure 80-1 Common pedigree symbols, definitions, and abbreviations. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

unaffected individual links 2 affected persons (Fig. 80-6). There are many potential reasons that a disorder exhibits incomplete penetrance, including the effect of modifier genes, environmental factors, gender, and age. Third, individuals with the same autosomal dominant mutation can manifest the disorder to different degrees. This is termed **variable expression** and is a characteristic of many autosomal dominant disorders. Fourth, some spontaneous genetic mutations occur not in the egg or sperm that forms a child, but rather in a cell in the developing embryo. Such events are referred to as **somatic mutations,** and because not all cells are affected, the change is said to be *mosaic*. The

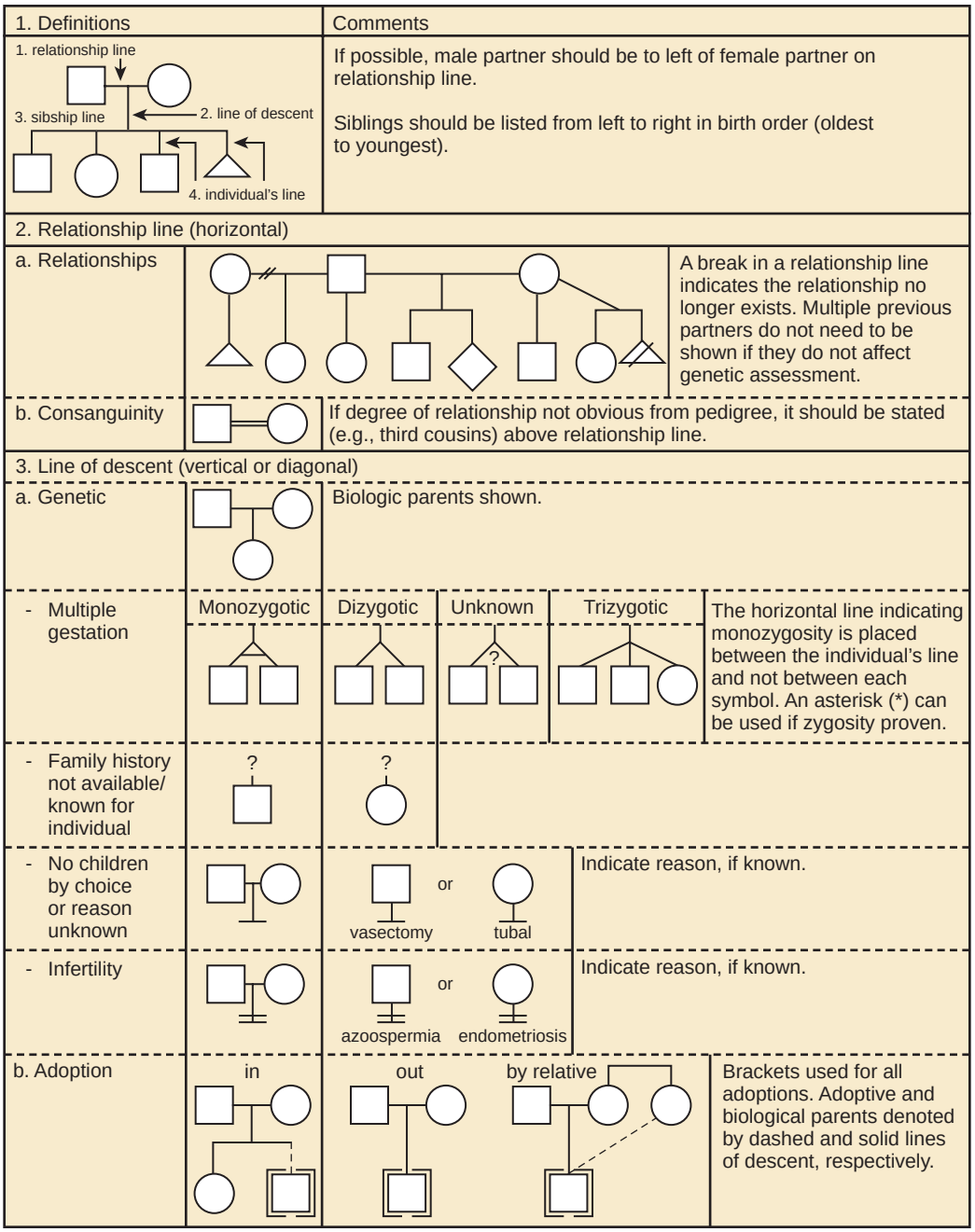


Figure 80-2 Pedigree line definitions. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

resulting phenotype caused by a somatic mutation can be varied, but it is usually milder than if all cells contain the mutation. In **germline mosaicism,** the mutation occurs in cells that populate the germline that produce eggs or sperm. A germline mosaic might not have any manifestations of the disorder but might produce multiple eggs or sperm that carry the mutation.

Autosomal Recessive Inheritance

Autosomal recessive inheritance involves mutations in both copies of a gene. Examples of autosomal recessive diseases are cystic fibrosis and sickle cell disease. Characteristics of autosomal recessive traits (Fig. 80-7) include **horizontal transmission,** the observation of multiple affected members of a kindred in the same generation, but no affected family members in other generations; recurrence risk of 25% for parents with a previous affected child; males and females being equally affected, although some traits exhibit different expression in males and females and increased incidence, particularly for rare traits, in the offspring of consanguineous parents. **Consanguinity** refers to the existence of a relationship by a common ancestor and increases the chance that both parents carry a gene affected by an identical mutation that they inherited. Consanguinity between parents of a child with a suspected genetic disorder implies (but does not prove) autosomal recessive inheritance. Although consanguineous unions are uncommon in Western society, in other parts of the world (southern India, Japan, and the Middle East) they are common; the incidence may be as high as 50%. The risk of a genetic disorder for the offspring of a first-cousin marriage (6-8%) is about double the risk in the general population (3-4%).

Every individual probably has several rare, harmful, recessive mutations. Because most mutations carried in the general population occur

Instructions:

— D represents egg or sperm donor
— S represents surrogate (gestational carrier)
— If the woman is both the ovum donor and a surrogate, in the interest of genetic assessment, she will only be referred to as a donor (e.g., 4 and 5); the pregnancy symbol and its line of descent are positioned below the woman who is carrying the pregnancy
— Available family history should be noted on the gamete donor and/or gestational carrier

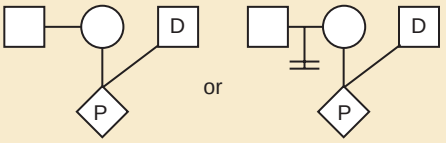
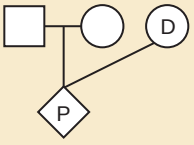
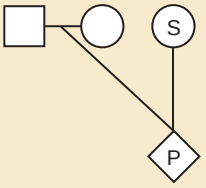
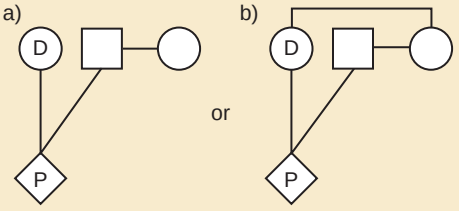
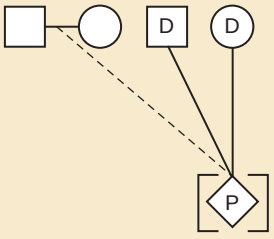
Possible Reproductive Scenarios		Comments
1. Sperm donor		Couple in which woman is carrying pregnancy using donor sperm. No relationship line is shown between the woman carrying the pregnancy and the sperm donor.
2. Ovum donor		Couple in which woman is carrying pregnancy using a donor egg and partner's sperm. The line of descent from the birth mother is solid because there is a biologic relationship that may affect the fetus (e.g., teratogens).
3. Surrogate only		Couple whose gamets are used to impregnate a woman (surrogate) who carries the pregnancy. The line of descent from the surrogate is solid because there is a biological relationship that may affect the fetus (e.g., teratogens).
4. Surrogate ovum donor		Couple in which male partner's sperm is used to inseminate (a) an unrelated woman or (b) a sister who is carrying the pregnancy for the couple.
5. Planned adoption		Couple contracts with a woman to carry a pregnancy using ovum of the woman carrying the pregnancy and donor sperm.

Figure 80-3 Assisted reproductive technology symbols and definitions. *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

at a very low frequency, it does not make economic sense to screen the entire population in order to identify the small number of persons who carry these mutations. As a result, these mutations typically remain undetected unless an affected child is born to a couple who both carry mutations affecting the same gene.

However, in some genetic isolates (small populations separated by geography, religion, culture, or language) certain rare recessive mutations are far more common than in the general population. Even though there may be no known consanguinity, couples from these genetic isolates have a greater chance of sharing mutant alleles inherited from a common ancestor. Screening programs have been developed among some such groups to detect persons who carry common disease-causing mutations and therefore are at increased risk for having affected children. For example, a variety of autosomal recessive conditions are more common among Ashkenazi Jews than in the general population. Couples of Ashkenazi Jewish ancestry should be offered prenatal or preconception screening for Gaucher disease type 1 (carrier rate 1:14), cystic fibrosis (1:25), Tay-Sachs disease (1:25), familial dysautonomia (1:30), Canavan disease (1:40), glycogen storage disease type 1A (1:71), maple syrup urine disease (1:81), Fanconi anemia type C (1:89), Niemann-Pick disease type A (1:90), Bloom syndrome (1:100), mucolipidosis IV (1:120), and possibly neonatal familial hyperinsulinemic hypoglycemia.

The prevalence of carriers of certain autosomal recessive genes in some larger populations is unusually high. In such cases, heterozygote advantage is postulated. For example, the carrier frequencies of sickle cell disease in the African population and of cystic fibrosis in the northern European population are much higher than would be expected from new mutations. It is possible that heterozygous carriers have had an advantage in terms of survival and reproduction over

Instructions:
- E is used for evaluation to represent clinical and/or test information on the pedigree
  a. E is to be defined in key/legend
  b. If more than one evaluation, use subscript (E_1, E_2, E_3) and define in key
  c. Test results should be put in parentheses or defined in key/legend
- A symbol is shaded only when an individual is clinically symptomatic
- For linkage studies, haplotype information is written below the individual. The haplotype of interest should be on left and appropriately highlighted
  Repetitive sequences, trinucleotides, and expansion numbers are written with affected allele first and placed in parentheses
- If mutation known, identify in parentheses

Definition	Symbol	Scenario
1. Documented evaluation (*) Use only if examined/evaluated by you or your research/clinical team or if the outside evaluation has been reviewed and verified.	*	Woman with negative echocardiogram. * E− (echo)
2. Carrier—not likely to manifest disease regardless of inheritance pattern		Male carrier of Tay-Sachs disease by patient report (* not used because results not verified).
3. Asymptomatic/presymptomatic carrier—clinically unaffected at this time but could later exhibit symptoms		Woman age 25 with negative mammogram and positive BRCA1 DNA test. * 25 y E_1− (mammogram) E_2+ (5385insC BRCA1)
4. Uninformative study (u)	Eu	Man age 25 with normal physical exam and uninformative DNA test for Huntington disease (E_2). * 25 y E_1− (physical exam) E_2u (36n/18n)
5. Affected individual with positive evaluation (E+)	E+	Individual with cystic fibrosis and positive mutation study; only one mutation has currently been identified. E+(ΔF508) Eu * E+(ΔF508/u)
		10 week male fetus with a trisomy 18 karyotype. P * 10 wk E+(CVS) 47,XY,+18

Figure 80-4 **Pedigree symbols of genetic evaluation and testing information.** *(From Bennett RL, French KS, Resta RG, et al: Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors,* J Genet Couns *17:424–433, 2008.)*

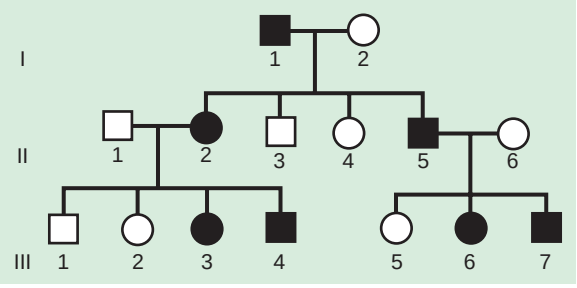


Figure 80-5 **Autosomal dominant pedigree.** Pedigree showing typical inheritance of a form of achondroplasia *(FGFR3)* inherited as an autosomal dominant trait. *Black*, affected patients.

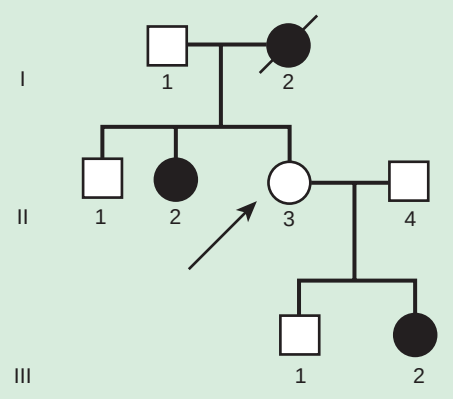


Figure 80-6 **Incomplete penetrance.** This family segregates a familial cancer syndrome, familial adenomatous polyposis. Individual II.3 is an obligate carrier, but there are no findings to suggest the disorder. This disorder is nonpenetrant in this individual.

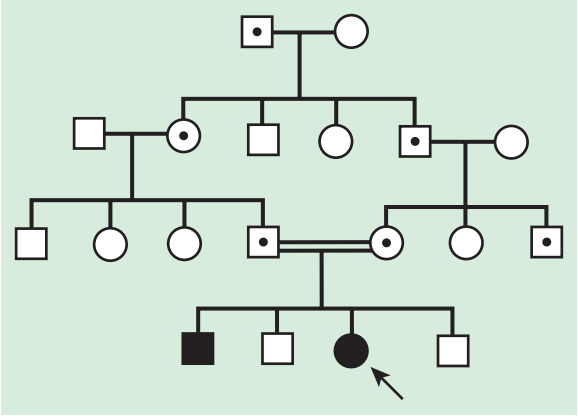


Figure 80-7 Autosomal recessive pedigree with parental consanguinity. *Central dot,* carriers; *black,* affected patients.

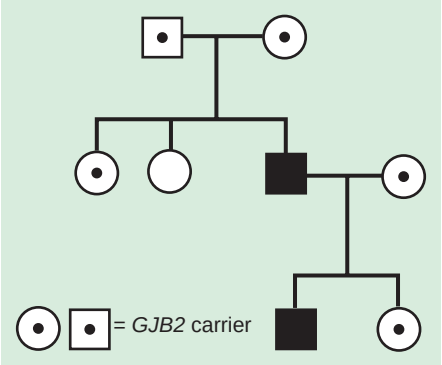


Figure 80-8 Pseudodominant inheritance. *Black,* affected (deaf); *central dot* shows carrier who is asymptomatic (unaffected).

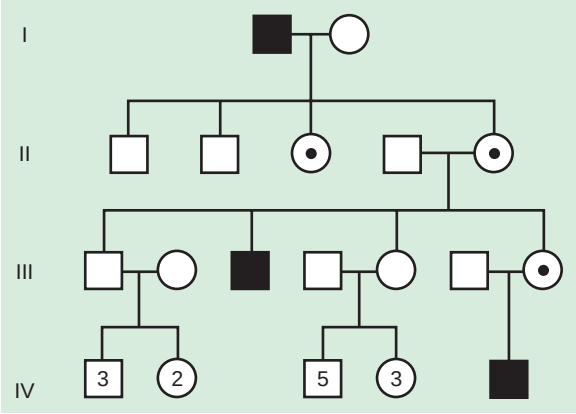


Figure 80-9 Pedigree demonstrating X-linked recessive inheritance.

noncarriers. In sickle cell disease, the carrier state might confer some resistance to malaria; in cystic fibrosis, the carrier state has been postulated to confer resistance to cholera or enteropathogenic *Escherichia coli* infections. Population-based carrier screening for cystic fibrosis is recommended for persons of northern European and Ashkenazi Jewish ancestry; population-based screening for sickle cell disease is recommended for persons of African ancestry.

If the frequency of an autosomal recessive disease is known, the frequency of the heterozygote or carrier state can be calculated from the **Hardy-Weinberg formula:**

$$p^2 + 2pq + q^2 = 1$$

where *p* is the frequency of one of a pair of alleles and *q* is the frequency of the other. For example, if the frequency of cystic fibrosis among white Americans is 1 in 2,500 (p^2), then the frequency of the heterozygote (2pq) can be calculated: If $p^2 = 1/2{,}500$, then $p = 1/50$ and $q = 49/50$; $2pq = 2 \times (1/50) \times (49/50) = 98/2500$ or 3.92%.

Pseudodominant Inheritance

Pseudodominant inheritance refers to the observation of apparent dominant (parent to child) transmission of a known autosomal recessive disorder (Fig. 80-8). This occurs when a homozygous affected individual has a partner who is a heterozygous carrier, and it is most likely to occur for relatively common traits, such as sickle cell anemia or nonsyndromic autosomal recessive hearing loss because of mutations in *GJB2*, the gene that encodes Connexin 26.

X-Linked Inheritance

Characteristics of X-linked inheritance (Fig. 80-9) include the following:

- Males are more commonly and more severely affected than females.
- Female carriers are generally unaffected, or if affected, they are affected more mildly than males.
- Female carriers have a 25% risk for having an affected son, a 25% risk for a carrier daughter, and a 50% chance of having a child that does not inherit the mutated X-linked gene.
- Affected males have carrier daughters and unaffected sons because they pass their X chromosome to all of their daughters and their Y chromosome to all of their sons. Male-to-male transmission excludes X-linkage but is seen with autosomal dominant and Y-linked inheritance.

A female occasionally exhibits signs of an X-linked trait similarly to a male. This occurs rarely owing to homozygosity for an X-linked trait or the presence of a sex chromosome abnormality (45,X or 46,XY female) or skewed or nonrandom X-inactivation. **X chromosome inactivation** occurs early in development and involves random and irreversible inactivation of most genes on one X chromosome in female cells (Fig. 80-10). In some cases, a preponderance of cells inactivates the same X chromosome, resulting in phenotypic expression of an X-linked mutation if it resides on the active chromosome. This can occur owing to chance, selection against cells that have inactivated the X chromosome carrying the normal gene, or X chromosome abnormalities that result in inactivation of the X chromosome carrying the normal gene.

Some X-linked disorders are inherited in an **X-linked dominant** fashion in which female carriers typically manifest abnormal findings. An affected man will have only affected daughters and unaffected sons, and half of the offspring of an affected woman will be affected (Fig. 80-11). Some X-linked dominant conditions are lethal in a high percentage of males. An example is incontinentia pigmenti (see Chapter 596.7). The pedigree shows only affected females and an overall ratio of 2:1 females to males with an increased number of miscarriages (Fig. 80-12).

Y-LINKED INHERITANCE

There are few Y-linked traits. These demonstrate *only* male-to-male transmission, and only males are affected (Fig. 80-13). Most Y-linked genes are related to male sex determination and reproduction and are associated with infertility. Therefore, it is rare to see familial transmission of a Y-linked disorder. However, advances in assisted reproductive technologies might make it possible to have familial transmission of male infertility.

Of special note are the pseudoautosomal regions on the Y chromosome that have homology that is shared by both Xp and Yp. Very few genes reside in this region. One of the few is *SHOX*. Heterozygous *SHOX* mutations cause **Leri-Weil dyschondrosteosis,** a rare skeletal dysplasia that involves bilateral bowing of the forearms with

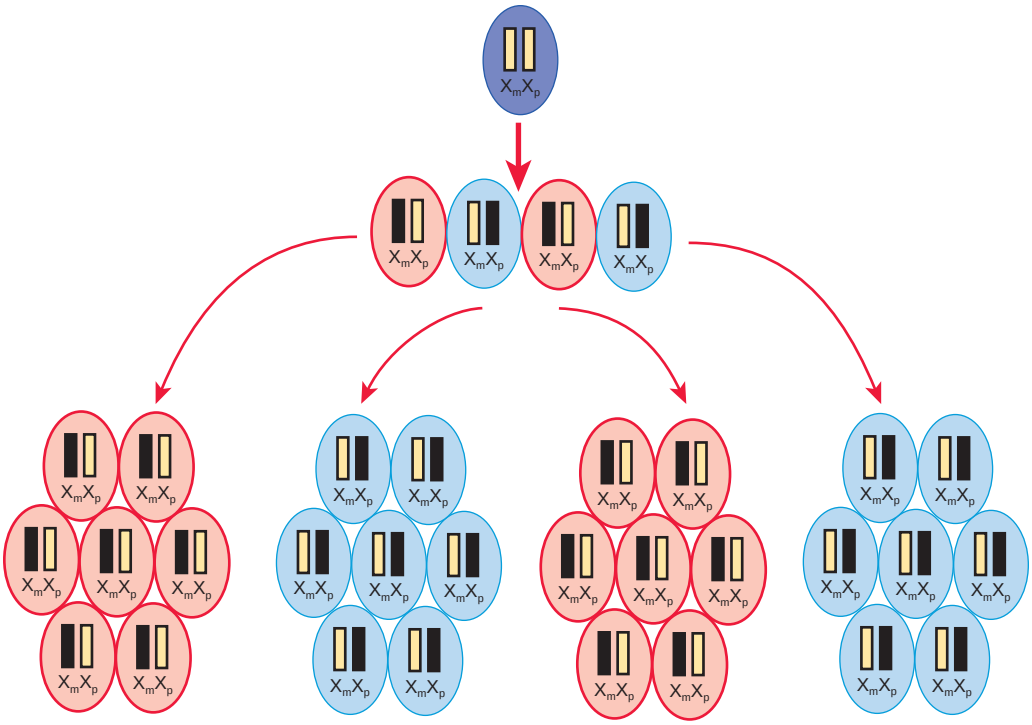


Figure 80-10 X-inactivation. *Black* marks the active X chromosome. Color of the cell represents its active X chromosome is paternally (X_p, *blue*) or maternally (X_m, *pink*) derived.

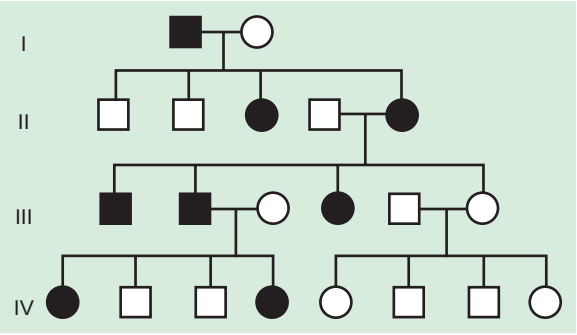


Figure 80-11 Pedigree pattern demonstrating X-linked dominant inheritance. Note there is no father-to-son transmission in this situation, and hemizygosity (i.e., X-linked gene in a male) is not lethal. In some X-linked dominant conditions, X-linked males have a more severe phenotype and might not survive. In that case, only females manifest the disease (see Fig. 80-12).

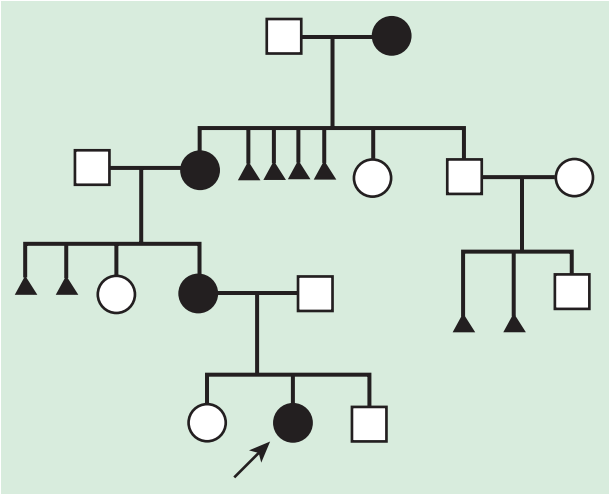


Figure 80-12 Pedigree of an X-linked dominant disorder with male lethality, such as incontinentia pigmenti.

dislocations of the ulna at the wrist and generalized short stature. Homozygous mutations cause the much more severe **Langer mesomelic dwarfism.**

DIGENIC INHERITANCE

Digenic inheritance explains the occurrence of **retinitis pigmentosa** (RP) in children of parents who each carry a mutation in a different RP-associated gene. Both parents have normal vision, as would be expected, but their offspring who are **double heterozygotes**—having inherited both mutations—develop RP. Digenic pedigrees (Fig. 80-14) can exhibit characteristics of both autosomal dominant (vertical transmission) and autosomal recessive inheritance (1 in 4 recurrence risk). For example, a couple in which the 2 unaffected partners are carriers for mutation in 2 different RP-associated genes that show digenic inheritance have a 1 in 4 risk of having an affected child similar to what is seen in autosomal recessive inheritance. However, their affected

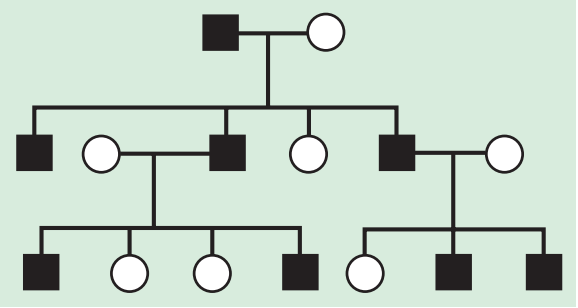


Figure 80-13 Y-linked inheritance. *Black*, affected patient.

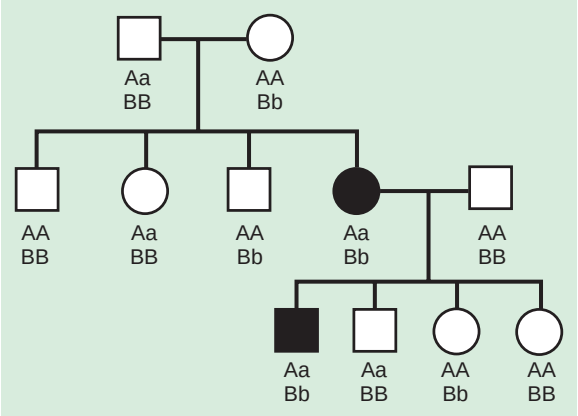


Figure 80-14 Digenic pedigree. Here, the disease alleles are *a* and *b* and they reside on distinct genetic loci or genes. For a person to have the disease, heterozygosity for mutant alleles in both genes (A/a;B/b) is required.

children, and affected children in subsequent generations, have a 1 in 4 risk of transmitting both mutations to their offspring, who would be affected (vertical transmission).

PSEUDOGENETIC INHERITANCE AND FAMILIAL CLUSTERING

Sometimes nongenetic reasons for the occurrence of a particular disease in multiple family members can produce a pattern that mimics genetic transmission. These nongenetic factors can include identifiable environmental factors, teratogenic exposures, or as yet undetermined and/or undefined factors. Examples of identifiable factors might include multiple siblings in a family having asthma as a result of exposure to cigarette smoke from their parents or having failure to thrive, developmental delay, and unusual facial appearance caused by exposure to alcohol during pregnancy.

In some cases the disease is sufficiently common in the general population that some familial clustering occurs simply by chance. Breast cancer affects 11% of all women, and it is possible that several women in a family will develop breast cancer even in the absence of a genetic predisposition. However, hereditary breast cancer associated with mutations in *BRCA1* and *BRCA2* should be suspected in any individual who has a personal history of breast cancer with onset before age 50 yr, early-onset breast and ovarian cancer at any age, bilateral or multifocal breast cancer, a family history of breast cancer or breast and ovarian cancer consistent with autosomal dominant inheritance, and/or a personal or family history of male breast cancer.

NONTRADITIONAL INHERITANCE

Some genetic disorders are inherited in a manner that does not follow classical Mendelian patterns. Nontraditional inheritance includes mitochondrial disorders, triplet repeat expansion diseases, and imprinting defects.

Mitochondrial Inheritance

An individual's mitochondrial genome is entirely derived from the mother because sperm contain few mitochondria, which are typically shed upon fertilization. It follows that mitochondrial disorders exhibit maternal inheritance. A woman with a mitochondrial genetic disorder can have affected offspring of either sex, but an affected father cannot pass on the disease to his offspring (Fig. 80-15). Mitochondrial DNA mutations are often deletions or point mutations; overall, 1:400 people has a maternally inherited pathogenic mitochondrial DNA mutation.

In individual families, mitochondrial inheritance may be difficult to distinguish from autosomal dominant or X-linked inheritance, but in many cases, paying close attention to the sex of the transmitting and nontransmitting parents can suggest a mitochondrial basis (Table 80-1).

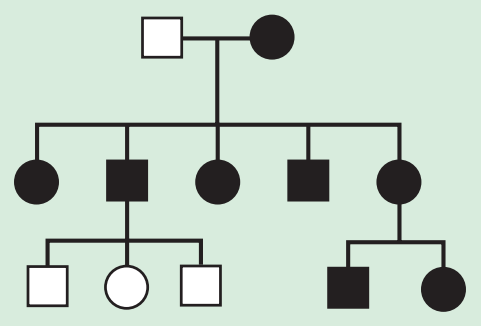


Figure 80-15 Pedigree of a mitochondrial disorder, exhibiting maternal inheritance. *Black,* affected patient.

The mitochondria are the cell's suppliers of energy, and it is not surprising that the organs that are most affected by the presence of abnormal mitochondria are those that have the greatest energy requirements, such as the brain, muscle, heart, and liver (see Chapters 87.4, 361, 598.2, and 611.4). Common manifestations include developmental delay, seizures, cardiac dysfunction, decreased muscle strength and tone, and hearing and vision problems. Examples of mitochondrial disorders include **MELAS** (*m*yopathy, *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes), **MERRF** (*m*yoclonic *e*pilepsy associated with *r*agged *r*ed *f*ibers), and **Kearns-Sayre syndrome** (ophthalmoplegia, pigmentary retinopathy, and cardiomyopathy) (see Chapter 598.2 and 611.4).

Mitochondrial diseases can be highly variable in clinical manifestation. This is partly because cells can contain multiple mitochondria, each bearing several copies of the mitochondrial genome. Thus, a cell can have a mixture of normal and abnormal mitochondrial genomes, which is referred to as **heteroplasmy.** Unequal segregation of mitochondria carrying normal and abnormal genomes and replicative advantage can result in varying degrees of heteroplasmy in the cells of an affected individual, including the individual ova of an affected female. Because of this, a mother may be asymptomatic and yet have children who are severely affected. The level of heteroplasmy at which disease symptoms typically appear can also vary based on the type of mitochondrial mutation. Detection of mitochondrial genome mutations can require sampling of the affected tissue for DNA analysis; testing for mitochondrial DNA mutations may in some tissues, such as blood, be inadequate because the mutation may be found primarily in affected tissues such as muscle.

Triplet Repeat Expansion Disorders

Triplet repeat expansion disorders are distinguished by the special dynamic nature of the disease-causing mutation. Triplet repeat expansion disorders include fragile X syndrome, myotonic dystrophy, Huntington disease, spinocerebellar ataxias, and several others (Table 80-2). These disorders are caused by expansion in the number of 3-bp repeats. The **fragile X gene,** *FMR1,* normally has 5-40 CGG triplets. An error in replication can result in expansion of that number to a level in the gray zone between 41 and 58 repeats, or to a level referred to as **premutation,** which comprises 59-200 repeats. Some male carriers of the premutation develop fragile X–associated tremor/ataxia syndrome (FXTAS) as adults, and female carriers of the premutation are at risk for fragile X-associated primary ovarian insufficiency (*FXPOI*). Persons with a premutation are also at risk for having the gene expand further in subsequent meiosis, hence crossing into the range of full mutation in offspring. In fragile X, the threshold for clinical diagnosis is above 200 repeats. With this number of repeats, the *FMR1* gene becomes hypermethylated, and protein production is lost.

Some triplet expansions associated with other genes can cause disease through a mechanism other than decreased protein production. In **Huntington disease,** the expansion causes the gene product

Table 80-1 Representative Examples of Disorders Caused by Mutations in Mitochondrial DNA and Their Inheritance

DISEASE	PHENOTYPE	MOST FREQUENT MUTATION IN MTDNA MOLECULE	HOMOPLASMY VS. HETEROPLASMY	INHERITANCE
Leber hereditary optic neuropathy	Rapid optic nerve death, leading to blindness in young adult life	Substitution Arg340His in *ND1* gene of complex I of electron transport chain; other complex I missense mutations	Homoplasmic (usually)	Maternal
NARP, Leigh disease	Neuropathy, ataxia, retinitis pigmentosa, developmental delay, mental retardation, lactic acidemia	Point mutations in ATPase subunit 6 gene	Heteroplasmic	Maternal
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; may manifest only as diabetes mellitus	Point mutation in $tRNA^{Leu}$	Heteroplasmic	Maternal
MERRF	Myoclonic epilepsy, ragged red fibers in muscle, ataxia, sensorineural deafness	Point mutation in $tRNA^{Lys}$	Heteroplasmic	Maternal
Deafness	Progressive sensorineural deafness, often induced by aminoglycoside antibiotics	A1555G mutation in 12S rRNA	Homoplasmic	Maternal
	Nonsyndromic sensorineural deafness	A7445G mutation in 12S rRNA	Homoplasmic	Maternal
Chronic progressive external ophthalmoplegia (CPEO)	Progressive weakness of extraocular muscles	The common MELAS point mutation in $tRNA^{Lys}$; large deletions similar to KSS	Heteroplasmic	Maternal if point mutations
Pearson syndrome	Pancreatic insufficiency, pancytopenia, lactic acidosis	Large deletions	Heteroplasmic	Sporadic, somatic mutations
Kearns-Sayre syndrome (KSS)	PEO of early onset with heart block, retinal pigmentation	5 kb large deletion	Heteroplasmic	Sporadic, somatic mutations

mtDNA, Mitochondrial DNA; rRNA, ribosomal RNA; tRNA, transfer RNA.
From Nussbaum RL, McInnes RR, Willard HF, editors: Thompson & Thompson genetics in medicine, *ed 6, Philadelphia, 2001, WB Saunders, p. 246.*

Table 80-2 Diseases Associated with Polynucleotide Repeat Expansions

DISEASE	DESCRIPTION	REPEAT SEQUENCE	NORMAL RANGE	ABNORMAL RANGE	PARENT IN WHOM EXPANSION USUALLY OCCURS	LOCATION OF EXPANSION
CATEGORY 1						
Huntington disease	Loss of motor control, dementia, affective disorder	CAG	6-34	36-100 or more	More often through father	Exon
Spinal and bulbar muscular atrophy	Adult-onset motor-neuron disease associated with androgen insensitivity	CAG	11-34	40-62	More often through father	Exon
Spinocerebellar ataxia type 1	Progressive ataxia, dysarthria, dysmetria	CAG	6-39	41-81	More often through father	Exon
Spinocerebellar ataxia type 2	Progressive ataxia, dysarthria	CAG	15-29	35-59	—	Exon
Spinocerebellar ataxia type 3 (Machado-Joseph disease)	Dystonia, distal muscular atrophy, ataxia, external ophthalmoplegia	CAG	13-36	68-79	More often through father	Exon
Spinocerebellar ataxia type 6	Progressive ataxia, dysarthria, nystagmus	CAG	4-16	21-27	—	Exon
Spinocerebellar ataxia type 7	Progressive ataxia, dysarthria, retinal degeneration	CAG	7-35	38-200	More often through father	—
Spinocerebellar ataxia type 17	Progressive ataxia, dementia, bradykinesia, dysmetria	CAG	29-42	47-55	—	Exon
Dentatorubral-pallidoluysian atrophy/ Haw River syndrome	Cerebellar atrophy, ataxia, myoclonic epilepsy, choreoathetosis, dementia	CAG	7-25	49-88	More often through father	Exon

Continued

Table 80-2 Diseases Associated with Polynucleotide Repeat Expansions—cont'd

DISEASE	DESCRIPTION	REPEAT SEQUENCE	NORMAL RANGE	ABNORMAL RANGE	PARENT IN WHOM EXPANSION USUALLY OCCURS	LOCATION OF EXPANSION
CATEGORY 2						
Pseudoachondroplasia, multiple epiphyseal dysplasia	Short stature, joint laxity, degenerative joint disease	GAC	5	6-7	—	Exon
Oculopharyngeal muscular dystrophy	Proximal limb weakness, dysphagia, ptosis	GCG	6	7-13	—	Exon
Cleidocranial dysplasia	Short stature, open skull sutures with bulging calvaria, clavicular hypoplasia, shortened fingers, dental anomalies	GCG, GCT, GCA	17	27 (expansion observed in 1 family)	—	Exon
Synpolydactyly	Polydactyly and syndactyly	GCG, GCT, GCA	15	22-25	—	Exon
CATEGORY 3						
Myotonic dystrophy (DM1; chromosome 19)	Muscle loss, cardiac arrhythmia, cataracts, frontal balding	CTG	5-37	100 to several thousand	Either parent, but expansion to congenital form through mother	3′ untranslated region
Myotonic dystrophy (DM2; chromosome 3)	Muscle loss, cardiac arrhythmia, cataracts, frontal balding	CCTG	<75	75-11,000	—	3′ untranslated region
Friedreich ataxia	Progressive limb ataxia, dysarthria, hypertrophic cardiomyopathy, pyramidal weakness in legs	GAA	7-2	200-900 or more	Autosomal recessive inheritance, so disease alleles are inherited from both parents	Intron
Fragile X syndrome (FRAXA)	Mental retardation, large ears and jaws, macroorchidism in males	CGG	6-52	200-2,000 or more	Exclusively through mother	5′ untranslated region
Fragile site (FRAXE)	Mild mental retardation	GCC	6-35	>200	More often through mother	5′ untranslated region
Spinocerebellar ataxia type 8	Adult-onset ataxia, dysarthria, nystagmus	CTG	16-37	107-127	More often through mother	3′ untranslated region
Spinocerebellar ataxia type 10	Ataxia and seizures	ATTCT	12-16	800-4,500	More often through father	Intron
Spinocerebellar ataxia type 12	Ataxia, eye movement disorders; variable age at onset	CAG	7-28	66-78	—	5′ untranslated region
Progressive myoclonic epilepsy type 1	Juvenile-onset convulsions, myoclonus, dementia	12-bp repeat motif	2-3	30-75	Autosomal recessive inheritance, so transmitted by both parents	5′ untranslated region

From Jorde LB, Carey JC, Bamshad MJ, et al: Medical genetics, *ed 3, St. Louis, 2006, Mosby, p. 82.*

to have a new, toxic effect on the neurons of the basal ganglia. For most triplet-repeat disorders, there is a clinical correlation to the size of the expansion, with a greater expansion causing more severe symptoms and/or earlier age of onset for the disease. The observation of increasing severity of disease and early age at onset in subsequent generations is termed **genetic anticipation** and is a defining characteristic of many triplet-repeat expansion disorders (Fig. 80-16).

Genetic Imprinting

The 2 copies of most autosomal genes are functionally equivalent. However, in some cases only 1 copy of a gene is transcribed and the other copy is silenced. This gene silencing is typically associated with methylation of DNA, which is an **epigenetic modification**, meaning it does not change the nucleotide sequence of the DNA (Fig. 80-17). In **imprinting**, gene expression depends on the parent of origin of the chromosome (see Chapter 81.8). Imprinting disorders result from an imbalance of active copies of a given gene, which can occur for several reasons. **Prader-Willi** and **Angelman syndromes**, two distinct disorders associated with developmental impairment, are illustrative. Both

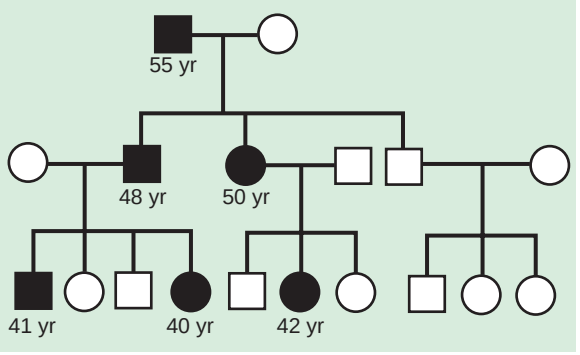


Figure 80-16 Myotonic dystrophy pedigree illustrating anticipation. In this case, the age at onset for family members affected with an autosomal dominant disease is lower in more recent generations. *Black,* affected patients.

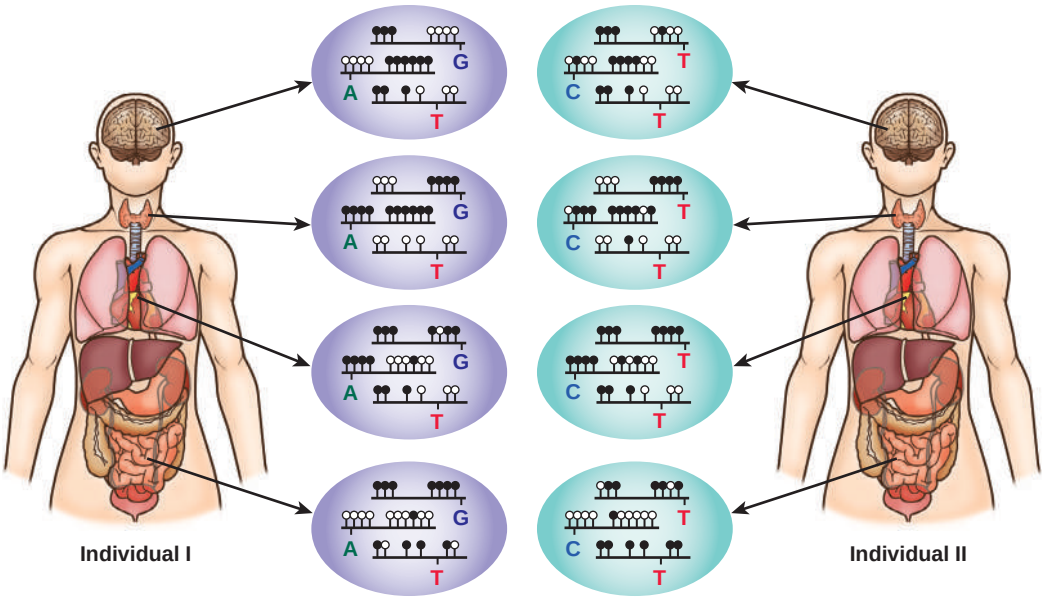


Figure 80-17 Tissue-specific DNA methylation and epigenetic heterogeneity among individuals. A subset of the DNA methylation patterns within a cell is characteristic of that cell type. Cell type–specific and tissue-specific DNA methylation are illustrated by organ-to-organ variations in the clusters of methylated CpGs within the same individual. Despite overall consistency in tissue-specific DNA methylation patterns, variations in these patterns exist among different individuals. Methylated CpGs are indicated by a *filled circle* and unmethylated CpGs by an *open circle*. SNPs are indicated by the corresponding base. *(Redrawn from Brena RM, Huang THM, Plass C: Toward a human epigenome,* Nat Genet *38:1359–1360, 2006.)*

can be caused by microdeletions of chromosome 15q11-12. The microdeletion in Prader-Willi syndrome is always on the paternally derived chromosome 15, whereas in Angelman syndrome it is on the maternal copy. *UBE3A* is the gene responsible for Angelman syndrome. The paternal copy of *UBE3A* is transcriptionally silenced in the brain and the maternal copy continues to be transcribed. If an individual has a maternal deletion, an insufficient amount of *UBE3A* protein is produced in the brain, resulting in the neurologic deficits seen in Angelman syndrome.

Uniparental disomy (UPD), the rare occurrence of a child inheriting both copies of a chromosome from the same parent, is another genetic mechanism that can cause Prader-Willi and Angelman syndromes. Inheriting both chromosomes 15 from the mother is functionally the same as deletion of the paternal 15q12 and results in Prader-Willi syndrome. Approximately 30% of cases of Prader-Willi syndrome is caused by paternal UPD15, whereas maternal UPD15 accounts for only 3% of Angelman syndrome (see Chapter 81.8).

A mutation in an imprinted gene is another cause. Mutations in *UBEA3* account for almost 11% of patients with Angelman syndrome and also result in familial transmission. The most uncommon cause is a mutation in the imprinting center, which results in an inability to correctly imprint the *UBE3A*. In a woman, the inability to reset the imprinting on her paternally inherited chromosome 15 imprint results in a 50% risk of passing on an incorrectly methylated copy of *UBE3A* to a child who would then develop Angelman syndrome.

Beside 15q12, other imprinted regions of clinical interest include the short arm of chromosome 11, where the genes for Beckwith-Wiedemann syndrome and nesidioblastosis map, and the long arm of chromosome 7 with maternal UPD of 7q, which has been associated with some cases of idiopathic short stature and Russell-Silver syndrome.

Imprinting of a gene can occur during gametogenesis or early embryonic development (reprogramming). Genes can become inactive or active by various mechanisms including DNA methylation or demethylation or histone acetylation or deacetylation, with different patterns of (de)methylation noted on paternal or maternal imprintable chromosome regions. Some genes demonstrate tissue-specific imprinting (see Fig. 80-17). Several studies suggest that there may be a small but significantly increased incidence of imprinting disorders, specifically Beckwith-Wiedemann and Angelman syndrome, associated with assisted reproductive technologies such as in vitro fertilization and intracytoplasmic sperm injection. However, the overall incidence of these disorders in children conceived using assisted reproductive technologies is likely to be <1%.

MULTIFACTORIAL AND POLYGENIC INHERITANCE

Multifactorial inheritance refers to traits that are caused by a combination of inherited, environmental, and stochastic factors (Fig. 80-18). Multifactorial traits differ from polygenic inheritance, which refers to traits that result from the additive effects of multiple genes. Multifactorial traits segregate within families but do not exhibit a consistent or recognizable inheritance pattern. Characteristics include the following:

- There is a similar rate of recurrence among all 1st-degree relatives (parents, siblings, offspring of the affected child). It is unusual to find a substantial increase in risk for relatives related more distantly than 2nd degree to the index case.
- The risk of recurrence is related to the incidence of the disease.
- Some disorders have a sex predilection, as indicated by an unequal male : female incidence. Pyloric stenosis, for example, is more common in males, whereas congenital dislocation of the hips is more common in females. Where there is an altered sex ratio, the risk is higher for the relatives of an index case whose gender is less commonly affected than relatives of an index case of the more commonly affected gender. For example, the risk to the son of an affected female with infantile pyloric stenosis is 18%, compared with the 5% risk for the son of an affected male. An affected female presumably has a greater genetic susceptibility, which she can then pass on to her offspring.
- The likelihood that both identical twins will be affected with the same malformation is less than 100% but much greater than the chance that both members of a nonidentical twin pair will be affected. This is in contrast with the pattern seen in mendelian

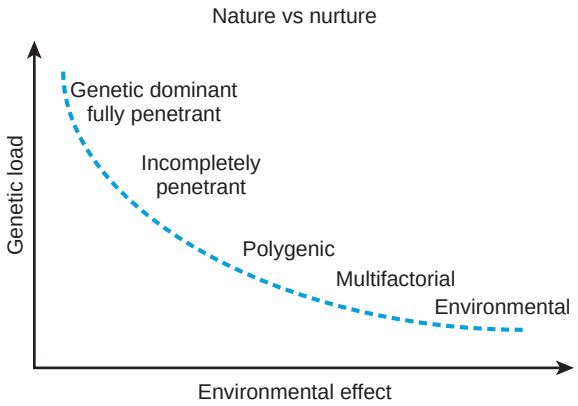


Figure 80-18 **The progressive decrease in the genetic load contributing to the development of a disease creates a smooth transition in the distribution of illnesses on an etiologic diagram.** In theory, no diseases are completely free from the influence of both genetic and environmental factors. *(From Bomprezzi R, Kovanen PE, Martin R: New approaches to investigating heterogeneity in complex traits,* J Med Genet *40:553–559, 2003. Reproduced with permission from the BMJ Publishing Group.)*

inheritance, in which identical twins almost always share fully penetrant genetic disorders.

- The risk of recurrence is increased when multiple family members are affected. A simple example is that the risk of recurrence for unilateral cleft lip and palate is 4% for a couple with 1 affected child and increases to 9% with 2 affected children. It is sometimes difficult to distinguish between a multifactorial and mendelian etiology in families with multiple affected individuals.
- The risk of recurrence may be greater when the disorder is more severe. For example, an infant who has long-segment Hirschsprung disease has a greater chance of having an affected sibling than the infant who has short-segment Hirschsprung disease.

There are 2 types of multifactorial traits. One exhibits continuous variation, with "normal" individuals falling within a statistical range—often defined as having a value 2 SDs above and/or below the mean—and "abnormals" falling outside that range. Examples include such traits as intelligence, blood pressure, height, and head circumference. For many of these traits, offspring values can be estimated based on a modified average of their parental values, with nutritional and environmental factors playing an important role.

With other multifactorial traits, the distinction between normal and abnormal is based on the presence or absence of a particular trait. Examples include pyloric stenosis, neural tube defects, congenital heart defects, and cleft lip and cleft palate. Such traits follow a threshold model (see Fig. 80-15). A distribution of liability because of genetic and nongenetic factors is postulated in the population. Individuals who exceed a threshold liability develop the trait, and those below the threshold do not.

The balance between genetic and environmental factors is demonstrated by **neural tube defects.** Genetic factors are implicated by the increased recurrence risk for parents of an affected child compared with the general population, yet the recurrence risk is about 3%, less than what would be expected if the trait was caused by a single, fully penetrant mutation. The role of nongenetic environmental factors can be seen in the fact that the recurrence risk can be lowered by up to 87% if the mother-to-be takes 4 mg of folic acid per day starting 3 mo before conception.

Many adult-onset diseases behave as if they are caused by multifactorial inheritance. Diabetes, coronary artery disease, and schizophrenia are examples.

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Chapter 81

Cytogenetics

Carlos A. Bacino and Brendan Lee

Clinical cytogenetics is the study of chromosomes: their structure, function, inheritance, and abnormalities. Chromosome abnormalities are very common and occur in approximately 1-2% of live births, 5% of stillbirths, and 50% of early fetal losses in the 1st trimester of pregnancy (Table 81-1). Chromosome abnormalities are more common among persons with intellectual disability and they play a significant role in the development of some neoplasias.

Chromosome analyses are indicated in persons presenting with multiple congenital anomalies, dysmorphic features, and/or intellectual disability. The specific indications for studies include advanced maternal age (>35 yr) or multiple abnormalities on fetal ultrasound (prenatal testing), multiple congenital anomalies, unexplained growth restriction in the fetus or postnatal problems in growth and development, ambiguous genitalia, unexplained intellectual disability with or without associated anatomic abnormalities, primary amenorrhea or infertility, recurrent miscarriages (≥3) or prior history of stillbirths and neonatal deaths, a 1st-degree relative with a known or suspected structural chromosome abnormality, clinical findings consistent with a known anomaly, some malignancies, and chromosome breakage syndromes (e.g., Bloom syndrome, Fanconi anemia).

Table 81-1 Incidence of Chromosomal Abnormalities in Newborn Surveys

TYPE OF ABNORMALITY	NUMBER	APPROXIMATE INCIDENCE
SEX CHROMOSOME ANEUPLOIDY		
Males (43,612 newborns)		
47,XXY	45	1/1,000
47,XYY	45	1/1,000
Other X or Y aneuploidy	32	1/1,350
Total	**122**	**1/360 male births**
Females (24,547 newborns)		
45,X	6	1/4,000
47,XXX	27	1/900
Other X aneuploidy	9	1/2,700
Total	**42**	**1/580 female births**
AUTOSOMAL ANEUPLOIDY (68,159 NEWBORNS)		
Trisomy 21	82	1/830
Trisomy 18	9	1/7,500
Trisomy 13	3	1/22,700
Other aneuploidy	2	1/34,000
Total	**96**	**1/700 live births**
STRUCTURAL ABNORMALITIES (68,159 NEWBORNS)		
Balanced rearrangements		
Robertsonian	62	1/1,100
Other	77	1/885
Unbalanced rearrangements		
Robertsonian	5	1/13,600
Other	38	1/1,800
Total	**182**	**1/375 live births**
All Chromosome Abnormalities	442	1/154 live births

Data from Hsu LYF: Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A, editor: Genetic disorders and the fetus, *ed 4, Baltimore, 1998, Johns Hopkins University Press, pp. 179-248.*

81.1 Methods of Chromosome Analysis

Carlos A. Bacino and Brendan Lee

Cytogenetic studies are usually performed on peripheral blood lymphocytes, although cultured fibroblasts may also be used. Prenatal (fetal) chromosome studies are performed with cells obtained from the amniotic fluid, chorionic villus tissue, and fetal blood or, in the case of preimplantation diagnosis, by analysis of a blastomere. Cytogenetic studies of bone marrow have an important role in tumor surveillance, particularly among patients with leukemia. These are useful to determine induction of remission and success of therapy or, in some cases, the occurrence of relapses.

Chromosome anomalies include abnormalities of number and structure and are the result of errors during cell division. There are 2 types of cell division: mitosis, which occurs in most somatic cells, and meiosis, which is limited to the germ cells. In **mitosis,** 2 genetically identical daughter cells are produced from a single parent cell. DNA duplication has already occurred during **interphase** in the S phase of the cell cycle (DNA synthesis). Therefore, at the beginning of mitosis the chromosomes consist of 2 double DNA strands joined together at the centromere known as *sister chromatids.* Mitosis can be divided into 4 stages: **prophase**, **metaphase**, **anaphase**, and **telophase**. Prophase is characterized by condensation of the DNA. Also during prophase, the nuclear membrane and the nucleolus disappear and the mitotic spindle forms. In metaphase, the chromosomes are maximally compacted and are clearly visible as distinct structures. The chromosomes align at the center of the cell and spindle fibers connect to the centromere of each chromosome and extend to centrioles at the 2 poles of the mitotic figure. In anaphase, the chromosomes divide along their longitudinal axes to form 2 daughter chromatids, which then migrate to opposite poles of the cell. Telophase is characterized by formation of 2 new nuclear membranes and nucleoli, duplication of the centrioles, and cytoplasmic cleavage to form the 2 daughter cells.

Meiosis begins in the female oocyte during fetal life and is completed years to decades later. In males, it begins in a particular spermatogonial cell sometime between adolescence and adult life and is completed in a few days. Meiosis is preceded by DNA replication so that at the outset each of the 46 chromosomes consists of 2 chromatids. In meiosis, a **diploid cell** (2n = 46 chromosomes) divides to form **haploid cells** (n = 23 chromosomes). Meiosis consists of 2 major rounds of cell division. In meiosis I, each of the homologous chromosomes pair precisely so that **genetic recombination,** involving exchange between 2 DNA strands **(crossing over),** can occur. This results in a reshuffling of the genetic information on the recombined chromosomes and allows further genetic diversity. Each daughter cell then receives 1 of each of the 23 homologous chromosomes. In oogenesis, 1 of the daughter cells receives most of the cytoplasm and becomes the egg, whereas the other smaller cell becomes the first polar body. Meiosis II is similar to a mitotic division but without a preceding round of DNA duplication (replication). Each of the 23 chromosomes divides longitudinally, and the homologous chromatids migrate to opposite poles of the cell. This produces 4 spermatogonia in males, or an egg cell and a second polar body in females, each with a haploid (n = 23) set of chromosomes. Consequently, meiosis fulfills 2 crucial roles: It reduces the chromosome number from diploid (46) to haploid (23) so that upon fertilization a diploid number is restored, and it allows genetic recombination.

Two errors of cell division commonly occur during meiosis or mitosis, and either can result in an abnormal number of chromosomes. The first is **nondisjunction,** in which 2 chromosomes fail to separate during meiosis and thus migrate together into 1 of the new cells, producing 1 cell with 2 copies of the chromosome and another with no copy. The second is **anaphase lag,** in which a chromatid or chromosome is lost during mitosis because it fails to move quickly enough during anaphase to become incorporated into 1 of the new daughter cells (Fig. 81-1).

For chromosome analysis, cells are cultured (for varying periods depending on cell type), with or without stimulation, and then artificially arrested in mitosis during metaphase (or prometaphase), later on

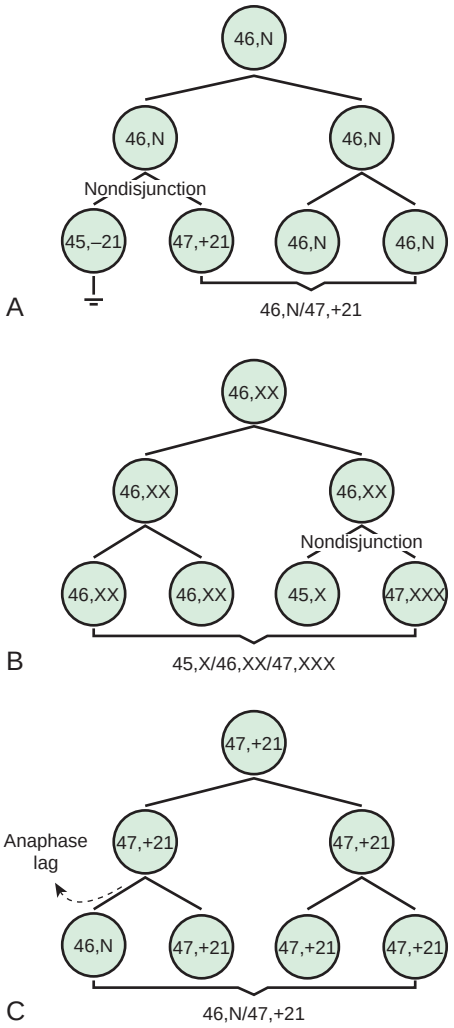

Figure 81-1 Generation of mosaicism. *A,* Postzygotic nondisjunction in an initially normal conceptus. In this example, 1 cell line (monosomic 21) is subsequently lost, with the final karyotype 46,N/47,+21. *B,* Postzygotic nondisjunction in an initially 46,XX conceptus, resulting in 45,X/46,XX/47,XXX mosaicism. *C,* Postzygotic anaphase lag in an initially 47,+21 conceptus. *(From Gardner RJM, Sutherland GR.* Chromosome abnormalities and genetic counseling, *ed 3 New York, 2003, Oxford University Press, p. 33, Figure 43.1. By permission of Oxford University Press, Inc.,* www.oup.com.*)*

subjected to a hypotonic solution to allow disruption of the nuclear cell membrane and proper dispersion of the chromosomes for analysis, fixed, banded, and finally stained. The most commonly used banding and staining method is the GTG banding (G-bands trypsin Giemsa), also known as G banding, which produces a unique combination of dark (G-positive) and light (G-negative) bands that permits recognition of all individual 23 chromosome pairs for analysis.

Other banding techniques, such as Q-banding using quinacrine, reverse banding (R-banding) using acridine orange, and C-banding (constitutive heterochromatin) using barium hydroxide, are available for use in certain circumstances but are losing ground to molecular technologies. Metaphase chromosome spreads are first evaluated microscopically, and then their images are photographed or captured by a video camera and stored on a computer to be later analyzed. Humans have 46 chromosomes or 23 pairs, which are classified as autosomes for chromosomes 1 to 22, and the sex chromosomes, often referred as sex complement: XX for females and XY for males. The homologous chromosomes from a metaphase spread can then be paired and arranged systematically to assemble a karyotype according to well-defined standard conventions like those established by International

System for Human Cytogenetic Nomenclature (ISCN), with chromosome 1 being the largest and 22 the smallest. According to nomenclature, the description of the karyotype includes the total number of chromosomes followed by the sex chromosome constitution. A normal karyotype is 46,XX for females and 46,XY for males (Fig. 81-2). Abnormalities are noted after the sex chromosome complement.

Although the internationally accepted system for human chromosome classification relies largely on the length and banding pattern of each chromosome, the position of the centromere relative to the ends of the chromosome also is a useful distinguishing feature (Fig. 81-3). The centromere divides the chromosome in 2, with the short arm designated as the **p arm** and the long arm designated as the **q arm**. A plus or minus sign before the number of a chromosome indicates that there is an extra or missing chromosome, respectively. Table 81-2 lists some of the abbreviations used for the descriptions of chromosomes and their abnormalities. A metaphase chromosome spread usually shows 450-550 bands. Prophase and prometaphase chromosomes are longer, are less condensed, and often show 550-850 bands. High-resolution analysis is useful for detecting subtle chromosome abnormalities that might otherwise go unrecognized.

Molecular techniques such as fluorescence in situ hybridization (FISH) and array comparative genomic hybridization studies (conventional CGH and array CGH [aCGH]) have filled a significant void for the diagnosing cryptic chromosomal abnormalities. These techniques identify subtle abnormalities that are often below the resolution of standard cytogenetic studies. **FISH** is used to identify the presence, absence, or rearrangement of *specific* DNA segments and is performed with gene- or region-specific DNA probes. Several FISH probes are used in the clinical setting: unique sequence or single-copy probes, repetitive-sequence probes (alpha satellites in the pericentromeric regions), and multiple-copy probes (chromosome specific or painting) (Fig. 81-4*A* and *B*). FISH involves using a unique known DNA sequence or probe labeled with a fluorescent dye that is complementary to the studied region of disease interest. The labeled probe is exposed to the DNA on a microscope slide, typically metaphase or interphase chromosomal DNA. When the probe pairs with its complementary DNA sequence, it can be then visualized by fluorescence microscopy (Fig. 81-5). In metaphase chromosome spreads, the exact chromosomal

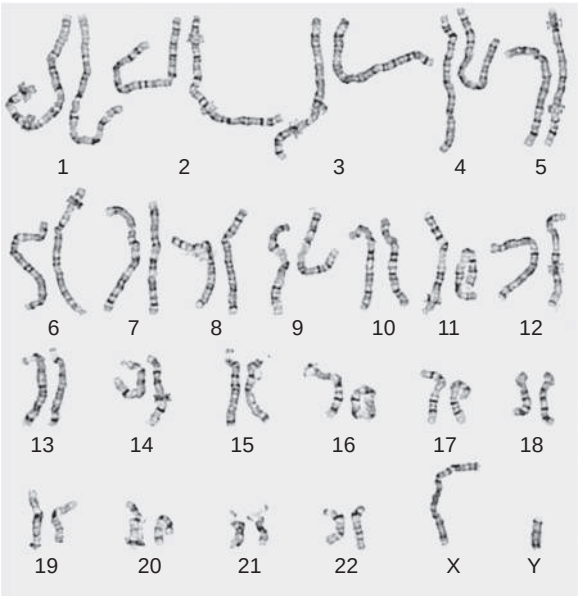

Figure 81-2 Karyotype of a normal male at the 550-600 band level. The longer the chromosomes are captured at metaphase or sometimes prometaphase, the more bands that can be visualized.

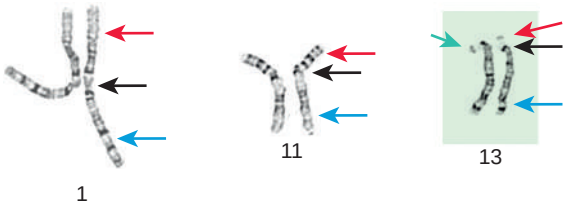

Figure 81-3 Example of different chromosome types according to the position of the centromere. On the *left* is a chromosome 1 pair with the centromere equidistant from the short and long arm (also known as metacentric). In the center is a chromosome 11 pair that is submetacentric. On the right is a chromosome 13 pair that is an example of an acrocentric chromosome. Acrocentric chromosomes contain a very small short arm, stalks, and satellite DNA. The *black arrow* indicates the position of the centromere. The *blue arrow* shows the long arm of a chromosome. The *red arrow* shows the short arm of a chromosome. The *green arrow* highlights the satellite region, which is made of DNA repeats. The *light area* between the short arm and the satellite is known as the stalk.

Table 81-2 Some Abbreviations Used for Description of Chromosomes and Their Abnormalities

ABBREVIATION	MEANING	EXAMPLE	CONDITION
XX	Female	46,XX	Normal female karyotype
XY	Male	46,XY	Normal male karyotype
[##]	Number [#] of cells	46,XY[12]/47,XXY[10]	Number of cells in each clone, typically inside brackets Mosaicism in Klinefelter syndrome with 12 normal cells and 10 cells with an extra X chromosome
cen	Centromere		
del	Deletion	46,XY,del(5p)	Male with deletion of chromosome 5 short arm
der	Derivative	46,XX,der(2),t(2p127q13)	Female with a structurally rearranged chromosome 2 that resulted from a translocation between chromosomes 2 and 7
dup	Duplication	46,XY,dup(15)(q11-13)	Male with interstitial duplication in the long arm of chromosome 15 in the Prader-Willi/Angelman syndrome region
ins	Insertion	46,XY,ins(3)(p13q21q26)	Male with an insertion within chromosome 3 A piece between q21q26 has reinserted on p13
inv	Inversion	46,XY,inv(2)(p21q31)	Male with pericentric inversion of chromosome 2 with breakpoints at bands p21 and q31

Table 81-2 Some Abbreviations Used for Description of Chromosomes and Their Abnormalities—cont'd

ABBREVIATION	MEANING	EXAMPLE	CONDITION
ish	Metaphase FISH	46,XX.ish del(7)(q11.23q11.23)	Female with deletion in the Williams syndrome region detected by in situ hybridization
nuc ish	Interphase FISH	nuc ish(DXZ1 × 3)	Interphase in situ hybridization showing 3 signals for the X chromosome centromeric region
mar	Marker	47,XY,+mar	Male with extra, unidentified chromosome material
mos	Mosaic	mos 45,X[14]/46,XX[16]	Turner syndrome mosaicism (analysis of 30 cells showed that 14 cells were 45,X and 16 cells were 46,XX)
p	Short arm	46,XY,del(5)(p12)	Male with a deletion on the short arm of chromosome 5, band p12 (short nomenclature)
q	Long arm	46,XY,del(5)(q14)	Male with a deletion on the long arm of chromosome 5, band 14
r	Ring chromosome	46,X,r(X)(p21q27)	Female with 1 normal X chromosome and a ring X chromosome
t	Translocation	t(2;8)(q33;q24.1)	The interchange of material between chromosomes 2 and 8 with breakpoints at bands 2q33 and 8q24.1
ter	Terminal	46,XY,del(5)(p12-pter)	Male with a deletion of chromosome 5 between p12 and the end of the short arm (long nomenclature)
/	Slash	45,X/46,XY	Separate lines or clones Mosaicism for monosomy X and a male cell line
+	Gain of	47,XX,+21	Female with trisomy 21
–	Loss of	45,XY,–21	Male with monosomy 21

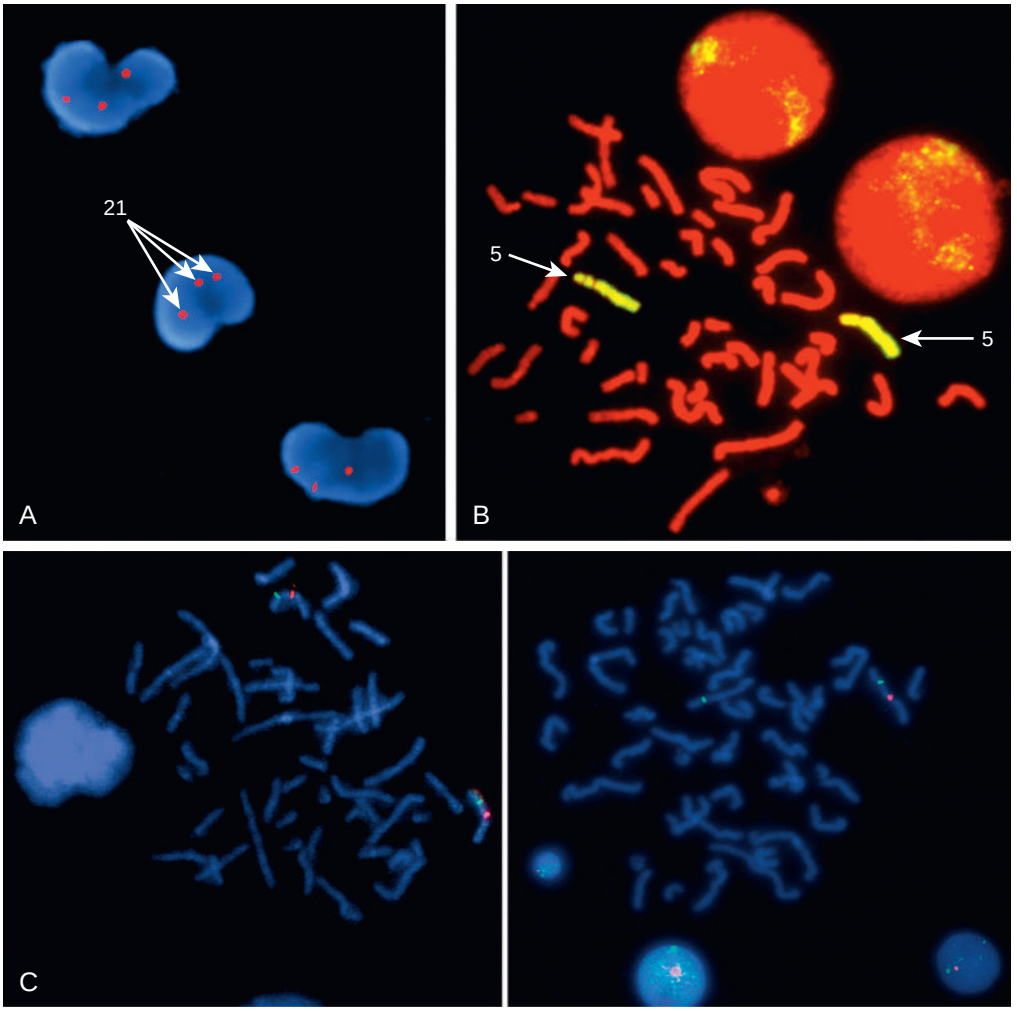

Figure 81-4 *A*, FISH analysis of interphase peripheral blood cells from a patient with Down syndrome using a chromosome 21-specific probe. The 3 red signals mark the presence of 3 chromosomes 21. *B*, FISH analysis of a metaphase chromosome spread from a clinically normal individual using a whole-chromosome paint specific for chromosome 5. Both chromosomes 5 are completely labeled *(yellow)* along their entire length. *C*, FISH on metaphase cells using a unique sequence probe that hybridizes to the elastin gene on chromosome 7q11.23, inside the Williams syndrome critical region. The elastin probe is labeled in *red*, and a control probe on chromosome 7 is labeled in *green*. The left image shows normal hybridization to chromosome 7, with 2 signals for the elastin region and 2 for the control probe. The right image shows a normal chromosome on the right with control and elastin signals, and a deleted chromosome 7 on the *left*, evidenced by a single signal for the control probe. This image corresponds to a patient with a Williams syndrome region deletion.

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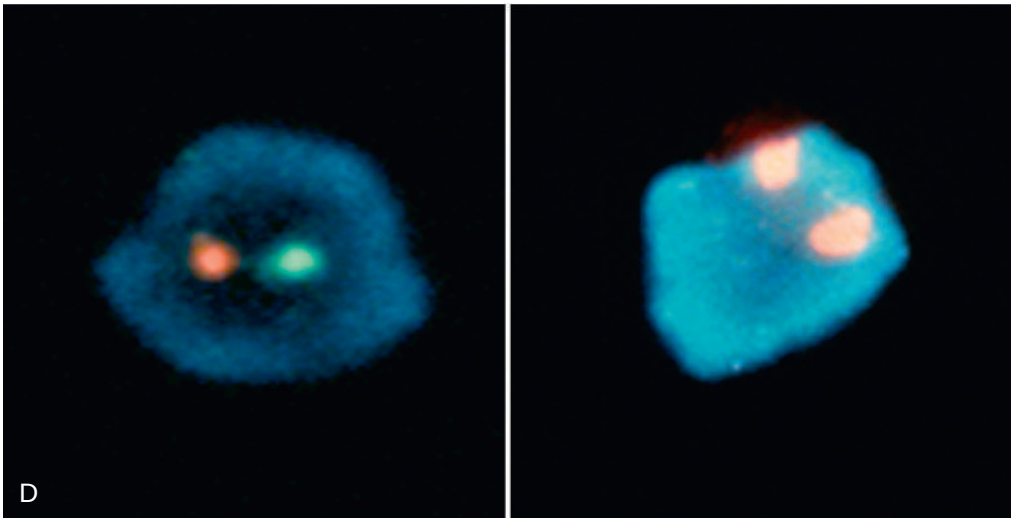

Figure 81-4, cont'd *D,* FISH in interphase cells using DNA probes that hybridize to repetitive α-satellite sequences in the pericentromeric region for the sex chromosomes. *Left,* interphase cells with 2 signals, 1 labeled in *red* for the X chromosome and *green* for the Y chromosome, consistent with a normal male chromosome complement. *Right,* interphase cell showing 2 *red* signals for the X chromosome, compatible with a normal female chromosome complement.

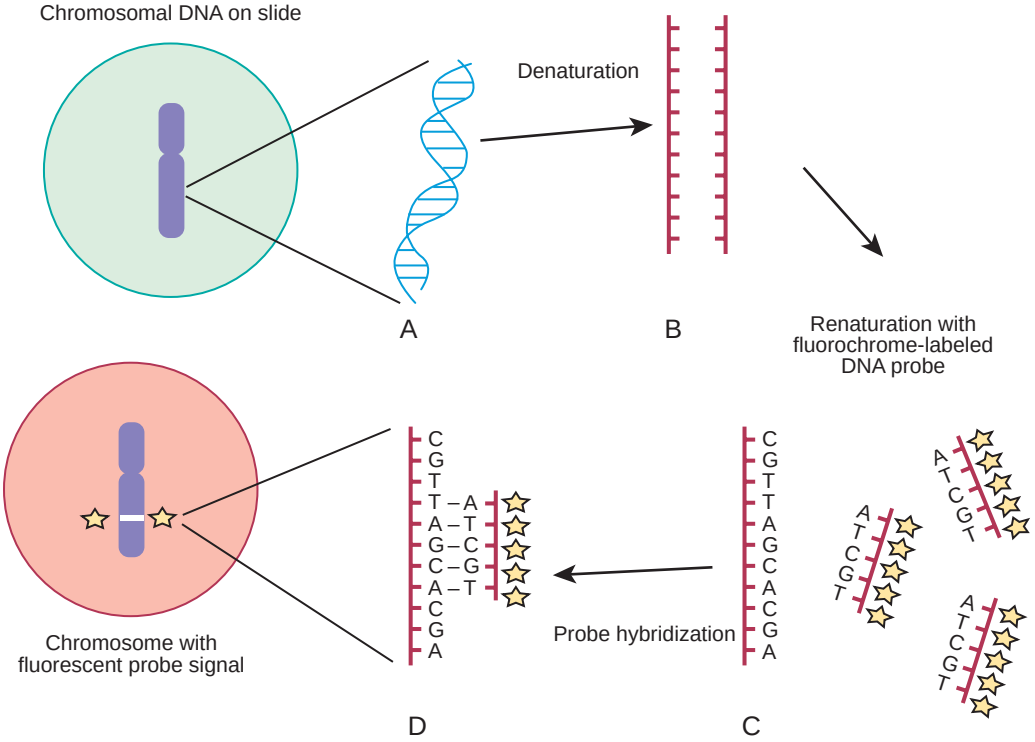

Figure 81-5 FISH involves denaturation of double-stranded DNA as present in metaphase chromosomes or interphase nuclei on cytogenetic slide preparations *(A)* into single-stranded DNA *(B).* The slide-bound (in situ) DNA is then renatured or reannealed in the presence of excess copies of a single-stranded, fluorochrome-labeled DNA base-pair sequence or probe *(C).* The probe anneals or "hybridizes" to sites of complementary DNA sequence *(D)* within the chromosomal genome. Probe signal is visualized and imaged on the chromosome by fluorescent microscopy. *(From Lin RL, Cherry AM, Bangs CD, et al: FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In Hyme HE, Greydanus D, editors:* Genetic disorders in adolescents: state of the art reviews. Adolescent medicine, *Philadelphia, 2002, Hanley and Belfus, pp. 305–313.)*

location of each probe copy can be documented and often the *number of copies* (deletions, duplications) of the DNA sequence as well. When the interrogated segments (as in genomic duplications) are close together, only interphase cells can accurately determine the presence of 2 or more copies or signals since in metaphase cells, some duplications might falsely appear as a single signal.

With high-resolution chromosome analysis it is very difficult to recognize deletions of <5 million bp (5 Mbp); FISH can reliably detect deletions as small as 50-200 kb of DNA. This has allowed the clinical characterization of a number of *microdeletion syndromes*. Other probes hybridize to repetitive sequences located to the pericentromeric regions. Pericentromeric probes are still widely used for the rapid identification of certain trisomies in interphase cells of blood smears, or even in the rapid analysis of prenatal samples from cells obtained through amniocentesis. Such probes are available for chromosomes 13, 18, and 21 and for the sex pair X and Y (see Fig. 81-4*C* and *D*). With regards to the detection of genomic disorders, FISH is no longer the first line of testing, and its role has also mostly changed to the confirmation of microarray findings.

Spectral karyotyping and **multicolor FISH** are similar molecular cytogenetic techniques that use 24 different chromosome painting probes and 5 fluorochromes to simultaneously visualize every chromosome in a metaphase spread. Each of the 24 different chromosome paints is labeled with a different combination of the 5 fluorescent dyes, which emit at different wavelengths. Each of the 22 autosomes and the X and Y chromosomes has its own unique spectrum of wavelengths of fluorescence. Special filters, cameras, and image-processing software are required to identify each chromosome. Spectral karyotyping and multicolor FISH are especially useful for identifying the complex chromosome rearrangements found in many tumors. This technique requires very special and costly equipment and is being displaced by comparative aCGH.

CGH is a molecular-based technique that involves differentially labeling the patient's DNA with a fluorescent dye (green) and a normal reference DNA with another fluorescent dye (red; Fig. 81-6). Equal amounts of the 2-label DNA samples are mixed and then used as a painting probe for FISH with normal metaphase chromosomes. The ratio of green : red fluorescence is measured along each chromosome. Regions of amplification of the patient's DNA display an excess of green fluorescence, and regions of loss show excess red fluorescence. If the patient's and the control DNA are equally represented, the green : red ratio is 1 : 1 and the chromosomes appear yellow.

A modified version of this technology, aCGH, uses DNA spotted onto a slide or **microarray** grid. In this case, instead of metaphase

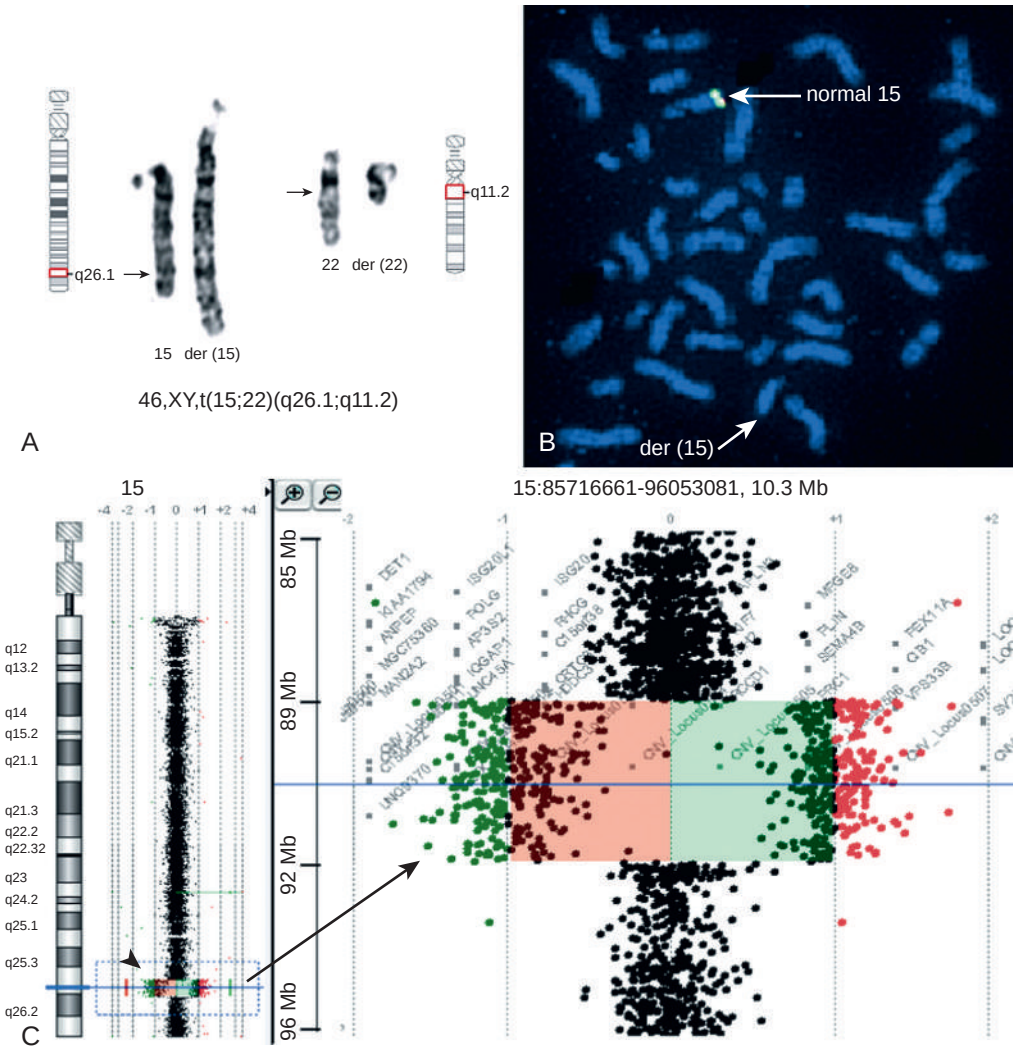

Figure 81-6 An example of a cryptic microdeletion at a translocation breakpoint of an apparently balanced translocation in a patient with DD and growth defect. *A*, Partial karyotype shows t(15;22)(q26.1;q11.2). *B*, FISH with clones 2O19 *(green)* and 354M14 *(red)* at 15q26.1; *arrows* indicate signals only present on the normal chromosome 15, suggesting a deletion on the der(15). *C*, Two-color aCGH with dye swap with 244 K oligo probes; *arrowhead* indicates a 3.3-Mbp deletion at chromosome 15q26.1-q26.2, *arrow* points to the close-up view of the deletion. *(From Li MM, Andersson HC: Clinical application of microarray-based molecular cytogenetics: an emerging new era of genomic medicine,* J Pediatr *155:311-317, 2009, with permission of the authors and publisher.)*

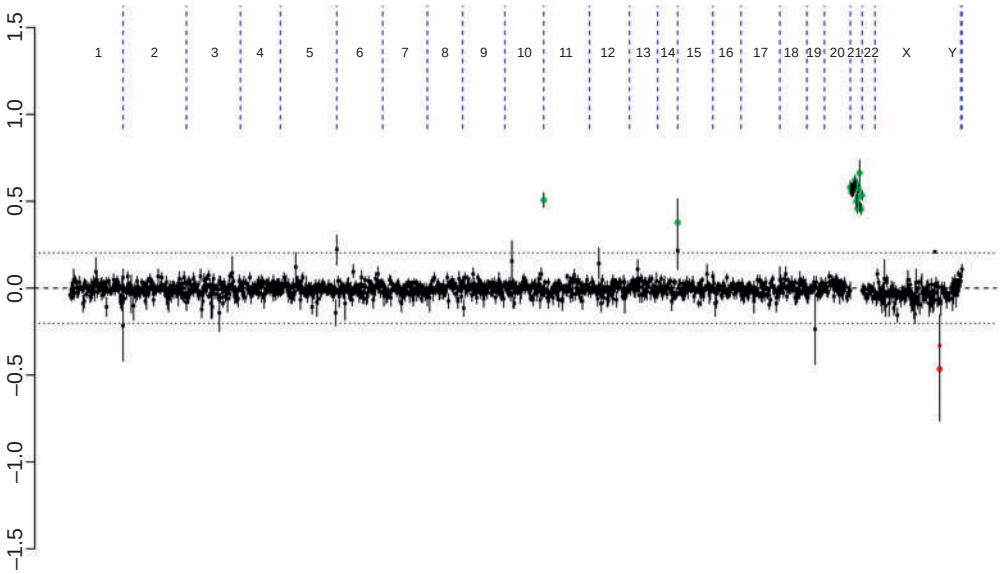

Figure 81-7 aCGH in a female patient with Down syndrome. Each *black dot* represents a piece of DNA segment specific for different chromosome location. Most of the dots displayed between the 0.0 and 0.2 axis are considered within normal range. Exceptions are often a result of polymorphic variations. A group of dots colored in *green* clusters on chromosome 21 and above 0.5. Those represent a *gain* in copy number of DNA segments for chromosome 21 as seen in Down syndrome and consistent with trisomy 21.

chromosomes, segments of DNA are represented by oligonucleotides (short DNA segments) distributed in a microarray that resembles the chromosomes in a metaphase. The detection is currently possible at the single exon resolution level depending on the arrays employed.

There are many advantages of aCGH. It can test all critical disease-causing regions in the genome at once; FISH requires the clinical knowledge and tests only 1 area at a time. aCGH can detect duplications and deletions not currently recognized as recurrent disease-causing regions probed by FISH. aCGH can detect single and contiguous gene deletion syndromes. aCGH does not always require cell culture to generate sufficient DNA, something that may be important in the context of prenatal testing because of timing. There are disadvantages to aCGH: It does not detect balanced translocations, inversions, or very low-levels of mosaicism.

There are different types of aCGH; some of them are more targeted while others have whole-genome coverage. **Targeted aCGH** is an effective and efficient technique for detecting clinically known cryptic chromosomal aberrations, which are typically associated with known disease phenotypes; many of these arrays have expanded detection to areas potentially susceptible to recurring deletion or duplication. **Whole-genome arrays** target the entire genome. The advantage of this latter technique is that it allows better and denser coverage of the entire genome in evenly spaced portions; its disadvantage is that interpretation of deletions or duplications may be difficult if it involves areas not previously known to be involved in disease. There is a new type of array being used in the clinical setting and that is the so-called single nucleotide polymorphism (SNP) array. SNPs are polymorphic variations between 2 nucleotides and when analyzed in massive parallel fashion, they can provide very valuable clinical information. Several million SNPs normally occur in the human genome. SNP arrays can help with the detection of uniparental disomies as well as consanguinity. Many arrays currently used in clinical practice combine the use of oligonucleotides for the detection of copy number variations in conjunction with SNPs.

There are many **copy number variations** causing deletion or duplication in the human genome. Thus, most detected genetic abnormalities, unless associated with very well-known clinical phenotypes, require *parental investigations* because a detected copy number variation that is inherited might turn out to be an incidental polymorphic variant. A de novo abnormality (i.e., one found only in the child and not the parents) is often more significant if it is associated with an abnormal phenotype found only in the child and if it involves genes with important functions. aCGH is a very valuable technology alone or when combined with FISH and conventional chromosome studies (Fig. 81-7).

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81.2 Down Syndrome and Other Abnormalities of Chromosome Number

Brendan Lee

ANEUPLOIDY AND POLYPLOIDY

Human cells contain a multiple of 23 chromosomes (n = 23). A haploid cell (n) has 23 chromosomes (typically in the ovum or sperm). If a cell's chromosomes are an exact multiple of 23 (46, 69, 92 in humans), those cells are referred to as euploid. **Polyploid** cells are euploid cells with more than the normal **diploid** number of 46 (2n) chromosomes: 3n, 4n. Polyploid conceptions are usually not viable, but the presence of mosaicism with a karyotypically normal line can allow survival. Mosaicism is an abnormality defined as the presence of 2 or more cell lines in a single individual. Polyploidy is a common abnormality seen in 1st-trimester pregnancy losses. **Triploid cells** are those with 3 haploid sets of chromosomes (3n) and are only viable in a mosaic form. Triploid infants can be liveborn but do not survive long. Triploidy is often the result of fertilization of an egg by 2 sperm (dispermy). Failure of 1 of the meiotic divisions, resulting in a diploid egg or sperm, can also result in triploidy. The phenotype of a triploid conception depends on the origin of the extra chromosome set. If the extra set is of **paternal** origin, it results in a partial hydatidiform mole with poor embryonic development, but triploid conceptions that have an extra set of **maternal** chromosomes results in severe embryonic retardation with a small fibrotic placenta that is typically spontaneously aborted.

Abnormal cells that do not contain a multiple of haploid number of chromosomes are termed **aneuploid** cells. Aneuploidy is the most common and clinically significant type of human chromosome abnormality, occurring in at least 3-4% of all clinically recognized pregnancies. **Monosomies** occur when only 1, instead of the normal 2, of a given chromosome is present in an otherwise diploid cell. In humans,

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most autosomal monosomies appear to be lethal early in development, and survival is possible in **mosaic forms** or by means of chromosome rescue (restoration of the normal number by duplication of single monosomic chromosome). An exception to this rule is monosomy for the X chromosome (45,X), seen in Turner syndrome; it has been estimated that the majority of 45,X conceptuses are lost early in pregnancy for as yet unexplained reasons.

The most common cause of aneuploidy is **nondisjunction,** the failure of chromosomes to disjoin normally during meiosis (see Fig. 81-1). Nondisjunction can occur during meiosis I or II or during mitosis. After meiotic nondisjunction, the resulting gamete either lacks a chromosome or has 2 copies instead of 1 normal copy, resulting in a monosomic or trisomic zygote, respectively.

Trisomy is characterized by the presence of 3 chromosomes, instead of the normal 2, of any particular chromosome. Trisomy is the most common form of aneuploidy. Trisomy can occur in all cells or it may be mosaic. Most individuals with trisomy exhibit a consistent and specific phenotype depending on the chromosome involved.

FISH is a technique that can be used for rapid diagnosis in the prenatal detection of common fetal aneuploidies including chromosomes 13, 18, and 21, as well as sex chromosomes (see Fig. 81-4*C* and *D*). The most common numerical abnormalities in liveborn children include trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome), and sex chromosomal aneuploidies: Turner syndrome (usually 45,X), Klinefelter syndrome (47,XXY), 47,XXX, and 47,XYY, By far the most common type of trisomy in liveborn infants is trisomy 21 (47,XX,+21 or 47,XY,+21) (see Table 81-1). Trisomy 18 and trisomy 13 are relatively less common and are associated with a characteristic set of congenital anomalies and severe intellectual disability (Table 81-3). The occurrence of trisomy 21 and other trisomies increases with advanced maternal age (≥35 yr). Owing to this increased risk, women who are ≥35 yr at the time of delivery should be offered genetic counseling and prenatal diagnosis (including serum screening, ultrasonography, and amniocentesis or chorionic villus sampling; see Chapter 96).

DOWN SYNDROME

Trisomy 21 is the most common genetic cause of moderate intellectual disability. The incidence of Down syndrome in live births is approximately 1 in 733; the incidence at conception is more than twice that rate; the difference is accounted by early pregnancy losses. In addition to cognitive impairment, Down syndrome is associated with congenital anomalies and characteristic dysmorphic features (Figs. 81-8 and 81-9; Table 81-4). Although there is variability in the clinical features, the constellation of phenotypic features is fairly consistent and permits clinical recognition of trisomy 21. Affected individuals are more prone to congenital heart defects (50%) such as atrioventricular septal defects, ventricular septal defects, isolated secundum atrial septal defects,

Table 81-3 Chromosomal Trisomies and Their Clinical Findings

SYNDROME	INCIDENCE	CLINICAL MANIFESTATIONS
Trisomy 13, Patau syndrome	1/10,000 births	Cleft lip often midline; flexed fingers with postaxial polydactyly; ocular hypotelorism, bulbous nose; low-set, malformed ears; microcephaly; cerebral malformation, especially holoprosencephaly; microphthalmia, cardiac malformations; scalp defects; hypoplastic or absent ribs; visceral and genital anomalies Early lethality in most cases, with a median survival of 7 days; ~91% die by 1 year. Survivors have significant neurodevelopmental delay
Trisomy 18, Edwards syndrome	1/6,000 births	Low birthweight, closed fists with index finger overlapping the 3rd digit and the 5th digit overlapping the 4th, narrow hips with limited abduction, short sternum, rocker-bottom feet, microcephaly, prominent occiput, micrognathia, cardiac and renal malformations, and intellectual disability ~92% of children die in the first year; with full support ~25% may survive 1 yr. Survivors have significant neurodevelopmental delay
Trisomy 8, mosaicism	1/20,000 births	Long face, high prominent forehead, wide upturned nose, thick everted lower lip, microretrognathia, low-set ears, high arched, sometimes cleft, palate; osteoarticular anomalies common (camptodactyly of 2nd to 5th digits, small patella); deep plantar and palmar creases; moderate intellectual disability

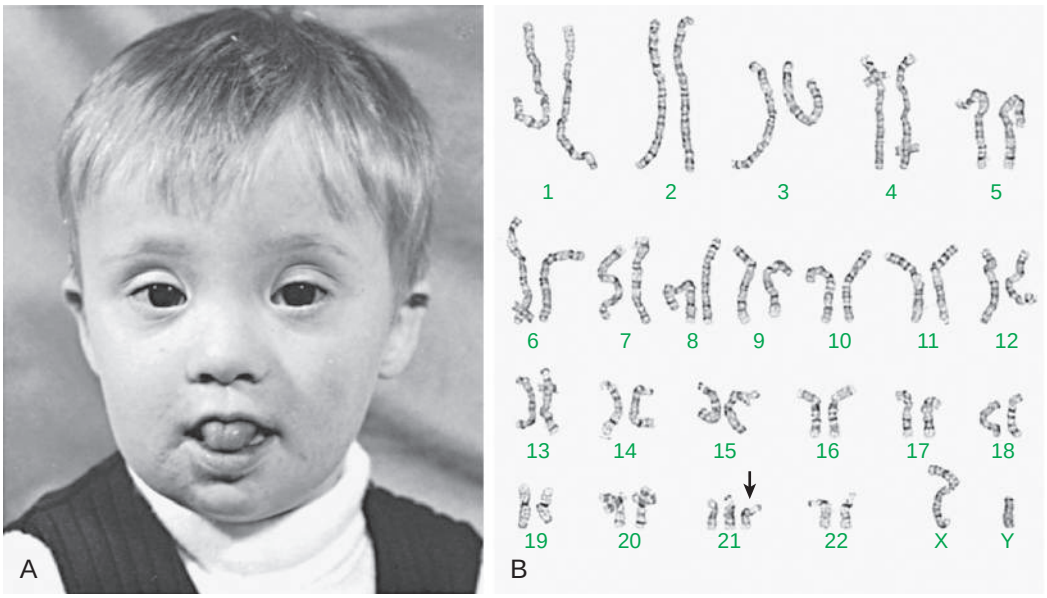

Figure 81-8 *A,* Face of a child with Down syndrome. *B,* Karyotype of a male with trisomy 21 as seen in Down syndrome. This karyotype reveals 47 chromosomes instead of 46, with an extra chromosome in pair 21.

Figure 81-9 Prehensile foot in a 1 mo old child with Down syndrome. *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

patent ductus arteriosus, and tetralogy of Fallot. Congenital and acquired gastrointestinal anomalies and hypothyroidism are common (Table 81-5). Other abnormalities include megakaryoblastic leukemia, immune dysfunction, diabetes mellitus, and problems with hearing and vision (Table 81-5). Alzheimer disease–like dementia is a known complication that occurs as early as the 4th decade and has an incidence 2-3 times higher than sporadic Alzheimer disease. Most males with Down syndrome are sterile, but some females have been able to reproduce, with a 50% chance of having trisomy 21 pregnancies. Two genes (*DYRK1A, DSCR1*) in the putative critical region of chromosome 21 may be targets for therapy.

Developmental delay is universal (Tables 81-6 and 81-7; Fig. 81-10). Cognitive impairment does not uniformly affect all areas of development. Social development is relatively spared, but children with Down syndrome have considerable difficulty using expressive language. Understanding these individual developmental strengths will maximize the educational process for children with Down syndrome. Persons with Down syndrome often benefit from programs aimed at stimulation, development, and education. These programs are most effective in addressing social skills that often appear advanced for the intellectual delay. Children with Down syndrome also benefit from anticipatory guidance, which establishes the protocol for screening, evaluation, and care for patients with genetic syndromes and chronic disorders (Table 81-8). Up to 15% of children with Down syndrome have misalignment of cervical vertebra C1, which places them at risk for spinal cord injury with neck hyperextension or extreme flexion. Special Olympics recommends sports participation and training but requires x-ray examination (full extension and flexion views) of the neck prior to participation in sports that may result in hyperextension or radical flexion or pressure on the neck or upper spine; sports include diving starts in swimming, butterfly stroke, diving, pentathlon, high jump, equestrian sports, gymnastics, football, soccer, alpine skinning, and warm up exercises placing stress on the head and neck. If atlantoaxial instability is diagnosed, Special Olympics will permit participation if the parents or guardians request so and only after obtaining written certification from a physician and acknowledgment of the risks by the parent or guardian.

The majority of children with Down syndrome do not have behavior problems. It is estimated that psychiatric comorbidity is 18-38% in this population. These estimates are higher than in unaffected children, but they are lower than in children with similar levels of intellectual disability from other etiologies. All maladaptive behaviors in persons with Down syndrome are thought to be inherently linked to cognitive impairment. Common behavioral difficulties that occur in children with Down syndrome include inattentiveness, stubbornness, and a need for routine and sameness. Aggression and self-injurious behavior are less common in this population. All of these behaviors can respond to educational or pharmacologic interventions.

The life expectancy for children with Down syndrome is reduced and is approximately 50-55 yr. Little prospective information about the secondary medical problems of adults with Down syndrome is known. Retrospective studies have shown premature aging and an increased risk of Alzheimer disease in adults with Down syndrome. These studies have also shown unexpected negative associations between Down syndrome and other medical comorbidities. Persons with Down syndrome have fewer than expected deaths caused by solid tumors and ischemic heart disease. This same study reported increased risk of adult deaths due to congenital heart disease, seizures, and leukemia. In one large study, leukemias accounted for 60% of all cancers in people with Down

Table 81-4 Clinical Features of Down Syndrome in the Neonatal Period

CENTRAL NERVOUS SYSTEM
Hypotonia*
Developmental delay
Poor Moro reflex*
CRANIOFACIAL
Brachycephaly with flat occiput
Flat face*
Upward slanted palpebral fissures*
Epicanthal folds
Speckled irises (Brushfield spots)
Three fontanels
Delayed fontanel closure
Frontal sinus and midfacial hypoplasia
Mild microcephaly
Short hard palate
Small nose, flat nasal bridge
Protruding tongue, open mouth
Small dysplastic ears*
CARDIOVASCULAR
Endocardial Cushing defects
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Aberrant subclavian artery
Pulmonary hypertension
MUSCULOSKELETAL
Joint hyperflexibility*
Short neck, redundant skin*
Short metacarpals and phalanges
Short 5th digit with clinodactyly*
Single transverse palmar creases*
Wide gap between 1st and 2nd toes
Pelvic dysplasia*
Short sternum
Two sternal manubrium ossification centers
GASTROINTESTINAL
Duodenal atresia
Annular pancreas
Tracheoesophageal fistula
Hirschsprung disease
Imperforate anus
Neonatal cholestasis
CUTANEOUS
Cutis marmorata

*Hall's criteria to aid in diagnosis.

Table 81-5 Additional Features of Down Syndrome That Can Develop or Become Symptomatic with Time

NEUROPSYCHIATRIC Developmental delay Seizures Autism spectrum disorders Behavioral disorders (disruptive) Depression Alzheimer disease
SENSORY Congenital or acquired hearing loss Serous otitis media Refractive errors (myopia) Congenital or acquired cataracts Nystagmus Strabismus Glaucoma Blocked tear ducts
CARDIOPULMONARY Acquired mitral, tricuspid, or aortic valve regurgitation Endocarditis Obstructive sleep apnea
MUSCULOSKELETAL Atlantoaxial instability Hip dysplasia Slipped capital femoral epiphyses Avascular hip necrosis Recurrent joint dislocations (shoulder, knee, elbow, thumb)
ENDOCRINE Congenital or acquired hypothyroidism Diabetes mellitus Infertility Obesity Hyperthyroidism
HEMATOLOGIC Transient myeloproliferative syndrome Acute lymphocytic leukemia Acute myelogenous leukemia
GASTROINTESTINAL Celiac disease Delayed tooth eruption Respiratory Obstructed sleep apnea Frequent infections (sinusitis, nasopharyngitis, pneumonia)
CUTANEOUS Hyperkeratosis Seborrhea Xerosis Perigenital folliculitis

syndrome and 97% of all cancers in children with Down syndrome. There was decreased risk of solid tumors in all age groups, including neuroblastomas and nephroblastomas in children with Down syndrome and epithelial tumors in adults with Down syndrome.

Most adults with Down syndrome are able to perform activities of daily living. However, most adults with Down syndrome have difficulty with complex financial, legal, or medical decisions. In most circumstances, a conservator is appointed for the adult with Down syndrome.

The risk of having a child with trisomy 21 is highest in women who conceive at >35 yr of age. Even though younger women have a lower risk, they represent half of all mothers with babies with Down syndrome because of their higher overall birth rate. *All women should be offered screening for Down syndrome* in their 2nd trimester by means of 4 maternal serum tests (free β-human chorionic gonadotropin [β-hCG], unconjugated estriol, inhibin, and α-fetoprotein). This is

Table 81-6 Developmental Milestones

	CHILDREN WITH DOWN SYNDROME		UNAFFECTED CHILDREN	
Milestone	**Average (mo)**	**Range (mo)**	**Average (mo)**	**Range (mo)**
Smiling	2	1.5-3	1	1.5-3
Rolling over	6	2-12	5	2-10
Sitting	9	6-18	7	5-9
Crawling	11	7-21	8	6-11
Creeping	13	8-25	10	7-13
Standing	10	10-32	11	8-16
Walking	20	12-45	13	8-18
Talking, words	14	9-30	10	6-14
Talking, sentences	24	18-46	21	14-32

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, Saunders.*

Table 81-7 Self-Help Skills

	DOWN SYNDROME CHILDREN		UNAFFECTED CHILDREN	
Skill	**Average (mo)**	**Range (mo)**	**Average (mo)**	**Range (mo)**
EATING				
Finger feeding	12	8-28	8	6-16
Using spoon/fork	20	12-40	13	8-20
TOILET TRAINING				
Bladder	48	20-95	32	18-60
Bowel	42	28-90	29	16-48
DRESSING				
Undressing	40	29-72	32	22-42
Putting clothes on	58	38-98	47	34-58

From Levine MD, Carey WB, Crocker AC, editors: Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, Saunders.*

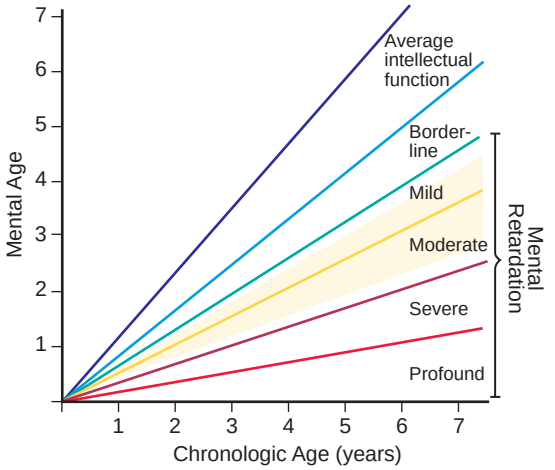

Figure 81-10 The area shaded in yellow denotes the range of intellectual function of the majority of children with Down syndrome. *(From Levine MD, Carey WB, Crocker AC, editors:* Developmental-behavioral pediatrics, *ed 2, Philadelphia, 1992, WB Saunders, p. 226.)*

Table 81-8 Health Supervision for Children with Down Syndrome

CONDITION	TIME TO SCREEN	COMMENT
Congenital heart disease	Birth; by pediatric cardiologist Young adult for acquired valve disease	50% risk of congenital heart disease; increased risk for pulmonary hypertension
Strabismus, cataracts, nystagmus	Birth or by 6 mo; by pediatric ophthalmologist **Check vision annually**	Cataracts occur in 15%, refractive errors in 50%
Hearing impairment or loss	Birth or by 3 mo with auditory brainstem response or otoacoustic emission testing; check hearing q6mo up to 3 yr if tympanic membrane is not visualized; **annually thereafter**	Risk for congenital hearing loss plus 50-70% risk of serous otitis media
Constipation	Birth	Increased risk for Hirschsprung disease
Celiac disease	At 2 yr or with symptoms	Screen with IgA and tissue transglutaminase antibodies
Hematologic disease	At birth and in adolescence or if symptoms develop	Increased risk for neonatal polycythemia (18%), leukemoid reaction, leukemia (<1%)
Hypothyroidism	Birth; repeat at 6-12 mo and **annually**	Congenital (1%) and acquired (5%)
Growth and development	At each visit Use Down syndrome growth curves	Discuss school placement options Proper diet to avoid obesity
Obstructive sleep apnea	Start at ~1 yr and at each visit	Monitor for snoring, restless sleep
Atlantoaxial subluxation or instability (incidence 10-30%)	At each visit by history and physical exam Radiographs at 3-5 yr or when planning to participate in contact sports Radiographs indicated wherever neurologic symptoms are present even if transient (neck pain, torticollis, gait disturbances, weakness) Many are asymptomatic	Special Olympics recommendations are to screen for high-risk sports, e.g., diving, swimming, contact sports
Gynecologic care	Adolescent girls	Menstruation and contraception issues
Recurrent infections	When present	Check IgG subclass and IgA levels
Psychiatric, behavioral disorders	At each visit	Depression, anxiety, obsessive-compulsive disorder, schizophrenia seem in 10-17% Autism spectrum disorder in 5-10% Early-onset Alzheimer disease

IgA, immunoglobulin A; IgG, immunoglobulin G.

Data from Committee on Genetics: Health supervision for children with Down syndrome, Pediatrics *107:442-449, 2001; and Baum RA, Spader M, Nash PL, et al: Primary care of children and adolescents with Down syndrome: an update,* Curr Probl Pediatr Adolesc Health Care *38:235–268, 2008.*

known as the *quad screen;* it can detect up to 80% of Down syndrome pregnancies compared to 70% in the triple screen. Both tests have a 5% false-positive rate. There is a method of screening during the 1st trimester using fetal nuchal translucency (NT) thickness that can be done alone or in conjunction with maternal serum β-hCG and pregnancy-associated plasma protein-A (PAPP-A). In the 1st trimester, NT alone can detect ≤70% of Down syndrome pregnancies, but with β-hCG and PAPP-A, the detection goes up to 87%. If both 1st and 2nd trimester screens are combined using NT and biochemical profiles (integrated screen), the detection rate goes up to 95%. If only 1st trimester quad screening is done, maternal serum α-fetoprotein (which is decreased in affected pregnancies) is recommended as a 2nd trimester follow-up.

Detection of cell free fetal DNA in maternal plasma is also diagnostic. The noninvasive detection of fetal trisomy 21 by analyzing cell-free fetal DNA in maternal serum is an important advance in prenatal diagnosis of Down syndrome. Next-generation DNA sequencing has reduced the cost of this procedure, which has a high degree of accuracy (98% detection rate) and applicability. The prenatal screens are also useful for other trisomies, although the detection rates may be different from those given for Down syndrome.

In approximately 95% of the cases of Down syndrome there are 3 copies of chromosome 21. The origin of the supernumerary chromosome 21 is maternal in 97% of the cases as a result of errors in meiosis. The majority of these occur in maternal meiosis I (90%). Approximately 1% of persons with trisomy 21 are mosaics, with some cells having 46 chromosomes, and another 4% have a **translocation** that involves chromosome 21. The majority of translocations in Down syndrome are fusions at the centromere between chromosomes 13, 14, 15, 21, and 22 known as *Robertsonian translocations.* The translocations can be de novo or inherited. Very rarely is Down syndrome diagnosed in a patient with only a part of the long arm of chromosome 21 in triplicate **(partial trisomy).** Isochromosomes and ring chromosomes are other rarer causes of trisomy 21. Down syndrome patients without a visible chromosome abnormality are the least common. It is not possible to distinguish the phenotypes of persons with full trisomy 21 and those with a translocation. Representative genes on chromosome 21 and their potential effects on development are noted in Table 81-9. Patients who are mosaic tend to have a milder phenotype.

Chromosome analysis is indicated in every person suspected of having Down syndrome. If a translocation is identified, parental chromosome studies must be performed to determine whether one of the parents is a translocation carrier, which carries a high recurrence risk for having another affected child. That parent might also have other family members at risk. Translocation (21;21) carriers have a 100% recurrence risk for a chromosomally abnormal child, and other Robertsonian translocations, such as t(14;21), have a 5-7% recurrence risk when transmitted by females. Genomic dosage imbalance contributes through direct and indirect pathways to the Down syndrome phenotype and its phenotypic variation.

Tables 81-10 and 81-11 provide more information on other aneuploidies and partial autosomal aneuploidies (Figs. 81-11 to 81-14).

Bibliography is available at Expert Consult.

Table 81-9 Genes Localized to Chromosome 21 That Possibly Affect Brain Development, Neuronal Loss, and Alzheimer Type Neuropathology

SYMBOL	NAME	POSSIBLE EFFECT IN DOWN SYNDROME	FUNCTION
SIM2	Single-minded homolog 2	Brain development	Required for synchronized cell division and establishment of proper cell lineage
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Brain development	Expressed during neuroblast proliferation Believed important homolog in regulating cell-cycle kinetics during cell division
GART	Phosphoribosylglycinamide formyltransferase Phosphoribosylglycinamide synthetase Phosphoribosylaminoimidazole synthetase	Brain development	Expressed during prenatal development of the cerebellum
PCP4	Purkinje cell protein 4	Brain development	Function unknown but found exclusively in the brain and most abundantly in the cerebellum
DSCAM	Down syndrome cell adhesion molecule	Brain development and possible candidate gene for congenital heart disease	Expressed in all molecule regions of the brain and believed to have a role in axonal outgrowth during development of the nervous system
GRIK1	Glutamate receptor, ionotropic kainite1	Neuronal loss	Function unknown, found in the cortex in fetal and early postnatal life and in adult primates, most concentrated in pyramidal cells in the cortex
APP	Amyloid beta (A4) precursor protein (protease nexin-II, Alzheimer disease)	Alzheimer type neuropathy	Seems to be involved in plasticity, neurite outgrowth, and neuroprotection
S100B	S100 calcium binding protein β (neural)	Alzheimer type neuropathy	Stimulates glial formation
SOD1	Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis, adult)	Accelerated aging?	Scavenges free superoxide molecules in the cell and might accelerate aging by producing hydrogen peroxide and oxygen

Table 81-10 Other Rare Aneuploidies and Partial Autosomal Aneuploidies

DISORDER	KARYOTYPE	CLINICAL MANIFESTATIONS
Trisomy 8	47,XX/XY,+8	Growth and mental deficiency are variable The majority of patients are mosaics Deep palmar and plantar furrows are characteristic
Trisomy 9	47,XX/XY,+9	The majority of patients are mosaics Clinical features include craniofacial (high forehead, microphthalmia, low-set malformed ears, bulbous nose) and skeletal (joint contractures) malformations and heart defects (60%)
Trisomy 16	47,XX/XY,+16	The most commonly observed autosomal aneuploidy in spontaneous abortion; the recurrence risk is negligible
Tetrasomy 12p	46,XX[12]/46,XX, +i(12p)[8] (mosaicism for an isochromosome 12p)	Known as Pallister-Killian syndrome. Sparse anterior scalp hair, eyebrows, and eyelashes, prominent forehead, chubby cheeks, long philtrum with thin upper lip and cupid-bow configuration, polydactyly, and streaks of hyper- and hypopigmentation

Table 81-11 Findings That May Be Present in Trisomy 13 and Trisomy 18

TRISOMY 13	TRISOMY 18
HEAD AND FACE	
Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60%-80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
CHEST	
Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, ASD) Short sternum, small nipples

Continued

Table 81-11 Findings That May Be Present in Trisomy 13 and Trisomy 18—cont'd

TRISOMY 13	TRISOMY 18
EXTREMITIES	
Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Limited hip abduction Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist Rocker-bottom feet Hypoplastic nails
GENERAL	
Severe developmental delays and prenatal and postnatal growth restriction Renal abnormalities Only 5% live >6 mo	Severe developmental delays and prenatal and postnatal growth restriction Premature birth, polyhydramnios Inguinal or abdominal hernias Only 5% live >1 yr

ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
From Behrman RE, Kliegman RM: Nelson essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders, p. 142.*

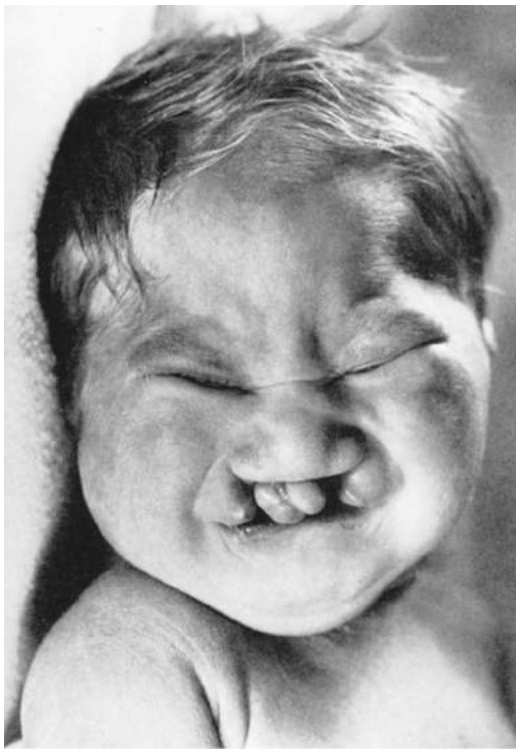

Figure 81-11 Facial appearance of a child with trisomy 13. *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

Figure 81-12 Trisomy 18: overlapping fingers and hypoplastic nails. *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

Figure 81-13 Trisomy 18: rocker-bottom feet (protruding calcanei). *(From Wiedemann HR, Kunze J, Dibbern H:* Atlas of clinical syndromes: a visual guide to diagnosis, *ed 3, St. Louis, 1989, Mosby.)*

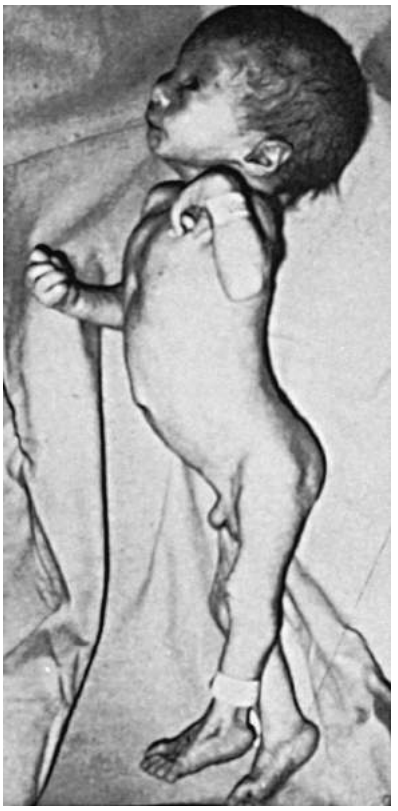

Figure 81-14 Male infant with trisomy 18 at age 4 days. Note prominent occiput, micrognathia, low-set ears, short sternum, narrow pelvis, prominent calcaneus, and flexion abnormalities of the fingers.

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81.3 Abnormalities of Chromosome Structure

Carlos A. Bacino and Brendan Lee

TRANSLOCATIONS

Translocations, which involve the transfer of material from 1 chromosome to another, occur with a frequency of 1 in 500 liveborn human infants. They may be inherited from a carrier parent or appear de novo, with no other affected family member. Translocations are commonly reciprocal or Robertsonian, involving 2 chromosomes (Fig. 81-15).

Reciprocal translocations are the result of breaks in nonhomologous chromosomes, with reciprocal exchange of the broken segments. Carriers of a reciprocal translocation are usually phenotypically normal but are at an increased risk for miscarriage caused by transmission of unbalanced reciprocal translocations and for bearing chromosomally abnormal offspring. Unbalanced translocations are the result of abnormalities in the segregation or crossover of the translocation carrier chromosomes in the germ cells.

Robertsonian translocations involve 2 acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22) that fuse near the centromeric region with a subsequent loss of the short arms. Because the short arms of all 5 pairs of acrocentric chromosomes have multiple copies of genes for ribosomal RNA, loss of the short arm of 2 acrocentric chromosomes has no deleterious effect. The resulting karyotype has only 45 chromosomes, including the translocated chromosome that is made up of the long arms of the 2 fused chromosomes. Carriers of Robertsonian translocations are usually phenotypically normal. However, they are at increased risk for miscarriage and unbalanced translocations in phenotypically abnormal offspring.

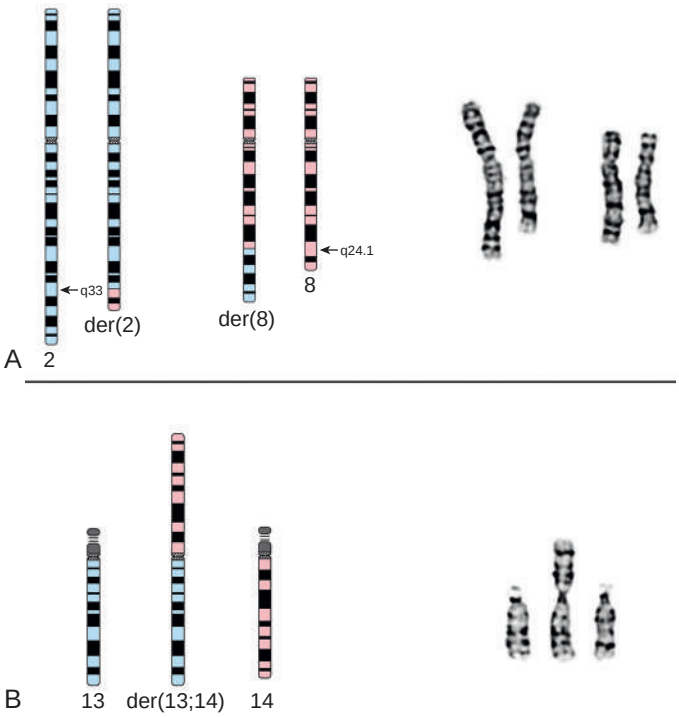

Figure 81-15 *A,* Schematic diagram *(left)* and partial G-banded karyotype *(right)* of a reciprocal translocation between chromosome 2 *(blue)* and chromosome 8 *(pink).* The breakpoints are on the long *(q)* arm of both chromosomes at bands 2q33 and 8q24.1, with the reciprocal exchange of material between the derivative *(der)* chromosomes 2 and 8. This translocation is balanced, with no net gain or loss of material. The nomenclature for this exchange is t(2;8)(q33:q24.1). *B,* Schematic diagram *(left)* and partial G-banded karyotype *(right)* of a Robertsonian translocation between chromosomes 13 *(blue)* and 14 *(pink).* The breakpoints are at the centromere (band q10) of both chromosomes, with fusion of the long arms into a single derivative chromosome and loss of the short *(p)* arm material. The nomenclature for this exchange is der(13;14)(q10;q10).

In some rare instances, translocations can involve 3 or more chromosomes, as seen in complex rearrangements. Another, less common type is the insertional translocation. Insertional translocations result from a piece of chromosome material that breaks away and later is reinserted inside the same chromosome at a different site or inserted in another chromosome.

INVERSIONS

An inversion requires that a single chromosome break at 2 points; the broken piece is then inverted and joined into the same chromosome. Inversions occur in 1 in 100 live births. There are 2 types of inversions: pericentric and paracentric. In **pericentric inversions,** the breaks are in the 2 opposite arms of the chromosome and include the centromere. They are usually discovered because they change the position of the centromere. The breaks in **paracentric inversions** occur in only 1 arm. Carriers of inversions are usually phenotypically normal, but they are at increased risk for miscarriages, typically in paracentric inversions, and chromosomally abnormal offspring in pericentric inversions.

DELETIONS AND DUPLICATIONS

Deletions involve loss of chromosome material and, depending on their location, they can be classified as **terminal** (at the ends of chromosomes) or **interstitial** (within the arms of a chromosome). They may be isolated or they may occur along with a duplication of another chromosome segment. The latter typically occurs in unbalanced reciprocal chromosomal translocation secondary to abnormal crossover or segregation in a translocation or inversion carrier.

A carrier of a deletion is monosomic for the genetic information of the missing segment. Deletions are usually associated with intellectual disability and malformations. The most commonly observed deletions in routine chromosome preparations include 1p–, 4p–, 5p–, 9p–, 11p–, 13q–, 18p–, 18q–, and 21q– (Table 81-12 and Fig. 81-16), all distal or terminal deletions of the short or the long arms of chromosomes. Deletions may be observed in routine chromosome preparations, and deletions and translocations larger than 5-10 Mbp are usually visible microscopically.

High-resolution banding techniques, FISH, and molecular studies like aCGH can reveal deletions that are too small to be seen in ordinary or routine chromosome spreads (see Fig. 81-7). **Microdeletions** involve loss of small chromosome regions, the largest of which are detectable only with prophase chromosome studies and/or molecular methods. For submicroscopic deletions, the missing piece can only be detected using molecular methodologies such as DNA-based studies like aCGH or FISH. The presence of extra genetic material from the same chromosome is referred to as **duplication.** Duplications can also be sporadic or result from abnormal segregation in translocation or inversion carriers.

Microdeletions and microduplications usually involve regions that include several genes, so that the affected individuals can have a distinctive phenotype depending on the number of genes involved. When such a deletion involves more than a single gene, the condition is referred to as a **contiguous gene deletion syndrome** (Table 81-13). With the advent of clinically available aCGH, a large number of duplications, most of them microduplications, have been uncovered. Most of those **microduplication syndromes** are the reciprocal duplications of the known deletions or microdeletion counterparts and have distinctive clinical features (Table 81-14).

Subtelomeric regions are often involved in chromosome rearrangements that cannot be visualized using routine cytogenetics. Telomeres, which are the distal ends of the chromosomes, are gene-rich regions. The distal structure of the telomeres is essentially common to all chromosomes, but proximal to those, there are unique regions known as subtelomeres, which typically involved in deletions and most other chromosome rearrangements. Small subtelomeric deletions, duplications, or rearrangements (translocations, inversions) may be relatively common in nonspecific intellectual disability with minor anomalies. Subtelomeric rearrangements have been found in 3-7% of children

Table 81-12 Common Deletions and Their Clinical Manifestations

DELETION	CLINICAL ABNORMALITIES
4p–	Wolf-Hirschhorn syndrome. The main features are a typical "Greek helmet" facies secondary to ocular hypertelorism, prominent glabella, and frontal bossing; microcephaly, dolichocephaly, hypoplasia of the orbits, ptosis, strabismus, nystagmus, bilateral epicanthic folds, cleft lip and palate, beaked nose with prominent bridge, hypospadias, cardiac malformations, and intellectual disability.
5p–	Cri-du-chat syndrome. The main features are hypotonia, short stature, characteristic shrill cry in the first few weeks of life (cat-like cry), microcephaly with protruding metopic suture, hypertelorism, bilateral epicanthic folds, high arched palate, wide and flat nasal bridge, and intellectual disability.
9p–	The main features are craniofacial dysmorphology with trigonocephaly, slanted palpebral fissures, discrete exophthalmos secondary to supraorbital hypoplasia, arched eyebrows, flat and wide nasal bridge, short neck with low hairline, genital anomalies, long fingers and toes with extra flexion creases, cardiac malformations, and intellectual disability.
13q–	The main features are low birthweight, failure to thrive, microcephaly, and severe intellectual disability. Facial features include high wide nasal bridge, hypertelorism, ptosis, micrognathia. Ocular malformations are common (retinoblastoma). The hands have hypoplastic or absent thumbs and syndactyly.
18p–	A few patients (15%) are severely affected and have cephalic and ocular malformations: holoprosencephaly, cleft lip and palate, ptosis, epicanthal folds, and varying degrees of intellectual disability. Most (80%) have only minor malformations and mild intellectual disability.
18q–	Growth deficiency, hypotonia with "frog-like" position with the legs flexed, externally rotated, and in hyperabduction. The face is characteristic with depressed midface and apparent protrusion of the mandible, deep-set eyes, short upper lip, everted lower lip ("carp-like" mouth); antihelix of the ears is very prominent; varying degrees of intellectual disability and belligerent personality. Myelination abnormalities in the central nervous system.

Table 81-13 Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations

DELETION	SYNDROME	CLINICAL MANIFESTATIONS
1p36	1p deletion	Growth restriction, dysmorphic features with midface hypoplasia, straight thin eyebrows, pointy chin, sensorineural hearing loss, progressive cardiomyopathy, hypothyroidism, seizures, intellectual disability
5q35	Sotos (50% are deletions of *NSD1* gene in Asians but only 6% in whites)	Overgrowth, macrocephaly, prominent forehead, prominence of extraaxial fluid spaces on brain imaging, large hands and feet, hypotonia, clumsiness, mental disabilities
6p25	Axenfeld-Rieger	Axenfeld-Rieger malformation, hearing loss, congenital heart defects, dental anomalies, developmental delays, facial dysmorphism
7q11.23	Williams	Round face with full cheeks and lips, long philtrum, stellate pattern in iris, strabismus, supravalvular aortic stenosis and other cardiac malformations, varying degrees of intellectual disability, friendly personality
8p11	8p11	Kallmann syndrome 2 (hypogonadotropic hypogonadism and anosmia), spherocytosis (deletions of ankyrin 1), multiple congenital anomalies, intellectual disability
8q24.1-q24.13	Langer-Giedion or trichorhinophalangeal type II	Sparse hair, multiple cone-shaped epiphyses, multiple cartilaginous exostoses, bulbous nasal tip, thickened alar cartilage, upturned nares, prominent philtrum, large protruding ears, mild intellectual disability
9q22	Gorlin	Multiple basal cell carcinomas, odontogenic keratocysts, palmoplantar pits, calcification falx cerebri
9q34	9q34 deletion	Distinct face with synophrys, anteverted nares, tented upper lip, protruding tongue, midface hypoplasia, conotruncal heart defects, intellectual disability
10p12-p13	DiGeorge 2	Many of the DiGeorge 1 and velocardiofacial 1 features (conotruncal defects, immunodeficiency, hypoparathyroidism, dysmorphic features)
11p11.2	Potocki-Shaffer	Multiple exostoses, parietal foramina, craniosynostosis, facial dysmorphism, syndactyly, intellectual disability
11p13	WAGR	Hypernephroma (Wilms tumor), aniridia, male genital hypoplasia of varying degrees, gonadoblastoma, long face, upward slanting palpebral fissures, ptosis, beaked nose, low-set poorly formed auricles, intellectual disability
11q24.1-11qter	Jacobsen	Growth restriction, intellectual disability, cardiac and digit anomalies, thrombocytopenia
15q11-q13 (paternal)	Prader-Willi	Severe hypotonia and feeding difficulties at birth, voracious appetite and obesity in infancy, short stature (responsive to growth hormone), small hands and feet, hypogonadism, intellectual disability

Table 81-13 Microdeletion and Contiguous Gene Syndromes and Their Clinical Manifestations—cont'd

DELETION	SYNDROME	CLINICAL MANIFESTATIONS
15q11-q13 (maternal)	Angelman	Hypotonia, feeding difficulties, gastroesophageal reflux, fair hair and skin, midface hypoplasia, prognathism, seizures, tremors, ataxia, sleep disturbances, inappropriate laughter, poor or absent speech, severe intellectual disability
16p13.3	Rubinstein-Taybi	Microcephaly, ptosis, beaked nose with low-lying philtrum, broad thumbs and large toes, intellectual disability
17p11.2	Smith-Magenis	Brachycephaly, midfacial hypoplasia, prognathism, myopia, cleft palate, short stature, severe behavioral problems, intellectual disability
17p13.3	Miller-Dieker	Microcephaly, lissencephaly, pachygyria, narrow forehead, hypoplastic male external genitals, growth restriction, seizures, profound intellectual disability
20p12	Alagille syndrome	Bile duct paucity with cholestasis; heart defects, particularly pulmonary artery stenosis; ocular abnormalities (posterior embryotoxon); skeletal defects such as butterfly vertebrae; long nose
22q11.2	Velocardiofacial-DiGeorge syndrome	Conotruncal cardiac anomalies, cleft palate, velopharyngeal incompetence, hypoplasia or agenesis of the thymus and parathyroid glands, hypocalcemia, hypoplasia of auricle, learning disabilities, psychiatric disorders
22q13.3 deletion		Hypotonia, developmental delay, normal or accelerated growth, severe expressive language deficits, autistic behavior
Xp21.2-p21.3		Duchenne muscular dystrophy, retinitis pigmentosa, adrenal hypoplasia, intellectual disability, glycerol kinase deficiency
Xp22.2-p22.3		Ichthyosis, Kallmann syndrome, intellectual disability, chondrodysplasia punctata
Xp22.3	Microphthalmia with linear defects (MLS)	Microphthalmia, linear skin defects, poikiloderma, congenital heart defects, seizures, intellectual disability

Table 81-14 Microduplications and Their Clinical Manifestations

DUPLICATION CHROMOSOME REGION	DISEASE REGION	CLINICAL FEATURES
1q21.1		Macrocephaly, DD, learning disabilities
3q29		Mild to moderate MR, microcephaly
7q11.23	Williams syndrome	DD and severe expressive language disorder, autistic features, subtle dysmorphisms
15q13.3	Prader-Willi/Angelman syndrome region	DD, MR, autistic features in duplications of maternal origin
15q24		Growth restriction, DD, microcephaly, digital anomalies, hypospadias, connective tissue abnormalities
16p11.2		FTT, severe DD, short stature, GH deficiency, dysmorphic features
17p11.2	Potocki-Lupski syndrome	Hypotonia, cardiovascular anomalies, FTT, DD, verbal apraxia, autism, anxiety
17q21.31		Severe DD, microcephaly, short and broad digits, dysmorphic features
22q11.2	Velocardiofacial-DiGeorge syndrome	Cardiovascular defects, velopharyngeal insufficiency
Xq28	*MECP2* gene region (Rett syndrome)	In males: infantile hypotonia, immune deficiency, dysmorphic features, DD, speech delay, autistic behavior, regression in childhood

DD, developmental delay; ID, intellectual disability; FTT, failure to thrive; GH, growth hormone; MR, mental retardation.

with moderate to mild intellectual disability and 0.5% of children with mild intellectual disability.

Clinical features (>30%) include short stature, microcephaly, hypertelorism, nose and ear abnormalities, and cryptorchidism. This group is also characterized by a family history of intellectual disability and an increased likelihood of restricted growth beginning in the prenatal period. Telomere mutations have also been associated with dyskeratosis congenita and other aplastic anemia syndromes as well as pulmonary or hepatic fibrosis. Both the subtelomeric rearrangements and the microdeletion and microduplication syndromes are typically diagnosed by molecular techniques like aCGH, FISH, and multiple ligation-dependent primer amplification. Recent studies show that aCGH can detect 14-18% of abnormalities in patients who are previously known to have normal chromosome studies.

INSERTIONS

Insertions occur when a piece of a chromosome broken at 2 points is incorporated into a break in another part of a chromosome. A total of 3 breakpoints are then required, and they can occur between 2 or within 1 chromosome. A form of nonreciprocal translocation, insertions are rare. Insertion carriers are at risk of having offspring with deletions or duplications of the inserted segment.

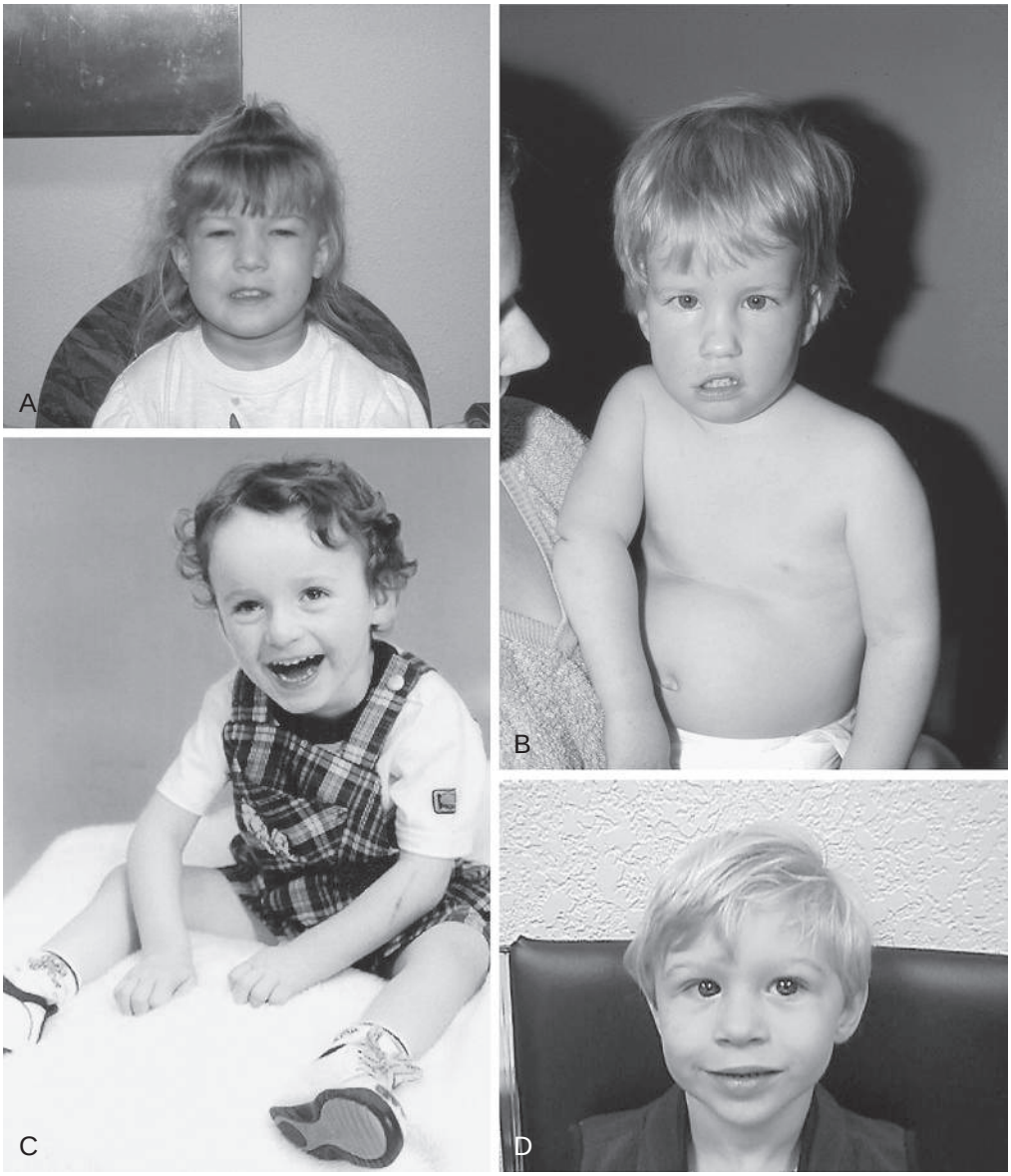

Figure 81-16 *A*, Child with velocardiofacial syndrome (deletion 22q11.2). *B*, Child with Prader-Willi syndrome (deletion 15q11-13). *C*, Child with Angelman syndrome (deletion 15q11-13). *D*, Child with Williams syndrome (deletion 7q11.23). *(From Lin RL, Cherry AM, Bangs CD, et al: FISHing for answers: the use of molecular cytogenetic techniques in adolescent medicine practice. In Hyme HE, Greydanus D, editors:* Genetic disorders in adolescents: state of the art reviews. Adolescent medicine, *Philadelphia, 2002, Hanley and Belfus, pp. 305–313.)*

ISOCHROMOSOMES

Isochromosomes consist of 2 copies of the same chromosome arm joined through a single centromere and forming mirror images of one another. The most commonly reported autosomal isochromosomes tend to involve chromosomes with small arms. Some of the more common chromosome arms involved in this formation include 5p, 8p, 9p, 12p, 18p, and 18q. There is also a common isochromosome abnormality seen in long arm of the X chromosome, and associated with Turner syndrome. Individuals who have 1 isochromosome within 46 chromosomes are monosomic for genes in the lost short arm and trisomic for the genes present in the long arm of the X chromosome.

MARKER AND RING CHROMOSOMES

Marker chromosomes are rare and are usually chromosome fragments that are too small to be identified by conventional cytogenetics; they usually occur in addition to the normal 46 chromosomes. Most are sporadic (70%); mosaicism is often (50%) noted because of the mitotic instability of the marker chromosome. The incidence in newborn infants is 1 in 3,300, and the incidence in persons with intellectual disability is 1 in 300. The associated phenotype ranges from normal to severely abnormal depending on the amount of chromosome material and number of genes associated with the fragment.

Ring chromosomes, which are found for all human chromosomes, are rare. A ring chromosome is formed when both ends of a chromosome are deleted and the ends are then joined to form a ring. Depending on the amount of chromosome material that is lacking or in excess (if the ring is in addition to the normal chromosomes), a patient with a ring chromosome can appear normal or nearly normal or can have intellectual disability and multiple congenital anomalies.

Marker and ring chromosomes can be found in the cells of solid tumors of children the cells of whose organs do not contain this additional chromosomal material.

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81.4 Sex Chromosome Aneuploidy

Carlos A. Bacino and Brendan Lee

About 1 in 400 males and 1 in 650 females have some form of sex chromosome abnormality. Considered together, sex chromosome abnormalities are the most common chromosome abnormalities seen in liveborn infants, children, and adults. Sex chromosome abnormalities can be either structural or numerical and can be present in all cells or in a mosaic form. Those affected with these abnormalities might have few or no physical or developmental problems (Table 81-15).

TURNER SYNDROME

Turner syndrome is a condition characterized by complete or partial monosomy of the X chromosome and defined by a combination of phenotypic features (Table 81-16). Half of the patients with Turner syndrome have a 45,X chromosome complement. The other half exhibits mosaicism and varied structural abnormalities of the X or Y chromosome. Maternal age is not a predisposing factor for children with 45,X. Turner syndrome occurs in approximately 1 in 5,000 female live births. In 75% of patients, the lost sex chromosome is of paternal origin (whether an X or a Y). 45,X is one of the chromosome abnormalities most often associated with spontaneous abortion. It has been estimated that 95-99% of 45,X conceptions are miscarried.

Clinical findings in the newborns can include small size for gestational age, webbing of the neck, protruding ears, and lymphedema of the hands and feet, although many newborns are phenotypically normal (Fig. 81-17). Older children and adults have short stature and exhibit variable dysmorphic features. Congenital heart defects (40%) and structural renal anomalies (60%) are common. The most common heart defects are bicuspid aortic valves, coarctation of the aorta, aortic stenosis, and mitral valve prolapse. The gonads are generally streaks of fibrous tissue **(gonadal dysgenesis).** There is primary amenorrhea and lack of secondary sex characters. These children should receive regular endocrinologic testing (see Chapter 586). Most patients tend to be of normal intelligence, but intellectual disability is seen in up to 6% of affected children. They are also at increased risk for behavioral problems and deficiencies in spatial and motor perception. Guidelines for health supervision for children with Turner syndrome are published by the American Academy of Pediatrics and include pubertal induction, as well as treatment with growth hormone and oxandrolone.

Patients with **45,X/46,XY mosaicism,** can have Turner syndrome, although this form of mosaicism can also be associated with male pseudohermaphroditism, male or female genitalia in association with

Table 81-15 Sex Chromosome Abnormalities

DISORDER	KARYOTYPE	APPROXIMATE INCIDENCE
Klinefelter syndrome	47,XXY 48,XXXY Other (48,XXYY; 49,XXXYY; mosaics)	1/575-1/1,000 males 1/50,000-1/80,000 male births
XYY syndrome	47,XYY	1/800-1,000 males
Other X or Y chromosome abnormalities		1/1,500 males
XX males	46,XX	1/20,000 males
Turner syndrome	45,X Variants and mosaics	1/2,500-1/5,000 females
Trisomy X	47,XXX 48,XXXX and 49,XXXXX	1/1,000 females Rare
Other X chromosome abnormalities		1/3,000 females
XY females	46,XY	1/20,000 females

Table 81-16 Signs Associated with Turner Syndrome

Short stature
Congenital lymphedema
Horseshoe kidneys
Patella dislocation
Increased carrying angle of elbow (cubitus valgus)
Madelung deformity (chondrodysplasia of distal radial epiphysis)
Congenital hip dislocation
Scoliosis
Widespread nipples
Shield chest
Redundant nuchal skin (in utero cystic hygroma)
Low posterior hairline
Coarctation of aorta
Bicuspid aortic valve
Cardiac conduction abnormalities
Hypoplastic left-heart syndrome and other left-heart abnormalities
Gonadal dysgenesis (infertility, primary amenorrhea)
Gonadoblastoma (increased risk if Y chromosome material is present)
Learning disabilities (nonverbal perceptual motor and visuospatial skills) (in 70%)
Developmental delay (in 10%)
Social awkwardness
Hypothyroidism (acquired in 15-30%)
Type 2 diabetes mellitus (insulin resistance)
Strabismus
Cataracts
Red-green color blindness (as in males)
Recurrent otitis media
Sensorineural hearing loss
Inflammatory bowel disease
Celiac disease (increased incidence)

Figure 81-17 Redundant nuchal skin *(A)* and puffiness of the hands *(B)* and feet *(C)* in Turner syndrome. *(From Sybert VP, McCauley E: Turner's syndrome,* N Engl J Med *351:1227–1238, 2004. Copyright © 2004 Massachusetts Medical Society.)*

mixed gonadal dysgenesis, or a normal male phenotype. This variant is estimated to represent approximately 6% of patients with mosaic Turner syndrome. Some of the patients with Turner syndrome phenotype and a Y cell line exhibit masculinization. Phenotypic females with 45,X/46,XY mosaicism have a 15-30% risk of developing **gonadoblastoma.** The risk for the patients with a male phenotype and external testes is not so high, but tumor surveillance is nevertheless recommended. The American Academy of Pediatrics has recommended the use of FISH analysis to look for Y-chromosome mosaicism in all 45,X patients. If Y chromosome material is identified, laparoscopic gonadectomy is recommended.

Noonan syndrome shares many clinical features with Turner syndrome (old name was pseudo-Turner syndrome), although it is an autosomal dominant disorder resulting from mutations in several genes that are involved in the RAS-MAPK (mitogen-activated protein kinase) pathway. The most common of these is *PTPN11* (50%), which encodes a protein-tyrosine phosphatase (SHP-2) on chromosome 12q24.1. Other genes include *SOS1* in 10-13%, *RAF1* in 3-17%, *KRAS* <5%, *BRAF* <2%, and *MAP2K* <2%. Overlapping phenotypes are seen in LEOPARD (lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth, deafness) syndrome, cardiofaciocutaneous syndrome, and Costello syndrome; these are Noonan-related disorders. Features common to Noonan syndrome include short stature, low posterior hairline, shield chest, congenital heart disease, and a short or webbed neck (Table 81-17). In contrast to Turner syndrome, Noonan syndrome affects both sexes and has a different pattern of congenital heart disease, typically involving right-sided lesions.

KLINEFELTER SYNDROME

Persons with Klinefelter syndrome are phenotypically male; this syndrome is the most common cause of hypogonadism and infertility in males and the most common sex chromosome aneuploidy in humans (see Chapter 583). Eighty percent of children with Klinefelter syndrome have a male karyotype with an extra chromosome X-47,XXY; the remaining 20% have multiple sex chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY), mosaicism (46,XY/47,XXY), or structurally abnormal X chromosomes. The greater the aneuploidy, the more severe the mental impairment and dysmorphism. Early studies showed that the birth prevalence is approximately 1 in 1,000 males. The current prevalence of 47,XXY appears to have increased to approximately 1 in 580 liveborn boys; the reasons for this are still unknown. Errors in paternal nondisjunction in meiosis I account for half of the cases.

Puberty occurs at the normal age, but the testes remain small. Patients develop secondary sex characters late; 50% develop gynecomastia. They have taller stature. Because many patients with Klinefelter syndrome are phenotypically normal until puberty, the syndrome often goes undiagnosed until they reach adulthood, when their infertility aids in their clinical identification. Patients with 46,XY/47,XXY have a better prognosis for testicular function. Their intelligence shows variability and ranges from above to below average. Persons with Klinefelter syndrome can show behavioral problems, learning disabilities, and deficits in language. Problems with self-esteem are often the case with adolescents and adults. Substance abuse, depression, and anxiety have been reported in adolescents with Klinefelter syndrome. Those who have higher X chromosome counts show impaired cognition. It has been estimated that each additional X chromosome reduces the IQ by 10-15 points, when comparing these persons with their normal siblings. The main effect is seen in language skills and social domains.

47,XYY

The incidence of 47,XYY is approximately 1 in 800-1,000 males, with many cases remaining undiagnosed, because most affected individuals have a normal appearance and normal fertility. The extra Y is the result of nondisjunction at paternal meiosis II. Those with this abnormality have normal intelligence but are at risk for learning disabilities. Behavioral abnormalities including hyperactive behavior, pervasive developmental disorder, and aggressive behavior have been reported. Early reports that assigned stigmata of criminality to this disorder have long been disproved.

Bibliography is available at Expert Consult.

Table 81-17 Signs Associated with Noonan Syndrome

Short stature
Failure to thrive (use Noonan growth curve)
Tall forehead
Epicanthal folds
Ptosis
Blue-green irises
Hypertelorism
Low nasal bridge, upturned nose
Downward-slanting palpebral fissures
Myopia
Nystagmus
Low-set auricles
Dental malocclusion
Low posterior hairline
Short webbed neck (excessive nuchal skin), cystic hygroma
Shield chest
Pectus carinatum superiorly
Scoliosis
Pigmented villonodular synovitis (polyarticular)
Cubitus valgus
Pulmonary valve stenosis (dysplastic valve)
Hypertrophic cardiomyopathy
Atrial septal defect, ventricular septal defect
Lymphedema
Nevi, lentigines, café-au-lait spots
Cryptorchidism
Small penis
Delayed puberty
Bleeding disorders, including thrombocytopenia and factor deficiencies
Leukemia, myeloproliferative disorders, other malignancies
Cognitive delay (*KRAS* mutation)

81.5 Fragile Chromosome Sites

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Fragile sites are regions of chromosomes that show a tendency for separation, breakage, or attenuation under particular growth conditions. They appear as a gap in the staining. At least 120 chromosomal loci, many of them heritable, have been identified as fragile sites in the human genome (see Table 80-2).

One fragile site that has clinical significance is the one on the distal long arm of chromosome Xq27.3 associated with the **fragile X syndrome.** Fragile X accounts for 3% of males with intellectual disability. There is another fragile site on the X chromosome (FRAXE on Xq28) that has also been implicated in mild intellectual disability. The FRA11B (11q23.3) breakpoints are associated with Jacobsen syndrome (condition caused by deletion of the distal long arm of chromosome 11). Fragile sites can also play a role in tumorigenesis. CGG repeat expansion silences the gene producing fragile X mental retardation protein (FMRP) that regulates the translation of multiple mRNAs to specific proteins, thus affecting synaptic function. FMRP deficiency upregulates the metabotropic glutamate receptor (mGluR) 5 pathway. FMRP deficiency also alters the expression of matrix metalloproteinase (MMP) 9.

The main **clinical manifestations** of fragile X syndrome in affected males are intellectual disability, autistic behavior, macroorchidism, hyperextensible finger joints, and characteristic facial features (Table 81-18). The macroorchidism may not be evident until puberty. The facial features, which include a long face, large ears, and a prominent square jaw, become more obvious with age. Females affected with

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Table 81-18 Clinical Features of Full and Premutation *FMR1* Alleles

Disorder	PHENOTYPE: Cognitive or Behavioral	PHENOTYPE: Clinical and Imaging Signs	Onset	Penetrance
FULL MUTATION				
FXS	Developmental delay: mean IQ = 42 in M; IQ is higher if significant residual FMRP is produced (e.g., females and mosaic males or unmethylated full mutations) Autism 20-30% ADHD 80% Anxiety 70-100%	Hypothalamic dysfunction: macroorchidism, 40%* Facial features, 60%,* large cupped ears, elongated face, high arched palate Connective tissue abnormalities: mitral valve prolapse, scoliosis, joint laxity, flat feet Others: seizures (20%), recurrent otitis media (60%), strabismus (8-30%)	Neonate	M 100%
PREMUTATION				
Female reproductive symptoms		POF (<40 yr) Early menopause (<45 yr)	Adult-/child hood	F 20%† F 30%†
FXTAS	Cognitive decline, dementia, apathy, disinhibition, irritability, depression	Gait ataxia, intention tremor, Parkinsonism, neuropathy, autonomic dysfunction	>50 yr	M 33%‡ F unknown
Neurodevelopmental disorder	ADHD, autism, or developmental delay	Mild features of FXS	Childhood	8% (1/13)*

*Frequency of those signs in prepubertal boys; {1/3} of boys with FXS are without classic facial features. Macroorchidism is present in 90% of men.
†Maximum penetrance reported for allele size approximately 80-90 CGG repeats.
‡Penetrance is correlated with age and repeat size.
ADHD, attention-deficit/hyperactivity disorder; F, female; FXS, fragile-X syndrome; M, male; POF, premature ovarian failure.
From Jacquemont S, Hagerman RJ, Hagerman PJ, et al: Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMRI, Lancet Neurol *6:45–55, 2007, Table 1.*

Table 81-19 Therapy for *FMR1* Related Disorders

DISORDER	SYMPTOM	THERAPY AND INTERVENTIONS	FUTURE POTENTIAL THERAPY
FULL MUTATION			
FXS*	ADHD	Stimulants	mGluR5 antagonists
	Anxiety, hyperarousal, aggressive outbursts	SSRIs, atypical antipsychotics, occupational therapy, behavioral therapy, counseling	mGluR5 antagonists
	Seizures	Carbamazepine, valproic acid	mGluR5 antagonists
	Cognitive deficit	Occupational therapy, speech therapy, special education support	mGluR5 antagonists
PREMUTATION			
POF	Premature ovarian failure	Reproductive counseling, egg donation Hormone replacement therapy	Cryopreservation of ovarian tissue
FXTAS†	Intention tremor	β-Blockers	
	Parkinsonism	Carbidopa/levodopa	
	Cognitive decline, dementia	Acetylcholinesterase inhibitors	
	Anxiety, apathy, disinhibition, irritability, depression	Venlafaxine, SSRIs	
	Neuropathic pain	Gabapentin	

*These data are based on a survey in 2 large referral centers. Drugs for anxiety were more frequently prescribed than those for neurologic signs.
†There have been no controlled studies to assess drugs for FXTAS. These data were collected through a questionnaire study (n = 56).
ADHD, attention-deficit/hyperactivity disorder; FXS, fragile-X syndrome; FXTAS, fragile X-associated tremor/ataxia syndrome; POF, premature ovarian failure; SSRI, selective serotonin reuptake inhibitor.
From Jacquemont S, Hagerman RJ, Hagerman PJ, et al: Fragile-X syndrome and fragile X-associated tremor/ataxia syndrome: two faces of FMRI, Lancet Neurol *2006:45–55, 2007, Table 2.*

fragile X show varying degrees of intellectual disability and/or learning disabilities. Diagnosis of fragile X is possible by DNA testing that shows an expansion of a triplet DNA repeat inside the *FMR1* gene on the X chromosome larger than 200 repeats. The expansion involves an area of the gene that contains a variable number of trinucleotide (CGG) repeats. The larger the triplet repeat expansion, the more significant the intellectual disability. In cases where the expansion is large, females can also manifest different degrees of intellectual disability. Males with premutation triple repeat expansions (50-200 repeats), have been found to have an adult, late onset progressive neurodegenerative disorder known as **fragile X-associated tremor/ataxia syndrome**. Therapy of the diverse neuropsychiatric manifestations associated with fragile X syndrome is noted in Table 81-19. Inhibitors of the mGluR (overexpressed in fragile X) are undergoing clinical trials. In preliminary trials, minocycline (lowers MMP9) has resulted in short term improvements in anxiety, mood, and the clinical Global Impression Scale.

Bibliography is available at Expert Consult.

81.6 Mosaicism

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Mosaicism describes an individual or tissue that contains ≥2 different cell lines typically derived from a single zygote and the result of mitotic nondisjunction (see Fig. 81-1). Study of placental tissue from chorionic

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villus samples collected at or before the 10th wk of gestation has shown that 2% or more of all conceptions are mosaic for a chromosome abnormality. With the exception of chromosomes 13, 18, and 21, complete autosomal trisomies are usually nonviable; the presence of a normal cell line might allow these other trisomic conceptions to survive to term. Depending on the point at which the new cell line arises during early embryogenesis, mosaicism may be present in some tissues but not in others. Germline mosaicism, which refers to the presence of mosaicism in the germ cells of the gonad, may be associated with an increased risk for recurrence of an affected child whether the germ cells are affected with a chromosomal abnormality or specific gene mutation.

PALLISTER-KILLIAN SYNDROME

Pallister-Killian syndrome is characterized by coarse facies (prominent full cheeks), abnormal ear lobes, localized alopecia, pigmentary skin anomalies, diaphragmatic hernia, cardiovascular anomalies, supernumerary nipples, seizures, and profound intellectual disability. The syndrome is due to mosaicism for an isochromosome 12p. The presence of the isochromosome 12p in cells gives 4 functional copies for the short arm of chromosome 12 in the affected cells. The isochromosome 12p is preferentially cultured from fibroblasts that can be readily obtained from a skin punch biopsy and is seldom present in lymphocytes. The abnormalities seen in affected persons probably reflect the presence of abnormal cells during early embryogenesis.

HYPOMELANOSIS OF ITO

Hypomelanosis of Ito is characterized by unilateral or bilateral macular hypo- or hyperpigmented whorls, streaks, and patches (see Chapter 653). Sometimes these pigmentary defects follow the lines of Blaschko. Hair and tooth anomalies are common. Abnormalities of the eyes, musculoskeletal system (growth asymmetry, syndactyly, polydactyly, clinodactyly), and central nervous system (microcephaly, seizures, intellectual disability) may also be present. Patients with hypomelanosis of Ito might have 2 genetically distinct cell lines. The mosaic chromosome anomalies that have been observed involve both autosomes and sex chromosomes and have been demonstrated in about 50% of patients. The mosaicism might not be visible in lymphocyte-derived chromosome studies; it is more likely to be found when chromosomes are analyzed from skin fibroblasts. The distinct cell lines might not always be due to observable chromosomal anomalies but might result from single gene mutations or other mechanisms.

81.7 Chromosome Instability Syndromes

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Chromosome instability syndromes, formerly known as chromosome breakage syndromes, are characterized by an increased risk of malignancy and specific phenotypes. They display autosomal recessive inheritance and have an increased frequency of chromosome breakage and/or rearrangement, either spontaneous or induced. They result from specific defects in DNA repair, cell cycle control, and apoptosis. The resulting chromosomal instability leads to the increased risk of developing neoplasms. The classic chromosome instability syndromes are Fanconi anemia, ataxia telangiectasia, Nijmegen syndrome, ICF (immunodeficiency, centromere instability, and facial anomalies) syndrome, Roberts syndrome, Werner syndrome, and Bloom syndrome.

81.8 Uniparental Disomy and Imprinting

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UNIPARENTAL DISOMY

Uniparental disomy (UPD) occurs when both chromosomes of a pair or areas from 1 chromosome in any individual have been inherited from a single parent. UPD can be of 2 types: uniparental isodisomy or uniparental heterodisomy. **Uniparental isodisomy** means that both chromosomes or chromosomal regions are identical (typically the result of monosomy rescue by duplication). **Uniparental heterodisomy** means that the 2 chromosomes are different members of a pair, both of which were still inherited from 1 parent. This results from a trisomy that is later reduced to disomy, leaving 2 copies from 1 parent. The phenotypical result of UPD varies according to the chromosome involved, the parent who contributed the chromosomes, and whether it is isodisomy or heterodisomy. Three types of phenotypic effects are seen in UPD: those related to imprinted genes (i.e., the absence of a gene that is normally expressed only when inherited from a parent of a specific sex), those related to the uncovering of autosomal recessive disorders, and those related to a vestigial aneuploidy producing mosaicism (see Chapter 80).

In uniparental isodisomy, both chromosomes or regions (and thus the genes) in the pair are identical. This is particularly important when the parent is a carrier of an autosomal recessive disorder. If the offspring of a carrier parent has UPD with isodisomy for a chromosome that carries an abnormal gene, the abnormal gene will be present in 2 copies and the phenotype will be that of the autosomal recessive disorder; the child has an autosomal recessive disorder even though only 1 parent is a carrier of that recessive disorder. It is estimated that all human beings carry approximately 20 abnormal autosomal recessive genes. Some autosomal recessive disorders like spinal muscular atrophy, cystic fibrosis, cartilage-hair hypoplasia, α- and β-thalassemias, and Bloom syndrome have been reported in cases of UPD. The possibility of uniparental isodisomy should also be considered when a person is affected with >1 recessive disorder because the abnormal genes for both disorders could be carried on the same isodisomic chromosome. Uniparental isodisomy is a *rare* cause of recessively inherited disorders. Uniparental isodisomies can also be detected by SNP microarrays.

Maternal UPD involving chromosomes 2, 7, 14, and 15 and **paternal UPD** involving chromosomes 6, 11, 15, and 20 are associated with phenotypic abnormalities of growth and behavior. UPD of maternal chromosome 7 is associated with a phenotype similar to Russell-Silver syndrome with intrauterine growth restriction. These phenotypic effects may be related to imprinting (see under Imprinting, below) (Fig. 81-18).

UPD for chromosome 15 is seen in some cases of Prader-Willi syndrome and Angelman syndrome. In **Prader-Willi syndrome**, approximately 25-29% of cases have maternal UPD (missing the paternal chromosome 15). In **Angelman syndrome**, paternal UPD of chromosome 15 is rarer and is observed in approximately 5% of the cases (missing the maternal chromosome 15). The phenotype for Prader-Willi syndrome (Fig. 81-19) and Angelman syndrome in cases of UPD is thought to result from the lack of the functional contribution from a particular parent of chromosome 15. In Prader-Willi syndrome the paternal contribution is missing, and the maternal contribution is missing in Angelman syndrome. Prader-Willi may be due to paternal deficiency of HB11-85 snoRNAs (small nucleolar RNAs). These findings suggest that there are differences in function of certain regions of chromosome 15, depending on whether it is inherited from the mother or from the father.

UPD most commonly arises when a pregnancy starts off as a **trisomic conception followed by trisomy rescue.** Because most trisomies are lethal, the fetus can only survive if a cell line loses 1 of the extra chromosomes to revert to the disomic state. One-third of the time, the disomic cell line is uniparental. This is the typical mechanism for Prader-Willi syndrome, and it is often associated with advanced maternal age. The embryo starts off as trisomy 15 secondary to maternal meiosis I nondisjunction, followed by random loss of the paternal chromosome. In this case, the disomic cell line becomes the more viable one and outgrows the trisomic cell line. When mosaic trisomy is found at prenatal diagnosis, care should be taken to determine whether UPD has resulted and whether the chromosome involved is one of the disomies known to be associated with phenotypic abnormalities. There must always be concern that some residual cells that are trisomic are present in some tissues, leading to malformations or

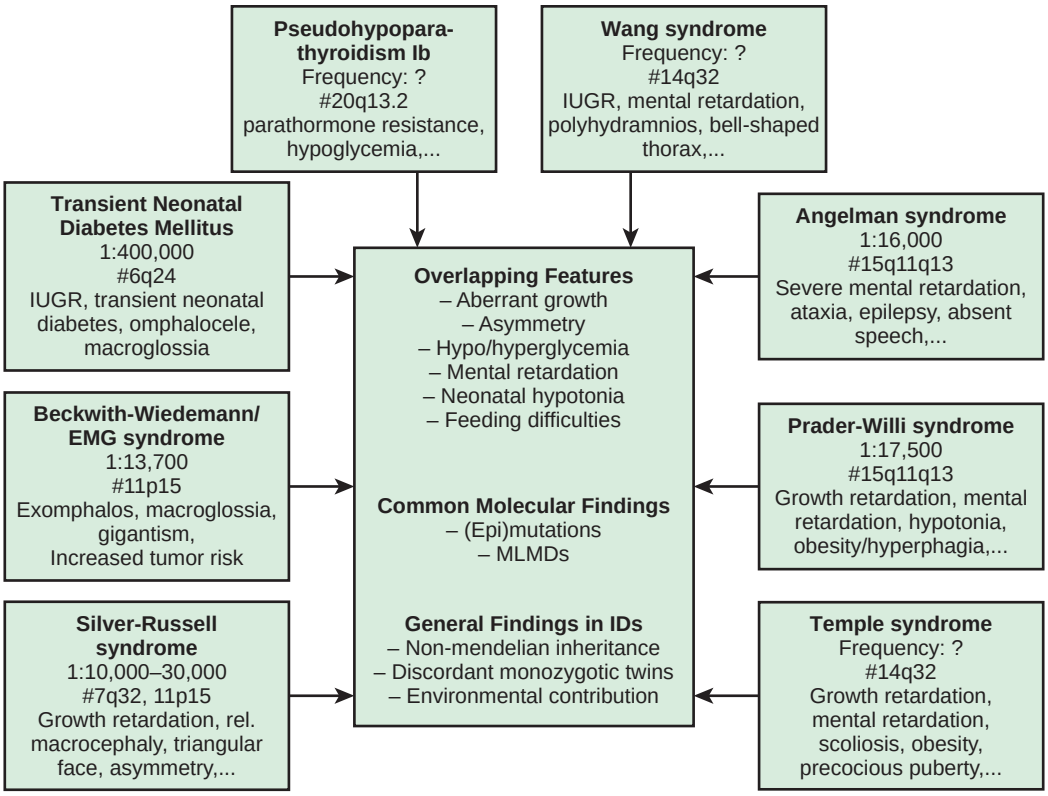

Figure 81-18 Overview of the common clinical and molecular findings in the 8 known imprinting disorders, including specific features, frequencies, and major chromosomal localization. *#6q24,* chromosome 6q24; *EMG,* exomphalos-macroglossia-gigantism; *IUGR,* intrauterine growth restriction. *(From Eggermann T, Elbracht M, Schröder C, et al: Congenital imprinting disorders: a novel mechanism linking seemingly unrelated disorders.* J Pediatr *163:1202-1207, 2013, Fig. 2, p. 1204).*

dysfunction. The presence of aggregates of trisomic cells might account for the spectrum of abnormalities seen in persons with UPD.

IMPRINTING

Traditional genetics has for many years suggested that most genes are equally expressed when inherited from maternal versus paternal lineages. The only exception to this rule were genes on the X chromosome that are subject to inactivation, and the immunoglobulin genes subject to allelic exclusion, a phenomenon that results in monoallelic expression of a particular immunoglobulin chain by switching on and off expression of parental alleles. Genomic imprinting occurs when the phenotypic expression of a gene depends on the parent of origin for certain genes or in some cases entire chromosome regions. Whether the genetic material is expressed or not depends on the sex of the parent from whom it was derived. Genomic imprinting can be suspected in some cases on the basis of a pedigree. In these pedigrees, the disease is always transmitted from 1 sex and could be passed on silently for several generations by the opposite sex (Figs. 81-20 and 81-21). Imprinting probably occurs in many different parts of the human genome and is thought to be particularly important in gene expression related to development, growth, cancer, and even behavior; over 60 genes have been classified as imprintable. Imprinting disorders may arise from UPD, deletions or duplications, epigenetic aberrant methylation patterns, or point mutations in a specific gene.

A classic example of imprinting disorder is seen in Prader-Willi syndrome and Angelman syndrome, 2 very different clinical conditions. These syndromes are usually associated with deletion of the same region in the proximal long arm of chromosome 15. A deletion on the paternally derived chromosome causes Prader-Willi syndrome, in which the maternally derived copy is still intact but some of the imprinted genes within this region normally remain silent. In contrast, a maternal deletion of the same region causes Angelman syndrome, leaving intact the paternal copy that in this case has genes that are also normally silent. In other situations, UPD can lead to the same diagnosis. Maternal UPD for chromosome 15 results in Prader-Willi syndrome due to lack of the paternal chromosome 15 contribution. In contrast, in Angelman syndrome, the UPD is always paternal, with no maternal contribution (Table 81-20). Many other disorders are associated with this type of parent of origin effect, as in some cases of Beckwith-Wiedemann syndrome, Russell-Silver syndrome, and neonatal diabetes.

Table 81-20 Molecular Mechanisms Causing Prader-Willi and Angelman Syndromes

	PRADER-WILLI SYNDROME	ANGELMAN SYNDROME
15q11-q13 deletion	~70% (paternal)	~70% (maternal)
Uniparental disomy	~30% (maternal)	~5% (paternal)
Single-gene mutation	None detected	E6-AP ubiquitin-protein ligase (10% of total but seen only in familial cases)
Imprinting center mutation	5%	5%
Unidentified	<1%	10-15%

Data from Nicholls RD, Knepper JL: Genome organization, function and imprinting in Prader-Willi and Angelman syndromes. Annu Rev Genomics Hum Genet *2:153-175, 2001; and Horsthemke B, Buiting K: Imprinting defects on human chromosome 15.* Cytogenet Genome Res *113:292–299, 2006.*

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Figure 81-19 *A* and *B*, Individual showing morbid obesity with facial features as shown. *C*, Upper extremities are notable for small hands relative to body size. *D*, External genitalia after laparoscopic orchiopexy at 13 mo. Parental informed consent, as approved by the Baylor College of Medicine Institutional Review Board, was obtained to publish the photographs. *(From Sahoo T, del Gaudio D, German JR, et al: Prader-Willi phenotype caused by paternal deficiency for the HBII-85 C/D box small nucleolar RNA cluster,* Nat Genet *40:719–721, 2008.)*

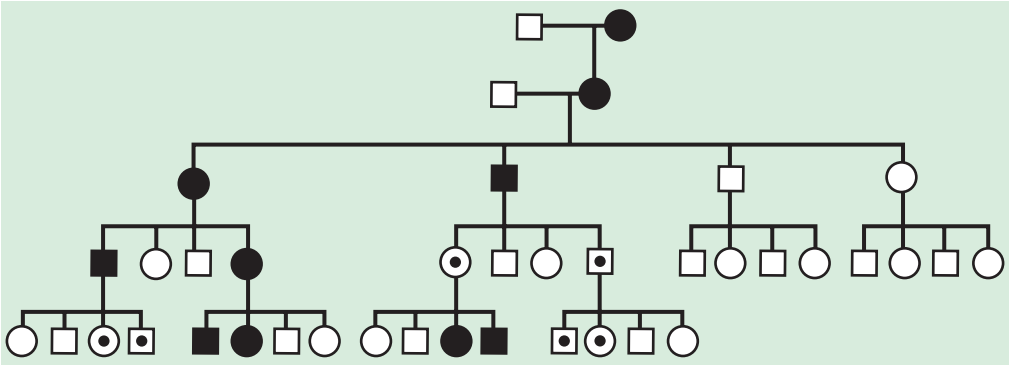

Figure 81-20 **In this hypothetical pedigree suggestive of imprinting, phenotypic effects occur only when the mutated gene is transmitted from the mother, but not when it is transmitted from the father, that is, maternal deficiency.** Equal numbers of males and females can be affected and not affected phenotypically in each generation. A nonmanifesting transmitter gives a clue to the sex of the parent who passes the expressed genetic information; that is, in maternal deficiency disorders (also termed paternal imprinting), there are "skipped" nonmanifesting females. This is theoretical, because in most clinical scenarios of maternal deficiency, such as Angelman syndrome, affected persons do not reproduce.

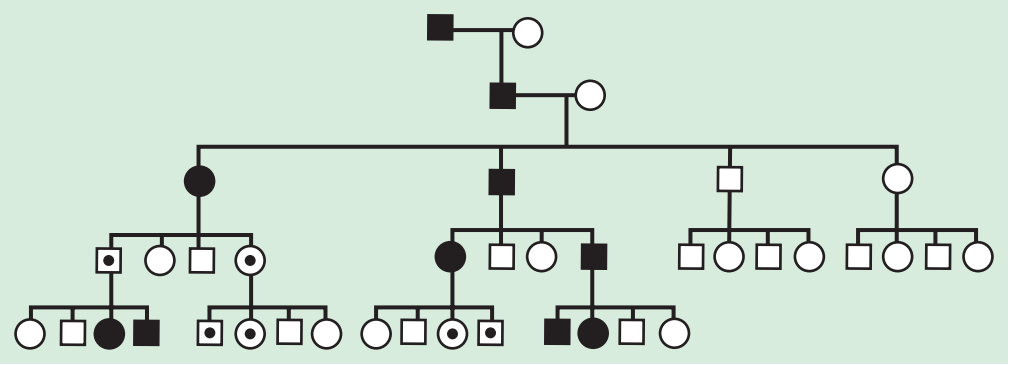

Figure 81-21 **In theoretical pedigrees suggestive of paternal deficiency (maternal imprinting), phenotypic effects occur only when the mutated gene is transmitted from the father, but not when transmitted from the mother.** Equal numbers of males and females can be affected and not affected phenotypically in each generation. In a theoretical situation, a nonmanifesting transmitter gives a clue to the sex of the parent who passes on the expressed genetic information; that is, in paternal deficiency (also known as maternal imprinting), there are "skipped" nonmanifesting males. In real-life clinical instances of Prader-Willi syndrome, affected persons do not reproduce.

Chapter 82

Genetics of Common Disorders

John W. Belmont and Brendan Lee

Genetic studies are useful in diagnosing and treating rare pediatric conditions, often alleviating suffering, extending life, and, in the case of neonatal metabolic and presymptomatic screening, preventing injury before symptoms develop. Genetic studies can also contribute to the understanding of more common diseases, such as asthma and diabetes. An understanding of the complex and potentially multiple pathways leading to disease is crucial for the development of new therapies and prevention strategies.

Common pediatric diseases are often multifactorial, and the combination of many genes and environmental factors triggers a complex sequence of events leading to disease. Each individual has variations in his or her set of genes; the cumulative effect of the individual's gene variants with each other and with the environment influence susceptibility to disease, response to various medications, and susceptibility to specific drug toxicities. The complexity of the combination of contributing factors increases the challenge of finding genetic variants that cause disease. Genetic tools include the completed human genome sequence, public databases of genetic variants, and the human haplotype map. In addition to public genetic databases, dramatic reduction in the cost of genotyping and DNA sequencing has allowed very large numbers of genetic variants to be efficiently tested in large numbers of patients. Most of these studies focus on common variants (those with frequencies >5%). New technologies for DNA sequencing are already allowing whole exome sequencing in many individuals at very low cost. This technology is being used to investigate the role of rare coding sequence variants in common diseases. The incorporation of these tools into large, well-designed population studies is the field of **genetic epidemiology.** Many new methods for analyzing genetic data have been developed, stimulating a renaissance in applied population genetics. So far, these methods of investigation have been used less extensively in pediatric diseases than in adult-onset conditions. This is a consequence of the relative lack of large-scale DNA sample sets for many common diseases of children.

We can now project that in the near future it will become routine to carry out "genomic profiling" by one technique or another for individual children. These methods will find clinical utility in decision algorithms for disease screening and initiation of treatment, drug selection, and targeted preventive strategies. The results will be of an unprecedented complexity, so that physicians and parents will increasingly rely on the coupling of genetic data to clinical decision support tools linked to the electronic health record.

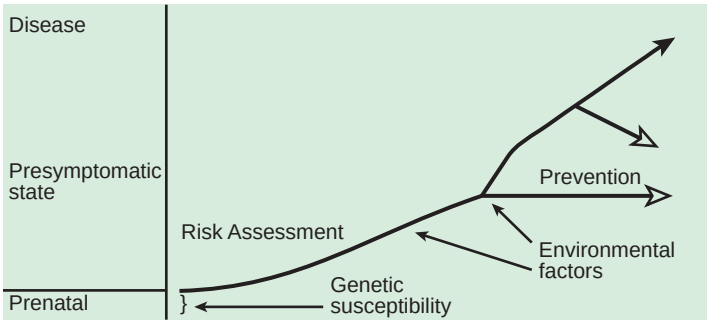

Figure 82-1 Model for the influence of genetics on health. Everyone inherits some genetic liability for disease risk, but for multifactorial disorders this is insufficient to produce disease on its own. Over time, exposure to environmental factors leads from a presymptomatic to a disease state. Identifying the genes responsible for risk can lead to prevention strategies or treatments.

82.1 Major Genetic Approaches to the Study of Common Pediatric Disorders

John W. Belmont and Brendan Lee

Figure 82-1 shows a model for the genetic contribution to health. Genetic variation that can have an impact on disease susceptibility is present in every person. Sometimes single-gene mutations cause a condition, as is the case for cystic fibrosis or sickle cell anemia. But other kinds of genetic variations can contribute much less strongly to the emergence of specific medical conditions, and the effect can depend upon exposure to certain environmental factors. One goal in medical genetics is to identify genes that contribute to disease in the hope of preventing the occurrence of disease, either by avoiding inciting environmental factors or by instituting interventions that reduce risk. For persons who cross the threshold of disease, the goal is to better understand the pathogenesis in the hope that this will suggest better approaches to treatment. Common genetic variation can also influence response to medications and the risk of toxicities of various medications and environmental toxins.

Complex traits may be inherently difficult to study if there are problems with the precision of clinical diagnosis. This is particularly true of neurobehavioral traits. A starting point in the genetic analysis of a complex trait is to obtain evidence in support of a genetic contribution and to estimate the relative strength of genetic and environmental factors. Complex traits typically exhibit familial clustering, but are not transmitted in a regular pattern like autosomal dominant or recessive inheritance. Complex traits often show variation among different ethnic or racial groups, possibly reflecting the differences in gene variants among these groups.

Assessing the potential genetic contribution begins by determining whether the trait is seen among related individuals more often than in the general population. A common measure of **familiality** is the first-degree relative risk (usually designated by the symbol λ_s), which is equal to the ratio of the prevalence rate in siblings and/or parents to the prevalence rate in the general population. For example, the λ_s for type 1 diabetes is about 15. The relative strength of genetic and nongenetic risk factors can be estimated by variance components analysis, and the **heritability** of a trait is the estimate of the fraction of the total variance contributed by genetic factors (Fig. 82-2).

It is not uncommon for a minority of cases of common diseases like diabetes to be caused by single-gene mutations (mendelian inheritance), chromosomal disorders, and other genomic disorders. These less-common causes of the disease can often provide important insight into the most important molecular pathways involved. Chromosomal regions with genes that might contribute to disease susceptibility could theoretically be located with **linkage mapping,** which locates regions of DNA that are inherited in families with the specific disease. But practically, this has turned out to be quite difficult for most complex traits either because of a dearth of families or because the effect of individual genetic loci is weak.

Genetic **association studies** are more powerful in identifying common gene variants (>5% in the population) that confer increased risk of disease, but they fail if the disease-causing gene variants are relatively rare. Detection of the modest effect of each variant and interactions with environmental factors requires well-powered studies that often include thousands of subjects. A number of parallel approaches for analyzing the aggregate effects of rare variants in genes have also been developed. Such rare variant association methods also seem to require large sample sizes because the gene effects have also proven to be relatively weak.

Linkage mapping and association studies require markers along the DNA that can be ascertained, or **genotyped,** with large-scale, high-throughput laboratory techniques. Markers that are typically used are in the forms of microsatellites and **single-nucleotide polymorphisms** (SNPs; Fig. 82-3). Although humans all have the same genetic material, each person's genome is slightly different. A sample of the same region of genome from 50 people will reveal that approximately 1 in every 200 bases varies from the more common form. Although most SNPs lack any obvious function, a few alter the amino acid sequence of the protein or affect regulation of gene expression. Some of these functional alterations directly affect susceptibility to disease. A complex clinical **phenotype** can be defined by the presence or absence of a disease as a **dichotomous trait**, or by selection of a clinically meaningful variable such as serum glucose in type 2 diabetes, which is a continuous or **quantitative trait**.

Although it might not be possible to define subgroups of patients in advance based on common disease mechanisms, the more uniform the phenotype, the more likely that a genetic study will be successful. **Locus heterogeneity** refers to the situation in which a trait results from the independent action of more than 1 gene. **Allelic heterogeneity** indicates that more than 1 variant in a particular gene can contribute to disease risk. The development of a trait or disease from a nongenetic mechanism results in a **phenocopy**. These 3 factors often contribute to the difficulty in identifying individual disease susceptibility genes because they reduce the effective size of the study population.

A person bearing any variant or **allele** (inherited unit, DNA segment, or chromosome) in a gene has a certain probability of being affected with a specific gene variant-associated disease. This is called the

Phenotypic variance		Genetic variance		Environmental variance		Measurement variance
V_P	=	V_G	+	V_E	+	V_M

$$h^2 = V_G / V_P$$

Heritability

Figure 82-2 Heritability concept. The phenotypic variance of a particular trait can be partitioned between the contributions of the genetic variance, the environmental variance, and the measurement variance. This is usually empirically determined. Heritability is defined by the proportion of the phenotypic variance that is accounted for by the genetic variance. One can estimate the heritability from correlation of a quantitative trait between relatives.

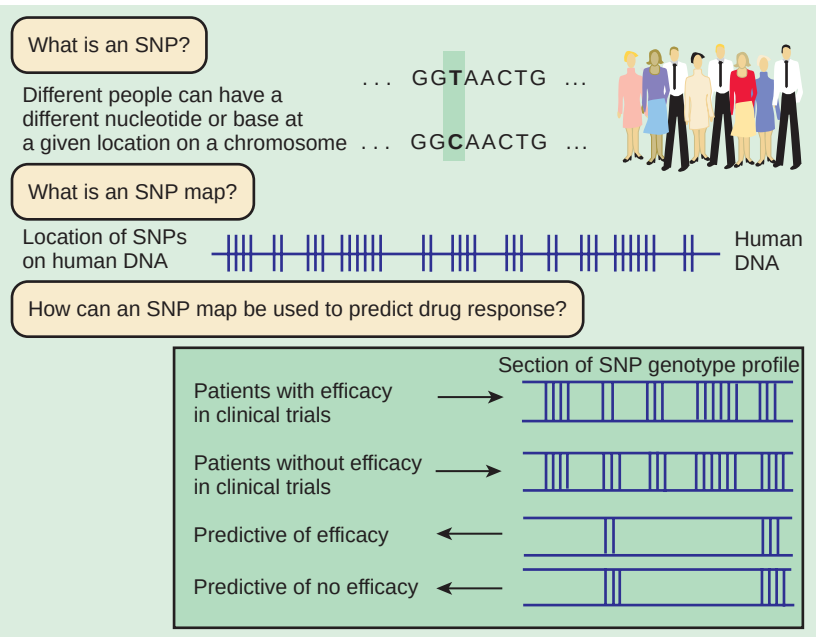

Figure 82-3 Different combinations of SNPs are found in different individuals. The locations of these SNPs can be pinpointed on maps of human genes. Subsequently, they can be used to create profiles that are associated with difference in response to a drug, such as efficacy and nonefficacy. *(Adapted from Roses A: Pharmacogenetics and the practice of medicine,* Nature *405:857-865, 2000. Copyright 2000. Reprinted by permission of Macmillan Publishers Ltd.)*

penetrance. Some diseases manifest signs only later in life (age-related penetrance), which could lead to misclassifying children who actually have the disease-producing gene as unaffected. Single-gene disorders are typically caused by mutations with relatively high penetrance, but some common variants have very low penetrance because their overall contribution to the disease is small. Many such common variants can contribute to disease risk for a complex trait. For example, normal human height is influenced by more than 400 genes.

Ideally, important environmental exposures should be measured and accounted for in a population because there may be a dependent interaction between the environmental factor and specific genetic variant. An example is the likely requirement for a viral infection preceding onset of type 1 diabetes. Although **gene X environment interactions** are strongly suspected to play an important role in common diseases, it is difficult to identify and measure them. Very large studies with uniform collection of information about environmental exposures are rare. New methods, such as genome-wide analysis of DNA methylation, may show evidence of environmental effects—so-called **developmental programming**. This information might be used to discover and validate gene-environment interactions.

LINKAGE MAPPING

Linkage studies were used in the past to isolate genes that cause rare genetic syndromes; modified methods have been used to identify chromosomal regions linked to more common diseases. Linkage studies involve tagging segments of a person's genome with markers that allow identification of segments that have been inherited through the family along with disease. The markers are typically **microsatellites** or **SNPs** that define and help to distinguish which type of an allele any person carries. The type of an allele is referred to as a **genotype.** Linkage analyses of common diseases have shown inconsistent results. Factors such as heterogeneity, pleiotropy, variable expressivity, and reduced penetrance, in addition to variability in environmental exposures, weaken the power of linkage studies in complex traits.

GENETIC ASSOCIATION

For multifactorial common diseases, association analyses may be used to identify causally important genes. There are two types of association study: **direct association,** in which the causal variant itself is tested to see whether its presence correlates with disease, and **indirect association,** in which markers that are physically close to the biologically important variant are used as proxies. The correlation of markers with other genetic variants in a small region of the genome is called **linkage disequilibrium**. Indirect association is enabled by the construction of a detailed genetic map in 3 reference populations (Europeans, Asians, West Africans) through the International HapMap Project. SNPs that tag most of the genome have been identified and can be genotyped at low cost using specially designed microarrays.

Three basic study designs are used for association testing: a case-control design, in which the frequency of an allele in the affected group is compared with the unaffected group; a family-based control design, in which parents or siblings of an affected individual are used as the controls; and a cohort design, in which large numbers of subjects are ascertained and then followed for the onset of any number of diseases. The cohort analysis is very expensive and there are few true cohort studies.

Family-based control study designs are somewhat attractive for pediatric diseases because it is usually possible to enroll parents. These studies solve a major problem in testing for association because the parents are perfectly matched for genetic background. When parents are collected, the statistical test used for these studies is called the **transmission disequilibrium test** (TDT). TDT compares the transmitted genotype with the inferred nontransmitted genotype. The success of all association analysis depends on the design of a well-powered study, with enough subjects, and an accurately measured trait to avoid phenotypical misclassification. In large, population-based studies, confounding by ethnicity or **population stratification** could distort results. Some genetic variants are more common in people from a particular ethnic group, which could cause an apparent association of a variant with a disease, when the disease rate happens to be higher in that group. This association would not be a true association between an allele and a disease, because the association would be confounded by genetic background. The family-based tests using the TDT are immune to population stratification. However, TDT and related study designs are inherently less efficient than case-control studies. Newer methods for measuring subtle mismatching between cases and controls using many thousands of markers routinely genotyped in genome-wide association studies allow this effect to be accounted for.

Association studies should be a powerful tool to find genetic variation that confers risk to an individual; the effect of any one genetic variant will be a very small contribution to the complex disease pathway. Genetic variants have been found that implicate a novel gene in a process, motivating more in-depth research into systems that will affect disease outcome. Associations such as the *ApoE4* variant with an increased risk of Alzheimer disease are noted by many studies. Many published association results are not reproducible; insufficient power and stratification might account for the inconsistencies. As of early 2014, more than 6000 disease associations for more than 600 medically important traits have been discovered and replicated in large studies.

New low-cost methods for sequencing the complete exomes and genomes of individuals will soon allow a more comprehensive evaluation of the full range of genetic variants involved in common diseases. The goal of the $1000 genome once seemed distant but may be achieved very soon. Rare genetic variants, including small insertions or deletions, could turn out to be extremely important in explaining the impact of genetic factors in important pediatric diseases such as autism, cardiovascular malformations, and other birth defects. Common traits such as obesity, diabetes, and autoimmune diseases might also be affected by rare variants. In common severe disorders like intellectual disability and complex heart malformations, de novo mutations (i.e., mutations not present in either parent) are likely to play an important role.

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Chapter 83

Genetic Approaches to Rare and Undiagnosed Diseases

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Rare and novel disorders often present in childhood and represent a diagnostic challenge that can be addressed using advanced genetic techniques.

SCOPE OF GENETIC DISEASE

An estimated 7000 rare disorders are recognized, and the existence of approximately 23,000 human genes suggests that many more genetic diseases will be discovered in the future. These genetic diseases comprise a set of maladies amenable to a variety of diagnostic approaches. Knowledge about the human genome creates a new opportunity to diagnose extremely rare disorders and discover new diseases. One

approach was taken by the National Institutes of Health (NIH) Undiagnosed Diseases Program (UDP).

Potential reasons patients may remain undiagnosed despite intensive prior investigation include:

- The genetic mutation had not previously been associated with the disease phenotype
- There is allelic heterogeneity (same gene but different mutation producing a different phenotype)
- There is locus heterogeneity (different genes producing similar phenotype)
- Presentation of monosymptomology or unusual features of a polysymptomatic or rare disease

The 3,000 patient applications to the UDP have involved collaboration between the referring healthcare team and the NIH group. Prior investigations are recounted in a summary letter from the referring clinician and documented with medical records that include photos, videos, imaging and histologic slides of biopsy material. Specialty consultants review the records and the UDP directors determine the next steps. The patients who are accepted come to the Clinical Center for a week-long inpatient admission. Approximately half of the patients with undiagnosed diseases have neurological disease; cardiovascular, rheumatology, immunology, and pulmonary problems are also frequent. Approximately 40% of accepted patients are children, among whom unknown multiple congenital anomalies and neurologic disorders are common.

CLINICAL EVALUATION

The term undiagnosed refers to patients who remain without a definitive diagnosis after an extensive workup. This occurs in part because every individual has a unique genetic and environmental background, and diseases express themselves in an unlimited number of ways. Undiagnosed conditions include those that have never been seen by the diagnostician, unusual presentations of otherwise recognizable conditions, and combinations of conditions that obfuscate each other's identities. A thorough clinical investigation allows the clinician to broaden the differential diagnosis through research, consultation, clinical testing and consideration of atypical presentations of previously known diseases. Extensive phenotyping, imaging, and other tests provide better documentation of the presentation and make the case available for association with future newly discovered diseases, genetic variants, and patient cohorts.

A complete history anchors the data, and includes prenatal and neonatal findings, developmental milestones, growth pattern, onset and progression of symptoms and signs, precipitating influences, response to medications, and a pedigree to determine which family members are affected. Pertinent physical findings include dysmorphisms, organomegaly, neurologic impairment, bone involvement, and dermatologic findings. Because many rare and novel disorders are multisystemic, consultants play a critical role in every diagnostic evaluation. Typical studies performed to address possible diagnoses are listed in Table 83-1. The evaluation of a pediatric neurology case involves even more extensive studies (Table 83-2).

An inpatient admission allows for close interaction among experts in different fields, informs the workup of complex cases, and often leads to a focus on the discovery of a new disease. In that situation, other family members need to be evaluated to definitively ascertain whether they are affected with the disorder under consideration.

AVAILABLE COMMERCIAL LABORATORY GENETIC STUDIES

Once phenotyping is complete, a differential list of genetic disorders can be compiled. Laboratory molecular testing is available for an increasingly large spectrum of molecular disorders. In many cases, several related diseases are included in a panel of molecular tests. Examples include X-linked cognitive impairment, hereditary spastic paraplegia, spastic paraplegia and gait, spinocerebellar ataxias, dystonias, and mitochondrial disorders. Some of these individual tests and panels are expensive, and added together they may exceed the cost of exome sequencing.

Table 83-1 Initial Studies to Generate New Diagnostic Hypotheses

TEST(S)	RELATED DISORDERS/ DISORDER GROUPS
Electrolytes, lactate, pyruvate	Energy metabolism defects, including mitochondrial disorders
Plasma amino acids	Renal disorders, amino acid disorders
Urine organic acids	Renal disorders, organic acid disorders, energy metabolism disorders, vitamin deficiencies
Aldolase, creatine phosphokinase	Muscle disorders
Carnitine (free, total, acyl, panel)	Fatty acid oxidation disorders, carnitine metabolism disorders
Cerebrospinal fluid (CSF) analysis	Neurotransmitter disorders, inborn errors of metabolism, select disorders that may present only in the CSF
Brain MRI/magnetic resonance spectroscopy	Structural clues to disorders affecting central nervous system
Mass spectrometry to detect *N*- and *O*-linked proteoglycan abnormalities	Congenital disorders of glycosylation
Lysosomal enzyme testing	Lysosomal storage diseases
White cell and skin electron microscopy	Lysosomal storage diseases; neuronal lipofuscinoses
Pathologic evaluation of affected tissues with special stains, DNA hybridization	Any
Echo-/electrocardiogram	Cardiac defects
Nerve conduction velocity/ electromyogram	Neurologic defects
Fibroblast cell line	Any
Single-nucleotide polymorphism/exome/ genome/karyotype	Any
Erythrocyte sedimentation rate, C-reactive protein	Inflammatory disorders

SINGLE-NUCLEOTIDE POLYMORPHISM ARRAYS

There are 2 technologies that are cost-effective for medical uses and can examine the entire genome with resolution at the level of a single base pair. These are single-nucleotide polymorphism (SNP) arrays (microarrays or chips) and next-generation sequencing. The human genome's 3.2 billion bases include many that are polymorphic. Polymorphisms are bases that are not the usual one at a defined position and yet occur with a frequency of >1% within a given population. For any 2 individuals who are not closely related, there are approximately 2.5×10^6 SNPs that vary between them (and between each individual and the canonical human reference), or about 1 polymorphism for every 1,000 bases in the genome on average. Within a single ethnic population there is about 1 common SNP per 3,000-7,000 bases, where common means a greater than 10% chance that any 1 patient will be polymorphic (heterozygous) at that position. A few hundred thousand to a few million of these common SNPs can be included on a DNA hybridization array and examined simultaneously in a single laboratory test. This technique produces genome-wide results that reveal copy number variations; mosaicism is also revealed, as are regions of

Table 83-2 Diagnostic Evaluation of the Neurologically Impaired Child

CONSULTATIONS Genetics/genetic counseling Neurology Endocrinology Immunology Rheumatology Dermatology Cardiology Neuropsychology Nutrition Rehabilitative medicine Physical therapy Occupational therapy Speech therapy	**ADDITIONAL TESTING IF CLINICALLY INDICATED** Electron microscopy of white blood cell buffy coat for inclusion bodies Electron microscopy of skin biopsy for evidence of storage Stool for ova and parasites, occult blood, fecal fat, or fecal calprotectin Autoimmune antibodies Vaccine response titers C3/C4 Quantitative immunoglobulins T-cell subsets Conjunctival or salivary gland biopsy
PROCEDURES Swallow study for aspiration Abdominal ultrasound (hepatosplenomegaly) Skeletal survey (dysostosis) Bone density scan (nonambulatory or growth-failure patients) Bone age Electroencephalogram Muscle biopsy for electron transport chain function and histology Nerve biopsy	**RESEARCH SPECIMENS** Cerebrospinal fluid Serum Plasma Skin biopsy for fibroblasts and/or melanocytes Isolated DNA/RNA Urine
LABORATORY EVALUATIONS Complete blood count with differential and peripheral smear Comprehensive metabolic panel Prothrombin time/partial thromboplastin time (for anesthesia sedation) Thyroid-stimulating hormone, thyroxine Vitamins A, E, 1,25-dihydroxyvitamin D Lactate/pyruvate Ammonia Amino acids (plasma and urine) Organic acids (urine) Acylcarnitine profile Total and free carnitine Lysosomal enzyme analysis in leukocytes and/or fibroblasts White blood cell coenzyme Q Purines and pyrimidines (urine) α-Glucosidase (plasma and urine) Peroxisomal panel Oxysterols Methylmalonic acid and homocystine (plasma) Copper/ceruloplasmin Vitamins A and E Transferrin isoelectric focusing *N*- and *O*-glycans (plasma) Oligosaccharides and free glycans (urine) Glycosaminoglycans (urine)	**STUDIES UNDER SEDATION** 3T MRI/magnetic resonance spectroscopy of brain (and spine if indicated) Skin biopsy Ophthalmologic exam Brainstem auditory evoked response Electroretinogram Lumbar puncture for biopterin, neopterin, neurotransmitters, folate, and inflammatory markers Dental exam Large blood draws Catheterization for urine Any part of the physical exam difficult to do in an awake child, including dysmorphology measurements and genital and rectal exam Electromyography and nerve conduction studies

identity by descent. These results are very useful in complementing the next-generation sequencing results. One example of this is the use of the SNP deletion regions to denote where to look for a point mutation in the next-generation sequence of the child (to detect the compound heterozygous recessive pairing of a deletion with a point mutation).

EXOME SEQUENCING

Technical advances have allowed for massive DNA sequencing at a reasonable price, making it feasible to determine the sequence of the coding regions of almost all of the human genes. Because this involves 1.7% of the 3.2 billion bases in the human genome, **exome sequences** comprise approximately 60,000,000 bases. These satisfactorily cover 80-85% of the known genes, and are determined by sequencing short "reads" (DNA fragments) and aligning them to a composite reference sequence of the human genome. In part because of SNP interference with hybridization, ambiguities in alignment, and chemistry error rates, the average exome has about 20,000 bases (0.03%) that differ from the "reference" sequence and from any other single, unrelated human sequence of the same ethnic group. Most of these variants are inconsequential polymorphisms. The problem is that each of the 20,000 variants of unknown significance is a **potential** disease-causing variant, yet only 1 is ***the*** disease-causing mutation for a monogenic disorder (with perhaps 2 or 3 additional loci modifying severity). The task of the clinician is to reduce the credible variants from 20,000 to a manageable number, such as 5.

This process involves using "filters," or programs that eliminate false-positive variants without eliminating the true variants. The single best filter uses the exome sequencing (ES) of nuclear family members (i.e., parents and siblings), but only if their true affected or unaffected status is certain. If, for example, an unaffected sibling's gene has 2 variants on opposite alleles that are the same as those of the affected proband, then those variants can be eliminated as causing the proband's disease. This emphasizes the importance of collecting family DNA and obtaining a very careful evaluation of family members. In general, having the proband, both parents and a sibling provides sufficient power to reduce the candidate variants to a reasonable number for all mendelian inheritance models, assuming complete penetrance.

As an example, if autosomal recessive inheritance is postulated, then the ES analysis should require mutations on both alleles of the proband, with 1 of the 2 mutations present in 1 parent and the other

mutation present in the other parent. Affected sibs must have both mutations, and unaffected sibs must have either 1 or none. Software programs have succeeded using a homozygous recessive model, and for significantly deleterious variants, using a compound heterozygous recessive model.

Base changes that result in amino acid changes (missense mutations) are evaluated by programs that gauge the pathogenicity of the change. This involves estimates of how tightly the base is conserved over evolution, whether the amino acid changes charge, size, or conformation, and, sometimes, where in the protein the amino acid change resides. Analyzing how changes in the genetic code influence protein function remains an inexact science, but approximations have been used with some success. Software programs, including PolyPhen-2, SIFT, and MutationTaster, rate the pathogenicity of amino acid changes. In addition, evolutionary consistency of a base can be evidence of deleteriousness of a change in that base, even if it is not involved in an amino acid change (promoter binding domains, methylation sites). Finally, some filters compare variants to databases that list changes considered to be benign (database of single-nucleotide polymorphisms), known to cause diseases other than those under investigation, or simply found frequently in many random genomes (1000 Genomes). These databases can be very helpful, but they are not entirely reliable because their entries have not been curated in all cases to a medically useful level of confidence.

The analysis of exome sequences is advancing rapidly, based upon the development of new filters and larger, better, and more informative databases. However, several key points need to be considered when employing genome-scale sequencing for clinical diagnostics.

Positive predictive value gives the likelihood that a positive test is a true positive. This is higher in a population in which a disease is frequent and lower in a population where the disease is rare. A person being tested with ES will show no clinical signs or symptoms of most of the genetic diseases for which the ES tests. Therefore, many apparently positive findings will be false positives. This manifests as the frequent occurrence of DNA variations in genes that are associated with phenotypes that do not match the person being tested. Such variants are difficult to interpret.

Individual versus family studies are relevant, as family data allow for variants to be substantially filtered. This advantage must be weighed against the financial costs of studying families versus individuals. Furthermore, family studies are useless if an affected person is called unaffected or *vice versa*. *Therefore, phenotyping family members is critical*. For later-onset conditions, younger siblings may not be suitable for inclusion in an exome study unless their affected status can be determined unambiguously.

Data revisiting policies must be addressed. Genome-scale sequencing generates data for many genes beside those involved in the current diagnostic effort. The sequencing data are of potential use in the future care of the patient. Even though some mutated genes are not reported because they are not currently associated with any medical condition, future advances may implicate such a gene in a human disease. The person ordering the exome study should be aware of the data reuse policy of the testing facility. In the current testing environment, time-limited data reuse and/or reuse fees are increasingly common.

Early discussion with a genetic specialist is critical. Genetic counseling should be sought before an exome study is sent rather than after the results become available. Proper consent for exome studies is an involved process, including information about disease risk factors, unrelated medical conditions, carrier states and cancer susceptibility. Consented individuals should be given the opportunity to consider which types of results they would like to have returned.

Anticipating findings that are difficult to use clinically is an important part of counseling. The problem of variants of unknown significance is well known for any type of genetic testing. Genome-scale sequencing amplifies this problem to include a wide variety of results that are difficult to use for medical decision making. Depending on the breadth of analysis and the resulting clinical report, different numbers of such findings will be returned to the ordering physician. Discussing such variants with families can be difficult; counseling families about the likelihood of receiving this type of result before testing is performed can help the family to cope when the report is returned (see Chapter 77).

When used as a gene panel, ES rules *in* but does not rule *out*. An exome study is a cost-effective way to test many genes at one time. However, there can be variation in coverage of any given exon among exome datasets. Therefore, even though exome studies are a powerful tool for variant discovery, they are not always sufficient to exclude variants in a panel of genes. With careful analysis involving laboratory validation on many similarly processed individuals, the exome coverage of any given gene can be assessed. However, commercial/clinical testing facilities may be unwilling to perform such an analysis when a large set of genes needs to be considered. Therefore, there is still a role for the use of a gene panel when the index of suspicion is high for a disorder caused by 1 of a large group of genes. Cerebellar ataxia and hereditary spastic paraparesis are examples.

Providing information to the testing facility improves the chances of a diagnosis. ES interpretation will benefit substantially from the incorporation of accurate and detailed clinical information about the presenting phenotype. The more clinical information that is provided to the testing lab, the more specific and useful the clinical report will be.

GENE FUNCTION STUDIES

Despite filtering for frequency and predicted deleteriousness, a variant identified by genomic sequencing cannot be interpreted as the cause of an individual's disease unless it has been previously demonstrated to cause a disease with a similar phenotype. To prove causality, medical genetics relies upon association (the recurrence of mutations within a gene among individuals with a similar phenotype). For rare diseases, there may be too few affected patients to demonstrate a statistically-significant association. In this setting, other evidence will be required to connect a specific genetic variant with an isolated phenotype. One approach is to accumulate additional diagnostic data about the patient that can be used to prioritize genetic variants (phenotype ontologies, metabolomics, glycomics, proteomics, and lipidomics). A second approach is to develop models that recapitulate the disease in question, such as mice, zebrafish, fruit flies, yeast, and cultured cells. Third, the variant in question can be linked to a biologic process or pathway that is known to cause a similar phenotype when disturbed. Finally, standardized and correlated phenotypic and genomic data are deposited into a database to identify other individuals with a similar phenotype and mutations in the same gene.

Physicians may apply their past biases to a group of variants that could be disease causing, but this is often misleading. A standardized computational approach would be preferable. For example, the Human Phenotype Ontology will standardize the description of a disease and, because the descriptors have been mapped to other human diseases and to mutant model organisms, will identify possible candidate genes and genetic networks for causing the disease. Similarly, untargeted laboratory screening tests provide an unbiased survey of patient cellular biology and physiology and a more informed prioritization of variants causing the patient's disease.

The ultimate proof of causality is to ameliorate the disease process by correcting the genetic defect, and this can sometimes be demonstrated in a model system that recapitulates the human disease. If model systems fail to identify the genetic cause of an individual's disease, one must search for other patients with a similar phenotype and mutations in the same gene. This can be accomplished using public databases that are interpreted using strict statistical and biologic standards.

PEDIATRIC ISSUES

During its first 4 yr, the UDP at NIH received 500 pediatric applications. In >10% of cases, more than 1 family member, usually a sibling, was similarly affected. There were 2 peaks in the age distribution of the children: 1 at 4-5 yr, reflecting patients with congenital disorders, and 1 at 16-18 yr representing disorders with symptom onset at early school age. The majority of applicants had been on a diagnostic odyssey for more than 5 yr. Of the 200 pediatric cases accepted, 175 were

evaluated to date and 25% received a diagnosis. Of the diagnoses, half were obtained using conventional diagnostic methods, including clinical suspicion with molecular confirmation, biochemical testing with molecular confirmation, or radiographic interpretation. In the remainder of cases the diagnosis was arrived at using SNP analysis and next-generation sequencing; all of these were rare diseases.

Pediatric medical records require attention to what has and what has not been completed previously. The electronic medical record is an important tool for medical practice, but *copy forward* functions can perpetuate errors, such as reports of normal testing when in fact the test was recommended or ordered but cancelled. Repetitive copying also fosters sloppiness in critical thinking, failure to take an adequate history, and missing the nuances of symptom progression. *A history and physical examination should be performed anew and all prior testing results confirmed via copies of original laboratory reports.*

Prolonged and painful procedures should be performed under sedation, but the risks associated with sedation must be weighed against the value of the information and samples to be obtained (see Table 83-2).

CONSIDERATIONS FOR FAMILIES OF UNDIAGNOSED CHILDREN

When a child comes to a genetics clinic for evaluation the parents want to know:

- What does my child have? (diagnosis)
- Why did it happen? (etiology/inheritance)
- What will happen in the future? (natural history)
- Is there a treatment? (therapy)
- Could the same thing happen to other family members? (recurrence risk)

The answers to all of these questions require an accurate diagnosis. The lack of a diagnosis also makes both the family and the physician uncomfortable, raises suspicion among relatives and acquaintances, and creates feelings of guilt about not having worked hard enough to find a diagnosis. As a consequence, families consult more and more specialists, and are often frustrated with the lack of coordination among providers. It is helpful for the family to save copies of every test and every visit from each institution and compile them in a binder for travel among institutions. A 2-3 page narrative summarizing the child's history, medications, list of healthcare providers with contact information, main medical issues, level of functioning on well days and sick days, and interventions that worked in the past, can be invaluable in an emergency room setting. An electronic copy is easily updated. Parents can always be the best advocates for their child, particularly an undiagnosed child.

Recommendations to parents of an undiagnosed child are similar to those that apply to any child with chronic illness:

- Keep copies of all records, electronic and otherwise, and organize them routinely, especially copies of original reports from "send-out" labs.
- Carry an updated emergency letter.
- Establish a medical home even if you obtain many second opinions.
- Find a physiatrist (rehabilitation medicine physician) to coordinate rehabilitative care.
- Be aggressive with the school system about services using, a legal advocate if necessary.
- Explore parent support groups for unknown disorders (Syndromes Without a Name, National Organization for Rare Disorders).
- Periodically check with providers (especially geneticists) for new diagnoses reported in the medical literature.
- Carve out time for yourselves as caregivers by engaging extended family members or respite care services.
- Work at supporting and being attentive to well children in the family.
- For the very sick dying child, consider an autopsy as a final attempt to establish a diagnosis especially when there is a possibility of future pregnancies.

THE DIAGNOSTIC SPECTRUM

The extent of determining the diagnosis varies considerably, from that of recognizing a clinical entity, to a largely molecular diagnosis, or to one in which the entire pathogenesis is known. In addition to known disorders, SNP and ES analyses may also identify variants in genes that are candidates for causing a new disease.

One example of a diagnosis involves 2 brothers whose parents were first cousins. The brothers had an early-onset spastic ataxia-neuropathy syndrome, with lower-extremity spasticity, peripheral neuropathy, ptosis, oculomotor apraxia, dystonia, cerebellar atrophy, and progressive myoclonic epilepsy. A homozygous missense mutation (c.1847G>A; p.Y616C) in *AFG3L2*, which encodes a subunit of a mitochondrial protease, was identified by ES. The AFG3L2 protein can bind to another AFG3L2 molecule or to paraplegin. UDP collaborators in Germany used a yeast model system to demonstrate that the patients' mutation affects the specific amino acid involved in the formation of both of these complexes. As a result, the brothers exhibited the signs and symptoms of a known AFG3L2 defect, autosomal dominant spinocerebellar ataxia type 28 (SCA28), and a known paraplegin defect, hereditary spastic paraplegia type 7 (SPG7). Other features of a mitochondrial disorder (oculomotor apraxia, extrapyramidal dysfunction, myoclonic epilepsy) were also present. The 2 brothers represent the first such cases in the world, and expand the phenotype of AFG3L2 disease.

A second example involves 2 siblings ages 5 and 10 yr with hypotonia, developmental delays, facial dysmorphisms, hearing loss, nystagmus, seizures, and atrophy on brain MRI. In this case, the leading clue was biochemical in nature, and genetic analysis confirmed the diagnosis. Urine thin-layer chromatography for oligosaccharides identified a strong band determined by mass spectrometry to consist of a tetrasaccharide containing 3 glucoses and one mannose. This suggested a defect of glucosidase I, the first enzyme involved in endoplasmic reticulum trimming of *N*-linked glycoproteins from a high-mannose to a complex form. Mutation analysis confirmed compound heterozygous mutations in the glucosidase I gene, establishing the diagnosis of congenital disorder of glycosylation IIb; the 2 siblings were the second and third patients in the world with this disorder.

The genetic analysis of rare and undiagnosed diseases has also yielded a variety of unique phenotypes that very likely represent new diseases. When variants in multiple genes are candidates for causing such a disorder, functional studies are required to demonstrate causality. This was successfully accomplished for a new disorder of vascular calcification identified and elucidated through the UDP at the NIH and found to be caused by a genetic deficiency of CD73, an enzyme on the surface of vascular cells that converts adenosine monophosphate to adenosine and inorganic phosphate.

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Metabolic Disorders

PART XI

Chapter 84

An Approach to Inborn Errors of Metabolism

Iraj Rezvani and Geoffrey A. Rezvani

Many childhood conditions are caused by single-gene mutations that encode specific proteins. These mutations can result in the alteration of primary protein structure or the amount of protein synthesized. The function of a protein, whether it is an enzyme, receptor, transport vehicle, membrane component, or structural element, may be compromised or abolished. These hereditary biochemical disorders are termed **inborn errors of metabolism** or **inherited metabolic disorders.**

Most mutations are clinically inconsequential and represent polymorphic differences that set individuals apart *(genetic polymorphism).* Some mutations produce disease states that range from very mild to lethal. Severe forms of these disorders usually become clinically apparent in the newborn period or shortly thereafter.

COMMON CHARACTERISTICS OF GENETIC DISORDERS OF METABOLISM

Although the manifestations of genetic metabolic disorders are quite variable, the following features are shared among most of these conditions:

1. The affected infant is normal at birth and becomes symptomatic later on in life. This differentiates these infants from those who appear sick at birth as a result of birth trauma, intrauterine insults, chromosomal abnormalities, or other genetic diseases.
2. The nature of the mutation that causes the dysfunction of the gene usually varies from family to family. This results in variation in severity of the phenotype in different families. An exception to this is found when a specific mutation has been preserved in an ethnic group primarily from inbreeding (the founder effect). An example is maple syrup urine disease in Old Order Mennonites in the United States (mainly in Lancaster County, PA), in whom all the affected infants have the same mutation and hence the same phenotype (see Chapter 85.6).
3. Mutations causing severe malfunction of the gene or its product result in clinical manifestations shortly after birth. In general, the earlier the appearance of clinical symptoms, the more severe the disease.
4. The majority of conditions are inherited as autosomal recessive traits. Therefore, a history of consanguinity in the parents or of an unexplained death of a family member in the neonatal period may raise the question of an inherited metabolic disease in the sick infant.
5. Most genetic metabolic conditions can be controlled successfully by some form of therapy, and a few can be potentially cured by the use of bone marrow or liver transplants. These patients can have a normal life if diagnosed and treated early, before irreversible damage to organs, especially to the brain, occurs. This underlines the importance of early diagnosis, which can be achieved through mass screening of all newborn infants.

MASS SCREENING OF NEWBORN INFANTS

Common characteristics of genetic metabolic conditions and the significance of early diagnosis make a strong argument for screening all newborn infants for the presence of these conditions. During the past half-century, methods have been developed to screen all infants inexpensively with accurate and fast-yielding results. Tandem mass spectrometry is the latest technical advance in the field. This method requires a few drops of blood to be placed on a filter paper and mailed to a central laboratory for assay. A large number of genetic conditions can be identified by this method when complemented by a few equally efficient assays for other specific disorders (Tables 84-1 and 84-2). Severe forms of some of these diseases may cause clinical manifestations before the results of the newborn screening become available. It should also be noted that these methods may identify mild forms of inherited metabolic conditions, some of which may never cause clinical manifestations in the lifetime of the individual. Potential psychosocial implications of such findings can be drastic and deserve serious consideration. An example of this is 3-methylcrotonyl-coenzyme A carboxylase deficiency, which has been identified with unexpectedly high frequency in screening programs using tandem mass spectrometry. The majority of these children have remained asymptomatic (see Chapter 85.6).

CLINICAL MANIFESTATIONS OF GENETIC METABOLIC DISEASES

Physicians and other healthcare providers who care for children should familiarize themselves with early manifestations of genetic metabolic disorders, because (1) severe forms of some of these conditions may cause symptoms before the results of screening studies become available, and (2) the current screening methods, although quite extensive, identify a small number of all inherited metabolic conditions. In the newborn period, the clinical findings are usually nonspecific and similar to those seen in infants with sepsis. A genetic disorder of metabolism should be considered in the differential diagnosis of a severely ill newborn infant, and special studies should be undertaken if the index of suspicion is high (Fig. 84-1).

Signs and symptoms such as lethargy, poor feeding, convulsions, and vomiting may develop as early as a few hours after birth. Occasionally, vomiting may be severe enough to suggest the diagnosis of pyloric stenosis, which is usually not present, although it may occur simultaneously in such infants. Lethargy, poor feeding, convulsions, and coma also may be seen in infants with hypoglycemia (see Chapters 92 and 107) or hypocalcemia (see Chapters 51 and 571). Measurements of blood concentrations of glucose and calcium and response to intravenous injection of glucose or calcium usually establish these diagnoses. Some of these disorders have a high incidence in specific population groups. Tyrosinemia type 1 is more common among French-Canadians of Quebec than in the general population. Therefore, knowledge of the ethnic background of the patient may be helpful in diagnosis. *Physical examination* usually reveals nonspecific findings; most signs are related to the central nervous system. Hepatomegaly is a common finding in a variety of inborn errors of metabolism. Occasionally, a peculiar odor may offer an invaluable aid to the diagnosis (Table 84-3). A physician caring for a sick infant should smell the patient and the patient's excretions; for example, patients with maple syrup urine disease have the unmistakable odor of maple syrup in their urine and on their bodies.

Occasionally, the onset of a genetic metabolic condition may occur months or years after birth. These children usually have mutations that render the gene partially nonfunctional. *Clinical manifestations,* such as intellectual disability, motor deficits, developmental regression, convulsions, myopathy, recurrent emesis, and cardiomyopathy, in a child beyond the neonatal period should raise the possibility of an inherited

Table 84-1 Disorders Recommended By the American College of Medical Genetics Task Force for Inclusion in Newborn Screening ("Primary Disorders")*

DISORDERS OF ORGANIC ACID METABOLISM
Isovaleric acidemia
Glutaric aciduria type I
3-Hydroxy-3-methylglutaric aciduria
Multiple carboxylase deficiency
Methylmalonic acidemia, mutase deficiency form
3-Methylcrotonyl-CoA carboxylase deficiency
Methylmalonic acidemia, cblA and cblB forms
Propionic acidemia
β-Ketothiolase deficiency
DISORDERS OF FATTY ACID METABOLISM
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency
Carnitine uptake defect
DISORDERS OF AMINO ACID METABOLISM
Phenylketonuria
Maple syrup urine disease
Homocystinuria
Citrullinemia
Argininosuccinic acidemia
Tyrosinemia type I
HEMOGLOBINOPATHIES
Sickle cell anemia (hemoglobin S)
Hemoglobin S-β-thalassemia
Hemoglobin SC disease
OTHER DISORDERS
Congenital hypothyroidism
Biotinidase deficiency
Congenital adrenal hyperplasia
Galactosemia
Hearing deficiency
Cystic fibrosis

*At this time, there is state-to-state variation in newborn screening; a list of the disorders that are screened for by each state is available at http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf.

cblA, Cobalamin A defect; cblB, cobalamin B defect; CoA, coenzyme A.

Table 84-2 Secondary Conditions Recommended By American College of Medical Genetics* Task Force for Inclusion in Newborn Screening

ORGANIC ACID METABOLISM DISORDERS
Methylmalonic acidemia, cblC and cblD forms
2-Methyl-3-hydroxybutyric aciduria
Isobutyryl-CoA dehydrogenase deficiency
2-Methylbutyryl-CoA dehydrogenase deficiency
3-Methylglutaconic aciduria
Malonic acidemia
FATTY ACID OXIDATION DISORDERS
Medium-/short-chain 3-OH acyl-CoA dehydrogenase deficiency
Short-chain acyl-CoA dehydrogenase deficiency
Medium-chain ketoacyl-CoA thiolase deficiency
Glutaric acidemia type 2
Carnitine palmitoyltransferase I deficiency
Carnitine palmitoyltransferase II deficiency
Carnitine acylcarnitine translocase deficiency
Dienoyl-CoA reductase deficiency
AMINO ACID METABOLISM DISORDERS
Hyperphenylalaninemia, benign (not phenylketonuria)
Tyrosinemia type II
Tyrosinemia type III
Defects of biopterin cofactor biosynthesis
Defects of biopterin cofactor regeneration
Argininemia
Hypermethioninemia
Citrullinemia type II
HEMOGLOBINOPATHICS
Hemoglobin variants (including hemoglobin E)
OTHERS
Galactose epimerase deficiency
Galactokinase deficiency

*The American College of Medical Genetics task force recommended reporting 25 disorders ("secondary targets") in addition to the primary disorders that can be detected through screening but that do not meet the criteria for primary disorders.

cblC, Cobalamin C defect; cblD, cobalamin D defect; CoA, coenzyme A.

Table 84-3 Inborn Errors of Amino Acid Metabolism Associated with Peculiar Odor

INBORN ERROR OF METABOLISM	URINE ODOR
Glutaric acidemia (type II)	Sweaty feet, acrid
Hawkinsinuria	Swimming pool
3-Hydroxy-3-methylglutaric aciduria	Cat urine
Isovaleric acidemia	Sweaty feet, acrid
Maple syrup urine disease	Maple syrup
Hypermethioninemia	Boiled cabbage
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
Phenylketonuria	Mousey or musty
Trimethylaminuria	Rotting fish
Tyrosinemia	Boiled cabbage, rancid butter

metabolic disease. There may be an episodic or intermittent pattern, with episodes of acute clinical manifestations separated by periods of seemingly disease-free states. The episodes are usually triggered by stress or a nonspecific catabolic insult such as an infection. The child may die during one of these acute attacks. A genetic disorder of metabolism should be considered in any child with 1 or more of the following manifestations: unexplained intellectual disability, developmental delay or regression, motor deficits or adventitious movements (e.g., dystonia, choreoathetosis), convulsions, unusual odor (particularly during an acute illness); intermittent episodes of unexplained vomiting, acidosis, mental deterioration, psychotic behavior or coma; hepatomegaly; renal stones; muscle weakness; or cardiomyopathy. For example, urea cycle defects may present with confusion, behavioral disturbances, catatonia, hallucinations, psychosis, or depression. Catatonia may also be seen in disorders of folate metabolism, porphyria, Wilson disease, and some storage diseases. Severe seizures may be noted in molybdenum cofactor deficiency, biotinidase deficiency, neuronal ceroid lipofuscinosis, nonketolic hyperglycinemia, or creatine deficiency.

Diagnosis usually requires a variety of specific *laboratory studies*. Measurements of serum concentrations of ammonia, bicarbonate, and pH are often very helpful initially in differentiating major causes of genetic metabolic disorders (see Fig. 84-1). Elevation of blood ammonia is usually caused by defects of urea cycle enzymes. Infants with elevated blood ammonia levels from urea cycle defects commonly have normal serum pH and bicarbonate values; without measurement of blood ammonia, they may remain undiagnosed and succumb to their disease. Elevation of serum ammonia is also observed in some infants with certain organic acidemias. These infants are severely acidotic because of accumulation of organic acids in body fluids.

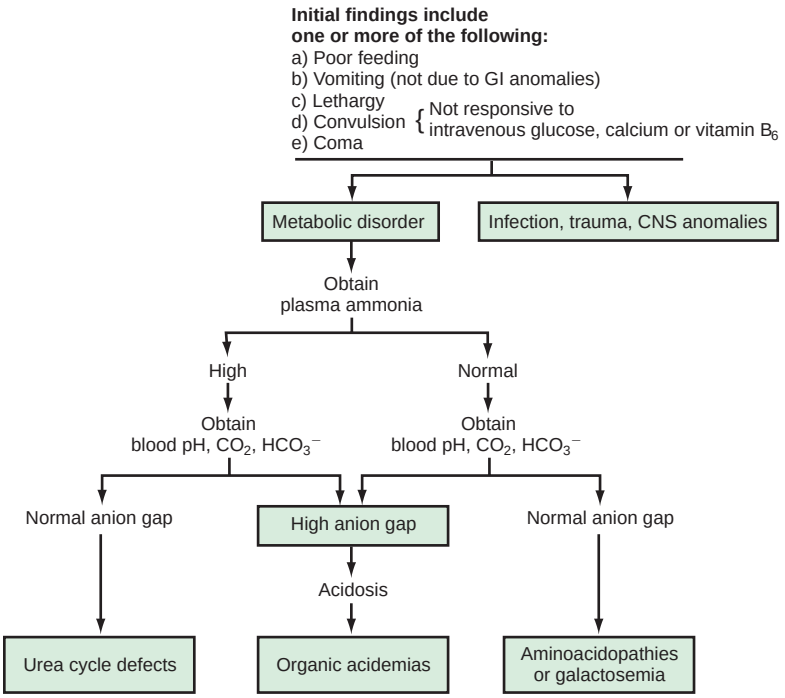

Figure 84-1 Initial clinical approach to a full term newborn infant with a suspected genetic metabolic disorder. This schema is a guide to the elucidation of some of the metabolic disorders in newborn infants. Although some exceptions to this schema exist, it is appropriate for most cases.

When blood ammonia, pH, and bicarbonate values are normal, other aminoacidopathies (such as hyperglycinemia) or galactosemia should be considered; galactosemic infants may also manifest cataracts, hepatomegaly, ascites, and jaundice.

TREATMENT

The majority of patients with genetic disorders of metabolism respond to 1 or all of the following treatments:

1. Special diets play an important role in the treatment of affected children. Dietary changes should be tailored to the pathophysiology of the condition and vary greatly among disorders.
2. Peritoneal dialysis or hemodialysis for expeditious removal of accumulated noxious compounds. This is a very effective modality for treatment of the acute phase of the condition.
3. Administration of the deficient metabolite.
4. Administration of the cofactor or coenzyme to maximize the residual enzyme activity.
5. Activation of alternate pathways to reduce the noxious compounds accumulated because of the genetic mutation.
6. Administration of the deficient enzyme.
7. Bone marrow transplantation.
8. Liver transplantation.

The bone marrow and liver transplantation modalities have the potential to cure the metabolic abnormalities. Replacement of the mutant gene with a normal one (gene therapy) is still in the experimental phase.

Treatment of genetic disorders of metabolism is complex and requires medical and technical expertise. The therapeutic regimen often needs to be tailored to the individual patient because of large phenotypic variations in the severity of the disease, even within a single family. Providing education and support for the family is the key to successful long-term therapy. Even in patients with hopeless prognoses every effort should be made to establish correct diagnoses premortem as the autopsy results are often noncontributory to the diagnosis. Effective treatment is best achieved by a team of specialists (physician metabolic genetics specialist, nutritionist, geneticist, neurologist, and psychologist) in a major medical center.

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Chapter 85

Defects in Metabolism of Amino Acids

85.1 Phenylalanine

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Phenylalanine is an essential amino acid. Dietary phenylalanine not utilized for protein synthesis is normally degraded by way of the tyrosine pathway (Fig. 85-1). Deficiency of the enzyme phenylalanine hydroxylase (PAH) or of its cofactor tetrahydrobiopterin (BH_4) causes accumulation of phenylalanine in body fluids and in the brain.

Hyperphenylalaninemia depends on the degree of enzyme deficiency and may vary from very high plasma concentrations (>20 mg/dL or >1,200 μmole/L, **classic phenylketonuria**) to mildly elevated levels (2-10 mg/dL or 120-600 μmole/L, **mild hyperphenylalaninemia**). In affected infants with plasma concentrations >20 mg/dL, excess phenylalanine is metabolized to phenylketones (phenylpyruvate and phenylacetate; see Fig. 85-1) that are excreted in the urine, giving rise to the term *phenylketonuria* (PKU). These metabolites have no role in pathogenesis of central nervous system (CNS) damage in patients with PKU; their presence in the body fluids simply signifies the severity of the condition. The term **hyperphenylalaninemia** implies lower plasma levels (<20 mg/dL) of phenylalanine. The brain is the main organ affected by hyperphenylalaninemia. The CNS damage in affected patients is caused by the elevated concentration of phenylalanine in brain tissue. The high blood levels of phenylalanine in PKU saturate the transport system across the blood–brain barrier causing inhibition of the cerebral uptake of other large neutral amino acids such as tyrosine and tryptophan. The exact mechanism of damage caused by elevated levels of intracerebral phenylalanine remains elusive. There have been a few adults with classic PKU and normal intelligence who have

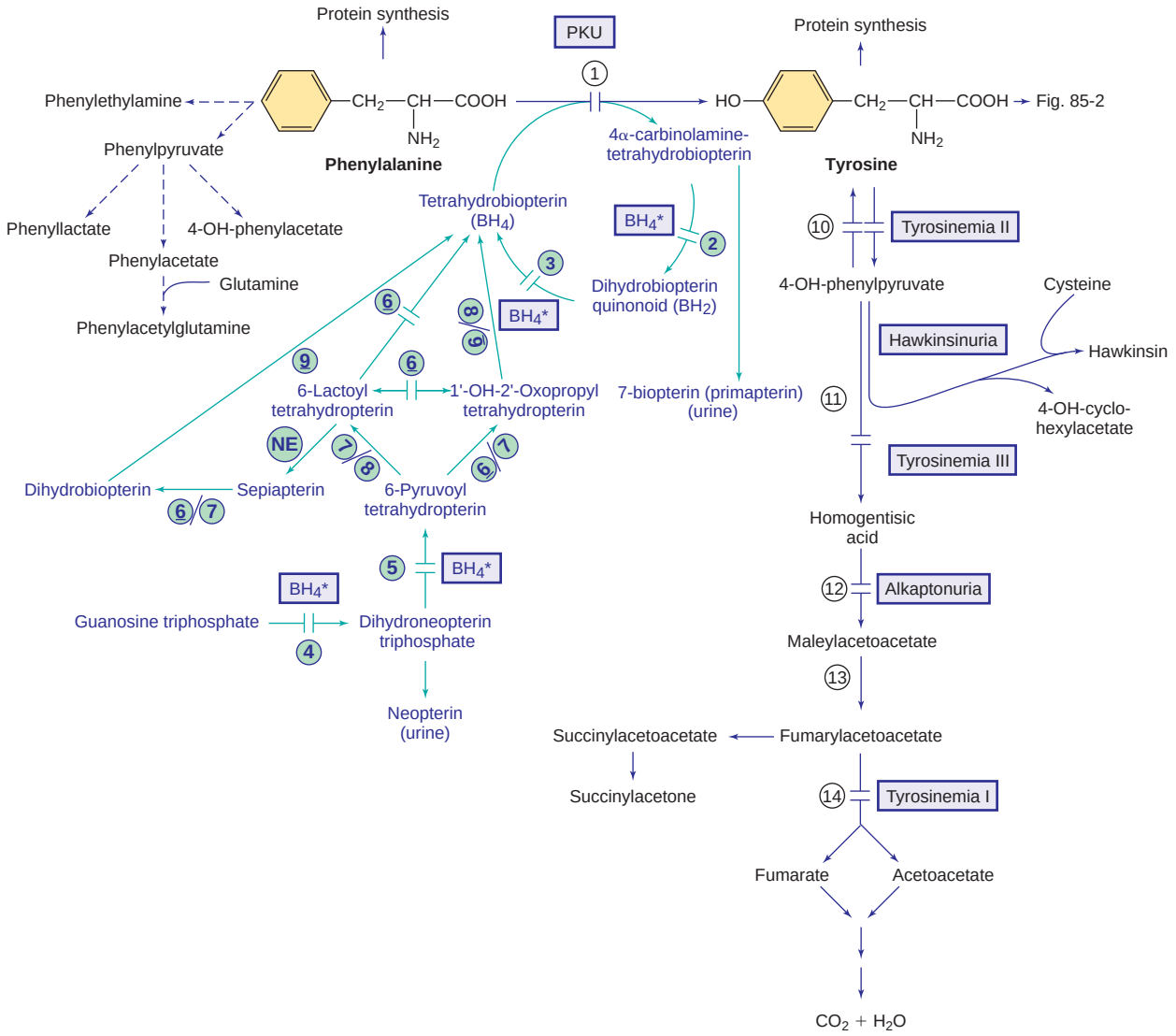

Figure 85-1 **Pathways of phenylalanine and tyrosine metabolism.** Enzyme defects causing genetic conditions are depicted as horizontal bars crossing the reaction arrow(s). Pathways for synthesis of cofactor BH_4 are shown in purple. PKU* refers to defects of BH_4 metabolism that affect the phenylalanine, tyrosine, and tryptophan hydroxylases (see Figs. 85-2 and 85-5). **Enzymes:** *(1)* Phenylalanine hydroxylase, *(2)* pterin-carbinolamine dehydratase, *(3)* dihydrobiopterin reductase, *(4)* guanosine triphosphate (GTP) cyclohydrolase, *(5)* 6-pyruvoyltetrahydropterin synthase, *(6)* sepiapterin reductase, *(7)* carbonyl reductase, *(8)* aldolase reductase, *(9)* dihydrofolate reductase, *(10)* tyrosine aminotransferase, *(11)* 4-hydroxyphenylpyruvate dioxygenase, *(12)* homogentisic acid dioxygenase, *(13)* maleylacetoacetate isomerase, *(14)* fumarylacetoacetate hydrolase, *(NE)* nonenzymatic.

never been treated with a phenylalanine-restricted diet. Phenylalanine content of the brain in these individuals was found to be close to that of normal subjects when studied by magnetic resonance spectroscopy (MRS).

CLASSIC PHENYLKETONURIA

Severe hyperphenylalaninemia (plasma phenylalanine levels >20 mg/dL), if untreated, invariably results in the development of signs and symptoms of classic PKU, except in rare unpredictable cases (see above).

Clinical Manifestations

The affected infant is normal at birth. Profound intellectual disability develops gradually if the infant remains untreated. Cognitive delay may not be evident for the first few months. In untreated patients, 50-70% will have an IQ below 35, and 88-90% will have an IQ below 65. Only 2-5% of untreated patients will have normal intelligence. Many patients require institutional care if the condition remains untreated. Vomiting, sometimes severe enough to be misdiagnosed as pyloric stenosis, may be an early symptom. Older untreated children become hyperactive with autistic behaviors, including purposeless hand movements, rhythmic rocking, and athetosis.

The infants are lighter in their complexion than unaffected siblings. Some may have a seborrheic or eczematoid rash, which is usually mild and disappears as the child grows older. These children have an unpleasant odor of phenylacetic acid, which has been described as musty or mousey. Neurologic signs include seizures (approximately 25%), spasticity, hyperreflexia, and tremors; more than 50% have electroencephalographic abnormalities. Microcephaly, prominent maxillae with widely spaced teeth, enamel hypoplasia, and growth retardation are other common findings in untreated children. The clinical manifestations of classic PKU are rarely seen in those countries in which neonatal screening programs for the detection of PKU are in effect.

Nonphenylketonuria Hyperphenylalaninemias (Milder Forms of Hyperphenylalaninemia)

In any screening program for PKU, a group of infants is identified in whom initial plasma concentrations of phenylalanine are above normal (i.e., >2 mg/dL or 120 μmole/L) but <20 mg/dL (1,200 μmole/L). These infants do not excrete phenylketones. Patients with non-PKU

hyperphenylalaninemia may still require dietary therapy, depending on their untreated plasma phenylalanine level. Attempts have been made to classify these patients in different subgroups depending on the degree of hyperphenylalaninemia, but such a practice has little clinical or therapeutic advantage. The possibility of deficiency of BH_4 should be investigated in all infants with the milder forms of hyperphenylalaninemia (see below).

Diagnosis

Because of the gradual and nonspecific nature of early clinical symptoms such as vomiting, developmental delay, or eczematoid rash, hyperphenylalaninemia is usually diagnosed through newborn screening in all developed countries. In infants with positive screening results, diagnosis should be confirmed by quantitative measurement of plasma phenylalanine concentration. Identification and measurement of phenylketones in the urine has no place in any screening program. In countries and places where such programs are not in effect, identification of phenylketones in the urine by ferric chloride may offer a simple test for diagnosis of infants with developmental and neurologic abnormalities. Once the diagnosis of hyperphenylalaninemia is established, additional studies for BH_4 metabolism should be performed to rule out BH_4 deficiency as the cause of hyperphenylalaninemia (see below).

Neonatal Screening for Hyperphenylalaninemia

Effective and relatively inexpensive methods for mass screening of newborn infants have been developed and are used in the United States and several other countries. A few drops of blood, which are placed on a filter paper and mailed to a central laboratory, are used for assay. The bacterial inhibition assay of Guthrie, which was the first method used for this purpose, has been replaced by more precise and quantitative methods (fluorometric and tandem mass spectrometry). The method of choice is tandem mass spectrometry, which identifies all forms of hyperphenylalaninemia with a low false-positive rate and excellent accuracy and precision. The addition of the phenylalanine:tyrosine molar ratio has further reduced the number of false-positive results. Diagnosis must be confirmed by measurement of plasma phenylalanine concentration. Blood phenylalanine in affected infants with PKU may rise to diagnostic levels as early as 4 hr after birth, even in the absence of protein feeding. It is recommended that the blood for screening be obtained in the first 24-48 hr of life after feeding protein to reduce the possibility of false-negative results, especially in the milder forms of the condition.

Treatment

The mainstay of treatment of PKU is a low–phenylalanine diet. The general consensus is to start diet treatment immediately in patients with blood phenylalanine levels above 10 mg/dL (600 μmole/L). Most physicians also advocate phenylalanine-restricted diet in patients with mild hyperphenylalaninemia whose levels are persistently above 6 mg/dL (360 μmole/L). It is generally accepted that infants with persistent (more than a few days) plasma levels of phenylalanine ≥6 mg/dL (360 μmole/L) should be treated with a phenylalanine-restricted diet similar to that for classic PKU. The goal of therapy is to reduce phenylalanine levels in the plasma and brain. Formulas free of or low in phenylalanine are commercially available. The diet should be started as soon as the diagnosis is established. Because phenylalanine is not synthesized endogenously, small amounts of phenylalanine should be added to the diet to prevent *phenylalanine deficiency*. Dietary deficiency of this amino acid is manifested by lethargy, failure to thrive, anorexia, anemia, rashes, diarrhea, and even death; moreover, tyrosine becomes an essential amino acid in this disorder and its adequate intake must be ensured. Special food items low in phenylalanine are commercially available for dietary treatment of affected children and adults.

There is no firm consensus concerning optimal level of blood phenylalanine in affected patients either across different countries or among treatment centers in the United States. In 2001, the National Institutes of Health Consensus Development Panel recommended that plasma phenylalanine levels be maintained between 2 and 6 mg/dL in neonates through 12 yr of age and between 2 and 15 mg/dL in older individuals. Given that brain development continues in adolescence and even in adulthood, maintenance of lower plasma phenylalanine levels (2-10 mg/dL) has been strongly encouraged even after 12 yr of age. The duration of diet therapy is also controversial. Discontinuation of therapy, even in adulthood, may cause deterioration of IQ and cognitive performance. The current recommendation from the 2001 National Institutes of Health Consensus Development Panel is that all patients be kept on a phenylalanine-restricted diet for life. Lifelong adherence to a low phenylalanine diet is extremely difficult. Patients, who maintain good control as children but discontinue the phenylalanine-restricted diet as teenagers or adults, may experience significant difficulties with executive function concentration, emotional liability, and depression. Executive dysfunction may also occur in early treated children in spite of diet treatment.

Given the difficulty of maintaining a strict low-phenylalanine diet, there are continuing attempts to find other modalities for treatment of these patients. Administration of large neutral amino acids (LNAAs) is another approach to diet therapy. LNAAs (tyrosine, tryptophan, arginine, leucine, isoleucine, valine, methionine, histidine, lysine, threonine and phenylalanine) share the same transporter protein (LNAA type 1, LAT-1) for transit through the intestinal cell membrane and blood–brain barrier. Binding of LNAA to the transporter protein is a competitive process. The rationale for use of LNAA is that these molecules compete with phenylalanine for transport across the blood–brain barrier; therefore, large concentrations of other LNAAs in the intestinal lumen and in the blood reduce the uptake of phenylalanine into bloodstream and the brain. Clinical trials to establish the efficacy of this treatment are lacking at this time. Oral administration of BH_4, the cofactor for PAH, may result in reduction of plasma levels of phenylalanine in some patients with PAH deficiency. Plasma levels of phenylalanine in these patients may decrease enough to allow for considerable modification of their dietary restriction. In very rare cases, the diet may be discontinued because the phenylalanine levels remain under 6 mg/dL. The response to BH_4 cannot be predicted consistently on the basis of genotype, especially in compound heterozygous patients. Sapropterin dihydrochloride (Kuvan), a synthetic form of BH_4, which acts as a cofactor in patients with residual PAH activity, is approved by the FDA to reduce phenylalanine levels in PKU. At a dose of 10 mg/kg/day, it reduces phenylalanine levels in up to 40% of patients. Preliminary trials with recombinant phenylalanine ammonia lyase have been encouraging and demonstrated reduced blood levels of phenylalanine during treatment.

Low mineral bone density and osteopenia have been reported in affected individuals of all ages. Although inadequate intake of natural proteins seems to be the major culprit, the exact pathogenesis of this sequela remains unclear.

Long-term care of patients with PKU is best achieved by a team of experienced professionals (metabolic specialist, nutritionist, and psychologist) in a regional treatment center.

Pregnancy in Women with Hyperphenylalaninemia (Maternal Phenylketonuria)

Pregnant women with hyperphenylalaninemia who are not on a phenylalanine-restricted diet have a very high risk of having offspring with intellectual disability, microcephaly, growth retardation, congenital malformations, and congenital heart disease. These complications are directly correlated with elevated maternal blood phenylalanine levels during pregnancy. Prospective mothers who have been treated for hyperphenylalaninemia should be maintained on a phenylalanine-restricted diet before and during pregnancy; the best observed outcomes occur when strict control of maternal blood phenylalanine concentration is instituted before pregnancy or by 8 wk of gestation at the latest. The currently recommended phenylalanine concentrations are between 2 and 6 mg/dL (120-360 μmol/L) throughout the pregnancy. All women with hyperphenylalaninemia who are of childbearing age should be counseled properly as to the risk of the just described congenital anomalies in their offspring.

HYPERPHENYLALANINEMIA CAUSED BY DEFICIENCY OF THE COFACTOR TETRAHYDROBIOPTERIN

In 1-3% of infants with hyperphenylalaninemia, the defect resides in 1 of the enzymes necessary for production or recycling of the cofactor BH_4 (see Fig. 85-1). If these infants are misdiagnosed as having PKU, they may deteriorate neurologically despite adequate control of plasma phenylalanine. BH_4 is synthesized from guanosine triphosphate (GTP) through several enzymatic reactions (see Fig. 85-1). In addition to acting as a cofactor for PAH, BH_4 is also a cofactor for tyrosine hydroxylase and tryptophan hydroxylase, which are involved in the biosynthesis of dopamine (Fig. 85-2) and serotonin (see Fig. 85-5), respectively. Therefore, patients with hyperphenylalaninemia as a result of BH_4 deficiency also manifest neurologic findings related to deficiencies of the neurotransmitters dopamine and serotonin. Four enzyme deficiencies leading to defective BH_4 formation cause hyperphenylalaninemia with concomitant deficiencies of dopamine and serotonin. These include autosomal recessive GTP cyclohydrolase deficiency, pterin-carbinolamine dehydratase deficiency, dihydropteridine reductase deficiency, and 6-pyruvoyltetrahydropterin synthase deficiency. More than half of the reported patients have had a deficiency of 6-pyruvoyltetrahydropterin synthase. Autosomal dominant forms of GTP deficiency and sepiapterin reductase deficiency result in deficiencies of neurotransmitters without hyperphenylalaninemia (see Chapter 85.11 and Fig. 85-1).

Clinical Manifestations

Infants with cofactor deficiency are identified during screening programs for PKU because of evidence of hyperphenylalaninemia. Plasma phenylalanine levels may be as high as those in classic PKU or in the range of milder forms of hyperphenylalaninemia. However, the clinical manifestations of the neurotransmitter disorders differ greatly from those of PKU. Neurologic symptoms of the neurotransmitter disorders often manifest in the first few months of life and include extrapyramidal signs (choreoathetotic or dystonic limb movements, axial and truncal hypotonia, hypokinesia), feeding difficulties, and autonomic abnormalities. Intellectual disability, seizures, hypersalivation, and swallowing difficulties are also seen. The symptoms are usually progressive and often have a marked diurnal fluctuation. Prognosis and outcome strongly depend on the age at which the diagnosis is made and treatment is introduced, but also on the specific nature of the mutation and resulting enzyme defect.

Diagnosis

Despite the low incidence of BH_4 defects, all newborns with hyperphenylalaninemia detected through newborn screening should be screened for BH_4 defects.

BH_4 deficiency and the responsible enzyme defect may be diagnosed by the following studies:

1. Measurement of neopterin (oxidative product of dihydroneopterin triphosphate) and biopterin (oxidative product of dihydrobiopterin and BH_4) in body fluids, especially urine (see Fig. 85-1). In patients with GTP cyclohydrolase deficiency, urinary excretion of both neopterin and biopterin is very low. In patients with 6-pyruvoyltetrahydropterin synthase deficiency, there is a marked elevation of neopterin excretion and a concomitant decrease in biopterin excretion. In patients with dihydropteridine reductase deficiency, neopterin is normal, but biopterin is very high. Excretion of biopterin increases in this enzyme deficiency because the quinonoid dihydrobiopterin cannot be recycled back to BH_4. Patients with pterin-carbinolamine dehydratase deficiency excrete 7-biopterin (an unusual isomer of biopterin) in their urine. In addition, examination of cerebrospinal fluid (CSF) reveals decreased levels of dopamine, serotonin, and their metabolites in all patients with BH_4 deficiency (see Chapter 85.11).
2. BH_4 loading test. An oral dose of BH_4 (20 mg/kg) normalizes plasma phenylalanine and phenylalanine : tyrosine ratio in patients with BH_4 deficiency within 4-8 hr. The blood phenylalanine should be elevated (>400 µmole/L) to enable interpretation of the results. This may be achieved by discontinuing diet therapy for 2 days before the test or by administering a loading dose of phenylalanine (100 mg/kg) 3 hr before the test. In BH_4-responsive PKU caused by PAH deficiency, blood phenylalanine levels may decrease during the BH_4 loading test, but increase later even with BH_4 supplementation. Patients who demonstrate phenylalanine levels within normal range over at least a week without a phenylalanine-restricted diet can be continued on BH_4 supplementation as the sole treatment for the hyperphenylalaninemia. However, it is imperative that plasma

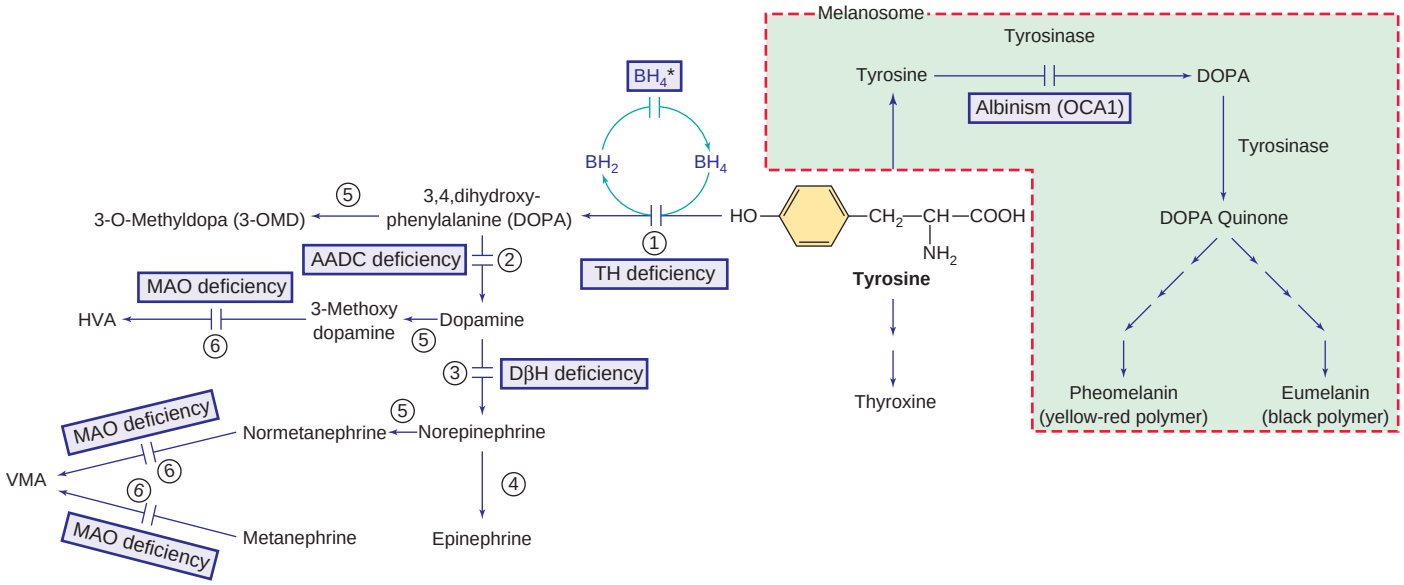

Figure 85-2 Other pathways involving tyrosine metabolism. PKU* indicates hyperphenylalaninemia caused by tetrahydrobiopterin (BH_4) deficiency (see Fig. 85-1). HVA, homovanillic acid; VMA, vanillylmandelic acid. **Enzymes:** *(1)* Tyrosine hydroxylase (TH), *(2)* aromatic L-amino acid decarboxylase (AADC), *(3)* dopamine β-hydroxylase (DβH), *(4)* phenylethanolamine-*N*-methyltransferase (PNMT), *(5)* catechol *O*-methyltransferase (COMT), *(6)* monoamine oxidase (MAO).

phenylalanine levels be monitored prospectively to ensure that phenylalanine levels remain within the normal range.
3. Enzyme assay. The activity of dihydropteridine reductase can be measured in the dry blood spots on the filter paper used for screening purposes. 6-Pyruvoyltetrahydropterin synthase activity can be measured in the liver, kidneys, and erythrocytes. Carbinolamine dehydratase activity can be measured in the liver and kidneys. GTP cyclohydrolase activity can be measured in the liver and in cytokine (interferon-γ) stimulated mononuclear cells or fibroblasts (the enzyme activity is normally very low in unstimulated cells).
4. Genetic test. Mutation analysis and deletion/duplication studies are clinically available for all these enzyme defects and help to confirm the diagnosis.

Treatment

The goals of therapy are to correct hyperphenylalaninemia and to restore neurotransmitter deficiencies in the CNS. The control of hyperphenylalaninemia is important in patients with cofactor deficiency, because high levels of phenylalanine cause intellectual disability and also interfere with the transport of neurotransmitter precursors (tyrosine, tryptophan) into the brain. Plasma phenylalanine should be maintained as close to normal as possible (<6 mg/dL). This can be achieved by oral supplementation of BH_4 (5-20 mg/kg/day). Sapropterin dihydrochloride (Kuvan), a synthetic form of BH_4, is commercially available, although it is expensive.

Lifelong supplementation with **neurotransmitter precursors** such as L-dopa and 5-hydroxytryptophan, along with carbidopa to inhibit degradation of L-dopa before it enters the CNS, is necessary in most of these patients even when treatment with BH_4 normalizes plasma levels of phenylalanine. BH_4 does not readily enter the brain to restore neurotransmitter production. To minimize untoward side effects (especially L-dopa–induced dyskinesia), the treatment should be started with low doses of L-dopa/carbidopa and 5-hydroxytryptophan, and should be adjusted based on response to therapy and clinical improvement for each individual patient. Supplementation with folinic acid is also recommended in patients with dihydropteridine reductase deficiency. Unfortunately, attempting to normalize neurotransmitter levels using neurotransmitter precursors usually does not fully resolve the neurologic symptoms as a result of the inability to attain normal levels of BH_4 in the brain. Patients often demonstrate intellectual disability, fluctuating abnormalities of tone, eye movement abnormalities, poor balance and coordination, decreased ability to ambulate, and seizures in spite of supplementation with neurotransmitter precursors.

Hyperprolactinemia occurs in patients with BH_4 deficiency and may be the result of hypothalamic dopamine deficiency. Measurement of serum prolactin levels may be a convenient method for monitoring adequacy of neurotransmitter replacement in affected patients.

Some drugs, such as trimethoprim sulfamethoxazole, methotrexate, and other antileukemic agents, are known to inhibit dihydropteridine reductase enzyme activity and should be used with great caution in patients with BH_4 deficiency.

Genetics and Prevalence

All defects causing hyperphenylalaninemia are inherited as autosomal recessive traits. The prevalence of PKU in the United States is estimated at 1 in 14,000 to 1 in 20,000 live births. The prevalence of non-PKU hyperphenylalaninemia is estimated at 1 in 50,000 live births. The condition is more common in whites and Native Americans and less prevalent in African-Americans, Hispanics, and Asians.

The gene for PAH is located on chromosome 12q23.2 and many disease-causing mutations have been identified in different families. The majority of patients are compound heterozygotes for 2 different mutant alleles. The gene for 6-pyruvoyl tetrahydropterin synthase *(PTS)*, the most common cause of BH_4 deficiency, resides on chromosome 11q23.1, the gene for dihydropteridine reductase *(QDPR)* is located on chromosome 4p15.2, and those of carbinolamine dehydratase *(PCBD1)* and GTP cyclohydrolase *(GCH1)* are on 10q22.1 and 14q22.2, respectively. Many disease-causing mutations of these genes have been identified. Prenatal diagnosis is possible using specific genetic probes in cells obtained from biopsy of the chorionic villi.

TETRAHYDROBIOPTERIN DEFECTS WITHOUT HYPERPHENYLALANINEMIA

See Chapter 85.11.

Bibliography is available at Expert Consult.

85.2 Tyrosine

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Tyrosine is derived from ingested proteins or is synthesized endogenously from phenylalanine. It is used for protein synthesis and is a precursor of dopamine, norepinephrine, epinephrine, melanin, and thyroxine. Excess tyrosine is metabolized to carbon dioxide and water (see Fig. 85-1). Hereditary causes of hypertyrosinemia include deficiencies of tyrosine aminotransferase, 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), and fumarylacetoacetate hydrolase. *Acquired hypertyrosinemia* may occur in severe hepatocellular dysfunction (liver failure), scurvy (vitamin C is the cofactor for 4-HPPD), and hyperthyroidism. Hypertyrosinemia is common in blood samples obtained soon after eating and in premature infants.

TYROSINEMIA TYPE I (TYROSINOSIS, HEREDITARY TYROSINEMIA, HEPATORENAL TYROSINEMIA)

This severe disease of the liver, kidney, and peripheral nerves is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase. Organ damage is believed to result from accumulation of metabolites of tyrosine degradation, especially fumarylacetoacetate and succinylacetone.

Clinical Manifestations and Natural History

Untreated, the affected infant appears normal at birth and typically presents between 2 and 6 mo of age but rarely may become symptomatic in the 1st mo or appear healthy beyond the 1st yr of life. The earlier the presentation, the poorer the prognosis. The 1 yr mortality of untreated children, which is approximately 60% in infants who develop symptoms before 2 mo of age, decreases to 4% in infants who become symptomatic after 6 mo of age.

An acute **hepatic crisis** commonly heralds the onset of the disease and is usually precipitated by an intercurrent illness that produces a catabolic state. Fever, irritability, vomiting, hemorrhage, hepatomegaly, jaundice, elevated levels of serum transaminases, and hypoglycemia are common. An odor resembling boiled cabbage may be present, resulting from increased methionine metabolites. Most hepatic crises resolve spontaneously, but may progress to liver failure and death. Between the crises, varying degrees of failure to thrive, hepatomegaly, and coagulation abnormalities often persist. Cirrhosis and eventually hepatocellular carcinoma occur with increasing age. Carcinoma is unusual before 2 yr of age.

Episodes of acute **peripheral neuropathy** resembling acute porphyria occur in approximately 40% of affected children. These crises, often triggered by a minor infection, are characterized by severe pain, often in the legs, associated with extensor hypertonia of the neck and trunk, vomiting, paralytic ileus, and, occasionally, self-induced injuries of the tongue or buccal mucosa. Marked weakness and paralysis occur in about 30% of episodes, which may lead to respiratory failure requiring mechanical ventilation. Crises typically last 1-7 days but recuperation from paralytic crises can require weeks to months.

Renal involvement is manifested as a Fanconi-like syndrome with hyperphosphaturia, hypophosphatemia, normal anion gap metabolic acidosis, and vitamin D–resistant rickets. Nephromegaly and nephrocalcinosis may be present on ultrasound examination. Glomerular failure may occur in adolescents and older patients.

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Hypertrophic cardiomyopathy and hyperinsulinism are seen in some infants.

Laboratory Findings

The presence of elevated levels of succinylacetone in serum and urine is diagnostic for tyrosinemia type I (see Fig. 85-1). In untreated patients, the blood level of α-fetoprotein is increased, often markedly, and liver-synthesized coagulation factors are decreased in most patients; serum levels of transaminases are often increased, with marked increases being possible during acute hepatic episodes. Serum concentration of bilirubin is usually normal but can be increased with liver failure. Increased levels of α-fetoprotein are present in the cord blood of affected infants, indicating intrauterine liver damage. Plasma tyrosine levels are usually elevated at diagnosis but this is a nonspecific finding and is dependent on dietary intake. Plasma levels of other amino acids, particularly methionine, may also be elevated in patients with liver damage. Hyperphosphaturia, hypophosphatemia, and generalized aminoaciduria may occur. The urinary level of 5-aminolevulinic acid is elevated because of inhibition of 5-aminolevulinic hydratase by succinylacetone.

Diagnosis is usually established by demonstration of elevated levels of succinylacetone in urine or blood. Neonatal screening for hypertyrosinemia detects only a minority of patients with tyrosinemia type I. Succinylacetone, which is now assayed by some neonatal screening programs, has higher sensitivity and specificity than tyrosine and is the preferred metabolite for screening. Tyrosinemia type I should be differentiated from other causes of hepatitis and hepatic failure in infants, including galactosemia, hereditary fructose intolerance, neonatal iron storage disease, giant cell hepatitis, and citrullinemia type II (see Chapter 85.12).

Treatment and Outcome

A diet low in phenylalanine and tyrosine can slow but does not halt the progression of the condition. The **treatment of choice** is nitisinone, which inhibits tyrosine degradation at 4-HPPD (see Fig. 85-1). This treatment prevents acute hepatic and neurologic crises. Although nitisinone stops or greatly slows disease progression, some pretreatment liver damage is not reversible. Therefore, patients must be followed for development of cirrhosis or **hepatocellular carcinoma**. On imaging, the presence of even a single liver nodule usually indicates underlying cirrhosis. Most liver nodules in tyrosinemic patients are benign but current imaging techniques do not accurately distinguish all malignant nodules. Liver transplantation is an effective therapy for tyrosinemia type I and alleviates the risk of hepatocellular carcinoma. The impact of nitisinone treatment on the need for liver transplantation is still under study but the greatest effect is in patients treated early, such as children detected by neonatal screening, prior to the development of clinical symptoms. In early-treated patients, nitisinone has greatly reduced the need for liver transplantation. At any age, nitisinone treatment eliminates the occurrence of acute episodes of liver failure and neurologic crises although they are at risk for impaired cognitive function. Because nitisinone treatment causes an increase in plasma tyrosine level, a diet restricted in tyrosine and phenylalanine is prescribed. Rarely, nitisinone-treated patients develop corneal crystals, presumably of tyrosine, which are reversible by strict dietary compliance. This finding, combined with observations of developmental delay in some patients with tyrosinemia type II who chronically have elevated tyrosine levels, suggest that a diet low in phenylalanine and tyrosine should be continued in patients treated with nitisinone. The dietary treatment of patients with tyrosine and phenylalanine restriction necessitates surveillance to ensure adequate intakes of other nutrients and amino acids.

Genetics and Prevalence

Tyrosinemia type I is inherited as an autosomal recessive trait. The gene for fumarylacetoacetate hydrolase (*FAH*) maps to chromosome 15q 25.1 and; numerous disease-causing mutations of the gene have been reported. DNA analysis is useful for molecular prenatal diagnosis if the familial mutations are known and for carrier testing in groups at risk for specific mutations such as French-Canadians from the Saguenay-Lac Saint-Jean region of Quebec. The prevalence of the condition is estimated to be 1 in 1,846 live births in the Saguenay-Lac Saint-Jean region and approximately 1 in 100,000 live births worldwide. But tyrosinemia type I is panethnic; lack of French-Canadian or Scandinavian ancestry does not exclude the diagnosis. Prenatal diagnosis is typically performed by measurement of succinylacetone in amniotic fluid, or if the familial mutations are known, by DNA analysis of amniocytes or of chorionic villi.

TYROSINEMIA TYPE II (RICHNER-HANHART SYNDROME, OCULOCUTANEOUS TYROSINEMIA)

This rare autosomal recessive disorder is caused by deficiency of tyrosine aminotransferase and results in palmar and plantar hyperkeratosis, herpetiform corneal ulcers, and intellectual disability (see Fig. 85-1). **Ocular manifestations,** which may occur as early as 6 mo of age, include excessive tearing, redness, pain, and photophobia. Corneal lesions are presumed to be because of tyrosine deposition. In contrast to herpetic ulcers, corneal lesions in tyrosinemia type II stain poorly with fluorescein and often are bilateral. **Skin lesions**, which may develop later in life, include painful, nonpruritic hyperkeratotic plaques on the soles, palms, and fingertips. Intellectual disability, which occurs in approximately 50% of patients, is usually mild to moderate.

The principal **laboratory finding** in untreated patients is marked hypertyrosinemia (20-50 mg/dL; 1,100-2,750 μmole/L). Surprisingly, 4-hydroxyphenylpyruvic acid and its metabolites are also elevated in urine despite being downstream from the metabolic block (see Fig. 85-1). This is hypothesized to occur via the action of other transaminases in the presence of high tyrosine concentrations, producing 4-hydroxyphenylpyruvic acid in cellular compartments like the mitochondrion in which it cannot be further degraded. In contrast to tyrosinemia type I, liver and kidney function are normal, as are serum concentrations of other amino acids and succinylacetone. Tyrosinemia type II is caused by *TAT* gene mutations, causing deficiency of cytosolic tyrosine aminotransferase activity in liver.

Diagnosis of type II tyrosinemia is established by assay of plasma tyrosine concentration in patients with suggestive findings. Molecular diagnosis is possible. Assay of liver tyrosine aminotransferase activity requires a liver biopsy and is rarely indicated.

Treatment with a diet low in tyrosine and phenylalanine improves the biochemical abnormalities and can normalize the skin and eye. The claim that intellectual disability may be prevented by early diet therapy is reasonable and is consistent with some case reports. The gene for tyrosine aminotransferase (*TAT)* maps to chromosome 16q22.2 and several disease-causing mutations have been identified. About half of reported cases are of Italian descent.

TYROSINEMIA TYPE III (PRIMARY DEFICIENCY OF 4-HYDROXYPHENYLPYRUVATE DIOXYGENASE [4-HPPD])

Only a few cases have been reported; most were detected by amino acid chromatography performed for various neurologic findings. Age at presentation has been from 1-17 mo. Developmental delay, seizures, intermittent ataxia, and self-destructive behavior are reported; a causal link to 4-HPPD deficiency is not formally established. Liver and renal abnormalities are absent. Asymptomatic infants with 4-HPPD deficiency have been identified by neonatal screening for hypertyrosinemia.

The **diagnosis** is suspected in children with sustained moderate increases in plasma levels of tyrosine (typically 350-700 μmole/L on a normal diet) and the presence of 4-hydroxyphenylpyruvic acid and its metabolites 4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids in urine. Diagnosis may be refined by demonstrating the presence of mutations in the gene (*HPD*) for 4-HPPD on chromosome 12q24.31, or rarely, by demonstrating a low activity of 4-HPPD enzyme; the latter requires a liver biopsy and is not usually indicated.

Given the possible association with neurologic abnormalities, dietary reduction of plasma tyrosine levels is prudent. It is also logical

to attempt a trial of vitamin C, the cofactor for 4-HPPD. The condition is inherited as an autosomal recessive trait.

HAWKINSINURIA

Certain missense mutations in the gene for 4-HPPD result in an abnormal enzyme activity. The mutant enzyme, incapable of normally oxidizing 4-hydroxyphenylpyruvate to homogentisic acid, forms an intermediate that reacts with cysteine to form the unusual organic acid hawkinsin ([2-L-cystein-*S*-yl-1,4-dihydroxycyclohex-5-en-1-yl]acetic acid, named after the first affected family, Fig. 85.1); secondary glutathione deficiency may occur. Hawkinsinuria is inherited as an autosomal dominant trait and a few specific causal missense mutations have been identified. The same mutation, a substitution of threonine for the normal alanine codon at position 33 of the 4-HPPD gene, has been identified in unrelated patients with hawkinsinuria. The condition is, perhaps, more prevalent than once realized.

Individuals with this disorder are symptomatic only during infancy. The symptoms usually appear in the first few months of life; commonly after weaning from breastfeeding and with the introduction of a high-protein diet. Severe metabolic acidosis, ketosis, failure to thrive, mild hepatomegaly, and an unusual odor (described as like that of a swimming pool) are reported manifestations of this disorder. Mental development is usually normal.

Symptomatic infants and asymptomatic affected children and adults excrete hawkinsin, 4-hydroxyphenylpyruvic acid, and its metabolites (4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids), 4-hydroxycyclohexylacetic acid and 5-oxoproline (owing to secondary glutathione deficiency) in their urine. The plasma tyrosine level, which is moderately elevated in the symptomatic infants, may become normal in the asymptomatic affected individuals. **Treatment** consists of a low-protein diet during infancy. Breastfeeding is encouraged. A trial with large doses of vitamin C (up to 1,000 mg/24 hr) is also recommended. The mutant enzyme is susceptible to inhibition by nitisinone; clinical studies showing the efficacy of this agent in symptomatic infants are lacking at this time, and the indications for its use are not known.

TRANSIENT TYROSINEMIA OF THE NEWBORN

In a small number of newborn infants, plasma tyrosine may be as high as 60 mg/dL (3,300 µmole/L) during the 1st 2 wk of life. Most affected infants are premature and are receiving high-protein diets. Transient tyrosinemia is felt to result from delayed maturation of 4-HPPD (see Fig. 85-1). Lethargy, poor feeding, and decreased motor activity are noted in some patients. Most are asymptomatic and are identified by a high blood phenylalanine or tyrosine level on routine screening. Laboratory findings include marked elevation of plasma tyrosine with a moderate increase in plasma phenylalanine. The finding of hypertyrosinemia differentiates this condition from PKU. 4-Hydroxyphenylpyruvic acid and its metabolites (see above) are present in the urine. Hypertyrosinemia usually resolves spontaneously in the 1st mo of life. It can be corrected promptly by reducing dietary protein to below 2 g/kg/24 hr and by administering vitamin C (200-400 mg/24 hr). Mild intellectual deficits have been reported in some infants who had this condition, but the causal relationship to hypertyrosinemia is not conclusively established.

ALKAPTONURIA

This rare (with an incidence of approximately 1 in 250,000 live births) autosomal recessive disorder is caused by a deficiency of homogentisic acid oxidase (homogentisate 1,2-dioxigenase). In alkaptonuria, large amounts of homogentisic acid are formed (see Fig. 85-1), which are excreted in urine or deposited in tissues.

The main **clinical manifestations** of alkaptonuria consist of ochronosis and arthritis in adulthood. The only sign in children is a blackening of the urine on standing, caused by oxidation and polymerization of homogentisic acid. A history of gray- or black-stained diapers should suggest the diagnosis. This sign may never be noted; hence, diagnosis is often delayed until adulthood. *Ochronosis,* which is seen clinically as dark spots on the sclera or ear cartilage, results from the accumulation of the black polymer of homogentisic acid. *Arthritis* is another result of this deposition and can be disabling with advancing age. It involves the large joints (spine, hip, and knee) and is usually more severe in males. Like rheumatoid arthritis, the alkaptonuric arthritis has acute exacerbations, but the radiologic findings are typical of osteoarthritis, with characteristic narrowing of the joint spaces and calcification of the intervertebral discs. High incidence of heart disease (mitral and aortic valvulitis, calcification of the heart valves, and myocardial infarction) has been noted.

The **diagnosis** is confirmed by finding massive excretion of homogentisic acid on urine organic acid testing. Tyrosine levels are normal. The enzyme is expressed only in the liver and kidneys.

Treatment of the arthritis is symptomatic. Nitisinone efficiently reduces homogentisic acid production in alkaptonuria. If presymptomatic individuals are detected, treatment with nitisinone, combined with a phenylalanine- and tyrosine-restricted diet, seems reasonable, although no experience is available regarding long-term efficacy.

The gene for homogentisic acid oxidase *(HGD)* maps to chromosome 3q13.3. Several disease-causing mutations have been identified. Alkaptonuria is commonest in the Dominican Republic and Slovakia.

TYROSINE HYDROXYLASE DEFICIENCY

See Chapter 85.11.

ALBINISM (See also Chapters 622 and 653)

Albinism is caused by deficiency of melanin, the main pigment of the skin and eye (Table 85-1). Melanin is synthesized by melanocytes from tyrosine in a membrane-bound intracellular organelle, the melanosome. Melanocytes originate from the embryonic neural crest and migrate to the skin, eyes (choroid and iris), hair follicles, and inner ear. The melanin in the eye is confined to the iris stromal and retinal pigment epithelia, whereas in skin and hair follicles, it is secreted into the epidermis and hair shaft. Albinism can be caused by deficiencies of melanin synthesis, by some hereditary defects of melanosomes, or by disorders of melanocyte migration. Neither the biosynthetic pathway of melanin nor many facets of melanocyte cell biology are completely elucidated (see Fig. 85-2). The end products are 2 pigments: *pheomelanin,* which is a yellow-red pigment, and *eumelanin,* a brown-black pigment.

Table 85-1 Classification of Major Causes of Albinism

TYPE	GENE	CHROMOSOME
OCULOCUTANEOUS ALBINISM (OCA)		
OCA1 (tyrosinase deficient)	*TYR*	11q14-q21
OCA1A (severe deficiency)	*TYR*	11q14-q21
OCA1B (mild deficiency)*	*TYR*	11q14-q21
OCA2 (tyrosinase positive)†	*OCA2*	15q12-q13
OCA3 (Rufous, red OCA)	*TYRP1*‡	9p23
OCA4	*SLC45A2*	5p13.3
Hermansky-Pudlak syndrome	*HPS1-9*	Different chromosomes
Chédiak-Higashi syndrome	*LYST*	1q42.1
OCULAR ALBINISM (OA)		
OA1 (Nettleship-Falls type)	*OA*	Xp22.3
LOCALIZED ALBINISM		
Piebaldism	*KIT*	4q12
Waardenburg syndrome (WS1-WS4)	See text	See text

*This includes Amish, minimal pigment, yellow albinism, and platinum and temperature-sensitive variants.
†Includes brown OCA.
‡Tyrosinase-related protein 1.

Clinically, primary albinism can be generalized or localized. Primary generalized albinism can be either ocular or oculocutaneous. Some syndromes feature albinism in association with platelet, immunological, or neurological dysfunction.

In generalized oculocutaneous albinism, hypopigmentation can be either complete or partial. Individuals with complete albinism do not develop either generalized (tanning) or localized (pigmented nevi) skin pigmentation.

The diagnosis of albinism is usually evident, but for some white children whose families are particularly light-skinned, normal variation may be a diagnostic consideration. Unlike patients with albinism, normal fair-skinned children progressively develop pigmentation with age, do not exhibit the eye manifestations of albinism, and have pigmentary development similar to other family members. The clinical diagnosis of oculocutaneous albinism, as opposed to other types of cutaneous hypopigmentation, requires the presence of characteristic eye findings.

The ocular manifestations of albinism include hypopigmentation of iris and retina with foveal hypoplasia along with, reduced visual acuity, refractive errors, nystagmus, alternating strabismus, and a red reflex (diffuse reddish hue of the iris produced during ophthalmoscopic or slit-lamp examination of the eye). There is also an abnormality in routing of the optic fibers at the chiasm. Unlike normally in pigmented individuals, in patients with albinism the majority of the nerve fibers from the temporal side of the retina cross to the contralateral hemisphere of the brain. This results in lack of biocular (stereoscopic) vision and depth perception, and in repeated switching of vision from eye to eye, causing alternating strabismus. This abnormality also causes a characteristic pattern of visual-evoked potentials. These findings are highly specific for albinism and can be used to formally establish the clinical diagnosis. Regular ophthalmologic follow-up is recommended for patients with oculocutaneous albinism; correction of refractive errors can maximize visual function. Normally the alternating strabismus does not result in amblyopia and does not require surgery.

Patients with albinism should be counseled to avoid UV radiation by wearing protective long-sleeved clothing and by using sunscreens with a sun protection factor rating above 30. All forms of oculocutaneous albinism are autosomal recessive traits.

Melanin is also present in the cochlea. Albino individuals may be more susceptible to ototoxic agents such as gentamicin.

Many clinical forms of albinism have been identified. Some of the seemingly distinct clinical forms are caused by different mutations of the same gene. Several genes located on different chromosomes are involved in melanogenesis (see Table 85-1). Attempts to differentiate types of albinism based on the mode of inheritance, tyrosinase activity, or the extent of hypopigmentation have failed to yield a comprehensive classification. The following classification is based on the distribution of albinism in the body and the type of mutated gene.

Mutation detection is clinically available for most albinism genes (see Table 85-1). Molecular diagnosis is of little use therapeutically in isolated albinism but can be helpful for precise genetic counseling of families.

Oculocutaneous (Generalized) Albinism

Lack of pigment is generalized, affecting skin, hair, and eyes. At least 4 genetically distinct forms of oculocutaneous albinism (OCA) have been identified: OCA_1, OCA_2, OCA_3, and OCA_4. The lack of pigment is complete in patients with OCA_1 A; the other types may not be clinically distinguishable from one another. All affected individuals have ocular manifestations of albinism (see above). All forms are inherited as autosomal recessive traits.

OCA_1 (Tyrosinase-Deficient Albinism)

The defect in these patients resides in the tyrosinase gene, *TYR*, located on chromosome 11q14.3. Many mutant alleles have been identified. Most affected individuals are genetic compounds, heterozygous for 2 different mutant alleles. A clinical clue to the diagnosis of OCA_1 is complete lack of pigment at birth. The condition can be subdivided to OCA_1 A and OCA_1 B, based on enzyme activity and difference in clinical manifestations as a function of age.

OCA_1 A (Tyrosinase-Negative OCA)

In these individuals, who have the most severe form of OCA, both *TYR* alleles have mutations that completely inactivate tyrosinase. Clinically, lack of pigment in the skin (milky white), hair (white hair), and eyes (red gray irides) is evident at birth and remains unchanged throughout life. They do not tan and do not develop pigmented nevi or freckles.

OCA_1 B

These patients have *TYR* gene mutations that preserve some residual activity. Clinically they completely lack pigment at birth, but with age become light blond with light blue or hazel eyes. They develop pigmented nevi and freckles and they may tan. OCA_1 B patients, depending on the degree of pigmentation, were once subdivided into different groups and thought to be genetically distinct.

OCA_2 (Tyrosinase-Positive OCA)

This is the most common form of generalized OCA, particularly in African blacks. Clinically, the phenotype is highly variable; most patients demonstrate some pigmentation of the skin and eyes at birth and continue to accumulate pigment throughout their lives. The hair is yellow at birth and may darken with age. They have pigmented nevi and freckles and some may tan. They may be clinically indistinguishable from OCA_1 B. Individuals with OCA_2, however, have normal tyrosinase activity in hair bulbs. The defect is in the *OCA_2* gene which is homologous to the *p* (pink-eyed dilution) gene in the mouse. This gene produces the P protein, a melanosome membrane protein. Patients with forms of Prader-Willi and Angelman syndromes caused by microdeletion of chromosome 15q12 that includes the *OCA_2* gene have mild pigmentary deficiency (see Chapter 81.8).

OCA_3 (Rufous Albinism)

This form has been identified only in Africans, African-Americans, and natives of New Guinea. Patients have reddish hair and reddish brown skin as adults. The skin color is peculiar to this form. In the young, the coloration may resemble that of OCA_2. Patients with OCA_3 can make pheomelanin but not eumelanin. The mutation is in the tyrosinase-related protein 1 (*TYRP1*) gene (located on chromosome 9p23), the function of which is not well-understood.

OCA_4

Similar manifestations to OCA_2 (both in the skin and the eyes) have been observed in patients (mostly from Japan) with mutations in the *SLC45A2* (previously called *MATP*) gene located on chromosome 5p13.2.

Ocular Albinism

Ocular albinism (OA) is limited to the eye. All the eye findings of albinism (see above) are present. Most cases are X-linked (OA_1).

Ocular Albinism 1 (Nettleship-Falls Type)

Only the hemizygous male has the complete manifestation. Segments of abnormal retinal pigmentation may be present in heterozygous females. An X-linked OA with late-onset sensorineural deafness has also been reported. The diagnosis of ocular albinism 1 (OA_1) is evident in males with the features of albinism in the eye, normal skin pigmentation, and a positive family history suggestive of an X-linked recessive transmission. Mild hypopigmentation of the skin (compared to unaffected siblings) may be present. It is a nonprogressive disorder and the eye findings, in fact, often improve with age. In patients who are the first of their families to be affected, electron microscopic demonstration of characteristic mega melanosomes in skin biopsies or hair root specimens is useful, as is mutation analysis of the *OA_1* gene on chromosome Xp22.2.

Syndromic Forms of Generalized Albinism

Hermansky-Pudlak Syndrome

This group of autosomal recessive disorders is caused by mutations of 1 of 9 different genes located on different chromosomes, *HPS1* to *HPS9*. Hermansky-Pudlak syndrome is suspected in patients with albinism and a bleeding diathesis. Disease subtype can be established with molecular studies.

The *HPS* genes are necessary for normal structure and function of lysosome-derived organelles, including melanosomes and platelet dense bodies. Patients have a tyrosinase-positive OCA of variable severity associated with platelet dysfunction (owing to the absence of platelet dense bodies). A ceroid-like material accumulates in tissues. Hermansky-Pudlak syndrome is most prevalent in 2 regions of Puerto Rico (type 1 in the northwest and type 3 in the central regions as a result of different founder effects). The cutaneous and ocular symptoms of albinism are present. Patients can develop epistaxis, postsurgical bleeding, or abundant menses. Bleeding time is prolonged but platelet count is normal. Major complications are progressive pulmonary fibrosis in young adults and Crohn-like inflammatory bowel disease in adolescents and young adults. Kidney failure and cardiomyopathy are reported. Neutropenia is described in HPS type 2. Treatment is symptomatic.

Chédiak-Higashi Syndrome

Patients with this rare autosomal recessive condition (see Chapter 130) have OCA of variable severity and susceptibility to infection. Bacterial infections of skin and upper respiratory tract are common. Giant peroxidase-positive lysosomal granules can be seen in granulocytes in a blood smear. Patients have a reduced number of melanosomes, which are abnormally large (macromelanosomes). The bleeding tendency is typically mild. The major, life-threatening complication is macrophage activation with hemophagocytic lymphohistiocytosis, manifested by fever, lymphadenopathy, hepatosplenomegaly, cytopenias, and elevated plasma ferritin level. Patients surviving childhood may develop cerebellar atrophy, peripheral neuropathy, and cognitive delay. Mutations in the *LYST* gene on chromosome 1q are the only known cause of this syndrome.

Hypopigmentation is a feature of other syndromes, some with abnormalities of lysosomal biogenesis or melanosome biology, such as *Griscelli syndrome* (silver-gray hair, pigmentary dilution of skin, and melanosomal clumping in hair shafts and the center of melanocytes, with intellectual disability or macrophage activation with hemophagocytosis in different subtypes), *Vici syndrome* (combined immunodeficiency, intellectual disability, agenesis of the corpus callosum, cataracts, and cleft lip and palate), and MAPBP interacting protein deficiency (short stature, recurrent infections, neutropenia).

Localized Albinism

Localized albinism refers to localized patches of hypopigmentation of skin and hair, which may be evident at birth or develop with time. These conditions are caused by abnormal migration of melanocytes during embryonic development.

Piebaldism

Piebaldism is an autosomal dominant inherited condition in which the individual is usually born with a white forelock. The underlying skin is depigmented and devoid of melanocytes. In addition, there are usually white macules on the face, trunk, and extremities. Mutations in the *KIT* gene have been shown in affected patients.

Waardenburg Syndrome

In this syndrome, a white forelock is associated with lateral displacement of inner canthi of the eyes, broad nasal bridge, heterochromia of irides, and sensorineural deafness. This condition is inherited as an autosomal dominant trait. Four major types of this syndrome have been identified. Patients with type 1 (WS1, the most common form) have all the above clinical findings including lateral displacement of inner canthi. The condition is caused by mutation (>90%) or deletion of the *PAX3* gene. Patients with type 2 (WS2) have all the clinical findings of WS1 except the lateral displacement of inner canthi. Genetically, this is a heterogeneous condition caused by mutations in different genes located on different chromosomes. Patients with type 3 (WS3) have all the findings seen in individuals with WS1 plus hypoplasia and contractures of the upper limbs. It is caused by heterozygous or homozygous mutations of *PAX3* gene. Type 4 (WS4), associated with Hirschsprung disease, is heterogeneous; mutations in different genes (*EDN3, EDNRB,* or *SOX10*) have been identified in different patients.

Other causes of localized hypopigmentation are discussed in other chapters (e.g., hypomelanosis of Ito, see Chapters 81 and 653; and vitiligo, see Chapter 653).

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85.3 Methionine

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The usual pathway for catabolism of methionine, an essential amino acid, produces *S*-adenosylmethionine, which serves as a methyl group donor for methylation of a variety of compounds in the body, and cysteine, which is formed through a series of reactions collectively called trans-sulfuration (Fig. 85-3).

HOMOCYSTINURIA (HOMOCYSTINEMIA)

Normally, most homocysteine, an intermediate compound of methionine degradation, is remethylated to methionine. This methionine-sparing reaction is catalyzed by the enzyme methionine synthase, which requires a metabolite of folic acid (5-methyltetrahydrofolate) as a methyl donor and a metabolite of vitamin B_{12} (methylcobalamin), as well as *S*-adenosylcobalamin, as cofactors (see Fig. 85-3). Only approximately 20% of total homocysteine (and its dimer homocystine) is in free form in the plasma of normal individuals. The rest is bound to proteins as mixed disulfides. Three major forms of homocystinemia and homocystinuria have been identified.

Homocystinuria Caused by Cystathionine β-Synthase Deficiency (Classic Homocystinuria)

This is the most common inborn error of methionine metabolism. Approximately 40% of affected patients respond to high doses of vitamin B_6 and usually have milder clinical manifestations than those who are unresponsive to vitamin B_6 therapy. These patients possess some residual enzyme activity.

Infants with this disorder are normal at birth. **Clinical manifestations** during infancy are nonspecific and may include failure to thrive and developmental delay. The diagnosis is usually made after 3 yr of age, when subluxation of the ocular lens **(ectopia lentis)** occurs. This causes severe myopia and iridodonesis (quivering of the iris). Astigmatism, glaucoma, staphyloma, cataracts, retinal detachment, and optic atrophy may develop later in life. Progressive **intellectual disability** is common. Normal intelligence has been reported. In an international survey of more than 600 patients, IQ scores ranged from 10-135. Higher IQ scores are seen in vitamin B_6–responsive patients. **Psychiatric and behavioral disorders** have been observed in more than 50% of affected patients. Convulsions occur in approximately 20% of patients. Affected individuals with homocystinuria manifest **skeletal abnormalities** resembling those of Marfan syndrome (see Chapter 702); they are usually tall and thin, with elongated limbs and arachnodactyly. Scoliosis, pectus excavatum or carinatum, genu valgum, pes cavus, high-arched palate, and crowding of the teeth are commonly seen. These children usually have fair complexions, blue eyes, and a peculiar malar flush. Generalized osteoporosis, especially of the spine, is the main roentgenographic finding. **Thromboembolic episodes** involving both large and small vessels, especially those of the brain, are common and may occur at any age. Optic atrophy, paralysis, cor pulmonale, and severe hypertension (from renal infarcts) are among the serious consequences of thromboembolism, which is caused by

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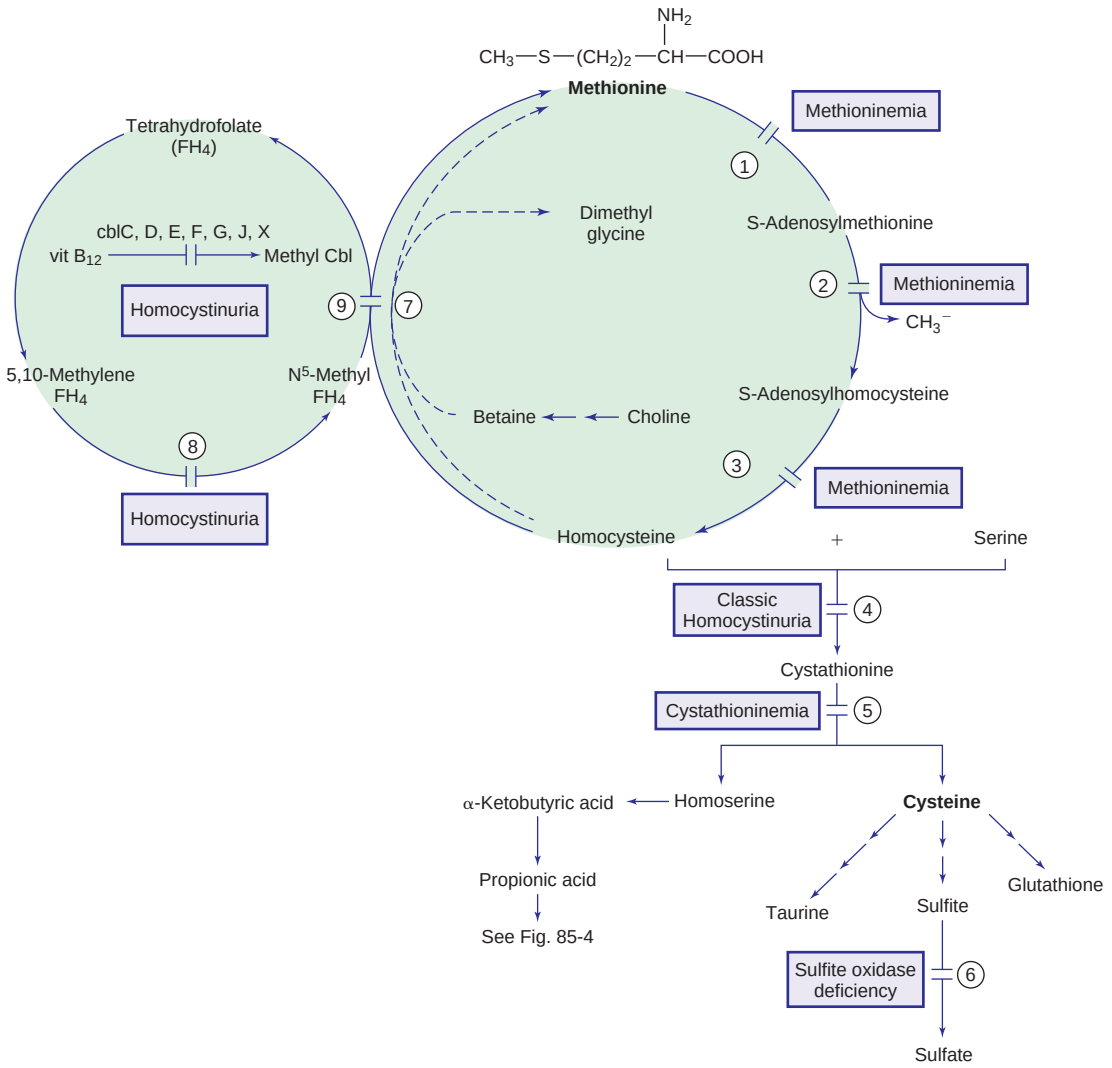

Figure 85-3 Pathways in the metabolism of sulfur-containing amino acids. **Enzymes:** *(1)* Methionine adenosyltransferase (MAT I/III), *(2)* glycine-N-methyltransferase, *(3)* adenosylhomocysteine hydrolase, *(4)* cystathionine synthase, *(5)* cystathionase, *(6)* sulfite oxidase, *(7)* betaine homocysteine methyltransferase, *(8)* methylene tetrahydrofolate reductase, *(9)* Methionine synthase (cblG).

changes in the vascular walls and increased platelet adhesiveness secondary to elevated homocystine levels. The risk of thromboembolism increases after surgical procedures. Spontaneous pneumothorax and acute pancreatitis are rare complications.

Elevations of both methionine and homocystine (or homocysteine) in body fluids are the diagnostic **laboratory findings**. Freshly voided urine should be tested for homocystine because this compound is unstable and may disappear as the urine is stored. Cystine is low or absent in plasma. The diagnosis may be established by assay of the enzyme in liver biopsy specimens, cultured fibroblasts, or phytohemagglutinin-stimulated lymphocytes or by DNA analysis.

Treatment with high doses of vitamin B_6 (200-1,000 mg/24 hr) causes dramatic improvement in most patients who are responsive to this therapy. The degree of response to vitamin B_6 treatment may be different in different families. Some patients may not respond because of folate depletion; a patient should not be considered unresponsive to vitamin B_6 until folic acid (1-5 mg/24 hr) has been added to the treatment regimen. Restriction of methionine intake in conjunction with cysteine supplementation is recommended for patients who are unresponsive to vitamin B_6. The need for dietary restriction and its extent remains controversial in patients with vitamin B_6–responsive form. In some patients with this form, addition of betaine may obviate the need for any dietary restriction. Betaine (trimethylglycine, 6-9 g/24 hr for adults or 200-250 mg/kg/day for children) lowers homocysteine levels in body fluids by remethylating homocysteine to methionine (see Fig. 85-3); this may result in further elevation of plasma methionine levels. This treatment has produced clinical improvement (preventing vascular events) in patients who are unresponsive to vitamin B_6 therapy. Cerebral edema has occurred in a patient with vitamin B_6–nonresponsive homocystinuria and dietary noncompliance during betaine therapy. Administration of large doses of vitamin C (1 g/day) has improved endothelial function; long-term clinical efficacy is not known.

More than 100 pregnancies in women with the classic form of homocystinuria have been reported with favorable outcomes for both mothers and infants. The majority of infants were full-term and normal. Postpartum thromboembolic events occurred in a few mothers. All but 1 of the 38 affected male patients has had normal offspring.

The screening of newborn infants for classic homocystinuria has been performed worldwide and a prevalence of 1 in 200,000 to 1 in 350,000 live births has been estimated. The condition seems more common in New South Wales, Australia (1 in 60,000 live births), and Ireland. Early treatment of patients identified by the screening process has produced favorable results. The mean IQ of 16 patients with vitamin B_6–unresponsive form treated in early infancy was 94 ± 4. Dislocation of the lens seemed to be prevented in some patients.

Homocystinuria is inherited as an autosomal recessive trait. The gene for cystathionine β-synthase *(CBS)* is located on chromosome 21q22.3. Prenatal diagnosis is feasible by performing an enzyme assay of cultured amniotic cells or chorionic villi or by DNA analysis. Many disease-causing mutations (>150) have been identified in different families. The majority of affected patients are compound heterozygotes for 2 different alleles. Heterozygous carriers are usually asymptomatic; thromboembolic events and coronary heart disease are more common in these individuals than in the normal population.

Homocystinuria Caused by Defects in Methylcobalamin Formation

Methylcobalamin is the cofactor for the enzyme methionine synthase, which catalyzes remethylation of homocysteine to methionine. There are at least 7 distinct defects in the intracellular metabolism of cobalamin that may interfere with the formation of methylcobalamin. To better understand the metabolism of cobalamin, see methylmalonic acidemia (Fig. 85-4; see Chapter 85.6 and Fig. 85-3). The 7 defects are designated as *cbl*C, *cbl*D (including *cbl*D variant 1), *cbl*E *(methionine synthase reductase)*, *cbl*G *(methionine synthase)*, and *cbl*F, *cblJ*, and *cbl*X. Patients with *cbl*C, *cbl*D (not including those with *cbl*D variant 1 or variant 2), *cbl*F, *cblJ*, and *cblX* defects have methylmalonic acidemia in addition to homocystinuria, because formation of both adenosylcobalamin and methylcobalamin is impaired (See Chapter 85.6 for further information about these defects.).

Patients with *cbl*E, *cbl*G, and *cbl*D variant 1 defects are unable to form methylcobalamin and develop homocystinuria without methylmalonic acidemia (see Fig. 85-4); fewer than 40 patients are known with each of these diseases.

The **clinical manifestations** are similar in patients with all of these defects. Vomiting, poor feeding, failure to thrive, lethargy, hypotonia, seizures, and developmental delay may occur in the first few months of life. One patient with the *cbl*G defect was not symptomatic (except for mild developmental delay) until she was 21 yr old when she developed difficulty in walking and numbness of the hands. **Laboratory findings** include megaloblastic anemia, homocystinuria, and hypomethioninemia. The presence of megaloblastic anemia differentiates these defects from homocystinuria due to methylenetetrahydrofolate reductase deficiency (see below). The absence of hypermethioninemia differentiates both of these conditions from cystathionine β-synthase deficiency (see above). Renal artery thrombosis, hemolytic uremic syndrome, pulmonary hypertension and optic nerve atrophy have been reported in some patients with these defects.

Diagnosis is established by complementation studies performed in cultured fibroblasts. Prenatal diagnosis has been accomplished by studies in amniotic cell cultures. These conditions (*cbl*E, *cbl*G, and *cbl*D variant 1) are inherited as autosomal recessive traits. The gene for *cbl*E is *MTRR*, encoding methionine synthase reductase (located on chromosome 5p15.3-p15.2) and the gene for *cbl*G is *MTR*, encoding methionine synthase (located on chromosome 1q43); *cbl*D variant 1 is caused by mutations affecting the C-terminal of the *MMADHC* gene (located on chromosome 2q23.2). Several disease-causing mutations, including a common missense mutation (P1173L) in the *MTR* gene, have been described.

Treatment with vitamin B_{12} in the form of hydroxycobalamin (1-2 mg/24 hr) is used to correct the clinical and biochemical findings. Results vary among both diseases and sibships.

Defects causing both homocystinuria and methylmalonic acidemias are discussed in Chapter 85.6.

Homocystinuria Caused by Deficiency of Methylenetetrahydrofolate Reductase

This enzyme reduces 5,10-methylenetetrahydrofolate to form 5-methyltetrahydrofolate, which provides the methyl group needed for remethylation of homocysteine to methionine (see Fig. 85-3).

The severity of the enzyme defect and the clinical manifestations varies considerably in different families. **Clinical findings** vary from apnea, seizure, microcephaly, coma, and death to developmental delay, ataxia, and motor abnormalities or even psychiatric manifestations. Premature vascular disease or peripheral neuropathy has been reported as the only manifestation of this enzyme deficiency in some patients. Adults with severe enzyme deficiency may even be completely asymptomatic. Exposure to the anesthetic nitrous oxide (which inhibits methionine synthase) in patients with methylenetetrahydrofolate reductase (MTHFR) deficiency may result in neurologic deterioration and death.

Laboratory findings include moderate homocystinemia and homocystinuria. The methionine concentration is low or low normal. This finding differentiates this condition from classic homocystinuria caused by cystathionine β-synthase deficiency. Absence of megaloblastic anemia distinguishes this condition from homocystinuria caused by methylcobalamin formation (see above). Thromboembolism of vessels has also been observed in these patients. Diagnosis may be confirmed by the enzyme assay in cultured fibroblasts or leukocytes or by finding causal mutation in the *MTHR* gene.

A number of polymorphisms have been described in the *MTHR* gene. Two of these (677C → T and 1298A → C) may affect levels of plasma total homocysteine and have been studied as possible risk factors for a wide variety of medical conditions, ranging from birth defects to vascular disease and even cancer, Alzheimer disease, and death from leukemia. To date, the best data support a role for 677C → T polymorphism as a risk factor for neural tube defects. Although a clinical test for this polymorphism is widely available, its predictive value in any given individual has yet to be determined.

Treatment of severe MTHFR deficiency with a combination of folic acid, vitamin B_6, vitamin B_{12}, methionine supplementation, and betaine has been tried. Of these, early treatment with betaine seems to have the most beneficial effect.

The condition is inherited as an autosomal recessive trait; the gene for the enzyme has been located on chromosome 1p36.3 and many disease-causing mutations have been reported in the *MTHFR* gene. Prenatal diagnosis can be offered by measuring MTHFR enzyme activity in cultured chorionic villus cells or amniocytes, by linkage analysis in informative families, or by DNA analysis of the mutation.

HYPERMETHIONINEMIA

Primary (Genetic) Hypermethioninemia

Elevation of plasma level of methionine occurs in the following genetic conditions:

1. **Classic homocystinuria (see above).**
2. **Hepatic methionine adenosyltransferase (MAT I/MAT III) deficiency:** This enzyme, which has 2 isoforms, MAT I (tetrameric) and MAT III (dimeric), is encoded by a single gene *(MAT 1A)* and is involved in the first step of methionine catabolism (see Fig. 85-3). Another structurally similar enzyme, MAT II, is encoded by a different gene (*MAT 2A* on chromosome 2p11.2) and is expressed predominately in nonhepatic tissues (kidney, brain, lymphocytes). Deficiency of MAT I/MAT III causes hypermethioninemia without homocystinuria. The majority of these patients have been diagnosed in the neonatal period through screening for homocystinuria. Most affected individuals have residual enzyme activity and remain asymptomatic throughout life despite persistent hypermethioninemia. Some complain of an unusual offensive odor to their breath (boiled cabbage). A few patients with complete enzyme deficiency have had neurologic abnormalities related to demyelination (intellectual disability, dystonia, dyspraxia).

   Laboratory studies reveal markedly elevated levels of plasma methionine with a low level of *S*-adenosylmethionine and normal concentrations of *S*-adenosylhomocysteine and homocysteine. These findings differentiate this condition from other causes of hypermethioninemia.

   No uniformly accepted therapeutic regimen has yet emerged. Diets low in methionine result in lowering of plasma methionine, but the advisability of such diets has been questioned since lowering of the plasma methionine level causes further lowering of *S*-adenosylmethionine in the body.

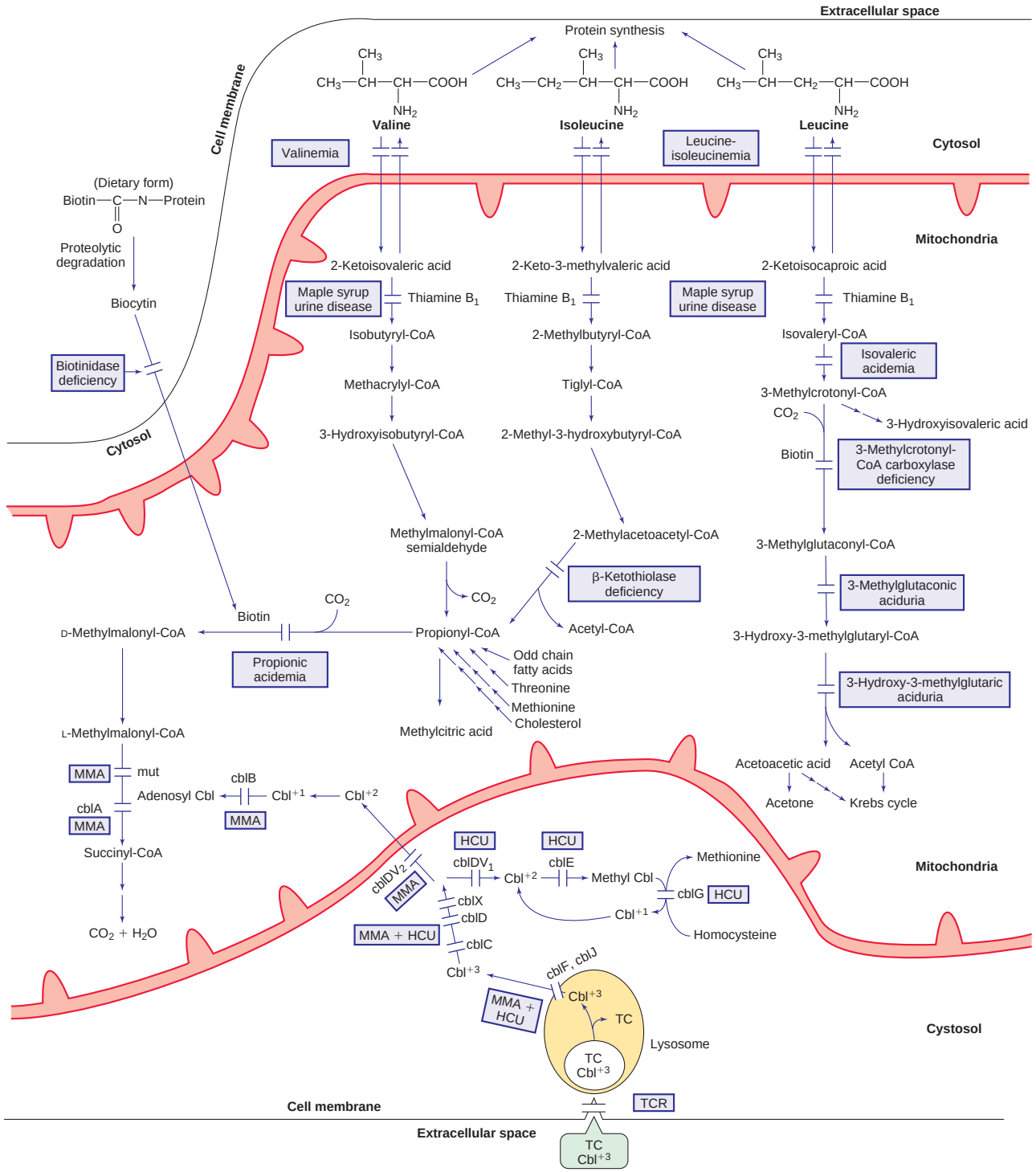

Figure 85-4 Pathways in the metabolism of the branched-chain amino acids, biotin, and vitamin B_{12} (cobalamin). Adenosyl Cbl, adenosylcobalamin; Cbl, cobalamin; cbl, defect in metabolism of cobalamin; cblDV1, cblD variant 1; cblDV2, cblD variant 2; HCU, homocystinuria; Methyl Cbl, methylcobalamin; MMA, methylmalonic acidemia; MUT, mutase; OHCbl, hydroxycobalamin; TC, transcobalamin; TCR, transcobalamin receptor. See text for the name of the enzymes.

Supplementation with *S*-adenosylmethionine in conjunction with a low methionine diet seems prudent, but no large clinical experience is yet available. Normal pregnancies producing normal offspring have been reported in mothers with MAT (MAT IA) deficiency. The condition is inherited as an autosomal recessive trait. The gene for hepatic MAT is on chromosome 10q22 and several disease-causing mutations have been identified.

3. **Glycine *N*-methyltransferase deficiency:** Although there are many methyltransferases present in the body, glycine *N*-methyltransferase is the critical one for catabolism of *S*-adenosylmethionine to *S*-adenosylhomocysteine (see Fig. 85-3). Three patients with deficiency of this enzyme have been reported to date. Clinically, patients were asymptomatic except for mild hepatomegaly and elevated serum levels of transaminases. Other laboratory findings included hypermethioninemia and very high

levels of serum *S*-adenosylmethionine. No specific treatment has yet been identified. The condition seems to be inherited as an autosomal recessive trait; the gene for the enzyme *(GNMT)* is on chromosome 6p21.1.

4. **Adenosylhomocysteine hydrolase deficiency:** Deficiency of this enzyme (see Fig. 85-3) has been reported in 6 patients from 5 different families. Psychomotor retardation and severe hypotonia were common clinical findings in affected individuals. Laboratory studies included elevated levels of serum creatine kinase, hypoalbuminemia (causing fetal hydrops in 1 family), hypoprothrombinemia and markedly elevated levels of serum *S*-adenosylhomocysteine with moderate elevations of plasma methionine and *S*-adenosylmethionine. Marked elevation in *S*-adenosylhomocysteine has been thought to cause inhibition of methyltransferases, including those involved in synthesis of creatine (see Fig. 85-10) and choline, resulting in their deficiencies. MRI of the brain showed delayed myelination of the white matter. Treatment with a low methionine diet in conjunction with creatine and phosphatidylcholine shows encouraging results in some patients.
5. **Tyrosinemia type I** (see Chapter 85.2).
6. **Citrin deficiency** (see Chapter 85.12).

Acquired (Nongenetic) Hypermethioninemia

Hypermethioninemia occurs in premature and some full-term infants receiving high-protein diets, in whom it may represent delayed maturation of the enzyme MAT. Lowering the protein intake usually resolves the abnormality. It is also commonly found in patients with various forms of liver disease.

CYSTATHIONINEMIA (CYSTATHIONINURIA)

Secondary cystathioninuria occurs in patients with vitamin B_6 or B_{12} deficiency, liver disease (particularly damage caused by galactosemia), thyrotoxicosis, hepatoblastoma, neuroblastoma, ganglioblastoma, or defects in remethylation of homocysteine.

Cystathionase deficiency results in massive cystathioninuria and mild to moderate cystathioninemia; cystathionine is not normally detectable in blood. Deficiency of this enzyme is inherited as an autosomal recessive trait and its prevalence is estimated to be about 1 in 14,000 live births. Affected subjects with a wide variety of clinical manifestations have been reported. Lack of a consistent clinical picture and the presence of cystathioninuria in a number of individuals free of clinical findings suggest that cystathionase deficiency may be of no clinical significance. A majority of reported cases are responsive to oral administration of large doses of vitamin B_6 (≥100 mg/24 hr). When cystathioninuria is discovered in a patient, vitamin B_6 treatment seems indicated, but its beneficial effect has not been established. The gene encoding for cystathionase (*CTH*) is located on chromosome16 1p31.1

Bibliography is available at Expert Consult.

85.4 Cysteine/Cystine

Iraj Rezvani

Cysteine is a sulfur-containing nonessential amino acid that is synthesized from methionine (see Fig. 85-3). In the presence of oxygen, 2 molecules of cysteine are oxidized to form cystine. The most common genetic disorders of cysteine/cystine metabolism are cystinuria (see Chapter 547) and cystinosis (see Chapter 529.3).

Sulfite Oxidase Deficiency (Molybdenum Cofactor Deficiency)

At the last step in cysteine metabolism, sulfite is oxidized to sulfate by sulfite oxidase, and the sulfate is excreted in the urine (see Fig. 85-3). This enzyme requires a molybdenum-pterin complex named molybdenum cofactor. This cofactor is also necessary for the function of 2 other enzymes in humans: xanthine dehydrogenase (which oxidizes xanthine and hypoxanthine to uric acid) and aldehyde oxidase (involved in oxidizing a number of natural compounds and drugs). Three enzymes, encoded by 3 different genes (*MOCS1*, *MOCS2,* and *GPHN*) are involved in the synthesis of the cofactor. The genes for these enzymes are mapped to chromosomes 6p21.2, 5q11.2, and 14q23.3, respectively. Deficiency of any of the 3 enzymes causes cofactor deficiency with identical phenotype. Most patients, who were originally diagnosed as having sulfite oxidase deficiency, have been proven to have molybdenum cofactor deficiency. Both conditions are inherited as autosomal recessive traits. The gene for sulfite oxidase (*SUOX*) is on chromosome 12q13.2.

The enzyme and or the cofactor deficiencies produce identical **clinical manifestations**. Refusal to feed, vomiting, severe intractable seizures (tonic, clonic, myoclonic), cortical atrophy with subcortical multicystic lesions, and severe developmental delay may develop within a few weeks after birth. Bilateral dislocation of ocular lenses is a common finding in patients who survive the neonatal period. The intractable seizures seen in this condition are, in large part, a consequence of secondary vitamin B_6 dependency. The accumulation of sulfites in body fluids in this condition causes the inhibition of antiquitin enzyme which is necessary for conversion of α-aminoadipic semialdehyde to α-aminoadipic acid; the resultant accumulation of α-aminoadipic semialdehyde and its cyclic form P6C causes the inactivation of pyridoxal-5-phosphate (active form of vitamin B_6) and, hence, the vitamin B_6–dependent epilepsy (see also Chapter 85.14).

These children excrete large amounts of sulfite, thiosulfate, *S*-sulfocysteine, xanthine, and hypoxanthine in their urine. Urinary and serum levels of uric acid and urinary concentration of sulfate are diminished. Fresh urine should be used for screening purposes and for quantitative measurements of sulfite, because oxidation of sulfite to sulfate at room temperature may produce false-negative results. Increased concentrations of α-aminoadipic semialdehyde and its cyclic form, P6C, and pipecolic acid are present in the CSF, plasma, and urine.

Diagnosis is confirmed by measurement of sulfite oxidase and molybdenum cofactor in fibroblasts and liver biopsies, respectively or by DNA studies. Prenatal diagnosis is possible by performing an assay of sulfite oxidase activity in cultured amniotic cells, in samples of chorionic villi or by DNA studies.

No effective **treatment** is available; large doses of vitamin B_6 (5-100 mg/kg) result in dramatic alleviation of seizures but do not seem to alter the devastating neurologic outcome. Most children die in the 1st 2 yr of life. One patient had an initial response to cyclic pyranopterin monophosphate (cPMP). The prevalence of these deficiencies in the general population is not known.

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85.5 Tryptophan

Iraj Rezvani

Tryptophan is an essential amino acid and a precursor for nicotinic acid (niacin) and serotonin (Fig. 85-5). The genetic disorders of metabolism of serotonin, one of the major neurotransmitters, are discussed in Chapter 85.11.

HARTNUP DISORDER

In this autosomal recessive disorder, named after the first affected family, there is a defect in the transport of monoamino-monocarboxylic amino acids (neutral amino acids), including tryptophan, by the intestinal mucosa and renal tubules. The transporter protein for these amino acids (B0AT1) is encoded by the *SLC6A19* gene located on chromosome 5p15.33. Two chemically close transcription factors, angiotensin-converting enzyme (ACE2) in the intestine and renal tubules, and collectrin in the renal tubules, are required for expression of B0AT1 transporter protein by the *SLC6A19* gene. The mutated gene in patients with Hartnup disorder, unable to interact with the above

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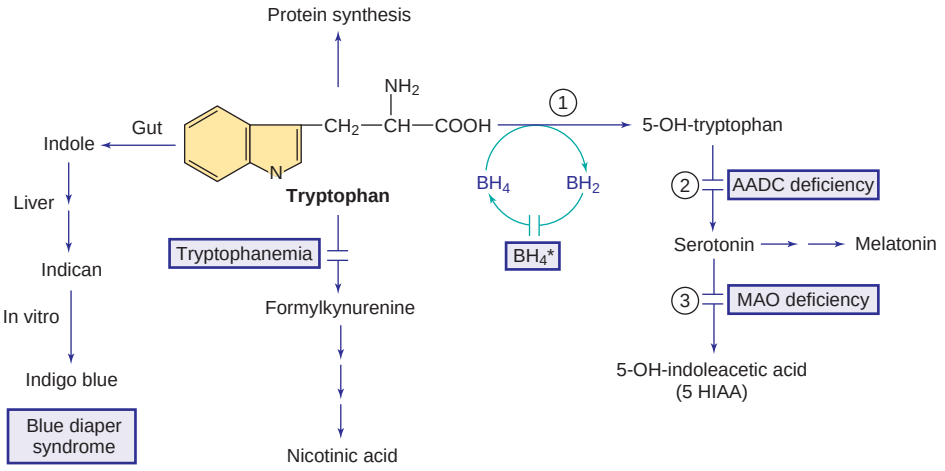

Figure 85-5 Pathways in the metabolism of tryptophan. PKU* indicates hyperphenylalaninemia caused by tetrahydrobiopterin deficiency (see Fig. 85-1). **Enzymes:** *(1)* Tryptophan hydroxylase, *(2)* aromatic L-amino acid decarboxylase (AADC), *(3)* monoamine oxidase (MAO).

transcription factors, results in deficiency of B0AT1 protein either in the intestine or in the renal tubules or in both. This explains the absence of renal or intestinal transport defect seen in some affected families. Decreased intestinal absorption of tryptophan in conjunction with its increased renal loss is believed to cause reduced availability of tryptophan for niacin synthesis in affected individuals. Most children with Hartnup defect remain asymptomatic. The major clinical manifestation in the rare symptomatic patient is cutaneous photosensitivity. The skin becomes rough and red after moderate exposure to the sun, and with greater exposure, a pellagra-like rash may develop. The rash may be pruritic, and a chronic eczema may develop. The skin changes have been reported in affected infants as young as 10 days of age. Some patients may have intermittent ataxia manifested as an unsteady, wide-based gait. The ataxia may last a few days and usually recovers spontaneously. Mental development is usually normal. Two individuals in the original kindred were cognitively impaired. Episodic psychiatric manifestations such as irritability, emotional instability, depression, and suicidal tendencies, have been observed; these changes are usually associated with bouts of ataxia. Short stature and atrophic glossitis are seen in some patients.

Most children diagnosed with Hartnup disorder by neonatal screening have remained asymptomatic. This indicates that other factors are also involved in pathogenesis of the clinical condition.

The main **laboratory finding** is aminoaciduria, which is restricted to neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine). Urinary excretion of proline, hydroxyproline, and arginine remains normal. This finding differentiates Hartnup disorder from other causes of generalized aminoaciduria, such as Fanconi syndrome. Plasma concentrations of neutral amino acids are usually normal. This seemingly unexpected finding occurs because these amino acids are absorbed as dipeptides and the transport system for small peptides is intact in Hartnup disorder. The indole derivatives (especially indican) may be found in large amounts in some patients, owing to bacterial breakdown of unabsorbed tryptophan in the intestines.

Diagnosis is established by the striking intermittent nature of symptoms and the previously described urinary findings.

Treatment with nicotinic acid or nicotinamide (50-300 mg/24 hr) and a high-protein diet results in a favorable response in symptomatic patients. Because of the intermittent nature of the clinical manifestations, the efficacy of these treatments is difficult to evaluate. The prevalence of the disorder is estimated to be 1 in 20,000 to 1 in 30,000 live births. Normal outcome both for mother and fetus is reported in affected pregnant women.

Bibliography is available at Expert Consult.

85.6 Valine, Leucine, Isoleucine, and Related Organic Acidemias

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The early steps in the degradation of these 3 essential amino acids, the **branched-chain amino acids**, are similar (see Fig. 85-4). The intermediate metabolites are all organic acids, and deficiency of any of the degradative enzymes, except for the transaminases, causes acidosis; in such instances, the organic acids proximal to the enzymatic block accumulate in body fluids and are excreted in the urine. These disorders commonly cause metabolic acidosis, which usually occurs in the first few days of life. Although most of the clinical findings are nonspecific, some manifestations may provide important clues to the nature of the enzyme deficiency. Figure 85-6 presents an approach to infants suspected of having an organic acidemia. Definitive diagnosis is usually established by identifying and measuring specific organic acids in body fluids (blood, urine), by the enzyme assay, and by identification of the mutant gene.

Organic acidemias are not limited to defects in the catabolic pathways of branched-chain amino acids. Disorders causing accumulation of other organic acids include those derived from lysine (see Chapter 85.14), those associated with lactic acid (see Chapter 87), and dicarboxylic acidemias associated with defective fatty acid degradation (see Chapter 86.1).

MAPLE SYRUP URINE DISEASE

Decarboxylation of leucine, isoleucine, and valine is accomplished by a complex enzyme system (branched-chain α-ketoacid dehydrogenase [BCKDH]) using thiamine (vitamin B_1) pyrophosphate as a coenzyme. This mitochondrial enzyme consists of 4 subunits: $E_{1\alpha}$, $E_{1\beta}$, E_2, and E_3. The E_3 subunit is shared with 2 other dehydrogenases in the body, namely pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Deficiency of any of these subunits causes maple syrup urine disease (MSUD) (see Fig. 85-4), named after the sweet odor of maple syrup found in body fluids, especially urine. Clinical conditions caused by defects in $E_{1\alpha}$, $E_{1\beta}$, E_2 and E_3 are designated as MSUD type IA, type IB, type 2, and type 3 respectively. This classification, however, is not very helpful clinically because the severity of clinical manifestations does not correlate with or correspond specifically to any single type. An affected infant with type 1A defect can have clinical manifestations ranging from relatively mild to very severe. A more useful classification, based on clinical findings and response to thiamine administration, has identified 5 phenotypes of MSUD as follows:

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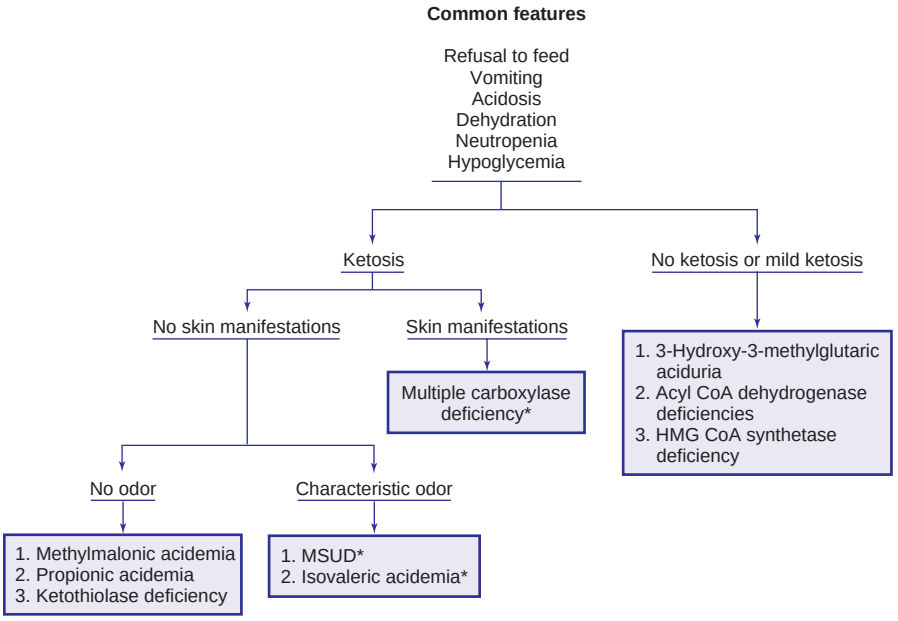

Figure 85-6 Clinical approach to infants with organic acidemia. *Asterisks* indicate disorders in which patients have a characteristic odor (see text and Table 85-2). MSUD, maple syrup urine disease.

Classic Maple Syrup Urine Disease

This form has the most severe clinical manifestations. Affected infants who are normal at birth develop poor feeding and vomiting in the 1st wk of life; lethargy and coma may ensue within a few days. Physical examination reveals hypertonicity and muscular rigidity with severe opisthotonos. Periods of hypertonicity may alternate with bouts of flaccidity manifested as repetitive movements of the extremities (boxing and bicycling). Neurologic findings are often mistakenly thought to be caused by generalized sepsis and meningitis. Cerebral edema may be present; convulsions occur in most infants, and hypoglycemia is common. In contrast to most hypoglycemic states, correction of the blood glucose concentration does not improve the clinical condition. Aside from the serum glucose, routine laboratory findings are usually unremarkable, except for varying degrees of metabolic acidosis. Death usually occurs in untreated patients in the first few weeks or months of life.

Diagnosis is often suspected because of the peculiar odor of maple syrup found in urine, sweat, and cerumen (see Fig. 85-6). It is usually confirmed by amino acid analysis showing marked elevations in plasma levels of leucine, isoleucine, valine, and alloisoleucine (a stereoisomer of isoleucine not normally found in blood) and depression of alanine. Leucine levels are usually higher than those of the other 3 amino acids. Urine contains high levels of leucine, isoleucine, and valine and their respective ketoacids. These ketoacids may be detected qualitatively by adding a few drops of 2,4-dinitrophenylhydrazine reagent (0.1% in 0.1N HCl) to the urine; a yellow precipitate of 2,4-dinitrophenylhydrazone, is formed in a positive test. Neuroimaging during the acute state may show cerebral edema, which is most prominent in the cerebellum, dorsal brainstem, cerebral peduncle, and internal capsule. After recovery from the acute state and with advancing age, hypomyelination and cerebral atrophy may be seen in neuroimaging of the brain. The enzyme activity can be measured in leukocytes and cultured fibroblasts.

Treatment of the acute state is aimed at hydration and rapid removal of the branched-chain amino acids and their metabolites from the tissues and body fluids. Because renal clearance of these compounds is poor, hydration alone may not produce a rapid improvement. Peritoneal dialysis or, preferably, hemodialysis is the most effective mode of therapy in critically ill infants and should be instituted promptly; significant decreases in plasma levels of leucine, isoleucine, and valine are usually seen within 24 hr of institution of treatment. Sufficient calories and nutrients should be provided intravenously or orally as soon as possible so as to reverse the patient's catabolic state. Cerebral edema, if present, may need to be treated with mannitol, diuretics (e.g., furosemide), or hypertonic saline.

Treatment after recovery from the acute state requires a diet low in branched-chain amino acids. Synthetic formulas devoid of leucine, isoleucine, and valine are available commercially. Because these amino acids cannot be synthesized endogenously, small amounts of them should be added to the diet; the amount should be titrated carefully by performing frequent analyses of the plasma amino acids. A clinical condition resembling **acrodermatitis enteropathica** (see Chapter 671) occurs in affected infants whose plasma isoleucine concentration becomes very low; addition of isoleucine to the diet causes a rapid and complete recovery. Patients with MSUD should remain on the diet for the rest of their lives. Liver transplantation has been performed in a number of patients with classic MSUD with promising results. These children have been able to tolerate a normal diet.

The long-term prognosis of affected children remains guarded. Severe ketoacidosis, cerebral edema, and death may occur during any stressful situation such as infection or surgery, especially in mid-childhood. Cognitive and other neurologic deficits are common sequelae.

Intermediate (Mild) Maple Syrup Urine Disease

In this form, affected children develop milder disease after the neonatal period. **Clinical manifestations** are insidious and limited to the CNS. Patients have mild to moderate intellectual disability (usually after 5 mo of age) with or without seizures. They have the odor of maple syrup and excrete moderate amounts of the branched-chain amino acids and their ketoacid derivatives in the urine. Plasma concentrations of leucine, isoleucine, and valine are moderately increased whereas those of lactate and pyruvate are normal. These children are commonly diagnosed during an intercurrent illness when signs and symptoms of classic MSUD may occur. The dehydrogenase activity is 3-40% of normal. Because patients with thiamine-responsive MSUD usually have manifestations similar to those seen in the mild form, a trial of thiamine therapy is recommended. Diet therapy, similar to that of classic MSUD, is needed.

Intermittent Maple Syrup Urine Disease

In this form of MSUD, seemingly normal children develop vomiting, odor of maple syrup, ataxia, lethargy, and coma during any stress or catabolic state such as infection or surgery. During these attacks, laboratory findings are indistinguishable from those of the classic form, and death may occur. **Treatment** of the acute attack of intermittent

MSUD is similar to that of the classic form. After recovery, although a normal diet is tolerated, a diet low in branched-chain amino acids is recommended. Activity of the dehydrogenase in patients with the intermittent form is higher than in the classic form and may reach 40% of the normal activity.

Thiamine-Responsive Maple Syrup Urine Disease

Some children with mild or intermediate forms of MSUD who are treated with high doses of thiamine have dramatic clinical and biochemical improvement. Although some respond to treatment with thiamine at 10 mg/24 hr, others may require as much as 200 mg/24 hr for at least 3 wk before a favorable response is observed. These patients also require diets deficient in branched-chain amino acids. The enzymatic activity in these patients is 30-40% of normal.

Maple Syrup Urine Disease Caused by a Deficiency of E_3 Subunit (Maple Syrup Urine Disease Type 3)

This is a very rare disorder. Patients develop lactic acidosis in addition to signs and symptoms similar to those of intermediate MSUD because the E_3 subunit is also a component of pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. Progressive neurologic impairment manifested by hypotonia and developmental delay occurs after 2 mo of age. Abnormal movements progress to ataxia. Death may occur in early childhood.

Laboratory findings include persistent lactic acidosis with high levels of plasma lactate, pyruvate, and alanine. Plasma concentrations of branched-chain amino acids are moderately increased. Patients excrete large amounts of lactate, pyruvate, α-glutarate, and the 3 branched-chain ketoacids in their urine.

No effective **treatment** is available. Dietary restrictions of branched-chain amino acids and treatment with high doses of thiamine, biotin, and lipoic acid have been ineffective.

Genetics and Prevalence of Maple Syrup Urine Disease

All forms of MSUD are inherited as an autosomal recessive trait. The gene for each subunit resides on different chromosomes. The gene for $E_{1\alpha}$ (*BCKDHA*) is on chromosome 19q13.1-q13.2; that for $E_{1\beta}$ (*BCKDHB*) is on chromosome 6q14.1; the gene for E_2 (*DBT*) is on chromosome 1p21.2; and that for E_3 (*DLD*) is on chromosome 7q31.1. Many different disease-causing mutations (>160) have been identified in patients with different forms of MSUD. A given clinical phenotype is caused by a variety of genotypes; as an example, patients from different pedigrees with the classic form of MSUD have been shown to have mutations in genes for $E_{1\alpha}$, $E_{1\beta}$, or E_2 subunits. The exception is the thiamine-responsive MSUD that is shown to be caused by mutations in the E_2 gene in all reported cases to date. Most patients are compound heterozygotes inheriting 2 different mutant alleles. Mutations in genes for $E_{1\alpha}$ (45%) and $E_{1\beta}$ (35%) account for approximately 80% of cases.

The prevalence is estimated at 1 in 185,000 live births. The classic form of MSUD is more prevalent in the Old Order Mennonites in the United States, with estimated prevalence of 1 in 380 live births. Affected patients in this population are homozygous for a specific mutation (c.1312T>A) in the $E_{1\alpha}$ subunit gene.

Early detection of MSUD is feasible by mass screening of newborn infants. In most cases (especially those with classic form of MSUD), however, the infant may be quite sick by the time the results of the screening becomes available (see Chapter 84). Prenatal diagnosis has been accomplished by enzyme assay of the cultured amniocytes, cultured chorionic villus tissue, or direct assay of samples of the chorionic villi and by identification of the mutant gene.

Several successful pregnancies have occurred in women with different forms of MSUD. No ill effects have been observed in the offspring of these patients. Episodes of metabolic decompensation have occurred in the mothers during pregnancy and the postpartum period.

ISOVALERIC ACIDEMIA

This condition is caused by the deficiency of the enzyme isovaleryl CoA dehydrogenase (see Fig. 85-4). Clinically, two forms of the condition are recognized in symptomatic patients: the acute form and the chronic intermittent form.

Clinical manifestations in the *acute form* include vomiting and severe acidosis in the first 2 wk of life. Lethargy, convulsions, and coma may ensue, and death may occur if proper therapy is not initiated. The vomiting may be severe enough to suggest pyloric stenosis. The characteristic odor of "sweaty feet" may be present (in body sweat and cerumen, but not in the urine; see Fig. 85-6). Infants who survive this acute episode will go on to have the chronic intermittent form later in life. In the *chronic intermittent form of the disease,* the first clinical manifestations (vomiting, lethargy, acidosis or coma) may not appear until the child is a few months or a few years old. In both forms, acute episodes of metabolic decompensations may occur during a catabolic state such as an infection. Acute episodes may be mistaken for diabetic ketoacidosis. With worldwide application of newborn screening technology (see Chapter 84) it is now becoming clear that the clinical spectrum in affected patients can range from completely asymptomatic to the acute form. Older siblings of symptomatic newborn infants have been reported with identical genotype and biochemical abnormalities but without any clinical manifestations.

Laboratory findings during the acute attacks include ketoacidosis, neutropenia, thrombocytopenia, and occasionally pancytopenia. Hypocalcemia, hyperglycemia, and moderate to severe hyperammonemia may be present in some patients. Increases in plasma ammonia may suggest a defect in the urea cycle (see Chapter 85.12). In urea cycle defects, the infant is not acidotic (see Fig. 85-6).

Diagnosis is established by demonstrating marked elevations of isovaleric acid and its metabolites (isovalerylglycine, 3-hydroxyisovaleric acid) in body fluids, especially urine. The main compound in plasma is isovalerylcarnitine, which can be measured even in a few drops of dried blood on a filter paper. Diagnosis can be confirmed by measurement of the enzyme activity in cultured skin fibroblasts or by the identification of the mutant gene.

Treatment of the acute attack is aimed at hydration, reversal of the catabolic state (by providing adequate calories orally or intravenously), correction of metabolic acidosis (by infusing sodium bicarbonate), and removal of the excess isovaleric acid. Because isovalerylglycine has a high urinary clearance, administration of glycine (250 mg/kg/24 hr) is recommended to enhance formation of isovalerylglycine. L-Carnitine (100 mg/kg/24 hr orally) also increases removal of isovaleric acid by forming isovalerylcarnitine, which is excreted in the urine. In patients with significant hyperammonemia (blood ammonia >200 μM), measures that reduce blood ammonia should be employed (see Chapter 85.12). Exchange transfusion and peritoneal dialysis may be needed if the previously described measures fail to induce significant clinical and biochemical improvement. After recovery from the acute attack, the patient should receive a low-protein diet (1.0-1.5 g/kg/24 hr) and should be given glycine and carnitine supplements. Pancreatitis (acute or recurrent forms) has been reported in survivors. Normal development can be achieved with early and proper treatment.

Prenatal diagnosis may be accomplished by measuring isovalerylglycine in amniotic fluid, by enzyme assay in cultured amniocytes, or by identification of the mutant gene. Successful pregnancy with favorable outcomes both for the mother and the infant has been reported. Mass screening of newborn infants for detection of this condition is in use in the United States and other countries (see Chapter 84). Isovaleric acidemia is inherited as an autosomal recessive trait. The gene (*IVD*) has been mapped to chromosome 15q15.1 and many disease-causing mutations have been identified. The prevalence of the condition is estimated from 1 in 62,500 (in parts of Germany) to 1 in 250,000 live births (in the United States).

MULTIPLE CARBOXYLASE DEFICIENCIES (DEFECTS IN UTILIZATION OF BIOTIN)

Biotin is a water-soluble vitamin that is a cofactor for all 4 carboxylase enzymes in humans: pyruvate carboxylase, acetyl CoA carboxylase,

propionyl CoA carboxylase, and 3-methylcrotonyl CoA carboxylase. The latter 2 are involved in the metabolic pathways of leucine, isoleucine, and valine (see Fig. 85-4).

Dietary biotin is bound to proteins; free biotin is generated in the intestine by the action of digestive enzymes, by intestinal bacteria, and perhaps by biotinidase. The latter enzyme, which is found in serum and most tissues in the body, is also essential for the recycling of biotin in the body by releasing it from the apoenzymes (carboxylases; see Fig. 85-4). Free biotin must form a covalent peptide bond with the apoprotein of the 4 carboxylases to form the activated enzyme (holocarboxylase). This binding is catalyzed by holocarboxylase synthetase. Deficiencies in this enzyme activity or in biotinidase result in malfunction of all the carboxylases and in organic acidemia.

Holocarboxylase Synthetase Deficiency (Multiple Carboxylase Deficiency Neonatal or Early Form)

Infants with this rare autosomal recessive disorder become symptomatic in the first few weeks of life. Symptoms may appear as early as a few hours after birth to 21 mo of age. **Clinically,** the affected infants who seem normal at birth develop breathing difficulties (tachypnea and apnea) shortly after birth. Feeding problems, vomiting, and hypotonia are also commonly present. If the condition remains untreated, generalized erythematous rash with exfoliation and alopecia (partial or total), failure to thrive, irritability, seizures, lethargy, and even coma may occur. Developmental delay is common. Immune deficiency manifests with susceptibility to infection. The urine may have a peculiar odor, which has been described as similar to tomcat urine. The rash, when present, differentiates this condition from other organic acidemias (see Fig. 85-6).

Laboratory findings include metabolic acidosis, ketosis, hyperammonemia, and the presence of a variety of organic acids (lactic acid, propionic acid, 3-methylcrotonic acid, 3-methylcrotonylglycine, tiglylglycine, methylcitrate, and 3-hydroxyisovaleric acid) in body fluids. Diagnosis is confirmed by the enzyme assay in lymphocytes or cultured fibroblasts or by identification of the mutant gene. Most mutations cause the enzyme to have an increased K_m (Michaelis-Menten dissociation constant) for biotin; the enzyme activity in such patients can be restored by the administration of large doses of biotin.

Treatment with biotin (10 mg/day orally) usually results in an improvement in clinical manifestations and may normalize the biochemical abnormalities. Early diagnosis and treatment are critical to prevent irreversible neurologic damage. In some patients, however, complete resolution may not be achieved even with large doses (up to 80 mg/day) of biotin.

The gene for holocarboxylase synthetase (*HLCS*) is located on chromosome 21q22.1 and many disease-causing mutations have been identified in different families. Prenatal diagnosis has been accomplished by assaying enzyme activity in cultured amniotic cells and by measurement of intermediate metabolites (3-hydroxyisovalerate and methylcitrate) in amniotic fluid or by DNA analysis. Pregnant mothers who had previous offspring with holocarboxylase synthetase deficiency have been treated with biotin late in pregnancy. Affected infants were normal at birth, but the efficacy of the treatment as related to the outcome remains unclear.

Biotinidase Deficiency (Multiple Carboxylase Deficiency—Juvenile or Late Form)

The absence of biotinidase results in biotin deficiency. Infants with this deficiency may develop **clinical manifestations** similar to those seen in infants with holocarboxylase synthetase deficiency but, unlike the latter, symptoms may appear later when the child is several months or years old; symptoms may develop as early as 1 wk of age. Therefore, the term "late form" does not apply to all cases and can be misleading. The delay is presumably because of the presence of sufficient free biotin derived from the mother or the diet. Clinical manifestations are mostly confined to skin and the nervous system. Atopic or seborrheic dermatitis, candidiasis, alopecia, ataxia, seizures (usually myoclonic type), hypotonia, developmental delay, optic atrophy, sensorineural hearing loss, and immunodeficiency (from T-cell abnormalities) may occur. A small number of children with intractable seborrheic dermatitis and partial (15-30% activity) deficiency of the enzyme, in whom the dermatitis resolved with biotin therapy, have been reported; these children were otherwise asymptomatic. Asymptomatic children and adults with this enzyme deficiency have been identified in screening programs. Most of these individuals have been shown to have partial deficiency of the enzyme activity. With the advent of mass screening of newborn infants and early identification and treatment of the affected patients, the clinical disease is predicted to become extinct.

Laboratory findings and the pattern of organic acids in body fluids resemble those associated with holocarboxylase synthetase deficiency (see above). Diagnosis can be established by measurement of the enzyme activity in the serum or by the identification of the mutant gene.

Treatment with free biotin (5-20 mg/24 hr) results in a dramatic clinical and biochemical response. Treatment with biotin is also suggested for individuals with partial biotinidase deficiency.

The prevalence of this autosomal recessive trait is estimated at 1 in 60,000 live births. The gene for biotinidase (*BTD*) is located on chromosome 3p25.1 and many disease-causing mutations (approximately 150) have been identified in different families. Prenatal diagnosis is possible by the measurement of the enzyme activity in the amniotic cells or by identification of the mutant gene.

Multiple Carboxylase Deficiency Because of Dietary Biotin Deficiency

Acquired deficiency of biotin may occur in infants receiving total parenteral nutrition without added biotin, in patients receiving prolonged anticonvulsant drugs (phenytoin, primidone, carbamazepine) or in children with short bowel syndrome or chronic diarrhea who are receiving formulas low in biotin. Excessive ingestion of raw eggs may also cause biotin deficiency because the protein avidin in egg white binds biotin and makes it unavailable for absorption. Infants with biotin deficiency may develop dermatitis, alopecia, and candidal skin infections.

ISOLATED 3-METHYLCROTONYL COENZYME A (CoA) CARBOXYLASE DEFICIENCY

This enzyme is 1 of 4 carboxylase enzymes in the body that require biotin as a cofactor (see Fig. 85-4). An isolated deficiency of this enzyme must be differentiated from disorders of biotin metabolism (multiple carboxylase deficiency), which causes diminished activity of all 4 carboxylases (see above). 3-Methylcrotonyl CoA carboxylase is a heteromeric enzyme consisting of α (biotin containing) and β subunits.

Clinical manifestations are highly variable, ranging from fatal neonatal onset (seizures, hypotonia, acidosis) to completely asymptomatic adults (including mothers of affected newborn infants). In the severe form of the condition, the affected infant who has been seemingly normal develops an acute episode of vomiting, hypotonia, lethargy, and convulsions after a minor infection. The onset is usually between 3 wk and 3 yr of age. Death may occur during the acute episode.

Laboratory findings during acute episodes include mild to moderate acidosis, ketosis, severe hypoglycemia, hyperammonemia, and elevated serum levels of liver transaminases. Large amounts of 3-hydroxyisovaleric acid and 3-methylcrotonylglycine are found in the urine. Urinary excretion of 3-methylcrotonic acid is not usually increased in this condition because the accumulated 3-methylcrotonyl CoA is converted to 3-hydroxyisovaleric acid. Severe secondary carnitine deficiency is common. The condition should be differentiated biochemically from multiple carboxylase deficiency (see above) in which lactic acid and metabolites of propionic acid are present in body fluids in addition to 3-hydroxyisovaleric acid. Diagnosis may be confirmed by measurement of the enzyme activity in cultured fibroblasts or by DNA analysis. Documentation of normal activities of other carboxylases is necessary for definitive diagnosis.

Treatment of acute episodes is similar to that of isovaleric acidemia (see above). Hydration and measures to correct metabolic acidosis and hypoglycemia (by infusing sodium bicarbonate and glucose) should be instituted promptly. Administration of L-carnitine and glycine is also recommended. These patients are unresponsive to biotin therapy. Patients who, in earlier reports, were found to be biotin-responsive were most probably suffering from multiple carboxylase deficiency as a result of biotinidase deficiency (see above). Long-term treatment includes a diet restricted in leucine in conjunction with the oral administration of L-carnitine (75-100 mg/kg/24 hr) and the prevention of catabolic states. Normal growth and development are expected in these patients.

The condition is inherited as an autosomal recessive trait. The gene for α subunit (*MCC1*) is located on chromosome 3q27.1 and that for the β subunit (*MCC2*) is mapped to chromosome 5q13.2. Mutation in either of these genes may result in the deficiency of the enzyme activity. Similar phenotype may be caused by different genotype. Several disease-causing mutations in either gene have been identified in different families. Newborn screening programs using tandem mass spectrometry have identified an unexpectedly high number of infants with 3-methylcrotonyl CoA carboxylase deficiency (1 : 50,000). Only a small number (<10%) of the affected infants become symptomatic; none of the symptoms reported so far could be clearly attributed to the degree of enzyme deficiency. These findings have questioned the advisability of including this condition in the routine newborn screening programs because the psychologic and financial burdens may outweigh the potential benefits.

3-METHYLGLUTACONIC ACIDURIA

Six inherited conditions are known to be associated with excessive excretion of 3-methylglutaconic acid in the urine. Deficiency of the enzyme 3-methylglutaconyl CoA hydratase (see Fig. 85-4) has been documented in only 1 condition (type I). In the other 5 conditions, the enzyme activity is normal despite a modest 3-methylglutaconic aciduria. The reason for increased urinary excretion of 3-methyglutaconic acid in these conditions is not completely understood; although these conditions are caused by mutations in different genes, the gene products are all critical for normal mitochondrial function. Only 3-methyglutaconic acidurias—types I, II, and III—are discussed here because the clinical pictures of types IV and V (dilated cardiomyopathy with ataxia) are not well delineated.

3-Methylglutaconic Aciduria Type I (3-Methylglutaconyl Coenzyme A Hydratase Deficiency)

See Figure 85-4.

Two main clinical forms of the condition have been described. In the childhood form, nonspecific neurodevelopmental findings such as speech delay or regression, choreoathetoid movements, optic atrophy, and mild psychomotor delay may be present. Metabolic acidosis may occur during a catabolic state. In the adulthood form, affected individuals remain asymptomatic until the 2nd or 3rd decades of life, when a clinical picture of slowly progressing leukoencephalopathy with optic atrophy, dysarthria, ataxia, spasticity, and dementia occurs. MRI of brain typically shows white matter abnormalities that may precede appearance of clinical symptoms by years. Asymptomatic affected children and adults have also been reported. Patients excrete large amounts of 3-methylglutaconic acid and moderate amounts of 3-hydroxyisovaleric and 3-methylglutaric acids in urine. Deficiency of 3-methylglutaconyl CoA hydratase has been shown in cultured fibroblasts and lymphoblasts. **Treatment** with a low leucine diet seems to be indicated even in asymptomatic affected individuals. Beneficial effects of this therapy on the clinical course of the disease remain to be determined. Administration of L-carnitine has resulted in clinical improvement in 1 patient. The condition is inherited as an autosomal recessive trait; the gene for the hydratase enzyme (*AUH*) is mapped to chromosome 9q22.3.

3-Methylglutaconic Aciduria Type II (X-Linked Cardiomyopathy, Neutropenia, Growth Retardation, and 3-Methylglutaconic Aciduria with Normal 3-Methylglutaconyl Coenzyme A Hydratase, Barth Syndrome)

This X-linked mitochondrial condition is caused by deficiency of tafazzin, a mitochondrial protein (enzyme), encoded by *TAZ* gene. This enzyme is necessary for processing of immature cardiolipin into the mature form (cardiolipin remodeling). Cardiolipin, a mitochondrial phospholipid, is critical for the integrity of inner mitochondrial membrane. **Clinical manifestations** of this condition, which usually occur in the first year of life in a male infant, include dilated cardiomyopathy (manifested as respiratory distress and heart failure), hypotonia, growth retardation, hypoglycemia, and moderate to severe cyclic neutropenia. The onset of clinical manifestations may be as late as 49 yr of age, but most affected individuals become symptomatic by adolescence. If patients survive infancy, relative improvement may occur with advancing age. Cognitive development is usually normal despite delayed motor function.

Laboratory findings include mild to moderate increases in urinary excretion of 3-methylglutaconic, 3-methylglutaric, and 2-ethylhydracrylic acids. Unlike 3-methylglutaconic aciduria type I, urinary excretion of 3-hydroxyisovaleric acid is not elevated. The activity of the enzyme 3-methylglutaconyl CoA hydratase is normal. Cyclic neutropenia is a common finding. Lactic acidosis, hypoglycemia, low serum cholesterol concentration and abnormal mitochondrial ultrastructure have been shown in some patients. Total cardiolipin and subclasses of cardiolipin are very low in skin fibroblast cultures from these patients. This finding may be useful for establishing the diagnosis.

The condition is inherited as an X-linked recessive trait. The gene (*TAZ*) has been mapped to chromosome Xq28 and several disease-causing mutations have been identified. The modest 3-methylglutaconic aciduria seen in this condition is thought to be related to the defect in mitochondrial membrane causing the leakage of this organic acid. No effective treatment is available. Older surviving patients may benefit from cardiac transplantation. There are reasons to believe that the condition is perhaps more common than realized; most affected patients remain undiagnosed or misdiagnosed as having viral cardiomyopathy.

3-Methylglutaconic Aciduria Type III (Costeff Optic Atrophy Syndrome)

Clinical manifestations in these patients include early onset optic atrophy and later development of choreoathetoid movements, spasticity, ataxia, dysarthria, and mild developmental delay. All reported patients except 1 were Iraqi Jews living in Israel. These patients excrete moderate amounts of 3-methylglutaconic and 3-methylglutaric acids. Activity of the enzyme 3-methylglutaconyl CoA hydratase is normal. The reason for the increased excretion of these organic acids remains unclear. The condition is inherited as an autosomal recessive trait. The gene for this condition (*OPA3*) is mapped to chromosome 19q13.2-q13.3. Mutation of this gene is believed to cause mitochondrial dysfunction. No effective treatment is available.

β-KETOTHIOLASE (3-OXOTHIOLASE) DEFICIENCY (MITOCHONDRIAL ACETOACETYL COENZYME A THIOLASE [T_2] DEFICIENCY)

This reversible mitochondrial enzyme is involved in final steps of catabolism of isoleucine and also in oxidation of fatty acids. It cleaves 2-methylacetoacetyl CoA to propionyl-CoA plus acetyl-CoA in isoleucine catabolic pathway (see Fig. 85-4). In the fatty acid oxidation pathway, the enzyme generates 2 moles of acetyl-CoA from 1 mole of acetoacetyl-CoA (Fig. 85-7). The same enzyme synthesizes 2-methyacetoacetate-CoA and acetoacetyl-CoA in the reverse direction (Fig. 85-7).

Clinical manifestations are quite variable, ranging from an asymptomatic course in an adult to severe episodes of acidosis starting in the

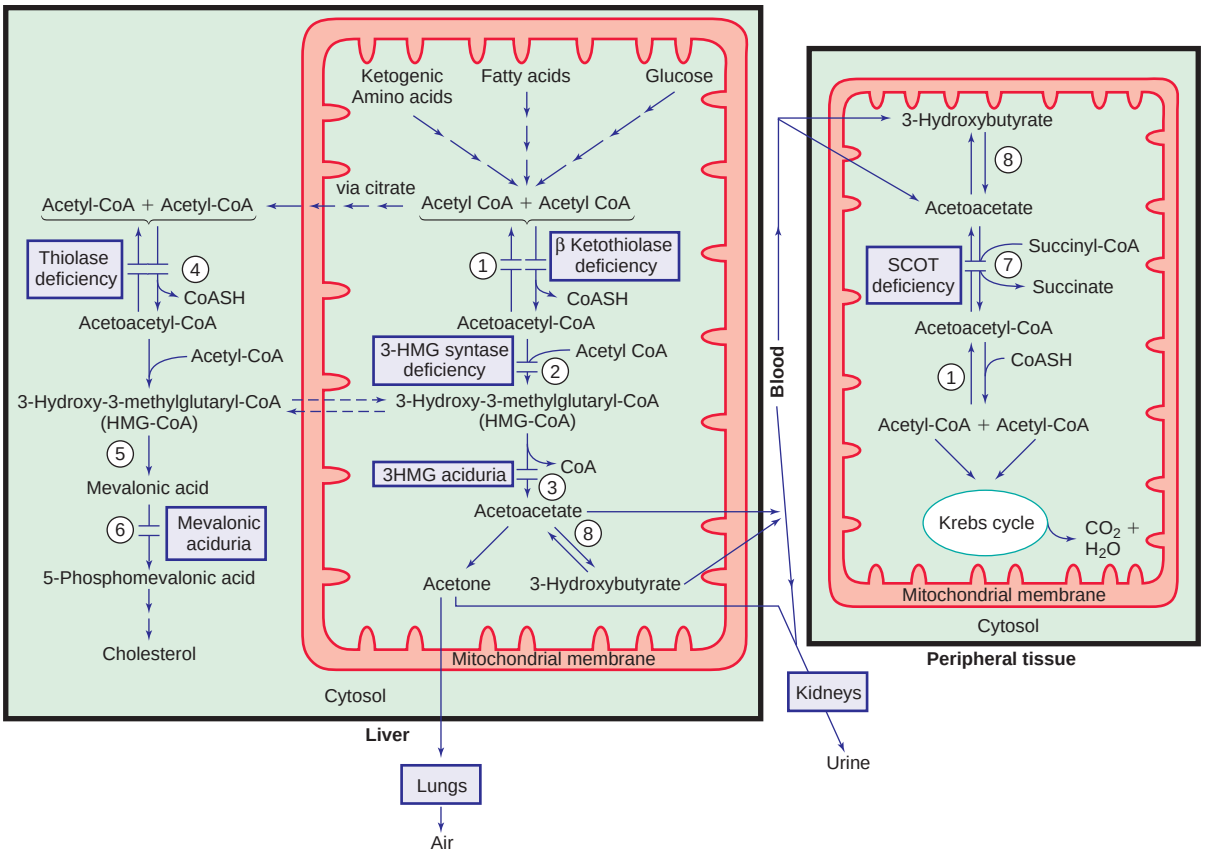

Figure 85-7 Formation (liver) and metabolism (peripheral tissues) of ketone bodies and cholesterol synthesis. **Enzymes:** *(1)* Mitochondrial acetoacetyl CoA thiolase, *(2)* HMG-CoA synthase, *(3)* HMG-CoA lyase, *(4)* cytosolic acetoacetyl CoA thiolase, *(5)* HMG-CoA reductase, *(6)* mevalonic kinase, *(7)* succinyl CoA:3-ketoacid CoA transferase (SCOT), *(8)* 3-hydroxybutyrate dehydrogenase.

1st yr of life. Typically, these children have intermittent episodes of unexplained ketosis and acidosis. These episodes usually occur after an intercurrent infection and respond quickly to intravenous fluids and bicarbonate therapy. Mild to moderate hyperammonemia may also be present during attacks. Both hypoglycemia and hyperglycemia have been reported in isolated cases. The child may be completely asymptomatic between episodes and may tolerate a normal protein diet well. Cognitive development is normal in most children. The episodes may be misdiagnosed as salicylate poisoning because of the similarity of the clinical findings and the interference of elevated blood levels of acetoacetate with the colorimetric assay for salicylate.

Laboratory findings during the acute attack include acidosis, ketosis, and hyperammonemia. The urine contains large amounts of 2-methylacetoacetate and its decarboxylated products butanone, 2-methyl-3-hydroxybutyrate, and tiglylglycine. Lower concentrations of these urinary metabolites persist during the seemingly well periods. Mass screening of newborn infants may yield false-negative results in affected infants who are well at the time of blood sampling. Mild hyperglycinemia may also be present. The clinical and biochemical findings should be differentiated from those seen with propionic and methylmalonic acidemias (see later). Diagnosis may be established by assay of the enzyme in leukocytes or cultured fibroblasts, or identification of the mutant gene.

Treatment of acute episodes includes hydration and infusion of bicarbonate to correct the acidosis; a 10% glucose solution with the appropriate electrolytes and intravenous lipids may be used to minimize the catabolic state. Restriction of protein intake (1-2 g/kg/24 hr) is recommended for long-term therapy. Oral L-carnitine (50-100 mg/kg/24 hr) is also recommended to prevent possible secondary carnitine deficiency. Long-term prognosis for achieving normal life seems very favorable. Three reported patients graduated from high school and 1 has attended college. All patients continued to have abnormal metabolites in body fluids. Successful pregnancy with normal outcomes for both mother and infant has been reported.

The pathogenesis of ketosis in this condition is not adequately explained because, in this enzyme deficiency, one expects impaired ketone formation (see Fig. 85-7). It is postulated that excess acetoacetyl CoA produced from other sources is used as a substrate for 3-hydroxy-3-methylglutaryl (HMG) CoA synthesis in the liver.

This condition is inherited as an autosomal recessive trait and may be more prevalent than has been appreciated. It is most prevalent in Tunisia. The gene (*ACAT1*) for this enzyme (T_2) is located on chromosome 11q22.3.

CYTOSOLIC ACETOACETYL COENZYME A THIOLASE DEFICIENCY

This enzyme catalyzes the cytosolic production of acetoacetyl CoA from 2 moles of acetyl CoA (see Fig. 85-7). Cytosolic acetoacetyl CoA is the precursor of hepatic cholesterol synthesis. Cytosolic acetoacetyl CoA thiolase is a completely different enzyme from mitochondrial thiolase (see above and Fig. 85-4). Clinical manifestations in patients with this very rare enzyme deficiency are similar to those in patients with mevalonic acidemia (see below). Severe progressive developmental delay, hypotonia, and choreoathetoid movements develop in the first few months of life. Laboratory findings are nonspecific; elevated levels of lactate, pyruvate, acetoacetate, and 3-hydroxybutyrate may be found in blood and urine. One patient had normal levels of acetoacetate and 3-hydroxybutyrate. Diagnosis can be established by demonstrating a deficiency in cytosolic thiolase activity in liver biopsy or in cultured fibroblasts or by DNA analysis. No effective treatment is available. The gene (*ACAT2*) for this condition is mapped to chromosome 6q25.3.

MITOCHONDRIAL 3-HYDROXY-3-METHYLGLUTARYL COENZYME A SYNTHASE DEFICIENCY

This enzyme catalyzes synthesis of 3-hydroxy-3-methylglutaryl (HMG)-CoA from acetoacetyl CoA in the mitochondria. This is a critical step in ketone body synthesis in the liver (see Fig. 85-7). A few patients with deficiency of this enzyme have been reported. All patients have had similar presentations and outcomes. Signs and symptoms of acute hypoglycemia have occurred after an acute illness (gastroenteritis). Age at presentation has ranged from 18 mo to 6 yr. All children were asymptomatic before the episodes and remained normal after the recovery (except for mild hepatomegaly with fatty infiltration). None of the patients has had a second episode, perhaps as a result of preventive measures to avoid prolonged fasting during ensuing intercurrent illnesses. Hepatomegaly was a consistent physical finding in all patients. Laboratory findings included hypoglycemia, acidosis with mild or no ketosis, elevation of liver function tests, and massive dicarboxylic aciduria. The clinical and laboratory findings may be confused with those of patients with defects in fatty acid metabolism (see Chapter 86.1). In contrast to the latter, blood concentrations of acylcarnitine conjugates are normal in patients with HMG-CoA synthase deficiency. Fasting of these patients has produced the abovementioned clinical and biochemical abnormalities.

Treatment consisted of provision of adequate calories and avoidance of prolonged periods of fasting. No dietary protein restriction was needed.

The condition is inherited as an autosomal recessive trait. The gene (*HMGCS2*) for this enzyme is located on chromosome 1p13-p12 and several disease-causing mutations have been identified. The condition should be considered in any child with fasting hypoglycemia and is perhaps more common than appreciated.

3-HYDROXY-3-METHYLGLUTARIC ACIDURIA

This condition is a result of a deficiency of HMG-CoA lyase (see Fig. 85-4). This enzyme catalyzes the conversion of HMG-CoA to acetoacetate and is a rate-limiting enzyme for ketogenesis (see Fig. 85-7). **Clinically,** more than 60% of patients become symptomatic between 3 and 11 mo of age (infantile form), whereas approximately 30% develop symptoms in the first few days of life (neonatal form). One child remained asymptomatic until 15 yr of age (childhood form). Episodes of vomiting, severe hypoglycemia, hypotonia, acidosis with mild or no ketosis, and dehydration may rapidly lead to lethargy, ataxia, and coma. These episodes often occur during a catabolic state such as fasting or an intercurrent infection. Hepatomegaly is common. These manifestations may be mistaken for Reye syndrome or medium-chain acyl-CoA dehydrogenase deficiency. Patients are usually clinically asymptomatic between the attacks; 1 patient died of acute cardiomyopathy at age 7 mo during a febrile illness. Development is usually normal, but intellectual disability and seizures with abnormalities of white matter (shown by MRI) have been observed in patients with prolonged episodes of hypoglycemia.

Laboratory findings include hypoglycemia, moderate to severe hyperammonemia, and acidosis. There is mild or no ketosis (see Fig. 85-7). Urinary excretion of 3-hydroxy-3-methylglutaric acid and other proximal intermediate metabolites of leucine catabolism (3-methylglutaconic acid and 3-hydroxyisovaleric acid) is markedly increased causing the urine to smell like cat urine. These organic acids are excreted in the urine as carnitine conjugates, resulting in secondary carnitine deficiency. Glutaric and adipic acids may also be increased in urine during acute attacks. **Diagnosis** may be confirmed by enzyme assay in cultured fibroblasts, leukocytes, or liver specimens or by identification of the mutant gene. Prenatal diagnosis is possible by the assay of the enzyme in cultured amniocytes or a chorionic villus biopsy or by DNA analysis.

Treatment of acute episodes includes hydration, infusion of glucose to control hypoglycemia, provision of adequate calories, and administration of bicarbonate to correct acidosis. Hyperammonemia should be treated promptly (see Chapter 85.12). Exchange transfusion and peritoneal dialysis may be required in patients with severe hyperammonemia. Restriction of protein and fat intake is recommended for long-term management. Oral administration of L-carnitine (50-100 mg/kg/24 hr) prevents secondary carnitine deficiency. Prolonged fasting should be avoided. One child died after routine immunization. The condition is inherited as an autosomal recessive trait. The gene (*HNGCL*) for HMG-CoA lyase resides on chromosome 1p36.11 and several disease-causing mutations have been identified in different families. The gene defect appears to be more common in the Arabic population, especially in Saudi Arabia.

SUCCINYL COENZYME A:3-KETOACID COENZYME A TRANSFERASE (SCOT) DEFICIENCY

This enzyme is necessary for the metabolism of ketone bodies (acetoacetate and 3-hydroxybutyrate) in peripheral tissues (see Fig. 85-7). A deficiency of this enzyme results in the underutilization and accumulation of ketone bodies and ketoacidosis. Only a few patients with succinyl coenzyme A:3-ketoacid coenzyme A transferase deficiency have been reported to date; the condition may not be rare because many cases are, perhaps, undiagnosed.

The **presentation** is an acute episode of unexplained severe ketoacidosis in an infant who had been growing and developing normally. About half of the patients become symptomatic in the 1st wk of life, and all become symptomatic before 2 yr of age. The acute episode is often precipitated by an intercurrent infection or a catabolic state. Death may occur during these episodes. A chronic subclinical ketosis usually persists between the attacks. Development is usually normal.

Laboratory findings during the acute episode are nonspecific and include metabolic acidosis and ketonuria with high levels of acetoacetate and 3-hydroxybutyrate in blood and urine. No other organic acids are found in the blood or in the urine. Blood glucose levels are usually normal, but hypoglycemia has been reported in 2 affected newborn infants with severe ketoacidosis. Plasma amino acids are usually normal. **Diagnosis** can be established by demonstrating a deficiency of enzyme activity in cultured fibroblasts or by DNA analysis.

Treatment of acute episodes consists of hydration, correction of acidosis, and the provision of a diet adequate in calories. Long-term treatment with a high-carbohydrate diet and avoidance of catabolic states is recommended. *This condition should be considered in any infant with unexplained bouts of ketoacidosis.* The condition is inherited as an autosomal recessive trait. The gene (*OXCT1*) for this enzyme is located on chromosome 5p13, and several disease-causing mutations have been found in different families.

MEVALONIC ACIDURIA

Mevalonic acid, an intermediate metabolite of cholesterol synthesis, is converted to 5-phosphomevalonic acid by the action of the enzyme mevalonate kinase (MVK) (see Fig. 85-7). Based on clinical manifestations and degree of enzyme deficiency, 2 forms of this condition have been recognized.

Mevalonic Aciduria, Severe Form

Clinical manifestations include intellectual disability, failure to thrive, growth retardation, hypotonia, ataxia, hepatosplenomegaly, cataracts, and facial dysmorphism (dolichocephaly, frontal bossing, low-set ears, downward slanting of the eyes, and long eyelashes). Recurrent crises, characterized by fever, vomiting, diarrhea, arthralgia, edema, lymphadenopathy, further enlargement of liver and spleen, and morbilliform rash have been observed in all patients. These episodes last 4-5 days and recur up to 25 times/yr. Death may occur during these crises.

Laboratory findings include marked elevation of mevalonic acid in urine; the concentration may be as high as 56,000 μmole/mole of creatinine (normal: <0.3). Plasma levels of mevalonic acid are also greatly increased (as high as 54 μmole/dL; normal: <0.004). This is the only abnormal organic acid found in these patients. The level of mevalonic acid tends to correlate with the severity of the condition and increases during crises. Serum cholesterol concentration is normal or mildly decreased. Serum concentration of creatine kinase is markedly increased. Sedimentation rate and serum leukotriene-4 are increased

during the crises. Serial examination of the brain by MRI reveals progressive atrophy of the cerebellum.

Diagnosis may be confirmed by assay of MVK activity in lymphocytes or in cultured fibroblasts or by DNA analysis. The enzyme activity in this form of the condition is below the detection level. No effective therapy is available. **Treatment** with high doses of prednisone (2 mg/kg/24 hr) causes improvement of the acute crises. The condition is inherited as an autosomal recessive trait. Prenatal diagnosis is possible by measurement of mevalonic acid in the amniotic fluid, by assay of the enzyme activity in cultured amniocytes or chorionic villus samples or by demonstration of the mutant gene. The gene (*MVK*) for the enzyme is on chromosome 12q24.

Periodic Fever with Hyperimmunoglobulinemia D (Mevalonic Aciduria, Mild Form)

See Chapter 163.

Some mutations of mevalonic kinase gene *(MVK)* cause mild deficiencies of the enzyme and produce the clinical picture of periodic fever with hyperimmunoglobulinemia D. These patients have periodic bouts of fever associated with abdominal pain, vomiting, diarrhea, arthralgia, arthritis, hepatosplenomegaly, lymphadenopathy, and morbilliform rash (even petechiae and purpura), which usually start before 1 yr of age. The attacks can be produced by vaccination, minor trauma, or stress; usually occur every 1-2 mo; and last 2-7 days. Patients are free of symptoms between acute attacks. The diagnostic laboratory finding is elevation of serum immunoglobulin D (IgD); IgA is also elevated in 80% of patients. During acute attacks, leukocytosis, increased C-reactive protein, and mild mevalonic aciduria may be present. High concentrations of serum IgD differentiate this condition from familial Mediterranean fever.

Treatment

See Chapter 163.

PROPIONIC ACIDEMIA (PROPIONYL COENZYME A CARBOXYLASE DEFICIENCY)

Propionic acid is an intermediate metabolite of isoleucine, valine, threonine, methionine, odd-chain fatty acids, and cholesterol catabolism. It is normally carboxylated to methylmalonic acid by the mitochondrial enzyme propionyl CoA carboxylase, which requires biotin as a cofactor (see Fig. 85-4). The enzyme is composed of 2 nonidentical subunits, α and β. Biotin is bound to the α subunit.

Clinical findings are nonspecific. In the severe form of the condition, patients develop symptoms in the first few days or weeks of life. Poor feeding, vomiting, hypotonia, lethargy, dehydration, and clinical signs of severe ketoacidosis progress rapidly to coma and death. Seizures occur in approximately 30% of affected infants. If an infant survives the first attack, similar episodes may occur during an intercurrent infection or constipation or after ingestion of a high-protein diet. Moderate to severe intellectual disability and neurologic manifestations reflective of extrapyramidal (dystonia, choreoathetosis, tremor), and pyramidal (paraplegia) dysfunction are common sequelae in the older survivors. Neuroimaging shows these abnormalities, which usually occur after an episode of metabolic decompensation, to be a result of damage to the basal ganglia, especially to the globus pallidus. This phenomenon has been referred to in the literature as **metabolic stroke**. This is the main cause of neurologic sequelae seen in the surviving affected children.

In the milder forms, the older infant may have intellectual disability without acute attacks of ketosis. Some affected children may have episodes of unexplained severe ketoacidosis separated by periods of seemingly normal health. Mass screening of newborn infants has identified milder forms of the condition; a few of these infants were completely asymptomatic at diagnosis. The severity of clinical manifestations may also be variable within a family; in 1 kindred, a brother was diagnosed at 5 yr of age whereas his 13 yr old sister, with the same level of enzyme deficiency, was asymptomatic.

Laboratory findings during the acute attack include severe metabolic acidosis with a large anion gap, ketosis, neutropenia, thrombocytopenia, and hypoglycemia. Moderate to severe hyperammonemia is common; plasma ammonia concentrations usually correlate with the severity of the disease. In contrast to other causes of hyperammonemia, plasma concentration of glutamine is within normal limits or even decreased. Presence of severe metabolic acidosis differentiates propionic academia from hyperammonemic states caused by urea cycle defects. Measurement of plasma ammonia is especially helpful in planning therapeutic strategy during episodes of exacerbation in a patient whose diagnosis has been established. Pathogenesis of hyperammonemia is not well understood. Glycine concentration is elevated in all body fluids (blood, urine, and spinal fluid) in almost all patients. This is the result of inhibition of glycine cleavage enzyme (Fig. 85-8) in the liver. Glycine elevation has also been observed in patients with methylmalonic acidemia. These disorders were collectively referred to as *ketotic hyperglycinemia* in the past before the specific enzyme deficiencies were elucidated. A decrease in plasma levels of branched-chain amino acids (leucine, isoleucine, valine) is a common finding. Mild to moderate increase in blood concentrations of lactate and lysine may also be present in these patients. Concentrations of propionic acid and methylcitric acid (presumably made by the condensation of propionyl CoA with oxaloacetic acid) are markedly elevated in the plasma and urine of infants with propionic acidemia. 3-Hydroxypropionic acid, propionylglycine, and other intermediate metabolites of isoleucine catabolism, such as tiglic acid, tiglylglycine, and 2-methyloacetoacetic acid, are also found in urine. Moderate elevations in blood levels of ammonia, glycine, and previously mentioned organic acids usually persist between the acute attacks. CT scan and MRI of the brain may reveal cerebral atrophy, demyelination, and abnormalities in the globus pallidus and basal ganglia as the evidence of a metabolic stroke in this condition (see above).

The **diagnosis** of propionic acidemia should be differentiated from multiple carboxylase deficiencies (see above and Fig. 85-6). Infants with the latter condition may have skin manifestations and excrete large amounts of lactic acid, 3-methylcrotonic acid, and 3-hydroxyisovaleric acid in addition to propionic acid. The presence of hyperammonemia may suggest a genetic defect in the urea cycle enzymes. Infants with defects in the urea cycle are usually not acidotic (see Fig. 85-1) and have elevated levels of plasma glutamine. Definitive diagnosis of propionic acidemia can be established by measuring the enzyme activity in leukocytes or cultured fibroblasts or by DNA analysis.

Treatment of acute attacks includes hydration, correction of acidosis, and amelioration of the catabolic state by provision of adequate calories through parenteral hyperalimentation. Minimal amounts of protein (0.25 g/kg/24 hr), preferably as a protein deficient in propionate precursors, should be provided in the hyperalimentation fluid very early in the course of treatment. To curtail the possible production of propionic acid by intestinal bacteria, sterilization of the intestinal tract flora by antibiotics (oral neomycin, or metronidazole) should be promptly initiated. Constipation should also be treated. Patients with propionic acidemia may develop carnitine deficiency, presumably as a result of urinary loss of propionylcarnitine formed from the accumulated organic acid. Administration of L-carnitine (50-100 mg/kg/24 hr orally or 10 mg/kg/24 hr intravenously) normalizes fatty acid oxidation and improves acidosis. In patients with concomitant hyperammonemia, measures to reduce blood ammonia should be employed (see Chapter 85.12). Very ill patients with severe acidosis and hyperammonemia require peritoneal dialysis or hemodialysis to remove ammonia and other toxic compounds rapidly and efficiently. Although no infant with true propionic acidemia has been found to be responsive to biotin, this compound should be administered (10 mg/24 hr orally) to all infants during the first attack and until the diagnosis is established.

Long-term treatment consists of a low-protein diet (1.0-1.5 g/kg/24 hr) and administration of L-carnitine (50-100 mg/kg/24 hr orally). Synthetic proteins deficient in propionate precursors (isoleucine, valine, methionine, and threonine) may be used to increase the amount of dietary protein (to 1.5-2.0 g/kg/24 hr) while causing minimal change in propionate production. Excessive supplementation with these proteins may cause a deficiency of the essential amino acids,

especially isoleucine (which may cause a condition resembling acrodermatitis enteropathica; see see Chapter 671). To avoid this problem, natural proteins should comprise most of the dietary protein (50-75%). Some patients may require chronic alkaline therapy to correct chronic acidosis. The concentration of ammonia in the blood usually normalizes between attacks, and chronic treatment of hyperammonemia is not usually needed. Catabolic states that may trigger acute attacks (infections, constipation) should be treated promptly and aggressively. Close monitoring of blood pH, amino acids, urinary content of propionate and its metabolites, and growth parameters is necessary to ensure the proper balance of the diet and the success of therapy.

Long-term prognosis is guarded. Death may occur during an acute attack. Normal psychomotor development is possible, especially in the mild forms identified through screening programs; most children identified clinically manifest some degree of permanent neurodevelopmental deficit such as tremor, dystonia, chorea, and pyramidal signs despite adequate therapy. These neurologic findings may be sequelae of a metabolic stroke occurring during an acute decompensation (see above). Cardiomyopathy with potential progression to heart failure and death may develop in older affected children despite adequate metabolic control. Acute pancreatitis has also been reported in these patients.

Prenatal diagnosis is achieved by measuring the enzyme activity in cultured amniotic cells or in samples of uncultured chorionic villi, by measurement of methylcitrate in amniotic fluid, or by identification of the mutant gene.

The condition is inherited as an autosomal recessive trait and can be identified by mass screening of newborns with a worldwide prevalence of 1:50,000 to 1:100,000 live births. It is more prevalent in Saudi Arabia (1:2,000 to 1:5,000 live births). The gene for the α subunit (*PCCA*) is located on chromosome 13q32 and that of the β subunit (*PCCB*) is mapped to the chromosome 3q21-q22. Mutations in either gene can cause the condition. Many mutations in either gene have been identified in different patients. Pregnancy with normal outcome has been reported in affected females.

METHYLMALONIC ACIDEMIA

Methylmalonic acid, a structural isomer of succinic acid, is usually derived from propionic acid as part of the catabolic pathways of isoleucine, valine, threonine, methionine, cholesterol, and odd-chain fatty acids. Two enzymes are involved in the conversion of D-methylmalonic acid to succinic acid: methylmalonyl CoA racemase, which forms the L isomer; and methylmalonyl CoA mutase, which converts the L-methylmalonic acid to succinic acid (see Fig. 85-4). The latter enzyme requires adenosylcobalamin, a metabolite of vitamin B_{12}, as a coenzyme. Deficiency of either the mutase or its coenzyme causes the accumulation of methylmalonic acid and its precursors in body fluids. A deficiency of the racemase can be associated with mild elevations of methylmalonic acid, but the clinical consequence of racemase deficiency is not known.

At least 2 forms of mutase apoenzyme deficiencies have been identified. These are designated mut^0, meaning no detectable enzyme activity, and mut^-, indicating residual, although abnormal, mutase activity. The majority of reported patients with methylmalonic acidemia have a deficiency of the mutase apoenzyme (mut^0 or mut^-). These patients are not responsive to vitamin B_{12} therapy. In the remaining patients with methylmalonic acidemia, the defect resides in the formation of adenosylcobalamin.

Defects in Metabolism of Vitamin B_{12} (Cobalamin)

Dietary vitamin B_{12} requires intrinsic factor, a glycoprotein secreted by the gastric parietal cells, for absorption in the terminal ileum. It is transported in the blood by haptocorrin and transcobalamin. The transcobalamin–cobalamin complex (TC-Cbl) is recognized by a specific receptor on the cell membrane and enters the cell by endocytosis. TC-Cbl is hydrolyzed in the lysosome, and free cobalamin is released into the cytosol (see Fig. 85-4). In the cytoplasm, cobalamin binds to the MMACHC protein (see *cbl*C later), which reduces the cobalt of the molecule from 3 valences (cob[III]alamin) to 2 (cob[II]alamin) before it enters the mitochondria, where it reacts with adenosine triphosphate and an unknown reductase to form adenosylcobalamin (coenzyme for methylmalonyl CoA mutase). Alternatively, partially reduced cobalamin in the cytosol may interact with methionine synthase and methionine synthase reductase to form methylcobalamin (coenzyme for methionine synthase; see Fig. 85-3). The MMADHC protein (see *cbl*D) appears to play a role in determining whether cobalamin enters the mitochondria or remains in the cytoplasm.

Uptake of TC-Cbl by cells is impaired in individuals with mutations affecting transcobalamin receptor which is located on the cell surface. Individuals homozygous for mutations at the *CD320* gene, which encodes the transcobalamin receptor, have elevations of serum methylmalonic acid, which can be detected by newborn screening using tandem mass spectroscopy, but it is not clear whether there is a clinical phenotype associated with this disorder.

Nine different defects in the intracellular metabolism of cobalamin have been identified. These are designated *cbl*A through *cbl*G, *cbl*J, and *cbl*X (*cbl* stands for a defect in any step of cobalamin metabolism). The *cbl*A, *cbl*B, and *cbl*D variant 2 defects cause methylmalonic acidemia alone. In patients with *cbl*C, classic *cbl*D, *cbl*F, *cbl*J, and *cbl*X defects, synthesis of both adenosylcobalamin and methylcobalamin is impaired, causing homocystinuria in addition to methylmalonic acidemia. The *cbl*D variant 1, *cbl*E, and the *cbl*G defects affect only the synthesis of methylcobalamin, resulting in homocystinuria without methylmalonic aciduria, but usually with megaloblastic anemia (see Chapter 85.3).

Clinical manifestations of patients with methylmalonic acidemia caused by mut^0, mut^-, *cbl*A, *cbl*B, and *cblD* variant 2 are similar. There are wide variations in clinical presentation, ranging from very sick newborn infants to asymptomatic adults, regardless of the nature of the enzymatic defect or the biochemical abnormalities. In severe forms, lethargy, feeding problems, vomiting, tachypnea (from acidosis), and hypotonia may develop in the first few days of life and may progress to coma and death if untreated. Infants who survive the first attack may go on to develop similar acute metabolic episodes during a catabolic state (such as infection) or after ingestion of a high-protein diet. Between the acute attacks, the patient commonly continues to exhibit hypotonia and feeding problems with failure to thrive. In milder forms, patients may present later in life with hypotonia, failure to thrive, and developmental delay. Asymptomatic patients with typical biochemical abnormalities of methylmalonic acidemia are also reported. It is important to note that mental development and IQ of patients with methylmalonic acidemia may remain within the normal range despite repeated acute attacks and regardless of the nature of the enzyme deficiency. In a study of patients with different forms of the condition, developmental delay was noted in 47%. One adolescent girl with a mut^- deficiency had an IQ of 129.

The episodic nature of the condition and its biochemical abnormalities may be confused with those of ethylene glycol (antifreeze) ingestion. The peak of propionate in a blood sample from an infant with methylmalonic acidemia has been mistaken for ethylene glycol when the sample was assayed by gas chromatography without mass spectrometry.

Laboratory findings include ketosis, acidosis, anemia, neutropenia, thrombocytopenia, hyperglycinemia, hyperammonemia, hypoglycemia, and the presence of large quantities of methylmalonic acid in body fluids (see Fig. 85-6). Propionic acid and its metabolites 3-hydroxypropionate and methylcitrate are also found in the urine. Hyperammonemia may suggest the presence of genetic defects in the urea cycle enzymes; patients with defects in urea cycle enzymes are not acidotic (see Fig. 85-12). The reason for hyperammonemia is not well understood.

Diagnosis can be confirmed by measuring propionate incorporation and performing complementation analysis in cultured fibroblasts, by measuring the specific activity of the mutase enzyme in biopsies or cell extracts or by identifying the mutations in the causal gene.

Treatment of acute attacks is similar to that of attacks in patients with propionic acidemia (see above), except that large doses (1 mg/24 hr) of vitamin B_{12} are used instead of biotin. Long-term treatment consists of administration of a low-protein diet (1.0-1.5 g/

kg/24 hr), L-carnitine (50-100 mg/kg/24 hr orally), and vitamin B_{12} (1 mg/24 hr for patients with defects in vitamin B_{12} metabolism; the dose can be decreased depending on the clinical response). The protein composition of the diet is similar to that prescribed for patients with propionic acidemia. Chronic alkaline therapy is usually required to correct chronic acidosis, especially during infancy and early childhood. Blood levels of ammonia usually normalize between the attacks, and chronic treatment of hyperammonemia is rarely needed. Stressful situations that may trigger acute attacks (such as infection) should be treated promptly.

Inadequate oral intake secondary to poor appetite is a common and bothersome complication in long-term management of these patients. Consequently, enteral feeding (through a nasogastric tube or gastrostomy) should be considered early in the course of the treatment. Close monitoring of blood pH, amino acid levels, blood and urinary concentrations of methylmalonate, and growth parameters is necessary to ensure proper balance in the diet and the success of therapy. Glutathione deficiency, responsive to high doses of ascorbate, has been described. Liver, kidney, and combined liver and kidney transplantations have been attempted in a small number of affected patients. Liver transplantation reduced but did not eliminate the metabolic abnormalities and did not prevent the occurrence of metabolic stroke. Kidney transplantation alone restored the renal function but caused only minor improvement in the methylmalonic acidemia.

Prognosis depends on the severity of symptoms and the occurrence of complications (see below). In general, patients with complete deficiency of mutase apoenzyme (mut^0) have the least-favorable prognosis and those with mut^- and *cbl*A defects have a better outcome than those with *cbl*B.

Complications have been noted in survivors. Metabolic strokes (see above) have been reported in a few patients during an acute episode of metabolic decompensation. These patients have survived with major extrapyramidal (tremor, dystonia) and pyramidal (paraplegia) sequelae.

Chronic renal failure necessitating renal transplant has been reported in a number of older patients with the condition. This complication has been observed in all genetic forms of the condition. **Tubulointerstitial nephritis** has been documented in some of these patients and is thought to be the major cause of renal failure. The pathogenesis remains unclear.

Acute and recurrent pancreatitis has been reported in affected patients as young as 13 mo of age. This complication may account for a fair number of hospitalizations of these children.

The prevalence of all forms of methylmalonic aciduria is estimated to be in the range of 1 in 48,000 live births. All defects causing isolated methylmalonic acidemia are inherited as autosomal recessive traits. Successful mass screening of newborn infants has been achieved by the tandem mass spectrometry method. The gene for the mutase (*MUT*) is on the short arm of chromosome 6p12.3; over 220 different mutations have been identified in the *MUT* gene, including a number of ethnic-specific mutations. Neonates with methylmalonic acidemia and severe diabetes owing to the absence of β cells, who have paternal uniparental isodisomy of chromosome 6, have been reported. Mutations in the genes for *cbl*A (*MMAA,* on chromosome 4q31-q31.2), *cbl*B (*MMAB,* on chromosome 12q24), and all forms of *cbl*D (*MMADHC,* on chromosome 2q23.2) have been identified in affected patients. The previously described *cbl*H group is identical to *cbl*D variant 2.

Successful pregnancy with normal outcomes for both the mother and the baby has been reported.

COMBINED METHYLMALONIC ACIDURIA AND HOMOCYSTINURIA (*cblC*, *cblD*, *cblF*, *cblJ*, AND *cblX* DEFECTS)

More than 550 patients with methylmalonic acidemia and homocystinuria because of *cbl*C have been reported. Indeed, with the advent of expanded newborn screening, it has become evident that *cbl*C may be as common as mutase deficiency. The other disorders are much rarer: 17 patients with *cbl*D, 15 with *cbl*F, 3 with *cblJ*, and 12 with *cbl*X have been identified to date (see Figs. 85-3 and 85-4). Neurologic findings are prominent in patients with *cbl*C and *cbl*D defects. Most patients with the *cbl*C defect present in the first year of life because of failure to thrive, lethargy, poor feeding, intellectual disability, and seizures. Intrauterine growth restriction and microcephaly may precede postnatal manifestations in some affected infants. Late-onset patients with sudden development of dementia and myelopathy have been reported, even with presentation in adulthood. Megaloblastic anemia is a common finding in patients with *cbl*C defect. Mild to moderate increases in concentrations of methylmalonic acid and homocysteine are found in body fluids. Unlike patients with classic homocystinuria, plasma levels of methionine are low to normal in these defects. Neither hyperammonemia nor hyperglycinemia are found in these patients. Like *cblC* patients, males with *cbl*X have elevations of both homocysteine and methylmalonic acid, but tend to have milder elevations of these metabolites. Clinically, patients with *cbl*X resemble those with *cbl*C but have more severe neurologic findings.

The **clinical findings** in the *cbl*F defect are quite variable; the first 2 patients had poor feeding, growth and developmental delay, and persistent stomatitis manifesting in the 1st 3 wk of life. One patient was not diagnosed until age 10 yr and had findings suggestive of rheumatoid arthritis, a pigmented skin abnormality, and encephalopathy. Vitamin B_{12} malabsorption has been noted in patients with *cbl*F defect. Clinical manifestations of *cblJ* are identical to those of *cbl*F.

Experience with **treatment** of patients with *cbl*C, *cbl*D, *cbl*F, *cblJ* and *cbl*X defects is limited. Large doses of hydroxycobalamin (1-2 mg/24 hr) in conjunction with betaine (6-9 g/24 hr) seem to produce biochemical improvement with variable clinical effect. Unexplained severe hemolytic anemia, hemolytic uremic syndrome, hydrocephalus, and congestive heart failure have been major complications in patients with *cbl*C defect.

The *cbl*C disorder is caused by mutations in the *MMACHC* gene located on chromosome 1p34.1. Approximately 75 different mutations have been identified, including a number of common mutations, and ones that are more common in specific ethnic groups. The *cbl*D disorder is caused by mutations in the *MMADHC* gene on chromosome 2q23.2. Mutations resulting in *cbl*D variant 1 (causing only homocystinuria) affect the C-terminal domain of the gene product; those resulting in *cbl*D variant 2 (causing only methylmalonic aciduria) affect the N terminus. Patients with classical form of *cbl*D, with both homocystinuria and methylmalonic, have mutations resulting in decreased protein expression. The *cbl*F disorder is caused by mutations in the *LMBRD1* gene (on chromosome 6q13) encoding a lysosomal membrane protein. The *cblJ* disorder is a phenocopy of *cbl*F and is associated with mutations in the *ABCD4* gene (on chromosome 14q24.3), encoding an adenosine triphosphate–binding cassette protein localized to the lysosomal membrane. Mutations in either *LMBRD1* or *ABCD4* genes result in failure of release of cobalamin from lysosomes. The *cbl*X disorder is caused by mutations in the *HCFC1* gene on the X chromosome, which encodes a DNA-binding protein that appears to be required for expression of the *MMACHC* gene.

Patients with *cbl*D variant 1, *cbl*E, and *cbl*G defects do not have methylmalonic acidemia (see Chapter 85.3).

Bibliography is available at Expert Consult.

85.7 Glycine

Iraj Rezvani

Glycine is a nonessential amino acid synthesized mainly from serine and threonine. Structurally, it is the simplest amino acid. It is involved in many reactions in the body, especially in the nervous system where it functions as a neurotransmitter (excitatory in the cortex, inhibitory in the brainstem and the spinal cord; see Chapter 85.11). Its main catabolic pathway requires the complex glycine cleavage enzyme to cleave the first carbon of glycine and convert it to carbon dioxide (see Fig. 85-8). The glycine cleavage protein, a mitochondrial multienzyme, is composed of 4 proteins: P protein (glycine decarboxylase), H protein, T protein, and L protein, which are encoded by 4 different genes.

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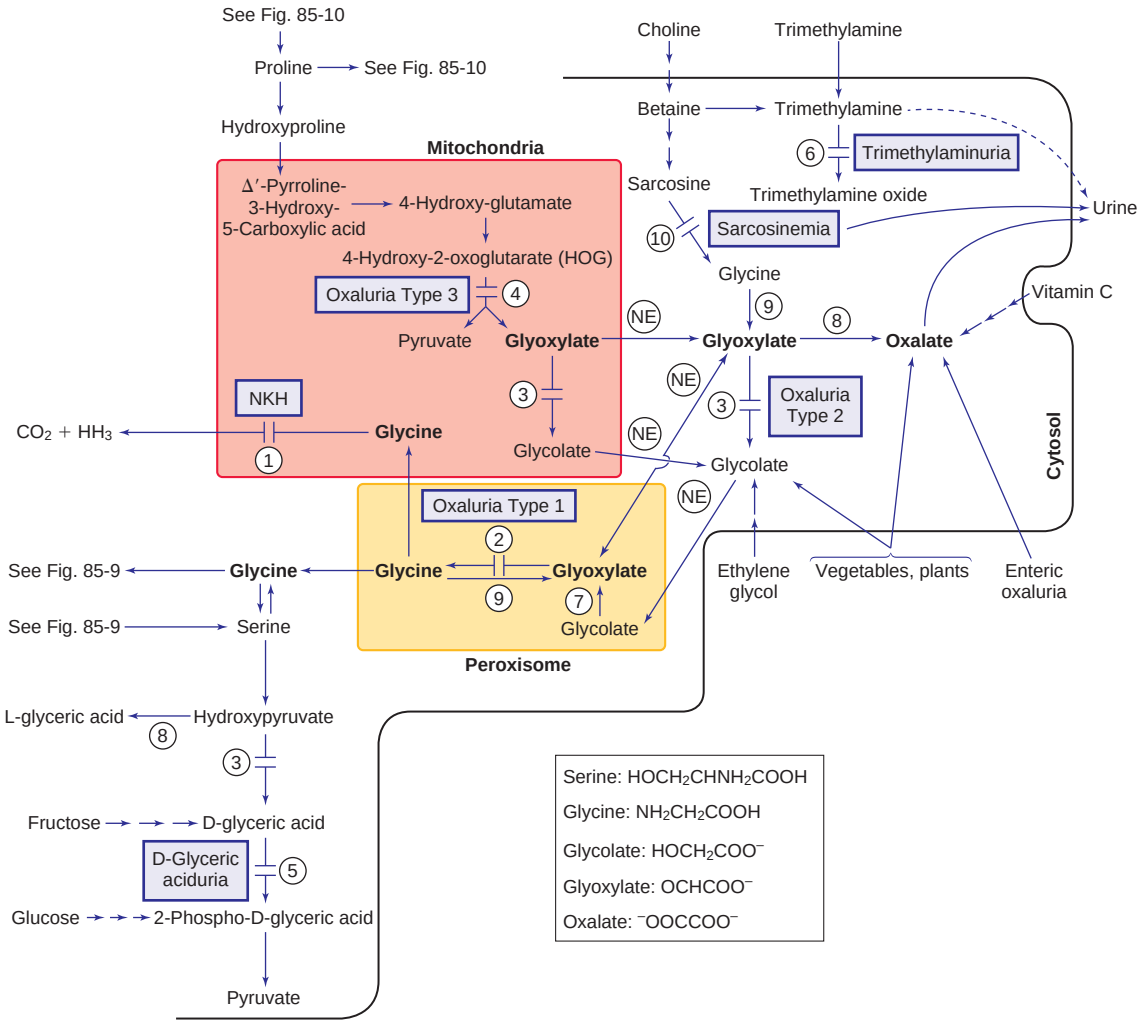

Figure 85-8 Pathways in the metabolism of glycine and glyoxylic acid. FH_4, tetrahydrofolate; (NE), nonenzymatic; NKH, nonketotic hyperglycinemia. **Enzymes:** *(1)* Glycine cleavage enzyme, *(2)* alanine: glyoxylate aminotransferase, *(3)* Glyoxylic reductase/hydroxypyruvate reductase (GR/HRP), *(4)* hydroxyoxoglutarate aldolase (HOGA), *(5)* glycerate kinase, *(6)* trimethylamine oxidase, *(7)* glycolate oxidase (D-amino acid oxidase), *(8)* lactate dehydrogenase, *(9)* glycine oxidase, *(10)* sarcosine dehydrogenase.

HYPOGLYCINEMIA

Defects in the biosynthetic pathway of serine (see Chapter 85.8) cause deficiency of glycine in addition to that of serine in body fluids, especially in the CSF. Isolated primary deficiency of glycine has not been reported.

HYPERGLYCINEMIA

Elevated levels of glycine in body fluids occur in propionic acidemia and methylmalonic acidemia that are collectively referred to as ketotic hyperglycinemia because of coexistence of acidosis and ketosis. The pathogenesis of hyperglycinemia in these disorders is not fully understood, but inhibition of the glycine cleavage enzyme system by the various organic acids has been shown to occur in some of the patients. The term **nonketotic hyperglycinemia** (NKH) is reserved for the clinical condition caused by the genetic deficiency of the glycine cleavage enzyme system (see Fig. 85-8). In this condition, hyperglycinemia is present without ketosis.

NONKETOTIC HYPERGLYCINEMIA, GLYCINE ENCEPHALOPATHY

Four forms of this condition have been identified: neonatal, infantile, late onset, and transient.

Neonatal Hyperglycemia

This is the most common form of NKH. **Clinical manifestations** develop in the first few days of life (between 6 hr and 8 days after birth). Poor feeding, failure to suck, lethargy, and profound hypotonia may progress rapidly to a deep coma, apnea, and death. Convulsions, especially myoclonic seizures and hiccups, are common.

Laboratory findings reveal moderate to severe hyperglycinemia (as high as 8 times normal) and hyperglycinuria. The unequivocal elevation of glycine concentration in the spinal fluid (15-30 times normal) and the high ratio of glycine concentration in spinal fluid to that in plasma (a value >0.08) are diagnostic of NKH. Serum pH is normal; plasma serine levels are usually low.

Approximately 30% of affected infants die despite supportive therapy. Those who survive develop profound psychomotor retardation and intractable seizure disorders (myoclonic and/or grand mal seizures). Hydrocephalus, requiring shunting, and pulmonary hypertension have been noted in some survivors.

Infantile Nonketotic Hyperglycinemia

These previously normal infants develop **signs and symptoms** of neonatal NKH (see above) after 6 mo of age. Seizures are the common presenting signs. This condition appears to be a milder form of

neonatal hyperglycinemia; infants usually survive and intellectual disability is not as profound as in the neonatal form.

Laboratory findings in these patients are identical to those seen in the neonatal form.

Late-Onset Nonketotic Hyperglycinemia, Mild Episodic Form

Progressive spastic diplegia, optic atrophy, and choreoathetotic movements are the main **clinical manifestations**. Age of onset has been between 2 and 33 yr. Symptoms of delirium, chorea, and vertical gaze palsy may occur episodically in some patients during an intercurrent infection. Mental development is usually normal, but mild cognitive impairment has been reported in some patients. Seizures have been reported in only 1 patient.

Laboratory findings are similar to but not as pronounced as in the neonatal form.

Transient Nonketotic Hyperglycinemia

Most **clinical and laboratory manifestations** of this form are indistinguishable from those of the neonatal form. By 2-8 wk of age, however, the elevated glycine levels in plasma and CSF normalize and a complete clinical recovery may occur. Most of these patients develop normally with no neurologic sequelae, but intellectual disability has been noted in some. The etiology of this condition is not known, but it is believed to be a consequence of immaturity of the enzyme system.

All forms of NKH should be differentiated from ketotic hyperglycinemia, D-glyceric aciduria (see below), and ingestion of valproic acid. The latter compound causes a moderate increase in blood and urinary concentrations of glycine. Repeat assays after discontinuation of the drug should establish the diagnosis.

Diagnosis can be established by assay of the enzyme in liver or brain specimens or by identification of the mutation. Enzyme activity in the neonatal form is close to zero, whereas in the other forms, some residual activity is present. In most patients with the neonatal form, the enzyme defect resides in the P protein; defects in the T protein account for the rest. The enzyme assay in 3 patients with the infantile and late-onset forms has revealed 2 patients with a defect in the T protein and 1 with a defect in the H protein.

No effective **treatment** is known. Exchange transfusion, dietary restriction of glycine, and administration of sodium benzoate or folate have not altered the neurologic outcome. Drugs that counteract the effect of glycine on neuronal cells, such as strychnine, diazepam, and dextromethorphan, have shown some beneficial effects only in patients with the mild forms of the condition.

NKH is inherited as an autosomal recessive trait. The prevalence is not known, but high frequency of the disorder has been noted in northern Finland (1 in 12,000 live births). The newborn screening method using tandem mass spectrometry may not identify affected infants. The gene for P protein (*GLDC*) is on chromosome 9p24.1. The gene for H protein (*GCSH*) is mapped to chromosome 16q23.2 and that for T protein (*AMT*) is on chromosome 3p21.31. The L protein gene (*DLD*) is on chromosome 7q31.7. Several disease-causing mutations have been identified. Prenatal diagnosis has been accomplished by performing an assay of the enzyme activity in chorionic villous biopsy specimens or by identification of the mutant gene.

SARCOSINEMIA

Increased concentrations of sarcosine (*N*-methylglycine) are observed in both blood and urine, but no consistent clinical picture has been attributed to this metabolic defect. This is a recessively inherited metabolic condition caused by a defect in sarcosine dehydrogenase, the enzyme that converts sarcosine to glycine (see Fig. 85-8). The gene for this enzyme (*SARDH*) is on chromosome 9q34.2.

D-GLYCERIC ACIDURIA

D-Glyceric acid is an intermediate metabolite of serine and fructose metabolism. This rare condition is caused by deficiency of glycerate kinase enzyme (see Fig. 85-8). **Clinical manifestations** are highly variable. In the severe form of the condition, signs and symptoms of encephalopathy (hypotonia, seizures, and mental and motor deficits) with laboratory findings of hyperglycinemia and hyperglycinuria are suggestive of NKH. These patients have elevated levels of D-glyceric acid in all body fluids and excrete large quantities of D-glyceric acid in urine. This compound is not normally detectable in urine. Mild forms of the condition with mild speech delay or even normal development have also been reported.

No effective therapy is available. Restriction of fructose reduced the incidence of seizures in 1 patient. The gene for glycerate kinase *(GLYCTK)* is on chromosome 3p21.1.

TRIMETHYLAMINURIA

Trimethylamine is normally produced in the intestine from the breakdown of dietary choline and trimethylamine oxide by bacteria. Egg yolk and liver are the main sources of choline, and fish is the major source of trimethylamine oxide. Trimethylamine is absorbed and oxidized in the liver by trimethylamine oxidase (flavin-containing monooxygenases) to trimethylamine oxide, which is odorless and excreted in the urine (see Fig. 85-8). Deficiency of this enzyme results in massive excretion of trimethylamine in urine. There is a foul body odor that resembles that of a rotten fish, which may have significant social and psychosocial ramifications. Transient symptomatic trimethylaminuria can occur in normal individuals following ingestion of large quantities of the abovementioned foods. Restriction of fish, eggs, liver, and other sources of choline (such as nuts and grains) in the diet significantly reduces the odor. **Treatment** with short courses of oral metronidazole, neomycin, or lactulose cause temporary reduction in the body odor. The gene for trimethylamine oxidase *(FMO3)* has been mapped to chromosome 1q24.3.

HYPEROXALURIA AND OXALOSIS

Normally, oxalic acid is derived mostly from oxidation of glyoxylic acid and, to a lesser degree, from oxidation of ascorbic acid (see Fig. 85-8). Glyoxylic acid is formed from oxidation of glycolic acid and glycine in the peroxisomes, and catabolism of hydroxyproline in the mitochondria (Figs. 85-8 and 85-9). Vegetables and foods containing oxalic acid, such as spinach and rhubarb, are the main *exogenous* sources of glycolic and oxalic acids; most of glyoxylic and oxalic acids are produced endogenously. Normally, a major portion of glyoxylate produced in the body is shuttled to peroxisomes where it is converted to glycine by the action of the enzyme alanine-glyoxylate aminotransferase. Deficiency of this enzyme causes hyperoxaluria type 1. Most of the remaining glyoxylate in the cytosol is reduced to glycolate by the action of the enzyme glyoxylate reductase/hydroxypyruvate reductase. Deficiency of this enzyme causes hyperoxaluria type 2. These 2 pathways protect the body from excessive production of oxalic acid (see Fig. 85-8). Any glyoxylate that cannot be disposed of through these pathways is readily converted to oxalic acid by the action of the enzyme lactate dehydrogenase (LDH). Oxalic acid cannot be further metabolized in humans and is excreted in the urine as oxalates. Calcium oxalate is relatively insoluble in water and precipitates in tissues (kidneys and joints) if its concentration increases in the body.

Secondary hyperoxaluria has been observed in pyridoxine deficiency (cofactor for alanine-glyoxylate aminotransferase; see Fig. 85-8), in patients with inflammatory bowel disease, extensive resection of small bowel, or jejunoileal bypass *(enteric hyperoxaluria)*, after ingestion of ethylene glycol or high doses of vitamin C, and after administration of the anesthetic agent methoxyflurane (which oxidizes directly to oxalic acid). Acute, fatal hyperoxaluria may develop after ingestion of plants with high oxalic acid content such as sorrel or intentional ingestion of oxalic acid. Precipitation of calcium oxalate in tissues causes hypocalcemia, liver necrosis, renal failure, cardiac arrhythmia, and death. The lethal dose of oxalic acid is estimated to be between 5 and 30 g.

Primary hyperoxaluria is a genetic disorder in which large amounts of oxalates accumulate in the body. Three types of primary hyperoxaluria have been identified to date. The term **oxalosis** refers to deposition of calcium oxalate in parenchymal tissues.

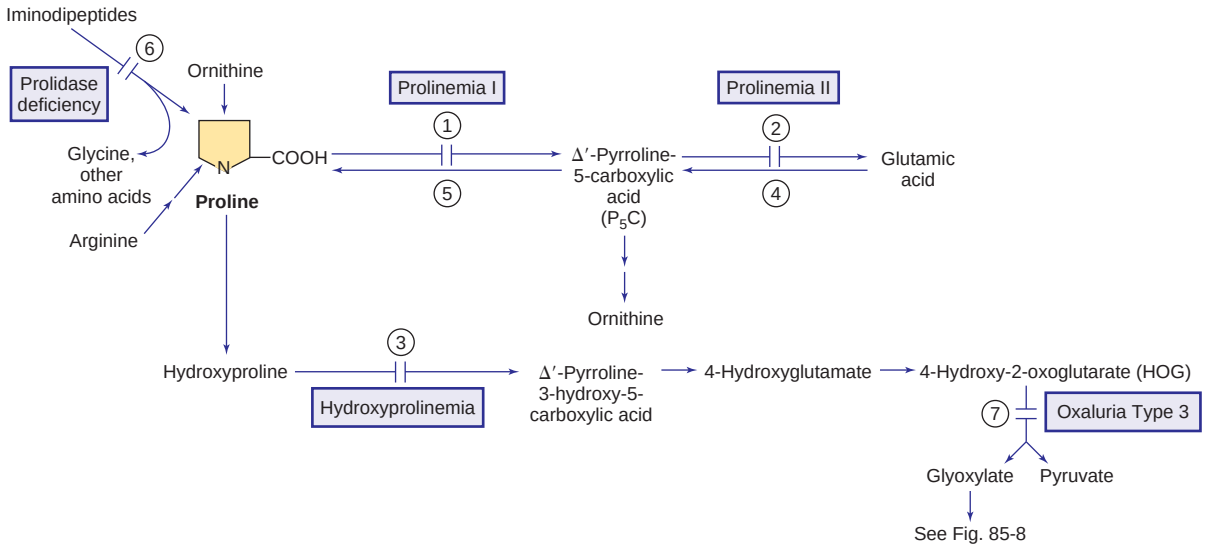

Figure 85-9 Pathways in the metabolism of proline. **Enzymes:** *(1)* Proline oxidase (dehydrogenase), *(2)* Δ^1-pyrroline-5-carboxylic acid (P5C) dehydrogenase, *(3)* hydroxyproline oxidase, *(4)* Δ^1-pyrroline-5-carboxylic acid (P5C) synthase, *(5)* Δ^1-pyrroline-5-carboxylic acid (P5C) reductase, *(6)* prolidase, *(7)* 4-hydroxyoxoglutarate aldolase (HOGA).

Primary Hyperoxaluria Type 1

This rare condition is the most common form of primary hyperoxaluria. It is caused by deficiency of the peroxisomal enzyme alanine-glyoxylate aminotransferase, which is expressed only in the liver peroxisomes and requires pyridoxine (vitamin B_6) as its cofactor. In the absence of this enzyme, glyoxylic acid, which cannot be converted to glycine, is transferred to the cytosol, where it is oxidized to oxalic acid (see above and Fig. 85-8).

There is a wide variation in the age of presentation (4 mo to 25 yr). The majority of patients become symptomatic in late childhood or early adolescence. In 19% of cases, symptoms develop before 1 yr of age (neonatal oxaluria). The initial **clinical manifestations** are related to renal stones and nephrocalcinosis. Renal colic and asymptomatic hematuria lead to a gradual deterioration of renal function, manifested by growth retardation and uremia. Most patients die before 20 yr of age from renal failure if the disorder is left untreated. Acute arthritis is a rare manifestation and may be misdiagnosed as gout because uric acid is usually elevated in patients with type 1 hyperoxaluria. Late forms of the disease presenting during adulthood have also been reported. Crystalline retinopathy and optic neuropathy causing visual loss have occurred in a few patients.

A marked increase in urinary excretion of oxalate (normal excretion 10-50 mg/24 hr) is the most important **laboratory finding**. The presence of oxalate crystals in urinary sediment is rarely helpful for diagnosis because such crystals are often seen in normal individuals. Urinary excretion of glycolic acid and glyoxylic acid is increased in most patients but not in all. **Diagnosis** can be confirmed by performing an assay of the enzyme in liver specimens or by identification of the mutant gene.

Treatment has been largely unsuccessful. In some patients (especially those whose condition is a result of mistargeting of the enzyme to the mitochondria; see below) administration of large doses of pyridoxine reduces urinary excretion of oxalate. Renal transplantation in patients with renal failure has not improved the outcome in most cases, because oxalosis has recurred in the transplanted kidney. Combined liver and kidney transplants have resulted in a significant decrease in plasma and urinary oxalate, and this may be the most effective treatment of this disorder, particularly in children.

The condition is inherited as an autosomal recessive trait. The gene for this enzyme *(AGXT)* is mapped to chromosome 2q37.3. Several mutations of the gene have been described in patients with this condition. The most common mutation results in the mistargeting of the enzyme to the mitochondria instead of the peroxisomes. The in vitro enzyme activity in these patients may reach the level found in obligate heterozygotes. In vivo function remains defective, however. Approximately 30% of patients with hyperoxaluria type 1 are estimated to have this defect.

Prenatal diagnosis has been achieved by the measurement of fetal hepatic enzyme activity obtained by needle biopsy or by DNA analysis of chorionic villous samples.

Primary Hyperoxaluria Type 2 (L-Glyceric Aciduria)

This rare condition is caused by a deficiency of D-glycerate dehydrogenase glyoxylate reductase/hydroxypyruvate reductase enzyme complex (see Fig. 85-8). A deficiency in the activity of this enzyme results in an accumulation of 2 intermediate metabolites, hydroxypyruvate (the ketoacid of serine) and glyoxylic acid. Both these compounds are further metabolized by LDH to L-glyceric acid and oxalic acid, respectively. Approximately 30% of reported patients are from the Saulteaux-Ojibway Indians of Manitoba.

These patients are indistinguishable from those with hyperoxaluria type 1. Renal stones presenting with renal colic and hematuria may develop before age 2 yr. Renal failure is less common in this condition than in hyperoxaluria type 1; the urine contains large amounts of L-glyceric acid in addition to high levels of oxalate. L-Glyceric acid is not normally present in urine. Urinary excretion of glycolic acid and glyoxylic acid is not increased. The presence of L-glyceric acid without increased levels of glycolic and glyoxylic acids in urine differentiate this type from type1 hyperoxaluria. **Diagnosis** can be confirmed by the enzyme assay in liver biopsy or by the identification of the mutant gene. The gene *(GRHPR)* is mapped to chromosome 9p13.2.

No effective **therapy** is available. As with the hyperoxaluria type 1 renal transplant does offer a cure because of recurrence of oxalosis in the transplanted kidney; no experience with kidney-liver transplantation is available at this time.

Primary Hyperoxaluria Type 3

Approximately 5% of patients with primary hyperoxaluria have neither type 1 nor type 2 hyperoxaluria. Genetic studies reveal mutations in the gene for 4-hydroxy-2-oxoglutarate aldolase enzyme. This mitochondrial enzyme catalyzes the final step in metabolic pathway of hydroxyproline generating pyruvate and glyoxylate from 4-hydroxy-2-oxoglutarate (HOG; see Figs. 85-8 and 85-9). In vitro studies show inhibition of glyoxylate reductase/hydroxypyruvate reductase enzyme activity by high concentration of HOG (the compound that

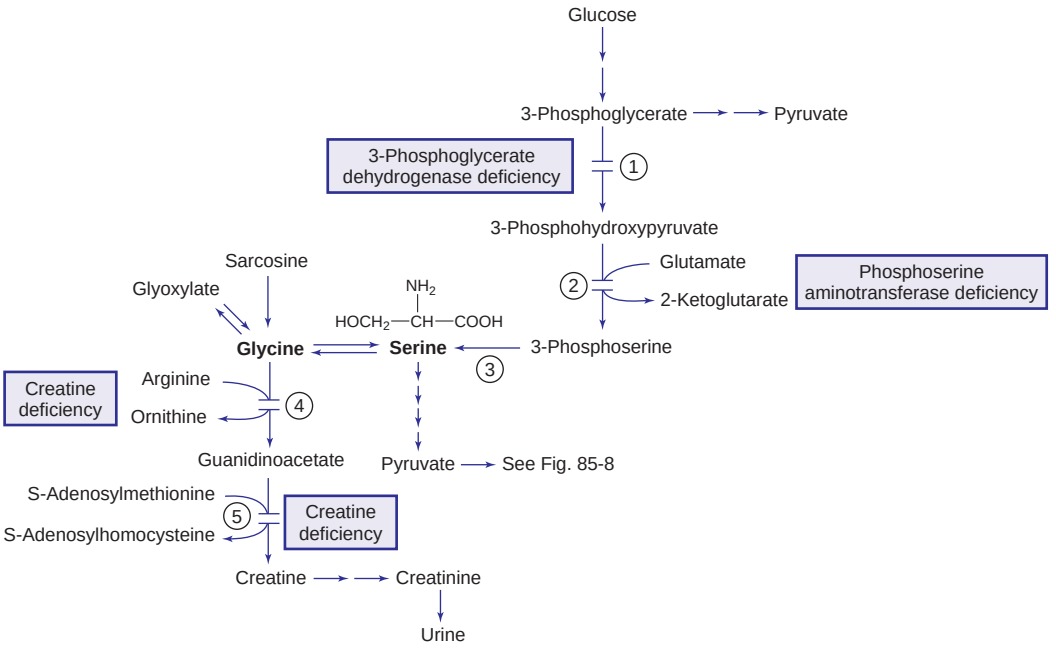

Figure 85-10 Pathways for the synthesis of serine and creatine. **Enzymes:** *(1)* 3-Phosphoglycerate dehydrogenase, *(2)* phosphoserine aminotransferase, *(3)* phosphoserine phosphatase, *(4)* arginine:glycine amidinotransferase (AGAT). *(5)* guanidinoacetate methyltransferase (GAMT).

accumulates in patients with hyperoxaluria type 3). This inhibition results in a biochemical phenotype similar to hyperoxaluria type 2 (see Fig. 85-8). It is also possible that the accumulated HOG is transferred into the cytosol and cleaved to form pyruvate and glyoxylate by the action of one of the cytosolic aldolases.

All probands in this cohort presented with calcium oxalate kidney stones in early childhood but asymptomatic older siblings were also identified. Renal function has remained normal in all patients. Increased levels of HOG have been found in urine, serum and liver biopsy samples of these patients. The gene for the enzyme *(HOGA1)* has been mapped to chromosome 10q24.2 and several different mutations have been identified in different families. The condition may be more common than type 2 hyperoxaluria.

Creatine Deficiency

Creatine is synthesized mainly in the liver, pancreas, and kidneys and to a lesser degree in the brain from arginine and glycine (Fig. 85-10) and is transported to muscles and the brain, where there is high activity of the enzyme creatine kinase. Phosphorylation and dephosphorylation of creatine in conjunction with adenosine triphosphate and diphosphate provide high-energy phosphate transfer reactions in these organs. Creatine is nonenzymatically metabolized to creatinine at a constant daily rate and is excreted in the urine. Three genetic conditions are known to cause creatine deficiency in the brain and other tissues. Two are because of deficiency of the enzymes involved in the biosynthesis of creatine. These enzymes are arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT; Fig. 85-10). Both conditions respond well to creatine supplementation. The third condition, an X-linked inherited defect, is caused by deficiency of the creatinine transporter (CRTR) protein and is not responsive to creatine administration.

Clinical manifestations of the 3 defects, which are similar, relate to the brain and muscles, and may appear in the first few weeks or months of life. Developmental delay, intellectual disability, speech delay, psychiatric symptoms (autistic behavior, hallucination), hypotonia, ataxia, and seizures are common findings. Dystonic movements are seen in severe GAMT deficiency.

Laboratory findings include decreased creatine and creatinine in blood and urine in patients with AGAT and GAMT defects. The urinary ratio of creatine to creatinine is increased in patients with a CRTR defect. Marked elevations of guanidinoacetate in blood, urine, and especially in spinal fluid (CSF), are diagnostic of GAMT defects. In contrast, low levels of guanidinoacetate are found in body fluids in the AGAT defect. Absence of creatine and creatine phosphate (in all 3 defects) and high levels of guanidinoacetate (in the GAMT defect) can be demonstrated in the brain by magnetic resonance spectroscopy (MRS). MRI of the brain shows signal hyperintensity in the globus pallidus. **Diagnosis** of AGAT or GAMT defects may be confirmed by measurement of the enzyme in the liver, cultured fibroblasts, or stimulated lymphoblasts or by the identification of the mutant gene DNA analysis of the gene. Diagnosis of CRTR is confirmed by DNA analysis or creatine uptake by fibroblasts.

Treatment with creatine monohydrate (350 mg-2 g/kg/day) orally results in a dramatic improvement in muscle tone and overall mental development and normalizes MRI and electroencephalographic findings in patients with AGAT and GAMT defects. It is believed that early treatment may assure normal development. No therapy is available for the CRTR defect; administration of creatine and its precursors (arginine and glycine) has failed to change the clinical course of the condition in affected patients. AGAT and GAMT defects are inherited as autosomal recessive traits. The gene for AGAT *(GATM)* is on chromosome 15q21.1 and that for GAMT *(GAMT)* is on chromosome 19p13.3. CRTR is an X-linked trait and the gene (*SLC6A8*) is on Xq28. CRTR defect is the most common cause of creatine deficiency, accounting for up to 1% of males with intellectual disability of unknown cause. AGAT defect is very rare (only 7 patients reported to date). Creatine deficiency must be considered in any patient with concomitant brain and muscle dysfunction, as treatment can produce a dramatic response in some cases.

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85.8 Serine

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Serine is a nonessential amino acid supplied through dietary sources and through its endogenous synthesis, mainly from glucose and glycine (see Fig. 85-10). The endogenous production of serine comprises an

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important portion of the daily requirement of this amino acid, especially in the synaptic junctions where it functions as a neurotransmitter (see Chapter 85.11). Consequently, deficiency of any of the enzymes involved in the biosynthesis of serine causes neurologic manifestations. Affected patients respond favorably to oral supplementation with serine and glycine provided that the treatment is initiated very early in life. Figure 85-8 shows the metabolic pathway for synthesis and catabolism of serine.

3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY

Deficiency of this enzyme causes deficiencies of serine and glycine in the body. Three forms of the condition have been recognized: infantile, juvenile, and adult forms. In the infantile form, which is the most common phenotype, the **clinical manifestations** appear typically in utero with microcephaly and intrauterine growth retardation. In 1 infant who was normocephalic at birth, the head failed to grow normally postnatally. Feeding problems, failure to thrive, vomiting, irritability, intractable seizures, severe developmental delay, and hypertonia progressing into spastic tetraplegia are common findings that develop shortly after birth. Nystagmus, cataracts, hypogonadism, and megaloblastic anemia have been observed in some affected infants.

Laboratory findings include low levels of serine and glycine in plasma and very low levels of serine and glycine in CSF. No abnormal organic acid metabolite is found in the urine. MRI of the brain shows cerebral atrophy with enlarged ventricles, significant attenuation of white matter and impaired myelination.

The juvenile form of the condition has been reported in 2 siblings who presented at 5 and 9 yr of age with mild intellectual disability and absence seizures. Head size and MRI of the brain were normal.

Only 1 adult patient with congenital cataracts and intellectual disability has been reported. This patient developed progressive polyneuropathy resembling Charcot-Marie-Tooth disease type 2.

Diagnosis can be confirmed by measurement of the enzyme activity in cultured fibroblasts and by DNA analysis.

Treatment with high doses of serine (500-700 mg/kg/24 hr, orally) alone or in conjunction with glycine (200-300 mg/kg/24 hr) normalizes the serine levels in the blood and CSF. This treatment produces significant improvement in all clinical findings except for the psychomotor retardation; seizure activity subsides within a few days of therapy and may be halted completely. Microcephaly improves in young affected infants. There is evidence to indicate that psychomotor retardation may be prevented if the treatment starts in the first few days of life or, even better, in utero.

The condition is inherited as an autosomal recessive trait. The gene for 3-phosphoglycerate dehydrogenase enzyme (*PHGDH*) has been mapped to chromosome 1p12 and a few disease-producing mutations have been identified in different families. Prenatal diagnosis has been achieved by DNA analysis in a family with previously affected offspring; administration of serine to the mother corrected the microcephaly in the affected fetus as evidenced by ultrasound imaging. Treatment with supplemental serine has continued postnatally; the patient remains normal neurologically at 12 yr of age. The favorable response of this condition to a simple treatment makes this diagnosis an important consideration in any child with microcephaly and neurologic defects such as psychomotor delay or a seizure disorder. Measurements of serine and glycine in the CSF are critical for diagnosis because mild decreases of these amino acids in the plasma can be easily overlooked.

PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY

This enzyme catalyzes conversion of 3-phosphohydroxypyruvate to 3-phosphoserine (see Fig. 85-10). Deficiency of this enzyme has been reported in 2 siblings from an English family. Poor feeding, cyanotic episodes, and jerky movements developed shortly after birth in the first affected infant and progressed to intractable seizures by 9 wk of age. The infant was microcephalic. Electroencephalography (EEG) was consistent with multifocal seizures. Neuroimaging showed generalized cerebral and cerebellar atrophies. **Laboratory studies** were all within normal limits except for a mild decrease in plasma levels of serine and glycine with pronounced deficiencies of these 2 amino acids in the CSF. **Treatment** with serine (500 mg/kg/day) and glycine (200 mg/kg/day) was started at 11 wk of age but resulted in only marginal clinical improvement; the child died at 7 mo of age. The younger affected sibling, who was treated with serine and glycine within a few hours after birth, remained asymptomatic at 3 yr of age.

The condition is inherited as an autosomal recessive trait and the gene for the enzyme (PSAT1) is mapped to chromosome 9q21.2. Based on this single report one can assume that this is a treatable genetic condition with a favorable outcome if the treatment is initiated early in life.

Bibliography is available at Expert Consult.

85.9 Proline

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Proline is a nonessential amino acid synthesized endogenously from glutamic acid, ornithine, and arginine (see Fig. 85-9). Proline and hydroxyproline are found in high concentrations in collagen. Neither of these amino acids is normally found in urine in the free form except in early infancy. Excretion of proline and hydroxyproline as iminopeptides (dipeptides and tripeptides containing proline or hydroxyproline) reflects collagen turnover and is increased in disorders of accelerated collagen turnover, such as rickets or hyperparathyroidism. Proline is also found at synaptic junctions and functions as a neurotransmitter (see Chapter 85.11). The catabolic pathway of proline/hydroxyproline produces glyoxylic acid which can be further metabolized to glycine or oxalic acid (see Fig. 85-8).

HYPERPROLINEMIA

Two types of primary hyperprolinemia have been described.

Hyperprolinemia Type I

This rare autosomal recessive condition is caused by deficiency of proline oxidase (proline dehydrogenase; see Fig. 85-9). Clinical manifestations are variable; some affected individuals are asymptomatic but patients with severe psychomotor retardation and seizures have been reported. Schizophrenia is a common finding in these patients. The gene for proline oxidase *(PRODH)* is located on chromosome 22q11.2 and several disease-causing mutations have been identified. Microdeletions involving this region of chromosome 22 cause velocardiofacial (DiGeorge, Shprintzen) syndrome; approximately 50% of patients with this syndrome have been reported to have hyperprolinemia type I. Therefore, all patients with hyperprolinemia type I should be screened (by fluorescence in situ hybridization analysis) for presence of DiGeorge syndrome.

Laboratory studies reveal high concentrations of proline in plasma, urine, and in the CSF. Approximately 30% of obligate heterozygous individuals (parents, siblings) also have hyperprolinemia. Increased urinary excretion of hydroxyproline and glycine is also present; this is from saturation of the shared tubular reabsorption mechanism by massive prolinuria.

No effective **treatment** has yet emerged. Restriction of dietary proline causes modest improvement in plasma proline with no proven clinical benefit.

Hyperprolinemia Type II

This is a rare autosomal recessive condition caused by the deficiency of pyrroline-carboxylic acid dehydrogenase (aldehyde dehydrogenase 4 [ALDH4]; see Fig. 85-9). Psychomotor retardation (modest to severe) and seizures (usually precipitated by an intercurrent infection) have been reported in most affected children, but asymptomatic patients have also been reported.

Laboratory studies reveal increased concentrations of proline and Δ^1-pyrroline-5-carboxylic acid (P5C) in blood, urine, and the CSF.

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Increased excretion of xanthurenic acid also has been reported in this condition. The presence of P5C differentiates this condition from hyperprolinemia type I (see above). Increased levels of P5C in body fluids, especially in the CNS, cause inactivation of vitamin B_6 and generate a state of vitamin B_6 dependency (see Chapter 85.14). Vitamin B_6 dependency is perhaps the main cause of seizures and neurologic findings in this condition and may explain the variability in clinical manifestations in different patients. **Treatment** with high doses of vitamin B_6 in conjunction with a diet low in proline is recommended but the experience remains very limited because of paucity of patients. The gene for P5C dehydrogenase (ALDH4) is on chromosome 1p36.13.

PROLIDASE DEFICIENCY

During collagen degradation, imidodipeptides (dipeptides containing proline such as glycylproline) are released and are normally cleaved by tissue prolidase. This enzyme requires manganese for its proper activity. Deficiency of prolidase, which is inherited as an autosomal recessive trait, results in the accumulation of imidodipeptides in body fluids.

The **clinical manifestations** of this rare condition and the age at onset are quite variable (19 mo to 19 yr) and include recurrent, painful skin ulcers, which are typically on hands and legs. Other skin lesions that may precede ulcers by several years may include scaly erythematous maculopapular rash, purpura, and telangiectasia. Most ulcers become infected. Healing of the ulcers may take 4-7 mo. Mild to severe cognitive and motor deficits and susceptibility to infections are also present in most patients (recurrent otitis media, sinusitis, respiratory infection, splenomegaly). Infection is the cause of death. Some patients may have craniofacial abnormalities such as ptosis, ocular proptosis, hypertelorism, small beaked nose and prominent cranial sutures. Asymptomatic cases have also been reported. Development of systemic lupus erythematosus has been noted in affected children of 1 family; young patients with systemic lupus erythematosus should be screened for prolidase deficiency. High levels of urinary excretion of imidodipeptides are diagnostic. Enzyme assay may be performed in erythrocytes or cultured skin fibroblasts.

Oral supplementation with proline, ascorbic acid, and manganese, and the topical use of proline and glycine, result in an improvement in leg ulcers. These treatments have not been found to be consistently effective in all patients.

The gene for prolidase enzyme *(PEPD)* has been mapped to chromosome 19q13.11 and several disease-causing mutations have been identified in different families.

Bibliography is available at Expert Consult.

85.10 Glutamic Acid

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Glutamic acid and its aminated derivative glutamine have a wide range of functions in the body. One of the major products of glutamic acid is glutathione (γ-glutamyl cysteinylglycine). This ubiquitous tripeptide, with its function as the major antioxidant in the body, is synthesized and degraded through a complex cycle called the γ-glutamyl cycle (Fig. 85-11). Because of its free sulfhydryl (-SH) group and its abundance in the cell, glutathione protects other sulfhydryl-containing compounds (such as enzymes and CoA) from oxidation. It is also involved in the detoxification of peroxides, including hydrogen peroxide, and in keeping the intracellular milieu in a reduced state. The common consequences of glutathione deficiency are hemolysis and hemolytic anemia. In addition, glutathione participates in amino acid transport

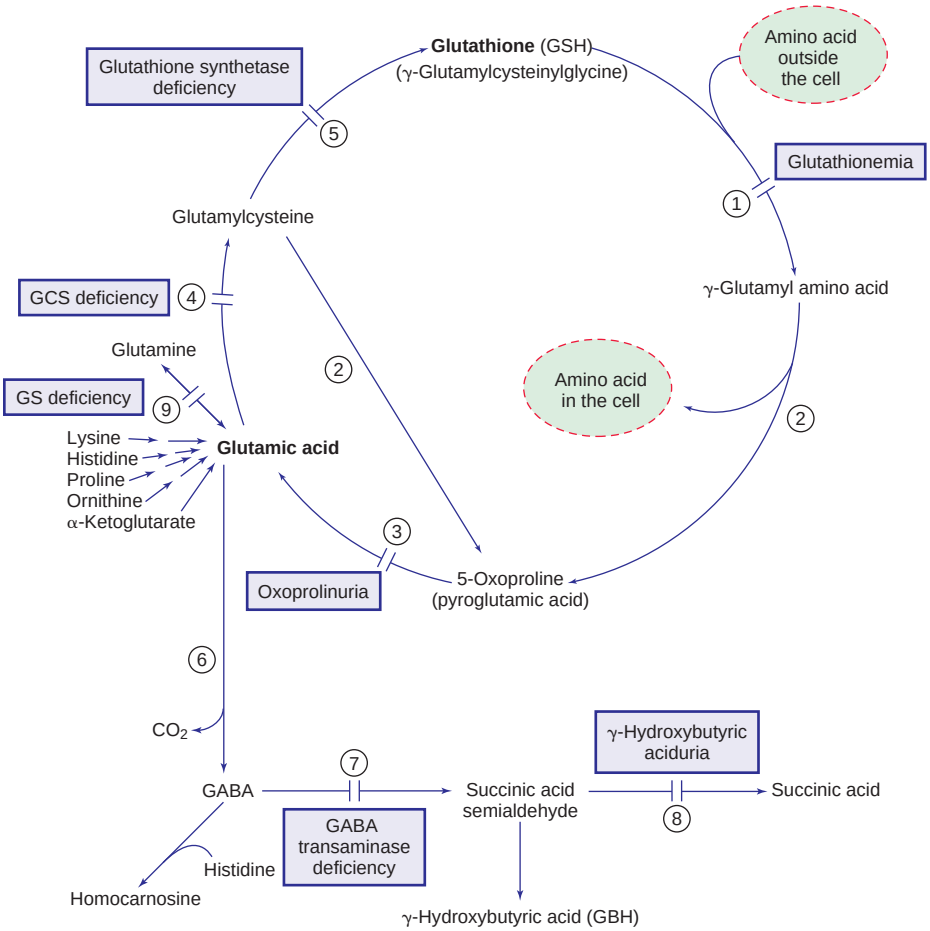

Figure 85-11 The γ-glutamyl cycle. Defects of the glutathione synthesis and degradation are noted. **Enzymes:** *(1)* γ-Glutamyl transpeptidase, *(2)* γ-glutamyl cyclotransferase, *(3)* 5-oxoprolinase, *(4)* γ-glutamyl-cysteine synthetase, *(5)* glutathione synthetase, *(6)* glutamic acid decarboxylase, *(7)* γ-aminobutyric acid (GABA) transaminase, *(8)* succinic semialdehyde dehydrogenase, *(9)* glutamine synthase.

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across the cell membrane through the γ-glutamyl cycle. Glutamic acid is also the precursor of γ-aminobutyric acid (GABA), a major neurotransmitter in the nervous system (see Chapter 85.11).

GLUTATHIONE SYNTHETASE DEFICIENCY

See Figure 85-11.

Three forms of this rare condition have been reported. In the **severe form**, which is a result of generalized deficiency of the enzyme, severe acidosis and massive 5-oxoprolinuria are the rule. In the **mild form**, in which the enzyme deficiency causes glutathione deficiency only in erythrocytes, neither 5-oxoprolinuria nor acidosis has been observed. A **moderate form** has also been observed in which the hemolytic anemia is associated with variable degrees of acidosis and 5-oxoprolinuria. In all forms, patients have hemolytic anemia secondary to glutathione deficiency.

Glutathione Synthetase Deficiency, Severe Form (Pyroglutamic Acidemia, Severe 5-Oxoprolinuria) and Moderate Form

Affected newborn infants with this rare condition usually develop acute symptoms of metabolic acidosis, jaundice, and mild to moderate hemolytic anemia in the first few days of life. Chronic acidosis continues after recovery. Similar episodes of life-threatening acidosis may occur during an infection such as gastroenteritis or after a surgical procedure. Progressive neurologic damage, manifested by intellectual disability, spastic tetraparesis, ataxia, tremor, dysarthria, and seizures, develops with age. Susceptibility to infection, presumably as a consequence of granulocyte dysfunction, is observed in some patients. Patients with the moderate form of the condition have milder acidosis and less 5-oxoprolinuria than is seen in the severe form, with no neurologic manifestations.

Laboratory findings include metabolic acidosis, mild to moderate degrees of hemolytic anemia, and 5-oxoprolinuria. High concentrations of 5-oxoproline are also found in blood. The urinary and blood levels of 5-oxoproline is less pronounced in patients with moderate form of the condition. The glutathione content of erythrocytes is markedly decreased. Increased synthesis of 5-oxoproline in this disorder is believed to be a result of the conversion of γ-glutamylcysteine to 5-oxoproline by the enzyme γ-glutamyl cyclotransferase (see Fig. 85-11). γ-Glutamylcysteine production increases greatly because the normal inhibitory effect of glutathione on the γ-glutamylcysteine synthetase enzyme is removed. A deficiency of glutathione synthetase has been demonstrated in a variety of cells including erythrocytes.

Treatment of acute attack includes hydration, correction of acidosis (by infusion of sodium bicarbonate), and measures to correct anemia and hyperbilirubinemia. Chronic administration of alkali is usually needed indefinitely. Administration of large doses of vitamins C and E has been recommended. Drugs and oxidants that are known to cause hemolysis and stressful catabolic states should be avoided. Oral administration of glutathione analogs has been tried with variable success.

Prenatal diagnosis can be achieved by the measurement of 5-oxoproline in amniotic fluid, by enzyme analysis in cultured amniocytes or chronic villous samples, or by DNA analysis of the gene. Successful pregnancy in an affected female (moderate form), with favorable outcomes for both mother and infant, has been reported.

Glutathione Synthetase Deficiency, Mild Form

This form has been reported in only a few patients. Mild to moderate hemolytic anemia has been the only **clinical finding** in these patients. Splenomegaly has been reported in some patients. Cognitive development is normal; metabolic acidosis and increased concentrations of 5-oxoproline do not occur. Similar to other types of glutathione synthase deficiency, this form is caused by mutations in the gene that encodes the enzyme. These mutations, however, decrease the half-life of the enzyme, which causes an increased rate of protein turnover without affecting its catalytic function. The expedited rate of enzyme turnover caused by these mutations is of no consequence for tissues with protein synthetic capability. However, inability of mature erythrocytes to synthesize protein, results in glutathione deficiency in the erythrocytes. **Treatment** is that of hemolytic anemia and avoidance of drugs and oxidants that can trigger the hemolytic process.

All forms of the condition are inherited as an autosomal recessive trait. The gene for this enzyme *(GSSD)* is located on chromosome 20q11.2. Several disease-causing mutations have been identified in different families.

5-Oxoprolinase Deficiency (5-Oxoprolinuria)

The main cause of massive 5-oxoprolinuria is glutathione synthetase deficiency (see above). Moderate 5-oxoprolinuria has been found in a variety of metabolic and acquired conditions, such as in patients with severe burns, Stevens-Johnson syndrome, homocystinuria, urea cycle defects, and tyrosinemia type I.

A few individuals with moderate 5-oxoprolinuria (4-10 g/day) as a result of 5-oxoprolinase (see Fig. 85-11) deficiency have been identified. No specific **clinical picture** has yet emerged; completely asymptomatic affected individuals have also been identified. It is, therefore, not clear whether 5-oxoprolinase deficiency is of any clinical consequence. No **treatment** has been recommended. The gene for the enzyme *(OPLAH)* is on chromosome 8q24.3.

γ-Glutamylcysteine Synthetase Deficiency

Only a few patients with this enzyme deficiency have been reported. The most consistent **clinical manifestation** has been mild chronic hemolytic anemia. Acute attacks of hemolysis have occurred after exposure to sulfonamides. Peripheral neuropathy and progressive spinocerebellar degeneration have been noted in 2 siblings in adulthood. **Laboratory findings** of chronic hemolytic anemia were present in all patients. Generalized aminoaciduria is also present because the γ-glutamyl cycle is involved in amino acid transport in cells (see Fig. 85-11). **Treatment** is that of hemolytic anemia and avoidance of drugs and oxidants that may trigger the hemolytic process. The condition is inherited as an autosomal recessive trait; the gene *(GCLC)* is mapped to chromosome 6p12.1.

GLUTATHIONEMIA (γ-GLUTAMYL TRANSPEPTIDASE DEFICIENCY)

This enzyme is present in any cell that has secretory or absorptive functions. It is especially abundant in the kidneys, pancreas, intestines, and liver. The enzyme is also present in the bile. Measurement of this enzyme in the blood is commonly performed to evaluate liver and bile duct diseases.

Deficiency of this enzyme causes elevation in glutathione concentrations in body fluids, but the cellular levels remain normal (see Fig. 85-11). Because only a few patients with enzyme deficiency have been reported, the scope of **clinical manifestations** has not yet been defined. Mild to moderate intellectual disability and severe behavioral problems were observed in 3 patients. One of the 2 sisters with this condition had normal intelligence as an adult, however, and the other had Prader-Willi syndrome.

Laboratory findings include marked elevations in urinary concentrations of glutathione (up to 1 g/day), γ-glutamylcysteine, and cysteine. None of the reported patients has had generalized aminoaciduria, a finding that would have been expected to occur in this enzyme deficiency (see Fig. 85-11).

Diagnosis can be confirmed by measurement of the enzyme activity in leukocytes or cultured skin fibroblasts. No effective **treatment** is available.

The condition is inherited as an autosomal recessive trait. The enzyme GGT (γ-glutamyl transpeptidase) is a complex protein and is encoded by at least 7 genes.

GENETIC DISORDERS OF METABOLISM OF γ-AMINOBUTYRIC ACID

See also Chapter 85.11.

Congenital Glutamine Deficiency

Glutamine is synthesized endogenously from glutamate and ammonia by a ubiquitous enzyme, glutamine synthetase (see Fig. 85-11).

Glutamine is known to be involved in several important functions, including detoxification of ammonia. Deficiency of this enzyme, resulting in glutamine deficiency, has been reported in 3 infants from 3 unrelated families. All affected infants manifested multiorgan involvement including significant brain malformations (abnormal gyrations, hypomyelination), facial abnormalities (broad nasal root, low-set ears) hypotonia and seizures at birth. Two of the patients died from multiorgan failure (respiratory and heart failure) in the neonatal period; 1 child was alive at 3 yr of age with severe developmental delay. Glutamine was absent in plasma, urine, and CSF, but plasma levels of glutamic acid were normal. Genetic defects of this enzyme underline the critical role of glutamine in embryogenesis especially in normal brain development. The condition is inherited as an autosomal recessive trait; the gene for glutamine synthetase *(GLUL)* is mapped to chromosome 1q25.3

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85.11 Genetic Disorders of Neurotransmitters

Iraj Rezvani and K. Michael Gibson

Neurotransmitters are chemical substances released from the axonal end of excited neurons at the synaptic junctions; they mediate initiation and amplification or inhibition of neural impulses. A number of amino acids and their metabolites comprise the bulk of neurotransmitters. Mutations in genes responsible for the synthesis or degradation of these substances may cause conditions that usually manifest neurologic and/or psychiatric abnormalities (Table 85-2). In the past, children affected by disorders of neurotransmitters have been given diagnoses such as cerebral palsy, seizure disorder, parkinsonism, dystonia, or autism. Diagnosis, in most cases, requires specialized laboratory studies of the **CSF,** because some of the neurotransmitters generated in the CNS (dopamine and serotonin) do not cross the blood–brain barrier and their abnormal concentrations are not detected in the serum or urine. An ever-growing number of these conditions are being identified; diseases that were once thought to be very rare are now diagnosed with increasing frequency.

TYROSINE HYDROXYLASE DEFICIENCY (INFANTILE PARKINSONISM, AUTOSOMAL RECESSIVE DOPA-RESPONSIVE DYSTONIA, SEGAWA SYNDROME, AUTOSOMAL RECESSIVE FORM)

Tyrosine hydroxylase catalyzes the formation of L-dopa from tyrosine. Deficiency of this enzyme, reported in several children, results in deficiencies of dopamine and norepinephrine (see Fig. 85-2). The clinical picture resembles that of autosomal dominant dystonia caused by GTP cyclohydrolase deficiency (see below); the clinical spectrum of the condition is still being elucidated.

Clinical manifestations range from mild to very severe. In general, 2 phenotypes have been recognized. In the mild form (dopa-responsive dystonia or type A), symptoms of unilateral limb dystonia causing gait incoordination and postural tremor occur in childhood and worsen with age if the condition remains untreated. Diurnal variation of symptoms (worse at the end of the day) may be present. Cognitive development is usually normal. In the severe form of the condition (infantile parkinsonism, infantile encephalopathy or type B), the clinical manifestations occur at birth or shortly thereafter. These include microcephaly, developmental delay, involuntary movements of the limbs with spasticity, dystonia, ptosis, expressionless face, oculogyric crises (upward rolling-eye movements) and autonomic dysfunction (temperature instability, excessive sweating, hypoglycemia, salivation, tremor, gastrointestinal reflux, constipation). Brisk reflexes, myoclonus, athetosis and distal chorea may be present. This form usually does not respond to treatment with L-dopa.

Laboratory findings include reduced levels of dopamine and its metabolite homovanillic acid (HVA), and normal concentrations of BH_4, neopterin, and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of serotonin) in the CSF. Serum prolactin levels are usually elevated. These findings are not diagnostic of the condition; diagnosis should be established by gene study.

Treatment with L-dopa/carbidopa results in significant clinical improvement in most patients, but is invariably associated with L-dopa induced dyskinesias. To minimize the side effects of therapy, the treatment should be started with a low dose and increased very slowly if needed. Other therapeutic interventions include anticholinergics, serotonergic agents and monoamine oxidase (MAO) B inhibitors, including amantadine, biperiden, and selegiline. Bilateral subthalamic nucleus deep brain stimulation has shown clinical efficacy in 1 case. The gene for tyrosine hydroxylase (TH) is located on chromosome 11p15.5; it is inherited as an autosomal-recessive trait.

Table 85-2 Genetic Disorders of Neurotransmitters in Children

TRANSMITTER	SYNTHESIS DEFECTS	DEGRADATION DEFECTS
MONOAMINES		
Dopamine	TH deficiency	MAO deficiency
Serotonin and dopamine	AADC deficiency	MAO deficiency
	BH_4 deficiency	
	With hyperphe	
	Without hyperphe	
Norepinephrine	DβH deficiency	MAO deficiency
GABA	?	GABA transaminase deficiency
		GHB aciduria
Histamine	HDC deficiency	?
TRANSPORTER PROTEINS		
Dopamine transporter	DAT deficiency	?
Vesicular monoamine transporter	VMAT2 deficiency	?
AMINO ACIDS		
Proline	?	Hyperprolinemia
Serine	3-PGD, PSAT deficiencies	?
Glycine	3-PDG, PSAT deficiencies	NKH

AADC, aromatic L-amino acid decarboxylase; BH_4, tetrahydrobiopterin; DAT, dopamine transporter; DβH, dopamine β-hydroxylase; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyric; HDC, histidine decarboxylase; hyperphe, hyperphenylalaninemia; MAO, monoamine oxidase; NKH, nonketotic hyperglycinemia; 3-PGD, 3-phosphoglycerate dehydrogenase; PSAT, phosphoserine aminotransferase; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2.

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Aromatic L-Amino Acid Decarboxylase Deficiency

Aromatic L-amino acid decarboxylase (AADC) catalyzes the decarboxylation of both 5-hydroxytryptophan (to form serotonin, see Fig. 85-5) and L-dopa (to generate dopamine, see Fig. 85-2). **Clinical manifestations** are related to underproduction of dopamine and serotonin. Poor feeding, lethargy, hypotension, hypothermia, eye rolling (oculogyric crises), and ptosis have been observed in affected neonates. Clinical findings in infants and older children include developmental delay, truncal hypotonia with hypertonia of limbs, oculogyric crises, extrapyramidal movements (choreoathetosis, dystonia, myoclonus), and autonomic abnormalities (sweating, salivation, irritability, temperature instability, hypotension). Symptoms often have a diurnal variation becoming worse by the end of the day.

Laboratory findings include decreased concentrations of dopamine and serotonin and their metabolites (HVA, 5-HIAA, vanillylmandelic acid [VMA] and norepinephrine), and increased levels of 5-hydroxytryptophan, L-dopa and its metabolite (3-*O*-methyldopa) in body fluids, especially in CSF. Elevated serum concentrations of prolactin (a result of dopamine deficiency) have also been observed. MRI of the brain reveals cerebral atrophy with degenerative changes in the white matter. A urine screening program, focused on 3-*O*-methyldopa and VMA, has demonstrated diagnostic promise in high-prevalence populations.

Treatment with neurotransmitter precursors has produced limited clinical improvement. Dopamine and serotonin have no therapeutic value because of their inability to cross the blood–brain barrier. Dopamine agonists (L-dopa/carbidopa, bromocriptine), MAO inhibitors (tranylcypromine), serotonergic agents and high doses of pyridoxine (cofactor for AADC enzyme) have been tried. No treatment of choice has yet emerged. Pyridoxine supplementation in patients harboring the S250F variant may be beneficial. Preimplantation genetic diagnosis after in vitro fertilization has been achieved in the high-prevalence Taiwanese population. The gene encoding AADC (*DDC*) is on chromosome 7p12.1. The condition is inherited as an autosomal recessive trait; several disease-causing mutations have been reported in different families.

TETRAHYDROBIOPTERIN DEFICIENCY

See Chapter 85.1.

BH_4 is the cofactor for PAH (see Fig. 85-1), tyrosine hydroxylase (see Fig. 85-2), tryptophan hydroxylase (see Fig. 85-5), and nitric oxide synthase. It is synthesized from GTP in many tissues (see Fig. 85-1). Deficiencies of enzymes involved in the biosynthesis of BH_4 result in inadequate production of this cofactor which causes deficiencies of monoamine neurotransmitters with or without concomitant hyperphenylalaninemia.

Tetrahydrobiopterin Deficiency with Hyperphenylalaninemia

See Chapter 85.1.

Tetrahydrobiopterin Deficiency Without Hyperphenylalaninemia

Hereditary Progressive Dystonia, Autosomal Dominant Dopa-Responsive Dystonia, Segawa Syndrome, Autosomal Dominant Form

See also Chapter 597.3.

This form of dystonia is caused by GTP cyclohydrolase I deficiency. It is inherited as an autosomal dominant trait and is more common in females than males (4:1).

Clinical manifestations usually start in early childhood with tremor and dystonia of the lower limbs (toe gait), which may spread to all extremities within a few years. Torticollis, dystonia of the arms, and poor coordination may precede dystonia of the lower limbs. Early development is generally normal. Symptoms have an impressive diurnal variation, becoming worse by the end of the day and improving with sleep. Autonomic instability is not uncommon. Parkinsonism may also be present or develop with advancing age. Late presentation in adult life has also been reported, associated with action dystonia (writer's cramp), torticollis or generalized rigid hypertonia with tremor but without postural dystonia. Additionally, limited data on adults suggest symptoms related to serotonin deficiency (sleep disturbance, cognitive impairment and impulsivity).

Laboratory findings show reduced levels of BH_4 and neopterin in the CSF without hyperphenylalaninemia. Dopamine and its metabolite (HVA) may also be reduced in CSF. The serotonergic pathway is less affected by this enzyme deficiency; thus, concentrations of serotonin and its metabolites are usually normal. Plasma phenylalanine is normal but an oral phenylalanine loading test (100 mg/kg) produces an abnormally high plasma phenylalanine level with an elevated phenylalanine/tyrosine ratio. The ratio, obtained at the 2nd and 3rd hr postload, in combination with urine neopterin level, has optimal diagnostic specificity and sensitivity. The existence of asymptomatic carriers indicates that other factors or genes may play a role in pathogenesis. The asymptomatic carrier may be identified by the phenylalanine loading test (see above).

Diagnosis may be confirmed by reduced levels of BH_4 and neopterin in CSF, through measurement of the enzyme activity, and via molecular genetic analysis (see Chapter 85.1). Clinically, the condition should be differentiated from other causes of dystonias and childhood parkinsonism, especially tyrosine hydroxylase, sepiapterin reductase, and aromatic amino acid decarboxylase deficiencies.

Treatment with L-dopa/carbidopa usually produces dramatic clinical improvement. Oral administration of BH_4 is also effective but is rarely used. The gene for GTP cyclohydroxylase I (*GCH1*) is located on chromosome 14q22.2.

Sepiapterin Reductase Deficiency

Sepiapterin reductase is involved in conversion of 6-pyruvoyl-tetrahydropterin to BH_4, and also participates in the salvage pathway of BH_4 synthesis (see Fig. 85-1). Sepiapterin reductase deficiency results in accumulation of 6-lactoyl-tetrahydropterin, which is converted to sepiapterin nonenzymatically. The majority of sepiapterin is metabolized to BH_4 through the salvage pathway in peripheral tissues (see Fig. 85-1), but because of the low activity of dihydrofolate reductase in brain, the amount of BH_4 remains insufficient for proper synthesis of dopamine and serotonin. This explains the absence of hyperphenylalaninemia, as well as an explanation for the often delayed diagnosis. Sepiapterin reductase deficiency may also be underdiagnosed as highly specialized CSF assays are required.

Clinical manifestations usually appear within a few months of life. Cardinal manifestations include paroxysmal stiffening, oculogyric crises, and hypotonia. Additional findings include motor and language delays, weakness, limb hypertonia, dystonia, hyperreflexia, and early onset parkinsonism. The symptoms usually have a diurnal variation. Misdiagnosis as cerebral palsy is common.

Diagnosis is established by measurement of CSF neurotransmitters and pterin metabolites which reveal decreased dopamine, HVA, norepinephrine, 5-HIAA and marked elevations of sepiapterin and dihydrobiopterin. The serum concentration of prolactin is elevated. The phenylalanine loading test (see above) may have diagnostic utility. Diagnosis may be confirmed by enzyme assay in fibroblasts or via molecular genetic analysis.

Treatment with slowly increasing doses of L-dopa/carbidopa and 5-hydroxytryptophan usually produces dramatic clinical improvement.

The condition is inherited as an autosomal recessive trait; the gene (SPR) for the enzyme is located on chromosome 2p13.2.

DOPAMINE β-HYDROXYLASE DEFICIENCY

See Figure 85-2.

This rare condition has been reported in only a few adult subjects with profound deficits of cardiovascular autonomic regulation resulting in predisposition to orthostatic hypotension. Past histories reveal ptosis, hypotension, hypothermia, hypoglycemia and nasal stuffiness in the neonatal and childhood periods. Presyncopal symptomatology includes dizziness, blurred vision, dyspnea, nuchal discomfort and chest pain; olfactory function remains relatively intact.

Laboratory findings include absence of norepinephrine and epinephrine and their metabolites with elevated levels of dopamine and its metabolite (HVA) in plasma, CSF, and urine. Elevated plasma dopamine may be pathognomonic for this disease. MRI of the brain shows decreased brain volume, consistent with the neurotrophic role of norepinephrine. **Treatment** with 3,4-dihydroxyphenylserine, which is converted to norepinephrine directly in vivo by the action of AADC, leads to significant improvement in orthostatic hypotension and normalizes noradrenaline and its metabolites. The condition is inherited as an autosomal recessive trait; the gene *(DBH)* for the enzyme resides on chromosome 9q34.2.

MONOAMINE OXIDASE (MAO) DEFICIENCY

There are 2 MAO isoenzymes: MAO A and MAO B. Both enzymes catalyze oxidative deamination of most biogenic amines in the body, including serotonin (see Fig. 85-5), norepinephrine, epinephrine, and dopamine (see Fig. 85-2). The genes for both isoenzymes are on the X chromosome (A, Xp11.3; B, Xp11.23). Male patients with MAO A deficiency manifest borderline intellectual deficiency and impaired impulse control. MAO B deficiency is found in patients with Norrie disease (see Chapter 622). Patients with isolated MAO B deficiency exhibit normal clinical characteristics and behavior. Combined MAO A and B deficiency causes severe intellectual disability and behavioral problems, associated with more extreme laboratory abnormalities (4-6–fold serotonin elevation in physiologic fluids, elevated *O*-methylated amine metabolites, and reduced deamination products [VMA, HVA]). A de novo microdeletion in Xp11.3 has been reported twice; the microdeletion in 1 male infant manifested with severe intellectual disability and episodic hypotonia. Dietary intervention (low tyramine, phenylethylamine and dopa/dopamine intake) did not improve the patients' blood serotonin levels.

γ-AMINOBUTYRIC ACID (GABA)

GABA is the main inhibitory neurotransmitter, which is synthesized in the synapses through decarboxylation of glutamic acid by glutamic acid decarboxylase (GAD). The same pathway is responsible for production of GABA in other organs, especially the kidneys and the β cells of the pancreas. GAD enzyme requires pyridoxine (vitamin B_6) as cofactor. Two GAD enzymes (GAD_{65} and GAD_{67}) have been identified. GAD_{67} is the main enzyme in the brain and GAD_{65} is the major enzyme in the β cells. Antibodies against GAD_{65} and GAD_{67} are the major markers for type1 diabetes and **stiff-person syndrome**, respectively. Deficiency of neither form of the enzyme has been reported in humans. GABA is catabolized to succinic acid by 2 enzymes, GABA transaminase and succinic semialdehyde dehydrogenase (SSADH) (see Fig. 85-11).

γ-Aminobutyric Acid Transaminase Deficiency

See Figure 85-11.

Clinical manifestations in the 2 index infant siblings included severe psychomotor retardation, hypotonia, hyperreflexia, lethargy, refractory seizures, and increased linear growth. Increased concentrations of GABA and β-alanine were found in CSF. Evidence of leukodystrophy was noted in the postmortem examination of the brain. A third case showed severe psychomotor retardation, recurrent episodic lethargy and intractable seizures with comparable CSF metabolite abnormalities to those of the index probands. GABA transaminase deficiency is demonstrated in brain and lymphocytes. No effective **treatment** has been identified. Intervention with vitamin B_6, the cofactor for the enzyme, was without therapeutic benefit. The gene *(ABAT),* maps to chromosome 16p13.2; the condition is inherited as an autosomal recessive trait.

Succinic Semialdehyde Dehydrogenase Deficiency (γ-Hydroxybutyric Aciduria)

SSADH deficiency is the most common genetic disorder of neurotransmitters (see Fig. 85-11). Clinical manifestations, which usually begin in early infancy, include intellectual disability with disproportionate deficit in expressive language, hypotonia and ataxia; seizures occur in approximately 50% of patients. A diagnosis of **autism spectrum** disorder occurs disproportionately. Neuropsychiatric morbidity (especially oppositional defiance, obsession-compulsion, and hyperactivity) can be disabling, especially in adolescents and adults. Abnormal EEG findings include background slowing and generalized spike-wave paroxysms, with variable lateralization in hemispheric onset and voltage predominance. Photosensitivity and electrographic status epilepticus of sleep have been reported in combination with difficulties in sleep maintenance and excessive daytime somnolence. MRI of the brain shows an increased T2-weighted hyperintensity involving the globus pallidi, cerebellar dentate nuclei, and subthalamic nuclei, usually in a bilaterally symmetrical distribution.

The biochemical hallmark, γ-hydroxybutyric acid (GHB), is elevated in physiologic fluids (CSF, plasma, urine) in all patients. Increased concentrations of GABA are also found in CSF. Heightened diagnostic suspicion evolves through documentation of elevated urinary γ-hydroxybutyric acid, and confirmation is achieved by molecular genetic testing.

Treatment remains elusive; vigabatrin (GABA-transaminase inhibitor) has been employed empirically, with mixed outcomes, and there is concern with its use as it further elevates CNS GABA in an already hyper-GABAergic disorder. Additionally, vigabatrin leads to constriction of the visual field and long-term use is contraindicated. Magnesium valproate has shown efficacy for behavioral problems and seizure control in a single case.

The gene for SSADH *(ALDH5A1)* is located on chromosome 6p22, and inheritance follows an autosomal-recessive pattern. Prenatal diagnosis has been achieved by measurement of GHB in the amniotic fluid, assay of the enzyme activity in the amniocytes or in biopsy specimens of chorionic villi or by DNA analysis.

DEFECTS IN NEUROTRANSMITTERS TRANSPORTER PROTEINS

More than 20 different proteins are involved in transporting different neurotransmitters across the neuronal membranes. The main function of most of these transporters is to remove the excess neurotransmitters from the synaptic junction (cleft) back into the presynaptic neurons (reuptake). This recycling process not only regulates the precise effect of neurotransmitters at the synaptic junction but also resupplies the presynaptic neurons with neurotransmitters for future use. A few transporter proteins are involved in shuttling neurotransmitters from the neuronal cytoplasm across the membrane of synaptic vesicles for storage (vesicular transporters). Upon neuronal stimulation, these vesicles release a bolus of neurotransmitters via exocytosis. As expected, mutations in transporter proteins interfere with the proper reuptake and storage of neurotransmitters and may result in clinical manifestations similar to those seen in deficiencies of neurotransmitters metabolism themselves. Two conditions caused by mutations of neurotransmitter protein transporters have been described.

Dopamine Transporter Protein Deficiency

This transporter protein is involved in reuptake of dopamine by the presynaptic neurons, and its deficiency causes depletion of dopamine, and hence a dopamine deficiency state. Dopamine transporter protein (DAT) is encoded by *SLC6A3* gene on chromosome 5p15.33. Mutation of this gene has been reported in 3 children from 2 unrelated consanguineous families. These children presented with **symptoms** of infantile parkinsonism-dystonia syndrome. Symptoms of irritability and feeding difficulties started shortly after birth and progressed to hypotonia, lack of head control, parkinsonism, dystonia and global developmental delay by early infancy. Two of the patients were misdiagnosed as having cerebral palsy. MRI of the brain showed no abnormalities.

Examination of the CSF revealed marked elevation of HVA and normal level of 5-HIAAs. The urinary level of HVA, as well as the serum concentration of prolactin, were increased. Diagnosis was established by demonstrating the loss of function mutation in the *SLC6A3* gene. No effective treatment has been identified. **Treatment** with L-dopa/carbidopa did not result in any improvements in clinical or biochemical parameters.

Dopamine–Serotonin Vesicular Transporter Disease (Vesicular Monoamine Transporter Deficiency)

This autosomal recessive condition, described in 8 children from a consanguineous Saudi Arabian family is caused by a mutation in the *SLC18A2* gene. This gene encodes the vesicular monoamine transporter 2 (*VMAT2*), which is involved in transporting dopamine and serotonin from the cytoplasm into the synaptic storage vesicles located in the axonal terminals of the presynaptic neurons. Affected children manifested symptoms consistent with deficiencies of dopamine (hypotonia progressing into dystonia, parkinsonism, oculogyric crises), serotonin (sleep and psychiatric disturbances), and norepinephrine-epinephrine (excessive sweating, tremors, temperature instability, postural hypotension and ptosis). Symptoms started at 4 mo of age with hypotonia, lack of head control, inconsolable crying and oculogyric crises. Cognitive development was initially normal but deteriorated with age. No diurnal variation of the symptoms was noted. EEG, MRI, and MRS of the brain, as well as concentrations of all neurotransmitters and their metabolites in the CSF, were within normal limits. Urinary concentrations of 5-HIAA and HVA were moderately increased, whereas those of norepinephrine and epinephrine were decreased.

The phenotype resembles that seen in AADC and BH_4 deficiencies (see above). Proper diagnosis requires mutation analysis of the *SLC18A2* gene (located on chromosome 10q25.3). **Treatment** with L-dopa/carbidopa caused exacerbation of symptoms, whereas treatment with pramipexole, a dopamine receptor agonist, resulted in a favorable clinical response.

HISTIDINE DECARBOXYLASE DEFICIENCY

Decarboxylation of histidine by histidine decarboxylase produces histamine, which functions as a neurotransmitter in the brain. Deficiency of this enzyme (expressed mainly in the posterior hypothalamus) results in deficiency of histamine in the CNS, and in 1 family caused an autosomal dominant form of Tourette syndrome (see Chapter 85.13).

HYPERPROLINEMIA

Psychomotor retardation and seizures are common findings in most patients with hyperprolinemia type I and type II. Patients with type I hyperprolinemia also have an increased risk of developing schizophrenia. The contribution of increased concentration of proline to the pathogenesis of these conditions, however, remains unclear. The neurologic abnormalities observed in hyperprolinemia type II are mainly because of development of vitamin B_6 dependency in this condition (see Chapter 85.9).

3-PHOSPHOGLYCERATE DEHYDROGENASE DEFICIENCY

See Chapter 85.8.

PHOSPHOSERINE AMINOTRANSFERASE DEFICIENCY

See Chapter 85.8.

NONKETOTIC HYPERGLYCINEMIA

See Chapter 85.7.

Bibliography is available at Expert Consult.

85.12 Urea Cycle and Hyperammonemia (Arginine, Citrulline, Ornithine)

Iraj Rezvani and Marc Yudkoff

Catabolism of amino acids results in the production of free ammonia, which, in high concentration, is toxic to the CNS. Mammals detoxify ammonia to urea through a series of reactions known as the urea cycle (Fig. 85-12), which is composed of 5 enzymes: carbamyl phosphate synthetase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL), and arginase. A 6th enzyme, *N*-acetylglutamate (NAG) synthetase, catalyzes synthesis of NAG, which is an obligatory activator (effector) of the CPS enzyme. Individual deficiencies of these enzymes have been observed and, with an overall estimated prevalence of 1 in 35,000 live births, they are the most common genetic causes of hyperammonemia in infants.

GENETIC CAUSES OF HYPERAMMONEMIA

Hyperammonemia, sometimes severe, occurs in inborn errors of metabolism other than the urea cycle defects (Table 85-3). The pathogenesis for hyperammonemia in some of these conditions is not fully understood, although it is probable that the accumulation of a toxic metabolite–usually an organic acid–compromises function of the urea cycle.

CLINICAL MANIFESTATIONS OF HYPERAMMONEMIA

In the **neonatal period**, *symptoms and signs* are mostly related to brain dysfunction and are similar regardless of the cause of the hyperammonemia. The affected infant is normal at birth but becomes symptomatic following the introduction of dietary protein. Refusal to eat, vomiting, tachypnea, and lethargy can quickly progress to a deep coma. Convulsions are common. Physical examination may reveal hepatomegaly in addition to obtundation. Hyperammonemia can trigger increased intracranial pressure that may be manifested by a bulging fontanelle and dilated pupils.

In **infants and older children** acute hyperammonemia is manifested by vomiting and neurologic abnormalities such as ataxia, mental confusion, agitation, irritability, and combativeness. These manifestations may alternate with periods of lethargy and somnolence that ultimately progress to coma.

Routine **laboratory studies** show no specific findings when hyperammonemia is caused by defects of the urea cycle enzymes. Blood urea nitrogen is usually low in these patients; serum pH is usually normal or mildly elevated. There may be mild increases in serum transaminases (alanine aminotransferase, aspartate aminotransferase) because ammonia can cause swelling of hepatic mitochondria. In some patients with severe OTC deficiency, criteria may be met for acute liver failure, as patients with severe OTC-related liver injury may have moderate hyperammonemia (100-400 μmol/L). In infants with organic acidemias, hyperammonemia is commonly associated with severe acidosis as well as ketonuria. Newborn infants with hyperammonemia are often misdiagnosed as having sepsis; they may succumb without a correct diagnosis. Neuroimaging with CT scanning may reveal cerebral edema. Autopsy is usually unremarkable. It is imperative to measure plasma ammonia levels in any ill infant whose clinical manifestations cannot be explained by an obvious infection.

DIAGNOSIS

The main criterion for diagnosis is hyperammonemia. Each clinical laboratory should establish its own normal values for blood ammonia. Normal newborn values are higher than those of the older child or adult. Levels as high as 100 μmole/L occur in healthy term infants and as high as 150 μmole/L in premature infants. An ill infant usually manifests a blood ammonia level >200 μmole/L. Figure 85-13 illustrates an approach to the differential diagnosis of hyperammonemia in the newborn infant. Careful inspection of individual plasma amino acids commonly reveals abnormalities that may help the diagnosis. In patients with deficiencies of either CPS, OTC, or NAG synthetase, frequent findings include elevations in plasma glutamine and alanine with concurrent decrements in citrulline and arginine. These disorders cannot be differentiated from one another by the plasma amino acid levels alone. A marked increase in urinary orotic acid in patients with OTC deficiency differentiates this defect from CPS deficiency. Differentiation between the CPS deficiency and the NAG synthetase deficiency may require an assay of the respective enzymes or sequencing of the relevant genes. Clinical improvement occurring after oral administration of carbamylglutamate, however, may suggest

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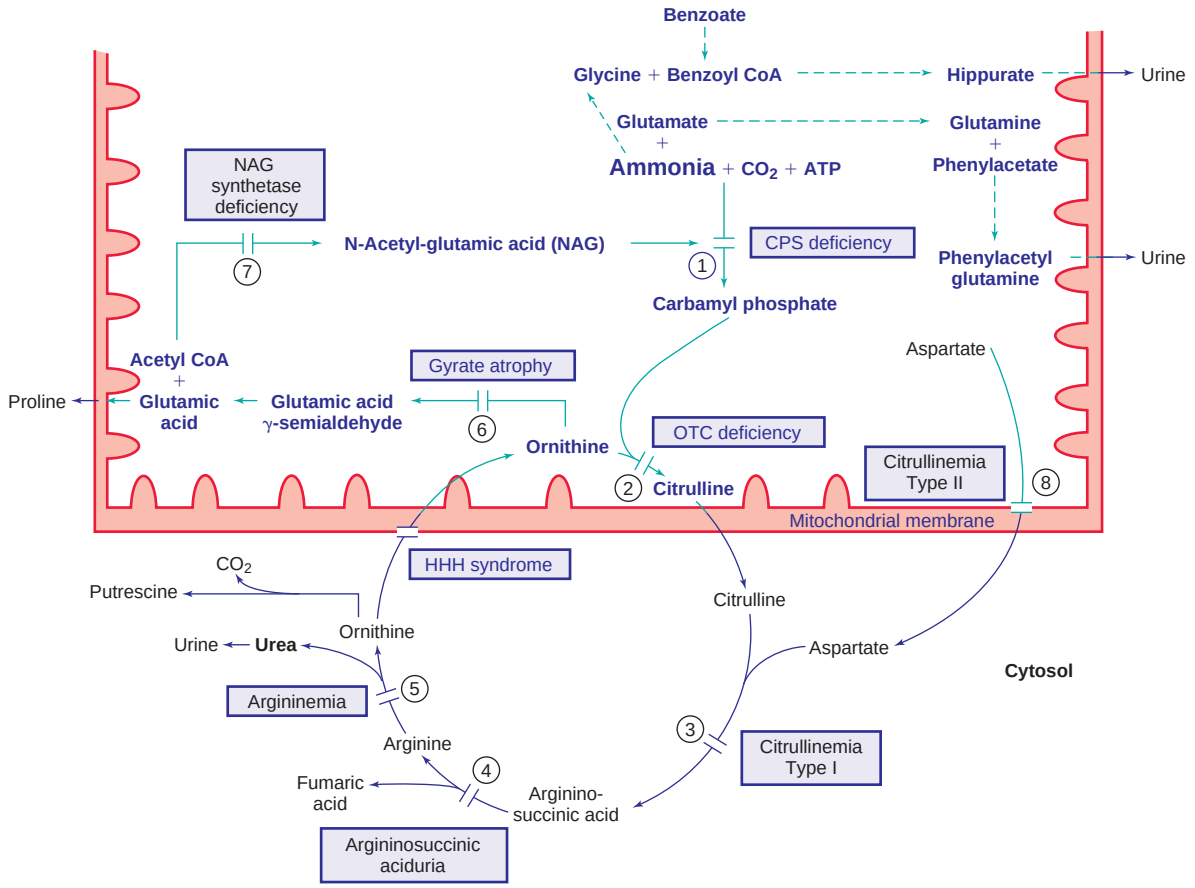

Figure 85-12 Urea cycle: pathways for ammonia disposal and ornithine metabolism. Reactions occurring in the mitochondria are depicted in *purple*. Reactions shown with *interrupted arrows* are the alternate pathways for the disposal of ammonia. **Enzymes:** *(1)* Carbamyl phosphate synthetase (CPS), *(2)* ornithine transcarbamylase (OTC), *(3)* argininosuccinic acid synthetase (AS), *(4)* argininosuccinic acid lyase (AL), *(5)* arginase, *(6)* ornithine 5-aminotransferase, *(7)* *N*-acetylglutamate (NAG) synthetase, *(8)* citrin. HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia.

Table 85-3	Inborn Errors of Metabolism Causing Hyperammonemia
Deficiencies of the urea cycle enzymes	
Carbamyl phosphate synthetase	
Ornithine transcarbamylase	
Argininosuccinate synthetase	
Argininosuccinate lyase	
Arginase *N*-acetylglutamate synthetase	
Organic acidemias	
Propionic acidemia	
Methylmalonic acidemia	
Isovaleric acidemia	
β-Ketothiolase deficiency	
Multiple carboxylase deficiencies	
Medium-chain fatty acid acyl-coenzyme A dehydrogenase deficiency	
Glutaric acidemia type I	
3-Hydroxy-3-methylglutaric aciduria	
Lysinuric protein intolerance	
Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome	
Transient hyperammonemia of the newborn	
Congenital hyperinsulinism with hyperammonemia	

NAG synthetase deficiency. Patients with a deficiency of ASS, ASL, or arginase have marked increases in the plasma levels of citrulline, argininosuccinic acid, or arginine, respectively. Indeed, the combination of hyperammonemia and marked hypercitrullinemia or argininosuccinic acidemia is virtually pathognomonic for these disorders. Children with urea cycle defects often self-select a low-protein, high-carbohydrate diet, especially those with late-onset disease or symptomatic females with OTC deficiency.

Mass screening of newborn infants identifies patients with ASS, ASL, and arginase deficiencies.

TREATMENT OF ACUTE HYPERAMMONEMIA

Clinical outcome depends mainly on the severity and the duration of hyperammonemia. Serious neurologic sequelae are likely in newborns with severe elevations in blood ammonia (>300 μmole/L) for more than 12 hr. Thus, acute hyperammonemia should be treated promptly and vigorously. The goal of therapy is to lower the concentration of ammonia. This is accomplished in 2 ways: (a) removal of ammonia from the body in a form other than urea and (b) minimizing endogenous protein breakdown and favoring endogenous protein synthesis by providing adequate calories and essential amino acids (Table 85-4). Fluid, electrolytes, glucose (5-15%), and lipids (1-2 g/kg/24 hr) should be infused intravenously together with minimal amounts of protein (0.25 g/kg/24 hr), preferably including essential amino acids. Oral feeding with a low-protein formula (0.5-1.0 g/kg/24 hr) through a nasogastric tube should be started as soon as sufficient improvement in the clinical condition is seen.

Because the kidneys clear ammonia poorly, its removal from the body must be expedited by formation of compounds with a high renal clearance. An important advance in the treatment of hyperammonemia has been the introduction of acylation therapy by using an exogenous organic acid which is acylated endogenously with nonessential amino acids to form a nontoxic compound with high renal clearances. The main organic acids used for this purpose are sodium salts of benzoic acid and phenylacetic acid. Benzoate forms hippurate with endogenous glycine in the liver (see Fig. 85-12). Each mole of benzoate

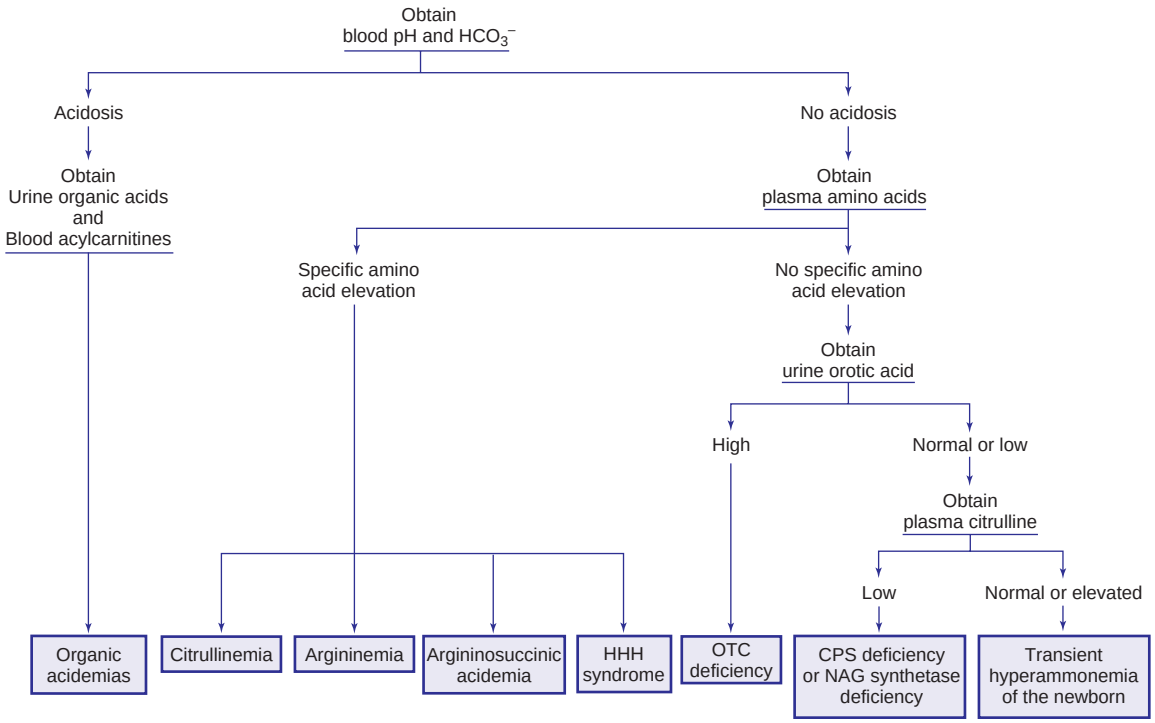

Figure 85-13 **Clinical approach to a newborn infant with symptomatic hyperammonemia.** CPS, carbamyl phosphate synthetase; HHH syndrome, hyperammonemia-hyperornithinemia-homocitrullinemia; NAG, *N*-acetylglutamate; OTC, ornithine transcarbamylase.

Table 85-4 Treatment of Acute Hyperammonemia in an Infant

1. Provide adequate calories, fluid, and electrolytes intravenously (10% glucose, NaCl* and intravenous lipids 1 g/kg/24 hr). Add minimal amounts of protein preferably as a mixture of essential amino acids (0.25 g/kg/24 hr) during the 1st 24 hr of therapy.
2. Give priming doses of the following compounds:
   (To be added to 20 mL/kg of 10% glucose and infused within 1-2 hr)
   - Sodium benzoate 250 mg/kg†
   - Sodium phenylacetate 250 mg/kg†
   - Arginine hydrochloride 200-600 mg/kg as a 10% solution
3. Continue infusion of sodium benzoate† (250-500 mg/kg/24 hr), sodium phenylacetate† (250-500 mg/kg/24 hr), and arginine (200-600 mg/kg/24 hr‡) following the above priming doses. These compounds should be added to the daily intravenous fluid.
4. Initiate peritoneal dialysis or hemodialysis if above treatment fails to produce an appreciable decrease in plasma ammonia.

*The concentration of sodium chloride should be calculated to be 0.45-0.9% including the amount of the sodium in the drugs.
†Sodium from these drugs should be included as part of the daily sodium requirement.
‡The higher dose is recommended in the treatment of patients with citrullinemia and argininosuccinic aciduria. Arginine is not recommended in patients with arginase deficiency and in those whose hyperammonemia is secondary to organic acidemia.

removes 1 mole of ammonia as glycine. Phenylacetate conjugates with glutamine to form phenylacetylglutamine, which is readily excreted in the urine. One mole of phenylacetate removes 2 moles of ammonia as glutamine from the body (see Fig. 85-12). A combined formulation of benzoate and phenylacetate (Ammonul) is commercially available for intravenous use.

Another valuable therapeutic adjunct is intravenous infusion of arginine, which is effective in all patients (except those with arginase deficiency). Arginine administration supplies the urea cycle with ornithine and NAG (see Fig. 85-12). In patients with citrullinemia, 1 mole of arginine reacts with 1 mole of ammonia (as carbamyl phosphate) to form citrulline. In patients with argininosuccinic acidemia, 2 moles of ammonia (as carbamyl phosphate and aspartate) react with arginine to form argininosuccinic acid. Citrulline and argininosuccinate are less toxic than ammonia and more readily excreted by the kidneys. In patients with CPS or OTC deficiency, arginine administration is indicated because this amino acid is not produced in sufficient amounts to enable endogenous protein synthesis. Patients with OTC deficiency benefit from supplementation with citrulline (200 mg/kg/24 hr) because 1 mole of citrulline reacts with 1 mole of ammonia (as aspartic acid) to form arginine. Administration of arginine or citrulline is **contraindicated** in patients with arginase deficiency, a rare condition in which the presenting clinical picture is one of spastic diplegia rather than hyperammonemia (see below). Arginine therapy is of no benefit if hyperammonemia is secondary to an organic acidemia. In a newborn infant with an initial episode of hyperammonemia, arginine should be used until the diagnosis is established.

Benzoate, phenylacetate, and arginine may be administered together for maximal therapeutic effect. A priming dose of these compounds is followed by continuous infusion until recovery from the acute state occurs (see Table 85-4). Both benzoate and phenylacetate are usually supplied as concentrated solutions and should be properly diluted (1-2% solution) for intravenous use. The recommended therapeutic doses of both compounds deliver a substantial amount of sodium to the patient; this amount should be included in calculation of the daily sodium requirement. Benzoate and phenylacetate (or the combined formulation, Ammonul) should be used with caution in newborn infants with hyperbilirubinemia because they may displace bilirubin from albumin; however, there are no documented cases of kernicterus (see Chapter 102.4) reported in neonates with hyperammonemia who have received such therapies. In infants at risk, it is advisable to reduce bilirubin to a safe level before administering benzoate or phenylacetate.

If the foregoing therapies fail within hours to produce any appreciable change in the blood ammonia level, peritoneal dialysis or, preferably, hemodialysis should be used. Exchange transfusion has little effect on reducing total body ammonia; it should be used only if dialysis cannot be employed promptly or when the patient is a newborn infant with hyperbilirubinemia (see above). Hemodialysis dramatically lowers blood ammonia within a few hours, but if it is unavailable or technically

unfeasible, peritoneal dialysis may be used as an alternative. When hyperammonemia is caused by an organic acidemia, peritoneal dialysis effectively removes both the offending organic acid and ammonia.

Oral administration of neomycin limits growth of intestinal bacteria that can produce ammonia. However, this modality is of limited use in patients (such as affected neonates) in whom reduction of hyperammonemia is an urgent priority. Oral lactulose acidifies the intestinal lumen, thereby reducing the diffusion of ammonia across the intestinal epithelium. This agent is of limited applicability in newborns in whom the risks of acidemia and dehydration are high.

There has been interest in the use of cooling as a therapeutic adjunct in newborn infants with metabolic encephalopathies like that caused by hyperammonemia. Clinical studies are in progress to evaluate the efficacy of this approach. There may be considerable lag between the normalization of ammonia and an improvement in the neurologic status of the patient. Several days may be needed before the infant becomes fully alert.

Long-Term Therapy

Once the infant is alert, therapy should be tailored to the underlying cause of the hyperammonemia. In general, all patients, regardless of the enzymatic defect, require some degree of protein restriction (1-2 g/kg/24 hr). In patients with defects in the urea cycle, chronic administration of benzoate (250-500 mg/kg/24 hr), phenylacetate (250-500 mg/kg/24 hr), and arginine (200-400 mg/kg/24 hr) or citrulline (in patients with OTC deficiency, 200-400 mg/kg/24 hr) is effective in maintaining blood ammonia levels within the normal range. Arginine and citrulline are contraindicated in patients with argininemia. Phenylbutyrate may be used in place of phenylacetate, because the patient and the family may not accept the latter owing to its offensive odor. A commercial preparation of the compound is available for oral use (Buphenyl). A significant innovation is the introduction of glycerol phenylbutyrate. This compound, unlike Buphenyl, is not a sodium salt and avoids the consequent coadministration of large amounts of sodium. It is approved for children ≥2 yr but is not yet approved for use in newborns. Benzoate and phenylacetate may lower carnitine levels, but clinical signs of carnitine deficiency or benefit from carnitine supplementation have not yet been demonstrated.

These compounds have been used during pregnancy without obvious teratogenic effect. However, experience is still quite limited and appropriate caution should be exercised.

Growth parameters, especially head circumference, and nutritional indices (blood albumin, prealbumin, pH, electrolytes, amino acids, zinc, selenium) should be followed closely. Long-term care of these patients is best achieved by a team of experienced professionals (pediatrician, nutritionist, child neurologist, metabolic geneticist). Skin lesions resembling **acrodermatitis enteropathica** (see Chapter 671) have been noted in a few patients with different types of urea cycle defects, presumably from deficiency of essential amino acids, especially arginine, caused by overzealous dietary protein restriction. Catabolic states (infections, fasting) that may trigger hyperammonemia should be avoided. They must be treated vigorously should they occur. It is important that all children with urea cycle defects avoid valproic acid (Depakote) because this drug elevates blood ammonia even in healthy subjects. In patients with CPS, OTC, and ASS deficiencies, acute hyperammonemic attacks may be precipitated by valproate administration.

CARBAMYL PHOSPHATE SYNTHETASE AND *N*-ACETYLGLUTAMATE SYNTHETASE DEFICIENCIES

See Figures 85-12 and 85-13.

Deficiencies of these 2 enzymes produce similar **clinical and biochemical manifestations**. There is a wide variation in severity of symptoms and in the age at presentation. In near complete enzymatic deficiency, symptoms appear during the first few days or even hours of life with signs and symptoms of hyperammonemia (refusal to eat, vomiting, lethargy, convulsion, and coma). Increased intracranial pressure is frequent. Late forms (as late as 32 yr of age) may present as an acute bout of hyperammonemia (lethargy, headache, seizures, psychosis) in a seemingly normal individual. Coma and death may occur during these episodes (a previously asymptomatic 26 yr old female died from hyperammonemia during childbirth). Diagnostic confusion with migraine is frequent. Intermediate forms with intellectual disability and chronic subclinical hyperammonemia interspersed with bouts of acute hyperammonemia have also been observed.

Laboratory findings include hyperammonemia. The plasma aminogram commonly shows a marked increase of glutamine and alanine with relatively low levels of citrulline and arginine. These are nondiagnostic changes that occur in hyperammonemia of diverse cause. Urinary orotic acid is usually low or may be absent (see Fig. 85-13).

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition is outlined above (see Table 85-4). Patients with NAG synthetase deficiency benefit from oral administration of carbamylglutamate. It is therefore important to differentiate between CPS and NAG synthetase deficiencies by gene sequencing. Deficiency of NAG synthetase is rare in North America.

CPS and NAG synthetase deficiencies are inherited as an autosomal recessive trait; the CPS enzyme is normally present in liver and intestine. The gene *(CPS1)* is mapped to chromosome 2q34; several disease-causing mutations have been found in different families. The prevalence of the condition is not known. The gene for NAG synthetase *(NAGS)* is located on chromosome 17q21.31. Neither of these conditions is identified by the mass screening of the newborn infants.

ORNITHINE TRANSCARBAMYLASE DEFICIENCY

See Figures 85-12 and 85-13.

In this X-linked partially dominant disorder, the hemizygous males are more severely affected than heterozygous females. The heterozygous females may have a mild form of the disease, but the majority (approximately 75%) is asymptomatic, although investigations indicate subtle neurologic defects even in women without a frank history of hyperammonemia. This is the most common form of all the urea cycle disorders, comprising approximately 40% of cases.

Clinical manifestations in a male newborn are usually those of severe hyperammonemia (see above) occurring in the first few days of life. Milder forms of the condition are commonly seen in heterozygous females and in some affected males. **Mild** forms characteristically have episodic manifestations, which may occur at any age (usually after infancy). Episodes of hyperammonemia (manifested by vomiting and neurologic abnormalities such as ataxia, mental confusion, agitation, combativeness and frank psychosis) are separated by periods of wellness. These episodes usually occur after ingestion of a high-protein diet or as a result of a catabolic state such as infection. Hyperammonemic coma, cerebral edema, and death may occur during one of these attacks. Cognitive development may proceed normally. Mild to moderate intellectual disability, however, is common. Gallstones have been seen in the survivors; the mechanism remains unclear.

The major **laboratory finding** during the acute attack is hyperammonemia accompanied by marked elevations of plasma concentrations of glutamine and alanine with low levels of citrulline and arginine. The blood level of urea is usually low. A marked increase in the urinary excretion of orotic acid differentiates this condition from CPS deficiency (see Fig. 85-13). Orotate may precipitate in urine as a pink-colored gravel or stones. In the mild form, these laboratory abnormalities may revert to normal between attacks. This form should be differentiated from all the episodic conditions of childhood. In particular, patients with lysinuric protein intolerance (see Chapter 85.14) may demonstrate some features of OTC deficiency, but the former can be differentiated by increased urinary excretion of lysine, ornithine, and arginine and elevated blood concentrations of citrulline.

The **diagnosis** is most conveniently confirmed by identification of the mutant gene, for which several commercial laboratories offer sequencing. As many as 20% of affected patients demonstrate a normal sequence, perhaps because the mutation involves an intron or a leader peptide. For these cases enzyme assay in a liver biopsy may be indicated. Prenatal diagnosis is feasible by analysis of DNA in amniocytes or chorionic villous samples. An oral protein load, which increases

plasma ammonia and urinary orotic acid levels, may identify asymptomatic heterozygous female carriers. A marked increase in urinary excretion of orotidine after an allopurinol loading test also detects obligate female carriers. Mild cerebral dysfunction may be present in asymptomatic female carriers. The importance of a detailed family history should be emphasized. A history of migraine or protein aversion is common in maternal female relatives of the proband. Indeed, careful scrutiny of the family history may reveal a pattern of unexplained deaths in male newborns in the maternal lineage.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined above. Citrulline is used in place of arginine in patients with OTC deficiency. Liver transplantation is a successful treatment for patients with OTC deficiency. It even has been performed during infancy.

The gene for OTC has been mapped to the X chromosome (Xp21.1). Many disease-causing mutations (>300) have been identified. The degree of enzyme deficiency and the genotype determine severity of the phenotype in most cases. Mothers of affected infants are expected to be carriers of the mutant gene unless a de novo mutation has occurred. A mother who gave birth to 2 affected male offspring was found to have a normal genotype, suggesting gonadal mosaicism in the mother. This condition is not identified by the mass screening of newborn infants.

ARGININOSUCCINATE SYNTHETASE (ASS) DEFICIENCY (CITRULLINEMIA)

See Figures 85-12 and 85-13.

Two clinically and genetically distinct forms of citrullinemia have been identified. The classic form (type I) is caused by the deficiency of the ASS enzyme. The adult form (type II) is caused by the deficiency of a mitochondrial transport protein named citrin.

Citrullinemia Type I (Classic Citrullinemia)

This condition is caused by the deficiency of ASS (see Fig. 85-12) and has variable **clinical manifestations** depending on the degree of the enzyme deficiency. Two major forms of the condition have been identified. The **severe or neonatal form**, which is most common, appears in the first few days of life with signs and symptoms of hyperammonemia (see above). In the **subacute or mild form**, clinical findings such as failure to thrive, frequent vomiting, developmental delay, and dry, brittle hair appear gradually after 1 yr of age. Acute hyperammonemia, triggered by an intercurrent catabolic state, may bring the diagnosis to light.

Laboratory findings are similar to those found in patients with OTC deficiency except that the plasma citrulline concentration is markedly elevated (50-100 times normal) (Fig. 85-13). Urinary excretion of orotic acid is moderately increased; crystalluria as a result of precipitation of orotates may also occur. The **diagnosis** is confirmed by assay of enzyme activity in cultured fibroblasts or by DNA analysis. Prenatal diagnosis is feasible with enzyme assay in cultured amniotic cells or by DNA analysis of cells obtained from chorionic villous biopsy.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter and in Table 85-3. Plasma concentration of citrulline remains elevated at all times and may increase further after administration of arginine. Although prognosis is poor for symptomatic neonates, patients with the mild disease usually do well on a protein-restricted diet in conjunction with sodium benzoate, phenylbutyrate, and arginine therapy. Mild to moderate cognitive impairment is a common sequela, even in a well-treated patient.

Citrullinemia is inherited as an autosomal recessive trait. The gene *(ASS 1)* is located on chromosome 9q34.11. Several disease-causing mutations have been identified in different families. The majority of patients are compound heterozygotes for 2 different alleles. The prevalence of the condition is not known. The recent introduction of neonatal screening for urea cycle defects has disclosed affected patients who are ostensibly asymptomatic, even with ingestion of a regular diet. Long-term follow-up is needed to be certain that these individuals do not sustain neurologic sequelae.

Citrullinemia Resulting From Citrin Deficiency (Citrullinemia Type II)

Citrin (aspartate-glutamate carrier protein) is a mitochondrial transporter encoded by a gene *(SLC25A13)* located on chromosome 7q21.3. One this protein's functions is to transport aspartate from mitochondria into cytoplasm; aspartate is required for converting citrulline to argininosuccinic acid (see Fig. 85-12). If aspartate is unavailable to the cytoplasmic component of the urea cycle, urea will not be formed at a normal rate and citrulline will accumulate. ASS activity is deficient in the liver of these patients, but no mutation in the gene for ASS has been found. It is postulated that citrin deficiency or its mutated gene interferes with translation of messenger RNA for ASS enzyme in the liver. Mutation in the gene for citrin produces 2 distinct clinical entities. The condition initially was reported almost exclusively in Japan but a few non-Japanese patients have been identified. Two clinical forms of citrin deficiency have been described.

Neonatal Intrahepatic Cholestasis (Citrullinemia Type II—Neonatal Form)

Clinical and laboratory manifestations, which usually start before 1 yr of age, include cholestatic jaundice with mild to moderate direct (conjugated) hyperbilirubinemia, marked hypoproteinemia, clotting dysfunction (increased prothrombin time and partial thromboplastin time), and increased serum GGTP and alkaline phosphatase activities; liver transaminases are usually normal. Plasma concentrations of ammonia and citrulline are usually normal, but moderate elevations are reported. There may be increases in plasma concentrations of methionine, tyrosine, alanine, and threonine. Elevated levels of serum galactose have been found even though the enzymes of galactose metabolism are normal. The reason for hypergalactosemia is not known. Marked elevation in the serum level of α-fetoprotein is also present. These findings resemble those of tyrosinemia type I, but unlike the latter condition, urinary excretion of succinylacetone is not elevated (see Chapter 85.2). Liver biopsy shows fatty infiltration, cholestasis with dilated canaliculi, and a moderate degree of fibrosis. The condition is usually self-limiting and the majority of infants recover spontaneously by 1 yr of age with only supportive and symptomatic treatment. Hyperammonemia and hypercitrullinemia, if present, should be treated with a low-protein diet and other appropriate measures (see above). Hepatic failure requiring liver transplantation has occurred in a few cases. Although the condition is commonly seen in Japan, the diagnosis should be considered in any case of unexplained neonatal hepatitis with cholestasis. Data on the long-term prognosis and the natural history of the condition are limited; development into the adult form of the condition (see below) after several years of seemingly asymptomatic hiatus has been observed.

Citrullinemia Type II, Adult Form (Adult-Onset Citrullinemia, Citrullinemia Type II—Mild Form)

This form starts suddenly in a previously normal individual and manifests with neuropsychiatric symptoms such as disorientation, delirium, delusion, aberrant behavior, tremors, and frank psychosis. Moderate degrees of hyperammonemia and hypercitrullinemia are present. The age at onset is usually between 20 and 40 yr (range: 11-85 yr). Patients who recover from the first episode may have recurrent attacks and most will die within a few years of diagnosis, mainly from cerebral edema. Pancreatitis, hyperlipidemia, and hepatoma are major complications among the survivors. Medical **treatment** has been mostly ineffective for prevention of future attacks. Indeed, some have speculated that the administration of large amounts of glucose might even prove deleterious, as the citrin transporter is important to the glycolytic pathway. Liver transplantation is the most effective therapy.

Several disease-causing mutations of the gene have been identified in affected Japanese families. The pathogenesis of citrullinemia type II (neonatal and adult forms) remains enigmatic. Although the frequency of homozygosity is relatively high in Japan (1 : 20,000 people), the clinical condition has a frequency of only 1 : 100,000 people. This indicates that a substantial number of homozygous individuals remain asymptomatic. Only a few non-Japanese patients have been identified.

ARGININOSUCCINATE LYASE DEFICIENCY (ARGININOSUCCINIC ACIDURIA)

See Figures 85-12 and 85-13.

The severity of the **clinical and biochemical manifestations** varies considerably. In the **neonatal form**, signs and symptoms of severe hyperammonemia (see above) develop in the first few days of life and mortality is high. Infants who survive the initial acute episode pursue a **subacute or late form** that is characterized by intellectual disability, failure to thrive, and hepatomegaly. A common finding is dry and brittle hair (trichorrhexis nodosa). Gallstones have been seen in some survivors. Acute attacks of severe hyperammonemia may occur during a catabolic state.

Laboratory findings include hyperammonemia, moderate elevations in liver enzymes, nonspecific increases in plasma levels of glutamine and alanine, a moderate increase in plasma levels of citrulline (less than that seen in citrullinemia), and marked increase in the concentration of argininosuccinic acid in plasma, urine and spinal fluid (see Fig. 85-13). The levels in the spinal fluid are usually higher than those in plasma. The enzyme is normally present in erythrocytes, the liver and cultured fibroblasts. Prenatal diagnosis is possible by measurement of the enzyme activity in cultured amniotic cells or by identification of the mutant gene. Argininosuccinic acid is also elevated in the amniotic fluid of affected fetuses.

Treatment of acute hyperammonemic attacks and the long-term therapy of the condition are outlined earlier in this chapter. Intellectual disability, persistent hepatomegaly with mild increases in liver enzymes, and bleeding tendencies as a result of abnormal clotting factors are common sequelae. This deficiency is inherited as an autosomal recessive trait with a prevalence of about 1 in 70,000 live births. The gene *(ASL)* is located on chromosome 7q11.21. Early detection is achieved through mass screening of newborn infants.

ARGINASE DEFICIENCY (HYPERARGININEMIA)

See Figures 85-12 and 85-13.

This defect is inherited as an autosomal recessive trait. There are 2 genetically distinct arginases in humans. One is cytosolic (ARG1) and is expressed in the liver and erythrocytes, and the other (ARG2) is found in renal and brain mitochondria. The gene for ARG1, the enzyme that is deficient in patients with arginase deficiency, is mapped to chromosome 6q23.2. The role of the mitochondrial enzyme is not well understood; its activity increases in patients with argininemia but has no protective effect. Several disease-causing mutations have been identified in different families.

Clinical manifestations of this rare condition are quite different from those of other urea cycle enzyme defects. The onset is insidious; the infant usually remains asymptomatic in the first few months or years of life. A **progressive spastic diplegia** with scissoring of the lower extremities, choreoathetotic movements, and loss of developmental milestones in a previously normal infant may suggest a degenerative disease of the CNS. Some children were treated for years as cases of cerebral palsy before their arginase deficiency was confirmed. Intellectual disability is progressive; seizures are common, but episodes of severe hyperammonemia are not usually seen. Hepatomegaly may be present. The acute neonatal form with intractable seizures, cerebral edema, and death has also been reported.

Laboratory findings include marked elevations of arginine in plasma and CSF (see Fig. 85-13). Urinary orotic acid is increased. Plasma ammonia levels may be normal or mildly elevated. Urinary excretion of arginine, lysine, cystine, and ornithine is usually increased, but normal levels have also been noted. Therefore, determination of amino acids in plasma is a critical step in the diagnosis of argininemia. The guanidino compounds (α-keto-guanidinovaleric acid and α-keto-argininic acid) are markedly increased in urine. The **diagnosis** is confirmed by assaying arginase activity in erythrocytes or by the identification of the mutant gene.

Treatment consists of a low-protein diet devoid of arginine. The composition of the diet and the daily intake of protein should be monitored by frequent plasma amino acid determinations. Sodium benzoate (250-375 mg/kg/24 hr) is also effective in controlling hyperammonemia and lowering plasma arginine levels. Intellectual disability is a common sequela of the condition. One patient developed type 1 diabetes at age 9 yr while his argininemia was under good control. Liver transplantation has produced promising results but no experience with long term outcome is available. Early detection is feasible through mass screening of newborn infants.

TRANSIENT HYPERAMMONEMIA OF THE NEWBORN

See Figure 85-13.

The blood concentration of ammonia in full-term infants may be as high as 100 μmole/L, or 2-3 times greater than that of the older child or adult. In premature infants, the upper limit of normal for blood ammonia may be as high as 150 μmole/L. Blood levels approximate the adult normal values after a few weeks of life. These infants are asymptomatic, and follow-up studies up to 18 mo of age have not revealed any significant neurologic deficits.

Severe transient hyperammonemia is observed in some newborn infants. The majority of affected infants are premature and have mild respiratory distress syndrome. Hyperammonemic coma may develop within 2-3 days of life, and the infant may succumb to the disease if treatment is not started immediately. **Laboratory studies** reveal marked hyperammonemia (plasma ammonia as high as 4,000 μmole/L) with moderate increases in plasma levels of glutamine and alanine. Plasma concentrations of urea cycle intermediate amino acids are usually normal except for citrulline, which may be moderately elevated. The cause of the disorder is unknown. Urea cycle enzyme activities are normal. **Treatment** of hyperammonemia should be initiated promptly and continued vigorously (see above). Recovery without sequelae is common, and hyperammonemia does not recur even with a normal protein diet.

ORNITHINE

Ornithine, a key intermediate of the urea cycle, is not incorporated into natural proteins. Rather, it is generated in the cytosol from arginine and must be transported into mitochondria, where it is a substrate for the OTC reaction, which forms citrulline. Excess ornithine is catabolized by 2 enzymes, ornithine 5-aminotransferase, which is a mitochondrial enzyme and converts ornithine to a proline precursor, and ornithine decarboxylase, which resides in the cytosol and converts ornithine to putrescine (see Fig. 85-12). Two genetic disorders feature hyperornithinemia: gyrate atrophy of the retina and hyperammonemia-hyperornithinemia-homocitrullinemia syndrome.

Gyrate Atrophy of the Retina and Choroid

This is a rare, autosomal recessive disorder caused by a deficiency of ornithine 5-aminotransferase (see Fig. 85-12). Approximately 30% of the reported cases are from Finland. **Clinical manifestations** are limited to the eyes and include night blindness, myopia, loss of peripheral vision, and posterior subcapsular cataracts. These eye changes start between 5 and 10 yr of age and progress to complete blindness by the 4th decade of life. Atrophic lesions in the retina resemble cerebral gyri. These patients usually have normal intelligence and a 10-20–fold increase in plasma levels of ornithine (400-1,400 μmole/L). They have neither hyperammonemia nor increases in plasma concentrations of any other amino acids; plasma levels of glutamate, glutamine, lysine, creatine, and creatinine are moderately decreased. Some patients respond partially to high doses of pyridoxine. An arginine-restricted diet in conjunction with supplemental lysine, proline, and creatine has been successful in reducing plasma ornithine concentration and has produced some clinical improvement. The gene for ornithine 5-aminotransferase *(OAT)* is mapped to chromosome 10q26.13. Many (at least 60) disease-causing mutations have been identified in different families.

HYPERAMMONEMIA-HYPERORNITHINEMIA-HOMOCITRULLINEMIA SYNDROME

In this rare autosomal recessive disorder, the defect is in the transport system of ornithine from the cytosol into the mitochondria, resulting in accumulation of ornithine in the cytosol and a deficiency of this

amino acid in mitochondria. The former causes hyperornithinemia and the latter results in disruption of the urea cycle and hyperammonemia (see Fig. 85-12). Homocitrulline is presumably formed from the reaction of mitochondrial carbamyl phosphate with lysine, which can become a substrate for the OTC reaction when ornithine is deficient. **Clinical manifestations** of hyperammonemia may develop shortly after birth or may be delayed until adulthood. Acute episodes of hyperammonemia manifest as refusal to feed, vomiting, and lethargy; coma may occur during infancy. Progressive neurologic signs, such as lower limb weakness, increased deep tendon reflexes, spasticity, clonus, seizures, and varying degrees of psychomotor retardation may develop if the condition remains undiagnosed. No clinical ocular findings have been observed in these patients.

Laboratory findings reveal marked increases in plasma levels of ornithine and homocitrulline in addition to hyperammonemia (see Fig. 85-13). Acute episodes of hyperammonemia should be treated promptly (see above). Restriction of protein intake improves hyperammonemia. Oral supplementation with ornithine and arginine (or citrulline) has produced clinical improvement in some patients. The gene for this disorder *(SLC25A15)* is located on chromosome 13q14.11.

Bibliography is available at Expert Consult.

85.13 Histidine

Iraj Rezvani

Histidine is an essential amino acid only during infancy. Its biosynthetic pathway in older children and adults is poorly understood. Histidine is degraded through the urocanic acid pathway to glutamic acid. Several genetic biochemical aberrations involving the degradative pathway of histidine have been reported, but none has any clinical consequence.

Decarboxylation of histidine by histidine decarboxylase produces histamine. Deficiency of this enzyme is the cause of familial form of **Tourette syndrome** (see Chapter 85.11).

Bibliography is available at Expert Consult.

85.14 Lysine

Iraj Rezvani

Lysine is catabolized through 2 pathways. In the first pathway, lysine is condensed with α-ketoglutaric acid to form saccharopine. Saccharopine is then catabolized to α-aminoadipic acid semialdehyde and glutamic acid. These first 2 steps are catalyzed by α-aminoadipic semialdehyde synthase, which has 2 activities: lysine-ketoglutarate reductase, and saccharopine dehydrogenase (see Fig. 85-14). In the second pathway, lysine is first transaminated and then condensed to its cyclic forms, pipecolic acid and piperidine-6-carboxylic acid (P6C). The latter compound (P6C) and its linear form, α-aminoadipic acid semialdehyde, are oxidized to α-aminoadipic acid by the enzyme antiquitin. This is the major pathway for D-lysine in the body and for the L-lysine in the brain (see Fig. 85-14).

Hyperlysinemia, *α-aminoadipic acidemia*, and *α-ketoadipic acidemia* are 3 biochemical conditions that are caused by inborn errors of metabolism of lysine. Individuals with these conditions are usually asymptomatic.

PYRIDOXINE (VITAMIN B_6)-DEPENDENT EPILEPSY

Pyridoxal 5′-phosphate, the active form of pyridoxine, is the cofactor for many enzymes including those involved in the metabolism of neurotransmitters. Intracellular deficiency of pyridoxal 5′-phosphate in the brain may result in a seizure disorder that is refractory to common anticonvulsant agents but is responsive to high doses of pyridoxine. This pyridoxine-dependent epilepsy is seen in the following genetic metabolic conditions:

Antiquitin (α-Aminoadipic Semialdehyde Dehydrogenase) Deficiency

This is the most common cause of pyridoxine-dependent epilepsy. Deficiency of antiquitin results in accumulation of P6C in brain tissue (see Fig. 85-14); P6C reacts with pyridoxal 5′-phosphate and renders it inactive. Large doses of pyridoxine are, therefore, needed to overcome this inactivation.

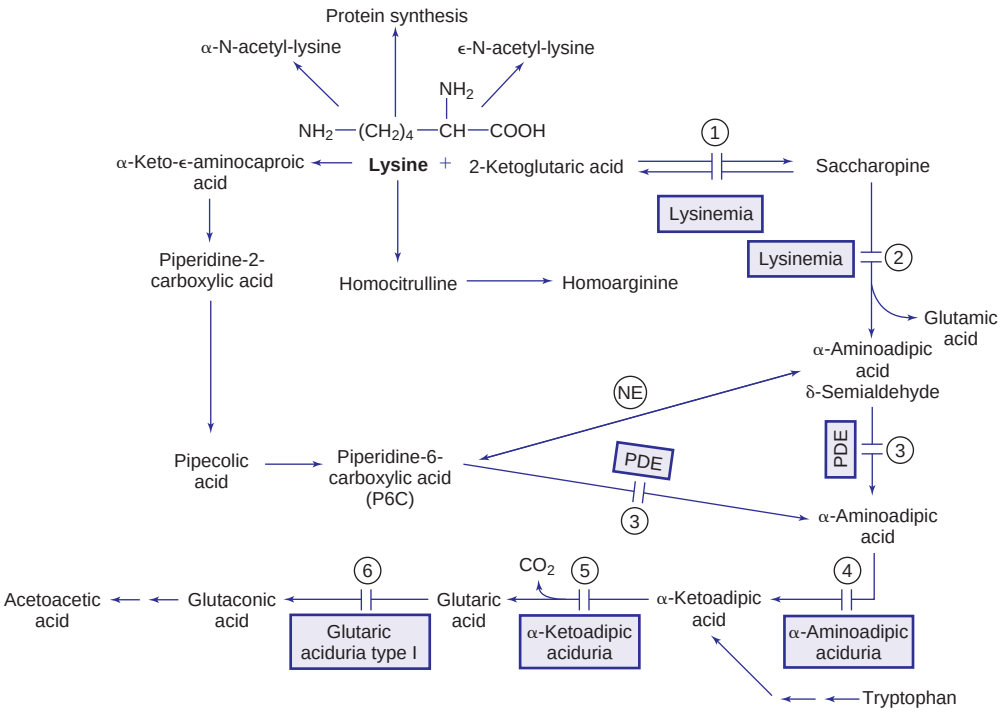

Figure 85-14 Pathways in the metabolism of lysine. **Enzymes:** *(1)* Lysine ketoglutarate reductase, *(2)* saccharopine dehydrogenase, *(3)* α-aminoadipic semialdehyde/piperidine-6-carboxylic acid (P6C) dehydrogenase (antiquitin), *(4)* α-aminoadipic acid transferase, *(5)* α-ketoadipic acid dehydrogenase, *(6)* glutaryl-CoA-dehydrogenase. NE, nonenzymatic; PDE, pyridoxine-dependent epilepsy.

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Sulfite Oxidase Deficiency (Molybdenum Cofactor Deficiency)

In this rare condition (see Chapter 85.4), accumulation of sulfites causes inhibition of enzymatic activity of antiquitin and accumulation of P6C, which, in turn, causes inactivation of pyridoxal-5′-phospate and vitamin B_6 dependency.

Hyperprolinemia Type II

In this condition, accumulation of P5C in brain tissue causes inactivation of pyridoxal-5′-phosphate and hence pyridoxine dependency (see Chapter 85.9 and Fig. 85-9).

Hypophosphatasia

Pyridoxal-5′-phosphate is the main circulating form of pyridoxine. Alkaline phosphatase is required for dephosphorylation of pyridoxal-5′-phosphate to generate free pyridoxine which is the only form of vitamin B_6 that can cross the blood–brain barrier and enter the brain cells. Pyridoxine is rephosphorylated intracellularly to form pyridoxal-5′-phosphate. In the infantile form of hypophosphatasia, pyridoxal-5′-phosphate cannot be dephosphorylated to free pyridoxine because of marked deficiency of tissue nonspecific alkaline phosphatase. This results in deficiency of pyridoxine in the brain and pyridoxine-dependent epilepsy (see Chapters 593 and 705).

The main **clinical manifestation** of pyridoxine-dependent epilepsy caused by antiquitin deficiency is generalized seizures, which usually occur in the first few hours of life and are unresponsive to conventional anticonvulsant therapies. Some mothers of affected fetuses report abnormal intrauterine fluttering movements. The seizures are usually tonic-clonic in nature but can be almost any type. Other manifestations such as dystonia, respiratory distress, and abdominal distention with vomiting, hepatomegaly, hypoglycemia and hypothermia may be present. Late-onset forms of the condition (as late as 5 yr of age) have been reported. Consequently, a trial with vitamin B_6 is recommended in any infant with intractable convulsions (see Chapters 593.4 and 593.6).

Laboratory studies reveal increased concentrations of α-aminoadipic semialdehyde and pipecolic acid in the CSF, plasma, and urine. EEG shows abnormalities corresponding to the type of seizures; these changes usually normalize after treatment. Neuroimaging may be normal but cerebellar and cerebral atrophy, periventricular hyperintensity, intracerebral hemorrhage, and hydrocephalus may be present.

Treatment with large doses of vitamin B_6 (50-100 mg/kg) usually results in a dramatic improvement of both seizures and the EEG abnormalities. The dependency and hence the therapy are lifelong. The therapeutic benefit of a lysine-restricted diet remains to be determined. Learning problems and speech delay are common sequelae. The condition is inherited as an autosomal recessive trait; the gene for antiquitin *(ALDH7A1)* is on chromosome 5q31.

GLUTARIC ACIDURIA TYPE I

Glutaric acid is an intermediate in the degradation of lysine (see Fig. 85-14), hydroxylysine, and tryptophan. Glutaric aciduria type I, a disorder caused by a deficiency of glutaryl CoA dehydrogenase, should be differentiated from glutaric aciduria type II, a distinct clinical and biochemical disorder caused by defects in the electron transport system (see Chapter 86.1).

Clinical Manifestations

Affected infants with glutaric aciduria type I may develop normally up to 2 yr of life; macrocephaly is a common finding in these infants and precedes onset of neurologic manifestations. Some affected infants may also show subtle neurologic symptoms, such as hypotonia, irritability, and feeding problems, during this seemingly asymptomatic period. The onset of the condition is usually heralded by acute encephalopathic findings such as loss of normal developmental milestones (head control, sitting), choreoathetosis, seizures, generalized rigidity, opisthotonos, and dystonia. These symptoms may occur suddenly in a seemingly normal infant after a minor infection. Recovery from the first attack usually occurs slowly, but some residual neurologic abnormalities, especially dystonia and extrapyramidal movements may persist. Additional acute attacks resembling the first one usually occur during episodes of intercurrent infections or catabolic states. In some patients, these signs and symptoms may develop gradually in the first few years of life; hypotonia and choreoathetosis may gradually progress into rigidity and dystonia ("insidious form"). Acute episodes of metabolic decompensation with vomiting, ketosis, seizures, and coma also occur in this form after infection or other catabolic states. Death usually occurs in the 1st decade of life during one of these episodes. The affected infants are prone to development of subdural hematoma and retinal hemorrhage following minor falls and head traumas. This may be misdiagnosed as child abuse. The intellectual abilities usually remain relatively normal in most patients.

Laboratory Findings

During acute episodes, mild to moderate metabolic acidosis and ketosis may occur. Hypoglycemia, hyperammonemia, and elevations of serum transaminases are seen in some patients. High concentrations of glutaric acid are usually found in urine, blood, and CSF. 3-Hydroxyglutaric acid may also be present in the urine. Plasma concentrations of amino acids are usually within normal limits. Laboratory findings may be unremarkable between attacks. Severely affected children without glutaric aciduria have also been reported ("low excretors"). In some of these patients, the glutaric acid is elevated only in the spinal fluid. In any child with progressive dystonia and dyskinesia, activity of the enzyme glutaryl CoA dehydrogenase should be measured in leukocytes or cultured fibroblasts as urinary glutaric acid may not be elevated in those patients who are the "low excretors." Neuroimaging of the brain may reveal macrocephaly, increased extraaxial (particularly frontal) fluid, striatal lesions, dilated lateral ventricles, cortical atrophy (mainly in frontotemporal region), and fibrosis.

Treatment

A low-protein diet (especially a diet restricted in lysine and tryptophan) and high doses (200-300 mg/24 hr) of riboflavin (the coenzyme for glutaryl CoA dehydrogenase) and L-carnitine (50-100 mg/kg/24 hr orally) produce a dramatic decrease in the levels of glutaric acid in body fluids, but their effects on the clinical outcome have been variable. Early diagnosis (through newborn screening) with prevention and aggressive treatment of intercurrent catabolic states (infections) are shown to minimize striatal insults and assure a more favorable prognosis. The addition of a GABA analog (baclofen) and valproic acid to the therapeutic regimen produces improvement in some affected children.

The condition is inherited as an autosomal recessive trait. The prevalence is estimated at 1 : 100,000 live births worldwide. The condition is more prevalent in some ethnic populations (Canadian Oji-Cree Indians, Irish travelers, black South Africans, Swedes, and the Old Order Amish population in the United States). The gene for glutaryl CoA dehydrogenase *(GCDH)* is located on chromosome 19p13.2 and many disease-causing mutations have been reported in different families. A single mutation *(A421V)* accounts for all the patients from the Lancaster County (Pennsylvania) Old Order Amish community.

Prenatal diagnosis may be accomplished by demonstrating increased concentrations of glutaric acid in amniotic fluid, by the assay of the enzyme activity in amniocytes or chorionic villous samples, or by identification of the mutant gene.

LYSINURIC PROTEIN INTOLERANCE (FAMILIAL PROTEIN INTOLERANCE)

This rare autosomal recessive disorder is caused by a defect in the transport of the cationic amino acids lysine, ornithine, and arginine in both intestine and kidneys. Unlike patients with cystinuria, urinary excretion of cystine is not increased in these patients. Deficiency of the transporter protein in this condition causes multisystem manifestations, which start initially with gastrointestinal symptoms. Refusal to feed, nausea, aversion to protein, vomiting, and mild diarrhea, which may result in failure to thrive, wasting, and hypotonia, start shortly

after birth. Breastfed infants usually remain asymptomatic until shortly after weaning. This may be because of the low protein content of breast milk. Episodes of hyperammonemia may occur after ingestion of a high-protein diet. Mild to moderate hepatosplenomegaly, osteoporosis, sparse brittle hair, thin extremities with moderate centripetal adiposity, and growth retardation are common physical findings in patients whose condition has remained undiagnosed. Mental development is usually normal, but moderate intellectual disability has been observed in 20% of patients.

Progressive **interstitial pneumonitis with bouts of acute exacerbation commonly occurs in these patients.** This usually progresses to severe **alveolar proteinosis**. **Clinical manifestations** include progressive exertional dyspnea, fatigue, cough, diminished breath sound, and inspiratory rales; cyanosis may develop in older patients. Some patients have remained undiagnosed until the appearance of pulmonary manifestations. Radiographic evidence of pulmonary fibrosis has been observed in up to 65% of patients without clinical manifestations of pulmonary involvement.

Renal involvement is manifested initially by proteinuria, hematuria, and elevation of serum creatinine, which may progress to end-stage renal failure. Renal tubular involvement with findings compatible with Fanconi syndrome may also be present. Renal biopsy reveals pathologic findings consistent with glomerulonephritis and tubulointerstitial nephritis. Hematologic findings of anemia, leukopenia, and thrombocytopenia may also be present. A condition resembling hemophagocytic lymphohistiocytosis/macrophage activation syndrome has also been reported. Immunologic abnormalities (impaired lymphocyte function, abnormalities in immune globulins, hypocomplementemia), hypercholesterolemia, hypertriglyceridemia, and acute pancreatitis have also been reported in these patients.

Laboratory findings may reveal hyperammonemia and an elevated concentration of urinary orotic acid, which develop after protein feeding. Plasma concentrations of lysine, arginine, and ornithine are usually mildly decreased, but urinary levels of these amino acids, especially lysine, are greatly increased. The pathogenesis of hyperammonemia is not well understood. All enzymes of the urea cycle are normal. Hyperammonemia may be related to disruption of the urea cycle secondary to deficiency of arginine and ornithine. However, in patients with cystinuria who also have defects in the transport of lysine, arginine, and ornithine in both intestine and kidneys, hyperammonemia is not observed. Plasma concentrations of alanine, glutamine, serine, glycine, proline, and citrulline are usually increased. Anemia, increased serum levels of ferritin, LDH, and thyroxine-binding globulin, have also been observed in these patients. This condition should be differentiated from hyperammonemia caused by urea cycle defects (see Chapter 85.12), especially in heterozygous females with OTC deficiency. Increased urinary excretion of lysine, ornithine, and arginine and elevated blood levels of citrulline are not seen in patients with OTC deficiency.

The transport defect in this condition resides in the basolateral (antiluminal) membrane of enterocytes and renal tubular epithelia. This explains the observation that cationic amino acids are unable to cross these cells even when administered as dipeptides. Lysine in the form of dipeptide crosses the luminal membrane of the enterocytes but hydrolyzes to free lysine molecules in the cytoplasm. Free lysine, unable to cross the basolateral membrane of the cells, diffuses back into the lumen.

Treatment with a low-protein diet (1.0-1.5 g/kg/24 hr) supplemented with citrulline (100 mg/kg/day) has produced biochemical and clinical improvements. Episodes of hyperammonemia should be treated promptly (see Chapter 85.12). Supplementation with lysine is not useful because it is poorly absorbed and tends to produce diarrhea and abdominal pain. Diet therapy has no effect in prevention or amelioration of the multisystem manifestations. Treatment with high doses of prednisone has been effective in the management of acute pulmonary complications in some patients. Bronchopulmonary lavage is the treatment of choice for patients with alveolar proteinosis. The condition is most prevalent in Finland and Japan where the prevalence is 1:60,000 and 1:57,000 live births, respectively.

The gene for lysinuric protein intolerance *(SLC7A7)* is mapped to chromosome 14q11.2, and several disease-causing mutations have been identified in different families. Pregnancies in affected mothers have been complicated by anemia, thrombocytopenia, toxemia, and bleeding, but offspring have been normal.

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85.15 Aspartic Acid (Canavan Disease)

Kimberlee M. Matalon and Reuben K. Matalon

N-Acetylaspartic acid, a derivative of aspartic acid, is synthesized in the brain and is found in a high concentration similar to glutamic acid. The exact function of *N*-acetylaspartic acid is unknown, but it may serve as a reservoir for acetate, which is needed for myelin synthesis. Aspartoacylase, cleaves the *N*-acetyl group from *N*-acetylaspartic acid. Deficiency of aspartoacylase, leads to Canavan disease, a severe **leukodystrophy**, characterized by excessive excretion of *N*-acetylaspartic acid and spongy degeneration of the white matter of the brain. Canavan disease is an autosomal recessive disorder and is more prevalent in individuals of Ashkenazi Jewish descent than in other ethnic groups. Aspartoacylase deficiency can be determined in skin fibroblasts, but the diagnosis is easy to ascertain by increased excretion of *N*-acetylaspartic acid in the urine. The gene for Canavan disease has been cloned, and mutations can be measured in patients, family members, and at-risk populations.

ETIOLOGY AND PATHOLOGY

The deficiency of the enzyme aspartoacylase leads to the accumulation of *N*-acetylaspartic acid in the brain, especially in white matter, and massive urinary excretion of this compound. Excessive amounts of *N*-acetylaspartic acid are also present in the blood and CSF. Brain biopsies of patients with Canavan disease show spongy degeneration of the myelin fibers, astrocytic swelling, and elongated mitochondria. There is striking vacuolization and astrocytic swelling in white matter. Electron microscopy reveals distorted mitochondria. As the disease progresses, the ventricles enlarge, owing to cerebral atrophy.

CLINICAL MANIFESTATIONS

The severity of Canavan disease covers a wide spectrum. Infants usually appear normal at birth and may not manifest symptoms of the disease until 3-6 mo of age, when they develop **progressive macrocephaly**, severe hypotonia, persistent head lag, and delayed milestones. As the disease progresses, there is spasticity, joint stiffness, and contractures. Optic atrophy and seizures develop. Feeding difficulties, poor weight gain, and gastroesophageal reflux may occur in the 1st yr of life; swallowing deteriorates, and nasogastric feeding or permanent gastrostomy may be required. Most patients die in the 1st decade of life; with improved nursing care, they may survive through the second decade.

ATYPICAL CANAVAN DISEASE

Juvenile or mildly affected patients with Canavan disease usually present with mild developmental delay, although 1 patient also had a large head and retinitis pigmentosa. These children have moderately increased urinary excretion of *N*-acetylaspartic acid, which suggests Canavan disease. Brain MRI demonstrates increased signal intensity in the basal ganglia rather than global white matter disease, sometimes leading to confusion with mitochondrial disease.

Diagnosis

In a typical patient with Canavan disease, CT scan and MRI reveal diffuse white matter degeneration, primarily in the cerebral hemispheres, with less involvement of the cerebellum and brainstem (Fig. 85-15). Repeated evaluations may be required. MRS performed at the time MRI is done can show the high peak of *N*-acetylaspartic acid, suggesting Canavan disease. The definitive diagnosis can be established by finding elevated amounts of *N*-acetylaspartic acid in the urine or

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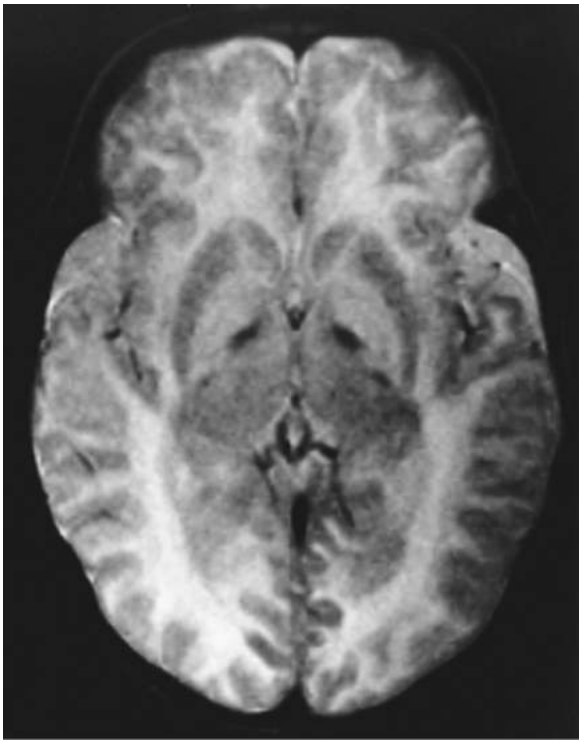

Figure 85-15 Axial T-weighted MRI of a 2 yr old patient with Canavan disease. Extensive thickening of the white matter is seen.

blood. A deficiency of aspartoacylase can be found in cultured skin fibroblasts. The biochemical method is the preferred choice for diagnosis. *N*-acetylaspartic acid is found only in trace amounts (24 ± 16 µmol/mmol creatinine) in the urine of unaffected individuals, whereas in patients with Canavan disease its concentration is in the range of 1,440 ± 873 µmol/mmol creatinine. High levels of *N*-acetylaspartic acid can also be detected in plasma, CSF, and brain tissue. The activity of aspartoacylase in the fibroblasts of obligate carriers is less than or equal to half of the activity found in normal individuals. The differential diagnosis of Canavan disease should include Alexander disease, which is another leukodystrophy associated with macrocephaly. Alexander disease is caused by a defect in the synthesis of glial fibrillary acidic protein and the diagnosis can be ruled out by molecular diagnosis on blood lymphocytes.

There are 2 mutations leading to Canavan disease predominant in the Ashkenazi Jewish population. The first is an amino acid substitution (E285A) in which glutamic acid is substituted for alanine. This mutation is the most frequent and encompasses 83% of 100 mutant alleles examined in Ashkenazi Jewish patients. The second common mutation is a change from tyrosine to a nonsense mutation, leading to a stop in the coding sequence (Y231X). This mutation accounts for 13% of the 100 mutant alleles. In the non-Jewish population, more diverse mutations have been observed, and the 2 mutations common in Jewish people are rare. A different mutation (A305E), the substitution of alanine for glutamic acid, accounts for 40% of 62 mutant alleles in non-Jewish patients. More than 50 mutations are described in the non-Jewish population. With Canavan disease, it is important to obtain a molecular diagnosis because this will lead to accurate counseling and prenatal guidance for the family. If the mutations are not known, prenatal diagnosis relies on the level of *N*-acetylaspartic acid in the amniotic fluid. In Ashkenazi Jewish patients, the carrier frequency can be as high as 1:36, which is close to that of Tay-Sachs disease. Carrier screening for Canavan disease is available for Jewish individuals. Genotype phenotype correlation and aspartoacylase expression show that expression studies may aid in understanding the disease.

Patients with juvenile or mild forms of Canavan disease have been compound heterozygotes with a mild mutation on one allele and a severe mutation on the other mutation. Mild mutations include p.Tyr288Cys and p.Arg71His.

Treatment and Prevention

No specific treatment is available. Feeding problems and seizures should be treated on an individual basis. Genetic counseling, carrier testing, and prenatal diagnosis are the only methods of prevention. Gene therapy attempts in children with Canavan disease have shown lack of long-term adverse events, some decrease in the brain elevation of *N*-acetylaspartic acid, improved seizure frequency, and stabilization of overall clinical status. There are ongoing trials of glycerol-triacetate as a supplement for acetate deficiency.

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Chapter 86

Defects in Metabolism of Lipids

86.1 Disorders of Mitochondrial Fatty Acid β-Oxidation

Charles A. Stanley and Michael J. Bennett

Mitochondrial β-oxidation of fatty acids is an essential energy-producing pathway. It is a particularly important pathway during prolonged periods of starvation, and during periods of reduced caloric intake because of gastrointestinal illness or increased energy expenditure during febrile illness. Under these conditions, the body switches from using predominantly carbohydrate to predominantly fat as its major fuel. Fatty acids are also important fuels for exercising skeletal muscle and are the preferred substrate for the heart. In these tissues, fatty acids are completely oxidized to carbon dioxide and water. The end products of hepatic fatty acid oxidation are the ketone bodies β-hydroxybutyrate and acetoacetate. These cannot be oxidized by the liver but are exported to and serve as important fuels in peripheral tissues, particularly the brain, which can partially substitute ketone bodies for glucose during periods of fasting.

Genetic defects have been identified in nearly all of the known steps in the fatty acid oxidation pathway; all are recessively inherited (Table 86-1).

Clinical manifestations characteristically involve those tissues with a high β-oxidation flux, including liver, skeletal, and cardiac muscle. The most common presentation is an acute episode of life-threatening coma and hypoglycemia induced by a period of fasting because of defective hepatic ketogenesis. Other manifestations may include chronic cardiomyopathy and muscle weakness or exercise-induced acute rhabdomyolysis. The fatty acid oxidation defects can often be asymptomatic during periods when there is no fasting stress. Acutely presenting disease may be misdiagnosed as **Reye syndrome** or, if fatal, as **sudden unexpected infant death**. Fatty acid oxidation disorders are easily overlooked because the only specific clue to the diagnosis may be the finding of inappropriately low concentrations of urinary ketones in an infant who has hypoglycemia. Genetic defects in ketone body utilization may also be overlooked because ketosis is an expected finding with fasting hypoglycemia. In some circumstances, clinical manifestations appear to arise from toxic effects of fatty acid metabolites rather than inadequate energy production. These include disorders (long chain 3-hydroxyacyl dehydrogenase

Table 86-1 Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features

ENZYME DEFICIENCY	GENE	CLINICAL PHENOTYPE	LABORATORY FINDINGS
Carnitine transporter	*OCTN2* *SLC22A5*	Cardiomyopathy, skeletal myopathy, liver disease, sudden death, endocardial fibroelastosis, prenatal and newborn screening diagnosis reported	↓ Total and free carnitine, normal acylcarnitines, acylglycine, and organic acids
Long-chain fatty acid transporter	*FATP1-6*	Rare, acute liver failure in childhood requiring liver transplantation	Reduced intracellular C_{14}-C_{18} fatty acids, reduced fatty acid oxidation
Carnitine palmitoyl transferase-I	*CPT-IA*	Liver failure, renal tubulopathy, and sudden death. Prenatal and newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome association described in a few patients	Normal or ↑ free carnitine, normal acylcarnitines, acylglycine, and organic acids
Carnitine acylcarnitine translocase	*CACT* *SLC25A20*	Chronic progressive liver failure, persistent ↑ NH_3, hypertrophic cardiomyopathy. Newborn screening diagnosis reported	Normal or ↓ free carnitine, abnormal acylcarnitine profile
Carnitine palmitoyl transferase-II	*CPT-II*	Early and late onset types. Liver failure, encephalopathy, skeletal myopathy, cardiomyopathy, renal cystic changes, newborn screening diagnosis reported. Adult form with acute rhabdomyolysis, myoglobinuria	Normal or ↓ free carnitine, abnormal acylcarnitine profile
Short-chain acyl-CoA dehydrogenase	*SCAD* *ACADS*	Clinical phenotype is unclear. Many individuals appear to be normal. Others have a variety of inconsistent signs and symptoms. Subset may have severe manifestations of unclear relationship to biochemical defects. Newborn screening diagnosis reported; significance being questioned	Normal or ↓ free carnitine, elevated urine ethylmalonic acid, inconsistently abnormal acylcarnitine profile
Medium-chain acyl-CoA dehydrogenase	*MCAD* *ACADM*	Hypoglycemia, hepatic encephalopathy, sudden death. Newborn screening diagnosis possible, maternal preeclampsia, HELLP syndrome association described rarely	Normal or ↓ free carnitine, ↑ plasma acylglycine, plasma C_6-C_{10} free fatty acids, ↑ C_8-C_{10} acyl-carnitine
Very long-chain acyl-CoA dehydrogenase	*VLCAD* *ACADVL*	Dilated cardiomyopathy, arrhythmias, hypoglycemia, and hepatic steatosis. Late-onset, stress-induced rhabdomyolysis, episodic myopathy. Prenatal and newborn screening diagnosis possible.	Normal or ↓ free carnitine, ↑ plasma $C_{14:1}$, C_{14} acylcarnitine, ↑ plasma C_{10}-C_{16} free fatty acids
ETF dehydrogenase*	*ETF-DH*	Nonketotic fasting hypoglycemia, congenital anomalies, milder forms of liver disease, cardiomyopathy, and skeletal myopathy. Newborn screening diagnosis reported	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
ETF-α*	*α-ETF*	Nonketotic fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
ETF-β*	*β-ETF*	Fasting hypoglycemia, congenital anomalies, liver disease, cardiomyopathy, and skeletal myopathy also described. Newborn screening diagnosis reported	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ acylcarnitine, urine organic acid and acylglycines
Short-chain L-3-hydroxyacyl-CoA dehydrogenase	*SCHAD* *HADH*	Hyperinsulinemic hypoglycemia, cardiomyopathy, myopathy. Newborn screening diagnosis reported	Normal or ↓ free carnitine, elevated free fatty acids, inconsistently abnormal urine organic acid, ↑3-OH glutarate. ↑ plasma C_4-OH acylcarnitine
Long-chain L-3-hydroxyacyl-CoA dehydrogenase	*LCHAD* *HADH-A*	Newborn screening diagnosis reported, maternal preeclampsia, HELLP syndrome, and AFLP association described frequently. See also MTP below for clinical manifestations	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines
MTP	*HADH-A,* *HADH-B*	Severe cardiac and skeletal myopathy, hypoglycemia, acidosis, hyper NH_3, sudden death, elevated liver enzymes, retinopathy. Maternal preeclampsia, HELLP syndrome, and AFLP association described frequently	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ C_{16}-OH and C_{18}-OH carnitines
Long-chain 3-ketoacyl-CoA thiolase	*LKAT* *HADH-B*	Severe neonatal presentation, hypoglycemia, acidosis, ↑ creatine kinase, cardiomyopathy, neuropathy, and early death	Normal or ↓ free carnitine, increased ratio of acyl:free carnitine, ↑ free fatty acids, ↑ 2-*trans*, 4-*cis*-decadienoylcarnitine
2,4-Dienoyl-CoA reductase	*DECR1*	Only 1 patient described, hypotonia in the newborn, mainly severe skeletal myopathy and respiratory failure. Hypoglycemia rare	Normal or ↓ free carnitine, ↑ acyl:free carnitine ratio, normal urine organic acids and acylglycines

Continued

Table 86-1 Mitochondrial Fatty Acid Oxidation Disorders—Clinical and Biochemical Features—cont'd

ENZYME DEFICIENCY	GENE	CLINICAL PHENOTYPE	LABORATORY FINDINGS
HMG CoA synthetase	*HMGCS2*	Hypoketosis and hypoglycemia, rarely myopathy	Elevated total plasma fatty acids, enzyme studies in biopsied liver may be diagnostic, genetic testing is preferred
HMG CoA lyase	*HMGCL*	Hypoketosis and hypoglycemia, rarely myopathy	Normal free carnitine, ↑ C_5-OH, and methylglutaryl-carnitine, enzymes studies in fibroblasts may be diagnostic

*Also known as glutaric acidemia type II or multiple acyl-CoA dehydrogenase deficiency (MADD).

AFLP, acute fatty liver of pregnancy; CoA, coenzyme A; ETF, electron transport flavoprotein; HELLP, hemolysis, elevated liver enzymes, low platelets; MTP, mitochondrial trifunctional protein; NH_3, ammonia.

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[LCHAD], carnitine palmitoyltransferase-1A [CPT-IA], mitochondrial trifunctional protein [MTP; also known as TFP] deficiencies) in which the presence of a homozygous affected fetus increases the risk of a life-threatening illness in the heterozygote mother, resulting in acute fatty liver of pregnancy or **preeclampsia with HELLP** (hemolysis, elevated liver enzymes, low platelets) syndrome. Malformations of the brain and kidneys have been described in severe electron transfer flavoprotein (ETF), ETF dehydrogenase (ETF-DH), and carnitine palmitoyltransferase-2 (CPT-II) deficiencies that might reflect in utero toxicity of fatty acid metabolites or a developmental role for these enzymes. Progressive retinal degeneration, peripheral neuropathy, and chronic progressive liver disease have been identified in LCHAD and MTP deficiency. Newborn screening programs using tandem mass spectrometry detect characteristic acylcarnitines seen in many of these disorders and permit presymptomatic diagnosis. Screening programs have provided evidence to demonstrate that all the fatty acid oxidation disorders combined are among the most common inborn errors of metabolism.

Figures 86-1 and 86-2 outline the steps involved in the oxidation of a typical long-chain fatty acid. In the *carnitine cycle*, fatty acids are transported across the barrier of the inner mitochondrial membrane as acylcarnitine esters. Within the mitochondria, successive turns of the 4-step β-*oxidation cycle* convert the coenzyme A (CoA)-activated fatty acid to acetyl-CoA units. Two to 3 different chain-length specific isoenzymes are needed for each of these β-oxidation steps to accommodate the different-sized fatty acyl-CoA species. The electron transfer pathway carries electrons generated in the first β-oxidation step (acyl-CoA dehydrogenase) to the *electron transport chain* at the level of coenzyme Q for adenosine triphosphate production, while electrons generated from the third step (3-hydroxyacyl-CoA dehydrogenase) enter the *electron transport chain* at the level of complex 1. Most of the acetyl-CoA generated from hepatic β-oxidation flows through the *pathway of ketogenesis* to form β-hydroxybutyrate and acetoacetate.

DEFECTS IN THE β-OXIDATION CYCLE

Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common fatty acid oxidation disorder. The disorder shows a strong founder effect; most patients have a northwestern European ancestry, and the majority of patients are homozygous for a single common missense mutation, an A-G transition at complementary DNA position 985 that changes a lysine to glutamic acid at residue 329 (K329E).

Clinical Manifestations

Previously undiagnosed affected patients usually present in the first 3 mo-5 yr of life with episodes of acute illness triggered by prolonged fasting (longer than 12-16 hr). Signs and symptoms include vomiting and lethargy, which rapidly progress to coma or seizures and cardiorespiratory collapse. Sudden unexpected infant death may occur. The liver may be slightly enlarged with fat deposition. Attacks are rare until the infant is beyond the first few months of life, presumably because of more frequent feedings at a younger age. Affected older infants are at higher risk of illness as they begin to fast through the night or are exposed to fasting stress during an intercurrent childhood illness. Presentation in the first days of life with neonatal hypoglycemia has been reported in newborns that were fasted inadvertently. Diagnosis of MCAD has occasionally been documented in previously healthy teenage and adult individuals, indicating that even patients who have been asymptomatic in infancy are still at risk for metabolic decompensation if exposed to sufficient periods of fasting. An unknown number may remain asymptomatic. Prior to routine newborn screening testing, as many as 25% of MCAD deficient cases died or suffered severe brain damage from their first episode. Most patients are now diagnosed in the newborn period by blood spot acylcarnitine screening, allowing the initiation of early treatment and prevention of many of the severe signs and symptoms.

Laboratory Findings

During acute episodes, hypoglycemia is usually present. Plasma and urinary ketone concentrations are inappropriately low (**hypoketotic hypoglycemia**). Because of the hypoketonemia, there is little or no metabolic acidosis, which is expected to be present in many children with hypoglycemia. Tests of liver function are abnormal, with elevations of liver enzymes (alanine aminotransferase, aspartate aminotransferase), elevated blood ammonia, and prolonged prothrombin and partial thromboplastin times. Liver biopsy at times of acute illness shows microvesicular or macrovesicular steatosis from triglyceride accumulation. During fasting stress or at times of acute illness, urinary organic acid profiles by gas chromatography/mass spectrometry show inappropriately low concentrations of ketones and elevated levels of medium-chain dicarboxylic acids (adipic, suberic, and sebacic acids) that derive from microsomal and peroxisomal omega oxidation of accumulated medium-chain fatty acids. Plasma and tissue concentrations of total carnitine are reduced to 25-50% of normal, and the fraction of total esterified carnitine is increased. This pattern of **secondary carnitine deficiency** is seen in most fatty acid oxidation defects and reflects competition between increased acylcarnitine levels and free carnitine for transport at the plasma membrane. Significant exceptions to this rule are the plasma membrane carnitine transporter, CPT-IA and β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase deficiencies that do not manifest secondary carnitine deficiency.

Diagnostic metabolite patterns include increased plasma $C_{8:0}$, $C_{10:0}$, and $C_{10:1}$ acylcarnitine species and increased urinary acylglycines including hexanoyl-propionyl, suberyl-propionyl, and 3-phenylpropionyl glycines. Newborn screening programs using tandem mass spectrometry, which almost all babies born in the United States receive, can diagnose presymptomatic MCAD deficiency based on the detection of the abnormal acylcarnitines in filter paper blood spots. In many cases, the diagnosis can be confirmed by finding the common A985G mutation. A second common variant, T199C, has been detected in infants with

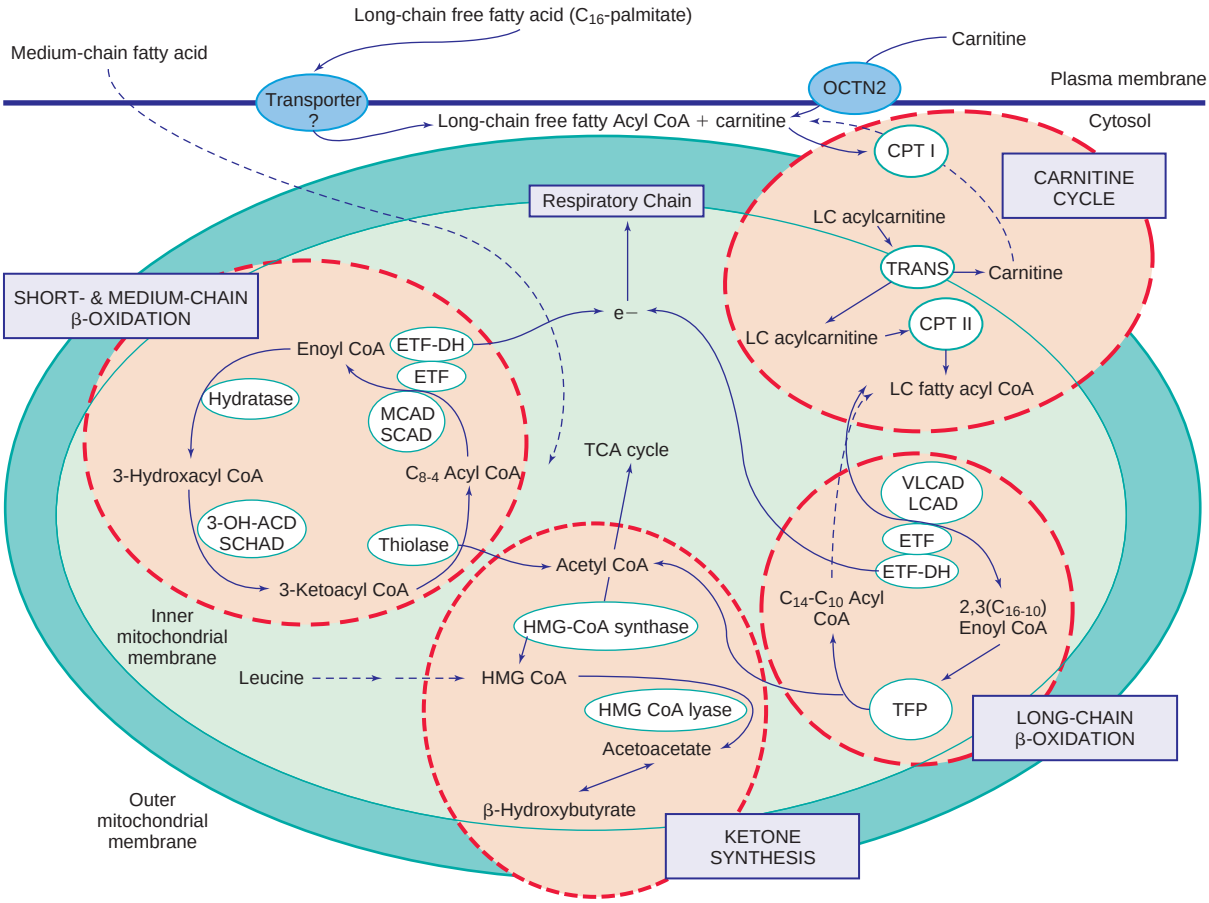

Figure 86-1 **Mitochondrial fatty acid oxidation.** Carnitine enters the cell through the action of the organic cation/carnitine transporter (OCTN2). Palmitate, a typical 16-carbon long-chain fatty acid, is transported across the plasma membrane and can be activated to form a long-chain (LC) fatty acyl coenzyme A (CoA). It then enters into the carnitine cycle, where it is transesterified by carnitine palmitoyltransferase-I (CPT-I), translocated across the inner mitochondrial membrane by carnitine/acylcarnitine translocase (TRANS), and then reconverted into a long-chain fatty acyl-CoA by carnitine palmitoyltransferase-II (CPT-II) to undergo β-oxidation. Very-long-chain acyl-CoA dehydrogenase (VLCAD/LCAD) leads to the production of (C_{16}-C_{10}) 2,3 enoyl CoA. Mitochondrial trifunctional protein (MTP) contains the activities of enoyl CoA hydratase (hydratase), 3-OH-hydroxyacyl-CoA dehydrogenase (3-OH-ACD), and β-ketothiolase (thiolase). Acetyl-CoA, reduced form of flavin adenine dinucleotide (FADH), and reduced form of nicotinamide adenine dinucleotide (NADH) are produced. Medium- and short-chain fatty acids (C8-4) can enter the mitochondrial matrix independent of the carnitine cycle. Medium-chain acyl-CoA dehydrogenase (MCAD), short-chain acyl-CoA dehydrogenase (SCAD), and short-chain hydroxy acyl-CoA dehydrogenase (SCHAD) are required. Acetyl-CoA can then enter the Krebs (TCA) cycle. Electrons are transported from FADH to the respiratory chain via the electron transfer flavoprotein (ETF) and the electron transfer flavoprotein dehydrogenase (ETF-DH). NADH enters the electron transport chain through complex I. In liver, acetyl-CoA can be converted into hydroxymethylglutaryl (HMG) CoA by β-hydroxy-β-methylglutaryl-CoA synthase (HMG CoA synthase) and then the ketone body acetoacetate by the action of β-hydroxy-β-methylglutaryl-CoA lyase (HMG-CoA lyase).

characteristic acylcarnitines in newborn screening tests. Interestingly, this allele has not been seen to date in symptomatic MCAD patients; it may represent a milder mutation.

Treatment

Acute illnesses should be promptly treated with intravenous fluids containing 10% dextrose to treat or prevent hypoglycemia and to suppress lipolysis as rapidly as possible (see Chapter 92). Chronic therapy consists of avoiding fasting. This usually requires simply adjusting the diet to ensure that overnight fasting periods are limited to <10-12 hr. Restricting dietary fat or treatment with carnitine is controversial. The necessity for active therapeutic intervention for individuals with the T199C variant has not yet been established.

Prognosis

Up to 25% of unrecognized patients may die during their first attack of illness. There is frequently a history of a previous sibling death that is presumed to be from an unrecognized MCAD deficiency. Some patients may suffer permanent brain injury during an attack of profound hypoglycemia. The prognosis for survivors without brain damage is excellent because progressive cognitive impairment or cardiomyopathy does not occur in MCAD deficiency. Muscle pain and reduced exercise tolerance may become evident with increasing age. Fasting tolerance improves with age and the risk of illness decreases. Because as many as 35% of affected patients have never had an episode, testing of siblings of affected patients is important to detect asymptomatic family members.

Very-Long-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is the second most commonly diagnosed disorder of fatty acid oxidation. It was originally termed long-chain acyl-CoA dehydrogenase deficiency before the existence of the inner mitochondrial membrane-bound VLCAD was known. *All patients previously diagnosed as having long-chain acyl-CoA dehydrogenase deficiency have VLCAD gene defects.* Patients with VLCAD deficiency have no ability to oxidize physiologic long-chain fatty acids and are usually more severely affected than those with MCAD deficiency who have a milder oxidative defect. VLCAD deficiency presents earlier in infancy and has more chronic problems

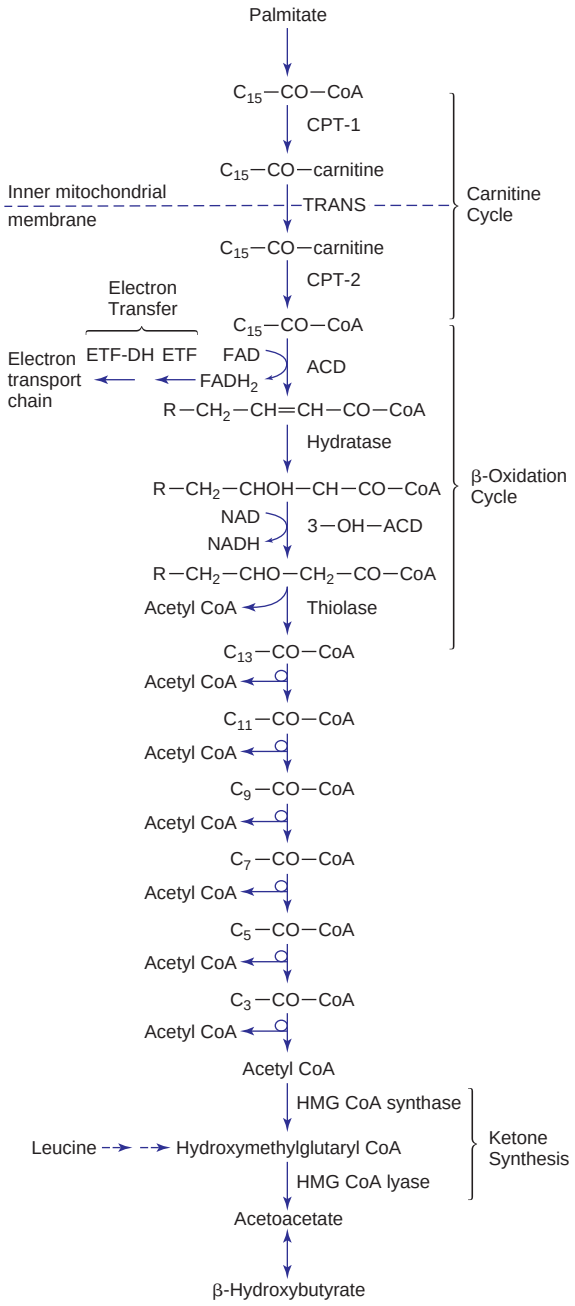

Figure 86-2 Pathway of mitochondrial oxidation of palmitate, a typical 16-carbon long-chain fatty acid. Enzyme steps include carnitine palmitoyltransferase (CPT) 1 and 2, carnitine/acylcarnitine translocase (TRANS), electron transfer flavoprotein (ETF), ETF dehydrogenase (ETF-DH), acyl-CoA dehydrogenase (ACD), enoyl CoA hydratase (hydratase), 3-hydroxy-acyl-CoA dehydrogenase (3-OH-ACD), β-ketothiolase (thiolase), β-hydroxy-β-methylglutaryl-CoA (HMG-CoA) synthase, and lyase.

with muscle weakness or episodes of muscle pain and rhabdomyolysis. Cardiomyopathy may be present during acute attacks provoked by fasting. The left ventricle may be hypertrophic or dilated and show poor contractility on echocardiography. Sudden unexpected death has occurred in several patients, but most who survived the initial episode showed improvement, including normalization of cardiac function. Other physical and routine laboratory features are similar to those of MCAD deficiency, including secondary carnitine deficiency. The urinary organic acid profile shows a nonketotic dicarboxylic aciduria with increased levels of $C_{6\text{-}12}$ dicarboxylic acids. Diagnosis may be suggested by an abnormal acylcarnitine profile with plasma or blood spot $C_{14:0,\ 14:1,\ 14:2}$ acylcarnitine species; however, the specific diagnosis requires mutational analysis of the VLCAD gene. Treatment is based primarily on avoidance of fasts for longer than 10-12 hr. Continuous intragastric feeding is useful in some patients.

Short-Chain Acyl-Coenzyme A Dehydrogenase Deficiency

A small number of patients with 2 clear null mutations in the short-chain acyl-CoA dehydrogenase (SCAD) gene have been described with variable phenotype. Most individuals classified as being SCAD deficient have polymorphic DNA changes in the SCAD gene; for example, 2 common polymorphisms are G185S and R147W, which are homozygously present in 7% of the population. Some investigators argue that these may be susceptibility changes, which require a second, as yet unknown, genetic mutation to express a clinical phenotype; while others believe that SCAD deficiency is a harmless biochemical condition. This autosomal recessive disorder presents with neonatal hypoglycemia and may have normal levels of ketone bodies. The diagnosis is indicated by elevated levels of butyrylcarnitine (C4-carnitine) on newborn blood spots or plasma and increased excretion of urinary ethylmalonic acid and butyrylglycine. These metabolic abnormalities are most pronounced in patients with null mutations and variably present in patients who are homozygous for the common polymorphisms.

The necessity for treatment in SCAD deficiency has not yet been established. It has been proposed that long-term evaluation of asymptomatic individuals is necessary to determine whether this is or is not a real disease. Although most individuals with SCAD deficiency remain asymptomatic throughout life, it has been proposed that there is a subset of individuals with SCAD deficiency with severe manifestations, including dysmorphic facial features, feeding difficulties/failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizures, hypotonia, dystonia, and myopathy.

Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase/Mitochondrial Trifunctional Protein Deficiency

The LCHAD enzyme is part of a MTP, which also contains 2 other steps in β-oxidation: long-chain enoyl CoA hydratase and long-chain β-ketothiolase. It is a heterooctameric protein composed of 4 α and 4 β chains that derive from distinct contiguous genes with a common promoter region. In some patients, only the LCHAD activity of the MTP is affected (LCHAD deficiency), whereas others have deficiencies of all 3 activities (MTP deficiency).

Clinical manifestations include attacks of acute hypoketotic hypoglycemia similar to MCAD deficiency; patients often show evidence of more severe disease, including cardiomyopathy, muscle cramps and weakness, and abnormal liver function (cholestasis). Toxic effects of fatty acid metabolites may produce pigmented retinopathy leading to blindness, progressive liver failure, peripheral neuropathy, and rhabdomyolysis. Life-threatening obstetric complications, acute fatty liver of pregnancy, and **HELLP** syndrome are observed in heterozygous mothers carrying homozygotic fetuses affected with LCHAD/MTP deficiency. Sudden unexpected infant death may occur. The diagnosis is indicated by elevated levels of blood spot or plasma 3-hydroxy acylcarnitines of chain lengths C_{16}-C_{18}. Urinary organic acid profile in patients may show increases in levels of 3-hydroxydicarboxylic acids of chain lengths C_6-C_{14}. Secondary carnitine deficiency is common. A common mutation in the α subunit, E474Q, is seen in more than 60% of LCHAD-deficient patients. This mutation in the fetus is especially associated with the obstetric complications, but other mutations in either subunit may also be linked to maternal illness.

Treatment is similar to that for MCAD or VLCAD deficiency; that is, avoiding fasting stress. Some investigators have suggested that dietary supplements with medium-chain triglyceride oil to bypass the defect in long-chain fatty acid oxidation and docosahexaenoic acid (for protection against the retinal changes) may be useful. Liver transplantation has been attempted in cases with severe liver failure, but does

not ameliorate the metabolic abnormalities or prevent the myopathic or retinal complications.

Short-Chain 3-Hydroxyacyl-Coenzyme A Dehydrogenase Deficiency

Only 12 patients with proven mutations of short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) have been reported, although a few additional unpublished cases are known to the authors. Most cases with recessive mutations of the SCHAD gene have presented with episodes of hypoketotic hypoglycemia that was caused by hyperinsulinism. In contrast to patients with other forms of fatty acid oxidation disorders, these cases required specific therapy with diazoxide for hyperinsulinism to avoid recurrent hypoglycemia. A single case with compound heterozygous mutations presented with fulminant hepatic failure at age 10 mo. The SCHAD protein has a nonenzymatic function (moonlighting) in which it directly interacts with glutamate dehydrogenase (GDH) to inhibit its activity. In the absence of an SCHAD protein, this inhibition is removed leading to upregulation of GDH enzyme activity, a recognized cause of hyperinsulinism usually caused by activating mutations of the GDH gene. This severe deficiency of SCHAD protein often presents predominantly as protein sensitive hypoglycemia rather than as fasting hypoglycemia. It appears that if a SCHAD protein is present the inhibition of GDH is maintained even when there is no SCHAD enzyme activity; these patients may present with a more traditional fatty acid oxidation defect. Specific metabolic markers for SCHAD deficiency include elevated plasma C4-hydroxy acylcarnitine and urine 3-hydroxyglutaric acid.

Treatment of SCHAD deficient patients with hyperinsulinism is with diazoxide. There is insufficient experience with the non-hyperinsulinemic form of SCHAD deficiency at present to recommend treatment modalities, but prevention of fasting seems advisable, which is similar to other fatty acid oxidation disorders.

DEFECTS IN THE CARNITINE CYCLE

Plasma Membrane Carnitine Transport Defect (Primary Carnitine Deficiency)

Primary carnitine deficiency is the only genetic defect in which carnitine deficiency is the cause, rather than the consequence, of impaired fatty acid oxidation. The most common presentation is progressive **cardiomyopathy** with or without **skeletal muscle weakness** beginning at 1-4 yr of age. A smaller number of patients may present with fasting hypoketotic hypoglycemia in the 1st yr of life before the cardiomyopathy becomes symptomatic. The underlying defect involves the plasma membrane sodium gradient-dependent carnitine transporter that is present in heart, muscle, and kidney. This transporter is responsible both for maintaining intracellular carnitine concentrations 20-50–fold higher than plasma concentrations and for renal conservation of carnitine.

Diagnosis of the carnitine transporter defect is aided by the fact that patients have extremely reduced carnitine levels in plasma and muscle (1-2% of normal). Heterozygote parents have plasma carnitine levels approximately 50% of normal. Fasting ketogenesis may be normal because liver carnitine transport is normal, but it may become impaired if dietary carnitine intake is interrupted. The fasting urinary organic acid profile may show a hypoketotic dicarboxylic aciduria pattern if hepatic fatty acid oxidation is impaired, but it is otherwise unremarkable. The defect in carnitine transport can be demonstrated clinically by the severe reduction in renal carnitine threshold or by in vitro assay of carnitine uptake using cultured fibroblasts or lymphoblasts. Mutations in the organic cation/carnitine transporter *(OCTN2)* underlie this disorder. Treatment with pharmacologic doses of oral carnitine (100-200 mg/kg/day) is highly effective in correcting the cardiomyopathy and muscle weakness, as well as any impairment in fasting ketogenesis. Muscle total carnitine concentrations remain <5% of normal on treatment.

Carnitine Palmitoyltransferase-IA Deficiency

Several dozen infants and children have been described with a deficiency of the liver and kidney carnitine palmitoyltransferase-I (CPT-I) isozyme (CPT-IA). Clinical manifestations include fasting hypoketotic hypoglycemia, occasionally with markedly abnormal liver function tests and, rarely, with renal tubular acidosis. The heart and skeletal muscle are not involved because the muscle isozyme is unaffected. Fasting urinary organic acid profile sometimes shows a hypoketotic C_6-C_{12} dicarboxylic aciduria but may be normal. Plasma acylcarnitine analysis demonstrates mostly free carnitine with very little acylated carnitine. This observation has been used to establish CPT-IA diagnosis on newborn screening by tandem mass spectrometry. CPT-IA deficiency is the only fatty acid oxidation disorder in which plasma total carnitine levels are elevated often to 150-200% of normal. This may be explained by the fact that the inhibitory effects of long-chain acylcarnitines on the renal tubular carnitine transporter are absent in CPT-IA deficiency. The enzyme defect can be demonstrated in cultured fibroblasts or lymphoblasts. CPT-IA deficiency in the fetus has been associated with acute fatty liver of pregnancy in the mother in a single case report. A common variant in the CPT-IA gene has been identified in individuals of Inuit background in the United States and First Nations tribes in Canada and Greenland. The variant is detected by a positive newborn acylcarnitine screen; enzyme activity is reduced by 80% and regulation by malonyl-CoA is lost. It has not been established if this is a pathologic DNA variant or an adaptation to ancient Inuit and First Nations high-fat diets. This variant is associated with an increased risk for sudden infant death syndrome. Treatment for the severe form of CPT-IA deficiency is similar to that for MCAD deficiency with avoidance of situations where fasting ketogenesis is necessary.

Carnitine:Acylcarnitine Translocase Deficiency

This defect of the inner mitochondrial membrane carrier protein for fatty acylcarnitines blocks the entry of long-chain fatty acids into the mitochondria for oxidation. The clinical phenotype of this disorder is characterized by a severe and generalized impairment of fatty acid oxidation. Most newborn patients present with attacks of fasting-induced hypoglycemia, hyperammonemia, and cardiorespiratory collapse. All symptomatic newborns have had evidence of cardiomyopathy and muscle weakness. Several patients with a partial translocase deficiency and milder disease without cardiac involvement have also been identified. No distinctive urinary or plasma organic acids are noted, although increased levels of plasma long-chain acylcarnitines of chain lengths C_{16}-C_{18} are reported. Diagnosis can be confirmed using genetic analysis. Functional carnitine:acylcarnitine translocase activity can be measured in cultured fibroblasts or lymphoblasts. Treatment is similar to that of other long-chain fatty acid oxidation disorders.

Carnitine Palmitoyltransferase-II Deficiency

Three forms of CPT-II deficiency have been described. The **severe neonatal lethal** presentation of this disorder is associated with a profound enzyme deficiency, and early death has been reported in several newborns with dysplastic kidneys, cerebral malformations, and mild facial anomalies. A milder, second defect, is associated with an **adult presentation** of episodic rhabdomyolysis. The first episode usually does not occur until late childhood or early adulthood. Attacks may be precipitated by prolonged exercise. There is aching muscle pain and myoglobinuria that may be severe enough to cause renal failure. Serum levels of creatine kinase are elevated to 5,000-100,000 units/L. Fasting hypoglycemia has not been described, but fasting may contribute to attacks of myoglobinuria. Muscle biopsy shows increased deposition of neutral fat. The myopathic presentation of CPT-II deficiency is associated with a common mutation S113L. This mutation produces a heat-labile protein that is unstable to increased muscle temperature during exercise resulting in the myopathic presentation. The **third intermediate** form of CPT-II deficiency presents in infancy/early childhood with fasting-induced hepatic failure, cardiomyopathy, and skeletal myopathy with hypoketotic hypoglycemia, but does not have the severe developmental changes seen in the neonatal lethal presentation. This pattern is similar to that seen in VLCAD deficiency and management is identical.

Diagnosis of all forms of CPT-II deficiency can be made by a combination of molecular analysis and demonstrating deficient enzyme activity in muscle or other tissues and in cultured fibroblasts.

DEFECTS IN THE ELECTRON TRANSFER PATHWAY

Electron Transfer Flavoprotein and Electron Transfer Flavoprotein Dehydrogenase Deficiencies (Glutaric Acidemia Type 2, Multiple Acyl-Coenzyme A Dehydrogenation Defects)

ETF and ETF-DH function to transfer electrons into the mitochondrial electron transport chain from dehydrogenation reactions catalyzed by VLCAD, MCAD, and SCAD, as well as by glutaryl-CoA dehydrogenase and 4 enzymes involved in branched-chain amino acid oxidation. Deficiencies of ETF or ETF-DH produce illness that combines the features of impaired fatty acid oxidation and impaired oxidation of several amino acids. Complete deficiencies of either protein are associated with severe illness in the newborn period, characterized by acidosis, hypoketotic hypoglycemia, coma, hypotonia, cardiomyopathy, and an unusual odor of sweaty feet caused by isovaleryl-CoA dehydrogenase inhibition. Some affected neonates have had facial dysmorphism and polycystic kidneys similar to that seen in severe CPT-II deficiency, which suggests that toxic effects of accumulated metabolites may occur in utero.

Diagnosis can be made from the urinary organic acid profile, which shows abnormalities corresponding to blocks in oxidation of fatty acids (ethylmalonate and C_6-C_{10} dicarboxylic acids), lysine (glutarate), and branched-chain amino acids (isovaleryl-, isobutyryl-, and α-methylbutyryl-glycine) and by molecular testing. Most severely affected infants do not survive the neonatal period.

Partial deficiencies of ETF and ETF-DH produce a disorder that may mimic MCAD deficiency or other milder fatty acid oxidation defects. These patients have attacks of fasting hypoketotic coma. The urinary organic acid profile reveals primarily elevations of dicarboxylic acids and ethylmalonate, derived from short-chain fatty acid intermediates. Secondary carnitine deficiency is present. Some patients with mild forms of ETF/ETF-DH deficiency benefit from treatment with high doses of riboflavin, which is a cofactor for the pathway of electron transfer.

DEFECTS IN KETONE SYNTHESIS PATHWAY

β-Hydroxy-β-Methylglutaryl-Coenzyme A Synthase Deficiency

See Chapter 85.6.

HMG-CoA synthase is the rate-limiting step in the conversion of acetyl-CoA derived from fatty acid β-oxidation in the liver to ketones. Several patients with this defect have recently been identified. The presentation is one of fasting **hypoketotic hypoglycemia** without evidence of impaired cardiac or skeletal muscle function. Urinary organic acid profile showed only a hypoketotic dicarboxylic aciduria. Plasma and tissue carnitine levels are normal, in contrast to all the other disorders of fatty acid oxidation. A separate synthase enzyme, present in cytosol for cholesterol biosynthesis, is not affected. The HMG-CoA synthase defect is expressed only in the liver and cannot be demonstrated in cultured fibroblasts. The gene has been cloned, and mutations in the affected patients have been characterized. Avoiding fasting is usually a successful treatment.

β-Hydroxy-β-Methylglutaryl-Coenzyme A Lyase Deficiency

See Chapter 85.6.

DEFECTS IN KETONE BODY UTILIZATION

The ketone bodies, β-hydroxybutyrate and acetoacetate, are the end products of hepatic fatty acid oxidation and are important metabolic fuels for the brain during fasting. Two defects in utilization of ketones in brain and other peripheral tissues present as episodes of **hyperketotic** coma, with or without hypoglycemia.

Succinyl-Coenzyme A:3-Ketoacid-Coenzyme A Transferase Deficiency

See Chapter 85.6.

Several patients with succinyl-CoA:3-ketoacid-CoA transferase (SCOT) deficiency have been reported. The characteristic presentation is an infant with recurrent episodes of severe ketoacidosis induced by fasting. Plasma acylcarnitine and urine organic acid abnormalities do not distinguish SCOT deficiency from other causes of ketoacidosis. Treatment of episodes requires infusion of glucose and large amounts of bicarbonate until metabolically stable. Patients usually exhibit inappropriate hyperketonemia even between episodes of illness. SCOT is responsible for activating acetoacetate in peripheral tissues using succinyl CoA as a donor to form acetoacetyl-CoA. Deficient enzyme activity can be demonstrated in brain, muscle, and fibroblasts from affected patients. The gene has been cloned, and numerous mutations have been characterized.

β-Ketothiolase Deficiency

See Chapter 85.6.

Bibliography is available at Expert Consult.

86.2 Disorders of Very Long Chain Fatty Acids

Gerald V. Raymond

PEROXISOMAL DISORDERS

The peroxisomal diseases are genetically determined disorders caused either by the failure to form or maintain the peroxisome or by a defect in the function of a single protein that is normally located in this organelle. These disorders cause serious disability in childhood and occur more frequently and present a wider range of phenotype than has been recognized in the past.

Etiology

Peroxisomal disorders are subdivided into 2 major categories (Table 86-2).

In category A, the **peroxisomal biogenesis disorders (PBDs)**, the basic defect is the failure to import 1 or more proteins into the organelle. In category B, **defects affect a single peroxisomal protein**. The peroxisome is present in all cells except mature erythrocytes and is a subcellular organelle surrounded by a single membrane; more than 50

Table 86-2 Classification of Peroxisomal Disorders

A: DISORDERS OF PEROXISOME IMPORT
A1: Zellweger syndrome
A2: Neonatal adrenoleukodystrophy
A3: Infantile Refsum disease
A4: Rhizomelic chondrodysplasia punctata
B: DEFECTS OF SINGLE PEROXISOMAL ENZYME
B1: X-linked adrenoleukodystrophy
B2: Acyl-CoA oxidase deficiency
B3: Bifunctional enzyme deficiency
B4: Peroxisomal thiolase deficiency
B5: Classic Refsum disease
B6: 2-Methylacyl-CoA racemase deficiency
B7: DHAP acyltransferase deficiency
B8: Alkyl-DHAP synthase deficiency
B9: Mevalonic aciduria
B10: Glutaric aciduria type III
B11: Hyperoxaluria type I
B12: Acatalasemia

CoA, coenzyme A; DHAP, dihydroxyacetone phosphate.

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peroxisomal enzymes are identified. Some enzymes are involved in the production and decomposition of hydrogen peroxide; others are concerned with lipid and amino acid metabolism. Most peroxisomal enzymes are first synthesized in their mature form on free polyribosomes and enter the cytoplasm. Proteins that are destined for the peroxisome contain specific peroxisome targeting sequences (PTSs). Most peroxisomal matrix proteins contain PTS1, a 3-amino acid sequence at the carboxyl terminus. PTS2 is an aminoterminal sequence that is critical for the import of enzymes involved in plasmalogen and branched-chain fatty acid metabolism. Import of proteins involves a complex series of reactions that involves at least 23 distinct proteins. These proteins, referred to as peroxins, are encoded by *PEX* genes.

Epidemiology

Except for X-linked adrenoleukodystrophy (ALD), all the peroxisomal disorders in Table 86-2 are **autosomal recessive traits**. ALD is the most common peroxisomal disorder, with an estimated incidence of 1 in 17,000 live births. The combined incidence of the other peroxisomal disorders is estimated to be 1 in 50,000 live births.

Pathology

Absence or reduction in the number of peroxisomes is pathognomonic for disorders of peroxisome biogenesis. In most disorders, there are membranous sacs that contain peroxisomal integral membrane proteins, which lack the normal complement of matrix proteins; these are peroxisome "ghosts." Pathologic changes are observed in most organs and include profound and characteristic defects in neuronal migration; micronodular cirrhosis of the liver; renal cysts; chondrodysplasia punctata; sensorineural hearing loss; retinopathy; congenital heart disease; and dysmorphic features.

Pathogenesis

It is likely that all pathologic changes are secondary to the peroxisome defect. Multiple peroxisomal enzymes fail to function in the PBDs (Table 86-3). The enzymes that are diminished or absent are synthesized but are degraded abnormally fast because they may be unprotected outside of the peroxisome. It is not clear how defective peroxisome functions lead to the widespread pathologic manifestations.

Mutations in 12 different *PEX* genes have been identified in PBDs. The pattern and severity of pathologic features vary with the nature of the import defects and the degree to which import is impaired. These gene defects lead to disorders that were named before their relationship to the peroxisome was recognized, namely, Zellweger syndrome, neonatal ALD, infantile Refsum disease, and rhizomelic chondrodysplasia punctata (RCDP). The first 3 disorders are considered to form a clinical continuum, with Zellweger syndrome the most severe, infantile Refsum disease the least severe, and neonatal ALD intermediate. They can be caused by mutations in any of the 11 genes involved in peroxisome assembly. The specific gene defects cannot be distinguished on the basis of clinical features. The clinical severity varies with the degree to which protein import is impaired. Mutations that abolish import completely are often associated with the Zellweger syndrome phenotype, whereas a missense mutation, in which some degree of import function is retained, leads to the somewhat milder phenotypes. A defect in *PEX7,* which involves the import of proteins that utilize PTS2, is associated with RCDP. *PEX7* defects that leave import partially intact are associated with milder phenotypes, some of which resemble classic Refsum disease.

The genetic disorders that involve single peroxisomal enzymes usually have clinical manifestations that are more restricted and relate to the single biochemical defect. The primary adrenal insufficiency of ALD is caused by accumulation of very-long-chain fatty acids (VLCFAs) in the adrenal cortex, and the peripheral neuropathy in Refsum disease is caused by the accumulation of phytanic acid in Schwann cells and myelin.

Table 86-3	Abnormal Laboratory Findings Common to Disorders of Peroxisome Biogenesis
Peroxisomes absent to reduced in number	
Catalase in cytosol	
Deficient synthesis and reduced tissue levels of plasmalogens	
Defective oxidation and abnormal accumulation of very-long-chain fatty acids	
Deficient oxidation and age-dependent accumulation of phytanic acid	
Defects in certain steps of bile acid formation and accumulation of bile acid intermediates	
Defects in oxidation and accumulation of L-pipecolic acid	
Increased urinary excretion of dicarboxylic acids	

Peroxisomal Biogenesis Disorders with Milder or Atypical Phenotypes

Newborn infants with **Zellweger syndrome** show striking and consistent recognizable abnormalities. Of central diagnostic importance are the typical facial appearance (high forehead, unslanting palpebral fissures, hypoplastic supraorbital ridges, and epicanthal folds; Fig. 86-3), severe weakness and hypotonia, neonatal seizures, and eye abnormalities. Because of the hypotonia and craniofacial appearance, Down syndrome may be suspected. Infants with Zellweger syndrome rarely live more than a few months. More than 90% show postnatal growth failure. Table 86-4 lists the main clinical abnormalities.

Patients with **neonatal ALD** show fewer, less-prominent craniofacial features. Neonatal seizures occur frequently. Some degree of psychomotor developmental delay is present; function remains in the severely or profoundly retarded range, and development may regress after 3-5 yr of age, probably from a progressive leukodystrophy. Hepatomegaly, impaired liver function, pigmentary degeneration of the retina, and severely impaired hearing are invariably present. Adrenocortical function is usually impaired and may require adrenal hormone replacement. Chondrodysplasia punctata and renal cysts are absent.

Figure 86-3 Four patients with Zellweger cerebrohepatorenal syndrome. Note the high forehead, epicanthal folds, and hypoplasia of supraorbital ridges and midface. *(Courtesy of Hans Zellweger, MD.)*

Table 86-4 Main Clinical Abnormalities in Zellweger Syndrome

ABNORMAL FEATURE	Cases in Which the Feature Was Present NO.	%
High forehead	58	97
Flat occiput	13	81
Large fontanelle(s), wide sutures	55	96
Shallow orbital ridges	33	100
Low/broad nasal bridge	23	100
Epicanthus	33	92
High arched palate	35	95
External ear deformity	39	97
Micrognathia	18	100
Redundant skin fold of neck	13	100
Brushfield spots	5	83
Cataract/cloudy cornea	30	86
Glaucoma	7	58
Abnormal retinal pigmentation	6	40
Optic disc pallor	17	74
Severe hypotonia	94	99
Abnormal Moro response	26	100
Hyporeflexia or areflexia	56	98
Poor sucking	74	96
Gavage feeding	26	100
Epileptic seizures	56	92
Psychomotor retardation	45	100
Impaired hearing	9	40
Nystagmus	30	81

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Patients with **infantile Refsum disease** have survived to adulthood. They are able to walk, although gait may be ataxic and broad based. Cognitive function is in the severely impaired range. All have sensorineural hearing loss and pigmentary degeneration of the retina. They have moderately dysmorphic features that may include epicanthal folds, a flat bridge of the nose, and low-set ears. Early hypotonia and hepatomegaly with impaired function are common. Levels of plasma cholesterol and high- and low-density lipoprotein are often moderately reduced. Chondrodysplasia punctata and renal cortical cysts are absent. Postmortem study in infantile Refsum disease reveals micronodular liver cirrhosis and small hypoplastic adrenals. The brain shows no malformations, except for severe hypoplasia of the cerebellar granule layer and ectopic locations of the Purkinje cells in the molecular layer. The mode of inheritance is autosomal recessive.

Some patients with PBDs have milder and atypical phenotypes. They may present with peripheral neuropathy or with retinopathy, impaired vision, or cataracts in childhood, adolescence, or adulthood and have been diagnosed to have **Charcot-Marie-Tooth** disease or **Usher syndrome**. Some patients have survived to the 5th decade. Defects in *PEX7,* which most commonly lead to the RCDP phenotype, may also lead to a milder phenotype with clinical manifestations similar to those of classical Refsum disease (phytanoyl-CoA hydroxylase deficiency).

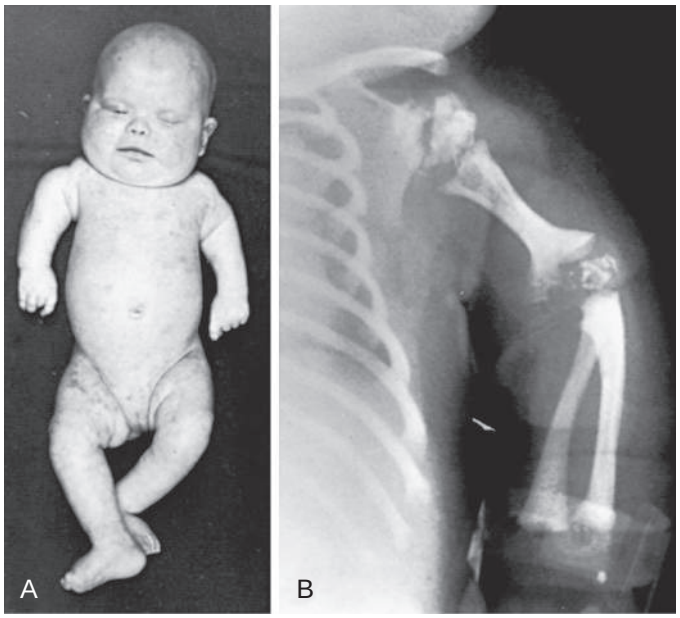

Figure 86-4 A, Newborn infant with rhizomelic chondrodysplasia punctata. Note the severe shortening of the proximal limbs, the depressed bridge of the nose, hypertelorism, and widespread scaling skin lesions. **B,** Note the marked shortening of the humerus and epiphyseal stippling at the shoulder and elbow joints. *(Courtesy of John P. Dorst, MD.)*

Rhizomelic Chondrodysplasia Punctata

RCDP is characterized by the presence of stippled foci of calcification within the hyaline cartilage and is associated with dwarfing, cataracts (72%), and multiple malformations caused by contractures. Vertebral bodies have a coronal cleft filled by cartilage that is a result of an embryonic arrest. Disproportionate short stature affects the proximal parts of the extremities (Fig. 86-4*A*). Radiologic abnormalities consist of shortening of the proximal limb bones, metaphyseal cupping, and disturbed ossification (Fig. 86-4*B*). Height, weight, and head circumference are less than the 3rd percentile, and these children have a severe intellectual disability. Skin changes such as those observed in ichthyosiform erythroderma are present in approximately 25% of patients.

Isolated Defects of Peroxisomal Fatty Acid Oxidation

The disorders labeled B1 through B3 (see Table 86-2) each involve 1 of 3 enzymes involved in peroxisomal fatty acid oxidation. Their clinical manifestations resemble those of the Zellweger spectrum disorder continuum; they can be distinguished from disorders of peroxisome biogenesis only by laboratory tests. Defects of bifunctional enzyme are common and are found in approximately 15% of patients with the Zellweger spectrum disorder. Patients with isolated acyl-CoA oxidase deficiency have a somewhat milder phenotype that resembles and come to attention because of the development of a childhood leukodystrophy.

Isolated Defects of Plasmalogen Synthesis

Plasmalogens are lipids in which the first carbon of glycerol is linked to an alcohol rather than a fatty acid. They are synthesized through a complex series of reactions, the first 2 steps of which are catalyzed by the peroxisomal enzymes dihydroxyacetone phosphate alkyl transferase and synthase. Deficiency of either of these enzymes (B4 and B5 in Table 86-2) leads to a phenotype that is clinically indistinguishable from the peroxisomal import disorder RCDP. This latter disorder is caused by a defect in *PEX7,* the receptor for PTS2. It shares the severe deficiency of plasmalogens with disorders B4 and B5 but, in addition, has defects of phytanic oxidation. The fact that disorders B4 and B5 are associated with the full phenotype of RCDP suggests that a deficiency of plasmalogens is sufficient to produce it.

Classic Refsum Disease

The defective enzyme (phytanoyl-CoA oxidase) is localized to the peroxisome. The manifestation of classic adult Refsum disease includes impaired vision from retinitis pigmentosa, ichthyosis, peripheral neuropathy, ataxia, and, occasionally, cardiac arrhythmias. In contrast to infantile Refsum disease, cognitive function is normal and there are no congenital malformations. Classic Refsum disease often does not manifest until young adulthood, but visual disturbances such as night blindness, ichthyosis, and peripheral neuropathy may already be present in childhood and adolescence. Early diagnosis is important because institution of a phytanic acid-restricted diet can reverse the peripheral neuropathy and prevent the progression of the visual and central nervous system manifestations. The classic Refsum disease phenotype may also be caused by defects in *PEX7*.

2-Methylacyl-Coenzyme A Racemase Deficiency

This disorder is caused by an enzyme defect that leads to the accumulation of the branched-chain fatty acids (phytanic and pristanic acid) and bile acids. Patients present with adult-type peripheral neuropathy and may also have pigmentary degeneration of the retina.

Laboratory Findings

Laboratory tests for peroxisomal disorders can be viewed at 3 levels of complexity.

Level 1: Does the Patient Have a Peroxisomal Disorder?

This can be resolved by noninvasive tests that are generally available (see Table 86-4). *Measurement of plasma VLCFA is the most commonly used assay*. Whereas plasma VLCFA levels are elevated in many patients with peroxisomal disorders, this is not always the case. The most important exception is RCDP, in which VLCFA levels are normal, but plasma phytanic acid levels are increased and red blood cell plasmalogen levels are reduced. In some other peroxisomal disorders, the biochemical abnormalities are still more restricted. Therefore, a panel of tests is recommended and includes plasma levels of VLCFA and phytanic, pristanic, and pipecolic acids and red blood cell levels of plasmalogens. Tandem mass spectrometry techniques also permit convenient quantitation of bile acids in plasma and urine. This panel of tests can be performed on 2 mL samples of venous blood and permits detection of most peroxisomal disorders. Furthermore, normal results make the presence of the typical peroxisomal disorder unlikely.

Level 2: What Is the Precise Nature of the Peroxisomal Disorder?

Table 86-5 lists the main biochemical abnormalities in the various peroxisomal disorders. When combined with the clinical presentation, the panel of level 1 tests (see above) is often sufficient to identify the precise nature of the defect. Marked reduction of erythrocyte plasmalogen levels combined with elevated plasma phytanic acid permits precise diagnosis in a patient with the clinical features of RCDP. Classic Refsum disease can be diagnosed by demonstration of increased plasma phytanic acid combined with normal or reduced levels of pristanic acid levels, while in D-bifunctional enzyme deficiency and 2-methylacyl-CoA racemase deficiency, the levels of pristanic and phytanic acid are both increased. Precise identification of some peroxisomal disorders may require more extensive studies in cultured skin fibroblasts. This may be required for the differentiation of PBDs from defects in bifunctional enzyme. In PBDs, the patient's peroxisomes are absent and catalase is in the soluble fraction, whereas in bifunctional enzyme defect, peroxisomes are present and catalase is in the particulate fraction. Fibroblast studies are required to identify the nature of the molecular defect in PBDs. Whether such specialized studies are clinically warranted depends on individual circumstances. Precise definition of the defect in a proband may improve the precision of prenatal diagnosis in at-risk pregnancies, and it is required for carrier detection. It is also of value in setting prognosis.

Level 3: What Is the Molecular Defect?

Definition of the molecular defect in the proband, which is now offered in several laboratories, is essential for carrier detection and speeds prenatal diagnosis. Characterization of the mutation may be of prognostic value in patients with *PEX1* defects. This defect is present in approximately 60% of PBD patients, and about half of the *PEX1* defects have the G843D allele, which is associated with a significantly milder phenotype than is found in other mutations.

Diagnosis

There are several noninvasive laboratory tests that permit precise and early diagnosis of peroxisomal disorders (see Table 86-4). The challenge in PBDs is to differentiate them from the large variety of other conditions that can cause hypotonia, seizures, failure to thrive, or dysmorphic features. Experienced clinicians can readily recognize classic Zellweger syndrome by its clinical manifestations. However, more mildly affected PBD patients often do not show the full clinical spectrum of disease and may be identifiable only by laboratory assays. Clinical features that serve as indications for these diagnostic assays include severe intellectual disability; weakness and hypotonia; dysmorphic features; neonatal seizures; retinopathy, glaucoma, or cataracts; hearing deficits; enlarged liver and impaired liver function; and chondrodysplasia punctata. The presence of 1 or more of these abnormalities increases the likelihood of this diagnosis. Atypical milder forms presenting as peripheral neuropathy have also been described.

Some patients with the isolated defects of peroxisomal fatty acid oxidation (group B) resemble those with group A disorders and can be detected by the demonstration of abnormally high levels of VLCFAs.

Patients with RCDP must be distinguished from patients with other causes of chondrodysplasia punctata. In addition to warfarin embryopathy and Zellweger syndrome, these disorders include the milder autosomal dominant form of chondrodysplasia punctata (Conradi-Hünermann syndrome), which is characterized by longer survival, absence of severe limb shortening, and usually intact intellect; an X-linked dominant form; and an X-linked recessive form associated with a deletion of the terminal portion of the short arm of the X chromosome. RCDP is suspected clinically because of the shortness of limbs, psychomotor retardation, and ichthyosis. The most decisive laboratory test is the demonstration of abnormally low plasmalogen levels in red blood cells and an impaired capacity to synthesize plasmalogens in cultured skin fibroblasts. These biochemical defects are not present in other types of chondrodysplasia punctata. Chondrodysplasia punctata may also be associated with a defect of 3β-hydroxysteroid-Δ^8,Δ^7-isomerase, an enzyme involved in biosynthesis of cholesterol.

Complications

Patients with Zellweger cerebrohepatorenal syndrome have multiple disabilities involving muscle tone, swallowing, cardiac abnormalities, liver disease, and seizures. These conditions are treated symptomatically, but the prognosis is poor, and most patients succumb in the first year of life. Patients with RCDP may develop quadriparesis owing to compression at the base of the brain.

Treatment

The most effective therapy is the dietary treatment of classic Refsum disease with a phytanic acid-restricted diet.

For patients with the somewhat milder variants of the peroxisome import disorders, success has been achieved with multidisciplinary early intervention, including physical and occupational therapy, hearing aids or cochlear implants, alternative communication, nutrition, and support for the parents. Although most patients continue to function in the severely delayed range, some make significant gains in self-help skills, and several are in stable condition in their teens or even early 20s.

Attempts to mitigate some of the secondary biochemical abnormalities include the oral administration of docosahexaenoic acid. The levels of this substance are greatly reduced in patients with disorders of peroxisome biogenesis and this therapy normalizes the plasma levels of

Table 86-5 Peroxisomal Disorders That Involve Fatty Acid Oxidation: Diagnostic Assays

DISEASE	ASSAY		FINDING
Zellweger syndrome Neonatal adrenoleukodystrophy Infantile Refsum disease	Plasma	VLCFA	Increased
		Phytanic acid	Age-dependent increase
		Pristanic acid	Age-dependent increase
		Pipecolic acid	Increased
		Bile acid	Increased, abnormal pattern
	RBCs	Plasmalogen levels	Variably decreased
	Fibroblasts	VLCFA levels	Increased
		VLCFA oxidation	Decreased
		Plasmalogen synthesis	Decreased
		Phytanic, pristanic oxidation	Decreased
		Catalase localization	Cytosolic
		Immunocytochemistry	Peroxisomes absent
		Complementation	Complementation between infantile Refsum disease and other peroxisomal disorder (except Zellweger) fibroblasts
		DNA	*PEX* gene mutations
Rhizomelic chondrodysplasia punctata	Plasma	Phytanic acid	Increased
		VLCFA	Normal
	RBCs	Plasmalogen levels	Decreased
	Fibroblasts	Plasmalogen synthesis	Decreased
		Phytanic acid oxidation	Decreased
		DNA	*PEX7* defect
X-linked ALD hemizygote	Plasma	VLCFA	Increased
	Fibroblasts	VLCFA levels	Increased
		VLCFA oxidation	Decreased
		ALDP immunoreactivity	Absent in 70%
		DNA	*ABCD1* mutation
X-linked ALD heterozygote	Plasma	VLCFA	Variable increase in 85% of heterozygotes
	Fibroblasts	VLCFA levels	Variable increase in 90% of heterozygotes
		ALDP immunoreactivity	Variable decrease
		DNA	*ABCD1* mutation
Bifunctional enzyme defect	Plasma	VLCFA	Increased
		Phytanic acid	Increased
		Pristanic acid	Increased
		Bile acids	Increased, abnormal pattern
	Fibroblasts	VLCFA levels	Increased
		Pristanic acid oxidation	Decreased
		Catalase localization	Peroxisomal
		Enzyme	D-bifunctional protein deficiency
Acyl-CoA oxidase deficiency	Plasma	VLCFA	Increased
	Fibroblasts	VLCFA levels	Increased
		VLCFA oxidation	Decreased
		Enzyme	Acyl-CoA oxidase defect
2-Methylacyl-CoA racemase deficiency	Plasma	Pristanic acid	Increased
		Bile acids	Increased, abnormal pattern
	Fibroblasts	Pristanic acid oxidation	Decreased
		Enzyme	2-Methylacyl-CoA oxidase defect
Classic Refsum disease	Plasma	Phytanic acid	Increased
		Pristanic acid	Decreased
	Fibroblasts	Enzyme	Phytanoyl-CoA deficiency

ALD, adrenoleukodystrophy; ALDP, adrenoleukodystrophy protein; CoA, coenzyme A; RBC, red blood cell; VLCFA, very-long-chain fatty acid.

this substance. Although there were anecdotal reports of clinical improvement, a randomized placebo-controlled study failed to find benefit.

Genetic Counseling

All the peroxisomal disorders, except hyperoxaluria type 1, can be diagnosed prenatally in the 1st or 2nd trimester. The tests are similar to those described for postnatal diagnosis (see Table 86-5) and use chorionic villus sampling or amniocytes. Because of the 25% recurrence risk, couples with an affected child must be advised about the availability of prenatal diagnosis. Heterozygotes can be identified in ALD and in those disorders in which the molecular defect has been identified.

ADRENOLEUKODYSTROPHY (X-LINKED)

ALD is a genetically determined disorder associated with the accumulation of saturated VLCFAs and a progressive dysfunction of the adrenal cortex and central and peripheral nervous system white matter.

Etiology

The key biochemical abnormality is the tissue accumulation of saturated VLCFAs, with a carbon chain length of 24 or more. Excess hexacosanoic acid ($C_{26:0}$) is the most striking and characteristic feature. This accumulation of fatty acids is caused by genetically deficient peroxisomal degradation of fatty acid. The gene that is defective *(ABCD1)* codes for a peroxisomal membrane protein (ALDP, the ALD protein). Most families have a mutation that is "private" (unique to that kindred)

and these are updated on the website, http://x-ald.nl. The mechanism by which the ALDP defect leads to VLCFA accumulation appears to be a disruption of transport of saturated fatty acids into the peroxisome with resultant continued elongation of progressively longer fatty acids.

Epidemiology

The minimum incidence of ALD in males is 1 in 21,000, and the combined incidence of ALD males and heterozygous females in the general population is estimated to be 1 in 17,000. All races are affected. The various phenotypes often occur in members of the same kindred.

Pathology

Characteristic lamellar cytoplasmic inclusions can be demonstrated with the electron microscope in adrenocortical cells, testicular Leydig cells, and nervous system macrophages. These inclusions probably consist of cholesterol esterified with VLCFA. They are most prominent in cells of the zona fasciculata of the adrenal cortex, which at first are distended with lipid and later atrophy.

The nervous system can display 2 types of lesions. In the severe childhood cerebral form and in the rapidly progressive adult forms, demyelination is associated with an inflammatory response manifested by the accumulation of perivascular lymphocytes that is most intense in the parietooccipital region. In the slowly progressive adult form, **adrenomyeloneuropathy**, the main finding is a distal axonopathy that affects the long tracts in the spinal cord. The inflammatory response is mild or absent.

Pathogenesis

The adrenal dysfunction is probably a direct consequence of the accumulation of VLCFAs. The cells in the zona fasciculata are distended with abnormal lipids. Cholesterol esterified with VLCFA is relatively resistant to adrenocorticotropic hormone (ACTH)-stimulated cholesterol ester hydrolases, and this limits the capacity to convert cholesterol to active steroids. In addition, $C_{26:0}$ excess increases the viscosity of the plasma membrane and this may interfere with receptor and other cellular functions.

There is no correlation between the neurologic phenotype and the nature of the mutation or the severity of the biochemical defect as assessed by plasma levels of VLCFAs or between the degree of adrenal involvement and nervous system involvement. The severity of the illness and rate of progression correlate with the intensity of the inflammatory response. The inflammatory response may be cytokine mediated and may involve an autoimmune response triggered in an unknown way by the excess of VLCFAs. Mitochondrial damage and oxidative stress also contribute. Approximately half of the patients do not experience the inflammatory response; this difference is not understood.

Clinical Manifestations

There are 5 relatively distinct phenotypes, 3 of which are present in childhood with symptoms and signs. In all the phenotypes, development is usually normal in the first 3-4 yr of life.

In the **childhood cerebral form** of ALD, symptoms are first noted most commonly between the ages of 4 and 8 yr. The most common initial manifestations are hyperactivity, which is often mistaken for an attention deficit disorder, and worsening school performance in a child who had previously been a good student. **Auditory discrimination** is often impaired, although tone perception is preserved. This may be evidenced by difficulty in using the telephone and greatly impaired performance on intelligence tests in items that are presented verbally. Spatial orientation is often impaired. Other initial symptoms are disturbances of vision, ataxia, poor handwriting, seizures, and strabismus. Visual disturbances are often caused by involvement of the cerebral cortex, which leads to variable and seemingly inconsistent visual capacity. **Seizures** occur in nearly all patients and may represent the first manifestation of the disease. Some patients present with increased intracranial pressure or with unilateral mass lesions. Impaired cortisol response to ACTH stimulation is present in 85% of patients, and mild hyperpigmentation is noted. In most patients with this phenotype, adrenal dysfunction is recognized only after the condition is diagnosed because of the cerebral symptoms. Cerebral childhood ALD tends to progress rapidly with increasing spasticity and paralysis, visual and hearing loss, and loss of ability to speak or swallow. The mean interval between the first neurologic symptom and an apparently vegetative state is 1.9 yr. Patients may continue in this apparently vegetative state for 10 yr or more.

Adolescent ALD designates patients who experience neurologic symptoms between the ages of 10 and 21 yr. The manifestations resemble those of childhood cerebral ALD except that progression is slower. Approximately 10% of patients present acutely with status epilepticus, adrenal crisis, acute encephalopathy, or coma.

Adrenomyeloneuropathy first manifests in late adolescence or adulthood as a progressive paraparesis caused by long tract degeneration in the spinal cord. Approximately half of the patients also have involvement of the cerebral white matter.

The **"Addison only"** phenotype is an important condition. Of male patients with Addison disease, 25% may have the biochemical defect of ALD. Many of these patients have intact neurologic systems, whereas others have subtle neurologic signs. Many acquire adrenomyeloneuropathy in adulthood.

The term "asymptomatic ALD" is applied to persons who have the biochemical defect of ALD but are free of neurologic or endocrinal disturbances. Nearly all persons with the gene defect eventually become neurologically symptomatic.

Approximately 50% of female heterozygotes acquire a syndrome that resembles adrenomyeloneuropathy but is milder and of later onset. Adrenal insufficiency and cerebral disease are rare.

Cases of typical ALD have occurred in relatives of those with adrenomyeloneuropathy. One of the most difficult problems in the management of X-linked ALD is the common observation that affected individuals in the same family may have quite different clinical courses. For example, in 1 family, 1 affected boy had severe classic ALD culminating in death by age 10 yr; another affected male (a brother) had late-onset adrenomyeloneuropathy, and a third had no symptoms at all.

Laboratory and Radiographic Findings

The most specific and important laboratory finding is the demonstration of abnormally high levels of VLCFA in plasma, red blood cells, or cultured skin fibroblasts. The test should be performed in a laboratory that has experience with this specialized procedure. Positive results are obtained in all male patients with ALD and in approximately 85% of female carriers of ALD. Mutation analysis is the most reliable method for the identification of carriers.

Neuroimaging

Patients with childhood cerebral or adolescent ALD show cerebral white matter lesions that are characteristic with respect to location and attenuation patterns on MRI. In 80% of patients, the lesions are symmetric and involve the periventricular white matter in the posterior parietal and occipital lobes. Approximately 50% show a garland of accumulated contrast material adjacent and anterior to the posterior hypodense lesions (Fig. 86-5*A*). This zone corresponds to the zones of intense perivascular lymphocytic infiltration where the blood–brain barrier breaks down. In 12% of patients, the initial lesions are frontal. Unilateral lesions that produce a mass effect suggestive of a brain tumor may occur. MRI provides a clearer delineation of normal and abnormal white matter than does CT (Fig. 86-5*B*).

Impaired Adrenal Function

More than 85% of patients with the childhood form of ALD have elevated levels of ACTH in plasma and a subnormal rise of cortisol levels in plasma following intravenous injection of 250 μg of ACTH (Cortrosyn).

Diagnosis and Differential Diagnosis

The earliest manifestations of childhood cerebral ALD are difficult to distinguish from the more common attention-deficit disorders or

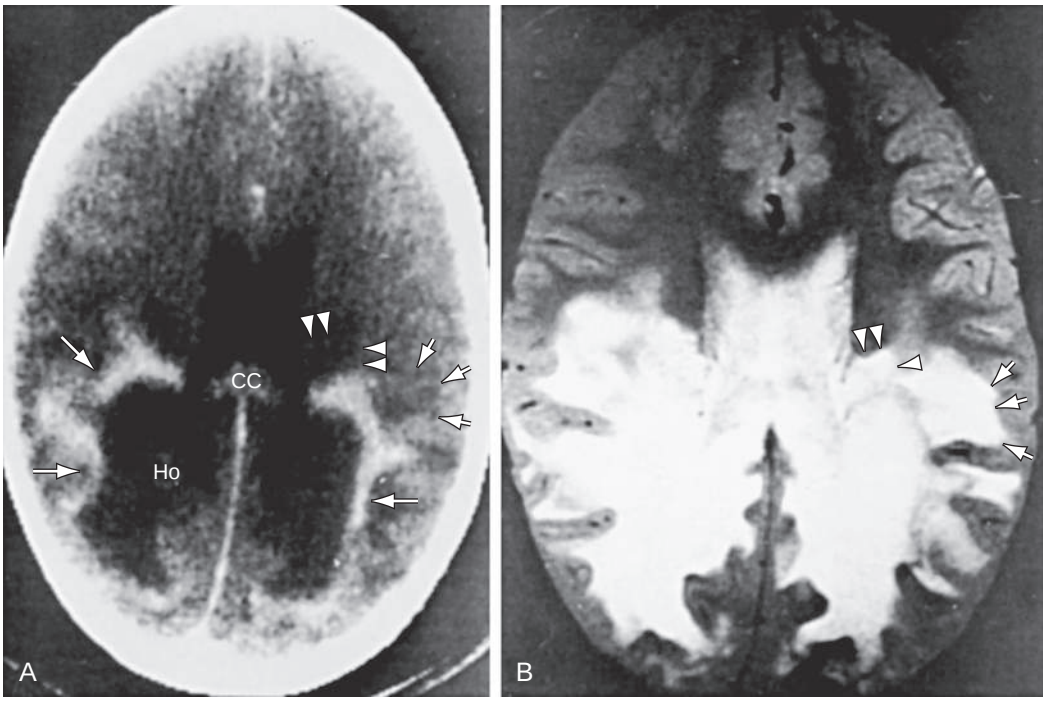

Figure 86-5 **A,** Contrast-enhanced CT abnormalities in adrenoleukodystrophy with typical parietooccipital location, showing symmetric bilateral hypodense inactive zones (Ho). The enhancing active periphery zone of hypodensity is demarcated by *arrows.* Compare the anterior zone of hypodensity *(arrowheads)* with that on the MRI in **B.** CC, corpus callosum. **B,** MRI of the same pattern and area shown by CT. MRI T2-weighted image shows a high-intensity signal of the abnormally bright parietooccipital white matter. Subcortical involvement is better identified on MRI. Separation of active zones may be better appreciated by CT, because both inactive and active zones are seen at high-signal areas on MRI. It is assumed, however, that such major distinctions afforded by CT will also be demonstrable when IV enhancement (paramagnetic enhancement) becomes readily available. Note the hypodense involvement of CT (*arrowheads* and *arrows* in **A**) compared with the well-resolved lesions on MRI in **B.** *(From Kumar AJ, Rosenbaum WE, Naidu S, et al: Adrenoleukodystrophy: corresponding MR imaging with CT,* Radiology *165:497–504, 1987.)*

learning disabilities. Rapid progression, signs of dementia, or difficulty in auditory discrimination suggest ALD. Even in early stages, CT or MRI may show strikingly abnormal changes. Other leukodystrophies or multiple sclerosis may mimic these radiographic findings, although early ALD has more of a predilection for the posterior brain than its mimics. Definitive diagnosis depends on demonstration of VLCFA excess, which occurs only in ALD and the other peroxisomal disorders.

Cerebral forms of ALD may present as increased intracranial pressure and unilateral mass lesions. These have been misdiagnosed as gliomas, even after brain biopsy, and several patients have received radiotherapy before the correct diagnosis was made. Measurement of VLCFA in plasma or brain biopsy specimens is the most reliable differentiating test.

Adolescent or adult cerebral ALD can be confused with **psychiatric disorders**, dementing disorders, or epilepsy. The first clue to the diagnosis of ALD may be the demonstration of white matter lesions by neuroimaging; assays of VLCFA are confirmatory.

ALD cannot be distinguished clinically from other forms of Addison disease; it is recommended that assays of VLCFA levels be performed in all male patients with Addison disease. ALD patients do not usually have antibodies to adrenal tissue in their plasma.

Complications

An avoidable complication is the occurrence of adrenal insufficiency. The most difficult neurologic problems are those related to bed rest, contracture, coma, and swallowing disturbances. Other complications involve behavioral disturbances and injuries associated with defects of spatial orientation, impaired vision and hearing, and seizures.

Treatment

Corticosteroid replacement for adrenal insufficiency or adrenocortical hypofunction is effective. It may be lifesaving and increase general strength and well-being, but it does not alter the course of the neurologic disability.

Bone Marrow Transplantation

Bone marrow transplantation (BMT) benefits patients who show early evidence of the inflammatory demyelination that is characteristic of the rapidly progressive neurologic disability in boys and adolescents with the cerebral ALD phenotype. BMT is a high-risk procedure, and patients must be selected with great care. The mechanism of the beneficial effect is incompletely understood. Bone marrow-derived cells do express ALDP, the protein that is deficient in ALD; approximately 50% of brain microglial cells are bone marrow derived. The favorable effect may be caused by modification of the brain inflammatory response. Five to 10 yr follow-up of boys and adolescents who had early cerebral involvement has shown stabilization. On the other hand, BMT has not shown favorable effects in patients who already had severe brain involvement and may accelerate disease progression under these circumstances. The nonverbal IQ has been found to be of predictive value, and transplant is not recommended in patients with performance IQ significantly below 80. Unfortunately, in more than half the patients who are diagnosed because of neurologic symptoms, the illness is so advanced at the time of diagnosis that they are not candidates for transplant.

Consideration of BMT is most relevant in neurologically asymptomatic or mildly involved patients. Screening at-risk relatives of symptomatic patients identifies these patients most frequently. Screening by measurement of plasma VLCFA levels in patients with Addison disease may also identify candidates for BMT. Because of its risk (10-20% mortality) and the fact that up to 50% of untreated patients with ALD do not develop inflammatory brain demyelination, transplant is not recommended in patients who are free of demonstrable brain involvement. The MRI is also of key importance for the crucial decision of whether transplant should be performed. MRI abnormalities precede

clinically evident neurologic or neuropsychologic abnormalities. The brain MRI should be monitored at 6 mo intervals in neurologically asymptomatic boys and adolescents between the ages of 3 and 15 yr. If the MRI is normal, BMT is not indicated. If brain MRI abnormalities develop, the patient should be evaluated at 3 mo intervals to determine if the abnormality is progressive, in combination with careful neurologic and neuropsychologic evaluation; and if early progressive involvement is confirmed, transplant should be considered. Magnetic resonance spectroscopy improves the capacity to determine whether the brain involvement is progressive. It is not known whether BMT has a favorable effect on the noninflammatory spinal cord involvement in adults with the adrenomyeloneuropathy phenotype.

Lorenzo's Oil Therapy

The administration of Lorenzo's oil to asymptomatic boys in an open study reduced the risk of developing the childhood cerebral phenotype by a factor of 2 or more. Lorenzo's oil (4:1 mixture of glyceryl trioleate and glyceryl trierucate) combined with a dietary regimen is under investigation for neurologically asymptomatic boys who have a normal brain MRI and are younger than 8 yr old. It has been determined that it must be supervised carefully. Adrenal function and brain MRI must be monitored. Patients who develop progressive MRI abnormalities are evaluated for hematopoietic stem cell transplant when changes are still in an early phase. Lorenzo's oil has not been shown to alter disease progression in patients who already have cerebral involvement.

Supportive Therapy

The progressive behavioral and neurologic disturbances associated with the childhood form of ALD are extremely difficult for the family. ALD patients require the establishment of a comprehensive management program and partnership among the family, physician, visiting nursing staff, school authorities, and counselors. In addition, parent support groups (e.g., United Leukodystrophy Foundation) are often helpful. Communication with school authorities is important because under the provisions of Public Law 94-142, children with ALD qualify for special services as "other health impaired" or "multihandicapped." Depending on the rate of progression of the disease, special needs might range from relatively low-level resource services within a regular school program to home- and hospital-based teaching programs for children who are not mobile.

Management challenges vary with the stage of the illness. The early stages are characterized by subtle changes in affect, behavior, and attention span. Counseling and communication with school authorities are of prime importance. Changes in the sleep–wake cycle can be benefited by the judicious use at night of medications for sleep.

As the leukodystrophy progresses, the modulation of muscle tone and support of bulbar muscular function are major concerns. Baclofen in gradually increasing doses (5 mg twice a day to 25 mg 4 times a day) is an effective pharmacologic agent for the treatment of acute episodic painful muscle spasms. Other agents may also be used, with care being taken to monitor the occurrence of side effects and drug interactions. As the leukodystrophy progresses, bulbar muscular control is lost. Although initially this can be managed by changing the diet to soft and pureed foods, most patients eventually require a gastrostomy tube. At least 30% of patients have focal or generalized seizures that usually readily respond to standard anticonvulsant medications.

Genetic Counseling and Prevention

Genetic counseling and primary and secondary prevention of ALD are of crucial importance. Extended family screening should be offered to all at-risk relatives of symptomatic patients; one program led to the identification of more than 250 asymptomatic affected males and 1,200 women heterozygous for ALD. The plasma assay permits reliable identification of affected males in whom plasma VLCFA levels are increased already on the day of birth. Identification of asymptomatic males permits institution of steroid replacement therapy when appropriate and prevents the occurrence of adrenal crisis, which may be fatal. Monitoring of brain MRI also permits identification of patients who are candidates for BMT at a stage when this procedure has the greatest chance of success. Plasma VLCFA assay is recommended in all male patients with Addison disease. ALD has been shown to be the cause of adrenal insufficiency in more than 25% of boys with Addison disease of unknown cause. Identification of women heterozygous for ALD is more difficult than that of affected males. Plasma VLCFA levels are normal in 15-20% of heterozygous women, and failure to note this has led to serious errors in genetic counseling. DNA analysis permits accurate identification of carriers, provided that the mutation has been defined in a family member, and is the procedure recommended for the identification of heterozygous women.

Prenatal diagnosis of affected male fetuses can be achieved by measurement of VLCFA levels in cultured amniocytes or chorionic villus cells and by mutation analysis. Whenever a new patient with ALD is identified, a detailed pedigree should be constructed and efforts should be made to identify all at-risk female carriers and affected males. These investigations should be accompanied by careful and sympathetic attention to social, emotional, and ethical issues during counseling.

Bibliography is available at Expert Consult.

86.3 Disorders of Lipoprotein Metabolism and Transport

William A. Neal and Collin C. John

EPIDEMIOLOGY OF BLOOD LIPIDS AND CARDIOVASCULAR DISEASE

The Seven Countries Study of geographic, social class, and ethnic differences in coronary heart disease (CHD) around the world found strong associations between average intake of saturated fats, plasma cholesterol, and mortality from CHD. Of all common chronic diseases, none is so clearly influenced by both environmental and genetic factors as CHD. This multifactorial disorder is strongly associated with increasing age and male gender, though it is increasingly apparent that heart disease is underrecognized in women. Tobacco use confers a 2-fold higher lifetime risk. Sedentary activity and high intake of saturated fats leading to adiposity increase risk through differences in the plasma levels of lipoproteins that are atherogenic. Family history is a reflection of the combined influence of lifestyle and genetic predisposition to early heart disease. Risk of premature heart disease associated with positive family history is 1.7 times higher than in families with no such history.

The pathogenesis of atherosclerosis begins during childhood. The Johns Hopkins Precursors Study demonstrated that white male medical students with blood cholesterol levels in the lowest quartile showed only a 10% incidence of CHD 3 decades later, whereas those in the highest quartile had a 40% incidence. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated a significant relationship between the weight of the abdominal fat pad and the extent of atherosclerosis found at autopsy on subjects 15-34 yr of age. The Bogalusa Heart Study of more than 3,000 black and white children and adolescents has provided the most comprehensive longitudinal data relating the presence and severity of CHD risk factors with semiquantifiable severity of atherosclerosis. Coronary atherosclerosis was present in 8.5% of military autopsies performed following combat or unintentional injuries.

The "fetal origins hypothesis" is based on the observation that infants born with low birthweight have a higher incidence of heart disease as adults. Epidemiologic studies support the idea that prenatal and early postnatal conditions may affect adult health status. Children who are large for gestational age at birth and exposed to an intrauterine environment of either diabetes or maternal obesity are at increased risk of eventually developing the "metabolic syndrome" (insulin resistance, type II diabetes, obesity, CHD). Breastfeeding preterm infants confers a long-term cardioprotective benefit 13-16 yr later. Those adolescents who were breastfed as infants had lower C-reactive protein

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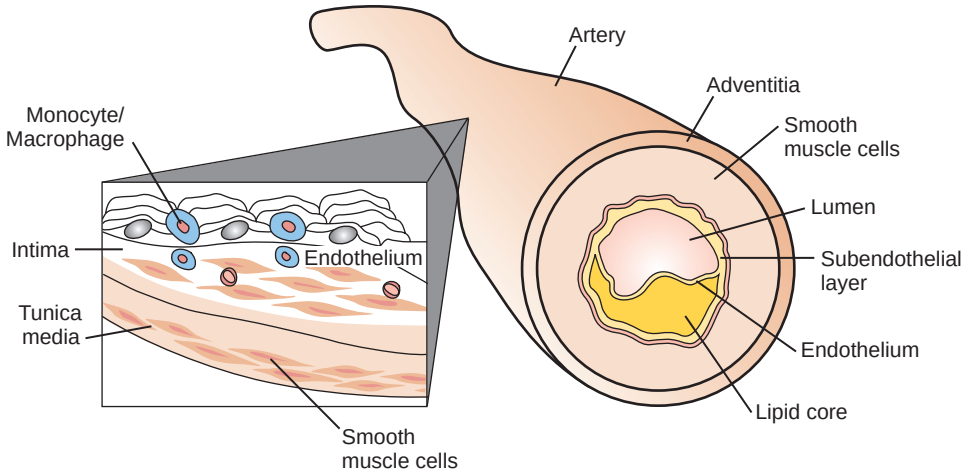


Figure 86-6 The early stage of development of atherosclerosis begins with penetration of the intimal lining of the vessel by inflammatory cells. Deposition of lipid within the subendothelial lining of the arterial wall eventually leads to disruption of smooth muscle cells to form an atheromatous lipid core that impinges on the lumen. Chronic inflammation leads to plaque instability, setting the stage for plaque rupture and complete occlusion of the vessel lumen by clot formation.

concentrations and a 14% lower low-density lipoprotein (LDL):high-density lipoprotein (HDL) ratio compared to those fed infant formulas. The impact of early nutrition and other lifestyle variables on gene expression, known as epigenetics, is an important mechanism by which adult metabolism and body composition may be determined.

In addition, secondary causes of hyperlipidemia may be the result of drugs (cyclosporine, steroids, isotretinoin, protease inhibitors, alcohol, thiazide diuretics, β-blocking agents, valproate) or various diseases (nephrotic syndrome, hypothyroidism, Cushing syndrome, anorexia nervosa, obstructive jaundice).

BLOOD LIPIDS AND ATHEROGENESIS

Numerous epidemiologic studies demonstrate the association of hypercholesterolemia, referring to elevated total blood cholesterol, with atherosclerotic disease. The ability to measure subcomponents within classes of lipid particles, as well as markers of inflammation, have further elucidated the process of atherogenesis and plaque rupture leading to acute coronary syndromes. Atherosclerosis affects primarily the coronary arteries but may also involve the aorta, arteries of the lower extremities, and carotid arteries.

The early stage of development of atherosclerosis is thought to begin with vascular endothelial dysfunction and intima-media thickness, which has been shown to occur in preadolescent children with risk factors such as obesity or familial hypercholesterolemia. The complex process of penetration of the intimal lining of the vessel may be a consequence of a variety of insults, including the presence of highly toxic oxidized LDL particles. Lymphocytes and monocytes penetrate the damaged endothelial lining, where they become macrophages laden with LDL lipids and then become foam cells. Such accumulation is counterbalanced by HDL particles capable of removing lipid deposits from the vessel wall. Fundamental to plaque formation is an inflammatory process (elevated C-reactive protein) involving macrophages and the arterial wall. The deposition of lipid within the subendothelial lining of the arterial wall appears macroscopically as fatty streaks, which may to some degree be reversible. A later stage of plaque development involves disruption of arterial smooth muscle cells stimulated by the release of tissue cytokines and growth factors. The atheroma is composed of a core of fatty substance separated from the lumen by collagen and smooth muscle (Fig. 86-6). Growth of the atherosclerotic plaque may result in ischemia of the tissue supplied by the artery. Chronic inflammation within the atheroma, results in plaque instability and subsequent rupture. Platelet adherence leads to clot formation at the site of rupture, resulting in myocardial infarction or a cerebrovascular event.

PLASMA LIPOPROTEIN METABOLISM AND TRANSPORT

Abnormalities of lipoprotein metabolism are associated with diabetes mellitus and premature atherosclerosis. Lipoproteins are soluble complexes of lipids and proteins that effect transport of fat absorbed from the diet, or synthesis by the liver and adipose tissues, for utilization and storage. Dietary fat is transported from the small intestine as chylomicrons. Lipids synthesized by the liver as very-low-density lipoproteins (VLDLs) are catabolized to intermediate-density lipoproteins (IDLs) and LDLs. HDLs are fundamentally involved in VLDL and chylomicron metabolism and cholesterol transport. Nonesterified free fatty acids are metabolically active lipids derived from lipolysis of triglycerides stored in adipose tissue bound to albumin for circulation in the plasma (Fig. 86-7).

Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins (Fig. 86-8). The density of the several classes of lipoproteins is inversely proportional to the ratio of lipid to protein (Fig. 86-9). Lipoproteins consist of a central core of triglycerides and cholesteryl esters surrounded by phospholipids, cholesterol, and proteins.

Constituent proteins are known as apolipoproteins (Table 86-6). They are responsible for a variety of metabolic functions in addition to their structural role, including cofactors or inhibitors of enzymatic pathways, and mediators of lipoprotein binding to cell surface receptors. ApoA is the major apolipoprotein (Apo) of HDL. ApoB is present in LDL, VLDL, IDL, and chylomicrons. ApoB-100 is derived from the liver, whereas apoB-48 comes from the small intestine. ApoC-I, C-II, and C-III are small peptides important in triglyceride metabolism. Loss of function and disruptive mutations of the *APOC3* gene are associated with low levels of triglycerides and a reduced risk of ischemic CHD. Likewise, apoE, which is present in VLDL, HDL, chylomicrons, and chylomicron remnants, plays an important role in the clearance of triglycerides.

Transport of Exogenous (Dietary) Lipids

All dietary fat with the exception of medium-chain triglycerides is efficiently carried into the circulation by way of lymphatic drainage from the intestinal mucosa. Triglyceride and cholesteryl esters combine with apoA and apoB-48 in the intestinal mucosa to form chylomicrons, which are carried into the peripheral circulation via the lymphatic system. HDL particles contribute apoC-II to the chylomicrons, required for the activation of lipoprotein lipase (LPL) within the capillary endothelium of adipose, heart, and skeletal muscle tissue. Free fatty acids are oxidized, esterified for storage as

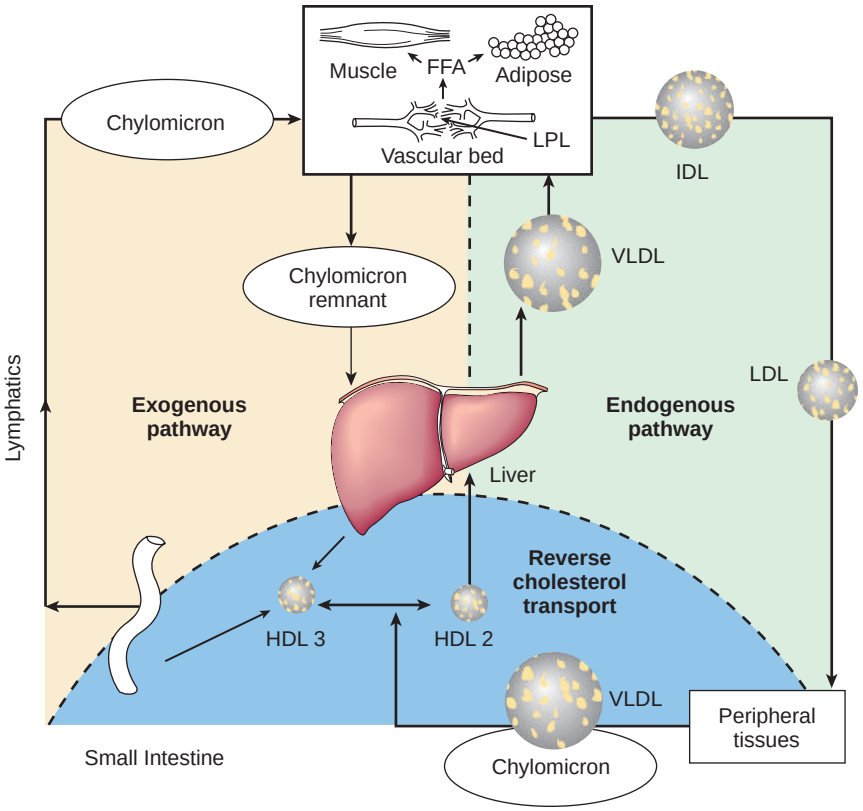


Figure 86-7 The exogenous, endogenous, and reverse cholesterol pathways. The exogenous pathway transports dietary fat from the small intestine as chylomicrons to the periphery and the liver. The endogenous pathway denotes the secretion of very-low-density lipoprotein (VLDL) from the liver and its catabolism to intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL). Triglycerides are hydrolyzed from the VLDL particle by the action of lipoprotein lipase (LPL) in the vascular bed, yielding free fatty acids (FFAs) for utilization and storage in muscle and adipose tissue. High-density lipoprotein (HDL) metabolism is responsible for the transport of excess cholesterol from the peripheral tissues back to the liver for excretion in the bile. Nascent HDL-3 particles derived from the liver and small intestine are esterified to more mature HDL-2 particles by enzyme-mediated movement of chylomicron and VLDL into the HDL core, which is removed from the circulation by endocytosis.

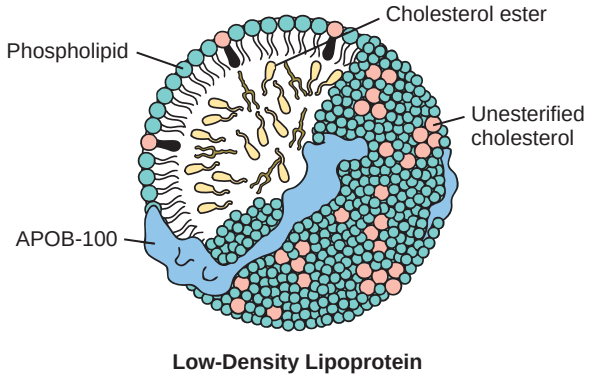


Figure 86-8 Schematic of low-density lipoprotein. Lipoprotein consists of a central core of cholesteryl esters, surrounded by phospholipids, cholesterol, and protein.

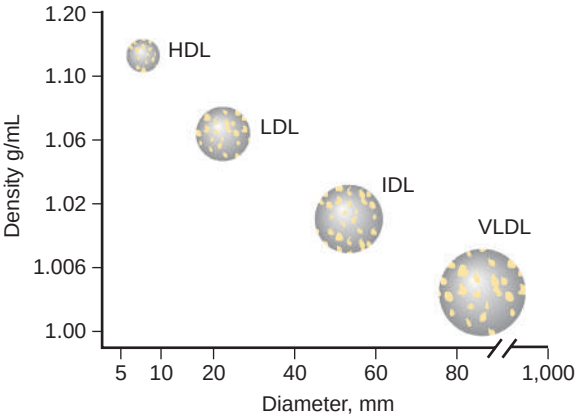


Figure 86-9 The density of the several classes of lipoprotein is inversely proportional to the ratio of lipid to protein. As lipid is less dense than protein, the more lipid contained in the particle increases its size and decreases its density. *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *IDL,* intermediate density lipoprotein; *VLDL,* very-low-density lipoprotein.

triglycerides, or released into the circulation bound to albumin for transport to the liver. After hydrolysis of the triglyceride core from the chylomicron, apoC particles are recirculated back to HDL. The subsequent contribution of apoE from HDL to the remnant chylomicron facilitates binding of the particle to hepatic LDL receptors (LDL-R). Within the hepatocyte, the chylomicron remnant may be incorporated into membranes, resecreted as lipoprotein back into the circulation, or secreted as bile acids. Normally, all dietary fat is disposed of within 8 hr after the last meal, an exception being individuals with a disorder of chylomicron metabolism. Postprandial hyperlipidemia is a risk factor for atherosclerosis. Abnormal transport of chylomicrons and their remnants may result in their absorption into the blood vessel wall as foam cells, caused by the ingestion of cholesteryl esters by macrophages, the earliest stage in the development of fatty streaks.

Transport of Endogenous Lipids from the Liver

The formation and secretion of VLDL from the liver and its catabolism to IDL and LDL particles describe the endogenous lipoprotein pathway. Fatty acids used in the hepatic formation of VLDL are derived primarily by uptake from the circulation. VLDL appears to be transported from the liver as rapidly as it is synthesized, and it consists of triglycerides, cholesteryl esters, phospholipids, and apoB-100. Nascent particles of VLDL secreted into the circulation combine with apoC and apoE. The size of the VLDL particle is determined by the amount of triglyceride present, progressively shrinking in size as triglyceride is hydrolyzed by the action of LPL, yielding free fatty acids for utilization

Table 86-6 Characteristics of the Major Lipoproteins

LIPOPROTEIN	SOURCE	SIZE (nm)	DENSITY (g/mL)	Composition %		
				PROTEIN	LIPID	APOLIPOPROTEINS
Chylomicrons	Intestine	80-1,200	<0.95	1-2	98-99	C-I, C-II, C-III, E, A-I, A-II, A-IV, B-48
Chylomicron remnants	Chylomicrons	40-150	<1.0006	6-8	92-94	B-48, E
VLDL	Liver, intestine	30-80	0.95-1.006	7-10	90-93	B-100, C-I, C-II, C-III
IDL	VLDL	25-35	1.006-1.019	11	89	B-100, E
LDL	VLDL	18-25	1.019-1.063	21	79	B-100
HDL	Liver, intestine VLDL, Chylomicrons	5-20	1.125-1.210	32-57	43-68	A-I, A-II, A-IV C-I, C-II, C-III D, E

HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

or storage in muscle and adipose tissue. Hydrolysis of approximately 80% of the triglyceride present in VLDL particles produces IDL particles containing an equal amount of cholesterol and triglyceride. The remaining remnant IDL is converted to LDL for delivery to peripheral tissues or to the liver. ApoE is attached to the remnant IDL particle to allow binding to the cell and subsequent incorporation into the lysosome. Individuals with deficiency of either apoE2 or hepatic triglyceride lipase accumulate IDL in the plasma.

LDL particles account for approximately 70% of the plasma cholesterol in normal individuals. LDL receptors are present on the surfaces of nearly all cells. Most LDL is taken up by the liver, and the rest is transported to peripheral tissues such as the adrenal glands and gonads for steroid synthesis. Dyslipidemia is greatly influenced by LDL-R activity. The efficiency with which VLDL is converted into LDL is also important in lipid homeostasis.

High-Density Lipoprotein and Reverse Cholesterol Transport

As hepatic secretion of lipid particles into the bile is the only mechanism by which cholesterol can be removed from the body, transport of excess cholesterol from the peripheral cells is a vitally important function of HDL. HDL is heavily laden with apoA-I containing lipoproteins, which is nonatherogenic in contrast to B lipoproteins. Cholesterol-poor nascent HDL particles secreted by the liver and small intestine are esterified to more mature HDL-2 particles by the action of the enzyme lecithin-cholesterol acyltransferase (LCAT), which facilitates movement of chylomicrons and VLDL into the HDL core. HDL-2 may transfer cholesteryl esters back to apoB lipoproteins mediated by cholesteryl ester transfer protein (CETP), or the cholesterol-rich particle may be removed from the plasma by endocytosis, completing reverse cholesterol transport. Low HDL may be genetic (deficiency of apoA-I) or secondary to increased plasma triglyceride.

LCAT deficiency results in diminished maturation of HDL particles, affecting their ability to do reverse cholesterol transport. This reduces its protective effect on atherosclerosis. There are rare reports, however, of less-than-expected severity of atherosclerosis despite low HDL secondary to LCAT deficiency, suggesting that the relationship may, for unknown reasons, be variable.

HYPERLIPOPROTEINEMIAS

Hypercholesterolemia

See Table 86-7.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is a monogenic autosomal codominant disorder characterized by strikingly elevated LDL cholesterol, premature cardiovascular disease (CVD), and tendon xanthomas. In the past, FH referred to defects of LDL receptor activity. However, genetic studies have broadened our understanding of the etiology of this lipoprotein abnormality to include defects in the genes for ApoB, as well as proprotein convertase subtilisin/kexin type 9. Severe hypercholesterolemia predisposing to premature CHD may be caused by other genetic abnormalities yet to be discovered. Of the nearly 800 mutations described, some result in failure of synthesis of the LDL receptor (receptor negative) and others cause defective binding or release at the lipoprotein-receptor interface. Receptor negative mutations result in more severe phenotypes than receptor defective mutations.

Homozygous Familial Hypercholesterolemia

FH homozygotes inherit 2 abnormal LDL receptor genes, resulting in markedly elevated plasma cholesterol levels ranging between 500 and 1,200 mg/dL. Triglyceride levels are normal to mildly elevated, and HDL levels may be slightly decreased. The condition occurs in 1 in 1,000,000 persons. Receptor-negative patients have <2% normal LDL receptor activity, whereas those who are receptor-defective may have as much as 25% normal activity and a better prognosis.

The prognosis is poor regardless of the specific LDL receptor aberration. Severe atherosclerosis involving the aortic root and coronary arteries is present by early to mid-childhood. These children usually present with xanthomas, which may cause thickening of the Achilles tendon or extensor tendons of the hands, or cutaneous lesions on the hands, elbows, knees, or buttocks (Figs. 86-10, 86-11, and 86-12). Corneal arcus may be present. Family history is informative because premature heart disease is strongly prevalent among relatives of both parents. The diagnosis may be confirmed by measuring LDL receptor activity in cultured skin fibroblasts. Phenotypic expression of the disease may also be assessed by measuring receptor activity on the surface of lymphocytes by using cell sorting techniques.

Untreated homozygous patients rarely survive to adulthood. Symptoms of coronary insufficiency may occur; sudden death is common. LDL apheresis to selectively remove LDL particles from the circulation is recommended for many children as it slows the progression of atherosclerosis. Liver transplantation is also successful in decreasing LDL cholesterol levels, but complications related to immunosuppression are common. HMG-CoA reductase inhibitors may be modestly effective depending on the specific class of LDL receptor defect present. Combination therapy with ezetimibe, selectively blocking cholesterol adsorption in the gut, usually results in further decline in LDL levels; it has largely replaced the use of bile acid sequestrants. Early clinical trials using microsomal triglyceride transfer protein inhibition with lomitapide resulted in a significant reduction in all apoB lipoproteins, including LDL, but hepatic fat deposition as a side effect limits consideration of this pharmacologic approach at this time. Mipomersen, an antisense oligonucleotide that binds to the sequence that encodes apolipoprotein B, reduces the synthesis of apoB and thus also VLDL and LDL; LDL cholesterol levels may decline approximately 25% with this treatment. Adverse effects include flu-like symptoms, hepatic steatosis, and cirrhosis.

Table 86-7 Hyperlipoproteinemias

DISORDER	LIPOPROTEINS ELEVATED	CLINICAL FINDINGS	GENETICS	ESTIMATED INCIDENCE
Familial hypercholesterolemia	LDL	Tendon xanthomas, CHD	AD	1 in 500
Familial defective ApoB-100	LDL	Tendon xanthomas, CHD	AD	1 in 1,000
Autosomal recessive hypercholesterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Sitosterolemia	LDL	Tendon xanthomas, CHD	AR	<1 in 1,000,000
Polygenic hypercholesterolemia	LDL	CHD		1 in 30?
Familial combined hyperlipidemia	LDL, TG	CHD	AD	1 in 200
Familial dysbetalipoproteinemia	LDL, TG	Tuberoeruptive xanthomas, peripheral vascular disease	AD	1 in 10,000
Familial chylomicronemia (Frederickson type I)	TG↑↑	Eruptive xanthomas, hepatosplenomegaly, pancreatitis	AR	1 in 1,000,000
Familial hypertriglyceridemia (Frederickson type IV)	TG↑	±CHD	AD	1 in 500
Familial hypertriglyceridemia (Frederickson type V)	TG↑↑	Xanthomas ± CHD	AD	
Familial hepatic lipase deficiency	VLDL	CHD	AR	<1 in 1,000,000

AD, autosomal dominant; AR, autosomal recessive; CHD, coronary heart disease; LDL, low-density lipoproteins, TG, triglycerides; VLDL, very-low-density lipoproteins.

Figure 86-10 Homozygous familial hypercholesterolemia. Tendon xanthomas in a 5 yr old male with homozygous familial hypercholesterolemia noted at the knee **(A),** wrist **(B),** and Achilles **(C).** *(Modified from Macchiaiolo M, Gagliardi MG, Toscano A, et al: Homozygous familial hypercholesterolaemia.* Lancet *379:1330, 2012.)*

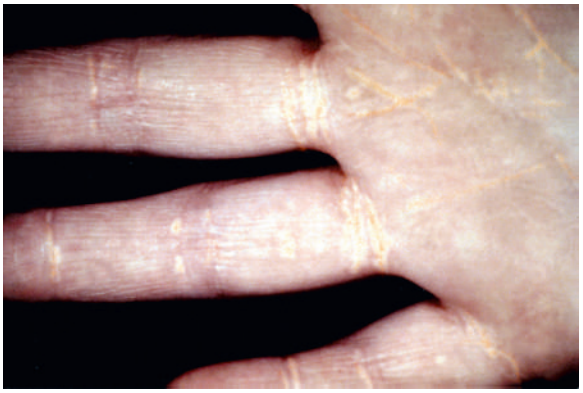


Figure 86-11 Striate palmar xanthomata. *(From Durrington P: Dyslipidaemia,* Lancet *362:717–731, 2003.)*

Figure 86-12 Eruptive xanthomata on extensor surface of forearm. *(From Durrington P: Dyslipidaemia,* Lancet *362:717–731, 2003.)*

Heterozygous Familial Hypercholesterolemia

Heterozygous FH is one of the most common single-gene mutations associated with acute coronary syndromes and atherosclerotic CHD in adults. Its prevalence is approximately 1 in 500 individuals worldwide, but the frequency may be as high as 1 in 250 in selected populations, such as French-Canadians, Afrikaners, and Christian Lebanese, as a result of the founder effect of unique new mutations.

Heart disease accounts for more than half of all deaths in Western society. The pathogenesis of CHD is both environmental and genetic, and the complex interrelationship between the 2 determines the phenotypic expression of disease. Chinese people with heterozygous FH living in China have a mean LDL cholesterol of 168 mg/dL, whereas immigrant Chinese with the disease living in Canada average 288 mg/dL. This dramatic disparity in lipoprotein levels between geographic locations is expected to narrow as dietary and physical activity practices in China approximate those of the industrialized West.

Because heterozygous FH is a codominant condition with nearly full penetrance, 50% of first-degree relatives of affected individuals will have the disease, as will 25% of 2nd-degree relatives. An estimated 10 million people have FH worldwide. Symptoms of CHD usually occur at the mean age of 45-48 yr in males, and a decade later in females. Genetic testing of individuals who fulfill clinical criteria for the diagnosis of heterozygous FH is positive approximately 80% of the time.

The World Health Organization has targeted FH for individualized intervention strategies because of its large effect on morbidity and mortality. A relatively small percentage of the population accounts for a disproportionately high share of the burden of CVD. The clinical expression of the disease is straightforward and treatment is effective.

One cannot overemphasize the importance of family history for suspecting the possibility of FH. Indeed, the whole basis for deciding which children should have blood cholesterol testing is determined by a family history of premature CHD and/or parental hypercholesterolemia. In fact, the risk of CHD in individuals with FH can be as high as 20 times greater than the general population.

Plasma levels of LDL cholesterol do not allow unequivocal diagnosis of FH heterozygotes, but values are generally twice normal for age because of 1 absent or dysfunctional allele. The U.S. MED-PED ("make early diagnosis–prevent early death") Program based in Utah has formulated diagnostic criteria. Similar criteria with minor variations exist in the United Kingdom and Holland. Within well-defined FH families, the diagnosis is reliably made according to LDL cutoff points. More stringent criteria are required to establish the diagnosis in previously undiagnosed families, requiring strong evidence of an autosomal inheritance pattern and higher LDL cutoff points. At a total cholesterol level of 310 mg/dL, only 4% of persons in the general population would have FH, whereas 95% of persons who were first-degree relatives of known cases would have the disease. The mathematical probability of FH, verified by molecular genetics, is derived from a U.S. population cohort and may not be applicable to other countries.

Very high cholesterol levels in children should prompt extensive screening of adult 1st- and 2nd-degree relatives ("reverse" cholesterol screening). A child younger than age 18 yr with total plasma cholesterol of 270 mg/dL and/or low-density lipoprotein-cholesterol (LDL-C) of 200 mg/dL has an 88% chance of having FH. *Formal clinical diagnosis of FH is based upon the presence of 2 or more family members having elevated LDL cholesterol levels greater than 220 mg/dL. It should be noted, however, that LDL-C level cutoff points vary with age* (Table 86-8). Conversely, criteria for diagnosing probable FH in a child whose first-degree relative has known FH require only modest elevation of total cholesterol to 220 mg/dL (LDL-C 155 mg/dL).

Treatment of children with FH should begin with a rather rigorous low-fat diet (see below). Diet alone is rarely sufficient for decreasing blood cholesterol levels to acceptable levels (LDL-C <130 mg/dL).

Ezetimibe blocks cholesterol adsorption in the gastrointestinal tract and has a low risk of side effects. Data suggest that ezetimibe will lower total cholesterol by 20-30 mg/dL. *HMG-CoA reductase inhibitors are the drug of choice for treatment of FH because of their remarkable effectiveness and acceptable risk profile*. There is sufficient clinical experience with this class of drugs in children to document that they are as effective in children as in adults, and the risks of elevated hepatic enzymes and myositis are no greater than in adults.

Familial Defective ApoB-100

Familial defective apoB-100 is an autosomal dominant condition that is indistinguishable from heterozygous FH. LDL cholesterol levels are increased, triglycerides are normal, adults often develop tendon

Table 86-8 Percentage of Youths Younger Than Age 18 Yr Expected to Have FH According to Cholesterol Levels and Closest Relative with FH

TOTAL CHOL (mg/dL)	LDL CHOL (mg/dL)	Percentage With FH at That Level: Degree of Relative: FIRST	SECOND	THIRD	GENERAL POPULATION
180	122	7.2	2.4	0.9	0.01
190	130	13.5	5.0	2.2	0.03
200	138	26.4	10.7	4.9	0.07
210	147	48.1	23.6	11.7	0.19
220	155	73.1	47.5	27.9	0.54
230	164	90.0	75.0	56.2	1.8
240	172	97.1	93.7	82.8	6.3
250	181	99.3	97.6	95.3	22.2
260	190	99.9	99.5	99.0	57.6
270	200	100.0	99.9	99.8	88.0
280	210	100.0	100.0	100.0	97.8
290	220	100.0	100.0	100.0	99.6
300	230	100.0	100.0	100.0	99.9
310	210	100.0	100.0	100.0	100.0

Chol, cholesterol; FH, familial hypercholesterolemia; LDL, low-density lipoprotein.

From Williams RR, Hunt SC, Schumacher MC, et al: Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics, Am J Cardiol *72:171–176, 1993.*

xanthomas, and premature CHD occurs. Familial defective apoB-100 is caused by mutation in the receptor binding region of apoB-100, the ligand of the LDL receptor, with an estimated frequency of 1 in 700 people in Western cultures. It is usually caused by substitution of glutamine for arginine in position 3500 in apoB-100, which results in reduced ability of the LDL receptor to bind LDL cholesterol, thus impairing its removal from the circulation. Specialized laboratory testing can distinguish familial defective apoB-100 from FH, but this is not necessary, except in research settings, because treatment is the same.

Autosomal Recessive Hypercholesterolemia

This rare condition, caused by a defect in LDL receptor–mediated endocytosis in the liver, clinically presents with severe hypercholesterolemia at levels intermediate between those found in homozygous and heterozygous FH. It is disproportionately present among Sardinians, and is modestly responsive to treatment with HMG-CoA reductase inhibitors.

Sitosterolemia

A rare autosomal recessive condition characterized by excessive intestinal adsorption of plant sterols, sitosterolemia is caused by mutations in the adenosine triphosphate-binding cassette transporter system, which is responsible for limiting adsorption of plant sterols in the small intestine and promotes biliary excretion of the small amounts adsorbed. Plasma cholesterol levels may be severely elevated, resulting in tendon xanthomas and premature atherosclerosis. Diagnosis can be confirmed by measuring elevated plasma sitosterol levels. Treatment with HMG-CoA reductase inhibitors is not effective, but cholesterol adsorption inhibitors, such as ezetimibe, and bile acid sequestrants are effective.

Polygenic Hypercholesterolemia

Primary elevation in LDL cholesterol among children and adults is most often polygenic; the small effects of many genes are impacted by environmental influences (diet). Plasma cholesterol levels are modestly elevated; triglyceride levels are normal. Polygenic hypercholesterolemia aggregates in families sharing a common lifestyle but does not follow predictable hereditary patterns found in single-gene lipoprotein defects. Treatment of children with polygenic hypercholesterolemia is directed toward adoption of a healthy lifestyle: reduced total and saturated fat consumption and at least 1 hr of physical activity daily. Cholesterol-lowering medication is rarely necessary.

Hypercholesterolemia with Hypertriglyceridemia

Familial Combined Hyperlipidemia

This is an autosomal dominant condition characterized by moderate elevation in plasma LDL cholesterol and triglycerides, and reduced plasma HDL cholesterol. It is the most common primary lipid disorder, occurring in approximately 1/200 people. Family history of premature heart disease is typically positive; the formal diagnosis requires that at least two first-degree relatives have evidence of one of three variants of dyslipidemia: (1) >90th percentile plasma LDL cholesterol; (2) >90th percentile LDL cholesterol and triglycerides; and (3) >90th percentile triglycerides. Individuals switch from one phenotype to another. Xanthomas are not a feature of familial combined hyperlipidemia (FCHL). Elevated plasma apoB levels with increased small dense LDL particles support the diagnosis.

Children and adults with FCHL have coexisting adiposity, hypertension, and hyperinsulinemia, suggesting the presence of the *metabolic syndrome.* Formal diagnosis in adults of this syndrome as defined by the National Cholesterol Education Program (NCEP)'s Adult Treatment Panel III identifies 6 major components: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance with or without impaired glucose tolerance, evidence of vascular inflammation, and prothrombotic state. It is estimated that 30% of overweight adults fulfill criteria for the diagnosis of metabolic syndrome, including 65% of those with FCHL. Hispanics and South Asians from the Indian subcontinent are especially susceptible. There is no official definition of metabolic syndrome for children. Absolute cutoffs for diagnosis in children do not account for continuous variables in aging, sexual maturation, and race/ethnicity.

FCHL and type II diabetes share many features of the metabolic syndrome, suggesting that they are less distinct entities than originally conceptualized. Genetic association studies reveal evidence for a common genetic background. The resultant metabolic overlap is associated with ectopic fat accumulation and insulin resistance. The mechanisms associating visceral adiposity with the metabolic syndrome and type II diabetes are not fully understood. A plausible unifying principle is that obesity causes endoplasmic reticulum stress, leading to suppression of insulin receptor signaling and thus insulin resistance and heightened inflammatory response. How this relates to atherogenesis is unclear. It is assumed that hypercholesterolemia and, with less certainty, hypertriglyceridemia confer risk for CVD in patients with FCHL. When features of the metabolic syndrome are included in logistic models shared etiologic features such as increased visceral adiposity become apparent. Visceral adiposity increases with age and its importance in children as a risk factor for heart disease and diabetes is limited by the relative paucity of data. Although longitudinal measurement of waist circumference and the presence of intraabdominal fat as determined by MRI is being conducted in the research setting, body mass index (BMI) remains the surrogate for adiposity in the pediatric clinical setting.

The metabolic syndrome is a dramatic illustration of the interaction of genetics and the environment. Genetic susceptibility is essential as an explanation for premature heart disease in individuals with FCHL. Unhealthy lifestyle, poor diet, and physical inactivity contribute to obesity and attendant features of the metabolic syndrome.

The cornerstone of management is lifestyle modification. This includes a diet low in saturated fats, trans fats, and cholesterol, as well as reduced consumption of simple sugars. Increased dietary intake of fruits and vegetables is important, as is 1 hr of moderate physical activity daily. Compliance among children and their parents is often a problem, but small incremental steps are more likely to succeed than aggressive weight-loss strategies. It is very important that the child's caregivers participate in the process. Plasma triglyceride levels are usually quite responsive to dietary restriction, especially reduction in the amount of sweetened drinks consumed. Blood cholesterol levels may decrease by 10-15%, but if LDL cholesterol remains >160 mg/dL, drug therapy should be considered.

Familial Dysbetalipoproteinemia (Type III Hyperlipoproteinemia)

Familial dysbetalipoproteinemia (FDBL) is caused by mutations in the gene for apoE, which when exposed to environmental influences such as high fat, high caloric diet, or excessive alcohol intake, results in a mixed type of hyperlipidemia. Patients tend to have elevated plasma cholesterol and triglycerides to a relatively similar degree. HDL cholesterol is typically normal in contrast to other causes of hypertriglyceridemia associated with low HDL. This rare disorder affects approximately 1 in 10,000 persons. ApoE mediates removal of chylomicron and VLDL remnants from the circulation by binding to hepatic surface receptors. The polymorphic *apoE* gene expresses in 3 isoforms: *apoE3, apoE2,* and *apoE4. E4* is the "normal" allele present in the majority of the population. The *apoE2* isoform has lower affinity for the LDL receptor and its frequency is approximately 7%. Approximately 1% of the population is homozygous for *apoE2/E2,* the most common mutation associated with FDBL, but only a minority expresses the disease. Expression requires precipitating illnesses such as diabetes, obesity, renal disease, or hypothyroidism. Individuals homozygous for *apoE4/E4* are at risk for late-onset Alzheimer disease and dementia from repeated sports-related head injuries.

Most patients with FDBL present in adulthood with distinctive xanthomas. Tuberoeruptive xanthomas resemble small grape-like clusters on the knees, buttocks, and elbows. Prominent orange-yellow discoloration of the creases of the hands (palmar xanthomas) is also typically present. Atherosclerosis, often presenting with peripheral vascular

disease, usually occurs in the 4th or 5th decade. Children may present with a less-distinctive rash and generally have precipitating illnesses.

The diagnosis of FDBL is established by lipoprotein electrophoresis, which demonstrates a broad beta band containing remnant lipoproteins. Direct measurement of VLDL by ultracentrifugation can be performed in specialized lipid laboratories. A VLDL:total triglyceride ratio >0.30 supports the diagnosis. *ApoE* genotyping for *apoE2* homozygosity can be performed, confirming the diagnosis in the presence of the distinctive physical findings. A negative result does not necessarily rule out the disease as other mutations in *apoE* may cause even more serious manifestations.

Pharmacologic treatment of FDBL is necessary to decrease the likelihood of symptomatic atherosclerosis in adults. HMG-CoA reductase inhibitors, nicotinic acid, and fibrates are all effective. FDBL is quite responsive to recommended dietary restriction.

Hypertriglyceridemias

The familial disorders of triglyceride-rich lipoproteins include both common and rare variants of the Frederickson classification system. These include chylomicronemia (type I), familial hypertriglyceridemia (type IV), and the more severe combined hypertriglyceridemia and chylomicronemia (type V). Hepatic lipase deficiency also results in a similar combined hyperlipidemia.

Familial Chylomicronemia (Type I Hyperlipidemia)

This rare single-gene defect, like FH, is caused by mutations affecting clearance of apoB-containing lipoproteins. Deficiency or absence of LPL or its cofactor apoC-II, which facilitates lipolysis by LPL, causes severe elevation of triglyceride rich plasma chylomicrons. HDL cholesterol levels are decreased. As clearance of these particles is markedly delayed, the plasma is noted to have a turbid appearance even after prolonged fasting (Fig. 86-13). Chylomicronemia caused by LPL deficiency is associated with modest elevation in triglycerides, whereas this is not the case when the cause is deficient or absent apoC-II. Both are autosomal recessive conditions with a frequency of approximately 1 in 1,000,000. The disease usually presents during childhood with acute pancreatitis. Eruptive xanthomas on the arms, knees, and buttocks may be present, and there may be hepatosplenomegaly. The diagnosis is established by assaying triglyceride lipolytic activity. Treatment of chylomicronemia is by vigorous dietary fat restriction supplemented by fat-soluble vitamins. Medium-chain triglycerides that are adsorbed into the portal venous system may augment total fat intake, and administration of fish oils may also be beneficial.

Figure 86-13 Milky plasma from patient with acute abdominal pain. *(From Durrington P: Dyslipidaemia,* Lancet *362:717–731, 2003.)*

Familial Hypertriglyceridemia (Type IV Hyperlipidemia)

Familial hypertriglyceridemia (FHTG) is an autosomal dominant disorder of unknown etiology that occurs in approximately 1 in 500 individuals. It is characterized by elevation of plasma triglycerides >90th percentile (250-1,000 mg/dL range), often accompanied by slight elevation in plasma cholesterol and low HDL. FHTG does not usually manifest until adulthood, although it is expressed in approximately 20% of affected children. In contrast to FCHL, FHTG is not thought to be highly atherogenic. It is most likely caused by defective breakdown of VLDL, or less often by overproduction of this class of lipoproteins.

The diagnosis should include the presence of at least one first-degree relative with hypertriglyceridemia. FHTG should be distinguished from FCHL and FDBL, as the latter require more vigorous treatment to prevent coronary or peripheral vascular disease. The differentiation is usually possible on clinical grounds, in that lower LDL cholesterol levels accompany FHTG, but measurement of normal apoB levels in FHTG may be helpful in ambiguous situations.

A more severe hypertriglyceridemia characterized by increased levels of chylomicrons as well as VLDL particles (Frederickson type V) may occasionally be encountered. Triglyceride levels are often >1,000 mg/dL. The disease is rarely seen in children. In contrast to chylomicronemia (Frederickson type I), LPL or apoC-II deficiency is not present. These patients often develop eruptive xanthomas in adulthood, whereas type IV hypertriglyceridemia individuals do not. Acute pancreatitis may be the presenting illness. As with other hypertriglyceridemias, excessive alcohol consumption and estrogen therapy can exacerbate the disease.

Secondary causes of transient hypertriglyceridemia should be ruled out before making a diagnosis of FHTG. A diet high in simple sugars and carbohydrates, or excessive alcohol consumption as well as estrogen therapy may exacerbate hypertriglyceridemia. Adolescents and adults should be questioned about excessive consumption of soda and other sweetened drinks, as it is common to encounter people who drink supersized drinks or multiple 12 oz cans of sweetened drinks daily. Cessation of this practice often results in dramatic fall in triglyceride levels as well as weight among those who are obese. HDL cholesterol levels will tend to rise as BMI stabilizes.

Pediatric diseases associated with hyperlipidemia include hypothyroidism, nephrotic syndrome, biliary atresia, glycogen storage disease, Niemann-Pick disease, Tay-Sachs disease, systemic lupus erythematosus, hepatitis, and anorexia nervosa (Table 86-9). Certain medications exacerbate hyperlipidemia, including isotretinoin (Accutane), thiazide diuretics, oral contraceptives, steroids, β blockers, immunosuppressants, and protease inhibitors used in the treatment of HIV.

Treatment of hypertriglyceridemia in children rarely requires medication unless levels >1,000 mg/dL persist after dietary restriction of fats, sugars, and carbohydrates, accompanied by increased physical activity. In such cases, the aim is to prevent episodes of pancreatitis. The common use of fibrates (fenofibric acid) and niacin in adults with hypertriglyceridemia is not recommended in children. HMG-CoA reductase inhibitors are reasonably effective in lowering triglyceride levels, and there is considerably more experience documenting the safety and efficacy of this class of lipid-lowering medications in children. In adults, prescription (Lovaza, Vascepa) and nonprescription fish oils have been approved by the FDA as adjuncts to diet in the treatment of severe hypertriglyceridemias.

Table 86-9 Secondary Causes of Hyperlipidemia

HYPERCHOLESTEROLEMIA
Hypothyroidism
Nephrotic syndrome
Cholestasis
Anorexia nervosa
Drugs: progesterone, thiazides, Tegretol, cyclosporine
HYPERTRIGLYCERIDEMIA
Obesity
Type II diabetes
Alcohol
Renal failure
Sepsis
Stress
Cushing syndrome
Pregnancy
Hepatitis
AIDS, protease inhibitors
Drugs: anabolic steroids, β blockers, estrogen, thiazides
REDUCED HIGH-DENSITY LIPOPROTEIN
Smoking
Obesity
Type II diabetes
Malnutrition
Drugs: β Blockers, anabolic steroids

Hepatic Lipase Deficiency

Hepatic lipase deficiency is a very rare autosomal recessive condition causing elevation in both plasma cholesterol and triglycerides. Hepatic lipase hydrolyzes triglycerides and phospholipids in VLDL remnants and IDL, preventing their conversion to LDL. HDL cholesterol levels tend to be increased rather than decreased, suggesting the diagnosis. Laboratory confirmation is established by measuring hepatic lipase activity in heparinized plasma.

Disorders of High-Density Lipoprotein Metabolism

Primary Hypoalphalipoproteinemia

Isolated low HDL cholesterol is a familial condition that often follows a pattern suggestive of autosomal dominant inheritance but may occur independent of family history. It is the most common disorder of HDL metabolism. It is defined as HDL cholesterol <10th percentile for gender and age with normal plasma triglycerides and LDL cholesterol. Whether it is associated with more rapid atherosclerosis is uncertain. It appears to be related to a reduction in apoA-I synthesis and increased catabolism of HDL. Secondary causes of low HDL cholesterol, such as the metabolic syndrome, and rare diseases such as LCAT deficiency and Tangier disease must be ruled out.

Familial Hyperalphalipoproteinemia

This is an unusual condition conferring deceased risk for CHD among family members. Plasma levels of HDL cholesterol exceed 80 mg/dL.

Familial Apolipoprotein A-I Deficiency

Mutations in the *apoA-I* gene may result in complete absence of plasma HDL. Nascent HDL is produced in the liver and small intestine. Free cholesterol from peripheral cells is esterified by LCAT, enabling formation of mature HDL particles. ApoA-I is required for normal enzymatic functioning of LCAT. The resultant accumulation of free cholesterol in the circulation eventually leads to corneal opacities, planar xanthomas, and premature atherosclerosis. Some patients, however, may have mutations of *apoA-I* that result in very rapid catabolism of the protein not associated with atherogenesis, despite HDL cholesterol levels in the 15-30 mg/dL range.

Tangier Disease

This is an autosomal codominant disease associated with levels of HDL cholesterol <5 mg/dL. It is caused by mutations in ABCA1, a protein that facilitates the binding of cellular cholesterol to apoA-I. This results in free cholesterol accumulation in the reticuloendothelial system manifested by tonsillar hypertrophy of a distinctive orange color and hepatosplenomegaly. Intermittent peripheral neuropathy may occur from cholesterol accumulation in Schwann cells. Diagnosis should be suspected in children with enlarged orange tonsils and extremely low HDL cholesterol levels.

Familial Lecithin–Cholesterol Acyltransferase Deficiency

Mutations affecting LCAT interfere with the esterification of cholesterol, thereby preventing formation of mature HDL particles. This is associated with rapid catabolism of apoA-I. Free circulating cholesterol in the plasma is greatly increased, which leads to corneal opacities and HDL cholesterol levels <10 mg/dL. Partial LCAT deficiency is known as "fish-eye" disease. Complete deficiency causes hemolytic anemia and progressive renal insufficiency early in adulthood. This rare disease is not thought to cause premature atherosclerosis. Laboratory confirmation is based on demonstration of decreased cholesterol esterification in the plasma.

Cholesteryl Ester Transfer Protein Deficiency

Mutations involving the *CETP* gene are localized to chromosome 16y21. CETP facilitates the transfer of lipoproteins from mature HDL to and from VLDL and chylomicron particles, thus ultimately regulating the rate of cholesterol transport to the liver for excretion in the bile. About half of mature HDL-2 particles are directly removed from the circulation by HDL receptors on the surface of the liver. The other half of cholesteryl esters in the core of HDL exchange with triglycerides in the core of apoB lipoproteins (VLDL, IDL, LDL) for transport to the liver. Homozygous deficiency of CETP has been observed in subsets of the Japanese population with extremely high HDL cholesterol levels (>150 mg/dL).

Conditions Associated with Low Cholesterol

Disorders of apoB-containing lipoproteins and intracellular cholesterol metabolism are associated with low plasma cholesterol.

Abetalipoproteinemia

This rare autosomal recessive disease is caused by mutations in the gene encoding microsomal triglyceride transfer protein necessary for the transfer of lipids to nascent chylomicrons in the small intestine and VLDL in the liver. This results in absence of chylomicrons, VLDL, LDL, and apoB, and very low levels of plasma cholesterol and triglycerides. Fat malabsorption, diarrhea, and failure to thrive present in early childhood. Spinocerebellar degeneration, secondary to vitamin E deficiency, manifests in loss of deep tendon reflexes progressing to ataxia and lower extremity spasticity by adulthood. Patients with abetalipoproteinemia also acquire a progressive pigmented retinopathy associated with decreased night and color vision and eventual blindness. The neurologic symptoms and retinopathy may be mistaken for Friedreich ataxia. Differentiation from Friedreich ataxia is suggested by the presence of malabsorption and acanthocytosis on peripheral blood smear in abetalipoproteinemia. Many of the clinical manifestations of the disease are a result of malabsorption of fat-soluble vitamins, such as vitamins E, A, and K. Early treatment with supplemental vitamins, especially E, may significantly slow the development of neurologic sequelae. Vitamin E is normally transported from the small intestine to the liver by chylomicrons, where it is dependent on the endogenous VLDL pathway for delivery into the circulation and peripheral tissues. Parents of children with abetalipoproteinemia have normal blood lipid and apoB levels.

Familial Hypobetalipoproteinemia

Familial homozygous hypobetalipoproteinemia is associated with symptoms very similar to those of abetalipoproteinemia, but the inheritance pattern is autosomal codominant. The disease is caused by mutations in the gene encoding apoB-100 synthesis. It is distinguishable from abetalipoproteinemia in that heterozygous parents of probands

Table 86-10 Major Clinical Characteristics of Smith-Lemli-Opitz Syndrome: Frequent Anomalies (>50% of Patients)

CRANIOFACIAL
Microcephaly
Blepharoptosis
Anteverted nares
Retromicrognathia
Low-set, posteriorly rotated ears
Midline cleft palate
Broad maxillary alveolar ridges
Cataracts (<50%)
SKELETAL ANOMALIES
Syndactyly of toes II/III
Postaxial polydactyly (<50%)
Equinovarus deformity (<50%)
GENITAL ANOMALIES
Hypospadias
Cryptorchidism
Sexual ambiguity (<50%)
DEVELOPMENT
Pre- and postnatal growth retardation
Feeding problems
Mental retardation
Behavioral abnormalities

From Haas D, Kelley RI, Hoffmann GF: Inherited disorders of cholesterol biosynthesis, Neuropediatrics *32:113–122, 2001.*

Table 86-11 Characteristic Malformations of Internal Organs in Severely Affected Smith-Lemli-Opitz Patients

CENTRAL NERVOUS SYSTEM
Frontal lobe hypoplasia
Enlarged ventricles
Agenesis of corpus callosum
Cerebellar hypoplasia
Holoprosencephaly
CARDIOVASCULAR
Atrioventricular canal
Secundum atrial septal defect
Patent ductus arteriosus
Membranous ventricular septal defect
URINARY TRACT
Renal hypoplasia or aplasia
Renal cortical cysts
Hydronephrosis
Ureteral duplication
GASTROINTESTINAL
Hirschsprung disease
Pyloric stenosis
Refractory dysmotility
Cholestatic and noncholestatic progressive liver disease
PULMONARY
Pulmonary hypoplasia
Abnormal lobation
ENDOCRINE
Adrenal insufficiency

From Haas D, Kelley RI, Hoffmann GF: Inherited disorders of cholesterol biosynthesis, Neuropediatrics *32:113–122, 2001.*

have plasma LDL cholesterol and apoB levels less than half normal. There are no symptoms or sequelae associated with the heterozygous condition.

The selective inability to secrete apoB-48 from the small intestine results in a condition resembling abetalipoproteinemia or homozygous hypobetalipoproteinemia. Sometimes referred to as Anderson disease, the failure of chylomicron absorption causes steatorrhea and fat-soluble vitamin deficiency. The blood level of apoB-100, derived from normal hepatocyte secretion, is normal in this condition.

Smith-Lemli-Opitz Syndrome

Patients with Smith-Lemli-Opitz syndrome (SLOS) often have multiple congenital anomalies and developmental delay caused by low plasma cholesterol and accumulated precursors (Tables 86-10 and 86-11). Family pedigree analysis has revealed its autosomal recessive inheritance pattern. Mutations in the *DHCR7* (7-dehydrocholesterol-Δ7 reductase) gene result in deficiency of the microsomal enzyme DHCR7, which is necessary to complete the final step in cholesterol synthesis. It is not known why defects in cholesterol synthesis result in congenital malformations, but as cholesterol is a major component of myelin and a contributor to signal transduction in the developing nervous system, neurodevelopment is severely impaired. The incidence of SLOS is estimated to be 1 in 20,000-60,000 births among whites, with a somewhat higher frequency in Hispanics and lower incidence in individuals of African descent.

Spontaneous abortion of SLOS fetuses may occur. Type II SLOS often leads to death by the end of the neonatal period. Survival is unlikely when the plasma cholesterol level is <20 mg/dL. Laboratory measurement should be performed by gas chromatography, as standard techniques for lipoprotein assay include measurement of cholesterol precursors, which may yield a false-positive result. Milder cases may not present until late childhood. Phenotypic variance ranges from microcephaly, cardiac and brain malformation, and multiorgan system failure to only subtle dysmorphic features and mild developmental delay. Treatment includes supplemental dietary cholesterol (egg yolk) and HMG-CoA reductase inhibition to prevent the synthesis of toxic precursors proximal to the enzymatic block.

Disorders of Intracellular Cholesterol Metabolism

Cerebrotendinous Xanthomatosis

This autosomal recessive disorder presents clinically in late adolescence with tendon xanthomas, cataracts, and progressive neurodegeneration. It is caused by tissue accumulation of bile acid intermediates shunted into cholestanol resulting from mutations in the gene for sterol 27-hydroxylase. This enzyme is necessary for normal mitochondrial synthesis of bile acids in the liver. Early treatment with chenodeoxycholic acid reduces cholesterol levels and prevents the development of symptoms.

Wolman Disease and Cholesterol Ester Storage Disease

These autosomal recessive disorders are caused by lack of lysosomal acid lipase. After LDL cholesterol is incorporated into the cell by endocytosis, it is delivered to lysosomes where it is hydrolyzed by lysosomal lipase. Failure of hydrolysis because of complete absence of the enzyme causes accumulation of cholesteryl esters within the cells. Hepatosplenomegaly, steatorrhea, and failure to thrive occur during early infancy, leading to death by the age of 1 yr. In cholesterol ester storage disease, a less-severe form than Wolman disease, there is low but detectable acid lipase activity.

Niemann-Pick Disease Type C

This is a disorder of intracellular cholesterol transport characterized by accumulation of cholesterol and sphingomyelin in the central nervous and reticuloendothelial systems. Death from this autosomal recessive neurologic disease usually occurs by adolescence.

Lipoprotein Patterns in Children and Adolescents

Table 86-12, derived primarily from the Lipid Research Clinics Population Studies, shows the distribution of lipoprotein levels in American

Table 86-12 Plasma Cholesterol and Triglyceride Levels in Childhood and Adolescence: Means and Percentiles

	Total Triglyceride (mg/dL)					Total Cholesterol (mg/dL)					Low-Density Lipoprotein Cholesterol (mg/dL)					High-Density Lipoprotein Cholesterol (mg/dL)*				
	5TH	MEAN	75TH	90TH	95TH	5TH	MEAN	75TH	90TH	95TH	5TH	MEAN	75TH	90TH	95TH	5TH	10TH	25TH	MEAN	95TH
Cord	14	34	—	—	84	42	68	—	—	103	17	29	—	—	50	13	—	—	35	60
1-4 YR																				
Male	29	56	68	85	99	114	155	170	190	203	—	—	—	—	—	—	—	—	—	—
Female	34	64	74	95	112	112	156	173	188	200	—	—	—	—	—	—	—	—	—	—
5-9 YR																				
Male	28	52	58	70	85	125	155	168	183	189	63	93	103	117	129	38	42	49	56	74
Female	32	64	74	103	126	131	164	176	190	197	68	100	115	125	140	36	38	47	53	73
10-14 YR																				
Male	33	63	74	94	111	124	160	173	188	202	64	97	109	122	132	37	40	46	55	74
Female	39	72	85	104	120	125	160	171	191	205	68	97	110	126	136	37	40	45	52	70
15-19 YR																				
Male	38	78	88	125	143	118	153	168	183	191	62	94	109	123	130	30	34	39	46	63
Female	36	73	85	112	126	118	159	176	198	207	59	96	111	29	137	35	38	43	52	74

*Note that different percentiles are listed for HDL cholesterol.

Data for cord blood from Strong W: Atherosclerosis: its pediatric roots. In Kaplan N, Stamler J, editors: Prevention of coronary heart disease, *Philadelphia, 1983, WB Saunders. Data for children 1-4 yr from Tables 6, 7, 20, and 21, and all other data from Tables 24, 25, 32, 33, 36, and 37 in* Lipid research clinics population studies data book, *Vol. 1, "The prevalence study," NIH publication No. 80-1527. Washington, DC, 1980, National Institutes of Health.*

youth at various ages. Total plasma cholesterol rises rapidly from a mean of 68 mg/dL at birth to a level approximately twice that by the end of the neonatal period. A very gradual rise in total cholesterol level occurs until puberty, at which time the mean level reaches 160 mg/dL. Total cholesterol falls transiently during puberty, in males because of a small decrease in HDL cholesterol, and in females secondary to a slight fall in LDL cholesterol. Blood cholesterol levels track reasonably well as individuals age.

High blood cholesterol tends to aggregate in families, a reflection of genetic and environmental influences.

Acceptable total cholesterol among children and adolescents is <170 mg/dL; borderline is 170-199 mg/dL; and high >200 mg/dL. Acceptable LDL cholesterol is <110 mg/dL; borderline 110-129 mg/dL; and high >130 mg/dL. HDL cholesterol should be >40 mg/dL.

Blood Cholesterol Screening

Previous guidelines for cholesterol measurement in children utilized a *targeted approach*. This meant obtaining a fasting lipid panel in a select group of children between the ages of 2 and 10 yr who met at least 1 of the following criteria:

- Parents or grandparents have documented premature coronary artery disease (before the age of 55 yr if male and 65 yr if female)
- Parents have been found to have high blood concentration of cholesterol (>240 mg/dL)
- Family history is unobtainable, particularly those with other risk factors such as obesity, hypertension, smoking, and/or diabetes mellitus.

Reliance on family history of premature heart disease or known parental heart disease, or known parental hypercholesterolemia was considered by some to be too insensitive and difficult to apply. Data from a large cohort of 5th grade school children who had comprehensive screening of CVD risk factors conducted by the Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project, which utilized a *universal screening* approach, found 36% of children with severe dyslipidemia did not fulfill criteria for the selective screening approach.

The American Academy of Pediatrics began recommending a universal screening approach for cholesterol screening to all children in 2011. They recommend a lipid profile to be checked for all children between the ages of 9 and 11 yr and then another between ages 17 and 21 yr as cholesterol levels may vary after puberty. However, if a child would have met the selective criteria from the previous guidelines, then screening can occur as early as age 2 yr. Of note, new data suggest that obtaining a nonfasting lipid profile can be just as useful in detecting severe genetic dyslipidemias as a fasting lipid profile, and thus, can be used as the first line of screening in children. Fasting lipid profiles may also be used depending on parental, child, and clinician preference, especially if there is concern for hypertriglyceridemia, as triglycerides are more affected by fasting status.

If a nonfasting lipid profile is used and reveals a non-HDL cholesterol (total cholesterol – HDL cholesterol) >145 mg/dL, then 2 separate **fasting** lipid profiles should be obtained at least 2 wk apart but within 3 mo of each other and the results averaged together to confirm the abnormality. If a fasting lipid profile is initially used and reveals an LDL-C ≥130 mg/dL, then another fasting lipid profile at least 2 wk apart but within 3 mo should be obtained and the results averaged together. In summary, children with suspected dyslipidemias should have results confirmed with 2 separate **fasting** lipid profiles.

Risk Assessment and Treatment of Hyperlipidemia

The NCEP recommends a population-based approach toward healthy lifestyle applicable to all children, and an individualized approach directed at those children at high risk (Fig. 86-14). The important focus on maintenance of a healthy lifestyle rather than aggressive weight reduction is recommended by the American Academy of Pediatrics.

All children with dyslipidemias are stratified according to the presence of "high-level" or "moderate-level" risk factors to determine their ultimate treatment. High-level risk factors are defined as the following: hypertension requiring drug therapy (blood pressure ≥99th percentile + 5 mm Hg), current cigarette smoker, BMI at the ≥ 97th percentile, presence of type I or type II diabetes mellitus, chronic kidney disease, postorthoptic heart transplant, and/or Kawasaki disease with current aneurysms. Moderate-level risk factors are defined as the following: hypertension that does not require drug therapy, BMI at the ≥95th percentile but <97th percentile, HDL cholesterol <40 mg/dL, Kawasaki disease with regressed coronary aneurysms, chronic inflammatory disease, HIV infection, and/or presence of nephrotic syndrome.

The initial treatment for dyslipidemia in a child always begins with a 6-mo trial of lifestyle modification, namely, changes in dietary and physical activity patterns. Being overweight confers special risk of CVD because of the strong association with the insulin resistance syndrome (metabolic syndrome). Although there is no standardized definition of metabolic syndrome defined for youth, it is likely that half of all severely obese children are insulin resistant. Data from the CARDIAC project noted that 49% of 5th grade children with the hyperpigmented rash, acanthosis nigricans, had 3 or more factors for the insulin resistance syndrome when using the definition classically used for adults, including evidence of insulin resistance, hypertension, HDL cholesterol <40 mg/dL, triglycerides >150 mg/dL, in addition to obesity.

The Cardiovascular Health Integrated Lifestyle Diet-1 (CHILD-1) diet is the first level of dietary change to be recommended for all children with dyslipidemias. The CHILD-1 diet is specially designed for children with risk factors for coronary artery disease and focuses on such things as limitation of dietary cholesterol to no more than 300 mg/day, limitation of sugary drink consumption, use of reduced fat/skim milk, avoiding foods high in *trans*-type fats, limitation of foods high in sodium, and encouraging consumption of foods high in fiber. Specific recommendations are dependent on the child's age.

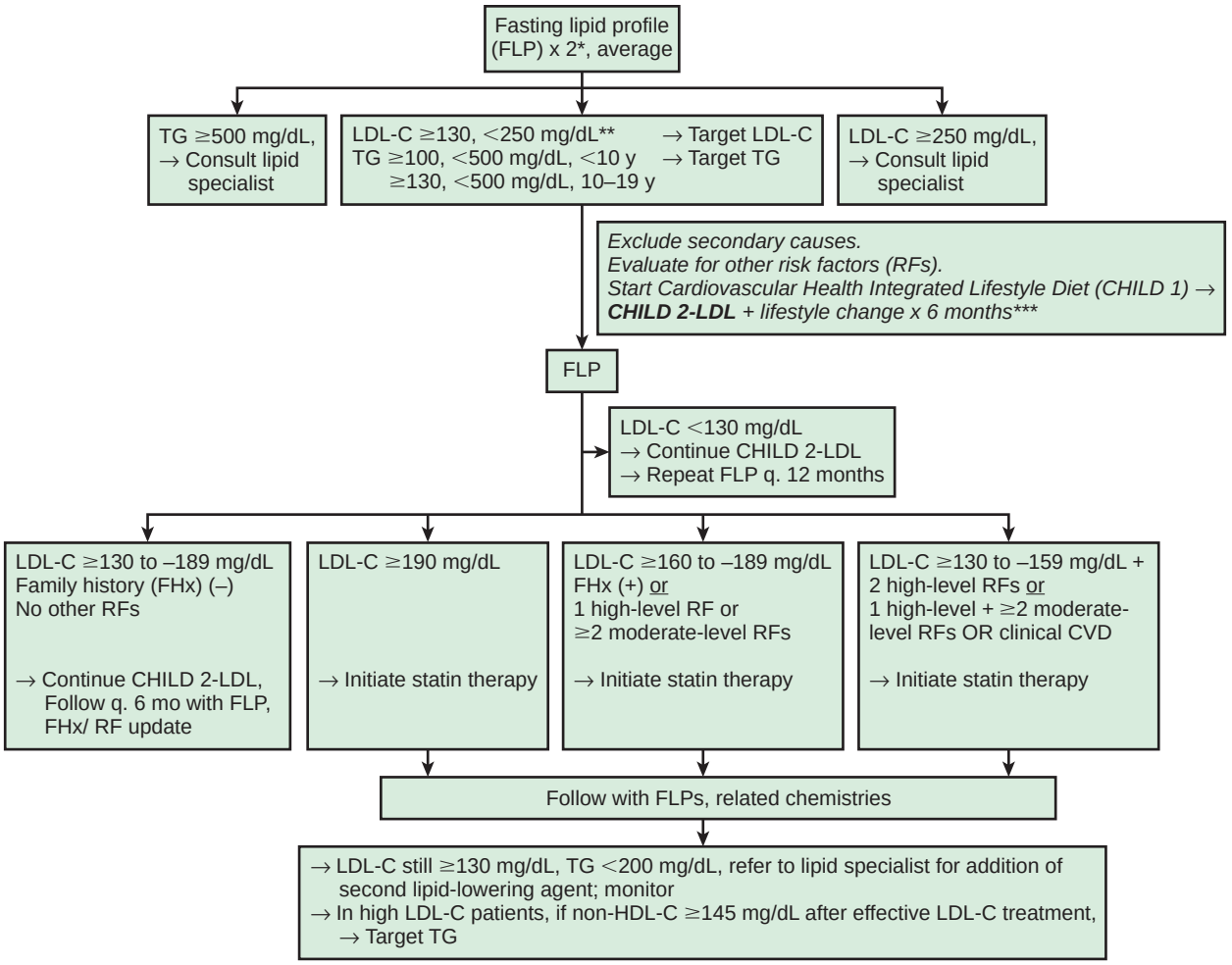
The use of the Cardiovascular Health Integrated Lifestyle Diet-2 (CHILD-2) diet is recommended if the CHILD-1 diet alone is unsuccessful. Although similar in many aspects to the CHILD-1 diet, the CHILD-2 diet is geared toward a specific dyslipidemia type, where the CHILD-2 LDL diet is recommended for those children with elevated LDL levels and the CHILD-2 TG diet is recommended for those children presenting with elevated triglycerides. The basic recommendations of calorie consumption for the CHILD-2 diet are as follows: only 25% to 30% of calories from fat, less than or equal to 7% of calories from saturated fat about 10% of calories from monounsaturated fat, less than 200 mg/d of cholesterol. If the CHILD-2 LDL diet is recommended, the use of plant sterols and water-soluble fiber is emphasized. If the CHILD-2 TG diet is recommended, the increasing consumption of complex carbohydrates and omega-3 fatty acids is emphasized.

If followed, these dietary recommendations will provide adequate calories for optimal growth and development without promoting obesity. Compliance on the part of children and their caregivers is challenging in today's society. Children learn eating habits from their parents. Successful adoption of a healthier lifestyle is far more likely to occur if meals and snacks in the home are applicable to the entire family rather than an individual child. A regular time for meals together as a family is desirable. Grandparents and other nonparental caregivers sometimes need to be reminded not to indulge the child who is on a restricted diet. Additionally, the rise in obesity is prompting some school districts to restrict sweetened drink availability, and offer more nutritious cafeteria selections.

As mentioned, changes in physical activity habits are also an important part of the initial lifestyle modification. The National Association for Sport and Physical Education recommends that children should accumulate at least 60 minutes of age-appropriate physical activity on most days of the week. Extended periods (2 hr or more) of daytime inactivity are discouraged, as is more than 2 hr of television and other forms of screen time. Unfortunately, the continued rise in sedentary activity among our youth contributes to the increase in obesity nationwide, which in turn, leads to the increasing prevalence of other risk factors such as hypertension.

Pharmacologic Therapy. See Tables 86-13 and 86-14.

The use of pharmacotherapy to treat dyslipidemias in children has been advocated by the American Academy of Pediatrics since the



* Obtain FLPs at least 2 weeks but no more than 3 months apart.
** Use of drug therapy is limited to children ≥10 y with defined risk profiles.
*** In a child with LDL-C >190 mg/dL and other RFs, trial of CHILD 2 LDL diet may be abbreviated.

Figure 86-14 Algorithm of the evaluation, risk assessment, follow-up, and treatment of children based on low-density lipoprotein (LDL) cholesterol levels. *FLP*, fasting lipid profile; *TG*, triglycerides. *(From Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary report.* Pediatrics *128(Suppl 5):S213–S256, 2011, Fig. 9-1.)*

Table 86-13 Drugs Used for the Treatment of Hyperlipidemia

DRUG	MECHANISM OF ACTION	INDICATION	STARTING DOSE
HMG-CoA reductase inhibitors (statins)	↓ Cholesterol and VLDL synthesis ↑ Hepatic LDL receptors	Elevated LDL	5-80 mg qhs
Bile acid sequestrants: Cholestyramine Colestipol	↑ Bile and excretion	Elevated LDL	 4-32 g daily 5-40 g daily
Nicotinic acid	↓ Hepatic VLDL synthesis	Elevated LDL Elevated TG	100-2,000 mg tid
Fibric acid derivatives: Gemfibrozil	↑ LPL ↓ VLDL	Elevated TG	600 mg bid
Fish oils	↓ VLDL production	Elevated TG	3-10 g daily
Cholesterol absorption inhibitors: Ezetimibe	↓ Intestinal absorption cholesterol	Elevated LDL	10 mg daily

LDL, low-density lipoprotein; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very-low-density lipoprotein.

Table 86-14 Side Effects of Lipid-Lowering Drugs

DRUG AND SITE OR TYPE OF EFFECT	EFFECT
STATINS	
Skin	Rash
Nervous system	Loss of concentration, sleep disturbance, headache, peripheral neuropathy
Liver	Hepatitis, loss of appetite, weight loss, and increases in serum aminotransferases to 2-3 times the upper limit of the normal range
Gastrointestinal tract	Abdominal pain, nausea, diarrhea
Muscles	Muscle pain or weakness, myositis (usually with serum creatine kinase >1,000U/L), rhabdomyolysis with renal failure
Immune system	Lupus-like syndrome (lovastatin, simvastatin, or fluvastatin)
Protein binding	Diminished binding of warfarin (lovastatin, simvastatin, fluvastatin)
BILE ACID-BINDING RESINS	
Gastrointestinal tract	Abdominal fullness, nausea, gas, constipation, hemorrhoids, anal fissure, activation of diverticulitis, diminished absorption of vitamin D in children
Liver	Mild serum aminotransferase elevations, which can be exacerbated by concomitant treatment with a statin
Metabolic system	Increases in serum triglycerides of ≈10% (greater increases in patients with hypertriglyceridemia)
Electrolytes	Hyperchloremic acidosis in children and patients with renal failure (cholestyramine)
Drug interactions	Binding of warfarin, digoxin, thiazide diuretics, thyroxine, statins
NICOTINIC ACID	
Skin	Flushing, dry skin, pruritus, ichthyosis, acanthosis nigricans
Eyes	Conjunctivitis, cystoid macular edema, retinal detachment
Respiratory tract	Nasal stuffiness
Heart	Supraventricular arrhythmias
Gastrointestinal tract	Heartburn, loose bowel movements or diarrhea
Liver	Mild increase in serum aminotransferases, hepatitis with nausea and fatigue
Muscles	Myositis
Metabolic system	Hyperglycemia (incidence: ≈5% higher in patients with diabetes), increase of 10% in serum uric acid
FIBRATES	
Skin	Rash
Gastrointestinal tract	Stomach upset, abdominal pain (mainly gemfibrozil), cholesterol-saturated bile, increase of 1-2% in gallstone incidence
Genitourinary tract	Erectile dysfunction (mainly clofibrate)
Muscles	Myositis with impaired renal function
Plasma proteins	Interference with binding of warfarin, requiring reduction in the dose of warfarin by ≈30%
Liver	Increased serum aminotransferases

From Knopp RH: Drug treatment of lipid disorders, N Engl J Med *341:498–512, 1999.*

inception of screening and treatment guidelines from the NCEP in 1992. Although the treatment guidelines have been slightly modified by the American Academy of Pediatrics since that time, pharmacologic therapy with cholesterol-lowering medication still remains a cornerstone of therapy for children who fail to respond to a 6 mo period of rigorous lifestyle modification. Drug therapy should be considered when one of the following conditions are met, which are also shown in Figure 86-14:

- LDL cholesterol remains >190 mg/dL
- LDL cholesterol remains >160 mg/dL with presence of 1 high-level risk factor and/or at least 2 moderate-level risk factors
- LDL cholesterol remains >130 mg/dL with presence of at least 2 high-level risk factors, 1 high-level risk factor, **and** at least 2 moderate-level risk factors, or evidence of coronary artery disease

Considerable experience with drug therapy in children and adolescents with hyperlipidemia over the past 20 yr has expanded therapeutic options, improved compliance, and enhanced efficacy. In the past, the mainstay of drug therapy was bile acid sequestrants such as cholestyramine and colestipol because they were not systemically absorbed. Interruption of the enterohepatic circulation of bile acids promotes synthesis in the liver of new bile acids from cholesterol. Gastrointestinal side effects and taste resulted in less than desirable compliance, even when there were few viable options.

HMG-CoA reductase inhibitors, also known as "statins" are remarkably effective in lowering LDL cholesterol levels and reducing plaque inflammation, thereby reducing the likelihood of a sudden coronary event in an at-risk adult within weeks of starting the medication. As a class, they work by blocking the intrahepatic biosynthesis of cholesterol, thereby stimulating the production of more LDL receptors on the cell surface and facilitating the uptake of LDL cholesterol from the bloodstream. The NCEP Adult Treatment Panel advocates aggressive lowering of LDL to below 70 mg/dL in individuals with known coronary artery disease. This information is relevant because a child who fulfills criteria for consideration of cholesterol-lowering medication will almost always have inherited the condition from one of the child's parents. Not infrequently, when providing care for the child, questions come up about screening and treatment of parents or grandparents. Statins are equally effective in children, capable of lowering LDL-C levels by 50% when necessary. They are considered first-line therapy for children who meet criteria for pharmacologic therapy. They also will effect a modest reduction in triglycerides and an inconsistent increase in HDL cholesterol. Their side–effect profile, mainly liver dysfunction and rarely rhabdomyolysis with secondary renal failure, should be taken into consideration before prescribing the drug. However, there has been no evidence to date that complications are any more frequent in children than adults, and skeletal muscle discomfort seems to be somewhat less of a problem. Drug interactions may occur as well, so careful attention should be paid to a child's active prescriptions to avoid potentiation of the aforementioned side effects. Children should have liver enzymes monitored regularly, and creatine phosphokinase measured if muscle aches or weakness occurs. Liver enzymes may be allowed to rise 3-fold before discontinuing the drug. There is a suggested link between the use of statins and increased risk of developing type II diabetes mellitus in

adults, but these results have not been replicated in children. It should be reemphasized that children with modest elevations in cholesterol, such as that seen in polygenic hypercholesterolemia, are not, as a rule, candidates for statins because of their side–effect profile. Statins should be started at the lowest effective dose and allowed at least 8 wk to achieve their peak effect. If LDL levels are not at goal, which in children who are treated is generally established to be <130 mg, then the medication may be titrated upwards with careful monitoring of side effects.

Other cholesterol-lowering medications such as nicotinic acid and fibrates have been used far less often in children than bile acid sequestrants and statins. Nicotinic acid and fibrates have been used selectively in children with marked hypertriglyceridemia (>500 mg/dL) at risk for acute pancreatitis, though dietary restriction of complex sugars and carbohydrates will usually result in significant lowering of triglyceride levels. Current guidelines recommend treatment of LDL cholesterol as the initial priority and after LDL levels are at goal, then if triglycerides remain between 200 and 499 mg/dL and non-HDL cholesterol remains ≥145 mg/dL treatment, pharmacologic treatment to reduce triglyceride levels is indicated. Omega-3 fatty acid supplementation, available both over the counter and in prescription form, is a safe and useful treatment thought to reduce triglyceride levels by decreasing the hepatic synthesis of triglycerides.

Ezetimibe has proven to be useful in the pediatric population because of its efficacy and low side–effect profile. Ezetimibe reduces plasma LDL cholesterol by blocking sterol absorption in enterocytes. The drug is marketed as an adjunct to statins when adult subjects are not achieving sufficient blood lipid lowering with statins alone. Not surprisingly, large clinical trials of ezetimibe used as monotherapy in children have not been conducted because the potential market in the pediatric age group is small. Nevertheless, there are sufficient reports in the literature documenting the effectiveness of this medication without worrisome side effects that one can feel on relatively safe grounds recommending it instead of a statin when moderate hypercholesterolemia is encountered, or apprehension from parents makes using a statin difficult.

Bibliography is available at Expert Consult.

86.4 Lipidoses (Lysosomal Storage Disorders)

Margaret M. McGovern and Robert J. Desnick

The lysosomal lipid storage diseases are diverse disorders, each caused by an inherited deficiency of a specific lysosomal hydrolase leading to the intralysosomal accumulation of the enzyme's particular substrate (Tables 86-15 and 86-16). With the exception of Wolman disease and cholesterol ester storage disease, the lipid substrates share a common structure that includes a ceramide backbone (2-*N*-acylsphingosine) from which the various sphingolipids are derived by substitution of hexoses, phosphorylcholine, or 1 or more sialic acid residues on the terminal hydroxyl group of the ceramide molecule. The pathway of sphingolipid metabolism in nervous tissue (Fig. 86-15) and in visceral organs (Fig. 86-16) is known; each catabolic step, with the exception of the catabolism of lactosylceramide, has a genetically determined metabolic defect and a resultant disease. Because sphingolipids are essential components of all cell membranes, the inability to degrade these substances and their subsequent accumulation results in the physiologic and morphologic alterations and characteristic clinical manifestations of the lipid storage disorders (see Table 86-15). Progressive lysosomal accumulation of glycosphingolipids in the central nervous system leads to neurodegeneration, whereas storage in visceral cells can lead to organomegaly, skeletal abnormalities, pulmonary infiltration, and other manifestations. The storage of a substrate in a specific tissue is dependent on its normal distribution in the body.

Diagnostic assays for the identification of affected individuals rely on the measurement of the specific enzymatic activity in isolated leukocytes or cultured fibroblasts or lymphoblasts. Figure 86-17 shows an approach to differentiating these disorders. For most disorders, carrier identification and prenatal diagnosis are available; a specific diagnosis is essential to permit genetic counseling. Neonatal screening using dried blood spots and performing enzyme assays and mutational analysis for Gaucher, Pompe, Fabry, and Niemann-Pick diseases are undergoing pilot studies. The characterization of the genes that encode the specific enzymes required for sphingolipid metabolism permit the development of therapeutic options, such as recombinant enzyme replacement therapy, as well as the potential of cell or gene therapy. Identification of specific disease-causing mutations improves diagnosis, prenatal detection, and carrier identification. For several disorders (Gaucher, Fabry, and Niemann-Pick types A and B disease), it has been possible to make genotype–phenotype correlations that predict disease severity and allow more precise genetic counseling. Inheritance is autosomal recessive except for X-linked Fabry disease.

GM_1 GANGLIOSIDOSIS

GM_1 gangliosidosis most frequently presents in early infancy, but has been described in patients with juvenile and adult onset subtypes. Inherited as an autosomal recessive trait, each subtype results from a different gene mutation that leads to the deficient activity of β-galactosidase, a lysosomal enzyme encoded by a gene on chromosome 3 (3p21.33). Although the disorder is characterized by the pathologic accumulation of GM_1 gangliosides in the lysosomes of both neural and visceral cells, GM_1 ganglioside accumulation is most marked in the brain. In addition, keratan sulfate, a mucopolysaccharide, accumulates in liver and is excreted in the urine of patients with GM_1 gangliosidosis. The β-galactosidase gene has been isolated and sequenced; mutations causing the disease subtypes have been identified.

The clinical manifestations of the infantile form of GM_1 gangliosidosis may be evident in the newborn as hepatosplenomegaly, edema, and skin eruptions (**angiokeratoma**). It most frequently presents in the first 6 mo of life with developmental delay followed by progressive psychomotor retardation and the onset of tonic–clonic seizures. A typical facies is characterized by low-set ears, frontal bossing, a depressed nasal bridge, and an abnormally long philtrum. Up to 50% of patients have a **macular cherry-red spot**. Hepatosplenomegaly and skeletal abnormalities similar to those of the mucopolysaccharidoses, including anterior beaking of the vertebrae, enlargement of the sella turcica, and thickening of the calvarium, are present. By the end of the first year of life, most patients are blind and deaf, with severe neurologic impairment characterized by decerebrate rigidity. Death usually occurs by 3-4 yr of age. The juvenile-onset form of GM_1 gangliosidosis is clinically distinct, with a variable age at onset. Affected patients present primarily with neurologic symptoms including ataxia, dysarthria, intellectual disability, and spasticity. Deterioration is slow; patients may survive through the 4th decade of life. These patients lack the visceral involvement, facial abnormalities, and skeletal features seen in type 1 disease. Adult-onset patients have been described who present with gait and speech abnormalities, dystonia and mild skeletal abnormalities. There is no specific treatment for either form of GM_1 gangliosidosis.

The diagnosis of GM_1 gangliosidosis should be suspected in infants with typical clinical features and is confirmed by the demonstration of the deficiency of β-galactosidase activity in peripheral leukocytes. Other disorders that share some of the features of the GM_1 gangliosidoses include Hurler disease (mucopolysaccharidosis type I), I-cell disease, and Niemann-Pick disease (NPD) type A, which can each be distinguished by the demonstration of their specific enzymatic deficiencies. Carriers of the disorder are detected by the measurement of the enzymatic activity in peripheral leukocytes or by identifying the specific gene mutations; prenatal diagnosis is accomplished by determination of the enzymatic activity in cultured amniocytes or chorionic villi or identification of the specific disease-causing mutations. Currently only supportive therapy is available for patients with GM_1 gangliosidosis. However studies in mice with GM_1-gangliosidosis have demonstrated that orally administered *N*-octyl-4-epi-β-valienamine

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Table 86-15 Clinical Findings in Lysosomal Storage Diseases

NOMENCLATURE	ENZYME DEFECT	HYDROPS FETALIS	COARSE FACIAL FEATURES DYSOSTOSIS MULTIPLEX	HEPATOSPLENOMEGALY
MUCOLIPIDOSES				
Mucolipidoses II, I-cell disease	*N*-Acetylglucosaminylphosphotransferase	(+)	++	+
Mucolipidosis III, Pseudo-Hurler	*N*-Acetylglucosaminylphosphotransferase	–	+	(+)
Mucolipidosis IV	Unknown	–	–	+
SS				
Fabry disease	α-Galactosidase	–	–	–
Farber disease	Ceramidase	–	–	(+)
Galactosialidosis	β-Galactosidase and sialidase	(+)	++	++
GM_1 gangliosidosis	β-Galactosidase	(+)	++	+
GM_2 gangliosidosis (Tay-Sachs disease, Sandhoff disease)	β-Hexosaminidases A and B	–	–	(+)
Gaucher type I	Glucocerebrosidase	–	–	++
Gaucher type II	Glucocerebrosidase	(+)	–	++
Gaucher type III	Glucocerebrosidase	(+)	–	+
Niemann-Pick type A	Sphingomyelinase	(+)	–	++
Niemann-Pick type B	Sphingomyelinase	–	–	++
Metachromatic leukodystrophy	Arylsulfatase A	–	–	–
Krabbe disease	β-Galactocerebrosidase	–	–	–
LIPID STORAGE DISORDERS				
Niemann-Pick type C	Intracellular cholesterol transport	–	–	(+)
Wolman disease	Acid lipase	(+)	–	+
Ceroid lipofuscinosis, infantile (Santavuori-Haltia)	Palmitoyl-protein thioesterase (CLN1)	–	–	–
Ceroid lipofuscinosis, late infantile (Jansky-Bielschowsky)	Pepstatin-insensitive peptidase (CLN2); variants in Finland (CLN5), Turkey (CLN7), and Italy (CLN6)	–	–	–
Ceroid lipofuscinosis, juvenile (Spielmeyer-Vogt)	CLN3, membrane protein	–	–	–
Ceroid lipofuscinosis, adult (Kufs, Parry)	CLN4, probably heterogeneous	(+)	–	–
OLIGOSACCHARIDOSES				
Aspartylglucosaminuria	Aspartylglucosylaminase	–	+	(+)
Fucosidosis	α-Fucosidase	–	++	(+)
α-Mannosidosis	α-Mannosidase	–	++	+
β-Mannosidosis	β-Mannosidase	–	+	(+)
Schindler disease	α-*N*-Acetylgalactosaminidase	–	–	–
Sialidosis I	Sialidase	(+)	–	–
Sialidosis II	Sialidase	(+)	++	+

++, Prominent; +, often present; (+), inconstant or occurring later in the disease course; –, not present; GAG, glycosaminoglycans.
Modified from Hoffmann GF, Nyhan WL, Zschoke J, et al: Storage disorders in inherited metabolic diseases, *Philadelphia, 2002, Lippincott Williams & Wilkins, pp. 346–351.*

(NOEV),which stabilizes the mutant enzyme protein produced by affected animals, crossed the brain and improved neurologic deterioration suggesting that this approach may be useful to study in humans.

THE GM_2 GANGLIOSIDOSES

The GM_2 gangliosidoses include Tay-Sachs disease and Sandhoff disease; each results from the deficiency of β-hexosaminidase activity and the lysosomal accumulation of GM_2 gangliosides, particularly in the central nervous system. Both disorders have been classified into infantile-, juvenile-, and adult-onset forms based on the age at onset and clinical features. β-Hexosaminidase occurs as 2 isozymes: β-hexosaminidase A, which is composed of 1 α and 1 β subunit, and β-hexosaminidase B, which has 2 β subunits. β-Hexosaminidase A deficiency results from mutations in the α subunit and causes Tay-Sachs disease, whereas mutations in the β-subunit gene result in the deficiency of both β-hexosaminidases A and B and cause Sandhoff

CARDIAC INVOLVEMENT CARDIAC FAILURE	MENTAL DETERIORATION	MYOCLONUS	SPASTICITY	PERIPHERAL NEUROPATHY	CHERRY-RED SPOT	CORNEAL CLOUDING	ANGIOKERATOMATA
++	++	–	–	–	–	(+)	–
–	(+)	–	–	–	–	+	–
–	(+)	–	–	–	–	–	–
+	–	–	–	–	–	+	++
++	+	–	–	+	(+)	–	–
+	++	(+)	+	–	+	+	+
(+)	++	–	(+)	–	(+)	+	+
–	++	+	+	–	++	–	–
–	–	–	–	–	–	–	–
–	++	+	+	–	–	–	–
–	+	(+)	(+)	–	–	–	–
–	+	(+)	–	(+)	(++)	–	–
–	–	–	–	(+)	(+)	–	–
–	++	–	+	++	(+)	–	–
–	++	–	+	++	(+)	–	–
–	+	–	–	–	(+)	–	–
(+)	–	–	–	–	(+)	–	–
–	+	+	+	–	–	–	–
–	+	+	+	–	–	–	–
–	+	–	(+)	–	–	–	–
–	+	–	–	–	–	–	–
(+)	+	–	–	–	–	(+)	(+)
+	++	+	+	–	–	–	(+)
–	++	–	(+)	–	–	++	(+)
–	+	–	+	+	–	–	(+)
–	+	+	+	–	–	–	–
–	–	++	+	+	++	(+)	–
+	++	(+)	–	–	++	–	+

disease. Both are autosomal recessive traits, with Tay-Sachs disease being more frequent in the Ashkenazi Jewish population, where the carrier frequency is approximately 1 in 25.

More than 50 mutations have been identified; most are associated with the infantile forms of disease. Three mutations account for >98% of mutant alleles among Ashkenazi Jewish carriers of Tay-Sachs disease, including 1 allele associated with the adult-onset form. Mutations that cause the subacute or adult-onset forms result in enzyme proteins with residual enzymatic activities, the levels of which correlate with the severity of the disease.

Patients with the infantile form of Tay-Sachs disease have clinical manifestations in infancy including loss of motor skills, increased startle reaction, and macular pallor and **retinal cherry-red spots** (see Table 86-15). Affected infants usually develop normally until 4-5 mo of age when decreased eye contact and an exaggerated startle response to noise (**hyperacusis**) are noted. **Macrocephaly**, not associated with

Table 86-16 Symptoms Encountered in Patients with Lysosomal Storage Disorders

SYSTEM	MANIFESTATIONS
Neurologic	Hypotonia Floppy-infant syndrome Trismus Strabismus Opisthotonus Spasticity Seizures Peripheral neuropathy Developmental delay Irritability Extrapyramidal movement disorder Hydrocephalus
Respiratory	Congenital lobar emphysema Recurrent respiratory infections Hoarseness
Endocrine	Osteopenia Metabolic bone disease Secondary hyperparathyroidism Congenital adrenal hyperplasia
Cardiovascular	Cardiomegaly Congenital heart failure Arrhythmias Wolff-Parkinson-White syndrome Cardiomyopathy
Dysmorphology	
Head and neck	Macrocephaly Enlarged nuchal translucency Microstomia Micrognathia/microretrognathia Long philtrum
Limbs	Bilateral broad thumbs and toes Bilateral club feet
Oral	Macroglossia Molar hypoplasia Hypertrophic gums
Facial	Bilateral epicanthal inferior orbital creases Palpebral edema Hypertelorism Coarse facies Low-set ears
Gastrointestinal	Hepatosplenomegaly Neonatal cholestasis
Bones and joints	Lytic bone lesions Joint contractures Dysostosis multiplex Hyperphosphatasemia Vertebral breaking Broadening of tubular bones Punctuate epiphysis Craniosynostosis Painful joint swelling
Skin	Congenital ichthyosis Collodion infant Hypopigmentation Telangiectasias Extended Mongolian spots
Ocular	Corneal clouding Megalocornea Glaucoma Cherry-red spots Fundi hypopigmentation Bilateral cataracts
Hematologic	Anemia Thrombocytopenia
Hydrops fetalis	Nonimmune hydrops fetalis Congenital ascites

From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn, Pediatrics *123:1191–1207, 2009.*

hydrocephalus, may develop. In the 2nd yr of life, seizures develop which may be refractory to anticonvulsant therapy. Neurodegeneration is relentless, with death occurring by the age of 4 or 5 yr. The juvenile and later-onset forms initially present with ataxia and dysarthria and may not be associated with a macular cherry-red spot.

The clinical manifestations of **Sandhoff** disease are similar to those of Tay-Sachs disease. Infants with Sandhoff disease have hepatosplenomegaly, cardiac involvement, and mild bony abnormalities. The juvenile form of this disorder presents as ataxia, dysarthria, and mental deterioration, but without visceral enlargement or a macular cherry red spot. There is no treatment available for Tay-Sachs disease or Sandhoff disease, although experimental approaches are being evaluated.

The diagnosis of infantile Tay-Sachs disease and Sandhoff disease is usually suspected in an infant with neurologic features and a cherry-red spot. Definitive diagnosis is made by determination of β-hexosaminidase A and B activities in peripheral leukocytes. The 2 disorders are distinguished by the enzymatic assay, because in Tay-Sachs disease only the β-hexosaminidase A isozyme is deficient, whereas in Sandhoff disease both of the β-hexosaminidase A and B isozymes are deficient. At-risk pregnancies for both disorders can be prenatally diagnosed by determining the enzyme levels in fetal cells obtained by amniocentesis or chorionic villus sampling. Identification of carriers in families is also possible by β-hexosaminidases A and B determination. Indeed, for Tay-Sachs disease, carrier screening of all couples in which at least 1 member is of Ashkenazi Jewish descent is recommended before the initiation of pregnancy to identify couples at risk. These studies can be conducted by the determination of the level of β-hexosaminidase A activity in peripheral leukocytes or plasma. Molecular studies to identify the exact molecular defect in enzymatically identified carriers should also be performed to permit more specific identification of carriers in the family and to allow prenatal diagnosis in at-risk couples by both enzymatic and genotype determinations. The incidence of Tay-Sachs disease has been markedly reduced since the introduction of carrier screening programs in the Ashkenazi Jewish population. Newborn screening may be possible by measuring specific glycosphingolipid markers, or the relevant enzymatic activities in dried blood spots.

GAUCHER DISEASE

This disease is a multisystemic lipidosis characterized by hematologic abnormalities, organomegaly, and skeletal involvement, the latter usually manifesting as bone pain and pathologic fractures (see Table 86-15). It is one of the most common lysosomal storage diseases and the most prevalent genetic defect among Ashkenazi Jews. There are 3 clinical subtypes delineated by the absence or presence and progression of neurologic manifestations: type 1 or the adult, nonneuronopathic form; type 2, the infantile or acute neuronopathic form; and type 3, the juvenile or subacute neuronopathic form. All are autosomal recessive traits. Type 1, which accounts for 99% of cases, has a striking predilection for Ashkenazi Jews, with an incidence of approximately 1 in 1,000 live births and a carrier frequency of approximately 1 in 18 adults.

Gaucher disease results from the deficient activity of the lysosomal hydrolase, acid β-glucosidase, which is encoded by a gene located on chromosome 1q21-q31. The enzymatic defect results in the

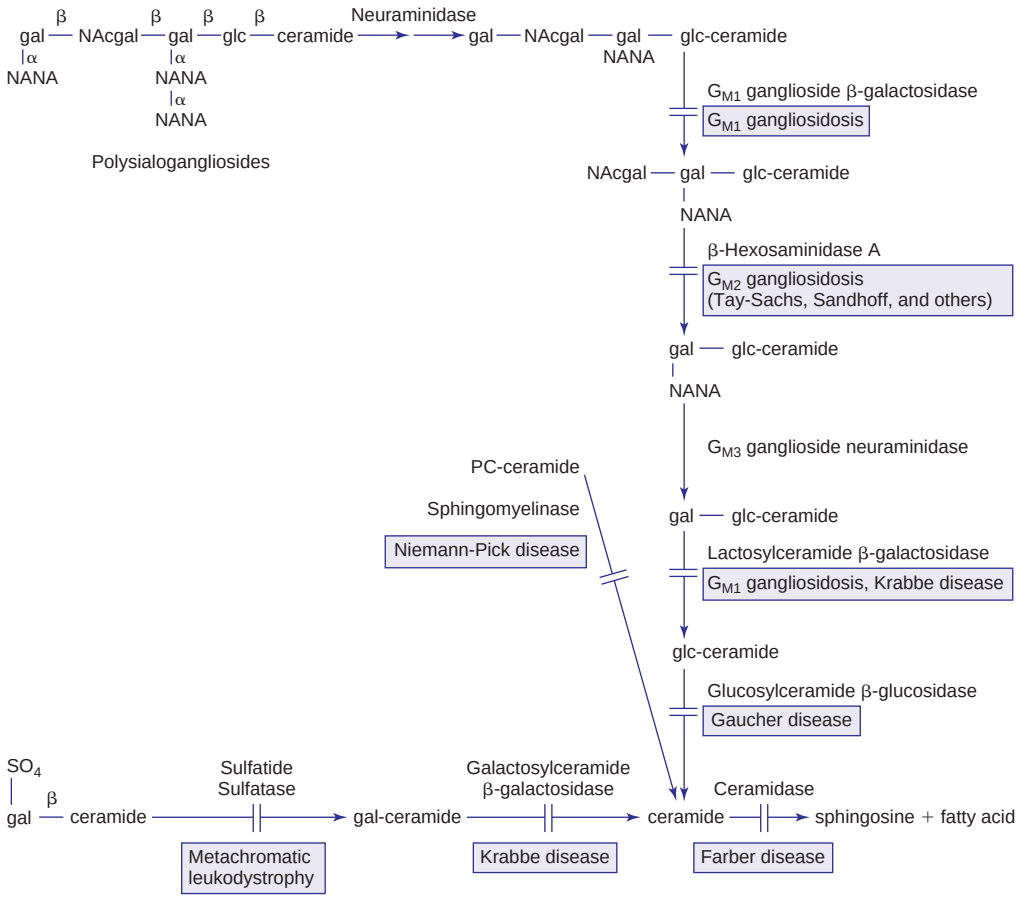

Figure 86-15 **Pathways in the metabolism of sphingolipids found in nervous tissues.** The name of the enzyme catalyzing each reaction is given with the name of the substrate that it hydrolyzes. Inborn errors are depicted as *bars* crossing the reaction *arrows,* and the name of the associated defect or defects is given in the nearest *box.* The gangliosides are named according to the nomenclature of Svennerholm. Anomeric configurations are given only at the largest starting compound. *Gal,* galactose; *glc,* glucose; *NAcgal, N*-acetylgalactosamine; *NANA, N*-acetylneuraminic acid; *PC,* phosphorylcholine.

accumulation of undegraded glycolipid substrates, particularly glucosylceramide, in cells of the reticuloendothelial system. This progressive deposition results in infiltration of the bone marrow, progressive hepatosplenomegaly, and skeletal complications. Four mutations—N370S, L444P, 84insG, and IVS2+2—account for approximately 95% of mutant alleles among Ashkenazi Jewish patients, permitting screening for this disorder in this population. Genotype–phenotype correlations have been noted, providing the molecular basis for the clinical heterogeneity seen in Gaucher disease type 1. Patients who are homozygous for the N370S mutation tend to have later onset, with a more indolent course than patients with 1 copy of N370S and another common allele.

Clinical manifestations of type 1 Gaucher disease have a variable age at onset, from early childhood to late adulthood, with most symptomatic patients presenting by adolescence. At presentation, patients may have bruising from thrombocytopenia, chronic fatigue secondary to anemia, hepatomegaly with or without elevated liver function test results, splenomegaly, and bone pain. Occasional patients have pulmonary involvement at the time of presentation. Patients presenting in the 1st decade frequently are not Jewish and have growth retardation and a more malignant course. Other patients may be discovered fortuitously during evaluation for other conditions or as part of routine examinations; these patients may have a milder or even a benign course. In symptomatic patients, splenomegaly is progressive and can become massive. Most patients develop radiologic evidence of skeletal involvement, including an Erlenmeyer flask deformity of the distal femur. Clinically apparent bony involvement, which occurs in most patients, can present as bone pain, a pseudoosteomyelitis pattern or pathologic fractures. Lytic lesions can develop in the long bones, including the femur, ribs, and pelvis; osteosclerosis may be evident at an early age. Bone crises with severe pain and swelling can occur. Bleeding secondary to thrombocytopenia may manifest as epistaxis or bruising and is frequently overlooked until other symptoms become apparent. With the exception of the severely growth-retarded child, who may experience developmental delay secondary to the effects of chronic disease, development and intelligence are normal.

The pathologic hallmark of Gaucher disease is the Gaucher cell in the reticuloendothelial system, particularly in the bone marrow (Fig. 86-18). These cells, which are 20-100 µm in diameter, have a characteristic wrinkled paper appearance resulting from the presence of intracytoplasmic substrate inclusions. The cytoplasm of the Gaucher cell reacts strongly positive with the periodic acid–Schiff stain. The presence of this cell in bone marrow and tissue specimens is highly suggestive of Gaucher disease, although it also may be found in patients with granulocytic leukemia and myeloma.

Gaucher disease type 2 is a rare form and does not have an ethnic predilection. It is characterized by a rapid neurodegenerative course with extensive visceral involvement and death within the first years of life. It presents in infancy with increased tone, strabismus, and organomegaly. Failure to thrive and stridor caused by laryngospasm are typical. After a several-year period of psychomotor regression, death typically occurs secondary to respiratory compromise. **Gaucher disease type 3** presents with clinical manifestations that are intermediate to those seen in types 1 and 2, with presentation in childhood

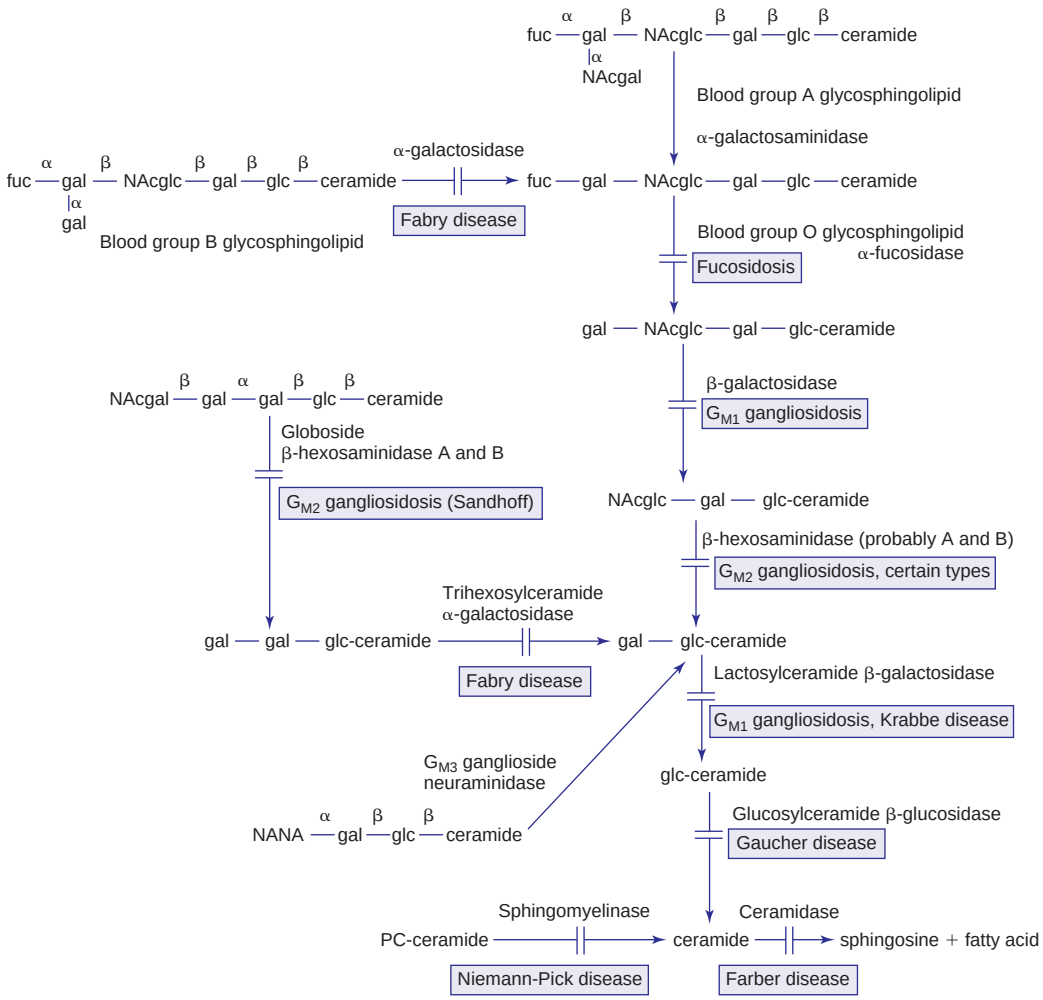

Figure 86-16 Pathways in the degradation of sphingolipids found in visceral organs and red or white blood cells. See also the legend for Figure 86-15. *Fuc,* fucose; *NAcglc, N*-acetylglucosamine.

and death by age 10-15 yr. It has a predilection for the Swedish Norrbottnian population, among whom the incidence is approximately 1 in 50,000. Neurologic involvement is present. Type 3 disease is further classified as types 3a and 3b based on the extent of neurologic involvement and whether there is progressive myotonia and dementia (type 3a) or isolated supranuclear gaze palsy (type 3b).

Gaucher disease should be considered in the differential diagnosis of patients with unexplained organomegaly, who bruise easily, have bone pain, or have a combination of these conditions. Bone marrow examination usually reveals the presence of Gaucher cells. All suspected diagnoses should be confirmed by determination of the acid β-glucosidase activity in isolated leukocytes or cultured fibroblasts, and by identification of their specific acid β-glucosidase gene mutations. In Ashkenazi Jewish individuals the identification of carriers can be achieved best by molecular testing for the common Ashkenazi mutations. Testing should be offered to all family members, keeping in mind that heterogeneity, even among members of the same kindred, can be so great that nonsymptomatic affected individuals may be diagnosed. Prenatal diagnosis is available by determination of enzyme activity and/or the specific family mutations in chorionic villi or cultured amniotic fluid cells.

Treatment of patients with Gaucher disease type 1 includes enzyme replacement therapy. The efficacy of enzyme replacement therapy with mannose-terminated recombinant human acid β-glucosidase has definitively been demonstrated. Most symptoms (organomegaly, hematologic indices, bone pain) are reversed by enzyme replacement therapy (60 IU/kg) administered by intravenous infusion every other week and the bone involvement can be stabilized or improved. Two additional enzyme preparations are approved by the FDA for the treatment of type 1 Gaucher disease, including velaglucerase alfa (VPRIV, Shire HGT), which is produced in human fibrosarcoma cells, and taliglucerase alfa (Uplyso, Protalix Biotherapeutics), which is produced in carrot cells.

Although enzyme replacement does not alter the neurologic progression of patients with Gaucher disease types 2 and 3, it has been used in selected patients as a palliative measure, particularly in type 3 patients with severe visceral involvement. Alternative treatments, including the use of oral substrate reduction agents designed to decrease the synthesis of glucosylceramide by chemical inhibition of glucosylceramide synthase (e.g., miglustat), also are available. A small number of patients have undergone bone marrow transplantation (BMT), which is curative but is associated with significant morbidity and mortality from the procedure, limiting the selection of appropriate candidates.

NIEMANN-PICK DISEASE

The original description of NPD was what is now known as **type A NPD**, a fatal disorder of infancy characterized by failure to thrive, hepatosplenomegaly, and a rapidly progressive neurodegenerative course that leads to death by 2-3 yr of age. **Type B** disease is a nonneuronopathic form observed in children and adults. **Type C** disease is a neuronopathic form that results from defective cholesterol transport. All subtypes are inherited as autosomal recessive traits and display variable clinical features (see Table 86-15).

NPD types A and B result from the deficient activity of acid sphingomyelinase, a lysosomal enzyme encoded by a gene on chromosome

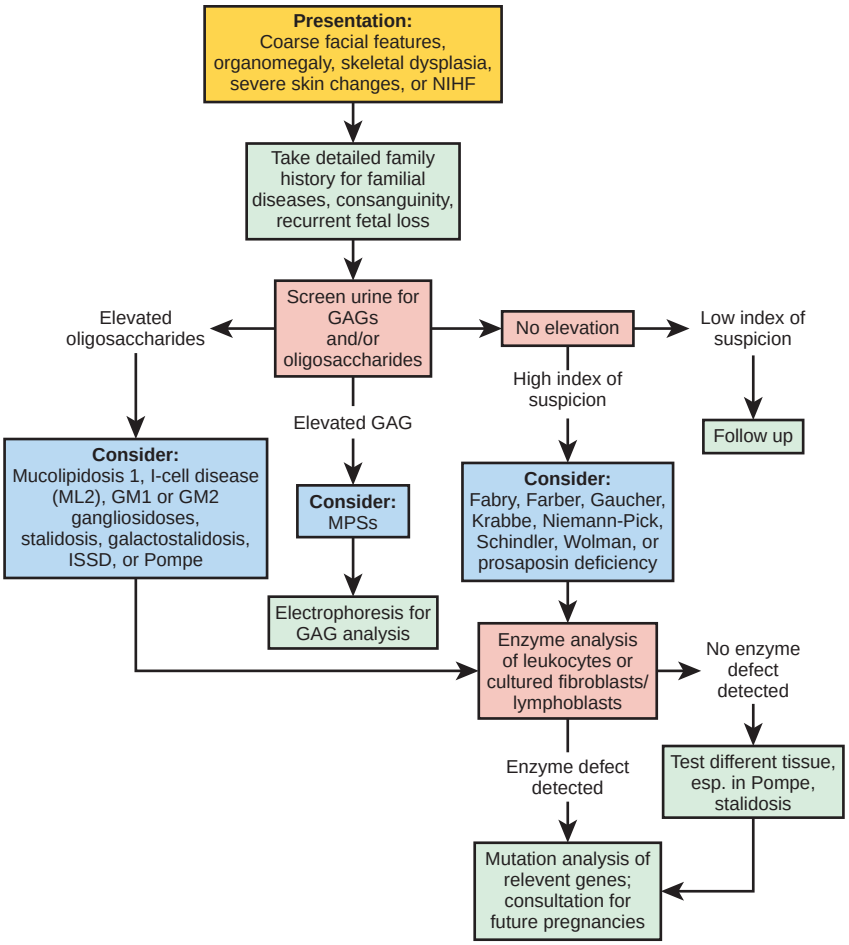

Figure 86-17 Algorithm of the clinical evaluation recommended for an infant with a suspected lysosomal storage disease. *GAGs,* glycosaminoglycans; *NIHF,* nonimmune hydrops fetalis. *(From Staretz-Chacham O, Lang TC, LaMarca ME, et al: Lysosomal storage disorders in the newborn,* Pediatrics *123:1191–1207, 2009.)*

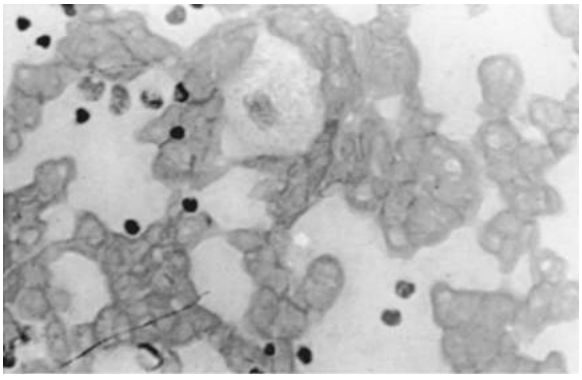

Figure 86-18 Cells from the spleen of a patient with Gaucher disease. A characteristic spleen cell is shown engorged with glucocerebroside.

11 (11p15.1-p15.4). The enzymatic defect results in the pathologic accumulation of sphingomyelin, a ceramide phospholipid, and other lipids in the monocyte–macrophage system, the primary pathologic site. The progressive deposition of sphingomyelin in the central nervous system results in the neurodegenerative course seen in type A, and in nonneural tissue in the systemic disease manifestations of type B, including progressive lung disease in some patients. A variety of mutations in the acid sphingomyelinase gene that cause types A and B NPD have been identified.

The clinical manifestations and course of type A NPD is uniform and is characterized by a normal appearance at birth. Hepatosplenomegaly, moderate lymphadenopathy, and psychomotor retardation are evident by 6 mo of age, followed by neurodevelopmental regression and death by 3 yr. With advancing age, the loss of motor function and the deterioration of intellectual capabilities are progressively debilitating; and in later stages, spasticity and rigidity are evident. Affected infants lose contact with their environment. In contrast to the stereotyped type A phenotype, the clinical presentation and course of patients with type B disease are more variable. Most are diagnosed in infancy or childhood when enlargement of the liver or spleen, or both, is detected during a routine physical examination. At diagnosis, type B NPD patients usually have evidence of mild pulmonary involvement, usually detected as a diffuse reticular or finely nodular infiltration on the chest radiograph. **Pulmonary symptoms** may present in adults. In most patients, hepatosplenomegaly is particularly prominent in childhood, but with increasing linear growth, the abdominal protuberance decreases and becomes less conspicuous. In mildly affected patients, the splenomegaly may not be noted until adulthood, and there may be minimal disease manifestations.

Severely affected patients may have liver involvement leading to life-threatening cirrhosis, portal hypertension, and ascites. Clinically significant pancytopenia caused by secondary **hypersplenism** may require partial or complete splenectomy; this should be avoided if possible because splenectomy frequently causes progression of pulmonary disease, which can be life-threatening. In general, type B patients do not have neurologic involvement and have a normal IQ. Some patients with type B disease have cherry-red maculae or haloes and subtle neurologic symptoms (peripheral neuropathy). In some type B patients, decreased pulmonary diffusion caused by alveolar infiltration becomes evident in late childhood or early adulthood and progresses with age.

Severely affected individuals may experience significant pulmonary compromise by 15-20 yr of age. Such patients have low PO_2 values and dyspnea on exertion. Life-threatening bronchopneumonias may occur, and cor pulmonale has been described.

Type C NPD patients often present with prolonged neonatal jaundice, appear normal for 1-2 yr, and then experience a slowly progressive and variable neurodegenerative course. Their hepatosplenomegaly is less severe than that of patients with types A or B NPD, and they may survive into adulthood. The underlying biochemical defect in type C patients is an abnormality in cholesterol transport, leading to the accumulation of sphingomyelin and cholesterol in their lysosomes and a secondary partial reduction in acid sphingomyelinase activity (see Chapter 86.3).

In type B NPD patients, splenomegaly is usually the first manifestation detected. The splenic enlargement is noted in early childhood; in very mild disease, the enlargement may be subtle and detection may be delayed until adolescence or adulthood. The presence of the characteristic NPD cells in bone marrow aspirates supports the diagnosis of type B NPD. Patients with type C NPD, however, also have extensive infiltration of NPD cells in the bone marrow and, thus, all suspected cases should be evaluated enzymatically to confirm the clinical diagnosis by measuring the acid sphingomyelinase activity level in peripheral leukocytes, cultured fibroblasts, or lymphoblasts, or a combination of these cells. Patients with types A and B NPD have markedly decreased levels (1-10%), whereas patients with type C NPD have normal or somewhat decreased acid sphingomyelinase activities. The enzymatic identification of NPD carriers is problematic. In families in which the specific molecular lesion has been identified, however, family members can be accurately tested for heterozygote status by DNA analysis. Prenatal diagnosis of types A and B NPD can be made reliably by the measurement of acid sphingomyelinase activity in cultured amniocytes or chorionic villi; molecular analysis of fetal cells to identify the specific acid sphingomyelinase mutations can provide the specific diagnosis or serve as a confirmatory test. The clinical diagnosis of type C NPD can be supported by the demonstration of filipin stain positivity in cultured fibroblasts and/or by identifying a specific mutation in the *NPC 1* or *2* gene.

Currently there is no specific treatment for NPD. Orthotopic liver transplantation in an infant with type A disease and cord blood transplantation in several type B NPD patients have been attempted with little or no success. BMT in a small number of type B NPD patients has been successful in reducing the spleen and liver volumes, the sphingomyelin content of the liver, the number of Niemann-Pick cells in the marrow, and radiologically detected infiltration of the lungs. In 1 patient, liver biopsies taken up to 33 mo posttransplantation showed only a moderate reduction in stored sphingomyelin. A phase I trial of enzyme replacement therapy for type B NPD has been completed which demonstrated elevated cytokine and bilirubin levels at the higher doses administered (0.6 and 1.0 mg/kg). The observed toxicity is presumably a result of the catabolism of the accumulated sphingomyelin to ceramide. Further clinical studies to evaluate effectiveness of this approach are planned. Clinical trials of miglustat (Actelion, Basel, Switzerland) have been performed and the drug has been approved in Europe for the treatment of type C disease. Treatment of type A disease by BMT has not been successful presumably because of the severe neurologic involvement.

FABRY DISEASE

This disease is an X-linked inborn error of glycosphingolipid metabolism caused by the absent or markedly deficient activity of α-galactosidase A (α-gal A). There are 2 major phenotypes. Affected males with the classic phenotype present in childhood with angiokeratomas (telangiectatic skin lesions), hypohidrosis, corneal and lenticular opacities, acroparesthesias, and with advancing age develop vascular disease of the kidney, heart, and/or brain (see Table 86-15). This classic phenotype is caused by the absent activity of the α-gal A and has an estimated prevalence of approximately 1 in 50,000 males. The later-onset phenotype occurs in affected males with residual α-gal A activity and presents in the 4th to 8th decades with cardiac disease and/or renal failure. This phenotype is more prevalent than the classic phenotype.

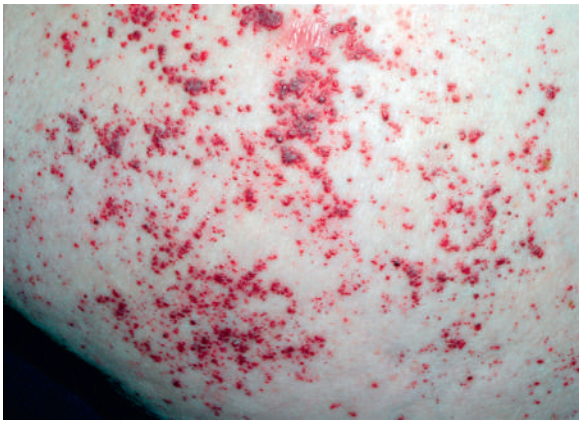

Figure 86-19 Typical angiokeratomas. Angiokeratomas are quite large and easily recognizable, but if only a few lesions exist or they are restricted only to the genitalia or umbilical regions, they can be easily missed. *(From Zarate VA, Hopkin RJ: Fabry's disease,* Lancet *372:1427, 2008.)*

Heterozygous females for the classic phenotype can be asymptomatic or as severely affected as the males, the variability a result of random X-inactivation. The enzyme deficiency results from mutations in the α-gal A gene located on the long arm of the X chromosome (Xq22). The enzymatic defect leads to the systemic accumulation of neutral glycosphingolipids, primarily globotriaosylceramide, particularly in the plasma and lysosomes of vascular endothelial and smooth muscle cells, cardiac myocytes, and renal podocytes. The progressive vascular glycosphingolipid deposition in classically affected males results in small vessel occlusion and ischemia, leading to the major disease manifestations. The complementary DNA and genomic sequences encoding α-gal A have been characterized and more than 500 different mutations in the α-gal A gene are responsible for this lysosomal storage disease.

The **angiokeratomas** usually occur in childhood and may lead to early diagnosis (Fig. 86-19). They increase in size and number with age and range from barely visible to several millimeters in diameter. The lesions are punctate, dark red to blue-black, and flat or slightly raised. They do not blanch with pressure, and the larger ones may show slight hyperkeratosis. Characteristically, the lesions are most dense between the umbilicus and knees, in the "bathing trunk area," but may occur anywhere, including the oral mucosa. The hips, thighs, buttocks, umbilicus, lower abdomen, scrotum, and glans penis are common sites, and there is a tendency toward symmetry. Variants without skin lesions have been described. Sweating is usually decreased or absent. Corneal opacities and characteristic lenticular lesions, observed under slit-lamp examination, are present in affected males, as well as in approximately 90% of heterozygotes from families with the classic phenotype. Conjunctival and retinal vascular tortuosity is common and results from the systemic vascular involvement.

Pain is the most debilitating symptom in childhood and adolescence. **Fabry crises,** lasting from minutes to several days, consist of agonizing, burning pain in the hands, feet, and proximal extremities and are usually associated with exercise, fatigue, fever, or a combination of these factors. These painful acroparesthesias usually become less frequent in the 3rd and 4th decades of life, although in some men, they may become more frequent and severe. Attacks of abdominal or flank pain may simulate appendicitis or renal colic.

The major morbid symptoms result from the progressive involvement of the vascular system. Early in the course of the classic phenotype, casts, red cells, and lipid inclusions with characteristic birefringent "Maltese crosses" appear in the urinary sediment. Proteinuria, isosthenuria, and gradual deterioration of renal function and development of azotemia occur in the 2nd through 4th decades in the classic phenotype and in the 4th to 8th decades in the later-onset form. Cardiovascular findings may include arrhythmias, left ventricular hypertrophy, angina, myocardial ischemia or infarction, and heart failure. Mitral insufficiency is the most common valvular lesion. Cerebrovascular

manifestations, including transient ischemic attacks and strokes, result from multifocal small vessel involvement. Other features may include chronic bronchitis and dyspnea, lymphedema of the legs without hypoproteinemia, episodic diarrhea, osteoporosis, retarded growth, and delayed puberty. Death most often results from renal failure or vascular disease of the heart or brain. Before hemodialysis or renal transplantation, the mean age at death for affected men was 40 yr. Patients with the later-onset phenotype with residual α-gal A activity have cardiac and/or renal disease. The cardiac manifestations include hypertrophy of the left ventricular wall and interventricular septum, and electrocardiographic abnormalities consistent with cardiomyopathy. Patients may progress to hypertrophic cardiomyopathy or myocardial infarction, or both.

The diagnosis in classically affected males is most readily made from the history of painful acroparesthesias, hypohidrosis, the presence of the characteristic skin lesions, and the observation of the corneal opacities and lenticular lesions. The disorder is often misdiagnosed as rheumatic fever, erythromelalgia, or neurosis. The skin lesions must be differentiated from the benign angiokeratomas of the scrotum (Fordyce disease) or from angiokeratoma circumscriptum. **Angiokeratomas** identical to those of Fabry disease have been reported in fucosidosis, aspartylglycosaminuria, late-onset GM_1 gangliosidosis, galactosialidosis, α-*N*-acetylgalactosaminidase deficiency, and sialidosis. Later-onset patients have been identified among patients on hemodialysis and among patients with hypertrophic cardiomyopathy or who have suffered cryptogenic strokes. Later-onset patients lack the early classic manifestations such as the angiokeratomas, acroparesthesias, hypohidrosis, and corneal opacities. The diagnosis of classic and later-onset patients is confirmed biochemically by the demonstration of markedly decreased α-gal A activity in plasma, isolated leukocytes, or cultured fibroblasts or lymphoblasts. The specific α-gal A mutation can be determined by gene sequencing.

Heterozygous females may have corneal opacities, isolated skin lesions, and intermediate activities of α-gal A in plasma or cells. Rare female heterozygotes may have manifestations as severe as those in affected males. Asymptomatic at-risk females in families affected by Fabry disease, however, should be optimally diagnosed by the direct analysis of their family's specific mutation. Prenatal detection of affected males can be accomplished by the demonstration of deficient α-gal A activity and/or the family's specific gene mutation in chorionic villi obtained in the 1st trimester or in cultured amniocytes obtained by amniocentesis in the 2nd trimester of pregnancy. Fabry disease can be detected by newborn screening and pilot studies have been conducted in Italy and Taiwan.

Treatment for Fabry disease may include the use of phenytoin and/or carbamazepine to decrease the frequency and severity of the chronic acroparesthesias and the periodic crises of excruciating pain. Renal transplantation and long-term hemodialysis are lifesaving procedures for patients with renal failure.

Enzyme replacement therapy for Fabry patients using recombinant human α-gal A preparations produced in Chinese hamster ovary cells (agalsidase beta, Fabrazyme, Genzyme Corporation) and in human fibrosarcoma cells (agalsidase alfa, Replagal, Shire HGT) has been developed. Both Fabrazyme and Replagal were approved by the European Medicines Agency in the European Union, but only Fabrazyme is approved by the FDA in the United States. The effectiveness of enzyme replacement therapy with Fabrazyme in stabilization of renal disease, regression of hypertrophic cardiomyopathy, reduction of pain, and improvement in quality of life has been demonstrated. Because most classically affected males produce no enzyme protein, these patients produce immunoglobulin G antibodies in response to the infused enzyme which can impact the effectiveness of substrate clearance. Treatment of classically affected males should begin in childhood.

FUCOSIDOSIS

This is a rare autosomal recessive disorder caused by the deficient activity of α-fucosidase and the accumulation of fucose-containing glycosphingolipids, glycoproteins, and oligosaccharides in the lysosomes of the liver, brain, and other organs (see Table 86-15). The α-fucosidase gene is on chromosome 1 (1p24), and specific mutations are known. Although the disorder is panethnic, most reported patients are from Italy and the United States. There is wide variability in the clinical phenotype, with the most severely affected patients presenting in the first year of life with developmental delay and somatic features similar to those of the mucopolysaccharidoses. These features include frontal bossing, hepatosplenomegaly, coarse facial features, and macroglossia. The central nervous system storage results in a relentless neurodegenerative course, with death in childhood. Patients with milder disease have angiokeratomas and longer survival. No specific therapy exists for the disorder, which can be diagnosed by the demonstration of deficient α-fucosidase activity in peripheral leukocytes or cultured fibroblasts. Carrier identification and prenatal diagnosis are possible by determination of the enzymatic activity or the specific family mutations.

SCHINDLER DISEASE

This is an autosomal recessive neurodegenerative disorder that results from the deficient activity of α-*N*-acetylgalactosaminidase and the accumulation of sialylated and asialoglycopeptides and oligosaccharides (see Table 86-15). The gene for the enzyme is located on chromosome 22 (22q11). The disease is clinically heterogeneous, and 2 major phenotypes have been identified. Type I disease is an infantile-onset neuroaxonal dystrophy. Affected infants have normal development for the first 9-15 mo of life followed by a rapid neurodegenerative course that results in severe psychomotor retardation, cortical blindness, and frequent myoclonic seizures. Type II disease is characterized by a variable age at onset, mild intellectual disability, and angiokeratomas. There is no specific therapy for either form of the disorder. The diagnosis is by demonstration of the enzymatic deficiency in leukocytes or cultured skin fibroblasts or specific gene mutations.

METACHROMATIC LEUKODYSTROPHY

This is an autosomal recessive white matter disease caused by a deficiency of arylsulfatase A (ASA), which is required for the hydrolysis of sulfated glycosphingolipids. Another form of metachromatic leukodystrophy (MLD) is caused by a deficiency of a sphingolipid activator protein (SAP1), which is required for the formation of the substrate–enzyme complex. The deficiency of this enzymatic activity results in the white matter storage of sulfated glycosphingolipids, which leads to demyelination and a neurodegenerative course. The *ASA* gene is on chromosome 22 (22q13.31qter); specific mutations tend to fall into 2 groups that correlate with disease severity.

The clinical manifestations of the late **infantile** form of MLD, which is most common, usually present between 12 and 18 mo of age as irritability, inability to walk, and hyperextension of the knee, causing genu recurvatum. The clinical progression of the disease relates to the pathologic involvement of both central and peripheral nervous system, giving a mixture of upper and lower motor neuron and cognitive and psychiatric signs. Deep tendon reflexes are diminished or absent. Gradual muscle wasting, weakness, and hypotonia become evident and lead to a debilitated state. As the disease progresses, nystagmus, myoclonic seizures, optic atrophy, and quadriparesis appear, with death in the 1st decade of life (see Table 86-15). The **juvenile** form of the disorder has a more indolent course with onset that may occur as late as 20 yr of age. This form of the disease presents with gait disturbances, mental deterioration, urinary incontinence, and emotional difficulties. The **adult** form, which presents after the 2nd decade, is similar to the juvenile form in its clinical manifestations, although emotional difficulties and psychosis are more prominent features. Dementia, seizures, diminished reflexes, and optic atrophy also occur in both the juvenile and adult forms. The pathologic hallmark of MLD is the deposition of metachromatic bodies, which stain strongly positive with periodic acid–Schiff and Alcian blue, in the white matter of the brain. Neuronal inclusions may be seen in the midbrain, pons, medulla, retina, and spinal cord; demyelination occurs in the peripheral nervous system. The diagnosis of MLD should be suspected in patients with the clinical features of leukodystrophy. Decreased nerve conduction velocities, increased cerebrospinal fluid protein, metachromatic deposits in sampled segments of sural nerve, and metachromatic granules in urinary

sediment are all suggestive of MLD. Confirmation of the diagnosis is based on the demonstration of the reduced activity of ASA in leukocytes or cultured skin fibroblasts. SAP deficiency is diagnosed by measuring the concentration of SAP1 in cultured fibroblasts using a specific antibody to the protein. The diagnosis, identification of carriers and prenatal diagnosis are available for both forms of the disorder by detection of the causative mutations in the ASA or SAP genes.

Unrelated donor umbilical cord blood transplantation has been undertaken in some pediatric patients with MLD. A longitudinal study of 6 patients with late-infantile onset and 14 with juvenile onset revealed that motor deficits present at the time of transplant did not improve and that neurologic symptoms continued to progress in those with late-infantile presentation. In contrast, in juvenile patients the brainstem auditory evoked responses, visual evoked potentials, electroencephalogram, and/or peripheral nerve conduction velocities stabilized or improved. Therefore consideration of umbilical cord blood transplantation for children with presymptomatic late-infantile MLD or minimally symptomatic juvenile MLD may be indicated.

MULTIPLE SULFATASE DEFICIENCY

This is an autosomal recessive disorder that results from the enzymatic deficiency of at least 9 sulfatases including arylsulfatases A, B, and C, and iduronate-2-sulfatase. The specific defect is an enzyme in the C-α-formylglycine generating system (the gene for which is located at 3p26), which introduces a common posttranslational modification in all of the affected sulfatases and explains the occurrence of these multiple enzyme defects. Because of the deficiency of these enzymes, sulfatides, mucopolysaccharides, steroid sulfates, and gangliosides accumulate in the cerebral cortex and visceral tissues, resulting in a clinical phenotype with features of a **leukodystrophy** as well as those of the **mucopolysaccharidoses**. Severe ichthyosis may also occur. Carrier testing and prenatal diagnosis by measurement of the enzymatic activities or the specific gene defects can be performed. There is no specific treatment for multiple sulfatase deficiency other than supportive care.

KRABBE DISEASE

This condition, also called globoid cell leukodystrophy, is an autosomal recessive fatal disorder of infancy. It results from the deficient activity of galactocerebrosidase and the white matter accumulation of galactosylceramide, which is normally found almost exclusively in the myelin sheath. Both peripheral and central myelin are affected, resulting in spasticity and cognitive impairment coupled with deceptively normal or even absent deep tendon reflexes. The galactocerebrosidase gene is on chromosome 14 (14q31), and specific disease-causing mutations are known. The **infantile** form of Krabbe disease is rapidly progressive and patients present in early infancy with irritability, seizures, and hypertonia (see Table 86-15). Optic atrophy is evident in the 1st yr of life, and mental development is severely impaired. As the disease progresses, optic atrophy and severe developmental delay become apparent; affected children exhibit opisthotonos and die before 3 yr of age. A **late infantile** form of Krabbe presents after the age of 2 yr. Affected individuals have a course similar to that of the early infantile form.

The diagnosis of Krabbe disease relies on the demonstration of the specific enzymatic deficiency in white blood cells or cultured skin fibroblasts. Causative gene mutations have been identified. Carrier identification and prenatal diagnosis are available. The development of methods to measure galactocerebrosidase activity on dried blood spots has led to the inclusion of Krabbe disease in the newborn screening programs of some states. Treatment of infants with Krabbe disease with umbilical cord blood cell transplantation has been reported in prenatally identified asymptomatic newborns and symptomatic infants. Transplanted infants appear to develop neurologic manifestations at a slower rate but succumb to a neurologic demise.

FARBER DISEASE

This is a rare autosomal recessive disorder that results from the deficiency of the lysosomal enzyme acid ceramidase and the accumulation of ceramide in various tissues, especially the joints. Symptoms can begin in the first year of life with painful joint swelling and nodule formation (Fig. 86-20), which is sometimes diagnosed as rheumatoid arthritis. As the disease progresses, nodule or granulomatous formation on the vocal cords can lead to hoarseness and breathing difficulties; failure to thrive is common. In some patients, moderate central nervous system dysfunction is present (see Table 86-15). Patients may die of recurrent pneumonias in their teens; there is currently no specific therapy. The diagnosis of this disorder should be suspected in patients who have nodule formation over the joints but no other findings of rheumatoid arthritis. In such patients, ceramidase activity should be determined in cultured skin fibroblasts or peripheral leukocytes. Various disease causing mutations have been identified in the acid ceramidase gene. Carrier detection and prenatal diagnosis are available.

Figure 86-20 Forearm of an 18 mo old girl with Farber disease. Note the painful joint swelling and the nodule formation. The infant was suspected of having rheumatoid arthritis.

WOLMAN DISEASE AND CHOLESTEROL ESTER STORAGE DISEASE

These are autosomal recessive lysosomal storage diseases that result from the deficiency of acid lipase and the accumulation of cholesterol esters and triglycerides in histiocytic foam cells of most visceral organs. The gene for lysosomal acid lipase is on chromosome 10 (10q24-q25). Wolman disease is the more severe clinical phenotype and is a fatal disorder of infancy. Clinical features become apparent in the first weeks of life and include failure to thrive, relentless vomiting, abdominal distention, steatorrhea, and hepatosplenomegaly (see Table 86-15). There usually is hyperlipidemia. Hepatic dysfunction and fibrosis may occur. **Calcification of the adrenal glands** occurs in about 50% of patients. Death usually occurs within the first 6 mo of life.

Cholesterol ester storage disease is a less-severe disorder that may not be diagnosed until adulthood. Hepatomegaly can be the only detectable abnormality, but affected individuals are at significant risk for premature cirrhosis and atherosclerosis. Adrenal calcification can occur in severe early onset patients.

Diagnosis and carrier identification are based on measuring acid lipase activity in peripheral leukocytes or cultured skin fibroblasts. Disease causing mutations have been identified in the acid ceramide gene. Prenatal diagnosis depends on measuring decreased enzyme levels or identifying specific mutations in cultured chorionic villi or amniocytes. There is no specific therapy available for either disorder. Although pharmacologic agents to suppress cholesterol synthesis, in combination with cholestyramine and diet modification, have been used in patients there is little to no clinical benefit. Enzyme

replacement therapy is currently being evaluated in clinical trials for both diseases (see Chapter 86.3).

Bibliography is available at Expert Consult.

86.5 Mucolipidoses

Margaret M. McGovern and Robert J. Desnick

I-cell disease (mucolipidosis II [ML-II]) and pseudo-Hurler polydystrophy (mucolipidosis III [ML-III]) are rare autosomal recessive disorders that share some clinical features with Hurler syndrome (see Chapter 88). These diseases result from the abnormal targeting of newly synthesized lysosomal enzymes that normally have phosphorylated mannose residues for binding to the mannose-6-phosphate receptors which transport the enzymes to the lysosomes. These mannose-6-phosphate residues are synthesized in a 2-step reaction that occurs in the Golgi apparatus and is mediated by 2 enzymatic activities. The enzyme that catalyzes the first step, the lysosomal enzyme *N*-acetylglucosamine-1-phosphotransferase, is defective in both ML-II and ML-III, which are allelic disorders resulting from mutations in the GlcNAc-phosphotransferase α/β-subunits precursor gene *(GNPTAB)*. This enzyme deficiency results in abnormal targeting of the lysosomal enzymes which are consequently secreted into the extracellular matrix. Because the lysosomal enzymes require the acidic environment of the lysosome to function, patients with this defect accumulate a variety of different substrates because of the intracellular deficiency of most lysosomal enzymes. The diagnosis of ML-II and ML-III can be made by the determination of the serum lysosomal enzymatic activities, which are markedly elevated, or by the demonstration of their reduced enzymatic activity levels in cultured skin fibroblasts. Direct measurement of the phosphotransferase activity is possible as well. Prenatal diagnosis is available for both disorders by measurement of lysosomal enzymatic activities in amniocytes or chorionic villus cells; carrier identification is available for both disorders by measurement of enzymatic activities using cultured skin fibroblasts or by mutation analysis of the causative gene. Neonatal screening by tandem mass spectroscopy may detect I-cell disease.

I-CELL DISEASE

This disorder, ML-II, shares many of the clinical manifestations of Hurler syndrome (see Chapter 88), although there is no mucopolysaccharidurias and the presentation is earlier (see Table 86-15). Some patients have clinical features evident at birth, including coarse facial features, craniofacial abnormalities, restricted joint movement, and hypotonia. Nonimmune hydrops may be present in the fetus. The remainder of patients present in the first year with severe psychomotor retardation, coarse facial features, and skeletal manifestations that include kyphoscoliosis and a lumbar gibbus. Patients may also have congenital dislocation of the hips, inguinal hernias, and gingival hypertrophy. Progressive, severe psychomotor retardation leads to death in early childhood. No treatment is available.

PSEUDO-HURLER POLYDYSTROPHY

Pseudo-Hurler polydystrophy (ML-III) is a less-severe disorder than I-cell disease, with later onset and survival to adulthood reported. Affected children may present around the age of 4 or 5 yr with joint stiffness and short stature. Progressive destruction of the hip joints and moderate dysostosis multiplex are evident. Radiographic evidence of low iliac wings, flattening of the proximal femoral epiphyses with valgus deformity of the femoral head, and hypoplasia of the anterior third of the lumbar vertebrae are characteristic findings. Ophthalmic findings include corneal clouding, retinopathy, and astigmatism; visual complaints are uncommon (see Table 86-15). Some patients have learning disabilities or intellectual disability. Treatment, which should include orthopedic care, is symptomatic.

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Chapter 87

Defects in Metabolism of Carbohydrates

Priya S. Kishnani and Yuan-Tsong Chen

Carbohydrate synthesis and degradation provide the energy required for most metabolic processes. The important carbohydrates include 3 monosaccharides—glucose, galactose, and fructose—and a polysaccharide, glycogen. Figure 87-1 shows the relevant biochemical pathways of these carbohydrates. Glucose is the principal substrate of energy metabolism. A continuous source of glucose from dietary intake, gluconeogenesis, and glycogenolysis of glycogen maintains normal blood glucose levels. Metabolism of glucose generates adenosine triphosphate (ATP) via glycolysis (conversion of glucose or glycogen to pyruvate), mitochondrial oxidative phosphorylation (conversion of pyruvate to carbon dioxide and water), or both. Dietary sources of glucose come from ingesting polysaccharides, primarily starch and disaccharides, including lactose, maltose, and sucrose. Oral intake of glucose is intermittent and unreliable. Glucose made de novo from amino acids, primarily alanine (gluconeogenesis), contributes to maintaining the euglycemic state, but this process requires time. The breakdown of hepatic glycogen provides the rapid release of glucose, which maintains a constant blood glucose concentration. Glycogen is also the primary stored energy source in muscle, providing glucose for muscle activity during exercise. Galactose and fructose are monosaccharides that provide fuel for cellular metabolism; their role is less significant than that of glucose. Galactose is derived from lactose (galactose + glucose), which is found in milk and milk products. Galactose is an important energy source in infants, but it is first metabolized to glucose. Galactose (exogenous or endogenously synthesized from glucose) is also an important component of certain glycolipids, glycoproteins, and glycosaminoglycans. The dietary sources of fructose are sucrose (fructose + glucose, sorbitol) and fructose itself, which is found in fruits, vegetables, and honey.

Defects in glycogen metabolism typically cause an accumulation of glycogen in the tissues, hence the name **glycogen storage disease** (Table 87-1). Defects in gluconeogenesis or the glycolytic pathway, including galactose and fructose metabolism, do not result in an accumulation of glycogen (Table 87-1). The defects in pyruvate metabolism in the pathway of the conversion of pyruvate to carbon dioxide and water via mitochondrial oxidative phosphorylation are more often associated with **lactic acidosis** and some tissue glycogen accumulation.

87.1 Glycogen Storage Diseases

Priya S. Kishnani and Yuan-Tsong Chen

The disorders of glycogen metabolism, the glycogen storage diseases (GSDs), result from deficiencies of various enzymes or transport proteins in the pathways of glycogen metabolism (see Fig. 87-1). The glycogen found in these disorders is abnormal in quantity, quality, or both. GSDs are categorized by numeric type in accordance with the chronological order in which these enzymatic defects were identified. This numeric classification is still widely used, at least up to number VII. The GSDs can also be classified by organ involvement and clinical manifestations into liver and muscle glycogenoses (see Table 87-1).

There are more than 12 forms of glycogenoses. Glucose-6-phosphatase deficiency (type I), lysosomal acid α-glucosidase deficiency (type II), debrancher deficiency (type III), and liver phosphorylase kinase

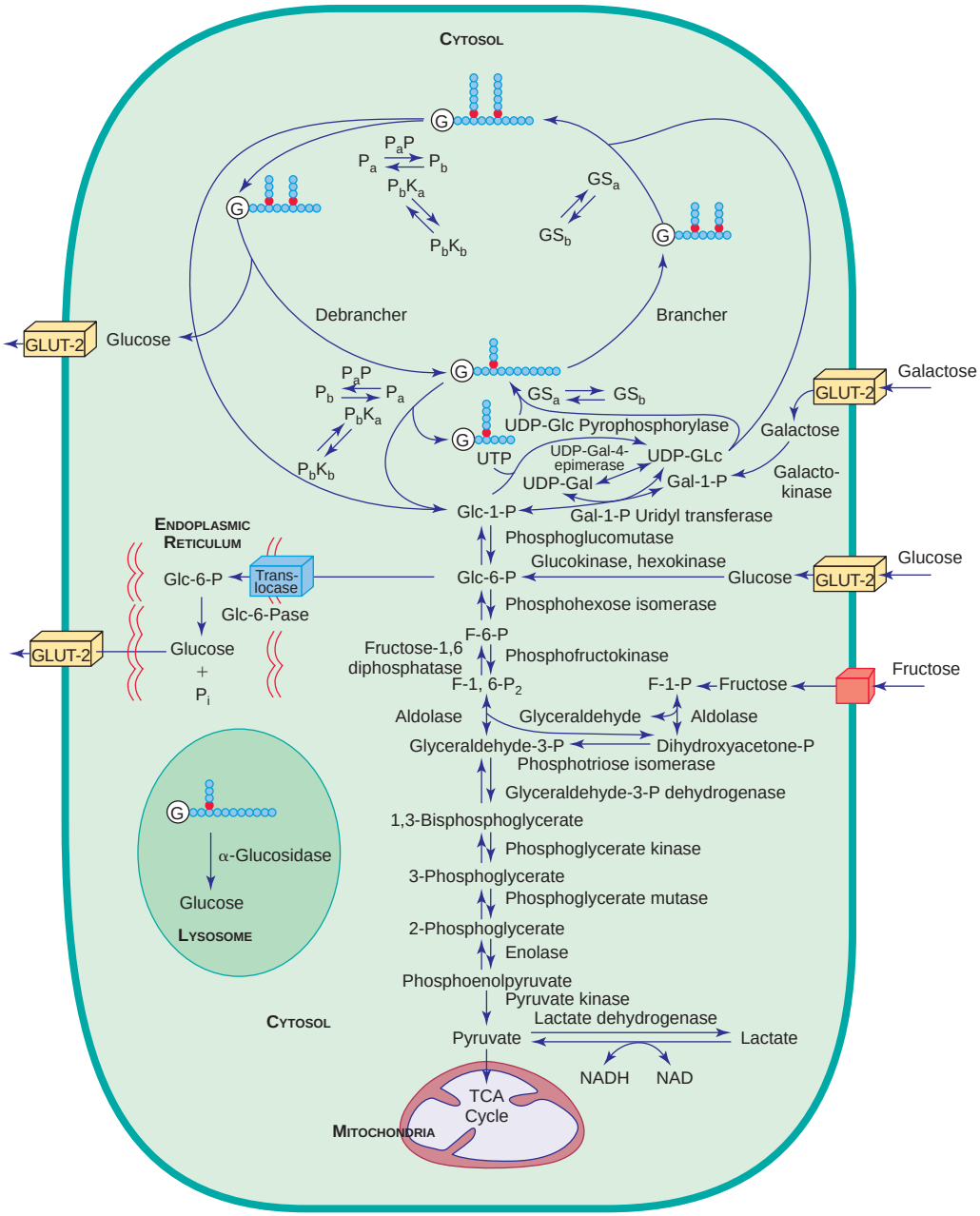

Figure 87-1 Pathway related to glycogen storage diseases and galactose and fructose disorders. *G*, glycogen, the primer for glycogen synthesis; *GLUT-2*, glucose transporter 2; *GSa*, active glycogen synthase; *GSb*, inactive glycogen synthase; *NAD/NADH*, nicotinamide-adenine dinucleotide; *Pa*, active phosphorylase; *PaP*, phosphorylase a phosphatase; *Pb*, inactive phosphorylase; *PbKa*, active phosphorylase b kinase; *PbKb*, inactive phosphorylase b kinase; *UDP*, uridine diphosphate. *(Modified from Beaudet AR: Glycogen storage disease. In Harrison TR, Isselbacher KJ, editors:* Harrison's principles of internal medicine, *ed 13, New York, 1994, McGraw-Hill. Reproduced with permission of The McGraw-Hill Companies.)*

deficiency (type IX) are the most common of those that typically present in early childhood; myophosphorylase deficiency (type V, McArdle disease) is the most common in adolescents and adults. The frequency of all forms of GSD is approximately 1 in 20,000 live births.

LIVER GLYCOGENOSES

The GSDs that principally affect the liver include glucose-6-phosphatase deficiency (type I), debranching enzyme deficiency (type III), branching enzyme deficiency (type IV), liver phosphorylase deficiency (type VI), phosphorylase kinase deficiency (type IX, formerly termed GSD VIa), glycogen synthase deficiency (type 0), and glucose transporter-2 defect. Because hepatic carbohydrate metabolism is responsible for plasma glucose homeostasis, this group of disorders typically causes fasting hypoglycemia and hepatomegaly. Some (types III, IV, IX) can be associated with liver cirrhosis. Other organs can also be involved and may manifest as renal dysfunction in type I, myopathy (skeletal and/or cardiomyopathy) in types III and IV, as well as in some rare forms of phosphorylase kinase deficiency, and neurologic involvement in types II (the brain, anterior horns cells), III (peripheral nerves), and IV (some patients can present with diffuse central and peripheral nervous system dysfunction).

Type I Glycogen Storage Disease (Glucose-6-Phosphatase or Translocase Deficiency, Von Gierke Disease)

Type I GSD is caused by the absence or deficiency of glucose-6-phosphatase activity in the liver, kidney, and intestinal mucosa. It can be divided into 2 subtypes: type Ia, in which the glucose-6-phosphatase

Table 87-1 Features of the Disorders of Carbohydrate Metabolism

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
LIVER GLYCOGENOSES			
Type/Common Name			
Ia/Von Gierke	Glucose-6-phosphatase	Growth retardation, hepatomegaly, hypoglycemia; elevated blood lactate, cholesterol, triglyceride, and uric acid levels	Common, severe hypoglycemia
Ib	Glucose-6-phosphate translocase	Same as type Ia, with additional findings of neutropenia and impaired neutrophil function	10% of type Ia
IIIa/Cori or Forbes	Liver and muscle debrancher deficiency (amylo-1,6-glucosidase)	Childhood: hepatomegaly, growth retardation, muscle weakness, hypoglycemia, hyperlipidemia, elevated transaminase levels; liver symptoms can progress to liver failure later in life	Common, intermediate severity of hypoglycemia
IIIb	Liver debrancher deficiency; normal muscle enzyme activity	Liver symptoms same as in type IIIa; no muscle symptoms	15% of type III
IV/Andersen	Branching enzyme	Failure to thrive, hypotonia, hepatomegaly, splenomegaly, progressive cirrhosis (death usually before 5th yr), elevated transaminase levels	Rare neuromuscular variants exist
VI/Hers	Liver phosphorylase	Hepatomegaly, typically mild hypoglycemia, hyperlipidemia, and ketosis	Rare, typically benign glycogenosis; severe presentation also known
Phosphorylase kinase deficiency	Phosphorylase kinase	Hepatomegaly, mild hypoglycemia, hyperlipidemia, and ketosis	Common, typically a benign glycogenosis, severe progressive forms also present
Glycogen synthase deficiency	Glycogen synthase	Early morning drowsiness and fatigue, fasting hypoglycemia, and ketosis, no hepatomegaly	Decreased liver glycogen store
Fanconi-Bickel syndrome	Glucose transporter 2 (GLUT-2)	Failure to thrive, rickets, hepatorenomegaly, proximal renal tubular dysfunction, impaired glucose and galactose utilization	GLUT-2 expressed in liver, kidney, pancreas, and intestine
MUSCLE GLYCOGENOSES			
Type/Common Name			
II/Pompe infantile	Acid α-glucosidase (acid maltase)	Cardiomegaly, hypotonia, hepatomegaly; onset: birth to 6 mo	Common, cardiorespiratory failure leading to death by age 1-2 yr; minimal to no residual enzyme activity
II/Late-onset Pompe (juvenile and adult)	Acid α-glucosidase (acid maltase)	Myopathy, variable cardiomyopathy, respiratory insufficiency; onset: childhood to adulthood	Residual enzyme activity
Danon disease	Lysosome-associated membrane protein 2 (LAMP2)	Hypertrophic cardiomyopathy	Rare, X-linked
PRKAG2 deficiency	Adenosine monophosphate (AMP)-activated protein kinase γ	Hypertrophic cardiomyopathy	Autosomal dominant
V/McArdle	Myophosphorylase	Exercise intolerance, muscle cramps, increased fatigability	Common, male predominance
VII/Tarui	Phosphofructokinase	Exercise intolerance, muscle cramps, hemolytic anemia, myoglobinuria	Prevalent in Japanese and Ashkenazi Jews
Phosphoglycerate kinase deficiency	Phosphoglycerate kinase	As with type V	Rare, X-linked
Phosphoglycerate mutase deficiency	M subunit of phosphoglycerate mutase	As with type V	Rare, majority of patients are African-American
Lactate dehydrogenase deficiency	M subunit of lactate dehydrogenase	As with type V	Rare
GALACTOSE DISORDERS			
Galactosemia with transferase deficiency	Galactose-1-phosphate uridyltransferase	Vomiting, hepatomegaly, cataracts, aminoaciduria, failure to thrive	African-American patients tend to have milder symptoms
Galactokinase deficiency	Galactokinase	Cataracts	Benign
Generalized uridine diphosphate galactose-4-epimerase deficiency	Uridine diphosphate galactose-4-epimerase	Similar to transferase deficiency with additional findings of hypotonia and nerve deafness	A benign variant also exists
FRUCTOSE DISORDERS			
Essential fructosuria	Fructokinase	Urine reducing substance	Benign
	Fructose-1-phosphate aldolase	Acute: vomiting, sweating, lethargy	
Hereditary fructose intolerance		Chronic: failure to thrive, hepatic failure	Prognosis good with fructose restriction

Continued

Table 87-1 Features of the Disorders of Carbohydrate Metabolism—cont'd

DISORDERS	BASIC DEFECTS	CLINICAL PRESENTATION	COMMENTS
DISORDERS OF GLUCONEOGENESIS			
Fructose-1,6-diphosphatase deficiency	Fructose-1,6-diphosphatase	Episodic hypoglycemia, apnea, acidosis	Good prognosis, avoid fasting
Phosphoenolpyruvate carboxykinase deficiency	Phosphoenolpyruvate carboxykinase	Hypoglycemia, hepatomegaly, hypotonia, failure to thrive	Rare
DISORDERS OF PYRUVATE METABOLISM			
Pyruvate dehydrogenase complex defect	Pyruvate dehydrogenase	Severe fatal neonatal to mild late onset, lactic acidosis, psychomotor retardation, and failure to thrive	Most commonly caused by $E_{1\alpha}$ subunit, defect X-linked
Pyruvate carboxylase deficiency	Pyruvate carboxylase	Same as above	Rare, autosomal recessive
Respiratory chain defects (oxidative phosphorylation disease)	Complexes I-V, many mitochondrial DNA mutations	Heterogeneous with multisystem involvement	Mitochondrial inheritance
DISORDERS IN PENTOSE METABOLISM			
Pentosuria	L-Xylulose reductase	Urine-reducing substance	Benign
Transaldolase deficiency	Transaldolase	Liver cirrhosis and failure, cardiomyopathy	Autosomal recessive
Ribose-5-phosphate isomerase deficiency	Ribose-5-phosphate isomerase	Progressive leukoencephalopathy and peripheral neuropathy	

enzyme is defective; and type Ib, in which a translocase that transports glucose-6-phosphate across the microsomal membrane is defective. The defects in both type Ia and type Ib lead to inadequate hepatic conversion of glucose-6-phosphate to glucose through normal glycogenolysis and gluconeogenesis and make affected individuals susceptible to fasting hypoglycemia.

Type I GSD is an autosomal recessive disorder. The structural gene for glucose-6-phosphatase is located on chromosome 17q21; the gene for translocase is on chromosome 11q23. Common mutations responsible for the disease are known. Carrier detection and prenatal diagnosis are possible with the DNA-based diagnosis.

Clinical Manifestations

Patients with type I GSD may present in the neonatal period with hypoglycemia and lactic acidosis; they more commonly present at 3-4 mo of age with hepatomegaly, hypoglycemic seizures, or both. These children often have **doll-like faces** with fat cheeks, relatively thin extremities, short stature, and a protuberant abdomen that is a consequence of massive hepatomegaly; the kidneys are also enlarged, whereas the spleen and heart are normal.

The biochemical hallmarks of the disease are hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Hypoglycemia and lactic acidosis can develop after a short fast. Hyperuricemia is present in young children; gout rarely develops before puberty. Despite marked hepatomegaly, the liver transaminase levels are usually normal or only slightly elevated. Intermittent diarrhea may occur in GSD I. In patients with GSD Ib, the loss of mucosal barrier function as a result of inflammation, which is likely related to the disturbed neutrophil function, seems to be the main cause of diarrhea. Easy bruising and epistaxis are common and are associated with a prolonged bleeding time as a result of impaired platelet aggregation and adhesion.

The plasma may be "milky" in appearance as a result of a striking elevation of triglyceride levels. Cholesterol and phospholipids are also elevated, but less prominently. The lipid abnormality resembles type IV hyperlipidemia and is characterized by increased levels of very-low-density lipoprotein, low-density lipoprotein, and a unique apolipoprotein profile consisting of increased levels of apolipoproteins B, C, and E, with relatively normal or reduced levels of apolipoproteins A and D. The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and fat. The lipid vacuoles are particularly large and prominent. There is little associated fibrosis.

All these findings apply to both type Ia and type Ib GSD, but **type Ib** has additional features of recurrent bacterial infections from **neutropenia** and impaired neutrophil function. Gut mucosa ulceration culminating in GSD enterocolitis is also common. Exceptional cases of type Ib without neutropenia and type Ia with neutropenia have been reported.

Although type I GSD affects mainly the liver, multiple organ systems are involved. Puberty is often delayed. Females can have ultrasound findings consistent with **polycystic ovaries;** other features of polycystic ovary syndrome (acne, hirsutism) are not seen. Nonetheless, fertility appears to be normal, as evidenced in several reports of successful pregnancy in women with GSD I. Increased bleeding during menstrual cycles, including life-threatening menorrhagia, has been noted and could be related to the impaired platelet aggregation. Symptoms of gout usually start around puberty from long-term hyperuricemia. Secondary to the lipid abnormalities, there is an increased risk of **pancreatitis.** The dyslipidemia, together with elevated erythrocyte aggregation, predisposes these patients to atherosclerosis. Premature atherosclerosis has not yet been clearly documented except for rare cases. Impaired platelet aggregation and increased antioxidative defense to prevent lipid peroxidation may function as a protective mechanism to help reduce the risk of atherosclerosis. Frequent fractures and radiographic evidence of **osteopenia** are common; bone mineral content is reduced even in prepubertal patients.

By the 2nd or 3rd decade of life, most patients with type I GSD exhibit **hepatic adenomas** that can hemorrhage and, in some cases, become malignant. **Pulmonary hypertension** has been seen in some long-term survivors of the disease. Iron refractory anemia and an increased prevalence of thyroid autoimmunity are also being recognized.

Renal disease is another complication, and most patients with type I GSD who are older than 20 yr of age have proteinuria. Many also have hypertension, renal stones, nephrocalcinosis, and altered creatinine clearance. Glomerular hyperfiltration, increased renal plasma flow, and microalbuminuria are often found in the early stages of renal dysfunction and can occur before the onset of proteinuria. In younger patients, hyperfiltration and hyperperfusion may be the only signs of renal abnormalities. With the advancement of renal disease, focal segmental glomerulosclerosis and interstitial fibrosis become evident. In some patients, renal function has deteriorated and progressed to failure, requiring dialysis and transplantation. Other renal

abnormalities include amyloidosis, a Fanconi-like syndrome, hypocitraturia, hypercalciuria, and a distal renal tubular acidification defect.

Diagnosis

The diagnosis of type I GSD is suspected on the basis of clinical presentation and the laboratory findings of hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. Neutropenia is noted in GSD Ib patients, typically before 1 yr of age. It has also been noted in some cases of GSD Ia, especially those with the mutation p.G188A. Administration of glucagon or epinephrine results in little or no rise in blood glucose level, but the lactate level rises significantly. Before the glucose-6-phosphatase and glucose-6-phosphate translocase genes were cloned, a definitive diagnosis required a liver biopsy. Gene-based mutation analysis provides a noninvasive way to diagnose most patients with types Ia and Ib disease.

Treatment

Treatment is designed to maintain normal blood glucose levels and is achieved by continuous nasogastric infusion of glucose or oral administration of uncooked cornstarch. Nasogastric drip feeding can be introduced in early infancy from the time of diagnosis. It can consist of an elemental enteral formula or contain only glucose or a glucose polymer to provide sufficient glucose to maintain euglycemia during the night. Frequent feedings with high-carbohydrate content are given during the day.

Uncooked cornstarch acts as a slow-release form of glucose and can be introduced at a dose of 1.6 g/kg every 4 hr for children younger than 2 yr of age. The response of young children is variable. As the child grows older, the cornstarch regimen can be changed to every 6 hr at a dose of 1.6-2.5 g/kg of body weight. New starch products, which are currently being developed, are thought to be longer acting, better tolerated, and more palatable. A short-term double-blind crossover pilot study comparing uncooked, physically modified cornstarch to traditional cornstarch showed that the majority of GSD I patients treated with the new starch had better short-term metabolic control and longer duration of euglycemia, especially at night. However, more extensive studies replicating these results are necessary. Because fructose and galactose cannot be converted directly to glucose in GSD type I, these sugars are restricted in the diet. Sucrose (table sugar, cane sugar, other ingredients), fructose (fruit, juice, high fructose corn syrup), lactose (dairy foods), and sorbitol should be avoided or limited. As a result of these dietary restrictions, vitamins and minerals such as calcium and vitamin D may be deficient and supplementation is required to prevent nutritional deficiencies. Dietary therapy improves hyperuricemia, hyperlipidemia, and renal function, slowing the development of renal failure. This therapy fails, however, to normalize blood uric acid and lipid levels completely in some individuals, despite good metabolic control, especially after puberty. The control of hyperuricemia can be further augmented by the use of allopurinol, a xanthine oxidase inhibitor. The hyperlipidemia can be reduced with lipid-lowering drugs such as beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors and fibrate (see Chapter 86). Microalbuminuria, an early indicator of renal dysfunction in type I disease, is treated with angiotensin-converting enzyme inhibitors. Citrate supplements can be beneficial for patients with hypocitraturia by preventing or ameliorating nephrocalcinosis and development of urinary calculi. Growth hormone should be used with extreme caution and limited to only those with a documented growth hormone deficiency. Even in those cases, there should be close monitoring of metabolic parameters and presence of adenomas.

In patients with type Ib GSD, granulocyte and granulocyte-macrophage colony-stimulating factors are successful in correcting the neutropenia, decreasing the number and severity of bacterial infections, and improving the chronic inflammatory bowel disease. The minimum effective dose should be used, as side effects are noted on these agents, including splenomegaly, hypersplenism, and bone pain.

Orthotopic liver transplantation is a potential cure of type I GSD. However, the inherent short- and long-term complications leave this as a treatment of last resort, usually for patients with liver malignancy, multiple liver adenomas, metabolic derangements refractory to medical management, and/or liver failure. Large adenomas (>2 cm) that are rapidly increasing in size and/or number may require partial hepatic resection. Smaller adenomas (<2 cm) can be treated with percutaneous ethanol injection or transcatheter arterial embolization. A challenge is the recurrence of liver adenomas with potential for malignant transformation in these patients, ultimately requiring a liver transplant.

Bone marrow transplantation has been reported to correct the neutropenia of type Ib GSD.

Before any surgical procedure, the bleeding status must be evaluated and good metabolic control established. Prolonged bleeding times can be normalized by the use of intensive intravenous glucose infusion for 24-48 hr before surgery. Use of 1-deamino-8-D-arginine vasopressin (DDAVP) can reduce bleeding complications. Lactated Ringer solution should be avoided because it contains lactate and no glucose. Glucose levels should be maintained in the normal range throughout surgery with the use of 10% dextrose. Overall, metabolic control is assessed by growth, improvement, and correction of the metabolic abnormalities such as elevated lactate, glucose, triglyceride, cholesterol, and uric acid levels.

Prognosis

Previously, many patients with type I GSD died at a young age, and the prognosis was guarded for those who survived. Long-term complications occur mostly in adults whose disease was not adequately treated during childhood. Early diagnosis and effective treatment have improved the outcome, although renal disease and formation of hepatic adenomas with potential risk for malignant transformation remain serious complications. The ability to identify transformation to hepatocellular carcinoma in the liver adenomas remains a challenge: α-fetoprotein and carcinoembryonic antigen levels often remain normal in the setting of hepatocellular carcinoma.

Type III Glycogen Storage Disease (Debrancher Deficiency, Limit Dextrinosis)

Type III GSD is caused by a deficiency of glycogen debranching enzyme activity. Debranching enzyme, together with phosphorylase, is responsible for complete degradation of glycogen. When debranching enzyme is defective, glycogen breakdown is incomplete and an abnormal glycogen with short outer branch chains and resembling limit dextrin accumulates. Deficiency of glycogen debranching enzyme causes hepatomegaly, hypoglycemia, short stature, variable skeletal myopathy, and variable cardiomyopathy. The disorder usually involves both liver and muscle and is termed type IIIa GSD. In approximately 15% of patients, the disease appears to involve only liver and is classified as type IIIb.

Type III glycogenosis is an autosomal recessive disease that has been reported in many different ethnic groups; the frequency is relatively high in Sephardic Jews from North Africa. The gene for debranching enzyme is located on chromosome 1p21. More than 40 different mutations are identified; 2 exon 3 mutations c.18_19delGA (previously described as c.17_18delAG) and p.Gln6X are specifically associated with glycogenosis IIIb. Carrier detection and prenatal diagnosis are possible using DNA-based linkage or mutation analysis.

Clinical Manifestations

During infancy and childhood, the disease may be indistinguishable from type I GSD, because hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation are common (Fig. 87-2). Splenomegaly may be present, but the kidneys are not enlarged. Hepatomegaly and hepatic symptoms in most patients with type III GSD improve with age; however, progressive liver cirrhosis and failure can occur. Hepatocellular carcinoma has also been reported, more typically in patients with progressive liver cirrhosis. The frequency of adenomas in individuals with GSD III is far less than in individuals with GSD I. Furthermore, the relationship of hepatic adenomas and malignancy in GSD III is unclear. α-Fetoprotein and carcinoembryonic antigen levels are not good predictors of the presence of hepatocellular adenomas or malignant transformation. A single case of malignant transformation

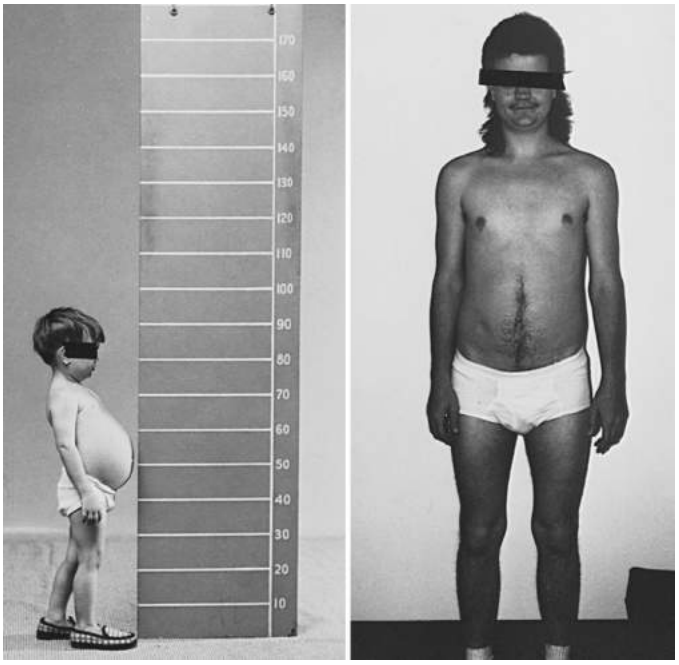

Figure 87-2 Growth and development in a patient with type IIIb glycogen storage disease. The patient has debrancher deficiency in liver but normal activity in muscle. As a child, he had hepatomegaly, hypoglycemia, and growth retardation. After puberty, he no longer had hepatomegaly or hypoglycemia, and his final adult height is normal. He had no muscle weakness or atrophy; this is in contrast to type IIIa patients, in whom a progressive myopathy is seen in adulthood.

at the site of adenomas has been noted. In patients with muscular involvement (type IIIa), muscle weakness can present in childhood but can become severe after the 3rd or 4th decade of life, as evidenced by slowly progressive weakness and wasting. Because patients with GSD III can have decreased bone density, they are at an increased risk of potential fracture. Myopathy does not follow any particular pattern of involvement; both proximal and distal muscles are involved. Electromyography reveals a widespread myopathy; nerve conduction studies are often abnormal. Ventricular hypertrophy is a frequent finding, but overt cardiac dysfunction is rare. Cardiac pathology has shown diffuse involvement of various cardiac structures including vacuolation of myocytes, atrioventricular conduction, and hyperplasia of smooth muscles. There have been some reports of life-threatening arrhythmia and need for heart transplant in some GSD III patients. Hepatic symptoms in some patients may be so mild that the diagnosis is not made until adulthood, when the patients show symptoms and signs of neuromuscular disease. The initial diagnosis has been confused with Charcot-Marie-Tooth disease. Polycystic ovaries are common; some patients can develop hirsutism, irregular menstrual cycles, and other features of polycystic ovarian syndrome. Fertility does not appear to be reduced; successful pregnancies in patients with GSD III have been reported.

Hypoglycemia and hyperlipidemia are common. In contrast to type I GSD, elevation of liver transaminase levels and fasting ketosis are prominent, but blood lactate and uric acid concentrations are usually normal. Serum creatine kinase levels can be useful to identify patients with muscle involvement; normal levels do not rule out muscle enzyme deficiency. The administration of glucagon 2 hr after a carbohydrate meal provokes a normal increase in blood glucose; after an overnight fast, glucagon may provoke no change in blood glucose level.

Diagnosis

The histologic appearance of the liver is characterized by a universal distention of hepatocytes by glycogen and the presence of fibrous septa. The fibrosis and the paucity of fat distinguish type III glycogenosis from type I. The fibrosis, which ranges from minimal periportal fibrosis to micronodular cirrhosis, appears in most cases to be nonprogressive. Overt cirrhosis has been seen in some patients with GSD III.

Patients with myopathy and liver symptoms have a generalized enzyme defect (type IIIa). The deficient enzyme activity can be demonstrated not only in liver and muscle, but also in other tissues such as heart, erythrocytes, and cultured fibroblasts. Patients with hepatic symptoms without clinical or laboratory evidence of myopathy have debranching enzyme deficiency only in the liver, with enzyme activity retained in the muscle (type IIIb). Definite diagnosis requires enzyme assay in liver, muscle, or both. Mutation analysis can provide a noninvasive method for diagnosis and subtype assignment in the majority of patients.

Treatment

Dietary management is less demanding than in type I GSD. Patients do not need to restrict dietary intake of fructose and galactose. If hypoglycemia is present, frequent meals high in carbohydrates with cornstarch supplements or nocturnal gastric drip feedings are usually effective. A high-protein diet during the daytime plus overnight protein enteral infusion is also effective in preventing hypoglycemia and preventing endogenous protein breakdown because protein can be used as a substrate for gluconeogenesis, a pathway that is intact in type III GSD. There is no satisfactory treatment for the progressive myopathy other than recommending a high-protein diet and an exercise program. Liver transplantation has been performed in GSD III patients with progressive cirrhosis and/or hepatic carcinoma. There are reports of cardiac transplant in GSD III patients with end stage cardiac disease.

Type IV Glycogen Storage Disease (Branching Enzyme Deficiency, Amylopectinosis, or Andersen Disease)

Deficiency of branching enzyme activity results in accumulation of an abnormal glycogen with poor solubility. The disease is referred to as type IV GSD or amylopectinosis because the abnormal glycogen has fewer branch points, more α 1-4 linked glucose units, and longer outer chains, resulting in a structure resembling amylopectin. Type IV GSD is an autosomal recessive disorder. The glycogen branching enzyme *(GBE)* gene is located on chromosome 3p21. More than 20 mutations responsible for type IV GSD have been identified, and their characterization in individual patients can be useful in predicting the clinical outcome. The nearly complete absence of GBE activity with null mutations has been associated with perinatal death and fatal neonatal hypotonia. Residual GBE enzyme activity of greater than 5% and at least 1 missense mutation are associated with a nonlethal phenotype and, in some situations, a lack of progressive liver disease.

Clinical Manifestations

This disorder is clinically variable. The most common and classic form is characterized by progressive cirrhosis of the liver and is manifested in the first 18 mo of life as hepatosplenomegaly and failure to thrive. The cirrhosis progresses to portal hypertension, ascites, esophageal varices, and liver failure that usually lead to death by 5 yr of age. Rare patients survive without progression of liver disease; these patients have a milder hepatic form and do not require a liver transplant.

A **neuromuscular** form of the disease has been reported with 4 main variants recognized based on age of presentation. The perinatal form presents as a fetal akinesia deformation sequence and death in the perinatal period. The congenital form presents at birth with severe hypotonia, muscle atrophy, and neuronal involvement with death in the neonatal period; some patients have cardiomyopathy. The childhood form presents primarily with myopathy or cardiomyopathy. The adult form presents with diffuse central and peripheral nervous system dysfunction accompanied by accumulation of polyglucosan material in the nervous system (**adult polyglucosan body disease**). For adult polyglucosan disease, a leukocyte or nerve biopsy is needed to establish the diagnosis as branching enzyme deficiency is limited to those tissues.

Diagnosis

Tissue deposition of amylopectin-like materials can be demonstrated in liver, heart, muscle, skin, intestine, brain, spinal cord, and peripheral nerve. The hepatic histologic findings are characterized by micronodular cirrhosis and faintly stained basophilic inclusions in the hepatocytes. The inclusions consist of coarsely clumped, stored material that is periodic acid–Schiff positive and partially resistant to diastase digestion. Electron microscopy shows, in addition to the conventional α and β glycogen particles, accumulation of the fibrillar aggregations that are typical of amylopectin. The distinct staining properties of the cytoplasmic inclusions, as well as electron microscopic findings, could be diagnostic. However, polysaccharides with histologic features reminiscent of type IV disease, but without enzymatic correlation, have been observed. The definitive diagnosis rests on the demonstration of the deficient branching enzyme activity in liver, muscle, cultured skin fibroblasts, or leukocytes, or on the identification of disease-causing mutations in the *GBE* gene. Prenatal diagnosis is possible by measuring the enzyme activity in cultured amniocytes, chorionic villi, or mutation analysis.

Treatment

There is no specific treatment for type IV GSD. Unlike patients with the other liver GSDs (I, III, VI, IX), those with GSD IV do not have hypoglycemia, which is only seen when there is overt liver cirrhosis. Liver transplantation has been performed for patients with progressive hepatic failure, but because it is a multisystem disorder involving many organ systems, the long-term success of liver transplantation is unknown. Individuals with significant diffuse reticuloendothelial involvement may have greater risk for morbidity and mortality, which may impact the success rate for liver transplants. Caution should be taken in selecting type IV patients for liver transplantation because these patients have variable phenotypes, which include a nonprogressive form of the liver disease and in some cases, extrahepatic manifestations of the disease.

Type VI Glycogen Storage Disease (Liver Phosphorylase Deficiency, Hers Disease)

There are few patients with documented liver phosphorylase deficiency. Such patients usually have a benign course and present with hepatomegaly and growth retardation in early childhood; however, some cases are more severe. Hypoglycemia, hyperlipidemia, and hyperketosis are of variable severity. Lactic acid and uric acid levels are normal. The heart and skeletal muscles are not involved. The hepatomegaly and growth retardation improve with age and usually disappear around puberty. Some patients with severe hepatomegaly, recurrent severe hypoglycemia, hyperketosis, and postprandial lactic acidosis have recently been reported. Treatment is symptomatic, as some patients require no specific treatment. A high-carbohydrate, high-protein diet and frequent feeding are effective in preventing hypoglycemia. Blood glucose and ketones should be monitored routinely, especially during periods of increased activity/illness.

GSD VI is an autosomal recessive disease. Diagnosis can be confirmed through molecular testing of the liver phosphorylase gene *(PYGL),* which is found on chromosome 14q21-22 and has 20 exons. Many mutations are known in this gene; a splice-site mutation in intron 13 has been identified in the Mennonite population. A liver biopsy showing elevated glycogen content and decreased hepatic phosphorylase enzyme activity can also be used to make a diagnosis.

Type IX Glycogen Storage Disease (Phosphorylase Kinase Deficiency)

This disorder represents a heterogeneous group of glycogenoses. Phosphorylase, the rate-limiting enzyme of glycogenolysis, is activated by a cascade of enzymatic reactions involving adenylate cyclase, cyclic adenosine monophosphate–dependent protein kinase (protein kinase A), and phosphorylase kinase. The latter enzyme has 4 subunits (α, β, γ, δ), each encoded by different genes on different chromosomes and differentially expressed in various tissues. This cascade of reactions is stimulated primarily by glucagon. Glycogenosis could be the result of any enzyme deficiency along this pathway; the most common is the deficiency of phosphorylase kinase. Phosphorylase kinase (PhK) deficiency varies clinically as a result of defects in the various genes encoding the four subunits of the protein. Mutations in the *PHKA1* gene causes muscle PhK deficiency; mutations in the *PHKA2* and *PHKG2* genes cause liver PhK deficiency; mutations in the *PHKB* gene cause PhK deficiency in liver and muscle. Mutations in the *PHKG1* gene have not been identified. Defects in subunits α, β, and γ are responsible for liver presentation. Liver PhK deficiency's physical features are usually recognizable within the first 2 yr of life and include short stature and abdominal distention from moderate to marked hepatomegaly. The clinical severity of liver PhK deficiency varies considerably. Hyperketotic hypoglycemia, if present, is usually mild but can be severe in some cases. Ketosis may occur even when glucose levels are normal. In some children, there may be mild delays in gross motor development and hypotonia. Liver fibrosis can occur and progress to cirrhosis in rare cases, particularly in patients with *PHKG2* mutations. Liver adenoma appears to be very rare. Cognitive and speech delays have been reported in a few individuals, but it is not clear whether these delays are caused by PhK deficiency or whether they are coincidental. Polycystic ovaries are common in females with liver PhK deficiency. Renal tubular acidosis has been reported in rare cases. Cardiac manifestations have not been reported. Unlike in GSD I, lactic acidosis, bleeding tendency, and loose bowel movements are not characteristic. Although growth is retarded during childhood, normal height and complete sexual development are eventually achieved. As with debrancher deficiency, abdominal distention and hepatomegaly usually decrease with age and may disappear by adolescence. Most adults with liver PhK deficiency are asymptomatic, although further long-term studies are needed to fully assess the impact of this disorder in adults. Phenotypic variability within each subtype is being uncovered with the availability of molecular testing. The incidence of all subtypes of PhK deficiency is approximately 1 : 100,000 live births.

X-Linked Liver Phosphorylase Kinase Deficiency

X-linked liver PhK deficiency is the most common form of liver glycogenoses. In addition to liver, enzyme activity can also be deficient in erythrocytes, leukocytes, and fibroblasts; it is normal in muscle. Typically, a 1-5 yr old male presents with growth retardation, an incidental finding of hepatomegaly, and a slight delay in motor development. Cholesterol, triglycerides, and liver enzymes are mildly elevated. Ketosis may occur after fasting. Lactate and uric acid levels are normal. Hypoglycemia is typically mild, if present, but can be severe. The response in blood glucose to glucagon is normal. Hepatomegaly and abnormal blood chemistries gradually improve and can normalize with age. Most adults achieve a normal final height and are usually asymptomatic despite a persistent PhK deficiency. In rare cases, liver fibrosis can occur and progress to cirrhosis. Liver histology shows glycogen-distended hepatocytes, steatosis, and potentially mild periportal fibrosis. The accumulated glycogen (β particles, rosette form) has a frayed or burst appearance and is less compact than the glycogen seen in type I or type III GSD. Fibrous septal formation and low-grade inflammatory changes may be present.

The structural gene for the common liver isoform of the PhK α subunit, *PHKA2,* is located on the X chromosome (αL at Xp22.2). Mutations in the *PHKA2* gene account for 75% of all PhK cases. X-linked liver PhK deficiency is further subdivided into 2 biochemical subtypes: XLG1, with measurable deficiency of PhK activity in both blood cells and liver, and XLG2, with normal in vitro PhK activity in blood cells and variable activity in liver. It is suspected that XLG2 may be caused by missense mutations that affect enzyme regulation, while nonsense mutations affecting the amount of protein result in XLG1.

Autosomal Liver and Muscle Phosphorylase Kinase Deficiency

PhK deficiency in liver and blood cells with an autosomal mode of inheritance has been reported. As with the X-linked form, hepatomegaly and growth retardation are the predominant symptoms in early

childhood. Some patients also exhibit muscle hypotonia. In a few cases where enzyme activity has been measured, reduced PhK activity has been demonstrated in muscle. Mutations causing milder autosomally transmitted liver and muscle PhK deficiency are found in the *PHKB* gene (chromosome 16q12-q13), which encodes the β subunit. Several nonsense mutations, a single-base insertion, a splice-site mutation, and a large intragenic mutation have been identified. In addition, a missense mutation was discovered in an atypical patient with normal blood cell PhK activity.

Autosomal Liver Phosphorylase Kinase Deficiency

This form of PhK deficiency is caused by mutations in the testis/liver isoform of the γ subunit gene (TL, *PHKG2*). In contrast to X-linked PhK deficiency, patients with mutations in the *PHKG2* gene typically have more severe phenotypes with recurrent hypoglycemia and often develop progressive liver cirrhosis. *PHKG2* maps to chromosome 16p12.1- p11.2; many disease-causing mutations are known for this gene.

Muscle-Specific Phosphorylase Kinase Deficiency

A few cases of PhK deficiency restricted to muscle are known. Patients, both male and female, present either with muscle cramps and myoglobinuria with exercise or with progressive muscle weakness and atrophy. PhK activity is decreased in muscle but normal in liver and blood cells. There is no hepatomegaly or cardiomegaly. The structural gene for the muscle-specific form α subunit (αM) is located at Xq12. Mutations of the gene have been found in some male patients with this disorder. The gene for muscle γ subunit (γM, *PHKG1*) is on chromosome 7p12. No mutations in this gene have been reported so far.

Phosphorylase Kinase Deficiency Limited to Heart

These patients present with **cardiomyopathy** in infancy and rapidly progress to heart failure and death. PhK deficiency is demonstrated in the heart with normal enzyme activity in skeletal muscle and liver. Studies have questioned the existence of cardiac-specific primary PhK deficiency. However, the disease presentation has now been linked to the γ2 subunit of adenosine monophosphate–activated protein kinase (see "Glycogen Storage Diseases Mimicking Hypertrophic Cardiomyopathy" below). The γ2 subunit is encoded by the *PRKAG2* gene.

Diagnosis

Definitive diagnosis of PhK deficiency requires demonstration of the enzymatic defect in affected tissues. PhK can be measured in leukocytes and erythrocytes, but because the enzyme has many isozymes, the diagnosis can be easily missed without studies of liver, muscle, or heart. Mutation analysis is necessary in many cases to determine the disease's subtype. Individuals with liver PhK deficiency also usually have elevated transaminases, mildly elevated triglycerides and cholesterol, normal uric acid and lactic acid concentrations, and normal glucagon responses.

The *PHKA2* gene encoding the α subunit is most commonly involved, followed by the *PHKB* gene encoding the β subunit, regardless of the presence of deficiency in erythrocytes. Mutations in the *PHKG2* gene underlying γ-subunit deficiency are typically associated with severe liver involvement with recurrent hypoglycemia and liver fibrosis.

Treatment

The treatment for liver PhK deficiency is symptomatic. It includes a high-carbohydrate, high-protein diet and frequent feedings to prevent hypoglycemia, although many patients require no specific treatment. Cornstarch can be administered with symptom-dependent dosage and timing (0.6-2.5 g/kg every 6 hr). Oral intake of glucose, if tolerated, should be used to treat hypoglycemia. If not, intravenous glucose should be given. Prognosis for the X-linked and certain autosomal forms is typically good, however, patients with mutations in the γ subunit typically have a more severe clinical course with progressive liver disease. There is no treatment for the fatal form of isolated cardiac PhK deficiency other than heart transplantation.

Glycogen Synthase Deficiency

Deficiency of hepatic glycogen synthase *(GYS2)* activity leads to a marked decrease of glycogen stored in the liver. The gene for GYS2 is located at 12p12.2. Several mutations of this gene have been identified in patients with GSD 0. The disease appears to be rare in humans, and in the true sense, this is not a type of GSD because the deficiency of the enzyme leads to decreased glycogen stores. Patients present in infancy with early morning (prebreakfast) drowsiness, pallor, emesis, and fatigue, and sometimes convulsions associated with hypoglycemia and hyperketonemia. Blood lactate and alanine levels are low, and there is no hyperlipidemia or hepatomegaly. Prolonged hyperglycemia, glycosuria, and elevation of lactate with normal insulin levels after administration of glucose or a meal suggest a possible diagnosis of deficiency of glycogen synthase. Definitive diagnosis requires a liver biopsy to measure the enzyme activity or identification of mutations in the liver glycogen synthase gene, located on chromosome 12p12.2. Treatment consists of frequent meals, rich in protein, and nighttime supplementation with uncooked cornstarch to prevent hypoglycemia and hyperketonemia. Most children with GSD 0 are cognitively and developmentally normal. Short stature and osteopenia are common features. The prognosis seems good for patients who survive to adulthood, including resolution of hypoglycemia, except during pregnancy.

Muscle Glycogen Synthase Deficiency

This GSD results from muscle glycogen synthase (glycogen synthase I, *GYS1*) deficiency. The gene for GYS1 has been localized to chromosome 19q13.3. The disease is extremely rare and was reported in 3 children of consanguineous parents of Syrian origin. Muscle biopsies showed lack of glycogen, predominantly oxidative fibers, and mitochondrial proliferation. Glucose tolerance was normal. Molecular study revealed a homozygous stop mutation (R462→ter) in the muscle glycogen synthase gene. The phenotype was variable in the 3 siblings and ranged from sudden cardiac arrest, muscle fatigability, hypertrophic cardiomyopathy, an abnormal heart rate, and hypotension while exercising, to mildly impaired cardiac function at rest.

Hepatic Glycogenosis with Renal Fanconi Syndrome (Fanconi-Bickel Syndrome)

This rare autosomal recessive disorder is caused by defects in the facilitative glucose transporter 2 (GLUT-2), which transports glucose in and out of hepatocytes, pancreatic β cells, and the basolateral membranes of intestinal and renal epithelial cells. The disease is characterized by proximal renal tubular dysfunction, impaired glucose and galactose utilization, and accumulation of glycogen in liver and kidney.

The affected child typically presents in the first year of life with failure to thrive, rickets, and a protuberant abdomen from hepatomegaly and nephromegaly. The disease may be confused with GSD type I because a Fanconi-like syndrome can also develop in type I disease patients. Adults commonly present with short stature, dwarfism, and excess fat in the abdomen and shoulders. Patients are more susceptible to fractures owing to early-onset generalized osteopenia. In addition, intestinal malabsorption and diarrhea may occur.

Laboratory findings include glucosuria, phosphaturia, generalized aminoaciduria, bicarbonate wasting, hypophosphatemia, increased serum alkaline phosphatase levels, and radiologic findings of rickets. Mild fasting hypoglycemia and hyperlipidemia may be present. Liver transaminase, plasma lactate, and uric acid levels are usually normal. Oral galactose or glucose tolerance tests show intolerance, which could be explained by the functional loss of GLUT-2 preventing liver uptake of these sugars. Tissue biopsy results show marked accumulation of glycogen in hepatocytes and proximal renal tubular cells, presumably owing to the altered glucose transport out of these organs. Diffuse glomerular mesangial expansion along with glomerular hyperfiltration and microalbuminuria similar to nephropathy in GSD Ia and diabetes have been reported.

Fanconi-Bickel syndrome is rare. Seventy percent of patients with a detectable GLUT-2 mutation have consanguineous parents. Most patients are homozygous for the disease-related mutations; some patients are compound heterozygotes. The majority of mutations detected thus far predict a premature termination of translation. The resulting loss of the C-terminal end of the GLUT-2 protein predicts a nonfunctioning glucose transporter with an inward-facing substrate-binding site.

There is no specific treatment. Symptom-dependent treatment with phosphate and bicarbonate can result in growth improvement. Symptomatic replacement of water, electrolytes, and vitamin D; restriction of galactose intake; and a diet similar to that used for diabetes mellitus presented in frequent and small meals with an adequate caloric intake may also improve growth.

MUSCLE GLYCOGENOSES

The role of glycogen in muscle is to provide substrates for the generation of ATP for muscle contraction. The muscle GSDs are broadly divided into 2 groups. The first group is characterized by hypertrophic cardiomyopathy, progressive skeletal muscle weakness and atrophy, or both, and includes deficiencies of acid α-glucosidase, a lysosomal glycogen degrading enzyme (type II GSD), lysosomal-associated membrane protein 2 (LAMP2), and adenosine monophosphate–activated protein kinase γ2 (PRKAG2). The second group comprises muscle energy disorders characterized by muscle pain, exercise intolerance, myoglobinuria, and susceptibility to fatigue. This group includes myophosphorylase deficiency (McArdle disease, type V) and deficiencies of phosphofructokinase (type VII), phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase. Some of these latter enzyme deficiencies can also be associated with compensated hemolysis, suggesting a more generalized defect in glucose metabolism.

Type II Glycogen Storage Disease (Lysosomal Acid α-1,4-Glucosidase Deficiency, Pompe Disease)

Pompe disease, also referred to as GSD type II or acid maltase deficiency, is caused by a deficiency of acid α-1,4-glucosidase (acid maltase), an enzyme responsible for the degradation of glycogen in lysosomes. This enzyme defect results in lysosomal glycogen accumulation in multiple tissues and cell types, with cardiac, skeletal, and smooth muscle cells being the most seriously affected. The disease is characterized by accumulation of glycogen in lysosomes, as opposed to its accumulation in cytoplasm in the other glycogenoses.

Pompe disease is an autosomal recessive disorder with an incidence of approximately 1 in 40,000 live births in whites and 1 in 18,000 live births in Han Chinese. The gene for acid α-glucosidase is on chromosome 17q25.2. Multiple pathogenic mutations have been identified that could be helpful in delineating the phenotypes. An example is a splice-site mutation (IVS1-13T→G; c.-32-13T>G), commonly seen in late-onset patients of white race.

Clinical Manifestations

The disorder encompasses a range of phenotypes, each including myopathy but differing in age at onset, organ involvement, and clinical severity. **Infantile Pompe disease** was uniformly lethal without enzyme replacement therapy with alglucosidase alfa. Affected infants present in the first few weeks to months of life with hypotonia, a generalized muscle weakness with a "floppy infant" appearance, neuropathic bulbar weakness, feeding difficulties, macroglossia, hepatomegaly, and a hypertrophic cardiomyopathy followed by death from cardiorespiratory failure or respiratory infection usually by 1 yr of age. **Late-onset Pompe disease (juvenile and adult-onset disease)** is characterized by a lack or absence of severe cardiac involvement and a less-severe short-term prognosis. Symptoms related to progressive dysfunction of skeletal muscles can start as early as 1 yr of age to as late as the 6th decade of life. The clinical picture is dominated by slowly progressive proximal muscle weakness with truncal involvement and greater involvement of the lower limbs than the upper limbs. The pelvic girdle, paraspinal muscles, and diaphragm are the muscle groups most seriously affected. Other symptoms may include lingual weakness, ptosis, and dilation of blood vessels such as the basilar artery and the ascending aorta. These patients often present with proximal or limb girdle muscle weakness. With disease progression, patients become confined to wheelchairs and require artificial ventilation. The initial symptoms in some patients may be respiratory insufficiency manifested by somnolence, morning headache, orthopnea, and exertional dyspnea, which eventually lead to sleep-disordered breathing and respiratory failure. Respiratory failure is the cause of significant morbidity and mortality in this form of the disease. Basilar artery aneurysms with rupture also contribute to mortality in some cases. The age of death varies from early childhood to late adulthood, depending on the rate of disease progression and the extent of respiratory muscle involvement. With the advent of enzyme replacement therapy, a new picture of the natural history is emerging for both infantile and late onset patients with Pompe disease.

Laboratory Findings

These include elevated levels of serum creatine kinase, aspartate aminotransferase, and lactate dehydrogenase. In the infantile form a chest x-ray showing massive cardiomegaly is frequently the first symptom detected. Electrocardiographic findings include a high-voltage QRS complex and a shortened PR interval. Echocardiography reveals thickening of both ventricles and/or the intraventricular septum and/or left ventricular outflow tract obstruction. Muscle biopsy shows the presence of vacuoles that stain positively for glycogen; acid phosphatase is increased, presumably from a compensatory increase of lysosomal enzymes. Electron microscopy reveals glycogen accumulation within the membranous sac and in the cytoplasm. Electromyography reveals myopathic features with excessive electrical irritability of muscle fibers and pseudomyotonic discharges. Serum creatine kinase is not always elevated in adult patients. Depending on the muscle sampled or tested, the muscle histologic appearance and electromyography may not be abnormal.

Some patients with infantile Pompe disease who had peripheral nerve biopsies demonstrated glycogen accumulation in the neurons and Schwann cells, too. Infantile Pompe disease may manifest both myopathic and neuropathic clinical signs. Generally, the former predominate.

Diagnosis

The confirmatory step for a diagnosis of Pompe disease is enzyme assay demonstrating deficient acid α-glucosidase or gene sequencing showing 2 pathogenic mutations in the *GAA* gene. The enzyme assay is usually done in dried blood spots, leukocytes, blood mononuclear cells, muscle, and cultured skin fibroblasts, using maltose, glycogen, or 4-methylumbelliferyl-α-D-glucopyranoside (4MUG) as a substrate. Deficiency is usually more severe in the infantile form than in the late-onset forms. The skin fibroblast assay is usually preferred to muscle biopsy because it is a less-invasive procedure with the advantage of maintaining a cell line for future use and providing information on residual enzyme activity. Blood-based assays, especially dried blood spots, have the advantage of a rapid turnaround time. A muscle biopsy can yield faster results and provide additional information about glycogen content and site of glycogen storage within and outside the lysosomes of muscle cells. A major limitation of a muscle biopsy in late-onset patients is the variable pathology and glycogen accumulation in different muscles and within muscle fibers; muscle histology and glycogen content can vary depending on the site of muscle biopsy. There is also a high risk from anesthesia in infantile patients. An electrocardiogram can be helpful in making the diagnosis in suspected cases of the infantile form and should be done for patients suspected of having Pompe disease before any procedure requiring anesthesia, including muscle biopsy, is performed. Urinary glucose tetrasaccharides are elevated in the urine of affected patients, and levels are extremely high in infantile patients. This biomarker is valuable for diagnosis and monitoring response to therapy in Pompe disease. Prenatal diagnosis using amniocytes or chorionic villi is available for the infantile form of the disease.

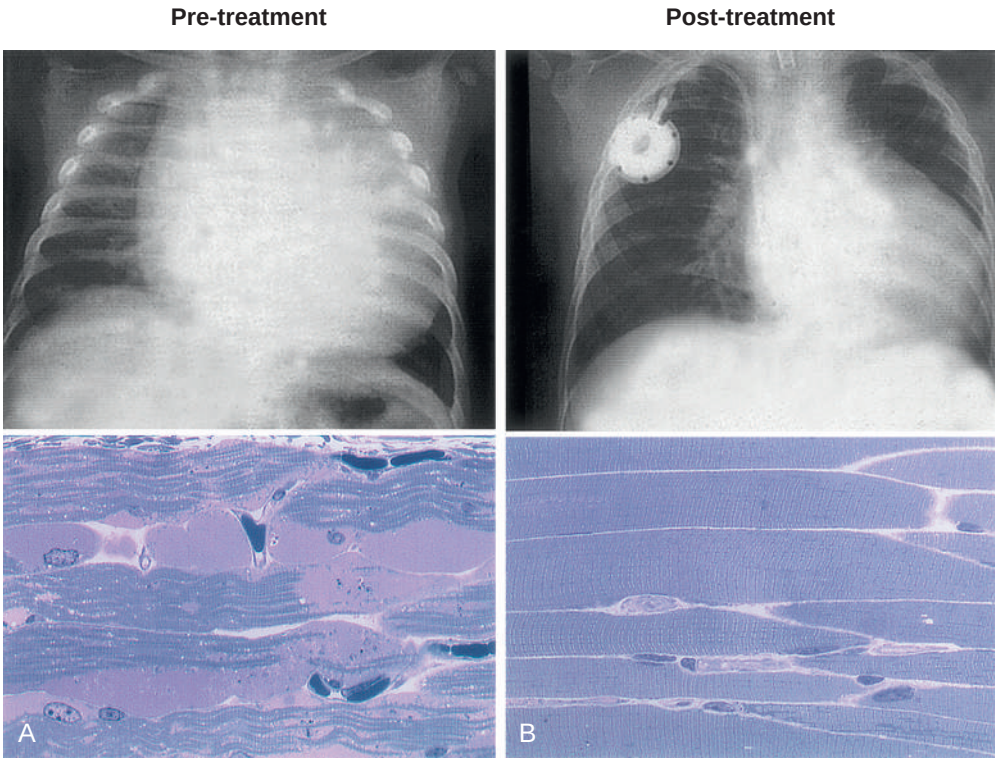

Figure 87-3 Chest x-ray and muscle histology findings of an infantile-onset Pompe disease patient before **(A)** and after **(B)** enzyme replacement therapy. Note the decrease in heart size and muscle glycogen with the therapy. *(Modified from Amalfitano A, Bengur AR, Morse RP, et al: Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial,* Genet Med *3:132–138, 2001.)*

Treatment

Treatment options were once limited to supportive or palliative care. Specific enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (alglucosidase alfa, [Myozyme or Lumizyme]) is available for treatment of Pompe disease. Recombinant acid α-glucosidase is capable of preventing deterioration or reversing abnormal cardiac and skeletal muscle functions (Fig. 87-3). ERT should be initiated as soon as possible across the disease spectrum, especially for babies with the infantile form who are diagnosed via newborn screening, as the disease is very rapidly progressive. The dosage is 20 mg/kg given every 2 wk. A high-protein diet and exercise therapy may also be beneficial. Nocturnal ventilatory support, when indicated, should be used. It has been shown to improve the quality of life and is particularly beneficial during a period of respiratory decompensation. Early diagnosis and treatment are necessary for optimal outcomes in Pompe disease. Newborn screening using blood-based assays in Taiwan has resulted in early identification of Pompe cases and, as a result, has improved disease outcomes through the early initiation of ERT.

Glycogen Storage Diseases Mimicking Hypertrophic Cardiomyopathy

Deficiencies of LAMP2 (also called Danon disease) and PRKAG2 result in accumulation of glycogen in the heart and skeletal muscle. Danon disease is transmitted as an X-linked trait and PRKAG2 deficiency as an autosomal dominant trait. These patients present primarily as a hypertrophic cardiomyopathy, but can be distinguished from the usual causes of hypertrophic cardiomyopathy caused by defects in sarcomere protein genes by their electrophysiologic abnormalities, particularly ventricular preexcitation and conduction defects. The onset of cardiac symptoms, including chest pain, palpitation, syncope, and cardiac arrest, can occur between the ages of 8 and 15 yr for LAMP2 deficiency, younger than the average age of 33 yr for patients with PRKAG2 deficiency. However, there are several reports of patients with mutations in the PRKAG2 gene presenting early. These cases present in early infancy with severe hypertrophic cardiomyopathy and a rapidly fatal course. In the past, several of these cases were misdiagnosed as GSD IX as a result of secondary low PhK activity in the heart. The p.Arg531Gln and p.Arg384Thr mutations in the PRKAG2 gene are incompatible with life. Other mutations (p.Arg302Gln, p.Thr400Ans, p.Asn488Ile, and p.His487Tyr) associated with Wolff-Parkinson-White syndrome and adult-onset hypertrophic cardiomyopathy are less disruptive.

The prognosis for LAMP2 deficiency is poor with progressive end-stage heart failure early in adulthood. With the exception of the fatal infantile presentation, cardiomyopathy caused by PRKAG2 mutations is compatible with long-term survival, although some patients may necessitate the implantation of a pacemaker and aggressive control of arrhythmias.

Type V Glycogen Storage Disease (Muscle Phosphorylase Deficiency, McArdle Disease)

GSD V is caused by the deficiency of muscle phosphorylase activity. Lack of this enzyme limits muscle ATP generation by glycogenolysis, resulting in muscle glycogen accumulation, and is the prototype of muscle energy disorders. A deficiency of myophosphorylase impairs the cleavage of glucosyl molecules from the straight chain of glycogen.

Clinical Manifestations

Symptoms usually first develop in late childhood or in the 2nd decade of life. In general, clinical heterogeneity is uncommon, but cases suggesting otherwise have been documented. Studies have shown that McArdle disease can manifest in individuals as old as 74 yr of age, as well as in infancy, in a fatal, early-onset form characterized by hypotonia, generalized muscle weakness, and respiratory complication. Symptoms are generally characterized by exercise intolerance with muscle cramps and pain. Two types of activity tend to cause symptoms: brief exercise of great intensity, such as sprinting or carrying heavy loads; and less intense but sustained activity, such as climbing stairs or walking uphill. Moderate exercise, such as walking on level ground,

can be performed by most patients for long periods. Many patients experience a characteristic "second wind" phenomenon. If they slow down or pause briefly at the first appearance of muscle pain, they can resume exercise with more ease. As a result of the underlying myopathy, these patients may be at risk for statin-induced myopathy and rhabdomyolysis. While patients typically experience episodic muscle pain and cramping from exercise, 35% of patients with McArdle disease report permanent pain that has a serious impact on sleep and other activities. Studies also suggest that there may also be a link between GSD V and levels of cognitive impairment.

Approximately 50% of patients report burgundy-colored urine after exercise, which is the consequence of exercise-induced **myoglobinuria** secondary to **rhabdomyolysis.** Intense myoglobinuria after vigorous exercise may cause acute renal failure. In rare cases, electromyographic findings may suggest an inflammatory myopathy and the diagnosis can be confused with polymyositis.

The level of serum creatine kinase is usually elevated at rest and increases more after exercise. Exercise also increases the levels of blood ammonia, inosine, hypoxanthine, and uric acid. The latter abnormalities are attributed to accelerated recycling of muscle purine nucleotides owing to insufficient ATP production. Type V GSD is an autosomal recessive disorder. The gene for muscle phosphorylase *(PYGM)* has been mapped to chromosome 11q13.

Diagnosis

The standard diagnosis for GSD V includes a muscle biopsy to measure glycogen content as well as enzyme and mutation analysis. An ischemic exercise test offers a rapid diagnostic screening for patients with a metabolic myopathy. Lack of an increase in blood lactate levels and exaggerated blood ammonia elevations indicate muscle glycogenosis and suggest a defect in the conversion of muscle glycogen or glucose to lactate. The abnormal ischemic exercise response is not limited to type V GSD. Other muscle defects in glycogenolysis or glycolysis produce similar results (deficiencies of muscle phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, or lactate dehydrogenase).

Phosphorus MRI allows for the noninvasive evaluation of muscle metabolism. Patients with type V GSD have no decrease in intracellular pH and have excessive reduction in phosphocreatine in response to exercise. The diagnosis should be confirmed by enzymatic evaluation of muscle. A common nonsense mutation p.R49X in exon 1 is found in 90% of white patients, and a deletion of a single codon in exon 17 is found in 61% of Japanese patients. The p.R49X mutation represents 55% of alleles in Spanish patients, whereas the p.W797R mutation represents 14% and the p.G204S represents 9% of mutant alleles in the Spanish population. There seems to be an association between clinical severity of GSD V and the presence of the D allele of the angiotensin-converting enzyme insertion/deletion polymorphism. This may help explain the spectrum of phenotypic variability manifested in this disorder.

Treatment

Avoidance of strenuous exercise prevents the symptoms; however, regular and moderate exercise is recommended to improve exercise capacity. Glucose or sucrose given before exercise or injection of glucagon can markedly improve tolerance in these patients. A high-protein diet may increase muscle endurance and creatine supplement has been shown to improve muscle function in some patients. The clinical response to creatine is dose-dependent: muscle pain may increase on high doses of creatine supplementation. Vitamin B_6 supplementation reduces exercise intolerance and muscle cramps. Longevity is not generally affected.

Type VII Glycogen Storage Disease (Muscle Phosphofructokinase Deficiency, Tarui Disease)

Type VII GSD is caused by a deficiency of muscle phosphofructokinase, which catalyzes the ATP-dependent conversion of fructose-6-phosphate to fructose-1,6-diphosphate and is a key regulatory enzyme of glycolysis. Phosphofructokinase is composed of 3 isoenzyme subunits (M [muscle], L [liver], and P [platelet]) that are encoded by different genes and differentially expressed in tissues. Skeletal muscle contains only the M subunit, and red blood cells contain a hybrid of L and M forms. Type VII disease is caused by a defective M isoenzyme, which causes a complete enzyme defect in muscle and a partial defect in red blood cells.

Type VII GSD is an autosomal recessive disorder and is prevalent among Japanese people and Ashkenazi Jews. The gene for muscle phosphofructokinase is located on chromosome 12q13.3. A splicing defect and a nucleotide deletion in the muscle phosphofructokinase gene account for 95% of mutant alleles in Ashkenazi Jews. Diagnosis based on molecular testing is thus possible in this population.

Clinical Manifestations

Six features of type VII are distinctive: (1) Exercise intolerance, usually evident in childhood, is more severe than in type V disease and may be associated with nausea, vomiting, and severe muscle pain; vigorous exercise causes severe muscle cramps and myoglobinuria. (2) Compensated hemolysis occurs as evidenced by an increased level of serum bilirubin and an elevated reticulocyte count. (3) Hyperuricemia is common and exaggerated by muscle exercise to a greater degree than that observed in type V or III GSD. (4) An abnormal polysaccharide is present in muscle fibers; it is periodic acid–Schiff-positive but resistant to diastase digestion. (5) Exercise intolerance is particularly acute after meals that are rich in carbohydrates because glucose cannot be utilized in muscle and because glucose inhibits lipolysis, thereby depriving muscle of fatty acid and ketone substrates. In contrast, patients with type V disease can metabolize bloodborne glucose derived from either liver glycogenolysis or exogenous glucose; indeed, glucose infusion improves exercise tolerance in type V patients. (6) There is no spontaneous second-wind phenomenon because of the inability to metabolize blood glucose.

Other rare type VII variants occur. One variant presents in infancy with hypotonia and limb weakness and proceeds to a rapidly progressive myopathy that leads to death by 4 yr of age. There is a second variant that occurs in infancy and results in congenital myopathy and arthrogryposis with a fatal outcome. A third variant presents in infancy with hypotonia, mild developmental delay and seizures. An additional presentation is hereditary nonspherocytic hemolytic anemia. Although these patients do not experience muscle symptoms, it remains unclear whether these symptoms will develop later in life. One variant presents in adults and is characterized by a slowly progressive, fixed muscle weakness rather than cramps and myoglobinuria. It may also cause mitral valve thickening from glycogen buildup.

Diagnosis

To establish a diagnosis, a biochemical or histochemical demonstration of the enzymatic defect in the muscle is required. The absence of the M isoenzyme of phosphofructokinase can also be demonstrated in blood cells and fibroblasts.

Treatment

There is no specific treatment. Avoidance of strenuous exercise is advisable to prevent acute attacks of muscle cramps and myoglobinuria. Drugs such as statins should be avoided. Precautionary measures should be taken to avoid hyperthermia while undergoing anesthesia. Carbohydrate meals and glucose infusions have demonstrated worsening symptoms because of the body's inability to utilize glucose. The administered glucose tends to lower the levels of fatty acids in the blood, a primary source of muscle fuel. One case of a child with a severe infantile form of GSD VII, demonstrated that the initiation of a ketogenic diet resulted in significant clinical improvement.

Other Muscle Glycogenoses with Muscle Energy Impairment

Six additional defects in enzymes—phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, fructose-1,6-bisphosphate aldolase A, muscle pyruvate kinase, and β-enolase in the pathway of the terminal glycolysis—cause symptoms and signs of muscle energy

impairment similar to those of types V and VII GSD. The failure of blood lactate to increase in response to exercise is a useful diagnostic test and can be used to differentiate muscle glycogenoses from disorders of lipid metabolism, such as carnitine palmitoyl transferase II deficiency and very long chain acyl-CoA dehydrogenase deficiency, which also cause muscle cramps and myoglobinuria. Muscle glycogen levels can be normal in the disorders affecting terminal glycolysis and assaying the muscle enzyme activity is needed to make a definite diagnosis. There is no specific treatment. Avoidance of strenuous exercise prevents acute attacks of muscle cramps and myoglobinuria. Avoidance of drugs such as statins, and malignant hyperthermia precautions for patients undergoing anesthesia should be followed.

Bibliography is available at Expert Consult.

87.2 Defects in Galactose Metabolism

Priya S. Kishnani and Yuan-Tsong Chen

Milk and dairy products contain lactose, the major dietary source of galactose. The metabolism of galactose produces fuel for cellular metabolism through its conversion to glucose-1-phosphate (see Table 87-1). Galactose also plays an important role in the formation of galactosides, which include glycoproteins, glycolipids, and glycosaminoglycans. Galactosemia denotes the elevated level of galactose in the blood and is found in 3 distinct inborn errors of galactose metabolism in 1 of the following enzymes: galactose-1-phosphate uridyl transferase, galactokinase, and uridine diphosphate galactose-4-epimerase. The term *galactosemia,* although adequate for the deficiencies in any of these disorders, generally designates the transferase deficiency.

GALACTOSE-1-PHOSPHATE URIDYL TRANSFERASE DEFICIENCY GALACTOSEMIA

Two forms of the deficiency exist: infants with complete or near complete deficiency of the enzyme (classic galactosemia) and those with partial transferase deficiency. **Classic galactosemia** is a serious disease with onset of symptoms typically by the second half of the 1st wk of life. The incidence is predicted to be 1 in 60,000 live births. The newborn infant receives high amounts of lactose (up to 40% in breast milk and certain formulas), which consists of equal parts of glucose and galactose. Without the transferase enzyme, the infant is unable to metabolize galactose-1-phosphate, the accumulation of which results in injury to kidney, liver, and brain. This injury may begin prenatally in the affected fetus by transplacental galactose derived from the diet of the heterozygous mother or by endogenous production of galactose in the fetus.

Clinical Manifestations

The diagnosis of uridyl transferase deficiency should be considered in newborn or young infants with any of the following features: jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain or failure to regain birth weight, aminoaciduria, nuclear cataracts, vitreous hemorrhage, hepatic failure, liver cirrhosis, ascites, splenomegaly, or intellectual disability. Symptoms are milder and improve when milk is temporarily withdrawn and replaced by intravenous or lactose-free nutrition. Patients with galactosemia are at increased risk for *Escherichia coli* neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia. Pseudotumor cerebri can occur and cause a bulging fontanel. Death from liver and kidney failure and sepsis may follow within days. When the diagnosis is not made at birth, damage to the liver (cirrhosis) and brain (intellectual disability) becomes increasingly severe and irreversible.

Partial transferase deficiency is generally asymptomatic. It is more frequent than classic galactosemia and is diagnosed in newborn screening because of moderately elevated blood galactose and/or low transferase activity. Galactosemia should be considered for the newborn or young infant who is not thriving or who has any of the preceding findings. Light and electron microscopy of hepatic tissue reveals fatty infiltration, the formation of pseudoacini, and eventual macronodular cirrhosis. These changes are consistent with a metabolic disease but do not indicate the precise enzymatic defect.

Diagnosis

The preliminary diagnosis of galactosemia is made by demonstrating a reducing substance in several urine specimens collected while the patient is receiving human milk, cow's milk, or any other formula containing lactose. The reducing substance found in urine by Clinitest (glucose, galactose, and others) can be identified by chromatography or by an enzymatic test specific for galactose. Galactosuria is present, provided the last milk feed does not date back more than a few hours and the child is not vomiting excessively. Clinistix urine test results are usually negative because the test materials rely on the action of glucose oxidase, which is specific for glucose and is nonreactive with galactose. Owing to a proximal renal tubular syndrome, the acutely ill baby may also excrete glucose together with amino acids. Because galactose is injurious to persons with galactosemia, diagnostic challenge tests dependent on administering galactose orally or intravenously should not be used. Direct enzyme assay using erythrocytes establishes the diagnosis. One needs to confirm that the patient did not receive a blood transfusion before the collection of the blood sample, as a diagnosis could be missed. A novel method utilizes nonradioactive UV and high-performance liquid chromatography to accurately detect levels of galactose-1-phosphate uridyl transferase in erythrocytes.

Genetics

Transferase deficiency is an autosomal recessive disorder. Based on newborn screening in the United States, the frequency of the disease is approximately 1 in 47,000 live births. There are several enzymatic variants of galactosemia. The *Duarte variant,* a single amino acid substitution (p.N314D), has diminished red cell enzyme activity (50% of normal), but usually no clinical significance. This variant is the most common, with a carrier frequency of 12% in the general population. Those who are heterozygous for the Duarte variant of galactosemia typically have 25% of normal galactose activity, few symptoms, elevated metabolites, and no need for intervention. Other similar variants expressing little enzyme activity typically require no intervention. Some African-American patients have milder symptoms despite the absence of measurable transferase activity in erythrocytes; these patients retain 10% enzyme activity in liver and intestinal mucosa, whereas most white patients have no detectable activity in any of these tissues. More than 230 identifiable mutations have been associated with transferase deficiency. In African-Americans, 62% of alleles are represented by the p.S135L mutation, a mutation that is responsible for a milder disease course. In the white population, 70% of alleles are represented by the p.Q188R and p.K285N missense mutations and are associated with severe disease. Carrier testing and prenatal diagnosis can be performed by direct enzyme analysis of amniocytes or chorionic villi; testing can also be DNA based.

Treatment and Prognosis

Because of newborn screening for galactosemia, patients are being identified and treated early. Various non–lactose-containing milk substitutes are available (casein hydrolysates, soybean-based formula). Elimination of galactose from the diet along with adequate calcium supplementation reverses growth failure and renal and hepatic dysfunction. Cataracts regress, and most patients have no impairment of vision. Early diagnosis and treatment have improved the prognosis of galactosemia; however, on long-term follow-up, patients still manifest ovarian failure with primary or secondary amenorrhea, decreased bone mineral density, developmental delay, and learning disabilities that increase in severity with age. **Hypergonadotrophic hypogonadism** is reported in 80% to more than 90% of female patients with classic galactosemia. Although most women with classic galactosemia are infertile when they reach childbearing age, a small number have given birth. Most patients manifest speech disorders, whereas a smaller number demonstrate poor growth and impaired motor function and balance (with or without overt ataxia). The relative control of

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galactose-1-phosphate levels does not always correlate with long-term outcome, leading to the belief that other factors, such as elevated galactitol, decreased uridine diphosphate galactose (a donor for galactolipids and proteins), and endogenous galactose production may be responsible.

GALACTOKINASE DEFICIENCY

The deficient enzyme is galactokinase, which normally catalyzes the phosphorylation of galactose. The principal metabolites accumulated are galactose and galactitol. Two genes are reported to encode galactokinase: *GK1* on chromosome 17q24 and *GK2* on chromosome 15. Cataracts are usually the sole manifestation of galactokinase deficiency; pseudotumor cerebri is a rare complication. The affected infant is otherwise asymptomatic. Heterozygote carriers may be at risk for presenile cataracts. Affected patients have an increased concentration of blood galactose levels, provided they have been fed a lactose-containing formula. The diagnosis is made by demonstrating an absence of galactokinase activity in erythrocytes or fibroblasts. Transferase activity is normal. Treatment is dietary restriction of galactose.

URIDINE DIPHOSPHATE GALACTOSE-4-EPIMERASE DEFICIENCY

The abnormally accumulated metabolites are similar to those in transferase deficiency; however, there is also an increase in cellular uridine diphosphate galactose. There are 2 distinct forms of epimerase deficiency. The first is a benign form discovered incidentally through neonatal screening programs. Affected persons are healthy and without problems; the enzyme deficiency is limited to leukocytes and erythrocytes. No treatment is required. The second form of epimerase deficiency is severe, and clinical manifestations resemble transferase deficiency, with the additional symptoms of hypotonia and nerve deafness. The enzyme deficiency is generalized, and clinical symptoms respond to restriction of dietary galactose. Although this form of galactosemia is rare, it must be considered in a symptomatic patient with measurable galactose-1-phosphate who has normal transferase activity. Diagnosis is confirmed by the assay of epimerase in erythrocytes.

Patients with the severe form of epimerase deficiency cannot synthesize galactose from glucose and are galactose-dependent. Because galactose is an essential component of many nervous system structural proteins, patients are placed on a galactose-restricted diet rather than a galactose-free diet.

Infants with the mild form of epimerase deficiency have not required treatment. It is advisable to follow urine specimens for reducing substances and exclude aminoaciduria within a few weeks of diagnosis while the infant is still on lactose-containing formula.

The gene for uridine diphosphate galactose-4-epimerase is located on chromosome 1 at 1p36. Carrier detection is possible by measurement of epimerase activity in the erythrocytes. Prenatal diagnosis for the severe form of epimerase deficiency, using an enzyme assay of cultured amniotic fluid cells, is possible.

Bibliography is available at Expert Consult.

87.3 Defects in Fructose Metabolism

Priya S. Kishnani and Yuan-Tsong Chen

Two inborn errors are known in the specialized pathway of fructose metabolism: benign or essential fructosuria and hereditary fructose intolerance (HFI). Fructose-1,6-bisphosphatase deficiency, although strictly speaking not a defect of the specialized fructose pathway, is discussed in Chapter 87.4.

DEFICIENCY OF FRUCTOKINASE (ESSENTIAL OR BENIGN FRUCTOSURIA)

Deficiency of fructokinase is not associated with any clinical manifestations. It is an accidental finding usually made because the asymptomatic patient's urine contains a reducing substance. No treatment is necessary and the prognosis is excellent. Inheritance is autosomal recessive with an incidence of 1 in 120,000 live births. The gene encoding fructokinase is located on chromosome 2p23.3.

Fructokinase catalyzes the first step of metabolism of dietary fructose: conversion of fructose to fructose-1-phosphate (see Fig. 87-1). Without this enzyme, ingested fructose is not metabolized. Its level is increased in the blood, and it is excreted in urine because there is practically no renal threshold for fructose. Clinitest results reveal the urinary-reducing substance, which can be identified as fructose by chromatography.

DEFICIENCY OF FRUCTOSE-1,6-BISPHOSPHATE ALDOLASE (ALDOLASE B, HEREDITARY FRUCTOSE INTOLERANCE)

Deficiency of fructose-1,6-bisphosphate aldolase is a severe condition of infants that appears with the ingestion of fructose-containing food and is caused by a deficiency of fructose aldolase B activity in the liver, kidney, and intestine. The enzyme catalyzes the hydrolysis of fructose-1,6-bisphosphate into triose phosphate and glyceraldehyde phosphate. The same enzyme also hydrolyzes fructose-1-phosphate. Deficiency of this enzyme activity causes a rapid accumulation of fructose-1-phosphate and initiates severe toxic symptoms when exposed to fructose.

Epidemiology and Genetics

The true incidence of HFI is unknown but may be as high as 1 in every 26,000 live births. The gene for aldolase B is on chromosome 9q22.3. At least 40 mutations causing HFI are known. A single missense mutation, a G→C transversion in exon 5 resulting in the normal alanine at position 149 being replaced by a proline, is the most common mutation identified in northern Europeans. This mutation, plus 2 other point mutations (p.A174D and p.N334K), account for 80-85% of HFI in Europe and the United States. Diagnosis of HFI can be made by direct DNA analysis and phosphorus magnetic resonance spectroscopy.

Clinical Manifestations

Patients with HFI are asymptomatic until fructose or sucrose (table sugar) is ingested (usually from fruit, fruit juice, or sweetened cereal). Symptoms may occur early in life, soon after birth if foods or formulas containing these sugars are introduced into the diet. Certain patients are very sensitive to fructose, whereas others can tolerate moderate intakes (up to 250 mg/kg/day). The average intake of fructose in Western societies is 1-2 g/kg/day. Early clinical manifestations resemble galactosemia and include jaundice, hepatomegaly, vomiting, lethargy, irritability, and convulsions. There may also be a higher incidence of celiac disease in HFI patients (>10%) than in the general population (1-3%). Laboratory findings include a prolonged clotting time, hypoalbuminemia, elevation of bilirubin and transaminase levels, and proximal tubular dysfunction. Acute fructose ingestion produces symptomatic hypoglycemia; the higher the intake, the more severe is the clinical picture. Chronic ingestion results in failure to thrive and hepatic disease. If the intake of the fructose persists, hypoglycemic episodes recur, and liver and kidney failure progress, eventually leading to death.

Diagnosis

Suspicion of the enzyme deficiency is fostered by the presence of a reducing substance in the urine during an episode. The fructose challenge, although an effective method of diagnosis, causes a rapid fall, first of serum phosphate and then of blood glucose, and a subsequent increase in uric acid and magnesium. Because of high risks to the patient who can become acutely ill after the oral tolerance test, it should not be performed. Definitive diagnosis is made by assay of fructaldolase B activity in the liver. Gene-based diagnosis is available for most patients with this disease; a common mutation (substitution of *Pro* for *Ala* at position 149) accounts for 53% of HFI alleles worldwide.

Treatment

Treatment consists of the complete elimination of all sources of sucrose, fructose, and sorbitol from the diet. It may be difficult because these

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sugars are widely used additives, found even in most medicinal preparations. With treatment, liver and kidney dysfunction improves, and catch-up in growth is common. Intellectual development is usually unimpaired. As the patient matures, symptoms become milder even after fructose ingestion; the long-term prognosis is good. Because of voluntary dietary avoidance of sucrose, affected patients have few dental caries.

Bibliography is available at Expert Consult.

87.4 Defects in Intermediary Carbohydrate Metabolism Associated with Lactic Acidosis

Priya S. Kishnani and Yuan-Tsong Chen

Lactic acidosis occurs with defects of carbohydrate metabolism that interfere with the conversion of pyruvate to glucose via the pathway of gluconeogenesis or to carbon dioxide and water via the mitochondrial enzymes of the Krebs cycle. Figure 87-4 depicts the relevant metabolic pathways. Type I GSD, fructose-1,6-diphosphatase deficiency, and phosphoenolpyruvate carboxylase deficiency are disorders of gluconeogenesis associated with lactic acidosis. Pyruvate dehydrogenase complex deficiency, respiratory chain defects, and pyruvate carboxylase deficiency are disorders in the pathway of pyruvate metabolism causing lactic acidosis. Lactic acidosis can also occur in defects of fatty acid oxidation, organic acidurias (see Chapters 85.6, 85.10, and 86.1), or biotin utilization diseases. These disorders are easily distinguishable by the presence of abnormal acylcarnitine profiles, amino acids in the blood, and unusual organic acids in the urine. Blood lactate, pyruvate, and acylcarnitine profiles and the presence of these unusual urine organic acids should be determined in infants and children with unexplained acidosis, especially if there is an increase of anion gap.

Lactic acidosis unrelated to an enzymatic defect occurs in hypoxemia. In this case, as well as in defects in the respiratory chain, the serum pyruvate concentration may remain normal (<1.0 mg/dL with an increased lactate: pyruvate ratio), whereas pyruvate is usually increased when lactic acidosis results from an enzymatic defect in gluconeogenesis or pyruvate dehydrogenase complex (both lactate and pyruvate are increased and the ratio is normal). Lactate and pyruvate should be measured in the same blood specimen and on multiple blood specimens obtained when the patient is symptomatic because lactic acidosis can be intermittent. Figure 87-5 is an algorithm for the differential diagnosis of lactic acidosis.

DISORDERS OF GLUCONEOGENESIS

Deficiency of Glucose-6-Phosphatase (Type I Glycogen Storage Disease)

Type I GSD is the only glycogenosis associated with significant lactic acidosis. The chronic metabolic acidosis predisposes these patients to osteopenia; after prolonged fasting, the acidosis associated with hypoglycemia is a life-threatening condition (see Chapter 87.1).

Fructose-1,6-Diphosphatase Deficiency

Fructose-1,6-diphosphatase deficiency impairs the formation of glucose from all gluconeogenic precursors, including dietary fructose. Hypoglycemia occurs when glycogen reserves are limited or exhausted. The clinical manifestations are characterized by life-threatening episodes of acidosis, hypoglycemia, hyperventilation, convulsions, and coma. In about half of the cases, the deficiency presents in the 1st wk of life. In infants and small children, episodes are triggered by febrile infections and gastroenteritis if oral food intake decreases. The frequency of the attacks decreases with age. Laboratory findings include low blood glucose, high lactate and uric acid levels, and metabolic acidosis. In contrast to HFI, there is usually no aversion to sweets; renal tubular and liver functions are normal.

The diagnosis is established by demonstrating an enzyme deficiency in either liver or intestinal biopsy. The enzyme defect can also be demonstrated in leukocytes in some cases. The gene coding for fructose-1,6-diphosphatase is located on chromosome 9q22; mutations are characterized, making carrier detection and prenatal diagnosis possible. Treatment of acute attacks consists of correction of hypoglycemia and acidosis by intravenous glucose infusion; the response is usually rapid. Avoidance of fasting, aggressive management of infections and restriction of fructose and sucrose from the diet can prevent further episodes. For long-term prevention of hypoglycemia, a slowly released carbohydrate such as cornstarch is useful. Patients who survive childhood develop normally.

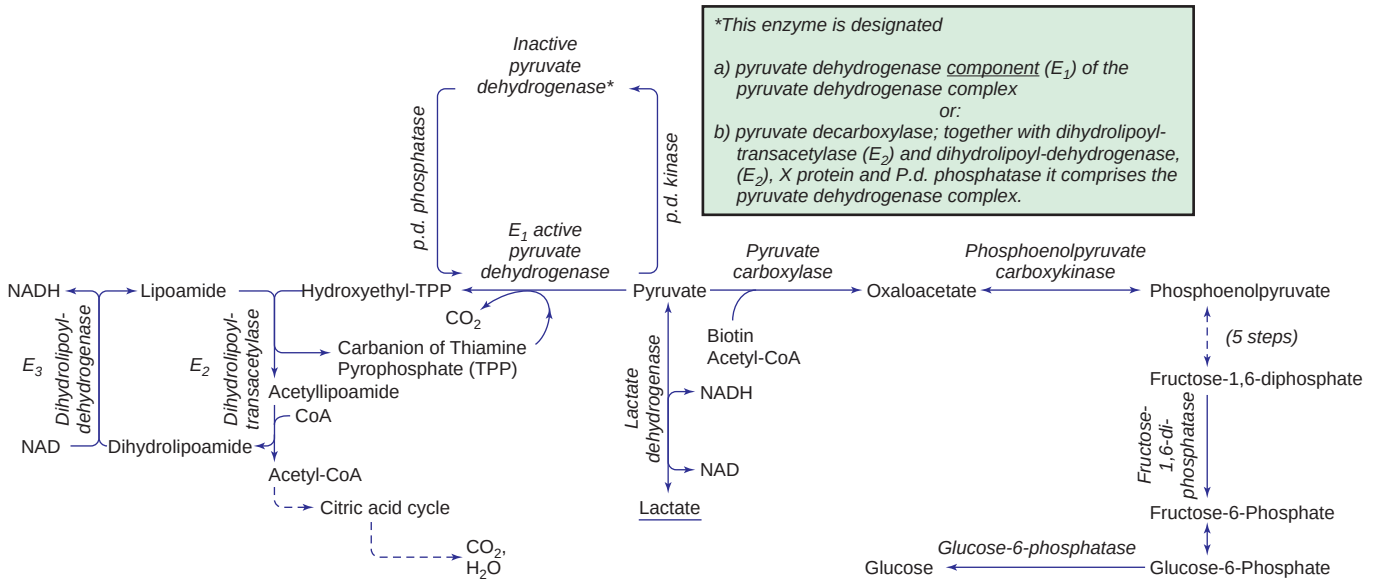

Figure 87-4 Enzymatic reactions of carbohydrate metabolism, deficiencies of which can give rise to lactic acidosis, pyruvate elevations, or hypoglycemia. The pyruvate dehydrogenase complex comprises, in addition to E_1, E_2, and E_3, an extra lipoate-containing protein (not shown), called protein X, and pyruvate dehydrogenase phosphatase.

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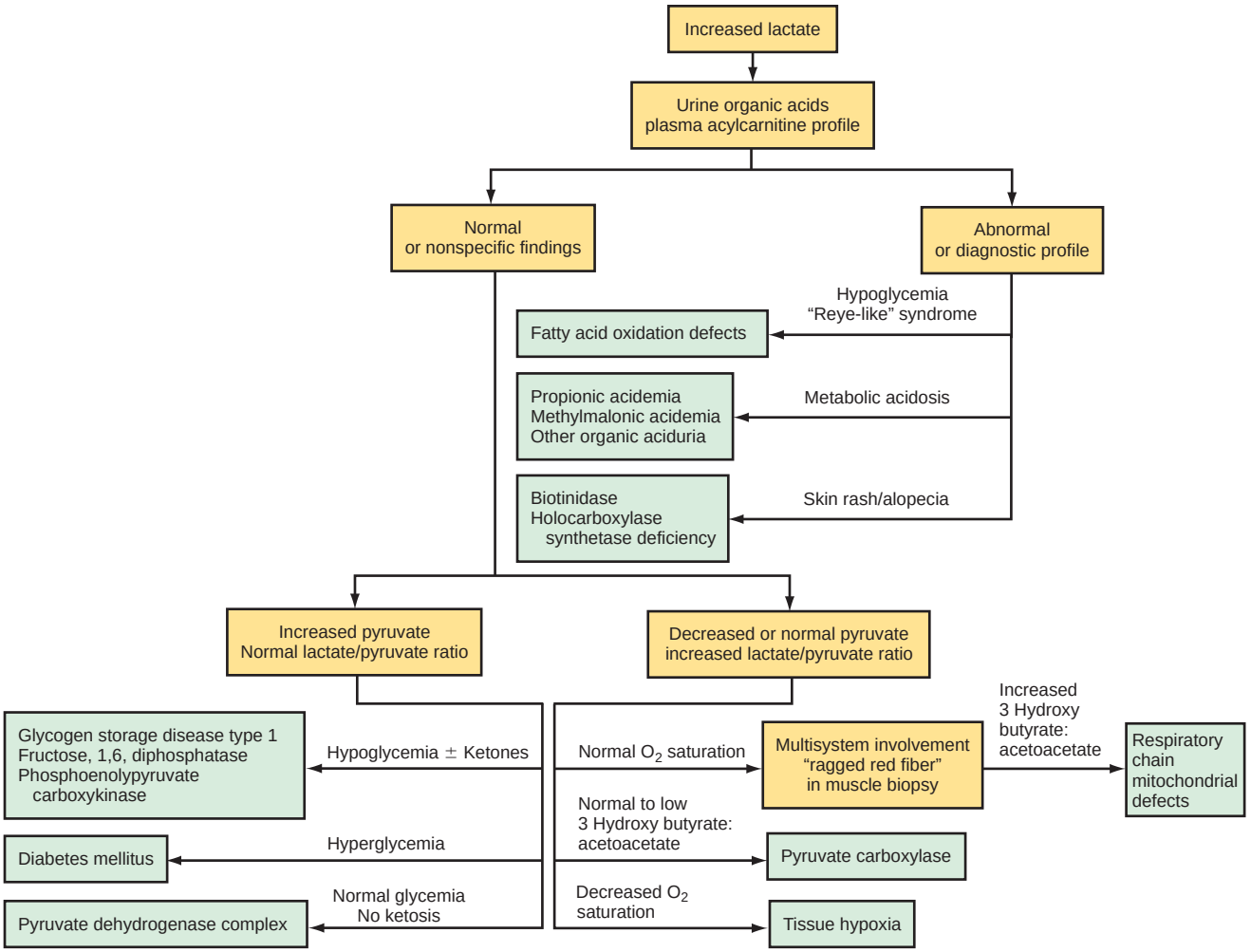

Figure 87-5 Algorithm of the differential diagnosis of lactic acidosis.

Phosphoenolpyruvate Carboxykinase Deficiency

Phosphoenolpyruvate carboxykinase (PEPCK) is a key enzyme in gluconeogenesis. It catalyzes the conversion of oxaloacetate to phosphoenolpyruvate (see Fig. 87-4). PEPCK deficiency is both a mitochondrial enzyme deficiency and a cytosolic enzyme deficiency, encoded by 2 distinct genes.

The disease has been reported in only a few cases. The clinical features are heterogeneous, with hypoglycemia, lactic acidemia, hepatomegaly, hypotonia, developmental delay, and failure to thrive as the major manifestations. There may be multisystem involvement, with neuromuscular deficits, hepatocellular damage, renal dysfunction, and cardiomyopathy. The diagnosis is based on the reduced activity of PEPCK in liver, fibroblasts, or lymphocytes. Fibroblasts and lymphocytes are not suitable for diagnosing the cytosolic form of PEPCK deficiency because these tissues possess only mitochondrial PEPCK. To avoid hypoglycemia, patients should be treated with slow-release carbohydrates such as cornstarch, and fasting should be avoided.

DISORDERS OF PYRUVATE METABOLISM

Pyruvate is formed from glucose and other monosaccharides, from lactate, and from alanine. It is metabolized through 4 main enzyme systems: lactate dehydrogenase, alanine aminotransferase, pyruvate carboxylase, and pyruvate dehydrogenase complex. Deficiency of the M subunit of lactate dehydrogenase causes exercise intolerance and myoglobinuria (see Chapter 87.1).

Pyruvate Dehydrogenase Complex Deficiency

After entering the mitochondria, pyruvate is converted into acetyl-CoA by the pyruvate dehydrogenase complex (PDHC), which catalyzes the oxidation of pyruvate to acetyl-CoA, which then enters the tricarboxylic acid cycle for ATP production. The complex comprises 5 components: E_1, an α-ketoacid decarboxylase; E_2, a dihydrolipoyl transacylase; E_3, a dihydrolipoyl dehydrogenase; protein X, an extra lipoate-containing protein; and pyruvate dehydrogenase phosphatase. The most common is a defect in the E_1 (see Fig. 87-4).

Deficiency of the PDHC is the most common of the disorders leading to lactic acidemia and central nervous system dysfunction. The central nervous system dysfunction occurs because the brain obtains its energy primarily from oxidation of glucose. Brain acetyl-CoA is synthesized nearly exclusively from pyruvate.

The E_1 defects are caused by mutations in the gene coding for E_1 α subunit, which is X-linked. Although X-linked, its deficiency is a problem in both males and females even though only 1 E_1 α allele in females carries a mutation.

Clinical Manifestations

The disease has a wide spectrum of presentations from the most severe neonatal presentation to a mild late-onset form. The **neonatal onset** is associated with lethal lactic acidosis, white matter cystic lesions, agenesis of the corpus callosum, and the most severe enzyme deficiency. **Infantile onset** can be lethal or associated with psychomotor delay and chronic lactic acidosis, cystic lesions in the brainstem and basal ganglia, and pathologic features resembling **Leigh disease** (see below).

Neurologic symptoms in PDHC can be categorized into 2 groups: the first, abnormal brain development seen in both males and females, and the second, brain lesions and epilepsy seen in male patients only. Older children, usually boys, may have less acidosis, have greater enzyme activity, and manifest ataxia with high-carbohydrate diets. Intelligence may be normal. Patients of all ages may have facial dysmorphology, features similar to those of fetal alcohol syndrome.

The E_2 and protein X-lipoate defects are rare and result in severe psychomotor retardation. The E_3 lipoamide dehydrogenase defect leads to deficient activity not only in the PDHC, but also in the α-ketoglutarate and branched-chain ketoacid dehydrogenase complexes. This deficiency is more common in the Ashkenazi Jewish population. Recent studies suggest that the reactive oxygen species generated by the mutations responsible for lipoamide dehydrogenase deficiency may in fact explain certain disease characteristics and suggest the utility of antioxidant therapy. Pyruvate dehydrogenase phosphatase deficiency has also been reported. These other PDHC defects have clinical manifestations within the variable spectrum associated with PDHC deficiency due to E_1 deficiency.

Treatment

The general prognosis is poor except in rare cases in which mutation is associated with altered affinity for thiamine pyrophosphate, which may respond to thiamine supplementation. Because carbohydrates can aggravate lactic acidosis, a ketogenic diet is recommended. The diet has been found to lower the blood lactate level; the long-term benefit to patient outcome is unclear. A potential treatment strategy is to maintain any residual PDHC in its active form by **dichloroacetate,** an inhibitor of E_1 kinase. Beneficial effects of controlling postprandial lactic acidosis in some patients have been shown. Young children with congenital acidosis generally tolerate oral dichloroacetate well, but continued exposure is associated with peripheral neuropathy, a condition that could be attributable to the drug or the disease.

Deficiency of Pyruvate Carboxylase

Pyruvate carboxylase is a mitochondrial, biotin-containing enzyme essential in the process of gluconeogenesis; it catalyzes the conversion of pyruvate to oxaloacetate. The enzyme is also essential for Krebs cycle function as a provider of oxaloacetate and is involved in lipogenesis and formation of nonessential amino acids. Clinical manifestations of this deficiency have varied from neonatal severe lactic acidosis accompanied by hyperammonemia, citrullinemia, and hyperlysinemia **(type B)** to late-onset mild to moderate lactic acidosis and developmental delay **(type A).** In both types, patients who survived usually had severe psychomotor retardation with seizures, spasticity, and microcephaly. Some patients have pathologic changes in the brainstem and basal ganglia that resemble **Leigh disease** (see below). The clinical severity appears to correlate with the level of the residual enzyme activity. A "benign" form of pyruvate carboxylase deficiency characterized by recurrent attacks of lactic acidosis and mild neurologic deficits has also been described (type C). Laboratory findings are characterized by elevated levels of blood lactate, pyruvate, alanine, and ketonuria. In the case of type B, blood ammonia, citrulline, and lysine levels are also elevated, which might suggest a primary defect of the urea cycle. The mechanism is likely caused by depletion of oxaloacetate, which leads to reduced levels of aspartate, a substrate for argininosuccinate synthase in the urea cycle (see Chapter 85.12). The gene for pyruvate carboxylase is located on chromosome 11q13.4-q13.5 and approximately 15 mutations have been identified.

Treatment consists of avoidance of fasting, and eating a carbohydrate meal before bedtime. During acute episodes of lactic acidosis, patients should receive continuous intravenous glucose. Aspartate and citrate supplements restore the metabolic abnormalities; whether this treatment can prevent the neurologic deficits is not known. Liver transplantation has been attempted; its benefit remains unknown. Diagnosis of pyruvate carboxylase deficiency is made by the measurement of enzyme activity in liver or cultured skin fibroblasts and must be differentiated from holocarboxylase synthase or biotinidase deficiency.

Deficiency of Pyruvate Carboxylase Secondary to Deficiency of Holocarboxylase Synthase or Biotinidase

Deficiency of either holocarboxylase synthase (HCS) or biotinidase, which are enzymes of biotin metabolism, result in multiple carboxylase deficiency (pyruvate carboxylase and other biotin-requiring carboxylases and metabolic reactions) and in clinical manifestations associated with the respective deficiencies, as well as rash, lactic acidosis, and alopecia (see Chapter 85.6). The course of HCS or biotinidase deficiency can be protracted, with intermittent exacerbation of chronic lactic acidosis, failure to thrive, seizures, and hypotonia leading to spasticity, lethargy, coma, and death. Auditory and optic nerve dysfunction can lead to deafness and blindness, respectively. Late-onset milder forms have also been reported. Laboratory findings include metabolic acidosis and abnormal organic acids in the urine. In HCS deficiency, biotin concentrations in plasma and urine are normal. Diagnosis can be made in skin fibroblasts or lymphocytes by assay for HCS activity, and in the case of biotinidase, in the serum by a screening blood spot.

Treatment consists of biotin supplementation, 5-20 mg/day, and is generally effective if treatment is started before the development of brain damage. Patients identified through newborn screening and treated with biotin have remained asymptomatic.

Both enzyme deficiencies are autosomal recessive traits. The incidence of HCS deficiency is approximately 1 in 87,000 live births. HCS and biotinidase are located on chromosome 21q22 and 3p25, respectively. Ethnic-specific mutations in the HCS gene have been identified. Two common mutations (del7/ins3 and p.R538C) in the biotinidase gene account for 52% of all mutant alleles in symptomatic patients with biotinidase deficiency.

Mitochondrial Respiratory Chain Defects (Oxidative Phosphorylation Disease)

The mitochondrial respiratory chain catalyzes the oxidation of fuel molecules and transfers the electrons to molecular oxygen with concomitant energy transduction into ATP (oxidative phosphorylation). The respiratory chain produces ATP from adenosine diphosphate and inorganic phosphate utilizing the energy from electrons transferred from nicotinamide adenine dinucleotide (NADH) or flavin adenine dinucleotide and includes 5 specific complexes (I: NADH–coenzyme Q reductase; II: succinate–coenzyme Q reductase; III: coenzyme QH_2 cytochrome C reductase; IV: cytochrome C oxidase; V: ATP synthase). Each complex is composed of 4-35 individual proteins and, with the exception of complex II (which is encoded solely by nuclear genes), is encoded by nuclear or mitochondrial DNA (inherited only from the mother by mitochondrial inheritance). Defects in any of these complexes or assembly systems produce chronic lactic acidosis presumably because of a change of the reduction-oxidation state with increased concentrations of NADH. In contrast to PDHC or pyruvate carboxylase deficiency, skeletal muscle and heart are usually involved in the respiratory chain disorders, and in muscle biopsy, "ragged red fibers" (indicating mitochondrial proliferation) are very suggestive when present (see Fig. 87-5). Because of the ubiquitous nature of oxidative phosphorylation, a defect of the mitochondrial respiratory chain accounts for a vast array of clinical manifestations and should be considered in patients in all age groups presenting with multisystem involvement. Some deficiencies resemble **Leigh disease** (see below), whereas others cause infantile myopathies such as **MELAS** (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), **MERRF** (myoclonic epilepsy and ragged red fibers), and **Kearns-Sayre syndrome** (external ophthalmoplegia, acidosis, retinal degeneration, heart block, myopathy, and high cerebrospinal fluid protein) (Table 87-2; Chapters 598.2 and 611.4). There is a higher incidence of psychiatric disorders in adults with a primary oxidative phosphorylation disease than in the general population. Diagnosis requires demonstration of abnormalities of oxidative phosphorylation enzyme complex activities in tissues or of mitochondrial DNA or a nuclear gene coding for mitochondrial functions, or both (Fig. 87-6). Muscle histology, including

Table 87-2 Clinical and Genetic Heterogeneity of Disorders Related to Mutations in Mitochondrial DNA*

SYMPTOMS, SIGNS, AND FINDINGS	Large Deletions in mtDNA			Mutation in Transfer RNA		Mutation in Ribosomal RNA	Mutation in Messenger RNA		
	KSS	PEO	PS	MERRF	MELAS	AID	NARP	MILS	LHON
CENTRAL NERVOUS SYSTEM									
Seizures	–	–	–	**+++**	+	–	–	+	–
Ataxia	+	–	–	+	+		+	±	–
Myoclonus	–	–	–	+	±	–	–	–	–
Psychomotor retardation	–	–	–	–	–	–	–	+	–
Psychomotor regression	+	–	–	±	+	–	–	–	–
Hemiparesis and hemianopia	–	–	–	–	**+++**	–	–	–	–
Cortical blindness	–	–	–	–	+	–	–	–	–
Migraine-like headaches	–	–	–	–	+	–	–	–	–
Dystonia	–	–	–	–	+	–	–	+	±
PERIPHERAL NERVOUS SYSTEM									
Peripheral neuropathy	±	–	–	±	±	–	**+**	–	–
MUSCLE									
Weakness and exercise intolerance	+	**+++**	–	+	+	–	+	+	–
Ophthalmoplegia	+	+	±	–	–	–	–	–	–
Ptosis		+	–	–	–	–	–	–	–
EYE									
Pigmentary retinopathy	**+**	–	–	–	–	–	**+**	±	–
Optic atrophy	–	–	–	–	–	–	±	±	
BLOOD									
Sideroblastic anemia	±	–	**+**	–	–	–	–	–	–
ENDOCRINE SYSTEM									
Diabetes mellitus	±	–	–	–	±	–	–	–	–
Short stature	+	–	–	+	+	–	–	–	–
Hypoparathyroidism	±	–	–	–	–	–	–	–	–
HEART									
Conduction disorder	**+**	**–**	–	–	±	–	–	–	±
Cardiomyopathy	±	–	–	–	±	**+**	–	±	–
GASTROINTESTINAL SYSTEM									
Exocrine pancreatic dysfunction	±	–	**+**	–	–	–	–	–	–
Intestinal pseudoobstruction	–	–	–	–	+	–	–	–	–
EAR, NOSE, AND THROAT									
Sensorineural hearing loss	±	–	–	+	+	**+**	±	–	–
KIDNEY									
Fanconi syndrome		–	**±**	–	**±**	–	–	–	–
LABORATORY FINDINGS									
Lactic acidosis	+	±	+	+	+	±	±	±	–
Ragged-red fibers on muscle biopsy	+	+	±	+	+	–	–	–	–
MODE OF INHERITANCE									
Maternal	–	–	–	+	+	–	+	+	+
Sporadic	+	+	+	–	–	–	–	–	–

*Characteristic constellations of symptoms and signs are bolded.

+, Presence of a symptom, sign, or finding; –, absence of a symptom, sign, or finding; ±, possible presence of a symptom, sign, or finding; AID, aminoglycoside-induced deafness; KSS, Kearns-Sayre syndrome; LHON, Leber's hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged-red fibers; MILS, maternally inherited Leigh syndrome; mtDNA, mitochondrial DNA; NARP, neuropathy, ataxia, and retinitis pigmentosa; PEO, progressive external ophthalmoplegia; PS, Pearson syndrome.

From DiMauro S, Schon EA: Mitochondrial respiratory-chain diseases, N Engl J Med *348:2656–2668, 2003. Copyright 2003 Massachusetts Medical Society. All rights reserved.*

electron microscopy can detect ragged red fibers and other abnormalities typical of mitochondrial myopathies. Analysis of oxidative phosphorylation complexes I-IV from intact mitochondria isolated from fresh skeletal muscle is the most sensitive assay for mitochondrial disorders; however, electron transport chain testing of flash-frozen muscle provides an alternative approach when fresh muscle testing is not available. Next-generation sequencing of mitochondrial DNA and panels of nuclear genes provides a noninvasive alternative to diagnosis, albeit with lower sensitivity. Specific criteria may assist in making a diagnosis (Table 87-3). Table 87-4 lists clues to the diagnosis of mitochondrial diseases.

Treatment remains largely symptomatic and does not significantly alter the outcome of disease. Some patients appear to respond to cofactor supplements, typically coenzyme Q_{10} ± L-carnitine at pharmacologic doses. The addition of creatine monohydrate and α-lipoic acid supplementation may add a significant benefit.

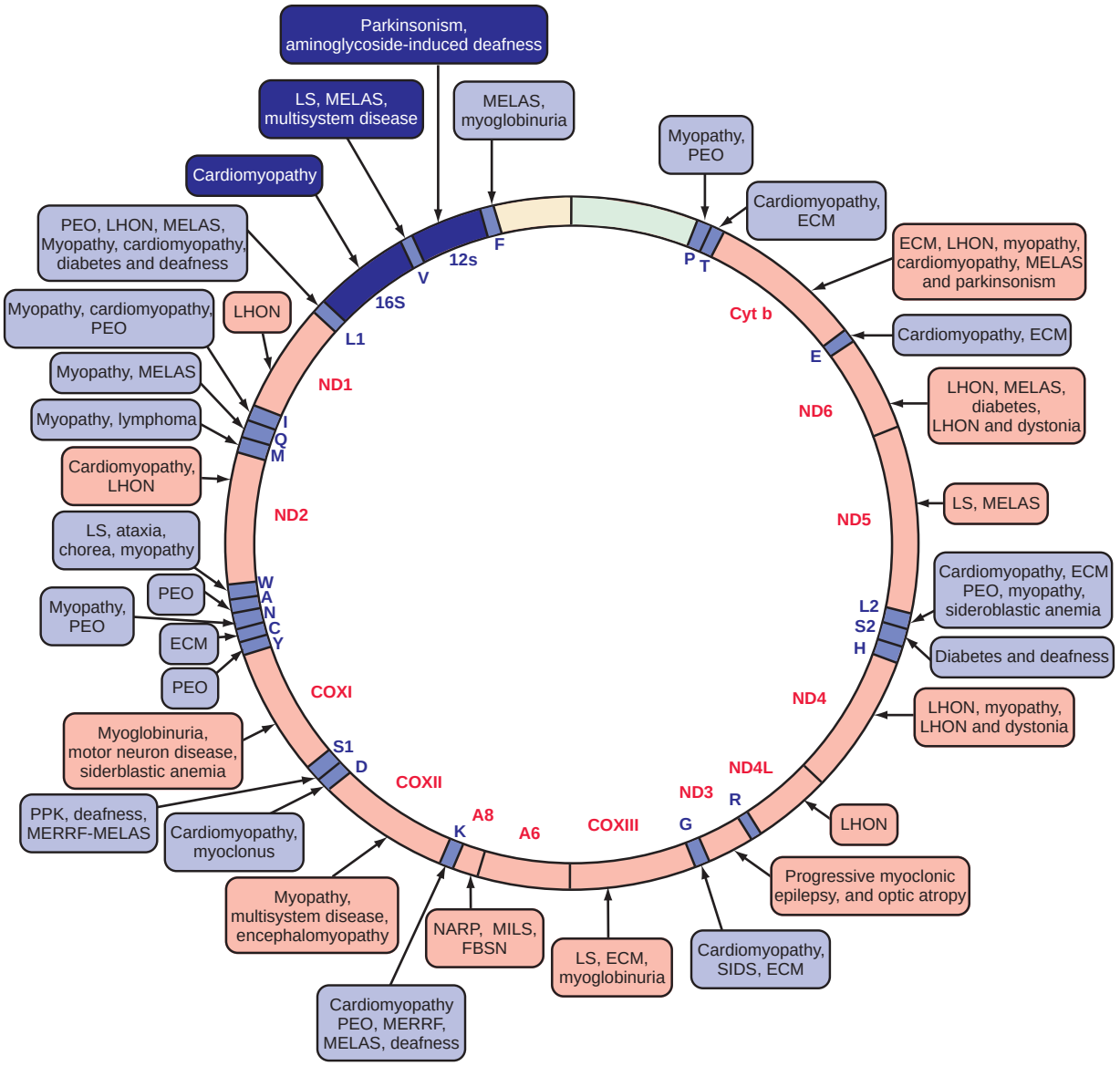

Figure 87-6 **Mutations in the human mitochondrial genome that are known to cause disease.** Disorders that are frequently or prominently associated with mutations in a particular gene are shown in *bold*. Diseases caused by mutations that impair mitochondrial protein synthesis are shown in *blue*. Diseases caused by mutations in protein-coding genes are shown in *red*. *ECM*, encephalomyopathy; *FBSN*, familial bilateral striatal necrosis; *LHON*, Leber hereditary optic neuropathy; *LS*, Leigh syndrome; *MELAS*, mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; *MERRF*, myoclonic epilepsy with ragged-red fibers; *MILS*, maternally inherited Leigh syndrome; *NARP*, neuropathy, ataxia, and retinitis pigmentosa; *PEO*, progressive external ophthalmoplegia; *PPK*, palmoplantar keratoderma; *SIDS*, sudden infant death syndrome. *(From DiMauro S, Schon EA: Mitochondrial respiratory-chain diseases,* N Engl J Med *348:2656–2668, 2003. Copyright 2003 Massachusetts Medical Society. All rights reserved.)*

Leigh Disease (Subacute Necrotizing Encephalomyelopathy)

Leigh disease is a heterogenous neurologic disease that remains a neuropathologic description characterized by demyelination, gliosis, necrosis, relative neuronal sparing, and capillary proliferation in specific brain regions. In decreasing order of severity, the affected areas are the basal ganglia, brainstem cerebellum, and cerebral cortex (see Chapter 598). The classic presentation is of an infant who presents with central hypotonia, developmental regression or arrest, and signs of brainstem or basal ganglia involvement. The clinical presentation is highly variable. Diagnosis is usually confirmed by radiologic or pathologic evidence of symmetric lesions affecting the basal ganglia, brainstem, and subthalamic nuclei. Patients with Leigh disease have defects in several enzyme complexes. Dysfunction in cytochrome C oxidase (complex IV) is the most commonly reported defect, followed by NADH-coenzyme Q reductase (complex I), PDHC, and pyruvate carboxylase. Mutations in the nuclear *SURF1* gene, which encodes a factor involved in the biogenesis of cytochrome C oxidase and mitochondrial DNA mutations in the adenosine triphosphatase 6 coding region, are common molecular findings in patients with Leigh disease. Patients with Leigh disease frequently present with developmental delay, seizures, altered consciousness, failure to thrive, pericardial effusion, and dilated cardiomyopathy. The prognosis for Leigh syndrome is poor. In a study of 14 cases, there were 7 fatalities before the age of 1.5 yr.

Lactic acidosis, hypoglycemia, and encephalopathy have also been reported in patients with thiamine transporter deficiency and with pyridoxine-dependent epilepsy. Both disorders should improve by the provision of thiamine and pyridoxine, respectively.

Bibliography is available at Expert Consult.

Table 87-3 Modified Walker Criteria Applied to Children Referred for Evaluation of Mitochondrial Disease

	MAJOR CRITERIA	MINOR CRITERIA
Clinical	Clinically complete RC encephalomyopathy* or a mitochondrial cytopathy defined as fulfilling 3 criteria†	Symptoms compatible with an RC defect‡
Histology	>2% RRF in skeletal muscle	Smaller numbers of RRF, SSAM, or widespread electron microscopy abnormalities of mitochondria
Enzymology	Cytochrome c oxidase–negative fibers or residual activity of an RC complex <20% in a tissue; <30% in a cell line, or <30% in 2 or more tissues	Antibody-based demonstration of an RC defect or residual activity of an RC complex 20-30% in a tissue, 30-40% in a cell line, or 30-40% in 2 or more tissues
Functional	Fibroblast ATP synthesis rates >3 SD below mean	Fibroblast ATP synthesis rates 2-3 SD below mean, or fibroblasts unable to grow in galactose media
Molecular	Nuclear or mtDNA mutation of undisputed pathogenicity	Nuclear or mtDNA mutation of probable pathogenicity
Metabolic		One or more metabolic indicators of impaired metabolic function

*Leigh disease, Alpers disease, lethal infantile mitochondrial disease, Pearson syndrome, Kearns-Sayre syndrome, MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), MERRF (myoclonic epilepsy associated with ragged red fibers), NARP (neuropathy, ataxia and retinitis pigmentosa), MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), and LHON (Leber hereditary optic neuropathy).

†(1) Unexplained combination of multisystemic symptoms that is essentially pathognomonic for an RC disorder, (2) a progressive clinical course with episodes of exacerbation or a family history strongly indicative of an mtDNA mutation, and (3) other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing.

‡Added pediatric features: stillbirth associated with a paucity of intrauterine movement, neonatal death or collapse, movement disorder, severe failure to thrive, neonatal hypotonia, and neonatal hypertonia as minor clinical criteria.

ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; RC, respiratory chain; RRF, ragged red fibers; SSAM, subsarcolemmal accumulation of mitochondria.

From Scaglia F, Towbin JA, Craigen WJ, et al: Clinical spectrum, morbidity and mortality in 113 pediatric patients with mitochondrial disease, Pediatrics *114:925–931, 2004.*

Table 87-4 Clues to the Diagnosis of Mitochondrial Disease

NEUROLOGIC
Cerebral stroke-like lesions in a nonvascular pattern
Basal ganglia disease
Encephalopathy: recurrent or with low/moderate dosing of valproate
Neurodegeneration
Epilepsia partialis continua
Myoclonus
Ataxia
MRI findings consistent with Leigh disease
Characteristic MRS peaks
Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
Succinate peak at 2.4 ppm
CARDIOVASCULAR
Hypertrophic cardiomyopathy with rhythm disturbance
Unexplained heart block in a child
Cardiomyopathy with lactic acidosis (>5 mM)
Dilated cardiomyopathy with muscle weakness
Wolff-Parkinson-White arrhythmia
OPHTHALMOLOGIC
Retinal degeneration with signs of night blindness, color vision deficits, decreased visual acuity, or pigmentary retinopathy
Ophthalmoplegia/paresis
Fluctuating, dysconjugate eye movements
Ptosis
Sudden- or insidious-onset optic neuropathy/atrophy
GASTROENTEROLOGIC
Unexplained or valproate-induced liver failure
Severe dysmotility
Pseudoobstructive episodes
OTHER
A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis

From Haas RH, Parikh S, Falk MJ, et al: Mitochondrial disease: a practical approach for primary care physicians, Pediatrics *120:1326–1333, 2007, Table 1, p. 1327.*

87.5 Defects in Pentose Metabolism

Priya S. Kishnani and Yuan-Tsong Chen

Approximately 90% of glucose metabolism in the body is via the glycolytic pathway, with the remaining 10% via the hexose monophosphate pathway. The hexose monophosphate shunt leads to formation of pentoses, as well as providing NADH. One of the metabolites is ribose-5-phosphate, which is used in the biosynthesis of ribonucleotides and deoxyribonucleotides. Through the transketolase and transaldolase reactions, the pentose phosphates can be converted back to fructose-6-phosphate and glucose-6-phosphate.

ESSENTIAL PENTOSURIA

Essential pentosuria is a benign disorder encountered principally in Ashkenazi Jews and is an autosomal recessive trait. The urine contains L-xylulose, which is excreted in increased amounts because of a block in the conversion of L-xylulose to xylitol as a result of xylitol dehydrogenase deficiency. The condition is usually discovered accidentally in a urine test for reducing substances; no treatment is required.

Transaldolase Deficiency

Few patients have reported symptoms that include liver cirrhosis, hepatosplenomegaly, severe neonatal hepatopathy, and cardiomyopathy. Biochemical abnormalities revealed elevated levels of arabitol, ribitol, and erythritol in the urine. Most recently, erythronic acid has been identified by urine nuclear magnetic resonance spectroscopy as another hallmark metabolite. Enzyme assay in the lymphoblasts and fibroblasts demonstrated low transaldolase activity, which was confirmed by mutations in the transaldolase gene. In addition, measurement of transaldolase activity in fibroblasts, lymphoblasts, or liver tissue, as well as assessing urinary concentrations of polyols also can be used to confirm the diagnosis.

Ribose-5-Phosphate Isomerase Deficiency

Only 1 case of this disorder has been reported. The affected male had psychomotor delay from early in life and developed epilepsy at 4 yr of age. Thereafter, a slow neurologic regression developed, with prominent cerebellar ataxia, some spasticity, optic atrophy, and a mild sensorimotor neuropathy. MRI of the brain at ages 11 yr and 14 yr showed

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extensive abnormalities of the cerebral white matter. Proton magnetic resonance spectroscopy (MRS) of the brain revealed elevated levels of ribitol and D-arabitol. These pentitols were also increased in urine and plasma similar to the patient found in transaldolase deficiency. Enzyme assays in cultured fibroblasts showed deficient ribose-5-phosphate isomerase activity, which was confirmed by a molecular study. These results combined with a study of ribose-5-phosphate isomerase–deficient mice converged to demonstrate that the specific genetic pairing of a null allele with an allele coding for a form of the enzyme that is only partly active, allowing for cell-type-dependent expression deficits, is a contributing factor to the rarity of the disease. Ribose-5-phosphate isomerase deficiency may represent an example of a single-gene disease that appears seldom because of its complex molecular etiology.

Bibliography is available at Expert Consult.

87.6 Disorders of Glycoprotein Degradation and Structure

Margaret M. McGovern and Robert J. Desnick

The disorders of glycoprotein degradation and structure include several lysosomal storage diseases that result from defects in glycoprotein degradation, and the congenital disorders of glycosylation (CDGs), which are pathophysiologically unrelated. Glycoproteins are macromolecules that are composed of oligosaccharide chains linked to a peptide backbone. They are synthesized by 2 pathways: the glycosyltransferase pathway, which synthesizes oligosaccharides linked *O*-glycosidically to serine or threonine residues; and the dolichol, lipid-linked pathway, which synthesizes oligosaccharides linked *N*-glycosidically to asparagine.

The glycoprotein lysosomal storage diseases result from the deficiency of the enzymes that normally participate in the degradation of oligosaccharides and include sialidosis, galactosialidosis, aspartylglucosaminuria, and α-mannosidosis. In some instances, the underlying abnormality that leads to glycoprotein accumulation also results in abnormal degradation of other classes of macromolecules that contain similar oligosaccharide linkages, such as certain glycolipids and proteoglycans. In these instances, the underlying enzymatic deficiency results in the accumulation of both glycoproteins and glycolipids. The classification of these types of disorders as lipidoses or glycoproteinoses is dependent on the nature of the predominantly stored substance. In general, the glycoprotein disorders are characterized by autosomal recessive inheritance and a progressive disease course with clinical features that resemble those seen in the mucopolysaccharidoses.

SIALIDOSIS AND GALACTOSIALIDOSIS

Sialidosis is an autosomal recessive disorder that results from the primary deficiency of neuraminidase because of mutations in the gene that encodes this protein, which is located on chromosome 10. In contrast, galactosialidosis is caused by the deficiency of 2 lysosomal enzymes—neuraminidase and β-galactosidase. The loss of these enzymatic activities results from mutations in a gene located on chromosome 20 that encodes protective protein/cathepsin A, which functions to stabilize these enzymatic activities. Neuraminidase normally cleaves terminal sialyl linkages of several oligosaccharides and glycoproteins. Its deficiency results in the accumulation of oligosaccharides, and the urinary excretion of sialic acid terminal oligosaccharides and sialylglycopeptides. Examination of tissues from affected individuals reveals pathologic storage of substrate in many tissues including liver, bone marrow, and brain.

The clinical phenotype associated with neuraminidase deficiency is variable and includes type I sialidosis which usually presents in the 2nd decade of life with myoclonus and the presence of a cherry-red spot. These patients typically come to attention secondary to gait disturbances, myoclonus, or visual complaints. In contrast, type II sialidosis occurs as congenital, infantile, and juvenile forms. The congenital and infantile forms result from isolated neuraminidase deficiency, whereas the juvenile form results from both neuraminidase and β-galactosidase deficiency. The congenital type II disease is characterized by hydrops fetalis, neonatal ascites, hepatosplenomegaly, stippling of the epiphyses, periosteal cloaking, and stillbirth or death in infancy. The type II infantile form presents in the 1st yr of life with dysostosis multiplex, moderate intellectual disability, visceromegaly, corneal clouding, cherry red spot, and seizures. The juvenile type II form of sialidosis, which is sometimes designated *galactosialidosis,* has a variable age of onset ranging from infancy to adulthood. In infancy, the phenotype is similar to that of GM_1 gangliosidosis, with edema, ascites, skeletal dysplasia, and cherry-red spot. Patients with later-onset disease have dysostosis multiplex, visceromegaly, mental retardation, dysmorphism, corneal clouding, progressive neurologic deterioration, and bilateral cherry red spots. No specific therapy exists for any form of the disease, although studies in animal models have demonstrated improvement in the phenotype after bone marrow transplantation. The diagnosis of sialidosis and galactosialidosis is achieved by the demonstration of the specific enzymatic deficiency. Prenatal diagnosis using cultured amniotic cells is also possible.

ASPARTYLGLUCOSAMINURIA

This is a rare autosomal recessive lysosomal storage disorder, except in Finland, where the carrier frequency is estimated at 1 in 36 adults. The disorder results from the deficient activity of aspartylglycosaminidase and the subsequent accumulation of aspartylglycosamine, particularly in the liver, spleen, and thyroid. The gene for the enzyme has been localized to the long arm of chromosome 4 and the complementary DNA has been cloned and sequenced. In the Finnish population, a single mutation in the gene *(C163S)* accounts for most mutant alleles, whereas outside of Finland, a large number of private mutations have been described. Affected individuals with aspartylglucosaminuria typically present in the 1st yr of life with recurrent infections, diarrhea, and hernias. Coarsening of the facies and short stature usually develop later. Other features include joint laxity, macroglossia, hoarse voice, crystal-like lens opacities, hypotonia, and spasticity. Psychomotor development is usually near normal until the age of 5 yr when a decline is noted. Behavioral abnormalities are typical and IQ values in affected adults are usually <40. Survival to adulthood is common, with most early deaths attributable to pneumonia or other pulmonary causes. Definitive diagnosis requires measurement of the enzyme in peripheral blood leukocytes. Molecular diagnosis by analysis of DNA for the C163S mutation is possible for Finnish patients. Several patients have undergone allogeneic bone marrow transplants with some reports of stabilization of the neurologic phenotype, but this approach has not been proven effective and no specific treatment is available. Prenatal diagnosis by the determination of the level of aspartylglycosaminidase in cultured amniocytes or chorionic villi has been reported.

α-MANNOSIDOSIS

This autosomal recessive disorder results from the deficient activity of α-mannosidase and the accumulation of mannose-rich compounds. The gene encoding the enzyme has been localized to chromosome 19p13.2-q12, although the complementary DNA has not been cloned. Affected patients with this disorder display clinical heterogeneity. There is a severe infantile form, or type I disease, and a milder juvenile variant, type II disease. All patients have psychomotor retardation, facial coarsening, and dysostosis multiplex. The infantile form of the disorder, however, is characterized by more rapid cognitive deterioration, with death occurring between the ages of 3 and 10 yr. Patients with the infantile form also have more severe skeletal involvement and hepatosplenomegaly. The juvenile disorder is characterized by onset of symptoms in early childhood or adolescence with milder somatic features and survival to adulthood. Hearing loss, destructive synovitis, pancytopenia, and spastic paraplegia have been reported in type II patients. No specific therapy exists for the disorder. The diagnosis is made by the demonstration of the deficiency of α-mannosidase activity in white blood cells or cultured fibroblasts, and prenatal diagnosis has also been achieved.

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Table 87-5 Congenital Disorders of Glycosylation: Disorders According to the New Nomenclature

	CLINICAL FEATURES	DIAGNOSTIC APPROACH
DEFECTS OF PROTEIN *N*-GLYCOSYLATION		
PMM2-CDG (CDG-Ia) MPI-CDG (CDG-Ib) ALG6-CDG (CDG-Ic) ALG3-CDG (CDG-Id) ALG12-CDG (CDG-Ig) ALG8-CDG (CDG-Ih) ALG2-CDG (CDG-Ii) DPAGT1-CDG (CDG-Ij) ALG1-CDG (CDG-Ik) ALG9-CDG (CDG-Il) RFT1-CDG (CDG-In) ALG11-CDG (CDG-Ip) TUSC3-CDG MAGT1-CDG MGAT2-CDG (CDG-IIa) GCS1-CDG (CDG-IIb)	Dysmorphic facial features, abnormal lipid distribution, strabismus, protein-losing enteropathy, frequent vomiting, failure to thrive, short stature, cardiomyopathy, pericardial fluid collection, proteinuria, hepatomegaly, liver cirrhosis, hypotonia, ataxia, speech delay, mental retardation, seizures, cataract, retinitis pigmentosa, visual loss, peripheral neuropathy, hypothyreosis, thrombosis, bleeding anomalies, osteoporosis, recurrent infections, thrombocytopenia	Screening by TIEF, confirming type I or type II pattern. In type I, measurement of PMM and PMI enzyme activity in leukocytes or fibroblasts. In case of normal results of PMM/PMI, lipid-linked oligosaccharides analysis in fibroblasts. In type II, mass spectrometry of isolated serum N-glycans or serum apoC-III isoelectrophoresis. Based on the findings, choose appropriate genetic testing. Normal TIEF results* necessitate direct mutation analysis
DEFECTS OF PROTEIN *O*-GLYCOSYLATION		
EXT1/EXT2-CDG B4GALT7-CDG GALNT3-CDG SLC35D1-CDG POMT1/POMT2-CDG POMGNT1-CDG SCDO3-CDG B3GALTL-CDG	Multiple exostosis; short stature/joint laxity/progeria; familial tumoral calcinosis; skeletal dysplasia; muscle dystrophy; brain developmental defect; spondylocostal dysostosis; congenital eye anomalies/cataract	Syndromic presentation and organ-specific expression of the disease necessitates a genetic approach; upon suspicion perform direct mutation analysis
DEFECTS OF GLYCOSPHINGOLIPID AND GPI-ANCHOR GLYCOSYLATION		
SIAT9-CDG PIGM-CDG PIGV-CDG	Epilepsy; hepatomegaly/portal vein thrombosis; hyperphosphatasia, mental retardation	Mutation analysis. Expression analysis of glycosylphosphatidylinositol-linked proteins (e.g., CD59 or CD24) on hematopoietic cells
DEFECTS OF MULTIPLE GLYCOSYLATION AND OTHER PATHWAYS		
DPM1-CDG (CDG-Ie) DPM3-CDG (CDG-Io) MPDU1-CDG (CDG-If) GNE-CDG B4GALT1-CDG (CDG-IId) SLC35A1-CDG (CDG-IIf) SLC35C1-CDG (CDG-IIc) DK1-CDG (CDG-Im) SRD5A3-CDG (CDG-Iq) COG-CDG (COG1, COG4, COG5, COG6, COG7, COG 8) ATP6VOA2-CDG SEC23B-CDG	Dysmorphic facial features, strabismus; cardiomyopathy, muscle dystrophy; hepatomegaly; recurrent infections; thrombosis/bleeding anomalies; hypotonia, mental retardation, seizures; cardiomyopathy; ichthyosis, ataxia, visual loss; skeletal dysplasia; hyperthermia, adducted thumbs; failure to thrive; cutis laxa; HEMPAS	Screening by TIEF, confirming type I or type II pattern. In type II pattern, additional apo-C III isoelectric focusing. In patients with normal TIEF, if there is a syndromic presentation upon suspicion perform direct mutation analysis. In patients with muscle dystrophy perform dystroglycan staining in muscle biopsy, in a syndromic presentation upon suspicion direct mutation analysis

Previous congenital disorders of glycosylation nomenclature are in parentheses.

*Normal TIEF results can be due to young age or also in GCS1-CDG, SLC35C1-CDG and SLC35A1-CDG.

Apo, apolipoprotein; GPI, glycophosphatidylinositol; HEMPAS, hereditary erythroblastic multinuclearity with a positive acidified serum; PMI, phosphomannoisomerase; PMM, phosphomannomutase; TIEF, transferrin isoelectric focusing.

From Theodore M, Morava E: Congenital disorders of glycosylation: sweet news. Curr Opin Pediatr *23(6):581–587, 2011.*

CONGENITAL DISORDERS OF GLYCOSYLATION

These are a heterogenous group of autosomal recessive disorders that result from defective protein and lipid glycosylation. The protein glycosylation disorders result from defects of *N*-glycosylation, combined *N*- and *O*-glycosylation, the dolichol pathway and the conserved oligomeric Golgi complex. The more recently discovered lipid-glycosylation disorders include defects of ganglioside synthesis (GM_3 synthase deficiency) and the glycophosphatidylinositol anchor system. In addition, there are patients with glycosylation defects for which the molecular and biochemical bases are not yet known.

To date, more than 30 CDG subtypes have been identified (Table 87-5). In general, most CDG disorders are multisystemic and present with variable involvement of the central nervous system (most often hypotonia and ataxia), abnormal fat distribution, ocular movement defects, coagulation abnormalities, gastrointestinal symptoms including protein-losing enteropathy, retinitis pigmentosa, hormonal abnormalities, and, in some cases, dysmorphic features. CDG type Ia, which results from mutations in the gene that encodes phosphomannomutase, is the most common form. The most consistent clinical features of this disorder include variable degrees of psychomotor retardation, subcutaneous fat pads and inverted nipples. Frequent neurologic findings in infancy include cerebellar atrophy (Fig. 87-7), hypotonia, weakness, hyperreflexia, and strokelike episodes (Table 87-6).

In childhood, ataxia, muscle atrophy, decreased deep tendon reflexes, toe walking, and continued stroke-like episodes are observed. The latter events may be related to coagulopathies characterized by reduced antithrombin III and proteins C and S, in conjunction with abnormal levels of factors VIII, IX, XI, and XIII, which together increase risk for bleeding and thrombosis. Growth failure, liver dysfunction, retinal

Table 87-6 Characteristics of Representative Congenital Disorders of Glycosylation

NAME	DEFECT	DYSMORPHOLOGY	NEUROLOGIC SIGNS	GASTROINTESTINAL SIGNS	OTHER SIGNS
CDG-Ia	Phosphomannomutase 2	Fat maldistribution: narrow waist, fat in axilla, groin, buttock High nasal bridge Prominent jaw Large ears Inverted nipples	Hypotonia Hyporeflexia Strabismus Ataxia: olivopontocerebellar atrophy or hypoplasia Mental retardation (IQ 40-60) Stroke-like episodes Hemorrhagic cerebral infarcts Polyneuropathy Muscle wasting Scoliosis Spinal stenosis Kyphosis Pigmentary retinal degeneration Contractures Seizures	Poor feeding, failure to thrive Carnitine deficiency Diarrhea Liver failure	Cardiomyopathy Pericardial effusions Nephrotic syndrome Renal tubulopathy Severe infections Hypogonadism Absent puberty TBG deficiency ↓ Levels of: antithrombin III, α_1-acid glycoprotein, α_1-antitrypsin, ferritin, ceruloplasmin, proteins C + S, factor XI, complement C1, C3a, C4a
CDG-Ib	Phosphomannose isomerase	None	Normal development	Protein-losing enteropathy Failure to thrive Chronic intractable diarrhea Hepatic fibrosis Hyperinsulinemic hypoglycemia Vomiting	Coagulopathy ↓ Proteins C, S, antithrombin III
CDG-Ic	Glucosyltransferase	None	Similar to CDG-Ia but milder Mild cerebellar hypoplasia Seizures		Frequent infections Coagulopathy Failure to thrive Recurrent eyelid edema Pigmentary retinal degeneration
CDGId	Mannosyltransferase	High-arched palate	Microcephaly Seizures (severe) Developmental delay CNS atrophy	Failure to thrive	Coagulopathy
CDG-Ie	Dolichol-phosphate-mannose synthetase Failure to thrive	High-arched palate Down-slanting palpebral fissures Hemangiomas Short arms Small hands Dysplastic nails	Microcephaly Hypotonia Developmental delay Seizures (severe) Cortical blindness Hyperreflexia Delayed myelination	Failure to thrive	↑ CPK
CDG-IIa	*N*-acetyl-glucosaminyl-transferase II	Facial dysmorphology	Stereotypic hand movements Seizures Developmental delay No neuropathy or cerebellar hypoplasia	Failure to thrive	Coagulopathy
CDG-IIb	Glucosidase I	Facial dysmorphology	Hypotonia Retardation Seizures	Hepatomegaly	Coagulopathy
CDG-IIc	GDP-fucose transporter I	Facial dysmorphology	Developmental delay Hypotonia	Failure to thrive	Recurrent infections with leukocytosis
CDG-x or CDG-Ix	Unknown	Like CDG-Ia Microcephaly	Hypotonia Seizures Cerebellar hypoplasia Developmental delay	Intractable diarrhea Failure to thrive	Nonimmune hydrops Cataracts Thrombocytopenia Renal tubulopathy Distal bone demineralization
CDG-Ih	Glucosyltransferase 2	Facial dysmorphology	Seizures Hypotonia Developmental delay	Chronic diarrhea Protein-losing enteropathy Chronic liver disease	Coagulopathy Renal microcysts Nephrotic syndrome
CDG-X variant	Unknown	None	None	Asymptomatic cryptogenic Chronic liver disease	Coagulopathy

Table 87-6 Characteristics of Representative Congenital Disorders of Glycosylation—cont'd

NAME	DEFECT	DYSMORPHOLOGY	NEUROLOGIC SIGNS	GASTROINTESTINAL SIGNS	OTHER SIGNS
CDG-IIX	Unknown	None	Developmental delay Hypotonia Cerebral atrophy	Chronic diarrhea Liver cirrhosis	Recurrent infections
CDG-XIV	Phosphoglucomutase 1 (previously a glycogenosis)	Bifid uvula	Muscle weakness Rhabdomyolysis	Hepatomegaly Elevated liver enzymes	Dilated cardiomyopathy Malignant hyperthermia Growth retardation Hypoglycemia May respond to galactose supplementation

CDG, congenital disorders of glycosylation; CNS, central nervous system; CPK, creatine phosphokinase; GDP, guanosine diphosphate; TBG, thyroid-binding globulin.

Figure 87-7 Sagittal T2-weighted MR image shows severe spinal cord compression with myelopathy *(white arrow)*, together with cerebellar atrophy *(black arrow)*, and cortical atrophy of the parietal lobe *(red arrow)*. *(From Schade van Westrum SM, Nederkoorn PJ, Schuurman PR, et al: Skeletal dysplasia and myelopathy in congenital disorder of glycosylation type 1A,* J Pediatr *148:115–117, 2006, Fig. 1.)*

degeneration, and skeletal abnormalities have also been described. The skeletal features can include contractures, kyphoscoliosis, and pectus carinatum, all of which may be secondary to the neurologic effects of the disorder. Pericardial effusion in older patients and hypertrophic obstructive cardiomyopathy in the infant also may occur.

Among the other types, few have distinctive phenotypes. These include CDG-Ib, which is characterized by protein-losing enteropathy and normal neurologic function; CDG-If, which includes ichthyosis and growth retardation; and CDG-IIf, in which macrothrombocytopenia is present.

Diagnostic testing for CDG types that result from defects of *N*-glycosylation begins with isoelectric focusing of *N*-glycosylated serum transferring. For some types further confirmation of the diagnosis by enzymatic analysis in fibroblasts or leukocytes and/or mutation analysis of the relevant gene is available. Although prenatal diagnosis by analysis of transferrin has been attempted, it has not proven reliable. Treatment of these disorders is symptomatic, except for CDG-Ib, which responds to oral mannose (100-150 mg/kg/day every 4-6 hr).

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Chapter 88

Mucopolysaccharidoses

Jürgen W. Spranger

Mucopolysaccharidoses are hereditary, progressive diseases caused by mutations of genes coding for lysosomal enzymes needed to degrade glycosaminoglycans (acid mucopolysaccharides). Glycosaminoglycans (GAGs) are long-chain complex carbohydrates composed of uronic acids, amino sugars, and neutral sugars. The major GAGs are chondroitin-4-sulfate, chondroitin-6-sulfate, heparan sulfate, dermatan sulfate, keratan sulfate, and hyaluronan. These substances are synthesized and, with the exception of hyaluronan, linked to proteins to form proteoglycans, major constituents of the ground substance of connective tissue, of nuclear and cell membranes. Degradation of proteoglycans starts with the proteolytic removal of the protein core followed by the stepwise degradation of the glycosaminoglycan moiety. Failure of this degradation because of absent or grossly reduced activity of mutated lysosomal enzymes results in the intralysosomal accumulation of glycosaminoglycan fragments (Fig. 88-1). Distended lysosomes accumulate in the cell, interfere with cell function and lead to characteristic pattern of clinical, radiologic, and biochemical abnormalities (Table 88-1, Fig. 88-2). Within this pattern, specific diseases can be recognized which evolve from the intracellular accumulation of different degradation products (Table 88-2). As a general rule, the impaired degradation of heparan sulfate is more closely associated with intellectual disability, and the impaired degradation of dermatan sulfate, chondroitin sulfates, and keratan sulfate with mesenchymal abnormalities. Variable expression within a given entity results from allelic mutations and varying residual activity of mutated enzymes. For instance, allelic mutations of the gene encoding L-iduronidase may result in severe Hurler disease with early death or in mild Scheie disease manifesting only with limited joint mobility, mild skeletal abnormalities and corneal opacities. Mucopolysaccharidoses are autosomal recessive disorders with the exception of Hunter disease, which is X-linked recessive. Their overall frequency is between 3.5 in 100,000 births and 4.5 in 100,000 births. The most common subtype is MPS-III, followed by MPS-I and MPS-II.

CLINICAL ENTITIES

Mucopolysaccharidosis I

Mucopolysaccharidosis (MPS)-I is caused by mutations of the *IDUA* gene on chromosome 4p16.3 encoding α-L-iduronidase. Mutation analysis has revealed 2 major alleles, W402X and Q70X, account for more than half the MPS-I alleles in the white population. The

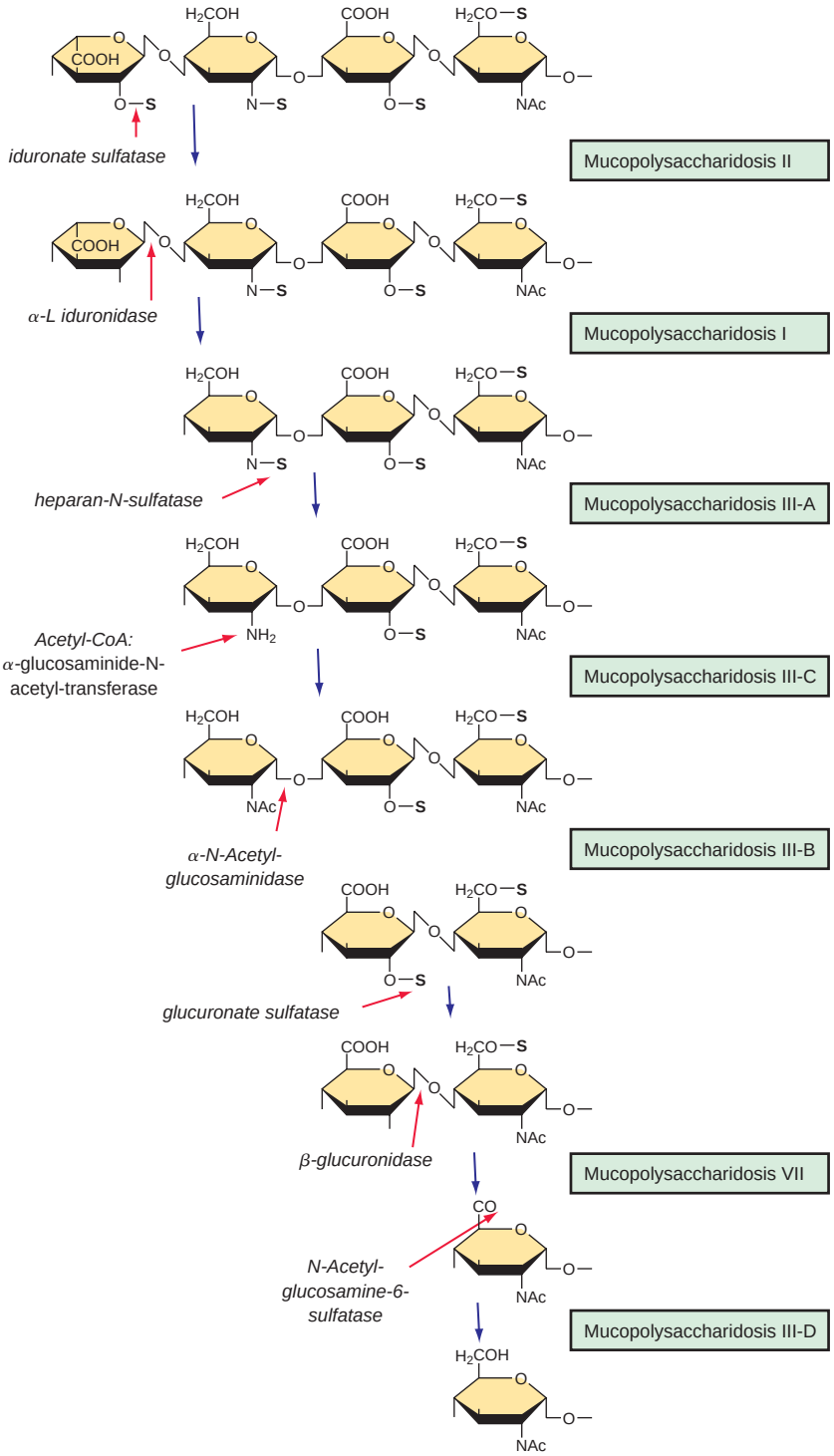

Figure 88-1 Degradation of heparan sulfate and mucopolysaccharidoses resulting from the deficiency of individual enzymes. Some of these enzymes are also involved in the degradation of other glycosaminoglycans (not shown).

mutations introduce stop codons with ensuing absence of functional enzyme (null alleles) and in homozygosity or compound heterozygosity give rise to Hurler disease. Other mutations occur in only 1 or a few individuals.

Deficiency of α-L-iduronidase results in a wide range of clinical involvement from severe Hurler disease to mild Scheie disease, which are ends of a broad clinical spectrum. Homozygous nonsense mutations result in severe forms of MPS-I, whereas missense mutations are more likely to preserve some residual enzyme activity associated with a milder form of the disease.

Hurler Disease

This form of MPS-I (MPS-IH) is a severe, progressive disorder with multiple organ and tissue involvement that results in premature death, usually by 10 yr of age. An infant with Hurler syndrome appears normal at birth, but inguinal herniae are often present. Diagnosis is usually made between 6 and 24 mo with evidence of hepatosplenomegaly, coarse facial features, corneal clouding, large tongue, prominent forehead, joint stiffness, short stature, and skeletal dysplasia. Acute cardiomyopathy has been found in some infants younger than 1 yr of age. Most patients have recurrent upper respiratory tract and

ear infections, noisy breathing, and persistent copious nasal discharge. Valvular heart disease with incompetence notably of the mitral and aortic valves regularly develops and narrowing of the coronary arteries occurs. Obstructive airway disease, notably during sleep, may necessitate tracheotomy. Obstructive airway disease, respiratory infection, and cardiac complications are the common causes of death.

Most children with Hurler syndrome acquire only limited language skills because of developmental delay, combined conductive and neurosensory hearing loss, and an enlarged tongue. Progressive ventricular enlargement with increased intracranial pressure caused by communicating hydrocephalus also occurs. Corneal clouding, glaucoma, and retinal degeneration are common. Radiographs show a characteristic skeletal dysplasia known as dysostosis multiplex (Figs. 88-3 and 88-4). The earliest radiographic signs are thick ribs and ovoid vertebral bodies. Skeletal abnormalities in addition to those shown in the figures include enlarged, coarsely trabeculated diaphyses of the long bones with irregular metaphyses and epiphyses. With progression of the disease macrocephaly develops with thickened calvarium, premature closure of lambdoid and sagittal sutures, shallow orbits, enlarged J-shaped sella, and abnormal spacing of teeth with dentigerous cyst.

Table 88-1 Recognition Pattern of Mucopolysaccharidoses

	Mucopolysaccharidosis Type						
MANIFESTATIONS	**I-H**	**I-S**	**II**	**III**	**IV**	**VI**	**VII**
Mental deficiency	+	–	±	+	–	–	±
Coarse facial features	+	(+)	+	+	–	+	±
Corneal clouding	+	+	–	–	(+)	+	±
Visceromegaly	+	(+)	+	(+)	–	+	+
Short stature	+	(+)	+	–	+	+	+
Joint contractures	+	+	+	–	–	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	–	+	+
Mucopolysacchariduria	+	+	+	+	+	+	+

I-H, Hurler disease; I-S, Scheie disease; II Hunter disease; III, Sanfilippo disease; IV, Morquio disease; VI, Maroteaux-Lamy disease; VII Sly disease.

Hurler-Scheie Disease

The clinical phenotype of MPS-IH/S is intermediate between Hurler and Scheie diseases and is characterized by progressive somatic involvement, including dysostosis multiplex with little or no intellectual dysfunction. The onset of symptoms is usually observed between 3 and 8 yr of age; survival to adulthood is common. Cardiac involvement and upper airway obstruction contribute to clinical morbidity. Some patients have spondylolisthesis, which may cause cord compression.

Scheie Disease

MPS-IS is a comparatively mild disorder characterized by joint stiffness, aortic valve disease, corneal clouding, and mild dysostosis multiplex. Onset of significant symptoms is usually after the age of 5 yr, with diagnosis made between 10 and 20 yr of age. Patients with Scheie disease have normal intelligence and stature but have significant joint and ocular involvement. A carpal tunnel syndrome often develops. Ophthalmic features include corneal clouding, glaucoma, and retinal degeneration. Obstructive airway disease, causing sleep apnea, develops in some patients, necessitating tracheotomy. Aortic valve disease is common and has required valve replacement in some patients.

Mucopolysaccharidosis II

Hunter disease, (MPS-II) is an X-linked disorder caused by the deficiency of iduronate 2-sulfatase (IDS). The gene encoding IDS is mapped to Xq28. Point mutations of the *IDS* gene have been detected in approximately 80% of patients with MPS-II. Major deletions or rearrangements of the *IDS* gene have been found in the rest, and these are usually associated with a more severe clinical phenotype. As an X-linked recessive disorder, Hunter disease manifests almost exclusively in males. However, it has been observed in females and this is

Figure 88-2 **Patients with various types of mucopolysaccharidoses.** MPS-I: Hurler disease, patient age 3 yr; MPS-II: Hunter disease, patient age 12 yr; MPS-III: Sanfilippo disease, patient age 4 yr; MPS-IV: Morquio disease, patient age 10 yr; MPS-VI: Maroteaux-Lamy disease, patient age 15 yr.

Table 88-2 Mucopolysaccharidoses: Clinical, Molecular, and Biochemical Aspects

MPS TYPE	EPONYM	INHERITANCE	GENE CHROMOSOME	MAIN CLINICAL FEATURES	DEFECTIVE ENZYME	ASSAY	MIM NUMBER
I-H	Pfaundler-Hurler	AR	*IDUA* 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr, Hurler phenotype, mental retardation, corneal clouding, death usually before age 14 yr	α-L-iduronidase	L,F,Ac,CV	252800 607014
I-S	Scheie	AR	*IDUA* 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α-L-iduronidase	L,F,Ac,CV	607016
I-HS	Hurler-Scheie	AR	*IDUA* 4p16.4	Phenotype intermediate between I-H and I-S	α-L-iduronidase	L,F,Ac,Cv	607015
II	Hunter	XLR	*IDS* Xq27.3-28	Severe course similar to I-H but clear corneae. Mild course: less pronounced features, later manifestation, survival to adulthood with mild or without mental deficiency	Iduronate sulfate sulfatase	S,F,Af,Ac,Cv	309900
III-A	Sanfilippo A	AR	*SGSH* 17q25.3	Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas; survival to adulthood possible	Heparan-S-sulfamidase	L,F,Ac,Cv	252900 605270
II-IB	Sanfilippo B	AR	*NAGLU* 17q21		*N*-Acetyl-α-D-glucosaminidase	S,F,Ac,Cv	252920
III-C	Sanfilippo C	AR	*HGSNAT* 8p11.21		Acetyl-CoA:α-glucosaminide *N*-acetyltransferase	F,Ac	252930
III-D	Sanfilippo D	AR	*GNS* 12q14		*N*-Acetylglucosamine-6-sulfatase	F,Ac	252940 607664
IV-A	Morquio A	AR	*GALNS* 16q24.3	Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height below 125 cm	*N*-Acetyl-galactosamine-6-sulfatase	L,F,Ac	253000
IV-B	Morquio B	AR	*GLB1* 3p21.33	Same as IV-A, but milder; adult height over 120 cm	β-Galactosidase	L,F,Ac,Cv	253010 230500
VI	Maroteaux-Lamy	AR	*ARSB* 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate and severe expression in different families	*N*-Acetyl-galactosamine-4-sulfatase (arylsulfatase B)	L,F,Ac	253200
VII	Sly	AR	*GUSB* 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	β-Glucuronidase	S,F,Ac,Cv	253220
IX	Hyaluronidase deficiency	AR	*HYAL1* 3p21.3	Periarticular masses, no Hurler phenotype H	Hyaluronidase 1	S	601492

Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villi; F, cultured fibroblasts; L, leukocytes; MIM, Mendelian Inheritance in Man Catalogue; S, serum.

explained by skewed inactivation of the X-chromosome carrying the normal gene.

Marked molecular heterogeneity explains the wide clinical spectrum of Hunter disease. Patients with severe MPS-II have features similar to those of Hurler disease except for the lack of corneal clouding and the somewhat slower progression of somatic and central nervous system (CNS) deterioration. Coarse facial features, short stature, dysostosis multiplex, joint stiffness, and intellectual disability manifest between 2 and 4 yr of age. Grouped skin papules are present in some patients. Extensive mongolian spots present at birth have been observed in African and Asian patients and may be an early marker of the disease. Gastrointestinal storage may produce chronic diarrhea. Communicating hydrocephalus and spastic paraplegia may develop due to thickened meninges. In severely affected patients, extensive, slowly progressive neurologic involvement precedes death, which usually occurs between 10 and 15 yr of age.

Patients with the mild form can have a near-normal or normal life span, minimal CNS involvement and slow progression of somatic deterioration with preservation of cognitive function in adult life. Survival to ages 65 and 87 yr has been reported and some patients have had children. Somatic features are Hurler-like but milder with a greatly reduced rate of progression. Adult height may exceed 150 cm. Airway involvement, valvular cardiac disease, hearing impairment, carpal tunnel syndrome, and joint stiffness are common and can result in significant loss of function in both the mild and severe forms.

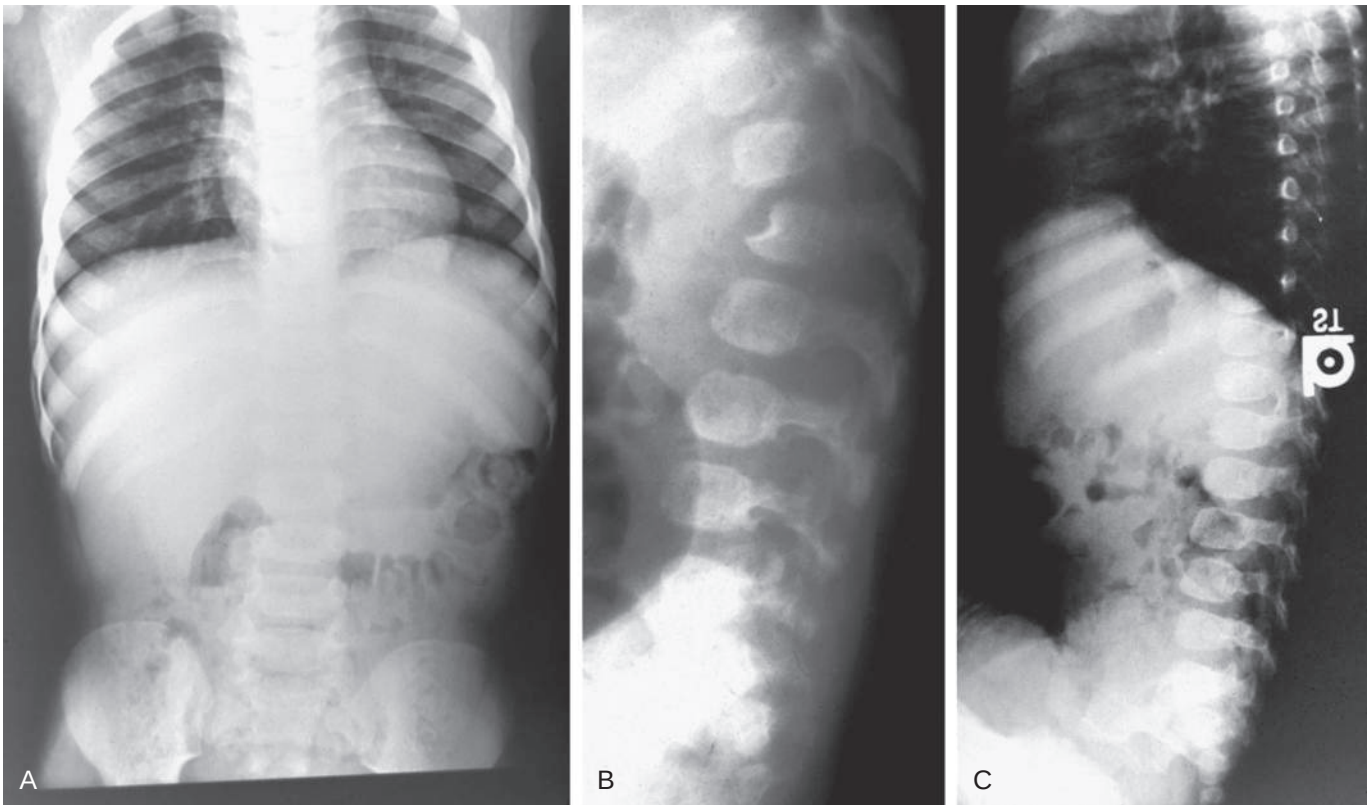

Figure 88-3 Dysostosis multiplex. **A,** Sanfilippo disease, patient age 4 yr: The ribs are wide. **B,** Sanfilippo disease, patient age 4 yr: immature, ovoid configuration of the vertebral bodies. **C,** Hurler disease, patient age 18 mo: anterosuperior hypoplasia of L-1 resulting in hook-shaped appearance.

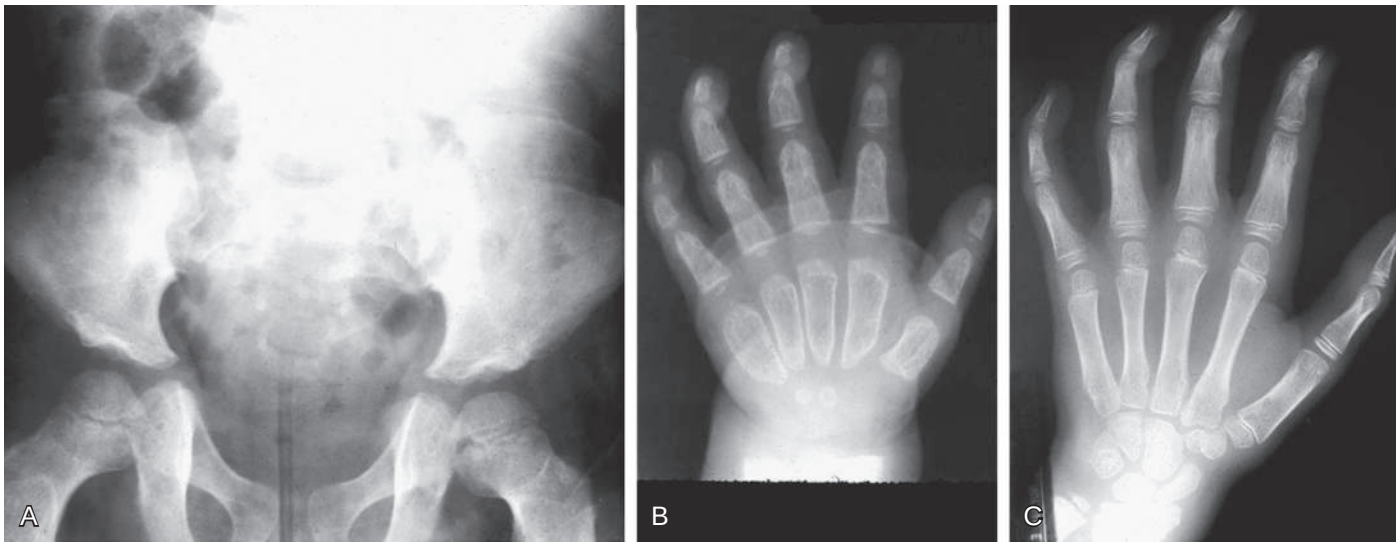

Figure 88-4 Dysostosis multiplex. **A,** MPS-IH, patient age 10 yr. The inferior portions of the ilia are hypoplastic with resulting iliac flare and shallow acetabular fossae. The femoral necks are in valgus position. **B,** MPS-IH, patient age 4 yr. Metacarpals and phalanges are abnormally short, wide and deformed with proximal pointing of the metacarpals and bullet-shaped phalanges. Bone trabeculation is coarse and the cortices are thin. **C,** MPS-IS, patient age 13 yr. The carpal bones are small leading to a V-shaped configuration of the digits. The short tubular bones are well modeled. Flexion of the middle and distal phalanges II-V is caused by joint contractures.

Mucopolysaccharidosis III

Sanfilippo disease makes up a genetically heterogeneous but clinically similar group of 4 recognized types. Each type is caused by a different enzyme deficiency involved in the degradation of heparan sulfate (see Fig. 88-1). Mutations have been found in all the MPS-III disorders for which the genes have been isolated.

Phenotypic variation exists in MPS-III patients, but to a lesser degree than in other MPS disorders. Patients with Sanfilippo disease are characterized by slowly progressive, severe CNS involvement with mild somatic disease. Such disproportionate involvement of the CNS is unique to MPS-III. Onset of clinical features usually occurs between 2 and 6 yr in a child who previously appeared normal. Presenting features include delayed development, hyperactivity with aggressive behavior, coarse hair, hirsutism, sleep disorders, and mild hepatosplenomegaly. Delays in diagnosis of MPS-III are common because of the mild physical features, hyperactivity, and slowly progressive neurologic disease. Severe neurologic deterioration occurs in most patients by 6-10 yr, accompanied by rapid deterioration of social and adaptive

skills. Severe behavior problems such as sleep disturbance, uncontrolled hyperactivity, temper tantrums, destructive behavior, and physical aggression are common. Profound developmental regression and behavior problems often occur in patients with normal physical strength, making management particularly difficult.

Mucopolysaccharidosis IV

Morquio disease (MPS-IV) is caused by a deficiency of *N*-acetylgalactosamine-6-sulfatase (MPS-IVA) or of β-galactosidase (MPS-IVB). Both result in the defective degradation of keratan sulfate. The gene encoding *N*-acetylgalactosamine-6-sulfatase is on chromosome 16q24.3 and the gene encoding β-galactosidase, *GLB1*, on chromosome 3p21.33. β-Galactosidase catalyzes hydrolysis of GM_1 ganglioside in addition to endohydrolysis of keratan sulfate, and most mutations of *GLB1* result in generalized gangliosidosis, a spectrum of neurodegenerative disorders associated with dysostosis multiplex. A W273L mutation of the *GLB1* gene, either in the homozygous state or as part of compound heterozygosity, commonly results in Morquio B disease.

Both types of Morquio disease are characterized by short-trunk dwarfism, fine corneal deposits, a skeletal dysplasia that is distinct from other mucopolysaccharidoses, and preservation of intelligence. MPS-IVA is usually more severe than MPS-IVB with adult heights of less than 125 cm in the former and more than 150 cm in the latter. However, there is considerable variability of expression in both subtypes. The appearance of genua valga, kyphosis, growth retardation with short trunk and neck, and waddling gait with a tendency to fall are early symptoms of MPS-IV. Extraskeletal manifestations include mild corneal clouding, small teeth with abnormally thin enamel, frequent caries formation and occasionally hepatomegaly and cardiac valvular lesions. Instability of the odontoid process and ligamentous laxity is regularly present and can result in life-threatening atlantoaxial instability and dislocation. Surgery to stabilize the upper cervical spine, usually by posterior spinal fusion, before the development of cervical myelopathy can be lifesaving.

Mucopolysaccharidosis VI

Maroteaux-Lamy disease is caused by mutations of the *ARSB* gene on chromosome 5q11-13 encoding *N*-acetylgalactosamine-4-sulfatase (arylsulfatase B). It is characterized by severe to mild somatic involvement, as seen in MPS-I, but with preservation of intelligence. The somatic involvement of the severe form of MPS-IV is characterized by corneal clouding, coarse facial features, joint stiffness, valvular heart disease, communicating hydrocephalus, and dysostosis multiplex. In the severe form, growth can be normal for the first few years of life but seems to virtually stop after age 6-8 yr. The mild to intermediate forms of Maroteaux-Lamy disease can be easily confused with Scheie syndrome. Spinal cord compression from thickening of the dura in the upper cervical canal with resultant myelopathy is a frequent occurrence in patients with MPS-VI.

Mucopolysaccharidosis VII

Sly syndrome (MPS-VII) is caused by mutations of the *GUSB* gene located on chromosome 7q21.11. Mutations result in a deficiency of β-glucuronidase, intracellular storage of glycosaminoglycan fragments and a very wide range of clinical involvement. The most severe form presents as lethal nonimmune fetal hydrops and may be detected in utero by ultrasound. Some severely affected newborns survive for some months and have, or develop, signs of lysosomal storage including thick skin, visceromegaly, and dysostosis multiplex. Less-severe forms of MPS-VII present during the first years of life with features of MPS-I but slower progression. Corneal clouding varies. Patients with manifestation after 4 yr of life have skeletal abnormalities of dysostosis multiplex but normal intelligence and usually clear corneae. They may be found incidentally on the basis of a blood smear that shows coarse granulocytic inclusions.

Mucopolysaccharidosis IX

The disorder is caused by a mutation in the *HYAL1* gene on chromosome 3p21.2-21.2 encoding one of 3 hyaluronidases. Clinical findings in the only known patient, a 14-year old girl, were bilateral nodular soft-tissue periarticular masses, lysosomal storage of GAGs in histiocytes, mildly dysmorphic craniofacial features, short stature, normal joint movement and normal intelligence. Small erosions in both acetabula were the only radiographic findings.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical suspicion of a MPS justifies a skeletal survey. Radiographs of chest, spine, pelvis and hands may show early signs of dysostosis multiplex. The next diagnostic step is to assay the urinary excretion of GAG. Semiquantitative spot tests are quick and inexpensive but subject to both false-positive and false-negative results. Quantitative analysis of single GAG by various methods, or of oligosaccharides by tandem mass spectrometry, is preferable and reveals type-specific profiles. Morquio disease is often missed in urinary assays but can reliably be diagnosed in serum using monoclonal antibodies to keratan sulfate.

Any individual who is suspected of an MPS disorder based on clinical features, radiographic results, or urinary GAG screening tests should have a definitive diagnosis established by enzyme assay. Serum, leukocytes, or cultured fibroblasts are used as the tissue source for measuring lysosomal enzymes (see Table 88-2).

Prenatal diagnosis is available for all MPSs and is carried out on cultured cells from amniotic fluid or chorionic villus biopsy. Measurement of GAGs in amniotic fluid is unreliable. Carrier testing in Hunter syndrome, an X-linked disorder, requires analysis of *IDS* gene once the specific mutation or chromosome arrangement in the family under consideration is known. Prenatal molecular analysis must be offered in a male fetus of a proven female carrier of the *IDS* gene. His risk to be affected is 50%. It is very small, but not zero, in a female fetus as a result of skewed maternal X-chromosome inactivation. Molecular analysis in patients with other enzymatically proven mucopolysaccharidoses or in known carriers is costly and usually not required. MPSs I, II, and VI are candidates for neonatal blood spot screening by tandem mass spectrometry allowing early diagnosis and enzyme replacement therapy.

Mucolipidoses and oligosaccharidoses manifest with the same clinical and radiographic features as mucopolysaccharidoses. In these conditions the urinary excretion of GAGs is not elevated. Hurler-like facial features, joint contractures, dysostosis multiplex and elevated urinary GAG excretion differentiate the mucopolysaccharidoses from congenital disorders of glycosylation and other neurodegenerative and dwarfing conditions.

TREATMENT

Hematopoietic stem cell transplantation and enzyme replacement therapy are performed in specialized institutions (Table 88-3). Experimental forms of therapy include substrate reduction by flavonoids, gene silencing, read-through attempts and transplantation of autologous hematopoietic stem cells that have been genetically modified ex vivo to express the missing protein. Symptomatic measures are listed in Table 88-4.

Bone marrow transplantation from related or unrelated donors and **cord blood transplantation** have resulted in significant clinical improvement of somatic disease in MPSs I, II, and VI. Clinical effects are increased life expectancy, resolution or improvement of growth, hepatosplenomegaly, joint stiffness, facial appearance, pebbly skin changes in MPS-II, obstructive sleep apnea, heart disease, communicating hydrocephalus, and hearing loss. Enzyme activity in serum and urinary GAG excretion normalize. Transplantation does not significantly improve the neuropsychologic outcome of MPS patients with impaired cognition at the time of transplantation. This is true for MPSs IH, II, and III. However, patients with MPS-I who have undergone transplantation before 24 mo of age and with a baseline mental development index greater than 70 have improved long-term outcome. Early transplantation in MPS-II may have the same effect. Transplantation in MPS-VI stabilizes or improves cardiac manifestations, posture and joint mobility. Stem cell transplantation does not correct skeletal and ocular anomalies and they have to be treated with appropriate orthopedic and ophthalmologic procedures. Cord blood

Table 88-3 Therapies Aimed at Proximate Causes of Mucopolysaccharidoses

MPS TYPE	STEM CELL TRANSPLANTATION (SCT)	ENZYME REPLACEMENT	REMARKS
I	Yes	Aldurazyme	Transplantation before age 2 yr. Enzyme replacement before and after transplantation
II	Questionable	Elaprase	Lack of neurologic improvement after stem cell transplantation
III	No	No	Experimental: Substrate reduction by flavanoids
IVA	No	Preclinical	Recombinant GALNS trial in course
VI	Yes	Naglazyme	Sustained improvement
VII	Questionable	?	Single SCT attempt without neurologic improvement

GALNS, galactosamine(*N*-acetyl)-6-sulfate sulfatase.

Table 88-4 Symptomatic Management of Mucopolysaccharidoses

PROBLEM	PREDOMINANTLY IN	MANAGEMENT
NEUROLOGIC		
Hydrocephalus	MPS-I, -II, -VI, -VII	Funduscopy, CT scan
Chronic headaches	All	Ventriculoperitoneal shunting
Behavioral disturbance	MPS-III	Behavioral medication, sometimes CT scan, ventriculoperitoneal shunting
Disturbed sleep/wake circle	MPS-III	Melatonin
Seizures	MPS-I, -II, -III	Electroencephalogram, anticonvulsants
Odontoid hypoplasia	MPS-IV	Cervical MRI, upper cervical fusion
Spinal cord compression	All	Laminectomy, dural excision
OPHTHALMOLOGIC		
Corneal opacity	MPS-I, -VI, -VII	Corneal transplant
Glaucoma	MPS-I, -VI, -VII	Medication, surgery
Retinal degeneration	MPS-I, -II	Night light
EARS, AIRWAYS		
Recurrent otitis media	MPS-I, -II, -VI, -VII	Ventilating tubes
Impaired hearing	All except MPS-IV	Audiometry, hearing aids
Obstruction	All except MPS-III	Adenotomy, tonsillectomy, bronchodilator therapy, continuous positive airway pressure at night, laser excision of tracheal lesions, tracheotomy
CARDIAC		
Cardiac valve disease	MPS-I, -II, -VI, -VII	Endocarditis prevention, valve replacement
Coronary insufficiency	MPS-I, -II, -VI, -VII	Medical therapy
Arrhythmias	MPS-I, -II, -VI, -VII	Antiarrhythmic medication, pacemaker
ORAL, GASTROINTESTINAL		
Hypertrophic gums, poor teeth	MPS-I, -II, -VI, -VII	Dental care
Chronic diarrhea	MPS-II	Diet modification, loperamide
MUSCULOSKELETAL		
Joint stiffness	All except MPS-IV	Physical therapy
Weakness	All	Physical therapy, wheelchair
Gross long bone malalignment	All	Corrective osteotomies
Carpal tunnel syndrome	MPS-I, -II, -VI, -VII	Electromyography, surgical decompression
ANESTHESIA	All except MPS-III	Avoid atlantoaxial dislocation, use angulated video intubation laryngoscope and small endotracheal tubes

transplantation is the therapy of choice in children with MPS-IH, and possibly MPS-II, before the age of 2 yr, but transplantation-related death or primary graft failure, which occur in approximately one-third of the patients, must be weighed against other therapeutic options.

Enzyme replacement using recombinant α-L-iduronidase has been approved for patients with MPS-I. It reduces organomegaly and ameliorates rate of growth, joint mobility, reduces the number of episodes of sleep apnea and urinary GAG excretion. The enzyme does not cross the blood–brain barrier and does not prevent deterioration of cognition and other neurologic functions. Consequently, this therapy is reserved for patients with mild CNS involvement. To stabilize extraneural manifestations, it is also recommended in young patients before stem cell transplantation. Recombinant iduronate-2-sulfatase ameliorates the nonneurologic manifestations of Hunter disease, and recombinant *N*-acetylgalactosamine-4-sulfatase has been successfully tested in patients with MPS-VI.

Primary prevention through genetic counseling and tertiary prevention to avoid or arrest complications remain the mainstay of pediatric care. Multidisciplinary attention to respiratory and cardiovascular complications, hearing loss, carpal tunnel syndrome, spinal cord compression, hydrocephalus and other problems can greatly improve the quality of life for patients and their families (see Table 88-4). The progressive nature of clinical involvement in MPS patients dictates the need for specialized and coordinated evaluation.

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Chapter 89

Disorders of Purine and Pyrimidine Metabolism

James C. Harris

The inherited disorders of purine and pyrimidine metabolism cover a broad spectrum of illnesses with various presentations. These include hyperuricemia, acute renal failure, renal stones, gout, unexplained neurologic deficits (seizures, muscle weakness, choreoathetoid and dystonic movements), developmental disability, intellectual disability, compulsive self-injury and aggression, autistic-like behavior, unexplained anemia, failure to thrive, susceptibility to recurrent infection (immune deficiency), and deafness. When identified, all family members should be screened.

Purines and pyrimidines form the basis of nucleotides and nucleic acids (DNA and RNA) and so are involved in all biologic processes. Metabolically active nucleotides are formed from heterocyclic nitrogen-containing purine bases (guanine and adenine) and pyrimidine bases (cytosine, uridine, and thymine): all cells require a balanced supply of nucleotides for growth and survival. Purines provide the primary source of cellular energy through adenosine triphosphate (ATP) and the basic coenzymes (nicotinamide adenine dinucleotide and its reduced form) for metabolic regulation and play a major role in signal transduction (guanosine triphosphate [GTP], cyclic adenosine monophosphate, cyclic guanosine monophosphate). Figure 89-1 shows the early steps in the biosynthesis of the purine ring. Purines are primarily produced from endogenous sources, and in the usual circumstances dietary purines have a small role. The end product of purine metabolism in humans is uric acid (2,6,8-trioxypurine).

Uric acid is not a specific disease marker so the cause of its elevation must be determined. The serum level of uric acid present at any time depends on the size of the purine nucleotide pool which is derived from de novo purine synthesis, catabolism of tissue nucleic acids, and increased turnover of preformed purines. Uric acid is poorly soluble and must be excreted continuously to avoid toxic accumulation in the body. Its renal excretion involves the following components: (1) glomerular filtration, (2) reabsorption in the proximal convoluted tubule, (3) secretion near the terminus of the proximal tubule, and (4) limited reabsorption near these secretory sites. Thus, renal loss of uric acid is a result of renal tube excretion and is a function of serum uric acid concentration and non-specific transporters that remove uric acid. Because renal tubule excretion is greater in children than in adults, serum uric acid levels are a less reliable indicator of uric acid production in children than in adults, and, consequently, measurement of the level in urine may be required to determine excessive production. Clearance of a smaller portion of uric acid is via the gastrointestinal tract (biliary and intestinal secretion). Owing to poor solubility of uric acid under normal circumstances, uric acid is near the maximal tolerable limits, and small alterations in production or solubility or changes in secretion may lead to hyperuricemia and can result in precipitation in extremities such as fingers or toes, which defines clinical gout. In renal insufficiency, urate excretion is increased by residual nephrons and by the gastrointestinal tract. Increased production of uric acid is found in malignancy, Reye syndrome, Down syndrome, psoriasis, sickle cell anemia, cyanotic congenital heart disease, pancreatic enzyme replacement, glycogen storage disease types I, III, IV, and V, hereditary fructose intolerance, and acyl-coenzyme A dehydrogenase deficiency.

The metabolism of both purines and pyrimidines can be divided into biosynthetic, salvage and catabolic pathways. The first, the de novo pathway, involves a multistep biosynthesis of phosphorylated ring structures from precursors such as CO_2, glycine, and glutamine. Purine and pyrimidine nucleotides are produced from ribose-5-phosphate or carbamyl phosphate, respectively. The second, a single-step salvage pathway, recovers purine bases and pyrimidine nucleosides derived from either dietary intake or the catabolic pathway (Figs. 89-2 and 89-3). In the de novo pathway, the nucleosides guanosine, adenosine, cytidine, uridine, and thymidine are formed by the addition of ribose-1-phosphate to the purine bases guanine or adenine, and to the pyrimidine bases cytosine, uracil, and thymine respectively. The phosphorylation of these nucleosides produces monophosphate, diphosphate, and triphosphate nucleotides, as well as the deoxy-nucleotides that are utilized for DNA formation. Under usual circumstances, the salvage pathway predominates over the biosynthetic pathway, as nucleotide salvage saves energy for cells. Only a small fraction of the nucleotides turned over by the body each day are degraded and excreted. Synthesis of nucleotides is most active in tissues with high rates of cellular turnover, such as gut epithelium, skin, and bone marrow. The third pathway is catabolism. The end product of the catabolic pathway of the purines in humans is uric acid, whereas catabolism of pyrimidines produces citric acid cycle intermediates.

Inborn errors in the **synthesis** of **purine nucleotides** comprise the phosphoribosylpyrophosphate synthetase spectrum of disorders, including deficiency and superactivity, adenylosuccinate lyase deficiency, and 5-amino-4-imizolecarboxamide (AICA) riboside deficiency (AICA-ribosiduria). Disorders resulting from abnormalities in purine **catabolism** comprise muscle adenosine monophosphate (AMP) deaminase deficiency, adenosine deaminase deficiency, purine nucleoside phosphorylase deficiency, and xanthine oxidoreductase deficiency. Disorders resulting from the purine **salvage** pathway comprise hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency, and adenine phosphoribosyltransferase (APRT) deficiency.

The sole inborn error of **pyrimidine synthesis** is hereditary orotic aciduria (uridine monophosphate synthase deficiency). Disorders resulting from abnormalities in pyrimidine catabolism comprise dihydropyrimidine dehydrogenase (DPD) deficiency, dihydropyrimidinase (DPH) deficiency, and β-ureidopropionase deficiency, pyrimidine 5′-nucleotidase deficiency, and mitochondrial thymidine phosphorylase deficiency. A disorder resulting from the **pyrimidine salvage** is thymidine kinase 2 deficiency.

GOUT

Gout presents with hyperuricemia, uric acid nephrolithiasis, and acute inflammatory arthritis. Gouty arthritis is caused by monosodium urate crystal deposits that result in inflammation in joints and surrounding tissues. The presentation is most commonly monoarticular, typically in the metatarsophalangeal joint of the big toe. Tophi, deposits of monosodium urate crystals, may occur over points of insertion of tendons at the elbows, knees, and feet or over the helix of the ears. Primary gout ordinarily occurs in middle-aged men, results mainly from decreased renal excretion of uric acid, or purine overconsumption, or high intake of alcohol or fructose, or a combination of these factors. Gout occurs in any condition that leads to reduced clearance of uric acid: during therapy for malignancy or with dehydration, lactic acidosis, ketoacidosis, starvation, diuretic therapy, and renal failure. Excessive purine, alcohol, or fructose ingestion may increase uric acid levels. The biochemical etiology of gout is unknown for most of those affected, and it is considered to be a polygenic trait. Purine overproduction is a rare cause of primary gout, and is associated with several genetic disorders discussed below. Secondary gout is either the result of another disorder in which there is rapid tissue breakdown or cellular turnover leading to increased production or decreased excretion of uric acid, or the result of some types of drug treatment, for example diuretics cause plasma volume reduction and can precipitate a gouty attack.

Gout resulting from endogenous purine overproduction is associated with hereditary disorders of 3 different enzymes that result in

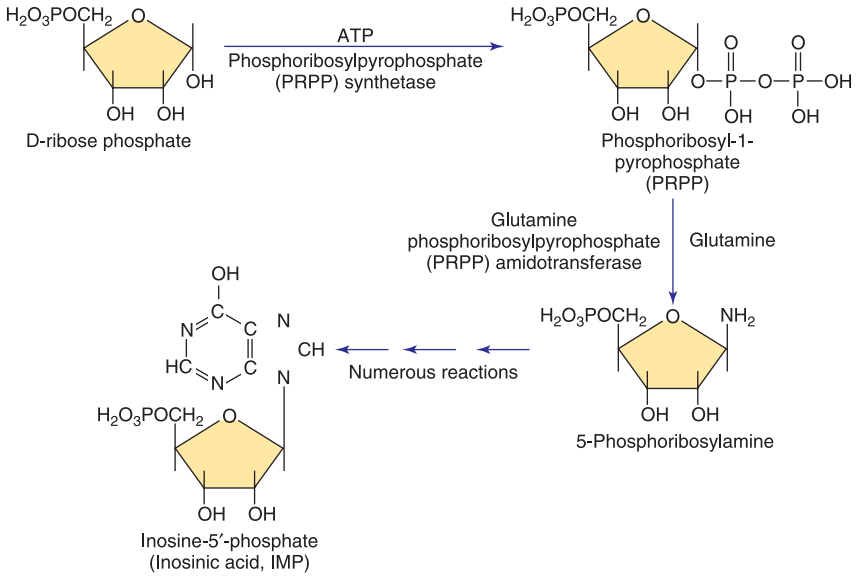

Figure 89-1 Early steps in the biosynthesis of the purine ring.

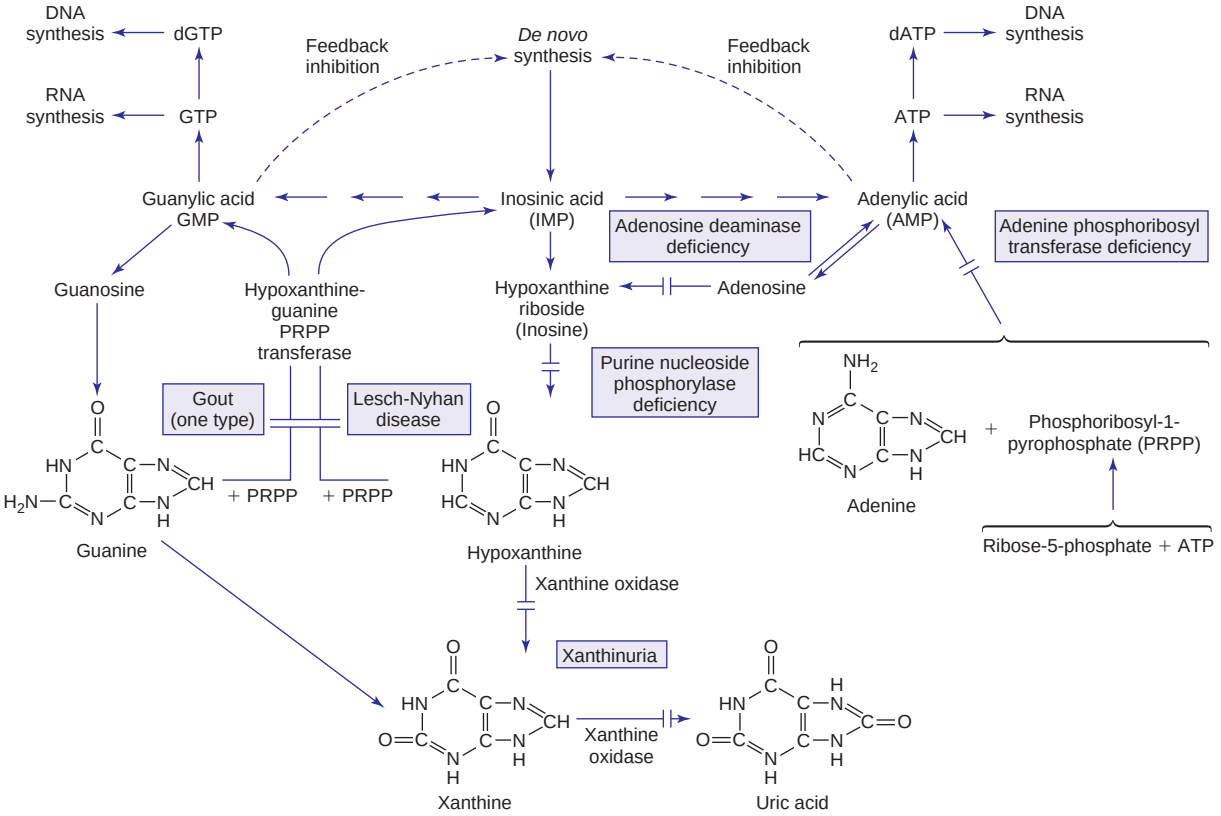

Figure 89-2 Pathways in purine metabolism and salvage.

hyperuricemia. These comprise the HPRT deficiency spectrum (ranging from severe deficiency or Lesch-Nyhan syndrome to partial HPRT deficiency), 2 forms of superactivity of PP-ribose-P synthetase, and glycogen storage disease type I (glucose-6-phosphatase deficiency; see Chapter 87.1). In the first two, the basis of hyperuricemia is purine nucleotide and uric acid overproduction, whereas in the third it is both excessive uric acid production and diminished renal excretion of urate. Glycogen storage disease types III, V, and VII are associated with exercise-induced hyperuricemia, the consequence of rapid ATP utilization and failure to regenerate it effectively during exercise (see Chapter 87.1).

Juvenile gout resulting from purine underexcretion is polygenic, consisting of the familial juvenile hyperuricemic nephropathy group of disorders. This includes medullary cystic kidney disease type 2, mapped to chromosome 16p11.2, which has been shown to result from uromodulin mutations; the term *uromodulin-associated kidney disease* has been proposed for them. Other genes classified as forms of familial juvenile hyperuricemic nephropathy include those for renin and hepatic nuclear factor-1β. Unlike the 3 inherited purine disorders that are X-linked and the recessively inherited glycogen storage disease, these are autosomal dominant conditions. Familial juvenile hyperuricemic nephropathy is associated with severe renal hypoexcretion of

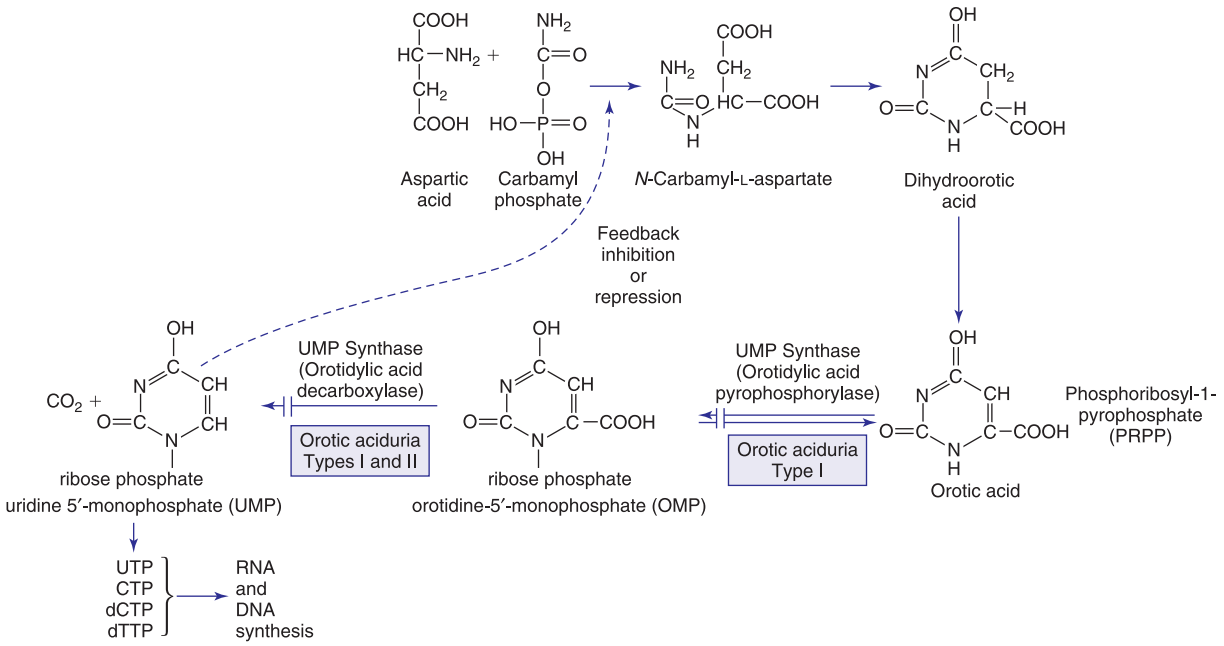

Figure 89-3 Pathways in pyrimidine biosynthesis.

uric acid. Although it most commonly presents from puberty up to the 3rd decade, it has been reported in infancy. It is characterized by early onset, hyperuricemia, gout, familial renal disease, and low urate clearance relative to glomerular filtration rate. It occurs in both males and females and is frequently associated with a rapid decline in renal function that may lead to death unless diagnosed and treated early. Once familial juvenile hyperuricemic nephropathy is recognized, presymptomatic detection is of critical importance to identify asymptomatic family members with hyperuricemia and to begin treatment, when indicated, to prevent nephropathy.

Genetics

Familial juvenile hyperuricemic nephropathy-2 (HNFJ2; 613092) is caused by mutation in the renin gene (*REN*; 179820) on chromosome 1q32. HNFJ3 (614227) has been mapped to chromosome 2p22.1-p21.

Treatment

Treatment of hyperuricemia involves the combination of allopurinol or febuxostat (xanthine oxidase inhibitors) to decrease uric acid production, probenecid to increase uric acid clearance in those with normal renal function, and increased fluid intake to reduce the concentration of uric acid. A low purine diet, weight reduction, and reduced alcohol and reduced fructose intake (as fructose both reduces urate clearance and accelerates ATP breakdown to uric acid) are recommended.

ABNORMALITIES IN PURINE SALVAGE

HPRT Deficiency

Lesch-Nyhan disease (LND) is a rare X-linked disorder of purine metabolism that results from HPRT deficiency. This enzyme is normally present in each cell in the body, but its highest concentration is in the brain, especially in the basal ganglia. Clinical manifestations include hyperuricemia, intellectual disability, dystonic movement disorder that may be accompanied by choreoathetosis and spasticity, dysarthric speech, and compulsive self-biting, usually beginning with the eruption of teeth.

There is a severity spectrum for the clinical presentations of HPRT deficiency. HPRT levels are related to the extent of motor symptoms, to the presence or absence of self-injury, and possibly to the level of cognitive function. Purine overproduction is present. The majority of individuals with classic LND have low or undetectable levels of the HPRT enzyme. Partial deficiency in HPRT **(Kelley-Seegmiller syndrome)** with more than 1.5-2.0% enzyme is associated with purine overproduction and variable neurologic dysfunction (neurologic HPRT deficiency). HPRT deficiency with activity levels >8% of normal still exhibit purine (and uric acid) overproduction but apparently normal cerebral functioning (HPRT-related hyperuricemia) although cognitive deficits may occur. Qualitatively similar cognitive deficit profiles have been reported in both LND and variant cases. Variants produced scores that are intermediate between those of patients with LND and normal controls on nearly every neuropsychological measure tested.

Genetics

The HPRT gene has been localized to the long arm of the X chromosome (q26-q27). The complete amino acid sequence for HPRT is known (approximately 44 kb; 9 exons). The disorder appears in males; occurrence in females is extremely rare and ascribed to nonrandom inactivation of the normal X chromosome. Absence of HPRT activity prevents the normal metabolism of hypoxanthine resulting in excessive uric acid production and manifestations of gout, necessitating specific drug treatment (allopurinol). Because of the enzyme deficiency, hypoxanthine accumulates in the cerebrospinal fluid, but uric acid does not; uric acid is not produced in the brain and does not cross the blood–brain barrier. The behavior disorder is not caused by hyperuricemia or excess hypoxanthine because patients with partial HPRT deficiency, the variants with hyperuricemia, do not self-injure and infants having isolated hyperuricemia from birth do not develop self-injurious behavior.

The prevalence of the classic LND has been estimated at 1 in 100,000 to 1 in 380,000 persons based on the number of known cases in the United States. The incidence of partial variants is not known. Those with the classic syndrome rarely survive the 3rd decade because of renal or respiratory compromise. The life span may be normal for patients with partial HPRT deficiency without severe renal involvement.

Pathology

No specific brain abnormality is documented after detailed histopathology and electron microscopy of affected brain regions. Magnetic resonance imaging has documented reductions in the volume of basal ganglia nuclei. Abnormalities in neurotransmitter metabolism have been identified in 3 autopsied cases. All 3 patients had very low HPRT levels (less than 1% in striatal tissue and 1-2% of control in thalamus cortex). There was a functional loss of 65-90% of the nigrostriatal and

mesolimbic dopamine terminals, although the cells of origin in the substantia nigra did not show dopamine reduction. The brain regions primarily involved were the caudate nucleus, putamen, and nucleus accumbens. It is proposed that the neurochemical changes may be linked to functional abnormalities, possibly resulting from a diminution of arborization or branching of dendrites rather than cell loss. A neurotransmitter abnormality is demonstrated by changes in cerebrospinal fluid neurotransmitters and their metabolites, and confirmed by positron emission tomography scans of dopamine function. Reductions in vivo in the presynaptic dopamine transporter have been documented in the caudate and putamen of 6 individuals.

The mechanism whereby HPRT leads to the neurologic and behavioral symptoms is unknown. However, both hypoxanthine and guanine metabolism are affected and GTP and adenosine have substantial effects on neural tissues. The functional link between purine nucleotides and the dopamine system is through salvage of guanine by HPRT to form GTP: this is essential for GTP cyclohydrolase activity, the first step in the synthesis of pterins and dopamine. Patients with inherited GTP cyclohydrolase deficiency show clinical features in common with LND. Dopamine reduction in brain is documented in HPRT-deficient strains of mutant mice. Dopamine binding to its receptor results in either an activation (D1 receptor) or an inhibition (D2 receptor) of adenylcyclase. Both receptor effects are mediated by G proteins (GTP-binding proteins) dependent on guanine diphosphate in the guanine diphosphate/GTP exchange for cellular activation. Dopamine and adenosine systems are also linked through the role of adenosine as a neuroprotective agent in preventing neurotoxicity. Adenosine derives from AMP which depends on hypoxanthine salvage in the brain by HPRT. Adenosine agonists mimic the biochemical and behavioral actions of dopamine antagonists, whereas adenosine receptor antagonists act as functional dopamine agonists. LND can thus be seen as arising ultimately from nucleotide depletion specifically in the brain, which relies upon the HPRT salvage pathway, leading to dopamine and adenosine depletions.

Clinical Manifestations

At birth, infants with LND have no apparent neurologic dysfunction. After several months, developmental delay, intellectual disability and neurologic signs become apparent. Before the age of 4 mo, hypotonia, recurrent vomiting, and difficulty with secretions may be noted. By approximately 8-12 mo, extrapyramidal signs appear, primarily dystonic movements. In some cases, spasticity may become apparent at this time; in some instances, it becomes apparent later in life.

Cognitive function is usually reported to be in the mild-to-moderate range of intellectual disability, although some individuals test in the low normal range. Because test scores may be influenced by difficulty in testing the subjects owing to their movement disorder and dysarthric speech, overall intelligence may be underestimated.

The age of onset of self-injury may be as early as 1 yr and occasionally as late as the teens. Self-injury occurs, although all sensory modalities, including pain, are intact. The self-injurious behavior usually begins with self-biting, although other patterns of self-injurious behavior emerge with time. Most characteristically, the fingers, mouth, and buccal mucosa are mutilated. Self-biting is intense and causes tissue damage and may result in the amputation of fingers and substantial loss of tissue around the lips. Extraction of primary teeth may be required. The biting pattern can be asymmetric, with preferential mutilation of the left or right side of the body. The type of behavior is different from that seen in other intellectual disability syndromes involving self-injury. Self-hitting and head-banging are the most common initial presentations in other syndromes. The intensity of the self-injurious behavior generally requires that the patient be restrained. When restraints are removed, the patient with LND may appear terrified, and stereotypically place a finger in the mouth. The patient may ask for restraints to prevent elbow movement; when the restraints are placed or replaced, he may appear relaxed and more good humored. Dysarthric speech may cause interpersonal communication problems; however, the higher-functioning children can express themselves fully and participate in verbal therapy.

The self-mutilation presents as a compulsive behavior that the child tries to control but frequently is unable to resist. Older individuals may enlist the help of others and notify them when they are comfortable enough to have restraints removed. In some instances, the behavior may lead to deliberate self-harm. The LND individual may also show compulsive aggression and inflict injury to others through pinching, grabbing, or hitting or by using verbal forms of aggression. Afterward he may apologize, stating that this behavior was out of his control. Other maladaptive behaviors include head- or limb-banging, eye-poking, and psychogenic vomiting.

Diagnosis

The presence of dystonia along with self-mutilation of the mouth and fingers suggests LND. With partial HPRT deficiency, recognition is linked to either hyperuricemia alone or hyperuricemia and a dystonic movement disorder. Serum levels of uric acid that exceed 4-5 mg uric acid/dL and a urine uric acid : creatinine ratio of ≥3-4 : 1 are highly suggestive of HPRT deficiency, particularly when associated with neurologic symptoms. The definitive diagnosis requires an analysis of the HPRT enzyme. This is assayed in an erythrocyte lysate. Individuals with classic LND have near 0% enzyme activity and those with partial variants show values between 1.5% and 60%. The intact cell HPRT assay in skin fibroblasts offers a good correlation between enzyme activity and the severity of the disease. Molecular techniques are used for gene sequencing and the identification of carriers.

Differential diagnosis includes other causes of infantile hypotonia and dystonia. Children with LND are often initially incorrectly diagnosed as having athetoid cerebral palsy. When a diagnosis of cerebral palsy is suspected in an infant with a normal prenatal, perinatal, and postnatal course, then LND should be considered. Partial HPRT deficiency may be associated with acute renal failure in infancy; therefore, clinical awareness of partial HPRT deficiency is of particular importance. The simplest test to exclude LND or partial deficiency is the urinary uric acid : creatinine ratio.

An understanding of the molecular disorder has led to effective drug treatment for uric acid accumulation and arthritic tophi, renal stones, and neuropathy. However, reduction in uric acid alone does not influence the neurologic and behavioral aspects of LND. Despite treatment from birth for uric acid elevation, behavioral and neurologic symptoms are unaffected. The most significant complications of LND are renal failure and self-mutilation.

Treatment

Medical management of this disorder focuses on the prevention of renal failure by pharmacologic treatment of hyperuricemia with high fluid intake along with alkalinization and allopurinol (or more febuxostat). A low purine diet and reduced fructose intake are desirable.

Allopurinol treatment must be monitored because urinary oxypurine excretion with all overproduction disorders is sensitive to allopurinol, resulting in an increased urine concentration of xanthine, which is extremely insoluble. Self-mutilation is reduced through behavior management, and the use of restraints or removal of teeth or both. Pharmacologic approaches to decrease anxiety and spasticity with medication have mixed results. Drug therapy focuses on symptomatic management of anticipatory anxiety, mood stabilization and reduction of self-injurious behavior. Although there is no standard drug treatment, diazepam may be helpful for anxiety symptoms, Risperdal for aggressive behavior and carbamazepine or gabapentin for mood stabilization. Each of these medications may reduce self-injurious behavior by helping to reduce anxiety and stabilize mood. *S*-adenosylmethionine (SAMe), which is thought to act by countering nucleotide depletion in the brain, has been reported to specifically reduce the rate of self-injury in some cases.

Bone marrow transplantation, based on the hypothesis that the central nervous system damage is produced by a circulating toxin, has been carried out in several patients. Several infant patients have died of complications of bone marrow transplantation. To date, there is no evidence that bone marrow transplantation is a beneficial treatment

approach; it remains an experimental and potentially dangerous therapy. Two patients received partial exchange transfusions every 2 mo for 3-4 yr. Erythrocyte HPRT activity was 10-70% of normal during this period, but no reduction of neurologic or behavioral symptoms was apparent. Successful preimplantation genetic diagnosis and in vitro fertilization for LND has been reported with the birth of an unaffected male infant.

Both the motivation for self-injury and its biologic basis must be addressed in treatment programs. Yet behavioral techniques alone, using operant conditioning approaches, have not proved to be an adequate general treatment. Although behavioral procedures have had some selective success in reducing self-injury, generalization outside the experimental setting limits this approach and patients under stress may revert to their previous self-injurious behavior. Behavioral approaches may also focus on reducing the self-injurious behavior through the treatment of phobic anxiety associated with being unrestrained. The most common techniques are systematic desensitization, extinction, and differential reinforcement of other (competing) behavior. Stress management has been recommended to assist patients to develop more effective coping mechanisms. Individuals with LND do not respond to contingent electric shock or similar aversive behavioral measures. An increase in self-injury may be observed when aversive methods are utilized.

Restraint (day and night) and dental procedures are common means to prevent self-injury. The time in restraints is linked to the age of onset of self-injury. Children with LND can participate in making decisions regarding restraints and the type of restraints. The time in restraints may potentially be reduced with systematic behavior treatment programs. Many patients have teeth extracted to prevent self-injury. Others use a protective mouth guard designed by a dentist. Most parents suggest that stress reduction and awareness of the patient's needs are the most effective in reducing self-injury. Positive behavioral techniques of reinforcing appropriate behavior are rated effective by almost half of the families.

Deep brain stimulation to the anteroventral internal globus pallidus is a procedure that has successfully treated self-injury and lessened dystonia in several case reports.

Adenine Phosphoribosyltransferase Deficiency (Dihydroxyadeninuria)

Adenine phosphoribosyltransferase (APRT), a purine salvage enzyme, catalyzes the synthesis of AMP from adenine and 5-phosphoribosyl-1-pyrophosphate (PP-ribose-P). The absence of this enzyme results in the cellular accumulation of adenine and its being oxidized as an alternative substrate by xanthine dehydrogenase to form 2,8-dihydroxyadenine, which is extremely insoluble. APRT deficiency is present from birth, becoming apparent as early as 5 mo and as late as the 7th decade.

Genetics

The disorder is an autosomal recessive trait with considerable clinical heterogeneity. The APRT gene is located on chromosome 16q (16q24.3) and encompasses 2.8 kb of genomic DNA.

Clinical Manifestations

Clinical manifestations include urinary calculus formation with crystalluria, urinary tract infections, hematuria, renal colic, dysuria and acute renal failure. The presence of brownish spots on the infant's diaper or of yellow-brown crystals in the urine is suggestive of the diagnosis. The 2,8-dihydroxyadenine is cleared efficiently by the kidneys and so does not accumulate in plasma, but precipitates readily in the renal lumen.

Laboratory

Urinary levels of adenine, 8-hydroxyadenine, and 2,8-dihydroxyadenine are elevated while plasma uric acid is normal. The deficiency may be complete (type I) or partial (type II); the partial deficiency is reported in Japan. The diagnosis is made based on the level of residual enzyme in erythrocyte lysates. The renal calculi, composed of 2,8-dihydroxyadenine, are radiolucent, soft, and easily crushed. These stones are not distinguishable from uric acid stones by routine tests but require high-performance liquid chromatography, UV, infrared, mass spectrometry, x-ray crystallography, or capillary electrophoresis for diagnosis, particularly to distinguish from stones in HPRT deficiency.

Treatment

Treatment includes high fluid intake, dietary purine restriction, and allopurinol, which inhibits the conversion of adenine to its metabolites, further 2,8-dihydroxyadenine excretion, and further stone formation. Alkalinization of the urine is to be avoided, because, unlike that of uric acid, the solubility of 2,8-dihydroxyadenine does not increase up to pH 9. Shockwave lithotripsy has been reported to be successful. The prognosis depends on renal function at the time of diagnosis. Early treatment is critical in the prevention of stones because severe renal insufficiency may accompany late recognition.

DISORDERS LINKED TO PURINE NUCLEOTIDE SYNTHESIS

Phosphoribosylpyrophosphate Synthetase Superactivity and Deficiency

Phosphoribosylpyrophosphate (PRPP) is a substrate involved in the synthesis of essentially all nucleotides and important in the regulation of the de novo pathways of purine and pyrimidine nucleotide synthesis. The synthetase enzyme (PRPS) produces PRPP from ribose-5-phosphate and ATP, as shown in Figures 89-1 and 89-2. PRPP is the first intermediary compound in the de novo synthesis of purine nucleotides that lead to the formation of inosine monophosphate, then to ATP and GTP.

Genetic disorders of this enzyme affect only the PRPS-1 isoform; PRPS-2 mutations have not been described. PRPS-1 disorders are all X-linked and are divided into "superactivity," which occurs as 2 phenotypes (infantile or early-childhood onset, and a milder form with late-juvenile or early-adult onset), and "deficiency," which is a spectrum disorder that is distinguished clinically according to severity as 3 disorders: Arts syndrome, Charcot-Marie-Tooth disease X-linked-5, and X-linked deafness-2 (DFN2).

Superactivity of the enzyme results in an increased generation of PRPP in dividing cells. Because PRPP aminotransferase, the first enzyme of the purine de novo pathway, is not physiologically saturated by PRPP, the synthesis of purine nucleotides increases, and, consequently, the production of uric acid is increased. PRPP synthetase superactivity is one of the few hereditary disorders in which there is enhancement of the activity of an enzyme. The infantile or early-childhood form of PRPS-1 superactivity has severe neurologic attributes accompanied by uric acid overproduction, whereas individuals with the late-juvenile or early-adult presentation are neurologically normal but still have uric acid overproduction.

Deficiency of PRPS-1 produces depleted purine nucleotide synthesis in tissues dependent upon PRPS-1, which includes brain as well as other neural tissues and lung.

Genetics

Three distinct complementary DNAs for PRPS have been cloned and sequenced. Two forms, PRPS-1 and PRPS-2, are X-linked to Xq22-q24 and Xp22.2-p.22.3 (escapes X inactivation), respectively, and are widely expressed; the third locus maps to human chromosome 7 and appears to be transcribed only in the testes. PRPS-1 defects are thus inherited as X-linked traits and present with varying degrees of severity. The late-onset form of superactivity arises from increased transcription of normal messenger RNA; the cause of this has not been discovered. The early-onset form of superactivity arises from mutations affecting allosteric regulation of the protein that controls feedback inhibition by inorganic phosphate and dinucleotides. At the same time, these mutations destabilize the protein, so that in slow or nonreplicating cells, such as neurons and red blood cells, the enzyme becomes inactive. In contrast, the deficiency phenotypes of PRPS-1 are produced by mutations directly affecting enzyme function, usually in the substrate

binding site. Even though the defect is X-linked it should be considered in a child or young adult of either sex with hyperuricemia and/or hyperuricosuria and normal HPRT activity in lysed red cells.

Clinical Manifestations

Clinical manifestations in affected hemizygous males with the early-onset form of superactivity include signs of uric acid overproduction that are apparent in infancy or early childhood and neurodevelopmental retardation and sensorineural deafness. Hypotonia, delays in motor milestones, ataxia, and autistic-like behavior have been described. Heterozygous female carriers may also develop gout and hearing impairment. The late-onset type is found in males who show only hyperuricemia and hyperuricosuria, but no neurologic signs. The mildest form of PRPS-1 deficiency manifests as progressive postlingual hearing loss in X-linked deafness-2. More severe mutations constitute the Charcot-Marie-Tooth disease X-linked-5 phenotype, which includes peripheral neuronopathy, hearing impairment, and optic atrophy. The most severe PRPS-1 mutations occur in patients with Arts syndrome who also have central neuropathy and an impaired immune system. Females appear to be unaffected, but hemizygous males have usually not survived beyond the 1st decade, typically succumbing to lung disease. Therapy with *S*-adenosylmethionine has prolonged survival, although the neurologic deficits, including the deafness, do not appear to be responsive.

A mechanism for the neurologic symptoms is unknown but it can be hypothesized that nucleotide depletion is present in neural tissues including the brain. Abnormalities of hearing and vision are typical of PRPS-1 deficiency, where the absence of this enzyme presumably compromises these highly energy-dependent neural functions. The high transcript level of PRPS-1 in lung and bone marrow also suggests that its absence may be causal for the recurrent lung infections that characterize Arts syndrome.

Laboratory

For PRPS-1 "superactivity" (both juvenile and adult presentations), serum uric acid may be grossly raised and the urinary excretion of uric acid increased. For PRPS "deficiency," uric acid is normal, not low, probably because PRPS-2 provides the major uric acid forming activity in liver and other major organs. Diagnosis requires that PRPS-1 activity be measured in erythrocytes and cultured fibroblasts. The adult superactivity disorder must be differentiated from partial HPRT deficiency involving the salvage pathway, which also presents with mild or absent neurologic traits accompanied by hyperuricemia.

Treatment

Treatment of PRPS deficiency, specifically Arts syndrome, has involved mainly experimental therapy with *S*-adenosylmethionine, as a dietary supplement to correct the depletion of purines. Dietary purines are usually not absorbed into the body but are degraded to uric acid by the gut. *S*-adenosylmethionine supplementation (beginning at 20 mg/kg/day orally) has been effective in greatly reducing the acute hospitalization episodes of 2 brothers with Arts syndrome, over a period of 10 yr. Treatment of PRPS superactivity is aimed at controlling the hyperuricemia with allopurinol, which inhibits xanthine oxidase, the last enzyme of the purine catabolic pathway. Uric acid production is reduced and is replaced by hypoxanthine, which is more soluble, and xanthine. The initial dose of allopurinol is 10-20 mg/kg/24 hr in children and is adjusted to maintain normal uric acid levels in plasma. The risk of xanthine stone formation is similar to that described for LND. A low purine diet (one free of organ meats, dried beans, and sardines), high fluid intake, and alkalinization of the urine to establish a urinary pH of 6.0-6.5 is necessary. These measures control the hyperuricemia and urate nephropathy but do not affect the neurologic symptoms. There is no known treatment for the neurologic complications.

Adenylosuccinate Lyase Deficiency (Succinylpurinuria)

Adenylosuccinase lyase deficiency is an inherited deficiency of de novo purine synthesis in humans. adenylosuccinase lyase is an enzyme that catalyzes 2 pathways in de novo synthesis and purine nucleotide recycling. These are the conversion of succinylaminoimidazole carboxamide ribotide into aminoimidazole carboxamide ribotide (AICAR) in the de novo synthesis of purine nucleotides and the conversion of adenylosuccinate (S-AMP) into AMP, the second step in the conversion of inosine monophosphate (IMP) into AMP, in the purine nucleotide cycle. Adenylosuccinase lyase deficiency results in the accumulation in urine, cerebrospinal fluid, and to a smaller extent, in plasma, of succinylaminoimidazole carboxamide riboside and succinyladenosine (S-Ado), the dephosphorylated derivatives of succinylaminoimidazole carboxamide ribotide and S-AMP, respectively.

Genetics

This is an autosomal recessive disorder; the gene has been mapped to chromosome 22q13.1-q13.2 and approximately 20 gene mutations have been identified. Laboratory investigations show grossly raised succinylpurines in urine and cerebrospinal fluid, which are normally undetectable.

Clinical Manifestations

Clinical manifestations include varying degrees of psychomotor retardation, generally accompanied by a seizure disorder and/or autistic-like behaviors (poor eye contact and repetitive behaviors). Neonatal seizures and a severe infantile epileptic encephalopathy are often the first manifestations of this disorder. Others demonstrate moderate to severe intellectual disability sometimes associated with growth retardation and muscle hypotonia. One reported case, a girl, tested in the mild range of intellectual disability. The form with profound intellectual disability has been designated type I; the variant case with mild intellectual disability as type II. Other patients have an intermediate clinical symptom pattern with moderately delayed psychomotor development, seizures, stereotypies, and agitation.

Pathology

CT and MRI of the brain may show hypotrophy or hypoplasia of the cerebellum, particularly the vermis. It is proposed that rather than being caused by purine nucleotide depletion, the symptoms are from the neurotoxic effects of accumulating succinylpurines. The ratio of S-Ado : succinylaminoimidazole carboxamide riboside has been linked to phenotype severity, suggesting that succinylaminoimidazole carboxamide riboside is the more toxic compound and that S-Ado might be neuroprotective.

The laboratory diagnosis is based on the presence in urine and cerebrospinal fluid of succinylaminoimidazole carboxamide riboside and S-Ado, both normally undetectable.

Treatment

No successful treatment has been demonstrated for this disorder. *S*-adenosylmethionine supplementation therapy was tested for 6 mo for a baby diagnosed in the early postnatal period, but no amelioration of symptoms were noted, providing further evidence that the disorder arises from nucleotide toxicity rather than depletion. Prenatal diagnosis has been reported. Systematic screening is suggested in infants and children with unexplained psychomotor retardation, and/or seizures disorder.

Aminoimidazole Carboxamide Ribotide Transformylase/Inosine Monophosphate Cyclohydrolase Deficiency

AICA riboside is the dephosphorylated product of AICAR, also termed ZMP. Along with its di- and triphosphates, ZMP accumulates in red blood cells and fibrocytes in inherited deficiency of the bifunctional enzyme AICAR transformylase/IMP cyclohydrolase (ATIC), which catalyzes the conversion of AICAR to formyl-AICAR.

Genetics

This is an inborn error of purine biosynthesis caused by a mutation of the *ATIC* gene effecting AICAR transformylase activity. In a single

reported case AICAR transformylase was profoundly deficient, whereas the IMP cyclohydrolase level was 40% of normal.

Clinical Features
The disorder is described in a female infant with profound intellectual disability, epilepsy, dysmorphic features (prominent forehead and metopic suture, brachycephaly, wide mouth with thin upper lip, low-set ears, and prominent clitoris because of fused labia minora), and congenital blindness.

Laboratory
Urinary screening with the Bratton-Marshall test to detect AICA resulted in the identification of this disorder. The transformylase was found to be deficient in fibroblasts in this disorder, confirming diagnosis.

Treatment
No successful treatment is described.

DISORDERS RESULTING FROM ABNORMALITIES IN PURINE CATABOLISM

Myoadenylate Deaminase Deficiency (Muscle Adenosine Monophosphate Deaminase Deficiency)
Myoadenylate deaminase is a muscle-specific isoenzyme of AMP deaminase that is active in skeletal muscle. During exercise, the deamination of AMP leads to increased levels of IMP and ammonia in proportion to the work performed by the muscle. Two forms of myoadenylate deaminase deficiency are known: an inherited (primary) form that may be asymptomatic or associated with cramps or myalgia with exercise, and a secondary form that may be associated with other neuromuscular or rheumatologic disorders.

Clinical Manifestations
Clinical manifestations are most commonly isolated muscle weakness, fatigue, myalgias following moderate-to-vigorous exercise, or cramps. Myalgia may be associated with an increased serum creatine kinase level and detectable electromyelographic abnormalities. Muscle wasting or histologic changes on biopsy are absent. The age of onset may be as early 8 mo of life with approximately 25% of cases recognized between 2 and 12 yr of age. The enzyme defect has been identified in asymptomatic family members. Secondary forms of muscle AMP deaminase deficiency have been identified in Werdnig-Hoffmann disease, Kugelberg-Welander syndrome, polyneuropathies, and amyotrophic lateral sclerosis (see Chapter 612.2). The metabolic disorder involves the purine nucleotide cycle. As shown in Figure 89-2, the enzymes involved in this cycle are AMP deaminase, S-AMP synthetase, and S-AMP lyase. It is proposed that muscle dysfunction in AMP deaminase deficiency results from impaired energy production during muscle contraction. It is unclear how individuals may carry the deficit and be asymptomatic. In addition to muscle dysfunction, a mutation of liver AMP deaminase has been proposed as a cause of primary gout, leading to overproduction of uric acid.

Genetics
The inherited form of the disorder is an autosomal recessive trait. *AMP-D1,* the gene responsible for encoding muscle AMP deaminase, is located on the short arm of chromosome 1 (1p13-21). Population studies reveal that a mutant allele is found at high frequency in white populations, but alternative splicing of the gene can result in removal of the mutation and normal enzyme function. As a result, the disorder is usually screened by performing the forearm ischemic exercise test. The elevation of venous plasma ammonia following exercise that is seen in normal subjects is absent in AMP deaminase deficiency.

Laboratory
The final diagnosis is made by histochemical or biochemical assays of a muscle biopsy. The primary form is distinguished by the finding of enzyme levels below 2% with little or no immunoprecipitable enzyme. Affected individuals are advised to exercise with caution to prevent rhabdomyolysis and myoglobinuria.

Treatment
Although there are no documented fully effective treatments, it has been proposed that enhancing the rate of replenishment of the ATP pool might be beneficial. Using this rationale treatment with ribose (2-60 g/24 hr orally, in divided doses) or xylitol, that is converted to ribose, has been reported to improve endurance and muscle strength in some cases but is ineffective in others. Genetic approaches may be feasible in the future for inherited cases while treatment of the underlying condition is essential in secondary cases.

Adenosine Deaminase Deficiency
See Chapter 126.1.

Purine Nucleoside Phosphorylase Deficiency
See Chapter 126.2.

Xanthine Oxidoreductase Deficiency (Hereditary Xanthinuria/Molybdenum Cofactor Deficiency)
Xanthine oxidoreductase (XOR) is the catalytic enzyme in the final step of the purine catabolic pathway and oxidizes hypoxanthine to xanthine and xanthine to uric acid. Because XOR exists in 2 forms, xanthine dehydrogenase and xanthine oxidase, the deficiency is also referred to as xanthine dehydrogenase/xanthine oxidase deficiency. Xanthine, the immediate precursor of uric acid, is less soluble than uric acid in urine and deficiency of the enzyme results in xanthinuria. XOR deficiency may occur in isolated form (xanthinuria type 1), in a combined form involving XOR and aldehyde oxidase deficiencies (xanthinuria type II), or multiple deficiencies of XOR, aldehyde oxidase, and sulfite oxidase (molybdenum cofactor deficiency). All 3 forms result in an almost total replacement of uric acid by hypoxanthine and xanthine in urine, while plasma uric acid is very low or undetectable.

Patients with the isolated form can be asymptomatic or have mild symptoms; renal stones, often not visible on radiography, are a risk for renal damage and may appear at any age, when patients may present with loin pain or renal insufficiency. For type II xanthinuria the clinical presentation is similar to type I, but patients also have aldehyde oxidase deficiency, which has no known clinical attributes. Molybdenum cofactor deficiency arises from inherited deficiency of molybdenum cofactor synthase, which affects all 3 molybdoenzymes, and like isolated sulfite oxidase deficiency, it usually presents with neonatal feeding problems, neonatal seizures, increased or decreased muscle tone, ocular lens dislocation, severe intellectual disability, and death in early childhood. Milder cases have presented with lens dislocation only.

Genetics
The inheritance of all 3 types of xanthinuria is complex and autosomal recessive. Type I results from mutations in the human *XDH* gene located on chromosome 2p22. Type II xanthinuria arises from mutations in the molybdenum cofactor synthase gene located on chromosome 18q12.2; this encodes molybdenum cofactor sulfurase, which is essential for the activity of both XOR and aldehyde oxidase. Type III xanthinuria (XOR, aldehyde oxidase and sulfite oxidase deficiencies) can arise from functional mutations in any of 3 genes: *MOCS1* (encoding 2 enzymes for synthesis of the precursor via a bicistronic transcript), *MOCS2* (encoding molybdopterin synthase), or *GPHN* (encoding gephyrin), located at 6p21.2, 5q11.2, and 14q23.3, respectively.

Laboratory
Diagnosis is made initially by measuring plasma and/or urinary concentrations of uric acid. Plasma uric acid is very low or absent (<1 mg/dL). Urinary uric acid is reduced, being replaced by xanthine and hypoxanthine. Type II patients can be distinguished by the absence in urine of methyl-2-pyridone-carboxamide, the product of nicotinamide (niacin) breakdown by aldehyde oxidase. Alternately, type II patients

can be distinguished from type I by their inability to oxidize a test dose of allopurinol to oxypurinol, via aldehyde oxidase. Molybdenum cofactor deficiency is distinguished by an additional excessive urinary excretion of sulfite and other sulfur-containing metabolites such as sulfocysteine.

Enzyme assay of XOR is not usually offered because it requires jejunal or liver biopsy, as these are the only human tissues that contain appreciable amounts of the enzyme. Sulfite oxidase and the molybdenum cofactor synthase can be measured in liver and fibroblasts. Molecular genetic analysis can be used to confirm diagnosis by searching for functional mutations among the three groups of genes.

Treatment

Although isolated deficiency is generally benign, treatment with a diet of low purines and low fructose (which reduces ATP breakdown to xanthine) with increased fluid intake is recommended. Allopurinol is not recommended. The prognosis for molybdenum cofactor deficiency has previously been very poor, but trials of cyclic pyranopterin monophosphate are promising.

DISORDERS OF PYRIMIDINE METABOLISM

The pyrimidines are the building blocks of DNA and RNA and involved in the formation of active intermediates in carbohydrate and phospholipid metabolism (e.g., uridine diphosphate glucose, cytidine diphosphate choline), glucuronidation in detoxification processes (uridine diphosphate), and glycosylation of proteins and lipids.

The essential precursor for pyrimidine biosynthesis is carbamyl-phosphate, which is shared with the urea cycle. Consequently, proximal blockages of the urea cycle results in carbamyl-phosphate overflowing into the pyrimidine pathway. Pyrimidine synthesis differs from that of purines in that the single pyrimidine ring is first assembled to form orotic acid and then linked to ribose phosphate to form the central pyrimidine nucleotide uridine monophosphate (UMP). The pyrimidine bases, uracil and thymine, are catabolized in 4 steps, as shown in Figure 89-3. Eight disorders of pyrimidine metabolism are reviewed. Purine catabolism has an easily measurable end point in uric acid; however, there is no equivalent compound in pyrimidine catabolism. The first defect (hereditary orotic aciduria) is in the de novo synthetic pathway, 1 defect (thymidine kinase) is part of pyrimidine salvage, and the other disorders involve overactivity (in 1 syndrome) or defects in the pyrimidine degradation pathway. Pyrimidine disorders may present as anemia, neuropathologies, or multisystem mitochondrial disorders. The first 3 steps of the degradation pathways for thymine and uracil, respectively, make use of the same enzymes (DPD, DPH, and UP). These 3 steps result in the conversion of uracil into β-alanine. There is increasing evidence that pyrimidines play an important role in the regulation of the nervous system. Reduced production of the neurotransmitter function of β-alanine is hypothesized to produce clinical symptoms. Clinically, pyrimidine disorders may be overlooked because they are rare and their symptoms are not highly specific; however, they should be considered as possible causes of anemia and neurologic disease and are a contraindication for treatment of cancer patients with certain pyrimidine analogs.

Uridine Monophosphate Synthase Type 1 Deficiency (Hereditary Orotic Aciduria)

Hereditary orotic aciduria is a disorder of pyrimidine synthesis associated with deficient activity of the last 2 steps of the de novo pyrimidine synthetic pathway, orotate phosphoribosyltransferase, orotidine-5′-monophosphate decarboxylase (ODC). The activities of these 2 steps reside in separate domains of a bifunctional protein, UMP synthase. This catalyzes the 2-step conversion of orotic acid to UMP, via orotidine monophosphate. Hereditary orotic aciduria (UMP synthase deficiency) results in the excessive accumulation of orotic acid.

Genetics

UMP synthase deficiency is inherited as an autosomal recessive disorder, with both functional domains encoded on a single gene, UMPS, which is located on the long arm of chromosome 3 (3q13). Theoretically, random mutations in the gene should have equal chances of producing either orotate phosphoribosyltransferase or ODC deficiency, but there has been only a single case of ODC deficiency reported. Genetic metabolic defects that involve 4 of the 6 enzymes associated with the urea cycle may also result in orotic aciduria, secondary to PPRP depletion resulting from a substantial increased flux through the pyrimidine synthesis pathway.

Clinical

Clinically patients with hereditary orotic aciduria (UMPS type 1 deficiency) have a macrocytic hypochromic megaloblastic anemia that is unresponsive to the usual forms of therapy (iron, folic acid, and vitamin B_{12}), and may develop leukopenia. Onset is usually in first months of life. Untreated, this disorder can lead to developmental disability, intellectual disability, failure to thrive, cardiac disease, strabismus, crystalluria, and occasional ureteric obstruction. Renal function is generally normal. Heterozygotes may have mild orotic aciduria but are not otherwise affected. The clinical features are thought to be related to pyrimidine nucleotide depletion. Metabolites derived from several pharmacologic agents (5-azauridine, allopurinol) can produce secondary orotic aciduria and orotidinuria by specifically inhibiting the ODC step of UMP synthase. Orotic aciduria may also occur in association with parenteral nutrition, essential amino acid deficiency, and Reye syndrome.

Laboratory

The enzymatic defect may be demonstrated in liver, lymphoblasts, erythrocytes, leukocytes, and cultured skin fibroblasts. A carrier detection test is available, as is prenatal diagnosis, although the condition is treatable.

Treatment

The administration of uridine in doses of 50-300 mg/kg/day has been used in treatment leading to clinical improvement and reduction in orotic acid excretion. Lifelong treatment is required. Uracil is ineffective because, unlike purines, pyrimidine salvage occurs at the nucleoside (uridine) level. The long-term prognosis in uncomplicated cases is good; however, congenital malformations and other associated features may adversely affect outcome.

Dihydropyrimidine Dehydrogenase Deficiency (Thymine-Uraciluria, Pyrimidinuria)

DPD catalyzes the initial and rate-limiting step in the degradation of the pyrimidine bases uracil and thymine. DPD has been identified in most tissues, with the highest activity being in lymphocytes.

Genetics

DPD deficiency is an autosomal recessive disorder, with the *DPYD* gene mapping to chromosome 1p22, with at least 32 polymorphisms detected. It is estimated that the frequency of heterozygosity may be as high as 3%.

The clinical manifestations in children may include seizure disorder, intellectual disability and motor delay. Less frequent are growth retardation, microcephaly, autistic-like behavior, and ocular anomalies. Others do not show developmental abnormalities but may have milder neurological symptoms and language disorder. Unaffected cases have been reported, raising discussion about possible secondary gene effects. In most cases, there is an initial period of normal psychomotor development, followed by subsequent developmental delays. Symptoms may be linked to altered uracil, thymine, or β-alanine homeostasis. Because β-alanine is a structural analog of γ-aminobutyric acid and glycine, it has been proposed that it may affect inhibitory neurotransmission. DPD is the initial and rate-limiting enzyme in the inactivation of the neoplastic drug 5-fluorouracil, being responsible for 80% of its catabolism. Patients with partial DPD deficiency are at risk for developing a severe 5-fluorouracil-associated toxicity. In adult patients, neurotoxicity (headache, somnolence, visual illusions and memory impairment) linked to pyrimidinemia following 5-fluorouracil treatment for cancer is reported in previously healthy individuals.

Laboratory
DPD deficiency is characterized by a variable phenotype and diagnosed by the gross accumulation of thymine and uracil in urine (thymine-uraciluria), plasma and cerebrospinal fluid. Uric acid levels have been reported to be normal. Prenatal diagnosis has been reported.

Treatment
There is no established treatment for this disorder, however, patients with seizures do respond to anticonvulsant medications. DPYD*5 (rs1801159) and 1896 T > C (rs17376848) are potentially useful predictive markers of patients' responses to 5-FU chemotherapy.

Dihydropyrimidinase Deficiency (Dihydropyrimidinuria)
DPH is the second enzyme in the 3-step degradation pathway of uracil and thymine. DPH deficiency is characterized by increased urinary excretion of dihydrouracil and dihydrothymine (dihydropyrimidinuria), as well as uracil and thymine. Similar to DPD deficiency, there is a variable clinical phenotype.

Genetics
This is an autosomal recessive disorder, with the *DPYS* gene mapped to chromosome 8q22. In 1 study there was no significant difference in residual activity between mutations observed in symptomatic and asymptomatic individuals, again similar to DPD deficiency. Population prevalence in a Japanese sample was 0.1%.

Clinical
Clinical manifestations are similar to DPD deficiency, which is evidence that defects in these sequential steps produce a common disorder. Symptoms in 3 unrelated affected cases include seizures with dysmorphic features and developmental delay in 2 of these cases. However, 3 unrelated infant and 2 adult asymptomatic cases were identified in a screening program for pyrimidine degradation disorders in Japan and were asymptomatic despite the accumulation of pyrimidine degradation products in body fluids.

Laboratory
Organic acid screening may identify increased amounts of uracil and thymine in urine. Oral loading tests with uracil, dihydrouracil, thymine, and dihydrothymine have been used to detect carriers of the deficiency. In symptomatic cases, treatment with β-alanine has been attempted with equivocal results. A single case of increased sensitivity to 5-fluorouracil has been reported.

Deficiency of β-Ureidopropionase (*N*-Carbamyl-β-Amino Aciduria)
The pyrimidine bases uracil and thymine are degraded via the consecutive action of 3 enzymes to β-alanine and β-aminoisobutyric acid, respectively. The third enzyme in the pathway is ureidopropionase, and its deficiency leads to *N*-carbamyl-β-amino aciduria. 3-ureidopropionic acid (3-UPA) acts as endogenous neurotoxin via inhibition of mitochondrial energy metabolism resulting in the initiation of secondary, energy-dependent excitotoxic mechanisms.

Genetics
Fluorescence in situ hybridization localized the human β-ureidopropionase gene, *UPB1,* to 22q11.2.

Clinical
Clinical manifestations in a reported case include muscular hypotonia, dystonic movements, and severe developmental delay.

Laboratory
Neuropathology involves both gray and white matter. Ureidopropionase deficiency leads to pathologic accumulation of 3-UPA in body fluids. Urinary analysis in a reported case showed elevated levels of *N*-carbamyl-β-alanine and *N*-carbamyl-β-aminoisobutyric acid (ureidoisobutyric acid). The enzyme is expressed only in the liver and no activity of β-ureidopropionase is detected in a liver biopsy.

Treatment
There is no known treatment for ureidopropionase deficiency.

Pyrimidine 5′-Nucleotidase Deficiency
Erythrocyte maturation is accompanied by RNA degradation and the release of mononucleotides. Pyrimidine 5′-nucleotidase is the first degradative enzyme of the pyrimidine salvage cycle and catalyzes the hydrolysis of pyrimidine 5′-nucleotides to the corresponding nucleosides. Enzyme deficiency results in the accumulation of high levels of cytidine and uridine nucleotides in the erythrocytes that, in turn, results in hemolysis. Deficiency of pyrimidine 5′-nucleotidase may be at least in part compensated in vivo by other nucleotidases or perhaps other nucleotide metabolic pathways.

Genetics
This is an autosomal recessive disorder involving the gene *pyrimidine 5′-nucleotidase deficiency* on chromosome 7 (7p15). Affected pyrimidine 5′-nucleotidase deficiency patients clinically present with a defect restricted to erythrocytes that is characterized by nonspherocytic hemolytic anemia with basophilic stippling. Other characteristic features include splenomegaly, increased indirect bilirubin, and hemoglobinuria. Lead is a powerful inhibitor of pyrimidine 5′-nucleotidase and assessment of lead levels should be included whenever hemolytic anemia, pyrimidine 5′-nucleotidase deficiency, and basophilic stippling are found together.

Laboratory
Diagnosis requires assay of erythrocyte UMP hydrolysis to form uridine and inorganic phosphate. The enzyme defect should be suspected in patients with nonspherocytic hemolytic anemia with basophilic stippling. The anemia is usually moderate, and transfusions are rarely necessary.

Treatment
There is no specific treatment. Splenectomy has not proved to be an effective treatment. Lead-induced acquired pyrimidine 5′ nucleotidase deficiency is treatable, unlike the congenital deficiency.

OVERACTIVE CYTOSOLIC 5′-NUCLEOTIDASE (PYRIMIDINE NUCLEOTIDE DEPLETION)
Pyrimidine nucleotide depletion and overactive cytosolic 5′-nucleotidase, may lead to a neurodevelopmental disorder. Four unrelated patients showed 6-10–fold elevation in the activity of pyrimidine 5′-nucleotidase in fibroblasts with both purine and pyrimidine substrates. Investigation in cultured fibroblasts derived from these patients showed normal incorporation of purine bases into nucleotides but decreased incorporation of uridine and orotic acid.

Clinical
Clinical manifestations include developmental delay, seizures, ataxia, recurrent infections, severe language deficit, hyperactivity, short attention span, and aggressive behavior appearing within the first few years of life. Affected patients show electroencephalogram abnormalities. Metabolic testing is normal except for persistent hypouricosuria. It is proposed that increased catabolic activity and decreased pyrimidine salvage cause a deficiency of pyrimidine nucleotides.

Treatment
Treatment is with oral uridine based on compensating for the increased nucleotide catabolism. All reported patients treated with uridine showed improved speech and behavior, decreased seizure activity with discontinuation of seizure medications, and decreased frequency of infections.

Thymidine Phosphorylase Deficiency (Mitochondrial Neurogastrointestinal Encephalomyopathy)
Thymidine phosphorylase catalyzes the catabolism in mitochondria of thymidine to thymine. This enzyme is also known as "platelet-derived

endothelial cell growth factor" because of its angiogenic properties, or "gliostatin" indicating its inhibitory effects on glial cell proliferation. It has been implicated in mitochondrial nucleoside metabolism. Plasma thymidine level is increased more than 20-fold in patients compared to controls. Loss of function of thymidine phosphorylase causes mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), which is inherited as a single autosomal recessive disorder, causing mitochondrial DNA depletion and instability. In MNGIE, loss of thymidine phosphorylase activity causes toxic accumulations of the nucleosides thymidine and deoxyuridine that are incorporated by the mitochondrial pyrimidine salvage pathway and cause deoxynucleoside triphosphate pool imbalances.

Genetics

The *TYMP* gene encoding thymidine phosphorylase has been identified as the MNGIE gene and is mapped to chromosome 22q13.32-qter, but the protein is imported into mitochondria.

Clinical Manifestations

Clinical manifestations of MNGIE include ptosis, progressive external ophthalmoparesis, gastrointestinal dysmotility and malabsorption, cachexia, peripheral neuropathy, skeletal muscle myopathy and leukoencephalopathy.

Laboratory

Muscle biopsies typically reveal mitochondrial abnormalities. Screening is performed by detection of grossly raised thymidine and deoxyuridine in urine, which are normally absent. Confirmation of the diagnosis can made by assay of thymidine phosphorylase activity in peripheral leukocytes. Molecular genetic analysis will show functional mutations in the *TYMP* gene. Increased thymidine and/or deoxyuridine nucleotides may cause mitochondrial nucleotide pool imbalance resulting in mitochondrial DNA alterations, in particular DNA depletion.

Treatment

Supportive treatment is indicated. There is no established therapy for MNGIE; bone marrow transplantation has been performed on several patients but no improvement in symptoms or progression of the disease has been reported. Allogeneic hematopoietic stem cell transplantation to restore thymidine phosphorylase activity and eliminate toxic metabolites is a potential therapy for MNGIE.

THYMIDINE KINASE 2 DEFICIENCY

Thymidine kinase 2 (TK2) is a key enzyme for the pyrimidine salvage pathway to provide precursor nucleotide for mitochondrial DNA. TK2 deficiency causes tissue-specific depletion of mitochondrial DNA. TK2 normally phosphorylates thymidine and deoxycytidine.

Genetics

The TK2 gene is located on chromosome 16q 22; the deficiency is inherited in an autosomal recessive manner.

Clinical

Clinically, affected individuals with TK2 deficiency have severe myopathy and depletion of muscular mitochondrial DNA in infancy.

Treatment

No specific treatment is available. Supportive treatment is indicated.

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Chapter 90

Hutchinson-Gilford Progeria Syndrome

Leslie B. Gordon

Hutchinson-Gilford progeria syndrome (progeria) is a rare, fatal, autosomal dominant segmental premature aging disease. With an estimated incidence of 1 in 4,000,000 live births and prevalence of 1 in 18 million, there were a total of 350 children living with progeria in 2013 worldwide. There is no gender, ethnic, or regional bias. Progeria is caused by a single base mutation in *LMNA*, which results in the production of a mutant lamin A protein called progerin. Progerin is found in increased concentration in skin and the vascular wall of normal older compared to younger individuals, suggesting a role in normal aging. Children develop progressive atherosclerosis and die of heart attacks or strokes at a median age of 14.5 yr, most often between ages 5 and 20 yr.

CLINICAL MANIFESTATIONS

Children develop the appearance of accelerated aging. Physical appearance changes dramatically each year that the children age (Fig. 90-1).

Dermatologic Changes

Skin findings are often apparent as initial signs of progeria. These are variable in severity and include areas of discoloration, stippled pigmentation, tightened areas that can restrict movement, and areas of the trunk or legs where small (1-2 cm) soft, bulging skin is present. Although usually born with normal hair present, patients lose cranial hair within the first few years, and are left with soft, downy, sparse immature hair on the scalp, no eyebrows, and scant eye lashes.

Failure to Thrive

Children with progeria experience apparently normal fetal and early postnatal development. Within the first year of life, abnormalities in growth and body composition are readily apparent; severe failure to thrive ensues, heralding generalized lipoatrophy, with apparent wasting of limbs, circumoral cyanosis, and prominent veins around the scalp, neck, and trunk. The mean weight, which is normal at birth, decreases to below the third percentile for normal children despite adequate caloric intake for normal growth and normal resting energy expenditure. A retrospective data set of 35 children showed an average weight gain of only 0.44 kg/year, beginning at 24 mo of age and persisting throughout life. There is interpatient variation in weight gain, but the projected weight gain over time in an individual patient is constant, linear, and very predictable. Children with progeria reach a final height of approximately 1 m and weight of approximately 14 kg. Head circumference is normal. Weight deficit is more pronounced than height deficit and this, associated with the loss of subcutaneous fat, results in the emaciated appearance characteristic of children with progeria. Clinical problems caused by the lack of subcutaneous fat include insulin resistance, sensitivity to cold temperatures, and foot discomfort because of a lack of fat cushioning. Although overt diabetes is very unusual in progeria, approximately 30-40% of children suffer from insulin resistance.

Ocular Abnormalities

Tightened skin and a paucity of subcutaneous fat around the eyes causes most patients to sleep with eyelids partially open, resulting in corneal dryness and eye tearing. Patients can develop exposure keratopathy and/or corneal ulcers, which can disrupt sight. Artificial tears

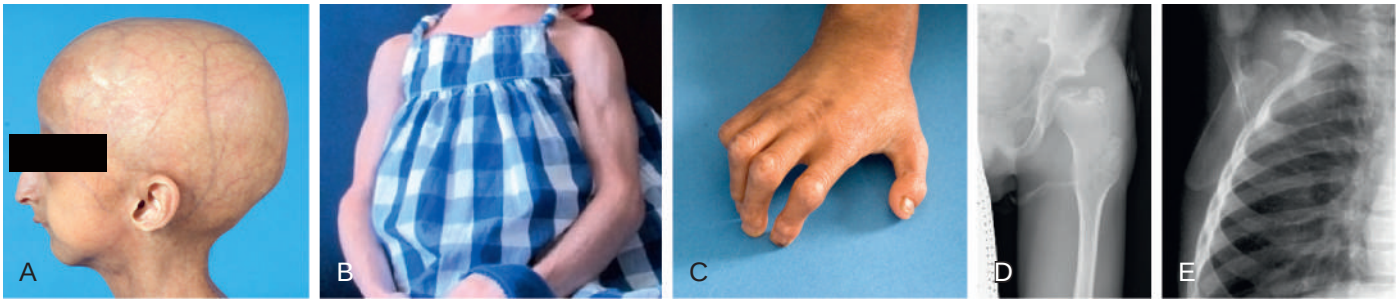

Figure 90-1 **A,** Profile of head and face of a child with progeria. Note the alopecia, beaked nose, and retrognathia. **B,** The arms of this child demonstrate absence of subcutaneous fat. **C,** Contractures in multiple joints including fingers, elbows, hips, knees, and ankles may be present at birth and/or in later years. **D,** Hip dysplasia is often progressive and may result in avascular necrosis, hip dislocation, and inability to bear weight. **E,** A pyriform chest structure and a small clavicle can lead to reducible shoulder dislocations. *(Photos courtesy of The Progeria Research Foundation and Boston Children's Hospital.)*

during the day and taping or covering the eyes at night are recommended. Some degree of photophobia is common.

Dental Abnormalities

Dentition is severely delayed in development and crowded due to micrognathia. Eruption may be delayed for many months, and primary teeth may persist for the duration of life. Secondary teeth are present, but may or may not erupt. They sometimes erupt on the lingual and palatal surfaces of the mandibular and maxillary alveolar ridges, rather than in place of the primary incisors. In some but not all cases, extracting primary teeth promotes movement of secondary teeth into place.

Bone and Cartilaginous Abnormalities

Aberrant development of bone structure and bone density represents a unique skeletal dysplasia which is not based in malnutrition. Acroosteolysis of the distal phalanges, distal clavicular resorption and thin, tapered ribs are early signs of progeria that appear as early as 3 mo of age. Facial disproportion, a narrowed nasal bridge and retrognathia make intubation extremely difficult, and fiberoptic intubation is recommended. A pyriform chest structure and a small clavicle can lead to reducible shoulder dislocations (Fig. 90-1*E*). Long bone remodeling of the femoral head–neck axis following knee and ankle contractures results in coxa valga, straightening of the femoral head-neck axis to >125 degrees. The bony pelvis is normal and these changes give rise to a "horse riding" stance. Hip dysplasia is often progressive and may result in avascular necrosis, hip dislocation, and inability to bear weight (Fig. 90-1*D*). Other long bone changes include flaring of the humeral and femoral metaphyses and constriction of the radial neck. Bone age is generally normal, with variable readings within a single radiograph. Growth plates are normal. Bone structure assessed by peripheral quantitative computed tomography of the radius demonstrates distinct and severe abnormalities in bone structural geometry and skeletal strength. Areal bone density Z scores by dual-energy X-ray absorptiometry are abnormally low, but improve after adjustment for height and age. Fracture rates in progeria are normal.

Joint contractures, a result of ligamentous and skin changes, limit range of motion. Contractures in multiple joints including fingers, elbows, hips, knees and ankles may be present at birth and/or in later years (Fig. 90-1*C*). Physical therapy is recommended routinely and throughout life to maximize joint function.

Hearing

Low tone conductive hearing loss is pervasive in progeria, and is indicative of a stiff tympanic membrane, and/or deficits in the middle ear bony and ligamentous structures. Overall, this does not affect ability to hear the usual spoken tones but preferential classroom seating is recommended.

Cardiovascular Disease

Death occurs primarily from myocardial infarction, and less often from strokes. Progeria is a primary vasculopathy, characterized by pervasive accelerated vascular stiffening, followed by large and small vessel occlusive disease as a result of atherosclerotic plaque formation, with valvular and cardiac insufficiency in later years. Hypertension, angina, cardiomegaly, metabolic syndrome, and heart failure are common end-stage events. Routine carotid ultrasound for plaque monitoring, carotid-femoral pulse wave velocity measures for vascular stiffening, and echocardiography are recommended.

Cerebrovascular Arteriopathy and Stroke

Cerebral infarction may occur while the child exhibits a normal electrocardiogram. The earliest incidence of stroke occurred at the age of 0.4 yr. More often they occur in the later yr. Radiographic evidence on MRI of infarction can be found in 60% of the patients, in whom half are clinically silent. Both large- and small-vessel disease is found; collateral vessel formation is extensive. Carotid artery occlusions are well documented, but infarction can occur in their absence. Propensity toward strokes and an underlying stiff vasculature make maintaining adequate blood pressure through hydration (i.e., habitually drinking well) a priority in progeria; special care should be taken when considering maintenance of consistent blood pressure during general anesthesia, airplane trips, and hot weather.

Normally Functioning Systems

Liver, kidney, thyroid, immune, gastrointestinal, and neurologic systems (other than stroke-related) remain intact. Intellect is normal for age.

Laboratory Findings

The most consistent laboratory findings are low serum leptin and insulin resistance. Platelet count is often moderately high. Lipid panels, blood chemistries, endocrine and coagulation and other tests are generally normal.

MOLECULAR PATHOGENESIS

Mutations in the *LMNA* gene cause progeria. The normal *LMNA/C* gene encodes the proteins lamins A and C, of which only lamin A is associated with human diseases. The lamin proteins are the principal proteins of the nuclear lamina, a complex molecular interface located between the inner membrane of the nuclear envelope and chromatin. The integrity of the lamina is central to many cellular functions, creating and maintaining structural integrity of the nuclear scaffold, DNA replication, RNA transcription, organization of the nucleus, nuclear pore assembly, chromatin function, cell cycling, and apoptosis.

Progeria is almost always a sporadic autosomal dominant disease. There is 1 proven case of mosaicism. Progeria is caused by the accelerated use of an alternative, internal splice site that results in the deletion of 150 base pairs in the 3' portion of exon 11 of the *LMNA* gene. In approximately 90% of cases, this results from a single C to T transition at nucleotide 1824 that is silent (Gly608Gly), but optimizes an internal splice site within exon 11. The remaining 10% of cases possess 1 of several single base mutations within the intron 11 splice donor site,

thus reducing specificity for this site and altering the splicing balance in favor of the internal splice. Subsequent to all of these mutations, translation followed by posttranslational processing of the altered messenger RNA produces progerin, a shortened abnormal lamin A protein with a 50-amino-acid deletion near its C-terminal end. An understanding of the posttranslational processing pathway and how it is altered to create progerin has led to a number of treatment prospects for the disease.

Both lamin A and progerin possess a farnesyl side group attached during posttranslational processing. This is a lipophilic moiety which facilitates intercalation of proteins into the inner nuclear membrane where most of the lamin and progerin functions are performed. For normal lamin A, loss of the farnesyl anchor releases prelamin from the nuclear membrane, rendering it soluble for autophagic degradation. However, progerin retains its farnesyl moiety. It remains anchored to the membrane, binding other proteins, causing blebbing of the nucleus, disrupting mitosis, and altering gene expression.

Disease in progeria is produced by a ***dominant negative*** mechanism; it is the action of progerin, not the diminution of lamin A that causes the disease phenotype. The severity of disease is determined in part by progerin levels, which are regulated by the particular mutation, tissue type, or other factors influencing use of the internal splice site.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Overall, the constellation of small body habitus, bone, hair, subcutaneous fat, and skin changes results in the marked physical resemblance among patients with progeria (Fig. 90-2). For this reason, clinical diagnosis can be achieved or excluded with relative confidence even at young ages, though there have been a few cases of low progerin-expressing patients with extremely mild signs. Clinical suspicion should be followed by *LMNA* genetic sequence testing. The disorders that resemble progeria are those grouped as the senile-like syndromes and include Wiedemann-Rautenstrauch syndrome, Werner syndrome, Cockayne syndrome, Rothmund-Thomson syndrome, restrictive dermopathy, and Nestor-Guillermo progeria syndrome (Table 90-1). Patients often fall under none of these diagnoses and represent ultrarare, unnamed progeroid laminopathies that carry either non–progerin-producing mutations in lamin or the lamin-associated enzyme Zmpste24, or progeroid syndromes without lamin mutations.

Figure 90-2 **Two unrelated children with progeria.** Note the physical resemblance of each to the other. *(Photo courtesy of The Progeria Research Foundation.)*

Table 90-1 Features of Hutchinson-Gilford Progeria Syndrome and Disorders That Resemble It

	HUTCHINSON-GILFORD PROGERIA SYNDROME	WIEDEMANN-RAUTENSTRAUCH SYNDROME	WERNER SYNDROME	COCKAYNE SYNDROME	ROTHMUND-THOMPSON SYNDROME	RESTRICTIVE DERMOPATHY
Causative gene	*LMNA*	Unknown	*WRN, LMNA*	*CSA, SP*	RecQL helicase gene w/8q24.3	LAMIN A/C mutations
Inheritance	Dominant	Recessive	Recessive	Recessive	Recessive	Recessive
Onset	Infancy	Newborn	Young Adult	Newborn	Infancy	Newborn
Hair loss	+Total	Scalp + patchy	Scalp + male pattern	–	+Diffuse	+Diffuse
Skin thinning	+	+	+	–	+	+
Subcutaneous fat loss	+	+	+	+	–	–
Skin calcification	–	–	+	–	–	–
Hyperkeratosis	–	–	+	–	+	–
Cataracts	–	–	+	+	+	–
Short stature	+	+	+	+	+	+
Coxa valga	+	–	–	–	–	–
Acroosteolysis	+	+	+	–	–	–
Mandibular dysplasia	+	+	–	–	–	+
Vasculopathy	+	–	+	+	–	–
Voice abnormality	+	–	+	–	–	–
Diabetes	–	+	+	–	–	–
Hypogonadism	+	–	+	+	+	–
Dental abnormality	+	+	+	+	+	+

Modified from Hegele RA: Drawing the line in progeria syndromes, Lancet 362;416–417, 2003.

PROGNOSIS, TREATMENT, AND PATIENT RESOURCES

Children with progeria develop a severe premature form of atherosclerosis. Prior to death, cardiac decline with left-sided hypertrophy, valvular insufficiency, and pulmonary edema develop; neurovascular decline with transient ischemic attack, strokes, and occasionally seizures can result in significant morbidity. Death occurs as a result of heart attack (~80%) and stroke (~20%), generally between age 5 and 20 yr, with a median life span of 14.5 yr.

No specific FDA-approved treatment for this condition exists. Growth hormone has resulted in increased rate of weight gain and overall size when administered at 0.05 mg/kg/day SC, but weight still remained well below that seen in normal children. Low-dose aspirin therapy is recommended at 2 mg/kg body weight per day, as an extension of what is known about decreasing cardiovascular risk in the general at-risk adult population. It is not known whether growth hormone or low-dose aspirin has any effect on morbidity or mortality.

The first potentially beneficial treatment prospect for progeria was published in 2011. Inhibiting posttranslational progerin farnesylation with a drug named lonafarnib was aimed at preventing this disease-causing protein from anchoring to the nuclear membrane where it carries out much of its damage. A prospective single-arm clinical trial was initiated with a cohort of 25 progeria patients between 3 and 16 yr of age, treated for a minimum of 2 yr (NCT00425607). Lonafarnib was well tolerated; the most common side effects were diarrhea, nausea, and loss of appetite, which generally improved with time. Subgroups of patients experienced increased rate of weight gain, decreased vascular stiffness measured via improved carotid-femoral wave velocity, and carotid artery echodensity, increased radial bone structural rigidity, improved sensorineural hearing, and early evidence of decreased headache, transient ischemic attack and stroke rates. Dermatologic, dental, joint contracture, insulin resistance, lipodystrophy, bone mineral density, and joint contractures were unaffected by drug treatment. The evidence for improved cardiovascular status in children with progeria is most encouraging. A study published in 2014 demonstrated increased estimated lifespan for children with progeria taking farnesylation inhibitors such as lonafarnib.

An ongoing clinical trial which adds pravastatin and zoledronate, 2 FDA-approved drugs, to the lonafarnib regimen is similarly aimed at inhibiting progerin farnesylation (NCT00916747).

The Progeria Foundation (www.progeriaresearch.org) maintains an international registry, diagnostics program, and complete patient care manual and coordinates clinical treatment trials.

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Chapter 91

The Porphyrias

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Porphyrias are metabolic diseases resulting from altered activities of specific enzymes of the heme biosynthetic pathway. These enzymes are most active in bone marrow and liver. Erythropoietic porphyrias, in which overproduction of heme pathway intermediates occurs primarily in bone marrow erythroid cells, usually present at birth or in early childhood with cutaneous photosensitivity, or in the case of congenital erythropoietic porphyria (CEP), even in utero as nonimmune hydrops. Erythropoietic protoporphyria (EPP) is the most common porphyria in children and of most interest to pediatricians. Most porphyrias are hepatic, with overproduction and initial accumulation of porphyrin precursors or porphyrins in the liver. Activation of hepatic porphyrias is very rare during childhood, reflecting the distinct hepatic regulatory mechanisms for heme biosynthesis that are influenced by pubertal development. Homozygous forms of the hepatic porphyrias may manifest clinically prior to puberty. Children who are heterozygous for inherited hepatic porphyrias may present with nonspecific and unrelated symptoms, and parents often request advice about long-term prognosis and express concerns about drugs that may exacerbate these conditions.

The DNA sequences and chromosomal locations are established for the human genes of the enzymes in this pathway, and multiple disease-related mutations have been found for each porphyria. The inherited porphyrias display autosomal dominant, recessive or X-linked inheritance. Although initial diagnosis of porphyria by biochemical methods remains essential, it is especially important to confirm the diagnosis by demonstrating a specific gene mutation(s).

THE HEME BIOSYNTHETIC PATHWAY

Heme is required for a variety of hemoproteins such as hemoglobin, myoglobin, respiratory cytochromes, and cytochrome P450 enzymes (CYPs). It is believed that the 8 enzymes in the pathway for heme biosynthesis are active in all tissues. Hemoglobin synthesis in erythroid precursor cells accounts for approximately 85% of daily heme synthesis in humans. Hepatocytes account for most of the rest, primarily for synthesis of CYPs, which are especially abundant in the liver endoplasmic reticulum, and turn over more rapidly than many other hemoproteins, such as the mitochondrial respiratory cytochromes. Pathway intermediates are the porphyrin precursors δ-aminolevulinic acid (ALA, also known as 5-aminolevulinic acid) and porphobilinogen (PBG), and porphyrins (mostly in their reduced forms, known as porphyrinogens) (Fig. 91-1). At least in humans, these intermediates do not accumulate in significant amounts under normal conditions or have important physiologic functions.

A deficiency of each enzyme in the pathway is associated with a specific porphyria (Table 91-1). The first enzyme, ALA synthase (ALAS), occurs in 2 forms. An erythroid specific form, termed ALAS2, is deficient in X-linked sideroblastic anemia, as a result of mutations of the *ALAS2* gene on chromosome Xp11.2. Gain of function mutations of *ALAS2* because of deletions in the last exon cause X-linked protoporphyria (XLP), a cutaneous porphyria which is phenotypically identical to EPP.

Regulation of heme synthesis differs in the 2 major heme-forming tissues. Liver heme biosynthesis is primary controlled by ALAS1. Synthesis of ALAS1 in liver is regulated by a "free" heme pool (see Fig. 91-1), which can be augmented by newly synthesized heme or by existing heme released from hemoproteins and destined for breakdown to biliverdin by heme oxygenase.

In the erythron, novel regulatory mechanisms allow for the production of the very large amounts of heme needed for hemoglobin synthesis. The response to stimuli for hemoglobin synthesis occurs during cell differentiation, leading to an increase in cell number. Also, unlike the liver, heme has a stimulatory role in hemoglobin formation, and the stimulation of heme synthesis in erythroid cells is accompanied by increases not only in ALAS2, but also by sequential induction of other heme biosynthetic enzymes. Separate erythroid-specific and nonerythroid or "housekeeping" transcripts are known for the first 4 enzymes in the pathway. The separate forms of ALAS are encoded by genes on different chromosomes, but for each of the other 3, erythroid and nonerythroid transcripts are transcribed by alternative promoters in the same gene. Heme also regulates the rate of its synthesis in erythroid cells by controlling the transport of iron into reticulocytes.

Intermediates of the heme biosynthetic pathway are efficiently converted to heme and, normally, only small amounts of the intermediates are excreted. Some may undergo chemical modifications before excretion. Whereas the porphyrin precursors ALA and PBG are colorless, nonfluorescent, and largely excreted unchanged in urine, PBG may degrade to colored products such as the brownish pigment called *porphobilin* or spontaneously polymerize to uroporphyrins. Porphyrins are red in color and display bright red fluorescence when exposed to long wavelength UV light. Porphyrinogens, which are colorless and nonfluorescent, are the reduced form of porphyrins, and when they

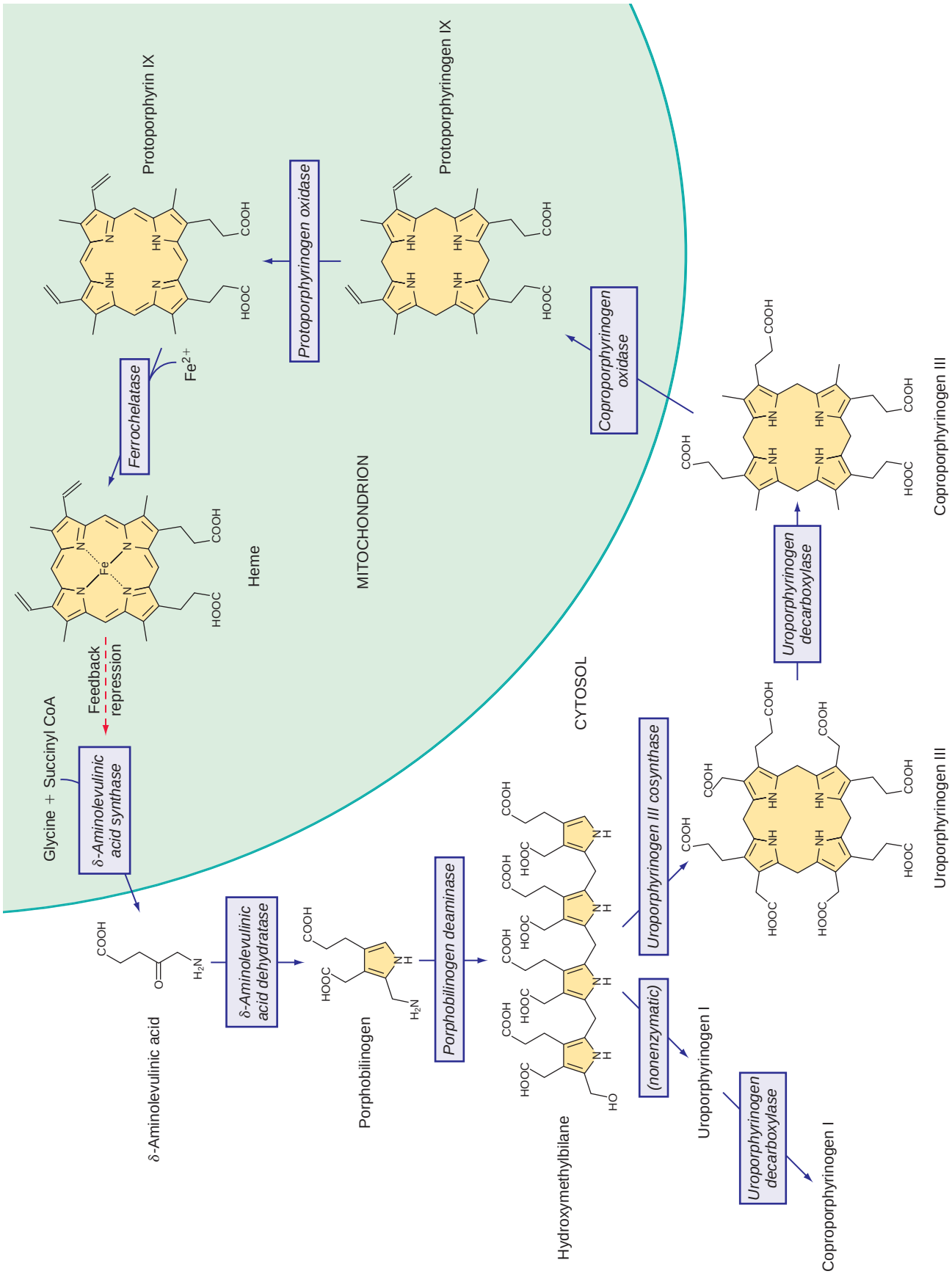

Figure 91-1 Enzymes and intermediates of the heme biosynthetic pathway. The pathway is regulated in the liver by the end product, heme, mainly by feedback repression *(dashed arrow)*.

Table 91-1 The Human Porphyrias: Mutations, Time of Presentation, and Tissue- and Symptom-Based Classifications

DISEASE (ABBREVIATION)	ENZYME (ABBREVIATION)	INHERITANCE	PRESENTATION	Classifications			
				HEPATIC	ERYTHROPOIETIC	ACUTE/ NEUROLOGIC	CUTANEOUS
X-Linked protoporphyria (XLP)	*δ-Aminolevulinate synthase 2 (ALAS2)*	X-linked	Childhood		X		X
δ-Aminolevulinic acid dehydratase porphyria (ADP)	*δ-Aminolevulinic acid dehydratase (ALAD)*	Autosomal recessive	Mostly post puberty	X	X*	X	
Acute intermittent porphyria (AIP)	*Porphobilinogen deaminase (PBGD)*	Autosomal dominant	Post puberty	X		X	
Homozygous AIP		Homozygous dominant	Childhood	X	X	X	
Congenital erythropoietic porphyria (CEP)	*Uroporphyrinogen III synthase (UROS)*	Autosomal recessive	In utero or infancy		X		X
Porphyria cutanea tarda (PCT) type 1	*Uroporphyrinogen decarboxylase (UROD)*	Sporadic	Adults	X			X
PCT type 2†		Autosomal dominant	Adults	X			X
PCT type 3		Unknown	Adults	X			X
Hepatoerythropoietic porphyria (HEP)		Homozygous dominant	Childhood	X	X*		X
Hereditary coproporphyria (HCP)	*Coproporphyrinogen oxidase (CPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous HCP		Homozygous dominant	Childhood	X	X	X	X
Variegate porphyria (VP)	*Protoporphyrinogen oxidase (PPOX)*	Autosomal dominant	Post puberty	X		X	X
Homozygous VP		Homozygous dominant	Childhood	X	X	X	X
Erythropoietic protoporphyria (EPP)	*Ferrochelatase (FECH)*	Autosomal recessive(most commonly heteroallelic with hypomorphic allele)	Childhood		X		X

*ADP and HEP are considered primarily hepatic porphyrias, but substantial increases in erythrocyte zinc protoporphyrin suggest an erythropoietic component.
†PCT is a result of inhibition of hepatic UROD. Autosomal dominant inheritance of a partial deficiency of UROD is a predisposing factor in cases defined as familial (type 2) PCT.

Table 91-2 The 3 Most Common Human Porphyrias and Their Major Features

	PRESENTING SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurologic, adult onset	Drugs (mostly P450-inducers), progesterone, dietary restriction	Urinary porphobilinogen	Hemin, glucose
Porphyria cutanea tarda	Skin blistering and fragility (chronic), adult onset	Iron, alcohol, smoking, estrogens, hepatitis C, HIV, halogenated hydrocarbons	Plasma (or urine) porphyrins	Phlebotomy, low-dose hydroxychloroquine
Erythropoietic protoporphyria	Skin pain and swelling (mostly acute), childhood onset		Erythrocyte (or plasma) porphyrins	Beta-carotene

accumulate are readily autoxidized to the corresponding porphyrins when outside the cell. Only the type III isomers of uroporphyrinogen and coproporphyrinogen are converted to heme (see Fig. 91-1).

ALA and PBG are excreted in urine. Excretion of porphyrins and porphyrinogens in urine or bile is determined by the number of carboxyl groups. Those with many carboxyl groups, such as uroporphyrin (octacarboxyl porphyrin) and heptacarboxyl porphyrin, are water soluble and readily excreted in urine. Those with fewer carboxyl groups, such as protoporphyrin (dicarboxyl porphyrin), are not water soluble and are excreted in bile and feces. Coproporphyrin (tetracarboxyl porphyrin) is excreted partly in urine and partly in bile. Because coproporphyrin I is more readily excreted in bile than is coproporphyrin III, impaired hepatobiliary function may increase total urinary coproporphyrin excretion and the ratio of these isomers.

CLASSIFICATION AND DIAGNOSIS OF PORPHYRIAS

Two classification schemes reflect either the underlying pathophysiology or clinical features, and both are useful for diagnosis and treatment (see Table 91-1). In **hepatic** and **erythropoietic** porphyrias, the source of excess production of porphyrin precursors and porphyrins is the liver and bone marrow, respectively. **Acute porphyrias** cause neurologic symptoms that are associated with increases of 1 or both of the porphyrin precursors, ALA and PBG. In the **cutaneous porphyrias,** photosensitivity results from transport of porphyrins in blood from the liver or bone marrow to the skin. **Dual porphyria** refers to the very rare cases of porphyria with deficiencies of 2 different heme pathway enzymes.

It is notable that, porphyria cutanea tarda (PCT), acute intermittent porphyria (AIP) and EPP in that order the 3 most common porphyrias considering all age groups are very different in clinical presentation, precipitating factors, methods of diagnosis, and effective therapy (Table 91-2). Two of the 4 acute porphyrias, hereditary coproporphyria (HCP) and variegate porphyria (VP), can also cause lesions indistinguishable from PCT (see Table 91-1). CEP causes more severe blistering lesions, often with secondary infection and mutilation. EPP and XLP have the same phenotype and are distinct from the other cutaneous porphyrias in causing nonblistering photosensitivity that occurs acutely after sun exposure. EPP is also the most common porphyria to become manifest before puberty.

First-Line Laboratory Diagnostic Testing

A few sensitive and specific first-line laboratory tests should be obtained whenever symptoms or signs suggest the diagnosis of porphyria. If a first-line or screening test is significantly abnormal, more comprehensive testing should follow to establish the type of porphyria. Overuse of laboratory tests for screening can lead to unnecessary expense and even delay in diagnosis. In patients who present with a past diagnosis of porphyria, laboratory reports that were the basis for the original diagnosis must be reviewed, and if these were inadequate, further testing considered.

Acute porphyria should be suspected in patients with neurovisceral symptoms such as abdominal pain after puberty, when initial clinical evaluation does not suggest another cause, and *urinary porphyrin precursors (ALA and PBG)* and *total porphyrins* should be measured. Urinary PBG is virtually always increased during acute attacks of acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP), and is not substantially increased in any other medical conditions. Therefore, this measurement is both sensitive and specific. A method for rapid, in-house testing for urinary PBG, such as the Trace PBG kit (Thermo Scientific, 1-800-640-0640), should be available in-house at all major medical facilities. Results from **spot** (**single void**) urine specimens are highly informative because very substantial increases are expected during acute attacks of porphyria. A 24 hr collection can unnecessarily delay diagnosis. The same spot urine specimen should be saved for quantitative determination of ALA and PBG to confirm the qualitative PBG result and total porphyrins. This will detect patients with ALA dehydratase porphyria (ADP) and some cases of HCP and VP, as urinary porphyrins may remain increased longer than porphyrin precursors in the latter disorders. Measurement of urinary porphyrins alone should be avoided for screening, because these are often increased in many disorders other than porphyrias, such as chronic liver disease, and misdiagnoses of porphyria can result from minimal increases in urinary porphyrins that have no diagnostic significance.

PBG is a colorless pyrrole that forms a violet pigment with Ehrlich reagent (*p*-dimethylaminobenzaldehyde). Other substances, principally urobilinogen, also react with Ehrlich aldehyde. A reliable quantitative method for both ALA and PBG, which uses small anion and cation exchange columns to separate interfering substances before adding Ehrlich reagent, has been available for many years. ALA is reacted to form a pyrrole, which is then also measured using Ehrlich reagent. The Trace PBG kit to detect increased PBG is based on this method.

Blistering Cutaneous Porphyrias

Blistering skin lesions caused by porphyria are virtually always accompanied by increases in *total plasma porphyrins.* A fluorometric method is preferred, because the porphyrins in plasma in VP are mostly covalently linked to plasma proteins and may be less readily detected by high-pressure liquid chromatography. The normal range for plasma porphyrins is somewhat increased in patients with end-stage renal disease. Urinary porphyrins are also increased in these porphyrias, but also in many other medical conditions.

Nonblistering Cutaneous Porphyria

Although a total plasma porphyrin determination will usually detect EPP and XLP, an erythrocyte protoporphyrin determination is more sensitive. Increases in erythrocyte protoporphyrin occur in many other conditions. Therefore, the diagnosis of EPP must be confirmed by showing a predominant increase in metal-free protoporphyrin rather than zinc protoporphyrin. In XLP, both free and zinc protoporphyrin can be elevated. Interpretation of laboratory reports can be misleading, because the term *free erythrocyte protoporphyrin* often refers to iron-free protoporphyrin (including zinc protoporphyrin) rather than metal-free protoporphyrin.

Second-Line Testing

More extensive testing is well justified when a first-line test is positive. A substantial increase in PBG may be caused by AIP, HCP, or VP. These acute porphyrias can be distinguished by measuring erythrocyte porphobilinogen deaminase (PBGD), urinary porphyrins (using the same spot urine sample), fecal porphyrins, and plasma porphyrins. The various porphyrias that cause blistering skin lesions are differentiated by measuring porphyrins in urine, feces, and plasma. Confirmation at the DNA level is important once the diagnosis is established by biochemical testing.

Testing for Subclinical Porphyria

It is often difficult to diagnose or "rule out" porphyria in patients who had suggestive symptoms months or years in the past, and in relatives of patients with acute porphyrias, because porphyrin precursors and porphyrins may be normal. More extensive testing and consultation with a specialist laboratory and physician may be needed. Before evaluating relatives, the diagnosis of porphyria should be firmly established in an index case, and the laboratory results reviewed to guide the choice of tests for the family members. The index case or another family member with confirmed porphyria should be retested if necessary. Identification of a disease-causing mutation in an index case greatly facilitates detection of additional gene carriers as biochemical tests in latent carriers may be normal.

δ-AMINOLEVULINIC ACID DEHYDRATASE PORPHYRIA

This porphyria is sometimes termed *Doss porphyria* after the investigator who described the first cases. The term *plumboporphyria* emphasizes the similarity of this condition to lead poisoning, but incorrectly implies that it is due to lead exposure.

Etiology

This porphyria results from a deficiency of δ-aminolevulinic acid dehydratase (ALAD), which is inherited as an autosomal recessive trait. Only 6 cases have been confirmed by mutation analysis. The prevalence of heterozygous ALAD deficiency was estimated to be <1% in Germany and approximately 2% in Sweden.

Pathology and Pathogenesis

ALAD catalyzes the condensation of 2 molecules of ALA to form the pyrrole PBG (see Fig. 91-1). The enzyme is subject to inhibition by a number of exogenous and endogenous chemicals. ALAD is the principal lead-binding protein in erythrocytes, and lead can displace the zinc atoms of the enzyme. Inhibition of erythrocyte ALAD activity is a sensitive index of lead exposure.

Eleven abnormal ALAD alleles, most with point mutations, have been identified, some expressing partial activity, such that heme synthesis is partially preserved. The amount of residual enzyme activity may predict the phenotypic severity of this disease. Immunochemical studies in 3 cases demonstrated nonfunctional enzyme protein that cross-reacted with anti-ALAD antibodies. Five of the 6 reported ADP cases inherited a different ALAD mutation from each parent. One reported patient with late-onset disease who was heterozygous for a mutant allele developed ADP associated with a myeloproliferative disorder and expansion of an affected clone of erythroid cells.

ADP is often classified as a hepatic porphyria, although the site of overproduction of ALA is not established. A patient with severe, early-onset disease underwent liver transplantation, without significant clinical or biochemical improvement, which might suggest that the excess intermediates did not originate in the liver. Excess urinary coproporphyrin III in ADP might originate from metabolism of ALA to porphyrinogens in a tissue other than the site of ALA overproduction. Administration of large doses of ALA to normal subjects also leads to substantial coproporphyrinuria. Increased erythrocyte protoporphyrin may, as in all other homozygous porphyrias, be explained by accumulation of earlier pathway intermediates in bone marrow erythroid cells during hemoglobin synthesis, followed by their transformation to protoporphyrin after hemoglobin synthesis is complete. Neurologic symptoms are attributed to neurotoxic effects of ALA, but this is unproven.

Clinical Manifestations

In most cases, symptoms resemble other acute porphyrias, including acute attacks of abdominal pain and neuropathy. Precipitating factors, such as exposure to harmful drugs, have not been evident in most cases. Four of the reported cases were adolescent males. A Swedish infant had more severe disease, with neurologic impairment and failure to thrive. A 63 yr old man in Belgium developed an acute motor polyneuropathy concurrently with a myeloproliferative disorder.

Laboratory Findings

Urinary ALA, coproporphyrin III, and erythrocyte zinc protoporphyrin are substantially increased. Urinary PBG is normal or slightly increased. Erythrocyte ALAD activity is markedly reduced and both parents should have approximately half-normal activity of this enzyme and normal urinary ALA.

Diagnosis and Differential Diagnosis

The 3 other acute porphyrias are characterized by substantial increases in both ALA and PBG. In contrast, ALA but not PBG is substantially increased in ADP. A marked deficiency of erythrocyte ALAD and half-normal activity in the parents support the diagnosis. Other causes of ALAD deficiency, such as **lead poisoning,** must be excluded. Succinylacetone accumulates in hereditary tyrosinemia type 1 and is structurally similar to ALA, inhibits ALAD, and can cause increased urinary excretion of ALA and clinical manifestations that resemble acute porphyria. Idiopathic acquired ALAD deficiency has been reported. Unlike lead poisoning, the deficient ALAD activity in ADP is not restored by the in vitro addition of sulfhydryl reagents such as dithiothreitol. Even if no other cause of ALAD deficiency is found, it is essential to confirm the diagnosis of ADP by molecular studies.

Treatment

Treatment experience is limited but is similar to other acute porphyrias. Glucose seems not very effective but may be tried for mild symptoms. Hemin therapy was apparently effective for acute attacks in adolescent male cases, and weekly infusions prevented attacks in 2 of these cases. Hemin was not effective either biochemically or clinically in the Swedish child with severe disease, and produced a biochemical response but no clinical improvement in the Belgian man with a late-onset form, who had a peripheral neuropathy but no acute attacks. Hemin is also effective in treating porphyria-like symptoms associated with hereditary tyrosinemia, and can significantly reduce urinary ALA and coproporphyrin in lead poisoning. Avoidance of drugs that are harmful in other acute porphyrias is advisable. Liver transplantation was not effective in the child with severe disease.

Prognosis

The outlook is generally good in typical cases, although recurrent attacks may occur. The course was unfavorable in the Swedish child with more severe disease, and is uncertain in adults with late-onset disease associated with myeloproliferative disorders.

Prevention and Genetic Counseling

Heterozygous parents should be aware that subsequent children are at risk for the disease, as in any autosomal recessive disorder. Prenatal diagnosis is possible, but has not been reported.

ACUTE INTERMITTENT PORPHYRIA

This disorder is also termed *pyrroloporphyria, Swedish porphyria,* and *intermittent acute porphyria* and is the most common type of acute porphyria in most countries.

Etiology

AIP results from the deficient activity of the housekeeping form of PBGD. This enzyme is also known as hydroxymethylbilane (HMB)

synthase; the prior term, uroporphyrinogen I synthase, is obsolete. PBGD catalyzes the deamination and head-to-tail condensation of 4 PBG molecules to form the linear tetrapyrrole, HMB (also known as preuroporphyrinogen; see Fig. 91-1). A unique dipyrromethane cofactor binds the pyrrole intermediates at the catalytic site until 6 pyrroles (including the dipyrrole cofactor) are assembled in a linear fashion, after which the tetrapyrrole HMB is released. The apo-deaminase generates the dipyrrole cofactor to form the holodeaminase, and this occurs more readily from HMB than from PBG. Indeed, high concentrations of PBG may inhibit formation of the holodeaminase. The product HMB can cyclize nonenzymatically to form nonphysiologic uroporphyrinogen I, but in the presence of the next enzyme in the pathway is more rapidly cyclized to form uroporphyrinogen III.

Erythroid and housekeeping forms of the enzyme are encoded by a single gene on human chromosome 11 (11q24.1→q24.2), which contains 15 exons. The 2 isoenzymes are both monomeric proteins and differ only slightly in molecular weight (approximately 40 and 42 kDa, respectively), and result from alternative splicing of 2 distinct messenger RNA (mRNA) transcripts arising from 2 promoters. The housekeeping promoter functions in all cell types, including erythroid cells.

The pattern of inheritance of AIP is autosomal dominant, with very rare homozygous cases that present in childhood. More than 380 *PBGD* mutations, including missense, nonsense, and splicing mutations, and insertions and deletions have been identified in AIP, and in many population groups, including blacks. Most mutations are found in only 1 or a few families. But because of founder effects, some are more common in certain geographic areas such as northern Sweden (W198X), Holland (R116W), Argentina (G116R), Nova Scotia (R173W), and Switzerland (W283X). De novo mutations may be found in approximately 3% of cases. *Chester porphyria* was initially described as a variant form of acute porphyria in a large English family but was found to be caused by a *PBGD* mutation. The nature of the *PBGD* mutation does not account for the severity of the clinical presentation, which varies markedly within families.

Most mutations lead to approximately half-normal activity of the housekeeping and erythroid isozymes and half-normal amounts of their respective enzyme proteins in all tissues of heterozygotes. In approximately 5% of unrelated AIP patients, the housekeeping isozyme is deficient, but the erythroid-specific isozyme is normal. Mutations causing this variant are usually found within exon 1 or its 5′ splice donor site or initiation of translation codon. Immunochemical methods can distinguish mutations that are cross-reactive immunologic material (CRIM)–positive (i.e., having excess CRIM relative to the mutant enzyme activity), whereas CRIM-negative mutations either do not synthesize a mutant enzyme protein, or the protein is not stable and not immunologically detectable using anti-PBGD antibodies. A child with homozygous AIP was found to have inherited a different CRIM-positive mutation from each parent.

Pathology and Pathogenesis

Induction of the rate-limiting hepatic enzyme ALAS1 is thought to underlie acute exacerbations of this and the other acute porphyrias. AIP remains latent (or asymptomatic) in the great majority of those who are heterozygous carriers of *PBGD* mutations, and this is almost always the case before puberty. In those with no history of acute symptoms, porphyrin precursor excretion is usually normal, suggesting that half-normal hepatic PBGD activity is sufficient and hepatic ALAS1 activity is not increased. Many nongenetic factors that lead to clinical expression of AIP, including certain drugs and steroid hormones, have the capacity to induce hepatic ALAS1 and CYPs. Under conditions in which heme synthesis is increased in the liver, half-normal PBGD activity may become limiting and ALA, PBG, and other heme pathway intermediates may accumulate. In addition, heme synthesis becomes impaired and heme-mediated repression of hepatic ALAS1 is less effective.

It is not proven, however, that hepatic PBGD remains constant at approximately 50% of normal activity during exacerbations and remission of AIP, as in erythrocytes. An early report suggested that the enzyme activity is considerably less than half-normal in the liver during an acute attack. Hepatic PBGD activity might be reduced further once AIP becomes activated if, as suggested, excess PBG interferes with assembly of the dipyrromethane cofactor for this enzyme. It also seems likely that currently unknown genetic factors play a contributing role in, for example, patients who continue to have attacks even when known precipitants are avoided.

The fact that AIP is almost always latent before puberty suggests that **endocrine factors,** and especially adult levels of steroid hormones, are important for clinical expression. Symptoms are more common in women suggesting a role for female hormones. Premenstrual attacks are probably the result of endogenous progesterone. Acute porphyrias are sometimes exacerbated by exogenous steroids, including oral contraceptive preparations containing progestins. Surprisingly, pregnancy is usually well tolerated, suggesting that beneficial metabolic changes may ameliorate the effects of high levels of progesterone.

Drugs that are unsafe in acute porphyrias (Table 91-3) include those having the capacity to induce hepatic ALAS1, which is closely associated with induction of CYPs. Some chemicals (e.g., griseofulvin) can increase heme turnover by promoting the destruction of specific CYPs to form an inhibitor (e.g., *N*-methyl protoporphyrin) of ferrochelatase (FECH, the final enzyme in the pathway). Sulfonamide antibiotics are harmful but apparently not inducers of hepatic heme synthesis. Ethanol and other alcohols are inducers of ALAS1 and some CYPs.

Nutritional factors, principally reduced intake of calories and carbohydrates, as may occur with illness or attempts to lose weight, can increase porphyrin precursor excretion and induce attacks of porphyria. Increased carbohydrate intake may ameliorate attacks. Hepatic ALAS1 is modulated by the peroxisome proliferator-activated receptor γ coactivator-1α, which is an important link between nutritional status and exacerbations of acute porphyria.

Other factors have been implicated. Chemicals in cigarette smoke, such as polycyclic aromatic hydrocarbons, can induce hepatic CYPs and heme synthesis. A survey of AIP patients found an association between smoking and repeated porphyric attacks. Attacks may result from metabolic stress and impaired nutrition associated with major illness, infection, or surgery.

The additive effect of multiple predisposing factors, including drugs, endogenous hormones, nutritional factors, and smoking, is suggested by clinical observations. Exposure to drugs and other precipitating factors is less likely to cause an attack in patients who have had no recent symptoms than in those with recent and frequent porphyric symptoms.

Neurologic Mechanisms

The mechanism of neural damage in acute porphyrias is poorly understood. The most favored hypothesis at present is that 1 or more heme precursors, or perhaps a derivative, are neurotoxic. Increased ALA in AIP, HCP, VP, ADP, plumbism, and hereditary tyrosinemia type 1, which have similar neurologic manifestations, suggests that this substance or a derivative may be neuropathic. Porphyrins derived from ALA after its uptake into cells may have toxic potential. ALA can also interact with γ-aminobutyric acid receptors. Severe AIP improves markedly after allogeneic liver transplantation, which supports the hypothesis that heme precursors from the liver cause the neurologic manifestations.

Epidemiology

AIP occurs in all races and is the most common acute porphyria, with a roughly estimated prevalence in most countries of approximately 5 in 100,000. In Sweden, prevalence was estimated to be 7.7 in 100,000, including latent cases with normal porphyrin precursors. A much higher prevalence of 60-100 in 100,000 in northern Sweden is the result of a founder effect. The combined prevalence of AIP and VP in Finland is approximately 3.4 in 100,000. A survey of chronic psychiatric patients in the United States using an erythrocyte PBGD determination found a high prevalence (210 in 100,000) of PBGD deficiency, but a study in Mexico found a similar prevalence in psychiatric patients and controls. Population screening by erythrocyte PBGD activity or DNA analysis revealed a prevalence of 200 heterozygotes per 100,000

Table 91-3 Drugs Regarded as Unsafe and Safe in Acute Porphyrias

UNSAFE	SAFE
Barbiturates	Narcotic analgesics
Sulfonamide antibiotics*	Aspirin
Meprobamate* (also mebutamate,* tybutamate*)	Acetaminophen
Carisoprodol*	Phenothiazines
Glutethimide*	Penicillin and derivatives
Methyprylon	Streptomycin
Ethchlorvynol*	Glucocorticoids
Mephenytoin	Bromides
Phenytoin*	Insulin
Succinimides	Atropine
Carbamazepine*	Cimetidine
Clonazepam‡	Ranitidine†
Primidone*	Acetaminophen (paracetamol)
Valproic acid*	Acetazolamide
Pyrazolones (aminopyrine, antipyrine)	Allopurinol
Griseofulvin*	Amiloride
Ergots	Bethanidine
Metoclopramide*‡	Bumetanide
Rifampin*	Cimetidine
Pyrazinamide*‡	Coumarins
Diclofenac*‡	Fluoxetine
Progesterone and synthetic progestins*	Gabapentin
Danazol*	Gentamicin
Alcohol	Guanethidine
Angiotensin-converting enzyme inhibitors (especially enalapril)‡	Ofloxacin
Calcium channel blockers (especially nifedipine)‡	Propranolol
Ketoconazole	Succinylcholine Tetracycline

This partial listing does not include all available information about drug safety in acute porphyrias. Other sources should be consulted for drugs not listed here.

*Porphyria has been listed as a contraindication, warning, precaution, or adverse effect in U.S. labeling for these drugs. Estrogens are also listed as harmful in porphyria, but have been implicated as harmful in acute porphyrias mostly based only on experience with estrogen-progestin combinations. Although estrogens can exacerbate PCT, there is little evidence they are harmful in the acute porphyrias.

†Porphyria has been listed as a precaution in U.S. labeling for this drug. However, this drug is regarded as safe by other sources.

‡These drugs have been classified as probably safe by some sources, but this is controversial and they should be avoided.

people in Finland, and 1 in approximately 1,675 (60 in 100,000 people) in France. Therefore, carriers of *PBGD* mutations that can cause AIP may be common.

Clinical Manifestations

Neurovisceral manifestations of acute porphyrias may appear any time after puberty, but rarely before. Very rare cases of homozygous AIP develop severe neurologic manifestations early in childhood.

In affected heterozygotes, acute attacks are characterized by a constellation of nonspecific symptoms, which may become severe and life-threatening. **Abdominal pain** occurs in 85-95% of cases, is usually severe, steady, and poorly localized, but sometimes cramping, and accompanied by signs of ileus, including abdominal distention and decreased bowel sounds. Nausea, vomiting, and constipation are common, but increased bowel sounds and diarrhea may occur. Bladder dysfunction may cause hesitancy and dysuria. **Tachycardia,** the most common physical sign, occurs in up to 80% of attacks. This is often accompanied by hypertension, restlessness, coarse or fine tremors, and excess sweating, which are attributed to sympathetic overactivity and increased catecholamines. Other common manifestations include mental symptoms; pain in the extremities, head, neck, or chest; muscle weakness; and sensory loss. Because all these manifestations are neurologic rather than inflammatory, there is little or no abdominal tenderness, fever, or leukocytosis.

Porphyric neuropathy is primarily motor and appears to result from axonal degeneration rather than demyelinization. Sensory involvement is indicated by pain in the extremities, which may be described as muscle or bone pain, and by numbness, paresthesias, and dysesthesias. Paresis may occur early in an attack, but is more often a late manifestation in an attack that is not recognized and adequately treated. Rarely, severe neuropathy develops when there is little or no abdominal pain. Motor weakness most commonly begins in the proximal muscles of the upper extremities and then progresses to the lower extremities and the periphery. It is usually symmetric, but occasionally asymmetric or focal. Initially, tendon reflexes may be little affected or hyperactive and become decreased or absent. Cranial nerves, most commonly X and VII, may be affected, and blindness from involvement of the optic nerves or occipital lobes has been reported. More common central nervous system manifestations include seizures, anxiety, insomnia, depression, disorientation, hallucinations, and paranoia. Seizures may result from hyponatremia, porphyria itself, or an unrelated cause. Chronic depression and other mental symptoms occur in some patients, but attribution to porphyria is often difficult.

Hyponatremia is common during acute attacks. Inappropriate antidiuretic hormone secretion is often the most likely mechanism, but salt depletion from excess renal sodium loss, gastrointestinal loss, and poor intake have been suggested as causes of hyponatremia in some patients. Unexplained reductions in total blood and red blood cell volumes are sometimes found, and increased antidiuretic hormone secretion might then be an appropriate physiologic response. Other electrolyte abnormalities may include hypomagnesemia and hypercalcemia.

The attack usually resolves within several days, unless treatment is delayed. Abdominal pain may resolve within a few hours and paresis within a few days. Even severe motor neuropathy can improve over months or several years, but may leave some residual weakness. Progression of neuropathy to respiratory and bulbar paralysis and death is uncommon with appropriate treatment and removal of harmful drugs. Sudden death may result from cardiac arrhythmia.

Laboratory Findings

Levels of ALA and PBG are substantially increased during acute attacks and these may decrease after an attack but usually remain increased unless the disease becomes asymptomatic for a prolonged period. A population-based study in Sweden indicated that symptoms suggestive of porphyria may occur in heterozygotes during childhood, in contrast to adults, even when urinary porphyria precursors are not elevated. This study lacked a comparison with the frequency of such nonspecific symptoms in a control group of children.

Porphyrins are also markedly increased, which accounts for reddish urine in AIP. These are predominantly uroporphyrins, which can form nonenzymatically from PBG. But because the increased urinary porphyrins in AIP are predominantly isomer III, their formation is likely to be largely enzymatic, which might occur if excess ALA produced in the liver enters cells in other tissues and is then converted to porphyrins via the heme biosynthetic pathway. Porphobilin, a degradation product of PBG, and dipyrrylmethenes appear to account for brownish

urinary discoloration. Total fecal porphyrins and plasma porphyrins are normal or slightly increased in AIP. Erythrocyte protoporphyrin may be somewhat increased in patients with manifest AIP.

Erythrocyte PBGD activity is approximately half-normal in most patients (70-80%) with AIP. The normal range is wide and overlaps with the range for AIP heterozygotes. As noted, some PBGD gene mutations cause the enzyme to be deficient only in nonerythroid tissues. PBGD activity is also highly dependent on erythrocyte age, and an increase in erythropoiesis from concurrent illness in an AIP patient may raise the activity into the normal range.

Diagnosis and Differential Diagnosis

An increased urinary PBG establishes that a patient has 1 of the 3 most common acute porphyrias (see Table 91-2). Measuring PBG in serum is preferred when there is coexistent severe renal disease, but is less sensitive when renal function is normal. Measurement of urinary ALA is less sensitive than PBG and also less specific, but will detect ADP, the fourth type of acute porphyria. Erythrocyte PBGD activity is decreased in most AIP patients and helps confirm the diagnosis in a patient with high PBG. A normal enzyme activity in erythrocytes does not exclude AIP.

Knowledge of the *PBGD* mutation in a family enables reliable identification of other gene carriers. PBGD deficiency can be documented in a fetus by finding a *PBGD* mutation in these cells.

Complications

AIP and other acute porphyrias are commonly associated with mild abnormalities in liver function tests. The risk of more advanced liver disease and hepatocellular carcinoma is also increased during adult life, perhaps 60-70–fold, even in asymptomatic individuals who have increased porphyrins or porphyrin precursors. Few patients who developed this neoplasm had increases in serum α-fetoprotein. Patients with acute porphyrias, especially older than age 50 yr must be screened at least yearly by ultrasound or an alternative imaging method.

The risk of chronic hypertension and impaired renal function, most often with evidence of interstitial nephritis, is increased in AIP. A nephrotoxic effect of ALA may contribute. This may progress to severe renal failure and require renal transplantation.

Increased serum thyroxin levels because of increased thyroxin-binding globulin occur in some AIP patients. Hypercholesterolemia and elevated low-density lipoprotein cholesterol appear to be less common in this disorder than previously thought.

Treatment

Hemin

Intravenous hemin, combined with symptomatic and supportive measures, is the treatment of choice for most acute attacks of porphyria. There is a favorable biochemical and clinical response to early treatment with hemin, but less rapid clinical improvement if treatment is delayed. It is no longer recommended that therapy with hemin for a severe attack be started only after an unsuccessful trial of intravenous glucose for several days. Mild attacks, without severe manifestations such as paresis and hyponatremia, may be treated initially with intravenous glucose. After intravenous administration, hemin binds to hemopexin and albumin in plasma and is taken up primarily in hepatocytes. Hemin then enters and augments the regulatory heme pool in hepatocytes, represses the synthesis of hepatic ALAS1, and dramatically reduces porphyrin precursor overproduction.

Hemin* is available for IV administration in the United States as a lyophilized hematin preparation (Panhematin, Recordati). Degradation products begin to form as soon as the lyophilized product is reconstituted with sterile water, and these are responsible for phlebitis at the site of infusion and a transient anticoagulant effect. Loss of venous access due to phlebitis is common after repeated administration. Stabilization of lyophilized hematin by reconstitution with 30% human albumin can prevent these adverse effects, and is recommended, especially if a peripheral vein is used for the infusion. Uncommon side effects of hemin include fever, aching, malaise, hemolysis, anaphylaxis, and circulatory collapse. Heme arginate, a more stable hemin preparation, is available in Europe and South Africa.

Hemin treatment should be instituted only after a diagnosis of acute porphyria has been initially confirmed by a marked increase in urinary PBG (determined most rapidly using a kit). When prior documentation of the diagnosis is available for review, it is not essential to confirm an increase in PBG with every recurrent attack, if other causes of the symptoms are excluded clinically. The standard regimen of hemin for treatment of acute porphyric attacks is 3-4 mg/kg daily for 4 days. Lower doses have less effect on porphyrin precursor excretion and probably less clinical benefit.

General and Supportive Measures

Drugs that may exacerbate porphyrias (see Table 91-3) should be discontinued whenever possible, and other precipitating factors identified. Hospitalization is warranted, except for mild attacks, for treatment of severe pain, nausea, and vomiting; for administration of hemin and fluids; and for monitoring vital capacity, nutritional status, neurologic function, and electrolytes. Pain usually requires a narcotic analgesic; there is low risk for addiction after recovery from the acute attack. Ondansetron or a phenothiazine such as chlorpromazine is needed for nausea, vomiting, anxiety, and restlessness. Chloral hydrate or low doses of short-acting benzodiazepines can be given for restlessness or insomnia. β-Adrenergic blocking agents may be useful during acute attacks to control tachycardia and hypertension, but may be hazardous in patients with hypovolemia and incipient cardiac failure.

Carbohydrate Loading

The effects of carbohydrates on repressing hepatic ALAS1 and reducing porphyrin precursor excretion are weak compared to those of hemin. Therefore, only mild attacks (mild pain, no paresis or hyponatremia) are treated with carbohydrate loading. Glucose polymer solutions by mouth are sometimes tolerated. At least 300 g of intravenous glucose, usually given as a 10% solution, has been recommended for adults hospitalized with attacks of porphyria. Amounts up to 500 g daily may be more effective, but large volumes may favor development of hyponatremia.

Other Therapies

Liver transplantation was effective in several patients with severe AIP. A group from the United Kingdom reported their experience with liver transplantation in 10 AIP patients with significantly impaired quality of life and recurrent attacks which were refractory to medical management. Patients had a complete biochemical and symptomatic resolution posttransplantation; 2 patients in this series, however, succumbed to multiorgan failure posttransplantation. Liver transplantation is a high-risk procedure and should be considered as a last resort in patients with severe recurrent attacks that are refractory to other treatment. Cimetidine, a well-known inhibitor of hepatic CYPs, can prevent experimental forms of porphyria induced by chemical agents that undergo activation by these enzymes, but these models are not highly relevant to human AIP. The drug's use is based on uncontrolled observations.

Seizures and Other Complications

Seizures caused by hyponatremia or other electrolyte imbalances may not require prolonged treatment with anticonvulsant drugs, most of which have at least some potential for exacerbating acute porphyrias. Bromides, gabapentin, and probably vigabatrin are safe. Clonazepam may be less harmful than phenytoin or barbiturates. Control of hypertension may help prevent chronic renal impairment, which can progress and require renal transplantation.

Safe and Unsafe Drugs

Patients often do well with avoidance of harmful drugs. Table 91-3 lists some drugs known or strongly suspected to be harmful or safe in the

*Hemin is the generic name for all heme preparations used for intravenous administration. Hemin is also a chemical term that refers to the oxidized (ferric) form of heme (iron protoporphyrin IX), and is usually isolated as hemin chloride. In alkaline solution, the chloride is replaced by the hydroxyl ion, forming hydroxyheme, or hematin.

acute porphyrias. More extensive listings are available on websites of the European Porphyria Network (www.porphyria-europe.com) and the American Porphyria Foundation (www.porphyriafoundation.com), but some listings are controversial. Information regarding safety is lacking for many drugs, especially for those recently introduced.

Exogenous progestins, usually in combination with estrogens, can induce attacks of porphyria. Estrogens are seldom reported to be harmful when given alone or in animal and hepatocyte culture systems. Synthetic steroids with an ethynyl substituent can cause a mechanism-based destruction of hepatic CYPs and should probably be avoided in patients with acute porphyria. Danazol is especially contraindicated.

Other Situations

Major surgery can be carried out safely in patients with acute porphyria, especially if barbiturates are avoided. Halothane has been recommended as an inhalation agent and propofol and midazolam as intravenous induction agents.

Pregnancy is usually well tolerated, which is surprising, because levels of progesterone, a potent inducer of hepatic ALAS1, are considerably increased during pregnancy. Some women do experience continuing attacks during pregnancy. This has sometimes been attributed to reduced caloric intake or metoclopramide, a drug sometimes used to treat hyperemesis gravidarum and considered harmful in acute porphyrias.

Diabetes mellitus and other endocrine conditions are not known to precipitate attacks of porphyria. In fact, the onset of diabetes mellitus and resulting high circulating glucose levels may decrease the frequency of attacks and lower porphyrin precursor levels in AIP.

Prognosis

The outlook for patients with acute porphyrias has improved markedly in the past several decades. In Finland, for example, 74% of patients with AIP or VP reported that they led normal lives, and <30% had recurrent attacks during several years of follow-up. In those presenting with acute symptoms, recurrent attacks were most likely within the next 1-3 yr. Moreover, only 6% of gene carriers who had never had attacks developed symptoms. The improved outlook may result from earlier detection, better treatment of acute attacks, and replacement of harmful drugs such as barbiturates and sulfonamides with safer drugs. Some patients continue to have recurrent attacks, chronic pain, and other symptoms even after avoiding known exacerbating factors.

Prevention

For prevention of attacks, it is important to identify multiple inciting factors and remove as many as possible. Drugs for concurrent medical conditions should be reviewed. Because dietary factors are often inapparent, consultation with a dietitian may be useful. A well-balanced diet that is somewhat high in carbohydrate (60-70% of total calories) and sufficient to maintain weight is recommended. There is little evidence that additional dietary carbohydrate helps further in preventing attacks, and it may lead to weight gain. Patients who wish to lose excess weight should do so gradually and when they are clinically stable. Rapid weight loss after bariatric surgery may exacerbate acute porphyrias. Iron deficiency, which can be detected by a low serum ferritin, should be corrected.

Gonadotropin-releasing hormone analogs, which reversibly suppress ovulation, can be dramatically effective for preventing frequently recurring luteal phase attacks, but baseline and continuing gynecologic evaluation and bone density measurements are important, and transdermal estrogen or a bisphosphonate may be added to prevent bone loss. Hemin administered once or twice weekly can prevent frequent, noncyclic attacks of porphyria in some patients.

Genetic Counseling

Children with a family history of porphyria are often seen by pediatricians for evaluation and counseling. Information and laboratory results from a relative with proven porphyria must be reviewed in order to guide testing of the child, which is different depending on the type of acute porphyria. A mutation identified in the index case can be sought in the child. If the child is found to have inherited the mutation, counseling to avoid potentially harmful drugs is appropriate. Counseling should also emphasize that the great majority of those who inherit a *PBGD* mutation never develop symptoms, and the prognosis of those who do is favorable. Therefore, a normal, healthy life is expected, especially with avoidance of harmful drugs and other factors and prompt recognition and treatment of symptoms should they occur. Given the favorable outlook for most mutation carriers, even during pregnancy, having children is not precluded, and prenatal diagnosis of acute porphyrias is less important than it is for many other inherited diseases.

CONGENITAL ERYTHROPOIETIC PORPHYRIA

Also termed *Günther disease,* this rare disease usually presents with photosensitivity shortly after birth or in utero as nonimmune hydrops.

Etiology

CEP is an autosomal recessive disease caused by a marked deficiency of uroporphyrinogen III synthase (UROS). Many *UROS* mutations have been identified among CEP families. Later-onset disease in adults is likely to be associated with myeloproliferative disorders and expansion of a clone of erythroblasts that carry a *UROS* mutation.

Pathology and Pathogenesis

UROS, which is markedly deficient in CEP, catalyzes inversion of pyrrole ring D of HMB (the pyrrole ring shown on the right end of the molecule in Fig. 91-1) and rapid cyclization of the linear tetrapyrrole to form uroporphyrinogen III. This enzyme is also termed *uroporphyrinogen III cosynthase.* The human enzyme is a monomer. The gene for the enzyme is found on chromosome 10q25.3→q26.3, and contains 10 exons. Erythroid and housekeeping transcripts are generated by alternative promoters but encode the same enzyme.

In CEP, HMB accumulates in erythroid cells during hemoglobin synthesis and cyclizes nonenzymatically to form uroporphyrinogen I, which is auto-oxidized to uroporphyrin I. Some of the uroporphyrinogen I that accumulates is metabolized to coproporphyrinogen I, which accumulates because it is not a substrate for coproporphyrinogen oxidase. Thus, both uroporphyrin I and coproporphyrin I accumulate in the bone marrow and are then found in circulating erythrocytes, plasma, urine, and feces.

A variety of *UROS* mutations have been identified in CEP, including missense and nonsense mutations, large and small deletions and insertions, splicing defects, and intronic branch point mutations. At least 4 mutations have been identified in the erythroid-specific promoter. Many patients inherited a different mutation from each parent, and most mutations have been detected in only 1 or a few families. An exception is a common mutation, C73R, which is at a mutational hotspot and was found in ≈33% of alleles. One child with CEP had a *GATA1* mutation, with no *UROS* mutation. The CEP phenotype may be modulated by gain of function *ALAS2* mutations, which were first identified as causing XLP.

Genotype–phenotype correlations have been based on the in vitro expression of various CEP mutations and the severity of associated phenotypic manifestations. The C73R allele, which is associated with a severe phenotype in homozygotes or in patients heteroallelic for C73R and another mutation expressing little residual activity, resulted in <1% of normal enzyme activity. Patients with the C73R allele and heteroallelic for other mutations expressing more residual activity have milder disease.

Hemolysis is a common feature of CEP. Excess porphyrins in circulating erythrocytes cause cell damage, perhaps by a phototoxic mechanism, leading to both intravascular hemolysis and increased splenic clearance of erythrocytes. Also important is ineffective erythropoiesis, with intramedullary destruction of porphyrin-laden erythroid cells and breakdown of heme. Expansion of the bone marrow as a result of erythroid hyperplasia may contribute to **bone loss.** Nutrient deficiencies sometimes cause erythroid hypoplasia. Despite the marked deficiency of UROS, heme production in the bone marrow is increased because of hemolysis and a compensatory increase in hemoglobin

Figure 91-2 Congenital erythropoietic porphyria. The diaper of an affected baby demonstrates the red color of urine. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)*

production. This occurs, however, at the expense of marked accumulation of HMB, which is converted to porphyrinogens and porphyrins.

Clinical Manifestations

In severe cases, CEP can cause fetal loss, or be recognized in utero as intrauterine hemolytic anemia and **nonimmune hydrops fetalis.** CEP may be associated with neonatal hyperbilirubinemia, and **phototherapy may unintentionally induce severe photosensitivity and scarring.**

The most characteristic presentation is reddish urine or pink staining of diapers by urine or meconium shortly after birth (Fig. 91-2). With sun exposure, severe blistering lesions appear on exposed areas of skin on the face and hands, and have been termed *hydroa aestivale* because they are more severe with greater sunlight exposure during summer (Fig. 91-3). Vesicles and bullae, as well as friability, hypertrichosis, scarring, thickening, and areas of hypopigmentation and hyperpigmentation are very similar to those seen in PCT but usually much more severe. Infection and scarring sometimes cause loss of facial features and fingers and damage to the cornea, ears, and nails. Porphyrins are deposited in dentine and bone in utero. Reddish-brown teeth in normal light, an appearance termed **erythrodontia,** display reddish fluorescence under long-wave UV light (Fig. 91-4). Unaffected children born to a mother with CEP may have erythrodontia. Hemolysis and splenomegaly are common in CEP. Bone marrow compensation may be adequate, especially in milder cases. Patients with severe phenotypes, however, are often transfusion-dependent. Splenomegaly may contribute to the anemia and cause leukopenia and thrombocytopenia, which may be complicated by significant bleeding. Neuropathic symptoms are absent, and there is no sensitivity to drugs, hormones, and carbohydrate restriction. The liver may be damaged by iron overload or viral hepatitis acquired from blood transfusions.

Milder cases of CEP with onset of symptoms in adult life and without erythrodontia may mimic PCT. These late-onset cases are likely to be associated with myeloproliferative disorders, and expansion of a clone of cells carrying a *UROS* mutation.

Laboratory Findings

Urinary porphyrin excretion and circulating porphyrin levels in CEP are much higher than in almost all other porphyrias. Urinary porphyrin excretion can be as high as 50-100 mg daily, and consists mostly of uroporphyrin I and coproporphyrin I. ALA and PBG are normal. Fecal porphyrins are markedly increased, with a predominance of coproporphyrin I.

Figure 91-3 Congenital erythropoietic porphyria. Vesicles, bullae, and crusts on sun-exposed areas. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)*

Figure 91-4 Congenital erythropoietic porphyria. Brownish teeth that fluoresce under Wood lamp examination. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3, Philadelphia, 2006, Elsevier Saunders, p. 517.)*

Marked increases in erythrocyte porphyrins in CEP consist mostly of uroporphyrin I and coproporphyrin I. These porphyrins are also increased in bone marrow, spleen, plasma, and, to a lesser extent, liver. The porphyrin pattern in erythrocytes is influenced by rates of erythropoiesis and erythroid maturation. A predominance of protoporphyrin has been noted in some CEP patients, and in 1 such patient, uroporphyrin and coproporphyrin increased when erythropoiesis was stimulated by blood removal.

Diagnosis and Differential Diagnosis

The diagnosis of CEP should be documented by full characterization of porphyrin patterns and identification of the underlying mutations. In later-onset cases, an underlying myeloproliferative disorder and a UROS somatic mutation should be suspected and studied in detail.

The clinical picture in hepatoerythropoietic porphyria (HEP) may be very similar, but the porphyrin patterns in urine and feces in HEP resemble PCT. A predominant increase in erythrocyte protoporphyrin is unusual in CEP but is characteristic of HEP, and rare homozygous cases of AIP, HCP, and VP. EPP is also distinguished by normal urinary porphyrins and by increases in erythrocyte metal-free protoporphyrin, whereas the increased protoporphyrin in other conditions is complexed with zinc.

CEP should be suspected as a cause of nonimmune hydrops or hemolytic anemia in utero. With recognition of the disease at this stage, intrauterine transfusion can be considered, and severe, scarring photosensitivity from phototherapy for hyperbilirubinemia avoided. Prenatal diagnosis is feasible by finding red-brown discoloration and increased porphyrins in amniotic fluid, and measuring porphyrins in fetal erythrocytes and plasma. UROS activity can be measured in cultured amniotic fluid cells, or *UROS* mutations identified in chorionic villi or cultured amniotic cells.

Treatment

Protection from sunlight exposure, minimizing skin trauma, and prompt treatment of any cutaneous infections are highly important in managing CEP. Sunscreen lotions and beta-carotene are sometimes beneficial. Transfusions to achieve a level of hemoglobin sufficient to suppress erythropoiesis significantly can be quite effective in reducing porphyrin levels and photosensitivity. Concurrent deferoxamine to reduce iron overload, and hydroxyurea to suppress erythropoiesis further may provide additional benefit. Splenectomy reduces hemolysis and transfusion requirements in some patients. Oral charcoal may increase fecal loss of porphyrins, but may contribute little in more severe cases. Intravenous hemin may be somewhat effective, but has not been extensively studied and seems unlikely to provide long-term benefit.

The most effective treatment is bone marrow or stem cell transplantation in early childhood, which has markedly reduced porphyrin levels and photosensitivity and increased long-term survival.

Prognosis

The outlook is favorable in milder cases and in patients with more severe disease especially after successful bone marrow or stem cell transplantation.

Prevention and Genetic Counseling

Genetic counseling is important for affected families, because CEP can be recognized before birth and a severe phenotype can often be predicted by identifying the nature of the UROS mutations.

PORPHYRIA CUTANEA TARDA

PCT is the most common and readily treated human porphyria (see Table 91-2). It occurs in mid or late adult life, and is rare in children. Previous terms include *symptomatic porphyria, PCT symptomatica,* and *idiosyncratic porphyria.* The underlying cause is a liver-specific, acquired deficiency of uroporphyrinogen decarboxylase (UROD) with contributions by several types of genetic and acquired factors. Heterozygous *UROD* mutations are found in familial PCT. HEP, the homozygous form of familial PCT, usually has a more severe presentation in childhood, resembling CEP clinically.

Etiology

PCT is caused by a reduction of hepatic UROD activity to 20% of normal activity or less. An inhibitor of hepatic UROD has been characterized as uroporphomethene, which is derived from partial oxidation of the enzyme substrate uroporphyrinogen. CYPs, such as CYP1A2, as well as iron, are involved in its formation (Fig. 91-5). Although enzyme activity is inhibited, the amount of hepatic enzyme protein measured immunochemically remains at its genetically determined level.

UROD catalyzes the decarboxylation of the 4 acetic acid side chains of uroporphyrinogen (an octacarboxyl porphyrinogen) to form coproporphyrinogen (a tetracarboxyl porphyrinogen) (see Fig. 91-1). The enzyme reaction occurs in a sequential, clockwise fashion, with the intermediate formation of hepta-, hexa-, and pentacarboxyl porphyrinogens. Uroporphyrinogen III, as compared with other uroporphyrinogen isomers, is the preferred substrate. Human UROD is a dimer with the 2 active site clefts juxtaposed. The UROD gene is on chromosome 1p34 and contains 10 exons, with only 1 promoter. Therefore, the gene is transcribed as a single mRNA in all tissues.

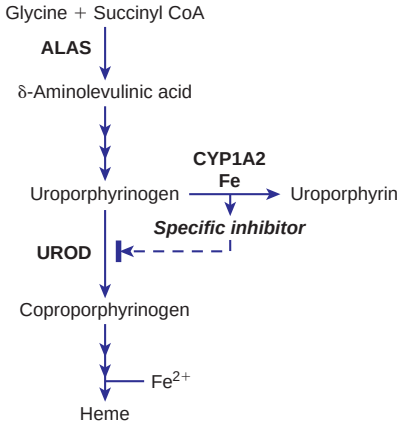

Figure 91-5 Formation of a specific inhibitor of uroporphyrinogen decarboxylase in the liver in porphyria cutanea tarda. ALAS, δ-aminolevulinic acid synthase; CYP1A2, cytochrome P450 1A2; UROD, uroporphyrinogen decarboxylase.

The majority of PCT patients (i.e., ≈80%) have no *UROD* mutations and are said to have sporadic (type 1) disease. Some are heterozygous for *UROD* mutations and are said to have familial (type 2) PCT. Described mutations include missense, nonsense, and splice-site mutations, several small and large deletions, and small insertions, with only a few identified in more than 1 family. A few of these mutations may be located near the active site cleft, but most appear to involve regions with important structural roles. Being heterozygous for a *UROD* mutation is insufficient to cause PCT unless a UROD inhibitor is also generated. Because penetrance of the genetic trait is low, many patients with familial PCT have no family history of the disease.

Induction of hepatic ALAS1 is not a prominent feature in PCT, although alcohol may increase this enzyme slightly. Iron and estrogens are also not potent inducers of ALAS1 and drugs that are potent inducers of ALAS1 and CYPs are much less commonly implicated in PCT than in acute porphyrias.

Blistering skin lesions result from porphyrins that are released from the liver. Sunlight exposure leads to generation of reactive oxygen species in the skin, complement activation, and lysosomal damage.

Epidemiology

Differences in prevalence probably relate to geographic variations in susceptibility factors such as hepatitis C and ethanol use. The yearly incidence in the United Kingdom was estimated at 2-5 in 1,000,000 in the general population, and the prevalence in the United States and Czechoslovakia was estimated at approximately 1 in 25,000 and 1 in 5,000 in the general population, respectively. The disease was reported to be prevalent in the Bantus of South Africa in association with iron overload. PCT is more common in males, possible because of greater alcohol intake, and in women it is commonly associated with estrogen use.

A massive outbreak of PCT occurred in eastern Turkey in the 1950s. Wheat intended for planting and treated with hexachlorobenzene as a fungicide was consumed by many at a time of food shortage. Cases and small outbreaks of PCT after exposure to other chemicals including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) have been reported. The manifestations improved in most cases when the exposure was stopped. There are reported cases of delayed onset many years after chemical exposure.

Pathology and Pathogenesis

PCT is currently classified into 3 clinically similar types. Generation of a UROD inhibitor in the liver plays an important role in all 3 types. The 80% of patients with **type 1 (sporadic)** PCT have no UROD mutations, and UROD activity is normal in nonhepatic tissues such as erythrocytes. In **familial (type 2)** PCT, a heterozygous *UROD* mutation results in a partial (approximately 50%) deficiency of UROD in all tissues from birth, and the disease becomes active in some heterozygotes when other susceptibility factors are present and a UROD inhibitor is generated in the liver, reducing hepatic UROD activity to 20% of normal or less. HEP results from inheritance of a *UROD* mutation from each parent and typically cause severe photosensitivity resembling CEP starting in early childhood. Some compound heterozygotes have developed symptoms in childhood more typical of PCT. **Type 3** is rare, and describes PCT with normal erythrocyte UROD activity occurring in more than 1 family member. Another genetic basis, such as *HFE* mutations, may be identified in type 3.

CYPs, especially CYP1A2, can catalyze the oxidation of uroporphyrinogen to uroporphyrin. This uroporphyrinogen oxidase activity is

enhanced by iron, and leads to formation of a UROD inhibitor (see Fig. 91-5). CYP1a2 seems essential for development of uroporphyria in rodents, because experimental uroporphyria does not develop in *CYP1a2* knockout mice.

Susceptibility Factors

The following factors are implicated in the development of PCT, and these occur in various combinations in individual patients.

Iron

A normal or increased amount of iron in the liver is essential for developing PCT, and treatment by phlebotomy to reduce hepatic iron leads to remission. Serum ferritin levels are usually in the upper part of the normal range or moderately increased and liver histology commonly shows increased iron staining. Prevalence of the C282Y mutation of the *HFE* gene, which is the major cause of hemochromatosis in people of northern European ancestry, is increased in both type 1 and type 2 PCT, and approximately 10% of patients are C282Y homozygotes. In southern Europe, the H63D mutation is more commonly associated. PCT may develop in patients with secondary iron overload. Reduced hepatic expression of the hormone hepcidin occurs in hemochromatosis and also in PCT, regardless of *HFE* genotype, which may explain hepatic siderosis in this condition.

Hepatitis C

This viral infection is highly prevalent in PCT in most geographic locations; in the United States, for example, it is present in 56-74% of cases, which is similar to rates in southern Europe. Prevalence of hepatitis C in PCT is lower in northern Europe (<20%). Steatosis and oxidative stress in hepatitis C may favor iron-mediated generation of reactive oxygen species and a UROD inhibitor. Dysregulation of hepcidin occurs in hepatitis C and may lead to increased iron absorption.

HIV

Many reports suggest that HIV infection can contribute to the development of PCT, although less commonly than does hepatitis C.

Ethanol

The long-recognized association between alcohol and PCT may be explained by the generation of active oxygen species, which may cause oxidative damage, mitochondrial injury, depletion of reduced glutathione and other antioxidant defenses, increased production of endotoxin, and activation of Kupffer cells. Alcohol may contribute to iron overload by impairing hepcidin production.

Smoking and Cytochrome P450 Enzymes

Smoking has not been extensively studied as a susceptibility factor but is commonly associated with alcohol use in PCT. It may act to induce hepatic CYPs and oxidative stress. Hepatic CYPs are thought to be important in oxidizing uroporphyrinogen and generating a UROD inhibitor (see Fig. 91-5). Genetic polymorphisms of *CYP1A2* and *1A1* have been implicated in human PCT. The frequency of an inducible *CYP1A2* genotype was more common in PCT patients than in controls in several studies.

Antioxidant Status

Ascorbic acid deficiency contributes to uroporphyria in laboratory models and perhaps in human PCT. In 1 series, plasma ascorbate levels were substantially reduced in 84% of patients with PCT. Low levels of serum carotenoids were also described, further suggesting that oxidant stress in hepatocytes is important in PCT.

Estrogens

Use of estrogen-containing oral contraceptives or postmenopausal estrogen replacement is very commonly associated with PCT (type 1 or 2) in women. PCT sometimes occurs during pregnancy, although it is not clear whether the risk is increased.

Clinical Manifestations

Cutaneous Manifestations

PCT is readily recognized by blistering and crusted skin lesions on the backs of the hands, which are the most sun-exposed areas of the body, and somewhat less commonly on the forearms, face, ears, neck, legs, and feet. The fluid-filled vesicles commonly rupture and become crusted or denuded areas, heal slowly, and are subject to infection. The skin on the backs of the hands is characteristically friable, and minor trauma may cause blisters or denudation of skin. Small white plaques, termed milia, may precede or follow vesicle formation. Facial hypertrichosis and hyperpigmentation are also common. Severe scarring and thickening of sun-exposed skin may resemble scleroderma. Skin biopsy findings include subepidermal blistering and deposition of periodic acid–Schiff-positive material around blood vessels and fine fibrillar material at the dermoepithelial junction, which may relate to excessive skin fragility. Immunoglobulin G, other immunoglobulins, and complement are also deposited at the dermoepithelial junction and around dermal blood vessels. The skin lesions and histologic changes are not specific for PCT. The same findings occur in VP and HCP, and resemble those of CEP and HEP, but are usually less severe. PCT usually develops in mid or late adult life. Earlier onset may be seen in those with UROD or *HFE* mutations. Childhood onset is rare, and suggests heterozygosity or even compound heterozygosity for UROD mutations.

Liver Abnormalities

PCT is almost always associated with nonspecific liver abnormalities, especially increased serum transaminases and γ-glutamyltranspeptidase, even in the absence of heavy alcohol intake or hepatitis C. Most histologic findings, such as necrosis, inflammation, increased iron, and increased fat, are nonspecific. Specific findings include red fluorescence of liver tissue, and fluorescent, birefringent, needle-like inclusions presumably consisting of porphyrins. Electron microscopy shows these inclusions are in lysosomes, and paracrystalline inclusions are found in mitochondria. Distorted lobular architecture and cirrhosis are more common with long-standing disease.

The risk of developing hepatocellular carcinoma is increased, with reported incidences ranging from 4-47% in PCT. These tumors seldom contain large amounts of porphyrins.

Other Findings and Associations

Mild or moderate erythrocytosis in some adult patients is not well understood, but chronic lung disease from smoking may contribute. An earlier onset of symptoms may be noted in patients with genetic predisposing factors, such as an inherited partial deficiency of UROD or the C282Y/C282Y *HFE* genotype. Iron overload secondary to conditions such as myelofibrosis and end-stage renal disease may be associated with PCT. The disease can be especially severe in patients with end-stage renal disease, because the lack of urinary excretion leads to much higher concentrations of porphyrins in plasma, and the excess porphyrins are poorly dialyzable. PCT occurs more frequently in patients with systemic lupus erythematosus and other immunologic disorders than would have been expected by chance.

Laboratory Findings

Porphyrins accumulate in the liver mostly as the oxidized porphyrins rather than porphyrinogens in PCT, as indicated by the immediate red fluorescence observed in liver tissue. This develops over weeks or months before porphyrins appear in plasma and are transported to the skin, causing photosensitivity. In contrast to the acute hepatic porphyrias, only a very small increase in synthesis of heme pathway intermediates and little or no increase in hepatic ALAS1 are required to account for the excess porphyrins excreted in PCT.

Hepatic UROD deficiency leads to a complex pattern of excess porphyrins, which initially accumulate as porphyrinogens, and then undergo nonenzymatic oxidation to the corresponding porphyrins (uro-, hepta-, hexa-, and pentacarboxyl porphyrins, and isocoproporphyrins). Uroporphyrin and heptacarboxyl porphyrin predominate in

urine, with lesser amounts of coproporphyrin and penta- and hexacarboxyl porphyrin. A normally minor pathway is accentuated by UROD deficiency, whereby pentacarboxyl porphyrinogen is oxidized by coproporphyrinogen oxidase (CPOX; the next enzyme in the pathway), forming isocoproporphyrinogen, an atypical tetracarboxyl porphyrinogen. Relative to normal values, urinary porphyrins are increased to a greater extent than fecal porphyrins. However, the total amount of porphyrins excreted in feces in PCT exceeds that in urine, and total excretion of type III isomers (including isocoproporphyrins, which are mostly derived from the type III series) exceeds that of type I isomers. Perhaps because uroporphyrinogen III is the preferred substrate for UROD, more uroporphyrinogen I than III accumulates and is excreted in PCT. Hepta- and hexacarboxyl porphyrin are mostly isomer III; and pentacarboxyl porphyrin and coproporphyrin are approximately equal mixtures of isomers I and III.

Diagnosis and Differential Diagnosis

Plasma porphyrins are always increased in clinically manifest PCT, and a total plasma porphyrin determination is most useful for screening. A normal value rules out PCT and other porphyrias that produce blistering skin lesions. If increased, it is useful to determine the plasma fluorescence emission maximum at neutral pH, because a maximum near 619 nm is characteristic of PCT (as well as CEP and HCP) and, most important, excludes VP, which has a distinctly different fluorescence maximum. Increased urinary porphyrins, with a predominance of uroporphyrin and heptacarboxyl porphyrin, is confirmatory. Urine porphyrins are less useful for initial screening because nonspecific increases, especially of coproporphyrin, occur in liver disease and other medical conditions. Urinary ALA may be increased slightly, and PBG is normal.

Familial (type 2) can be distinguished from sporadic (type 1) PCT by finding decreased erythrocyte UROD activity (in type 2), or more reliably by finding a disease-related *UROD* mutation. Type 3 is distinguished from type 1 only by occurrence of PCT in a relative. Biochemical findings in HEP are similar to those in PCT, but with an additional marked increase in erythrocyte zinc protoporphyrin.

Pseudoporphyria (also known as pseudo-PCT) presents with skin lesions that closely resemble PCT, but without significant increases in plasma porphyrins. A photosensitizing drug such as a nonsteroidal antiinflammatory agent is sometimes implicated. Both PCT and pseudoporphyria may occur in patients with end-stage renal disease.

Complications

Cutaneous blisters may rupture and become infected, sometimes leading to cellulitis. In more-severe disease in patients with end-stage renal disease, repeated infections can be mutilating, as in CEP. Pseudoscleroderma, with scarring, contraction, and calcification of skin and subcutaneous tissue, is a rare complication. Other complications include advanced liver disease and hepatocellular carcinoma.

Treatment

Two specific and effective forms of treatment, namely phlebotomy or low-dose hydroxychloroquine, are available. Susceptibility factors should be removed when possible. The diagnosis of PCT must be firmly established, because conditions that produce identical cutaneous lesions do not respond to these treatments. Treatment can usually be started after demonstrating an increase in plasma total porphyrins and excluding VP by analysis of the fluorescence spectrum at neutral pH, while urine and fecal studies are still pending. Use of alcohol, estrogens (in women), and smoking should be stopped, and patients tested for hepatitis C, HIV, and *HFE* mutations. Some susceptibility factors and the degree of iron overload as assessed by the serum ferritin concentration, influence the choice of treatment.

Phlebotomy is considered standard therapy, and is effective both in children and adults with PCT because it reduces hepatic iron content. Treatment is guided by plasma (or serum) ferritin and porphyrin levels. Hemoglobin or hematocrit levels should be followed to prevent symptomatic anemia. For adults, a unit of blood (≈450 mL) is removed at about 2 wk intervals until a target serum ferritin near the lower limit of normal (≈15 ng/mL) is achieved. A total of 6-8 phlebotomies is often sufficient. After this, plasma porphyrin concentrations continue to fall from pretreatment levels (generally 10-25 μg/dL) to below the upper limit of normal (≈1 μg/dL), usually after several more weeks. This is followed by gradual clearing of skin lesions, sometimes including pseudoscleroderma. Liver function abnormalities may improve, and hepatic siderosis, needle-like inclusions, and red fluorescence of liver tissue will disappear. Although remission usually persists even if ferritin levels later return to normal, it is advisable to follow porphyrin levels and reinstitute phlebotomies if these begin to rise. Infusions of deferoxamine, an iron chelator, may be used when phlebotomy is contraindicated.

An alternative when phlebotomy is contraindicated or poorly tolerated is a low-dose regimen of hydroxychloroquine (or chloroquine). Normal doses of these 4-aminoquinoline antimalarials increase plasma and urinary porphyrin levels and increase photosensitivity in PCT, reflecting an outpouring of porphyrins from the liver. This is accompanied by acute hepatocellular damage, with fever, malaise, nausea, and increased serum transaminases, but is followed by complete remission of the porphyria. These adverse consequences of normal doses are largely avoided by a low-dose regimen (hydroxychloroquine 100 mg or chloroquine 125 mg, of a normal tablet, twice weekly), which can be continued until plasma or urine porphyrins are normalized. There is at least some risk of retinopathy, which may be lower with hydroxychloroquine. The mechanism of action of 4-aminoquinolines in PCT is not known but is quite specific, because these drugs are not useful in other porphyrias. Recent studies indicate that low-dose hydroxychloroquine is as safe and effective as phlebotomy in PCT.

In patients with PCT and hepatitis C, PCT should be treated first because this condition is more symptomatic and can be treated more quickly and effectively. Treatment of PCT by phlebotomy may not be possible once interferon-ribavirin treatment is complicated by anemia. Moreover, treatment of hepatitis C may be more effective after iron reduction.

PCT in patients with end-stage renal disease is often more severe and difficult to treat. However, erythropoietin administration can correct anemia, mobilize iron, and support phlebotomy in many cases. Improvement after renal transplantation may be partly from resumption of endogenous erythropoietic production.

Liver imaging and a serum α-fetoprotein determination may be advisable in all PCT patients, perhaps at 6-12 mo intervals, for early detection of hepatocellular carcinoma. Finding low-erythrocyte UROD activity or a *UROD* mutation identifies those with an underlying genetic predisposition, which does not alter treatment but is useful for genetic counseling.

Prognosis

PCT is the most readily treated form of porphyria, and complete remission is expected with treatment either by phlebotomy or low-dose hydroxychloroquine. There is little information on rates of recurrence and long-term outlook. Risk for hepatocellular carcinoma is increased, and some susceptibility factors such as hepatitis C can lead to complications even after PCT is in remission.

Prevention and Genetic Counseling

Patients with PCT may have concerns about risk to other family members. A heritable *UROD* mutation can usually be detected or excluded by measuring erythrocyte UROD activity, although DNA studies are more sensitive. Relatives of patients with *UROD* mutations have an increased risk for developing PCT, and may have increased motivation to avoid adverse behaviors such as ethanol and tobacco use and exposures to hepatitis C and HIV. Such counseling would be given to anyone, however. The finding of *HFE* mutations, and especially C282Y, should prompt screening of relatives, some of whom may be C282Y homozygotes and warrant lifelong monitoring of serum ferritin.

HEPATOERYTHROPOIETIC PORPHYRIA

HEP, which is the homozygous form of familial (type 2) PCT, resembles CEP clinically. Excess porphyrins originate mostly from liver, with

a pattern consistent with severe UROD deficiency. This rare disorder has no particular racial predominance.

Etiology
HEP is an autosomal recessive disorder, although most patients have inherited a different mutation from unrelated parents. In contrast to most mutations in familial (type 2) PCT, most causing HEP are associated with expression of some residual enzyme activity. At least 1 genotype is associated with the predominant excretion of pentacarboxyl porphyrin.

Pathology and Pathogenesis
Excess porphyrins originate primarily from the liver in HEP, although the substantial increase in erythrocyte zinc protoporphyrin indicates that the heme biosynthetic pathway is also impaired in bone marrow erythroid cells. Apparently, porphyrinogens accumulate in the marrow while hemoglobin synthesis is most active, and are metabolized to protoporphyrin after hemoglobin synthesis is complete. The cutaneous lesions are a result of photoactivation of porphyrins in skin, as in other cutaneous porphyrias.

Clinical Manifestations
Like CEP, this disease usually presents with blistering skin lesions, hypertrichosis, scarring, and red urine in infancy or childhood. Sclerodermoid skin changes are sometimes prominent. Unusually mild cases have been described. Concurrent conditions that affect liver function can alter disease severity. For example, the disease became manifest because of hepatitis A in a 2 yr old child, and then improved with recovery of liver function.

Laboratory Findings
Biochemical findings resemble those in PCT with accumulation and excretion of uroporphyrin, heptacarboxyl porphyrin, and isocoproporphyrin. But in addition, erythrocyte zinc protoporphyrin is substantially increased.

Diagnosis and Differential Diagnosis
HEP is distinguished from CEP by increases in both uroporphyrin and heptacarboxyl porphyrin, and isocoproporphyrins. In CEP, the excess erythrocyte porphyrins are predominantly uroporphyrin and coproporphyrin rather than protoporphyrin. Blistering skin lesions are unusual in EPP, the excess erythrocyte protoporphyrin in that disease is free and not complexed with zinc, and urinary porphyrins are normal.

Treatment and Prognosis
Avoiding sunlight exposure is most important in managing this disease, as in CEP. Oral charcoal was helpful in a severe case associated with dyserythropoiesis. Phlebotomy has shown little or no benefit. The outlook depends on the severity of the enzyme deficiency and may be favorable if sunlight can be avoided.

Prevention and Genetic Counseling
As part of genetic counseling in affected families, it is feasible to diagnose HEP in utero, either by analysis of porphyrins in amniotic fluid or DNA studies.

HEREDITARY COPROPORPHYRIA
This autosomal dominant hepatic porphyria is caused by a deficiency of CPOX. The disease presents with acute attacks, as in AIP. Cutaneous photosensitivity may occur, but much less commonly than in VP. Rare homozygous cases present in childhood.

Etiology
A partial (50%) deficiency in CPOX activity has been found in all cells studied from patients with HCP. A much more profound deficiency is found in homozygous cases. Human CPOX is a homodimer composed of 39 kDa subunits, and contains no metals or prosthetic groups. The enzyme requires molecular oxygen, and is localized in the mitochondrial intermembrane space. A single active site on the enzyme catalyzes the oxidative decarboxylation of 2 of the 4 propionic acid groups of coproporphyrinogen III to form the 2 vinyl groups at positions 2 and 4, on rings A and B, respectively, of protoporphyrinogen IX (see Fig. 91-1). Most of the intermediate tricarboxyl porphyrinogen, termed *harderoporphyrinogen,* is not released before undergoing the second decarboxylation to protoporphyrinogen IX. Coproporphyrinogen I is not a substrate for this enzyme.

The human *CPOX* gene contains 7 exons and is located on chromosome 3q12.1. A single promoter contains elements for both housekeeping and erythroid-specific expression. A variety of *CPOX* gene mutations have been described in HCP, with a predominance of missense mutations and no genotype-phenotype correlations. Harderoporphyria, an autosomal recessive biochemical variant form of HCP, is caused by *CPOX* mutations that impair substrate binding, leading to premature release of harderoporphyrinogen.

Epidemiology
HCP is less common than AIP and VP, but its prevalence has not been carefully estimated. There is no obvious racial predominance. Homozygous HCP is rare and presents during childhood. Harderoporphyria, a biochemically distinguishable variant of HCP, has been recognized in heteroallelic and homoallelic forms.

Pathology and Pathogenesis
Increased ALA and PBG during acute attacks of HCP may be explained by induction of ALAS1 and by the normally relatively low activity of PBGD in the liver. Hepatic ALAS1 is increased during acute attacks, but is normal when the disease is latent and porphyrin precursor excretion is normal. Because coproporphyrinogen III concentration in the liver is probably less than the K_m for CPOX, the reaction rate is likely to be determined in part by substrate concentration. The substrate coproporphyrinogen appears to be lost more readily from the liver cell than, for example, uroporphyrinogen, especially when heme synthesis is stimulated. Coproporphyrin and coproporphyrinogen are both transported into bile and excreted in urine, and do not appear to accumulate in the liver in HCP.

Clinical Manifestations
Symptoms are identical to those of AIP except that attacks are generally milder, and cutaneous lesions that resemble those in PCT develop occasionally. Severe motor neuropathy and respiratory paralysis can occur. Like other acute porphyrias, HCP is almost always latent before puberty, and symptoms are most common in adult women. Attacks are precipitated by the same factors that cause attacks in AIP, including fasting, oral contraceptive steroids, and hormone increases during the luteal phase of the menstrual cycle. Concomitant liver diseases may increase porphyrin retention and photosensitivity. The risk of hepatocellular carcinoma is increased, as in other acute porphyrias.

The clinical features of homozygous HCP or harderoporphyria, which begin in early childhood, may include jaundice, hemolytic anemia, hepatosplenomegaly, and skin photosensitivity. These symptoms are generally quite distinct from those seen in heterozygotes.

Laboratory Findings
The porphyrin precursors ALA and PBG are increased during acute attacks, but may decrease more rapidly than in AIP. Marked increases in coproporphyrin III in urine and feces are more persistent. In homozygous cases, porphyrin excretion may be more markedly increased and is accompanied by substantial increases in erythrocyte zinc protoporphyrin. Harderoporphyria is characterized by a marked increase in fecal excretion of harderoporphyrin (tricarboxyl porphyrin) as well as coproporphyrin. Plasma porphyrins are usually normal or only slightly increased.

Diagnosis and Differential Diagnosis
The diagnosis of HCP is readily established in patients with clinically manifest disease, although urinary ALA, PBG, and uroporphyrin may revert to normal more quickly than in AIP. Urinary coproporphyrin

III is increased. Urinary porphyrins, especially coproporphyrin, can be increased in many medical conditions such as liver disease, and small increases may not be clinically significant and lead to an incorrect diagnosis of HCP. Fecal porphyrins are mostly coproporphyrin (isomer III) in HCP, whereas in VP, coproporphyrin III and protoporphyrin are often increased approximately equally. Plasma porphyrins are usually normal in HCP and increased in VP.

The ratio of fecal coproporphyrin III to coproporphyrin I is especially sensitive for detecting latent heterozygotes (especially adults). Assays for CPOX, a mitochondrial enzyme, require cells such as lymphocytes and are not widely available. Identification of a *CPOX* mutation in an index case greatly facilitates screening family members.

Treatment and Prognosis

Acute attacks of HCP are treated as in AIP, which includes intravenous hemin and identifying and avoiding precipitating factors. Cholestyramine may be of some value for photosensitivity occurring with liver dysfunction. Phlebotomy and chloroquine are not effective. Gonadotropin-releasing hormone analogs can be effective for prevention of cyclic attacks. The prognosis is generally better than in AIP.

Prevention and Genetic Counseling

These are the same as in other acute porphyrias.

Variegate Porphyria

This hepatic porphyria is caused by a deficiency of protoporphyrinogen oxidase (PPOX), which is inherited as an autosomal dominant trait. The disorder is termed *variegate* because it can present with neurologic or cutaneous manifestations. Other terms have included *porphyria variegata, protocoproporphyria,* and *South African genetic porphyria.* Rare cases of homozygous VP are symptomatic in childhood.

Etiology

PPOX is approximately half normal in all cells studied in patients with VP. The enzyme is more markedly deficient in rare cases of homozygous VP, with approximately half-normal enzyme activity in parents.

Human PPOX is a homodimer that contains flavin adenine dinucleotide and is localized to the cytosolic side of the inner mitochondrial membrane. Membrane-binding domains may be docked onto human FECH, the next enzyme in the pathway, which is embedded in the opposite side of the membrane. PPOX catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX by the removal of 6 hydrogen atoms (see Fig. 91-1). The enzyme requires molecular oxygen. The substrate is readily oxidized nonenzymatically to protoporphyrin under aerobic conditions, or if exported into the cytosol. PPOX is highly specific for protoporphyrinogen IX, and is inhibited by tetrapyrroles such as heme, biliverdin, and bilirubin and by certain herbicides that cause protoporphyrin to accumulate and induce phototoxicity in plants. Inhibition by bilirubin may account for decreased PPOX activity in Gilbert disease.

The human *PPOX* gene on chromosome 1q22-q23 consists of 1 noncoding and 12 coding exons. A single PPOX transcript is produced in a variety of tissues, but putative transcriptional element binding sequences may allow for erythroid-specific expression. Many *PPOX* mutations have been reported in VP families. A missense mutation, R59W, is prevalent in South Africa. No convincing genotype–phenotype correlations have been identified. Mutations in homozygous cases of VP are more likely to encode enzyme proteins with residual activity.

Epidemiology

VP is less common than AIP in most countries. The R59W mutation is highly prevalent in South African whites (3 in 1,000 in this population). This example of genetic drift or "founder effect" has been traced to a man or his wife who emigrated from Holland to South Africa in 1688. In Finland, the prevalence is 1.3 in 100,000 people and is about as common as AIP.

Pathology and Pathogenesis

Acute attacks develop in a minority (approximately 25%) of heterozygotes for PPOX deficiency, and are often attributable to drugs, steroids, and nutritional factors that play a role in other acute porphyrias. Protoporphyrinogen IX accumulates and undergoes autoxidation to protoporphyrin IX. Coproporphyrinogen III may accumulate as the result of a close functional association between PPOX in the inner mitochondrial membrane and CPOX in the intermembrane space. Liver porphyrin content is not increased. The increased porphyrin content in plasma consists of porphyrin–peptide conjugates, which may be formed from protoporphyrinogen. Increased ALA and PBG during acute attacks may be explained, as in HCP, by induction of ALAS1 by exacerbating factors, and by the normally relatively low activity of PBGD in liver. Furthermore, PBGD is inhibited by protoporphyrinogen, the substrate for PPOX.

Clinical Manifestations

Symptoms develop in some heterozygotes after puberty. Neurovisceral symptoms occurring as acute attacks are identical to AIP but are generally milder and less often fatal. Drugs, steroids, and nutritional alterations such as fasting, which are harmful in AIP, can also induce attacks of VP. Attacks occur equally in males and females, at least in South Africa. Cutaneous fragility, vesicles, bullae, hyperpigmentation, and hypertrichosis of sun-exposed areas are much more common than in HCP. They are likely to occur apart from and be more long lasting than the neurovisceral symptoms. Oral contraceptives can precipitate cutaneous manifestations. Acute attacks have become less common, and skin manifestations are more frequently the initial presentation; this may be due to earlier diagnosis and counseling. The risk of hepatocellular carcinoma is increased.

Symptoms of homozygous VP begin in infancy or childhood. These children generally have severe photosensitivity, neurologic symptoms, convulsions, developmental disturbances, and sometimes growth retardation, but do not have acute attacks.

Laboratory Findings

Urinary ALA, PBG, and uroporphyrin are increased during acute attacks but often less so than in AIP, and may be normal or only slightly increased during remission. Plasma porphyrins, urinary coproporphyrin III, and fecal coproporphyrin III and protoporphyrin are more persistently increased between attacks. Erythrocyte zinc protoporphyrin levels are markedly increased in homozygous VP, and may be modestly increased in heterozygous cases.

Diagnosis and Differential Diagnosis

VP is readily distinguished from AIP and HCP, which also present with acute attacks and increases in PBG. Plasma porphyrin analysis is especially useful, because the plasma porphyrins in VP are tightly protein bound, resulting in a characteristic fluorescence emission spectrum at neutral pH. Fecal porphyrins are increased, with approximately equal amounts of coproporphyrin III and protoporphyrin. Fluorometric detection of plasma porphyrins is more sensitive than stool porphyrin analysis in asymptomatic VP. PPOX assays using cells that contain mitochondria, such as lymphocytes, are sensitive for identifying asymptomatic carriers but are not widely available. Knowing the *PPOX* mutation in an index case enables the identification of relatives who carry the same mutation.

Treatment

Acute attacks are treated as in AIP. Hemin is beneficial for acute attacks but not for cutaneous symptoms. Light protection is important in patients with skin manifestations, using long-sleeved clothing, gloves, a broad-brimmed hat, and opaque sunscreen preparations. Exposure to short-wavelength UV light, which does not excite porphyrins, may increase skin pigmentation and provide some protection. Phlebotomy and chloroquine are not effective. Surprisingly, oral activated charcoal was reported to increase porphyrin levels and worsen skin manifestations.

Prognosis and Prevention

The outlook of patients with VP has improved, which may be attributed to improved treatment, earlier diagnosis, and detection of latent cases. Cyclic acute attacks in women can be prevented with a gonadotropin-releasing hormone analog, as in AIP. A diagnosis of VP or any other acute porphyria should not lead to difficulty obtaining insurance, because the prognosis is usually good once the diagnosis is established.

Genetic Counseling

This is the same as in other acute porphyrias.

ERYTHROPOIETIC PROTOPORPHYRIA

In this autosomal recessive disorder, protoporphyrin accumulates as the result of a marked deficiency of FECH, the last enzyme in the heme biosynthetic pathway, because of *FECH* mutations. EPP is sometimes termed *protoporphyria* or *erythrohepatic protoporphyria,* although the liver does not contribute substantially to production of excess protoporphyrin in uncomplicated cases. XLP is a genetically distinct form of porphyria that is less common than EPP but with the same phenotype, and is a result of gain of function *ALAS2* mutations.

Etiology

FECH, the enzyme that is deficient in EPP, catalyzes the final step in heme synthesis, which is insertion of ferrous iron (Fe^{2+}) into protoporphyrin IX (see Fig. 91-1). The enzyme is also termed *heme synthetase* or *protoheme ferrolyase.* The human enzyme is a dimer, and each homodimer contains a [2Fe-2S] cluster, which may have a role in bridging homodimers. FECH is found in the mitochondrial inner membrane where its active site faces the mitochondrial matrix. It may be associated with complex I of the mitochondrial electron transport chain, and the ferrous iron substrate may be produced upon nicotinamide adenine dinucleotide oxidation. FECH is specific for the reduced form of iron, but can utilize other metals such as Zn^{2+} and Co^{2+} and other dicarboxyl porphyrins. Accumulation of free protoporphyrin rather than zinc protoporphyrin in EPP indicates that formation of the latter is dependent on FECH activity in vivo.

The human *FECH* gene is located on chromosome 18q21.3, has a single promoter sequence, and contains 11 exons. Two mRNAs of 1.6 and 2.5 kb were described, which may be explained by the use of 2 alternative polyadenylation signals. The larger transcript is more abundant in murine erythroid cells, suggesting erythroid-specific regulation of FECH. A variety of *FECH* mutations have been reported in EPP, including missense, nonsense, and splicing mutations, small and large deletions, and an insertion.

The inheritance of 2 alleles associated with reduced FECH activity is required for disease expression. This is consistent with FECH activities as low as 15-25% of normal in EPP patients. In most patients, a disabling mutation on 1 *FECH* allele is combined with a common variant affecting the other allele. This common variant *FECH* allele (IVS3-48T > C) produces less-than-normal amounts of enzyme because it expresses an aberrantly spliced mRNA that is degraded by a nonsense-mediated RNA decay mechanism. The IVS3-48T > C *FECH* variant by itself does not cause disease, even when homozygous. In a few families, 2 severe *FECH* mutations have been found, without the IVS3-48T > C allele. EPP with autosomal recessive inheritance occurs naturally in cattle and in mouse models.

XLP is associated with gain-of-function deletions in the last exon of *ALAS2*. These lesions delete the last 10-20 amino acids of the ALAS2 polypeptide and apparently make the enzyme more stable. Free protoporphyrin predominates in erythrocytes in these cases, but because FECH activity is normal the proportion of zinc protoporphyrin is greater than in classic EPP. XLP accounts for approximately 2% of cases with the EPP phenotype in Europe and approximately 10% of cases in North America.

EPP is sometimes associated with myelodysplastic syndromes and expansion of a clone of hematopoietic cells with deletion of one *FECH* allele or other *FECH* mutations. In such cases, there is late onset of the disease.

Epidemiology

EPP is the most common porphyria to cause symptoms in children, but is often not diagnosed until adult life. Overall it is the third most common porphyria, although its prevalence is not precisely known (see Table 91-2). It is described mostly in white people, but occurs in other races. The IVS3-48T > C splice variant is common in whites and East Asians, but rare in Africans, which explains lower disease prevalence in populations of African origin.

Pathology and Pathogenesis

FECH is deficient in all tissues in EPP, but bone marrow reticulocytes are thought to be the primary source of the excess protoporphyrin, some of which enters plasma and circulates to the skin. Circulating erythrocytes are no longer synthesizing heme and hemoglobin, but they contain excess free protoporphyrin, which also contributes. In XLP caused by terminal deletions in exon 11 of ALAS2, all intermediates of the heme pathway are overproduced and ultimately accumulate in bone marrow erythroblasts as protoporphyrin. FECH is not deficient in the variant form, and this enzyme chelates some of the excess protoporphyrin with zinc. An aberrantly spliced mitoferrin transcript, which limits iron transport into mitochondria, has also been described in this condition. The liver functions as an excretory organ rather than a major source for excess protoporphyrin. But FECH deficiency in the skin and liver may be important, as tissue transplantation studies in mice suggest that skin photosensitivity and liver damage occur only when FECH is deficient in these tissues.

Patients with EPP and XLP are maximally sensitive to light in the 400 nm range, which corresponds to the so-called Soret band (the narrow peak absorption maximum that is characteristic for protoporphyrin and other porphyrins). Having absorbed light, porphyrins enter an excited energy state and release energy as fluorescence, singlet oxygen, and other reactive oxygen species. Tissue damage is accompanied by lipid peroxidation, oxidation of amino acids, crosslinking of proteins in cell membranes, and damage to capillary endothelial cells. Such damage may be mediated by photoactivation of the complement system and release of histamine, kinins, and chemotactic factors. Repeated acute damage leads to thickening of the vessel walls and perivascular deposits from accumulation of serum components. Deposition of amorphous material containing immunoglobulin, complement components, glycoproteins, acid glycosaminoglycans, and lipids around blood vessels occurs in the upper dermis.

There is little evidence for impaired erythropoiesis or hemolysis in EPP. However, mild anemia with microcytosis, hypochromia and reticulocytosis is common. Iron accumulation in erythroblasts and ring sideroblasts have been noted in bone marrow in some patients. Decreased transferrin saturation and low or low-normal serum ferritin suggest iron deficiency. Iron status should be carefully evaluated in EPP patients, keeping in mind that iron deficiency may lead to further increases in protoporphyrin and increase the risk for cholestasis. Oral iron supplements are often poorly absorbed in EPP, which is unexplained. Some patients report increased photosensitivity when given iron supplements, but whether this is from transient increases in porphyrins when iron deficiency is corrected and erythropoiesis increases is not known.

Liver damage that develops in a small proportion of EPP and XLP patients is attributed to excess protoporphyrin, which is cholestatic, insoluble in water and excreted only by hepatic uptake and biliary excretion. Some may be reabsorbed by the intestine and undergo enterohepatic circulation. With cholestasis the excess protoporphyrin that accumulates in the liver can form crystalline structures in hepatocytes, and impair mitochondrial function.

Clinical Manifestations

Symptoms of cutaneous photosensitivity begin in childhood, and consist of pain, redness, and itching occurring within minutes of sunlight exposure. Swelling may resemble angioneurotic edema, and *solar urticaria.* Symptoms are usually worse in the spring and summer. Petechiae and purpuric lesions may be seen, but blisters are usually absent. Chronic changes may include lichenification, leathery pseudovesicles,

labial grooving, and nail changes, but changes in pigmentation and pronounced scarring are unusual. Although physical findings in EPP and XLP may not be impressive, the symptoms significantly impair quality of life to a greater extent than in PCT and VP. An association between autosomal recessive EPP and seasonal palmar keratoderma is unexplained. Neuropathy develops only in some patients with severe hepatic decompensation.

Unless hepatic or other complications develop, protoporphyrin levels and symptoms of photosensitivity remain remarkably stable for many years in most patients. Factors that exacerbate hepatic porphyrias play little or no role in EPP or XLP. Mild, unexplained hypertriglyceridemia has been described. Erythrocyte protoporphyrin levels may decrease and sunlight tolerance may improve during pregnancy, which is unexplained.

Laboratory Findings

Protoporphyrin is substantially increased in circulating erythrocytes in EPP, and consists almost entirely of free protoporphyrin. In a variant form of EPP caused by ALAS2 exon 11 deletions, both zinc protoporphyrin and free protoporphyrin are increased, although the latter still predominates. Protoporphyrin is also increased in bone marrow, plasma, bile, and feces. Other porphyrins and porphyrin precursors are normal in uncomplicated EPP.

Diagnosis and Differential Diagnosis

A diagnosis of EPP is confirmed primarily by finding a substantially elevated concentration of erythrocyte protoporphyrin, which is predominantly metal-free and not complexed with zinc. In XLP, both free and zinc complexed protoporphyrins are elevated. Erythrocyte total protoporphyrin levels are on average higher in XLP more variable in EPP, possible reflecting differences in severity of the many reported *FECH* mutations. Erythrocyte zinc protoporphyrin concentration is increased in some homozygous porphyrias, iron deficiency, lead poisoning, anemia of chronic disease, hemolytic conditions, and many other erythrocytic disorders. Many assays for erythrocyte protoporphyrin or "free erythrocyte protoporphyrin" measure only zinc protoporphyrin (i.e., iron-free rather than metal-free protoporphyrin). Therefore, reports must be interpreted with care, and confirmation obtained from a laboratory that reliably fractionates metal-free and zinc protoporphyrin.

Plasma total porphyrin concentration is often less increased in EPP than in other cutaneous porphyrias, and may be normal. Great care must be taken to avoid light exposure during sample processing, because plasma porphyrins in EPP are particularly subject to photodegradation. Urinary porphyrin precursors and porphyrins are not increased.

Measurement of FECH activity requires cells containing mitochondria and is not widely available. A greater than expected proportion of zinc protoporphyrin (more than ~15% of the total) in erythrocytes is important in identifying XLP. DNA studies are increasingly important for confirming *FECH* or *ALAS2* mutations and for genetic counseling.

Life-threatening protoporphyric hepatopathy is heralded by increasingly abnormal liver function tests, increasing erythrocyte and plasma protoporphyrin levels, and worsening photosensitivity. Increases in urinary porphyrins, especially coproporphyrin, in this setting are attributable to liver dysfunction.

Complications

Biliary stones containing protoporphyrin are sometimes symptomatic and require cholecystectomy. Protoporphyric hepatopathy occurs in less than 5% of EPP patients, including children, and may be chronic or progress rapidly to death from liver failure. This liver disease is sometimes the major presenting feature of EPP. In XLP, liver disease may be more frequent and in 1 report of 8 families, 17% of patients had overt liver dysfunction. Protoporphyric hepatopathy can cause acute upper abdominal pain suggesting biliary obstruction, and unnecessary laparotomy to exclude this possibility can be detrimental. Concurrent conditions that impair liver function, such as viral hepatitis, alcohol intake, iron deficiency, fasting, or oral contraceptive steroids, may contribute. Liver histology shows marked deposition of protoporphyrin in liver cells and bile canaliculi. Patients with protoporphyric liver failure most often have *FECH* "null mutations" and the IVS3–48T>C hypoexpression allele, but some may have 2 severe mutant *FECH* alleles or XLP caused by *ALAS2* exon 11 deletions. The bone marrow is probably the major source of protoporphyrin, even in EPP patients with hepatic failure.

Treatment

Exposure to sunlight should be avoided, which is aided by wearing closely woven clothing. Oral beta-carotene leads to clinical improvement and greater tolerance to light in some patients, usually 1-3 mo after starting treatment. In most adults, doses of 120-180 mg daily will maintain serum carotene levels in the recommended range of 600-800 mg/dL, but doses up to 300 mg daily may be needed. Mild skin discoloration from carotenemia is expected. The recommended product is Lumitene, which was initially developed as a drug for treating this disease, rather than nutritional products that are less standardized. Beta-carotene may quench singlet oxygen or free radicals, but does not substantially alter circulating porphyrin levels. Better tolerance of sunlight may result in tanning, which provides additional protection. Oral cysteine may also quench excited oxygen species and was found to increase tolerance to sunlight in EPP.

Measures to darken the skin may also be helpful. This may be accomplished by narrow-band UV-B phototherapy or with topical products such as dihydroxyacetone and lawsone (naphthoquinone). Afamelanotide, a synthetic analog of melanocyte-stimulating hormone shows promise for increasing sunlight tolerance in EPP and XLP and is currently in Phase 3 trials in the United States. Caloric restriction and drugs or hormone preparations that impair hepatic excretory function should be avoided, and iron deficiency should be corrected if present. Vitamin D supplementation and hepatitides A and B vaccination are recommended.

Treatment of protoporphyric hepatopathy must be individualized and results are unpredictable. Ursodeoxycholic acid may be of some value in early stages. Cholestyramine or activated charcoal may interrupt the enterohepatic circulation of protoporphyrin, promote its fecal excretion, and reduce liver protoporphyrin content. Spontaneous resolution may occur, especially if another reversible cause of liver dysfunction, such as viral hepatitis or alcohol abuse, is contributing. In patients with severe hepatic decompensation, combined treatment with plasmapheresis, transfusion to suppress erythropoiesis, intravenous hemin to suppress erythroid and hepatic protoporphyrin production, ursodeoxycholic acid, vitamin E, and cholestyramine may be beneficial.

Motor neuropathy resembling that seen in acute porphyrias sometimes develops in EPP patients with liver disease before or after transfusion or liver transplantation and is sometimes reversible. Artificial lights, such as operating room lights during liver transplantation or other surgery, may cause severe photosensitivity, with extensive burns of the skin and peritoneum and photodamage of circulating erythrocytes.

With continued progression of liver disease, liver transplantation may be considered. Although liver disease may recur in the transplanted liver as a result of continued bone marrow production of excess protoporphyrin, outcomes are comparable to transplantation for other types of liver disease. Bone marrow transplantation should also be considered after liver transplantation if a suitable donor is available.

Prognosis

Typical EPP patients have lifelong photosensitivity but can otherwise expect normal longevity. Protoporphyric liver disease is often life-threatening; however, the incidence is low.

Prevention

Symptoms can be prevented by avoiding sunlight. Avoiding agents that may cause liver damage may help prevent liver complications.

Genetic Counseling

DNA studies to identify *FECH* mutations, the common IVS3–48T>C *FECH* hypoexpression allele, or ALAS2 exon 11 deletions are increasingly important for genetic counseling. EPP may improve during pregnancy. In classic EPP, DNA studies in both parents can predict the risk for EPP occurring in an offspring.

Dual Porphyria

Dual porphyria refers to patients with porphyria who have deficiencies of more than 1 enzyme of the heme biosynthetic pathway. An unusual pattern of porphyrin precursors and porphyrins may suggest the presence of 2 enzyme deficiencies. Mutations of 2 heme pathway enzymes have been documented in only 2 patients with porphyria. One presented with acute porphyria and had heterozygous mutations in both the *CPOX* and *ALAD* genes. The other had symptoms of AIP and PCT and was documented to have both *PBGD* and *UROD* mutations. In other reported cases, 1 or both enzyme deficiencies were based on enzyme measurements.

Porphyria Resulting from Tumors

Very rarely, hepatocellular tumors contain and presumably produce excess porphyrins, but such cases have not been studied carefully. Hepatocellular carcinomas complicating PCT and acute hepatic porphyrias usually are not described as containing large amounts of porphyrins. Erythropoietic porphyrias can develop late in life from clonal expansion of erythroid cells containing a specific enzyme deficiency in patients who have developed myelodysplastic or myeloproliferative syndromes.

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Chapter 92

Hypoglycemia

Mark A. Sperling

Glucose has a central role in fuel economy and is a source of energy storage in the form of glycogen, fat, and protein (see Chapter 87). As an immediate source of energy, glucose provides 38 mol of adenosine triphosphate (ATP) per mole of glucose oxidized. Glucose is essential for energy metabolism in the brain where it is usually the preferred substrate and where its utilization accounts for nearly all of the brain's oxygen consumption. Cerebral glucose uptake occurs through a glucose transporter molecule or molecules that are not regulated by insulin. Cerebral transport of glucose is a Glut1, carrier-mediated, facilitated diffusion process that is dependent on blood glucose concentration. Hence, low concentrations of blood glucose result in cerebral glucopenia. Deficiency of brain glucose transporters can result in seizures because of low cerebral and cerebrospinal fluid (CSF) glucose concentrations (hypoglycorrhachia) despite normal blood glucose levels. To maintain the blood glucose concentration and prevent it from falling precipitously to levels that impair brain function, an elaborate regulatory system has evolved.

The defense against hypoglycemia is integrated by the autonomic nervous system and by hormones that act in concert to enhance glucose production through enzymatic modulation of glycogenolysis and gluconeogenesis, while simultaneously limiting peripheral glucose utilization which conserves glucose for cerebral metabolism. Hypoglycemia represents a defect in one or several of the complex interactions that normally integrate glucose homeostasis during feeding and fasting. This process is particularly important for neonates, in whom there is an abrupt transition from intrauterine life, characterized by dependence on transplacental glucose supply, to extrauterine life, characterized ultimately by the autonomous ability to maintain euglycemia. Because prematurity or placental insufficiency may limit tissue nutrient deposits, and genetic abnormalities in enzymes or hormones may become evident in the neonate, hypoglycemia is common in the neonatal period.

DEFINITION

In neonates, there is not always an obvious correlation between blood glucose concentration and the classic clinical manifestations of hypoglycemia. The absence of symptoms does not indicate that glucose concentration is normal and has not fallen to less than some optimal level for maintaining brain metabolism. There is evidence that hypoxemia and ischemia may potentiate the role of hypoglycemia in causing permanent brain damage. Consequently, the lower limit of accepted normality of the blood glucose level in newborn infants with associated illness that already impairs cerebral metabolism has not been determined (see Chapter 107). Out of concern for possible neurologic, intellectual, or psychologic sequelae in later life, most authorities recommend that any value of blood glucose <55 mg/dL in neonates be viewed with suspicion and vigorously treated. This is particularly applicable after the initial 2-3 hr of life, when glucose normally has reached its nadir; subsequently, blood glucose levels begin to rise and achieve values of 50 mg/dL or higher after 12-24 hr. By day 3 of life in normal full-term newborns, blood glucose averages approximately 60 mg/dL. In older infants and children, a whole blood glucose concentration of <55 mg/dL (10-15% higher for serum or plasma) represents hypoglycemia, because counterregulatory mechanisms are activated at these glucose concentrations.

SIGNIFICANCE AND SEQUELAE

Most of the endogenous hepatic glucose production in infants and young children, which occurs several hours after feeding and during fasting, can be accounted for by brain metabolism.

Because the brain grows most rapidly in the 1st yr of life and because the larger proportion of glucose turnover is used for brain metabolism, sustained or repetitive hypoglycemia in infants and children can retard brain development and function. Transient isolated and asymptomatic hypoglycemia of short duration does not appear to be associated with these severe sequelae. In the rapidly growing brain, glucose may also be a source of membrane lipids and, together with protein synthesis it can provide structural proteins and myelination that are important for normal brain maturation. Under conditions of severe and sustained hypoglycemia, these cerebral structural substrates may become degraded to energy-usable intermediates such as lactate, pyruvate, amino acids, and ketoacids, which can support brain metabolism at the expense of brain growth. The capacity of the newborn brain to take up and oxidize ketone bodies is about 5-fold greater than that of the adult brain. However, the capacity of the liver to produce ketone bodies is limited in the immediate newborn period, especially in the presence of hyperinsulinism, which acutely inhibits hepatic glucose output, lipolysis, and ketogenesis, thereby depriving the brain of any alternate fuel sources. Although the brain may metabolize ketones, these alternate fuels cannot completely replace glucose as an essential central nervous system (CNS) fuel. The deprivation of the brain's major energy source during hypoglycemia and the limited availability of alternate fuel sources during hyperinsulinism have predictable adverse consequences on brain metabolism and growth: decreased brain oxygen consumption and increased breakdown of endogenous structural components with destruction of functional membrane integrity.

The major long-term sequelae of severe, prolonged hypoglycemia are cognitive impairment, recurrent seizure activity, cerebral palsy and autonomic dysregulation. Subtle effects on personality are also possible but have not been clearly defined. Permanent neurologic sequelae are present in 25-50% of patients with severe recurrent symptomatic hypoglycemia who are younger than 6 mo of age. These sequelae may be reflected in pathologic changes characterized by reduced myelination in cerebral white matter and atrophy of the cerebral cortex, reflected in enlargement of the sulci and thinning of the gyri of the brain. These sequelae also are more likely when alternative fuel sources are limited,

as occurs with hyperinsulinism, when the episodes of hypoglycemia are repetitive or prolonged, or when they are compounded by hypoxia. There is no precise knowledge relating the duration or severity of hypoglycemia to subsequent neurologic development of children in a predictable manner. Although less common, hypoglycemia in older children may also produce long-term neurologic defects through neuronal death mediated, in part, by cerebral excitotoxins released during hypoglycemia.

SUBSTRATE, ENZYME, AND HORMONAL INTEGRATION OF GLUCOSE HOMEOSTASIS

In the Newborn

See Chapter 107.

Under nonstressed conditions, fetal glucose is derived entirely from the mother through placental transfer. Therefore, fetal glucose concentration usually reflects, but is slightly lower than, maternal glucose levels. Catecholamine release, which occurs with fetal stress such as hypoxia, mobilizes fetal glucose and free fatty acids (FFAs) through β-adrenergic mechanisms, reflecting β-adrenergic activity in fetal liver and adipose tissue. Catecholamines may also inhibit fetal insulin and stimulate glucagon release.

The acute interruption of maternal glucose transfer to the fetus at delivery imposes an immediate need to mobilize endogenous glucose. Three related events facilitate this transition: changes in hormones, changes in their receptors, and changes in key enzyme activity. There is a 3-5–fold abrupt increase in glucagon concentration within minutes to hours of birth. The level of insulin usually falls initially and remains in the basal range for several days without demonstrating the usual brisk response to physiologic stimuli such as glucose. A dramatic surge in spontaneous catecholamine secretion is also characteristic. Epinephrine can also augment growth hormone secretion by α-adrenergic mechanisms; growth hormone levels are elevated at birth. Acting in concert, these hormonal changes at birth mobilize glucose via glycogenolysis and gluconeogenesis, activate lipolysis, and promote ketogenesis. As a result of these processes, plasma glucose concentration stabilizes after a transient decrease immediately after birth, liver glycogen stores become rapidly depleted within hours of birth, and gluconeogenesis from alanine, a major gluconeogenic amino acid, can account for approximately 10% of glucose turnover in the human newborn infant by several hours of age. FFA concentrations also increase sharply in concert with the surges in glucagon and epinephrine, and are followed later by rises in ketone bodies. Glucose is thus partially spared for brain utilization while FFAs and ketones provide alternative fuel sources for muscle as well as essential gluconeogenic factors such as acetyl coenzyme A (CoA) and the reduced form of nicotinamide adenine dinucleotide from hepatic fatty acid oxidation, which is required to drive gluconeogenesis.

In the early postnatal period, responses of the endocrine pancreas favor glucagon secretion so that blood glucose concentration can be maintained. These adaptive changes in hormone secretion are paralleled by similarly striking adaptive changes in hormone receptors. Key enzymes involved in glucose production also change dramatically in the perinatal period. Thus, there is a rapid fall in glycogen synthase activity and a sharp rise in phosphorylase activity after delivery. Similarly, the amount of the rate-limiting enzyme for gluconeogenesis, phosphoenolpyruvate carboxykinase, rises dramatically after birth, activated in part by the surge in glucagon and the fall in insulin. This framework can explain several causes of neonatal hypoglycemia based on inappropriate changes in hormone secretion and unavailability of adequate reserves of substrates in the form of hepatic glycogen, muscle as a source of amino acids for gluconeogenesis, and lipid stores for the release of fatty acids. In addition, appropriate activities of key enzymes governing glucose homeostasis are required (see Fig. 87-1 in Chapter 87).

In Older Infants and Children

Hypoglycemia in older infants and children is analogous to that of adults, in whom glucose homeostasis is maintained by glycogenolysis in the immediate postfeeding period and by gluconeogenesis several hours after meals. The liver of a 10 kg child contains 20-25 g of glycogen, which is sufficient to meet normal glucose requirements of 4-6 mg/kg/min for only 6-12 hr. Beyond this period, hepatic gluconeogenesis must be activated. Both glycogenolysis and gluconeogenesis depend on the metabolic pathway summarized in Figure 87-1. Defects in glycogenolysis or gluconeogenesis may not be manifested in infants until the frequent feeding at 3-4 hr intervals ceases and infants sleep through the night, a situation usually present by 3-6 mo of age. The source of gluconeogenic precursors is derived primarily from muscle protein. The muscle bulk of infants and small children is substantially smaller relative to body mass than that of adults, whereas glucose requirements/unit of body mass are greater in children, so the ability to compensate for glucose deprivation by gluconeogenesis is more limited in infants and young children, as is the ability to withstand fasting for prolonged periods. The ability of muscle to generate alanine, the principal gluconeogenic amino acid, may also be limited. Thus, in normal young children, the blood glucose level falls after 24 hr of fasting, insulin concentrations fall appropriately to levels of <5-10 μU/mL, lipolysis and ketogenesis are activated, and ketones may appear in the urine.

The switch from glycogen synthesis during and immediately after meals to glycogen breakdown and later gluconeogenesis is governed by hormones, of which insulin is of central importance. Plasma insulin concentrations increase to peak levels of 5-10–fold greater than their baseline of approximately 5-10 μU/mL after meals, which serve to lower the blood glucose concentration through the activation of glycogen synthesis, enhancement of peripheral glucose uptake, and inhibition of glucose production. In addition, lipogenesis is stimulated, whereas lipolysis and ketogenesis are curtailed. During fasting, plasma insulin concentrations fall to ≤5-10 μU/mL, and together with the rise of counterregulatory hormones, this fall in insulin results in activation of gluconeogenic pathways (see Fig. 87-1). Fasting glucose concentrations are maintained through the activation of glycogenolysis and gluconeogenesis, inhibition of glycogen synthesis, and activation of lipolysis and ketogenesis. It should be emphasized that a plasma insulin concentration of >5 μU/mL, in association with a blood glucose concentration of ≤50-55 mg/dL (2.8-3.0 mM), is abnormal, indicating a **state** of excessive insulin action, here termed **hyperinsulinism,** because of failure of the mechanisms that normally result in suppression of insulin secretion during fasting or hypoglycemia.

The hypoglycemic effects of insulin are opposed by the actions of several hormones whose concentration in plasma increases as blood glucose falls. These **counterregulatory hormones**—glucagon, growth hormone, cortisol, and epinephrine—act in concert by increasing blood glucose concentrations via activating glycogenolytic enzymes (glucagon, epinephrine); inducing gluconeogenic enzymes (glucagon, cortisol); inhibiting glucose uptake by muscle (epinephrine, growth hormone, cortisol); mobilizing amino acids from muscle for gluconeogenesis (cortisol); activating lipolysis and thereby providing glycerol for gluconeogenesis and fatty acids for ketogenesis (epinephrine, cortisol, growth hormone, glucagon); and inhibiting insulin release and promoting growth hormone and glucagon secretion (epinephrine).

Congenital or acquired deficiency of any one of these hormones is uncommon but will result in hypoglycemia, which occurs when endogenous glucose production cannot be mobilized to meet energy needs in the postabsorptive state, that is, 8-12 hr after meals or during fasting. Concurrent deficiency of several hormones (**hypopituitarism**) may result in hypoglycemia that is more severe or appears earlier during fasting than that seen with isolated hormone deficiencies. Most of the causes of hypoglycemia in neonates, infants and children reflect inappropriate adaptation to fasting as a result of excess insulin action, or inadequate counter-regulatory hormone response primarily of cortisol and growth hormone, or enzymatic defects in the mechanisms for glycogen storage and release, or defects in gluconeogenesis.

CLINICAL MANIFESTATIONS

See Chapter 107.

Clinical features generally fall into 2 categories. The first includes symptoms associated with the activation of the autonomic nervous system and epinephrine release, usually seen with a rapid decline in blood glucose concentration (Table 92-1). The second category includes

Table 92-1 Manifestations of Hypoglycemia in Childhood

FEATURES ASSOCIATED WITH ACTIVATION OF AUTONOMIC NERVOUS SYSTEM AND EPINEPHRINE RELEASE*
Anxiety†
Perspiration†
Palpitation (tachycardia)†
Pallor‡
Tremulousness‡
Weakness
Hunger
Nausea
Emesis
FEATURES ASSOCIATED WITH CEREBRAL GLUCOPENIA
Headache†
Mental confusion†
Visual disturbances (↓ acuity, diplopia)†
Organic personality changes†
Inability to concentrate†
Dysarthria
Staring
Paresthesias
Dizziness
Amnesia
Ataxia, incoordination
Refusal to feed‡
Somnolence, lethargy‡
Seizures‡
Coma
Stroke, hemiplegia, aphasia
Decerebrate or decorticate posture

*Some of these features will be attenuated if the patient is receiving β-adrenergic blocking agents.
†Common.
‡Most common manifestations in the newborn.

symptoms caused by decreased cerebral glucose utilization (cerebral glycopenia), usually associated with a slow decline in blood glucose level or prolonged hypoglycemia (Table 92-1). Although these classic symptoms occur in older children, the symptoms of hypoglycemia in newborns and infants may be subtler and include cyanosis, apnea, hypothermia, hypotonia, poor feeding, lethargy, and seizures. Some of these symptoms may be so mild that they are missed. Occasionally, hypoglycemia may be asymptomatic in the immediate newborn period. Newborns with hyperinsulinism are often large for gestational age; older infants with hyperinsulinism may eat excessively because of chronic hypoglycemia and become obese. In childhood, hypoglycemia may present as behavior problems, inattention, ravenous appetite, or seizures. It may be misdiagnosed as epilepsy, inebriation, personality disorders, headache, hysteria, and developmental delay. A blood glucose determination should always be performed in sick neonates, who should be vigorously treated if concentrations are <50 mg/dL. At any age, hypoglycemia should be considered a cause of an initial episode of convulsions or a sudden deterioration in psychobehavioral functioning or level of consciousness.

Many neonates have asymptomatic (chemical) hypoglycemia. The incidence of symptomatic hypoglycemia is highest in small for gestational age infants (Fig. 92-1). The exact incidence of symptomatic hypoglycemia has been difficult to establish because many of the symptoms in neonates occur **together** with other conditions such as infections, especially sepsis and meningitis; CNS anomalies, hemorrhage, or edema; hypocalcemia and hypomagnesemia; asphyxia; drug withdrawal; apnea of prematurity; congenital heart disease; or polycythemia.

The onset of symptoms in neonates varies from a few hours to a week after birth. In approximate order of frequency, symptoms include jitteriness or tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, weak or high-pitched cry, limpness or lethargy, difficulty feeding, and eye rolling. Episodes of sweating, sudden pallor, hypothermia, and cardiac arrest and failure also occur.

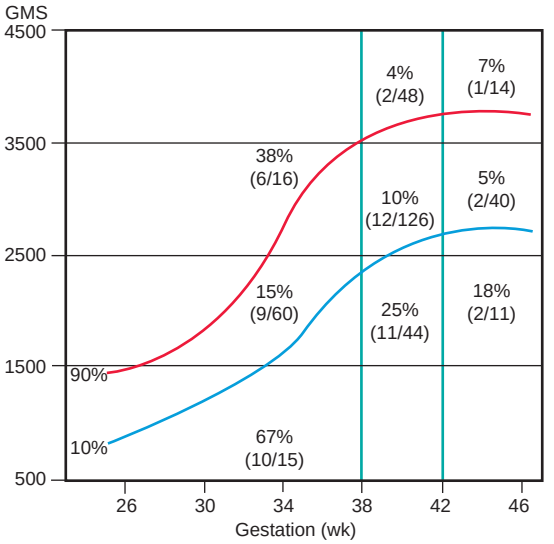

Figure 92-1 Incidence of hypoglycemia by birthweight, gestational age, and intrauterine growth. *(From Lubchenco LO, Bard H: Incidence of hypoglycemia in newborn infants classified by birthweight and gestational age,* Pediatrics *47:831–838, 1971.)*

Frequently, a clustering of episodic symptoms may be noted. Because these clinical manifestations may result from various causes, it is critical to measure serum glucose levels and determine whether symptoms disappear with the administration of sufficient glucose to raise the blood glucose to normal levels; if they do not, other diagnoses must be considered.

CLASSIFICATION OF HYPOGLYCEMIA IN INFANTS AND CHILDREN

Classification is based on knowledge of the control of glucose homeostasis in infants and children (Table 92-2).

Neonatal, Transient, Small for Gestational Age, and Premature Infants

See Chapter 107.

The estimated incidence of symptomatic hypoglycemia in newborns is 1-3 in 1,000 live births. This incidence is increased severalfold in certain high-risk neonatal groups (see Table 92-2 and Fig. 92-1). The premature and small for gestational age (SGA) infants are vulnerable to the development of hypoglycemia. The factors responsible for the high frequency of hypoglycemia in this group, as well as in other groups outlined in Table 92-2, are related to the inadequate stores of liver glycogen, muscle protein, and body fat needed to sustain the substrates required to meet energy needs. These infants are small by virtue of prematurity or impaired placental transfer of nutrients. Their enzyme systems for gluconeogenesis may not be fully developed. **Transient hyperinsulinism** responsive to diazoxide has also been reported as contributing to hypoglycemia in asphyxiated, SGA, and premature newborn infants. This form of hyperinsulinism associated with perinatal asphyxia, intrauterine growth restriction, maternal toxemia and other perinatal stressors, is probably the most common cause of hyperinsulinemic hypoglycemia in neonates and may be quite severe. In most cases, the condition resolves quickly, but it may persist to 7 mo of life or longer.

In contrast to deficiency of substrates or enzymes, the hormonal system appears to be functioning normally at birth in most low-risk neonates. Despite hypoglycemia, plasma concentrations of alanine, lactate, and pyruvate are higher, implying their diminished rate of utilization as substrates for gluconeogenesis. Infusion of alanine elicits further glucagon secretion but causes no significant rise in glucose. During the initial 24 hr of life, plasma concentrations of acetoacetate and β-hydroxybutyrate are lower in SGA infants than in full-term infants, implying diminished lipid stores, diminished fatty acid mobilization, impaired ketogenesis, or a combination of these

Table 92-2 Classification of Hypoglycemia in Infants and Children

NEONATAL TRANSITIONAL (ADAPTIVE) HYPOGLYCEMIA

Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates
Prematurity
Small for gestational age
Normal newborn

Transient Neonatal Hyperinsulinism
Infant of diabetic mother
Small for gestational age
Discordant twin
Birth asphyxia
Infant of toxemic mother

NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS

Hyperinsulinism
Recessive K_{ATP} channel HI
Recessive HADH (hydroxyl acyl-CoA dehydrogenase) mutation HI
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI
Focal K_{ATP} channel HI
Dominant K_{ATP} channel HI
Atypical congenital hyperinsulinemia (no mutations in *ABCC8* or *KCN11* genes)
Dominant glucokinase HI
Dominant glutamate dehydrogenase HI (hyperinsulinism/hyperammonemia syndrome)
Dominant mutations in HNF-4A and HNF-1A (hepatic nuclear factors 4α and 1α) HI with monogenic diabetes of youth later in life
Dominant mutation in SLC16A1(the pyruvate transporter)—exercise-induced hypoglycemia
Acquired islet adenoma
Beckwith-Wiedemann syndrome
Insulin administration (Munchausen syndrome by proxy)
Oral sulfonylurea drugs
Congenital disorders of glycosylation

Counterregulatory Hormone Deficiency
Panhypopituitarism
Isolated growth hormone deficiency
Adrenocorticotropic hormone deficiency
Addison disease
Epinephrine deficiency

Glycogenolysis and Gluconeogenesis Disorders
Glucose-6-phosphatase deficiency (GSD 1a)
Glucose-6-phosphate translocase deficiency (GSD 1b)
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3)
Liver phosphorylase deficiency (GSD 6)
Phosphorylase kinase deficiency (GSD 9)
Glycogen synthetase deficiency (GSD 0)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
Galactosemia
Hereditary fructose intolerance

Lipolysis Disorders

Fatty Acid Oxidation Disorders
Carnitine transporter deficiency (primary carnitine deficiency)
Carnitine palmitoyltransferase-1 deficiency
Carnitine translocase deficiency
Carnitine palmitoyltransferase-2 deficiency
Secondary carnitine deficiencies
Very-long-, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency

OTHER ETIOLOGIES

Substrate-Limited
Ketotic hypoglycemia
Poisoning—drugs
Salicylates
Alcohol
Oral hypoglycemic agents
Insulin
Propranolol
Pentamidine
Quinine
Disopyramide
Ackee fruit (unripe)—hypoglycin
Vacor (rat poison)
Trimethoprim-sulfamethoxazole (with renal failure)

Liver Disease
Reye syndrome
Hepatitis
Cirrhosis
Hepatoma

AMINO ACID AND ORGANIC ACID DISORDERS
Maple syrup urine disease
Propionic acidemia
Methylmalonic acidemia
Tyrosinosis
Glutaric aciduria
3-Hydroxy-3-methylglutaric aciduria

SYSTEMIC DISORDERS
Sepsis
Carcinoma/sarcoma (secreting—insulin-like growth factor II)
Heart failure
Malnutrition
Malabsorption
Antiinsulin receptor antibodies
Antiinsulin antibodies
Neonatal hyperviscosity
Renal failure
Diarrhea
Burns
Shock
Postsurgical
Pseudohypoglycemia (leukocytosis, polycythemia)
Excessive insulin therapy of insulin-dependent diabetes mellitus
Factitious
Nissen fundoplication (dumping syndrome)
Falciparum malaria

GSD, glycogen storage disease; HI, hyperinsulinemia; K_{ATP}, regulated potassium channel.

conditions. Diminished lipid stores are most likely because fat (triglyceride) feeding of newborns results in a rise in the plasma levels of glucose, ketones such as β OH butyrate and FFA. For infants with perinatal asphyxia, and some SGA newborns who have transient hyperinsulinism, hypoglycemia and diminished concentrations of β OH butyrate and FFAs are the hallmark of hyperinsulinism.

The role of FFAs and their oxidation in stimulating neonatal gluconeogenesis is essential. The provision of FFAs as triglyceride feedings from formula or human milk together with gluconeogenic precursors may prevent the hypoglycemia that usually ensues after neonatal fasting. For these and other reasons, milk feedings are introduced early (at birth or within 2-4 hr) after delivery. In the hospital setting, when feeding is precluded by virtue of respiratory distress or when feedings alone cannot maintain blood glucose concentrations at levels >50 mg/dL, intravenous glucose at a rate that supplies 4-8 mg/kg/min should be started. Infants with transient neonatal hypoglycemia can usually maintain the blood glucose level spontaneously after 2-3 days of life, but some require longer periods of support. In these latter infants,

insulin values >5 μU/mL at the time of hypoglycemia should be treated with diazoxide.

Infants Born to Diabetic Mothers

See Chapter 107.1.

Of the transient hyperinsulinemic states, infants born to diabetic mothers are the most common. Gestational diabetes affects some 2% of pregnant women, and ≈1 in 1,000 pregnant women have insulin-dependent diabetes. At birth, infants born to these mothers may be large and plethoric, and their body stores of glycogen, protein, and fat are replete.

Hypoglycemia in infants of diabetic mothers is mostly related to hyperinsulinemia and partly related to diminished glucagon secretion. Hypertrophy and hyperplasia of the islets is present, as is a brisk, biphasic, and typically mature insulin response to glucose; this brisk insulin response is absent in normal infants. Infants born to diabetic mothers also have a subnormal surge in plasma glucagon immediately after birth, subnormal glucagon secretion in response to stimuli, and, initially, excessive sympathetic activity that may lead to adrenomedullary exhaustion as reflected by decreased urinary excretion of epinephrine. The normal plasma hormonal pattern of low insulin, high glucagon, and high catecholamines is reversed to a pattern of high insulin, low glucagon, and low epinephrine. As a consequence of this abnormal hormonal profile, endogenous glucose production is significantly inhibited compared with that in normal infants, thus predisposing them to hypoglycemia.

Mothers whose diabetes has been well controlled during pregnancy, labor, and delivery generally have infants near normal size who are less likely to develop neonatal hypoglycemia and other complications formerly considered typical of such infants (see Chapter 107.1). In supplying exogenous glucose to these hypoglycemic infants, it is important to avoid hyperglycemia that evokes a prompt exuberant insulin release, which may result in rebound hypoglycemia. When needed, glucose should be provided at continuous infusion rates of 4-8 mg/kg/min, but the appropriate dose for each patient must be individually adjusted. During labor and delivery, maternal hyperglycemia should be avoided because it results in fetal hyperglycemia, which predisposes to hypoglycemia when the glucose supply is interrupted at birth. Hypoglycemia persisting or occurring after 1 wk of life requires an evaluation for the causes listed in Table 92-2.

Infants born with **erythroblastosis fetalis** may also have hyperinsulinemia and share many physical features, such as large body size, with infants born to diabetic mothers. The cause of the hyperinsulinemia in infants with erythroblastosis is not clear.

PERSISTENT OR RECURRENT HYPOGLYCEMIA IN INFANTS AND CHILDREN

Hyperinsulinism

Most children with hyperinsulinism that causes hypoglycemia present in the neonatal period or later in infancy; hyperinsulinism is the most common cause of persistent hypoglycemia in early infancy. Infants who have hyperinsulinism may be macrosomic at birth, reflecting the anabolic effects of insulin in utero. There is no history or biochemical evidence of maternal diabetes. The onset of symptoms is from birth to 18 mo of age, but occasionally it only becomes evident in older children. Insulin concentrations are inappropriately elevated at the time of documented hypoglycemia; with nonhyperinsulinemic hypoglycemia, plasma insulin concentrations should be <5 μU/mL and no higher than 10 μU/mL. In affected infants, plasma insulin concentrations at the time of hypoglycemia are commonly >5-10 μU/mL. Some authorities set more stringent criteria, arguing that any value of insulin >2 μU/mL with hypoglycemia is abnormal. The insulin (μU/mL):glucose (mg/dL) ratio is commonly >0.4; plasma insulin-like growth factor binding protein-1 (IGFBP-1), β OH butyrate, and FFA levels are low with hyperinsulinism. Rare instances of activating mutations in the insulin receptor signaling pathway have been reported where the clinical and biochemical features are similar to states of excessive insulin secretion, yet insulin concentrations are low to the point of being undetectable. Hence, the preferred term is **hyperinsulinism**, to describe a state of increased insulin action. Macrosomic infants may present with hypoglycemia from the first days of life. Infants with lesser degrees of hyperinsulinism may manifest hypoglycemia only after the first few weeks to months, when the frequency of feedings has been decreased to permit the infant to sleep through the night, and hyperinsulinism prevents the mobilization of endogenous glucose. Increasing appetite and demands for feeding, wilting spells, jitteriness, and frank seizures are the most common presenting features. Additional clues include the rapid development of fasting hypoglycemia within 4-8 hr of food deprivation compared with other causes of hypoglycemia (Tables 92-3 and 92-4); the need for high rates of exogenous glucose infusion to prevent hypoglycemia, often at rates >10-15 mg/kg/min; the absence of ketonemia or acidosis; and elevated C-peptide or proinsulin levels at the time of hypoglycemia. The latter insulin-related products are absent in **factitious hypoglycemia** from exogenous administration of insulin as a form of child abuse (Munchausen by proxy syndrome; see Chapter 40.2). Hypoglycemia is invariably provoked by withholding feedings for several hours, permitting simultaneous measurement of glucose, insulin, ketones, and FFAs in the same sample at the time of clinically manifested hypoglycemia. This is termed the **critical sample.** The glycemic response to glucagon at the time of hypoglycemia reveals a brisk increment in glucose concentration of at least 40 mg/dL, which implies that glucose mobilization has been restrained by insulin but that glycogenolytic mechanisms are intact (Tables 92-5, 92-6, and 92-7).

The measurement of serum IGFBP-1 concentration may help diagnose hyperinsulinism. The secretion of IGFBP-1 is acutely inhibited by insulin action; IGFBP-1 concentrations are low during hyperinsulinism-induced hypoglycemia. In patients with spontaneous or fasting-induced hypoglycemia with a low insulin level (ketotic hypoglycemia, normal fasting), IGFBP-1 concentrations are significantly higher.

The differential diagnosis of endogenous hyperinsulinism includes **diffuse β-cell hyperplasia** or **focal β-cell microadenoma.**

The distinction between these 2 major entities is important because the former, if unresponsive to medical therapy, requires near total pancreatectomy, despite which hypoglycemia may persist or diabetes mellitus may ensue at some later time. Some affected infants may respond to sirolimus. By contrast, focal adenomas diagnosed

Table 92-3 Hypoglycemia in Infants and Children: Clinical and Laboratory Features

GROUP	AGE AT DIAGNOSIS (mo)	GLUCOSE* (mg/dL)	INSULIN (μU/mL)	FASTING TIME TO HYPOGLYCEMIA (hr)
HYPERINSULINEMIA (*N* = 12)				
Mean	7.4	23.1	22.4	2.1†
SEM	2.0	2.7	3.2	0.6
NONHYPERINSULINEMIA (*N* = 16)				
Mean	41.8	36.1	5.8	18.2
SEM	7.3	2.4	0.9	2.9

*In hypoglycemia caused by hyperinsulinism β OH butyrate and FFA are low compared with normal at same duration of fasting.
†Milder forms of hyperinsulinism may require up to 18 hr of fasting to provoke hypoglycemia.
SEM, standard error of mean.
Adapted from Antunes JD, Geffner ME, Lippe BM, et al: Childhood hypoglycemia: differentiating hyperinsulinemic from nonhyperinsulinemic causes, J Pediatr *116:105–108, 1990.*

Table 92-4 Correlation of Clinical Features with Molecular Defects in Persistent Hyperinsulinemic Hypoglycemia in Infancy

TYPE	MACROSOMIA	HYPOGLYCEMIA/ HYPERINSULINEMIA	FAMILY HISTORY	MOLECULAR DEFECTS	ASSOCIATED CLINICAL, BIOCHEMICAL, OR MOLECULAR FEATURES	RESPONSE TO MEDICAL MANAGEMENT	RECOMMENDED SURGICAL APPROACH	PROGNOSIS
Sporadic	Present at birth	Moderate/severe in first days to weeks of life	Negative	? *SUR1*/K_{IR} 6.2 Mutations not always identified in diffuse hyperplasia	Loss of heterozygosity in microadenomatous tissue	Generally poor; may respond better to somatostatin than to diazoxide	Partial pancreatectomy if frozen section shows β-cell crowding with small nuclei—suggests microadenoma Subtotal >95% pancreatectomy if frozen section shows giant nuclei in β-cells—suggests diffuse hyperplasia	Excellent if focal adenoma is removed, thereby curing hypoglycemia and retaining sufficient pancreas to avoid diabetes Guarded if subtotal (>95%) pancreatectomy is performed because diabetes develops in, and hypoglycemia persists in
Autosomal recessive	Present at birth	Severe in first days to weeks of life	Positive	*SUR*/K_{IR} 6.2	Consanguinity a feature in some populations	Poor	Subtotal pancreatectomy	Guarded
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glucokinase (activating) Some cases gene unknown	None	Very good to excellent	Surgery usually not required Partial pancreatectomy only if medical management fails	Excellent
Autosomal dominant	Unusual	Moderate onset usually post 6 mo of age	Positive	Glutamate dehydrogenase (activating)	Modest hyperammonemia	Very good to excellent	Surgery usually not required	Excellent
Beckwith-Wiedemann syndrome	Present at birth	Moderate, spontaneously resolves post 6 mo of age	Negative	Duplicating/ imprinting in chromosome 11p15.1	Macroglossia, omphalocele, hemihypertrophy	Good	Not recommended	Excellent for hypoglycemia; guarded for possible development of embryonal tumors (Wilms hepatoblastoma)
Congenital disorders of glycosylation	Not usual	Moderate/onset post 3 mo of age	Negative	Phosphomannose isomerase deficiency	Hepatomegaly, vomiting, intractable diarrhea	Good with mannose supplement	Not recommended	Fair

Table 92-5 Analysis of Critical Blood Sample During Hypoglycemia and 30 Minutes After Glucagon*

SUBSTRATES
Glucose
Free fatty acids
Ketones
Lactate
Uric acid
Ammonia
HORMONES
Insulin
Cortisol
Growth hormone
Thyroxine, thyroid-stimulating hormone
Insulin-like growth factor binding protein-1†

*Glucagon 50 μg/kg with maximum of 1 mg IV or IM.
†Measure once only before or after glucagon administration. Rise in glucose of ≥40 mg/dL after glucagon given at the time of hypoglycemia strongly suggests a hyperinsulinemic state with adequate hepatic glycogen stores and intact glycogenolytic enzymes. If ammonia is elevated to 100-200 μM, consider activating mutation of glutamate dehydrogenase.

Table 92-6 Criteria for Diagnosing Hyperinsulinism Based on "Critical" Samples (Drawn at a Time of Fasting Hypoglycemia: Plasma Glucose <50 mg/dL)

1. Hyperinsulinemia (plasma insulin >2 μU/mL)*
2. Hypofatty acidemia (plasma free fatty acids <1.5 mmol/L)
3. Hypoketonemia (plasma β-hydroxybutyrate: <2.0 mmol/L)
4. Inappropriate glycemic response to glucagon, 1 mg IV (change in glucose >40 mg/dL)

*Depends on sensitivity of insulin assay.
From Stanley CA, Thomson PS, Finegold DN, et al: Hypoglycemia in infants and neonates. In Sperling MA, editor: Pediatric endocrinology, *ed 2, Philadelphia, 2002, WB Saunders, pp. 135–159.*

Table 92-7 Diagnosis of Acute Hypoglycemia in Infants and Children

ACUTE SYMPTOMS PRESENT

1. Obtain blood sample before and 30 min after glucagon administration.
2. Obtain urine as soon as possible. Examine for ketones; if not present and hypoglycemia confirmed, suspect hyperinsulinemia or fatty acid oxidation defect; if present, suspect ketotic, hormone deficiency, inborn error of glycogen metabolism, or defective gluconeogenesis.
3. Measure glucose in the original blood sample. If hypoglycemia is confirmed, proceed with substrate-hormone measurement as in Table 92-5.
4. If glycemic increment after glucagon exceeds 40 mg/dL above basal, suspect hyperinsulinemia.
5. If insulin level at time of confirmed hypoglycemia is >5 μU/mL, suspect endogenous hyperinsulinemia; if >100 μU/mL, suspect factitious hyperinsulinemia (exogenous insulin injection). Admit to hospital for supervised fast.
6. If cortisol is <10 μg/dL or growth hormone is <5 ng/mL, or both, suspect adrenal insufficiency or pituitary disease, or both. Admit to hospital for hormonal testing and neuroimaging.

HISTORY SUGGESTIVE: ACUTE SYMPTOMS NOT PRESENT

1. Careful history for relation of symptoms to time and type of food intake, bearing in mind age of patient. Exclude possibility of alcohol or drug ingestion. Assess possibility of insulin injection, salt craving, growth velocity, intracranial pathology.
2. Careful examination for hepatomegaly (glycogen storage disease; defect in gluconeogenesis); pigmentation (adrenal failure); stature and neurologic status (pituitary disease).
3. Admit to hospital for provocative testing:
   a. 24 hr fast under careful observation; when symptoms provoked, proceed with steps 1-4 as when acute symptoms present.
   b. Pituitary–adrenal function using arginine-insulin stimulation test if indicated.
4. Consider molecular diagnostic test before liver biopsy for histologic and enzyme determinations.
5. Oral glucose tolerance test (1.75 g/kg; max 75 g) if reactive hypoglycemia suspected (dumping syndrome, etc.).

preoperatively or intraoperatively permit localized curative resection with subsequent normal glucose metabolism. Approximately 50% of the autosomal recessive or sporadic forms of neonatal/infantile hyperinsulinism are caused by focal microadenomas, which may be distinguished from the diffuse form by the pattern of insulin response to selective insulin secretagogues infused into an arterial branch supplying the pancreas, with sampling via the hepatic vein. However, these invasive and technically difficult procedures have been largely abandoned in favor of positron emission tomography using 18-fluoro-L-dopa. This technique can distinguish the diffuse form (uniform fluorescence throughout the pancreas) from the focal form (focal uptake of 18-fluoro-L-dopa and localized fluorescence) with an extremely high degree of reliability, success, specificity, and sensitivity (see Fig. 92-3 and below).

Insulin-secreting macroadenomas are rare in childhood and may be diagnosed preoperatively via CT or MRI. The plasma levels of insulin alone, however, cannot distinguish the aforementioned entities. The diffuse or microadenomatous forms of islet cell hyperplasia represent a variety of genetic defects responsible for abnormalities in the endocrine pancreas characterized by autonomous insulin secretion that is not appropriately reduced when blood glucose declines spontaneously or in response to provocative maneuvers such as fasting (see Tables 92-4, 92-7, and 92-8 and Fig. 92-2). Clinical, biochemical, and molecular genetic approaches now permit classification of congenital hyperinsulinism, formerly termed **nesidioblastosis,** into distinct entities. **Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)** may be inherited or sporadic, is severe, and is caused by mutations that affect the regulation of the potassium channel intimately involved in insulin secretion by the pancreatic β cell (Fig. 92-2). Normally, glucose entry into the β cell is enabled by the non–insulin-responsive glucose transporter GLUT-2. On entry, glucose is phosphorylated to glucose-6-phosphate by the enzyme glucokinase, enabling glucose metabolism to generate ATP. The rise in the molar ratio of ATP relative to adenosine diphosphate closes the ATP-sensitive potassium channel in the cell membrane (K_{ATP} channel). This channel is composed of 2 subunits, the K_{IR} 6.2 channel, part of the family of inward-rectifier potassium channels, and a regulatory component in intimate association with K_{IR} 6.2 known as the sulfonylurea receptor (SUR1). Together, K_{IR} 6.2 and SUR1 constitute the potassium-sensitive ATP channel K_{ATP}. Normally, the K_{ATP} is open, but with the rise in ATP and closure of the channel, potassium accumulates intracellularly, causing depolarization of the membrane, opening of voltage-gated calcium channels, influx of calcium into the cytoplasm, and secretion of insulin via exocytosis. The genes for both SUR1 and K_{IR} 6.2 are located close together on the short arm of chromosome 11, the site of the insulin gene. **Inactivating** mutations in the gene for SUR1 or, less often, K_{IR} 6.2 prevent the potassium channel from opening; it remains variably closed with constant depolarization and, therefore, constant inward flux of calcium; hence, insulin secretion is continuous and not governed by the glucose concentration. A milder autosomal dominant form of these defects is also reported. Likewise, an **activating** mutation in glucokinase or glutamate dehydrogenase enzyme activity results in closure of the potassium channel through overproduction of ATP which causes hyperinsulinism. Genetic defects in fatty acid metabolism, in the insulin transcription factor HNF-4α and HNF-1α, and in the uncoupling protein UCP-2 of the mitochondrial gene complex also have been involved in

Table 92-8 Clinical Manifestations and Differential Diagnosis in Childhood Hypoglycemia

Condition	Hypoglycemia	Urinary Ketones or Reducing Sugars	Hepatomegaly	Serum		Effect of 24-36 hr Fast on Plasma					Glycemic Response to Glucagon		Glycemic Response to Infusion of	
				LIPIDS	URIC ACID	GLUCOSE	INSULIN	KETONES	ALANINE	LACTATE	FED	FASTED	ALANINE	GLYCEROL
Normal	0	0	0	Normal	Normal	↓	↓	↑	↓	Normal	↑	↓		Not indicated
Hyperinsulinemia	Recurrent severe	0	0	Normal or ↑	Normal	↓↓	↑↑	↓↓	Normal	Normal	↑	↑		Not indicated
Ketotic hypoglycemia	Severe with missed meals	Ketonuria +++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓		Not indicated
Fatty acid oxidation disorder	Severe with missed meals	Absent	0 to + Abnormal liver function test results	Abnormal	↑		Contraindicated				↑	↓		Not indicated
Hypopituitarism	Moderate with missed meals	Ketonuria ++		Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Adrenal insufficiency	Severe with missed meals	Ketonuria ++	0	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	↓↓	↑	↑
Enzyme deficiencies	Severe-constant	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	0	0-↓↓	0	0
Glucose-6-phosphatase debrancher	Moderate with fasting	++	++	Normal	Normal	↓↓	↓	↑↑	↓↓	Normal	↑	0-↓↓	↑	↑
Phosphorylase	Mild-moderate	Ketonuria ++	+	Normal	Normal	↓	↓	↑↑	↓↓	Normal	0-↑	0-↓↓	↑	↑
Fructose-1, 6-diphosphatase	Severe with fasting	Ketonuria +++	+++	↑↑	↑↑	↓↓	↓	↑↑	↑↑	↑↑	↑	0-↓↓	↓	↓
Galactosemia	After milk or milk products	0 Ketones;(s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑
Fructose intolerance	After fructose	0 Ketones;(s) +	+++	Normal	Normal	↓	↓	↑	↓	Normal	↑	0-↓↓	↑	↑

Details of each condition are discussed in the text.
0, absence; ↑ or ↓ indicates respectively small increase or decrease; ↑↑ or ↓↓ indicates respectively large increase or decrease.

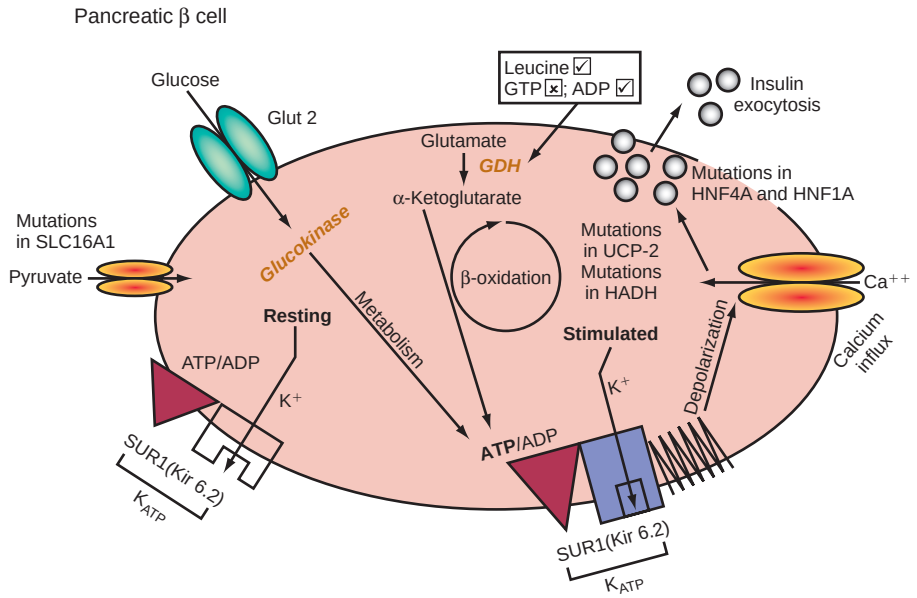

Figure 92-2 **Schematic of the pancreatic cell with some important steps in insulin secretion.** The membrane-spanning, adenosine triphosphate (ATP)-sensitive potassium (K^+) channel (K_{ATP}) consists of 2 subunits: the sulfonylurea receptor (SUR) and the inward rectifying K channel (K_{IR} 6.2). In the resting state, the ratio of ATP to adenosine diphosphate (ADP) maintains K_{ATP} in an open state, permitting efflux of intracellular K^+. When blood glucose concentration rises, its entry into the β cell is facilitated by the GLUT-2 glucose transporter, a process not regulated by insulin. Within the β cell, glucose is converted to glucose-6-phosphate by the enzyme glucokinase and then undergoes metabolism to generate energy. The resultant increase in ATP relative to ADP closes K_{ATP}, preventing efflux of K^+, and the rise of intracellular K^+ depolarizes the cell membrane and opens a calcium (Ca^{2+}) channel. The intracellular rise in Ca^{2+} triggers insulin secretion via exocytosis. Sulfonylureas trigger insulin secretion by reacting with their receptor (SUR) to close K_{ATP}; diazoxide inhibits this process, whereas somatostatin, or its analog octreotide, inhibits insulin secretion by interfering with calcium influx. Genetic mutations in SUR1 or K_{IR} 6.2 that prevent K_{ATP} from being open, tonically maintain inappropriate insulin secretion and are responsible for autosomal recessive forms of persistent hyperinsulinemic hypoglycemia of infancy (PHHI). One form of autosomal dominant PHHI is caused by an activating mutation in glucokinase. The amino acid leucine also triggers insulin secretion by closure of K_{ATP}. Metabolism of leucine is facilitated by the enzyme glutamate dehydrogenase (GDH), and overactivity of this enzyme in the pancreas leads to hyperinsulinemia with hypoglycemia, associated with hyperammonemia from overactivity of GDH in the liver. Mutations in the pyruvate channel SLC16A1 can cause ectopic expression in the β cell and permit pyruvate, accumulated during exercise, to induce insulin secretion and hence exercise-induced hypoglycemia. Mutations in the mitochondrial uncoupling protein 2 (UCP2) and hydroxyl acyl-CoA dehydrogenase (HADH) are associated with hyperinsulinism (HI) by mechanisms yet to be defined. Mutations in the transcription factors hepatic nuclear factors (HNF) 4α and 1α can be associated with neonatal macrosomia and HI, but progress to monogenic diabetes of youth (MODY) later in life. √, stimulation; GTP, guanosine triphosphate; X, inhibition.

hyperinsulinemic hypoglycemia. **Inactivating** mutations of the glucokinase gene or **activating** mutations of the ATP regulated potassium channel which prevent or limit closure of the channel, are responsible for inadequate insulin secretion and form the basis of some forms of maturity-onset diabetes of youth or of neonatal diabetes mellitus (see Chapter 589).

The familial forms of PHHI are more common in certain populations, notably Arabic and Ashkenazi Jewish communities, where it may reach an incidence of approximately 1 in 2,500, compared with the sporadic rates in the general population of approximately 1 in 50,000. These **autosomal recessive forms** of PHHI typically present in the immediate newborn period as macrosomic newborns with a weight frequently >4.0 kg and severe recurrent or persistent hypoglycemia manifesting in the initial hours or days of life. Glucose infusions as high as 15-20 mg/kg/min and frequent feedings fail to maintain euglycemia. Diazoxide, which acts by opening K_{ATP} channels (see Fig. 92-2) fails to control hypoglycemia adequately. Somatostatin (octreotide), which also opens K_{ATP} channels and inhibits calcium flux, may be partially effective in approximately 50% of patients (see Fig. 92-2). Calcium channel blocking agents have had inconsistent effects. Some affected infants have responded to sirolimus. When affected patients are unresponsive to these measures, pancreatectomy is strongly recommended to avoid the long-term neurologic sequelae of hypoglycemia. If surgery is undertaken, preoperative CT or MRI rarely reveals an isolated adenoma, which would then permit local resection. Intraoperative ultrasonography may identify a small impalpable adenoma, permitting local resection. Adenomas often present in late infancy or early childhood.

Distinguishing between **focal** and **diffuse** cases of **persistent hyperinsulinism** has been attempted in several ways. Preoperatively, transhepatic portal vein catheterization and selective pancreatic venous sampling to measure insulin may localize a focal lesion from the step-up in insulin concentration at a specific site. Selective catheterization of arterial branches supplying the pancreas, followed by infusion of a secretagogue such as calcium and portal vein sampling for insulin concentration (arterial stimulation-venous sampling) may localize a lesion. Both approaches are highly invasive, restricted to specialized centers, and not uniformly successful in distinguishing the focal from the diffuse forms, hence, these techniques are not recommended. 18F-labeled L-dopa combined with positron emission tomography scanning is a highly promising means to distinguish the focal from the diffuse lesions of hyperinsulinism unresponsive to medical management (Fig. 92-3). The "gold standard" remains intraoperative histologic characterization. Diffuse hyperinsulinism is characterized by large β cells with abnormally large nuclei, whereas focal adenomatous lesions display small and normal β cell nuclei. Although *SUR1* mutations are present in both types, the focal lesions arise by a random loss of a maternally imprinted growth-inhibitory gene on maternal chromosome 11p in association with paternal transmission of a mutated *SUR1* or K_{IR} 6.2 paternal chromosome 11p expressing the insulin-like growth factor 2 *(IGF2)* gene. Thus the focal form represents a double hit–loss of maternal repressor and transmission of a paternal mutation that contains a growth-promoting gene. Local excision of focal adenomatous islet cell hyperplasia results in a cure with little or no recurrence. For the diffuse form, near-total resection of 85-90% of the pancreas is recommended. The near-total pancreatectomy required for the diffuse

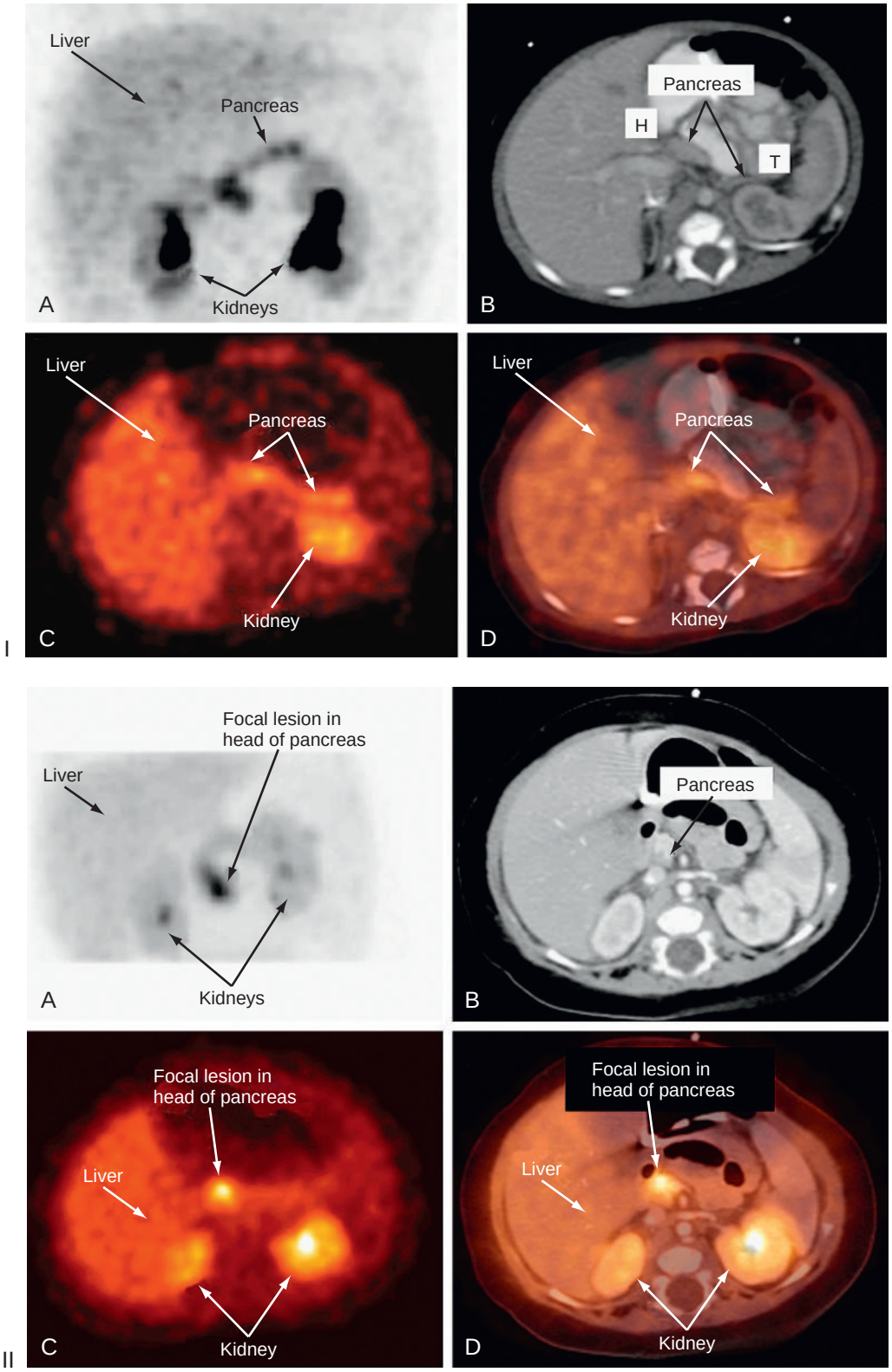

Figure 92-3 **Congenital hyperinsulinism. I** Panels (diffuse): [18F]-DOPA positron emission tomography (PET) of patient with diffuse form of congenital hyperinsulinism. **A,** Diffuse uptake of [18F]-DOPA is visualized throughout the pancreas. Transverse views show **(B)** normal pancreatic tissue on abdominal CT; **(C)** diffuse uptake of [18F]-DOPA in pancreas; and **(D)** confirmation of pancreatic uptake of [18F]-DOPA with coregistration. H, head of pancreas; T, tail of pancreas. **II** Panels (focal): [18F]-DOPA PET of patient with focal form of congenital hyperinsulinism. **A,** Discrete area of increased [18F]-DOPA uptake is visualized in the head of the pancreas. The intensity of this area is greater than that observed in the liver and neighboring normal pancreatic tissue. Transverse views show **(B)** normal pancreatic tissue on abdominal CT; **(C)** focal uptake of [18F]-DOPA in pancreatic head; and **(D)** confirmation of [18F]-DOPA uptake in the pancreatic head with coregistration. *(Courtesy of Dr. Olga Hardy, Children's Hospital of Philadelphia.)*

hyperplastic lesions is, however, often associated with persistent hypoglycemia with the later development of hyperglycemia or frank, insulin-requiring diabetes mellitus.

Further resection of the remaining pancreas may occasionally be necessary if hypoglycemia recurs and cannot be controlled by medical measures, such as the use of octreotide or diazoxide.

Experienced pediatric surgeons in medical centers equipped to provide the necessary preoperative and postoperative care, diagnostic evaluation, and management should perform surgery. In some patients who have been managed medically, hyperinsulinism and hypoglycemia regress over months. This is similar to what occurs in children with the hyperinsulinemic hypoglycemia seen in the epigenetic and genetic imprinting disorder **Beckwith-Wiedemann syndrome.**

If hypoglycemia first manifests between 3 and 6 mo of age or later, a therapeutic trial using medical approaches with diazoxide, octreotide, and frequent feedings can be attempted for up to 2-4 wk. Failure to maintain euglycemia without undesirable side effects from the drugs may prompt the need for surgery. Some success in suppressing insulin release and correcting hypoglycemia in patients with PHHI has been reported with the use of the long-acting somatostatin analog octreotide. Most cases of neonatal PHHI are sporadic; familial forms permit genetic counseling on the basis of anticipated autosomal recessive inheritance.

A second form of familial PHHI suggests **autosomal dominant inheritance.** The clinical features tend to be less severe, and onset of hypoglycemia is most likely, but not exclusively, to occur beyond the immediate newborn period and usually beyond the period of weaning at an average age at onset of about 1 yr. At birth, macrosomia is rarely observed, and response to diazoxide is almost uniform. The initial presentation may be delayed and rarely occur as late as 30 yr, unless provoked by fasting. The genetic basis for this autosomal dominant form has not been delineated; it is not always linked to K_{IR} 6.2/*SUR1*. The activating mutation in glucokinase is transmitted in an autosomal dominant manner. If a family history is present, genetic counseling for a 50% recurrence rate can be given for future offspring.

A third form of persistent PHHI is associated with **mild and asymptomatic hyperammonemia,** usually as a sporadic occurrence, although dominant inheritance occurs. Presentation is more like the autosomal dominant form than the autosomal recessive form. Diet and diazoxide control symptoms, but pancreatectomy may be necessary in some cases. The association of hyperinsulinism and hyperammonemia is caused by an inherited or de novo gain-of-function mutation in the enzyme glutamate dehydrogenase. The resulting increase in glutamate oxidation in the pancreatic β cell raises the ATP concentration and, hence, the ratio of ATP:adenosine diphosphate, which closes K_{ATP}, leading to membrane depolarization, calcium influx, and insulin secretion (see Fig. 92-2). In the liver, the excessive oxidation of glutamate to β-ketoglutarate may generate ammonia and divert glutamate from being processed to *N*-acetylglutamate, an essential cofactor for removal of ammonia through the urea cycle via activation of the enzyme carbamoyl phosphate synthetase. The hyperammonemia is mild, with concentrations of 100-200 μM/L, and produces no CNS symptoms or consequences, as seen in other hyperammonemic states. Leucine, a potent amino acid for stimulating insulin secretion and implicated in leucine-sensitive hypoglycemia, acts by allosterically stimulating glutamate dehydrogenase. Thus, **leucine-sensitive hypoglycemia** may be a form of the hyperinsulinemia–hyperammonemia syndrome or a potentiation of mild disorders of the K_{ATP} channel; it need not always be associated with a modest increase in serum ammonia.

Hypoglycemia associated with hyperinsulinemia is also seen in approximately 50% of patients with the **Beckwith-Wiedemann syndrome.** This syndrome is caused by an imprinting disorder (see Chapter 81) and characterized by omphalocele, gigantism, macroglossia, microcephaly, and visceromegaly (Fig. 92-4). Distinctive lateral earlobe fissures and facial nevus flammeus are present; hemihypertrophy occurs in many of these infants. Diffuse islet cell hyperplasia occurs in infants with hypoglycemia. The diagnostic and therapeutic approaches are the same as those discussed previously, although

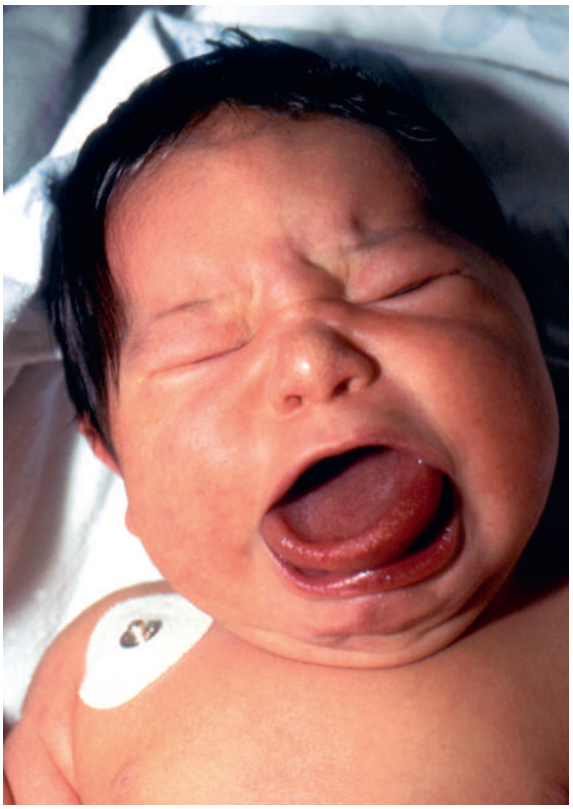

Figure 92-4 Beckwith-Wiedemann syndrome. *(Courtesy of Dr. Michael Cohen, Dalhousie University, Halifax, Nova Scotia. From Jones KL:* Smith's recognizable patterns of human malformation, *ed 6, Philadelphia, 2006, WB Saunders.)*

microcephaly and slowing of brain development may occur independently of hypoglycemia. Patients with the Beckwith-Wiedemann syndrome may acquire tumors, including Wilms tumor, hepatoblastoma, adrenal carcinoma, gonadoblastoma, and rhabdomyosarcoma. This overgrowth syndrome is caused by mutations in the chromosome 11p15.5 region close to the genes for insulin, SUR1, K_{IR} 6.2, and IGF2. Duplications in this region and genetic imprinting from a defective or absent copy of the maternally derived gene are involved in the variable features and patterns of transmission. Hypoglycemia may resolve in weeks to months of medical therapy. Pancreatic resection may rarely be needed.

Hyperinsulinemic hypoglycemia in infancy is reported as a manifestation of one form of **congenital disorder of glycosylation**. Disorders of protein glycosylation usually present with neurologic symptoms but may also include liver dysfunction with hepatomegaly, intractable diarrhea, protein-losing enteropathy, and hypoglycemia (see Chapter 87.6). These disorders are often underdiagnosed. One entity associated with hyperinsulinemic hypoglycemia is caused by phosphomannose isomerase deficiency, and clinical improvement followed supplemental treatment with oral mannose at a dose of 0.17 g/kg 6 times per day.

After the first 12 mo of life, hyperinsulinemic states are uncommon until islet cell adenomas reappear as a cause after the patient is several years of age. Hyperinsulinemia as a result of **islet cell adenoma** should be considered in any child 5 yr or older who presents with hypoglycemia. Islet cell adenomas do not "light up" during scanning with L-dopa labeled with fluorine-18. An islet cell adenoma in a child should arouse suspicion of the possibility of **multiple endocrine neoplasia** type 1 (Wermer syndrome), which involves mutations in the menin gene and may be associated with hyperparathyroidism and with pituitary tumors. Tables 92-7 and 92-8 outline the diagnostic approach. Fasting for up to 24-36 hr usually provokes hypoglycemia; coexisting hyperinsulinemia confirms the diagnosis,

provided that factitious administration of insulin by the parents, a form of **Munchausen syndrome by proxy,** is excluded. Occasionally, provocative tests may be required. Exogenously administered insulin can be distinguished from endogenous insulin by simultaneous measurement of C-peptide concentration. If C-peptide levels are elevated, endogenous insulin secretion is responsible for the hypoglycemia; if C-peptide levels are low but insulin values are high, exogenous insulin has been administered, perhaps as a form of child abuse. Islet cell adenomas at this age are treated by surgical excision. Antibodies to insulin or the insulin receptor (**insulin mimetic action**) are also rarely associated with hypoglycemia. Activating mutations in the Akt2 signaling complex of the insulin receptor also can cause hyperinsulinism. Some **tumors** produce insulin-like growth factors, thereby provoking hypoglycemia by interacting with the insulin receptor. The astute clinician must also consider the possibility of deliberate or accidental ingestion of drugs such as a sulfonylurea or related compound that stimulates insulin secretion. In such cases, insulin and C-peptide concentrations in blood will be elevated. Inadvertent substitution of an insulin secretagogue by a dispensing error should be considered in those taking medications who suddenly develop documented hypoglycemia.

A rare form of hyperinsulinemic hypoglycemia has been reported after **exercise**. Whereas glucose and insulin remain unchanged in most people after moderate, short-term exercise, rare patients manifest severe hypoglycemia with hyperinsulinemia 15-50 min after the same standardized exercise. This form of exercise-induced hyperinsulinism is caused by an abnormal responsiveness of β-cell insulin release in response to pyruvate generated during exercise. The gene responsible for this syndrome, *SLC16A1,* regulates a transporter, MCT1R, that controls the entry of pyruvate into cells. Dominant mutations in *SLC16A1* that increase the ectopic expression of MCTR1 transporter in pancreatic β cells permit excessive entry of pyruvate into β cells and act to increase insulin secretion with resultant hypoglycemia during exercise.

Hypoglycemia with so-called nesidioblastosis has also rarely been reported after **bariatric surgery** for obesity. The mechanism for this form of hyperinsulinemic hypoglycemia remains to be defined.

Infants and children with **Nissen fundoplication,** a relatively common procedure used to ameliorate gastroesophageal reflux, frequently have an associated "dumping" syndrome with hypoglycemia. Characteristic features include significant hyperglycemia of 200 mg/dL and up to 500 mg/dL 30 min postprandially, and severe hypoglycemia (average 32 mg/dL in one series) 1.5-3.0 hr later. The early hyperglycemia phase is associated with brisk and excessive insulin release that causes the rebound hypoglycemia. A role for exaggerated GLP1 secretion has been proposed and glucagon responses have been reported to be inappropriately low in some cases. However, the physiologic mechanisms are not always clearly understood, and attempted treatments not always effective; **acarbose,** an inhibitor of glucose absorption, was reported to be successful in one small series.

Endocrine Deficiency

Hypoglycemia associated with endocrine deficiency is usually caused by adrenal insufficiency with or without associated growth hormone deficiency (see Chapters 557 and 575). In panhypopituitarism, isolated adrenocorticotropic hormone (ACTH) or growth hormone deficiency, or combined ACTH deficiency plus growth hormone deficiency, the incidence of hypoglycemia is as high as 20%. In the newborn period, hypoglycemia may be the presenting feature of hypopituitarism; in males, a microphallus may provide a clue to a coexisting deficiency of gonadotropin. Newborns with hypopituitarism often have a form of "hepatitis" associated with cholestatic jaundice and hypoglycemia. The combination of hypoglycemia and cholestatic jaundice requires exclusion of hypopituitarism as a cause, as the jaundice resolves with replacement treatment of growth hormone, cortisol, and thyroid as required. This constellation is often associated with the syndrome of **septooptic dysplasia.** When adrenal disease is severe, as in congenital adrenal hyperplasia caused by enzyme defects in cortisol synthesis, adrenal hemorrhage, or congenital hypoplasia of the adrenal glands, disturbances in serum electrolytes with hyponatremia and hyperkalemia or ambiguous genitals may provide diagnostic clues (see Chapter 576). In older children, failure of growth should suggest growth hormone deficiency. Hyperpigmentation or salt-craving may provide the clue to Addison disease with increased ACTH levels or adrenal unresponsiveness to ACTH owing to a defect in the adrenal receptor for ACTH, congenital adrenal hypoplasia, adrenoleukodystrophy, or the Allgrove triple A syndrome. The frequent association of Addison disease in childhood with hypoparathyroidism (hypocalcemia), chronic mucocutaneous candidiasis, and other endocrinopathies which constitute the autoimmune polyendocrinopathy syndrome type 1 should be considered. Adrenoleukodystrophy, and congenital adrenal hypoplasia are sex-linked conditions and should be considered in the differential diagnosis of primary Addison disease in male children (see Chapter 86.2).

Hypoglycemia in cortisol–growth hormone deficiency may be caused by decreased gluconeogenic enzymes with cortisol deficiency, increased glucose utilization because of a lack of the antagonistic effects of growth hormone on insulin action, or failure to supply endogenous gluconeogenic substrate in the form of alanine and lactate with compensatory breakdown of fat and generation of ketones. Deficiency of these hormones results in reduced gluconeogenic substrate, which resembles the syndrome of ketotic hypoglycemia. Investigation of a child with hypoglycemia, therefore, requires exclusion of ACTH-cortisol or growth hormone deficiency and, if diagnosed, its appropriate replacement with cortisol or growth hormone.

Epinephrine deficiency could theoretically be responsible for hypoglycemia. Urinary excretion of epinephrine has been diminished in some patients with spontaneous or insulin-induced hypoglycemia in whom absence of pallor and tachycardia was also noted, suggesting that failure of catecholamine release, as the result of a defect anywhere along the hypothalamic–autonomic–adrenomedullary axis, might be responsible for the hypoglycemia. This possibility has been challenged, owing to the rarity of hypoglycemia in patients with bilateral adrenalectomy, provided that they receive adequate glucocorticoid replacement, and because diminished epinephrine excretion is found in normal patients with repeated insulin-induced hypoglycemia. Many of the patients described as having hypoglycemia with failure of epinephrine excretion fit the criteria for ketotic hypoglycemia. Also, repetitive hypoglycemia leads to diminished cortisol plus epinephrine responses, as seen most commonly in insulin-treated diabetes mellitus and the syndrome of hypoglycemia unawareness, associated with autonomic failure.

Glucagon deficiency in infants or children may theoretically be associated with hypoglycemia but has never been documented.

Substrate Limited

Ketotic Hypoglycemia

Ketotic hypoglycemia is the **most common** form of *childhood* hypoglycemia. This condition usually presents between the ages of 18 mo and 5 yr and commonly remits spontaneously by the age of 8-9 yr. Hypoglycemic episodes typically occur during periods of intercurrent illness when food intake is limited. The classic history is of a child who eats poorly or completely avoids the evening meal, is difficult to arouse from sleep the following morning and hence eats poorly again, and may have a seizure or be comatose by mid-morning. Another common presentation occurs when parents sleep late and the affected child is unable to eat breakfast, thus prolonging the overnight fast.

At the time of documented hypoglycemia, there is associated ketonuria and ketonemia; plasma insulin concentrations are appropriately low, ≤5-10 μU/mL, thus excluding hyperinsulinemia. A ketogenic provocative diet, formerly used as a diagnostic test, is no longer used to establish the diagnosis because fasting alone provokes a hypoglycemic episode with ketonemia and ketonuria within 12-18 hr in susceptible individuals. Normal children of similar age can withstand fasting without hypoglycemia developing during the same period, although

even normal children may acquire these features by 36 hr of fasting.

Children with ketotic hypoglycemia have plasma alanine concentrations that are markedly reduced in the basal state after an overnight fast and decline even further with prolonged fasting. Alanine, produced in muscle, is a major gluconeogenic precursor. Alanine is the only amino acid that is significantly lower in these children, and infusions of alanine (250 mg/kg) produce a rapid rise in plasma glucose without causing significant changes in blood lactate or pyruvate levels, indicating that the entire gluconeogenic pathway from the level of pyruvate is intact, but that there is a deficiency of substrate. Glycogenolytic pathways are also intact because glucagon induces a normal glycemic response in affected children in the fed state. The levels of hormones that counter hypoglycemia are appropriately elevated, and insulin is appropriately low.

The etiology of ketotic hypoglycemia may be a defect in any of the complex steps involved in protein catabolism, oxidative deamination of amino acids, transamination, alanine synthesis, or alanine efflux from muscle. Children with ketotic hypoglycemia are frequently smaller than age-matched controls and often have a history of transient neonatal hypoglycemia. Any decrease in muscle mass may compromise the supply of gluconeogenic substrate at a time when glucose demands per unit of body weight are already relatively high, thus predisposing the patient to the rapid development of hypoglycemia, with ketosis representing the attempt to switch to an alternative fuel supply. Children with ketotic hypoglycemia may represent the low end of the spectrum of children's capacity to tolerate fasting. Similar relative intolerance to fasting is present in normal children, who cannot maintain blood glucose after 30-36 hr of fasting, compared with the adult's capacity for prolonged fasting. Although the defect may be present at birth, it may not be evident until the child is stressed by more prolonged periods of calorie restriction. Moreover, the spontaneous remission observed in children at age 8-9 yr might be explained by the increase in muscle bulk with its resultant increase in supply of endogenous substrate and the relative decrease in glucose requirement per unit of body mass with increasing age.

In anticipation of spontaneous resolution of this syndrome, treatment of ketotic hypoglycemia consists of frequent feedings of a high-protein, high-carbohydrate diet. During intercurrent illnesses, parents should be taught to test the child's urine for the presence of ketones, the appearance of which precedes hypoglycemia by several hours. In the presence of ketonuria, liquids of high carbohydrate content should be offered to the child. If these cannot be tolerated, the child should be treated with intravenous glucose administration in a hospital.

Branched-Chain Ketonuria (Maple Syrup Urine Disease)

See Chapter 85.6.

The hypoglycemic episodes were once attributed to high levels of leucine, but evidence indicates that interference with the production of alanine and its availability as a gluconeogenic substrate during calorie deprivation is responsible for hypoglycemia.

Glycogen Storage Disease

See Chapter 87.1.

Glucose-6-Phosphatase Deficiency (Type I Glycogen Storage Disease)

Affected children usually display a remarkable tolerance to their chronic hypoglycemia; blood glucose values in the range of 20-50 mg/dL are not associated with the classic symptoms of hypoglycemia, possibly reflecting the adaptation of the CNS to ketone bodies and lactate as alternative fuels. Hepatomegaly and poor growth are consistent physical features. Hypoglycemia is associated with acidosis (HCO_3 <18 mEq/L), increased β O-B and lactate; hyperuricemia also is frequent. Management is discussed in detail in Chapter 87.

Amylo-1,6-Glucosidase Deficiency (Debrancher Enzyme Deficiency; Type III Glycogen Storage Disease)

See Chapter 87.

Liver Phosphorylase Deficiency (Type VI Glycogen Storage Disease)

See Chapter 87.

Low hepatic phosphorylase activity may result from a defect in any of the steps of activation; a variety of defects have been described. Hepatomegaly, excessive deposition of glycogen in liver, growth retardation, and occasional symptomatic hypoglycemia occur. A diet high in protein and reduced in carbohydrate usually prevents hypoglycemia.

Glycogen Synthetase Deficiency

See Chapter 87.

The inability to synthesize glycogen is rare. There is hypoglycemia and hyperketonemia after fasting because glycogen reserves are markedly diminished or absent. After feeding, however, hyperglycemia with glucosuria may occur because of the inability to assimilate some of the glucose load into glycogen. During fasting hypoglycemia, levels of the counterregulatory hormones, including catecholamines, are appropriately elevated or normal, and insulin levels are appropriately low. The liver is not enlarged. Protein-rich feedings at frequent intervals result in dramatic clinical improvement, including growth velocity. This condition mimics the syndrome of ketotic hypoglycemia and should be considered in the differential diagnosis of that syndrome.

Disorders of Gluconeogenesis

Fructose-1,6-Diphosphatase Deficiency

See Chapter 87.3.

A deficiency of this enzyme results in a block of gluconeogenesis from all possible precursors below the level of fructose-1,6-diphosphate. Infusion of these gluconeogenic precursors results in lactic acidosis without a rise in glucose; acute hypoglycemia may be provoked by inhibition of glycogenolysis. Glycogenolysis remains intact, and glucagon elicits a normal glycemic response in the fed, but not in the fasted, state. Accordingly, affected individuals have hypoglycemia only during caloric deprivation, as in fasting, or during intercurrent illness. As long as glycogen stores remain normal, hypoglycemia does not develop. In affected families, there may be a history of siblings with known hepatomegaly who died in infancy with unexplained metabolic acidosis.

Defects in Fatty Acid Oxidation

See Chapter 86.

The important role of fatty acid oxidation in maintaining gluconeogenesis is underscored by examples of congenital or drug-induced defects in fatty acid metabolism that may be associated with fasting hypoglycemia.

Various congenital enzymatic deficiencies causing defective carnitine or fatty acid metabolism occur. A severe and relatively common form of fasting hypoglycemia with hepatomegaly, cardiomyopathy, and hypotonia occurs with long- and medium-chain fatty acid CoA dehydrogenase deficiency. Plasma carnitine levels are low, ketones are not present, but dicarboxylic aciduria is present in urine. Clinically, patients with **acyl-CoA dehydrogenase deficiency** present with a Reye-like syndrome (see Chapter 361), recurrent episodes of severe fasting hypoglycemic coma, and cardiorespiratory arrest (sudden infant death syndrome-like events). Severe hypoglycemia and metabolic acidosis without ketosis also occur in patients with multiple acyl-CoA dehydrogenase disorders. Hypotonia, seizures, and acrid odor are other clinical clues. Survival depends on whether the defects are severe or mild; diagnosis is established from studies of enzyme activity in liver biopsy tissue or in cultured fibroblasts from affected patients. Tandem mass spectrometry can be employed for blood samples, even those on filter paper, for screening of congenital inborn errors. Molecular diagnosis also is available for most entities. The frequency of this disorder

is at least 1 in 10,000-15,000 births. Avoidance of fasting and supplementation with carnitine may be lifesaving in these patients who generally present in infancy.

Interference with fatty acid metabolism also underlies the fasting hypoglycemia associated with Jamaican vomiting sickness, with atractyloside, and with the drug valproate. In **Jamaican vomiting sickness,** the unripe ackee fruit contains a water-soluble toxin, hypoglycin, which produces vomiting, CNS depression, and severe hypoglycemia. The hypoglycemic activity of hypoglycin derives from its inhibition of gluconeogenesis secondary to its interference with the acyl-CoA and carnitine metabolism essential for the oxidation of long-chain fatty acids. The disease is almost totally confined to Jamaica, where ackee forms a staple of the diet for the poor. The ripe ackee fruit no longer contains this toxin. *Atractyloside* is a reagent that inhibits oxidative phosphorylation in mitochondria by preventing the translocation of adenine nucleotides, such as ATP, across the mitochondrial membrane. Atractyloside is a perhydrophenanthrenic glycoside derived from *Atractylis gummifera.* This plant is found in the Mediterranean basin; ingestion of this "thistle" is associated with hypoglycemia and a syndrome similar to Jamaican vomiting sickness. The anticonvulsant drug **valproate** is associated with side effects, predominantly in young infants, which include a Reye-like syndrome, low serum carnitine levels, and the potential for fasting hypoglycemia. In all these conditions, hypoglycemia *is not associated with ketonuria.*

Acute Alcohol Intoxication

The liver metabolizes alcohol as a preferred fuel, and generation of reducing equivalents during the oxidation of ethanol alters the reduced form of nicotinamide adenine dinucleotide : nicotinamide adenine dinucleotide ratio, which is essential for certain gluconeogenic steps. As a result, gluconeogenesis is impaired and hypoglycemia may ensue if glycogen stores are depleted by starvation or by preexisting abnormalities in glycogen metabolism. In toddlers who have been unfed for some time, even the consumption of small quantities of alcohol can precipitate these events. The hypoglycemia promptly responds to intravenous glucose, which should always be considered in a child who presents initially with coma or seizure, after taking a blood sample to determine glucose concentration. The possibility of the child's ingesting alcoholic drinks must also be considered if there was a preceding adult evening party. A careful history allows the diagnosis to be made and may avoid needless and expensive hospitalization and investigation.

Salicylate Intoxication

See Chapter 63.

Both hyperglycemia and hypoglycemia occur in children with salicylate intoxication. Accelerated utilization of glucose, resulting from augmentation of insulin secretion by salicylates, and possible interference with gluconeogenesis may contribute to hypoglycemia. Infants are more susceptible than are older children. Monitoring of blood glucose levels with appropriate glucose infusion in the event of hypoglycemia should form part of the therapeutic approach to salicylate intoxication in childhood. Ketosis may occur.

Phosphoenolpyruvate Carboxykinase Deficiency

Deficiency of this rate-limiting gluconeogenic enzyme is associated with severe fasting hypoglycemia and variable onset after birth. Hypoglycemia may occur within 24 hr after birth, and defective gluconeogenesis from alanine can be documented in vivo. Liver, kidney, and myocardium demonstrate fatty infiltration, and atrophy of the optic nerve and visual cortex may occur. Hypoglycemia may be profound. Lactate and pyruvate levels in plasma have been normal, but a mild metabolic acidosis may be present. The fatty infiltration of various organs is caused by increased formation of acetyl-CoA, which becomes available for fatty acid synthesis. Diagnosis of this rare entity can be made with certainty only through appropriate enzymatic determinations in liver biopsy material or molecular diagnosis. Avoidance of periods of fasting through frequent feedings rich in carbohydrate should be helpful because glycogen synthesis and breakdown are intact.

Pyruvate Carboxylase Deficiency

See Chapter 87.

Other Enzyme Defects

Galactosemia (Galactose-1-Phosphate Uridyl Transferase Deficiency)

See Chapter 87.

Fructose Intolerance (Fructose-1-Phosphate Aldolase Deficiency)

See Chapter 87.

Acute hypoglycemia is caused by the inhibition by fructose-1-phosphate of glycogenolysis via the phosphorylase system and of gluconeogenesis at the level of fructose-1,6-diphosphate aldolase. Affected individuals usually learn spontaneously to eliminate fructose from their diet.

Defects in Glucose Transporters

Glut-1 Deficiency

Rarely infants with a seizure disorder are found to have low CSF glucose concentrations despite normal plasma glucose. Lactate concentrations in CSF are low, suggesting decreased glycolysis rather than bacterial infection, which causes low CSF glucose with high lactate. The erythrocyte glucose transporter is defective, suggesting a similar defect in the brain glucose transporter responsible for the clinical features. A ketogenic diet reduces the severity of seizures by supplying an alternate source of brain fuel that bypassed the defect in glucose transport.

Glut-2 Deficiency

Children with hepatomegaly, galactose intolerance, and renal tubular dysfunction **(Fanconi-Bickel syndrome)** have a deficiency of the GLUT-2 glucose transporter of plasma membranes. In addition to liver and kidney tubules, GLUT-2 is also expressed in pancreatic β cells. Hence, the clinical manifestations reflect impaired glucose release from liver and defective tubular reabsorption of glucose plus phosphaturia and aminoaciduria**.**

Systemic Disorders

Several systemic disorders are associated with hypoglycemia in infants and children. Neonatal sepsis is often associated with hypoglycemia, possibly as a result of diminished caloric intake with impaired gluconeogenesis. Similar mechanisms may apply to the hypoglycemia found in severely malnourished infants or those with severe malabsorption. Hyperviscosity with a central hematocrit of >65% is associated with hypoglycemia in at least 10-15% of affected infants. **Falciparum malaria** is associated with hyperinsulinemia and hypoglycemia. Heart and renal failure are also associated with hypoglycemia, but the mechanism is obscure.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Table 92-8 and Figure 92-5 list the pertinent clinical and biochemical findings in the common childhood disorders associated with hypoglycemia. A careful and detailed history is essential in every suspected or documented case of hypoglycemia (see Table 92-7). Specific points to be noted include age at onset, temporal relation to meals or caloric deprivation, and a family history of prior infants known to have had hypoglycemia or of unexplained infant deaths. In the 1st wk of life, the majority of infants have the transient form of neonatal hypoglycemia either as a result of prematurity/intrauterine growth restriction or by virtue of being born to diabetic mothers. The absence of a history of maternal diabetes, but the presence of macrosomia and the characteristic large plethoric appearance of an "infant of a diabetic mother" should arouse the possibility of hyperinsulinemic hypoglycemia of infancy, probably resulting from a K_{ATP} channel defect that is familial (autosomal recessive) or sporadic; decreased β OH butyrate, low FFAs, and plasma insulin concentrations >5-10 μU/mL in the presence of documented hypoglycemia confirm this diagnosis. The presence of

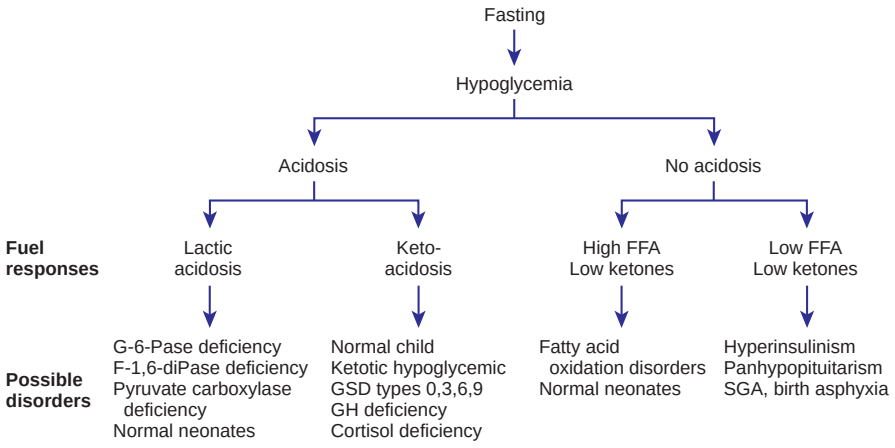

Figure 92-5 Algorithm for diagnosis of hypoglycemia based on fasting fuel responses. F1,6-diPase, fructose-1,6-diphosphatase; FFA, free fatty acid; G-6Pase, glucose-6-phosphatase; GH, growth hormone; GSD, glycogen storage disease; SGA, small for gestational age. *(From Kliegman RM, Greenbaum LA, Lye PS, editors:* Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier Saunders.)*

hepatomegaly should arouse suspicion of an enzyme deficiency such as glucose-6-phosphate in glycogen storage disease-1 or other glycogen storage diseases; if a non–glucose-reducing sugar is present in the urine (e.g., Clinitest positive but Clinistix negative), galactosemia is most likely. In males, the presence of a microphallus suggests the possibility of hypopituitarism, which also may be associated with cholestatic jaundice in both sexes; evidence of a midline facial defect such as cleft palate also suggests possible hypopituitarism as the cause of hypoglycemia via deficiency in growth hormone and/or cortisol. A high index of suspicion and awareness of hypoglycemia as the cause for unusual behavior of any "sick" newborn should prompt a **bedside glucose determination**. However, because glucose meters have an accuracy of only ±20%, any blood glucose value <60 mg/dL must be confirmed by a formal laboratory measurement that is performed without delay on a blood sample preserved in a tube that prevents glycolysis, which can cause spurious low values.

Past the newborn period, clues to the cause of persistent or recurrent hypoglycemia may be obtained through a careful history, physical examination, and initial laboratory findings. The temporal relation of the hypoglycemia to food intake may suggest that the defect is one of gluconeogenesis, if symptoms occur 6 hr or more after meals. If hypoglycemia occurs shortly after meals, hyperinsulinism should be suspected and confirmed or excluded via measurement of β OH butyrate, insulin, and FFA in a sample in which blood glucose is <50 mg/dL. The autosomal dominant forms of hyperinsulinemic hypoglycemia need to be considered, with measurement of glucose, insulin, and ammonia, and careful history for other affected family members of any age. Measurement of IGFBP-1 may be useful; it is low in states of hyperinsulinism and high in other forms of hypoglycemia. The presence of hepatomegaly suggests one of the enzyme deficiencies in glycogen breakdown or in gluconeogenesis, as outlined in Table 92-8. The absence of ketonemia or ketonuria at the time of initial presentation strongly suggests hyperinsulinism or a defect in fatty acid oxidation. In most other causes of hypoglycemia, with the exception of galactosemia and fructose intolerance, ketonemia and ketonuria are present at the time of fasting hypoglycemia. At the time of the hypoglycemia, serum should be obtained for determination of substrates especially β OH butyrate, lactate and FFA as well as hormones especially insulin, cortisol, ACTH, and growth hormone, followed by repeated measurement after an intramuscular or intravenous injection of glucagon, as outlined in Table 92-7. Table 92-8 summarizes the interpretation of the findings. Hypoglycemia with ketonuria in children between ages 18 mo and 5 yr is most likely to be ketotic hypoglycemia, especially if hepatomegaly is absent. The ingestion of a toxin, including alcohol or salicylate, can usually be excluded rapidly by the history. Inadvertent or deliberate drug ingestion and errors in dispensing medicines should also be considered. Munchhausen by proxy should be considered when parents or other caregivers have access to insulin or insulin secretagogues—high insulin concentrations in the sample with low concentrations of C-peptide confirm exogenous insulin administration. Deliberate or accidental ingestion of drugs that stimulate endogenous insulin secretion will result in both high insulin and C-peptide concentrations and may require specialized laboratory methods that identify the offending substance.

When the history is suggestive, but acute symptoms are not present, a 24 hr supervised fast can usually provoke hypoglycemia and resolve the question of hyperinsulinism or other conditions (see Table 92-8). Rarely, such a fast needs to be extended to 36 hr, but only in older children. Such a fast is contraindicated if a fatty acid oxidation defect is suspected; other approaches such as mass tandem spectrometry or molecular diagnosis, or both, should be considered. Because adrenal insufficiency may mimic ketotic hypoglycemia, plasma cortisol and ACTH levels should be determined at the time of documented hypoglycemia; increased buccal or skin pigmentation may provide the clue to primary adrenal insufficiency with elevated ACTH (melanocyte-stimulating hormone) activity. Short stature or a decrease in the growth rate may provide the clue to pituitary insufficiency involving growth hormone as well as ACTH. Definitive tests of pituitary–adrenal function, such as the arginine-insulin stimulation test for growth hormone insulin-like growth factor-1, IGFBP-1, and cortisol release, may be necessary.

In the presence of hepatomegaly and hypoglycemia, a presumptive diagnosis of the enzyme defect can often be made through the clinical manifestations, presence of hyperlipidemia, acidosis, hyperuricemia, response to glucagon in the fed and fasted states, and response to infusion of various appropriate precursors (see Tables 92-7 and 92-8). Table 92-8 summarizes these clinical findings and investigative approaches. Definitive diagnosis of the glycogen storage disease may require molecular diagnosis (see Chapter 87). Occasional patients with all the manifestations of glycogen storage disease are found to have normal enzyme activity. These definitive studies require special expertise available only in certain institutions.

TREATMENT

The prevention of hypoglycemia and its resultant effects on CNS development are critically important in the newborn period. For neonates with hyperinsulinism not associated with maternal diabetes, subtotal or focal pancreatectomy may be needed, unless hypoglycemia can be readily controlled with long-term diazoxide, somatostatin analogs (e.g., octreotide), or sirolimus.

Treatment of **acute symptomatic** neonatal or infant hypoglycemia includes intravenous administration of 2 mL/kg of 10% dextrose in water ($D_{10}W$), followed by a continuous infusion of glucose at 6-8 mg/kg/min, adjusting the rate to maintain blood glucose levels in the normal range. If hypoglycemic seizures are present, some recommend a 4 mL/kg bolus of $D_{10}W$.

Treatment of asymptomatic hyperglycemia in at risk infants usually includes enteral feedings rather than parenteral glucose. If symptoms develop or the hypoglycemia persists despite enteral feedings, intravenous glucose is indicated. Dextrose gel (40% at 400 mg/kg)

administered into the mouth may be an alternative to enteral feedings if breast milk or if formula is not available.

The management of **persistent** neonatal or infantile hypoglycemia includes increasing the rate of intravenous glucose infusion to 10-15 mg/kg/min or more, if needed. This may require a central venous or umbilical venous catheter to administer a hypertonic 15-25% glucose solution. If hyperinsulinism is present, it should be medically managed initially with diazoxide and then somatostatin analogs. If hypoglycemia is unresponsive to intravenous glucose plus diazoxide (maximal doses up to 15-20 mg/kg/day) and somatostatin analogs, surgery via partial or near-total pancreatectomy should be considered. Such surgery should be performed in centers with the requisite facilities, and trained staff experienced in the procedures. If possible, surgery should be preceded by [18F]-L-DOPA scanning to localize a lesion which can then provide guidance to the surgeon for curative resection before the operation is undertaken.

Oral diazoxide, 5-15 mg/kg/24 hr given in divided doses twice daily, may reverse hyperinsulinemic hypoglycemia but may also produce hirsutism, edema, nausea, hyperuricemia, electrolyte disturbances, advanced bone age, immunoglobulin G deficiency, and, rarely, hypotension with prolonged use. The long-acting somatostatin analog octreotide may be helpful in controlling hyperinsulinism causing hypoglycemia in patients with islet cell disorders, including genetic mutations in K_{ATP} channel and islet cell adenoma. Glucagon given by continuous IV infusion at 5 μg/kg/hr together with octreotide administered subcutaneously every 6-12 hr in doses of 20-50 μg/kg/day in neonates and young infants may maintain blood glucose, but generally these agents are used as a temporizing measure before surgery for partial or more complete pancreatectomy. Potential but unusual complications of octreotide include poor growth because of inhibition of growth hormone release, pain at the injection site, vomiting, diarrhea, and hepatic dysfunction (hepatitis, cholelithiasis), and necrotizing enterocolitis; tachyphylaxis to the drug's effects is more common. It may be particularly useful for the treatment of refractory hypoglycemia despite subtotal pancreatectomy. Total pancreatectomy is not optimal therapy, owing to the risks of surgery, permanent diabetes mellitus, and exocrine pancreatic insufficiency. Continued prolonged medical therapy without pancreatic resection if hypoglycemia is controllable is worthwhile, because over time some children have a spontaneous resolution of the hyperinsulinism-induced hypoglycemia. This should be balanced against the risk of hypoglycemia-induced CNS injury and the toxicity of drugs.

PROGNOSIS

The prognosis is good in asymptomatic neonates with hypoglycemia of short duration. Hypoglycemia recurs in 10-15% of infants after adequate treatment. Recurrence is more common if intravenous fluids are extravasated or discontinued too rapidly before oral feedings are well tolerated. Children who had transient neonatal hypoglycemia have an increased incidence of ketotic hypoglycemia later in life.

The prognosis for normal intellectual function must be guarded because prolonged, recurrent, and severe symptomatic hypoglycemia is associated with neurologic sequelae. Symptomatic infants with hypoglycemia, particularly low-birthweight infants, those with persistent hyperinsulinemic hypoglycemia, and severely hypoglycemic infants born to poorly controlled diabetic mothers, have a poorer prognosis for subsequent normal intellectual development than asymptomatic infants do.

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The Fetus and the Neonatal Infant

PART XII

Chapter 93

Overview of Mortality and Morbidity

Waldemar A. Carlo

The risk for mortality in fetuses and neonates is very high around the time of birth. The perinatal period is most often defined as the period from the 28th wk of gestation through the 7th day after birth. The neonatal period is defined as the 1st 28 days after birth and may be further subdivided into the very early (birth to <24 hr), early (birth to <7 days), and late neonatal periods (7 days to <28 days). Infancy is defined as the 1st yr after birth.

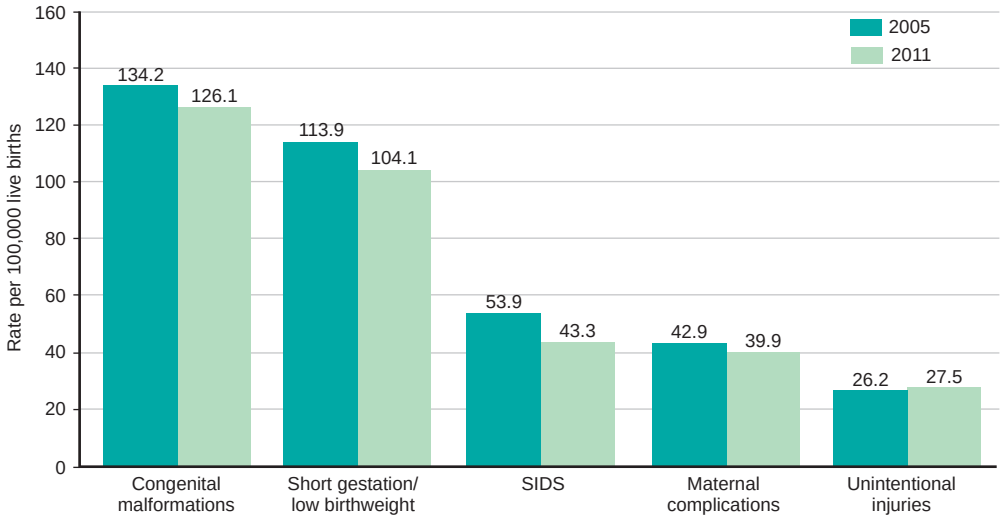
Perinatal mortality is influenced by prenatal, maternal, and fetal conditions and by circumstances surrounding delivery. Perinatal deaths are associated with intrauterine growth restriction (IUGR); conditions that predispose the fetus to asphyxia, such as placental insufficiency; severe congenital malformations; and overwhelming early-onset neonatal infections (Table 93-1). The major causes of neonatal mortality are prematurity/low birthweight (LBW) and congenital anomalies (Fig. 93-1). Mortality is highest during the 1st 24 hr after birth. Neonatal mortality (4.04/1,000 in 2011) accounts for about two-thirds of all infant deaths (deaths before 1 yr of age). Neonatal and postneonatal mortality rates in the United States have declined slightly in the last decade (Fig. 93-2). Factors related to the decline in mortality include improved obstetric and neonatal intensive care management with a significant reduction in birthweight-specific neonatal mortality (Fig. 93-3). Further reduction in neonatal mortality will depend on prevention of preterm delivery and LBW, prenatal diagnosis and early management of congenital anomalies, and effective diagnosis and treatment of diseases that result from adverse factors during pregnancy, labor, and/or delivery (see Table 93-1). In the United States each year, approximately 6 million pregnancies, 4 million live births, 19,000 neonatal deaths, and 28,000 infant deaths occur. Approximately 10% of births are to teenage women between the ages of 15 and 19 yr, a proportion that has been decreasing for approximately 50 yr (Fig. 93-4). Births to girls 10-14 yr of age, very young mothers who are at great social and medical risk, declined substantially over this period.

Infant mortality rates (deaths occurring from birth to 12 mo per 1,000 live births) vary by country; in 2010, rates were lowest in Hong Kong (1.7/1,000 births), moderate in the United States (6.1/1,000), and highest in developing, resource-poor countries (30-150/1,000). Medical, socioeconomic, and cultural factors influence perinatal and neonatal mortality. Preventive variables such as health education, prenatal care, nutrition, social support, risk identification, and obstetric care can effectively reduce perinatal, neonatal, and infant mortality. A number of reasons can explain in part the relatively higher infant mortality in the United States than in other countries. There is evidence of differential reporting of live births versus fetal deaths or stillbirths among countries. Many countries do not report as live births those of infants as mature as up to 27 wk if they die early after birth. The reporting of vital events in the United States is more complete than in many countries, including developed countries. This situation in part explains the larger proportion of LBW/preterm infants in the United States than in other countries. Increases in recorded preterm live births, especially of the most immature infants (<500 g body weight) in the United States, result in increases in both neonatal and infant mortality rates. Nonetheless, continuing healthcare disparities in part account for the higher infant mortality rate in the United States. Infants of African-American women continue to have a high infant mortality rate (12.76/1,000), which is more than twice the rates of infants of white (5.52/1,000) and Hispanic mothers (4.76/1,000 Central and South American vs. 7.29/1,000 Puerto Rican).

In the United States, approximately 50% of infant deaths in 2011 were a consequence of 4 conditions (classified according to the *International Classification of Diseases*, 10th revision): congenital malformations (20.1%), disorders relating to prematurity and unspecified LBW (16.9%), sudden infant death syndrome (8.2%), and newborns affected by maternal complications of pregnancy (6.3%). LBW (as a result of preterm delivery and/or IUGR) is a major determinant of both neonatal and infant mortality rates and, together with congenital anomalies (cardiac, central nervous system, respiratory), contributes significantly to childhood morbidity. In developing countries, LBW/prematurity, birth asphyxia, and infections are the major causes of infant deaths.

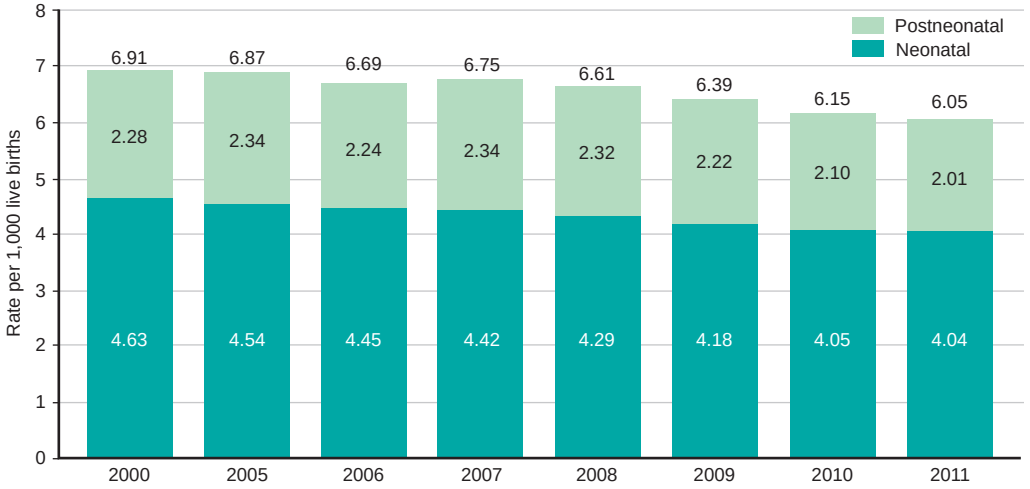
The LBW rate (infants weighing ≤2,500 g at birth each year) in the United States increased from 6.6% to 8.2% between 1981 and 2008, whereas the very-low birthweight (VLBW) rate (infants weighing ≤1,500 g at birth) increased from 1.1% to 1.46% of all births. In the past decade, LBW has increased among white infants, mainly because of a rise in the number of multiple births (often associated with assisted reproduction). Nonetheless, LBW and VLBW rates remain highest among black infants. Reasons for the racial disparity in LBW remain unclear. Despite advances in prenatal and obstetric care, racial disparity in birthweight persists, thus suggesting the need for novel prevention programs. Furthermore, although preterm LBW survival is better among black neonates, overall neonatal and infant mortality rates remain highest among blacks (Fig. 93-5), even for infants born to extremely low-risk mothers (married, age 20-34 yr, ≥13 yr of education, adequate prenatal care, no medical risk factors, no alcohol or tobacco use during pregnancy). A reduction in the racial disparity in mortality is an important public health issue reflected in *Healthy People 2020*, the U.S. national health objectives for the year 2020.

LBW is caused by preterm birth, IUGR, or both. The predominant cause of LBW in the United States is preterm birth, whereas in developing countries, the cause is more often IUGR. Although IUGR does not appear to further increase the risk of mortality in preterm infants, both morbidity and mortality are increased in term growth-restricted infants. VLBW infants are most often premature (<37 wk of gestation), although IUGR may also complicate their early delivery. Even though VLBW occurs in only 1-2% of all infants in the United States, their births represent a large proportion of the neonatal and infant mortality, as well as of infants with both short- and long-term complications, including neurodevelopmental handicaps. The etiology of preterm birth is complex, multifactorial, and not completely understood. Causes include maternal diseases such as severe preeclampsia requiring elective delivery, premature rupture of membranes, uterine abnormalities, placental bleeding (abruptio, previa), multiple-fetus gestation, drug misuse, maternal chronic illnesses, fetal distress, and infection. A complex interaction can be noted among infection, inflammation, and both preterm premature rupture of membranes and preterm birth. Infectious antecedents include maternal urinary tract infection, chorioamnionitis, bacterial vaginosis, and upper and lower genitourinary tract infection with a variety of agents (*Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis, Gardnerella vaginalis,* and group B streptococcus). Preconceptional dietary folate supplementation may effectively reduce the rate of spontaneous



NOTE: Data for 2011 are preliminary. SIDS is sudden infant death syndrome.
SOURCE: CDC/NCHS, National Vital Statistics System, mortality data set.

Figure 93-1 Infant mortality rates for the 5 leading causes of infant death in 2011: United States, 2005 and 2011. *(From CDC/NCHS, National Vital Statistics, mortality data set.* NCHS Data Brief, *No. 120, April 2013.)*



NOTE: Data for 2011 are preliminary.
SOURCE: CDC/NCHS, National Vital Statistics System, mortality data set.

Figure 93-2 Infant, neonatal, and postneonatal mortality rates: United States, 2000 and 2005-2011. *(From CDC/NCHS, National Vital Statistics, mortality data set.* NCHS Data Brief, *No. 120, April 2013.)*

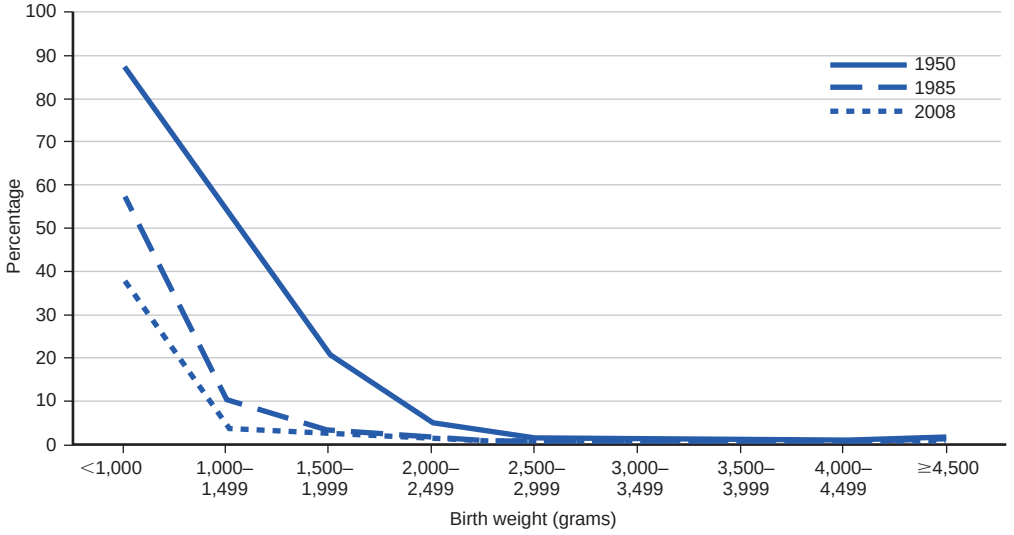
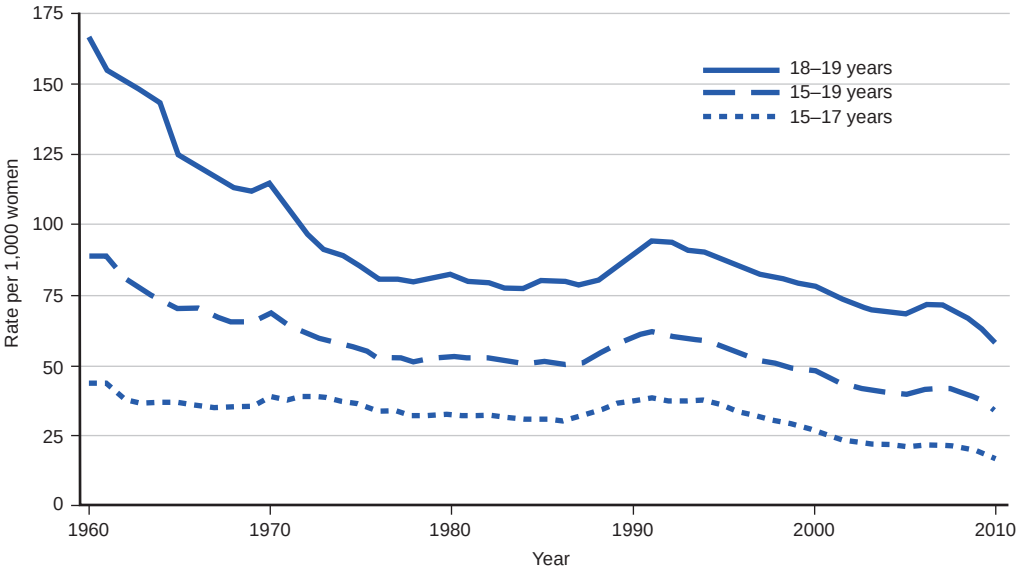
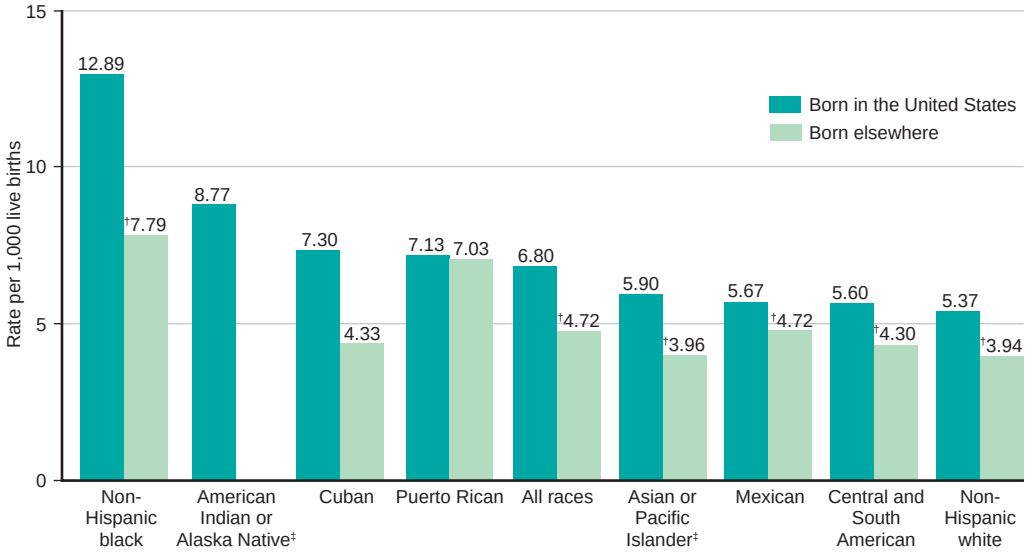


Figure 93-3 Birthweight-specific neonatal mortality—United States, 1950, 1985, and 2008. *(From Centers for Disease Control and Prevention: Grand rounds: public health approaches to reducing U.S. infant mortality.* MMWR Morb Mortal Wkly Rep *62(31):625–628, 2013, Fig. 3, p. 627.)*



NOTES: Rates for 2001–2009 have been revised using population estimates based on the 2010 census, and may differ from rates previously published; see Technical Notes.
SOURCE: CDC/NCHS, National Vital Statistics System.

Figure 93-4 Birth rates for teenagers ages 15-19 yr, by age: United States, 1960-2010. *(From Martin JA, Hamilton BE, Ventura SJ, et al: Birth: final data for 2010.* Natl Vital Stat Rep *61(1):1–72, 2012, Fig. 3, p. 4.)*



†Significant difference.
‡Includes persons of Hispanic and non-Hispanic origin.
NOTE: "Born elswhere" category for American Indian or Alaska Native mothers is not applicable; there are fewer than 20 infant deaths.
SOURCE: CDC/NCHS, National Vital Statistics System.

Figure 93-5 Infant mortality rates, by place of birth and by race and ethnicity of mother: United States, 2009. *(From Mathews TJ, MacDorman MF: Infant mortality statistics from the 2009 period linked birth/infant death data set.* Natl Vital Stat Rep *61(8):1–27, 2013.)*

preterm birth. In many cases, the cause of preterm delivery is unknown. The number of late preterm births (34-36 wk) has increased owing in part to elective deliveries; late preterm neonates are also at increased risk for morbidity and mortality. If possible, elective delivery should be delayed until ≥39 wk.

Although 99% of births occur in hospitals, only 80-85% of pregnant women receive ideal prenatal care in the 1st trimester. Many women who receive inadequate prenatal care are at risk for perinatal complications. Barriers to prenatal care include lack or insufficiency of money or insurance to pay for care; poor coordination of services, including language and cultural issues; and inadequate effective education about the importance of prenatal care. Successful and adequate provision of high-quality prenatal care requires competent healthcare professionals and coordination of services among physicians' offices, clinics, community hospitals, specially regionalized programs for high-risk mothers and infants, and tertiary care centers. Regional perinatal programs should provide continuing education and consultation in both the community and the referral center and transportation for pregnant women and newborn infants to appropriate hospitals; they should also include a regional hospital with facilities, equipment, and personnel for obstetric and neonatal intensive care (Table 93-2).

Fetal deaths slightly exceed neonatal deaths in their contribution to perinatal mortality. The fetal mortality rate in the United States has been declining steadily during the last 2 decades and decreased to 6.2/1000 in 2004. Obstetricians and maternal–fetal medicine subspecialists have a central role in reducing perinatal mortality and

morbidity. The overall decrease in fetal death has been from a reduction in late fetal deaths (≥28 wk). Intrapartum fetal deaths have declined more than antepartum fetal deaths, reflecting improvements in care during labor and delivery. It is important to emphasize the ability to predict the maturity and functional reserve of a fetus both before and during labor so that fetuses and infants at greatest risk can be identified as early as possible. The obstetrician and pediatrician must interact effectively to anticipate perinatal problems and take prompt preventive and therapeutic measures.

Causes of intrauterine fetal demise include obstetric conditions (preeclampsia, others), placental and umbilical cord abnormalities, genetic and syndromic disorders, intrauterine infections, fetal growth restriction, and preexisting maternal diseases. In approximately 40% of intrauterine fetal demise, there is no identifiable etiology.

Postneonatal mortality refers to deaths between 28 days and 1 yr of life. Historically, these infant deaths were a result of causes outside the neonatal period, such as sudden infant death syndrome, infections (respiratory, enteric), and trauma. With the advent of modern neonatal care, many VLBW and preterm infants who would have died in the 1st mo of life now survive the neonatal period only to succumb to the sequelae listed in Table 93-3. This delayed neonatal mortality is an important contributor to postneonatal mortality and explains its lack of decline during the last years.

Late preterm infants are at risk for hypothermia, hypoglycemia, respiratory distress, apnea, jaundice, feeding difficulties, dehydration, and suspected sepsis. They are also at risk of having rehospitalizations. Even term infants born at 37 and 38 wk by cesarean section are at increased risk for respiratory distress syndrome, transient tachypnea of the newborn, suspected sepsis, hypoglycemia, need for ventilatory support, and admission to the neonatal intensive care unit (Table 93-4).

For the most immature infants at the limit of viability (22-25 wk gestation), decision making about care is a complex process that involves the physician, other health professionals, and the family. The challenge for all premature infants is not only to improve survival, but also to reduce short-term complications and improve long-term neurodevelopmental outcome. Adverse neurodevelopmental sequelae include cerebral palsy, seizures, hydrocephalus requiring a shunt, blindness, deafness, and cognitive impairment. The risk of an adverse outcome increases with decreasing gestational age at birth. Higher birthweight, female gender, singleton birth, and antenatal steroids reduce the risk of neurodevelopment impairment or death. Early morbidity and prognostic variables that contribute to adverse neurodevelopmental outcomes include intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis requiring extensive bowel resection, neonatal infection, and bronchopulmonary dysplasia. Many studies have documented the impact of adverse social and family risk factors on poor outcome.

Table 93-1 Major Causes of Perinatal and Neonatal Mortality

FETAL
Placental insufficiency
Intrauterine infection
Severe congenital malformations (anomalies)
Umbilical cord accident
Abruptio placentae
Hydrops fetalis
PRETERM
Severe immaturity
Respiratory distress syndrome
Intraventricular hemorrhage
Congenital anomalies
Infection
Necrotizing enterocolitis
Bronchopulmonary dysplasia (BPD)
FULL TERM
Congenital anomalies
Birth asphyxia
Trauma
Infection
Meconium aspiration pneumonia
Persistent pulmonary hypertension (PPHN)

Table 93-2 Levels of In-Hospital Perinatal Care

MATERNAL	NEONATE
BASIC	
Monitor and care for low-risk patients	Resuscitation
	Stabilization
Triage for high risk for transfer	Well neonatal care
Detection and care of unanticipated labor problems	Nursery care
Emergency cesarean delivery within 30 min	Visitation
	General pediatrician staff (capable of neonatal resuscitation)
Blood bank, anesthesia, radiology, ultrasound, and laboratory support	
Care of postpartum problems	
Obstetrician, nurse, midwife staff	
SPECIAL CARE	
Basic services plus:	*Basic services plus:*
Care of high-risk pregnancies	Care of high-risk neonate with short-term problems
Triage, transfer of high-risk pregnancies (<32 wk, intrauterine growth retardation, preeclampsia, severe maternal medical illness)	Stabilization before transfer (<1,500 g, <32 wk, critically ill)
	Accept convalescing back (reverse) transfers
SUBSPECIALTY CARE	
Basic plus specialty care plus:	*Basic plus specialty care plus:*
Experienced perinatologist (24-hr coverage)	Experienced neonatologist (24-hr coverage)
Evaluation of high-risk therapies	Inborn plus transferred patients
Care for severe maternal medical or obstetric illnesses	Evaluation of high-risk therapies
	All pediatric medical, radiologic, and surgical subspecialties
High-risk fetal care (Rh disease, nonimmune hydrops, life-threatening anomalies)	Neonatal intensive care unit with operating room capabilities
	High-risk follow-up
Outcomes research	Outcomes research
Community education	Community education

From American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, *ed 5, Elk Grove Village, IL, 2002, American Academy of Pediatrics.*

Table 93-3 Morbidities and Sequelae of Perinatal and Neonatal Illness

MORBIDITIES	EXAMPLES
CENTRAL NERVOUS SYSTEM	
Spastic diplegic-quadriplegic cerebral palsy	Hypoxic–ischemic encephalopathy, periventricular leukomalacia, undetermined antenatal factors
Choreoathetotic cerebral palsy	Bilirubin encephalopathy (kernicterus)
Microcephaly	Hypoxic-ischemic encephalopathy, intrauterine infection (rubella, CMV)
Communicating hydrocephalus	Intraventricular hemorrhage, meningitis
Seizures	Hypoxic-ischemic encephalopathy, hypoglycemia
Encephalopathy	Congenital infections (rubella, CMV, HIV, toxoplasmosis)
Educational failure and/or mental retardation	Immaturity, hypoxia, hypoglycemia, cerebral palsy, intraventricular hemorrhage, low socioeconomic status
SENSATION—PERIPHERAL NERVES	
Reduced visual acuity (blindness)	Retinopathy of prematurity
Strabismus	Undetermined, prematurity
Hearing impairment (deafness)	Drug toxicity (furosemide, aminoglycosides), bilirubin encephalopathy, hypoxia ± hyperventilation
Poor speech	Immaturity, chronic illness, hypoxia, prolonged endotracheal intubation, hearing deficit
Paralysis–paresis	Birth trauma—brachial plexus, phrenic nerve, spinal cord
RESPIRATORY	
BPD	Oxygen toxicity, barotrauma
Subglottic stenosis	Endotracheal tube injury
Sudden infant death syndrome	Prematurity, BPD, infant of illicit drug user
Choanal stenosis, nasal septum destruction	Nasotracheal intubation Growth failure
CARDIOVASCULAR	
Cyanosis	Precorrective palliative care of congenital cyanotic heart disease, cor pulmonale from BPD, reactive airway
Heart failure	Precorrective palliative care of complex congenital heart disease, BPD, ventricular septal defect
GASTROINTESTINAL	
Short-gut syndrome	Necrotizing enterocolitis, gastroschisis, malrotation-volvulus, cystic fibrosis, intestinal atresia
Cholestatic liver disease (cirrhosis, hepatic failure)	Hyperalimentation toxicity, sepsis, short-gut syndrome
Failure to thrive	Short-gut syndrome, cholestasis, BPD, cerebral palsy, severe congenital heart disease
Inguinal hernia	Unknown
MISCELLANEOUS	
Cutaneous scars	Chest tube or intravenous catheter placement, hyperalimentation, subcutaneous infiltration, fetal puncture, intrauterine varicella, cutis aplasia
Absence of radial artery pulse	Frequent arterial puncture
Hypertension	Renal thrombi, repair of coarctation of aorta

BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus.

Table 93-4 Incidence of Adverse Outcome According to Completed Week of Gestation at Delivery for Infants Born by Caesarean Section

OUTCOME	WK 37 (N = 934)	WK 38 (N = 3909)	WK 39 (N = 6512)	WK 40 (N = 1385)	WK 41 (N = 1385)	WK 42 (N = 113)
Respiratory distress syndrome	3.7	1.9	0.9	0.9	0.8	1.8
Transient tachypnea of the newborn	4.8	3.9	2.7	2.5	4.8	6.2
Admission to the neonatal intensive care unit	12.8	8.1	5.9	4.8	7.9	14.2
Suspected sepsis	6.6	3.9	2.4	2.6	3.6	10.6
Treated hypoglycemia	2.4	0.9	0.7	0.8	1.6	1.8
Ventilation	1.9	0.9	0.4	0.4	0.4	

From Tita AT, Landon MB, Spong CY, et al: Timing of elective repeat cesarean delivery at term and neonatal outcomes, N Engl J Med *360:111–120, 2009.*

High-risk infants must be monitored after discharge so that neurodevelopmental impairment is detected as early as possible and to ensure that children and families receive any interventions indicated and adequate support to optimize long-term outcome. At school age, former VLBW and preterm infants have poorer physical growth, cognitive function, and school performance. Although disadvantages may persist into adulthood, data now suggest that there may be cognitive improvement throughout childhood.

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Chapter 94

The Newborn Infant

Waldemar A. Carlo

See also Chapter 9.

The neonatal period is a highly vulnerable time for infants as they are completing many of the physiologic adjustments required for extrauterine existence. The high neonatal morbidity and mortality rates attest to the fragility of life during this period; of all deaths occurring in the 1st yr of life in the United States, two-thirds are in the neonatal period. The annual rate of deaths during the 1st yr is unequaled by the rate in any other period of life until the 7th decade.

94.1 History in Neonatal Pediatrics

Waldemar A. Carlo

The perinatal history should include the following information:

- Demographic and social data: socioeconomic status, age, race
- Past medical illnesses in the mother and family, including previous siblings: cardiopulmonary disorders, infectious diseases, genetic disorders, anemia, jaundice, diabetes mellitus
- Previous maternal reproductive problems: stillbirth, prematurity, blood group sensitization
- Events occurring in the present pregnancy: preterm labor, fetal assessments, vaginal bleeding, medications, acute illness, duration of rupture of membranes
- Description of the labor (duration, fetal presentation, fetal distress, fever) and delivery (cesarean section, anesthesia or sedation, use of forceps, Apgar scores, need for resuscitation)

94.2 Physical Examination of the Newborn Infant

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Many physical and behavioral characteristics of a normal newborn infant are described in Chapters 9 and 590.

The **initial examination** of a newborn infant should be performed as soon as possible after delivery. Temperature, pulse, respiratory rate, color, signs of respiratory distress, tone, activity, and level of consciousness of infants should be monitored frequently until stabilization. For high-risk deliveries, this examination should take place in the delivery room and should focus on congenital anomalies, maturation and growth, and pathophysiologic problems that may interfere with normal cardiopulmonary and metabolic adaptation to extrauterine life. Congenital anomalies of varying degrees of severity may be present in 3-5% of infants. After a stable delivery room course, a second and more detailed examination should be performed within 24 hr of birth. If an infant remains in the hospital longer than 48 hr, a **discharge examination** should be performed within 24 hr of discharge. For a healthy infant, the mother should be present during this examination; even minor, seemingly insignificant anatomic variations may worry the parents and should be explained. The explanation must be careful and skillful so that otherwise unworried parents are not unduly alarmed. Infants should not be discharged from the hospital without a final examination because certain abnormalities, particularly cyanosis and heart murmurs, often appear or disappear in the immediate neonatal period; in addition, evidence of disease that has just been acquired may be noted. The pulse (normal: 120-160 beats/min), respiratory rate (normal: 30-60 breaths/min), temperature, weight, length, head circumference, and dimensions of any visible or palpable structural abnormality should be assessed. Blood pressure is determined if a neonate appears ill or has a heart murmur. Pulse oximetry should be performed to screen for critical congenital heart disease and is part of the routine screening for newborn infants. An oxygen saturation ≥95% test after 24 hr after birth in otherwise healthy appearing term infants has >99% sensitivity and specificity to rule out critical congenital heart disease. Neonates with oxygen saturations <95% should be referred for evaluation and possible echocardiogram (see Chapter 425).

Examining a newborn requires patience, gentleness, and procedural flexibility. Thus, if the infant is quiet and relaxed at the beginning of the examination, palpation of the abdomen or auscultation of the heart should be performed first, before other, more disturbing manipulations are attempted.

GENERAL APPEARANCE

Physical activity may be absent during normal sleep, or it may be decreased by the effects of illness or drugs; an infant may be either lying with the extremities motionless, to conserve energy for the effort of difficult breathing, or vigorously crying, with accompanying activity of the arms and legs. Both active and passive muscle tone and any unusual posture should be noted. Coarse, tremulous movements with ankle or jaw **myoclonus** are more common and less significant in newborn infants than at any other age. Such movements tend to occur when an infant is active, whereas convulsive twitching usually occurs in a quiet state. **Edema** may produce a superficial appearance of good nutrition. Pitting after applied pressure may or may not be noted, but the skin of the fingers and toes lacks the normal fine wrinkles when filled with fluid. Edema of the eyelids commonly results from irritation caused by the administration of silver nitrate. Generalized edema may occur with prematurity, hypoproteinemia secondary to severe erythroblastosis fetalis, nonimmune hydrops, congenital nephrosis, Hurler syndrome, and from unknown causes. Localized edema suggests a congenital malformation of the lymphatic system; when confined to one or more extremities of a female infant, it may be the initial sign of Turner syndrome (see Chapters 81 and 586).

SKIN

Vasomotor instability and peripheral circulatory sluggishness are revealed by deep redness or purple lividity in a crying infant, whose color may darken profoundly with closure of the glottis preceding a vigorous cry, and by harmless cyanosis (**acrocyanosis**) of the hands and feet, especially when they are cool. Mottling, another example of general circulatory instability, may be associated with serious illness or related to a transient fluctuation in skin temperature. An extraordinary division of the body from the forehead to the pubis into red and pale halves is known as **harlequin color change**, a transient and harmless condition. Significant **cyanosis** may be masked by the pallor of circulatory failure or anemia; alternatively, the relatively high hemoglobin content of the 1st few days and the thin skin may combine to produce an appearance of cyanosis at a higher Pa_{O_2} (partial pressure arterial oxygen) than in older children. Localized cyanosis is differentiated from ecchymosis by the momentary blanching pallor (with cyanosis) that occurs after pressure. The same maneuver also helps in demonstrating icterus. **Pallor** may be caused by anemia, asphyxia, shock, or edema. Early recognition of anemia may lead to a diagnosis of fetomaternal blood transfusion, erythroblastosis fetalis, subcapsular hematoma of the liver or spleen, subdural hemorrhage, or fetal–maternal or twin–twin transfusion. Without being anemic, postmature infants tend to have paler and thicker skin than term or premature infants. The ruddy appearance of plethora is seen with polycythemia.

The vernix and common transitory macular capillary hemangiomas of the eyelids and neck are described in Chapter 647. Cavernous

hemangiomas are deeper, blue masses that, if large, may trap platelets and produce disseminated intravascular coagulation or interfere with local organ function. Scattered petechiae may be seen on the presenting part (usually the scalp or face) after a difficult delivery. Slate-blue, well-demarcated areas of pigmentation called **Mongolian spots** are seen over the buttocks, back, and sometimes other parts of the body in more than 50% of black, Native American, and Asian infants, and occasionally in white infants. These benign patches have no known anthropologic significance despite their name; they tend to disappear within the 1st year. The vernix, skin, and especially the cord may be stained brownish yellow if the amniotic fluid has been colored by the passage of meconium during or before birth.

The skin of premature infants is thin and delicate and tends to be deep red; in extremely premature infants, the skin appears almost gelatinous and translucent. Fine, soft, immature hair called **lanugo** frequently covers the scalp and brow and may also cover the face of premature infants. Lanugo has usually been lost or replaced by vellus hair in term infants. **Tufts of hair** over the lumbosacral spine suggest an underlying abnormality, such as occult spina bifida, a sinus tract, or a tumor. The nails are rudimentary in very premature infants, but they may protrude beyond the fingertips in infants born past term. Postterm infants may have a peeling, parchment-like skin (Fig. 94-1), a severe degree of which may mimic ichthyosis congenita (see Chapter 658).

In many neonates, small, white papules on an erythematous base develop 1-3 days after birth. This benign rash, **erythema toxicum**, persists for as long as 1 wk, contains eosinophils, and is usually distributed on the face, trunk, and extremities (see Chapter 647). **Pustular melanosis**, a benign lesion seen predominantly in black neonates, contains neutrophils and is present at birth as a vesiculopustular eruption around the chin, neck, back, extremities, and palms or soles; it lasts 2-3 days. Both lesions need to be distinguished from more dangerous vesicular eruptions such as herpes simplex (see Chapter 252) and staphylococcal disease of the skin (see Chapter 181.1).

Figure 94-1 Infant with intrauterine growth retardation as a result of placental insufficiency. Note the long, thin appearance with peeling, parchment-like dry skin, alert expression, meconium staining of the skin, and long nails. *(From Clifford S:* Advances in pediatrics, *vol 9, Chicago, 1962, Year Book.)*

Amniotic bands may disrupt the skin, extremities (amputation, ring constriction, syndactyly), face (clefts), or trunk (abdominal or thoracic wall defects). Their cause is uncertain but may be related to amniotic membrane rupture or vascular compromise with fibrous band formation. Excessive skin fragility and extensibility with joint hypermobility suggest Ehlers-Danlos syndrome, Marfan syndrome, congenital contractural arachnodactyly, and other disorders of collagen synthesis.

SKULL

The head circumference of all infants should be plotted on a growth chart to rule out **microcephalus** and **megalencephaly**. The skull may be molded, particularly if the infant is the first-born and if the head has been engaged in the pelvic canal for a considerable time. The parietal bones tend to override the occipital and frontal bones. The head of an infant born by cesarean section or from a breech presentation is characterized by its roundness. The suture lines and the size and fullness of the anterior and posterior fontanels should be determined digitally by palpation. Premature fusion of sutures (**cranial synostosis**) is identified as a hard nonmovable ridge over the suture and an abnormally shaped skull. Great variation in the size of the **fontanels** exists at birth; if small, the anterior fontanel usually tends to enlarge during the first few mo after birth. The persistence of excessively large anterior (normal: 20 ± 10 mm) and posterior fontanels has been associated with several disorders (Table 94-1). Persistently small fontanels suggest microcephaly, craniosynostosis, congenital hyperthyroidism, or wormian bones; presence of a third fontanel suggests trisomy 21, but is seen in preterm infants. Soft areas (**craniotabes**) are occasionally found in the parietal bones at the vertex near the sagittal suture; they are more common in preterm infants and in infants who have been exposed to uterine compression. Although such soft areas are usually insignificant, their possible pathologic cause should be investigated if they persist. Soft areas in the occipital region suggest the irregular calcification and wormian bone formation associated with osteogenesis imperfecta, cleidocranial dysostosis, lacunar skull, cretinism, and, occasionally, Down syndrome. Transillumination of an abnormal skull in a dark room followed by ultrasound or magnetic resonance imaging will rule out hydranencephaly and hydrocephaly (see Chapter 591). An excessively large head (megalencephaly) suggests hydrocephaly, storage disease, achondroplasia, cerebral gigantism, neurocutaneous syndromes, or inborn errors of metabolism, or may be familial. The skull of a premature infant may suggest hydrocephaly because of the relatively larger brain growth in comparison with growth of other organs. Depression of the skull (indentation, fracture, ping pong ball deformity) is usually of prenatal onset and a result of prolonged focal

Table 94-1 Disorders Associated with a Large Anterior Fontanel

Achondroplasia
Apert syndrome
Athyrotic hypothyroidism
Cleidocranial dysostosis
Congenital rubella syndrome
Hallermann-Streiff syndrome
Hydrocephaly
Hypophosphatasia
Intrauterine growth restriction
Kenny syndrome
Osteogenesis imperfecta
Prematurity
Pyknodysostosis
Russell-Silver syndrome
Trisomies 13-, 18-, and 21
Vitamin D deficiency rickets

pressure by the bony pelvis. Atrophic or alopecic scalp areas may represent aplasia cutis congenita, which may be sporadic, or autosomal dominant, or associated with trisomy 13, chromosome 4 deletion, or Johanson-Blizzard syndrome. Deformational plagiocephaly may be the result of in utero positioning forces on the skull and manifests as an asymmetric skull and face with ear malalignment (see Chapter 592). It is associated with torticollis and vertex positioning.

FACE

The general appearance of the face should be noted with regard to dysmorphic features, such as epicanthal folds, widely or narrowly spaced eyes, microphthalmos, asymmetry, long philtrum, and low-set ears, which are often associated with congenital syndromes. The face may be asymmetric as a result of a 7th nerve palsy, hypoplasia of the depressor muscle at the angle of the mouth, or an abnormal fetal posture (see Chapter 108); when the jaw has been held against a shoulder or an extremity during the intrauterine period, the mandible may deviate strikingly from the midline. Symmetric facial palsy suggests absence or hypoplasia of the 7th nerve nucleus (**Möbius syndrome**).

Eyes

The eyes often open spontaneously if the infant is held up and tipped gently forward and backward. This maneuver, a result of labyrinthine and neck reflexes, is more successful for inspecting the eyes than is forcing the lids apart. Conjunctival and retinal hemorrhages are usually benign. Retinal hemorrhages are more common with vacuum- or forceps-assisted deliveries, than spontaneous vaginal delivery, and least common after cesarean section. They are usually bilateral, intraretinal, and in the posterior pole. They resolve in most infants by 2 wk of age (85%) and in all infants by 4 wk. **Pupillary reflexes** are present after 28-30 wk of gestation. The iris should be inspected for colobomas and heterochromia. A cornea >1 cm in diameter in a term infant (with photophobia and tearing) suggests congenital glaucoma and requires prompt ophthalmologic consultation. The presence of bilateral red reflexes suggests the absence of cataracts and intraocular pathology (see Chapters 619, 627-633). **Leukokoria** (white pupillary reflex) suggests cataracts, tumor, chorioretinitis, retinopathy of prematurity, or a persistent hyperplastic primary vitreous and warrants an immediate ophthalmologic consultation.

Ears

Deformities of the pinnae are occasionally seen. Unilateral or bilateral preauricular skin tags occur frequently; if pedunculated, they can be tightly ligated at the base, resulting in dry gangrene and sloughing. The tympanic membrane, easily seen otoscopically through the short and straight external auditory canal, normally appears dull gray.

Nose

The nose may be slightly obstructed by mucus accumulated in the narrow nostrils. The nares should be symmetric and patent. Dislocation of the nasal cartilage from the vomerian groove results in asymmetric nares. Anatomic obstruction of the nasal passages secondary to unilateral or bilateral choanal atresia results in respiratory distress.

Mouth

A normal mouth may rarely have precocious dentition, with natal (present at birth) or neonatal (eruption after birth) teeth in the lower incisor position or aberrantly placed; these teeth are shed before the deciduous ones erupt (see Chapter 307). Alternatively, such teeth occur in Ellis-van Creveld, Hallermann-Streiff, and other syndromes. Extraction is not usually indicated. Premature eruption of deciduous teeth is even more unusual. The soft and hard palate should be inspected and palpated for a complete or submucosal cleft, and the contour noted if the arch is excessively high or the uvula is bifid. On the hard palate on either side of the raphe, there may be temporary accumulations of epithelial cells called **Epstein pearls**. Retention cysts of similar appearance may also be seen on the gums. Both disappear spontaneously, usually within a few weeks of birth. Clusters of small white or yellow follicles or ulcers on erythematous bases may be found on the anterior tonsillar pillars, most frequently on the 2nd or 3rd day of life. Of unknown cause, they clear without treatment in 2-4 days.

Neonates do not have active salivation. The tongue appears relatively large; the frenulum may be short, but its shortness (**tongue-tied** or **ankyloglossia**) is rarely a reason for cutting it. If there are problems with feedings (breast or bottle) and the frenulum is short, frenulotomy (frenotomy) may be indicated. Frenotomy may reduce maternal nipple pain and improve breastfeeding scores more rapidly than no treatment, but over time neonates not treated with frenotomy also had successful feeding. The sublingual mucous membrane occasionally forms a prominent fold. The cheeks have fullness on both the buccal and the external aspects as a result of the accumulation of fat making up the sucking pads. These pads, as well as the labial tubercle on the upper lip (**sucking callus**), disappear when suckling ceases. A marble-sized buccal mass is usually caused by benign idiopathic fat necrosis.

The throat of a newborn infant is hard to see because of the low arch of the palate; it should be clearly viewed because posterior palatal or uvular clefts are easy to miss. The tonsils are small.

NECK

The neck appears relatively short. Abnormalities are not common but include goiter, cystic hygroma, branchial cleft rests, teratoma, hemangioma, and lesions of the sternocleidomastoid muscle that are presumably traumatic or due to a fixed positioning in utero that produces either a hematoma or fibrosis, respectively. Congenital **torticollis** causes the head to turn toward and the face to turn away from the affected side. Plagiocephaly, facial asymmetry, and hemihypoplasia may develop if it is untreated (see Chapter 592.1). Redundant skin or webbing in a female infant suggests intrauterine lymphedema and Turner syndrome (see Chapters 81 and 586). Both clavicles should be palpated for fractures.

CHEST

Breast hypertrophy is common, and milk may be present (but should not be expressed). Asymmetry, erythema, induration, and tenderness suggest mastitis or a breast abscess. Supernumerary nipples, inverted nipples, or widely spaced nipples with a shield-shaped chest may be seen; the last finding suggests Turner syndrome.

LUNGS

Much can be learned by observing breathing. Normal variations in rate and rhythm are characteristic and fluctuate according to the infant's physical activity, the state of wakefulness, or the presence of crying. Because fluctuations are rapid, the respiratory rate should be counted for a full minute with the infant in the resting state, preferably asleep. Under these circumstances, the usual rate for normal term infants is 30-60 breaths/min; in premature infants the rate is higher and fluctuates more widely. A rate consistently greater than 60 breaths/min during periods of regular breathing that persists for more than an hour after birth is an indication to rule out pulmonary, cardiac, or metabolic disease (acidosis) etiologies. Preterm infants may breathe with a Cheyne-Stokes rhythm, known as periodic respiration, or with complete irregularity. Irregular gasping, sometimes accompanied by spasmodic movements of the mouth and chin, strongly indicates serious impairment of the respiratory centers.

The breathing of newborn infants at rest is almost entirely diaphragmatic, so during inspiration, the soft front of the thorax is usually drawn inward while the abdomen protrudes. If the baby is quiet, relaxed, and with good color, this "paradoxic movement" does not necessarily signify insufficient ventilation. On the other hand, labored respiration with retractions is important evidence of respiratory distress syndrome, pneumonia, anomalies, or mechanical disturbance of the lungs. A weak persistent or intermittent groaning, whining cry, or **grunting** during expiration can signify potentially serious cardiopulmonary disease or sepsis and warrants immediate attention. When benign, the grunting resolves between 30 and 60 min after birth. Flaring of the alae nasi and retraction of the intercostal muscles and sternum are common signs of pulmonary pathology.

Normally, the breath sounds are bronchovesicular. Suspicion of pulmonary pathology because of diminished breath sounds, rhonchi, retractions, or cyanosis should always be verified with a chest radiograph.

HEART

Normal variation in the size and shape of the chest makes it difficult to estimate the size of the heart. The location of the heart should be determined to detect dextrocardia. Transitory murmurs usually represent a closing ductus arteriosus. Although congenital heart disease may not initially produce a murmur, a substantial portion of infants in whom persistent murmurs are detected during routine neonatal examination have underlying malformation. Evaluation of the heart by echocardiography is essential when the possibility of a significant lesion exists, particularly if oxygen saturations are below 95%.

The pulse is usually 110-140 beats/min at rest, but may vary normally from 90 beats/min in relaxed sleep to 180 beats/min during activity. The still higher rate of supraventricular tachycardia (>220 beats/min) may be determined better with a cardiac monitor or electrocardiogram than by auscultation. Preterm infants usually have a higher resting heart rate, up to about 160 beats/min, but may have a sudden onset of sinus bradycardia secondary to apnea. On both admission to and discharge from the nursery, the infant's pulses should be palpated in the upper and lower extremities to detect coarctation of the aorta.

Blood pressure measurements may be a valuable diagnostic aid in ill infants (see Chapter 425). The oscillometric method is the easiest and most accurate noninvasive method available. Continuous direct measurement of blood pressure with an umbilical artery catheter may be indicated in special circumstances for critically ill infants in an intensive care unit (Fig. 94-2).

ABDOMEN

The liver is usually palpable, sometimes as much as 2 cm below the rib margin. Less commonly, the tip of the spleen may be felt. The approximate size and location of each kidney can usually be determined on deep palpation. At no other period of life does the amount of air in the gastrointestinal tract vary so much, nor is it usually so great under normal circumstances. The intestinal tract is gasless at birth. Gas is swallowed soon after birth, and gas should normally be present in the rectum on roentgenogram by 24 hr of age. The abdominal wall is normally weak (especially in premature infants), and diastasis recti and umbilical hernias are common, particularly among black infants.

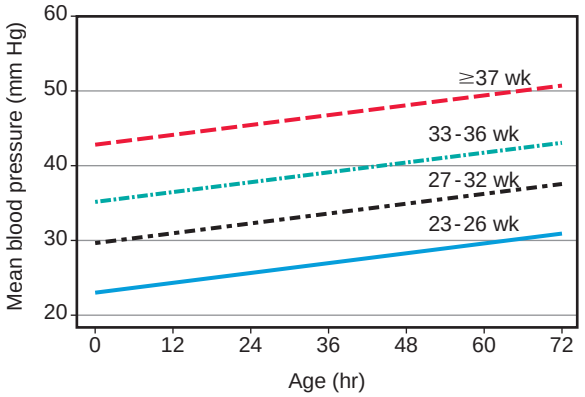

Figure 94-2 **Nomogram for mean blood pressure (BP) in neonates with gestational ages of 23-43 wk derived from continuous arterial BP measurements obtained from 103 infants admitted to the neonatal intensive care unit.** The graph shows the predicted mean BP of neonates of different gestational ages during the 1st 72 hr of life. Each line represents the lower limit of the 80% confidence interval (2-tail) of the mean BP for each gestational age group; 90% of infants for each gestational age group will be expected to have a mean BP value equal to or above the value indicated by the corresponding line, the lower limit of the confidence interval. *(From Nuntnarumit P, Yang W, Bada-Ellzey SB: Blood pressure measurements in the newborn,* Clin Perinatol *26:976–996, 1999.)*

Unusual masses should be investigated immediately with ultrasonography. Renal pathology is the cause of most neonatal abdominal masses. **Cystic abdominal masses** include hydronephrosis, multicystic-dysplastic kidneys, adrenal hemorrhage, hydrometrocolpos, intestinal duplication, and choledochal, ovarian, omental, or pancreatic cysts. **Solid masses** include neuroblastoma, congenital mesoblastic nephroma, hepatoblastoma, and teratoma. A solid flank mass may be caused by **renal vein thrombosis**, which becomes clinically apparent with hematuria, hypertension, and thrombocytopenia. Renal vein thrombosis in infants is associated with polycythemia, dehydration, maternal diabetes, asphyxia, sepsis, nephrosis, and hypercoagulable states such as antithrombin III and protein C deficiency.

Abdominal distention at birth or shortly afterward suggests either obstruction or perforation of the gastrointestinal tract, often as a result of meconium ileus; later distention suggests lower bowel obstruction, sepsis, or peritonitis. A scaphoid abdomen in a newborn suggests diaphragmatic hernia. Abdominal wall defects produce an omphalocele (see Chapter 105) when they occur through the umbilicus and gastroschisis when they occur lateral to the midline. Omphaloceles are associated with other anomalies and syndromes such as Beckwith-Wiedemann, conjoined twins, trisomy 18, meningomyelocele, and imperforate anus. **Omphalitis** is an acute local inflammation of the periumbilical tissue that may extend to the abdominal wall, the peritoneum, the umbilical vein or portal vessels, or the liver and may result in later portal hypertension. The umbilical cord should have 2 arteries and 1 vein. A single umbilical artery is associated with an increased risk for an occult renal anomaly.

GENITALS

The genitals and mammary glands normally respond to transplacentally acquired maternal hormones to produce enlargement and secretion of the breasts in both sexes and prominence of the genitals in females, often with considerable nonpurulent discharge. These transitory manifestations require no intervention.

An imperforate hymen or other causes of vaginal obstruction may result in **hydrometrocolpos** and a lower abdominal mass. A normal scrotum at term is relatively large; its size may be increased by the trauma of breech delivery or by a transitory hydrocele, which is distinguished from a hernia by palpation and transillumination. The testes should be in the scrotum or should be palpable in the canals in term infants. Black male infants usually have dark pigmentation of the scrotum before the rest of the skin assumes its permanent color. The scrotum may be ecchymotic from breech presentation or a retroperitoneal hemorrhage; it may contain meconium particles associated with meconium peritonitis.

The prepuce of a newborn infant is normally tight and adherent. Severe hypospadias or epispadias should always lead one to suspect either that abnormal sex chromosomes are present (see Chapter 81) or that the infant is actually a masculinized female with an enlarged clitoris, because this finding may be the first evidence of adrenogenital syndrome (see Chapter 576). Erection of the penis is common and has no significance. Urine is usually passed during or immediately after birth; a period without voiding may normally follow. Most neonates void by 12 hr, and approximately 95% of preterm and term infants void within 24 hr.

ANUS

Some passage of meconium usually occurs within the 1st 12 hr after birth; 99% of term infants and 95% of premature infants pass meconium within 48 hr of birth. Imperforate anus is not always visible and may require evidence obtained by gentle insertion of the examiner's little finger or a rectal tube. Radiographic study is required. Passage of meconium does not rule out an imperforate anus if a rectal–vaginal fistula is present. The dimple or irregularity in skinfold often normally

present in the sacrococcygeal midline may be mistaken for an actual or potential neurocutaneous sinus.

EXTREMITIES

During examination of the extremities, the effects of fetal posture (see Chapter 672) should be noted so that their cause and usual transitory nature can be explained to the mother. Such explanations are particularly important after breech presentations. A fracture or nerve injury associated with delivery can be detected more commonly by observation of the extremities in spontaneous or stimulated activity than by any other means. The hands and feet should be examined for polydactyly, syndactyly, and abnormal dermatoglyphic patterns such as a simian crease.

The hips of all infants should be examined with specific maneuvers to rule out congenital dislocation (see Chapter 678.1).

NEUROLOGIC EXAMINATION

See Chapters 9 and 590.

In utero neuromuscular diseases associated with limited fetal motion produce a constellation of signs and symptoms that are independent of the specific disease. Severe positional deformations and contractures produce arthrogryposis. Other manifestations of fetal neuromuscular disease include breech presentation, polyhydramnios, failure to breathe at birth, pulmonary hypoplasia, dislocated hips, undescended testes, thin ribs, and clubfoot. Many congenital disorders manifest as hypotonia, hypertonia, or seizures.

Bibliography is available at Expert Consult.

94.3 Routine Delivery Room and Initial Care

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Low-risk infants may initially be placed on the mother's abdomen after delivery; clearing the mouth of secretions with gentle suction with a bulb syringe or soft catheter is indicated if there is an excessive (copious) amount of fluid in the mouth or nares. In resource-poor countries, gentle wiping of the face, nose, and mouth with a soft cloth may be equally effective as a bulb syringe. Nonetheless, spontaneously breathing neonates with no distress do not need any assisted method to clear their airway. Most healthy infants who appear to be in satisfactory condition should be given directly to their mothers for immediate bonding and nursing. Delayed clamping of the umbilical cord (~30 sec) has value in reducing the incidence of anemia in infancy. If respiratory distress is a concern, infants should be placed under warmers for observation.

The **Apgar score** is a practical method of systematically assessing newborn infants immediately after birth (Table 94-2). A low score may be the result of fetal distress but may also be caused by a number of factors, including prematurity and drugs given to the mother during labor (Table 94-3). The Apgar score was not designed to predict neurologic outcome. Indeed, the score is normal in most patients in whom cerebral palsy subsequently develops, and the incidence of cerebral palsy is low in infants with Apgar scores of 0-3 at 5 min (but higher than in infants with Apgar scores of 7-10). Low Apgar scores and umbilical artery blood pH predict neonatal death. An Apgar score of 0-3 at 5 min is uncommon but is a better predictor of neonatal death (in both term and preterm infants) than an umbilical artery pH ≤7.0; the presence of both variables increases the relative risk of neonatal mortality in term and preterm infants (Table 94-4). Infants who fail to initiate respiration should receive prompt resuscitation and close observation (see Chapter 100).

MAINTENANCE OF BODY HEAT

Newborn infants are at risk for heat loss and hypothermia for several reasons. Relative to body weight, the body surface area of a newborn infant is approximately 3 times that of an adult. Generation of body heat depends in large part on body weight, but heat loss depends on surface area. In low birthweight and preterm infants, the insulating layer of subcutaneous fat is thin. The estimated rate of heat loss in a newborn is approximately 4 times that of an adult. Under the usual delivery room conditions (20-25°C [68-77°F]), an infant's skin temperature falls approximately 0.3°C (0.54°F)/min and deep body temperature decreases approximately 0.1°C (0.18°F)/min during the period immediately after delivery; these rates generally result in a

Table 94-3 Factors Affecting the Apgar Score*

FALSE-POSITIVE (NO FETAL ACIDOSIS OR HYPOXIA; LOW APGAR SCORE)
Prematurity
Analgesics, narcotics, sedatives
Magnesium sulfate
Acute cerebral trauma
Precipitous delivery
Congenital myopathy
Congenital neuropathy
Spinal cord trauma
Central nervous system anomaly
Lung anomaly (diaphragmatic hernia)
Airway obstruction (choanal atresia)
Congenital pneumonia and sepsis
Previous episodes of fetal asphyxia (recovered)
Hemorrhage-hypovolemia
FALSE-NEGATIVE (ACIDOSIS; NORMAL APGAR SCORE)
Maternal acidosis
High fetal catecholamine levels
Some full-term infants

*Regardless of the etiology, a low Apgar score because of fetal asphyxia, immaturity, central nervous system depression, or airway obstruction identifies an infant needing immediate resuscitation.

Table 94-2 Apgar Evaluation of Newborn Infants*

SIGN	0	1	2
Heart rate	Absent	Below 100	Over 100
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Response to catheter in nostril (tested after oropharynx is clear)	No response	Grimace	Cough or sneeze
Color	Blue, pale	Body pink, extremities blue	Completely pink

*Sixty sec after complete birth of the infant (disregarding the cord and placenta), the 5 objective signs listed here are evaluated, and each is given a score of 0, 1, or 2. A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0-3 requires immediate resuscitation.

Modified from Apgar V: A proposal for a new method of evaluation of the newborn infant, Curr Res Anesth Analg *32:260–267, 1953.*

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Table 94-4 Incidence of Neonatal Death in 132,228 Singleton Infants Born at Term (37th wk of Gestation or Later) in Relation to Apgar Scores at 5 Minutes of Age*

5-MIN APGAR SCORE	NO. OF LIVE BIRTHS	NO. NEONATAL DEATHS (PER 1,000 BIRTHS)	RELATIVE RISK (95% CI)
0-3	86	21 (244)	1,460 (835-2,555)
4-6	561	5 (9)	53 (20-140)
7-10	131,581	22 (0.2)	1

*Infants with 5-min Apgar scores of 7-10 served as the reference group.
CI, confidence interval.
From Casey BM, McIntire DD, Leveno KJ: The continuing value of the Apgar score for the assessment of newborn infants, N Engl J Med *344:467–471, 2001.*

cumulative loss of 2-3°C (3.6-5.4°F) in deep body temperature (corresponding to a heat loss of approximately 200 kcal/kg). The heat loss occurs by 4 mechanisms: (1) **convection** of heat energy to the cooler surrounding air, (2) **conduction** of heat to the colder materials touching the infant, (3) **heat radiation** from the infant to other nearby cooler objects, and (4) **evaporation** from skin and lungs.

Metabolic acidosis, hypoxemia, hypoglycemia, and increased renal excretion of water and solutes may develop in term infants exposed to cold after birth because of their effort to compensate for heat loss. Heat production is augmented by increasing the metabolic rate and oxygen consumption in part by releasing norepinephrine, which results in nonshivering thermo-genesis through oxidation of fat, particularly brown fat. In addition, muscular activity may increase. Hypoglycemic or hypoxic infants cannot increase their oxygen consumption when exposed to a cold environment, and their central temperature decreases. After labor and vaginal delivery, many newborn infants have mild to moderate metabolic acidosis, for which they may compensate by hyperventilating, a response that is more difficult for infants with central nervous system depression (asphyxia, drugs) and infants exposed to cold stress in the delivery room. Therefore, to reduce heat loss, it is desirable to ensure that infants are dried and either wrapped in blankets or placed with the mother or under radiant warmers. **Skin-to-skin contact** with the mother is the optimal method of maintaining temperature in the stable newborn. Because carrying out resuscitative measures on a covered infant or one enclosed in an incubator is difficult, a radiant heat source should be used to warm the baby during resuscitation.

ANTISEPTIC SKIN AND CORD CARE

Careful removal of the amniotic fluid and blood from the skin shortly after birth may reduce the risk of infection with bloodborne agents. Once a healthy infant's temperature has stabilized, the entire skin and cord should be cleansed with warm water or a mild nonmedicated soap solution and rinsed with water to reduce the incidence of skin and periumbilical colonization with pathogenic bacteria and subsequent infectious complications. To avoid heat loss, the infant is then dried and wrapped in clean blankets. To reduce colonization with *Staphylococcus aureus* and other pathogenic bacteria, the umbilical cord may be treated daily with a bactericidal or antimicrobial agents such as chlorhexidine, triple dye, or bacitracin. One application of triple dye followed by twice-daily alcohol swabbing (until the cord falls off) reduces colonization, exudates, and foul odor of the umbilicus in comparison with dry care (soap and water when soiled). On the rare occasion of *S. aureus* nursery epidemics, a single hexachlorophene bath may be used. Topical ointments should not be applied to preterm infants in neonatal intensive care units because this treatment increases the risk of bacterial sepsis. Routine or repeated total-body exposure to hexachlorophene may be neurotoxic, particularly in low-birthweight infants, and is thus contraindicated. Nursery personnel should use alcohol-based solutions or chlorhexidine or iodophor-containing antiseptic soaps for routine handwashing before caring for each infant. Rigid enforcement of hand-to-elbow washing for 2 min in the initial wash and 15-30 sec in subsequent washes is essential for staff and visitors entering the nursery.

OTHER MEASURES

The eyes of all infants, including those born by cesarean section, must be protected against gonococcal ophthalmia neonatorum by application of a 1-cm ribbon of erythromycin (0.5%) or tetracycline (1.0%) sterile ophthalmic ointments in each lower conjunctival sac. This procedure may be delayed during the initial short-alert period after birth to promote bonding, but once applied, drops should not be rinsed out (see Chapters 192 and 226.3). A 1% silver nitrate solution is an acceptable alternative, but leads to a transient chemical conjunctivitis in 10-20% of cases.

Although hemorrhage in newborn infants can be a result of factors other than vitamin K deficiency, an intramuscular injection of 0.5-1 mg of water-soluble vitamin K_1 (phytonadione) should be given to all infants shortly after birth to prevent hemorrhagic disease of the newborn (see Chapter 103.4). Oral vitamin K is not as effective as the parenteral dosage.

Hepatitis B immunization before discharge from the nursery is recommended for newborns with weight >2 kg irrespective of maternal hepatitis status.

Neonatal screening is available for various genetic, metabolic, hematologic, and endocrine disorders. All states in the United States have adopted the Advisory Committee on Heritable Disorders in Newborns and Children, although the specific tests performed vary by state based in part to disease prevalence, detection rates, and costs (see Chapter 84). The most commonly identified disorders (and their rates) include hypothyroidism (52/100,000 births), cystic fibrosis (30/100,000), hemoglobinopathies (26/100,000), medium-chain acyl–coenzyme A dehydrogenase deficiency (6/100,000), galactosemia (5/100,000), phenylketonuria (5/100,000), and adrenal hyperplasia (5/100,000). To be effective in the timely identification and prompt management of treatable diseases, screening programs must include not only high-quality laboratory tests but also follow-up of infants with abnormal test results; education, counseling, and psychologic support for families; and prompt referral of the identified neonate for accurate diagnosis and appropriate treatment.

Hearing impairment, a serious morbidity that affects speech and language development, may be severe in 2/1,000 births and overall affects 5/1,000 births. Universal screening of infants is recommended to ensure early detection of hearing loss and appropriate, timely intervention.

Universal screening with pulse oximetry provides early detection of ductal dependent cyanotic congenital heart disease (see Chapter 425).

Universal screening for hyperbilirubinemia should include risk assessment in all infants with measurement of serum or transcutaneous bilirubin levels before hospital discharge.

Universal screening for congenital hip dysplasia with physical examination with the Ortolani (sensation of the dislocated hip reducing) and Barlow (unstable hip dislocating from the acetabulum) tests is recommended but routine hip ultrasound is not indicated.

Routine measurement of the hematocrit or blood glucose value is not necessary in the absence of risk factors.

Bibliography is available at Expert Consult.

94.4 Nursery Care

Waldemar A. Carlo

Non–high-risk, healthy infants may be taken to the "regular" (normal) newborn nursery or may be placed in the mother's room if the hospital has rooming-in facilities.

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The bassinet, preferably of clear plastic to allow for easy visibility and care, should be cleaned frequently. All professional care should be given to the infant in the bassinet, including the physical examination, clothing changes, temperature taking, skin cleansing, and other procedures that, if performed elsewhere, would establish a common contact point and possibly provide a channel for cross infection. The clothing and bedding should be minimal, only enough needed for an infant's comfort; the nursery temperature should be kept at approximately 22-26°C (72-78°F). The infant's temperature should be taken by axillary measurement. Although the interval between temperature measurements depends on many circumstances, it need not be shorter than 4 hr during the 1st 2-3 days and 8 hr thereafter. Axillary temperatures of 36.5-37.4°C (97.7-99.3°F) are within normal limits. Weighing at birth and daily thereafter is sufficient. Healthy infants should be placed supine to reduce the risk of sudden infant death syndrome.

Vernix is spontaneously shed within 2-3 days, much of it adhering to the clothing, which should be completely changed daily. The diaper should be checked before and after feeding and when the baby cries; it should be changed when wet or soiled. The perineal area can be cleaned with baby wipes or with mild soap and warm water. Meconium or feces should be cleansed from the buttocks with sterile cotton moistened with sterile water. The foreskin of a male infant should not be retracted.

Infants should meet minimum criteria before hospital discharge (Table 94-5). Late preterm infants (34-36 wk) and infants with early discharge (<48 hr) or very early discharge (<24 hr) are at increased risk of rehospitalization. Early discharge requires careful ambulatory follow-up at home (by a visiting nurse) or in the office within 48 hr of discharge.

Table 94-5 Criteria for Discharge from the Normal Newborn Nursery*

Uncomplicated antepartum, intrapartum, postpartum courses
Vaginal delivery
Singleton at 38-42 wk: appropriate for gestational age
Normal vital signs including respiratory rate <60 breaths/min; axillary temperature 36.1-37°C (97.0-98.6°F) in open crib
Physical examination reveals no abnormalities requiring continued hospitalization
Urination; stool × 1
At least 2 uneventful, successful feedings
No excessive bleeding 2 hr after circumcision
No jaundice within 24 hr of birth; if jaundice, appropriate management and follow-up are in place
Evidence of parental knowledge, ability, and confidence to care for the baby at home:
Feeding
Cord, skin, genital care
Recognition of illness (jaundice, poor feeding, lethargy, fever, etc.)
Infant safety (car seat, supine sleep position, etc.)
Availability of family and physician support (physician follow-up)
Laboratory evaluation:
Syphilis
Hepatitis B surface antigen and vaccination or appointment for vaccination
Coombs test and blood type if clinically indicated
Expanded metabolic screening: phenylketonuria, thyroid, galactosemia, sickle cell
Hearing screening
No social risks:
Substance abuse
History of child abuse
Domestic violence
Mental illness
Teen mother
Homelessness
Barriers to follow-up
Source of continuing medical care is identified

*It is not likely that all these criteria will be met before 48 hr of age.

Adapted from American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Guidelines for perinatal care, *ed 7, Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Bibliography is available at Expert Consult.

94.5 Parent–Infant Bonding

Waldemar A. Carlo

See also Chapter 9.

Normal infant development depends partly on a series of affectionate responses exchanged between a mother and her newborn infant that binds them psychologically and physiologically. This bonding is facilitated and reinforced by the emotional support of a loving family. The attachment process may be important in enabling some mothers to provide loving care during the neonatal period and subsequently during childhood. The power of this attachment is so great that it enables the mother and the father to make unusual sacrifices necessary for the day-to-day care of the infant, care night after night, giving feedings 24 hr a day, attending to crying, and so on. The sacrifices continue for many years as parents dedicate much of their lives to their children.

Parent–infant bonding is initiated before birth with the planning and confirmation of the pregnancy. Subsequently, there is a growing awareness of the baby as an individual, starting usually with the remarkably powerful event of "quickening" or sensation of fetal movements. After delivery and during the ensuing weeks, sensory (visual, auditory, olfactory) and physical contact between the mother and baby triggers various mutually rewarding and pleasurable interactions, such as the mother touching the infant's extremities and face with her fingertips and encompassing and gently massaging the infant's trunk with her hands. Touching an infant's cheek elicits responsive turning toward the mother's face or toward the breast with nuzzling and licking of the nipple, a powerful stimulus for prolactin secretion. An infant's initial quiet alert state provides the opportunity for eye-to-eye contact, which is particularly important in stimulating the loving and possessive feelings of many parents for their babies. An infant's crying elicits the maternal response of touching the infant and speaking in a soft, soothing, higher-toned voice. Initial contact between the mother and infant should take place in the delivery room, and opportunities for extended intimate contact and breastfeeding should be provided within the 1st hours after birth. Delayed or abnormal maternal–infant bonding, as occurs because of prematurity, infant or maternal illness, birth defects, or family stress, may harm infant development and maternal caretaking ability. Hospital routines should be designed to encourage parent–infant contact. Open nurseries, rooming-in arrangements, care by parents, and family-centered care increase the opportunities for better parent–infant interaction.

NURSERIES AND BREASTFEEDING

See Chapter 45 for full discussions of breastfeeding and formula feeding.

Ample evidence indicates that there are infant and maternal benefits to breastfeeding. Practices that encourage successful breastfeeding include antepartum education and encouragement, immediate postpartum mother–infant contact with suckling, rooming-in arrangements, demand feeding, inclusion of fathers in breastfeeding education, and support from experienced women. Nursing at first for least 5 min at each breast is reasonable, allows a baby to obtain most of the available breast contents, and provides effective stimulation for increasing the milk supply. Nursing episodes should then be extended according to the comfort and desire of the mother and infant. A confident and relaxed mother, supported by an encouraging home and hospital environment, is likely to nurse well. The Baby-Friendly Hospital Initiative, a global effort (sponsored by the World Health Organization and the United Nations Children's Fund) to promote breastfeeding, recommends 10 steps to successful breastfeeding (Table 94-6). Some hospital practices contribute to difficulties in breastfeeding by enforcing 4-hr feeding schedules, limiting nursing time, using only 1 breast at a

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feeding, washing nipples with substances other than water, delaying the first feeding, providing formula supplements, and using heavy intrapartum sedation.

DRUGS AND BREASTFEEDING

Maternal medications may affect the production and safety of breast milk (Table 94-7). Although most commonly used medications are safe, the safety of any new drug to be used while a woman is breastfeeding must be confirmed before the drug is initiated and/or breastfeeding is continued. Maternal sedatives may result in sedation of the infant. Maternal drugs that are weak acids, composed of large molecules, plasma bound, or poorly absorbed from the maternal or neonatal intestine are less likely to affect a neonate.

CONTRAINDICATIONS TO BREASTFEEDING

Medical contraindications to breastfeeding in the United States include infants with galactosemia, maple syrup urine disease, and phenylketonuria. Maternal conditions that contraindicate breastfeeding include infection with HIV, human T-cell lymphotropic virus types 1 and 2, active tuberculosis (until appropriately treated ≥2 wk and not considered contagious), herpes virus infection on breast, and maternal treatment with some radioactive compounds (Table 94-8).

Table 94-6 | Ten Steps to Successful Breastfeeding

Every facility providing maternity services and care for newborn infants should accomplish the following:

1. Have a written breastfeeding policy that is routinely communicated to all healthcare staff.
2. Train all healthcare staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within a half hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk unless *medically* indicated.
7. Practice rooming-in (allow mothers and infants to remain together) 24 hr a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called *dummies* or *soothers*) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

From Protecting, promoting and supporting breastfeeding: the special role of maternity services. A joint WHO/UNICEF statement. *Geneva, 1989, World Health Organization.*

Table 94-7 | Drugs and Breastfeeding

CONTRAINDICATED	
Amphetamines	Metoclopramide
Antineoplastic agents	Metronidazole
Bromocriptine	Meperidine
Chloramphenicol	Oxycodone
Clozapine	Phenobarbital*
Cocaine	Primidone
Cyclophosphamide	Psychotropic drugs
Diethylstilbestrol	Reserpine
Doxorubicin	Salicylazosulfapyridine (sulfasalazine)
Ecstasy	**PROBABLY SAFE**
Ergots	Acetaminophen
Gold salts	Acyclovir
Heroin	Aldomet
Immunosuppressants	Anesthetics
Iodides	Antibiotics (not chloramphenicol)
Kava	Antiepileptics
Lithium	Antihistamines*
Methimazole	Antithyroid (not methimazole)
Methamphetamine	Bishydroxycoumarin (dicumarol)
Phencyclidine (PCP)	Chlorpromazine*
Radiopharmaceuticals	Cyclosporine
Thiouracil	Depo-Provera
Yohimbe	Digoxin
AVOID OR GIVE WITH CAUTION	Dilantin (phenytoin)
Alcohol	Diuretics
Amiodarone	Fluoxetine
Anthraquinones (laxatives)	Furosemide
Aspirin (salicylates)	Haloperidol*
Atropine	Hydralazine
β-Adrenergic blocking agents	Indomethacin, other nonsteroidal antiinflammatory drugs
Benzodiazepines	Low-molecular-weight heparins
Birth control pills	Metformin
Bromides	Methadone*
Buprenorphine/naltrexone	Morphine
Bupropion	Muscle relaxants
Calciferol	Paroxetine
Cascara	Prednisone
Ciprofloxacin	Propranolol
Codeine	Propylthiouracil
Dicumarol	Sedatives*
Dihydrotachysterol	Sertraline
Domperidone	Theophylline
Estrogens	Vitamins
Hydrocodone	Warfarin
Marijuana	

*Watch for sedation.

Table 94-8 | Summary of Infectious Agents Detected in Milk and Newborn Disease

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
BACTERIA			
Mastitis/*Staphylococcus aureus*	Yes	No	No, unless breast abscess present
Mycobacterium tuberculosis:			
Active disease	Yes	No	Yes, because of aerosol spread, or tuberculosis mastitis
Purified protein derivative skin test result positive, chest radiograph findings negative	No	No	No
Escherichia coli, other Gram-negative rods	Yes, stored	Yes, stored	—
Group B streptococci	Yes	Yes	No*
Listeria monocytogenes	Yes	Yes	No*
Coxiella burnetii	Yes	Yes	No*
Syphilis	No	No	No†

Continued

Table 94-8 Summary of Infectious Agents Detected in Milk and Newborn Disease—cont'd

INFECTIOUS AGENT	DETECTED IN BREAST MILK?	BREAST MILK REPORTED AS CAUSE OF NEWBORN DISEASE?	MATERNAL INFECTION CONTRAINDICATION TO BREASTFEEDING?
VIRUSES			
HIV	Yes	Yes	Yes, developed countries
Cytomegalovirus:			
Term infant	Yes	Yes	No
Preterm infant	Yes	Yes	Evaluate on an individual basis
Hepatitis B virus	Yes, surface antigen	No	No, developed countries[‡]
Hepatitis C virus	Yes	No	No[§]
Hepatitis E virus	Yes	No	No
Human T-cell leukemia virus (HTLV)-1	Yes	Yes	Yes, developed countries
HTLV-2	Yes	?	Yes, developed countries
Herpes simplex virus	Yes	No/?yes	No, unless breast vesicles present
Rubella			
Wild type	Yes	Yes, rare	No
Vaccine	Yes	No	No
Varicella-zoster virus	Yes	No	No, cover active lesions[¶]
Epstein-Barr virus	Yes	No	No
Human herpesvirus (HHV)-6	No	No	No
HHV-7	Yes	No	No
West Nile virus	Possible	Possible	Unknown
PARASITES			
Toxoplasma gondii	Yes	Yes, 1 case	No

*Provided that the mother and child are taking appropriate antibiotics.
[†]Treat mother and child if active disease.
[‡]Immunize and immune globulin at birth.
[§]Provided that the mother is HIV-seronegative. Mothers should be counseled that breast milk transmission of hepatitis C virus has not been documented, but is theoretically possible.
[¶]Provide appropriate antivaricella therapy or prophylaxis to newborn.
Modified from Jones CA: Maternal transmission of infectious pathogens in breast milk, J Paediatr Child Health *37:576–582, 2001.*

Donor human milk, particularly purchased through the Internet, may be contaminated with potential pathogens. Contamination is much less of a concern with unpasteurized human milk obtained from a milk bank.

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Chapter 95

High-Risk Pregnancies

Waldemar A. Carlo and Namasivayam Ambalavanan

High-risk pregnancies are those that increase the likelihood of abortion, fetal death, preterm delivery, intrauterine growth restriction, poor cardiopulmonary or metabolic transitioning at birth, fetal or neonatal disease, congenital malformations, or mental retardation and other handicaps (Table 95-1; see Chapter 96). Some factors, such as ingestion of a teratogenic drug in the 1st trimester, are causally related to the risk; others, such as hydramnios, are associations that alert a physician to determine the etiology and avoid the inherent risks associated with excessive amniotic fluid. On the basis of their history, 10-20% of pregnant women can be identified as being at high risk; nearly half of all perinatal mortality and morbidity is associated with these high-risk pregnancies. Although assessing antepartum risk is important in reducing perinatal mortality and morbidity, some pregnancies become high risk only during labor and delivery; therefore, careful monitoring is critical throughout the intrapartum course.

Identifying high-risk pregnancies is important not only because it is the first step toward prevention but also because therapeutic steps may often be taken to reduce the risks to the fetus or neonate if the physician knows of the potential for difficulty.

GENETIC FACTORS

The occurrence of chromosomal abnormalities, congenital anomalies, inborn errors of metabolism, mental retardation, or any familial disease in blood relatives increases the risk of the same condition in the infant. Because many parents recognize only obvious clinical manifestations of genetically determined diseases, specific inquiry should be made about any disease affecting 1 or more blood relatives.

MATERNAL FACTORS

The lowest neonatal mortality rate occurs in infants of mothers who receive adequate prenatal care and who are 20-30 yr of age. Pregnancies in both teenagers and women older than 40 yr, particularly primiparous women, are at increased risk for intrauterine growth restriction, fetal distress, and intrauterine death. Advanced maternal age increases the risk of both chromosomal and nonchromosomal fetal malformations (Fig. 95-1).

Maternal illness (Table 95-2), multiple pregnancies (particularly those involving monochorionic twinning), infections (Table 95-3), and certain drugs (see Chapter 96) increase the risk for the fetus. The use of assisted reproductive technology (in vitro fertilization, intracytoplasmic sperm injection) increases the risk of perinatal mortality, infant morbidity, prematurity, low and very-low birthweight, and cerebral palsy, largely because of the increase in multiple-fetus pregnancies with such technology; the risks for birth defects are also increased, in part, because of epigenetic effects on gene expression.

Table 95-1	Factors Associated with High-Risk Pregnancy
ECONOMIC	
Poverty	
Unemployment	
Uninsured, underinsured health insurance	
Poor access to prenatal care	
CULTURAL–BEHAVIORAL	
Low educational status	
Poor healthcare attitudes	
No care or inadequate prenatal care	
Cigarette, alcohol, illicit drug use	
Age <20 or >40 yr	
Unmarried	
Short interpregnancy interval	
Lack of support group (husband, family, religion)	
Stress (physical, psychologic)	
Black race	
BIOLOGIC–GENETIC	
Previous low birthweight or preterm infant	
Low weight for height	
Poor weight gain during pregnancy	
Short stature	
Poor nutrition	
Consanguinity	
Intergenerational effects	
Low maternal birthweight	
Hereditary diseases (inborn error of metabolism)	
REPRODUCTIVE	
Previous cesarean section	
Previous infertility	
Conception by reproductive technology	
Prolonged gestation	
Prolonged labor	
Previous infant with cerebral palsy, mental retardation, birth trauma, congenital anomalies	
Abnormal lie (breech)	
Multiple gestations	
Premature rupture of membranes	
Infection (systemic, amniotic, extra-amniotic, cervical)	
Preeclampsia or eclampsia	
Uterine bleeding (abruptio placentae, placenta previa)	
Parity (0 or >5 previous deliveries)	
Uterine or cervical anomalies	
Fetal disease	
Abnormal fetal growth	
Idiopathic premature labor	
Iatrogenic prematurity	
High or low levels of maternal serum α-fetoprotein	
MEDICAL	
Diabetes mellitus	
Hypertension	
Congenital heart disease	
Autoimmune disease	
Sickle cell anemia	
Intercurrent surgery or trauma	
Sexually transmitted infection	
Maternal hypercoagulable states	
Exposure to prescription medications	
TORCH (*t*oxoplasmosis, *o*ther agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex) infection	

Preterm birth is common in high-risk pregnancies (see Chapter 97). Factors associated with prematurity, noted in Table 95-1, include biologic markers such as cervical shortening, genital infection, fetal fibronectin in cervicovaginal secretions, serum α-fetoprotein, and preterm premature rupture of membranes (PROM). PROM occurs in 30-40% of preterm deliveries, and it is a leading identifiable cause of prematurity. Preterm delivery is often difficult to predict.

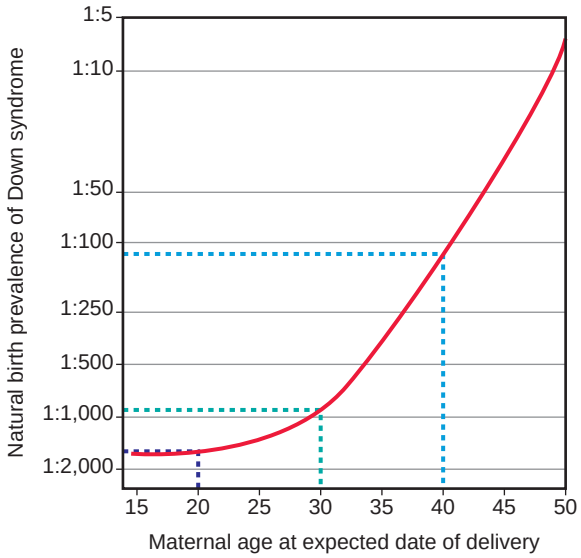

Figure 95-1 Natural birth prevalence of Down syndrome according to maternal age. *(From Wald NJ, Leck I:* Antenatal and neonatal screening, *ed 2, Oxford, 2000, Oxford University Press.)*

Polyhydramnios and **oligohydramnios** indicate high-risk pregnancies. Although the turnover rate of amniotic fluid is rapid, during normal pregnancy the amniotic fluid volume gradually increases at a rate of <10 mL/day until about the 34th wk of pregnancy, after which it slowly diminishes. Volumes vary widely in normal pregnancy; term volume may be 500-2,000 mL. A volume estimated at greater than 2,000 mL in the 3rd trimester constitutes polyhydramnios, and a volume estimated at <500 mL indicates oligohydramnios. Polyhydramnios complicates 1-3%, and oligohydramnios 1-5%, of pregnancies. The ultrasonographic criteria for these diagnoses are based on the amniotic fluid index, which is determined by measuring the vertical diameter of amniotic fluid pockets in four quadrants; an index >24 cm suggests polyhydramnios, whereas an index <5 cm suggests oligohydramnios.

Acute polyhydramnios is rare and is usually associated with preterm labor and delivery. **Chronic polyhydramnios** is diagnosed in the 3rd trimester from the discrepancy between uterine size and gestational age; it is occasionally not diagnosed until the patient has dysfunctional labor or an abnormally large amount of amniotic fluid is noted during delivery. Polyhydramnios is associated with preterm labor, abruptio placentae, multiple congenital anomalies, and fetal neuromuscular dysfunction or obstruction of the gastrointestinal tract that interferes with reabsorption of the amniotic fluid that is normally swallowed by the fetus (Table 95-4). Increased fetal urination or edema formation is also associated with excessive amniotic fluid volume. Ultrasound demonstrates the increased amniotic fluid surrounding the fetus and detects associated fetal anomalies, hydrops, pleural effusions, and ascites. In 60% of patients, no cause is identified. Symptomatic polyhydramnios may be managed by serial amniocenteses or by short-course maternal indomethacin if the problem is caused by excessive fetal urination. Treatment is indicated for acute maternal respiratory distress and threatened preterm labor or to provide time for the administration of corticosteroids to enhance fetal lung maturity.

Oligohydramnios is associated with congenital anomalies; intrauterine growth restriction; severe renal, bladder, or urethral anomalies; and drugs that interfere with fetal urination (see Table 95-4). Oligohydramnios becomes most evident after 20 wk of gestation, when fetal urination is the major source of amniotic fluid. Rupture of the membranes is the most common cause of oligohydramnios and must be ruled out if oligohydramnios is suspected, especially if a normal-sized

Table 95-2 Maternal Conditions Affecting the Fetus or Neonate

DISORDER	EFFECT(S)	MECHANISM(S)
Autoantibody against folate receptors	Neural tube defects	Blockage of cellular uptake of folate
Cervical neoplasia	Preterm premature rupture of membranes	Associated with loop electrosurgical excision procedure or cone therapy
Cholestasis	Preterm delivery, intrauterine fetal demise	Unknown, possibly hepatitis E
Cyanotic heart disease	Intrauterine growth restriction	Low fetal oxygen delivery
Diabetes mellitus:		
Mild	Large for gestational age, hypoglycemia	Fetal hyperglycemia—produces hyperinsulinemia; insulin promotes growth
Severe	Growth restriction	Vascular disease, placental insufficiency
Drug addiction	Intrauterine growth restriction, neonatal withdrawal	Direct drug effect plus poor diet
Endemic goiter	Hypothyroidism	Iodine deficiency
Graves disease	Transient neonatal thyrotoxicosis	Placental immunoglobulin passage of thyroid-stimulating antibody
Herpes gestationis (noninfectious)	Bullous rash, intrauterine fetal demise	Autoantibody similar to that in bullous pemphigoid
Hyperparathyroidism	Neonatal hypocalcemia	Maternal calcium crosses to fetus and suppresses fetal parathyroid gland
Hypertension	Intrauterine growth restriction, intrauterine fetal demise	Placental insufficiency, fetal hypoxia
Idiopathic thrombocytopenic purpura	Thrombocytopenia	Nonspecific maternal platelet antibodies cross placenta
Isoimmune neutropenia or thrombocytopenia	Neutropenia or thrombocytopenia	Specific antifetus neutrophil or platelet antibody crosses placenta after sensitization of mother
Malignant melanoma	Placental or fetal tumor	Metastasis
Myasthenia gravis	Transient neonatal myasthenia	Immunoglobulin to acetylcholine receptor crosses placenta
Myotonic dystrophy	Neonatal myotonic dystrophy, congenital contractures, respiratory insufficiency	Genetic anticipation
Obesity	Macrosomia, hypoglycemia	Unknown
Phenylketonuria	Microcephaly, retardation	Elevated fetal phenylalanine values
Poor nutrition	Intrauterine growth restriction, adult insulin resistance	Reduced fetal nutrients, nutritional programming
Preeclampsia, eclampsia	Intrauterine growth restriction, thrombocytopenia, neutropenia, fetal demise	Uteroplacental insufficiency, fetal hypoxia, vasoconstriction
Renal transplantation	Intrauterine growth restriction	Uteroplacental insufficiency
Rhesus or other blood group sensitization	Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice	Antibody crosses placenta and is directed to fetal cells with antigen
Sickle cell anemia	Preterm birth, intrauterine growth restriction, stillbirth	Maternal sickling producing fetal hypoxia
Systemic lupus erythematosus	Congenital heart block, rash, anemia, thrombocytopenia, neutropenia	Antibody directed to fetal heart, red and white blood cells, and platelets

bladder is seen on fetal ultrasound. Oligohydramnios causes fetal compression abnormalities such as fetal distress, clubfoot, spadelike hands, and a flattened nasal bridge. The most serious complication of chronic oligohydramnios is **pulmonary hypoplasia.** The risk of umbilical cord compression during labor and delivery is increased in pregnancies complicated by oligohydramnios and may be alleviated by saline amnioinfusion. Prophylactic intrapartum amnioinfusion reduces the need for cesarean section and improves Apgar scores.

Antenatal screening can be used to detect a number of disorders, including Down syndrome and other chromosomal abnormalities, neural tube defects and other structural anomalies, Tay-Sachs disease and other metabolic genetic diseases, hemoglobinopathies and other blood disorders, and cystic fibrosis. Screening methods include maternal blood tests, fetal ultrasound, and diagnostic tests on cells or fluid obtained by amniocentesis or chorionic villus sampling and by fetal blood or tissue sampling. Cell-free fetal DNA in maternal blood has higher sensitivity (>99%) and lower false-positive rates for trisomy 21 (Down syndrome) and other chromosomal abnormalities than a combination of maternal serum analytes and ultrasound.

Second-trimester screening (15-18 wk) of maternal serum α-fetoprotein (MSAFP) values is used to screen for open neural tube defects. Approximately 90% of affected pregnancies can be detected by an elevated MSAFP value. Gastroschisis, omphalocele, congenital nephrosis, twins, and other abnormal conditions can also be identified.

Table 95-3 Maternal Infections Affecting the Fetus or Newborn

INFECTION	MODE(S) OF TRANSMISSION	OUTCOME
BACTERIA		
Group B streptococcus	Ascending cervical	Sepsis, pneumonia
Escherichia coli	Ascending cervical	Sepsis, pneumonia
Listeria monocytogenes	Transplacental	Sepsis, pneumonia
Ureaplasma urealyticum	Ascending cervical	Pneumonia, meningitis
Mycoplasma hominis	Ascending cervical	Pneumonia
Chlamydia trachomatis	Vaginal passage	Conjunctivitis, pneumonia
Syphilis	Transplacental, vaginal passage	Congenital syphilis
Borrelia burgdorferi	Transplacental	Prematurity, fetal demise
Neisseria gonorrhoeae	Vaginal passage	Ophthalmia (conjunctivitis), sepsis, meningitis
Mycobacterium tuberculosis	Transplacental	Prematurity, fetal demise, congenital tuberculosis
Granulocytic ehrlichiosis	Transplacental	Sepsis
VIRUS		
Rubella	Transplacental	Congenital rubella
Cytomegalovirus	Transplacental, breast milk (rare)	Congenital cytomegalovirus or asymptomatic
HIV	Transplacental, vaginal passage, breast milk	Congenital acquired immunodeficiency syndrome
Hepatitis B	Vaginal passage, transplacental, breast milk	Neonatal hepatitis, chronic hepatitis B surface antigen carrier state
Hepatitis C	Transplacental	Uncommon, but neonatal hepatitis, chronic carrier state possible
Lymphocytic choriomeningitis	Transplacental	Fetal, neonatal death; hydrocephalus, chorioretinitis
Herpes simplex type 2 or 1	Transplacental	Congenital herpes simplex virus
	Vaginal passage, ascending	Neonatal encephalitis, disseminated viremia
Varicella-zoster	Transplacental:	
	Early	Congenital anomalies
	Late	Neonatal varicella
Parvovirus	Transplacental	Fetal anemia, hydrops
Coxsackie B	Fecal-oral	Myocarditis, meningitis, hepatitis
Poliomyelitis	Transplacental	Congenital poliomyelitis
Epstein-Barr	Transplacental	Anomalies(?)
Rubeola	Transplacental	Abortion, fetal measles
West Nile	Transplacental	Chorioretinitis, focal cerebral necrosis
Dengue virus	Transplacental	Thrombocytopenia, lymphocytosis
PARASITES		
Toxoplasmosis	Transplacental	Congenital toxoplasmosis or asymptomatic
Malaria	Transplacental	Abortion, prematurity, intrauterine growth restriction
Trypanosomiasis	Transplacental	Congenital Chagas disease
Hookworm	None	Maternal anemia, low birthweight
FUNGI		
Candida	Ascending, cervical	Sepsis, pneumonia, rash
PRION		
Creutzfeldt-Jakob disease	Transplacental, colostrum	Hypothetical route, no long-term data

Low MSAFP is associated with incorrect gestational age estimates, trisomy 18 or 21, and intrauterine growth restriction.

A pregnancy should be considered high risk when the uterus is inappropriately large or small. A uterus large for the estimated stage of gestation suggests the presence of multiple fetuses, hydramnios, or an excessively large infant; an inappropriately small infant suggests oligohydramnios or poor intrauterine growth. PROM more than 24 hr before delivery carries a risk of fetal infection; it also increases the risk of premature birth. PROM at term usually results in the onset of labor within 48 hr but poses a risk of chorioamnionitis and umbilical cord compression. With **PROM** before 37 wk, there is a longer latency until labor starts, and its occurrence has the added risks of cord prolapse, oligohydramnios, abruptio placentae, fetal malposition; also, if membrane rupture is present for >7 days in a fetus during the 2nd trimester, pulmonary hypoplasia, uterine-induced deformations, and extremity contractures can develop. Prolonged and difficult labor increases the risk for mechanical and hypoxic damage. A tumultuous short labor with a precipitous delivery increases the risk of birth asphyxia and intracranial hemorrhage. **Placental separation** at any time before delivery and abnormal implantation or compression of the cord increase the possibility of brain damage from fetal hypoxia; brown or muddy amniotic fluid suggests that meconium has been passed, possibly during an episode of fetal hypoxia.

Although the safety of any type of delivery depends on the skill of the obstetrician, additional hazards accompany particular methods and result from the circumstances that dictated them. The risk of **intracranial hemorrhage** is greater in infants delivered by vacuum extraction or forceps than in those born unassisted in spontaneous vaginal deliveries. Neonatal deaths after mid-forceps delivery, breech extraction, and version are likely to be related to traumatic intracranial injury.

Infants born by **cesarean section** present problems possibly related to the unfavorable obstetric circumstance that necessitated the operation. In normal term pregnancies without any indication of fetal distress, cesarean section delivery carries a greater risk than delivery through the birth canal. Controversy exists regarding the safest type of delivery for a nondistressed, viable immature fetus, especially in a breech presentation; cesarean section may involve less risk than the "stress" of labor and the potentially hypoxic effects of uterine contractions during vaginal delivery. Term infants in breech position (≈3-4% of term births) that do not assume vertex position after external cephalic version attempts may also benefit from cesarean section.

Table 95-4	Conditions Associated with Disorders of Amniotic Fluid Volume
OLIGOHYDRAMNIOS	
Amniotic fluid leak/rupture of membranes	
Intrauterine growth restriction	
Fetal anomalies	
Twin–twin transfusion (donor)	
Renal agenesis (Potter syndrome)	
Urethral atresia	
Prune-belly syndrome	
Pulmonary hypoplasia	
Amnion nodosum	
Indomethacin	
Angiotensin-converting enzyme inhibitors or receptor antagonists	
Intestinal pseudoobstruction	
POLYHYDRAMNIOS	
Congenital anomalies:	
Anencephaly	
Hydrocephaly	
Tracheoesophageal fistula	
Duodenal atresia	
Spina bifida	
Cleft lip or palate	
Cystic adenomatoid lung malformation	
Diaphragmatic hernia	
Syndromes:	
Achondroplasia	
Klippel-Feil	
Trisomy 18	
Trisomy 21	
TORCH (toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex)	
Hydrops fetalis	
Multiple congenital anomalies	
Other:	
Diabetes mellitus	
Twin–twin transfusion (recipient)	
Fetal anemia	
Fetal heart failure	
Polyuric renal disease	
Neuromuscular diseases	
Nonimmune hydrops	
Chylothorax	
Teratoma	
Idiopathic	

Although transient tachypnea is the most frequently associated problem with cesarean section, respiratory distress syndrome and persistent pulmonary hypertension may develop, particularly in infants born by cesarean section to women who are not in labor, in those with uncertain dates, and in those born to diabetic mothers or after asphyxia. A trial of labor after a previous low segment cesarean section may have benefits and harms but there are limited data to make firm recommendations. In women with more than one previous cesarean section, there is an increased risk of uterine rupture. An elective cesarean section should be delayed until ≥39 wk of gestation. Earlier delivery increases the risk to the newborns.

Anesthesia and analgesia affect the fetus as well as the mother; severe maternal hypoxemia secondary to hypoventilation or hypotension resulting from epidural anesthesia may lead to severe fetal hypoxia and shock. Skilled use of medication avoids severe fetal narcosis while securing the benefits of gentle and unhurried delivery. Even skilled administration may result in a mildly depressed infant whose crying and breathing may be delayed 1-2 min and who may be somewhat inactive for several hours.

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Chapter 96

The Fetus

Waldemar A. Carlo and Namasivayam Ambalavanan

The major emphasis in fetal medicine involves (1) assessment of fetal growth and maturity, (2) evaluation of fetal well-being or distress, (3) assessment of the effects of maternal disease on the fetus, (4) evaluation of the effects of drugs administered to the mother on the fetus, and (5) identification and treatment of fetal disease or anomalies. Some aspects of human fetal growth and development are summarized in Chapter 8.

96.1 Fetal Growth and Maturity

Waldemar A. Carlo and Namasivayam Ambalavanan

Ultrasonography of the fetus, a common obstetric procedure, is both safe and reasonably accurate. Indications for antenatal ultrasonography include estimation of gestational age (unknown dates, discrepancy between uterine size and dates or suspected growth restriction), assessment of amniotic fluid volume, estimation of fetal weight, determination of the location of the placenta and the number and position of fetuses, and identification of congenital anomalies.

Fetal growth can be assessed by ultrasonography as early as 6-8 wk. The most accurate assessment of gestational age is by 1st-trimester ultrasound measurement of crown–rump length. The biparietal diameter is used to assess gestational age beginning in the 2nd trimester. Through 30 wk the biparietal diameter accurately estimates gestation to within ± 10 days. Later in gestation, accuracy falls to ± 3 wk. Methods used to assess gestational age closer to term include measurement of abdominal circumference and femoral length. If a single ultrasound examination is performed, the most information can be obtained with a scan at 18-20 wk, when both gestational age and fetal anatomy can be evaluated. Serial scans may be useful in assessing fetal growth. Two patterns of fetal growth restriction have been identified: continuous fetal growth 2 SD below the mean for gestational age or a normal fetal growth curve that abruptly slows or flattens later in gestation (Fig. 96-1).

Fetal maturity and dating are usually assessed by history (last menstrual period), physical examination, auscultation of fetal heart sounds at 16-18 wk, maternal perception of fetal movements at 18-20 wk, fundal height, and ultrasound (growth). Lung maturation may be estimated by determining the surfactant content of amniotic fluid (see Chapter 101.3).

Bibliography is available at Expert Consult.

96.2 Fetal Distress

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Fetal compromise may occur during the antepartum or intrapartum period; it may be asymptomatic in the antenatal period. Antepartum fetal surveillance is warranted for women at increased risk for fetal death, including those with a history of stillbirth, intrauterine growth restriction (IUGR), oligohydramnios or polyhydramnios, multiple gestation, rhesus sensitization, hypertensive disorders, diabetes mellitus or other chronic maternal disease, decreased fetal movement, and postterm pregnancy. The predominant cause of antepartum fetal distress is uteroplacental insufficiency, which may manifest clinically as IUGR, fetal hypoxia, increased vascular resistance in fetal blood vessels (Figs. 96-2 and 96-3), and, when severe, mixed respiratory and

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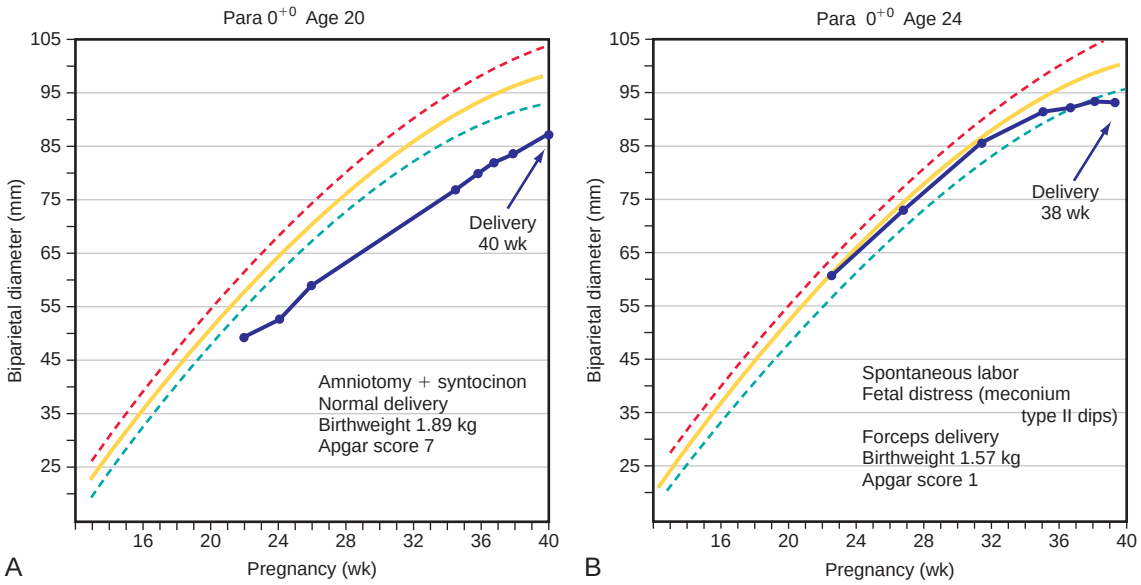

Figure 96-1 **A,** Example of a "low-profile" growth retardation pattern in an uneventful pregnancy and labor. The baby cried at 1 min and hypoglycemia did not develop. Birthweight was below the 5th percentile for gestational age. **B,** Example of a "late-flattening" growth retardation pattern. The mother had a typical history of preeclampsia, and the infant had intrapartum fetal distress, a low Apgar score, and postnatal hypoglycemia. Birthweight was below the 5th percentile for gestational age. *(From Campbell S: Fetal growth,* Clin Obstet Gynecol *1:41–65, 1974.)*

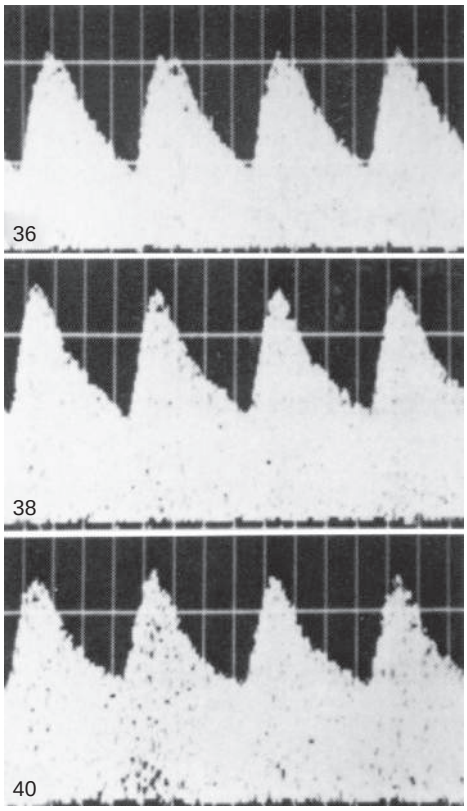

Figure 96-2 Normal Doppler velocity in sequential studies of fetal umbilical artery flow velocity waveforms from one normal pregnancy. Note the systolic peak flow with lower but constant heart flow during diastole. The systolic:diastolic ratio can be determined and, in normal pregnancies, is less than 3 after the 30th wk of gestation. The *numbers* indicate the weeks of gestation. *(From Trudinger B: Doppler ultrasound assessment of blood flow. In Creasy RK, Resnik R, editors:* Maternal-fetal medicine: principles and practice, *ed 5, Philadelphia, 2004, WB Saunders.)*

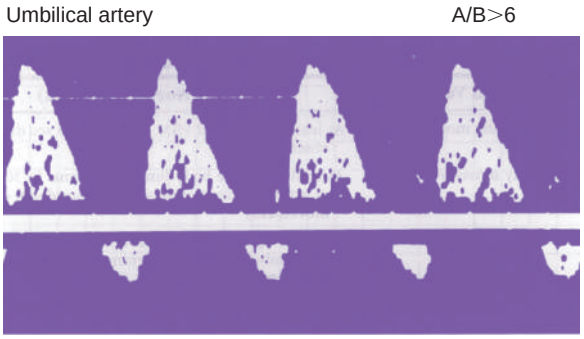

Figure 96-3 Abnormal umbilical artery Doppler in which the diastolic component shows flow in a reverse direction. This finding occurs in severe intrauterine hypoxia and intrauterine growth restriction. *(From Trudinger C: Doppler ultrasound assessment of blood flow. In Creasy RK, Resnik R, editors:* Maternal-fetal medicine: principles and practice, *ed 5, Philadelphia, 2004, WB Saunders.)*

metabolic (lactic) acidosis. The goals of antepartum fetal surveillance are to prevent intrauterine fetal demise, to prevent hypoxic brain injury, and to either prolong gestation in women at risk for preterm delivery when such prolongation is safe or deliver a fetus when it is in jeopardy. Table 96-1 lists methods for assessing fetal well-being.

The most commonly used noninvasive tests are the nonstress test (NST), the full and modified biophysical profile (BPP), and, less commonly, the contraction stress test (CST). The **NST** monitors the presence of fetal heart rate accelerations that follow fetal movement. A reactive (normal) NST result demonstrates 2 fetal heart rate accelerations of at least 15 beats/min lasting 15 sec. A nonreactive NST result suggests fetal compromise and requires further assessment with a CST or the BPP. A **CST** observes the fetal heart rate response to spontaneous, nipple-stimulated, or oxytocin-stimulated uterine contractions. Fetal compromise is suggested when the majority of contractions in 10 min are followed by late decelerations. A CST is relatively contraindicated in women with preterm premature rupture of membranes, a previous uterine scar from a classic cesarean section, multiple

Table 96-1 Fetal Diagnosis and Assessment

METHOD	COMMENT(S) AND INDICATION(S)
IMAGING	
Ultrasound (real-time)	Biometry (growth), anomaly (morphology) detection Biophysical profile Amniotic fluid volume, hydrops
Ultrasound (Doppler)	Velocimetry (blood flow velocity) Detection of increased vascular resistance secondary to fetal hypoxia
Embryoscopy	Early diagnosis of limb anomaly
Fetoscopy	Detection of facial, limb, cutaneous anomalies
MRI	Defining of lesions before fetal surgery
FLUID ANALYSIS	
Amniocentesis	Fetal maturity (L:S ratio), karyotype (cytogenetics), biochemical enzyme analysis, molecular genetic DNA diagnosis, bilirubin, or α-fetoprotein determination Bacterial culture, pathogen antigen, or genome detection
Cordocentesis (percutaneous umbilical blood sampling)	Detection of blood type, anemia, hemoglobinopathies, thrombocytopenia, acidosis, hypoxia, polycythemia, immunoglobulin M antibody response to infection Rapid karyotyping and molecular DNA genetic diagnosis Fetal therapy (see Table 96-5)
FETAL TISSUE ANALYSIS	
Chorionic villus biopsy	Karyotype, molecular DNA genetic analysis, enzyme assays
Skin biopsy	Hereditary skin disease*
Liver biopsy	Enzyme assay*
Circulating fetal DNA or cells in maternal blood or plasma	Molecular DNA genetic analysis including microarray analysis, chromosome number, specific gene testing, or genetic sequencing
MATERNAL SERUM α-FETOPROTEIN CONCENTRATION	
Elevated	Twins, neural tube defects (anencephaly, spina bifida), intestinal atresia, hepatitis, nephrosis, fetal demise, incorrect gestational age
Reduced	Trisomies, aneuploidy
MATERNAL CERVIX	
Fetal fibronectin	Indicates risk of preterm birth
Bacterial culture	Identifies risk of fetal infection (group B streptococcus, *Neisseria gonorrhoeae*)
Fluid	Determination of premature rupture of membranes
ANTEPARTUM BIOPHYSICAL MONITORING	
Nonstress test	Fetal distress; hypoxia
Contraction stress test	Fetal distress; hypoxia
Biophysical profile and modified biophysical profile	Fetal distress; hypoxia
Intrapartum fetal heart rate monitoring	See Fig. 96-4

*DNA genetic analysis on chorionic villus samples, amniocytes from amniocentesis, or fetal cells recovered from the maternal circulation may obviate the need for direct fetal tissue biopsy if the gene or genetic marker is available (e.g., the gene for Duchenne muscular dystrophy).
L:S, lecithin:sphingomyelin ratio.

gestations, incompetent cervix, and placenta previa. The goals of fetal monitoring are to prevent intrauterine fetal demise and hypoxic brain injury. Although the CST and NST have low false-negative rates, both have high false-positive rates. The full **BPP** assesses fetal breathing, body movement, tone, heart rate, and amniotic fluid volume, and it is used to improve the accurate and safe identification of fetal compromise (Table 96-2). A score of 2 is given for each observation present. A total score of 8-10 is reassuring; a score of 6 is equivocal, and retesting should be done in 12-24 hr; and a score of 4 or less warrants immediate evaluation and possible delivery. The BPP has good negative predictive value. The modified BPP consists of the combination of an ultrasound estimate of amniotic fluid volume (the amniotic fluid index) and the NST. When results of both are normal, fetal compromise is very unlikely. Signs of progressive compromise seen on Doppler ultrasonography include reduced, absent, or reversed diastolic waveform velocity in the fetal aorta or umbilical artery (see Fig. 96-3 and Table 96-1). High-risk fetuses often have combinations of abnormalities, such as oligohydramnios, reversed diastolic Doppler umbilical artery blood flow velocity, and a low BPP.

Fetal compromise *during labor* may be detected by monitoring the fetal heart rate, uterine pressure, and fetal scalp blood pH (Fig. 96-4). **Continuous fetal heart rate monitoring** detects abnormal cardiac patterns by instruments that compute the beat-to-beat fetal heart rate from a fetal electrocardiographic signal. Signals are derived from an electrode attached to the fetal presenting part, from an ultrasonic transducer placed on the maternal abdominal wall to detect continuous ultrasonic waves reflected from the contractions of the fetal heart, or from a phonotransducer placed on the mother's abdomen. Uterine contractions are simultaneously recorded from an amniotic fluid catheter and pressure transducer or from a tocotransducer applied to the maternal abdominal wall overlying the uterus. Fetal heart rate patterns show various characteristics, some of which suggest fetal compromise. The baseline fetal heart rate is the average rate between uterine contractions, which gradually decreases from approximately 155 beats/min in early pregnancy to approximately 135 beats/min at term; the normal range at term is 110-160 beats/min. **Tachycardia** (>160 beats/min) is associated with early fetal hypoxia, maternal fever, maternal hyperthyroidism, maternal β-sympathomimetic drug or atropine therapy, fetal anemia, infection, and some fetal arrhythmias. The last do not generally occur with congenital heart disease and may resolve spontaneously at birth. **Fetal bradycardia** (<110 beats/min) may be normal (e.g., 105-110 beats/min) but may occur with fetal hypoxia, placental transfer of local anesthetic agents and β-adrenergic blocking agents, and, occasionally, heart block with or without congenital heart disease.

Normally, the baseline fetal heart rate is variable. **Variability** is classified as follows: **absence of variability**, if an amplitude change is undetectable; **minimal variability** if amplitude range is ≤5 beats/min

Table 96-2 Biophysical Profile Scoring: Technique and Interpretation

BIOPHYSICAL VARIABLE	NORMAL SCORE (2)	ABNORMAL SCORE (0)
Fetal breathing movements (FBMs)	At least 1 episode of FBM of at least 30 sec duration in 30 min observation	Absence of FBM or no episode ≥30 sec in 30 min
Gross body movement	At least 3 discrete body/limb movements in 30 min (episodes of active continuous movement considered a single movement)	2 or fewer episodes of body/limb movements in 30 min
Fetal tone	At least 1 episode of active extension with return to flexion of fetal limb(s) or trunk Opening and closing of hand considered evidence of normal tone	Either slow extension with return to partial flexion or movement of limb in full extension or absence of fetal movement with the hand held in complete or partial deflection
Reactive fetal heart rate (FHR)	At least 2 episodes of FHR acceleration of ≥15 beats/min and at least 15 sec in duration associated with fetal movement in 30 min	Less than 2 episodes of acceleration of FHR or acceleration of <15 beats/min in 30 min
Qualitative amniotic fluid (AF) volume*	At least 1 pocket of AF that measures at least 2 cm in 2 perpendicular planes	Either no AF pockets or a pocket <2 cm in 2 perpendicular planes

*Modification of the criteria for reduced amniotic fluid from less than 1 cm to less than 2 cm would seem reasonable. Ultrasound is used for biophysical assessment of the fetus.

From Creasy RK, Resnik R, Iams JD, editors: Maternal-fetal medicine: principles and practice, *ed 5, Philadelphia, 2004, Saunders.*

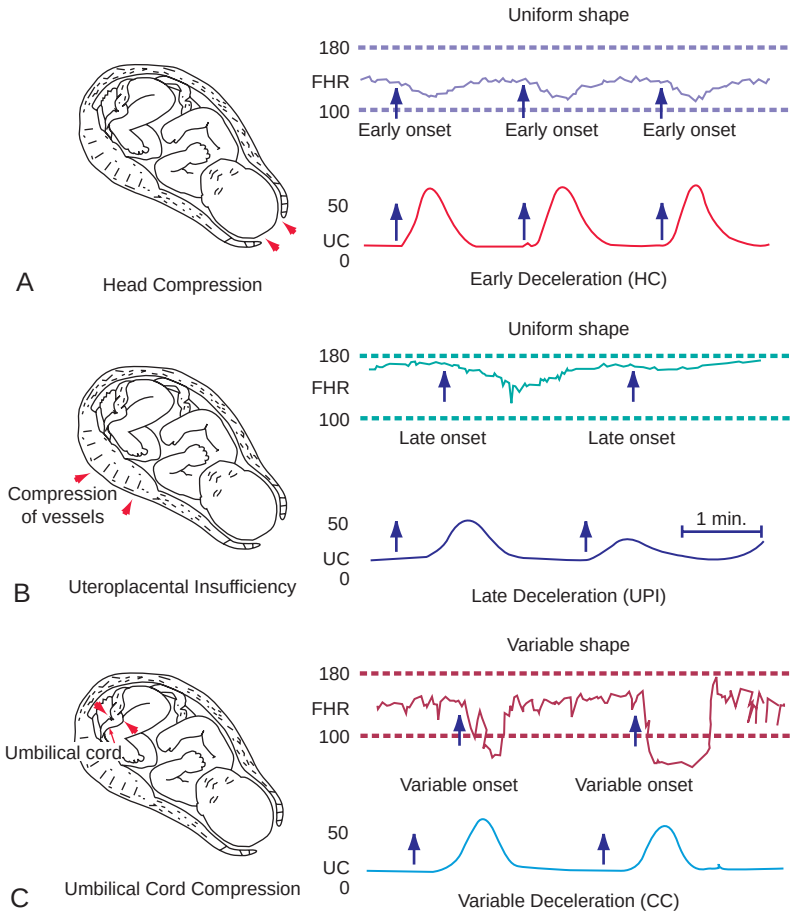

Figure 96-4 Patterns of periodic fetal heart rate deceleration. The tracing in **A** shows early deceleration occurring during the peak of uterine contractions as a result of pressure on the fetal head. **B,** Late deceleration caused by uteroplacental insufficiency. **C,** Variable deceleration as a result of umbilical cold compression. *Arrows* denote the time relationship between the onset of fetal heart rate changes and uterine contractions. *(From Hon EH:* An atlas of fetal heart rate patterns, *New Haven, CT, 1968, Harty Press.)*

(beats/min); **moderate variability** if amplitude range is 6-25 beats/min; **marked variability** if amplitude range is >25 beats/min. Variability may be decreased or lost with fetal hypoxemia or the placental transfer of drugs such as atropine, diazepam, promethazine, magnesium sulfate, and most sedative and narcotic agents. Prematurity, the sleep state, and fetal tachycardia may also diminish beat-to-beat variability.

Periodic accelerations or decelerations of the fetal heart rate in response to uterine contractions may also be monitored (see Fig. 96-4). An **acceleration** is an abrupt increase in fetal heart rate of ≥15 beats/

Table 96-3 Characteristics of Decelerations of the Fetal Heart Rate

LATE DECELERATION
- Visually apparent, usually symmetric *gradual* decrease and return of the fetal heart rate (FHR) associated with a uterine contraction.
- A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the nadir of the FHR.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The deceleration is delayed in timing, with the nadir of the deceleration occurring after the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration occur after the beginning, peak, and ending of the contraction, respectively.

EARLY DECELERATION
- Visually apparent, usually symmetric *gradual* decrease and return of the FHR associated with a uterine contraction.
- A *gradual* FHR decrease is defined as duration of ≥30 sec from the onset to the FHR nadir.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The nadir of the deceleration occurs at the same time as the peak of the contraction.
- In most cases, the onset, nadir, and recovery of the deceleration are coincident with the beginning, peak, and ending of the contraction, respectively.

VARIABLE DECELERATION
- Visually apparent, *abrupt* decrease in FHR.
- An *abrupt* FHR decrease is defined as duration <30 sec from the onset of the deceleration to the beginning of the FHR nadir of the deceleration.
- The decrease in FHR is calculated from the onset to the nadir of the deceleration.
- The decrease in FHR is ≥15 beats/min, lasting ≥15 sec, and <2 min in duration.
- When variable decelerations are associated with uterine contractions, their onset, depth, and duration commonly vary with successive uterine contractions.

From Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, Obstet Gynecol *112:661–666, 2008.*

min in ≥15 sec. The presence of accelerations or moderate variability reliably predicts the absence of fetal metabolic acidemia. However, their absence does not reliably predict fetal acidemia or hypoxemia. **Early deceleration** associated with head compression is a repetitive pattern of gradual decrease and return of the fetal heart rate that is coincidental with the uterine contraction (Table 96-3). **Variable deceleration** (associated with cord compression) is characterized by variable shape, abrupt onset and occurrence with consecutive contractions, and return to baseline at or after the conclusion of the contraction. **Late deceleration,** associated with fetal hypoxemia, occurs repetitively after a uterine contraction is well established and persists into the interval following contractions. The late deceleration pattern is usually associated with maternal hypotension or excessive uterine activity, but it may be a response to any maternal, placental, umbilical cord, or fetal factor that limits effective oxygenation of the fetus. Reflex late decelerations with normal beat-to-beat variability are associated with chronic compensated fetal hypoxia, and they occur during uterine contractions that temporarily impede oxygen transport to the heart. Nonreflex late decelerations are more ominous and indicate severe hypoxic depression of myocardial function. Approximately 10-15% of term fetuses have terminal (just before delivery) fetal heart rate decelerations that are usually benign if they lasted <10 min prior to delivery. Neonates with longer terminal decelerations without recovery (persistent bradycardia) are associated with fetal acidosis and need neonatal ICU observation or treatment.

If late decelerations are unresponsive to oxygen supplementation, hydration, discontinuation of labor stimulation, and position changes, prompt delivery is indicated. A 3-tier system has been developed by a panel of experts for interpretation of fetal heart rate tracings (Table 96-4). **Category I tracings** are normal and are strongly predictive of normal fetal acid–base status at the time of the observation. **Category II tracings** are not predictive of abnormal fetal status, but there is insufficient evidence to categorize them as category I or III; further evaluation, surveillance, and reevaluation are indicated. **Category III tracings** are abnormal and predictive of abnormal fetal acid–base status at the time of observation. Category III tracings require prompt evaluation and efforts to expeditiously resolve the abnormal fetal heart rate as previously discussed for late decelerations.

Fetal scalp blood sampling during labor through a slightly dilated cervix may aid in confirming fetal distress suspected on the basis of variations in fetal heart rate or the presence of meconium in amniotic

Table 96-4 Three-Tier Fetal Heart Rate Interpretation System

CATEGORY I

Category I fetal heart rate (FHR) tracings include all of the following:
- Baseline rate: 110-160 beats per minute (beats/min)
- Baseline FHR variability: moderate
- Late or variable decelerations: absent
- Early decelerations: present or absent
- Accelerations: present or absent

CATEGORY II

Category II FHR tracings include all FHR tracings not categorized as category I or category III. Category II tracings may represent an appreciable fraction of those encountered in clinical care. Examples of category II FHR tracings include any of the following:

Baseline rate
- Bradycardia not accompanied by absence of baseline variability
- Tachycardia

Baseline FHR variability
- Minimal baseline variability
- Absence of baseline variability not accompanied by recurrent decelerations
- Marked baseline variability

Accelerations
- Absence of induced accelerations after fetal stimulation

Periodic or episodic decelerations
- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration, ≥2 min but <10 min
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics, such as slow return to baseline, "overshoots," and "shoulders"

CATEGORY III

Category III FHR tracings include either:
- Absence of baseline FHR variability and any of the following:
- Recurrent late decelerations
- Recurrent variable decelerations
- Bradycardia
- Sinusoidal pattern

From Macones GA, Hankins GDV, Spong CY, et al: The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring: update on definitions, interpretation, and research guidelines, Obstet Gynecol *112:661–666, 2008.*

fluid. The proper use of this technique may result in earlier delivery of depressed infants, who thus have a better chance of successful resuscitation, increased survival, and less morbidity. Alternatively, when continuous fetal heart rate monitoring or general clinical evaluation suggests that a fetus is at risk, a normal fetal scalp blood sample may help avert obstetric intervention.

Fetal scalp blood pH in normal labor decreases from approximately 7.33 early in labor to approximately 7.25 at the time of vaginal delivery; the base deficit is approximately 4-6 mEq/L. Changes in the buffer base may be particularly helpful in assessing fetal status, because they correspond to the accumulation of fetal lactic acid. A pH <7.25 suggests fetal distress, and a pH <7.20 is an indication for further assessment and intervention. Determination of the lactate concentration in fetal scalp blood is another tool for monitoring the condition of the fetus.

Umbilical cord blood samples obtained at the time of delivery are useful to document fetal acid–base status. Although the exact cord blood pH value that defines significant fetal acidemia is unknown, an umbilical artery pH <7.0 has been associated with greater need for resuscitation and a higher incidence of respiratory, gastrointestinal, cardiovascular, and neurologic complications. Nonetheless, in many cases, even when a low pH is detected, newborn infants are neurologically normal.

Intrapartum fetal pulse oximetry is another measure of fetal status. Even though initial data suggested that intrapartum fetal pulse oximetry could help identify fetuses with a nonreassuring status, a large randomized controlled trial showed that intrapartum fetal pulse oximetry does not lead to a reduction in cesarean section rates or improvement in the condition of newborns at birth.

Bibliography is available at Expert Consult.

96.3 Maternal Disease and the Fetus

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INFECTIOUS DISEASES

See Table 95-3.

Almost any maternal infection with severe systemic manifestations may result in miscarriage, stillbirth, or premature labor. Whether these results are a consequence of infection of the fetus or are secondary to maternal illness is not always clear. Maternal hyperthermia may be associated with an increased incidence of congenital anomalies, including neural tube defects (NTDs). Regardless of the severity of the maternal infection, certain agents frequently infect the fetus and have serious sequelae. Fetuses of mothers infected with these agents are often small for gestational age and sometimes microcephalic. Some infections, such as rubella, may also produce congenital malformations if they occur during the period of organogenesis. Intrauterine infection/chorioamnionitis may be an important risk factor for cerebral white matter injury and subsequent cerebral palsy. Infections that affect maternal nutrition (e.g., hookworm) may also result in IUGR.

NONINFECTIOUS DISEASES

See Table 95-2.

Maternal diabetes increases the risk for neonatal hypoglycemia, hypocalcemia, respiratory distress syndrome and other respiratory problems, polycythemia, macrosomia, myocardial dysfunction, jaundice, and congenital malformations (see Chapter 107.1). There is increased risk for incidence of uteroplacental insufficiency, polyhydramnios, and intrauterine death in poorly controlled diabetic mothers. **Eclampsia–preeclampsia** of pregnancy, **chronic hypertension**, and **chronic renal disease** can result in IUGR, prematurity, and intrauterine death, all probably caused by diminished uteroplacental perfusion. Uncontrolled maternal **hypothyroidism** or **hyperthyroidism** is responsible for relative infertility, spontaneous abortion, premature labor, and fetal death. Hypothyroidism in pregnant women (even if mild or asymptomatic) can adversely affect neurodevelopment of the child. Maternal **immunologic diseases** such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, myasthenia gravis, and Graves disease, all of which are mediated by immunoglobulin G autoantibodies that can cross the placenta, frequently cause transient illness in the newborn. Maternal autoantibodies to the folate receptor are associated with NTDs, whereas maternal immunologic sensitization to paternal antigens may be associated with neonatal hemochromatosis. Untreated maternal **phenylketonuria** results in miscarriage, congenital cardiac malformations, and injury to the brain of a nonphenylketonuric heterozygotic fetus.

Bibliography is available at Expert Consult.

96.4 Maternal Medication and Toxin Exposure and the Fetus

Waldemar A. Carlo and Namasivayam Ambalavanan

The use of medications or herbal remedies during pregnancy is potentially harmful to the fetus. Consumption of medications occurs during the majority of pregnancies. The average mother has taken 4 drugs other than vitamins or iron during pregnancy. Almost 40% of pregnant women receive a drug for which human safety during pregnancy has not been established (category C pregnancy risk; see later). Moreover, many women are exposed to potential reproductive toxins, such as occupational, environmental, or household chemicals, including solvents, pesticides, and hair products. The effects of drugs taken by the mother vary considerably, especially in relation to the time in pregnancy when they are taken and the fetal genotype for drug-metabolizing enzymes. Miscarriage or congenital malformations result from the maternal ingestion of teratogenic drugs during the period of organogenesis. Maternal medications taken later, particularly during the last few weeks of gestation or during labor, tend to affect the function of specific organs or enzyme systems, and they adversely affect the neonate rather than the fetus (Tables 96-5 and 96-6).

The effects of drugs may be evident immediately in the delivery room or later in the neonatal period, or they may be delayed even longer. The administration of diethylstilbestrol during pregnancy, for instance, increased the risk for vaginal adenocarcinoma in female offspring in the 2nd or 3rd decade of life.

Evidence has confirmed an interaction between genetic factors and susceptibility to certain drugs or environmental toxins. Phenytoin teratogenesis may be mediated by genetic differences in the enzymatic production of epoxide metabolites; specific genes may influence the adverse effects of benzene exposure during pregnancy. Polymorphisms of genes encoding enzymes that metabolize the polycyclic aromatic hydrocarbons in cigarette smoke influence the growth-restricting effects of smoking on the fetus.

Often the risk of controlling maternal disease must be balanced with the risk of possible complications in the fetus. The majority of women with epilepsy have normal fetuses. Nonetheless, several commonly used antiepileptic drugs are associated with congenital malformations. Infants exposed to valproic acid may have multiple anomalies, including NTDs, hypospadias, facial anomalies, cardiac anomalies, and limb defects. In addition, they have lower developmental index scores than unexposed infants and infants exposed to other commonly used antiepileptic drugs.

Methotrexate is used for medical termination of pregnancy; surviving exposed infants may be at higher risk for congenital anomalies, IUGR, hypotonia, and developmental delay.

Moderate or high alcohol intake (≥7 drinks per week or ≥3 drinks on multiple occasions) is a risk for fetal alcohol syndrome. The exposed fetuses are at risk for growth failure, central nervous system abnormalities, cognitive defects, and behavioral problems. Smoking during pregnancy is associated with IUGR and facial clefts.

In view of the limits of current knowledge about the fetal effects of maternal medication, drugs and herbal agents should not be prescribed

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during pregnancy without weighing of maternal need against the risk of fetal damage. All women should be specifically counseled to abstain from the use of alcohol, tobacco, and illicit drugs during pregnancy.

Bibliography is available at Expert Consult.

96.5 Teratogens

Waldemar A. Carlo and Namasivayam Ambalavanan

When an infant or child has a congenital malformation or is developmentally delayed, the parents often wrongly blame themselves and attribute the child's problems to events that occurred during pregnancy. Because benign infections occur and several nonteratogenic drugs are often taken during many pregnancies, the pediatrician must evaluate the presumed viral infections and the drugs ingested to help parents understand their child's birth defect. The causes of approximately 40% of congenital malformations are unknown. Although only a relatively few agents are recognized to be teratogenic in humans (see Tables 96-5 and 96-6), new agents continue to be identified. Overall, only 10% of anomalies are due to recognizable teratogens (see Chapter 108). The time of exposure is usually during organogenesis at less than 60 days of gestation. Specific agents produce predictable lesions. Some agents have a dose or threshold effect; below the threshold, no alterations in growth, function, or structure occur. Genetic variables such as the presence of specific enzymes may metabolize a benign agent into a more toxic-teratogenic form (e.g., phenytoin conversion to its

Table 96-5 Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn

DRUG	EFFECT ON FETUS
Accutane (isotretinoin)	Facial-ear anomalies, heart disease, CNS anomalies
Alcohol	Congenital cardiac, CNS, limb anomalies; IUGR; developmental delay; attention deficits; autism
Aminopterin	Abortion, malformations
Amphetamines	Congenital heart disease, IUGR, withdrawal
Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists	Oligohydramnios, IUGR, renal failure, Potter-like syndrome
Azathioprine	Abortion
Busulfan (Myleran)	Stunted growth; corneal opacities; cleft palate; hypoplasia of ovaries, thyroid, and parathyroids
Carbamazepine	Spina bifida, possible neurodevelopmental delay
Carbimazole	Scalp defects, choanal atresia, esophageal atresia, developmental delay
Carbon monoxide	Cerebral atrophy, microcephaly, seizures
Chloroquine	Deafness
Chorionic villus sampling	Probably no effect, possibly limb reduction
Cigarette smoking	LBW for gestational age
Cocaine/crack	Microcephaly, LBW, IUGR, behavioral disturbances
Cyclophosphamide	Multiple malformations
Danazol	Virilization
17α-Ethinyl testosterone (Progestoral)	Masculinization of female fetus
Hyperthermia	Spina bifida
Infliximab	Possible increased risk of live vaccine associated disease in infant; neutropenia
Lithium	Ebstein anomaly, macrosomia
Lopinavir-ritonavir	Transient adrenal dysfunction
6-Mercaptopurine	Abortion
Methyl mercury	Minamata disease, microcephaly, deafness, blindness, mental retardation
Methyltestosterone	Masculinization of female fetus
Misoprostol	Arthrogryposis, cranial neuropathies (Möbius syndrome), equinovarus
Mycophenolate mofetil	Craniofacial, limb, cardiovascular, CNS anomalies
Norethindrone	Masculinization of female fetus
Penicillamine	Cutis laxa syndrome
Phenytoin	Congenital anomalies, IUGR, neuroblastoma, bleeding (vitamin K deficiency)
Polychlorinated biphenyls	Skin discoloration—thickening, desquamation, LBW, acne, developmental delay
Prednisone	Oral clefts

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Table 96-5 Agents Acting on Pregnant Women That May Adversely Affect the Structure or Function of the Fetus and Newborn—cont'd

DRUG	EFFECT ON FETUS
Progesterone	Masculinization of female fetus
Quinine	Abortion, thrombocytopenia, deafness
Selective serotonin reuptake inhibitors	Small increased risk of congenital anomalies, persistent pulmonary hypertension of newborn
Statins	IUGR, limb deficiencies, VACTERAL
Stilbestrol (diethylstilbestrol [DES])	Vaginal adenocarcinoma in adolescence
Streptomycin	Deafness
Tetracycline	Retarded skeletal growth, pigmentation of teeth, hypoplasia of enamel, cataract, limb malformations
Thalidomide	Phocomelia, deafness, other malformations
Toluene (solvent abuse)	Craniofacial abnormalities, prematurity, withdrawal symptoms, hypertonia
Topiramate	Cleft lip
Trimethadione and paramethadione	Abortion, multiple malformations, mental retardation
Valproate	CNS (spina bifida), facial and cardiac anomalies, limb defects, impaired neurologic function, autism spectrum disorder
Vitamin D	Supravalvular aortic stenosis, hypercalcemia
Warfarin (Coumadin)	Fetal bleeding and death, hypoplastic nasal structures

CNS, central nervous system; IUGR, intrauterine growth restriction; LBW, low birthweight. VACTERAL, vertebral, anal, cardiac, tracheoesophageal fistula, renal, arterial, limb.

Table 96-6 Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant*

Acebutolol—IUGR, hypotension, bradycardia
Acetazolamide—metabolic acidosis
Amiodarone—bradycardia, hypothyroidism
Anesthetic agents (volatile)—CNS depression
Adrenal corticosteroids—adrenocortical failure (rare)
Ammonium chloride—acidosis (clinically inapparent)
Aspirin—neonatal bleeding, prolonged gestation
Atenolol—IUGR, hypoglycemia
Baclofen—withdrawal
Blue cohosh herbal tea—neonatal heart failure
Bromides—rash, CNS depression, IUGR
Captopril, enalapril—transient anuric renal failure, oligohydramnios
Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of baby)—bradypnea, apnea, bradycardia, convulsions
Cholinergic agents (edrophonium, pyridostigmine)—transient muscle weakness
CNS depressants (narcotics, barbiturates, benzodiazepines) during labor—CNS depression, hypotonia
Cephalothin—positive direct Coombs test reaction
Dexamethasone—periventricular leukomalacia
Fluoxetine and other SSRIs—transient neonatal withdrawal, hypertonicity, minor anomalies, preterm birth, prolonged QT interval
Haloperidol—withdrawal
Hexamethonium bromide—paralytic ileus
Ibuprofen—oligohydramnios, pulmonary hypertension
Imipramine—withdrawal
Indomethacin—oliguria, oligohydramnios, intestinal perforation, pulmonary hypertension
Intravenous fluids during labor (e.g., salt-free solutions)—electrolyte disturbances, hyponatremia, hypoglycemia
Iodide (radioactive)—goiter
Iodides—goiter
Lead—reduced intellectual function
Magnesium sulfate—respiratory depression, meconium plug, hypotonia
Methimazole—goiter, hypothyroidism
Morphine and its derivatives (addiction)—withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)
Naphthalene—hemolytic anemia (in G6PD-deficient infants)
Nitrofurantoin—hemolytic anemia (in G6PD-deficient infants)
Oxytocin—hyperbilirubinemia, hyponatremia
Phenobarbital—bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation
Primaquine—hemolytic anemia (in G6PD-deficient infants)
Propranolol—hypoglycemia, bradycardia, apnea

Continued

Table 96-6 Agents Acting on Pregnant Women That May Adversely Affect the Newborn Infant—cont'd

Propylthiouracil—goiter, hypothyroidism
Pyridoxine—seizures
Reserpine—drowsiness, nasal congestion, poor temperature stability
Sulfonamides—interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolysis with G6PD deficiency
Sulfonylurea agents—refractory hypoglycemia
Sympathomimetic (tocolytic β-agonist) agents—tachycardia
Thiazides—neonatal thrombocytopenia (rare)
Tumor necrosis factor blocking agents—neutropenia
Valproate—developmental delay
Zolpidem (Ambien)—low birthweight

*See also Table 96-5.
CNS, central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; SSRI, selective serotonin reuptake inhibitor.

epoxide). In many circumstances, the same agent and dose may not consistently produce the lesion.

Reduced enzyme activity of the folate methylation pathway, particularly the formation of 5-methyltetrahydrofolate, may be responsible for neural tube or other birth defects. The common thermolabile mutation of 5,10-methylene tetrahydrofolate reductase may be one of the enzymes responsible. Folate supplementation for all pregnant women (by direct fortification of cereal grains, mandatory in the United States), and oral folic acid tablets taken during organogenesis may overcome this genetic enzyme defect, thus reducing the incidence of neural tube and perhaps other birth defects.

The U.S. Food and Drug Administration (FDA) classifies drugs into 5 pregnancy risk categories. **Category A** drugs pose no risk on the basis of evidence from controlled human studies. For **category B** drugs, either no risk has been shown in animal studies but no adequate studies in humans *or* some risk has been shown in animal studies but these results are not confirmed by human studies. For **category C** drugs, either definite risk has been shown in animal studies but no adequate human studies have been performed *or* no data is available from either animal or human studies. **Category D** includes drugs with some risk but with a benefit that may exceed that risk for the treated life-threatening condition, such as streptomycin for tuberculosis. **Category X** is for drugs that are contraindicated in pregnancy on the basis of animal and human evidence and for which the risk exceeds the benefits.

The specific mechanism of action is known or postulated for very few teratogens. Warfarin, an anticoagulant because it is a vitamin K antagonist, prevents the carboxylation of γ- carboxyglutamic acid, which is a component of osteocalcin and other vitamin K–dependent bone proteins. The teratogenic effect of warfarin on developing cartilage, especially nasal cartilage, appears to be avoided if the pregnant woman's anticoagulation treatment is switched from warfarin to heparin for the period between weeks 6 and 12 of gestation. Hypothyroidism in the fetus may be caused by the maternal ingestion of an excessive amount of iodides or propylthiouracil; each interferes with the conversion of inorganic to organic iodides. Phenytoin may be teratogenic because of the accumulation of a metabolite as a result of deficiency of epoxide hydrolase.

Recognition of teratogens offers the opportunity to prevent related birth defects. If a pregnant woman is informed of the potentially harmful effects of alcohol on her unborn infant, she may be motivated to avoid alcohol consumption during pregnancy. A woman with insulin-dependent diabetes mellitus may significantly decrease her risk for having a child with birth defects by achieving good control of her disease before conception.

Bibliography is available at Expert Consult.

96.6 Radiation

Waldemar A. Carlo and Namasivayam Ambalavanan

See also Chapter 718.

Accidental exposure of a pregnant woman to radiation is a common cause for anxiety about whether her fetus will have genetic abnormalities or birth defects. It is unlikely that exposure to diagnostic radiation will cause gene mutations; no increase in genetic abnormalities has been identified in the offspring exposed as unborn fetuses to the atomic bomb explosions in Japan in 1945.

A more realistic concern is whether the exposed human fetus will show birth defects or a higher incidence of malignancy. The estimated radiation dose for most radiographs is less than 0.1 rad, and for most CT scans it is less than 5 rad. Imaging studies with high radiation exposure (such as CT scans) can be modified to ensure that radiation doses are kept as low as possible. Thus, single diagnostic studies do not result in radiation doses high enough to affect the embryo or fetus. Therapeutic abortion should not be recommended, given the low likelihood for high radiation exposure. Most of the evidence suggests that usual fetal radiation exposure does not increase the risk of childhood leukemia and other cancers. The limited data on human fetuses show that large doses of radiation (20-50 rad) may cause fetal death (the most sensitive period is the 3rd and 4th postconception wk) as well as microcephaly, severe mental retardation, and growth retardation (the most sensitive period is 4th to 15th wk). The available data suggest no harmful fetal effect of diagnostic MRI or ultrasonography.

Bibliography is available at Expert Consult.

96.7 Intrauterine Diagnosis of Fetal Disease

Waldemar A. Carlo and Namasivayam Ambalavanan

See Table 96-1 and Chapter 96.2.

Diagnostic procedures are used to identify fetal diseases when abortion is being considered, when direct fetal treatment is possible, or when a decision is made to deliver a viable but premature infant to avoid intrauterine fetal demise. Fetal assessment is also indicated in a broader context when the family, medical, or reproductive history of the mother suggests the presence of a high-risk pregnancy or a high-risk fetus (see Chapters 95 and 96.3).

Various methods are used for identifying fetal disease (see Table 96-1). Fetal ultrasonographic imaging may detect fetal growth abnormalities (by biometric measurements of biparietal diameter, femoral length, or head or abdominal circumference) or fetal malformations (Fig. 96-5). Although 89% of fetuses whose biparietal diameter is 9.5 cm or more are at least in the 37th wk of gestation, the lungs of these fetuses may not be mature. Serial determinations of growth velocity and the head-to-abdomen circumference ratio enhance the ability to detect IUGR. Real-time ultrasonography may identify placental abnormalities (abruptio placentae, placenta previa) and fetal anomalies such as hydrocephalus, NTDs, duodenal atresia, diaphragmatic hernia, renal agenesis, bladder outlet obstruction, congenital heart disease, limb abnormalities, sacrococcygeal teratoma, cystic hygroma, omphalocele, gastroschisis, and hydrops (Table 96-7).

Real-time ultrasonography also facilitates performance of cordocentesis and the BPP by imaging fetal breathing, body movements, tone, and amniotic fluid volume (see Table 96-2). Doppler velocimetry

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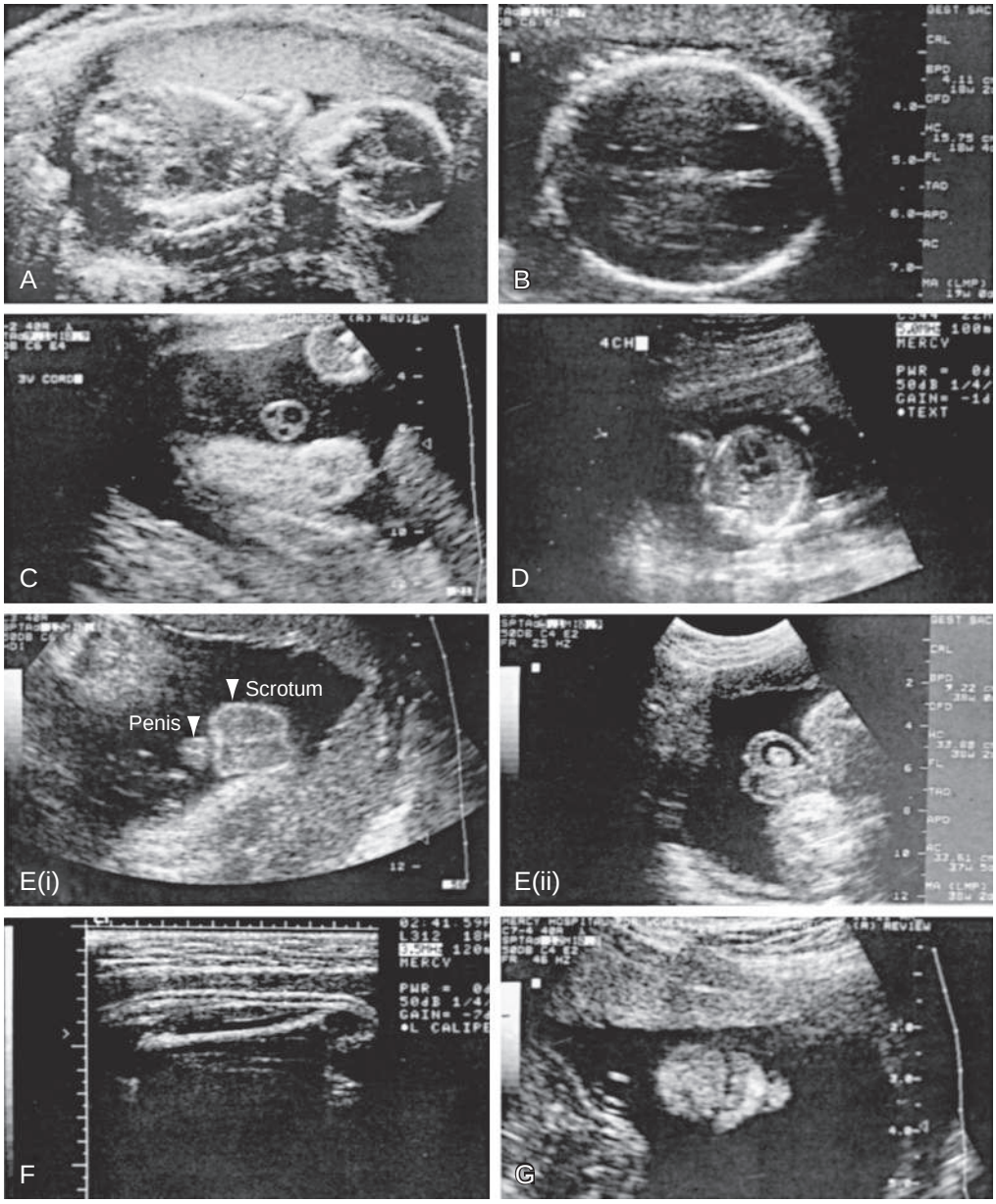

Figure 96-5 Assessment of fetal anatomy. **A,** Overall view of the uterus at 24 wk showing a longitudinal section of the fetus and an anterior placenta. **B,** Transverse section at the level of the lateral ventricle at 18 wk showing (*on the right*) prominent anterior horns of the lateral ventricles on either side of the midline echo of the falx. **C,** Cross-section of the umbilical cord showing that the lumen of the umbilical vein is much wider than that of the 2 umbilical arteries. **D,** Four-chambered view of the heart at 18 wk with equal-sized atria. **E(i),** Normal male genitals near term. **E(ii),** Hydrocele outlining a testicle within the scrotum projecting into a normal-size pocket of amniotic fluid at 38 wk. Approximately 2% of male infants after birth have clinical evidence of a hydrocele that is often bilateral, not to be confused with subcutaneous edema occurring during vaginal breech birth. **F,** Section of a thigh near term showing thick subcutaneous tissue (4.6 mm between markers) above the femur of a fetus with macrosomia. **G,** Fetal face viewed from below, showing (*from right to left*) the nose, alveolar margin, and chin at 20 wk. *(From Special investigative procedures. In Beischer NA, Mackay EV, Colditz PB, editors:* Obstetrics and the newborn, *ed 3, Philadelphia, 1997, WB Saunders.)*

assesses fetal arterial blood flow (vascular resistance) (see Figs. 96-2 and 96-3). Radiographic examination of the fetus has been replaced by real-time ultrasonography, MRI, and fetoscopy.

Amniocentesis, the transabdominal withdrawal of amniotic fluid during pregnancy for diagnostic purposes (see Table 96-1), is frequently performed to determine the timing of delivery of fetuses with erythroblastosis fetalis or the need for fetal transfusion. It is also done for genetic indications, usually between the 15th and 16th wk of gestation, with results available within 1-2 wk. The most common indication for genetic amniocentesis is advanced maternal age (the risk for chromosome abnormality at age 21 yr is 1:526, vs. 1:8 at age 49 yr). The amniotic fluid may be directly analyzed for amino acids, enzymes, hormones, and abnormal metabolic products, and amniotic fluid cells may be cultivated to permit detailed cytologic analysis for prenatal detection of chromosomal abnormalities and DNA-gene or enzymatic analysis for the detection of inborn metabolic errors. Analysis of amniotic fluid may also help in identifying NTDs (elevation of α-fetoprotein), adrenogenital syndrome (elevation of 17-ketosteroids and pregnanetriol), and thyroid dysfunction. Chorionic villus biopsy (transvaginal or transabdominal) performed in the 1st trimester also provides fetal cells but may pose a slightly increased risk for fetal loss and limb reduction defects. Fetal DNA in maternal plasma and fetal cells circulating in maternal blood are potential noninvasive sources of material for prenatal diagnosis. This technology may eliminate the need for amniocentesis or chorionic villus sampling.

Table 96-7 Significance of Fetal Ultrasonographic Anatomic Findings

PRENATAL OBSERVATION	DEFINITION	DIFFERENTIAL DIAGNOSIS	SIGNIFICANCE	POSTNATAL EVALUATION
Dilated cerebral ventricles	Ventriculomegaly ≥10 mm	Hydrocephalus Hydranencephalous Dandy-Walker cyst Agenesis of corpus callosum	Transient isolated ventriculomegaly is common and usually benign Persistent or progressive ventriculomegaly more worrisome Identify associated cranial and extracranial anomalies Bilateral ventriculomegaly increases risk of developmental delay Unilateral ventriculomegaly may be normal variant	Serial head US or CT Evaluate for extracranial anomalies
Choroid plexus cysts	Size ~10 mm: unilateral or bilateral 1-3% incidence	Abnormal karyotype (trisomy 18, 21) Aneuploidy risk 1:100 if isolated. ↑ Risk (1:3) with other anomalies. Risk ↑ if large, complex, or bilateral cysts or advanced maternal age	Often isolated, benign; resolves by 24-28 wk Fetus should be examined for other organ anomalies; then amniocentesis should be performed for karyotype	Head US or CT Examine for extracranial anomalies; karyotype if indicated
Nuchal pad thickening	≥6 mm at 15-20 wk	Cystic hygroma trisomy 21, 18 Turner syndrome (XO) Nonchromosomal syndromes Normal (~25%)	≈50% of affected fetuses have chromosome abnormalities Amniocentesis for karyotype needed	Evaluate for multiple organ malformations; karyotype if indicated
Dilated renal pelvis	Pyelectasis ≥5 to 10 mm 0.6-1% incidence	Uteropelvic junction obstruction Vesicoureteral reflux Posterior ureteral valves Entopic ureterocele Large-volume nonobstruction	Often "physiologic" and transient Reflux is common If dilation is >10 mm or associated with caliectasis, pathologic cause should be considered If large bladder present, posterior urethral valves and megacystics-megaduodenum syndrome should be considered	Repeat ultrasonography on day 5 and at 1 mo; voiding cystourethrogram, prophylactic antibiotics
Echogenic bowel	0.6% incidence	CF, meconium peritonitis, trisomy 21 or 18, other chromosomal abnormalities cytomegalovirus, toxoplasmosis, GI obstruction	Often normal (65%) 10% of affected fetuses have CF; 1.5% have aneuploidy	Sweat chloride and DNA testing Karyotype Surgery for obstruction Evaluation for TORCH (toxoplasmosis, other agents, rubella, CMV, herpes simplex) syndrome
Stomach appearance	Small or absent or with double bubble	Upper GI obstruction (esophageal atresia) Double bubble signifies duodenal atresia Abnormal karyotype Polyhydramnios Stomach in chest signifies diaphragmatic hernia	Must also consider neurologic disorders that reduce swallowing Over 30% with double bubble have trisomy 21	Chromosomes, kidney, ureter, and bladder radiograph if indicated, upper GI series, neurologic evaluation

CF, cystic fibrosis; CMV, cytomegalovirus; GI, gastrointestinal; US, ultrasound.

The best available chemical indices of fetal maturity are provided by determination of amniotic fluid creatinine and lecithin levels, which reflect the maturity of the fetal kidneys and lungs, respectively. Lecithin is produced in the lungs by type II alveolar cells and eventually reaches the amniotic fluid via the effluent from the trachea. Until the middle of the 3rd trimester, its concentration nearly equals that of sphingomyelin; thereafter, the sphingomyelin concentration remains constant in amniotic fluid while the lecithin concentration increases. By 35 wk, the lecithin:sphingomyelin (L:S) ratio averages about 2:1, indicative of lung maturity.

Earlier lung maturation may occur in the presence of severe premature separation of the placenta, premature rupture of the fetal membranes, narcotic addiction, or maternal hypertensive and renal vascular disease. A delay in pulmonary maturation may be associated with hydrops fetalis or maternal diabetes without vascular disease. The likelihood of hyaline membrane disease is greatly reduced with L:S ratios of 2:1 or more, although hypoxia, acidosis, and hypothermia may increase the risk despite this "mature" L:S ratio. Maternal and fetal blood have an L:S ratio of about 1:4; thus, contamination will not alter the significance of a ratio of 2:1 or more. Meconium contamination,

sample storage, and sample centrifugation may reduce the reliability of the L:S ratio.

Saturated phosphatidylcholine or phosphatidylglycerol concentrations in amniotic fluid may be more specific and sensitive predictors of pulmonary maturity, especially in high-risk pregnancies such as those occurring in women with diabetes (see Chapters 95 and 107.1).

Amniocentesis can be carried out with little discomfort to the mother, but even in experienced hands, the procedure entails some small risk, such as direct damage to the fetus, placental puncture and bleeding with secondary damage to the fetus, stimulation of uterine contraction and premature labor, amnionitis, and maternal sensitization to fetal blood. The earlier in gestation that amniotic puncture is done, the greater the risk to the fetus. Using ultrasound for placental and fetal localization can reduce the risk of complications. The procedure should be limited to cases in which the potential benefits of the findings will outweigh the risk.

Cordocentesis, or percutaneous umbilical blood sampling, is used to diagnose fetal hematologic abnormalities, genetic disorders, infections, and fetal acidosis (see Table 96-1). Under direct ultrasonographic visualization, a long needle is passed into the umbilical vein at its entrance to the placenta or fetal abdominal wall. Umbilical blood may be withdrawn to determine fetal hemoglobin, platelet concentration, lymphocyte DNA, the presence of infection, or Pa_{O_2}, pH, P_{CO_2}, and lactate levels.

Transfusion or administration of drugs can be performed through the umbilical vein (Table 96-8). Serum screening is offered to pregnant women at midgestation to evaluate the risk for Down syndrome (trisomy 21) and congenital malformations known to cause elevations of various markers, including abdominal wall and NTDs. A combination of these biochemical markers (including α-fetoprotein, inhibin A, estriol, pregnancy-associated plasma protein A, and β-HCG [human chorionic gonadotropin]) and ultrasound increases the positive

Table 96-8 Fetal Therapy

DISORDER	POSSIBLE TREATMENT
HEMATOLOGIC	
Anemia with hydrops (erythroblastosis fetalis)	Umbilical vein packed red blood cell transfusion
Thalassemia	Fetal stem cell transplantation
Isoimmune thrombocytopenia	Umbilical vein platelet transfusion, maternal IVIG
Autoimmune thrombocytopenia (ITP)	Maternal steroids and IVIG
Chronic granulomatous disease	Fetal stem cell transplantation
METABOLIC-ENDOCRINE	
Maternal phenylketonuria (PKU)	Phenylalanine restriction
Fetal galactosemia	Galactose-free diet (?)
Multiple carboxylase deficiency	Biotin if responsive
Methylmalonic acidemia	Vitamin B_{12} if responsive
21-Hydroxylase deficiency	Dexamethasone
Maternal diabetes mellitus	Tight insulin control during pregnancy, labor, and delivery
Fetal goiter	Maternal hyperthyroidism—maternal propylthiouracil Fetal hypothyroidism—intra-amniotic thyroxine
Bartter syndrome	Maternal indomethacin may prevent nephrocalcinosis and postnatal sodium losses
Neonatal iron storage disease (alloimmune)	Maternal IVIG
FETAL DISTRESS	
Hypoxia	Maternal oxygen, position
Intrauterine growth restriction	Maternal oxygen, position, improve macronutrients and micronutrients if deficient
Oligohydramnios, premature rupture of membranes with variable deceleration	Amnioinfusion (antepartum and intrapartum)
Polyhydramnios	Amnioreduction (serial), indomethacin (if from increased urine output) if indicated
Supraventricular tachycardia	Maternal digoxin,* flecainide, procainamide, amiodarone, quinidine
Lupus anticoagulant	Maternal aspirin, prednisone
Meconium-stained fluid	Amnioinfusion
Congenital heart block	Dexamethasone, pacemaker (with hydrops)
Premature labor	Magnesium sulfate, antibiotics sympathomimetics, indomethacin
RESPIRATORY	
Pulmonary immaturity	Betamethasone
Bilateral chylothorax—pleural effusions	Thoracentesis, pleuroamniotic shunt
CONGENITAL ABNORMALITIES†	
Neural tube defects	Folate, vitamins (prevention); fetal surgery‡
Posterior urethral valves, urethral atresia (lower urinary tract obstruction)	Percutaneous vesicoamniotic shunt
Cystic adenomatoid malformation (with hydrops)	Pleuroamniotic shunt or resection‡
Fetal neck masses	Secure an airway with EXIT procedure‡
INFECTIOUS DISEASE	
Group B streptococcus colonization	Ampicillin, penicillin
Chorioamnionitis	Antibiotics
Toxoplasmosis	Spiramycin, pyrimethamine, sulfadiazine, and folic acid
Syphilis	Penicillin
Tuberculosis	Antituberculosis drugs
Lyme disease	Penicillin, ceftriaxone
Parvovirus	Intrauterine red blood cell transfusion for hydrops, severe anemia
Chlamydia trachomatis	Erythromycin
HIV-AIDS	Maternal and neonatal antiretroviral therapy (see Chapter 276)
Cytomegalovirus	Ganciclovir by umbilical vein

Continued

Table 96-8 Fetal Therapy

DISORDER	POSSIBLE TREATMENT
OTHER	
Nonimmune hydrops (anemia)	Umbilical vein packed red blood cell transfusion
Narcotic abstinence (withdrawal)	Maternal low-dose methadone
Severe combined immunodeficiency disease	Fetal stem cell transplantation
Sacrococcygeal teratoma (with hydrops)	In utero resection or catheter directed vessel obliteration
Twin-twin transfusion syndrome	Repeated amniocentesis, yttrium-aluminum-garnet (YAG) laser photocoagulation of shared vessels
Twin reversed arterial perfusion (TRAP) syndrome	Digoxin, indomethacin, cord occlusion
Multifetal gestation	Selective reduction
Neonatal hemochromatosis	Maternal IVIG

*Drug of choice (may require percutaneous umbilical cord sampling and umbilical vein administration if hydrops is present). Most drug therapy is given to the mother, with subsequent placental passage to the fetus.

†Detailed fetal ultrasonography is needed to detect other anomalies; karyotype is also indicated.

‡EXIT permits surgery and other procedures.

EXIT, ex utero intrapartum treatment; IVIG, intravenous immunoglobulin; (?), possible but not proved efficacy.

predictive value of these screening tests. Nonetheless fetal karyotyping by analysis of fetal DNA in maternal plasma is another accurate method to diagnose trisomy 21. Additionally, families with a known genetic syndrome may be offered prenatal genetic testing from amniotic fluid or amniocytes obtained via amniocentesis or chorionic villus sampling.

Bibliography is available at Expert Consult.

96.8 Treatment and Prevention of Fetal Disease

Waldemar A. Carlo and Namasivayam Ambalavanan

Management of a fetal disease depends on coordinated advances in diagnostic accuracy and knowledge of the disease's natural history; an understanding of fetal nutrition, pharmacology, immunology, and pathophysiology; the availability of specific active drugs that cross the placenta; and therapeutic procedures. Progress in providing specific treatments for accurately diagnosed diseases has improved with the advent of real-time ultrasonography and cordocentesis (see Tables 96-1 and 96-8).

The incidence of sensitization of Rh-negative women by Rh-positive fetuses has been reduced by prophylactic administration of Rh(D) immunoglobulin to mothers early in pregnancy and after each delivery or abortion, thus reducing the frequency of hemolytic disease in their subsequent offspring. Fetal erythroblastosis (see Chapter 103.2) may be accurately diagnosed by amniotic fluid analysis and treated with intrauterine intraperitoneal or, more often, intraumbilical vein transfusions of packed Rh-negative blood cells to maintain the fetus until it is mature enough to have a reasonable chance of survival.

Fetal hypoxia or distress may be diagnosed with moderate success. Treatment, however, remains limited to supplying the mother with high concentrations of oxygen, positioning the uterus to avoid vascular compression, and initiating operative delivery before severe fetal injury occurs.

Pharmacologic approaches to fetal immaturity (e.g., administration of steroids to the mother to accelerate fetal lung maturation and decrease the incidence of respiratory distress syndrome [Chapter 101.3] in prematurely delivered infants) are successful. Inhibiting labor with tocolytic agents is unfortunately not successful in most patients with premature labor. Management of definitively diagnosed fetal genetic disease or congenital anomalies consists of parental counseling or abortion; rarely, high-dose vitamin therapy for a responsive inborn error of metabolism (biotin-dependent disorders) or fetal transfusion (with red blood cells or platelets) may be indicated. Fetal surgery (see Table 96-8) remains an a largely experimental approach to therapy and is available only in a few highly specialized perinatal centers. The nature of the defect and its consequences, as well as ethical implications for the fetus and the parents, must be considered. In a randomized controlled trial, fetal surgery for myelomeningocele improved neurological function (mental and motor development) and decreased the need for shunts by 50% but increased the prematurity rate.

Folic acid supplementation decreases the incidence and recurrence of (NTDs). Because the neural tube closes within the 1st 28 days of conception, periconceptional supplementation is needed for prevention. It is recommended that women without a prior history of a NTD ingest 400 μg/day of folic acid throughout their reproductive years. Women with a history of a prior pregnancy complicated by an NTD or a 1st-degree relative with an NTD should have preconceptional counseling and should ingest 4 mg/day of supplemental folic acid beginning at least 1 mo before conception. Fortification of cereal grain flour with folic acid is established policy in the United States and some other countries. The optimal concentration of folic acid in enriched grains is somewhat controversial. The incidence of NTD in the United States and other countries has decreased significantly since these public health initiatives were implemented. Use of some antiepileptic drugs (valproate, carbamazepine) during pregnancy is associated with an increased risk of NTD. Women taking these medications should ingest 1-5 mg of folic acid/day in the preconception period.

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Chapter 97

The High-Risk Infant

Waldemar A. Carlo

Neonates at risk should be identified as early as possible prenatally or after birth to decrease neonatal morbidity and mortality (see Chapter 93). The term *high-risk infant* designates an infant who should be under close observation by experienced physicians and nurses. Table 97-1 lists the factors that define infants as being high risk. Approximately 10-20% of all births require special or neonatal intensive care. Usually needed for only a few days, such care may last from a few hours to several months. In some institutions, initial care for high-risk infants is provided in a special or transitional care nursery, often within the labor and delivery suite. This facility should be equipped and staffed like a neonatal intensive care area.

Examination of the fresh **placenta**, **cord**, and **membranes** may alert the physician to a newborn infant at high risk and may help confirm a diagnosis in a sick infant. **Fetal blood loss** may be indicated by

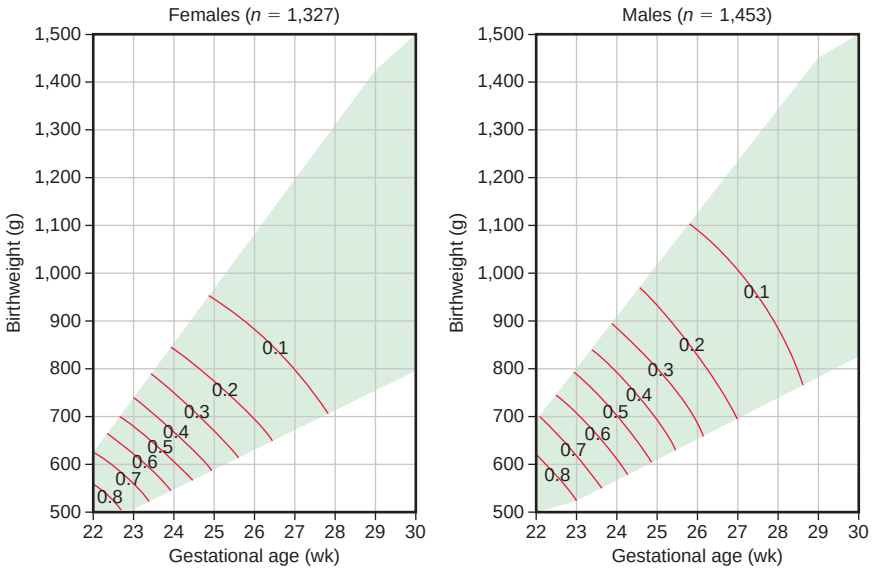

Figure 97-1 Estimated mortality risk by birthweight and gestational age based on singleton infants in National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers between January 1, 1995, and December 31, 1996. *(From Lemons JA, Bauer CR, Oh W, et al: Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996,* Pediatrics *107:E1, 2001; available at* www.pediatrics.org.cgi/content/full/107/1/el.*)*

Table 97-1 Factors That Define an Infant as Being High Risk

DEMOGRAPHIC SOCIAL FACTORS Maternal age <16 or >40 yr Illicit drug, alcohol, cigarette use Poverty Unmarried Emotional or physical stress	Multiple gestation Preeclampsia Premature rupture of membranes Short interpregnancy time Poly-/oligohydramnios Acute medical or surgical illness Inadequate prenatal care Familial or acquired hypercoagulable states Abnormal fetal ultrasonographic findings Treatment of infertility
PAST MEDICAL HISTORY Genetic disorders Diabetes mellitus Hypertension Asymptomatic bacteriuria Rheumatologic illness (systemic lupus erythematosus) Immune-mediated diseases (immunoglobulin G crossing placenta) Long-term medication (see Tables 96-5 and 96-6 in Chapter 96)	LABOR AND DELIVERY Premature labor (<37 wk) Postdates pregnancy (≥42 wk) Fetal distress Immature lethicin:sphingomyelin ratio; absence of phosphatidylglycerol Breech presentation Meconium-stained fluid Nuchal cord Cesarean section Forceps delivery Apgar score <4 at 1 min
PREVIOUS PREGNANCY Intrauterine fetal demise Neonatal death Prematurity Intrauterine growth restriction Congenital malformation Incompetent cervix Blood group sensitization, neonatal jaundice Neonatal thrombocytopenia Hydrops Inborn errors of metabolism	NEONATE Birthweight <2,500 or >4,000 g Birth <37 or ≥42 wk of gestation Small or large for gestational age Respiratory distress, cyanosis Congenital malformation Pallor, plethora, petechiae
PRESENT PREGNANCY Vaginal bleeding (abruptio placentae, placenta previa) Sexually transmitted infections (colonization: herpes simplex, group B streptococcus, chlamydia, syphilis, hepatitis B, HIV)	

placental pallor, retroplacental hematoma, and tears in the velamentous cords or chorionic blood vessels supplying the succenturiate lobes. Placental edema and secondary possible immunoglobulin G deficiency in a newborn may be associated with fetofetal transfusion syndrome, hydrops fetalis, congenital nephrosis, or hepatic disease. **Amnion nodosum** (granules on the amnion) and **oligohydramnios** are associated with pulmonary hypoplasia and renal agenesis, whereas small whitish nodules on the cord suggest a candidal infection. Short cords and noncoiled cords occur with chromosome abnormalities and omphalocele. True umbilical cord knots are seen in approximately 1% of births and are associated with a long cord, small fetal size, polyhydramnios, monoamniotic twinning, fetal demise, and low Apgar scores.

Chorioangiomas are associated with prematurity, abruptio placentae, polyhydramnios, and intrauterine growth restriction (IUGR). **Meconium staining** suggests in utero stress, and opacity of the fetal surface of the placenta suggests infection. Single umbilical arteries are associated with an increased incidence of congenital renal abnormalities and syndromes.

For many infants who are born prematurely, are small for gestational age (SGA), have significant perinatal asphyxia, are breech, or are born with life-threatening congenital anomalies, there are no previously identified risk factors. For any given duration of gestation, the lower the birthweight, the higher the neonatal mortality; for any given birthweight, the shorter the gestational duration, the higher the neonatal mortality (Fig. 97-1). The highest risk of neonatal and infant mortality occurs in infants who weigh <1,000 g at birth and whose gestation was <28 wk. The lowest risk of neonatal mortality occurs in infants with a birthweight of 3,000-4,000 g and a gestational age of 39-41 wk. As

birthweight increases from 400 to 3,000 g and gestational age increases from 23 to 39 wk, a logarithmic decrease in neonatal mortality occurs. In the United States, approximately 50% of all infant deaths occur in infants born after less than 27 wk of gestation or infants weighing less than 1,000 g. Neonatal mortality rates rise sharply for infants weighing more than 4,000 g at birth and for those whose gestational period is 42 wk or longer. Because neonatal mortality largely depends on birthweight and gestational age, Figure 97-1 can be used to help identify high-risk infants quickly. This analysis is based on total live births and therefore describes the mortality risk only at birth. Because most neonatal mortality occurs within the 1st hours and days after birth, the outlook improves dramatically with increasing postnatal survival. Prediction of death as well as neurodevelopmental impairment improves after birth and continues to improve over the first days and weeks after birth. The importance of gestational age, birth weight, and other perinatal factors for prediction of outcomes decline whereas the importance of respiratory illnesses and other morbidities increase.

97.1 Multiple-Gestation Pregnancies

Waldemar A. Carlo

INCIDENCE

The incidence of spontaneous twinning is highest among blacks and East Indians, followed by northern European whites, and is lowest in the Asian races. Specific rates are 1/56 in Belgium, 1/70 among American blacks, 1/86 in Italy, 1/88 among American whites, 1/130 in Greece, 1/150 in Japan, and 1/300 in China. Differences in the incidence of twins mainly involve fraternal (polyovular) dizygotic twins. Triplets are estimated to occur in 1 in 86^2 pregnancies and quadruplets in 1 in 86^3 pregnancies in the United States. The incidence of monozygotic twins (3-5/1,000) is unaffected by racial or familial factors. The incidence of twins detected by ultrasonography at 12 wk of gestation (3-5%) is much higher than that occurring later in pregnancy; the **vanishing twin syndrome** results in a singleton fetus. Although the incidence of spontaneous multifetal gestation has been stable over the years, the overall incidence of multifetal gestation is increasing as a result of treatment of infertility with ovarian stimulants (clomiphene, gonadotropins) and in vitro fertilization. Twins account for about 2.5% of births but approximately 15% of extremely low birthweight (ELBW, ≤1,000 g) infants.

ETIOLOGY

The occurrence of monovular twins appears to be independent of genetic influence. Polyovular pregnancies are more frequent beyond the second pregnancy, in older women, and in families with a history of polyovular twins. They may result from simultaneous maturation of multiple ovarian follicles, but follicles containing 2 ova have been described as a genetic trait leading to twin pregnancies. Twin-prone women have higher levels of gonadotropin. Polyovular pregnancies occur in many women treated for infertility.

Conjoined twins (Siamese twins—incidence 1/50,000) result from relatively late monovular separation. The prognosis for conjoined twins depends on the possibility of surgical separation, which, in turn, depends on the extent to which vital organs are shared. The site of connections varies: thoracoomphalopagus (28% of conjoined twins), thoracopagus (18%), omphalopagus (10%), craniopagus (6%), and incomplete duplication (10%). Difficult-to-separate conjoined twins have occasionally survived to adulthood. Most conjoined twins are female.

Superfecundation, or fertilization of an ovum by an insemination that takes place after 1 ovum has already been fertilized, and **superfetation,** or fertilization and subsequent development of an embryo when a fetus is already present in the uterus, have been proposed as uncommon explanations for differences in size and appearance of certain twins at birth.

A prenatal diagnosis of pregnancy with twins is suggested by a uterine size that is greater than that expected for gestational age, auscultation of 2 fetal hearts, and elevated maternal serum α-fetoprotein or human chorionic gonadotropin levels, and it is confirmed by ultrasonography.

MONOZYGOTIC VERSUS DIZYGOTIC TWINS

Identifying twins as monozygotic or dizygotic (monovular or polyovular) is useful in determining the relative influence of heredity and environment on human development and disease. Twins not of the same sex are dizygotic. In twins of the same sex, zygosity should be determined and recorded at birth through careful examination of the placenta. Detailed blood typing, gene analysis, or tissue (human leukocyte antigen) typing can also be used to determine zygosity. Monozygotic twins may have physical and cognitive differences because their in utero environment may have been different; differences may exist in the mitochondrial genome, in posttranslational gene product modification, and in the epigenetic modification of nuclear genes in response to environmental factors.

Examination of the Placenta

If the placentas are separate, they are always dichorionic (present in 75%), but the twins are not necessarily dizygotic, because initiation of monovular twinning at the first cell division or during the morula stage may result in 2 amnions, 2 chorions, and even 2 placentas. One-third of monozygotic twins are dichorionic and diamnionic.

An apparently single placenta may be present with either monovular or polyovular twins; yet inspection of a polyovular placenta usually reveals that each twin has a separate chorion that crosses the placenta between the attachments of the cords and two amnions. Separate or fused dichorionic placentas may be disproportionate in size. The fetus attached to the smaller placenta or the smaller portion of the placenta is usually smaller than its twin or is malformed. **Monochorionic twins** are usually diamnionic, and almost invariably, the placenta is a single mass.

Problems of twin gestation include polyhydramnios, hyperemesis gravidarum, preeclampsia, premature rupture of membranes, vasa previa, velamentous insertion of the umbilical cord, abnormal presentations (breech), and premature labor. **Monoamniotic twins** have a high fatality rate owing to obstruction of the circulation secondary to intertwining of the umbilical cords. Twins of widely discrepant size are usually monochorionic.

When compared with the first-born twin, the second twin is at increased risk for respiratory distress syndrome and asphyxia. Twins are at risk for IUGR, twin–twin transfusion, and congenital anomalies, which occur predominantly in monozygotic twins. Anomalies are a result of compression deformation of the uterus from crowding (hip dislocation), vascular communication with embolization (ileal atresia, porencephaly, cutis aplasia) or without embolization (acardiac twin), and unknown factors that cause twinning (conjoined twins, anencephaly, meningomyelocele).

Placental vascular anastomoses occur with high frequency only in monochorionic twins. In monochorionic placentas, the fetal vasculature is usually joined, sometimes in a very complex manner. The vascular anastomoses in monochorionic placentas may be artery to artery, vein to vein, or artery to vein. They are usually balanced so that neither twin suffers. Artery-to-artery communications cross over placental veins, and when anastomoses are present, blood can readily be stroked from one fetal vascular bed to the other. Vein-to-vein communications are similarly recognized but are less common. A combination of artery-to-artery and vein-to-vein anastomoses is associated with the condition of **acardiac fetus.** This rare lethal anomaly (1/35,000) is secondary to the **TRAP** (twin reversed arterial perfusion) **syndrome**. In utero neodynium:yttrium-aluminum-garnet (Nd:YAG) laser ablation of the anastomosis or cord occlusion can be used to treat heart failure in the surviving twin. In rare cases, 1 umbilical cord may arise from the other after leaving the placenta. In such cases, the twin attached to the secondary cord usually is malformed or dies in utero.

In the **fetal transfusion syndrome,** an artery from 1 twin acutely or chronically delivers blood that is drained into the vein of the other. The

Table 97-2 Characteristic Changes in Monochorionic Twins with Uncompensated Placental Arteriovenous Shunts

TWIN ON	
Arterial Side—Donor	**Venous Side—Recipient**
Prematurity	Prematurity
Oligohydramnios	Polyhydramnios
Small premature	Hydrops
Malnourished	Large premature
Pale	Well nourished
Anemic	Plethoric
Hypovolemia	Polycythemic
Hypoglycemia	Hypervolemic
Microcardia	Cardiac hypertrophy
Glomeruli small or normal	Myocardial dysfunction
Arterioles thin walled	Tricuspid valve regurgitation Right ventricular outflow obstruction Glomeruli large Arterioles thick walled

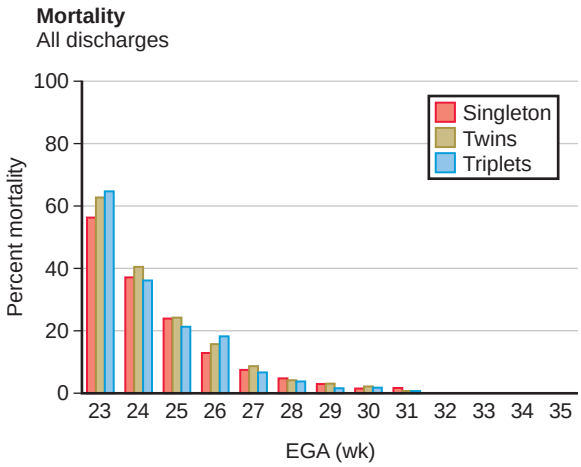

Figure 97-2 Mortality, all discharges. The neonatal mortality rate for all babies who died during the original hospitalization at each week of gestational age is given. The *bars on the left* represent singletons; the *middle bars* represent twins, and the *bars on the right* represent triplets. There are no differences among singleton births, twin births, and triplet births. EGA, estimated gestational age. *(From Garite TJ, Clark RH, Elliott JP, et al: Twins and triplets: the effect of plurality and growth on neonatal outcome compared with singleton infants,* Am J Obstet Gynecol *191:700–707, 2004.)*

latter becomes plethoric and large, and the former is anemic and small. Generally, with chronicity, 5 g/dL hemoglobin and 20% body weight differences can be noted in this syndrome. Maternal hydramnios in a twin pregnancy suggests fetal transfusion syndrome. Anticipating this possibility by preparing to transfuse the donor twin or bleed the recipient twin may be lifesaving. Death of the donor twin in utero may result in generalized fibrin thrombi in the smaller arterioles of the recipient twin, possibly as the result of transfusion of thromboplastin-rich blood from the macerating donor fetus. Disseminated intravascular coagulation may develop in the surviving twin. Table 97-2 lists the more frequent changes associated with a large uncompensated arteriovenous shunt from the placenta of 1 twin to that of the other. Treatment of this highly lethal problem includes maternal digoxin, aggressive amnioreduction for polyhydramnios, selective twin termination, and Nd:YAG laser or fetoscopic ablation of the anastomosis.

Postnatal Identification

The following physical criteria can be used to determine whether twins are monovular: (1) both must be of the same sex; (2) their features, including ears and teeth, must be obviously alike (but they need not resemble each other more than the lateral halves of one individual); (3) their hair must be identical in color, texture, natural curl, and distribution; (4) their eyes must be of the same color and shade; (5) their skin must be of the same texture and color (nevi may be differently apportioned and distributed); (6) their hands and feet must be of the same conformation and of similar size; and (7) their anthropometric values must show close agreement.

PROGNOSIS

Most twins are born prematurely, and maternal complications of pregnancy are more common than with single pregnancies. The risk for twins is most often associated with twin–twin transfusion, assisted reproductive technology, and early-onset discordant growth. Although monochorionic twins have a significantly higher perinatal mortality, there is no significant difference between the neonatal mortality rates of twin births and single births in comparable weight and gestational age groups (Fig. 97-2). Because most twins are premature, their overall mortality is higher than that of single-birth infants. The perinatal mortality of twins is about 4 times that of singletons. Monoamnionic twins have an increased likelihood of entangling the cords, which may lead to asphyxia. Theoretically, the second twin is more subject to anoxia than the first because the placenta may separate after birth of the first twin and before birth of the second. In addition, delivery of the second twin may be difficult because it may be in an abnormal presentation (breech, entangled), uterine tone may be decreased, or the cervix may begin to close after the first twin's birth. Triplet or higher-order births are associated with an increased risk of death or neurodevelopmental impairment when compared with ELBW singleton and twin infants.

The mortality for multiple gestations with 4 or more fetuses is excessively high for each fetus. Because of this poor prognosis, selective fetal reduction (with transabdominal intrathoracic fetal injection of KCl) to 2 or3 fetuses has been offered as a treatment option. Monozygotic twins have an increased risk of 1 twin dying in utero. The surviving twin has a greater risk for cerebral palsy and other neurodevelopmental sequelae.

The risk of multiple gestation pregnancies using assisted reproductive technologies may be reduced by elective single embryo transfers. In addition, elective delivery of twins at 37 wk reduces the complication rate for the fetuses and the mother. Furthermore, in twin pregnancies between 32 and 39 wk of gestation, planned vaginal delivery is preferred if the first twin is in the cephalic presentation.

TREATMENT

Prenatal diagnosis enables the obstetrician and pediatrician to anticipate the birth of infants who are at high risk because of twinning. Close observation is indicated during labor and in the immediate neonatal period so that prompt treatment of asphyxia or fetal transfusion syndrome can be initiated. The decision to perform an immediate blood transfusion in a severely anemic "donor twin" or to perform a partial exchange transfusion of a "recipient twin" must be based on clinical judgment.

Bibliography is available at Expert Consult.

97.2 Prematurity and Intrauterine Growth Restriction

Waldemar A. Carlo

DEFINITIONS

Traditionally, a delivery date is determined 280 days after the last menstrual period; however, only 4% deliver at 280 days and only 70%

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deliver within 10 days of the estimated delivery date. Human gestation length from ovulation to birth may be 268 days, with a range of 37 days.

Liveborn infants delivered before 37 wk from the 1st day of the last menstrual period are termed premature by the World Health Organization. Low birthweight (LBW; birthweight of 2,500 g or less) is a consequence of prematurity, poor intrauterine growth (IUGR, also referred to as SGA), or both.

The American College of Obstetrics and Gynecology redefines term into subgroups: early term (37 0/7 wk of gestation to 38 6/7 wk), full term (39 0/7–40 6/7 wk), and late term (41 0/7–41 6/7 wk). Early term was previously referred to as late preterm.

Prematurity and IUGR are associated with increased neonatal morbidity and mortality. Ideally, definitions of LBW for individual populations should be based on data that are as genetically and environmentally homogeneous as possible. As previously mentioned, Figure 97-1 presents variations in mortality based on birthweight, gestational age, and gender.

INCIDENCE

There is an increasing percentage of deaths in children <5 yr of age that occur in the neonatal period. More than 5% of deaths in children <5 yr of age occur within the 1st mo of life, with about half of the deaths attributable to prematurity. Approximately 8% of liveborn neonates in the United States weigh <2,500 g; the rate for blacks is almost twice that for whites. Over the past 2 decades, the LBW rate has increased primarily because of an increased number of preterm births registered as live births. Women whose first births are delivered before term are at increased risk for recurrent preterm delivery. Approximately 30% of LBW infants in the United States have IUGR and are born after 37 wk of gestation. At LBW rates >10%, the contribution of IUGR increases and that of prematurity decreases. In developing countries, approximately 70% of LBW infants have IUGR. Infants with IUGR have greater morbidity and mortality than do appropriately grown, gestational age–matched infants (see Fig. 97-1). Although U.S. infant mortality rates have fallen since 1971, the ethnic disparity between black infants and white or Hispanic infants remains unchanged. Black infants have higher neonatal mortality rates and comprise a larger percentage of low birthweight births in the United States.

The incidence of preterm births in the United States continues to rise (Figs. 97-3 and 97-4) and is partly a result of multiple gestation pregnancies and increased reporting as live births of the most immature babies.

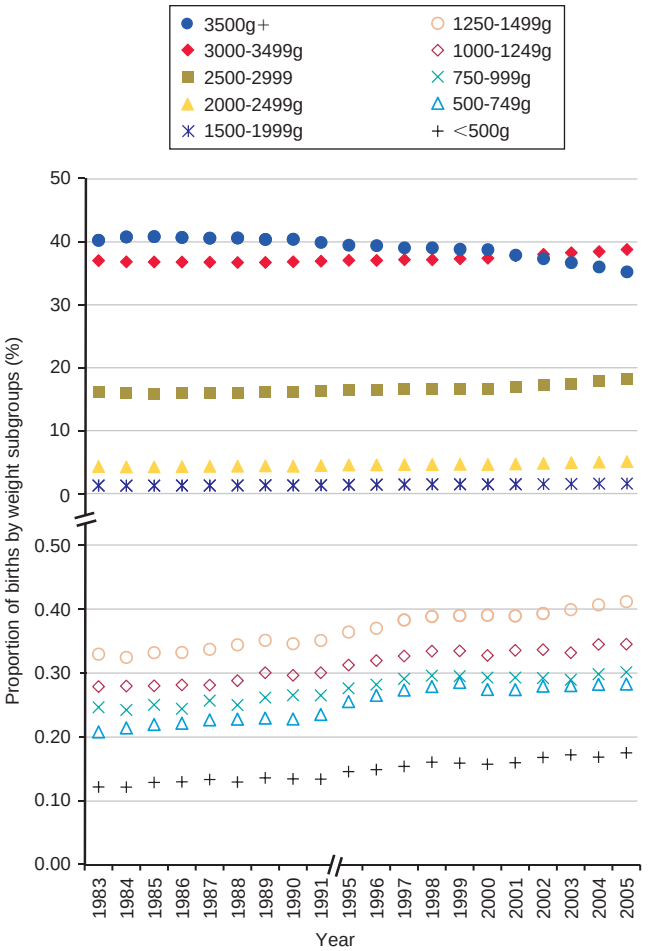

Figure 97-3 Percentage contributions of infants in each very-low birthweight subgroup to total births for 1983-2005. The contribution of infants in each very-low birthweight subgroup increased during the study period. *(From Lau C, Ambalavanan N, Chakraborty H, et al: Extremely low birth weight and infant mortality rates in the United States,* Pediatrics *131:855–860, 2013.)*

VERY LOW BIRTHWEIGHT INFANTS

Very-low birthweight (VLBW) infants weigh <1,500 g and are predominantly premature. In the United States in 2011, the VLBW rates were approximately 1.44% overall, 2.99% among blacks, and 1.14% among whites. The VLBW rate is an accurate predictor of the infant mortality rate. VLBW infants account for more than 50% of neonatal deaths and 50% of handicapped infants; their survival is directly related to birthweight, with approximately 20% of those between 500 and 600 g and >90% of those between 1,250 and 1,500 g surviving. The VLBW rate has remained unchanged for black Americans but has increased among whites, perhaps because of a rise in multiple births among whites. Perinatal care has improved the rate of survival of VLBW infants. When compared with term infants, VLBW neonates have a higher incidence of rehospitalization during the 1st yr of life for sequelae of prematurity, infections, neurologic complications, and psychosocial disorders.

FACTORS RELATED TO PREMATURE BIRTH AND LOW BIRTHWEIGHT

It is difficult to separate completely the factors associated with prematurity from those associated with IUGR (see Chapters 94 and 95). A strong positive correlation exists between both preterm birth and IUGR and low socioeconomic status. Families of low socioeconomic status have higher rates of maternal undernutrition, anemia, and illness; inadequate prenatal care; drug misuse; obstetric complications; and maternal history of reproductive inefficiency (abortions, stillbirths, premature or LBW infants). Other associated factors, such as single-parent families, teenage pregnancies, short interpregnancy interval, and mothers who have borne more than 4 previous children, are also encountered more frequently in such families. Systematic differences in fetal growth have also been described in association with maternal size, birth order, sibling weight, social class, maternal smoking, and other factors. The degree to which the variance in birthweight among various populations is caused by environmental (extrafetal) rather than genetic differences in growth potential is difficult to determine.

The etiology of preterm birth is multifactorial and involves a complex interaction between fetal, placental, uterine, and maternal factors (Table 97-3).

Premature birth of infants whose LBW is appropriate for their preterm gestational age is associated with medical conditions characterized by an inability of the uterus to retain the fetus, interference with the course of the pregnancy, premature rupture of the amniotic membranes or premature separation of the placenta, multifetal gestation, or an undetermined stimulus to effective uterine contractions before term.

Overt or asymptomatic bacterial infection (group B streptococci, *Listeria monocytogenes, Ureaplasma urealyticum, Mycoplasma hominis, Chlamydia, Trichomonas vaginalis, Gardnerella vaginalis, Bacteroides* spp.) of the amniotic fluid and membranes (chorioamnionitis) may initiate preterm labor. Bacterial products may stimulate the production

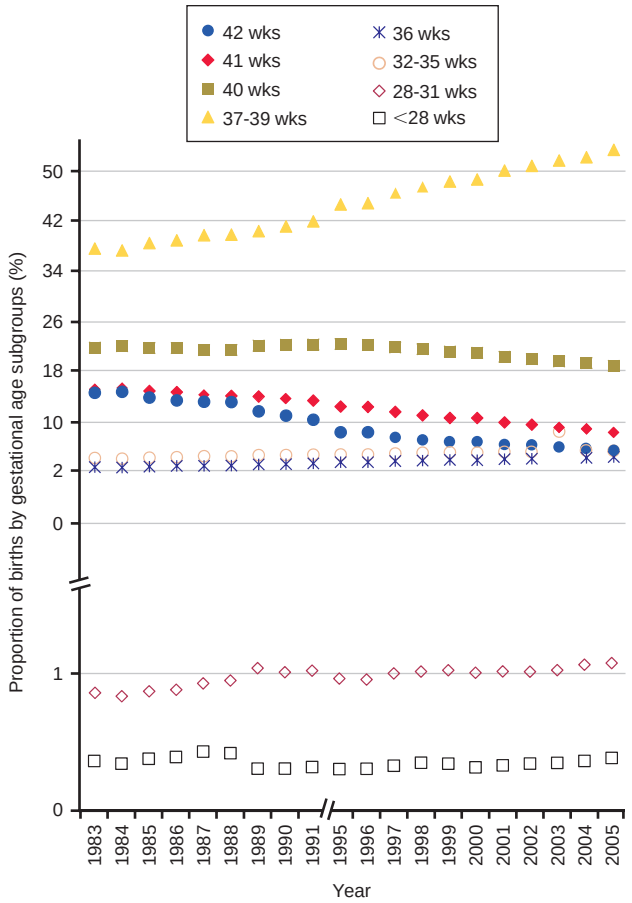

Figure 97-4 Percentage contributions of infants in gestational age subgroups to total births for 1983-2005. *(From Lau C, Ambalavanan N, Chakraborty H, et al: Extremely low birth weight and infant mortality rates in the United States,* Pediatrics *131:855–860, 2013.)*

of local inflammatory mediators (interleukin-6, prostaglandins), which may induce premature uterine contractions or a local inflammatory response with focal amniotic membrane rupture. Appropriate antibiotic therapy reduces the risk of fetal infection and may prolong gestation.

Most preterm births are "spontaneous" without an identifiable cause; genetic predisposition may increase the risk of prematurity. In one study, 6 genes were associated with prematurity. In addition, attempts at prevention of prematurity with hydroxyprogesterone caproate intramuscular injections or vaginal progesterone therapy, suggest a role for an endocrine–genetic relationship.

IUGR is associated with medical conditions that interfere with the circulation and efficiency of the placenta, with the development or growth of the fetus, or with the general health and nutrition of the mother (Table 97-4). Many factors are common to both prematurely born and LBW infants with IUGR. IUGR is associated with decreased insulin production or insulin (or insulin-like growth factor) action at the receptor level. Infants with insulin-like growth factor-1 receptor defects, pancreatic hypoplasia, or transient neonatal diabetes have IUGR. Genetic mutations affecting the glucose-sensing mechanisms of the pancreatic islet cells that result in decreased insulin release (loss of function of the glucose-sensing glucokinase gene) give rise to IUGR.

IUGR may be a normal fetal response to nutritional or oxygen deprivation. Therefore, the issue is not the IUGR but rather the ongoing risk of fetal malnutrition or hypoxia. Similarly, some preterm births signify a need for early delivery from a potentially disadvantageous intrauterine environment. IUGR is often classified as reduced growth that is symmetric (head circumference, length, and weight equally affected) or asymmetric (with relative sparing of head growth) (see Fig. 96-1 in Chapter 96). **Symmetric IUGR** often has an earlier onset and is associated with diseases that seriously affect fetal cell number, such as conditions with chromosomal, genetic, malformation, teratogenic, infectious, or severe maternal hypertensive etiologies. It is important to assess gestational age carefully in infants suspected to have symmetric IUGR because incorrect overestimation of gestational age may lead to the diagnosis of symmetric IUGR. **Asymmetric IUGR** is often of late onset, demonstrates preservation of Doppler waveform velocity to the carotid vessels, and is associated with poor maternal nutrition or with late onset or exacerbation of maternal vascular

Table 97-3 Identifiable Causes of Preterm Birth

FETAL
Fetal distress
Multiple gestation
Erythroblastosis
Nonimmune hydrops
PLACENTAL
Placental dysfunction
Placenta previa
Abruptio placentae
UTERINE
Bicornuate uterus
Incompetent cervix (premature dilation)
MATERNAL
Preeclampsia
Chronic medical illness (cyanotic heart disease, renal disease)
Infection (*Listeria monocytogenes,* group B streptococcus, urinary tract infection, bacterial vaginosis, chorioamnionitis)
Drug abuse (cocaine)
OTHER
Premature rupture of membranes
Polyhydramnios
Iatrogenic
Trauma

Table 97-4 Factors Often Associated with Intrauterine Growth Restriction

FETAL
Chromosomal disorders
Chronic fetal infections (cytomegalic inclusion disease, congenital rubella, syphilis)
Congenital anomalies—syndrome complexes
Irradiation
Multiple gestation
Pancreatic hypoplasia
Insulin deficiency (production or action of insulin)
Insulin-like growth factor type I deficiency
PLACENTAL
Decreased placental weight, cellularity, or both
Decrease in surface area
Villous placentitis (bacterial, viral, parasitic)
Infarction
Tumor (chorioangioma, hydatidiform mole)
Placental separation
Twin transfusion syndrome
MATERNAL
Toxemia
Hypertension or renal disease, or both
Hypoxemia (high altitude, cyanotic cardiac or pulmonary disease)
Malnutrition (micronutrient or macronutrient deficiencies)
Chronic illness
Sickle cell anemia
Drugs (narcotics, alcohol, cigarettes, cocaine, antimetabolites)

disease (preeclampsia, chronic hypertension). Table 97-5 lists the problems of infants with IUGR.

ASSESSMENT OF GESTATIONAL AGE AT BIRTH

When compared with a premature infant of appropriate weight, an infant with IUGR has a reduced birthweight and may appear to have a disproportionately larger head relative to body size; infants in both groups lack subcutaneous fat. Neurologic maturity (nerve conduction velocity) in the absence of asphyxia correlates with gestational age despite reduced fetal weight. Physical signs may be useful in estimating gestational age at birth. Commonly used, the Ballard scoring system is accurate to ±2 wk (Figs. 97-5 to 97-7). An infant should be presumed to be at high risk for mortality or morbidity if a discrepancy exists between the estimation of gestational age by physical examination, the mother's estimated date of her last menstrual period, and fetal ultrasonographic evaluation.

Table 97-5 Problems of Infants Small for Gestational Age or with Intrauterine Growth Retardation*

PROBLEM	PATHOGENESIS
Intrauterine fetal demise	Hypoxia, acidosis, infection, lethal anomaly
Perinatal asphyxia	↓ Uteroplacental perfusion during labor ± chronic fetal hypoxia–acidosis; meconium aspiration syndrome
Hypoglycemia	↓ Tissue glycogen stores, ↓ gluconeogenesis, hyperinsulinism, ↑ glucose needs of hypoxia, hypothermia, large brain
Polycythemia–hyperviscosity	Fetal hypoxia with ↑ erythropoietin production
Reduced oxygen consumption/hypothermia	Hypoxia, hypoglycemia, starvation effect, poor subcutaneous fat stores
Dysmorphology	Syndrome anomalads, chromosomal-genetic disorders, oligohydramnios-induced deformation, TORCH (*t*oxoplasmosis, other agents, *r*ubella, *c*ytomegalovirus, *h*erpes simplex) infection

*Other problems include pulmonary hemorrhage and those common to the gestational age-related risks of prematurity if born at less than 37 wk.
↓, Decreased; ↑, increased.

SPECTRUM OF DISEASE IN LOW-BIRTHWEIGHT INFANTS

Immaturity increases the severity but reduces the distinctiveness of the clinical manifestations of most neonatal diseases. Immature organ function, complications of therapy, and the specific disorders that caused the premature onset of labor contribute to the neonatal

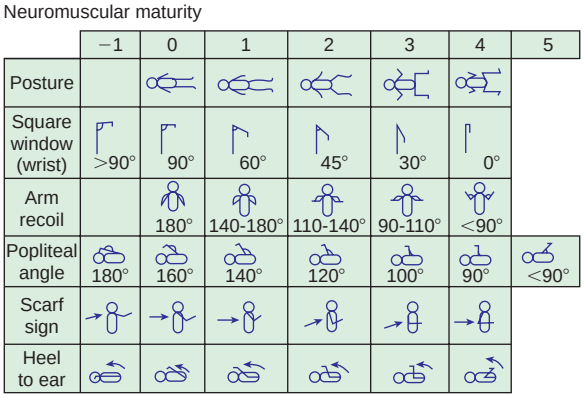

Figure 97-6 **Neuromuscular criteria for maturity.** The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants,* J Pediatr *119:417–423, 1991.)*

Physical maturity

	−1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40-50 mm:·–1 <40 mm: –2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola–no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (–1), tightly (–2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Figure 97-5 **Physical criteria for maturity.** The expanded New Ballard score includes extremely premature infants and has been refined to improve accuracy in more mature infants. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants,* J Pediatr *119:417–423, 1991.)*

Maturity Rating

Score	Weeks
– 10	20
– 5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Figure 97-7 **Maturity rating.** The physical and neurologic scores are added to calculate gestational age. *(From Ballard JL, Khoury JC, Wedig K, et al: New Ballard score, expanded to include extremely premature infants,* J Pediatr *119:417–423, 1991.)*

Table 97-6 Neonatal Problems Associated with Premature Infants

RESPIRATORY
Respiratory distress syndrome (hyaline membrane disease)*
Bronchopulmonary dysplasia
Pneumothorax, pneumomediastinum; interstitial emphysema
Congenital pneumonia
Apnea*
CARDIOVASCULAR
Patent ductus arteriosus*
Hypotension
Bradycardia (with apnea)*
HEMATOLOGIC
Anemia (early or late onset)
GASTROINTESTINAL
Poor gastrointestinal function—poor motility*
Necrotizing enterocolitis
Hyperbilirubinemia—direct and indirect*
Spontaneous gastrointestinal isolated perforation
METABOLIC-ENDOCRINE
Hypocalcemia*
Hypoglycemia*
Hyperglycemia*
Late metabolic acidosis
Hypothermia*
Euthyroid but low thyroxine status
Osteopenia
CENTRAL NERVOUS SYSTEM
Intraventricular hemorrhage*
Periventricular leukomalacia
Seizures
Retinopathy of prematurity
Deafness
Hypotonia*
RENAL
Hyponatremia*
Hypernatremia*
Hyperkalemia*
Renal tubular acidosis
Renal glycosuria
Edema
OTHER
Infections* (congenital, perinatal, nosocomial: bacterial, viral, fungal, protozoal)

*Common.

morbidity and mortality associated with premature, LBW infants (Table 97-6). Among VLBW infants, morbidity is inversely related to birthweight. Respiratory distress syndrome is noted in approximately 80% of infants weighing 501-750 g; in 65% of those weighing 751-1,000 g; in 45% of those weighing 1,001-1,250 g; and in 25% of those weighing 1,251-1,500 g. Severe intraventricular hemorrhage (IVH) is noted in approximately 25% of infants weighing 501-750 g; in 12% of those weighing 751-1,000 g; in 8% of those weighing 1,001-1,250 g; and in 3% of those weighing 1,251-1,500 g. Overall, the risk of late sepsis (24%), bronchopulmonary dysplasia (23%), severe IVH (11%), necrotizing enterocolitis (7%), and prolonged hospitalization (45-125 days) is high in VLBW infants. Problems associated with IUGR LBW infants are noted in Table 97-5; these added problems are often superimposed on those noted in Table 97-6 if an infant with IUGR is also premature. Poor postnatal growth is an important problem for both preterm and IUGR infants.

NURSERY CARE

At birth, the measures needed to clear the airway, initiate breathing, care for the umbilical cord and eyes, and administer vitamin K are the same for immature infants as for those of normal weight and maturity (see Chapter 94). Special care is required to maintain a patent airway. Additional considerations are the need for (1) thermal control and monitoring of the heart rate and respiration, (2) oxygen therapy, and (3) special attention to the details of fluid requirements and nutrition. Safeguards against infection can never be relaxed. Routine procedures that disturb these infants may result in hypoxia. The need for regular and active participation by the parents in the infant's care in the nursery, the need to instruct the mother in at-home care of her infant, and the question of prognosis for later growth and development require special consideration.

Thermal Control

The survival rate of LBW and sick infants is higher when they are cared for at or near their **neutral thermal environment.** This environment is a set of thermal conditions, including air and radiating surface temperatures, relative humidity, and airflow, at which heat production (measured experimentally as oxygen consumption) is minimal and the infant's core temperature is within the normal range. The neutral thermal environment is a function of the size and postnatal age of an infant; larger, older infants require lower environmental temperatures than smaller, younger infants do. Incubators or radiant warmers can be used to maintain body temperature. Body heat is conserved through provision of a warm environment and humidity. The optimal environmental temperature for minimal heat loss and oxygen consumption for an unclothed infant is one that maintains the infant's core temperature at 36.5-37.0°C (97.7-98.6°F). It depends on an infant's size and maturity; the smaller and more immature the infant, the higher the environmental temperature required. An additional acrylic resin (Plexiglas) heat shield or head cap and body clothing may be required to keep an extremely LBW (ELBW) preterm infant warm. Infant warmth can be maintained by heating the air to a desired temperature or by servocontrolling the infant's body temperature at a desired set point. Continuous monitoring of the infant's temperature is required so that the environmental temperature can be adjusted to maintain optimal body temperature. **Kangaroo mother care** with direct skin-to-skin contact and a hat and blanket covering the infant is a safe alternative, with careful monitoring to avoid the risk of serious hypothermia when

incubators are unavailable or when the infant is stable and the parent desire close contact with their infant.

Maintaining a relative humidity of 40-60% aids in stabilizing body temperature by reducing heat loss at lower environmental temperatures; by preventing drying and irritation of the lining of respiratory passages, especially during the administration of oxygen and after or during endotracheal intubation (usually 100% humidity); and by thinning viscid secretions and reducing insensible water loss from the lungs. An infant should be weaned and then removed from the incubator or radiant warmer only when the gradual change to the atmosphere of the nursery does not result in a significant change in the infant's temperature, color, activity, or vital signs.

Administering oxygen to reduce the risk of injury from hypoxia and circulatory insufficiency must be balanced against the risk of hyperoxia to the eyes (retinopathy of prematurity) and oxygen injury to the lungs. Oxygen should be administered via a head hood, nasal cannula, continuous positive airway pressure apparatus, or endotracheal tube to maintain stable and safe inspired oxygen concentrations. Although cyanosis must be treated immediately, oxygen is a drug, and its use must be carefully regulated to maximize benefit and minimize potential harm. The concentration of inspired oxygen must be adjusted in accordance with the oxygen tension of arterial blood (Pa_{O_2}) or a noninvasive method such as continuous pulse oximetry or transcutaneous oxygen measurements. Capillary blood gas determinations are inadequate for estimating arterial oxygen levels.

Fluid Requirements

Fluid needs vary according to gestational age, environmental conditions, and disease states. Assuming minimal water loss in the stool of infants not receiving oral fluids, their water needs are equal to their insensible water loss, excretion of renal solutes, growth, and any unusual ongoing losses. Insensible water loss is indirectly related to gestational age; very immature preterm infants (<1,000 g) may lose as much as 2-3 mL/kg/hr, partly because of immature skin, lack of subcutaneous tissue, and a large exposed surface area. Insensible water loss is increased under radiant warmers, during phototherapy, and in febrile infants. High humidity can be used to reduce insensible water losses. The loss is diminished when an infant is clothed, is covered by an acrylic resin inner heat shield, breathes humidified air, or is of advanced postnatal age. A larger premature infant (2,000-2,500 g) nursed in an incubator may have an insensible water loss of approximately 0.6-0.7 mL/kg/hr.

Adequate fluid intake is essential for excretion of the urinary solute load (urea, electrolytes, phosphate). The amount varies with dietary intake and the anabolic or catabolic state of nutrition. Formulas with a high solute load, high protein intake, and catabolism increase the end products that require urinary excretion and thus increase the requirement for water. **Renal solute loads** may vary between 7.5 and 30 mOsm/kg. Newborn infants, especially VLBW ones, are also less able to concentrate urine, so they need higher fluid intake to excrete solutes.

Fluid intake in term infants is usually begun at 60-70 mL/kg on day 1 and increased to 100-120 mL/kg by days 2-3. Smaller, more premature infants may need to start with 70-80 mL/kg on day 1 and advance gradually to 150 mL/kg/day. Fluid volumes should be titrated individually, although it is unusual to exceed 150 mL/kg/24 hr. Infants weighing <750 g in the 1st wk of life have immature skin and a large surface area, characteristics that lead to a high rate of transepidermal fluid loss, at times requiring higher rates of intravenous fluids. Daily weights, urine output, and serum urea nitrogen and sodium levels should be monitored carefully to determine water balance and fluid needs. Clinical observation and physical examination are poor indicators of the state of hydration of premature infants. Conditions that increase fluid loss, such as glycosuria, the polyuric phase of acute tubular necrosis, and diarrhea, may place additional strain on kidneys that have not yet acquired their maximal capacity to conserve water and electrolytes, the result of which may be severe dehydration. Alternatively, fluid overload may lead to edema, heart failure, patent ductus arteriosus, and bronchopulmonary dysplasia.

Parenteral Nutrition

Before complete enteral feeding has been established or when enteral feeding is impossible for prolonged periods, total intravenous alimentation may provide sufficient fluid, calories, amino acids, electrolytes, and vitamins to sustain the growth of ill infants. This technique has been lifesaving for VLBW and preterm infants and infants who have had intractable diarrheal syndromes or extensive bowel resection. Infusions may be administered through a percutaneously or, less often, surgically placed indwelling central venous catheter or through a peripheral vein. The umbilical vein may also be used for up to 2 wk.

The goal of parenteral alimentation is to deliver sufficient calories from glucose, protein, and lipids to promote optimal growth. The infusate should contain 2.5-3.5 g/dL of synthetic amino acids and usually 10-15 g/dL of glucose, in addition to appropriate quantities of electrolytes, trace minerals, and vitamins. If a peripheral vein is used, it is advisable to keep the glucose concentration below 12.5 g/dL. If a central vein is used, glucose concentrations as high as 25 g/dL may be used (rarely). Intravenous fat emulsions such as Intralipid 20% (2.2 kcal/mL) may be administered to provide calories without an appreciable osmotic load, thereby decreasing the need for infusion of the higher concentrations of glucose by central or peripheral vein while preventing the development of essential fatty acid deficiency. A 20% fat emulsion may be initiated at 0.5 g/kg/24 hr and advanced to 3 g/kg/24 hr, if triglyceride levels remain normal; 0.5 g/kg/24 hr is sufficient to prevent essential fatty acid deficiency. Electrolytes, trace minerals, and vitamin additives are included in amounts approximating established intravenous maintenance requirements. The content of each day's infusate should be determined after careful assessment of the infant's clinical and biochemical status. Slow and continuous infusion is advisable. A well-trained pharmacist should mix all solutions under a laminar flow hood.

After a caloric intake of >100 kcal/kg/24 hr is established by total parenteral intravenous nutrition, the infants can be expected to gain about 15 g/kg/24 hr, with a positive nitrogen balance of 150-200 mg/kg/24 hr, in the absence of episodes of sepsis, surgical procedures, and other severe stress. This goal can usually be achieved (and the catabolic tendency during the 1st wk of life reversed, with subsequent weight gain) by peripheral vein infusion of 2.5-3.5 g/kg/24 hr of an amino acid mixture, 10 g/dL of glucose, and 2-3 g/kg/24 hr of a 20% fat emulsion.

Complications of intravenous alimentation are related to both the catheter and the metabolism of the infusate. Sepsis, the most important problem of central vein infusions, can be minimized only by meticulous catheter care and aseptic preparation of the infusate; a vancomycin–heparin solution also reduces the risk of line sepsis. Coagulase-negative *Staphylococcus* is the most common infecting organism. Treatment includes appropriate antibiotics. If an infection persists (repeatedly positive blood culture results while the infant is receiving appropriate antibiotics), the line must be removed. Thrombosis, extravasation of fluid, and accidental dislodgment of catheters have also occurred. Although sepsis is less often attributable to peripheral vein infusion, phlebitis, cutaneous sloughing, and superficial infection may occur. Metabolic complications of parenteral nutrition include hyperglycemia from the high glucose concentration of the infusate, which may lead to osmotic diuresis and dehydration; azotemia; a possible increased risk of nephrocalcinosis; hypoglycemia from sudden accidental cessation of the infusate; hyperlipidemia and possibly hypoxemia from intravenous lipid infusions; and hyperammonemia, which may result from high levels of certain amino acids. Metabolic bone disease and/or cholestatic jaundice and liver disease may develop in infants who require long-term parenteral nutrition and receive no enteral nutrition. Biochemical and physiologic monitoring of infants receiving intravenous alimentation is indicated because of the frequency and seriousness of complications.

Feeding

The method of feeding each LBW or preterm infant should be individualized. It is important to avoid fatigue and aspiration of food

through regurgitation or the feeding process. No feeding method averts these problems unless the person feeding the infant has been well trained in the method. Oral feeding (nipple) should not be initiated or should be discontinued in infants with respiratory distress, hypoxia, circulatory insufficiency, excessive secretions, gagging, sepsis, central nervous system depression, severe immaturity, or signs of serious illness. These high-risk infants require parenteral nutrition or gavage feeding to supply calories, fluid, and electrolytes. The process of oral alimentation requires, in addition to a strong sucking effort, coordination of swallowing, epiglottal and uvular closure of the larynx and nasal passages, and normal esophageal motility, a synchronized process that is usually absent before 34 wk of gestation.

Preterm infants at 34 wk of gestation or more can often be fed by bottle or at the breast. Because the effort of sucking is usually the limiting factor, direct breastfeeding is less likely to succeed in very preterm infants until they mature. Bottle-feeding of expressed breast milk may be a temporary alternative. In bottle-feeding, the infant's effort may be reduced by use of special small, soft nipples with large holes. Smaller or less vigorous infants should be fed by gavage: A soft plastic tube with No. 5 French external and approximately 0.05 cm internal diameters and with a rounded atraumatic tip and two holes on alternate sides is preferable. The tube is passed through the nose until approximately 2.5 cm (1 inch) of the lower end is in the stomach. The free end of the tube has an adapter into which the tip of a syringe is fitted, and a measured amount of fluid is given by pump or by gravity. Such a tube may be left in place for 3-7 days before being replaced by a similar tube through the other nostril. Infants occasionally have enough local irritation from an indwelling tube that they may gag or troublesome secretions may gather around it in the nasopharynx. In such cases, a catheter may be passed through the mouth by a skilled person and removed at the end of each feeding.

The infant may be fed with intermittent bolus feedings or continuous feeding. In the occasional infant with feeding intolerance, nasojejunal feeding may be successful. Intestinal perforation is a risk with nasojejunal feeding. A change to breast- or bottle-feeding may be instituted gradually as soon as an infant displays general vigor adequate for oral feeding without fatigue.

Gastrostomy feeding is not usually indicated in premature or LBW infants except as an adjunct to surgical management of specific gastrointestinal conditions or in patients with permanent neurologic injuries who are unable to suck and swallow normally.

Initiation of Feeding

The optimal time to introduce enteral feeding to a sick premature or LBW infant is controversial. **Trophic feeding** is the practice of feeding very small amounts of enteral nourishment to VLBW preterm infants to stimulate development of the immature gastrointestinal tract. The benefits of trophic feeding include enhanced gut motility, improved growth, decreased need for parenteral nutrition, fewer episodes of sepsis, and shortened hospital stay. Once the infant is stable, small-volume feedings are given in addition to intravenous fluids/nutrition. Feeding is gradually advanced, and parenteral nutrition decreased. This approach may reduce the incidence of necrotizing enterocolitis. The main principle in feeding premature infants is to proceed cautiously and gradually. Careful early feeding of breast milk or formula tends to reduce the risk of hypoglycemia, dehydration, and hyperbilirubinemia without the additional risk of aspiration, provided that there is no indication for withholding oral feedings, such as the presence of respiratory distress or other disorders.

If an infant is well, is making sucking movements, and is in no distress, oral feeding may be attempted, although most infants weighing <1,500 g require tube feeding because they are unable to coordinate breathing, sucking, and swallowing. Intestinal tract readiness for feeding may be determined by active bowel sounds, passage of meconium, and the absence of abdominal distention, bilious gastric aspirates, and emesis. For infants <1,000 g, the initial trophic feedings can be given at 10-20 mL/kg/24 hr as a continuous nasogastric tube drip (or given by intermittent gavage every 2-3 hr) for

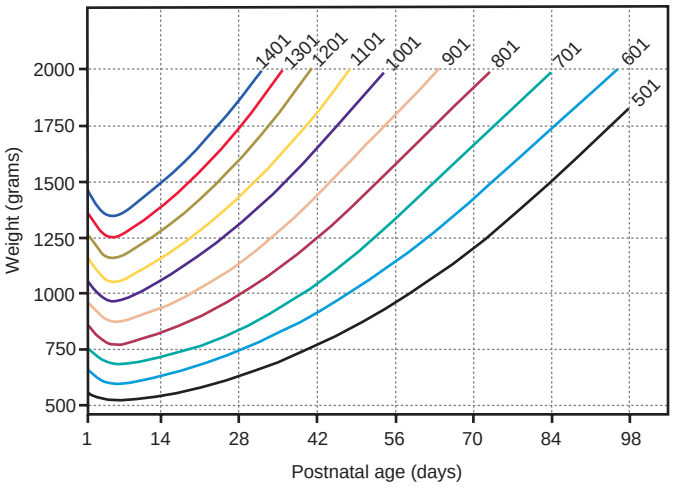

Figure 97-8 Average daily body weight versus postnatal age in days for infants stratified by 100-g birthweight intervals. *(From Ehrenkranz RA, Younes N, Lemons JA, et al: Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 104:280-289, 1999.)*

5-10 days. If the initial feedings are tolerated, the volume is increased by 20-30 mL/kg/24 hr. Once a volume of 150 mL/kg/24 hr has been achieved, the caloric content may be increased to 24 or 27 kcal/oz. With high caloric density, infants are at risk for dehydration, edema, lactose intolerance, diarrhea, flatus, and delayed gastric emptying with emesis. Intravenous fluids are needed until feedings provide approximately 120 mL/kg/24 hr. The feeding protocol for premature infants weighing >1,500 g is initiated at a volume of 20-30 mL/kg/24 hr with increments in total daily formula volume of 20-30 mL/kg/24 hr. Figure 97-8 projects the expected weight increments for premature infants of various birthweights. Infants with IUGR may not demonstrate the marked initial weight loss noted in premature infants.

Regurgitation, vomiting, abdominal distention, or gastric residuals from previous feedings should arouse suspicion of sepsis, necrotizing enterocolitis, or intestinal obstruction; these conditions are indications to stop feedings, at least temporarily, and to increase subsequent feedings slowly only as tolerated or to change to intravenous alimentation and evaluate the infant for more serious problems (see Chapter 102.2). Weight gain may not be achieved for 10-12 days. Alternatively, in infants whose feeding schedule is advanced successfully in calories or volume, weight gain may appear within a few days.

When tube feeding is used, the contents of the stomach should be aspirated before each feeding. If only air or small amounts of mucus are obtained, the feeding is given as planned. If all or a substantial part of the previous feeding is aspirated, it is advisable to withhold feedings or to reduce the amount of the feeding and proceed more gradually with subsequent increases, depending on the physical findings and other evidence of feeding intolerance.

The digestive enzyme systems of infants older than 28 wk of gestation are mature enough to permit adequate digestion and absorption of protein and carbohydrate. Fat is less-well absorbed, primarily because of inadequate amounts of bile salt; unsaturated fats and the fat of human milk are absorbed better than the fat of cow's milk. The weight gain of infants weighing <2,000 g at birth should be adequate when either human milk or "humanized" milk premature formula (40% casein and 60% whey) with a protein intake of 2.25-2.75 g/kg/24 hr is fed. These 2 alternatives should provide all amino acids essential for premature infants, including tyrosine, cystine, and histidine. Higher protein intake may be well tolerated and is generally safe, especially in older, rapidly growing infants. Protein intake >4-5 g/kg/24 hr may be hazardous. Although they may promote linear growth, high-protein formulas may cause abnormal plasma

aminogram results; elevations in blood urea nitrogen, ammonia, and sodium concentrations; metabolic acidosis (cow's milk formulas); and untoward effects on neurologic development. Furthermore, the high protein and mineral contents of balanced cow's milk formulas with a high caloric content constitute a large solute load for the kidneys, a fact important in maintaining water balance, especially in infants with diarrhea or fever.

Breast milk from their mothers is the preferred milk for all infants, including VLBW infants. In addition to nutritional advantages, the benefits of breast milk include protection against a wide range of infections (through both specific and nonspecific anti-infective factors in breast milk and beneficial effects on intestinal flora), a decreased risk of necrotizing enterocolitis in preterm infants, a lower risk of sudden infant death syndrome, and possible long-term effects, including a lower risk of childhood/adolescent obesity and improved neurodevelopmental outcome. Once a premature infant takes 120 mL/kg/24 hr, **breast milk fortifiers** are added to supplement breast milk with protein, calcium, and phosphorus. If breast milk is unavailable, special preterm formulas should be used.

Properly fed premature infants may have from 1 to 8 daily stools of semisolid consistency; a sudden increase in their number, the appearance of occult or gross blood, or change to a watery consistency is more reason for concern than any arbitrarily stated stooling frequency.

Vitamins

Although formula in amounts necessary for adequate growth probably contains adequate quantities of all vitamins, the volume of milk sufficient to satisfy these requirements may not be ingested for several weeks. Therefore, LBW and preterm infants should be given supplemental vitamins. Because requirements for these infants have not been precisely established, the recommended daily allowances for term infants should be given (see Chapter 44). Furthermore, infants may have a special need for certain vitamins. Intermediary metabolism of phenylalanine and tyrosine depends, in part, on vitamin C. Decreased fat absorption with increased fecal fat loss may be associated with decreased absorption of vitamin D, other fat-soluble vitamins, and calcium in premature infants. VLBW infants are particularly prone to the development of osteopenia, but their total intake of vitamin D should not exceed 1,500 IU/24 hr. Folic acid is essential for the formation of DNA and production of new cells; serum and erythrocyte levels decrease in preterm infants during the 1st few wk of life and remain low for 2-3 mo. Therefore, folic acid supplementation is recommended, although it does not result in improved growth or an increased hemoglobin concentration. Deficiency of vitamin E is uncommon, but is associated with increased hemolysis and, if severe, with anemia and edema in premature infants. Vitamin E functions as an antioxidant to prevent the peroxidation of excessive polyunsaturated fatty acids in red blood cell membranes; its need may increase because of the higher membrane content of these fatty acids when formulas with high polyunsaturated fatty acids are used. Vitamin A supplementation reduces bronchopulmonary dysplasia in ELBW infants. Vitamin K deficiency is discussed in Chapter 97.4.

In LBW and premature infants, **physiologic anemia** from postnatal suppression of erythropoiesis is exacerbated by smaller fetal iron stores and greater expansion of blood volume from the more rapid growth than that of term infants; therefore, the anemia develops earlier and reaches a lower ultimate level. Fetal or neonatal blood loss accentuates this problem. Iron stores, even in a VLBW neonate, are usually adequate until an infant's birthweight has doubled; iron supplementation (2 mg/kg/24 hr) should then be started. If erythropoietin is used, iron supplementation is also required.

Prevention of Infection

Premature infants have an increased susceptibility to infection, and thus meticulous attention to infection control is required. Prevention strategies include strict compliance with handwashing and universal precautions, minimizing the risk of catheter contamination and duration, meticulous skin care, encouraging early appropriate advancement of enteral feeding, education and feedback to staff, and surveillance of nosocomial infection rates in the nursery. Although no one with an active infection should be permitted in the nursery, the risks of infection must be balanced against the disadvantages of limiting the infant's contact with the family. Early and frequent participation by parents in the nursery care of their infant does not increase the risk of infection when preventive precautions are maintained.

Preventing transmission of infection from infant to infant is difficult because often neither term nor premature newborn infants have clear clinical evidence of an infection early in its course. When epidemics occur within a nursery, cohort nursing and isolation rooms should be used. Universal precautions require gloves to be worn with all patient contact. Because premature infants have immature immune function, some will develop nosocomial infection even when all precautions are followed.

Routine immunizations should be given on the regular schedule at standard doses (see Chapter 172).

IMMATURITY OF DRUG METABOLISM

Renal clearance of almost all substances excreted in the urine is diminished in newborn infants, but more so in premature ones. The glomerular filtration rate rises with increasing gestational age; therefore drug dosing recommendations vary with age. Intervals between doses may therefore need to be extended with administration of drugs excreted chiefly by the kidneys. Longer intervals are required for many drugs administered to preterm infants. Drugs that are detoxified in the liver or require chemical conjugation before renal excretion should also be given with caution and in doses smaller than usual.

When possible, blood levels should be determined for potentially toxic drugs, especially if renal or hepatic dysfunction is present. Decisions about the choice and dose of antibacterial agents and the route of administration should be made on an individual basis rather than routinely because of the dangers of (a) development of infections with organisms resistant to antibacterial agents, (b) inhibition of intestinal bacteria that manufacture significant amounts of essential vitamins (vitamin K and thiamine), and (c) harmful interference in important metabolic processes.

Many drugs apparently safe for adults on the basis of toxicity studies may be harmful to newborn infants, especially premature ones. Oxygen and a number of drugs have proved toxic to premature infants in amounts not harmful to term infants (Table 97-7). Thus, administering any drug, particularly in high doses, that has not undergone pharmacologic testing in premature infants should be undertaken carefully after risks have been weighed against benefits.

PROGNOSIS

Infants born weighing 1,501-2,500 g have a 95% or greater chance of survival, but those weighing still less have significantly higher mortality (see Fig. 97-1). Intensive care has extended the period during which a VLBW infant is at increased risk of dying of complications of prematurity, such as bronchopulmonary dysplasia, necrotizing enterocolitis, and nosocomial infection (Table 97-8). The postdischarge mortality rate of LBW infants is higher than that of term infants during the 1st 2 yr of life. Because many of the deaths are attributable to infection (e.g., respiratory syncytial virus), they are at least theoretically preventable. In addition, premature infants have an increased incidence of failure to thrive, sudden infant death syndrome, child abuse, and inadequate maternal-infant bonding. The biologic risk associated with poor cardiorespiratory regulation as a result of immaturity or complications of underlying perinatal disease and the social risk associated with poverty also contribute to the high mortality and morbidity of these infants. Congenital anomalies are present in approximately 3-7% of LBW infants.

In the absence of congenital abnormalities, central nervous system injury, VLBW, or marked IUGR, the **physical growth** of LBW infants tends to approximate that of term infants by the 2nd yr; the approximation occurs earlier in premature infants with larger birth size. VLBW infants may not catch up, especially if they have severe chronic sequelae, insufficient nutritional intake, or an inadequate caretaking

Table 97-7 Potential Adverse Reactions to Drugs Administered to Premature Infants

DRUG	REACTION(S)
Oxygen	Retinopathy of prematurity, bronchopulmonary dysplasia
Sulfisoxazole	Kernicterus
Chloramphenicol	Gray baby syndrome—shock, bone marrow suppression
Vitamin K analogs	Jaundice
Novobiocin	Jaundice
Hexachlorophene	Encephalopathy
Benzyl alcohol	Acidosis, collapse, intraventricular bleeding
Intravenous vitamin E	Ascites, shock
Phenolic detergents	Jaundice
$NaHCO_3$	Intraventricular hemorrhage
Amphotericin	Anuric renal failure, hypokalemia, hypomagnesemia
Reserpine	Nasal stuffiness
Indomethacin	Oliguria, hyponatremia, intestinal perforation
Cisapride	Prolonged QTc interval
Tetracycline	Enamel hypoplasia
Tolazoline	Hypotension, gastrointestinal bleeding
Calcium salts	Subcutaneous necrosis
Aminoglycosides	Deafness, renal toxicity
Enteric gentamicin	Resistant bacteria
Prostaglandins	Seizures, diarrhea, apnea, hyperostosis, pyloric stenosis
Phenobarbital	Altered state, drowsiness
Morphine	Hypotension, urine retention, withdrawal
Pancuronium	Edema, hypovolemia, hypotension, tachycardia, vecuronium contractions, prolonged hypotonia
Iodine antiseptics	Hypothyroidism, goiter
Fentanyl	Seizures, chest wall rigidity, withdrawal
Dexamethasone	Gastrointestinal bleeding, hypertension, infection, hyperglycemia, cardiomyopathy, reduced growth
Furosemide	Deafness, hyponatremia, hypokalemia, hypochloremia, nephrocalcinosis, biliary stones
Heparin (not low-dose prophylactic use)	Bleeding, intraventricular hemorrhage, thrombocytopenia
Erythromycin	Pyloric stenosis

environment (see Table 97-8). Infrequently, infants with IUGR (SGA) grow poorly and do not demonstrate catch-up growth. These infants may benefit from recombinant human growth hormone therapy beginning at age 4 yr.

Premature birth in itself may adversely affect later development. The greater the immaturity and the lower the birthweight, the greater the likelihood of intellectual and neurologic deficit; as many as 50% of 500-750 g infants have significant neurodevelopmental impairment

Table 97-8 Sequelae of Low Birthweight

IMMEDIATE	LATE
Hypoxia, ischemia	Mental retardation, spastic diplegia, microcephaly, seizures, poor school performance
Intraventricular hemorrhage	Mental retardation, spasticity, seizures, hydrocephalus
Sensorineural injury	Hearing, visual impairment, retinopathy of prematurity, strabismus, myopia
Respiratory failure	Bronchopulmonary dysplasia, cor pulmonale, bronchospasm, malnutrition, subglottic stenosis
Necrotizing enterocolitis	Short-bowel syndrome, malabsorption, malnutrition, infectious diarrhea
Cholestatic liver disease	Cirrhosis, hepatic failure, malnutrition
Nutrient deficiency	Osteopenia, fractures, anemia, growth failure
Social stress	Child abuse or neglect, failure to thrive, divorce
Other	Sudden infant death syndrome, infections, inguinal hernia, cutaneous scars (chest tube, patent ductus arteriosus ligation, intravenous infiltration), gastroesophageal reflux, hypertension, craniosynostosis, cholelithiasis, nephrocalcinosis, cutaneous hemangiomas

(mental retardation, cerebral palsy, blindness, deafness). Small head circumference at birth may be related to a poor neurobehavioral prognosis. Many surviving LBW infants have hypotonia before 8 mo corrected age, which improves by the time they are 8 mo to 1 yr old. This transient hypotonia is not a poor prognostic sign. Thirty percent to 50% of VLBW children have poor school performance at 7 yr of age (repeating of grades, special classes, learning disorders, poor speech and language), despite a normal IQ. Factors posing a risk for poor academic performance include birthweight below 750 g, severe IVH, periventricular leukomalacia, bronchopulmonary dysplasia, cerebral atrophy, posthemorrhagic hydrocephalus, IUGR, low socioeconomic status, and, possibly, low thyroxine levels. Antenatal exposure to magnesium sulfate may have neuroprotective effects and may reduce the incidence of cerebral palsy in high-risk neonates. Adolescents who were VLBW report satisfactory health; 94% are integrated in regular classes despite neurosensory disabilities (hearing, vision, cerebral palsy, cognition) in 24%.

Both premature and IUGR infants are at risk for significant metabolic conditions (obesity, type II diabetes) and cardiovascular disorders (ischemic heart disease, hypertension) as adults. This **fetal origins** hypothesis of adult morbidities may involve insulin resistance, which may be evident in early childhood.

PREDICTING NEONATAL MORTALITY

Birthweight and gestational age have traditionally been used as strong indicators for the risk of neonatal death. Indeed, survival at 22 wk of gestation is poor, particularly in those infants requiring aggressive resuscitation in the delivery room. With increasing gestational age, survival rates rise to approximately 15% at 23 wk, 56% at 24 wk, and 79% at 25 wk. The survival of infants of <24 wk gestation, weighing <750 g, and with a 1-min Apgar score <3 is 30%. Antenatal steroids to increase lung maturation, female sex, and singleton pregnancy increase the chance for survival. However, extremely premature infants are also at risk for poor neurodevelopmental outcome.

Birthweight-specific neonatal diseases such as IVH, group B streptococcal sepsis/pneumonia, and pulmonary hypoplasia also contribute to a poor outcome. **Scoring systems** that have been developed take into consideration physiologic abnormalities (hypotension–hypertension, acidosis, hypoxia, hypercapnia, anemia, neutropenia), as in the **Score for Neonatal Acute Physiology,** or clinical parameters (gestational age, birthweight, anomalies, acidosis, FIO_2), as in the **Clinical Risk Index for Babies.** The Clinical Risk Index for Babies includes 6 parameters collected in the 1st 12 hr after birth, and the Score for Neonatal Acute Physiology has 26 variables collected in the 1st 24 hr. Prediction models can be used before birth, but additional data from throughout the hospitalization improve the identification of infants at high risk for death or neurodevelopmental impairment. Combining a physician's judgment and an objective score may produce a more accurate assessment of the risk of death.

DISCHARGE FROM THE HOSPITAL

Before discharge, a premature infant should be taking all nutrition by nipple, either bottle or breast (Table 97-9). Some medically fragile infants may be discharged home while receiving gavage feedings after the parents have received appropriate training and education. Growth should be occurring at steady increments of approximately 30 g/day. Temperature should be stabile in an open crib. Infants should have had no recent episodes of apnea or bradycardia, and parenteral drug administration should have been discontinued or converted to oral dosing. Stable infants recovering from bronchopulmonary dysplasia may be discharged on a regimen of oxygen given by nasal cannula as long as careful follow-up is arranged with frequent pulse oximetry monitoring and outpatient visits. All infants with birthweight <1,500 g and those with birthweights between 1,500 and 2,000 g with an unstable clinical course requiring oxygen should undergo an eye examination to screen for retinopathy of prematurity. All infants should have a hearing test prior to discharge. In those who had indwelling umbilical arterial catheters, blood pressure should be measured to check for renal vascular hypertension. The hemoglobin level or hematocrit should be determined to evaluate for possible anemia. If all major medical problems have resolved and the home setting is adequate, premature infants may then be discharged when their weight approaches 1,800-2,100 g; close follow-up plus easy access to healthcare providers is essential for early discharge protocols. Alternatively, if the medical or social environment is not ideal, high-risk neonates who have been transported to neonatal intensive care units and whose major illnesses have resolved may be returned to their hospital of birth for an additional period of hospitalization. Standard vaccinations with full doses should commence after discharge or, if infants are still in the hospital, with vaccines that do not contain live viruses. For respiratory syncytial virus prophylaxis, see Chapter 260.

Table 97-9 Readiness for Discharge of High-Risk Infants Criteria

Resolution of acute life-threatening illnesses
Ongoing follow-up for chronic but stable problems:
Bronchopulmonary dysplasia
Intraventricular hemorrhage
Necrotizing enterocolitis after surgery or recovery
Ventricular septal defect, other cardiac lesions
Anemia
Retinopathy of prematurity
Hearing problems
Apnea
Cholestasis
Stable temperature regulation
Gain of weight with oral feedings:
Breastfeeding
Bottle-feeding
Gastric tube
Free of significant apnea; home monitoring for apnea if needed
Appropriate immunizations and planning for respiratory syncytial virus prophylaxis if indicated
Hearing screenings
Ophthalmologic examination if <27 wk of gestation or <1,250 g at birth
Mother's knowledge, skill, confidence documented in:
Administration of medications (diuretics, methylxanthines, aerosols, etc.)
Use of oxygen, apnea monitors, oximeters
Nutritional support:
Timing
Volume
Mixing concentrated formulas
Recognition of illness and deterioration
Basic cardiopulmonary resuscitation
Infant safety (see Table 97-1)
Scheduling of referrals:
Primary care provider
Neonatal follow-up clinic
Occupational therapy/physical therapy
Imaging (head ultrasound)
Assessment of and solution to social risks (see Table 97-1)

Adapted from American Academy of Pediatrics, American College of Obstetricians: Guidelines for perinatal care, *ed 7, Elk Grove Village, IL, 2013, American Academy of Pediatrics.*

HOME CARE

While the infant is in the hospital, the mother should receive instruction on how to care for the baby after discharge and should be allowed to provide infant care in the hospital. Ideally, a home care program should include at least 1 home visit by someone capable of evaluating domestic arrangements and advising about any needed improvements. Early developmental intervention programs focused on parent-infant relationship and/or infant development after discharge improve cognitive development in the short to medium term (up to preschool) but do not improve motor outcomes. However these benefits are not sustained at school age.

Bibliography is available at Expert Consult.

97.3 Postterm Infants

Waldemar A. Carlo

Postterm infants are those born after 42 completed weeks of gestation, as calculated from the mother's last menstrual period, regardless of weight at birth. Historically, approximately 12% of pregnancies ended after the 294th day. Obstetric interventions often occur earlier, and the rate of postterm births is decreasing. The cause of postterm birth or postmaturity is unknown.

CLINICAL MANIFESTATIONS

Postterm infants have normal length and head circumference but may have decreased weight if there is placental insufficiency. Infants born postterm in association with presumed placental insufficiency may have various physical signs. Desquamation, long nails, abundant hair, pale skin, alert faces, and loose skin, especially around the thighs and buttocks, give them the appearance of having recently lost weight; meconium-stained nails, skin, vernix, umbilical cord, and placental membranes may also be noted (see Fig. 88-1 in Chapter 88). Common complications of postmaturity include perinatal depression, meconium aspiration, persistent pulmonary hypertension, hypoglycemia, hypocalcemia, and polycythemia.

PROGNOSIS

When delivery is delayed 3 wk or more beyond term, mortality is significantly increased and, in some series, has been approximately 3 times that of a control group of infants born at term. Mortality has been lowered markedly through improved obstetric management.

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MANAGEMENT

Careful obstetric monitoring, including nonstress testing, biophysical profile, or Doppler velocimetry, usually provides a rational basis for choosing one of three courses: nonintervention, induction of labor, or cesarean section. Induction of labor or cesarean section may be indicated in older primigravidas more than 2-4 wk beyond term, particularly if evidence of fetal distress is present. Medical problems in the newborn are treated if they arise.

97.4 Large-for-Gestational-Age Infants

Waldemar A. Carlo

See also Chapter 101.1.

Infants with birthweight > the 90th percentile for gestational age are called **large for gestational age** (LGA). Neonatal mortality rates decrease with increasing birthweight until approximately 4,000 g, after which they increase. These oversized infants are usually born at term, but preterm infants with weights high for gestational age also have a significantly higher mortality than infants of the same size born at term; maternal diabetes and obesity are predisposing factors. Some infants are constitutionally large because of large parental size. LGA infants, regardless of their gestational age, have a higher incidence of birth injuries, such as cervical and brachial plexus injuries, phrenic nerve damage with paralysis of the diaphragm, fractured clavicles, cephalohematomas, subdural hematomas, and ecchymoses of the head and face. LGA infants are also at increased risk for hypoglycemia and polycythemia.

The incidence of congenital anomalies, particularly congenital heart disease, is also higher in LGA infants than in term infants of normal weight. Intellectual and developmental retardation is statistically more common in high birthweight term and preterm infants than in babies of appropriate weight for gestational age.

97.5 Infant Transport

Waldemar A. Carlo

With the advent of regionalized care of high-risk neonates, increasing numbers of high-risk mothers and sick infants are transported to hospitals with neonatal intensive care units. Neonatal transport should include consultation about the infant's problem and care before transport, ease of access to the transport team, and transport and stabilization by the team before moving the infant. Securing an airway, providing oxygen, assisting with infant ventilation, providing antimicrobial therapy, maintaining the circulation, providing a warmed environment, and placing intravenous or arterial lines or chest tubes should be initiated, if indicated, before transport. Infant and maternal records and laboratory reports should also be provided. Before departure of an infant, the mother should be briefly reassured and allowed to see her stabilized infant; the father should enter his car and follow the transport vehicle to the unit. The transport officer or nurse should also call ahead to inform the receiving unit about the nature of the patient's illness.

The transport vehicle should be equipped with appropriate medicines, fluids, oxygen tanks, catheters, chest tubes, endotracheal tubes, laryngoscopes, and an infant warming device. It should be well illuminated and have ample room for emergency procedures and monitoring equipment. With efficient transport and appropriately educated nursing and medical staff at the referring hospitals, the mortality of "outborn" neonates should be no higher than that of those born within the tertiary care center.

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Chapter 98

Clinical Manifestations of Diseases in the Newborn Period

Waldemar A. Carlo

The wide varieties of disorders that affect the newborn originate in utero, during birth, or in the immediate postnatal period. These disorders may be caused by prematurity, genetic mutations, chromosomal aberrations, or acquired diseases and injuries. Recognizing disease in newborn infants depends on knowledge of the disorder and evaluation of a limited number of relatively nonspecific clinical signs and symptoms.

Central cyanosis has respiratory, cardiac, central nervous system (CNS), hematologic, and metabolic causes (Table 98-1). Respiratory insufficiency may be a result of pulmonary conditions or may be secondary to CNS depression from drugs, intracranial hemorrhage, or anoxia. If respiratory insufficiency is caused by pulmonary conditions, respirations tend to be rapid and may be accompanied by retraction of the thoracic cage. If it is caused by the CNS depression, respirations tend to be irregular and weak and are often slow. Cyanosis unaccompanied by obvious signs of respiratory difficulty suggests cyanotic congenital heart disease or methemoglobinemia. Cyanosis resulting from congenital heart disease may, however, be difficult to distinguish clinically from cyanosis caused by respiratory disease. Episodes of cyanosis may also be the initial sign of hypoglycemia, bacteremia, meningitis, shock, or pulmonary hypertension. Peripheral acrocyanosis is common in neonates and does not usually warrant concern unless poor perfusion is suspected.

Pallor, in addition to anemia or acute hemorrhage, should suggest hypoxia, asphyxia, hypoglycemia, sepsis, shock, or adrenal failure.

Hypotension in term infants suggests shock from hypovolemia (hemorrhage, dehydration), the systemic inflammatory response syndrome (bacterial sepsis, intrauterine infection, necrotizing enterocolitis), cardiac dysfunction (left heart obstructive lesions—hypoplastic left-heart syndrome, myocarditis, asphyxia-induced myocardial stunning, anomalous coronary artery), pneumothorax, pneumopericardium, pericardial effusion, or metabolic disorders (hypoglycemia, adrenal insufficiency–salt-losing adrenogenital syndrome). Hypotension is a common problem in sick preterm infants and may also be caused by any of the problems noted in a term infant. Hypotension may develop in preterm infants with severe respiratory distress syndrome. Strategies used to support blood pressure include volume expansion (normal saline is equally as effective as 5% albumin), pressors (dopamine, dobutamine, epinephrine, norepinephrine, vasopressin), and corticosteroids. Hypotension in some infants weighing <1,000 g does not respond to fluids or inotropic agents but may respond to therapy with intravenous hydrocortisone. Sudden onset of hypotension in a very-low birthweight infant suggests pneumothorax, intraventricular hemorrhage, or subcapsular hepatic hematoma.

Seizures (see Chapter 593.7) usually point to a disorder of the CNS and suggest hypoxic–ischemic encephalopathy, intracranial hemorrhage, cerebral anomaly, subdural effusion, meningitis, hypocalcemia, hypoglycemia, cerebral infarction, benign familial seizures, or, rarely, pyridoxine dependence, hyponatremia, hypernatremia, inborn errors of metabolism, or drug withdrawal. Seizures beginning in the delivery room or shortly thereafter may be the result of the unintentional injection of maternal local anesthetic into the fetus. Seizures may also result from hyponatremia and water intoxication in the infant after the administration of large amounts of hypotonic fluid to the mother shortly before and during delivery.

Table 98-1 Differential Diagnosis of Cyanosis in the Newborn

CENTRAL OR PERIPHERAL NERVOUS SYSTEM HYPOVENTILATION
Birth asphyxia
Intracranial hypertension, hemorrhage
Oversedation (direct or through maternal route)
Diaphragm palsy
Neuromuscular diseases
Seizures
RESPIRATORY DISEASE
Airway
Choanal atresia/stenosis
Pierre Robin syndrome
Intrinsic airway obstruction (laryngeal/bronchial/tracheal stenosis)
Extrinsic airway obstruction (bronchogenic cyst, duplication cyst, vascular compression)
Lung
Respiratory distress syndrome
Transient tachypnea
Meconium aspiration
Pneumonia (sepsis)
Pneumothorax
Congenital diaphragmatic hernia
Pulmonary hypoplasia
CARDIAC RIGHT-TO-LEFT SHUNT
Abnormal connections (pulmonary blood flow normal or increased)
Transposition of great vessels
Total anomalous pulmonary venous return
Truncus arteriosus
Hypoplastic left heart syndrome
Single ventricle or tricuspid atresia with large ventricular septal defect but without pulmonic stenosis
Obstructed pulmonary blood flow (pulmonary blood flow decreased)
Pulmonic atresia with intact ventricular septum
Tetralogy of Fallot
Critical pulmonic stenosis with patent foramen ovale or atrial septal defect
Tricuspid atresia
Single ventricle with pulmonic stenosis
Ebstein malformation of the tricuspid valve
Persistent fetal circulation (persistent pulmonary hypertension of newborn)
METHEMOGLOBINEMIA
Congenital (hemoglobin M, methemoglobin reductase deficiency)
Acquired (nitrates, nitrites)
Inadequate ambient O_2 or less O_2 delivered than expected (rare)
Disconnection of O_2 supply to nasal cannula, head hood
Connection of air, rather than O_2, to a mechanical ventilator
SPURIOUS/ARTIFACTUAL
Oximeter artifact (poor contact between probe and skin, poor pulse searching)
Arterial blood gas artifact (contamination with venous blood)
OTHER
Hypoglycemia
Adrenogenital syndrome
Polycythemia
BLOOD LOSS

From Smith F: Cyanosis. In Kliegman RM: Practical strategies in pediatric diagnosis and therapy, *Philadelphia, 1996, WB Saunders.*

Seizures should be distinguished from the jitteriness that may be present in normal newborns, in infants of diabetic mothers, in those who experienced birth asphyxia or drug withdrawal, and in polycythemic neonates. An examiner may stop the jitteriness resembling simple tremors by holding the infant's extremity; this jitteriness often depends on sensory stimuli and occurs when the infant is active, and it is not associated with abnormal eye movements. Tremors are often more rapid with a smaller amplitude than those of tonic-clonic seizures. Seizures in premature infants are often subtle and associated with abnormal eye (fluttering, deviation, stare) or facial (chewing, tongue thrusting) movements; the motor component is often that of tonic extension of the limbs, neck, and trunk. Term infants may have focal or multifocal, clonic or myoclonic movements, but they may also have more subtle seizure activity. Apnea may be the first manifestation of seizure activity, particularly in a premature infant. Seizures may adversely affect the subsequent neurodevelopmental outcome and may even predispose an infant to nonneonatal seizures. Seizures should be treated aggressively.

After severe birth asphyxia, infants may have **motor automatisms** characterized by oral-buccal-lingual movements, rotary limb activities (rowing, pedaling, swimming), tonic posturing, or myoclonus. These motor activities are not usually accompanied by time-synchronized electroencephalographic discharges, may not signify cortical epileptic activity, respond poorly to anticonvulsant therapy, and are associated with a poor prognosis. Such automatisms may represent cortical depression that produces a brainstem release phenomenon or subcortical seizures.

Lethargy may be a manifestation of infection, asphyxia, hypoglycemia, hypercapnia, sedation from maternal analgesia or anesthesia, a cerebral defect, or, indeed, almost any severe disease, including an inborn error of metabolism. Lethargy appearing after the 2nd day should, in particular, suggest infection. Lethargy with emesis suggests increased intracranial pressure or an inborn error of metabolism.

Irritability may be a sign of discomfort accompanying intraabdominal conditions, meningeal irritation, drug withdrawal, infections, congenital glaucoma, or any condition producing pain. As in later infancy, the eardrums should always be examined as a possible source of pain. Hyperactivity, especially in a premature infant, may be a sign of hypoxia, pneumothorax, emphysema, hypoglycemia, hypocalcemia, CNS damage, drug withdrawal, neonatal thyrotoxicosis, bronchospasm, esophageal reflux, or discomfort from a cold environment.

Failure to feed well is seen in most sick newborn infants and should lead a careful search for infection, a central or peripheral nervous system disorder, intestinal obstruction, and other abnormal conditions.

Fever may be the result of too high an environmental temperature because of weather, overheated nurseries or incubators/radiant warmers, or too many clothes. It is also noted in "dehydration fever" of newborn infants. If these causes of fever can be eliminated, serious infection (pneumonia, bacteremia, meningitis, and viral infections, particularly herpes simplex or enteroviruses) must be considered, although such infections often occur without provoking a febrile response in newborn infants (see Chapters 176 and 177). Unexplained **hypothermia** may accompany infection or other serious disturbances of the circulation or CNS. A sudden servocontrolled increase in incubator ambient temperature to maintain body temperature is a sign of temperature instability and may be associated with sepsis or any of the conditions already mentioned.

Periods of **apnea**, particularly in premature infants, may be associated with various disturbances (see Chapter 101.2). When apnea recurs, or when the intervals are longer than 20 sec, or are associated with cyanosis or bradycardia, an immediate diagnostic evaluation is needed.

Jaundice during the 1st 24 hr of life warrants diagnostic evaluation and should be considered to be due to hemolysis until proven otherwise. Septicemia and intrauterine infections, such as syphilis, cytomegalovirus, and toxoplasmosis, should also be considered, especially in infants with an increase in direct bilirubin value.

Jaundice after the 1st 24 hr may be "physiologic" or may be caused by septicemia, hemolytic anemia, galactosemia, hepatitis, congenital atresia of the bile ducts, inspissated bile syndrome after erythroblastosis fetalis, syphilis, herpes simplex, other congenital infections, or other conditions (see Chapter 102.3).

Vomiting during the 1st day of life suggests obstruction in the upper digestive tract or increased intracranial pressure. Roentgenographic studies are indicated when obstruction is suspected. Vomiting may also be a nonspecific symptom of an illness such as septicemia. It is a common manifestation of overfeeding, inexperienced feeding technique, or normal reflux and is rarely caused by pyloric stenosis, milk allergy, duodenal ulcer, stress ulcer, an inborn error of metabolism

Table 98-2 Pain in the Neonate: General Considerations

- Pain in newborns is often unrecognized and/or undertreated.
- If a procedure is painful in adults, it should be considered painful in newborns.
- Healthcare institutions should develop and implement patient care policies to assess, prevent, and manage pain in neonates.
- Pharmacologic agents with known pharmacokinetic and pharmacodynamic properties and demonstrated efficacy in neonates should be used. Agents known to compromise cardiorespiratory function should be administered only by persons experienced in neonatal airway management and in settings with the capacity for continuous monitoring.
- Educational programs to increase the skills of healthcare professionals in the assessment and management of stress and pain in neonates should be provided.
- Further research is needed to develop and validate neonatal pain assessment tools that are useful in the clinical setting; to determine optimal behavioral and pharmacologic interventions; and to study long-term effects of pain and pain management.

Adapted from Prevention and management of pain and stress in the neonate: American Academy of Pediatrics. Committee on Fetus and Newborn. Committee on Drugs. Section on Anesthesiology. Section on Surgery. Canadian Paediatric Society. Fetus and Newborn Committee, Pediatrics *105:454–461, 2000; and Anand KJS; International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn,* Arch Pediatr Adolesc Med *155:173–180, 2001.*

Table 98-3 Common Life-Threatening Congenital Anomalies

NAME	MANIFESTATIONS
Choanal atresia	Respiratory distress in delivery room, nasogastric tube cannot be passed through nares Suspect CHARGE (coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies) syndrome
Pierre Robin syndrome Stickler syndrome	Micrognathia, cleft palate, airway obstruction
Diaphragmatic hernia	Scaphoid abdomen, bowel sounds present in chest, respiratory distress
Tracheoesophageal fistula	Polyhydramnios, aspiration pneumonia, excessive salivation, nasogastric tube cannot be placed in stomach Suspect VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, and radial and renal dysplasia) syndrome
Intestinal obstruction: volvulus, duodenal atresia, ileal atresia	Polyhydramnios, bile-stained emesis, abdominal distention Suspect trisomy 21, cystic fibrosis, cocaine
Gastroschisis, omphalocele	Polyhydramnios, intestinal obstruction
Renal agenesis, Potter syndrome	Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax
Neural tube defects: anencephalus, meningomyelocele	Polyhydramnios, elevated α-fetoprotein, decreased fetal activity
Ductus-dependent congenital heart disease	Cyanosis, hypotension, murmur

(hyperammonemia, metabolic acidosis), or adrenal insufficiency. Vomitus containing dark blood is usually a sign of a serious illness; the benign possibility of swallowed maternal blood should also be considered. Bile-stained vomitus strongly suggests obstruction below the ampulla of Vater and warrants contrast-enhanced radiography in many cases.

Diarrhea may be a symptom of overfeeding (especially high–caloric density formula), acute gastroenteritis, or malabsorption, or it may be a nonspecific symptom of infection. Diarrhea may occur in conditions accompanied by compromised circulation of part of the intestinal or genital tract, such as mesenteric thrombosis, necrotizing enterocolitis, strangulated hernia, intussusception, and torsion of the ovary or testis.

Abdominal distention, usually a sign of intestinal obstruction or an intraabdominal mass, may also be seen in infants with enteritis, necrotizing enterocolitis, isolated intestinal perforation, ileus accompanying sepsis, respiratory distress, ascites, or hypokalemia.

Failure to move an extremity **(pseudoparalysis)** suggests fracture, dislocation, or nerve injury. It is also seen in osteomyelitis and other infections that cause pain on movement of the affected part.

Pain in neonates may be unrecognized and/or undertreated. The intensive care of neonates may involve a number of painful procedures, including blood sampling (heelstick, venous or arterial puncture), endotracheal intubation and suctioning, mechanical ventilation, and insertion of chest tubes and intravascular catheters. Pain in neonates results in obvious distress and acute physiologic stress responses, which may have developmental implications for pain in later life. Moreover, the knowledge that infants may experience pain contributes to the stress of parents of sick newborns.

Pain and discomfort are potentially avoidable problems during the treatment of sick infants. Preemptive relief from painful stimuli should be provided before pain or anxiety develops. The most frequently used drugs are intermittent or continuous doses of opioids (morphine, fentanyl) and benzodiazepines (midazolam, lorazepam). Although the long-term effects of opioids and sedatives are not well established, the first concern should be the treatment and/or prevention of acute pain. Continuous opiate infusions should be used with caution. Some minor but painful procedures performed in well neonates can be managed with oral sucrose solutions (Table 98-2).

CONGENITAL ANOMALIES

Congenital anomalies are a major cause of stillbirths and neonatal deaths. In the United States and other developed countries, congenital anomalies are one of the main causes of neonatal mortality. In addition, congenital anomalies are a major cause of acute illness and long-term morbidity. Anomalies are discussed in general in Chapters 81 and 108, and specifically in the chapters on the various systems of the body. Early recognition of anomalies is important for planning care; with some, such as congenital heart disease, tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, and intestinal obstruction, immediate medical and/or surgical therapy is essential for survival (Table 98-3). Parents are likely to feel anxious and guilty upon learning of the existence of a congenital anomaly and require sensitive counseling.

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Chapter 99

Nervous System Disorders

Waldemar A. Carlo and Namasivayam Ambalavanan

Central nervous system (CNS) disorders are important causes of neonatal mortality and both short- and long-term morbidity. The CNS can be damaged as a result of asphyxia, hemorrhage, trauma, hypoglycemia, or direct cytotoxicity. The etiology of CNS damage is often multifactorial and includes perinatal complications, postnatal hemodynamic instability, and developmental abnormalities that may be genetic and/or environmental. Predisposing factors for brain injury include chronic and acute maternal illness resulting in uteroplacental dysfunction, intrauterine infection, macrosomia/dystocia, malpresentation, prematurity, and intrauterine growth restriction. Acute and often unavoidable emergencies during the delivery process sometimes result in mechanical and/or hypoxic–ischemic brain injury.

99.1 The Cranium

Waldemar A. Carlo and Namasivayam Ambalavanan

Erythema, abrasions, ecchymoses, and subcutaneous fat necrosis of facial or scalp soft tissues may be noted after a normal delivery or after forceps or vacuum-assisted deliveries. Their location depends on the area of contact with the pelvic bones or of application of the forceps. Traumatic hemorrhage may involve any layer of the scalp as well as intracranial contents (Fig. 99-1).

Caput succedaneum is a diffuse, sometimes ecchymotic, edematous swelling of the soft tissues of the scalp involving the area presenting during vertex delivery (see Fig. 99-1). It may extend across the midline and across suture lines. The edema disappears within the 1st few days of life. Molding of the head and overriding of the parietal bones are frequently associated with caput succedaneum and become more evident after the caput has receded; they disappear during the 1st few wk of life. Rarely, a hemorrhagic caput may result in shock and require blood transfusion. Analogous swelling, discoloration, and distortion of the face are seen in face presentations. No specific treatment is needed, but if extensive ecchymoses are present, hyperbilirubinemia may develop.

Cephalohematoma (Fig. 99-2) is a subperiosteal hemorrhage, hence always limited to the surface of 1 cranial bone. Cephalohematomas occur in 1-2% of live births. No discoloration of the overlying scalp occurs, and swelling is not usually visible for several hours after birth because subperiosteal bleeding is a slow process. The lesion becomes a firm tense mass with a palpable rim localized over 1 area of the skull. Most cephalohematomas are resorbed within 2 wk-3 mo, depending on their size. They may begin to calcify by the end of the 2nd wk. A few remain for years as bony protuberances and are detectable on radiographs as widening of the diploic space; cystlike defects may persist for months or years. An underlying skull fracture, usually linear and not depressed, may be associated with 10-25% of cases. A sensation of central depression suggesting but not indicative of an underlying fracture or bony defect is usually encountered on palpation of the organized rim of a cephalohematoma. Cephalohematomas require no treatment, although phototherapy may be necessary to treat hyperbilirubinemia. Infection of the hematoma is a very rare complication.

A **subgaleal hemorrhage** is a collection of blood beneath the aponeurosis that covers the scalp and serves as the insertion for the occipitofrontalis muscle. Bleeding can be very extensive into this large potential space and may even dissect into the subcutaneous tissues of the neck. There is often an association with vacuum-assisted delivery. The mechanism of injury is most likely secondary to rupture of emissary veins connecting the dural sinuses within the skull with the superficial veins of the scalp, sometimes associated with skull fractures, suture diastasis, and fragmentation of the superior margin of the parietal bone. Extensive subgaleal bleeding is occasionally secondary to a hereditary coagulopathy (hemophilia). A subgaleal hemorrhage manifests as a fluctuating mass that straddles cranial sutures or fontanels that increases in size after birth. Some patients have a consumptive coagulopathy owing to massive blood loss. Patients should be monitored for hypotension, anemia, and the development of hyperbilirubinemia. These lesions typically resolve over 2-3 wk.

Fractures of the skull may occur as a result of pressure from forceps or from the maternal symphysis pubis, sacral promontory, or ischial spines. Linear fractures, the most common, cause no symptoms and require no treatment. Depressed fractures are usually indentations of the calvaria similar to the dents in a ping-pong ball; they are generally a complication of forceps delivery or fetal compression. Affected infants may be asymptomatic unless they have associated intracranial injury; it is advisable to elevate severe depressions to prevent cortical injury from sustained pressure. Although some may elevate spontaneously, some require treatment. Percutaneous microscrew elevation is one method successfully used to elevate depressed skull fractures. Fracture of the occipital bone with separation of the basal and squamous portions frequently causes fatal hemorrhage because of disruption of the underlying vascular sinuses. Such fractures may result

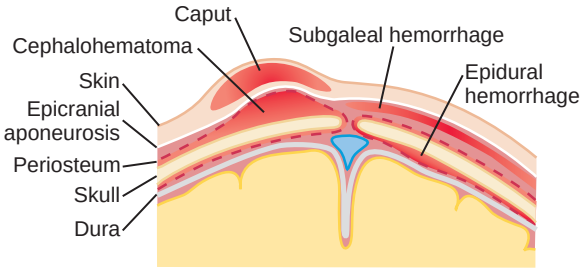

Figure 99-1 Sites of extracranial (and extradural) hemorrhages in the newborn. Schematic diagram of important tissue planes from skin to dura. *(From Volpe JJ:* Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders.)*

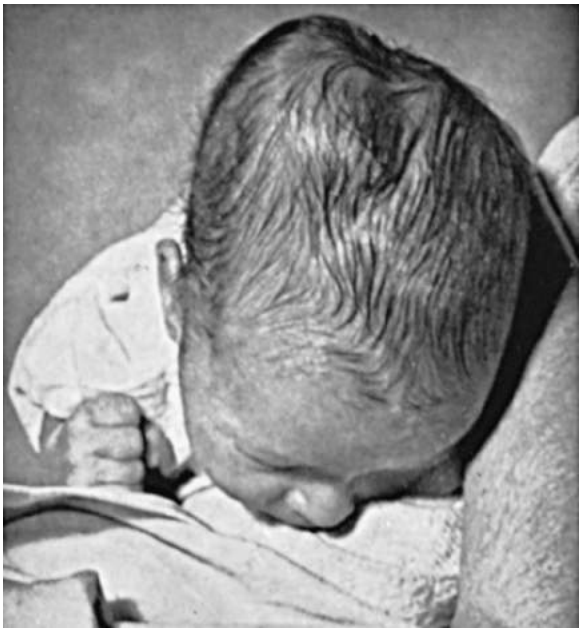

Figure 99-2 Cephalohematoma of the right parietal bone.

during breech deliveries from traction on the hyperextended spine of the infant while the head is fixed in the maternal pelvis.

Subconjunctival and **retinal hemorrhages** are frequent; petechiae of the skin of the head and neck are also common. All are probably secondary to a sudden increase in intrathoracic pressure during passage of the chest through the birth canal. Parents should be assured that these hemorrhages are temporary and the result of normal events of delivery. The lesions resolve rapidly within the 1st 2 wk of life.

99.2 Traumatic, Epidural, Subdural, and Subarachnoid Hemorrhage

Waldemar A. Carlo and Namasivayam Ambalavanan

Traumatic **epidural, subdural, or subarachnoid hemorrhage** is especially likely when the fetal head is large in proportion to the size of the mother's pelvic outlet, with prolonged labor, in breech or precipitous deliveries, or as a result of mechanical assistance with delivery. Asymptomatic subdural hemorrhage may be noted within 48 hr of birth after vaginal or cesarean delivery. Massive **subdural hemorrhage**, often associated with tears in the tentorium cerebelli or, less frequently, in the falx cerebri, is rare but is encountered more often in full-term than in premature infants. Patients with massive hemorrhage caused by tears of the tentorium or falx cerebri rapidly deteriorate and may die soon after birth. The majority of **subdural and epidural hemorrhages** resolve without intervention; consultation with a neurosurgeon is recommended. The diagnosis of subdural hemorrhage may be delayed until the chronic subdural fluid volume expands and produces megalocephaly, frontal bossing, a bulging fontanel, anemia, and, sometimes, seizures. CT scan and MRI are useful imaging techniques to confirm these diagnoses. Symptomatic subdural hemorrhage in large term infants should be treated by removal of the subdural fluid collection with a needle placed through the lateral margin of the anterior fontanel. In addition to birth trauma, **child abuse** must be suspected in all infants with subdural effusion after the immediate neonatal period; asymptomatic subdural hemorrhages following labor should resolve by 4 wk of age.

Subarachnoid hemorrhage is rare and typically is clinically silent. The anastomoses between the penetrating leptomeningeal arteries or the bridging veins are the most likely source of the bleeding. The majority of affected infants have no clinical symptoms, but the subarachnoid hemorrhage may be detected because of an elevated number of red blood cells in a lumbar puncture sample. Some infants experience benign seizures, which tend to occur on the 2nd day of life. Rarely, an infant has a life-threatening catastrophic hemorrhage and dies. There are usually no neurologic abnormalities during the acute episode or on follow-up. Significant neurologic findings should suggest an arteriovenous malformation; this lesion can easily be detected on CT or MRI; ultrasonography is a less-sensitive tool.

99.3 Intracranial–Intraventricular Hemorrhage and Periventricular Leukomalacia

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ETIOLOGY

Intracranial hemorrhage usually develops spontaneously; less commonly, it may be caused by trauma or asphyxia, and rarely, it occurs from a primary hemorrhagic disturbance or congenital vascular anomaly. Intracranial hemorrhage often involves the ventricles (**intraventricular hemorrhage** [IVH]) of premature infants delivered spontaneously without apparent trauma. Primary hemorrhagic disturbances and vascular malformations are rare and usually give rise to subarachnoid or intracerebral hemorrhage. In utero hemorrhage associated with maternal idiopathic or, more often, fetal alloimmune thrombocytopenia may occur as severe cerebral hemorrhage or a porencephalic cyst after resolution of a fetal cortical hemorrhage. Intracranial bleeding may be associated with disseminated intravascular coagulopathy, isoimmune thrombocytopenia, and neonatal vitamin K deficiency, especially in infants born to mothers receiving phenobarbital or phenytoin.

EPIDEMIOLOGY

The overall incidence of IVH has decreased over the past decades as a result of improved perinatal care and increased use of antenatal corticosteroids, surfactant to treat respiratory distress syndrome (RDS), and, possibly, prophylactic indomethacin; however, it continues to be an important cause of morbidity in preterm infants. Approximately 30% of premature infants <1,500 g have IVH. The risk is inversely related to gestational age and birthweight, with the smallest and most immature infants being at the highest risk; 7% of infants weighing 1,001-1,500 g have a severe IVH (grade III or IV), compared with 14% of infants weighing 751-1,000 g and 24% of infants weighing ≤750 g. In 3% of infants weighing <1,000 g, **periventricular leukomalacia (PVL)** develops.

PATHOGENESIS

The major neuropathologic lesions associated with very-low-birthweight (VLBW) infants are IVH and PVL. IVH in premature infants occurs in the gelatinous subependymal germinal matrix. This periventricular area is the site of origin for embryonal neurons and fetal glial cells, which migrate outwardly to the cortex. Immature blood vessels in this highly vascular region of the developing brain combined with poor tissue vascular support predispose premature infants to hemorrhage. The germinal matrix involutes as the infant approaches full-term gestation and the tissue's vascular integrity improves; therefore IVH is much less common in the term infant. **Periventricular hemorrhagic infarction** often develops after a large IVH owing to venous congestion. Predisposing factors for IVH include prematurity, RDS, hypoxic–ischemic or hypotensive injury, reperfusion injury of damaged vessels, increased or decreased cerebral blood flow, reduced vascular integrity, increased venous pressure, pneumothorax, thrombocytopenia, hypervolemia, and hypertension.

Understanding of the pathogenesis of PVL is evolving, and it appears to involve both intrauterine and postnatal events. A complex interaction exists between the development of the cerebral vasculature and the regulation of cerebral blood flow (both of which are gestational age-dependent), disturbances in the oligodendrocyte precursors required for myelination, and maternal/fetal infection and/or inflammation. Similar factors (hypoxia–ischemia), venous obstruction from an IVH, or undetected fetal stress may result in decreased perfusion to the brain, leading, in turn, to periventricular hemorrhage and necrosis. PVL is characterized by focal necrotic lesions in the periventricular white matter and/or more diffuse white matter damage. The risk for PVL increases in infants with severe IVH and/or ventriculomegaly. The corticospinal tracts descend through the periventricular white matter, hence the association between cerebral white matter injury/PVL and motor abnormalities, including cerebral palsy.

CLINICAL MANIFESTATIONS

The majority of patients with IVH, including some with moderate to severe hemorrhages, have no initial clinical signs. Some premature infants in whom severe IVH develops may have acute deterioration on the 2nd or 3rd day of life. Hypotension, apnea, pallor, or cyanosis; poor suck; abnormal eye signs; a high-pitched, shrill cry; convulsions, or decreased muscle tone; metabolic acidosis; shock; and a decreased hematocrit or failure of the hematocrit to increase after transfusion may be the first clinical indications. IVH may rarely manifest at birth; 50% of cases are diagnosed within the 1st day of life, and up to 75% within the 1st 3 days. A small percentage of infants have late hemorrhage, between days 14 and 30. IVH as a primary event is rare after the 1st mo of life.

PVL is usually clinically asymptomatic until the neurologic sequelae of white matter damage become apparent in later infancy as spastic motor deficits. PVL may be present at birth but usually occurs later as

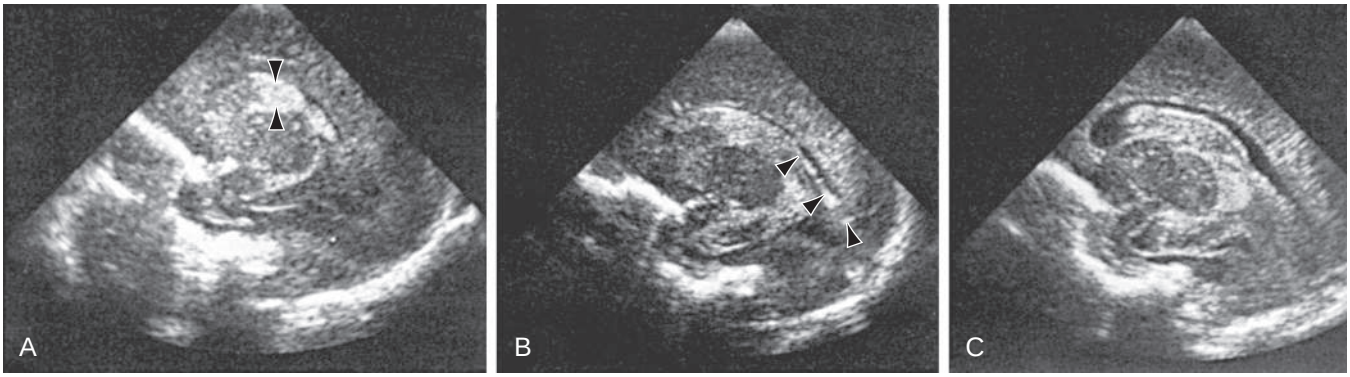

Figure 99-3 Grading the severity of germinal matrix intraventricular hemorrhage with parasagittal ultrasound scans. *A,* Grade I: Note the echogenic blood in the germinal matrix *(arrowheads)* just anterior to the anterior tip of the choroid plexus, which (normally) is also echogenic. *B,* Grade II: Note the echogenic blood *(arrowheads)* filling <50% of the ventricular area. *C,* Grade III: Note the large blood clot nearly completely filling and distending the entire lateral ventricle. *(From Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage of the premature infant. In Volpe JJ:* Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders.)*

an early echodense phase (3-10 days of life), followed by the typical echolucent (cystic) phase (14-20 days of life).

The severity of hemorrhage may be defined on cranial imaging by the location and degree of bleeding and ventricular dilation. In a **grade I** hemorrhage, bleeding is isolated to the subependymal area. In **Grade II** hemorrhage, there is bleeding within the ventricle but without evidence of ventricular dilation. **Grade III** hemorrhage consists of IVH with ventricular dilation. In **Grade IV** hemorrhage, there is intraventricular and parenchymal hemorrhage. Another grading system describes 3 levels of increasing severity of IVH detected on ultrasound: In **grade I,** bleeding is confined to the germinal matrix–subependymal region or to <10% of the ventricle (≈35% of IVH cases); **grade II** is defined as intraventricular bleeding with 10-50% filling of the ventricle (≈40% of IVH cases) and in **grade III**, more than 50% of the ventricle is involved, with dilated ventricles (Fig. 99-3). **Ventriculomegaly** is defined as mild (0.5-1 cm dilation), moderate (1.0-1.5 cm dilation), or severe (>1.5 cm dilation).

DIAGNOSIS

Intracranial hemorrhage is suspected on the basis of the history, clinical manifestations, and knowledge of the birthweight-specific risks for IVH. The associated clinical signs of IVH are typically nonspecific or absent; therefore, it is recommended that premature infants <32 wk of gestation be evaluated with routine real-time cranial ultrasonography through the anterior fontanel to screen for IVH. Infants <1,000 g are at highest risk and should undergo cranial ultrasonography within the 1st 3-7 days of age, when approximately 75% of lesions will be detectable. Ultrasonography is the preferred imaging technique for screening because it is noninvasive, portable, reproducible, and sensitive and specific for detection of IVH. All at-risk infants should undergo follow-up ultrasonography at 36-40 wk of postmenstrual age to evaluate adequately for PVL, because cystic changes related to perinatal injury may not be visible for at least 2-4 wk. In one study, 29% of low-birthweight (LBW) infants who later experienced cerebral palsy did not have radiographic evidence of PVL until after 28 days of age. Ultrasonography also detects the precystic and cystic symmetric lesions of PVL and the asymmetric intraparenchymal echogenic lesions of cortical hemorrhagic infarction. Furthermore, the delayed development of cortical atrophy, porencephaly, and the severity, progression, or regression of posthemorrhagic hydrocephalus can be determined by serial ultrasonographic examinations.

Approximately 3-5% of VLBW infants develop **posthemorrhagic hydrocephalus (PHH)** that sometimes requires ventriculoperitoneal shunt insertion; if the initial ultrasonography findings are abnormal, additional interval ultrasonographic studies are indicated to monitor for the development of hydrocephalus.

IVH represents only 1 facet of brain injury in the term or preterm infant. MRI is a more sensitive tool for evaluation of extensive periventricular injury and may be more predictive of adverse long-term outcome. CT or, more reliably, diffusion-weighted MRI is indicated for term infants in whom brain injury or stroke is suspected, because ultrasonography may not reveal edema or intraparenchymal hemorrhage and infarction.

PROGNOSIS

The degree of IVH and the presence of PVL are strongly linked to neurodevelopmental impairment. For infants with a birthweight of <1,000 g, the incidences of severe neurologic impairment (defined as Bayley Scales of Infant Development II mental developmental index <70, psychomotor development index <70, cerebral palsy, blindness, or deafness) are approximately 50%, 55%, and 70% for infants with grade II, grade III, and grade IV IVH, respectively (Table 99-1). In contrast, the rate of neurodevelopmental impairment is approximately 40% in infants (weighing <1,000 g) without IVH and those with grade I IVH. PVL, cystic PVL, and progressive hydrocephalus requiring shunt insertion are each independently associated with a poorer prognosis.

Most infants with IVH and acute ventricular distention do not have **PHH.** Ten percent to 15% of LBW neonates with IVH demonstrate PHH, which may initially be present without clinical signs, such as an enlarging head circumference, lethargy, a bulging fontanel or widely split sutures, apnea, and bradycardia. In infants in whom symptomatic hydrocephalus develops, clinical signs may be delayed 2-4 wk despite progressive ventricular distention with compression and thinning of the cerebral cortex. Many infants with PHH have spontaneous regression; 3-5% of VLBW infants with PHH require shunt insertion. Infants with PHH requiring shunt insertion have lower cognitive and psychomotor performance at 18-22 mo.

PREVENTION

Improved perinatal care is imperative to minimize traumatic brain injury and decrease the risk of preterm delivery. The incidence of traumatic intracranial hemorrhage may be reduced by judicious management of cephalopelvic disproportion and operative (forceps, vacuum) delivery. Fetal or neonatal hemorrhage caused by maternal idiopathic thrombocytopenic purpura or alloimmune thrombocytopenia may be reduced by maternal treatment with steroids, intravenous immunoglobulin, fetal platelet transfusion, or cesarean section. Meticulous care of the LBW infant's respiratory status and fluid and electrolyte management—including avoidance of acidosis, hypocarbia, hypoxia, hypotension, wide fluctuations in neonatal blood pressure or P_{CO_2}, and pneumothorax—are important factors that may affect the risk for development of IVH and PVL.

A single course of antenatal corticosteroids is recommended in pregnancies 24-34 wk of gestation that are at risk for preterm delivery. Antenatal steroids decrease the risk of death, grades III and IV IVH,

Table 99-1 Percentage of Infants with Each Neurologic Outcome at 18 to 22 Mo Corrected Age by Head Ultrasound Findings*

HEAD ULTRASOUND VARIABLE	NDI (N = 929)	MDI > 70 (N = 174)	PDI < 70 (N = 478	CEREBRAL PALSY (N = 478)	BLINDNESS (N = 66)	DEAFNESS (N = 42)	NONINDEPENDENT WALKING (N = 260)	NONINDEPENDENT FEEDING (N = 318)
Normal (n = 1308)	39.4	31.9	18.8	10.1	1.6	1.5	7.7	12.8
Intracranial hemorrhage:								
Grade 1 (n = 244)	40.6	31.5	18.0	17.2	2.9	1.2	10.7	13.9
Grade 2 (n = 151)	51.0	36.9	22.3	17.2	4.0	3.3	9.3	13.9
Grade 3 (n = 215)	55.4	43.3	36.7	31.3	7.0	2.8	25.1	23.4
Grade 4 (n = 145)	69.7	52.6	55.5	51.4	11.2	4.9	42.4	28.5
Periventricular leukomalacia (n = 134)	72.4	60.3	52.8	50.0	10.5	3.7	44.0	29.1
Cystic periventricular leukomalacia (n = 50)	76.0	60.4	64.6	64.0	18.0	6.3	50.0	32.0

*All infants were counted only once and were assigned the highest grade of intracranial hemorrhage/leukomalacia from either head ultrasound scan. Missing values in either the row or column variable were excluded from the analysis.

MDI, Mental Developmental Index; NDI, neurodevelopment impairment; PDI, Psychomotor Developmental Index.

Data from Broitman E, Ambalavanan N, Higgins RD, et al: Clinical data predict neurodevelopmental outcome better than head ultrasound in extremely low birth weight infants, J Pediatr *151:500–505, 2007.*

and PVL in the neonate. The prophylactic administration of low-dose indomethacin (0.1 mg/kg/day for 3 days) to VLBW preterm infants reduces the incidence of severe IVH.

TREATMENT

Although no treatment is available for IVH, it may be associated with other complications that require therapy. Seizures should be treated with anticonvulsant drugs. Anemia and coagulopathy require transfusion with packed red blood cells or fresh-frozen plasma. Shock and acidosis are treated with the judicious and slow administration of sodium bicarbonate and fluid resuscitation.

Insertion of a ventriculoperitoneal shunt is the preferred method to treat progressive and symptomatic PHH; some infants require temporary cerebrospinal fluid diversion before a permanent shunt can be safety inserted. Diuretics and acetazolamide are not effective. Serial lumbar punctures, ventricular taps or reservoirs, and externalized ventricular drains are potential temporizing interventions; they have an associated risk of infection and of "puncture porencephaly" owing to injury to the surrounding parenchyma. A ventriculosubgaleal shunt inserted from the ventricle into a surgically created subgaleal pocket provides a closed system for constant ventricular decompression without these additional risk factors. Decompression is regulated by the pressure gradient between the ventricle and the subgaleal pocket.

Bibliography is available at Expert Consult.

99.4 Brain Injury from Inflammation, Infection, and Medications

Waldemar A. Carlo and Namasivayam Ambalavanan

Severe IVH and PVL are the most commonly associated risk factors for adverse outcome in the VLBW infant. Other factors are also involved in the etiology of perinatal brain injury. Cytokines and prenatal or postnatal infection or inflammation may contribute to brain injury. A systemic inflammatory response syndrome in the mother, fetus, or infant may induce the production of various inflammatory mediators that are directly cytotoxic or cause decreased CNS perfusion (Fig. 99-4). Preterm infants with evidence (often subclinical) of intrauterine or postnatal infection or maternal chorioamnionitis are more likely than uninfected infants to have adverse neurodevelopmental outcome including cerebral palsy.

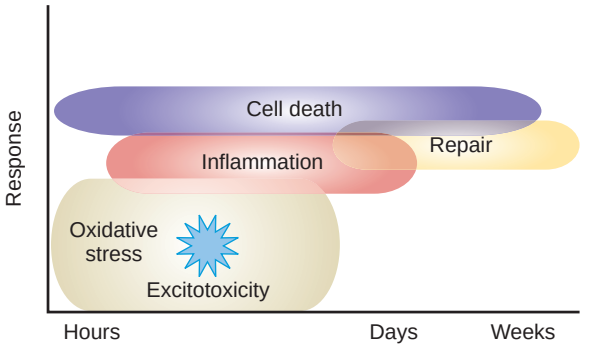

Figure 99-4 Mechanisms of brain injury in the term neonate. Oxidative stress and excitotoxicity, through downstream intracellular signaling, produce both inflammation and repair. Cell death begins immediately and continues during a period of days to weeks. The cell-death phenotype changes from an early necrotic morphology to a pathology resembling apoptosis. This evolution is called the necrosis-apoptosis continuum. *(From Ferriero DM: Neonatal brain injury,* N Engl J Med *351:1985–1995, 2004.Copyright © 2004 Massachusetts Medical Society. All rights reserved.)*

In utero infections may involve the developing CNS and directly impair cell growth or produce cell neurosis, resulting in microcephaly, developmental delay, mental retardation, or cerebral palsy. These specific congenital or perinatal acquired infections include those caused by cytomegalovirus (see Chapter 255), toxoplasmosis (see Chapter

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290), herpes simplex (see Chapter 252), syphilis (see Chapter 218), rubella (see Chapter 247), and human immunodeficiency virus (see Chapter 276). Postnatal acquired bacterial meningitis in the 1st yr, but even more so in the 1st mo of life, is another major risk factor for CNS injury and associated adverse neurodevelopmental outcome (see Chapter 603).

Long-term adverse neurodevelopmental outcomes are also associated with high-dose postnatal corticosteroid use in VLBW infants. Early postnatal exposure to dexamethasone, within the 1st wk of life, is associated with metabolic derangements, poor growth, increased risk for sepsis, and an increased risk of spontaneous bowel perforation. Infants exposed to postnatal steroids after the 1st wk of life have an increased risk of cerebral palsy and developmental delay. The risk may be increased with prolonged steroid use (>6 wk). At 8 yr of age, dexamethasone-treated children are smaller, have smaller head circumferences, poorer motor skills and coordination, more difficulty with visual motor integration, and lower full-scale verbal IQ and performance IQ scores. It is recommended that postnatal corticosteroid use in VLBW infants be limited to exceptional clinical circumstances and that parents of infants in whom corticosteroids are used be informed of the potential adverse side effects, including increased risk for developmental delay, cerebral palsy, and impaired growth.

Necrotizing enterocolitis (NEC) affects approximately 9-14% of LBW infants and is associated with significant morbidity and mortality (see Chapter 102.2). Patients with NEC requiring surgery are more likely to have Mental Developmental Index (MDI) scores <70, Psychomotor Developmental Index (PDI) scores <70, and evidence of overall neurodevelopmental impairment. Infants with severe NEC are reported to have a higher incidence of PVL, postnatal infections, and poor growth.

Bibliography is available at Expert Consult.

99.5 Hypoxic–Ischemic Encephalopathy

Namasivayam Ambalavanan and Waldemar A. Carlo

Anoxia is a term used to indicate the consequences of complete lack of oxygen as a result of a number of primary causes. **Hypoxemia** refers to decreased arterial concentration of oxygen. **Hypoxia** refers to a decreased oxygenation to cells or organs. **Ischemia** refers to blood flow to cells or organs that is insufficient to maintain their normal function. **Hypoxic–ischemic encephalopathy (HIE)** is an important cause of permanent damage to CNS tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay. Approximately 20-30% of infants with HIE die in the neonatal period, and ≈33-50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation). The greatest risk of adverse outcome is seen in infants with severe fetal acidosis (pH <6.7) (90% death/impairment) and a base deficit >25 mmol/L (72% mortality). Multiorgan failure and insult can occur (Table 99-2).

Table 99-2 Multiorgan Systemic Effects of Asphyxia

SYSTEM	EFFECT(S)
CNS	HIE, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stunning, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, RDS
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

ETIOLOGY

Most neonatal encephalopathic or seizure disorders, in the absence of major congenital malformations or syndromes, appear to be caused by perinatal events. Brain MRI or autopsy findings in full-term neonates with encephalopathy demonstrate that 80% have acute injuries, <1% have prenatal injuries, and 3% have non–hypoxic-ischemic diagnoses. Fetal hypoxia may be caused by various disorders in the mother, including (1) inadequate oxygenation of maternal blood from hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning; (2) low maternal blood pressure from acute blood loss, spinal anesthesia, or compression of the vena cava and aorta by the gravid uterus; (3) inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin; (4) premature separation of the placenta; (5) impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord; and (6) placental insufficiency from toxemia or postmaturity.

Placental insufficiency often remains undetected on clinical assessment. Intrauterine growth restriction may develop in chronically hypoxic fetuses without the traditional signs of fetal distress. Doppler umbilical waveform velocimetry (demonstrating increased fetal vascular resistance) and cordocentesis (demonstrating fetal hypoxia and lactic acidosis) identify a chronically hypoxic infant (see Chapter 96). Uterine contractions may further reduce umbilical oxygenation, depressing the fetal cardiovascular system and CNS and resulting in low Apgar scores and respiratory depression at birth.

After birth, hypoxia may be caused by (1) failure of oxygenation as a result of severe forms of cyanotic congenital heart disease or severe pulmonary disease; (2) severe anemia (severe hemorrhage, hemolytic disease); or (3) shock severe enough to interfere with the transport of oxygen to vital organs from overwhelming sepsis, massive blood loss, and intracranial or adrenal hemorrhage.

PATHOPHYSIOLOGY AND PATHOLOGY

The topography of injury typically correlates with areas of decreased cerebral blood flow. After an episode of hypoxia and ischemia, anaerobic metabolism occurs and generates increased amounts of lactate and inorganic phosphates. Excitatory and toxic amino acids, particularly glutamate, accumulate in the damaged tissue. Increased amounts of intracellular sodium and calcium may result in tissue swelling and cerebral edema. There is also increased production of free radicals and nitric oxide in these tissues. The initial circulatory response of the fetus is increased shunting through the ductus venosus, ductus arteriosus, and foramen ovale, with transient maintenance of perfusion of the brain, heart, and adrenals in preference to the lungs, liver, kidneys, and intestine.

The pathology of hypoxia–ischemia depends on the affected organ and the severity of the injury. Early congestion, fluid leak from increased capillary permeability, and endothelial cell swelling may then lead to signs of coagulation necrosis and cell death. Congestion and petechiae are seen in the pericardium, pleura, thymus, heart, adrenals, and meninges. Prolonged intrauterine hypoxia may result in inadequate perfusion of the periventricular white matter, resulting, in turn, in PVL. Pulmonary arteriole smooth muscle hyperplasia may develop, which predisposes the infant to pulmonary hypertension (see Chapter 101.7). If fetal distress produces gasping, the amniotic fluid contents (meconium, squames, lanugo) may be aspirated into the trachea or lungs.

The combination of chronic fetal hypoxia and acute hypoxic-ischemic injury around the time of birth results in gestational age–specific neuropathology (Table 99-3). Term infants demonstrate neuronal necrosis of the cortex (later, cortical atrophy) and parasagittal

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Table 99-3 Topography of Brain Injury in Term Infants with HIE and Clinical Correlates

AREA OF INJURY	LOCATION OF INJURY	CLINICAL CORRELATE(S)	LONG-TERM SEQUELA(E)
Selective neuronal necrosis	Entire neuraxis, deep cortical area, brainstem and pontosubicular	Stupor or coma Seizures Hypotonia Oculomotor abnormalities Suck/swallow abnormalities	Cognitive delay Cerebral palsy Dystonia Seizure disorder Ataxia Bulbar and pseudobulbar palsy
Parasagittal injury	Cortex and subcortical white matter Parasagittal regions, especially posterior	Proximal limb weakness Upper extremities affected more than lower extremities	Spastic quadriparesis Cognitive delay Visual and auditory processing difficulty
Focal ischemic necrosis	Cortex and subcortical white matter Vascular injury (usually middle cerebral artery distribution)	Unilateral findings Seizures common and typically focal	Hemiparesis Seizures Cognitive delays
Periventricular injury	Injury to motor tracts, especially lower extremity	Bilateral and symmetric weakness in lower extremities More common in preterm infants	Spastic diplegia

Modified from Volpe JJ: Neurology of the newborn, *ed 4, Philadelphia, 2001, WB Saunders.*

ischemic injury. Preterm infants demonstrate PVL (later, spastic diplegia), status marmoratus of the basal ganglia, and IVH. Term more often than preterm infants have focal or multifocal cortical infarcts that manifest clinically as focal seizures and hemiplegia.

CLINICAL MANIFESTATIONS

Intrauterine growth restriction with increased vascular resistance may be the first indication of fetal hypoxia. During labor, the fetal heart rate slows and beat-to-beat variability declines. Continuous heart rate recording may reveal a variable or late deceleration pattern (see Fig. 96-4). Particularly in infants near term, these signs should lead to the administration of high concentrations of oxygen to the mother and consideration of immediate delivery to avoid fetal death and CNS damage.

At delivery, the presence of meconium-stained amniotic fluid indicates that fetal distress may have occurred. At birth, affected infants may be depressed and may fail to breathe spontaneously. During the ensuing hours, they may remain hypotonic or change from a hypotonic to a hypertonic state, or their tone may appear normal (Tables 99-4 and 99-5). Pallor, cyanosis, apnea, a slow heart rate, and unresponsiveness to stimulation are also signs of HIE. Cerebral edema may develop during the next 24 hr and result in profound brainstem depression. During this time, seizure activity may occur; it may be severe and refractory to the usual doses of anticonvulsants. Though most often a result of the HIE, seizures in asphyxiated newborns may also be a result of hypocalcemia, hypoglycemia, or infection.

In addition to CNS dysfunction, systemic organ dysfunction is noted in up to 80% of affected neonates; heart failure and cardiogenic shock, persistent pulmonary hypertension, RDS, gastrointestinal perforation, and acute kidney injury are associated with perinatal asphyxia secondary to inadequate perfusion (see Table 99-2).

The severity of neonatal encephalopathy depends on the duration and timing of injury. Symptoms develop over a series of days, making it important to perform serial neurologic examinations (see Tables 99-4 and 99-5). During the initial hours after an insult, infants have a depressed level of consciousness. Periodic breathing with apnea or bradycardia is present, but cranial nerve functions are often spared with intact pupillary responses and spontaneous eye movement. Seizures are common with extensive injury. Hypotonia is also common as an early manifestation.

DIAGNOSIS

Diffusion-weighted MRI is the preferred imaging modality in neonates with HIE because of its increased sensitivity and specificity early in the process and its ability to outline the topography of the lesion (Figs. 99-5 to 99-8, Table 99-6). CT scans are helpful in identifying focal hemorrhagic lesions, diffuse cortical injury, and damage to the basal ganglia; CT has limited ability to identify cortical injury during the 1st few days of life. Ultrasonography has limited utility in evaluation of hypoxic injury in the term infant; it is the initial preferred modality in evaluation of the preterm infant.

Table 99-4 Predictor Variables, Odds Ratios, and Scores Assigned to Each Variable for Death/Disability Scoring in Infants with HIE

VARIABLE	LEVEL OF VARIABLE	ODDS RATIO	SCORE*
Posture	Normal Distal flexion Decerebrate	0.037 0.401 1	1 11 27
Spontaneous activity	Normal/decreased None	0.147 1	1 7
Base deficit of first postnatal blood gas analysis	<15 mmol/L 15-22 mmol/L >22 mmol/L	0.073 0.304 1	1 4 14
Apgar score at 5 min	7-10 4-6 0-3	0.082 0.676 1	14 8 12
Chronic hypertension/ preeclampsia/eclampsia	Yes No	0.2 1	1 5

*The total score is obtained by adding the scores for each of the variables. Interpretation of the total score is as follows: <23: no death or moderate/severe disability even without hypothermia; 23-28: probable benefit from hypothermia; 29-52: possible benefit; >52: death/disability likely despite hypothermia. =172.

From Ambalavanan, N, Carlo WA, Shankaran S, et al; National Institute of Child Health and Human Development Neonatal Research Network: Predicting outcomes of neonates diagnosed with hypoxemic-ischemic encephalopathy, Pediatrics *118:2084–2093, 2006.*

Amplitude-integrated electroencephalography (aEEG) may help to determine which infants are at highest risk for long-term brain injury. A single-channel tracing is generated from 2 electrodes placed in the biparietal area. A filter is used to filter and attenuate the signal between 2 Hz and 15 Hz. This technique is simple to perform and correlates with standard electroencephalogram (EEG) It has good reliability, a positive predictive value of 85%, and a negative predictive value of 91-96% for infants who will have adverse neurodevelopmental outcome. The technique provides information quickly within the window during which intervention is most likely to be useful. Also, aEEG is able to detect seizure activity, which is common in patients

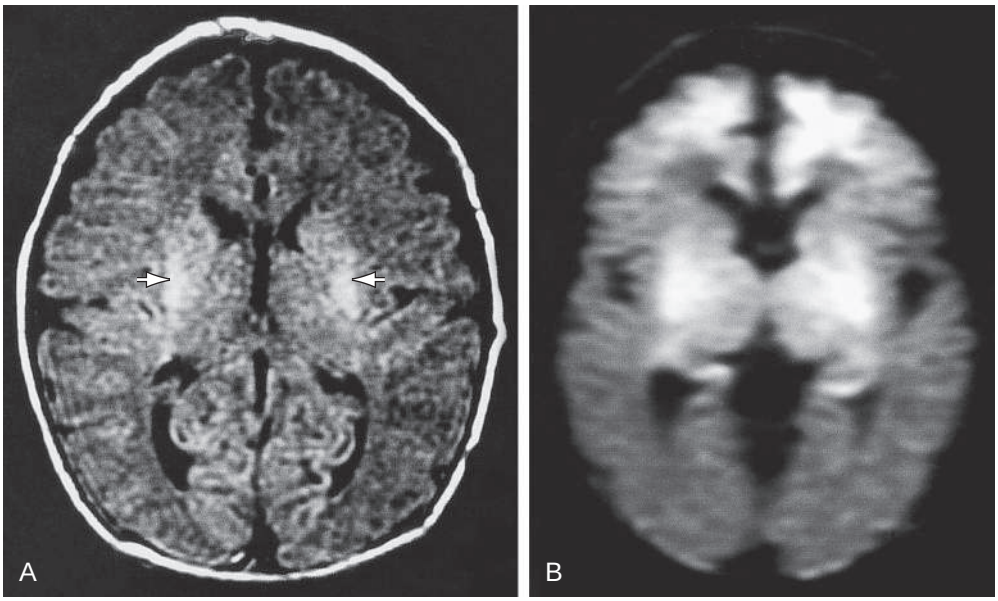

Figure 99-5 **MR images of selective neuronal injury.** The infant experienced intrapartum asphyxia and had seizures on the 1st postnatal day. MRI was performed on the 5th postnatal day. *A*, An axial, fluid-attenuated inversion recovery image shows increased signal in the putamen bilaterally *(arrows)* but no definite abnormality in the cerebral cortex. *B*, By contrast, a diffusion-weighted image shows striking increased signal intensity (i.e., decreased diffusion) in the frontal cortex (in addition to a more pronounced basal ganglia abnormality). *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 420.)*

Table 99-5 HIE in Term Infants

SIGNS	STAGE 1	STAGE 2	STAGE 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
Electroencephalographic findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	<24 hr if progresses; otherwise, may remain normal	24 hr-14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

Modified from Sarnat HB, Sarnat MS: Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study, Arch Neurol *33:696–705, 1976. Copyright 1976, American Medical Association.*

with HIE. Continuous aEEG monitoring detects subclinical seizure activity during the subacute phase.

TREATMENT

Whole body (systemic) or selective cerebral therapeutic hypothermia reduces mortality or major neurodevelopmental impairment in term and near-term infants with HIE. Hypothermia decreases the rate of apoptosis and suppresses production of mediators known to be neurotoxic, including extracellular glutamate, free radicals, nitric oxide, and lactate.

Isolated cerebral cooling or more often systemic induced servo controlled hypothermia to a core (rectal) temperature of 33.5°C (92.3°F) within the 1st 6 hr after birth (duration 72 hr) reduces mortality and major neurodevelopmental impairment at 18 mo of age. Systemic hypothermia may result in more uniform cooling of the brain and deeper CNS structures. Infants treated with systemic hypothermia have a lower incidence of cortical neuronal injury on MRI. Complications of induced hypothermia include thrombocytopenia (usually without bleeding), reduced heart rate, and subcutaneous fat necrosis (associated with hypercalcemia in some) and the potential for overcooling and the cold injury syndrome. The latter is avoided with a servocontrolled cooling system. Therapeutic hypothermia may theoretically alter drug metabolism, prolong the QT interval, and effect the interpretation of blood gases. In practice, none of these concerns have been observed during therapeutic hypothermia.

Phenobarbital, the drug of choice for seizures, is given with an intravenous loading dose (20 mg/kg); additional doses of 5-10 mg/kg (up to 40-50 mg/kg total) may be needed. Phenytoin (20 mg/kg

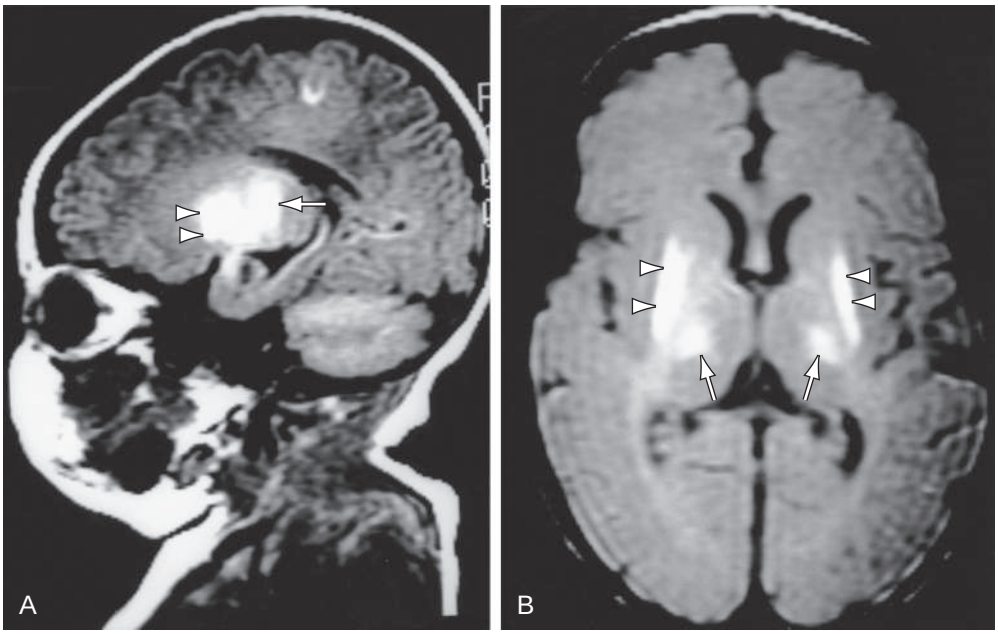

Figure 99-6 MR images of hypoxic-ischemic injury to basal ganglia and thalamus. MRI was performed in a 5 day old infant who experienced severe perinatal asphyxia. *A,* Note, in this parasagittal T1-weighted image, the markedly increased signal intensity in the basal ganglia, especially the putamen *(arrowheads)* and the thalamus *(arrow). B,* An axial proton density image also demonstrates the injury well in the same distribution. *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 420.)*

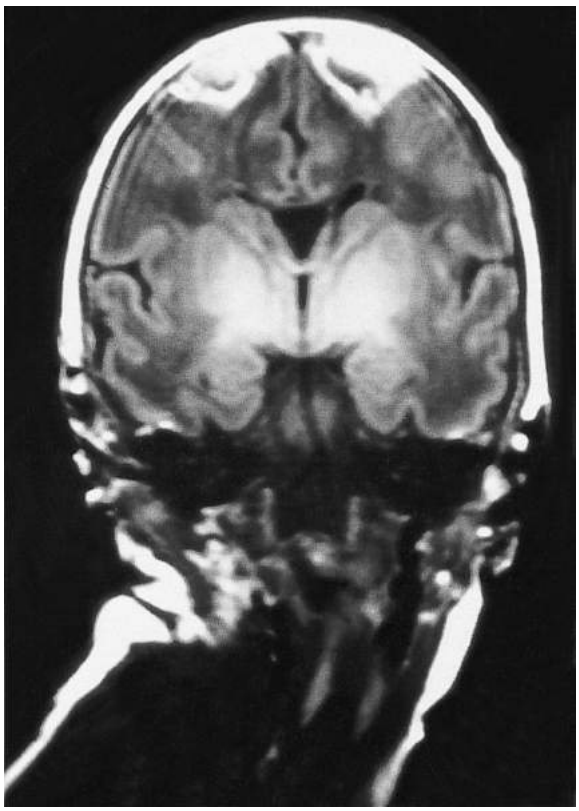

Figure 99-7 MR image of a parasagittal cerebral injury. A coronal T1-weighted image, obtained on the 5th postnatal day in an asphyxiated term infant, shows striking triangular lesions in the parasagittal areas bilaterally; increased signal intensity is also apparent in the basal ganglia and thalamus bilaterally. *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 421.)*

Table 99-6 Major Aspects of MRI in the Diagnosis of HIE in the Term Infant

Major Conventional MRI Findings in the First Week
Cerebral cortical gray-white differentiation lost (on T1W or T2W)
Cerebral cortical high signal (T1W and FLAIR), especially in parasagittal perirolandic cortex
Basal ganglia–thalamus, high signal (T1W and FLAIR, usually associated with the cerebral cortical changes but possibly alone with increased signal in brainstem tegmentum in cases of acute severe insults
Parasagittal cerebral cortex, subcortical white matter, high signal (T1W and FLAIR)
Periventricular white matter, decreased signal (T1W) or increased signal (T2W)
Posterior limb of internal capsule, decreased signal (T1W or FLAIR)
Cerebrum in a vascular distribution, decreased signal (T1W), but much better visualized as decreased diffusion (increased signal) on diffusion-weighted MRI
Diffusion-weighted MRI more sensitive than conventional MRI, especially in 1st days after birth, when former shows decreased diffusion (increased signal) in injured areas

FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; T1W and T2W, T1- and T2-weighted images.

(From Volpe JJ, editor: Neurology of the newborn, *ed 5, Philadelphia, 2008, Elsevier, Table 9-16, p. 419.)*

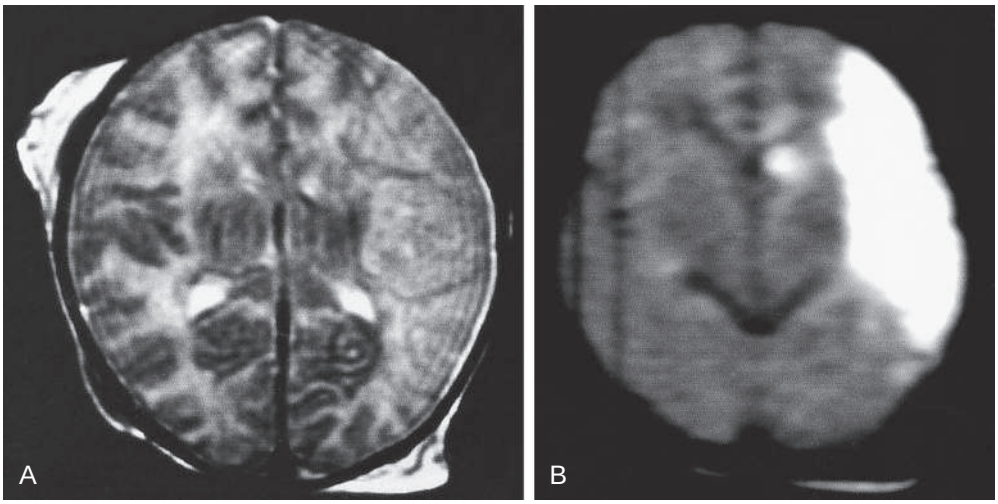

Figure 99-8 MR images of focal ischemic cerebral injury. MRI was performed on the 3rd postnatal day. *A,* An axial T2-weighted image shows a lesion in the distribution of the main branch of the left middle cerebral artery. *B,* A diffusion-weighted image demonstrates the lesion more strikingly. *(From Volpe JJ, editor:* Neurology of the newborn, *ed 5, Philadelphia, 2008, Saunders/Elsevier, p. 422.)*

loading dose) or lorazepam (0.1 mg/kg) may be needed for refractory seizures. Phenobarbital levels should be monitored 24 hr after the loading dose has been given and maintenance therapy (5 mg/kg/24hr) is begun. Therapeutic phenobarbital levels are 20-40 µg/mL. There is some clinical evidence that high-dose prophylactic phenobarbital may decrease neurodevelopmental impairment in infants with HIE. Status epilepticus, multifocal seizures and multiple anticonvulsant medications during therapeutic hypothermia, is associated with a poor prognosis. Subclinical (EEG detected) seizures have a better prognosis.

Additional therapy for infants with HIE includes supportive care directed at management of organ system dysfunction. Hyperthermia has been found to be associated with impaired neurodevelopment, so it is important to prevent hyperthermia before initiation of hypothermia. Careful attention to ventilatory status and adequate oxygenation, blood pressure, hemodynamic status, acid–base balance, and possible infection is important. Secondary hypoxia or hypotension from complications of HIE must be prevented. Aggressive treatment of seizures is critical and may necessitate continuous EEG monitoring. In addition hyperoxia, hypocarbia, and hypoglycemia are associated with poor outcomes so careful attention to resuscitation, ventilation, and blood glucose homeostasis are essential.

PROGNOSIS

The outcome of HIE, which correlates with the timing and severity of the insult, ranges from complete recovery to death. The prognosis varies depending on the severity of the insult and the treatment. Infants with initial cord or initial blood pH <6.7 have a 90% risk for death or severe neurodevelopmental impairment at 18 mo of age. In addition, infants with Apgar scores of 0-3 at 5 min, high base deficit (>20-25 mmol/L), decerebrate posture, severe basal ganglia–thalamic lesions, persistence of severe HIE at 72 hr, and lack of spontaneous activity are also at increased risk for death or impairment. These predictor variables can be combined to determine a score that helps with prognosis (see Table 99-4). Infants with the highest risk are likely to die or have severe disability despite aggressive treatment including hypothermia. Those with intermediate scores are likely to benefit from treatment. In general, severe encephalopathy, characterized by flaccid coma, apnea, absence of oculocephalic reflexes, and refractory seizures, is associated with a poor prognosis (see Table 99-5). A low Apgar score at 20 min, absence of spontaneous respirations at 20 min of age, and persistence of abnormal neurologic signs at 2 wk of age also predict death or severe cognitive and motor deficits. The combined use of early EEG and MRI is of some help in predicting outcome in term infants with HIE. Normal MRI and EEG findings are associated with a good recovery, whereas severe MRI and EEG abnormalities predict a poor outcome. Microcephaly and poor head growth during the 1st year of life also correlate with injury to the basal ganglia and white matter and adverse developmental outcome at 12 mo. All survivors of moderate to severe encephalopathy require comprehensive high-risk medical and developmental follow-up. Early identification of neurodevelopmental problems allows prompt referral for developmental, rehabilitative, neurologic care, and early intervention services so that the best possible outcome can be achieved.

Brain death after neonatal HIE is diagnosed from the clinical findings of coma unresponsive to pain, auditory, or visual stimulation; apnea with P_{CO_2} rising from 40 to >60 mm Hg without ventilatory support; and absence of brainstem reflexes (pupillary, oculocephalic, oculovestibular, corneal, gag, sucking) (see Chapter 68.1). These findings must occur in the absence of hypothermia, hypotension, and elevations of depressant drugs (phenobarbital). An absence of cerebral blood flow on radionuclide scans and of electrical activity on EEG (electrocerebral silence) is inconsistently observed in clinically brain-dead neonatal infants. Persistence of the clinical criteria for 2 days in term infants and 3 days in preterm infants predicts brain death in most asphyxiated newborns. Nonetheless, no universal agreement has been reached regarding the definition of neonatal brain death. Consideration of withdrawal of life support should include discussions with the family, the healthcare team, and, if there is disagreement, an ethics committee. The best interest of the infant involves judgments about the benefits and harm of continuing therapy or avoiding ongoing futile therapy.

Bibliography is available at Expert Consult.

99.6 Spine and Spinal Cord

Waldemar A. Carlo and Namasivayam Ambalavanan

Injury to the spine/spinal cord during birth is rare but can be devastating. Strong traction exerted when the spine is hyperextended or when the direction of pull is lateral, or forceful longitudinal traction on the trunk while the head is still firmly engaged in the pelvis, especially when combined with flexion and torsion of the vertical axis, may produce fracture and separation of the vertebrae. Such injuries are most likely to occur when difficulty is encountered in delivering the shoulders in cephalic presentations and the head in breech presentations. The injury occurs most commonly at the level of the 4th cervical vertebra with cephalic presentations and the lower cervical–upper thoracic vertebrae with breech presentations. Transection of the cord may

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occur with or without vertebral fractures; hemorrhage and edema may produce neurologic signs that are indistinguishable from those of transection except that they may not be permanent. Areflexia, loss of sensation, and complete paralysis of voluntary motion occur below the level of injury, although the persistence of a withdrawal reflex mediated through spinal centers distal to the area of injury is frequently misinterpreted as representing voluntary motion. If the injury is severe, the infant, who from birth may be in poor condition because of respiratory depression, shock, or hypothermia, may deteriorate rapidly to death within several hours before any neurologic signs are obvious. Alternatively, the course may be protracted, with symptoms and signs appearing at birth or later in the 1st wk; immobility, flaccidity, and associated brachial plexus injuries may not be recognized for several days. Constipation may also be present. Some infants survive for prolonged periods, their initial flaccidity, immobility, and areflexia being replaced after several weeks or months by rigid flexion of the extremities, increased muscle tone, and spasms. Apnea on day 1 and poor motor recovery by 3 mo are poor prognostic signs.

The **differential diagnosis** of spine/spinal cord injury includes amyotonia congenita and myelodysplasia associated with spina bifida occulta. Ultrasonography or, more often, MRI confirms the diagnosis. Treatment of the survivors is supportive, including home ventilation; patients often remain permanently disabled. When a fracture or dislocation is causing spinal compression, the prognosis is related to the time elapsed before the compression is relieved.

Bibliography is available at Expert Consult.

99.7 Peripheral Nerve Injuries

Waldemar A. Carlo and Namasivayam Ambalavanan

BRACHIAL PALSY

Brachial plexus injury is a common problem, with an incidence of 0.6-4.6/1,000 live births. Injury to the brachial plexus may cause paralysis of the upper part of the arm with or without paralysis of the forearm or hand or, more commonly, paralysis of the entire arm. These injuries occur in macrosomic infants and when lateral traction is exerted on the head and neck during delivery of the shoulder in a vertex presentation, when the arms are extended over the head in a breech presentation, or when excessive traction is placed on the shoulders. Approximately 45% of brachial plexus injuries are associated with shoulder dystocia. In **Erb-Duchenne paralysis**, the injury is limited to the 5th and 6th cervical nerves. The infant loses the power to abduct the arm from the shoulder, rotate the arm externally, and supinate the forearm. The characteristic position consists of adduction and internal rotation of the arm with pronation of the forearm. Power to extend the forearm is retained, but the biceps reflex is absent; the Moro reflex is absent on the affected side (Fig. 99-9). The outer aspect of the arm may have some sensory impairment. Power in the forearm and hand grasps is preserved unless the lower part of the plexus is also injured; the presence of hand grasp is a favorable prognostic sign. When the injury includes the phrenic nerve, alteration in diaphragmatic excursion may be observed with ultrasonography or fluoroscopy. **Klumpke paralysis** is a rare form of brachial palsy, in which injury to the 7th and 8th cervical nerves and the 1st thoracic nerve produces a paralyzed hand and ipsilateral ptosis and miosis **(Horner syndrome)** if the sympathetic fibers of the 1st thoracic root are also injured. Mild cases may not be detected immediately after birth. Differentiation must be made from cerebral injury; from fracture, dislocation, or epiphyseal separation of the humerus; and from fracture of the clavicle. MRI demonstrates nerve root rupture or avulsion.

Full recovery occurs in most patients; prognosis depends on whether the nerve was merely injured or was lacerated. If the paralysis was a result of edema and hemorrhage about the nerve fibers, function should return within a few months; if it was because of laceration, permanent damage may result. Involvement of the deltoid is usually the most serious problem and may result in shoulder drop secondary to muscle atrophy. In general, paralysis of the upper part of the arm has a better prognosis than paralysis of the lower part.

Figure 99-9 Brachial palsy of the left arm (asymmetric Moro reflex).

Treatment consists of initial conservative management with monthly follow-up and a decision for surgical intervention by 3 mo if function has not improved. Partial immobilization and appropriate positioning are used to prevent the development of contractures. In upper arm paralysis, the arm should be abducted 90 degrees with external rotation at the shoulder, full supination of the forearm, and slight extension at the wrist with the palm turned toward the face. This position may be achieved with a brace or splint during the 1st 1-2 wk. Immobilization should be intermittent throughout the day while the infant is asleep and between feedings. In lower arm or hand paralysis, the wrist should be splinted in a neutral position, and padding placed in the fist. When the entire arm is paralyzed, the same treatment principles should be followed. Gentle massage and range-of-motion exercises may be started by 7-10 days of age. Infants should be closely monitored with active and passive corrective exercises. If the paralysis persists without improvement for 3 mo, neuroplasty, neurolysis, end-to-end anastomosis, and nerve grafting offer hope for partial recovery.

The type of treatment and the prognosis depend on the mechanism of injury and the number of nerve roots involved. The mildest injury to a peripheral nerve (neurapraxia) is due to edema and heals spontaneously within a few weeks. Axonotmesis is more severe and is a consequence of nerve fiber disruption with an intact myelin sheath; function usually returns in a few months. Total disruption of nerves (neurotmesis) or root avulsion is the most severe, especially if it involves C5-T1; microsurgical repair may be indicated. Fortunately, most (75%) injuries are at the root level C5-C6, involve neurapraxia and axonotmesis, and should heal spontaneously. Botulism toxin may be used to treat biceps-triceps co-contractions.

PHRENIC NERVE PARALYSIS

Phrenic nerve injury (3rd, 4th, 5th cervical nerves) with diaphragmatic paralysis must be considered when cyanosis and irregular and labored respirations develop. Such injuries, usually unilateral, are associated with ipsilateral upper brachial palsy. Because breathing is thoracic in type, the abdomen does not bulge with inspiration. Breath

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sounds are diminished on the affected side. The thrust of the diaphragm, which may often be felt just under the costal margin on the normal side, is absent on the affected side. The diagnosis is established by ultrasonographic or fluoroscopic examination, which reveals elevation of the diaphragm on the paralyzed side and seesaw movements of the 2 sides of the diaphragm during respiration.

No specific treatment is available; infants should be placed on the involved side and given oxygen if necessary. Initially, intravenous feedings may be needed; later, progressive gavage or oral feeding may be started, depending on the infant's condition. Pulmonary infections are a serious complication. Recovery usually occurs spontaneously by 1-3 mo; rarely, surgical plication of the diaphragm may be indicated.

FACIAL NERVE PALSY

Facial palsy is usually a peripheral paralysis that results from pressure over the facial nerve in utero, from efforts during labor, or from forceps use during delivery. Rarely, it may result from nuclear agenesis of the facial nerve. Peripheral paralysis is flaccid and, when complete, involves the entire side of the face, including the forehead. When the infant cries, movement occurs only on the nonparalyzed side of the face, and the mouth is drawn to that side. On the affected side the forehead is smooth, the eye cannot be closed, the nasolabial fold is absent, and the corner of the mouth droops. The forehead wrinkles on the affected side with central paralysis because only the lower 2/3 of the face is involved. The infant also usually has other manifestations of intracranial injury, most commonly 6th nerve palsy. The prognosis depends on whether the nerve was injured by pressure or the nerve fibers were torn. Improvement occurs within a few weeks in the former instance. Care of the exposed eye is essential. Neuroplasty may be indicated when the paralysis is persistent. Facial palsy may be confused with absence of the depressor muscles of the mouth, which is a benign problem.

Other peripheral nerves are seldom injured in utero or at birth except when they are involved in fractures or hemorrhage.

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Chapter 100

Delivery Room Emergencies

Waldemar A. Carlo

Most infants complete the transition to extrauterine life without difficulty; however, a small percentage requires resuscitation after birth. The most common delivery room emergency for neonates is secondary to failure to initiate and maintain effective respirations. Less frequent, but of major importance, are shock (see Chapter 98), severe anemia (see Chapter 103.1), plethora (see Chapter 103.3), convulsions (see Chapter 593.7), and management of life-threatening congenital malformations (see Chapter 98). Improved perinatal care and prenatal diagnosis of fetal anomalies allow for appropriate maternal transports for high-risk deliveries.

RESPIRATORY DISTRESS AND FAILURE

Disorders of respiration in newborn infants can be categorized as either central nervous system (CNS) failure, representing depression or failure of the respiratory center, or peripheral respiratory difficulty, indicating interference with the alveolar exchange of oxygen and carbon dioxide. Cyanosis occurs in both groups (see Table 98-1). Respiratory problems encountered in the delivery room are most frequently those of airway obstruction and depression of the CNS (maternal medications, asphyxia) with an absence of adequate respiratory effort. Respiratory distress in the presence of good respiratory effort should lead to an immediate consideration of the underlying cause and is an indication for radiographic examination of the chest.

If respiratory movements are made with the mouth closed but the infant fails to move air in and out of the lungs, bilateral **choanal atresia** (see Chapter 376) or other obstruction of the upper respiratory tract should be suspected. The mouth should be opened, and the mouth and pharynx cleared of secretions with gentle suction. An oropharyngeal airway should be inserted, and the source of the obstruction sought immediately. If effective respiratory flow is not produced by opening the infant's mouth and clearing the airway, laryngoscopy is indicated. With obstructive malformations of the mandible, epiglottis, larynx, or trachea, an endotracheal tube should be inserted; prolonged endotracheal intubation or tracheostomy may be required. Respiratory failure caused by CNS depression or injury may require continuous mechanical ventilation.

Hypoplasia of the mandible (Pierre Robin, Stickler, DiGeorge, and other syndromes; see Chapters 308 and 311) with posterior displacement of the tongue may result in symptoms similar to those of choanal atresia and may be temporarily relieved by pulling the tongue or mandible forward or placing the infant in the prone position. A scaphoid abdomen suggests a **diaphragmatic hernia** or **eventration,** as does asymmetry in contour or movement of the chest or a shift of the apical impulse of the heart; these latter manifestations are also compatible with **tension pneumothorax.** A pneumothorax can be the presenting symptom in infants with pulmonary hypoplasia, renal malformations, or both.

Pulmonary causes of respiratory difficulty are discussed in Chapter 101.

FAILURE TO INITIATE OR SUSTAIN RESPIRATION

Failure to initiate or sustain respiratory effort is common at birth. Infants with **primary apnea** respond to stimulation by establishing normal breathing. Infants with secondary apnea need ventilatory assistance. **Secondary apnea** usually originates in the CNS as a result of asphyxia or peripherally because of neuromuscular disorders. Prematurity alone is seldom a causative factor, except in infants weighing <1,500 g. Intrapulmonary problems, such as respiratory distress syndrome, pulmonary hypoplasia associated with oligohydramnios as in Potter syndrome or neuromuscular diseases, bilateral pleural effusions (hydrops fetalis), pneumothorax, and severe intrauterine pneumonia, may at times result in poor ventilation despite strong respiratory efforts. The lungs in affected infants may be noncompliant, and efforts to begin respirations may be inadequate to initiate sufficient ventilation.

Respiratory depression may occur from administration of morphine, meperidine, fentanyl, barbiturates, or tranquilizers to the mother shortly before delivery or from maternal anesthesia given during the 2nd stage of labor. This sequela may be minimized by the use of appropriate analgesic and anesthetic practices. Treatment includes initial physical stimulation and securing of a patent airway. If effective ventilation is not initiated, artificial breathing with a bag and mask must be instituted. At the same time, if the respiratory depression is caused by an opiate, naloxone hydrochloride (Narcan), 0.1 mg/kg, should be given intravenously or intramuscularly. Naloxone is contraindicated in infants born to mothers with opiate addiction as it may precipitate acute neonatal withdrawal with seizures. If depression is a consequence of other anesthetics or analgesics, artificial respiration should be continued until the infant is able to sustain ventilation. CNS-stimulant drugs should not be used because they are ineffective and may be harmful. External cardiac massage, correction of acidosis, and circulatory support with drugs may be important adjuncts to ventilation in the severely asphyxiated infant.

NEONATAL RESUSCITATION

Although the majority of babies undergo a smooth physiologic transition and breathe effectively after delivery, 5-10% requires active intervention to establish normal cardiorespiratory function. The goals of neonatal resuscitation are to prevent the morbidity and mortality

associated with hypoxic–ischemic tissue (brain, heart, kidney) injury and to reestablish adequate spontaneous respiration and cardiac output. High-risk situations should be anticipated from the history of the pregnancy, labor, and delivery and identification of signs of fetal distress. Infants who are born limp, cyanotic, apneic, or pulseless require immediate resuscitation before assignment of the 1-min Apgar score. Rapid and appropriate resuscitative efforts improve the likelihood of preventing brain damage and achieving a successful outcome.

Guidelines for neonatal resuscitation propose an "integrated" assessment/response approach for the initial evaluation of an infant, consisting of simultaneous assessment of infant color, general appearance, and risk factors. The fundamental principles include evaluation of the airway, establishing effective respiration and adequate circulation; the guidelines also highlight the assessment and response to the neonatal heart rate and the management of infants with meconium-stained amniotic fluid.

Immediately after birth, an infant *in need of resuscitation* should be placed under a radiant heater and dried (to avoid passive hypothermia), positioned with the head down and slightly extended; the airway should be cleared by suctioning, and gentle tactile stimulation provided (slapping the foot, rubbing the back). Simultaneously, the infant's color, heart rate, and respiratory effort should be assessed (Fig. 100-1).

The steps in neonatal resuscitation follow the ABCs: **A,** anticipate and establish a patent airway by suctioning and, if necessary, performing endotracheal intubation; **B,** initiate breathing by using tactile stimulation or positive-pressure ventilation with a bag-and-mask or through an endotracheal tube; **C,** maintain the circulation with chest compression and medications, if needed. Figure 100-1 outlines the steps to follow for immediate neonatal evaluation and resuscitation (see also Chapter 67).

If no respirations are noted, or if the heart rate is <100 beats/min, positive-pressure ventilation is given through a tightly fitted face-bag-and-mask for 15-30 sec. In infants with severe respiratory depression that does not respond to positive-pressure ventilation via bag-and-mask, endotracheal intubation should be performed. Many authorities recommend early intubation for extremely low birthweight preterm infants. Table 100-1 lists guidelines for endotracheal tube size and depth of insertion in infants with different birthweights. If the heart rate does not improve after 30 sec with bag-and-mask (or endotracheal) ventilation and remains below 100 beats/min, ventilation is continued and chest compression should be initiated over the lower third of the sternum at a rate of 90 compressions/min. The ratio of compressions to ventilation is 3 : 1 (90 compressions:30 breaths). If the heart rate remains <60 beats/min despite effective compressions and ventilation, administration of epinephrine should be considered. Persistent bradycardia in neonates is usually attributable to hypoxia resulting from respiratory arrest and often responds rapidly to effective ventilation alone. Persistent bradycardia despite what appears to be adequate resuscitation suggests inadequate ventilation or more severe cardiac compromise. Poor response to ventilation may be a result of a loosely fitted mask, poor positioning of the endotracheal tube, intraesophageal intubation, airway obstruction, insufficient pressure, pleural effusions, pneumothorax, excessive air in the stomach, asystole, hypovolemia, diaphragmatic hernia, or prolonged intrauterine asphyxia.

In the past, the inspired gas for neonatal resuscitation had been 100% oxygen. *Resuscitation with room air in term infants is equally effective and may reduce the risk of hyperoxia, which is associated with decreased cerebral blood flow and generation of oxygen free radicals.* Room air is the preferred initial gas for neonatal resuscitation in term infants; if the neonate does not achieve normal oxygen saturation levels within 90 sec, increasing concentrations of oxygen should be blended in (up to 100% oxygen) until normal oxygen saturation levels are achieved. If pulmonary hypertension is suspected (meconium aspiration, diaphragmatic hernia) one may consider 100% oxygen as the initial gas for resuscitation. Particular attention is required during the resuscitation of very-low birthweight neonates, to monitor oxygen saturation and adjust oxygen concentration using an oxygen blender so as to minimize the risk of hyperoxia and hypoxia.

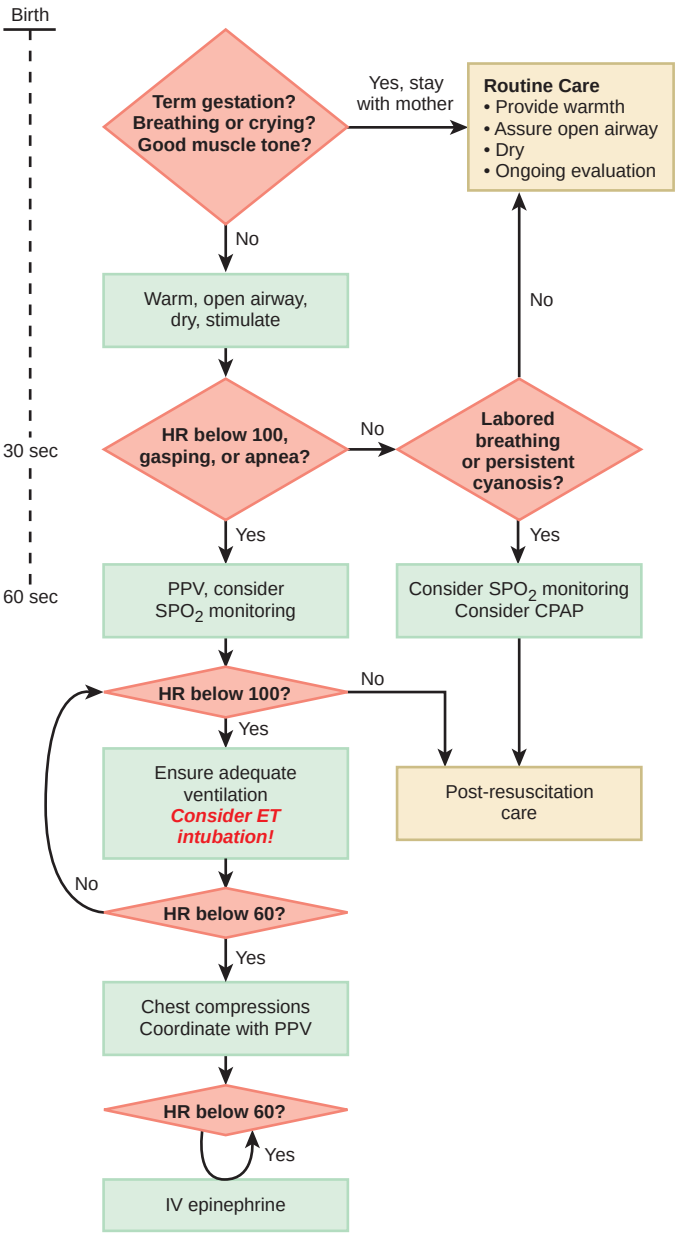

Figure 100-1 Newborn resuscitation algorithm. CPAP, continuous positive airway pressure; ET, endotracheal; HR, heart rate; IV, intravenous; PPV, positive pressure ventilation. *(From the American Academy of Pediatrics:* Textbook of Neonatal Resuscitation, *ed 6, Elk Grove Village, IL, 2011, AAP.)*

Although the first breath normally requires pressures as low as 15-20 cm H_2O, pressures as high as 30-40 cm H_2O may be needed. Subsequent breaths are given at a rate of 40-60/min with a pressure of 15-20 cm H_2O. Noncompliant stiff lungs secondary to respiratory distress syndrome, congenital pneumonia, pulmonary hypoplasia, or meconium aspiration may require higher pressures. Successful ventilation is signified by adequate chest rise, symmetric breath sounds, improved pink color, heart rate >100 beats/min, spontaneous respirations, presence of end-tidal CO_2, and improved tone. Various devices to detect exhaled CO_2 and to confirm accurate placement of an endotracheal tube are available commercially. A laryngeal mask airway may be an effective tool to establish an airway, especially if bag and mask ventilation is ineffective or intubation is unsuccessful.

Table 100-1 Guidelines for Tracheal Tube Size and Depth of Insertion

TUBE SIZE (MM INTERNAL DIAMETER)	DEPTH OF INSERTION FROM UPPER LIP (cm)	WEIGHT (g)	GESTATION (wk)
2.5	6.5-7	<1,000	<28
3	7-8	1,000-2,000	28-34
3/3.5	8-9	2,000-3,000	34-38
3.5/4.0	≥9	>3,000	>38

From Kattwinkel J, Niermeyer S, Nadkarni V, et al: ILCOR advisory statement: resuscitation of the newly born infant: an advisory statement from the Pediatric Working Group of the International Liaison Committee on Resuscitation, Circulation *99:1927–1938, 1999. By permission of the American Heart Association, Inc.*

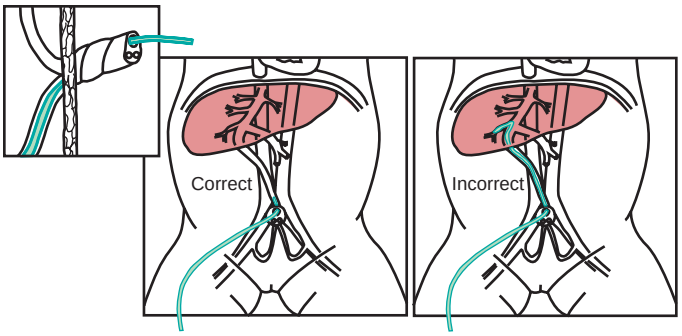

Figure 100-2 Use of the umbilical vein for administration of medications during neonatal resuscitation. *(From Kattwinkel J, Bloom RS, editors:* Neonatal resuscitation textbook, *ed 5, Elk Grove, IL, 2006, American Academy of Pediatrics, American Heart Association.)*

If the infant has respiratory depression and the mother has received an analgesic narcotic drug within 4 hr prior to delivery, naloxone hydrochloride (0.1 mg/kg) is given while adequate ventilation is maintained. Breathing in the depressed infant should be maintained until a response to naloxone is noted. Continuous observation of the infant is important because repeated doses of naloxone may be needed even after the infant has been transferred to the nursery owing to the short half-life of naloxone.

Medications are rarely required but should be administered when the heart rate is <60 beats/min after 30 sec of combined ventilation and chest compressions or during asystole. The umbilical vein can generally be readily cannulated and used for immediate administration of medications during neonatal resuscitation (Fig. 100-2). The endotracheal tube may be used for the administration of epinephrine if intravenous access is not available and/or for naloxone. Epinephrine (0.1-0.3 mL/kg of a 1:10,000 solution, given intravenously or intratracheally) is given for asystole or for failure to respond to 30 sec of combined resuscitation. The dose may be repeated every 3-5 min. Data in neonates are insufficient to recommend higher doses in infants who are unresponsive to the standard dose. Emergency volume expansion is accomplished with 10-20 mL/kg of an isotonic crystalloid solution or type O Rh-negative red blood cells (in acute hemorrhage). Volume infusions should be used cautiously during the resuscitation of a very-low birthweight infant. Sodium bicarbonate (2 mEq/kg, 0.5 mEq/mL of a 4.2% solution) is sometimes given and should be administered slowly (1 mEq/kg/min) if metabolic acidosis has been documented and the resuscitation is prolonged. Sodium bicarbonate should be given only after effective ventilation has been established, because such therapy may increase the blood CO_2 concentration and produce respiratory acidosis, complicating an existing metabolic acidosis. Restoration of oxygenation and tissue perfusion is the main treatment of metabolic acidosis associated with asphyxia.

Severe asphyxia may also depress myocardial function and cause cardiogenic shock despite the recovery of heart and respiratory rates. Dopamine or dobutamine administered as a continuous infusion (5-20 μg/kg/min) and fluids should be started after the initial resuscitation effort, to improve cardiac output in an infant with poor peripheral perfusion, weak pulses, hypotension, tachycardia, and poor urine output. Epinephrine (0.1-1.0 μg/kg/min) may be indicated for infants in severe shock that does not respond to dopamine or dobutamine (see Chapter 67).

Less-severe degrees of poor cardiopulmonary transition in the delivery room can usually be managed by brief periods of bag-and-mask ventilation. Chest compression and medications are not needed for most neonates who have mild to moderate birth depression. Regardless of the severity of asphyxia or the response to resuscitation, asphyxiated infants should be monitored closely for signs of multiorgan hypoxic–ischemic tissue injury (see Table 99-1 in Chapter 99).

MECONIUM

Meconium staining of the amniotic fluid may be an indication of fetal stress; therefore, personnel skilled at endotracheal intubation and resuscitation should be present at the delivery. Previously the decision to intubate a neonate was based on the presence and thickness/consistency of the meconium-stained fluid; *current evidence no longer supports this practice*. If the infant is vigorous with good respiratory effort and a heart rate >100 beats/min, tracheal intubation to aspirate meconium **should not be attempted**; the mouth and nose may be suctioned with a bulb or suction catheter. If the infant is depressed with poor muscle tone and/or a heart rate <100 beats/min, tracheal intubation and suctioning should be performed. The endotracheal tube should be attached to a suction device, and free-flow oxygen should be provided throughout the procedure.

SHOCK

Circulatory insufficiency may be present at birth as a result of severe asphyxia or hemorrhage during gestation, labor, or delivery. Causes of blood loss include hemolysis; placental abruption or tear, placenta previa; traumatic injury to the umbilical cord or internal organs; and intracranial bleeding. Clinical manifestations include signs of respiratory distress, cyanosis, pallor, flaccidity, cold mottled skin, tachycardia or bradycardia, hepatosplenomegaly, and, rarely, convulsions. Edema and hepatosplenomegaly suggest hydrops fetalis or heart failure without shock. Shock from overwhelming infection may be present immediately after birth.

Supportive treatment with type O Rh-negative blood or normal saline is indicated for hemorrhage or hypovolemia, respectively. Oxygen should be administered and the metabolic acidosis corrected with sodium bicarbonate. A sympathomimetic agent such as dopamine or dobutamine may be needed to support cardiac output and blood pressure. The diagnosis and treatment of erythroblastosis fetalis are discussed in Chapter 103.2. If infection is present, appropriate antibiotics must be started as soon as possible.

After supportive measures have stabilized the infant's condition, a specific diagnosis should be established, and appropriate continuing treatment instituted.

PNEUMOTHORAX

Infants may experience pneumothorax in the delivery room, resulting in respiratory distress and hypoxia. Approximately 1-2% of infants have pneumothorax after birth; only 0.05-0.07% have symptoms (see Chapter 101.12). The risk is higher in infants requiring positive pressure ventilation or those with meconium-stained amniotic fluid. Rarely, an infant has a congenital malformation that results in lung hypoplasia, such as congenital diaphragmatic hernia or renal agenesis. Clinically, the infant demonstrates respiratory distress and has diminished breath sounds on the affected side. Transillumination may be helpful to confirm the diagnosis, particularly in the low birthweight infant. Emergency evacuation of a pneumothorax without

radiographic confirmation is indicated in an infant who is unresponsive to resuscitation efforts, and has asymmetric breath sounds, bradycardia, and cyanosis. A 23-gauge butterfly needle or angiocatheter attached to a stopcock and syringe should be inserted perpendicular to the chest wall above the rib in the 4th intercostal space at the level of the nipple (Fig. 100-3). The air is evacuated. The catheter is then inserted with constant negative pressure, and the air evacuated.

AIRWAY OBSTRUCTION

Critical fetal and then neonatal airway obstruction represents an emergency in the delivery room. The **ex utero intrapartum treatment (EXIT) procedure** allows time to secure the airway in an infant known to have airway obstruction for a variety of causes, including laryngeal atresia or stenosis, teratomas, hygromas, and oral tumors, before the infant is separated from the placenta. Uteroplacental gas exchange is maintained throughout the procedure. High-risk perinatal care has led to more frequent prenatal diagnosis of many disorders known to cause the **critical high airway obstruction syndrome (CHAOS)** (Fig. 100-4).

ABDOMINAL WALL DEFECTS

Appropriate management of patients with abdominal wall defects (omphalocele, gastroschisis) in the delivery room prevents excessive fluid loss and minimizes the risk for injury to the exposed viscera.

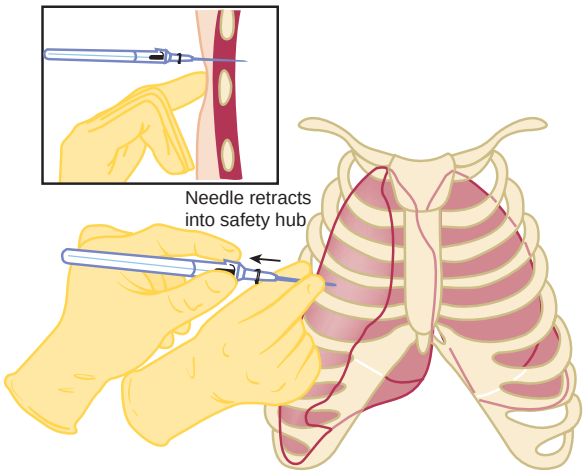

Figure 100-3 Decompression of a pneumothorax. *(From Kattwinkel J, Bloom RS, editors:* Neonatal resuscitation textbook, *ed 5, Elk Grove, IL, 2006, American Academy of Pediatrics, American Heart Association.)*

Gastroschisis is the more common defect and typically the intestines are not covered by a membrane. The exposed intestines should be gently placed in a sterile clear plastic bag after delivery. A membrane often covers an omphalocele, and care should be taken to prevent its rupture. The infant should be transferred to a tertiary referral center for surgical consultation and evaluation for other associated anomalies (see Chapter 105).

INJURY DURING DELIVERY

Central Nervous System

See Chapter 99.

Viscera

The **liver** is the only internal organ other than the brain that is injured with any frequency during the delivery process. Damage usually results from pressure on the liver during delivery of the head in breech presentations. Large infant size, intrauterine asphyxia, coagulation disorders, extreme prematurity, and hepatomegaly are contributing factors. Incorrect cardiac massage is a less-frequent cause. Hepatic rupture may result in the formation of a **subcapsular hematoma,** but the capsule may tamponade further bleeding. Affected infants may appear normal for the 1st 1-3 days. Nonspecific signs related to loss of blood into the hematoma may appear early and include poor feeding, listlessness, pallor, jaundice, tachypnea, and tachycardia. A mass may be palpable in the right upper quadrant, and the abdomen or inguinal area may appear blue. The hematoma may be large enough to cause anemia. Shock and death may occur if the hematoma ruptures into the peritoneal cavity, where the reduced pressure may allow fresh hemorrhage. Early suspicion, ultrasonographic diagnosis, and prompt supportive therapy can decrease the mortality associated with this disorder. Surgical repair of a laceration may be required. Rupture of the spleen may occur alone or in connection with rupture of the liver. The causes, complications, treatment, and prevention are similar.

Although **adrenal hemorrhage** occurs with some frequency, especially after breech delivery, in infants who are large for gestational age or have diabetic mothers, its cause is often undetermined; it may be due to trauma, anoxia, or severe stress, as in overwhelming infection. Ninety percent of adrenal hemorrhages are unilateral; 75% are right-sided. Calcified central hematomas of the adrenal, identified on radiographs or at autopsy in older infants and children, suggest that not all adrenal hemorrhages are immediately fatal. In severe cases, the diagnosis is usually made at postmortem examination. The symptoms are profound shock and cyanosis. A mass may be present in the flank along with overlying skin discoloration; jaundice may also develop. If adrenal hemorrhage is suspected, abdominal ultrasonography may be helpful, and treatment of acute adrenal failure may be indicated (see Chapter 569).

Figure 100-4 EXIT procedure. Baby with teratoma and critical high airway obstruction syndrome (CHAOS). Trachea is displaced to the lateral neck. *(Courtesy of Dr. Mark Wulkan, Pediatric Surgery, Emory University.)*

Fractures

Clavicle

The clavicle is fractured during labor and delivery more frequently than any other bone; it is particularly vulnerable with difficult delivery of the shoulder in vertex presentations and the extended arms in breech deliveries. The infant characteristically does not move the arm freely on the affected side; crepitus and bony irregularity may be palpated, and discoloration is occasionally visible over the fracture site. The Moro reflex is absent on the affected side, and spasm of the sternocleidomastoid muscle with obliteration of the supraclavicular depression at the site of the fracture can be noted. Infants with greenstick clavicle fractures may not have any limitation of movement, and the Moro reflex may be present. The prognosis for this fracture is excellent. **Treatment,** if any, consists of immobilization of the arm and shoulder on the affected side. A remarkable degree of palpable callus develops at the site within a week and may be the initial evidence of the fracture. Fracture of the humerus or brachial palsy may also be responsible for limitation of movement of an arm and absence of a Moro reflex on the affected side.

Extremities

In fractures of the long bones, spontaneous movement of the extremity is usually absent (**pseudoparalysis**). The Moro reflex is often absent from the involved extremity. Associated nerve involvement may occur. Satisfactory results of treatment of a fractured humerus are obtained with 2-4 wk of immobilization, during which the arm is strapped to the chest, a triangular splint and a Velpeau bandage are applied, or a cast is applied. For fracture of the femur, good results are achieved with traction-suspension of both lower extremities, even if the fracture is unilateral; the legs are immobilized in a spica cast. Splints are effective for treatment of fractures of the forearm or leg. Healing is usually accompanied by excess callus formation. The prognosis is excellent for fractures of the extremities. Fractures in very-low birthweight infants may be related to osteopenia of prematurity (see Chapter 106).

Dislocations and epiphyseal separations rarely result from birth trauma. The upper femoral epiphysis may be separated by forcible manipulation of the infant's leg as, for example, in breech extraction or after version. The affected leg shows swelling, slight shortening, limitation of active motion, painful passive motion, and external rotation. The diagnosis is established radiographically. The prognosis is good for milder injuries, but coxa vara frequently results from extensive displacement.

Nose

The most prevalent injury to the nose is dislocation of the cartilaginous portion of the septum from the vomerine groove and the columella. The affected infant may have difficulty nursing and some impairment of nasal respiration. On physical examination, the nares appear asymmetric and the nose is flattened. An oral airway is rarely needed, and surgical consultation should be obtained for definitive treatment.

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Chapter 101

Respiratory Tract Disorders

Waldemar A. Carlo and Namasivayam Ambalavanan

Respiratory disorders are the most frequent cause of admission for neonatal intensive care in both term and preterm infants. Signs and symptoms of respiratory distress include cyanosis, grunting, nasal flaring, retractions, tachypnea, decreased breath sounds with or without rales and/or rhonchi, and pallor. A wide variety of pathologic lesions may be responsible for respiratory disturbances, including pulmonary, airway, cardiovascular, central nervous, infection, and other disorders (Fig. 101-1).

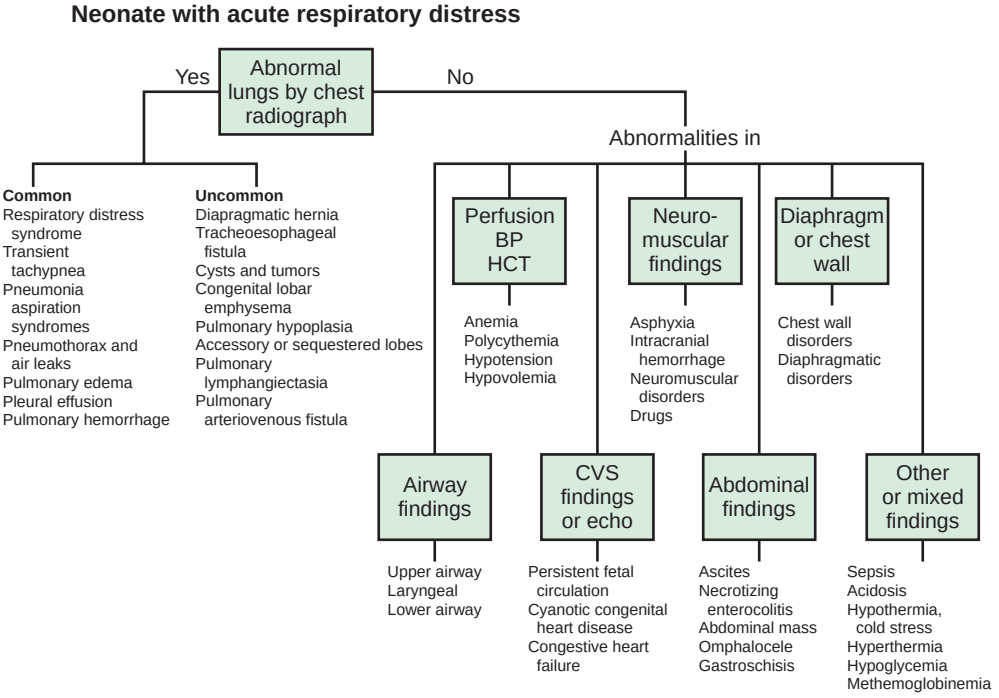

Figure 101-1 Neonate with acute respiratory distress. BP, blood pressure; CVS, cardiovascular system; HCT, hematocrit. *(From Battista MA, Carlo WA: Differential diagnosis of acute respiratory distress in the neonate. In Frantz ID, editor:* Tufts University of School of Medicine and Floating Hospital for Children reports on neonatal respiratory diseases, *vol 2, issue 3, Newtown, PA, 1992, Associates in Medical Marketing Co.)*

It is occasionally difficult to distinguish respiratory from nonrespiratory etiologies on the basis of clinical signs alone. Signs of respiratory distress are an indication for a physical examination and diagnostic evaluation, including a blood gas or pulse oximetry determination and chest x-ray. Timely and appropriate therapy is essential to improve outcome.

101.1 Transition to Pulmonary Respiration

Waldemar A. Carlo

Successful establishment of adequate lung function at birth depends on airway patency, functional lung development, and maturity of respiratory control. Fetal lung fluid must be removed and replaced with gas. This process begins before birth as active sodium transport across the pulmonary epithelium drives liquid from the lung lumen into the interstitium with subsequent absorption into the vasculature. Increased levels of circulating catecholamines, vasopressin, prolactin, and glucocorticoids enhance lung fluid adsorption and trigger the change in lung epithelia from a chloride-secretory to a sodium-reabsorptive mode. Functional residual capacity (FRC) must be established and maintained in order to develop a ventilation–perfusion relationship that will provide optimal exchange of oxygen and carbon dioxide between alveoli and blood (see Chapter 421).

THE FIRST BREATH

During vaginal delivery, intermittent compression of the thorax facilitates removal of lung fluid. Surfactant lining the alveoli enhances the aeration of gas-free lungs by reducing surface tension, thereby lowering the pressure required to open alveoli. Although spontaneously breathing infants do not need to generate an opening pressure to create airflow, infants requiring positive-pressure ventilation at birth need an opening pressure of 13-32 cm H_2O and are more likely to establish FRC if they generate a spontaneous, negative pressure breath. Expiratory esophageal pressures associated with the first few spontaneous breaths in term newborns range from 45-90 cm H_2O. This high pressure, due to expiration against a partially closed glottis, may aid in the establishment of FRC but would be difficult to mimic safely with use of artificial ventilation. The higher pressures needed to initiate respiration are required to overcome the opposing forces of surface tension (particularly in small airways) and the viscosity of liquid remaining in the airways, as well as to introduce about 50 mL/kg of air into the lungs, 20-30 mL/kg of which remains after the first breath to establish FRC. Air entry into the lungs displaces fluid, decreases hydrostatic pressure in the pulmonary vasculature, and increases pulmonary blood flow. The greater blood flow, in turn, increases the blood volume of the lung and the effective vascular surface area available for fluid uptake. The remaining fluid is removed via the pulmonary lymphatics, upper airway, mediastinum, and pleural space. Fluid removal may be impaired after cesarean section or as a result of surfactant deficiency, endothelial cell damage, hypoalbuminemia, high pulmonary venous pressure, or neonatal sedation.

Initiation of the first breath is caused by a decline in Pa_{O_2} and pH and a rise in Pa_{CO_2} as a result of interruption of the placental circulation, a redistribution of cardiac output, a decrease in body temperature, and various tactile and sensory inputs. The relative contributions of these stimuli to the onset of respiration are uncertain.

When compared with term infants, preterm infants have a very compliant chest wall and may be at a disadvantage in establishing FRC. The FRC is lowest in the most immature infants because of the decrease in alveolar number. Abnormalities in ventilation : perfusion ratio are greater and persist for longer periods in preterm infants and may lead to hypoxemia and hypercarbia as a result of atelectasis, intrapulmonary shunting, hypoventilation, and gas trapping. The smallest immature infants have the most profound disturbances as a consequence of respiratory distress syndrome (RDS). However, even in healthy term infants, oxygenation is impaired immediately after birth, and oxygen saturation improves to exceed 90% only around 5 min. In addition, right-to-left shunting is common soon after birth; if pulse oximetry is performed soon after birth, the recommendation is to measure oxygen saturation in the right upper extremity.

BREATHING PATTERNS IN NEWBORNS

During sleep in the 1st few mo after birth, normal full-term infants may have episodes when regular breathing is interrupted by short pauses. This **periodic breathing** pattern, which shifts from a regular rhythmicity to cyclic brief episodes of intermittent apnea, is more common in preterm infants, who may have apneic pauses of 5-10 sec followed by a burst of rapid respirations at a rate of 50-60 breaths/min for 10-15 sec. They rarely have an associated change in color or heart rate, and periodic breathing often stops without apparent reason. Periodic breathing, a normal characteristic of neonatal respiration, has no prognostic significance.

101.2 Apnea

Waldemar A. Carlo

Apnea is a common problem in preterm infants that may be the result of prematurity or an associated illness. In term infants, apnea is always worrisome and demands prompt diagnostic evaluation. Periodic breathing must be distinguished from prolonged apneic pauses, because the latter may be associated with serious illnesses. Apnea is a feature of many primary diseases that affect neonates (Table 101-1). These disorders produce apnea by direct depression of the central nervous system's control of respiration (hypoglycemia, meningitis, drugs, hemorrhage, seizures), disturbances in oxygen delivery (shock, sepsis, anemia), or ventilation defects (obstruction of the airway, pneumonia, muscle weakness).

Idiopathic apnea of prematurity occurs in the absence of identifiable predisposing diseases. Apnea is a disorder of respiratory control and may be obstructive, central, or mixed. **Obstructive apnea** (pharyngeal instability, neck flexion) is characterized by absence of airflow but persistent chest wall motion. Pharyngeal collapse may follow the negative airway pressures generated during inspiration or it may result from incoordination of the tongue and other upper airway muscles

Table 101-1 Potential Causes of Neonatal Apnea and Bradycardia

Central nervous system	Intraventricular hemorrhage, drugs, seizures, hypoxic injury, herniation, neuromuscular disorders, Leigh syndrome, brainstem infarction or anomalies (e.g., olivopontocerebellar atrophy), spinal cord injury after general anesthesia
Respiratory	Pneumonia, obstructive airway lesions, upper airway collapse, atelectasis, extreme prematurity, laryngeal reflex, phrenic nerve paralysis, pneumothorax, hypoxia
Infectious	Sepsis, meningitis (bacterial, fungal, viral), respiratory syncytial virus, pertussis
Gastrointestinal	Oral feeding, bowel movement, necrotizing enterocolitis, intestinal perforation
Metabolic	↓ Glucose, ↓ calcium, ↓/↑ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia
Cardiovascular	Hypotension, hypertension, heart failure, anemia, hypovolemia, vagal tone
Other	Immaturity of respiratory center, sleep state

involved in maintaining airway patency. In **central apnea,** which is caused by decreased central nervous system (CNS) stimuli to respiratory muscles, both airflow and chest wall motion are absent. Gestational age is the most important determinant of respiratory control, with the frequency of apnea being inversely related to gestational age. The immaturity of the brainstem respiratory centers is manifested by an attenuated response to carbon dioxide and a paradoxical response to hypoxia that results in apnea rather than the hyperventilation observed after the 1st few mo of life. The most common pattern of idiopathic apnea in preterm neonates is **mixed apnea** (50-75% of cases), with obstructive apnea preceding (usually) or following central apnea. Short episodes of apnea are usually central, whereas prolonged ones are often mixed. Apnea depends on the sleep state; its frequency increases during active (rapid eye movement) sleep.

CLINICAL MANIFESTATIONS

The incidence of idiopathic apnea of prematurity varies inversely with gestational age. The onset of idiopathic apnea can be during the 1st 1-2 wk after birth but is often delayed if there is RDS or other causes of respiratory distress. Apneic episodes have been noted to be as frequent on day 1 as throughout the 1st wk in premature infants without respiratory disease. In preterm infants, **serious apnea** is defined as cessation of breathing for longer than 20 sec or for any duration if accompanied by cyanosis and bradycardia. The incidence of associated bradycardia increases with the length of the preceding apnea and correlates with the severity of hypoxia. Short apnea episodes (10 sec) are rarely associated with bradycardia, whereas longer episodes (>20 sec) have a higher incidence of bradycardia. Bradycardia follows the apnea by 1-2 sec in more than 95% of cases and is most often sinus, but on occasion it can be nodal. Vagal responses and, rarely, heart block are causes of bradycardia without apnea. Short oxygen desaturation episodes noted with oxygen saturation monitoring are normal in neonates, and treatment is not necessary.

TREATMENT

Infants at risk for apnea should get cardiorespiratory monitoring. Gentle tactile stimulation is often adequate therapy for mild and intermittent episodes. The onset of apnea in a previously well preterm neonate after the 2nd wk of life or in a term infant at any time is a critical event that warrants prompt investigation. Recurrent apnea of prematurity may be treated with caffeine or theophylline. Methylxanthines increase central respiratory drive by lowering the threshold of response to hypercapnia as well as enhancing contractility of the diaphragm and preventing diaphragmatic fatigue. Caffeine and theophylline are as effective, *but caffeine has fewer side effects (less tachycardia and feeding intolerance)*. Loading doses of 5-7 mg/kg of theophylline (orally) or aminophylline (intravenously) should be followed by doses of 1-2 mg/kg given every 6-12 hr by the oral or intravenous route. Loading doses of 20 mg/kg of **caffeine citrate** are followed 24 hr later by maintenance doses of 5 mg/kg/24 hr qd, either orally or intravenously. These doses should be monitored through observation of vital signs and clinical response. Serum drug determinations (therapeutic levels: theophylline, 6-10 μg/mL; caffeine, 8-20 μg/mL) are optional because important side effects of these medications are rare. Higher doses of methylxanthines may be more effective, do not necessarily result in more frequent side effects, and may reduce major neurodevelopmental disabilities. Withholding respiratory stimulants in infants with RDS may result in ventilator dependency, increased bronchopulmonary dysplasia (BPD), and death. Doxapram, known to be a potent respiratory stimulant, acts predominantly on peripheral chemoreceptors and is effective in neonates with apnea of prematurity that is unresponsive to methylxanthines. Transfusion of packed red blood cells to reduce the incidence of idiopathic apnea is reserved for severely anemic infants. Gastroesophageal reflux is common in neonates, but data do not support a causal relationship between gastroesophageal reflux and apneic events or the use of antireflux medications to reduce the frequency of apnea in preterm infants.

Nasal continuous positive airway pressure (continuous positive airway pressure [CPAP], 3-5 cm H_2O) and high-flow humidification using nasal cannula (1-2.5 L/min) are therapies for mixed or obstructive apnea, but CPAP is preferred because of its proven efficacy and safety. The efficacy of CPAP is related to its ability to splint the upper airway and prevent airway obstruction.

PROGNOSIS

Apnea of prematurity does not alter an infant's prognosis unless it is severe, recurrent, and refractory to therapy. The associated problems of intraventricular hemorrhage (IVH), BPD, and retinopathy of prematurity are critical in determining the prognosis for apneic infants. Apnea of prematurity usually resolves by 37 wk of postconceptional age, although it may persist beyond term gestation, particularly in extremely preterm infants born at <28 wk of gestation, and does not predict future episodes of sudden infant death syndrome (SIDS). Some infants with persistent apnea are discharged with cardiorespiratory monitoring performed at home. In the absence of significant events, home monitoring can be safely discontinued after 44 wk postconceptional age.

APNEA AND SUDDEN INFANT DEATH SYNDROME

Although preterm infants are at higher risk for SIDS, apnea of prematurity is not a risk factor for SIDS. The epidemiologic evidence that positioning the babies to sleep on their backs reduces the rate of SIDS deaths by more than 50% suggests that position, and not prematurity, has been the primary cause of SIDS. Avoidance of cigarette smoke exposure and of overheating the infant are also important in the prevention of SIDS.

Bibliography is available at Expert Consult.

101.3 Respiratory Distress Syndrome (Hyaline Membrane Disease)

Waldemar A. Carlo and Namasivayam Ambalavanan

INCIDENCE

Respiratory distress syndrome occurs primarily in premature infants; its incidence is inversely related to gestational age and birthweight. It occurs in 60-80% of infants <28 wk of gestational age, in 15-30% of those between 32 and 36 wk of gestational age, and rarely in those >37 wk of gestational age. The risk for development of RDS increases with maternal diabetes, multiple births, cesarean delivery, precipitous delivery, asphyxia, cold stress, and a maternal history of previously affected infants. The incidence is highest in preterm male or white infants. The risk of RDS is reduced in pregnancies with chronic or pregnancy-associated hypertension, maternal heroin use, prolonged rupture of membranes, and antenatal corticosteroid prophylaxis.

ETIOLOGY AND PATHOPHYSIOLOGY

Surfactant deficiency (decreased production and secretion) is the primary cause of RDS. The failure to attain an adequate FRC and the tendency of affected lungs to become atelectatic correlate with high surface tension and the absence of pulmonary surfactant. The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, SP-B, SP-C, and SP-D), and cholesterol (Fig. 101-2). With advancing gestational age, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells (Fig. 101-3). These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability by preventing the collapse of small air spaces at end-expiration. Because of immaturity, the amounts produced or released may be insufficient to meet postnatal demands. Surfactant is present in high concentrations in fetal lung homogenates by 20 wk of gestation, but it does not reach the surface of the lungs until later. It appears in amniotic fluid between 28 and 32 wk of gestation. Mature levels of pulmonary surfactant are present usually after 35 wk of gestation.

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Although rare, genetic disorders may contribute to respiratory distress. Abnormalities in surfactant protein B and C genes as well as a gene responsible for transporting surfactant across membranes (ABC transporter 3 *[ABCA3]*) are associated with severe and often lethal familial respiratory disease. Other familial causes of neonatal respiratory distress (not RDS) include alveolar capillary dysplasia, acinar dysplasia, pulmonary lymphangiectasia, and mucopolysaccharidosis.

Synthesis of surfactant depends in part on normal pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia, particularly in association with hypovolemia, hypotension, and cold stress, may suppress surfactant synthesis. The epithelial lining of the lungs may also be injured by high oxygen concentrations and the effects of respirator management, thereby resulting in a further reduction in surfactant.

Alveolar atelectasis, hyaline membrane formation, and interstitial edema make the lungs less compliant in RDS, so greater pressure is required to expand the alveoli and small airways. The chest wall of the preterm infant, which is highly compliant, offers less resistance than that of the mature infant to the natural tendency of the lungs to collapse. Thus, at end-expiration, the volume of the thorax and lungs tends to approach residual volume, and atelectasis may develop.

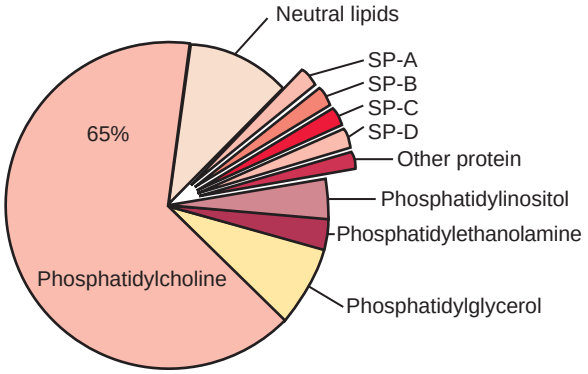

Figure 101-2 Composition of surfactant recovered by alveolar wash. The quantities of the different components are similar for surfactant from the mature lungs of mammals. SP, surfactant protein. *(From Jobe AH: Fetal lung development, tests for maturation, induction of maturation, and treatment. In Creasy RK, Resnick R, editors:* Maternal-fetal medicine: principles and practice, *ed 3, Philadelphia, 1994, WB Saunders.)*

Deficient synthesis or release of surfactant, together with small respiratory units and a compliant chest wall, produces atelectasis and results in perfused but not ventilated alveoli, causing **hypoxia.** Decreased lung compliance, small tidal volumes, increased physiologic dead space, and insufficient alveolar ventilation eventually result in **hypercapnia.** The combination of hypercapnia, hypoxia, and acidosis produces pulmonary arterial vasoconstriction with increased right-to-left shunting through the foramen ovale and ductus arteriosus and within the lung itself. Progressive injury to epithelial and endothelial cells from atelectasis (atelectrauma), volutrauma, ischemic injury, and oxygen toxicity results in effusion of proteinaceous material into the alveolar spaces (Fig. 101-4).

CLINICAL MANIFESTATIONS

Signs of RDS usually appear within minutes of birth, although they may not be recognized for several hours in larger premature infants until rapid, shallow respirations become more obvious. A later onset of tachypnea should suggest other conditions. Some patients require resuscitation at birth because of intrapartum asphyxia or initial severe respiratory distress (especially with a birthweight <1,000 g). Characteristically, tachypnea, prominent (often audible) grunting, intercostal and subcostal retractions, nasal flaring, and cyanosis are noted. Breath sounds may be normal or diminished with a harsh tubular quality, and on deep inspiration, fine crackles may be heard. The natural course of untreated RDS is characterized by progressive worsening of cyanosis and dyspnea. If the condition is inadequately treated, blood pressure may fall; cyanosis and pallor increase, and grunting decreases or disappears, as the condition worsens. Apnea and irregular respirations are ominous signs requiring immediate intervention. Untreated patients may also have a mixed respiratory-metabolic acidosis, edema, ileus, and oliguria. Respiratory failure may occur in infants with rapid progression of the disease. In most cases, the signs reach a peak within 3 days, after which improvement is gradual. Improvement is often heralded by spontaneous diuresis and improved blood gas values at lower inspired oxygen levels and/or lower ventilator support. Death can result from severe impairment of gas exchange, alveolar air leaks (interstitial emphysema, pneumothorax), pulmonary hemorrhage, or IVH. BPD is a form of chronic lung disease that often develops in infants with severe RDS.

DIAGNOSIS

The clinical course, chest x-ray findings, and blood gas and acid–base values help establish the clinical diagnosis. On x-ray, the lungs may have a characteristic but not pathognomonic appearance that includes

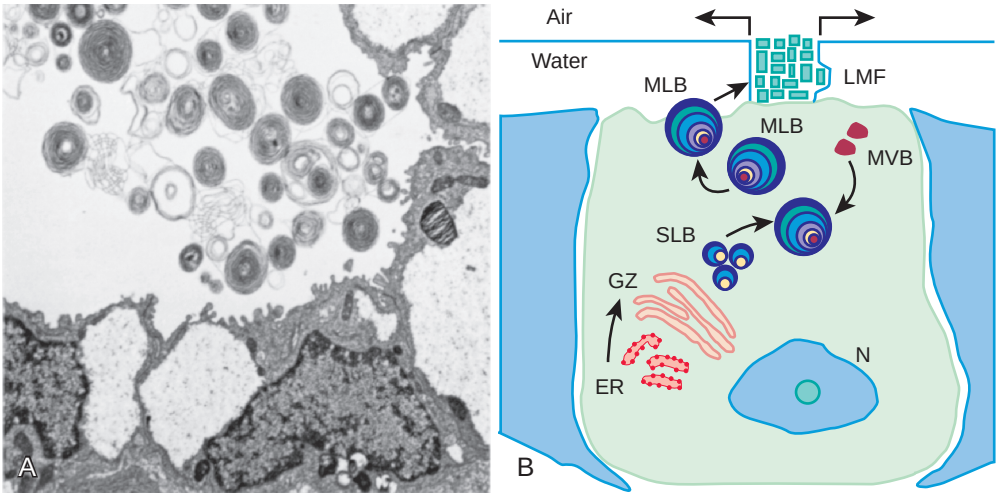

Figure 101-3 **A,** Fetal rat lung (low magnification), day 20 (term: day 22) showing developing type II cells, stored glycogen *(pale areas)*, secreted lamellar bodies, and tubular myelin. **B,** Possible pathway for transport, secretion, and reuptake of surfactant. ER, endoplasmic reticulum; GZ, Golgi zone; LMF, lattice (tubular) myelin figure; MLB, mature lamellar body; MVB, multivesicular body; N, nucleus; SLB, small lamellar body. *(**A** courtesy of Mary Williams, MD, University of California, San Francisco; **B** from Hansen T, Corbet A: Lung development and function. In Taeusch HW, Ballard RA, Avery MA, editors:* Schaffer and Avery's diseases of the newborn, *ed 6, Philadelphia, 1991, WB Saunders.)*

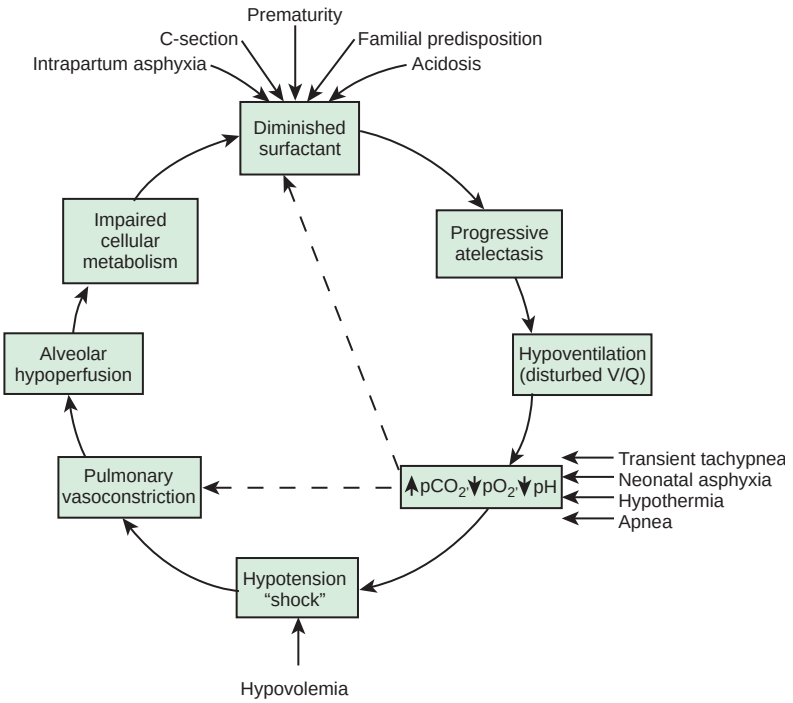

Figure 101-4 Contributing factors in the pathogenesis of hyaline membrane disease. The potential "vicious circle" perpetuates hypoxia and pulmonary insufficiency. *(From Farrell P, Zachman R: Pulmonary surfactant and the respiratory distress syndrome. In Quilligan EJ, Kretchmer N, editors:* Fetal and maternal medicine, *New York, 1980, Wiley. Reprinted by permission of John Wiley and Sons, Inc.)*

a fine reticular granularity of the parenchyma and air bronchograms, which are often more prominent early in the left lower lobe because of superimposition of the cardiac shadow (Fig. 101-5). The initial x-ray appearance is occasionally normal, with the typical pattern developing during the first day. Considerable variation in radiographic findings may be seen, depending on the phase of respiration (inspiratory vs. expiratory radiograph) and the use of CPAP or positive end-expiratory pressure (PEEP); this variation often results in poor correlation between radiographic findings and the clinical course. Laboratory findings are characterized initially by hypoxemia and later by progressive hypoxemia, hypercapnia, and variable metabolic acidosis.

In the differential diagnosis**, early-onset sepsis** may be indistinguishable from RDS. In neonates with **pneumonia**, the chest radiograph may be identical to that for RDS. Maternal group B streptococcal colonization, identification of organisms on Gram staining of gastric or tracheal aspirates or a buffy coat smear, and/or the presence of marked neutropenia may suggest the diagnosis of early-onset sepsis. **Cyanotic heart disease** (in particular, total anomalous pulmonary venous return) can also mimic RDS both clinically and radiographically. Echocardiography with color-flow imaging should be performed in infants who show no response to surfactant replacement to rule out cyanotic congenital heart disease as well as ascertain patency of the ductus arteriosus and assess pulmonary vascular resistance (PVR). **Persistent pulmonary hypertension, aspiration (meconium, amniotic fluid) syndromes, spontaneous pneumothorax, pleural effusions**, and **congenital anomalies,** such as cystic adenomatoid malformation, pulmonary lymphangiectasia, diaphragmatic hernia, and lobar emphysema, must be considered in patients with an atypical clinical course, but can generally be differentiated from RDS through radiographic and other evaluations. **Transient tachypnea** may be distinguished by its shorter and milder clinical course and is characterized by low or no need for oxygen supplementation. Congenital alveolar proteinosis (congenital surfactant protein B deficiency) is a rare familial disease that manifests as severe and lethal RDS in predominantly term and near-term infants (see Chapter 405). In atypical cases of RDS, a lung profile (lecithin : sphingomyelin ratio and phosphatidylglycerol determination) performed on a tracheal aspirate can be helpful in establishing a diagnosis of surfactant deficiency.

PREVENTION

Avoidance of unnecessary or poorly timed early cesarean section (<39 wk) or induction of labor, appropriate management of high-risk pregnancy and labor (including administration of antenatal corticosteroids), and prediction of pulmonary immaturity with possible in utero acceleration of maturation (see Chapter 98) are important preventive strategies. Antenatal and intrapartum fetal monitoring may decrease the risk of fetal asphyxia; asphyxia is associated with an increased incidence and severity of RDS.

Administration of antenatal corticosteroids to women before 34 wk of gestation significantly reduces the incidence and mortality of RDS as well as overall neonatal mortality. Antenatal steroids also reduce (1) overall mortality, (2) the need for and duration of ventilatory support and admission to a neonatal ICU, and (3) the incidence of severe IVH, necrotizing enterocolitis, and neurodevelopmental impairment. Postnatal growth is not adversely affected. Antenatal steroids do not increase the risk of maternal death, chorioamnionitis, or puerperal sepsis. Steroid administration is recommended for all women in preterm labor who are likely to deliver a fetus within 1 wk. Antenatal steroids act synergistically with postnatal exogenous surfactant therapy so they should be given even though surfactant therapy is effective. Betamethasone and dexamethasone have both been used antenatally. Betamethasone may reduce neonatal death to a greater extent as compared to dexamethasone.

In the past administration of surfactant into the trachea of symptomatic premature infants immediately after birth (prophylactic) or during the 1st few hr of life (early rescue) showed reduced air leak and mortality from RDS. *CPAP started at birth is as effective as prophylactic or early surfactant and is the approach of choice for the delivery room management of a preterm neonate at risk for RDS.*

TREATMENT

The basic defect requiring treatment in RDS is inadequate pulmonary exchange of oxygen and carbon dioxide; metabolic acidosis and circulatory insufficiency are secondary manifestations. Early supportive care of premature infants, especially in the treatment of acidosis, hypoxia, hypotension (see Chapter 98), and hypothermia, may lessen the severity of RDS. Therapy requires careful and frequent monitoring

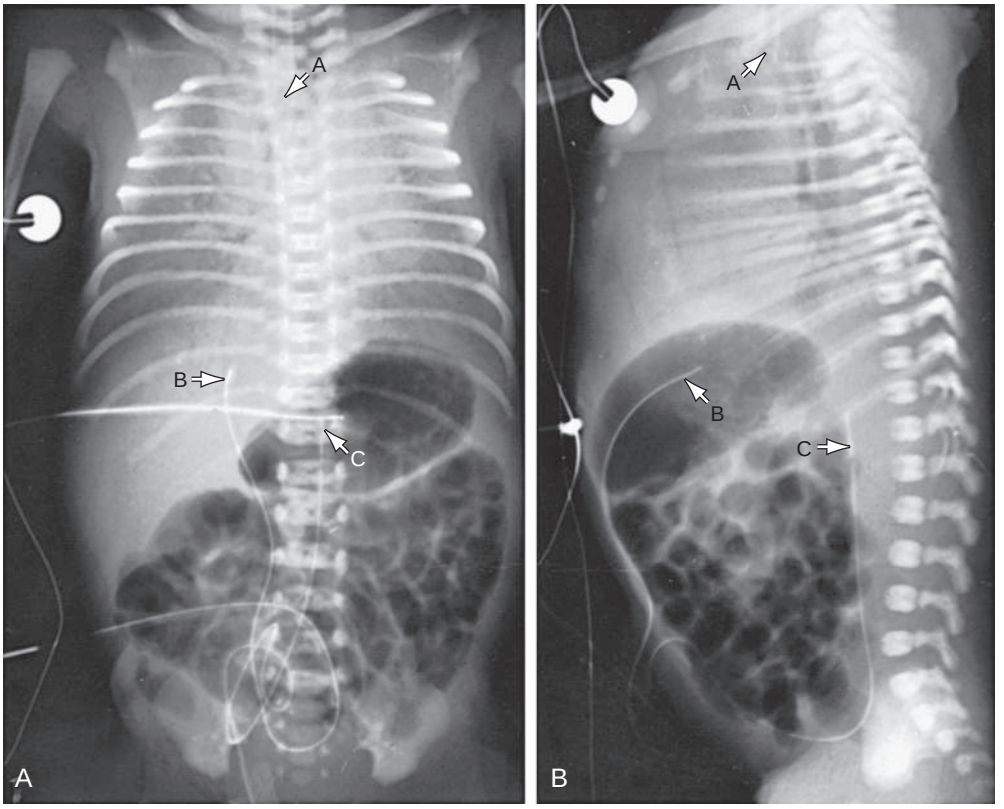

Figure 101-5 **Infant with respiratory distress syndrome.** Note the granular lungs, air bronchogram, and air-filled esophagus. Anteroposterior (**A**) and lateral (**B**) roentgenograms are needed to distinguish the umbilical artery from the vein catheter and to determine the appropriate level of insertion. The lateral view clearly shows that the catheter has been inserted into an umbilical vein and is lying in the portal system of the liver. *A* indicates endotracheal tube; *B* indicates the umbilical venous catheter at the junction of the umbilical vein, ductus venosus, and portal vein; *C* indicates the umbilical artery catheter passed up the aorta to T12. *(Courtesy of Walter E. Berdon, Babies Hospital, New York City.)*

of heart and respiratory rates, oxygen saturation, Pa_{O_2}, Pa_{CO_2}, pH, serum bicarbonate, electrolytes, glucose, hematocrit, blood pressure, and temperature. Arterial catheterization is frequently necessary. Because most cases of RDS are self-limited, the goal of treatment is to minimize abnormal physiologic variations and superimposed iatrogenic problems. Treatment of infants with RDS is best carried out in the neonatal ICU.

The general principles for supportive care of any premature infant should be adhered to, including developmental care and scheduled "touch times." To avoid hypothermia and minimize oxygen consumption, the infant should be placed in an incubator or radiant warmer, and core temperature maintained between 36.5 and 37°C (97.7 and 98.6°F) (see Chapters 97 and 98). Use of an incubator is preferable in very-low birthweight (VLBW) infants owing to the high insensible water losses associated with radiant heat. Calories and fluids should initially be provided intravenously. For the 1st 24 hr, 10% glucose solution with additional amino acids in extremely premature infants, should be infused through a peripheral vein at a rate of 65-75 mL/kg/24 hr. Electrolytes should be added on day 2 in the most mature infants and on days 3-7 in the more immature ones. Fluid volume is increased gradually over the 1st wk. Excessive fluids (>140 mL/kg/day) contribute to the development of patent ductus arteriosus (PDA) and BPD.

Warm humidified oxygen should be provided at a concentration initially sufficient to keep arterial oxygen pressure between 50 and 70 mm Hg (91-95% saturation) in order to maintain normal tissue oxygenation while minimizing the risk of oxygen toxicity. If oxygen saturation cannot be kept >90% at inspired oxygen concentrations of 40-70% or greater, applying CPAP at a pressure of 5-10 cm H_2O via nasal prongs is indicated and usually produces a rapid improvement in oxygenation. CPAP reduces collapse of surfactant-deficient alveoli and improves both FRC and ventilation–perfusion matching. *Early use of CPAP for stabilization of at-risk preterm infants beginning as early as in the delivery room reduces ventilatory needs.* Another approach is to intubate the preterm infant, administer intratracheal surfactant and then extubate the infant and begin CPAP. The amount of CPAP required usually decreases after approximately 72 hr of age, and most infants can be weaned from CPAP shortly thereafter. If an infant with RDS undergoing CPAP cannot keep oxygen saturation >90% while breathing 40-70% oxygen, assisted ventilation and surfactant are indicated.

Infants with respiratory failure or persistent apnea require assisted mechanical ventilation. Reasonable measures of respiratory failure are: (1) arterial blood pH <7.20, (2) arterial blood P_{CO_2} of 60 mm Hg or higher, and (3) oxygen saturation <90% at oxygen concentrations of 40-70% and CPAP of 5-10 cm H_2O. Infants with persistent apnea also need mechanical ventilation. Intermittent positive pressure ventilation delivered by time-cycled, pressure-limited, continuous flow ventilators is a common method of conventional ventilation for newborns. Other methods of conventional ventilation are synchronized intermittent mandatory ventilation (the set rate and pressure synchronized with the patient's own breaths), pressure support (the patient triggers each breath and a set pressure is delivered), and volume ventilation (a mode in which a specific tidal volume is set and the delivered pressure varies), and combinations thereof. Assisted ventilation for infants with RDS should always include appropriate PEEP (see Chapter 71.1). High ventilatory rates (≥60/min) with lower tidal volumes result in fewer air leaks. With use of high ventilatory rates, sufficient expiratory time should be allowed to avoid the inadvertent PEEP.

The **goal of mechanical ventilation** is to improve oxygenation and elimination of carbon dioxide without causing pulmonary injury or oxygen toxicity. Acceptable ranges of blood gas values, after the risks of hypoxia and acidosis are balanced against those of mechanical ventilation, vary among institutions: Pa_{O_2} 50-70 mm Hg, Pa_{CO_2} 45-65 mm

Hg (and higher after the first few days when the risk of IVH is less), and pH 7.20-7.35. During mechanical ventilation, **oxygenation** is improved by increasing either the fraction of inspired oxygen (FIO_2) or the mean airway pressure. The latter can be increased by raising the peak inspiratory pressure, PEEP gas flow, or inspiratory-expiratory ratio. Pressure changes are usually most effective. However, excessive PEEP may impede venous return, thereby reducing cardiac output and decreasing oxygen delivery despite improvement in PaO_2. PEEP levels of 4-6 cm H_2O are usually safe and effective. **Carbon dioxide elimination** is achieved by increasing the peak inspiratory pressure (tidal volume) or the rate of the ventilator.

A strategy to minimize ventilator-associated lung injury is the use of CPAP instead of endotracheal intubation. The decreased need for ventilator support with the use of CPAP may allow lung inflation to be maintained but may prevent volutrauma from overdistention and/or atelectasis. Early nasal CPAP is beneficial as compared to intubation and prophylactic surfactant, including lower mortality or BPD with CPAP treatment.

An effective strategy with conventional mechanical ventilation is the use of high rates and presumably small tidal volumes as $PaCO_2$ levels were kept in comparable ranges. Meta-analyses of the randomized controlled trials comparing high (>60 breaths/min) and low (usually 30-40 breaths/min) rates (and presumed low vs. high tidal volumes, respectively) revealed that the high ventilatory rate strategy led to fewer air leaks and a trend for increased survival.

If mechanical ventilation is needed, a ventilatory approach using small tidal volumes and permissive hypercapnia can be employed. **Permissive hypercapnia** is a strategy for the management of patients receiving ventilatory support in which priority is given to the prevention or limitation of lung injury from the ventilator by tolerating relatively high levels of $PaCO_2$ rather than maintenance of normal blood gas values. Permissive hypercapnia can be implemented during CPAP and mechanical ventilation. Volume-targeted ventilation allows the clinician to set a tidal volume that may prevent volutrauma. There are limited data on volume-targeted ventilation, but this mode of ventilation may decrease the rates of pneumothorax and BPD.

Hyperoxia may also contribute to lung injury in preterm infants. However, a lower target range of oxygenation (85-89%), as compared with a higher range (91-95%) increases mortality, and does not alter rates of BPD, BPD/death, blindness, or neurodevelopmental impairment. **Therefore, the currently recommended range of oxygen saturation targets is 91-95%.**

Many ventilated neonates receive sedation or pain relief with benzodiazepines or opiates (morphine, fentanyl), respectively. Midazolam is approved for use in neonates and has demonstrated sedative effects. Adverse hemodynamic effects and myoclonus have been associated with its use in neonates. If midazolam is used, a continuous infusion or administration of individual doses over at least 10 min is recommended to reduce these risks. Data are insufficient to assess the efficacy and safety of lorazepam. Diazepam is not recommended owing to its long half-life, its long-acting metabolites, and concern about the benzyl alcohol content of diazepam injection. Continuous infusion of morphine in VLBW neonates requiring mechanical ventilation does not reduce mortality rates, severe IVH, or periventricular leukomalacia. The need for additional doses of morphine is associated with poor outcome.

High-frequency ventilation (HFV) achieves desired alveolar ventilation by using smaller tidal volumes and higher rates (300-1,200 breaths/min or 5-20 Hz). HFV may improve elimination of carbon dioxide and improve oxygenation in patients who show no response to conventional ventilators and those who have severe RDS, interstitial emphysema, recurrent pneumothoraces, or meconium aspiration pneumonia. High-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation are the most frequently used methods of HFV. HFOV reduces BPD but may raise the risk for intracranial hemorrhage. HFOV strategies that promote lung recruitment, combined with surfactant therapy, may improve gas exchange. High-frequency jet ventilation facilitates resolution of air leaks. Elective use of either method, in comparison with conventional ventilation, generally does not offer advantages if used as the initial ventilation strategy to treat infants with RDS.

Surfactant deficiency is the primary pathophysiology of RDS. Immediate effects of surfactant replacement therapy include improved alveolar-arterial oxygen gradients, reduced ventilatory support, increased pulmonary compliance, and improved chest radiograph appearance. In neonates with RDS who fail CPAP, **treatment** with endotracheal surfactant should be initiated immediately after intubation. Repeated dosing is given every 6-12 hr for a total of 2 to 4 doses, depending on the preparation. Exogenous surfactant should be given by a physician who is qualified in neonatal resuscitation and respiratory management. Additional onsite staff support required includes nurses and respiratory therapists experienced in the ventilatory management of preterm infants. Appropriate monitoring equipment (radiology, blood gas laboratory, pulse oximetry) must also be available. Complications of surfactant therapy include transient hypoxia, hypercapnia, bradycardia and hypotension, blockage of the endotracheal tube, and pulmonary hemorrhage (see Chapter 101.13).

A number of surfactant preparations are available, including synthetic surfactants and natural surfactants derived from animal sources. The lack of reduction in BPD rates following surfactant replacement is probably, in part, a result of the survival of infants with severe RDS who would have died without surfactant administration. Infants requiring ventilator support after 1 wk of age may experience transient episodes of surfactant dysfunction associated with deficiencies of SP-B and SP-C, which are temporally associated with episodes of infection and respiratory deterioration. Surfactant treatment may be beneficial in these infants.

Strategies for weaning infants from ventilators vary widely and are influenced by lung mechanics as well as the availability of ventilatory modes (pressure support). Once extubated, many infants are transitioned to nasal CPAP to avoid postextubation atelectasis and reduce re-intubation. Synchronized nasal intermittent ventilation decreases the need for re-intubation in premature infants. High flow (1-2 L/min) or warmed, humidified high-flow (2-8 L/min) nasal cannula oxygen is commonly used to support term and near-term infants following extubation and to wean premature infants from nasal CPAP. Preloading with methylxanthines may enhance the success of extubation.

Pharmacologic Therapies

Systemic corticosteroids have been used to treat infants with RDS, to selectively treat infants who continue to require respiratory support, and to treat those in whom BPD develops. Mortality and/or BPD at 36 wk decrease with moderately early (7-14 days) administration of corticosteroids. Early (<96 hr) and delayed (>2-3 wk) administration of systemic steroids has also been assessed with meta-analyses, and the results are qualitatively similar. However, there are **short-term adverse** effects, including hyperglycemia, hypertension, gastrointestinal bleeding, gastrointestinal perforation, hypertrophic obstructive cardiomyopathy, poor weight gain, poor growth of the head, and a trend toward a higher incidence of periventricular leukomalacia. Furthermore, data showing an increased incidence of neurodevelopmental delay and cerebral palsy in infants randomly assigned to receive systemic corticosteroids raise serious concerns about adverse long-term outcomes of this therapy. Thus, routine use of systemic corticosteroids for the prevention or treatment of BPD is not recommended by the Consensus Group of the American Academy of Pediatrics and the Canadian Pediatric Society. Administration of inhaled steroids to ventilated preterm infants during the 1st 2 wk after birth reduced the need for systemic steroids and tended to decrease rates of death and/or BPD at 36 wk without an increase in adverse effects.

Inhaled nitric oxide has been evaluated in preterm infants following the observation of its effectiveness in term and near-term infants with hypoxemic respiratory failure. **Inhaled nitric oxide (iNO)** decreases the need for extracorporeal membrane oxygenation (ECMO) in term and near-term infants with hypoxic respiratory failure or persistent pulmonary hypertension of the neonate. Trials in preterm infants report heterogeneous effects on BPD, mortality, and other important outcomes. The most current data do not support the

routine administration of iNO in preterm infants with hypoxemic respiratory failure.

Prevention of extubation failure has been attempted with use of various pharmacologic approaches. Methylxanthines appear to have a large effect on reducing extubation failure. Similarly, use of systemic steroids before extubation reduces the need for reintubation (from 10% to 1%). In contrast, administration of racemic epinephrine after extubation does not improve pulmonary function or the rate of extubation failure.

Metabolic acidosis in RDS may be a result of perinatal asphyxia and hypotension and is often encountered when an infant has required prolonged resuscitation (see Chapter 100). Sodium bicarbonate, 1-2 mEq/kg, may be administered over 15-20 min through a peripheral or umbilical vein, followed by an acid–base determination within 30 min, or it may be administered over several hours. Often, sodium bicarbonate is administered on an emergency basis through an umbilical venous catheter. Alkali therapy may result in skin sloughing from infiltration, increased serum osmolarity, hypernatremia, hypocalcemia, hypokalemia, and liver injury when concentrated solutions are administered rapidly through an umbilical vein catheter wedged in the liver.

Monitoring of aortic blood pressure through an umbilical or peripheral arterial catheter or by oscillometric technique is useful in managing the shock-like state that may occur during the 1st hr or so in premature infants who have been asphyxiated or have severe RDS (see Fig. 100-2 in Chapter 100). The position of a radiopaque umbilical catheter should be checked radiographically after insertion (see Fig. 101-5). The tip of an umbilical artery catheter should lie at L3-L5 just above the bifurcation of the aorta or at T6-T10. Preferred sites for peripheral catheters are the radial or posterior tibial arteries. The placement and supervision should be carried out by skilled and experienced personnel. Catheters should be removed as soon as patients no longer have any indication for their continued use—usually when an infant is stable and the F_{IO_2} is <40%. Hypotension and low flow in the superior vena cava have been associated with higher rates of CNS morbidity and mortality and should be treated with cautious administration of volume (crystalloid) and early use of vasopressors. Dopamine is more effective in raising blood pressure than dobutamine. Hypotension may be refractory to pressors, but responsive to glucocorticoids, especially in neonates <1,000 g. This hypotension may result from transient adrenal insufficiency in the ill premature infant, which may be treated with intravenous hydrocortisone at 1-2 mg/kg/dose q 6-12 hr (see Chapter 98).

Periodic **monitoring of Pa_{O_2}, Pa_{CO_2}, and pH** is an important part of the management; if assisted ventilation is being used, such monitoring is essential. Oxygenation may be assessed continuously from transcutaneous electrodes or pulse oximetry (oxygen saturation). Capillary blood samples are of limited value for determining P_{O_2} but may be useful for evaluating P_{CO_2} and pH.

Because of the difficulty of distinguishing **group B streptococcal** or other bacterial infections from RDS, empirical antibiotic therapy is indicated until the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is suggested, although the choice of antibiotics should be based on the recent pattern of bacterial sensitivity in the hospital where the infant is being treated (see Chapter 109).

COMPLICATIONS OF RESPIRATORY DISTRESS SYNDROME AND INTENSIVE CARE

The most serious complications of **tracheal intubation** are pneumothorax and other air leaks, asphyxia from obstruction or dislodgment of the tube, bradycardia during intubation or suctioning, and the subsequent development of subglottic stenosis. Other complications include bleeding from trauma during intubation, posterior pharyngeal pseudodiverticula, need for tracheostomy, ulceration of the nares caused by pressure from the tube, permanent narrowing of the nostril as a result of tissue damage and scarring from irritation or infection around the tube, erosion of the palate, avulsion of a vocal cord, laryngeal ulcer, papilloma of a vocal cord, and persistent hoarseness, stridor, or edema of the larynx.

Measures to reduce the incidence of these complications include skillful intubation, adequate securing of the tube, use of polyvinyl endotracheal tubes, use of the smallest tube that will provide effective ventilation in order to reduce local pressure necrosis and ischemia, avoidance of frequent changes and motion of the tube in situ, avoidance of too frequent or too vigorous suctioning, and prevention of infection through meticulous cleanliness and frequent sterilization of all apparatus attached to or passed through the tube. The personnel inserting and caring for the endotracheal tube should be experienced and skilled in such care.

Risks associated with **umbilical arterial catheterization** include vascular embolization, thrombosis, spasm, and vascular perforation; ischemic or chemical necrosis of abdominal viscera; infection; accidental hemorrhage; hypertension; and impairment of circulation to a leg with subsequent gangrene. Aortography has demonstrated that clots form in or about the tips of 95% of catheters placed in an umbilical artery. Aortic ultrasonography can also be used to investigate for the presence of thrombosis. The risk of a serious clinical complication resulting from umbilical catheterization is probably between 2% and 5%.

Transient blanching of the leg may occur during catheterization of the umbilical artery. It is usually caused by reflex arterial spasm, the incidence of which is lessened by using the smallest available catheter, particularly in very small infants. The catheter should be removed immediately; catheterization of the other artery may then be attempted. Persistent spasm after removal of the catheter may be relieved by a small amount of topical nitroglycerin paste applied to the affected area or by warming the other leg. Blood sampling from a radial artery may similarly result in spasm or thrombosis, and the same treatment is indicated. Intermittent severe spasm or unrelieved spasm may respond to the cautious use of topical nitroglycerin. Spasm or thrombosis unresponsive to treatment may result in gangrene of the organ or area supplied by the vessel.

Serious hemorrhage upon removal of the catheter is rare. Thrombi may form in the artery or in the catheter, the incidence of which can be lowered by using a smooth-tipped catheter with a hole only at its end, by rinsing the catheter with a small amount of saline solution containing heparin, or by continuously infusing a solution containing 1-2 units/mL of heparin. The risk of thrombus formation with potential vascular occlusion can also be reduced by removing the catheter when early signs of thrombosis, such as narrowing of pulse pressure and disappearance of the dicrotic notch, are noted. Some authorities prefer to use the umbilical artery for blood sampling only and to leave the catheter filled with heparinized saline between samplings. **Renovascular hypertension** may occur days to weeks after umbilical arterial catheterization in a small proportion of neonates.

Umbilical vein catheterization is associated with many of the same risks as umbilical artery catheterization. Additional risks are cardiac perforation and pericardial tamponade; portal hypertension can develop from portal vein thrombosis, especially in the presence of omphalitis.

Air leaks are a common complication of the management of infants with RDS (see Chapter 101.12).

Some neonates with RDS may have clinically significant shunting through a **PDA.** Delayed closure of the PDA is associated with hypoxia, acidosis, increased pulmonary pressure secondary to vasoconstriction, systemic hypotension, immaturity, and local release of prostaglandins, which dilate the ductus. Shunting through the PDA may initially be bidirectional or right-to-left. As RDS resolves, PVR decreases, and left-to-right shunting may occur, leading to left ventricular volume overload and pulmonary edema. Manifestations of PDA may include (1) a hyperdynamic precordium, bounding peripheral pulses, wide pulse pressure, and a continuous or systolic murmur with or without extension into diastole or an apical diastolic murmur, or multiple clicks resembling the shaking of dice; (2) radiographic evidence of cardiomegaly and increased pulmonary vascular markings; (3) hepatomegaly; (4) increasing oxygen dependence; and (5) carbon dioxide retention. The **diagnosis** is confirmed by echocardiographic visualization of a PDA with Doppler flow imaging that demonstrates left-to-right or

bidirectional shunting. Prophylactic "closure" before signs of a PDA, closure of the asymptomatic but clinically detected PDA, and closure of the symptomatic PDA are 3 strategies to manage a PDA. Interventions include fluid restriction, the use of cyclooxygenase inhibitors (indomethacin or ibuprofen) to close the ductus, and surgical closure. Short-term benefits have to be balanced against adverse effects such as transient renal dysfunction and a possible increase in the risk of intestinal perforation with indomethacin. Much uncertainty about "best practice" in the management of a PDA remains. Many cases respond to general supportive measures, including fluid restriction. Medical and/or surgical ductal closure is indicated in the premature infant with a large PDA when there is a delay in clinical improvement or deterioration after initial clinical improvement of RDS. Intravenous indomethacin (0.1-0.2 mg/kg/dose) is given in 3 doses every 12-24 hr; treatment may be repeated once. A second course may be needed in a few symptomatic patients. If closure does not occur in a symptomatic patient, surgical ligation is usually the next step. Prophylactic low-dose indomethacin given soon after birth reduces the incidence of both IVH and PDA and improves the rate of permanent ductus closure even in the most immature infants. **Contraindications** to indomethacin include thrombocytopenia (<50,000 platelets/mm^3), bleeding disorders, oliguria (urine output <1 mL/kg/hr), necrotizing enterocolitis, isolated intestinal perforation, and an elevated plasma creatinine value (>1.8 mg/dL). The infant whose symptomatic PDA fails to close with indomethacin or who has contraindications to indomethacin is a candidate for surgical closure. Surgical mortality is very low even in the extremely low-birthweight infants. Complications of surgery include Horner syndrome, injury to the recurrent laryngeal nerve, chylothorax, transient hypertension, pneumothorax, and bleeding from the surgical site. Inadvertent ligation of the left pulmonary artery or the transverse aortic arch has rarely been reported.

Intravenous ibuprofen may be an alternative to indomethacin; it can be as effective in closing a PDA without reducing cerebral, mesenteric, or renal blood flow velocity. Compared with indomethacin, therapeutic ibuprofen has a lower risk of oliguria.

BPD is a result of lung injury in infants requiring mechanical ventilation and supplemental oxygen. The clinical, radiographic, and lung histology of **classic BPD** described in 1967, in an era before the widespread use of antenatal steroids and postnatal surfactant, was that of a disease of more mature preterm infants with RDS who were treated with positive-pressure ventilation and oxygen. The **new BPD** is a disease primarily of infants with birthweight <1,000 g who were born at <28 wk of gestation, some of whom have little or no lung disease at birth but experience progressive respiratory failure over the 1st few wk of life.

The lung histology currently found in infants with the new BPD include alveolar hypoplasia, variable saccular wall fibrosis, and minimal airway disease. Some specimens also have decreased pulmonary microvasculature development. The histopathology of BPD indicates interference with normal alveolar septation and microvascular maturation, which may prevent subsequent lung growth and development. The pathogenesis of BPD is multifactorial and affects both the lungs and the heart. RDS is a disease of progressive alveolar collapse. Alveolar collapse (**atelectrauma**) as a consequence of surfactant deficiency, together with ventilator-induced phasic overdistention of the lung (**volutrauma**), promotes injury. Oxygen induces injury by producing free radicals that cannot be metabolized by the immature antioxidant systems of VLBW neonates. Mechanical ventilation and oxygen injure the lung through their effect on alveolar and vascular development. Inflammation (detected with measurement of circulating neutrophils, neutrophils and macrophages in alveolar fluid, and proinflammatory cytokines) contributes to the progression of lung injury. Several clinical factors, including immaturity, chorioamnionitis, infection, symptomatic PDA, and malnutrition, contribute to the development of BPD.

The occurrence of BPD is inversely related to gestational age. Additional associations include the presence of interstitial emphysema, male sex, low Pa_{CO_2} during the treatment of RDS, PDA, high peak inspiratory pressure, increased airway resistance in the 1st wk of life, increased pulmonary artery pressure, and, possibly, a family history of atopy or asthma. Genetic polymorphisms may increase the risk for development of BPD. In some VLBW infants without RDS who require mechanical ventilation for apnea or respiratory insufficiency, BPD that does not follow the classic pattern may develop. Overhydration during the 1st days of life may also contribute to the development of BPD. Vitamin A supplementation (5,000 IU intramuscularly 3 times/wk for 4 wk) in VLBW infants reduces the risk of BPD (1 case prevented for every 14-15 infants treated). Early use of nasal CPAP and rapid extubation with transition to nasal CPAP are associated with a decreased risk of BPD.

Instead of showing improvement on the 3rd or 4th day, which would be consistent with the natural course of RDS, some infants demonstrate an increased need for oxygen and ventilatory support. Respiratory distress persists or worsens and is characterized by hypoxia, hypercapnia, oxygen dependence, and, in severe cases, the development of right-sided heart failure. The chest radiograph may reveal pulmonary interstitial emphysema, wandering atelectasis with concomitant hyperinflation, and cyst formation (Fig. 101-6). Four distinct pathologic stages of classic BPD have been identified: acute lung injury, exudative bronchiolitis, proliferative bronchiolitis, and obliterative fibroproliferative bronchiolitis. Histologic study at this stage (10-20 days) shows residual hyaline membrane formation, progressive alveolar coalescence with atelectasis of the surrounding alveoli, interstitial edema, coarse focal thickening of the basement membrane, and widespread bronchial and bronchiolar mucosal metaplasia and hyperplasia. These findings correspond to a severe maldistribution of ventilation. Pathologic examination of infants who die later in the course of BPD reveals cardiac enlargement and pulmonary changes consisting of focal areas of emphysema with hypertrophy of the peribronchial smooth muscle of the tributary bronchioles, perimucosal fibrosis, widespread metaplasia of the bronchiolar mucosa, thickening of basement membranes, and separation of the capillaries from the alveolar epithelial cells.

BPD can be classified according to the need for oxygen supplementation (Table 101-2). Neonates receiving positive pressure support or ≥30% supplemental oxygen at 36 wk or at discharge (whichever occurs first) are diagnosed as having severe BPD. Those needing supplementation with 22-29% oxygen at this age are diagnosed as having moderate BPD. Those who need oxygen supplementation for >28 days but are breathing room air at 36 wk or at discharge are diagnosed as having mild BPD. Those receiving <30% oxygen should undergo a stepwise 2% reduction in supplemental oxygen to room air while under continuous observation and with oxygen saturation monitoring to determine whether they can be weaned off oxygen (physiologic definition of BPD). This test is highly reliable and correlated with discharge home on oxygen, length of hospital stay, and hospital readmissions in the 1st yr of life.

Severe BPD requires prolonged mechanical ventilation. Gradual weaning should be attempted despite elevations in Pa_{CO_2}, because hypercapnia may be the result of gas trapping rather than inadequate minute ventilation. Acceptable blood gas concentrations include hypercapnia with pH >7.20 and a Pa_{O_2} of 50-70 mm Hg with an oxygen saturation of 91-95%. Lower levels of Pa_{O_2} may exacerbate pulmonary hypertension with resultant cor pulmonale, so the lower limit of oxygenation targets in neonates with BPD are higher than those in neonates with RDS. Airway obstruction in BPD may be due to mucus and edema production, bronchospasm, and airway collapse from acquired tracheobronchomalacia. These events may contribute to "blue spells." Alternatively, blue spells may be the result of acute pulmonary vasospasm or right ventricular dysfunction.

Treatment of BPD includes nutritional support, fluid restriction, drug therapy, maintenance of adequate oxygenation, and prompt treatment of infection. Growth must be monitored because recovery depends on the growth of lung tissue and remodeling of the pulmonary vascular bed. Nutritional supplementation to provide added calories (24-30 calories/30 mL formula), protein (3-3.5 g/kg/24 hr), and fat (3 g/kg/24 hr) is needed for growth. Diuretic therapy results in a short-term improvement in lung mechanics and may lead to decreased oxygen and ventilatory requirements. Furosemide (1 mg/kg/dose

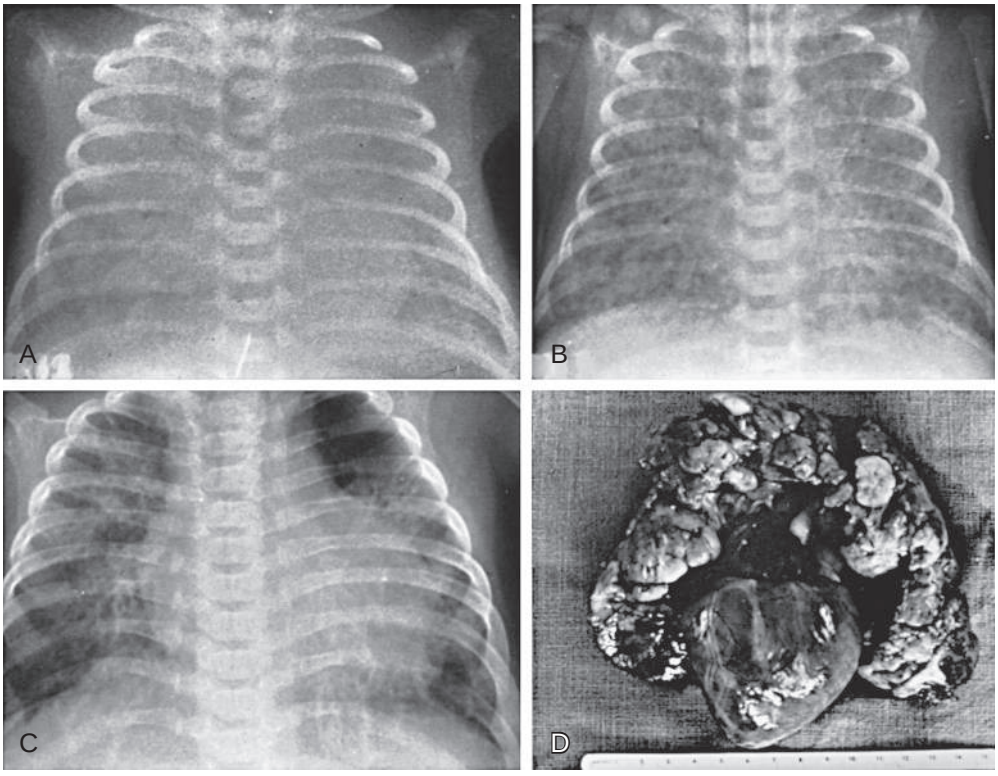

Figure 101-6 **Pulmonary changes in infants treated with prolonged, intermittent positive-pressure breathing with air containing 80-100% oxygen in the immediate postnatal period for the clinical syndrome of hyaline membrane disease. A,** A 5 day old infant with nearly complete opacification of the lungs. **B,** A 13 day old infant with "bubbly lungs" simulating the roentgenographic appearance of the Wilson-Mikity syndrome. **C,** A 7 mo old infant with irregular, dense strands in both lungs, hyperinflation, and cardiomegaly suggestive of chronic lung disease. **D,** Large right ventricle and a cobbly, irregular aerated lung of an infant who died at 11 mo of age. This infant also had a PDA. *(From Northway WH Jr, Rosan RC, Porter DY: Pulmonary disease following respirator therapy of hyaline-membrane disease,* N Engl J Med *276:357–368, 1967.)*

Table 101-2 Definition of BPD: Diagnostic Criteria*

	GESTATIONAL AGE	
	<32 Wk	**≥32 Wk**
Time point of assessment	36 wk postmenstrual age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**	>28 days but <56 days postnatal age or discharge home, whichever comes first Treatment with >21% oxygen for at least 28 days **plus**
Mild BPD	Breathing room air at 36 wk postmenstrual age or discharge home, whichever comes first	Breathing room air by 56 days postnatal age or discharge home, whichever comes first
Moderate BPD	Need† for <30% oxygen at 36 wk postmenstrual age or discharge home, whichever comes first	Need† for <30% oxygen at 56 days postnatal age or discharge home, whichever comes first
Severe BPD	Need† for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 wk postmenstrual age or discharge home, whichever comes first	Need† for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge home, whichever comes first

*BPD usually develops in neonates being treated with oxygen and PPV for respiratory failure, most commonly respiratory distress syndrome. Persistence of the clinical features of respiratory disease (tachypnea, retractions, crackles) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with >21% oxygen and/or PPV for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless parenchymal lung disease also develops and they have clinical features of respiratory distress. A day of treatment with >21% oxygen means that the infant received >21% oxygen for more than 12 hr on that day. Treatment with >21% oxygen and/or PPV at 36 wk postmenstrual age or at 56 days postnatal age or discharge should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and after 36 wk postmenstrual age, 56 days postnatal age, or discharge.

†A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD, bronchopulmonary dysplasia; NCPAP, nasal continuous positive airway pressure; PPV, positive-pressure ventilation.

From Jobe AH, Bancalari E: Bronchopulmonary dysplasia, Am J Respir Crit Care Med *163:1723–1729, 2001.*

intravenously twice daily [bid] or 2 mg/kg/dose orally bid) is the treatment of choice for acute fluid overload in infants with BPD. This loop diuretic has been demonstrated to decrease pulmonary interstitial emphysema and PVR, improve pulmonary function, and facilitate weaning from mechanical ventilation and oxygen. Adverse effects of long-term diuretic therapy are common and include hyponatremia, hypokalemia, alkalosis, azotemia, hypocalcemia, hypercalciuria, cholelithiasis, renal stones, nephrocalcinosis, and ototoxicity. Potassium chloride supplementation is often necessary. Hyponatremia should be treated with fluid restriction and a decrease in the dose or frequency of furosemide. Thiazide diuretics have been used in infants with BPD. Several trials of thiazide diuretics combined with spironolactone have

shown increased urine output with or without improvement in pulmonary mechanics in infants with BPD. Adverse effects include electrolyte imbalance.

Inhaled bronchodilators improve lung mechanics by decreasing airway resistance. Albuterol is a specific β_2-agonist used to treat bronchospasm in infants with BPD. Albuterol may improve lung compliance by decreasing airway resistance secondary to smooth muscle cell relaxation. Changes in pulmonary mechanics may last as long as 4-6 hr. Adverse effects include hypertension and tachycardia. Ipratropium bromide is a muscarinic antagonist related to atropine, but with more potent bronchodilator effects. Improvements in pulmonary mechanics have been demonstrated in BPD after ipratropium bromide inhalation. Combination therapy using albuterol and ipratropium bromide may be more effective than either agent alone. Few adverse effects have been noted. With current aerosol administration strategies, exactly how much medication is delivered to the airways and lungs of infants with BPD, especially if they are ventilator dependent, is unclear. Because significant smooth muscle relaxation does not appear to occur within the 1st few wk of life, aerosol therapy in the early stages of BPD is not indicated. Methylxanthines are used to increase respiratory drive, decrease apnea, and improve diaphragmatic contractility. Methylxanthines may also decrease PVR and increase lung compliance in infants with BPD, probably through direct smooth muscle relaxation. They also exhibit diuretic effects. These effects may accelerate weaning from mechanical ventilation. Synergy between theophylline and diuretics has been demonstrated. Theophylline has a half-life of 30-40 hr, is metabolized primarily to caffeine in the liver and may have adverse effects, such as tachycardia, gastroesophageal reflux, agitation, and seizures. Caffeine has a longer half-life than theophylline. Both are available in intravenous and enteral formulations.

Preventive therapy of BPD with postnatal dexamethasone may reduce the time to extubation and may decrease the risk of BPD but is associated with substantial short- and long-term risks, including hypertension, hyperglycemia, gastrointestinal bleeding and perforation, hypertrophic cardiomyopathy, sepsis, and poor weight gain and head growth. Survival is not improved, and infants who have been treated with dexamethasone have an increased risk of neurodevelopmental delay and cerebral palsy. The use of dexamethasone for the prevention of BPD is not recommended unless an infant has severe pulmonary disease, for example is ventilator dependent for at least 1 to 2 wk after birth. A rapid tapering course of therapy, starting at 0.25 mg/kg/day and lasting for 5-7 days, may be adequate. Inhaled beclomethasone does not prevent BPD but does decrease the need for systemic steroids. Inhaled corticosteroids facilitate earlier extubation of ventilated infants with BPD.

Physiologic abnormalities of the pulmonary circulation in BPD include elevated PVR and abnormal vasoreactivity. Acute exposure to even modest levels of hypoxemia causes large elevations in pulmonary artery pressure in infants with BPD with pulmonary hypertension. Higher oxygen saturations are effective in lowering pulmonary artery pressure. The current recommendation for treatment of patients with BPD and pulmonary hypertension is to maintain oxygen saturation values in the 91-95% range.

Low-dose iNO has no acute effects on lung function, cardiac function, or oxygenation in evolving BPD. The use of low-dose iNO may improve oxygenation in some infants with severe BPD, allowing decreased F_{IO_2} and ventilator support.

PROGNOSIS

Early provision of intensive observation and care of high-risk newborn infants can significantly reduce the morbidity and mortality associated with RDS and other acute neonatal illnesses. Antenatal steroids, postnatal surfactant use, and improved modes of ventilation have resulted in low mortality from RDS (≈10%). Mortality increases with decreasing gestational age. Optimal results depend on the availability of experienced and skilled personnel, care in specially designed and organized regional hospital units, proper equipment, and lack of complications such as severe asphyxia, intracranial hemorrhage, or irremediable congenital malformation. Surfactant therapy has reduced mortality from RDS by approximately 40%, but the incidence of BPD has not been measurably affected.

Although 85-90% of all infants surviving RDS after requiring ventilatory support with respirators are normal, the outlook is much better for those weighing >1,500 g. The long-term prognosis for normal pulmonary function in most infants surviving RDS is excellent. Survivors of severe neonatal respiratory failure may have significant pulmonary and neurodevelopmental impairment.

Prolonged ventilation, IVH, pulmonary hypertension, cor pulmonale, and oxygen dependence beyond 1 yr of life are poor prognostic signs. Mortality in infants with BPD ranges from 10-25% and is highest in infants who remain ventilator dependent for longer than 6 mo. Cardiorespiratory failure associated with cor pulmonale and acquired infection (respiratory syncytial virus) are common causes of death. Survivors with BPD often go home on a regimen of oxygen, diuretics, and bronchodilator therapy.

Pulmonary function slowly improves in most survivors owing to continued lung and airway growth and healing. Rehospitalization for impaired pulmonary function is most common during the 1st 2 yr of life. There is a gradual decrease in symptom frequency in children ages 6-9 yr from the frequency during the 1st 2 yr of life. Persistence of respiratory symptoms and abnormal pulmonary function test results are present in children ages 7-10 yr. Pulmonary function testing in children with a history of BPD shows persistent abnormalities in clinical moderate expiratory flow obstruction. Approximately 25-50% of very-low birthweight infants and more than 50% of children born at less than 26 wk of gestation continue to have abnormal spirometry as preadolescents. Many have asthma and respond to bronchodilators. Infants are at risk for severe respiratory syncytial virus infections and must receive prophylactic therapy (see Chapter 260). Airway obstruction and hyperactivity and hyperinflation are noted in some adolescent and adult survivors of BPD. High-resolution chest CT scanning or MRI studies in children and adults with a history of BPD reveal lung abnormalities that correlate directly with the degree of pulmonary function abnormality.

Noncardiorespiratory complications of BPD include growth failure, psychomotor retardation, and parental stress, as well as sequelae of therapy, such as nephrolithiasis, osteopenia, and electrolyte imbalance. Airway problems, such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, and tracheomalacia, are common and may aggravate or cause pulmonary hypertension. Subglottic stenosis may require tracheotomy or an anterior cricoid split procedure to relieve upper airway obstruction. Cardiac complications of BPD include pulmonary hypertension, cor pulmonale, systemic hypertension, left ventricular hypertrophy, and the development of aortopulmonary collateral vessels, which, if large, may cause heart failure.

Bibliography is available at Expert Consult.

101.4 Transient Tachypnea of the Newborn

Namasivayam Ambalavanan and Waldemar A. Carlo

Transient tachypnea is most common after term cesarean delivery. It is characterized by the early onset of tachypnea, sometimes with retractions, or expiratory grunting and, occasionally, cyanosis that is relieved by minimal oxygen supplementation (<40%). Most infants recover rapidly, usually within 3 days. The chest generally sounds clear without crackles or wheeze, and the chest radiograph shows prominent pulmonary vascular markings, fluid in the intralobar fissures, overaeration, flat diaphragms, and, rarely, small pleural effusions. Hypercapnia and acidosis are uncommon. Distinguishing the disease from RDS and other respiratory disorders (e.g., pneumonia) may be difficult, and transient tachypnea is frequently a diagnosis of exclusion; the distinctive features of transient tachypnea are rapid recovery of the infant and the absence of radiographic findings for RDS (hypoaeration, diffuse reticulogranular pattern, air bronchograms) and other lung disorders. The syndrome is believed to be secondary to slow absorption of fetal

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lung fluid, resulting in decreased pulmonary compliance and tidal volume and increased dead space. In severe cases, retained fetal lung fluid may interfere with the normal postnatal fall in PVR, resulting in persistent pulmonary hypertension; a mild surfactant deficiency may be present. Treatment is supportive. There is no evidence supporting the use of oral furosemide or racemic epinephrine in this disorder. One study demonstrated efficacy of inhaled salbutamol in enhancing resolution of transient tachypnea of the newborn.

Severe respiratory morbidity and mortality have been reported in infants born by elective cesarean section before full term (late preterm infants) who initially present with signs and symptoms of transient tachypnea. These infants often demonstrate refractory hypoxemia as a result of pulmonary hypertension and require ECMO support. The term "malignant transient tachypnea of the newborn" has been used to describe this condition. The initial approach to these infants is similar to that of RDS plus the concern for pulmonary hypertension.

Bibliography is available at Expert Consult.

101.5 Aspiration of Foreign Material (Fetal Aspiration Syndrome, Aspiration Pneumonia)

Waldemar A. Carlo

With fetal distress, infants often initiate vigorous respiratory movements in utero because of interference with the supply of oxygen through the placenta. Under such circumstances, the infant may aspirate amniotic fluid containing vernix caseosa, epithelial cells, meconium, blood, or material from the birth canal, which may block the smallest airways and interfere with alveolar exchange of oxygen and carbon dioxide. Pathogenic bacteria may accompany the aspirated material, and pneumonia may ensue, but even in noninfected cases, respiratory distress accompanied by radiographic evidence of aspiration is seen (Fig. 101-7).

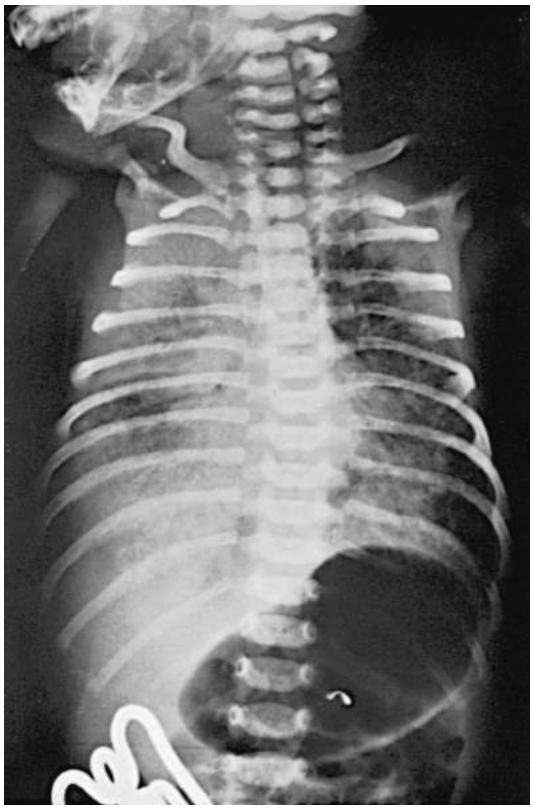

Figure 101-7 Fetal aspiration syndrome (aspiration pneumonia). Note the coarse granular pattern with irregular aeration typical of fetal distress from the aspiration of material contained in amniotic fluid, such as vernix caseosa, epithelial cells, and meconium. *(From Goodwin SR, Grave SA, Haberkern CM: Aspiration in intubated premature infants,* Pediatrics *75:85–88, 1985.)*

Postnatal pulmonary aspiration may also occur in newborn infants as a result of prematurity, tracheoesophageal fistula, esophageal and duodenal obstruction, gastroesophageal reflux, improper feeding practices, and administration of depressant medicines. To avoid aspiration of gastric contents, the stomach should be aspirated using a soft catheter just before surgery or other major procedures that require anesthesia or conscious sedation. The treatment of aspiration pneumonia is symptomatic and may include respiratory support and systemic antibiotics (see Chapters 109.8 and 397). Gradual improvement generally occurs over 3-4 days.

101.6 Meconium Aspiration

Namasivayam Ambalavanan and Waldemar A. Carlo

Meconium-stained amniotic fluid is found in 10-15% of births and usually occurs in term or postterm infants. Meconium aspiration syndrome (MAS) develops in 5% of such infants; 30% require mechanical ventilation and 3-5% die. Usually, but not invariably, fetal distress and hypoxia occur before the passage of meconium into amniotic fluid. The infants are meconium stained and may be depressed and require resuscitation at birth. Figure 101-8 shows the pathophysiology of the MAS. Infants with MAS are at increased risk of persistent pulmonary hypertension (see Chapter 101.7).

CLINICAL MANIFESTATIONS

Either in utero or with the first breath, thick, particulate meconium is aspirated into the lungs. The resulting small airway obstruction may produce respiratory distress within the first hours, with tachypnea, retractions, grunting, and cyanosis observed in severely affected infants. Partial obstruction of some airways may lead to pneumomediastinum, pneumothorax, or both. Overdistention of the chest may be prominent. The condition usually improves within 72 hr, but when its course requires assisted ventilation, it may be severe with a high risk for mortality. Tachypnea may persist for many days or even several weeks. The typical chest radiograph is characterized by patchy infiltrates, coarse streaking of both lung fields, increased anteroposterior diameter, and flattening of the diaphragm. A normal chest roentgenogram in an infant with severe hypoxemia and no cardiac malformation suggests the diagnosis of pulmonary hypertension (see Chapter 101.7).

PREVENTION

The risk of meconium aspiration may be decreased by rapid identification of fetal distress and initiation of prompt delivery in the presence of late fetal heart rate deceleration or poor beat-to-beat fetal heart rate variability. Despite initial enthusiasm for amnioinfusion, it does not reduce the risk of MAS, cesarean delivery, or other major indicators of maternal or neonatal morbidity. Intrapartum nasopharyngeal suctioning in infants with meconium-stained amniotic fluid does not reduce the risk for MAS.

TREATMENT

Routine intubation to aspirate the lungs of vigorous infants born through meconium-stained fluid is not effective in reducing the MAS or other major adverse outcomes. Depressed infants (those with hypotonia, bradycardia, or decreased respiratory effort) are at higher risk of MAS and may benefit from endotracheal intubation and suction to remove meconium from the airway before the first breath in the delivery room, but the data are inconclusive.

Treatment of the MAS includes supportive care and standard management for respiratory distress. The beneficial effect of mean airway pressure on oxygenation must be weighed against the risk of

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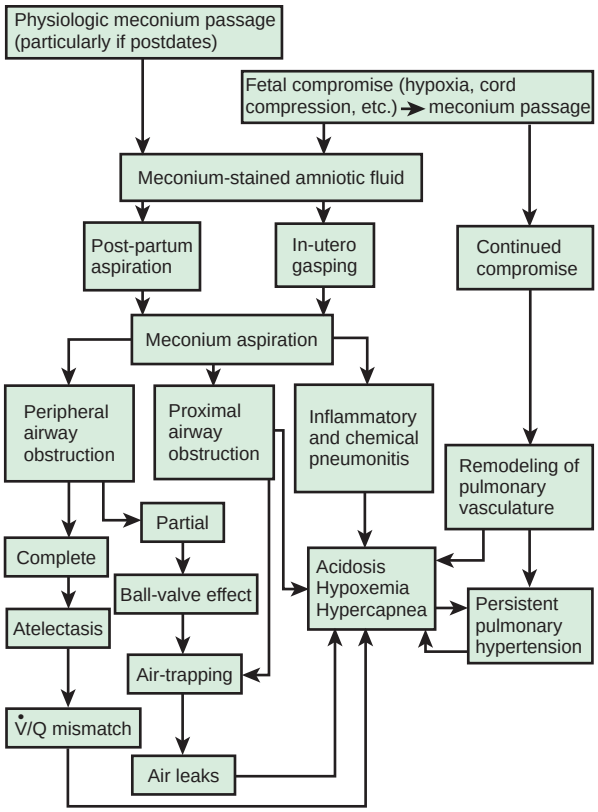

Figure 101-8 Pathophysiology of meconium passage and the meconium aspiration syndrome. V̇/Q̇, ventilation-perfusion ratio. *(From Wiswell TE, Bent RC: Meconium staining and the meconium aspiration syndrome: unresolved issues,* Pediatr Clin North Am *40:955–981, 1993.)*

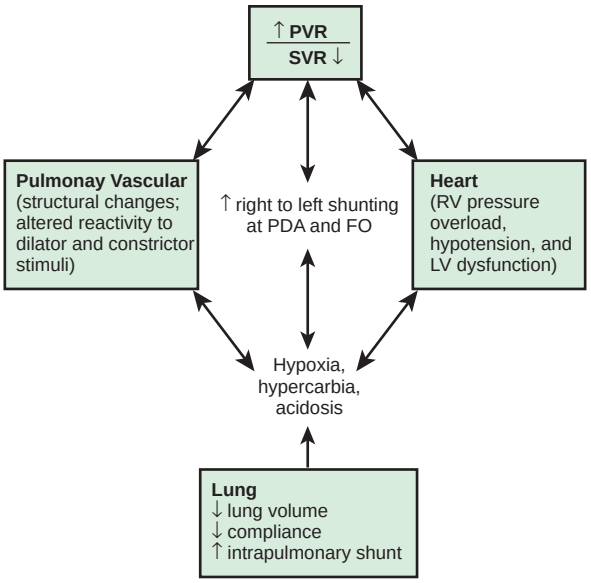

Figure 101-9 Cardiopulmonary interactions in PPHN. FO, foramen ovale; LV, left ventricular; PDA, patent ductus arteriosus; PVR, pulmonary vascular resistance; RV, right ventricular; SVR, systemic vascular resistance. *(From Kinsella JP, Abman SH: Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn,* J Pediatr *126:853–864, 1995.)*

pneumothorax. Administration of exogenous surfactant and/or iNO to infants with MAS and hypoxemic respiratory failure, or pulmonary hypertension requiring mechanical ventilation, decreases the need for ECMO, which is needed by the most severely affected infants who show no response to therapy. Severe meconium aspiration may be complicated by persistent pulmonary hypertension. Patients with MAS that is refractory to conventional mechanical ventilation may benefit from HFV or ECMO (see Chapter 101.7).

PROGNOSIS

The mortality rate of meconium-stained infants is considerably higher than that of nonstained infants. The decline in neonatal deaths caused by MAS during the last decades is related to improvements in obstetric and neonatal care. Residual lung problems are rare, but include symptomatic cough, wheezing, and persistent hyperinflation for up to 5-10 yr. The ultimate prognosis depends on the extent of CNS injury from asphyxia and the presence of associated problems such as pulmonary hypertension.

Bibliography is available at Expert Consult.

101.7 Persistent Pulmonary Hypertension of the Newborn (Persistent Fetal Circulation)

Namasivayam Ambalavanan and Waldemar A. Carlo

Persistent pulmonary hypertension of the newborn (PPHN) occurs mostly in in term and postterm infants. Predisposing factors include birth asphyxia, MAS, early-onset sepsis, RDS, hypoglycemia, polycythemia, maternal use of nonsteroidal antiinflammatory drugs with in utero constriction of the ductus arteriosus, maternal late trimester use of selective serotonin reuptake inhibitors, and pulmonary hypoplasia caused by diaphragmatic hernia, amniotic fluid leak, oligohydramnios, or pleural effusions. PPHN is often idiopathic. Some patients with PPHN have low plasma arginine and NO metabolite concentrations and polymorphisms of the carbamoyl phosphate synthase gene, findings suggestive of a possible subtle defect in NO production. The incidence is 1/500-1,500 live births with a wide variation among clinical centers.

PATHOPHYSIOLOGY

Persistence of the fetal circulatory pattern of right-to-left shunting through the PDA and foramen ovale after birth is a result of excessively high PVR. Fetal PVR is usually elevated relative to fetal systemic or postnatal pulmonary pressure. This fetal state normally permits shunting of oxygenated umbilical venous blood to the left atrium (and brain) through the foramen ovale, from which it bypasses the lungs through the ductus arteriosus and passes to the descending aorta. After birth, PVR normally declines rapidly as a consequence of vasodilation secondary to lung inflation, a rise in postnatal Pa_{O_2}, a reduction in Pa_{CO_2}, increased pH, and release of vasoactive substances. Increased neonatal PVR may be (1) maladaptive from an acute injury (not demonstrating normal vasodilation in response to increased oxygen and other changes after birth); (2) the result of increased pulmonary artery medial muscle thickness and extension of smooth muscle layers into the usually nonmuscular, more peripheral pulmonary arterioles in response to chronic fetal hypoxia; (3) a consequence of pulmonary hypoplasia (diaphragmatic hernia, Potter syndrome); or (4) obstructive as a result of polycythemia or total anomalous pulmonary venous return, or of alveolar capillary dysplasia, which is a lethal autosomal recessive disorder characterized by thickened alveolar septa, increased muscularization of the pulmonary arterioles, a reduced number of capillaries, and misalignment of the intrapulmonary veins. Regardless of etiology, profound hypoxemia from right-to-left shunting and normal or elevated Pa_{CO_2} are present (Fig. 101-9).

CLINICAL MANIFESTATIONS

Infants with PPHN usually become ill in the delivery room or within the 1st 12 hr after birth. PPHN related to polycythemia, idiopathic

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causes, hypoglycemia, hypothermia, or asphyxia may result in severe cyanosis with tachypnea, although initial signs of respiratory distress may be minimal. Infants who have PPHN associated with meconium aspiration, group B streptococcal pneumonia, diaphragmatic hernia, or pulmonary hypoplasia usually exhibit cyanosis, grunting, flaring, retractions, tachycardia, and shock. Multiorgan involvement may be present (see Table 98-1 in Chapter 98). Myocardial ischemia, papillary muscle dysfunction with mitral and tricuspid regurgitation, and biventricular dysfunction produce cardiogenic shock with decreases in pulmonary blood flow, tissue perfusion, and oxygen delivery. The hypoxemia is often labile and out of proportion to the findings on chest radiographs.

DIAGNOSIS

PPHN should be suspected in all term infants who have cyanosis independent of a history of fetal distress, intrauterine growth restriction, meconium-stained amniotic fluid, hypoglycemia, polycythemia, diaphragmatic hernia, pleural effusions, or birth asphyxia. Hypoxemia is universal and is at least intermittently unresponsive to 100% oxygen given by oxygen hood, but it may respond transiently to hyperoxic hyperventilation administered after endotracheal intubation or to the application of a bag and mask. A Pa_{O_2} or oxygen saturation gradient between a preductal (right radial artery) and a postductal (umbilical artery) site of blood sampling suggests right-to-left shunting through the ductus arteriosus. Foramen ovale shunting does not lead to a Pa_{O_2} or oxygen saturation gradient.

Real-time echocardiography combined with Doppler flow imaging is very helpful in evaluating PPHN. Systolic flattening of the interventricular septum as the right ventricular systolic pressure approaches the left ventricular systolic pressure can be used to estimate the degree of pulmonary hypertension. The peak velocity of the tricuspid valve regurgitation jet, when present, yields a quantitative estimate of the right ventricular systolic pressure. Likewise, the direction and velocity of a shunt across the PDA provides a quantitative comparison between the aortic and pulmonary artery pressures. In advanced cases, right-to-left or bidirectional shunting across a PDA and/or a patent foramen ovale can be observed.

In asphyxia-associated and idiopathic PPHN, chest x-ray findings are normal, whereas in PPHN associated with pneumonia and diaphragmatic hernia, parenchymal opacification and bowel and/or liver in the chest, respectively, are seen. The **differential diagnosis** of PPHN includes cyanotic heart disease (especially obstructed total anomalous pulmonary venous return) congenital surfactant deficiency syndromes, alveolar-capillary dysplasia, and the associated etiologic entities that predispose to PPHN (hypoglycemia, polycythemia, sepsis, hypothermia).

TREATMENT

Therapy is directed toward correcting any predisposing condition (hypoglycemia, polycythemia, others) and improving poor tissue oxygenation. The response to therapy is often unpredictable, transient, and complicated by the adverse effects of drugs or mechanical ventilation. Initial management includes oxygen administration and correction of acidosis, hypotension, and hypercapnia. Persistent hypoxemia should be managed with intubation and mechanical ventilation.

The optimal approach to mechanical ventilation has evolved. In the pre-iNO era, treatment of severe PPHN consisted of instituting mechanical ventilation with 1 or more of the following: muscle relaxants, hyperventilation, and alkalinization with sodium bicarbonate. These therapies may lead to complications associated with hypocarbia including reduced cerebral blood flow, cerebral palsy, and deafness; volutrauma; and impaired cardiac function which have resulted in less use of these practices. Currently, infants with PPHN are usually managed without hyperventilation and/or alkalinization. In skilled hands, "gentle ventilation" with normocarbia or permissive hypercarbia and avoidance of hypoxemia result in excellent outcomes and a low incidence of chronic lung disease and ECMO use.

Because of their instability and ability to fight the ventilator, newborns with PPHN usually require sedation. The use of paralytic agents is controversial and reserved for the newborn that cannot be treated with sedatives alone. Muscle relaxants may promote atelectasis of dependent lung regions and ventilation–perfusion mismatch and may be associated with an increased risk of death.

Inotropic therapy is frequently needed to support blood pressure and perfusion. Whereas dopamine is frequently used as a first-line agent, other agents, such as dobutamine, epinephrine, and milrinone may be helpful when myocardial contractility is poor. Some of the sickest newborns with PPHN demonstrate hypotension refractory to vasopressor administration. This results from desensitization of the cardiovascular system to catecholamines by overwhelming illness and relative adrenal insufficiency. Hydrocortisone rapidly upregulates cardiovascular adrenergic receptor expression and serves as a hormone substitute in cases of adrenal insufficiency.

NO is an endothelium-derived signaling molecule that relaxes vascular smooth muscle and can be delivered to the lung by inhalation. Use of iNO reduces the need for ECMO support by approximately 40%. The optimal starting dose is 20 ppm. Higher doses have not been shown to be more effective and are associated with side effects including methemoglobinemia and increased levels of nitrogen dioxide, a pulmonary irritant. Most newborns require iNO for <5 days. Although NO has been used as long-term therapy in children and adults with primary pulmonary hypertension, prolonged dependency is rare in neonates and suggests the presence of lung hypoplasia, congenital heart disease, or alveolar capillary dysplasia. The maximal safe duration of iNO therapy is unknown. The dose can be weaned to 5 ppm after 6-24 hr of therapy. The dose can then be weaned slowly and discontinued when the F_{IO_2} is <0.6 and the iNO dose is 1 ppm. Abrupt discontinuation should be avoided as it may cause rebound pulmonary hypertension. iNO should be used only at institutions that offer ECMO support or have the capability of transporting an infant on iNO therapy if a referral for ECMO is necessary. Some infants with PPHN do not respond adequately to iNO. Therapy with continuous inhaled or intravenous prostacyclin (prostaglandin I_2) has improved oxygenation and outcome in infants with PPHN. The safety and efficacy of sildenafil (a type 5 phosphodiesterase inhibitor) in newborns with PPHN is under investigation; initial results are promising.

Extracorporeal Membrane Oxygenation

In 5-10% of patients with PPHN, the response to 100% oxygen, mechanical ventilation, and drugs is poor. In such patients, two parameters have been used to predict mortality, the alveolar-arterial oxygen gradient (P_{AO_2}–Pa_{O_2}), and the oxygenation index, which is calculated as follows: F_{IO_2} (as %) × MAP/Pa_{O_2}.

An alveolar–arterial gradient >620 for 8-12 hr and an oxygenation index >40 that is unresponsive to iNO predict a high mortality rate (>80%) and are indications for ECMO. ECMO is used to treat carefully selected, severely ill infants with hypoxemic respiratory failure caused by RDS, meconium aspiration pneumonia, congenital diaphragmatic hernia, PPHN, or sepsis.

ECMO is a form of cardiopulmonary bypass that augments systemic perfusion and provides gas exchange. Most experience has been with venoarterial bypass, which requires carotid artery ligation and the placement of large catheters in the right internal jugular vein and carotid artery. Venovenous bypass avoids carotid artery ligation and provides gas exchange, but it does not support cardiac output. Blood is initially pumped through the ECMO circuit at a rate that approximates 80% of the estimated cardiac output, 150-200 mL/kg/min. Venous return passes through a membrane oxygenator, is rewarmed, and returns to the aortic arch in venoarterial ECMO and to the right atrium in venovenous ECMO. Venous oxygen saturation values are used to monitor tissue oxygen delivery and subsequent extraction for infants undergoing venoarterial ECMO, whereas arterial oxygen saturation values are used to monitor oxygenation for infants receiving venovenous ECMO.

Because ECMO requires complete heparinization to prevent clotting in the circuit, it cannot be used in patients with or at high risk for IVH (weight <2 kg, gestational age <34 wk). In addition, infants for whom ECMO is being considered should have reversible lung

disease, no signs of systemic bleeding, an absence of severe asphyxia or lethal malformations, and they should have been ventilated for less than 10 days. Complications of ECMO include thromboembolism, air embolization, bleeding, stroke, seizures, atelectasis, cholestatic jaundice, thrombocytopenia, neutropenia, hemolysis, infectious complications of blood transfusions, edema formation, and systemic hypertension.

PROGNOSIS

Survival in patients with PPHN varies with the underlying diagnosis. The long-term outcome for infants with PPHN is related to the associated hypoxic-ischemic encephalopathy and the ability to reduce PVR. The long-term prognosis for infants who have PPHN and who survive after treatment with hyperventilation is comparable to that for infants who have underlying illnesses of equivalent severity (birth asphyxia, hypoglycemia, polycythemia). The outcome for infants with PPHN who are treated with ECMO is also favorable; >80-90% survive, and 60-75% of survivors appear normal at 1-3.5 yr of age. Survival of infants born with congenital diaphragmatic hernia (CDH) has increased over the past 10 yr to 67%; benchmark institutions are reporting survival rates >80%. Those infants with CDH who require ECMO continue to have a lower survival than the general neonatal population undergoing ECMO (~50%).

Bibliography is available at Expert Consult.

101.8 Diaphragmatic Hernia

Akhil Maheshwari and Waldemar A. Carlo

A diaphragmatic hernia is defined as a communication between the abdominal and thoracic cavities with or without abdominal contents in the thorax (Fig. 101-10). The etiology is usually congenital but may be traumatic. The symptoms and prognosis depend on the location of the defect and associated anomalies. The defect may be at the esophageal hiatus (hiatal), paraesophageal (adjacent to the hiatus), retrosternal (Morgagni), or at the posterolateral (Bochdalek) portion of the diaphragm. The term *congenital diaphragmatic hernia* typically refers to the Bochdalek form. These lesions may cause significant respiratory distress at birth, can be associated with other congenital anomalies, and have significant mortality and long-term morbidity. The overall survival from the CDH Study Group is 67%. The Bochdalek hernia accounts for up to 90% of the hernias seen in the newborn period, with 80-90% occurring on the left side. The Morgagni hernia accounts for 2-6% of congenital diaphragmatic defects. The size of the defect is highly variable, ranging from a small hole to complete agenesis of this area of the diaphragm.

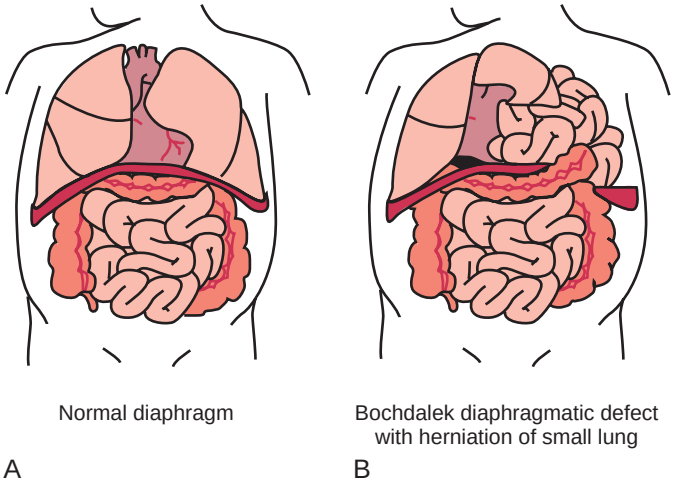

Figure 101-10 A, A normal diaphragm separating the abdominal and thoracic cavity. **B,** Diaphragmatic hernia with a small lung and abdominal contents in the thoracic cavity.

CONGENITAL DIAPHRAGMATIC HERNIA (BOCHDALEK)

Pathology and Etiology

Although CDH is characterized by a structural diaphragmatic defect, a major limiting factor for survival is the associated **pulmonary hypoplasia.** Lung hypoplasia was initially thought to be solely caused by the compression of the lung from the herniated abdominal contents, which impaired lung growth. However, emerging evidence indicates that pulmonary hypoplasia, at least in some cases, may precede the development of the diaphragmatic defect.

Pulmonary hypoplasia is characterized by a reduction in pulmonary mass and the number of bronchial divisions, respiratory bronchioles, and alveoli. The pathology of pulmonary hypoplasia and CDH includes abnormal septa in the terminal saccules, thickened alveoli, and thickened pulmonary arterioles. Biochemical abnormalities include relative surfactant deficiencies, increased glycogen in the alveoli, and decreased levels of phosphatidylcholine, total DNA, and total lung protein, all of which contribute to limited gas exchange.

Epidemiology

The incidence of CDH is between 1/2,000 and 1/5,000 live births, with females affected twice as often as males. Defects are more common on the left (85%) and are occasionally (<5%) bilateral. Pulmonary hypoplasia and malrotation of the intestine are part of the lesion, not associated anomalies. Most cases of CDH are sporadic, but familial cases have been reported. Associated anomalies have been reported in up to 30% of cases; these include CNS lesions, esophageal atresia, omphalocele, and cardiovascular lesions. CDH is recognized as part of several chromosomal syndromes: trisomy 21, trisomy 13, trisomy 18, Fryns, Brachmann-de Lange, Pallister-Killian, and Turner.

Diagnosis and Clinical Presentation

CDH can be diagnosed on prenatal ultrasonography (between 16 and 24 wk of gestation) in >50% of cases. High-speed fetal MRI can further define the lesion. Findings on ultrasonography may include polyhydramnios, chest mass, mediastinal shift, gastric bubble or a liver in the thoracic cavity, and fetal hydrops. Certain imaging features may predict outcome; these include lung : head size ratio. Nonetheless, no definitive characteristic reliably predicts outcome. After delivery, a chest radiograph is needed to confirm the diagnosis (Fig. 101-11). In some infants with an echogenic chest mass, further imaging is required. The **differential diagnosis** may include other diaphragm disorders such as eventration, a cystic lung lesion (pulmonary sequestration, cystic adenomatoid malformation), and others.

Arriving at the diagnosis early in pregnancy allows for prenatal counseling, possible fetal interventions, and planning for postnatal care. A referral to a center providing high-risk obstetrics, pediatric surgery, and tertiary care neonatology is advised. Careful evaluation for other anomalies should include echocardiography and amniocentesis. To avoid unnecessary pregnancy termination and unrealistic expectations, an experienced multidisciplinary group must carefully counsel the parents of a child diagnosed with a diaphragmatic hernia.

Respiratory distress is a cardinal sign in babies with CDH. It may occur immediately after birth or there may be a "honeymoon" period of up to 48 hr during which the baby is relatively stable. Early respiratory distress, within 6 hr after birth, is thought to be a poor prognostic sign. Respiratory distress is characterized clinically by tachypnea, grunting, use of accessory muscles, and cyanosis. *Children with CDH may also have a scaphoid abdomen and increased chest wall diameter.* Bowel sounds may also be heard in the chest with decreased breath sounds bilaterally. The point of maximal cardiac impulse may be displaced away from the side of the hernia if mediastinal shift has occurred. A chest x-ray and passage of a nasal gastric tube are all that is usually required to confirm the diagnosis.

A small group of infants with CDH present beyond the neonatal period. Patients with a delayed presentation may experience vomiting

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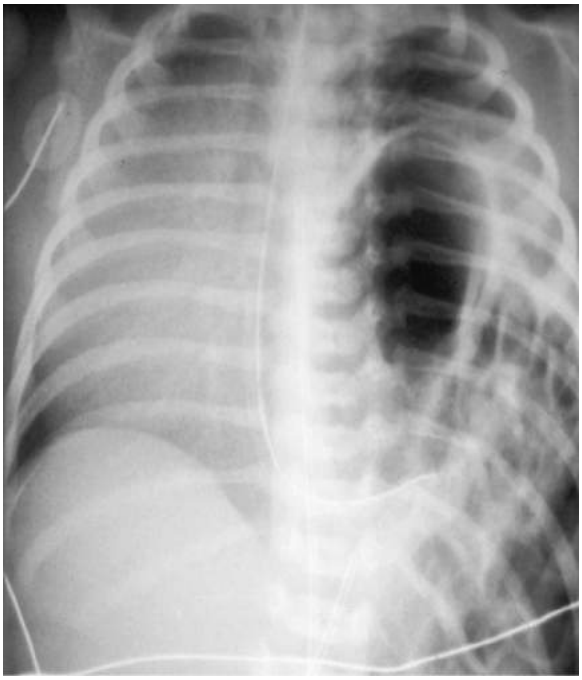

Figure 101-11 This chest radiograph shows a stomach, nasogastric tube, and small bowel contents in the thoracic cavity, consistent with a CDH.

as a result of intestinal obstruction or mild respiratory symptoms. Occasionally, incarceration of the intestine proceeds to ischemia with sepsis and shock. Unrecognized diaphragmatic hernia is a rare cause of sudden death in infants and toddlers. Group B streptococcal sepsis has been associated with delayed onset of symptoms and a CDH (often right side).

Treatment

Initial Management

Aggressive respiratory support is often needed in children with CDH. This includes rapid endotracheal intubation, sedation, and possibly paralysis. Arterial (preductal and postductal) and central venous (umbilical) lines are mandated, as are a urinary catheter and nasogastric tube. A preductal arterial oxygen saturation (Spo_2) value ≥85% should be the minimum goal. *Prolonged mask ventilation in the delivery room, which enlarges the stomach and small bowel and thus makes oxygenation more difficult, must be avoided.* Volutrauma is a significant problem. Gentle ventilation with **permissive hypercapnia** reduces lung injury, need for ECMO, and mortality. Factors that contribute to pulmonary hypertension (hypoxia, acidosis, hypothermia) should be avoided. Echocardiography is important to guide therapeutic decisions by measuring pulmonary and system vascular pressures and defining the presence of cardiac dysfunction. Routine use of inotropes is indicated in the presence of left ventricular dysfunction. Babies with CDH may be surfactant deficient. Although surfactant is commonly used, no study has proven that it is beneficial in treatment of CDH.

Ventilation Strategies

Conventional mechanical ventilation, HFOV, and ECMO are the 3 main strategies to support respiratory failure in the newborn with CDH. The goal is to maintain oxygenation and carbon dioxide elimination without inducing volutrauma. The first modality to be used is conventional ventilation. Hyperventilation to induce alkalosis and decrease ductal shunting has not proved effective and should be avoided. Permissive hypercapnia has reduced lung injury and mortality rates in several studies. HFOV can be used early to prevent lung injury by using lower airway pressures.

NO is a selective pulmonary vasodilator. Its use reduces ductal shunting and pulmonary pressures and results in improved oxygenation. Although it has been helpful in PPHN, randomized trials have not demonstrated improved survival or reduced need for ECMO when NO is used in newborns with CDH. Nonetheless, it is used in patients with CDH before ECMO is started (see Chapter 101.7).

Extracorporeal Membrane Oxygenation

The availability of ECMO and the utility of preoperative stabilization have improved survival of babies with CDH. ECMO is the therapeutic option in children in whom conventional ventilation or conventional ventilation and HFOV fail. ECMO is most commonly used before repair of the defect. Several objective criteria for ECMO have been developed (see Chapter 101.7).

Birthweight and the 5-min Apgar score may be the best predictors of outcome in patients treated with ECMO. The lower limit of weight for ECMO is 2,000 g.

The duration of ECMO for neonates with diaphragmatic hernia is longer (7-14 days) than for those with persistent fetal circulation or meconium aspiration, and may last up to 2-4 wk. Timing of repair of the diaphragm while the infant receives ECMO is controversial; some experts prefer early repair to allow a greater duration of ECMO after the repair, whereas many defer repair until the infant has demonstrated the ability to tolerate weaning from ECMO. The recurrence of pulmonary hypertension is associated with a high mortality, and weaning from ECMO support should be cautious. If the patient cannot be weaned from ECMO after repair of CDH, options include discontinuing support and, in rare cases, lung transplantation.

Novel Strategies for Infants with Congenital Diaphragmatic Hernia

The most reliable prenatal prognosticators of outcomes in children with CDH studied is fetal ultrasonography. A prospective study using this modality at 24-26 wk compared fetal lung:head size ratio. There were no survivors when the lung:head size ratio was <1, and all babies with lung:head size ratio >1.4 survived. A second important consideration was the presence of liver in the thoracic cavity, which is a poor prognostic feature. Human studies have shown no benefit for in utero repair of CDH.

Tracheal occlusion in utero is based on the observation that in utero fetal lung fluid plays a critical role in lung growth and maturity. A deficiency of lung fluid results in pulmonary hypoplasia. Initial studies in affected fetuses have not demonstrated success, but new preliminary reports are showing some efficacy. Partial liquid ventilation after birth is an experimental therapy under investigation in adults and children with severe respiratory failure. Partial liquid ventilation increases FRC by recruiting collapsed alveoli, thereby improving ventilation–perfusion mismatches and compliance. It also may reduce lung injury and increase surfactant production.

Surgical Repair

The ideal time to repair the diaphragmatic defect is under debate. Most experts wait at least 48 hr after stabilization and resolution of the pulmonary hypertension. Good relative indicators of stability are the requirement for conventional ventilation only, a low peak inspiratory pressure, and a FIO_2 <50. If the newborn is on ECMO, an ability to be weaned from this support should be a consideration before surgical repair. In some centers, the repair is done with the cannulas in place; in other centers, the cannulas are removed. A subcostal approach is the most frequently used (Fig. 101-12). This allows for good visualization of the defect and, if the abdominal cavity cannot accommodate the herniated contents, a polymeric silicone (Silastic) patch can be placed. Both laparoscopic and thoracoscopic repairs have been reported, but these should be reserved for only the most stable infants.

The defect size and amount of native diaphragm present are variable. Whenever possible, a primary repair using native tissue is performed. If the defect is too large, a porous polytetrafluoroethylene (Gore-Tex) patch is used.

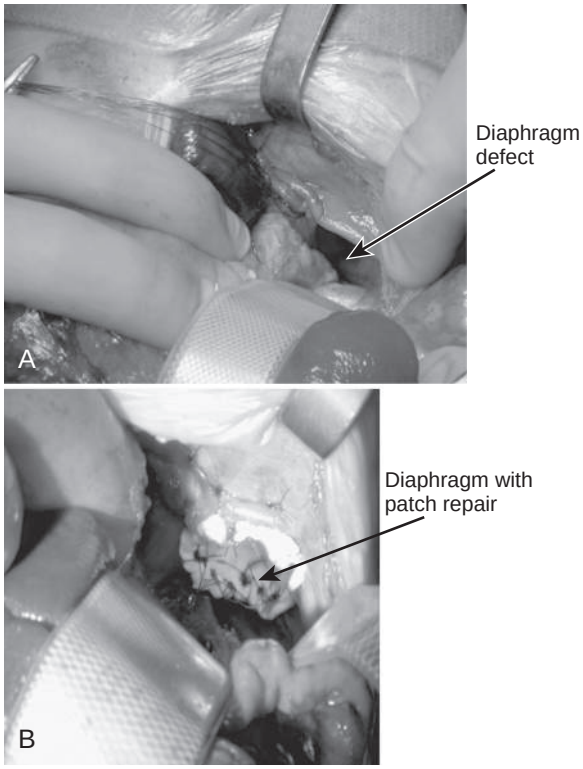

Figure 101-12 **A,** An intraoperative picture of a CDH before repair. **B,** An intraoperative picture of a patch repair of a CDH.

There is a higher recurrence rate of CDH among children with patches (the patch does not grow as the child grows) than among those with repairs with native tissue. A loosely fitted patch may reduce the recurrence rates. Pulmonary hypertension must be monitored carefully, and in some instances, a postoperative course of ECMO is needed. Other recognized complications include bleeding, chylothorax, and bowel obstruction.

Outcome and Long-Term Survival

Overall survival of liveborn infants with CDH is 67%. The incidence of spontaneous fetal demise is 7-10%. Relative predictors of a poor prognosis include an associated major anomaly, symptoms before 24 hr of age, severe pulmonary hypoplasia, herniation to the contralateral lung, and the need for ECMO.

Pulmonary problems continue to be a source of morbidity for long-term survivors of CDH. Children receiving CDH repair who were studied at 6-11 yr of age demonstrated significant decreases in forced expiratory flow at 50% of vital capacity and decreased peak expiratory flow. Both obstructive and restrictive patterns can occur. Those without severe pulmonary hypertension and barotrauma do the best. Those at highest risk include children who required ECMO and patch repair, but the data clearly show that CDH survivors who did not require ECMO also need frequent attention to pulmonary issues. At discharge, up to 20% of infants require oxygen, but only 1-2% require oxygen past 1 yr of age. **BPD** is frequently documented radiographically but will improve as more alveoli develop and the child ages.

Gastroesophageal reflux disease is reported in more than 50% of children with CDH. It is more common in those children whose diaphragmatic defect involves the esophageal hiatus. Intestinal obstruction is reported in up to 20% of children and may result from a midgut volvulus, adhesions, or a recurrent hernia that became incarcerated. Recurrent diaphragmatic hernia is reported in 5-20% in most series. Children with patch repairs are at highest risk.

Children with CDH typically have **delayed growth** in the 1st 2 yr of life. Contributing factors include poor intake, gastroesophageal reflux disease, and a caloric requirement that may be higher because of the energy required to breathe. Many children normalize and "catch up" in growth by the time they are 2 yr old.

Neurocognitive defects are common and may result from the disease or the interventions. The incidence of neurologic abnormalities is higher in infants who require ECMO (67% vs. 24% of those who do not). The abnormalities are similar to those seen in neonates treated with ECMO for other diagnoses and include transient and permanent developmental delay, abnormal hearing or vision, and seizures. Serious hearing loss may occur in up to 28% of children who underwent ECMO. The majority of neurologic abnormalities are classified as mild to moderate.

Other long-term problems occurring in this population include pectus excavatum and scoliosis. Survivors of CDH repair, particularly those requiring ECMO support, have a variety of long-term abnormalities that appear to improve with time but require close monitoring and multidisciplinary support.

Bibliography is available at Expert Consult.

Figure 101-13 A chest radiograph demonstrating a Morgagni hernia.

101.9 Foramen of Morgagni Hernia

Akhil Maheshwari and Waldemar A. Carlo

The anteromedial diaphragmatic defect through the foramen of Morgagni accounts for 2-6% of diaphragmatic hernias. Failure of the sternal and crural portions of the diaphragm to meet and fuse produces this defect. These defects are usually small, with a greater transverse than anteroposterior diameter, and are more commonly right-sided (90%) but may be bilateral (Fig. 101-13). The transverse colon or small intestine or liver is usually contained in the hernial sac. The majorities of children with these defects are asymptomatic and are diagnosed beyond the neonatal period. The diagnosis is usually made on chest radiograph when a child is evaluated for another reason. The anteroposterior radiograph shows a structure behind the heart, and a lateral film localizes the mass to the retrosternal area. Chest CT or MRI will confirm the diagnosis. When symptoms occur, they can be recurrent respiratory infections, cough, vomiting, or reflux; in rare instances, incarceration may occur. Repair is recommended for all patients, in view of the risk of bowel strangulation, and can be accomplished laparoscopically or by an open approach. Prosthetic material is rarely required.

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101.10 Paraesophageal Hernia

Akhil Maheshwari and Waldemar A. Carlo

Paraesophageal hernia is differentiated from hiatal hernia in that the gastroesophageal junction is in the normal location. The herniation of the stomach alongside or adjacent to the gastroesophageal junction is prone to incarceration with strangulation and perforation. A previous Nissen fundoplication and other diaphragmatic procedures are risk factors. This unusual diaphragmatic hernia should be repaired promptly after identification.

101.11 Eventration

Akhil Maheshwari and Waldemar A. Carlo

Eventration of the diaphragm is an abnormal elevation, consisting of a thinned diaphragmatic muscle that causes elevation of the entire hemidiaphragm or, more commonly, the anterior aspect of the hemidiaphragm. This elevation produces a paradoxical motion of the affected hemidiaphragm. Most eventrations are asymptomatic and do not require repair. A congenital form is the result of either incomplete development of the muscular portion or central tendon or abnormal development of the phrenic nerves. Congenital eventration may affect lung development, but it has not been associated with pulmonary hypoplasia. The **differential diagnosis** includes diaphragmatic paralysis, diaphragmatic hernia, traction injury, and iatrogenic injury after heart surgery. Eventration is also associated with pulmonary sequestration, congenital heart disease, and chromosomal trisomies. Most eventrations are asymptomatic and do not require repair. The indications for surgery include continued need for mechanical ventilation, recurrent infections, and failure to thrive. Large or symptomatic eventrations can be repaired by plication through an abdominal or thoracic approach that is minimally invasive.

Bibliography is available at Expert Consult.

101.12 Extrapulmonary Air Leaks (Pneumothorax, Pneumomediastinum, Pulmonary Interstitial Emphysema, Pneumopericardium)

Waldemar A. Carlo

Asymptomatic pneumothorax, usually unilateral, is estimated to occur in 1-2% of all newborn infants; symptomatic pneumothorax and pneumomediastinum are less common (see Chapter 94). The incidence of pneumothorax is increased in infants with lung diseases such as meconium aspiration and RDS; in those who receive assisted ventilation, especially if high ventilator support is necessary; and in infants with urinary tract anomalies or oligohydramnios.

ETIOLOGY AND PATHOPHYSIOLOGY

The most common cause of pneumothorax is overinflation resulting in alveolar rupture. It may be "spontaneous" or caused by underlying pulmonary disease, such as lobar emphysema or rupture of a congenital lung cyst or pneumatocele, to trauma, or to a "ball-valve" type of bronchial or bronchiolar obstruction resulting from aspiration.

Pneumothorax associated with **pulmonary hypoplasia** is common, tends to occur during the 1st few hr after birth, and is caused by reduced alveolar surface area and poorly compliant lungs. It is associated with disorders of decreased amniotic fluid volume (Potter syndrome, renal agenesis, renal dysplasia, chronic amniotic fluid leak), decreased fetal breathing movement (oligohydramnios, neuromuscular disease), pulmonary space-occupying lesions (diaphragmatic hernia, pleural effusion, chylothorax), and thoracic abnormalities (thoracic dystrophies).

Gas from a ruptured alveolus escapes into the interstitial spaces of the lung, where it may cause interstitial emphysema or dissect along the peribronchial and perivascular connective tissue sheaths to the hilum of the lung. If the volume of escaped air is great enough, it may collect in the mediastinal space (**pneumomediastinum**) or rupture into the pleural space (**pneumothorax**), subcutaneous tissue (**subcutaneous emphysema**), peritoneal cavity (**pneumoperitoneum**), and/or pericardial sac (**pneumopericardium**). Rarely, increased mediastinal pressure may compress the pulmonary veins at the hilum and thereby interfere with pulmonary venous return to the heart and cardiac output. On occasion, air may embolize into the circulation (**pulmonary air embolism**) and produce cutaneous blanching, air in intravascular catheters, an air-filled heart and vessels on chest roentgenograms, and death.

Tension pneumothorax occurs if an accumulation of air within the pleural space is sufficient to elevate intrapleural pressure above atmospheric pressure. Unilateral tension pneumothorax results in impaired ventilation not only in the ipsilateral lung but also in the contralateral lung owing to a shift in the mediastinum toward the contralateral side. Compression of the vena cava and torsion of the great vessels may interfere with venous return.

CLINICAL MANIFESTATIONS

The physical findings of a clinically asymptomatic **pneumothorax** are hyperresonance and diminished breath sounds over the involved side of the chest with or without tachypnea.

Symptomatic pneumothorax is characterized by respiratory distress, which varies from merely high respiratory rate to severe dyspnea, tachypnea, and cyanosis. Irritability and restlessness or apnea may be the earliest signs. The onset is usually sudden but may be gradual; an infant may rapidly become critically ill. The chest may appear asymmetric with an increased anteroposterior diameter and bulging of the intercostal spaces on the affected side; other signs may be hyperresonance and diminished or absence of breath sounds. The heart is displaced toward the unaffected side, resulting in displacement of the cardiac apex and point of maximal impulse of the heart. The diaphragm is displaced downward, as is the liver with right-sided pneumothorax, and may result in abdominal distention. Because pneumothorax may be bilateral in approximately 10% of patients, symmetry of findings does not rule it out. In tension pneumothorax, signs of shock may be noted.

Pneumomediastinum can occur in patients with pneumothorax and is usually asymptomatic. The degree of respiratory distress depends on the amount of trapped gas. If it is great, bulging of the midthoracic area is observed, the neck veins are distended, and blood pressure is low. The last 2 findings are a result of tamponade of the systemic and pulmonary veins. Although often asymptomatic, subcutaneous emphysema in newborn infants is almost pathognomonic of pneumomediastinum.

Pulmonary interstitial emphysema may precede the development of a pneumothorax or may occur independently and lead to increasing respiratory distress as a result of decreased compliance, hypercapnia, and hypoxemia. Hypoxemia is caused by an increased alveolar–arterial oxygen gradient and intrapulmonary shunting. Progressive enlargement of blebs of gas may result in cystic dilation and respiratory deterioration resembling pneumothorax. In severe cases, pulmonary interstitial emphysema precedes the development of BPD. Avoidance of high inspiratory or mean airway pressures may prevent the development of pulmonary interstitial emphysema. Treatment may include bronchoscopy in patients with evidence of mucous plugging, selective intubation and ventilation of the uninvolved bronchus, oxygen, general respiratory care, and HFV.

DIAGNOSIS

Pneumothorax and other air leaks should be suspected in newborn infants who show signs of respiratory distress, are restless or irritable, or have a sudden change in condition. The diagnosis of pneumothorax is established by radiography, with the edge of the collapsed

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lung standing out in relief against the pneumothorax (Fig. 101-14); pneumomediastinum is signified by hyperlucency around the heart border and between the sternum and the heart border (Fig. 101-15). Transillumination of the thorax is often helpful in the emergency diagnosis of pneumothorax; the affected side transmits excessive light. Associated renal anomalies are identified by ultrasonography. Pulmonary hypoplasia is suggested by signs of uterine compression (extremity contractures), a small thorax on chest roentgenograms, severe hypoxia with hypercapnia, and signs of the primary disease (hypotonia, diaphragmatic hernia, Potter syndrome).

Pneumopericardium may be asymptomatic, requiring only general supportive treatment, but it usually manifests as sudden shock with tachycardia, muffled heart sounds, and poor pulses suggesting tamponade. **Pneumoperitoneum** from air dissecting through the diaphragmatic apertures during mechanical ventilation may be confused with intestinal perforation. Abdominal paracentesis can be helpful in differentiating the two conditions. The presence of organisms on Gram stain of intestinal contents suggests the latter. Occasionally, pneumoperitoneum can result in an abdominal compartment syndrome requiring decompression.

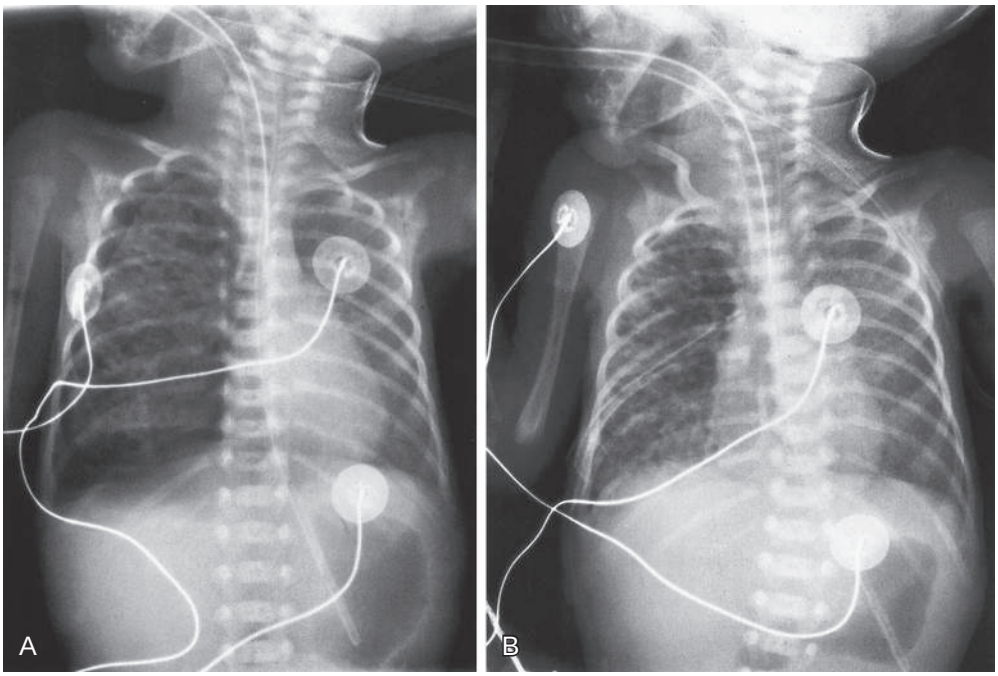

Figure 101-14 A, Right-sided tension pneumothorax and widespread right lung pulmonary interstitial emphysema in a preterm infant receiving intensive care. **B,** Resolution of pneumothorax with a chest tube in place. Pulmonary interstitial emphysema (PIE) persists. *(From Meerstadt PWD, Gyll C:* Manual of neonatal emergency x-ray interpretation, *Philadelphia, 1994, WB Saunders, p. 73.)*

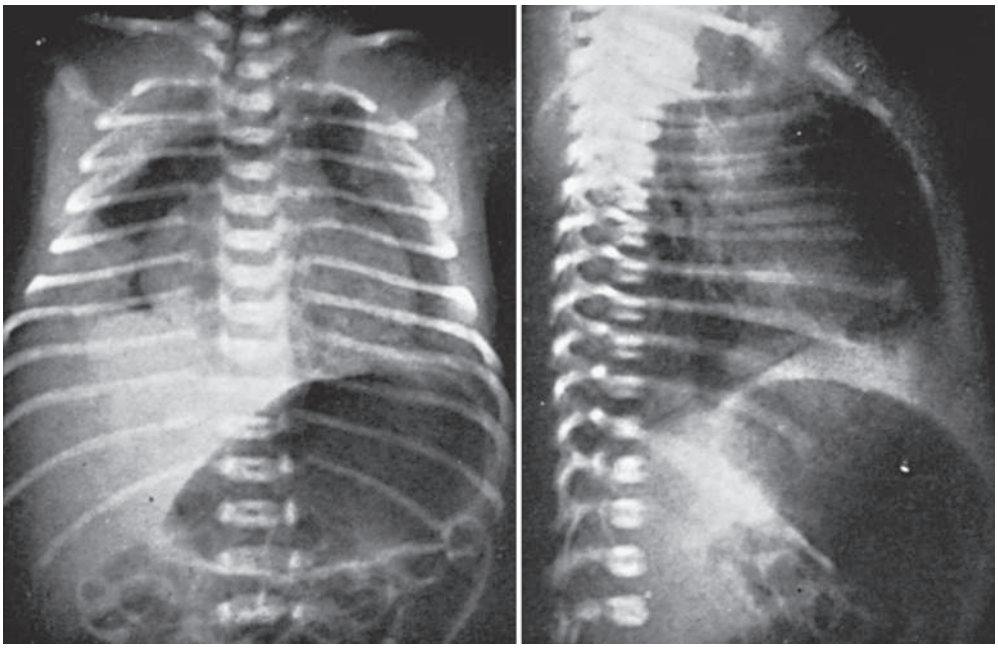

Figure 101-15 Pneumomediastinum in a newborn infant. The anteroposterior view (*left*) demonstrates compression of the lungs, and the lateral view (*right*) shows bulging of the sternum, each resulting from distention of the mediastinum by trapped air.

TREATMENT

Without a continued air leak, asymptomatic and mildly symptomatic small pneumothoraces require only close observation. Conservative management of a pneumothorax is effective even in selected infants requiring ventilatory support. Frequent small feedings may prevent gastric dilation and minimize crying, which can further compromise ventilation and worsen the pneumothorax. Breathing 100% oxygen in term infants may accelerate the resorption of free pleural air into blood by reducing the nitrogen tension in blood and producing a resultant nitrogen pressure gradient from the trapped gas in the blood, but the clinical effectiveness is not proven and the benefit must be weighed against the risks of oxygen toxicity. With severe respiratory or circulatory embarrassment, emergency aspiration using a soft small catheter introduced with a needle is indicated. Either immediately or after catheter aspiration, a chest tube should be inserted and attached to underwater seal drainage (see Fig. 101-14). If the air leak is ongoing, continuous suction (−5 to −20 cm H_2O) may be needed to evacuate the pneumothorax completely. A pneumopericardium requires prompt evacuation of entrapped air. Severe localized interstitial emphysema may respond to selective bronchial intubation. Judicious use of sedation in an infant fighting a ventilator may reduce the risk of pneumothorax. Surfactant therapy for RDS reduces the incidence of pneumothorax.

Bibliography is available at Expert Consult.

101.13 Pulmonary Hemorrhage

Namasivayam Ambalavanan and Waldemar A. Carlo

Massive pulmonary hemorrhage is a relatively uncommon, but catastrophic complication with a high risk of morbidity and mortality. Some degree of pulmonary hemorrhage occurs in about 10% of extremely preterm infants. However, massive pulmonary hemorrhage is less common and can be fatal. Autopsy demonstrates massive pulmonary hemorrhage in 15% of neonates who die in the 1st 2 wk of life. The reported incidence at autopsy varies from 1 to 4/1,000 live births. Approximately 75% of affected patients weigh <2,500 g at birth. Prophylactic indomethacin in extremely low birthweight infants reduces the incidence of pulmonary hemorrhage.

Most infants with pulmonary hemorrhage have had symptoms of respiratory distress that are indistinguishable from those of RDS. The onset may occur at birth or may be delayed several days. Hemorrhagic pulmonary edema is the source of blood in many cases and is associated with significant ductal shunting and high pulmonary blood flow or severe left-sided heart failure resulting from hypoxia. In severe cases, sudden cardiovascular collapse, poor lung compliance, profound cyanosis, and hypercapnia may be present. Radiographic findings are varied and nonspecific, ranging from minor streaking or patchy infiltrates to massive consolidation.

The incidence of pulmonary hemorrhage is increased in association with acute pulmonary infection, severe asphyxia, RDS, assisted ventilation, PDA, congenital heart disease, erythroblastosis fetalis, hemorrhagic disease of the newborn, thrombocytopenia, inborn errors of ammonia metabolism, and cold injury. Pulmonary hemorrhage is the only severe complication whose rate is *increased* with surfactant treatment. Pulmonary hemorrhage is seen with all surfactants; the incidence ranges from 1-5% of treated infants and is higher with natural surfactant. Bleeding is predominantly alveolar in approximately 65% of cases and interstitial in the rest. Bleeding into other organs is observed at autopsy of severely ill neonates, suggesting the possibility of an additional bleeding diathesis such as disseminated intravascular coagulation.

Treatment of pulmonary hemorrhage includes blood replacement, suctioning to clear the airway, intratracheal administration of epinephrine, and, in some cases, HFV. Although surfactant treatment has been associated with the development of pulmonary hemorrhage, administration of exogenous surfactant after the bleeding has occurred can improve lung compliance, because the presence of intra-alveolar blood and protein can inactivate surfactant.

Acute pulmonary hemorrhage may rarely occur in previously healthy full-term infants. The cause is unknown. Pulmonary hemorrhage may manifest as hemoptysis or blood in the nasopharynx or airway with no evidence of upper respiratory or gastrointestinal bleeding. Patients present with acute, severe respiratory failure requiring mechanical ventilation. Chest radiographs usually demonstrate bilateral alveolar infiltrates. The condition usually responds to intensive supportive treatment (see Chapter 407).

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Chapter 102

Digestive System Disorders

Akhil Maheshwari and Waldemar A. Carlo

VOMITING

Vomiting or, more often, regurgitation is a relatively frequent symptom during the neonatal period. In the 1st few hr after birth, infants may vomit mucus, occasionally blood streaked. This vomiting rarely persists after the first few feedings; it may be caused by irritation of the gastric mucosa by material swallowed during delivery. If vomiting is protracted, gastric lavage with physiologic saline solution may relieve it.

When vomiting occurs shortly after birth and is persistent, the possibilities of intestinal obstruction, metabolic disorders, and increased intracranial pressure must be considered. A history of maternal polyhydramnios suggests upper gastrointestinal (esophageal, duodenal, ileal) atresia. Bile-stained emesis suggests intestinal obstruction beyond the duodenum but may also be idiopathic. Abdominal radiographs (kidney-ureter-bladder and cross-table lateral views) should be performed in neonates with persistent emesis and in all infants with bile-stained emesis to detect air–fluid levels, distended bowel loops, characteristic patterns of obstruction (double bubble: duodenal atresia), and pneumoperitoneum (that may be a result of intestinal perforation). A contrast swallow roentgenogram with small bowel follow-through is indicated in the presence of bilious emesis.

Obstructive lesions of the digestive tract are the most frequent gastrointestinal anomalies (see Chapters 319, 329, 330, and 332). Vomiting (and drooling) from esophageal obstruction occurs before or with the first feeding. The diagnosis of esophageal atresia can be suspected if unusual drooling from the mouth is observed and if resistance is encountered during an attempt to pass a catheter into the stomach. The diagnosis should be made before the infant has trouble with oral feedings and aspiration pneumonia develops. Infantile achalasia (cardiospasm), a rare cause of vomiting in newborn infants, is demonstrable radiographically as obstruction at the cardiac end of the esophagus without organic stenosis. Regurgitation of feedings because of continuous relaxation of the esophageal–gastric sphincter, or chalasia, is a cause of vomiting. Keeping the infant in a semiupright position, thickening the feeding, or administering prokinetic drugs can control it.

Vomiting caused by obstruction of the small intestine usually begins on the 1st day of life and is frequent, persistent, usually nonprojectile, copious, and, unless the obstruction is above the ampulla of Vater, bile-stained; it is associated with abdominal distention, visible deep peristaltic waves, and reduction or absence of bowel movements. Malrotation with obstruction from **midgut volvulus** is an acute emergency that must be not only considered but also urgently evaluated by an upper gastrointestinal contrast radiographic series. Radiographs of the

abdomen show the distribution of air in the intestine, which may point to the anatomic location of an obstruction; malrotation can be identified only by contrast studies. Normally, air can be demonstrated by radiographs in the jejunum by 15-60 min, in the ileum by 2-3 hr, and in the colon by 3 hr after birth. Absence of rectal gas at 24 hr is abnormal. Persistent vomiting may occur with congenital diaphragmatic hernia. The vomiting associated with pyloric stenosis may begin any time after birth but may not assume its characteristic pattern before the 2nd-3rd wk. Vomiting with obstipation is a common early sign of **Hirschsprung disease.** Vomiting may occur with many other disturbances that do not obstruct the digestive tract, such as milk allergy, adrenal hyperplasia of the salt-losing variety, galactosemia, hyperammonemias, organic acidemias, increased intracranial pressure, septicemia, meningitis, and urinary tract infection. In many infants, it is simply regurgitation from overfeeding or from failure to permit the infant to eructate swallowed air. (See Chapter 323 for a discussion of gastric emptying and gastroesophageal reflux.)

DIARRHEA

See Chapters 340 and 341.

CONSTIPATION

More than 90% of full-term newborn infants pass meconium within the 1st 24 hr. The possibility of intestinal obstruction should be considered in any infant who does not pass meconium by 24-36 hr. Intestinal atresia, stricture, or stenosis; Hirschsprung disease; milk bolus obstruction; meconium ileus; or meconium plugs may manifest as constipation or, more often, obstipation. Approximately 20% of very-low birthweight (VLBW) infants do not pass meconium within the 1st 24 hr. Constipation not present from birth but appearing during the 1st mo of life may be a sign of short-segment congenital aganglionic megacolon, hypothyroidism, strictures after necrotizing enterocolitis (NEC), or anal stenosis. It must be kept in mind that infrequent bowel movements do not necessarily mean constipation. A breastfed infant usually has frequent bowel movements, whereas a formula-fed infant may have 1-2 movements a day or every other day.

MECONIUM PLUGS

Lower colonic or anorectal plugs (Fig. 102-1) with a lower-than-normal water content may cause intestinal obstruction. Rarely, a firm mass of meconium may form elsewhere in the intestine and cause intrauterine intestinal obstruction and meconium peritonitis unrelated to cystic fibrosis (CF). Anorectal plugs may also cause mucosal ulceration and intestinal perforation. **Meconium plugs** are associated with small left colon syndrome in infants of diabetic mothers and with CF, rectal aganglionosis, maternal opiate use, and magnesium sulfate therapy for preeclampsia. The plug may be evacuated by glycerin suppository or rectal irrigation with isotonic saline. Enemas with the iodinated contrast medium Gastrografin (meglumine diatrizoate, a hyperosmolar, water-soluble, radiopaque solution containing 0.1% polysorbate 80 [Tween 80] and 37% organically bound iodine) usually induce passage of the plug, presumably because the high osmolarity (1,900 mOsm/L) of the solution draws fluid rapidly into the intestinal lumen and loosens inspissated material. Such rapid loss of fluid into the bowel may result in acute dehydration and shock, so it is advisable to dilute the contrast material with an equal amount of water, correct any existing dehydration, and provide intravenous fluids during and for several hours after the procedure. After removal of a meconium plug, the infant should be observed closely for the possible presence of congenital aganglionic megacolon.

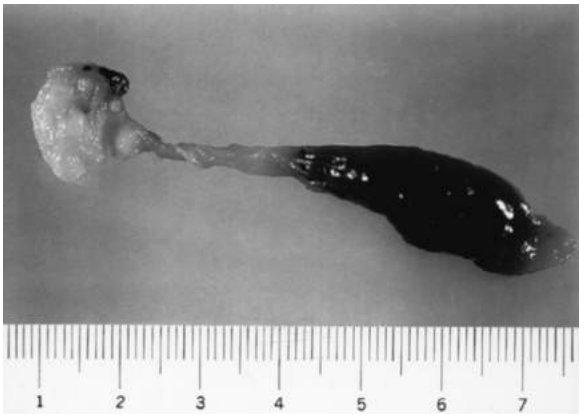

Figure 102-1 This plug of meconium and mucus (scale in cm) caused bowel obstruction in a premature infant. A radiograph showed marked gaseous distention and multiple fluid levels at 30 hr of age. Dramatic improvement occurred when the plug was passed after an enema. *(From The abnormal fetus. In Beischer NA, Mackay EV, Colditz PB, editors:* Obstetrics and the newborn, *ed 3, Philadelphia, 1997, WB Saunders.)*

102.1 Meconium Ileus in Cystic Fibrosis

Akhil Maheshwari and Waldemar A. Carlo

Impaction of meconium causes intestinal obstructions and may be associated with CF. The absence of fetal pancreatic enzymes in CF limits normal digestive activities in the intestine, and meconium becomes viscid and mucilaginous. It clings to the intestinal wall and moves with difficulty. The inspissated and impacted meconium fills the intestinal canal but is most concentrated in the lower part of the ileum. Clinically, the pattern is that of congenital intestinal obstruction with or without intestinal perforation. Abdominal distention is prominent, and vomiting becomes persistent. Infrequently, 1 or more inspissated meconium stools may be passed shortly after birth.

Meconium ileus is primarily associated with CF transmembrane regulator (CFTR) mutations F508del, G542X, W1282X, R553X, and G551D. Patients with 2 copies of the F508del mutation have a 25% chance of presenting with meconium ileus. F508del plus any "other" CF mutation confers 17% chance, and 2 "other" CF mutations confer a 12% chance of meconium ileus. In addition, non-CFTR genetic "modifier" genes influence meconium ileus. In families that already have at least 1 child with CF complicated by meconium ileus, there is a 39% recurrence rate for meconium ileus in subsequent children, which is more than the rates expected with autosomal recessive inheritance. In a twin study, 82% of monozygotic twins showed concordance for meconium ileus, whereas only 22% of dizygotic and 24% of 2 affected siblings showed concordance.

The **differential diagnosis** involves other causes of intestinal obstruction, including intestinal pseudoobstruction and other causes of pancreatic insufficiency (see Chapter 349). A presumptive diagnosis can be made on the basis of a history of CF in a sibling, via palpation of doughy or cordlike masses of intestines through the abdominal wall, and from the radiographic appearance. In contrast to the generally evenly distended intestinal loops above an atresia, the loops may vary in width and are not as evenly filled with gas. At points of heaviest meconium concentration, the infiltrated gas may create a bubbly granular appearance (Figs. 102-2 and 102-3). It is technically difficult to perform a sweat test in a neonate. Genetic testing confirms the diagnosis of CF.

Treatment for meconium ileus is high Gastrografin enema as described previously for meconium plugs. If the procedure is unsuccessful or perforation of the bowel wall is suspected, a laparotomy is performed and the ileum is opened at the point of largest diameter of the impaction. Approximately 50% of these infants have associated intestinal atresia, stenosis, or volvulus that requires surgery. The inspissated meconium is removed by gentle and patient irrigation with warm isotonic sodium chloride or *N*-acetylcysteine (Mucomyst) solution through a catheter passed between the impaction and the bowel wall. Most infants with meconium ileus survive the neonatal period. If meconium ileus is associated with CF, the long-term prognosis depends on the severity of the underlying disease (see Chapter 403).

Figure 102-2 **Meconium ileus.** Impacted meconium with small amounts of air interspersed can be seen in loops of intestine on the right side of the abdomen. The intestinal loops above this impaction are greatly distended.

Figure 102-3 **Meconium ileus.** The colon, outlined by contrast material, is small because meconium has not reached it.

MECONIUM PERITONITIS

Perforation of the intestine may occur in utero or shortly after birth. Frequently, the intestinal perforation seals naturally with relatively little meconium leakage into the peritoneal cavity. In some cases, with long-standing perforation, meconium peritonitis is more pronounced. Perforations occur most often as a complication of meconium ileus in infants with CF but are occasionally the result of a meconium plug or in utero intestinal obstruction of another cause. Cases at the most severe end of the spectrum may be diagnosed on prenatal ultrasonography with fetal ascites, polyhydramnios, bowel dilation, intraabdominal calcifications, and hydrops fetalis. At the other end are cases in which an intestinal perforation may seal spontaneously with only a minor meconium leak, so the event may never be detected except when meconium becomes calcified and is later discovered on radiographs of the abdomen. Alternatively, the clinical picture may be dominated by the signs of intestinal obstruction (as in meconium ileus) or chemical peritonitis. Characteristic clinical findings include abdominal distention, vomiting, and absence of stools. Treatment consists primarily of elimination of the intestinal obstruction and drainage of the peritoneal cavity.

102.2 Necrotizing Enterocolitis

Akhil Maheshwari and Waldemar A. Carlo

NEC is the most common life-threatening emergency of the gastrointestinal tract in the newborn period. The disease is characterized by various degrees of mucosal or transmural necrosis of the intestine. The cause of NEC remains unclear but is most likely multifactorial. The incidence of NEC is 1-5% of infants in neonatal ICUs. Both incidence and case fatality rates increase with decreasing birth weight and gestational age. Because very small, ill preterm infants are particularly susceptible to NEC, a rising incidence may reflect improved survival of this high-risk group of patients.

PATHOLOGY AND PATHOGENESIS

Many factors may contribute to the development of a the pathologic findings of NEC including necrotic segment of intestine, gas accumulation in the submucosa of the bowel wall **(pneumatosis intestinalis),** and progression of the necrosis to perforation, peritonitis, sepsis, and death. The distal part of the ileum and the proximal segment of colon are involved most frequently; in fatal cases, gangrene may extend from the stomach to the rectum. Although NEC is a multifactorial disease primarily associated with intestinal immaturity, the concept of "risk factors" for NEC is controversial. The triad of intestinal ischemia (injury), enteral nutrition (metabolic substrate), and bacterial translocation has classically been linked to NEC. The greatest risk factor for NEC is prematurity. The disorder probably results from an interaction between loss of mucosal integrity due to a variety of factors (ischemia, infection, inflammation) and the host's response to that injury (circulatory, immunologic, inflammatory), leading to necrosis of the affected area. Coagulation necrosis is the characteristic histologic finding in intestinal specimens. Clustering of cases suggests a primary role for an infectious agent. Various bacterial and viral agents, including *Escherichia coli, Klebsiella, Clostridium perfringens, Staphylococcus epidermidis,* astrovirus, norovirus, and rotavirus, have been recovered from cultures. Nonetheless, in most situations, a pathogen is not identified. NEC rarely occurs before the initiation of enteral feeding and is much less common in infants fed human milk. Aggressive enteral feeding may predispose to the development of NEC.

Although nearly 90% of all cases of NEC occur in preterm infants, the disease can occur in full-term neonates. NEC in term infants is often a "secondary" disease, seen more frequently in infants with history of birth asphyxia, Down syndrome, congenital heart disease, rotavirus infections, and Hirschsprung disease.

CLINICAL MANIFESTATIONS

Infants with NEC have a variety of signs and symptoms and may have an insidious or sudden catastrophic onset (Table 102-1). The onset of NEC is usually in the 2nd or 3rd wk of life but can be as late as 3 mo in VLBW infants. Age of onset is inversely related to gestational age. The first signs of impending disease may be nonspecific, including lethargy and temperature instability, or related to gastrointestinal pathology, such as abdominal distention and gastric retention. In some

Table 102-1 Signs and Symptoms Associated with Necrotizing Enterocolitis

GASTROINTESTINAL
Abdominal distention
Abdominal tenderness
Feeding intolerance
Delayed gastric emptying
Vomiting
Occult/gross blood in stool
Change in stool pattern/diarrhea
Abdominal mass
Erythema of abdominal wall
SYSTEMIC
Lethargy
Apnea/respiratory distress
Temperature instability
"Not right"
Acidosis (metabolic and/or respiratory)
Glucose instability
Poor perfusion/shock
Disseminated intravascular coagulopathy
Positive results of blood cultures

From Kanto WP Jr, Hunter JE, Stoll BJ: Recognition and medical management of necrotizing enterocolitis, Clin Perinatol *21:335–346, 1994.*

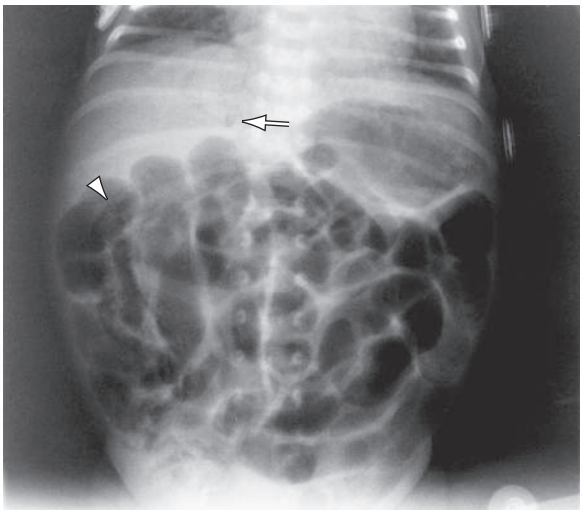

Figure 102-4 NEC. A kidney-ureter-bladder film demonstrates abdominal distention, hepatic portal venous gas *(arrow),* and a bubbly appearance of pneumatosis intestinalis (*arrowhead;* right lower quadrant). The latter 2 signs are thought to be pathognomonic for neonatal NEC.

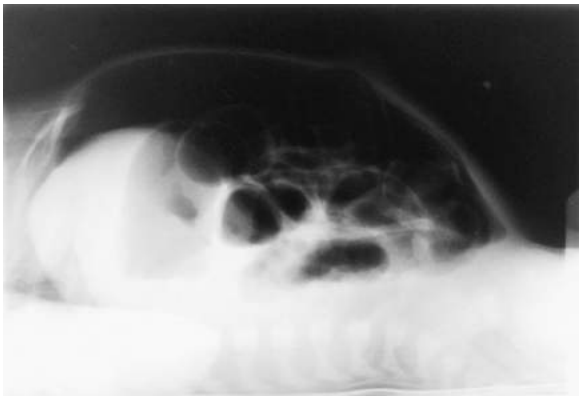

Figure 102-5 Intestinal perforation. A cross-table abdominal roentgenogram in a patient with a neonatal NEC demonstrates marked distention and massive pneumoperitoneum as evidenced by the free air below the anterior abdominal wall.

extremely low birthweight infants, NEC may develop following a red cell transfusion. Bloody stools are seen in 25% of patients. Because of nonspecific signs, sepsis may be suspected before NEC. The spectrum of illness is broad, ranging from mild disease with only guaiac-positive stools to severe illness with bowel perforation, peritonitis, systemic inflammatory response syndrome, shock, and death. Progression may be rapid, but it is unusual for the disease to progress from mild to severe after 72 hr.

DIAGNOSIS

A very high index of suspicion in treating preterm at-risk infants is crucial. Plain abdominal radiographs are essential to make a diagnosis of NEC. The finding of pneumatosis intestinalis (air in the bowel wall) confirms the clinical suspicion of NEC and is diagnostic; 50-75% of patients have pneumatosis when treatment is started (Fig. 102-4). Portal venous gas is a sign of severe disease, and pneumoperitoneum indicates a perforation (Figs. 102-4 and 102-5). Hepatic sonography may detect portal venous gas in some infants with normal abdominal x-rays.

The **differential diagnosis** of NEC includes specific infections (systemic or intestinal), gastrointestinal obstruction, volvulus, and isolated intestinal perforation. Idiopathic focal intestinal perforation can occur spontaneously or after the early use of postnatal steroids and indomethacin. Pneumoperitoneum develops in such patients, but they are usually less ill than those with NEC.

TREATMENT

Rapid initiation of therapy is required for suspected as well as proven cases of NEC. There is no definitive treatment for established NEC, so therapy is directed at giving supportive care and preventing further injury with cessation of feeding, nasogastric decompression, and administration of intravenous fluids. Careful attention to respiratory status, coagulation profile, and acid–base and electrolyte balances are important. Once blood has been drawn for culture, systemic antibiotics (with broad coverage based on the antibiotic sensitivity patterns of the gram-positive, Gram-negative, and anaerobic organisms in the particular neonatal ICU) should be started immediately. If present, umbilical catheters should be removed, but good intravenous access needs to be maintained. Ventilation should be assisted in the presence of apnea or if abdominal distention is contributing to hypoxia and hypercapnia. Intravascular volume replacement with crystalloid or blood products, cardiovascular support with fluid boluses and/or inotropes, and correction of hematologic, metabolic, and electrolyte abnormalities are essential to stabilize the infant with NEC.

The patient's course should be monitored closely by means of frequent physical assessments; sequential anteroposterior and cross-table lateral or lateral decubitus abdominal radiographs to detect intestinal perforation; and serial determinations of hematologic, electrolyte, and acid–base status. Gown and glove isolation and grouping of infants at similar increased risks into cohorts separate from other infants should be instituted to contain an epidemic.

A surgeon should be consulted early in the course of treatment. **Indications for surgery** include evidence of perforation on abdominal x-ray (pneumoperitoneum) or positive result of abdominal paracentesis (stool or organism on Gram stain preparation from peritoneal fluid). Failure of medical management, a single fixed bowel loop on radiographs, abdominal wall erythema, and a palpable mass are relative indications for exploratory laparotomy. Ideally, surgery should be performed after intestinal necrosis develops but before perforation and peritonitis occur. In unstable premature infants with perforated NEC, **peritoneal drainage** can be cautiously considered as an alternative to **exploratory laparotomy**, although the best surgical approach in these infants remains unresolved. The type of surgical operation did not

influence survival or other clinically important early outcomes in one multicenter study, but another large randomized trial showed that a majority of infants who were initially treated with peritoneal drains required a delayed secondary laparotomy. There are also some concerns about the long-term outcome (death or neurodevelopmental outcome) for infants treated with peritoneal drainage.

Patients with isolated intestinal perforation (not related to NEC) tend to have a lower birthweight, are less likely to be receiving oral feeding, and are prone to perforation at an earlier postnatal age than are patients with perforation related to NEC. In many patients with isolated intestinal perforation treated by drainage, no further surgical procedure is needed; a small subgroup may require later surgery to repair an intestinal stricture or fistula.

PROGNOSIS

Medical management fails in approximately 20-40% of patients with pneumatosis intestinalis at diagnosis; of these, 10-30% die. Early postoperative complications include wound infection, dehiscence, and stomal problems (prolapse, necrosis). Later complications include **intestinal strictures**, which develop at the site of the necrotizing lesion in approximately 10% of surgically or medically managed patients. Resection of the obstructing stricture is curative. After massive intestinal resection, complications from postoperative NEC include **short-bowel syndrome** (malabsorption, growth failure, malnutrition), complications related to central venous catheters (sepsis, thrombosis), and cholestatic jaundice. Preterm infants with NEC who require surgical intervention or who have concomitant bacteremia are at increased risk for adverse growth and neurodevelopmental outcome.

PREVENTION

Newborns exclusively breastfed have a reduced risk of NEC. There have been concerns about early and aggressive increase in feeding volumes in raising the risk of NEC in VLBW infants, although a safe feeding regimen remains unknown. Gut stimulation protocols consisting of minimal enteral feeds followed by judicious volume advancement decreased the incidence of NEC in smaller study cohorts, but significant benefits were not detected in a meta-analysis of all randomized studies. In other studies, slow advancement or delayed introduction of enteral feedings did not protect against NEC. Emerging evidence indicates that the use of inhibitors of gastric acid secretion (H_2-receptor blockers, proton pump inhibitors) or prolonged empirical antibiotics in early neonatal period is associated with increased risk of NEC. Prophylactic enteral antibiotics reduced the risk of NEC in a study but although concerns about adverse outcomes persist, particularly related to the development of resistant bacteria. Extensive data and meta-analyses show that probiotic preparations decrease the incidence of severe NEC (stage II or higher) and mortality in preterm infants but an FDA-approved preparation is not available.

Bibliography is available at Expert Consult.

102.3 Jaundice and Hyperbilirubinemia in the Newborn

Namasivayam Ambalavanan and Waldemar A. Carlo

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st wk after birth in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. This unconjugated bilirubin (designated **indirect-acting** by nature of the Van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and nonenzymatic reducing agents in the reticuloendothelial cells. It may also be partly caused by deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)–glucuronyl transferase to form the polar, water-soluble glucuronide of bilirubin **(direct-reacting).** Although bilirubin may have a physiologic role as an antioxidant, elevations of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates a potentially serious hepatic disorders or a systemic illness.

ETIOLOGY

During the neonatal period, metabolism of bilirubin is in transition from the fetal stage, during which the placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, to the adult stage, during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract. Unconjugated hyperbilirubinemia may be caused or increased by any factor that (a) increases the load of bilirubin to be metabolized by the liver (hemolytic anemias, polycythemia, bruising or internal hemorrhage, shortened red blood cell life as a result of immaturity or transfusion of cells, increased enterohepatic circulation, infection); (b) damages or reduces the activity of the transferase enzyme or other related enzymes (genetic deficiency, hypoxia, infection, thyroid deficiency); (c) competes for or blocks the transferase enzyme (drugs and other substances requiring glucuronic acid conjugation); or (d) leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells (genetic defect, and prematurity). Gene polymorphisms in the hepatic uridine diphosphate glucuronosyltransferase isoenzyme 1A1 (*UGT1A1*) and the solute carrier organic anion transporter 1B1 (*SLCO1B1*) alone or in combination influence the incidence of neonatal hyperbilirubinemia. The toxic effects of elevated serum concentrations of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation (hypoproteinemia, displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia). Neurotoxic effects are directly related not only to the permeability of the blood–brain barrier and nerve cell membranes but also to neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases, whereas breastfeeding and dehydration increase, serum levels of bilirubin. Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic recirculation after deconjugation by intestinal glucuronidase (Fig. 102-6). Drugs such as oxytocin (in the mother) and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia. Table 102-2 lists the risk factors for unconjugated hyperbilirubinemia. Additional risk factors include polycythemia, infection, prematurity, and having a diabetic mother.

CLINICAL MANIFESTATIONS

Jaundice usually appears during the early neonatal period, depending on etiology. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Dermal pressure may reveal the anatomic progression of jaundice (face, ≈ 5 mg/dL; mid-abdomen, ≈ 15 mg/dL; soles, ≈ 20 mg/dL), but clinical examination cannot be depended on to estimate serum levels. Jaundice to the midabdomen, signs or symptoms, high-risk factors that suggest nonphysiologic jaundice, or hemolysis must be evaluated further (see Tables 102-2 and 102-3). Noninvasive techniques for transcutaneous measurement of bilirubin that correlate with serum levels may be used to screen infants, but determination of serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for either hemolysis or sepsis. Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast. Infants with severe hyperbilirubinemia may present with lethargy and poor feeding and, without

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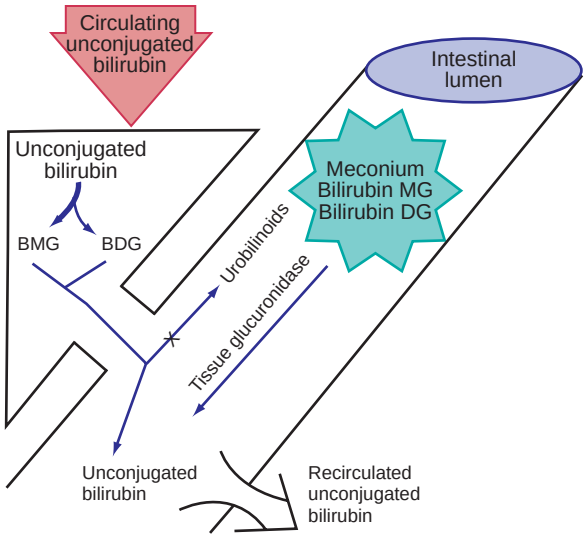

Figure 102-6 The neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilitranslocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione S-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults do. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucuronide (BDG) must be deconjugated by tissue β-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

Table 102-2 Risk Factors for Development of Severe Hyperbilirubinemia in Infants ≥35 Wk of Gestation (in Approximate Order of Importance)

MAJOR RISK FACTORS
Predischarge TSB or TcB level in the high-risk zone (see Fig. 102-8)
Jaundice observed in the 1st 24 hr
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), elevated end-title CO concentration
Gestational age 35-36 wk
Previous sibling received phototherapy
Cephalohematoma or significant bruising
Exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive
East Asian race*
MINOR RISK FACTORS
Predischarge TSB or TcB level in the high intermediate-risk zone
Gestational age 37-38 wk
Jaundice observed before discharge
Previous sibling with jaundice
Macrosomic infant of a diabetic mother
Maternal age ≥25 yr
Male gender
DECREASED RISK (THESE FACTORS ARE ASSOCIATED WITH DECREASED RISK OF SIGNIFICANT JAUNDICE, LISTED IN ORDER OF DECREASING IMPORTANCE)
TSB or TcB level in the low-risk zone (see Fig. 102-8)
Gestational age ≥41 wk
Exclusive bottle-feeding
Black race
Discharge from hospital after 72 hr

*Race as defined by mother's description.
TcB, transcutaneous bilirubin; TSB, total serum bilirubin.
From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics *114:297–316, 2004.*

Table 102-3 Laboratory Evaluation of the Jaundiced Infant ≥35 Wk of Gestation

INDICATIONS	ASSESSMENTS
Jaundice in 1st 24 hr	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (i.e., crossing percentiles [see Fig. 102-8]) and unexplained by history and physical examination	Blood type and Coombs test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and $ETCO_c$, if available Repeat TSB in 4-24 hr depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, ETCO if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

$ETCO_c$, end tidal carbon monoxide concentration; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.
From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics *114:297–316, 2004.*

treatment, can progress to acute bilirubin encephalopathy (kernicterus) (see Chapter 102.4).

DIFFERENTIAL DIAGNOSIS

Jaundice, consisting of either indirect or direct bilirubin, that is present at birth or appears within the 1st 24 hr after birth requires immediate attention and may be due to erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital infections, including syphilis, cytomegalovirus, rubella, and toxoplasmosis. Hemolysis is suggested by a rapid rise in serum bilirubin concentration (>0.5 mg/dL/hr), anemia, pallor, reticulocytosis, hepatosplenomegaly, and a positive family history. An unusually high proportion of direct-reacting bilirubin may characterize jaundice in infants who have received intrauterine transfusions for erythroblastosis fetalis. Jaundice that first appears on the 2nd or 3rd day is usually **physiologic** but may represent a more severe form. Familial nonhemolytic icterus **(Crigler-Najjar syndrome)** and early-onset breastfeeding jaundice are seen initially on the 2nd or 3rd day. Jaundice appearing after the 3rd day and within the 1st wk suggests bacterial sepsis or urinary tract infection; it may also be due to other infections, notably syphilis, toxoplasmosis, cytomegalovirus, and enterovirus. Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the 1st day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

There is a long differential diagnosis for jaundice first recognized *after* the 1st wk of life, including breast milk jaundice, septicemia, congenital atresia or paucity of the bile ducts, hepatitis, galactosemia, hypothyroidism, CF, and congenital hemolytic anemia crises related to red blood cell morphology and enzyme deficiencies (Fig. 102-7). The differential diagnosis for persistent jaundice during the 1st mo of life includes hyperalimentation-associated cholestasis, hepatitis, cytomegalic inclusion disease, syphilis, toxoplasmosis, familial nonhemolytic icterus, congenital atresia of the bile ducts, galactosemia, and inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several weeks, as in infants with hypothyroidism or pyloric stenosis.

Full-term, low-risk, asymptomatic infants with jaundice may be evaluated by monitoring of total serum bilirubin levels. Regardless of gestation or time of appearance of jaundice, patients with significant hyperbilirubinemia and those with symptoms or signs require a complete diagnostic evaluation, which includes determination of direct and indirect bilirubin fractions, hemoglobin, reticulocyte count, blood type, Coombs test, and examination of a peripheral blood smear. Indirect hyperbilirubinemia, reticulocytosis, and a smear with evidence of red blood cell destruction suggest hemolysis (see Table 102-3). In the absence of blood group incompatibility, nonimmunologically induced hemolysis should be considered. If the reticulocyte count, Coombs test result, and direct bilirubin value are normal, physiologic or pathologic indirect hyperbilirubinemia may be present (see Fig. 102-7). If direct hyperbilirubinemia is present, hepatitis, congenital bile duct disorders (biliary atresia, paucity of bile ducts, Byler disease), cholestasis, inborn errors of metabolism, CF, and sepsis are diagnostic possibilities.

PHYSIOLOGIC JAUNDICE (ICTERUS NEONATORUM)

Under normal circumstances, the level of indirect bilirubin in umbilical cord serum is 1-3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus, jaundice becomes visible on the 2nd or 3rd day, usually peaking

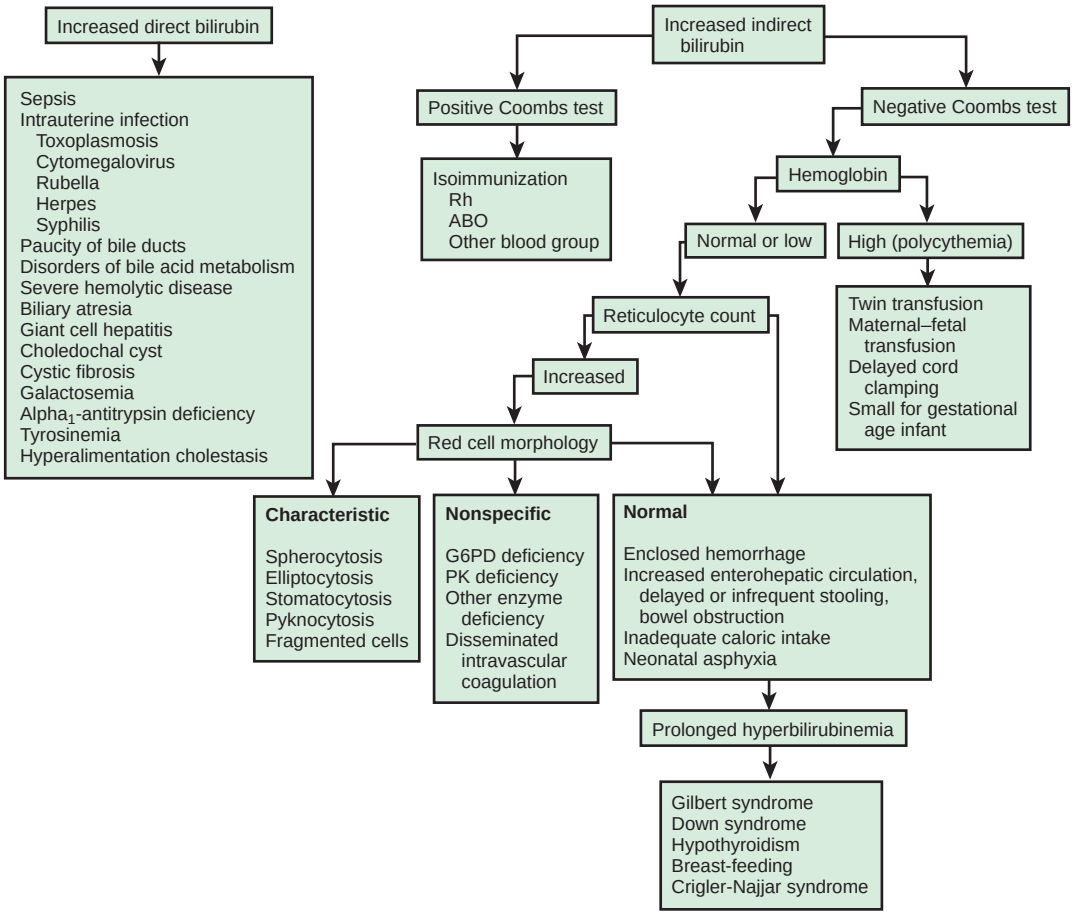

Figure 102-7 Schematic approach to the diagnosis of neonatal jaundice. G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase. *(From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA, editors:* Schaffer and Avery's diseases of the newborn, *ed 6, Philadelphia, 1991, WB Saunders.)*

between the 2nd and 4th days at 5-6 mg/dL and decreasing to <2 mg/dL between the 5th and 7th days after birth. Jaundice associated with these changes is designated *physiologic* and is believed to be the result of increased bilirubin production from the breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

Overall, 6-7% of full-term infants have indirect bilirubin levels >13 mg/dL and less than 3% have levels >15 mg/dL. Risk factors for elevated indirect bilirubin include maternal age, race (Chinese, Japanese, Korean, and Native American), maternal diabetes, prematurity, drugs (vitamin K_3, novobiocin), altitude, polycythemia, male sex, trisomy 21, cutaneous bruising, blood extravasation (cephalohematoma), oxytocin induction, breastfeeding, weight loss (dehydration or caloric deprivation), delayed bowel movement, and a family history of or a sibling who had physiologic jaundice (see Table 102-2). In infants without these variables, indirect bilirubin levels rarely rise above 12 mg/dL, whereas infants with several risk factors are more likely to have higher bilirubin levels. A combination of breastfeeding, variant-glucuronosyltransferase activity (1A1), and alterations of the organic anion transporter 2 gene increases the risk of hyperbilirubinemia. Predicting which neonates are at risk for exaggerated physiologic jaundice can be based on hour-specific bilirubin levels in the 1st 24-72 hr of life (Fig. 102-8). Transcutaneous measurements of bilirubin are linearly correlated with serum levels and can be used for screening. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life. Persistent indirect hyperbilirubinemia beyond 2 wk suggests hemolysis, hereditary glucuronyl transferase deficiency, breast milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated with pyloric stenosis may be the result of caloric deprivation, relative deficiency of hepatic UDP-glucuronyl transferase, or an increase in the enterohepatic circulation of bilirubin from the ileus. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12 mg/dL are not usually reached until the 4th-7th day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice on the basis of the history, clinical findings, and laboratory data (Table 102-4). In general, a search to determine the cause of jaundice should be made if (1) it appears in the 1st 24-36 hr after birth, (2) serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr, (3) serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant, (4) jaundice persists after 10-14 days after birth, or (5) direct bilirubin fraction is >2 mg/dL at any time. Other factors suggesting a nonphysiologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, and signs of kernicterus (see Chapter 102.4).

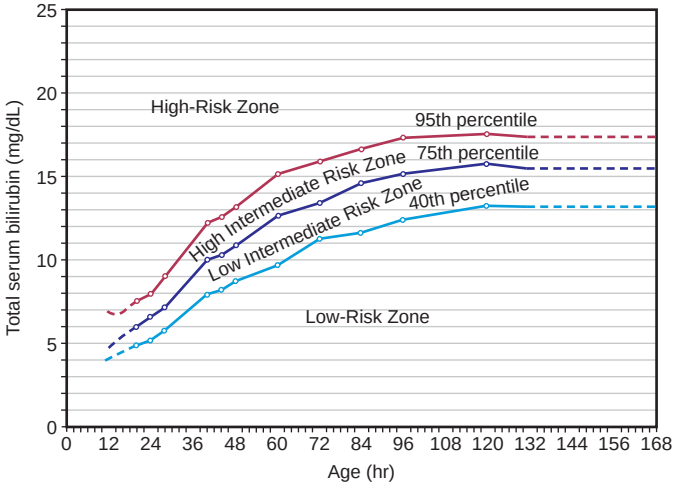

Figure 102-8 Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values. The high-risk zone is subdivided by the 95th percentile track. The intermediate -risk zone is subdivided into upper and lower risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. *(From Bhutani VK, Johnson L, Sivieri EM: Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns,* Pediatrics *103:6–14, 1999.)*

PATHOLOGIC HYPERBILIRUBINEMIA

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity. It may not be possible to determine the precise cause of an abnormal elevation of unconjugated bilirubin, but many infants with this finding have associated risk factors such as Asian race, prematurity, breastfeeding, and weight loss. Frequently, the terms *exaggerated physiologic jaundice* and *hyperbilirubinemia of the newborn* are used in infants whose primary problem is probably a deficiency or inactivity of bilirubin glucuronyl transferase (**Gilbert syndrome**) rather than an excessive load of bilirubin for excretion (see Table 102-2). The combination of glucose-6-phosphate dehydrogenase (G6PD) deficiency and a mutation of the promoter region of UDP-glucuronyl transferase-1 produces indirect hyperbilirubinemia in the absence of signs of hemolysis. Nonphysiologic hyperbilirubinemia may also be caused by mutations in the gene for bilirubin UDP-glucuronyl transferase.

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels (see Chapter 102.4). The development of kernicterus (bilirubin encephalopathy) depends on the level of indirect bilirubin, duration of exposure to bilirubin elevation, the cause of jaundice, and the infant's well-being. Neurologic injury including kernicterus may occur at lower bilirubin levels in preterm infants and in the presence of asphyxia, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. The exact serum indirect bilirubin level that is harmful for VLBW infants is unclear.

JAUNDICE ASSOCIATED WITH BREAST-FEEDING

Significant elevation in unconjugated bilirubin (*breast milk jaundice*) develops in an estimated 2% of breastfed term infants after the 7th day, with maximal concentrations as high as 10-30 mg/dL reached during the 2nd-3rd wk. If breastfeeding is continued, the bilirubin gradually decreases but may persist for 3-10 wk at lower levels. If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal range within a few days. With resumption of breastfeeding, bilirubin seldom returns to previously high levels. Phototherapy may be of benefit (see Chapter 102.4). Although uncommon, kernicterus can occur in patients with breast milk jaundice. The etiology of breast milk jaundice is not entirely clear but may be attributed to the presence of glucuronidase in some breast milk.

The late jaundice associated with breastfeeding should be distinguished from an early-onset, accentuated unconjugated hyperbilirubinemia known as *breastfeeding jaundice*, which occurs in the 1st wk after birth in breastfed infants, who normally have higher bilirubin levels than formula-fed infants (Fig. 102-9). Hyperbilirubinemia (>12 mg/dL) develops in 13% of breastfed infants during the 1st wk and may be a result of decreased milk intake with dehydration and/or reduced caloric intake. Prophylactic supplements of glucose water to breastfed infants are associated with higher bilirubin levels, in part because of reduced intake of the higher–caloric density breast milk. Frequent breastfeeding (>10/24 hr), rooming-in with night feeding,

Table 102-4 Diagnostic Features of the Various Types of Neonatal Jaundice

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	REMARKS
		Appears	Disappears	mg/dL	Age in Days		
"Physiologic jaundice":							Usually relates to degree of maturity
Full-term	Indirect	2-3 days	4-5 days	10-12	2-3	<5	
Premature	Indirect	3-4 days	7-9 days	15	6-8	<5	
Hyperbilirubinemia caused by metabolic factors:							Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate
Full-term	Indirect	2-3 days	Variable	>12	1st wk	<5	Hormonal influences: cretinism, hormones, Gilbert syndrome
Premature	Indirect	3-4 days	Variable	>15	1st wk	<5	Genetic factors: Crigler-Najjar syndrome, Gilbert syndrome Drugs: vitamin K, novobiocin
Hemolytic states and hematoma	Indirect	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Erythroblastosis: Rh, ABO, Kell congenital hemolytic states: spherocytic, nonspherocytic Infantile pyknocytosis Drug: vitamin K Enclosed hemorrhage—hematoma
Mixed hemolytic and hepatotoxic factors	Indirect and direct	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Infection: bacterial sepsis, pyelonephritis, hepatitis, toxoplasmosis, cytomegalic inclusion disease, rubella, syphilis Drug: vitamin K
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by 2nd wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary atresia; paucity of bile ducts, familial cholestasis, galactosemia; hepatitis and infection

From Brown AK: Neonatal jaundice, Pediatr Clin North Am *9:575–603, 1962.*

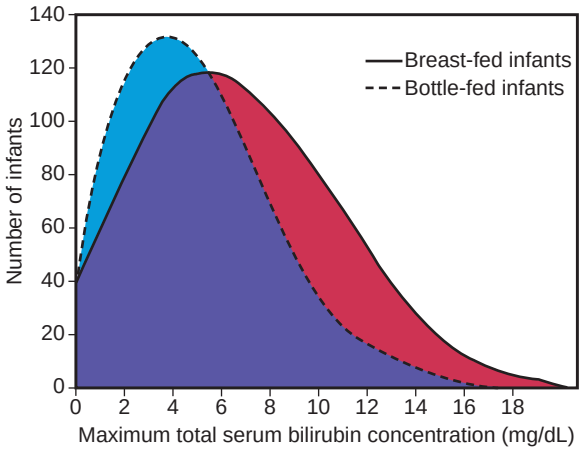

Figure 102-9 Distribution of maximal bilirubin levels during the 1st wk of life in breastfed and formula-fed white infants weighing more than 2,500 g. *(From Maisels MJ, Gifford K: Normal serum bilirubin levels in the newborn and the effect of breast-feeding,* Pediatrics *78:837–843, 1986.)*

and ongoing lactation support may reduce the incidence of early breastfeeding jaundice. Even when breastfeeding jaundice develops, breastfeeding should be continued if possible. It is an option to temporarily interrupt breast-feedings and substitute formula for a day or two. In addition, frequent feeding and supplementation with formula or expressed breast milk is appropriate if the intake seems inadequate, weight loss is excessive, or the infant appears dehydrated.

NEONATAL HEPATITIS

See Chapter 356.1.

CONGENITAL ATRESIA OF THE BILE DUCTS

See Chapter 356.1.

Jaundice persisting for more than 2 wk or associated with acholic stools and dark urine suggests biliary atresia. All infants with such findings must undergo an immediate diagnostic evaluation, including determination of direct bilirubin.

INSPISSATED BILE SYNDROME

See Late Complications in Chapter 103.2.

Bibliography is available at Expert Consult.

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102.4 Kernicterus

Namasivayam Ambalavanan and Waldemar A. Carlo

Kernicterus, or bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the blood-brain barrier, and neuronal susceptibility to injury. Disruption of the blood–brain barrier by disease, asphyxia, and other factors and maturational changes in blood–brain barrier permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but in a large series, kernicterus occurred only in infants with a bilirubin >20 mg/dL. Ninety percent of the infants in whom kernicterus developed were in previously healthy, predominantly breastfed term and near-term infants. The duration of exposure to high bilirubin levels needed to produce toxic effects are unknown. The more immature the infant is, the greater the susceptibility to kernicterus. Chapter 102.3 discusses the factors that potentiate the movement of bilirubin across the blood–brain barrier and into brain cells.

CLINICAL MANIFESTATIONS

Signs and symptoms of kernicterus usually appear 2-5 days after birth in term infants and as late as the 7th day in preterm infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrate, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched (Table 102-5). Rigidity is rare at this late stage.

Many infants who progress to these severe neurologic signs die; the survivors are usually seriously damaged but may appear to recover and for 2-3 mo show few abnormalities. Later in the 1st yr, opisthotonos, muscle rigidity, irregular movements, and convulsions tend to recur. In the 2nd yr, the opisthotonos and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 yr of age, the complete neurologic syndrome is often apparent; it consists of bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dysarthric speech, high-frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or "minimal brain dysfunction," occurring singly or in combination; these problems may be unapparent until the child enters school (see Table 102-5).

Table 102-5 Clinical Features of Kernicterus

ACUTE FORM
Phase 1 (1st 1-2 days): poor suck, stupor, hypotonia, seizures
Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever
Phase 3 (after the 1st wk): hypertonia
CHRONIC FORM
1st year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills
After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

From Dennery PA, Seidman DS, Stevenson DK: Neonatal hyperbilirubinemia, N Engl J Med *344:581–590, 2001.*

INCIDENCE AND PROGNOSIS

By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic preterm infants is 2-16% and is related to the risk factors discussed in Chapter 102.3. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs have a grave prognosis; more than 75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common.

PREVENTION

Although kernicterus has been thought to be a disease of the past, there are reports of neurotoxic effects of bilirubin in term and near-term infants who were discharged as healthy newborns. Experts recommend universal screening for hyperbilirubinemia in the 1st 24-48 hr after birth to detect infants at high risk for severe jaundice and bilirubin-induced neurologic dysfunction.

Effective prevention requires ongoing vigilance and a practical, system-based approach in order to distinguish infants with benign newborn jaundice from those whose course may be less predictable and potentially harmful. Protocols using the hour-specific bilirubin nomogram (see Fig. 102-8), physical examination, and clinical risk factors have been successful in identifying patients at risk for hyperbilirubinemia and candidates for targeted management. The American Academy of Pediatrics has identified potentially preventable causes of kernicterus, as follows: (1) early discharge (<48 hr) with no early follow-up (within 48 hr of discharge); this problem is particularly important in near-term infants (35-37 wk of gestation); (2) failure to check the bilirubin level in an infant noted to be jaundiced in the 1st 24 hr; (3) failure to recognize the presence of risk factors for hyperbilirubinemia; (4) underestimation of the severity of jaundice by clinical (visual) assessment; (5) lack of concern regarding the presence of jaundice; (6) delay in measuring the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy. Figure 102-10 is an evidence-based management algorithm for infants. In addition, it is recommended to determine before discharge each infant's risk factors from established protocols (see Table 102-2).

The following approach is further recommended: (1) any infant who is jaundiced before 24 hr requires measurement of total and direct serum bilirubin levels and, if it is elevated, evaluation for possible hemolytic disease and (2) follow-up should be provided within 2-3 days of discharge to all neonates discharged earlier than 48 hr after birth. Early follow-up is particularly important for infants younger than 38 wk of gestation. The timing of follow-up depends on the age at discharge and the presence of risk factors. In some cases, follow-up within 24 hr is necessary. Postdischarge follow-up is essential for early recognition of problems related to hyperbilirubinemia and disease progression. Parental communication with regard to concerns about infant's skin color and behavioral activities should be addressed early and frequently, including education about potential risks and neurotoxicity. Ongoing lactation promotion, education, support, and follow-up services are essential throughout the neonatal period. Mothers should be advised to nurse their infants every 2-3 hr and to avoid routine supplementation with water or glucose water in order to ensure adequate hydration and caloric intake.

TREATMENT OF HYPERBILIRUBINEMIA

Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin while not causing undue harm. Phototherapy and, if it is unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below pathologic levels (Figs. 102-11 and 102-12;

Table 102-6 Suggested Maximal Indirect Serum Bilirubin Concentrations (mg/dL) in Preterm Infants

BIRTHWEIGHT (g)	UNCOMPLICATED*	COMPLICATED*
<1,000	12-13	10-12
1,000-1,250	12-14	10-12
1,251-1,499	14-16	12-14
1,500-1,999	16-20	15-17
2,000-2,500	20-22	18-20

*Complications include perinatal asphyxia, acidosis, hypoxia, hypothermia, hypoalbuminemia, meningitis, intraventricular hemorrhage, hemolysis, hypoglycemia, or signs of kernicterus. Phototherapy is usually started at 50-70% of the maximal indirect level. If values greatly exceed this level, if phototherapy is unsuccessful in reducing the maximal bilirubin level, or if signs of kernicterus are evident, exchange transfusion is indicated.

Table 102-6). The risk of injury to the central nervous system from bilirubin must be balanced against the potential risk of treatment. There is lack of consensus regarding the exact bilirubin level at which to initiate phototherapy. Because phototherapy may require 6-12 hr to have a measurable effect, it must be started at bilirubin levels below those indicated for exchange transfusion. When identified, underlying medical causes of elevated bilirubin and physiologic factors that contribute to neuronal susceptibility should be treated, with antibiotics for septicemia and correction of acidosis (Table 102-7).

Phototherapy

Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to a high intensity of light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420-470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. Bilirubin in the skin absorbs light energy, causing several photochemical reactions. One major product from phototherapy is a result of a reversible photoisomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state.

The therapeutic effect of phototherapy depends on the light energy emitted in the effective range of wavelengths, the distance between the lights and the infant, and the surface area of exposed skin, as well as the rate of hemolysis and in vivo metabolism and excretion of bilirubin. Available commercial phototherapy units vary considerably in spectral output and the intensity of radiance emitted; therefore, the wattage can be accurately measured only at the patient's skin surface. Dark skin does not reduce the efficacy of phototherapy. Maximal intensive phototherapy should be used when indirect bilirubin levels approach those noted in Figure 102-11 and Table 102-7. Such therapy includes using "special blue" fluorescent tubes, placing the lamps within 15-20 cm of the infant, and putting a fiberoptic phototherapy blanket under the infant's back to increase the exposed surface area. Aggressive phototherapy may improve neurodevelopmental outcome in infants <1,000 g.

The use of phototherapy has decreased the need for exchange transfusion in term and preterm infants with hemolytic and nonhemolytic jaundice. When indications for exchange transfusion are present, phototherapy should not be used as a substitute; however, phototherapy may reduce the need for repeated exchange transfusions in infants with hemolysis. Conventional phototherapy is applied continuously, and the infant is turned frequently for maximal skin surface area exposure. It should be discontinued as soon as the indirect bilirubin concentration has reduced to levels considered safe with respect to the infant's age and condition. Serum bilirubin levels and hematocrit should be monitored every 4-8 hr in infants with hemolytic disease and those with bilirubin levels near toxic range for the individual infant. Others, particularly older neonate, may be monitored less frequently. Serum bilirubin monitoring should continue for at least 24 hr after cessation of phototherapy in patients with hemolytic disease, because unexpected rises in bilirubin may occur, requiring further treatment. Skin color cannot be relied on for evaluating the effectiveness of phototherapy; the skin of babies exposed to light may appear to be almost without jaundice in the presence of marked hyperbilirubinemia. Although not necessary for all affected infants, intravenous fluid supplementation added to oral feedings may be beneficial in dehydrated patients or infants with bilirubin levels nearing those requiring exchange transfusion.

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrinemia, overheating, dehydration (increased insensible water loss, diarrhea), hypothermia from exposure, and a benign condition called bronze baby syndrome (which occurs in the presence of direct hyperbilirubinemia). Phototherapy is contraindicated in the presence of porphyria. Before phototherapy is initiated, the infant's eyes should be closed and adequately covered to prevent light exposure and corneal damage. Body temperature should be monitored, and the infant should be shielded from bulb breakage. Irradiance should be measured directly. In infants with hemolytic disease, care must be taken to monitor for the development of anemia, which may require transfusion. *Anemia may develop despite lowering of bilirubin levels.* Clinical experience suggests that long-term adverse biologic effects of phototherapy are absent, minimal, or unrecognized.

The term **bronze baby syndrome** refers to a sometimes-noted dark, grayish brown skin discoloration in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may result from photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Intravenous Immunoglobulin

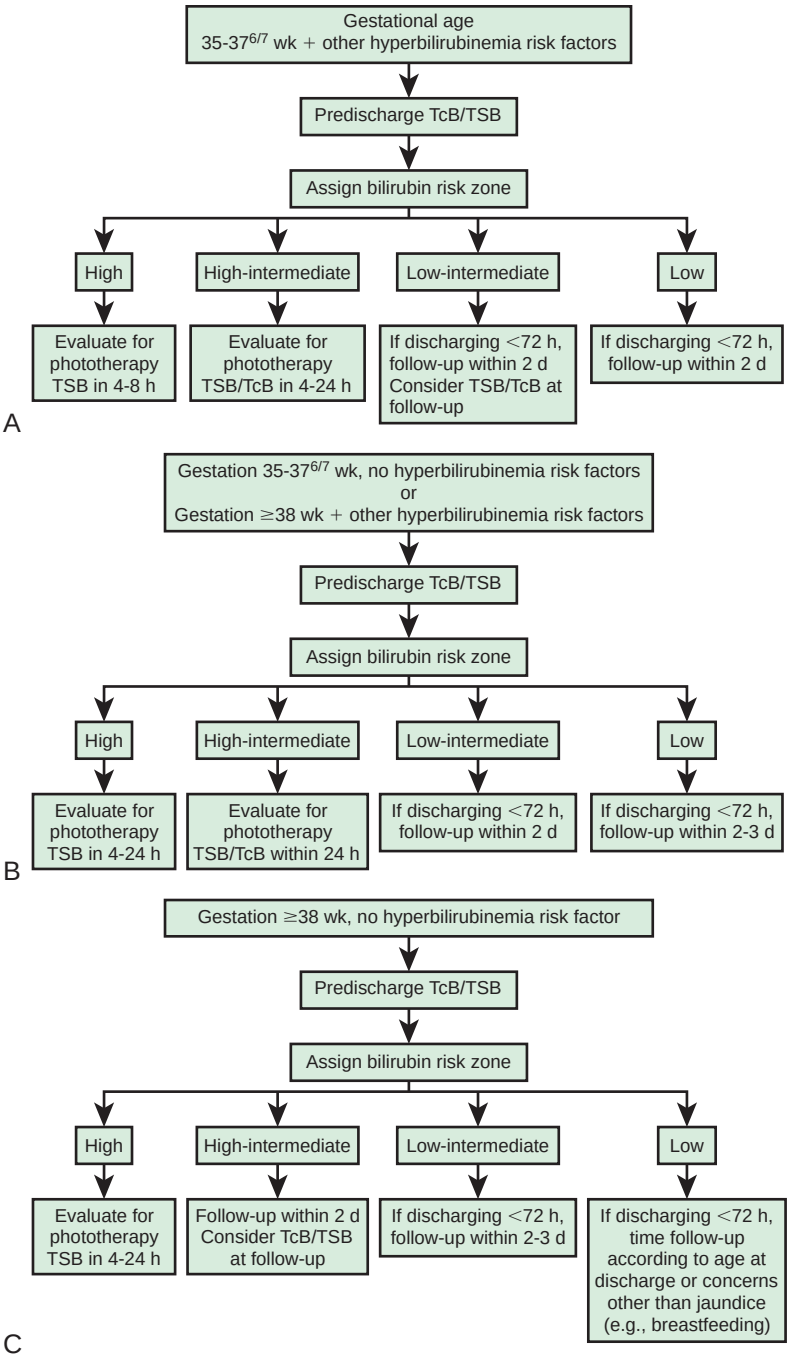
The administration of intravenous immunoglobulin is an adjunctive treatment for hyperbilirubinemia caused by *isoimmune hemolytic disease*. Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions including phototherapy. Intravenous immunoglobulin (0.5-1.0 g/kg/dose; repeat in 12 hr) reduces the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.

Metalloporphyrins

A potentially important alternative therapy is the use of metalloporphyrins for hyperbilirubinemia. The metalloporphyrin Sn-mesoporphyrin (SnMP) offers promise as a drug candidate. The proposed mechanism of action is competitive enzymatic inhibition of the rate-limiting conversion of heme-protein to biliverdin (an intermediate metabolite in the production of unconjugated bilirubin) by heme-oxygenase. A single intramuscular dose on the 1st day of life may reduce the need for subsequent phototherapy. Such therapy may be beneficial when jaundice is anticipated, particularly in patients with ABO incompatibility or G6PD deficiency, or when blood products are objected to, as with Jehovah's Witness patients. Complications from metalloporphyrins include transient erythema if the infant is receiving phototherapy. Administration of SnMP may reduce bilirubin levels and decrease both the need for phototherapy and the duration of hospital stay; however, it remains unclear whether treatment with metalloporphyrins for unconjugated hyperbilirubinemia will alter the risk of kernicterus or long-term neurodevelopment impairment. Data on efficacy, toxicity, and long-term benefit are currently being evaluated.

Exchange Transfusion

Double-volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and if the

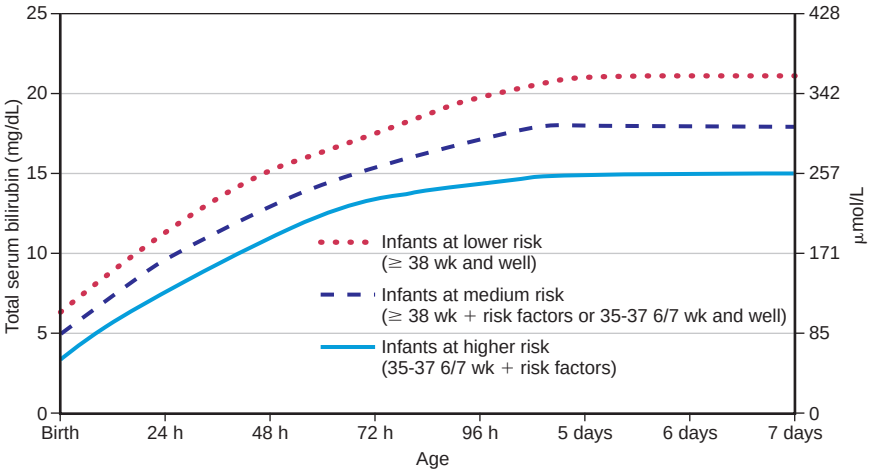


- Provide lactation evaluation and support for all breastfeeding mothers.
- Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile. Higher and earlier initial TSB levels require an earlier repeat TSB measurment.
- Perform standard clinical evaluation at all follow-up visits.
- For evaluation of jaundice see 2004 AAP guideline.
- In hospital or as outpatient. Follow-up recommendations can be modified according to level of risk for hyperbilirubinemia; depending on the circumstances in infants at low risk, later follow-up can be considered.

Figure 102-10 Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. TcB, transcutaneous bilirubin; TSB, total serum bilirubin. *(From Maisels MJ, Bhutani VK, Bogen D, et al: Hyperbilirubinemia in the newborn infant ≥35 weeks' gestation: an update with clarifications,* Pediatrics *124:1193–1198, 2009.)*

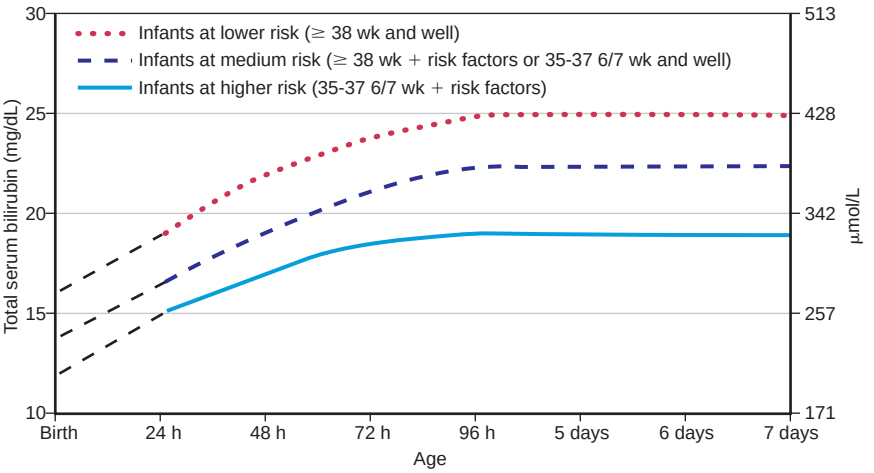
risk of kernicterus exceeds the risk of the procedure. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, NEC, infection, graft-versus-host disease, and death. This widely accepted treatment is repeated if necessary to keep indirect bilirubin levels in a safe range (see Fig. 102-12 and Table 102-7). See "Exchange Transfusion" in Chapter 103.

Various factors may influence the decision to perform a double-volume exchange transfusion in an individual patient. The appearance of clinical signs suggesting kernicterus is an indication for exchange transfusion at any level of serum bilirubin. A healthy full-term infant



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0 g/dL (if measured).
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

Figure 102-11 **Guidelines for phototherapy in hospitalized infants of ≥35 wk of gestation.** *Note:* These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood–brain barrier, and the susceptibility of the brain cells to damage by bilirubin. "Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths approximately 430-490 nm) of at least 30 μW/cm^2/nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's skin surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the manufacturer of the phototherapy system. If TSB levels approach or exceed the exchange transfusion line (see Fig. 102-12), the sides of the bassinette, incubator, or warmer should be lined with aluminum foil or white material, to increase both the surface area of the infant exposed and the efficacy of phototherapy. The presence of hemolysis is strongly suggested if the TSB does not decrease or continues to rise in an infant who is receiving intensive phototherapy. Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin value (cholestatic jaundice) may inconsistently have the bronze-baby syndrome. G6PD, glucose-6-phosphate dehydrogenase. *(From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation,* Pediatrics *114:297–316, 2004.)*



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dL (85 μmol/L) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

Figure 102-12 **Guidelines for exchange transfusion in hospitalized infants of ≥35 wk of gestation.** *Note:* These suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite intensive phototherapy. In a readmitted infant, if the TSB level is above the exchange level, TSB measurement should be repeated every 2-3 hr; exchange transfusion should be considered if the TSB remains above the levels indicated after intensive phototherapy for 6 hr. The following B : A (bilirubin : albumin) ratios can be used together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion. G6PD, glucose-6-phosphate dehydrogenase. *(From American Academy of Pediatrics Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation,* Pediatrics *114:297–316, 2004.)*

Table 102-7	Example of a Clinical Pathway for Management of the Newborn Infant Readmitted for Phototherapy or Exchange Transfusion
TREATMENT	
Use intensive phototherapy and/or exchange transfusion as indicated in Figs. 102-11 and 102-12	
LABORATORY TESTS	
TSB and direct bilirubin levels	
Blood type (ABO, Rh)	
Direct antibody test (Coombs)	
Serum albumin	
Complete blood cell count with differential and smear for red cell morphology	
Reticulocyte count	
End-tidal CO concentration (if available)	
Glucose-6-phosphate dehydrogenase if suggested by ethnic or geographic origin or if poor response to phototherapy	
Urine for reducing substances	
If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture	
INTERVENTIONS	
If TSB ≥25 mg/dL (428 μmol/L) or ≥20 mg/dL (342 μmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary	
In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2-3 mg/dL (34-51 μmol/L) of exchange level (see Fig. 102-12), administer intravenous immunoglobulin 0.5-1 g/kg over 2 hr and repeat in 12 hr if necessary	
If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids	
FOR INFANTS RECEIVING INTENSIVE PHOTOTHERAPY:	
Breastfeed or bottle-feed (formula or expressed breast milk) every 2-3 hr	
If TSB ≥25 mg/dL (428 μmol/L), repeat TSB within 2-3 hr	
If TSB 20-25 mg/dL (342-428 μmol/L), repeat within 3-4 hr. If TSB <20 mg/dL (342 μmol/L), repeat in 4-6 hr. If TSB continues to fall, repeat in 8-12 hr	
If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig. 102-12, consider exchange transfusion (see Fig. 102-12 for exchange transfusion recommendations)	
When TSB is <13-14 mg/dL (239 μmol/L), discontinue phototherapy	
Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hr after discharge to check for rebound	

TSB, total serum bilirubin.

From AAP Subcommittee on Hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, Pediatrics *114:297–316, 2004.*

with physiologic or breast milk jaundice may tolerate a concentration slightly higher than 25 mg/dL with no apparent ill effect, whereas kernicterus may develop in a sick premature infant at a significantly lower level. A level approaching that considered critical for the individual infant may be an indication for exchange transfusion during the 1st or 2nd day after birth when a further rise is anticipated, but not typically after the 4th day in a term infant or after the 7th day in a preterm infant because an imminent fall may be anticipated as the hepatic conjugating mechanism becomes more effective.

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Chapter 103

Blood Disorders

Akhil Maheshwari and Waldemar A. Carlo

103.1 Anemia in the Newborn Infant

Akhil Maheshwari and Waldemar A. Carlo

Hemoglobin increases with advancing gestational age: at term, cord blood hemoglobin is 16.8 g/dL (14-20 g/dL); hemoglobin levels in very-low birthweight (VLBW) infants are 1-2 g/dL below those in term infants (Fig. 103-1). A hemoglobin value less than the normal range of hemoglobin for birthweight and postnatal age is defined as anemia (Table 103-1). A "physiologic" decrease in hemoglobin content is noticed at 8-12 wk in term infants (hemoglobin, 11 g/dL) and at approximately 6 wk in premature infants (7-10 g/dL).

Infants born by cesarean section may have a lower hematocrit than those born vaginally. **Anemia at birth** manifests as pallor, heart failure, or shock (Fig. 103-2). It may be caused by acute or chronic fetal blood loss, hemolysis, or underproduction of erythrocytes. Specific causes include hemolytic disease of the newborn, tearing or cutting of the umbilical cord during delivery, abnormal cord insertion, communicating placental vessels, placenta previa or abruptio, nuchal cord, incision into the placenta, internal hemorrhage (liver, spleen, intracranial), α-thalassemia, congenital parvovirus infection or other hypoplastic anemias, and twin–twin transfusion in monozygotic twins with arteriovenous placental connections (see Chapter 98).

Transplacental hemorrhage with bleeding from the fetal into the maternal circulation has been reported in 5-15% of pregnancies, but, unless severe, it is not usually sufficient to cause clinically apparent anemia at birth. The cause of transplacental hemorrhage is not clear, but its occurrence has been proven by demonstration of significant amounts of fetal hemoglobin and red blood cells (RBCs) in maternal blood on the day of delivery by the **Kleihauer-Betke** test or by flow cytometry methods to detect fetal cells in maternal blood. If the infant has severe anemia with heart failure, emergency exchange transfusion to restore hematocrit and oxygen-carrying capacity may be needed.

Acute blood loss usually results in severe distress at birth, initially with a normal hemoglobin level, no hepatosplenomegaly, and early onset of shock. In contrast, chronic blood loss in utero produces

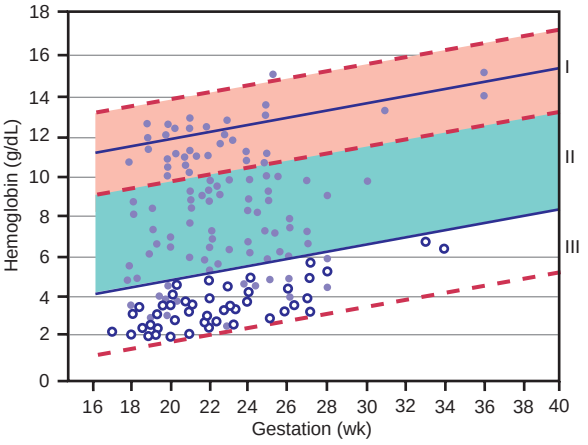

Figure 103-1 Range (mean and 95% confidence limits) of hemoglobin concentration from 10-40 wk of gestational age in normal (zone I) fetuses obtained by cordocentesis (percutaneous umbilical blood sample). *Solid circles* depict maternal red blood cell isoimmunization; *open circles* indicate hemoglobin levels in fetuses with ultrasonographic evidence of hydrops (zone III). *(From Soothill PW: Cordocentesis: role in assessment of fetal condition,* Clin Perinatol *16:755–770, 1989.)*

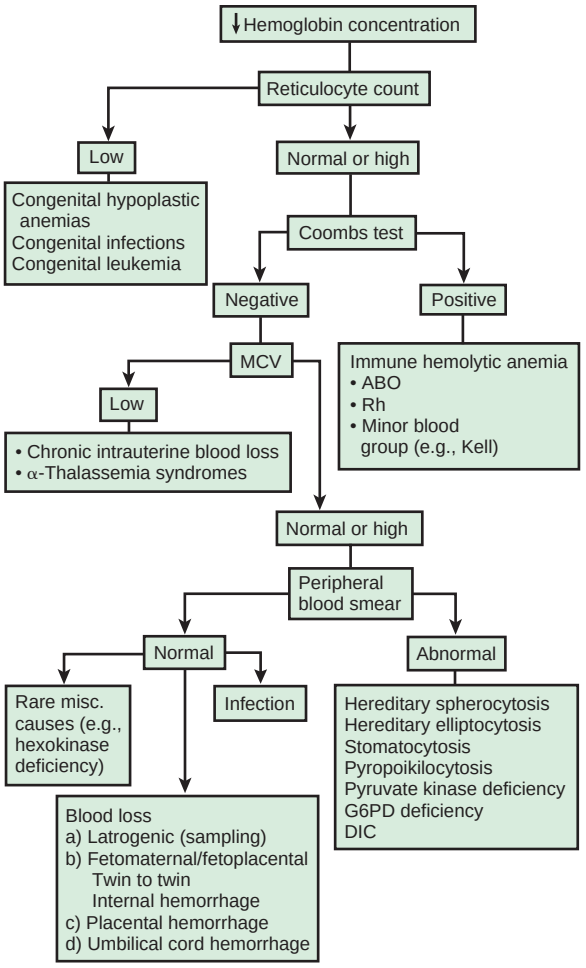

Figure 103-2 Diagnostic approach to anemia in newborn infants. DIC, disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; MCV, mean corpuscular volume. *(Modified from Blanchette VS, Zipursky A: Assessment of anemia in newborn infants,* Clin Perinatol *11:489–510, 1984.)*

marked pallor, less distress, a low hemoglobin level with microcytic indices, and, if severe, heart failure.

Anemia appearing in the first few days after birth is also most frequently a result of hemolytic disease of the newborn. Other causes are hemorrhagic disease of the newborn, bleeding from an improperly tied or clamped umbilical cord, large cephalohematoma, intracranial hemorrhage, and subcapsular bleeding from rupture of the liver, spleen, adrenals, or kidneys. Rapid decreases in hemoglobin or hematocrit values during the first few days of life may be the initial clue to these conditions.

Later in the neonatal period, delayed anemia may develop as a result of hemolytic disease of the newborn, with or without exchange transfusion or phototherapy. Congenital hemolytic anemia (spherocytosis) occasionally appears during the 1st mo of life, and hereditary nonspherocytic hemolytic anemia has been described during the neonatal period secondary to deficiency of glucose-6-phosphate dehydrogenase and pyruvate kinase. Bleeding from hemangiomas of the upper gastrointestinal tract or from ulcers caused by aberrant gastric mucosa in a Meckel diverticulum or duplication is a rare source of anemia in newborns. Repeated blood sampling of infants requiring frequent monitoring of blood gas and chemistry parameters is a common cause of anemia among hospitalized infants. Deficiency of minerals such as copper may cause anemia in infants maintained on total parenteral nutrition.

Anemia of prematurity occurs in low birthweight infants 1-3 mo after birth, is associated with hemoglobin levels <7-10 g/dL, and is clinically manifested as pallor, poor weight gain, decreased activity, tachypnea, tachycardia, and feeding problems. Repeated phlebotomy for blood tests, shortened RBC survival, rapid growth, and the physiologic effects of the transition from fetal (low Pa_{O_2} and hemoglobin saturation) to neonatal life (high Pa_{O_2} and hemoglobin saturation) contribute to anemia of prematurity. The oxygen available to neonatal tissue is lower than that in adults, but a neonate's erythropoietin response is attenuated for the degree of anemia, and as a result, hemoglobin and reticulocyte levels are low. In VLBW infants, delayed clamping of the umbilical cord with the infant held below the level of the placenta may enhance placental-infant transfusion and reduce postnatal transfusion needs. This maneuver should not delay any needed resuscitation and may lead to hyperviscosity.

Delayed cord clamping (30-180 sec or after cessation of cord pulsation) may be beneficial in otherwise well newborns in preventing anemia in full-term infants, with effects extending beyond the neonatal period. The benefits of delayed cord clamping persist for 2-6 mo as improved hematocrit, iron status as measured by ferritin concentration and stored iron, and a clinically important reduction in the risk of anemia in infancy. Late clamping may result in delivery of an extra 20-40 mL of blood and 30-35 mg of iron to the newborn. Polycythemia is a risk with delayed clamping but is often asymptomatic.

Treatment of neonatal anemia by blood transfusion depends on the severity of symptoms, the hemoglobin level, and the presence of comorbid diseases (bronchopulmonary dysplasia, cyanotic congenital heart disease, respiratory distress syndrome) that interfere with oxygen delivery. The need for treatment with blood should be balanced against the risks of transfusion, including hemolytic transfusion reactions, exposure to blood product preservatives and other potential toxins, volume overload, possible increased risk of retinopathy of prematurity and necrotizing enterocolitis, graft-versus-host (GVH) reaction, and transfusion-acquired infection (cytomegalovirus [CMV], HIV, parvovirus, hepatitides B and C) (see Chapter 474). The risk of CMV infection can be almost eliminated by the use of leukoreduced blood. In the infant who weighs <1,500 g, CMV antibody-negative leukoreduced blood should be used. The risk of acquiring HIV and hepatitides B and C viruses is reduced but not eliminated by antibody screening of donated blood. Blood-banking techniques that limit multiple donor exposure should be encouraged.

Although transfusion guidelines for preterm infants have been proposed (Table 103-2), they have not been subjected to rigorous clinical study. Nonetheless, these guidelines have led to a decline in the number of unnecessary transfusions. The use of restrictive vs more liberal transfusion guidelines has been examined in 2 randomized trials, one conducted at University of Iowa and a second multicentric trial known as the PINT (Premature Infants in Need of Transfusion) study. The restrictive guidelines in the 2 groups were generally similar. In the Iowa trial, the transfusion thresholds in the liberal- and restrictive-transfusion groups were <46% and <34%, respectively, in tracheally intubated infants receiving assisted ventilation; <38% and <28%, respectively, in infants receiving nasal continuous positive airway pressure or supplemental oxygen; and <30% and <22%, respectively, in infants breathing room air. The transfusion thresholds for the liberal groups were higher in the Iowa trial than in the PINT study. In both trials, the use of restrictive thresholds resulted in fewer transfusions and also increased the number of infants who received no transfusions at all. However, in the Iowa trial (but not in the PINT study), restrictive transfusion thresholds were associated with increases in major cranial ultrasonographic abnormalities and in the frequency of apneic spells. Although these findings need further evaluation in clinical studies, the issue of finding an appropriate transfusion threshold in premature infants remains unresolved.

Asymptomatic full-term infants with a hemoglobin level of 10 g/dL may be monitored, whereas symptomatic neonates born after abruptio placentae or with severe hemolytic disease of the newborn need immediate transfusion. Preterm infants who have repeated episodes of apnea and bradycardia despite theophylline therapy and a hemoglobin level ≤8 g/dL may benefit from RBC transfusion. In addition, infants with respiratory distress syndrome or severe bronchopulmonary dysplasia

Table 103-1 Normal Red Blood Cell Values from 18 Wk of Gestation to 14 Wk of Life

AGE	HEMOGLOBIN (g/dL)	HEMATOCRIT (%)	MCV (μ^3)	RETICULOCYTES (%)
GESTATIONAL (WK)				
18-20*	11.5 ± 0.8	36 ± 3	134 ± 8.8	N/A
21-22*	12.3 ± 0.9	39 ± 3	130 ± 6.2	N/A
23-25*	12.4 ± 0.8	39 ± 2	126 ± 6.2	N/A
26-27	19.0 ± 2.5	62 ± 8	132 ± 14.4	9.6 ± 3.2
28-29	19.3 ± 1.8	60 ± 7	131 ± 13.5	7.5 ± 2.5
30-31	19.1 ± 2.2	60 ± 8	127 ± 12.7	5.8 ± 2.0
32-33	18.5 ± 2.0	60 ± 8	123 ± 15.7	5.0 ± 1.9
34-35	19.6 ± 2.1	61 ± 7	122 ± 10.0	3.9 ± 1.6
36-37	19.2 ± 1.7	64 ± 7	121 ± 12.5	4.2 ± 1.8
38-40	19.3 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
POSTNATAL (DAYS)				
1	19.0 ± 2.2	61 ± 7	119 ± 9.4	3.2 ± 1.4
2	19.0 ± 1.9	60 ± 6	115 ± 7.0	3.2 ± 1.3
3	18.7 ± 3.4	62 ± 9	116 ± 5.3	2.8 ± 1.7
4	18.6 ± 2.1	57 ± 8	114 ± 7.5	1.8 ± 1.1
5	17.6 ± 1.1	57 ± 7	114 ± 8.9	1.2 ± 0.2
6	17.4 ± 2.2	54 ± 7	113 ± 10.0	0.6 ± 0.2
7	17.9 ± 2.5	56 ± 9	118 ± 11.2	0.5 ± 0.4
POSTNATAL (WK)				
1-2	17.3 ± 2.3	54 ± 8	112 ± 19.0	0.5 ± 0.3
2-3	15.6 ± 2.6	46 ± 7	111 ± 8.2	0.8 ± 0.6
3-4	14.2 ± 2.1	43 ± 6	105 ± 7.5	0.6 ± 0.3
4-5	12.7 ± 1.6	36 ± 5	101 ± 8.1	0.9 ± 0.8
5-6	11.9 ± 1.5	36 ± 6	102 ± 10.2	1.0 ± 0.7
6-7	12.0 ± 1.5	36 ± 5	105 ± 12.0	1.2 ± 0.7
7-8	11.1 ± 1.1	33 ± 4	100 ± 13.0	1.5 ± 0.7
8-9	10.7 ± 0.9	31 ± 3	93 ± 12.0	1.8 ± 1.0
9-10	11.2 ± 0.9	32 ± 3	91 ± 9.3	1.2 ± 0.6
10-11	11.4 ± 0.9	34 ± 2	91 ± 7.7	1.2 ± 0.7
11-12	11.3 ± 0.9	33 ± 3	88 ± 7.9	0.7 ± 0.3
12-14	11.9	37	86.8	0.9

*Based on samples collected in utero. Results expressed as mean value ±1 standard deviation from the mean except for postnatal weeks 12-14 in which only the mean value is given.

From Bizzarro MJ, Colson E, Ehrenkranz RA: Differential diagnosis and management of anemia in the newborn, Pediatr Clin North Am *51:1087–1107, 2004.*

Table 103-2 Transfusion Protocol

HEMATOCRIT (%)	HEMOGLOBIN (g/dL)	RESPIRATORY SUPPORT AND/OR SYMPTOMS	TRANSFUSION VOLUME
≤35	≤11	Infants requiring moderate or significant mechanical ventilation (mean arterial pressure >8 cm H_2O and FIO_2 >0.4)	15 mL/kg PRBCs* over 2-4 hr
≤30	≤10	Infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal continuous positive airway pressure >6 cm H_2O and FIO_2 ≤0.4)	15 mL/kg PRBCs over 2-4 hr
≤25	≤8	Infants not requiring mechanical ventilation but who are receiving supplemental O_2 or CPAP with an FIO_2 ≤0.4 and in whom 1 or more of the following is present: • ≤24 hr of tachycardia (heart rate >180 beats/min) or tachypnea (respiratory rate >80 breaths/min) • An increased oxygen requirement from the previous 48 hr, defined as a ≥4-fold increase in nasal canula flow (i.e., from 0.25 to 1 L/min) or an increase in nasal CPAP ≥20% from the previous 48 hr (i.e., 5-6 cm H_2O) • Weight gain <10 g/kg/day over the previous 4 days while infant is receiving ≥100 kcal/kg/day • An increase in episodes of apnea and bradycardia (>9 episodes in a 24-hr period or ≥2 episodes in 24 hr requiring bag and mask ventilation) while infant is receiving therapeutic doses of methylxanthines • Undergoing surgery	20 mL/kg PRBCs over 2-4 hr (divide into 2 10-mL/kg volumes if infant is fluid sensitive)
≤20	≤7	Asymptomatic and an absolute reticulocyte count <100,000 cells/μL	20 mL/kg PRBCs over 2-4 hr (2 10-mL/kg volumes)

*RBCs should be irradiated prior to transfusion.

CPAP, continuous positive airway pressure; FIO_2, fractional inspired oxygen; PRBCs, packed red blood cells.

From Ohls RK, Ehrenkranz RA, Wright LL, et al: Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial, Pediatrics *108:934–942, 2001.*

may need hemoglobin levels of 12-14 g/dL to improve oxygen delivery. No transfusion is needed to replace blood removed for testing or for mild asymptomatic anemia. Asymptomatic neonates with reticulocytopenia and hemoglobin levels ≤7 g/dL may require transfusion; if a transfusion is not provided, close observation is essential. Packed RBC transfusion (10-20 mL/kg) is given at a rate of 2-3 mL/kg/hr to raise the hemoglobin concentration; 2 mL/kg raises the hemoglobin level 0.5-1 g/dL. Hemorrhage should be treated with whole blood if available; alternatively, fluid resuscitation is initiated, followed by packed RBC transfusion.

Recombinant human erythropoietin (rHuEPO) may be considered in the treatment of chronic or anticipated anemia in an attempt to decrease or eliminate transfusions when families, for religious reasons, request all possible measures to avoid transfusions. Therapy with rHuEPO must be supplemented with oral iron. Doses and regimens vary. In anemia of prematurity, rHuEPO does not provide a major reduction in transfusion requirements or the number of donors; therefore, *routine* use of erythropoietin in VLBW infants is not recommended. Early initiation of rHuEPO therapy may produce a small reduction in the total transfusion volume per infant. There were concerns about an increased risk of severe retinopathy of prematurity in the rHuEPO group. The effects of *late* initiation of rHuEPO (≥8 days) have also been associated with small reductions in the total blood volume transfused per infant and the number of transfusions per infant. In pilot studies, a single-dose treatment with darbepoetin alfa, a long-acting form of recombinant erythropoietin, has shown promise as a stimulant of erythropoiesis in convalescing premature infants.

Bibliography is available at Expert Consult.

103.2 Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)

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Erythroblastosis fetalis is caused by the transplacental passage of maternal antibody active against paternal RBC antigens of the infant and is characterized by an increased rate of RBC destruction. It is an important cause of anemia and jaundice in newborn infants despite the development of a method of preventing maternal isoimmunization by Rh antigens. Although more than 60 different RBC antigens are capable of eliciting an antibody response, significant disease is associated primarily with the D antigen of the Rh group and with incompatibility of ABO factors. Rarely, hemolytic disease may be caused by C or E antigens or by other RBC antigens, such as C^W, C^X, D^U, K (Kell), M, Duffy, S, P, MNS, Xg, Lutheran, Diego, and Kidd. Anti-Lewis antibodies do not cause disease.

HEMOLYTIC DISEASE OF THE NEWBORN CAUSED BY RH INCOMPATIBILITY

The Rh antigenic determinants are genetically transmitted from each parent, determine the Rh type, and direct the production of a number of blood group factors (C, c, D, d, E, and e). Each factor can elicit a specific antibody response under suitable conditions; 90% are caused by D antigen and the remainder to C or E antigen.

Pathogenesis

Isoimmune hemolytic disease from D antigen is approximately 3 times more frequent among white persons than among black persons. When Rh-positive blood is infused into an Rh-negative woman through error, or when small quantities (usually >1 mL) of Rh-positive fetal blood containing D antigen inherited from an Rh-positive father enter the maternal circulation during pregnancy, with spontaneous or induced abortion, or at delivery, antibody formation against D antigen may be induced in the unsensitized Rh-negative recipient mother. Once sensitization has taken place, considerably smaller doses of antigen can stimulate an increase in antibody titer. Initially, a rise in immunoglobulin (Ig) M antibody occurs, which is later replaced by IgG antibody; the latter readily crosses the placenta to cause hemolytic manifestations.

Hemolytic disease rarely occurs during a first pregnancy because transfusion of Rh-positive fetal blood into an Rh-negative mother occurs near the time of delivery, too late for the mother to become sensitized and transmit antibody to her infant before delivery. The facts that 55% of Rh-positive fathers are heterozygous (D/d) and may have Rh-negative offspring and that fetal-to-maternal transfusion occurs in only 50% of pregnancies, reduce the chance of sensitization, as does small family size, in which the opportunities for its reoccurrence are reduced. The disparity between the numbers of incompatible versus alloimmunized maternal-fetal pairs can also be the result of a threshold effect of fetomaternal transfusions (a certain amount of the immunizing blood cell antigen is required to activate the maternal immune system), the type of antibody response (IgG antibodies are more efficiently transferred across the placenta to the fetus), differential immunogenicity of blood group antigens, and differences in maternal immune response, presumably related to differences in the efficiency of antigen presentation by various major histocompatibility loci. Thus, the overall incidence of isoimmunization of Rh-negative mothers at risk is low, with antibody to antigen D detected in >10% of those studied, even after five or more pregnancies; only approximately 5% ever have babies with hemolytic disease.

When the mother and fetus are also incompatible with respect to group A or B, the mother is partially protected against sensitization by the rapid removal of Rh-positive cells from her circulation by her preexisting anti-A or anti-B antibodies, which are IgM antibodies and do not cross the placenta. Once a mother has been sensitized, her infant is likely to have hemolytic disease. The severity of Rh illness worsens with successive pregnancies. The possibility that the first affected infant after sensitization may represent the end of the mother's childbearing potential for Rh-positive infants argues urgently for the prevention of sensitization. *The injection of anti-D gammaglobulin (RhoGAM) into the mother immediately after the delivery of each Rh-positive infant has been a successful strategy to reduce Rh hemolytic disease.*

Clinical Manifestations

A wide spectrum of hemolytic disease occurs in affected infants born to sensitized mothers, depending on the nature of the individual immune response. The severity of the disease may range from only laboratory evidence of mild hemolysis (15% of cases) to severe anemia with compensatory hyperplasia of erythropoietic tissue leading to massive enlargement of the liver and spleen. When the compensatory capacity of the hematopoietic system is exceeded, profound anemia occurs and results in pallor, signs of cardiac decompensation (cardiomegaly, respiratory distress), massive anasarca, and circulatory collapse. This clinical picture of excessive abnormal fluid in 2 or more fetal compartments (skin, pleura, pericardium, placenta, peritoneum, amniotic fluid), termed **hydrops fetalis,** frequently results in death in utero or shortly after birth. With the use of RhoGAM to prevent Rh sensitization, nonimmune (nonhemolytic) conditions have become frequent causes of hydrops (Table 103-3). The severity of hydrops is related to the level of anemia and the degree of reduction in serum albumin (oncotic pressure), which is partly a result of hepatic dysfunction. Alternatively, heart failure may increase right heart pressure, with the subsequent development of edema and ascites. Failure to initiate spontaneous effective ventilation because of pulmonary edema or bilateral pleural effusions results in birth asphyxia; after successful resuscitation, severe respiratory distress may develop. Petechiae, purpura, and thrombocytopenia may also be present in severe cases as a result of decreased platelet production or the presence of concurrent disseminated intravascular coagulation.

Jaundice may be absent at birth because of placental clearance of lipid-soluble unconjugated bilirubin, but in severe cases, bilirubin pigments stain the amniotic fluid, cord, and vernix caseosa yellow. Jaundice is generally evident on the 1st day of life because the infant's bilirubin-conjugating and excretory systems are unable to cope with the load resulting from massive hemolysis. Indirect-reacting bilirubin

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Table 103-3 Etiology of Hydrops Fetalis*

CATEGORY	DISORDER(S)
Anemia	Immune (Rh, Kell) hemolysis α-Thalassemia Red blood cell enzyme deficiencies (glucose-6-phosphate dehydrogenase) Fetomaternal hemorrhage Donor in twin-to-twin transfusion Diamond-Blackfan syndrome
Cardiac dysrhythmias	Supraventricular tachycardia Atrial flutter Congenital heart block
Structural heart lesions	Premature closure of foramen ovale Tricuspid insufficiency Hypoplastic left heart Endocardial cushion defect Cardiomyopathy Endocardial fibroelastosis Tuberous sclerosis with cardiac rhabdomyoma Pericardial teratoma
Vascular	Chorioangioma of placenta, chorionic vessels, or umbilical vessels Umbilical artery aneurysm Angiomyxoma of umbilical cord True knot of umbilical cord Hepatic hemangioma Cerebral arteriovenous malformation (aneurysm of vein of Galen) Angioosteohypertrophy (Klippel-Trénaunay syndrome) Thrombosis of renal or umbilical vein or inferior vena cava Recipient in twin-to-twin transfusion
Lymphatic	Lymphangiectasia Cystic hygroma Chylothorax, chylous ascites Noonan syndrome Multiple pterygium syndrome
Central nervous system	Absent corpus callosum Encephalocele Intracranial hemorrhage Holoprosencephaly
Thoracic lesions	Cystic adenomatoid malformation of lung Mediastinal teratoma Diaphragmatic hernia Sequestered lung
Teratomas	Choriocarcinoma Sacrococcygeal teratoma
Tumors and storage diseases	Neuroblastoma Hepatoblastoma Gaucher disease Niemann-Pick disease Mucolipidosis GM_1 gangliosidosis Mucopolysaccharidosis
Chromosome abnormalities	Trisomy 13, 15, 16, 18, 21 XX/XY, 45XO Partial duplication of chromosomes 11, 15, 17, 18 Partial deletion of chromosomes 13, 18 Triploidy Tetraploidy
Bone diseases	Osteogenesis imperfecta Asphyxiating thoracic dystrophy Skeletal dysplasias
Congenital infections	Cytomegalovirus Parvovirus Rubella Toxoplasmosis Syphilis Leptospirosis Chagas disease
Others	Bowel obstruction with perforation and meconium peritonitis, volvulus Hepatic fibrosis Beckwith-Wiedemann syndrome Prune-belly syndrome Congenital nephrosis Infant of a diabetic mother Myotonic dystrophy Neu-Laxova syndrome Maternal therapy with indomethacin Fetal akinesia
Idiopathic	Multiple congenital anomaly syndromes

*The incidence of nonimmune (nonhemolytic) hydrops fetalis is 1/2,000-1/3,500 live births.
Modified from Phibbs R. In Polin N, Fox W, editors: Fetal and neonatal physiology, *ed 2, Philadelphia, 1998, WB Saunders.*

therefore accumulates postnatally and may rapidly reach extremely high levels and present a significant risk of bilirubin encephalopathy. The risk of development of kernicterus from hemolytic disease is greater than from comparable nonhemolytic hyperbilirubinemia, although the risk in an individual patient may be affected by other complications (hypoxia, acidosis). Hypoglycemia occurs frequently in infants with severe isoimmune hemolytic disease and may be related to hyperinsulinism and hypertrophy of the pancreatic islet cells in these infants.

Infants born after intrauterine transfusion for prenatally diagnosed erythroblastosis may be severely affected because the indications for transfusion are evidence of already severe disease in utero (hydrops, fetal anemia). Such infants usually have very high (but extremely variable) cord levels of bilirubin, reflecting the severity of the hemolysis and its effects on hepatic function. Infants treated with intraumbilical vein transfusions in utero may also have a benign postnatal course if the anemia and hydrops resolve before birth. Anemia from continuing hemolysis may be masked by the previous intrauterine transfusion, and the clinical manifestations of erythroblastosis may be superimposed on various degrees of immaturity resulting from spontaneous or induced premature delivery.

Laboratory Data

Before treatment, the direct Coombs test result is usually positive and anemia is generally present. The cord blood hemoglobin content varies and is usually proportional to the severity of the disease; with hydrops fetalis it may be as low as 3-4 g/dL. Alternatively, despite hemolysis, it may be within the normal range because of compensatory bone marrow and extramedullary hematopoiesis. The blood smear typically shows polychromasia and a marked increase in nucleated RBCs. The reticulocyte count is increased. The white blood cell count is usually normal but may be elevated; thrombocytopenia may develop in severe cases. Cord bilirubin is generally between 3 and 5 mg/dL; the direct-reacting (conjugated) bilirubin content may also be elevated, especially if there was an intrauterine transfusion. Indirect- reacting bilirubin content rises rapidly to high levels in the 1st 6 hr of life.

After intrauterine transfusions, cord blood may show a normal hemoglobin concentration, negative direct Coombs test result, predominantly type O Rh-negative adult RBCs, and relatively normal smear findings.

Diagnosis

Definitive diagnosis of erythroblastosis fetalis requires demonstration of blood group incompatibility and corresponding antibody bound to the infant's RBCs.

Antenatal Diagnosis

In Rh-negative women, a history of previous transfusions, abortion, or pregnancy should suggest the possibility of sensitization. Expectant parents' blood types should be tested for potential incompatibility, and the maternal titer of IgG antibodies to D antigen should be assayed at 12-16, 28-32, and 36 wk of gestation. Fetal Rh status may be determined by isolating fetal cells or fetal DNA (plasma) from the maternal circulation. The presence of elevated antibody titers at the beginning of pregnancy, a rapid rise in titer, or a titer of 1:64 or greater suggests significant hemolytic disease, although the exact titer correlates poorly with the severity of disease. If a mother is found to have antibody against D antigen at a titer of 1:16 (15 IU/mL in Europe) or greater at any time during a subsequent pregnancy, the severity of fetal disease should be monitored by Doppler ultrasonography of the middle cerebral artery and then percutaneous umbilical blood sampling (PUBS) if indicated (see Chapter 96). If the mother has a history of a previously affected infant or a stillbirth, an Rh-positive infant is usually equally or more severely affected than the previous infant, and the severity of disease in the fetus should be monitored.

Assessment of the fetus may require information obtained from ultrasonography and PUBS. Real-time ultrasonography is used to detect the progression of disease, with hydrops defined as skin or scalp edema, pleural or pericardial effusions, and ascites. Early ultrasonographic signs of hydrops include organomegaly (liver, spleen, heart), the double–bowel wall sign (bowel edema), and placental thickening. Progression to polyhydramnios, ascites, pleural or pericardial effusions, and skin or scalp edema may then follow. If pleural effusions precede ascites and hydrops by a significant time, causes other than fetal anemia should be suspected (see Table 96-2 in Chapter 96). Extramedullary hematopoiesis and, less so, hepatic congestion compress the intrahepatic vessels and produce venous stasis with portal hypertension, hepatocellular dysfunction, and decreased albumin synthesis.

Hydrops is present with a fetal hemoglobin level <5 g/dL, frequent with a level <7 g/dL, and variable with levels between 7 and 9 g/dL. Real-time ultrasonography predicts fetal well-being by means of the biophysical profile (see Table 96-2 in Chapter 96), whereas Doppler ultrasonography assesses fetal distress by demonstrating increased vascular resistance in fetal arteries (middle cerebral). In pregnancies with ultrasonographic evidence of hemolysis (hepatosplenomegaly), early or late hydrops, or fetal distress, further and more direct assessment of fetal hemolysis should be performed.

Amniocentesis was classically used to assess fetal hemolysis. Hemolysis of fetal RBCs produces hyperbilirubinemia before the onset of severe anemia. Bilirubin is cleared by the placenta, but a significant proportion enters the amniotic fluid and can be measured by spectrophotometry. Ultrasonographically guided transabdominal aspiration of amniotic fluid may be performed as early as 18-20 wk of gestation. Spectrophotometric scanning of amniotic fluid wavelengths demonstrates a positive optical density deviation of absorption for bilirubin from normal at 450 nm. Amniocentesis and cordocentesis are invasive procedures with risks to both the fetus and mother, including fetal death, bleeding, or bradycardia, worsening of alloimmunization, premature rupture of membranes, preterm labor, and chorioamnionitis. *Noninvasive measurements to detect fetal anemia are desirable*. In fetuses without hydrops, moderate to severe anemia can be detected noninvasively by demonstration of an increase in the peak velocity of systolic blood flow in the middle cerebral artery by Doppler ultrasonography.

PUBS is the standard approach to assessment of the fetus if Doppler and real-time ultrasonography findings suggest that the fetus has erythroblastosis fetalis. PUBS is performed to determine fetal hemoglobin levels and to transfuse packed RBCs in those with serious fetal anemia (hematocrit 25-30%).

Postnatal Diagnosis

Immediately after the birth of any infant to an Rh-negative woman, blood from the umbilical cord or from the infant should be examined for ABO blood group, Rh type, hematocrit and hemoglobin, and reaction to the direct Coombs test. If the Coombs test result is positive, a baseline serum bilirubin level should be measured, and a commercially available RBC panel should be used to identify RBC antibodies present in the mother's serum, both tests being performed not only to establish the diagnosis but also to ensure selection of the most compatible blood for exchange transfusion should it be necessary. The direct Coombs test result is usually strongly positive in clinically affected infants and may remain so for a few days up to several months.

Treatment

The main goals of therapy are to (1) prevent intrauterine or extrauterine death from severe anemia and hypoxia, and (2) avoid neurotoxicity from hyperbilirubinemia.

Treatment of an Unborn Infant

Survival of severely affected fetuses has been improved by the use of fetal ultrasonography to identify the need for in utero transfusion. Intravascular (umbilical vein) transfusion of packed RBCs is the treatment of choice for fetal anemia, replacing intrauterine transfusion into the fetal peritoneal cavity. Hydrops or fetal anemia (hematocrit < 30%) is an indication for umbilical vein transfusion in infants with pulmonary immaturity (see Fig. 103-1). **Intravascular fetal transfusion** is facilitated by maternal and hence fetal sedation with diazepam and by fetal paralysis with pancuronium. Packed RBCs are given by slow-push infusion after being cross-matched against the mother's serum. The cells should be obtained from a CMV-negative donor and irradiated to kill lymphocytes to avoid GVH disease. *Of note, leukoreduction alone (without irradiation) does not prevent GVH disease*. Transfusions should achieve a posttransfusion hematocrit of 45-55% and can be repeated every 3-5 wk. Indications for delivery include pulmonary maturity, fetal distress, complications of PUBS, and 35-37 wk of gestation. The survival rate for intrauterine transfusions is 89%; the complication rate is 3%. Complications include rupture of the membranes and preterm delivery, infection, fetal distress requiring emergency cesarean section, and perinatal death.

Treatment of a Liveborn Infant

The birth should be attended by a physician skilled in neonatal resuscitation. Fresh, low-titer, group O, leukoreduced, and irradiated Rh-negative blood cross-matched against maternal serum should be immediately available. If clinical signs of severe hemolytic anemia (pallor, hepatosplenomegaly, edema, petechiae, ascites) are evident at birth, immediate resuscitation and supportive therapy, temperature stabilization, and monitoring before proceeding with exchange transfusion may save some severely affected infants. Such therapy should include correction of acidosis with 1-2 mEq/kg of sodium bicarbonate; a small transfusion of compatible packed RBCs to correct anemia; volume expansion for hypotension, especially in those with hydrops; and provision of assisted ventilation for respiratory failure.

Exchange Transfusion

When an infant's clinical condition at birth does not require an immediate full or partial exchange transfusion, the decision to perform one should be based on a judgment that the infant has a high risk of rapid development of a dangerous degree of anemia or hyperbilirubinemia. Cord hemoglobin value of 10 g/dL or less and bilirubin concentration of 5 mg/dL or more suggest severe hemolysis but inconsistently predict the need for exchange transfusion. Some physicians consider previous kernicterus or severe erythroblastosis in a sibling, reticulocyte counts

>15%, and prematurity to be additional factors supporting a decision for early exchange transfusion (see Chapters 102.3 and 102.4). Intrauterine, intravascular transfusions have decreased the need for exchange transfusion.

The hemoglobin concentration, hematocrit, and serum bilirubin level should be measured at 4-6 hr intervals initially, with extension to longer intervals if and as the rate of change diminishes. The decision to perform an exchange transfusion is based on the likelihood that the trend of bilirubin levels plotted against hours of age indicates that serum bilirubin will reach the levels indicated in Figure 102-12 and Table 102-7, both in Chapter 102. Term infants with bilirubin levels ≥20 mg/dL have an increased risk of kernicterus. Ordinary transfusions of compatible Rh-negative, leukoreduced, and irradiated RBCs may be necessary to correct anemia at any stage of the disease up to 6-8 wk of age, when the infant's own blood-forming mechanism may be expected to take over. Weekly determinations of hemoglobin or hematocrit values should be performed until a spontaneous rise has been demonstrated.

Careful monitoring of the serum bilirubin level is essential until a falling trend has been demonstrated in the absence of phototherapy (see Chapter 102.3). Even then, an occasional infant, particularly if premature, may experience an unpredicted significant rise in serum bilirubin as late as the 7th day of life. Attempts to predict the attainment of dangerously high levels of serum bilirubin on the basis of observed levels exceeding 6 mg/dL in the 1st 6 hr or 10 mg/dL in the 2nd 6 hr of life or on rates of rise exceeding 0.5-1.0 mg/dL/hr can be unreliable.

Blood for exchange transfusion should be as fresh as possible. Heparin or citrate-phosphate-dextrose-adenine solution may be used as an anticoagulant. If the blood is obtained before delivery, it should be taken from a type O, Rh-negative donor with a low titer of anti-A and anti-B antibodies and should be determined compatible with the mother's serum by the indirect Coombs test. After delivery, blood should be obtained from an Rh-negative donor whose cells are compatible with both the infant's and the mother's sera; when possible, type O donor cells are generally used, but cells of the infant's ABO blood type may be used when the mother has the same type. A complete cross match, including an indirect Coombs test, should be performed before the second and subsequent transfusions. Blood should be gradually warmed and maintained at a temperature between 35 and 37°C (95 and 98.6°F) throughout the exchange transfusion. It should be kept well mixed by gentle squeezing or agitation of the bag to avoid sedimentation; otherwise, the use of supernatant serum with a low RBC count at the end of the exchange will leave the infant anemic. Whole blood or packed leukoreduced and irradiated RBCs reconstituted with fresh-frozen plasma to an hematocrit of 40% should be used. The infant's stomach should be emptied before transfusion to prevent aspiration, and body temperature should be maintained and vital signs monitored. A competent assistant should be present to help monitor, tally the volume of blood exchanged, and perform emergency procedures.

With strict aseptic technique, the umbilical vein is cannulated with a polyvinyl catheter to a distance no greater than 7 cm in a full-term infant. When free flow of blood is obtained, the catheter is usually in a large hepatic vein or the inferior vena cava. Alternatively, the exchange may be performed through peripheral arterial (drawn out) and venous (infused in) lines. The exchange should be carried out over 45-60 min, with aspiration of 20 mL of infant blood alternating with infusion of 20 mL of donor blood. Smaller aliquots (5-10 mL) may be indicated for sick and premature infants. The goal should be an isovolumetric exchange of approximately two blood volumes of the infant (2 × 85 mL/kg).

Infants with acidosis and hypoxia from respiratory distress, sepsis, or shock may be further compromised by the significant acute acid load contained in citrated blood, which usually has a pH between 7 and 7.2. The subsequent metabolism of citrate may result in metabolic alkalosis later if citrated blood is used. Fresh heparinized blood avoids this problem. During the exchange, blood pH and Pa_{O_2} should be serially monitored because infants often become acidotic and hypoxic during exchange transfusions. Symptomatic hypoglycemia may occur before or during an exchange transfusion in moderately to severely affected infants; it may also occur 1-3 hr after exchange. Acute complications, noted in 5-10% of infants, include transient bradycardia with or without calcium infusion, cyanosis, transient vasospasm, thrombosis, apnea with bradycardia requiring resuscitation, and death. Infectious risks include CMV, HIV, and hepatitis. Necrotizing enterocolitis is a rare complication of exchange transfusion.

The risk of death from an exchange transfusion performed by an experienced physician is 0.3/100 procedures. With the decreasing use of this procedure because of the use of phototherapy and prevention of sensitization, the general level of physician competence is diminishing. Thus, it is best if this procedure is performed in experienced neonatal referral centers.

After exchange transfusion, the bilirubin level must be determined at frequent intervals (every 4-8 hr) because bilirubin may rebound 40-50% within hours. Repeated exchange transfusions should be carried out to keep the indirect fraction from exceeding the levels indicated in Table 102-7 in Chapter 102 for preterm infants and 20 mg/dL for term infants. Symptoms suggestive of kernicterus are mandatory indications for exchange transfusion at any time.

Intravenous Immunoglobulin

Early administration of intravenous immunoglobulin (IVIG) may reduce hemolysis, peak serum bilirubin levels, and the need for exchange transfusions. IVIG administration reduces the need for exchange transfusion, the duration of phototherapy, and the length of hospitalization. A dose of 0.5-1 g/kg may be used.

Late Complications

Infants who have hemolytic disease or who have had an exchange or an intrauterine transfusion must be observed carefully for the development of anemia and cholestasis. **Late anemia** may be hemolytic or hyporegenerative. Treatment with supplemental iron, blood transfusion, or erythropoietin may be indicated. A mild GVH reaction may manifest as diarrhea, rash, hepatitis, or eosinophilia.

Inspissated bile syndrome refers to the rare occurrence of persistent icterus in association with significant elevations in direct and indirect bilirubin levels in infants with hemolytic disease. The cause is unclear, but the jaundice clears spontaneously within a few weeks or months.

Portal vein thrombosis and portal hypertension may occur in children who have been subjected to exchange transfusion as newborn infants. It is probably associated with prolonged, traumatic, or septic umbilical vein catheterization.

Prevention of Rh Sensitization

The risk of initial sensitization of Rh-negative mothers has been reduced to less than 1% by the intramuscular injection of 300 µg of human anti-D globulin (1 mL of RhoGAM) within 72 hr of delivery of an Rh-positive infant, ectopic pregnancy, abdominal trauma in pregnancy, amniocentesis, chorionic villus biopsy, or abortion. This quantity is sufficient to eliminate ≈ 10 mL of potentially antigenic fetal cells from the maternal circulation. Large fetal-to-maternal transfers of blood may require proportionately more human anti-D globulin. RhoGAM administration of human anti-D globulin at 28-32 wk and again at birth (40 wk) is more effective than a single dose. The use of this technique, combined with improved methods of detecting maternal sensitization and measuring the extent of fetal-to-maternal transfusion, plus the use of fewer obstetric procedures that increase the risk of such fetal-to-maternal bleeding (version, manual separation of the placenta), should further reduce the incidence of erythroblastosis fetalis.

HEMOLYTIC DISEASE OF THE NEWBORN CAUSED BY BLOOD GROUP A AND B INCOMPATIBILITY

ABO incompatibility is the most common cause of hemolytic disease of the newborn. Approximately 15% of live births are at risk, but

Table 103-4 Hemolytic Disease of the Newborn

	Rh	ABO	KELL
BLOOD GROUPS			
Mother	Rh-negative	O (occasionally B)	K1-negative
Infant	Positive (D, sometimes C)	A (sometimes B)	K1-positive
CLINICAL FEATURES OF HEMOLYTIC DISEASE IN THE NEWBORN			
Occurrence in first-born	5%	40-50%	Rare
Severity in subsequent pregnancies:	Predictable	Difficult to predict	Somewhat predictable
Stillbirth/hydrops	Frequent	Rare	10%
Severe anemia	Frequent	Rare	Frequent
Jaundice	Prominent, severe	Mild-moderate	Mild
LABORATORY TESTS:			
Direct Coombs test result (infant)	Positive	Positive or negative	Positive or negative
Reticulocyte count	High	High	May not be high
Maternal antibodies	Usually detectable	May not be detectable	Usually detectable
	Maternal antibody titers can help predict the severity of fetal disease	Titers may not correlate with fetal disease	Titers may not correlate with fetal disease; fetus affected at titers lower than for Rh-mediated hemolysis

manifestations of disease develop in only 0.3-2.2%. Major blood group incompatibility between the mother and fetus generally results in milder disease than Rh incompatibility does. Maternal antibody may be formed against B cells if the mother is type A or against A cells if the mother is type B. Usually, the mother is type O and the infant is type A or B. Although ABO incompatibility occurs in 20-25% of pregnancies, hemolytic disease develops in only 10% of the offspring in such pregnancies, and the infants are generally type A_1, which is more antigenic than A_2. Low antigenicity of the ABO factors in the fetus and newborn infant may account for the low incidence of severe ABO hemolytic disease relative to the incidence of incompatibility between the blood groups of the mother and child. Although antibodies against A and B factors occur without previous immunization ("natural" antibodies), they are usually IgM antibodies that do not cross the placenta. However, IgG antibodies to A antigen may be present and these do cross the placenta, so A-O isoimmune hemolytic disease may be found in first-born infants. Mothers who have become immunized against A or B factors from a previous incompatible pregnancy also exhibit IgG antibody. These "immune" antibodies are the primary mediators in ABO isoimmune disease.

Clinical Manifestations

Most cases are mild, with jaundice being the only clinical manifestation. The infant is not generally affected at birth; pallor is not present, and hydrops fetalis is extremely rare. The liver and spleen are not greatly enlarged, if at all. Jaundice usually appears during the 1st 24 hr. Rarely, it may become severe, and symptoms and signs of kernicterus develop rapidly.

Diagnosis

A presumptive diagnosis is based on the presence of ABO incompatibility, a weakly to moderately positive direct Coombs test result, and spherocytes in the blood smear, which may at times suggest the presence of hereditary spherocytosis. Hyperbilirubinemia is often the only other laboratory abnormality. The hemoglobin level is usually normal but may be as low as 10-12 g/dL. Reticulocytes may be increased to 10-15%, with extensive polychromasia and increased numbers of nucleated RBCs. In 10-20% of affected infants, the unconjugated serum bilirubin level may reach 20 mg/dL or more unless phototherapy is administered.

Treatment

Phototherapy may be effective in lowering serum bilirubin levels (see Chapter 102.4). In severe cases, IVIG administration can reduce the rate of hemolysis and the need for exchange transfusion. Exchange transfusions with type O blood of the same Rh type as the infant may be needed in some cases to correct dangerous degrees of anemia or hyperbilirubinemia. Indications for this procedure are similar to those previously described for hemolytic disease caused by Rh incompatibility. Some infants with ABO hemolytic disease may require transfusion of packed RBCs at several weeks of age because of slowly progressive anemia. Postdischarge monitoring of hemoglobin or hematocrit is essential in newborns with ABO hemolytic disease.

OTHER FORMS OF HEMOLYTIC DISEASE

Blood group incompatibilities other than Rh or ABO account for <5% of hemolytic disease of the newborn. The direct Coombs test result is invariably positive, and exchange transfusion may be indicated for hyperbilirubinemia and anemia. Hemolytic disease, anemia, and hydrops fetalis as a result of anti-Kell antibodies are not predictable from the previous obstetric history, amniotic fluid bilirubin determinants, or the maternal antibody titer. Erythroid suppression may contribute to the anemia; PUBS is beneficial in actually measuring the fetal hematocrit. Kell-alloimmunized infants often have inappropriately low numbers of circulating reticulocytes in comparison with other forms of hemolytic disease, which can cause difficulties in the laboratory confirmation of the hemolytic etiology of hyperbilirubinemia. The clinical characteristics of hemolytic disease caused by Rh, ABO, and Kell antigen systems are summarized in Table 103-4.

Bibliography is available at Expert Consult.

103.3 Plethora in the Newborn Infant (Polycythemia)

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See also Chapter 467.

Plethora, a ruddy, deep red-purple appearance associated with a high hematocrit, is often due to polycythemia, defined as a central hematocrit of 65% or higher. Peripheral (heelstick) hematocrit values are higher than central values, whereas Coulter counter results are lower than hematocrit values determined by microcentrifugation. The incidence of neonatal polycythemia is increased at high altitudes (5% in Denver vs. 1.6% in Texas); in postmature (3%) versus term (1-2%) infants; in small for gestational age (8%) versus large for gestational age (3%) versus average for gestational age (1-2%) infants; during the 1st day of life (peak, 2-3 hr); in the recipient infant of a twin–twin transfusion; after delayed clamping of the umbilical cord; in infants of diabetic mothers; in trisomy 13, 18, or 21; in adrenogenital syndrome;

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in neonatal Graves disease; in hypothyroidism; in infants of hypertensive mothers or those on propranolol; and in Beckwith-Wiedemann syndrome. Infants of diabetic or hypertensive mothers and those with growth restriction may have been exposed to chronic fetal hypoxia, which stimulates erythropoietin production and increases RBC production.

Clinical manifestations include irritability, lethargy, tachypnea, respiratory distress, cyanosis, feeding disturbances, hyperbilirubinemia, hypoglycemia, and thrombocytopenia. Severe complications include seizures, stroke, pulmonary hypertension, necrotizing enterocolitis, renal vein thrombosis, and renal failure. *Many affected infants are asymptomatic*. Hyperviscosity is present in many infants with central hematocrit values of 65% or higher and accounts for the symptoms of polycythemia. Hyperviscosity determined at constant shear rates (11.5 sec^{-1}) is present when whole blood viscosity is >18 cycles/sec. Hyperviscosity is accentuated because neonatal RBCs have decreased deformability and filterability, which predispose to stasis in the microcirculation.

The treatment of polycythemia is controversial. Asymptomatic infants whose central hematocrits are between 60% and 70% can be monitored closely and aggressively hydrated with adequate enteral intake or administration of intravenous fluids. **Treatment** of symptomatic polycythemic newborns is partial exchange transfusion (with normal saline). A partial exchange transfusion should be considered if the hematocrit is ≥70-75% or even lower if signs of hyperviscosity are present. Partial exchange transfusion lowers the Hematocrit and viscosity and improves acute symptoms, but may not affect long-term outcome in these infants. The volume to be exchanged is calculated from the following formula:

$$\text{Volume of exchange (mL)} = \text{Blood volume} \times (\text{Observed} - \text{Desired hematocrit}) / \text{Observed hematocrit}$$

Infants treated with partial exchange may be at increased risk of necrotizing enterocolitis and should be carefully monitored. The long-term prognosis of polycythemic infants is unclear. Reported adverse outcomes include speech deficits, abnormal fine motor control, reduced IQ, school problems, and other neurologic abnormalities. The underlying etiology (chronic intrauterine hypoxia) and hyperviscosity is thought to contribute to adverse outcomes. It is unclear whether partial exchange transfusion improves the long-term outcome. Most asymptomatic infants develop normally.

Bibliography is available at Expert Consult.

103.4 Hemorrhage in the Newborn Infant

Akhil Maheshwari and Waldemar A. Carlo

HEMORRHAGIC DISEASE OF THE NEWBORN

A moderate decrease in factors II, VII, IX, and X normally occurs in all newborn infants by 48-72 hr after birth, with a gradual return to birth levels by 7-10 days of age. This transient deficiency of vitamin K–dependent factors is probably caused by lack of free vitamin K from the mother and absence of the bacterial intestinal flora normally responsible for the synthesis of vitamin K. Rarely in term infants, and more frequently in premature infants, accentuation and prolongation of this deficiency between the 2nd and 7th days of life result in spontaneous and prolonged bleeding. Breast milk is a poor source of vitamin K, but hemorrhagic complications are more frequent in breastfed than in formula-fed infants. This classic form of hemorrhagic disease of the newborn, which is responsive to and prevented by vitamin K therapy, must be distinguished from disseminated intravascular coagulopathy and from the more infrequent congenital deficiencies of one or more of the other factors that are unresponsive to vitamin K (see Chapter 476). Early-onset life-threatening vitamin K deficiency–induced bleeding (onset from birth to 24 hr) also occurs if the mother has been treated with drugs (phenobarbital, phenytoin) that interfere with vitamin K function. Late onset (>2 wk) is often associated with vitamin K malabsorption, as noted in neonatal hepatitis or biliary atresia (Table 103-5).

Hemorrhagic disease of the newborn resulting from severe transient deficiencies in vitamin K–dependent factors is characterized by bleeding that tends to be gastrointestinal, nasal, subgaleal, intracranial, or post-circumcision. Prodromal or warning signs (mild bleeding) may occur before serious intracranial hemorrhage. The prothrombin time, blood coagulation time, and partial thromboplastin time are prolonged, and levels of prothrombin (II) and factors VII, IX, and X are decreased. Vitamin K facilitates posttranscriptional carboxylation of factors II, VII, IX, and X. In the absence of carboxylation, such factors form PIVKA (proteins induced in vitamin K absence), which is a sensitive marker for vitamin K status. Bleeding time, fibrinogen, factors V and VIII, platelets, capillary fragility, and clot retraction are normal for maturity.

Intramuscular administration of 1 mg of vitamin K at the time of birth **prevents** the decrease in vitamin K–dependent factors in full-term infants, but it is not uniformly effective in the prophylaxis of hemorrhagic disease of the newborn, particularly in breastfed and in

Table 103-5 Hemorrhagic Disease of the Newborn

	EARLY-ONSET DISEASE	CLASSIC DISEASE	LATE-ONSET DISEASE
Age	0-24 hr	2-7 days	1-6 mo
Site of hemorrhage	Cephalohematoma Subgaleal Intracranial Gastrointestinal Umbilicus Intraabdominal	Gastrointestinal Ear-nose-throat-mucosal Intracranial Circumcision Cutaneous Gastrointestinal Injection sites	Intracranial Gastrointestinal Cutaneous Ear-nose-throat-mucosal Injection sites Thoracic
Etiology/risks	Maternal drugs (phenobarbital, phenytoin, warfarin, rifampin, isoniazid) that interfere with vitamin K Inherited coagulopathy	Vitamin K deficiency Breastfeeding	Cholestasis—malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis) Abetalipoprotein deficiency Idiopathic in Asian breastfed infants Warfarin ingestion
Prevention	Possibly, administrations of vitamin K to infant at birth or to mother (20 mg) before birth Avoid high-risk medications	Prevented by parenteral vitamin K at birth Oral vitamin K regimens require repeated dosing over time	Prevented by parenteral and high-dose oral vitamin K during periods of malabsorption or cholestasis
Incidence	Very rare	≈ 2% if infant not given vitamin K	Dependent on primary disease

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premature infants. The disease may be effectively **treated** with a slow intravenous infusion of 1-5 mg of vitamin K_1, with improvement in coagulation defects and cessation of bleeding noted within a few hours. Serious bleeding, particularly in premature infants or those with liver disease, may require a transfusion of **fresh-frozen plasma** or whole blood. The mortality rate is low in treated patients.

A particularly severe form of deficiency of vitamin K–dependent coagulation factors has been reported in infants born to mothers receiving anticonvulsive medications (phenobarbital and phenytoin) during pregnancy. The infants may have severe bleeding, with onset within the 1st 24 hr of life; the bleeding is usually corrected by vitamin K_1, although in some the response is poor or delayed. A prothrombin time should be measured in cord blood, and the infant given 1-2 mg of vitamin K intravenously. If the prothrombin time is greatly prolonged and fails to improve, 10 mL/kg of fresh-frozen plasma should be administered.

The routine use of intramuscular vitamin K for prophylaxis in the United States is safe and is not associated with an increased risk of childhood cancer or leukemia. Although oral vitamin K (birth, discharge, 3-4 wk: 1-2 mg) has been suggested as an alternative, oral vitamin K is less effective in preventing the late onset of bleeding due to vitamin K deficiency and thus cannot be recommended for routine therapy. The intramuscular route remains the method of choice.

Other forms of bleeding may be clinically indistinguishable from hemorrhagic disease of the newborn responsive to vitamin K, but they are neither prevented nor successfully treated with vitamin K. A clinical pattern identical to that of hemorrhagic disease of the newborn may also result from any of the congenital defects in blood coagulation (see Chapters 476 and 477). Hematomas, melena, and postcircumcision and umbilical cord bleeding may be present; only 5-35% of cases of factor VIII and IX deficiency become clinically apparent in the newborn period. Treatment of the rare congenital deficiencies of coagulation factors requires fresh-frozen plasma or specific factor replacement.

Disseminated intravascular coagulopathy in newborn infants results in consumption of coagulation factors and bleeding. Affected infants are often premature; the clinical course is frequently characterized by asphyxia, hypoxia, acidosis, shock, hemangiomas, or infection. Treatment is directed at correcting the primary clinical problem, such as infection, interrupting consumption of clotting factors, and replacing them (see Chapter 483).

Infants with central nervous system or other bleeding posing an immediate threat to life should receive fresh-frozen plasma, vitamin K, and blood if needed as soon as possible after a blood specimen has been obtained for coagulation studies, which should include a determination of the number of platelets.

The **swallowed blood syndrome,** in which blood or bloody stools are passed, usually on the 2nd or 3rd day of life, may be confused with hemorrhage from the gastrointestinal tract. The blood may be swallowed during delivery or from a fissure in the mother's nipple. Differentiation from gastrointestinal hemorrhage is based on the fact that the infant's blood contains mostly fetal hemoglobin, which is alkali-resistant, whereas swallowed blood from a maternal source contains adult hemoglobin, which is promptly changed to alkaline hematin after the addition of alkali. Apt devised the following test for this differentiation: (1) Rinse a blood-stained diaper or some grossly bloody (red) stool with a suitable amount of water to obtain a distinctly pink supernatant hemoglobin solution; (2) centrifuge the mixture and decant the supernatant solution; (3) add 1 part of 0.25 N (1%) sodium hydroxide to 5 parts of the supernatant fluid. Within 1-2 min, a color reaction takes place: A yellow-brown color indicates that the blood is maternal in origin; a persistent pink indicates that it is from the infant. A control test with known adult or infant blood, or both, is advisable.

Widespread subcutaneous ecchymoses in premature infants at or immediately after birth are apparently a result of fragile superficial blood vessels rather than a coagulation defect. Administering vitamin K_1 to the mother during labor has no effect on the incidence of ecchymoses. Occasionally, an infant is born with petechiae or a generalized bluish suffusion limited to the face, head, and neck, probably as a result of venous obstruction by a nuchal cord or sudden increases in intrathoracic pressure during delivery. It may take 2-3 wk for such suffusions to disappear.

NEONATAL THROMBOCYTOPENIC PURPURA

See Chapter 484.

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Chapter 104

Genitourinary System

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See also Part XXIV.

Urinary tract anomalies (hydronephrosis, dysplasia, agenesis, cystic or solitary kidney) can often be identified by prenatal ultrasonography (see Table 96-1). After birth, the presence/extent of anomalies needs to be confirmed and followed by detailed evaluation and appropriate management. Multicystic and polycystic forms of kidney disease have high risk for mortality and renal morbidity. In contrast, the majority of mild dilatations have no clinical consequences but cause unnecessary anxiety in many cases.

One or both kidneys are often easily palpable in a newborn infant. When both are palpable and similar, infants usually do not have any particular diagnostic problems, but when only one kidney can be felt, a frequent impression is that it is larger than normal or is displaced by an intrinsic or extrinsic mass. Fetal lobulation may contribute to this impression. The problem usually resolves as the kidney becomes progressively less easily palpable during the early months of life. Because palpable enlargement or displacement of a kidney in a newborn may be due to hydronephrosis, neuroblastoma, mesoblastic nephroma, adrenal hemorrhage, or a cystic malformation, ultrasound examination is indicated.

RENAL VEIN THROMBOSIS

See Chapter 519.7.

Circumcision

Male circumcision is an elective procedure currently performed in many countries and in some religious and cultural groups. In the United States, the rate of male circumcision varies between 50% and 75% among various populations but has been declining recently. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologist have endorsed a policy statement in support of circumcision because of the health benefits.

The health benefits of circumcision include reduced acquisition and/or transmission of several sexually transmitted diseases (human immunodeficiency virus, human papillomavirus, herpes simplex virus type 2, and syphilis), possible prevention of urinary tract infections, and penile cancer. There is fair evidence that there are no significant differences in sexual function between circumcised and uncircumcised males. Even though the benefits of circumcision outweigh the rare but important complications (amputation of the penis or glans, infection), the health benefits are not large enough to recommend circumcision of all male infants. With appropriate counseling, parents can make a decision on what they think is the best interest of their baby in the context of their medical, ethical, religious, and cultural beliefs (see also Chapter 544).

Male circumcision entails the surgical removal of some of the foreskin (prepuce) of the penis. The surgery is performed under penile

nerve block anesthesia and under sterile conditions. The surgery includes dilation of the preputial orifice to visualize the glans, freeing the preputial epithelium from the epithelium of the glans, placement of the circumcision device (Gomco clamp, Plastibell, or Mogen clamp) to enhance hemostasis, and removal of foreskin.

Parents should be instructed on the care of the penis. The circumcised penis should be washed gently. A gauze with petroleum jelly can be used to cover the glans until the glans heals. The uncircumcised penis should be washed with soap and water on the outside. At birth, the foreskin is attached to the glans and cannot be retracted. The foreskin will separate naturally over several months. After separation, the foreskin is pulled back and the penis and inside of the foreskin can be washed with soap and water. After cleaning, the foreskin should be pulled back over the glans.

Bibliography is available at Expert Consult.

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Chapter 105

The Umbilicus

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UMBILICAL CORD

The umbilical cord contains the 2 umbilical arteries, the umbilical vein, the rudimentary allantois, the remnant of the omphalomesenteric duct, and a gelatinous substance called Wharton jelly. The sheath of the umbilical cord is derived from the amnion. The muscular umbilical arteries contract readily, but the vein does not. The vein retains a fairly large lumen after birth. The normal cord at term is 55 cm long on average. Abnormally short cords are associated with antepartum abnormalities, including fetal hypotonia, oligohydramnios, and uterine constraint, and with increased risk for complications of labor and delivery for both mother and infant. Long cords (>70 cm) increase risk for true knots, wrapping around fetal parts (neck, arm), and/or prolapse. Straight untwisted cords are associated with fetal distress, anomalies, and intrauterine fetal demise.

When the cord sloughs after birth, portions of these structures remain in the base. The blood vessels are functionally closed but anatomically patent for 10-20 days. The arteries become the lateral umbilical ligaments; the vein, the ligamentum teres; and the ductus venosus, the ligamentum venosum. During this interval, the umbilical vessels are potential portals of entry for infection. The umbilical cord usually sloughs within 2 wk. Delayed separation of the cord, after more than 1 mo, has been associated with neutrophil chemotactic defects and overwhelming bacterial infection (see Chapter 130).

A single umbilical artery is present in approximately 5-10/1,000 births; the frequency is approximately 35-70/1,000 in twin births. Approximately 30% of infants with a single umbilical artery have congenital abnormalities, usually more than one; many such infants are stillborn or die shortly after birth. Trisomy 18 is one of the more frequent abnormalities. Because abnormalities may not be apparent on physical examination, it is important that at every delivery, the cut cord and the maternal and fetal surfaces of the placenta be inspected. The number of arteries present is an aid to the early suspicion and identification of abnormalities in the infants. For infants with a single umbilical artery but no other anomalies, the need for renal ultrasonography is controversial.

Patency of the omphalomesenteric (vitelline) duct may be responsible for intestinal obstruction, intestinal fistula with fecal or bilious draining, prolapse of the bowel, a polyp (cyst), or a Meckel diverticulum (see Chapter 331.2). **Therapy** is surgical excision of the anomaly.

A persistent urachus (urachal cyst, sinus, patent urachus, or diverticulum) is a result of failure of closure of the allantoic duct and is associated with bladder outlet obstruction. Patency should be suspected if a clear, light yellow, urine-like fluid is being discharged from the umbilicus. Symptoms include drainage, a mass or cyst, abdominal pain, local erythema, and infection. Urachal anomalies should be investigated by ultrasonography and a cystogram. **Therapy** is surgical excision of the anomaly and correction of any bladder outlet obstruction if present.

CONGENITAL OMPHALOCELE

An omphalocele is a herniation or protrusion of the abdominal contents into the base of the umbilical cord (Figs. 105-1 and 105-2). In contrast to the more common umbilical hernia, the sac is covered with peritoneum without overlying skin. The size of the sac that lies outside the abdominal cavity depends on its contents. Herniation of intestines into the cord occurs in approximately 1/5,000 births, and herniation of liver and intestines in 1/10,000 births. The abdominal cavity is

Figure 105-1 Small intact sac at the base of the umbilical cord. *(From Clark DA, Thompson JE, Barnemeyer BM:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders.)*

Figure 105-2 Intact sac with healthy organs visible. *(From Clark DA, Thompson JE, Barnemeyer BM:* Atlas of neonatology, *ed 7, Philadelphia, 2000, WB Saunders.)*

proportionately small because the impetus to grow and develop is deficient. Immediate surgical repair, before infection has taken place and before the tissues have been damaged by drying (saline-soaked sterile dressings should be applied immediately) or by rupture of the sac, is essential for survival. Mersilene mesh or similar synthetic material may be used to cover the viscera if the sac has ruptured or if excessive mobilization of the skin would be necessary to cover the mass and its intact sac. The majority (≈75%) of infants with omphalocele have associated congenital anomalies/syndromes, including Beckwith-Wiedemann syndrome (omphalocele, macrosomia, hypoglycemia), and other chromosomal (29%, including trisomies 13 and 18) and nonchromosomal (45%) multiple and isolated congenital anomalies (musculoskeletal, 24%; urogenital, 20%; cardiovascular, 15%; and central nervous system, 9%). The survival rate is approximately 80% overall, but in infants with isolated omphalocele, the survival rate is >90%.

TUMORS

Tumors of the umbilicus are rare and include angioma, enteroteratoma, dermoid cyst, myxosarcoma, and cysts of urachal or omphalomesenteric duct remnants.

HEMORRHAGE

Hemorrhage from the umbilical cord may be the result of trauma, inadequate ligation of the cord, or failure of normal thrombus formation. It may also indicate hemorrhagic disease of the newborn or other coagulopathies (especially factor XIII deficiency), septicemia, or local infection. The infant should be observed frequently during the first few days of life so that if hemorrhage does occur, it will be detected promptly.

GRANULOMA

The umbilical cord usually dries and separates within 6-8 days after birth. The raw surface becomes covered by a thin layer of skin; scar tissue forms, and the wound is usually healed within 12-15 days. The presence of saprophytic organisms delays separation of the cord and increases the possibility of invasion by pathogenic organisms. Mild infection or incomplete epithelialization may result in a moist granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Good results are usually obtained by cleansing with alcohol several times daily.

Persistence of granulation tissue at the base of the umbilicus is common. The tissue is soft, 3-10 mm in size, vascular and granular, and dull red or pink, and it may have a seropurulent secretion. **Treatment** is cauterization with silver nitrate, repeated at intervals of several days until the base is dry.

Umbilical granuloma must be differentiated from **umbilical polyp,** a rare anomaly resulting from persistence of all or part of the omphalomesenteric duct or the urachus. The tissue of the polyp is firm and resistant, is bright red, and has a mucoid secretion. If the polyp is communicating with the ileum or bladder, small amounts of fecal material or urine may be discharged intermittently. Histologically, the polyp consists of intestinal or urinary tract mucosa. **Treatment** is surgical excision of the entire omphalomesenteric or urachal remnant.

INFECTIONS

Although aseptic delivery and routine cord care (application of triple dye and other antiseptics to the umbilical stump and surrounding skin) decrease bacterial colonization and umbilical infection, the necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. In a meta-analysis, triple dye was found to be more effective than alcohol in reducing omphalitis. Soap and water or dry care is not as effective in the prevention of omphalitis. Topical application of 4% chlorhexidine to the umbilical cord reduces neonatal mortality and omphalitis in community and primary care settings in developing countries. **Omphalitis** may remain localized or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, or the liver. Infants with abdominal wall cellulitis or those with **necrotizing fasciitis** have a high incidence of associated bacteremia. Portal vein phlebitis may develop and result in the later onset of **extrahepatic portal hypertension.** The general manifestations may be minimal (periumbilical erythema), even when septicemia or hepatitis has resulted. Treatment includes prompt antibiotic therapy (with agents effective against *Staphylococcus aureus* and *Escherichia coli*) and, if abscess formation has occurred, surgical incision and drainage. Necrotizing fasciitis is often polymicrobial and has a high mortality.

UMBILICAL HERNIA

Often associated with diastasis recti, an umbilical hernia is due to imperfect closure or weakness of the umbilical ring. Predisposing factors include black race and low birthweight. The hernia appears as a soft swelling covered by skin that protrudes during crying, coughing, or straining and can be reduced easily through the fibrous ring at the umbilicus. The hernia consists of omentum or portions of the small intestine. The size of the defect varies from <1 cm in diameter to as much as 5 cm, but large defects are rare. Most umbilical hernias that appear before the age of 6 mo disappear spontaneously by 1 yr of age. Even large hernias (5-6 cm in all dimensions) have been known to disappear spontaneously by 5-6 yr of age. Strangulation is extremely rare. It is generally agreed that "strapping" is ineffective. Surgery is not advised unless the hernia persists to the age of 4-5 yr, causes symptoms, becomes strangulated, or becomes progressively larger after the age of 1-2 yr. Defects exceeding 2 cm are less likely to close spontaneously.

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Chapter 106

Metabolic Disturbances

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HYPERTHERMIA IN THE NEWBORN

Elevations in temperature (38-39°C [100-103°F]) are occasionally noted on the 2nd or 3rd day after birth in infants whose clinical course has been otherwise satisfactory. This disturbance is especially likely to occur in breastfed infants whose intake of fluid has been particularly low or in infants who are overdressed or are exposed to high environmental temperatures, either in an incubator, in a bassinette near a radiator, or in the sun.

The infant may lose weight. A consistent relationship may not be seen between the fever and the extent of weight loss or inadequacy of fluid intake. Urinary output and the frequency of voiding diminish. The fontanel may be depressed. The infant takes fluids avidly, and the apparent vigor of the infant is not consistent with the usual appearance of "being sick" from an infection. The rise in temperature may be associated with increases in serum levels of protein and sodium and in hematocrit. The possibility of local or systemic infection should be evaluated. Lowering the environmental temperature leads to prompt reduction of the fever and alleviation of symptoms. Oral hydration should be accomplished with additional breast milk or formula feeding and not with water, because of the risk of hyponatremia.

A more severe form of neonatal hyperthermia occurs in both newborn and older infants when they are warmly dressed. The diminished sweating capacity of newborn infants is a contributing factor. Warmly dressed infants left near stoves or radiators, traveling in well-heated automobiles, or left with bright sunlight shining directly on them through the windows of a closed room or automobile are likely to be victims. Body temperature may become as high as 41-44°C (106-111°F). The skin is hot and dry, and initially the infant usually appears

flushed and apathetic. The extremities are warm. Tachypnea and irritability may be noted. This stage may be followed by stupor, grayish pallor, coma, and convulsions. Hypernatremia may contribute to the convulsions. Mortality and morbidity (brain damage) rates are high. Hyperthermia has been associated with sudden infant death, and **hemorrhagic shock and encephalopathy syndrome** (see Chapter 70). The condition is prevented by dressing infants in clothing suitable for the temperature of the immediate environment. In newborn infants, exposure of the body to usual room temperature or immersion in tepid water usually suffices to bring the temperature back to normal levels. Older infants may require cooling for a longer time by repeated immersion. Attention to possible fluid and electrolyte disturbance is essential.

Hyperthermia a few days after birth can result from infection, particularly herpes sepsis. Infants with infection appear ill with cold extremities, in contrast to the warm extremities of those in whom hyperthermia is from environmental causes.

NEONATAL COLD INJURY

Neonatal cold injury usually occurs in abandoned infants, infants in inadequately heated homes during cold spells when the outside temperature is low, and in preterm infants (see Chapter 76). The initial features are apathy, refusal of food, oliguria, and coldness to touch. The body temperature is usually between 29.5 and 35°C (85 and 95°F), and immobility, edema, and redness of the extremities, especially the hands and feet, and of the face are observed. Bradycardia and apnea may also occur. The facial erythema frequently gives a false impression of health and delays recognition that the infant is ill. Local hardening over areas of edema may lead to confusion with scleredema. Hypoglycemia and acidosis are common. Hemorrhagic manifestations are frequent; massive pulmonary hemorrhage is a common finding at autopsy. Hypothermia in preterm infants can be prevented with special plastic wraps that reduce evaporation and heat loss. Because of their high ratio of surface area to body mass, preterm infants are very vulnerable to evaporation heat loss. Infants at <28-30 wk of gestation should be placed inside a clear polyethylene bag without prior drying at birth. Neonatal cold injury occurs in even late preterm infants in low-resource settings and can be prevented with skin-to-skin (kangaroo mother) care and polyethylene plastic wraps. **Treatment** consists of warming and paying scrupulous attention to recognition and correction of hypotension and metabolic imbalances, particularly hypoglycemia. Prevention consists of providing adequate environmental heat. The mortality rate is approximately 10%; approximately 10% of survivors have evidence of brain damage.

EDEMA

Generalized edema occurs in association with **hydrops fetalis** (see Chapter 103.2) and in the offspring of diabetic mothers. In preterm infants, edema is often a consequence of a decreased ability to excrete water or sodium, although some have considerable edema without identifiable cause. Infants with respiratory distress syndrome may become edematous without heart failure. Edema of the face and scalp may be caused by pressure from the umbilical cord around the neck, and transient localized swelling of the hands or feet may similarly be caused by intrauterine pressure. Edema may be associated with heart failure. A lag in renal excretion of electrolytes and water may result in edema after a sudden large increase in intake of electrolytes, particularly with feeding of concentrated cow's milk formulas. Rarely, idiopathic hypoproteinemia with edema lasting weeks or months is observed in term infants. The cause is unclear, and the disturbance is benign. Persistent edema of 1 or more extremities may represent congenital lymphedema (Milroy disease) or, in females, Turner syndrome. Generalized edema with hypoproteinemia may be seen in the neonatal period with congenital nephrosis and rarely with Hurler syndrome or after feeding hypoallergenic formulas to infants with cystic fibrosis of the pancreas. Chapter 647 describes sclerema.

HYPOCALCEMIA (TETANY)

See also Chapter 51.

Metabolic Bone Disease

Metabolic bone disease is a common complication in preterm infants. The smallest, sickest infants are at greatest risk. Progressive osteopenia with demineralized bones and, occasionally, pathologic fractures may develop. The major cause is inadequate intake of calcium and phosphorus to meet the requirements for growth. Poor intake of vitamin D is an additional risk factor. Contributing factors include prolonged parenteral nutrition, vitamin D and calcium malabsorption, intake of unsupplemented human milk, immobilization, and urinary calcium losses from long-term diuretic use. The serum alkaline phosphatase level is used to monitor metabolic bone disease and can be >1,000 units/L in severe cases. Fortified human milk and formulas designed for preterm infants provide higher amounts of calcium, phosphorus, and vitamin D; promote bone mineralization; and reduce metabolic bone disease. Treatment of fractures requires immobilization and administration of calcium, phosphorus, and, if needed, vitamin D (not more than 1,000 IU/day unless severe cholestasis or vitamin D resistance is present). See also Chapters 51 and 570.

Hypomagnesemia

Rarely, hypomagnesemia of unknown cause may occur in newborn infants, usually in association with hypocalcemia. It may also be associated with insufficient stores of skeletal magnesium secondary to deficient placental transfer, decreased intestinal absorption, neonatal hypoparathyroidism, hyperphosphatemia, renal loss (primary or secondary to drugs, e.g., amphotericin B), a defect in magnesium and calcium homeostasis, or iatrogenic deficiency caused by loss incurred during exchange transfusion or insufficient replacement during total intravenous alimentation. Infants of diabetic mothers may have lower than normal serum magnesium levels. The clinical manifestations of hypomagnesemia are indistinguishable from those of hypocalcemia and tetany and may, in fact, contribute to the accompanying hypocalcemia.

Hypomagnesemia occurs when serum magnesium levels fall below 1.5 mg/dL (0.62 mmol/L), although clinical signs do not usually develop until serum magnesium levels fall below 1.2 mg/dL. During exchange transfusion with citrated blood, which is low in magnesium because of binding by citrate, serum magnesium decreases about 0.5 mg/dL (0.2 mmol/L); approximately 10 days are required for return to normal. In noniatrogenic hypomagnesemia, the serum magnesium level may be <0.5 mg/dL. Serum calcium in either instance is usually at levels noted in hypocalcemic tetany, but the serum phosphorus value is normal or high. Because the hypocalcemia accompanying hypomagnesemia is inadequately corrected by administration of calcium alone, hypomagnesemia should also be suspected in any patient with tetany not responding to calcium therapy.

Immediate **treatment** consists of intramuscular injection of magnesium sulfate. For newborn infants, 25-50 mg/kg/dose every 8 hr for 3-4 doses usually suffices. The accompanying hypocalcemia usually corrects itself as the hypomagnesemia resolves. The same daily dose can be given for oral maintenance therapy. Four to 5 times higher doses may be required in malabsorptive states. In most cases, the metabolic defect is transient, and treatment can be discontinued after 1-2 wk. A few patients appear to have a permanent form of the disease that requires continuous oral supplementation with magnesium to prevent recurrence of hypomagnesemia. No residual damage to the central nervous system is evident after prompt treatment.

HYPERMAGNESEMIA

Hypermagnesemia may occur in newborn infants of mothers treated with magnesium sulfate during labor. At high serum levels, the central nervous system is depressed and infants have respiratory depression that may require mechanical ventilation. Lower levels may result in hypoventilation, lethargy, flaccidity, hyporeflexia, and poor sucking. Hypermagnesemia may be associated with failure to pass meconium. The upper limit of normal magnesium is 2.8 mg/dL (1.15 mmol/L), but serious symptoms rarely occur at levels <5 mg/dL (2.1 mmol/L). In most cases, no specific therapy (beyond supportive care and maintenance of respiratory support) is required. Intravenous calcium and

diuresis will reduce the magnesium levels. In rare cases, exchange transfusion has been used for rapid removal of magnesium ion from the blood.

SUBSTANCE ABUSE AND NEONATAL ABSTINENCE (WITHDRAWAL)

Substance abuse during pregnancy can be a serious problem for both the mother and her newborn. The mother may suffer adverse consequences of her addiction, including episodes of drug withdrawal during pregnancy and illnesses related to high-risk behavior. Effects on the fetus and newborn include chronic or intermittent drug exposure, poor maternal nutrition, acute withdrawal shortly after birth, and long-term effects on physical growth and neurodevelopment. Because infants with in utero drug exposure often have social and environmental risk factors and may have been exposed to multiple substances, it may be difficult to evaluate the effects of specific in utero drug exposure on long-term neurodevelopmental outcome.

Pregnancies in women who use illegal drugs or alcohol are high risk. Prenatal care is usually inadequate, and these women have a higher incidence of sexually transmitted infections, including syphilis, HIV, and hepatitis. In addition, the risk of preterm labor, intrauterine growth restriction, premature rupture of membranes, and perinatal morbidity and mortality is higher. Physiologic addiction to narcotics occurs in most infants born to actively addicted mothers because opiates cross the placenta. Withdrawal may manifest even before birth as increased activity of the fetus when the mother feels a need for the drug or withdrawal symptoms develop. The clinical syndrome associated with opioid withdrawal has been termed the neonatal abstinence syndrome. Withdrawal signs develop during the 1st wk after birth in 55-94% of newborn infants exposed to opioids in utero. Neonatal withdrawal signs have also been described in infants exposed antenatally to benzodiazepines, barbiturates, alcohol, and other drugs. **Heroin addiction** results in a 50% incidence of low birthweight infants, half of whom are small for gestational age. Chronic infections, maternal undernutrition, and a direct fetal growth–inhibiting effect are possible causes. The rate of stillbirths increases, but not the incidence of congenital anomalies. Clinical manifestations of withdrawal occur in 50-75% of infants, usually beginning within the 1st 48 hr, depending on the daily maternal dose (<6 mg/24 hr is associated with no or mild symptoms), the duration of addiction (duration >1 yr has a >70% incidence of withdrawal), and the time of the last maternal dose (the incidence is higher if the last dose was taken within 24 hr of birth). Rarely, symptoms may appear as late as 4-6 wk of age. The incidence of respiratory distress syndrome and hyperbilirubinemia may be decreased in preterm infants of heroin users; accelerated production of pulmonary surfactant may explain the former, and enzyme induction of hepatic glucuronyl transferase the latter.

Tremors and hyperirritability are the most prominent symptoms. The tremors may be fine or jittery and indistinguishable from those of hypoglycemia, but they are more often coarse, "flapping," and bilateral; the limbs are frequently rigid, hyperreflexic, and resistant to flexion and extension. Irritability and hyperactivity are generally marked and may lead to skin abrasions. Other signs include wakefulness, hyperacusis, hypertonicity, tachypnea, diarrhea, vomiting, high-pitched cry, fist sucking, poor feeding with weight loss (disorganized sucking), and fever. Sneezing, yawning, hiccups, myoclonic jerks, convulsions, abnormal sleep cycles, nasal stuffiness, apnea, flushing alternating rapidly with pallor, and lacrimation are less common. The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) is a useful way to evaluate neonates exposed to opiates or other drugs (Table 106-1). The risk of sudden infant death syndrome is higher in such neonates. The diagnosis is generally established from the history and clinical findings. Examining the urine for opiates may reveal only low levels during withdrawal, but quinine, which is often mixed with heroin, may be present in higher concentrations. Meconium testing is more accurate than neonatal urine drug testing. Hypoglycemia and hypocalcemia should be excluded.

Methadone treatment of the mother is associated with severe withdrawal symptoms, the incidence varying from 20-90%. Mothers taking methadone usually have better prenatal care than those taking heroin; these mothers have a high incidence of polysubstance abuse, including alcohol, barbiturates, and tranquilizers, and they are often heavy smokers. The incidence of congenital anomalies is not increased. The average birthweight of infants of mothers taking methadone is higher than that of infants of heroin-addicted mothers; the clinical manifestations are similar, except that the former group has a higher incidence of seizures (10-20%) and later onset (2-6 wk of age) of withdrawal. Women who continue to abuse heroin, even if they enter a methadone program, are more likely to have preterm and/or low birthweight infants than those born to women who stop using heroin. They are also more likely to suffer withdrawal and have a higher risk of neonatal mortality.

Table 106-1 Neurobehavioral Scale

DOMAIN	ITEMS
Physiologic	Labored breathing Nasal flaring
Autonomic	Sweating Spit-up Hiccoughing Sneezing Nasal stuffiness Yawning
Central nervous system	Abnormal sucking Choreiform movements Athetoid postures and movements Tremors Cogwheel movements Startles Hypertonia Back arching Fisting Cortical thumb Myoclonic jerks Generalized seizures Abnormal posture
Skin	Pallor Mottling Lividity Overall cyanosis Circumoral cyanosis Periocular cyanosis
Visual	Gaze aversion during orientation Pull-down during orientation Fuss/cry during orientation Obligatory following during orientation End-point nystagmus during orientation Sustained spontaneous nystagmus Visual locking Hyperalertness Setting sun sign Roving eye movements Strabismus Tight blinking Other abnormal eye signs
Gastrointestinal	Gagging/choking Loose stools, watery stools Excessive gas, bowel sounds
State	High-pitched cry Monotone-pitch cry Weak cry No cry Extreme irritability Abrupt state changes Inability to achieve quiet awake state (state 4)

From Lester BM, Tronick EZ, Brazelton TB: The Neonatal Intensive Care Unit Network Neurobehavioral Scales procedures, Pediatrics *113:641–667, 2004.*

Table 106-2 Pharmacologic Therapy for Neonatal Abstinence Syndrome

DRUG	INITIAL DOSING	DOSING INCREASES	RESCUE DOSING	ADD ADJUVANT THERAPY	WEANING SCHEDULE
Morphine	0.1 mg kg^{-1} $dose^{-1}$ orally every 4 hr	Increase by 20–30% every 12 hr until scores <8 × 24 hr	Repeat previous dose between scheduled dose intervals	At morphine dose of 1.25 mg kg^{-1} $dose^{-1}$, add phenobarbital or clonidine	Decrease by 10% every 24 hr, while scores <8. Discontinue when 0.15 kg^{-1} $dose^{-1}$
Methadone	0.1 mg kg^{-1} $dose^{-1}$ orally every 12 hr	Calculate entire methadone dose for previous 24 hr and divide by two for BID dosing	Additional dosing of 0.025 mg kg^{-1} $dose^{-1}$ every 4 hr while scoring >8. Max dose 0.5 mg kg^{-1} $dose^{-1}$	When max dosing has been reached	Decrease by 10% every 1-2 wk. Discontinue when 0.05 mg kg^{-1} $dose^{-1}$
Buprenorphine	15.9 μg kg^{-1} $dose^{-1}$ divided in 3 doses, orally	Increase by 25%	Max dose 60 μg kg^{-1} $dose^{-1}$		After 3 days of stabilization, decrease by 10% while scores <8. Discontinue when dose is 10% of initial dose
Phenobarbital	20 mg/kg loading	Maintenance dose 5 mg/kg		Adjuvant	
Clonidine	0.5 to 1.5 μg/kg orally	Increase by over 1 to 2 days to target dose 3 to 5 μg kg^{-1} day^{-1}, divided every 4–6 hr		Adjuvant	No taper required

From Cramton REM, Gruchala NE: Babies breaking bad: neonatal and iatrogenic withdrawal syndromes. Curr Opin Pediatr *25:532–542, 2013, Table 4, p. 538.*

Buprenorphine (a partial μ-opioid agonist) is a synthetic opioid often used for the treatment of opioid dependence, used either alone (Subutex) or in combination with naloxone (Suboxone), Although the incidence of neonatal symptoms after maternal treatment with methadone and buprenorphine may be similar, the pattern of symptoms may be different; more tremor and hyperactive Moro reflex with methadone and more nasal stuffiness, sneezing, and loose stools with buprenorphine. Infants born to mothers treated with buprenorphine develop abstinence symptoms 1-2 days later than those of mothers on methadone. Infants born to buprenorphine-treated mothers also require less postnatal morphine doses, have a shorter duration of treatment, and are discharged from the hospital approximately 5 days sooner than methadone-exposed infants.

Alcohol withdrawal is uncommon. Infants of women who have been drinking immediately before delivery may have alcohol on their breath for several hours because it rapidly crosses the placenta. Blood levels in the infant are similar to those in the mother. Hypoglycemia and metabolic acidosis may be present. Infants in whom withdrawal symptoms develop often become agitated and hyperactive, with marked tremors lasting 72 hr, followed by about 48 hr of lethargy before return to normal activity. Seizures may develop.

Phenobarbital withdrawal usually occurs in infants of mothers addicted to the drug. Symptoms begin at a median age of 7 days (range: 2-14 days). Infants may have a brief acute stage consisting of irritability, constant crying, sleeplessness, hiccups, and mouthing movements, followed by a subacute stage consisting of voracious appetite, frequent regurgitation and gagging, episodic irritability, hyperacusis, sweating, and a disturbed sleep pattern, all of which may last 2-4 mo.

Cocaine abuse in pregnant women is common, but withdrawal in their infants is unusual; the pregnancy may be complicated by premature labor, abruptio placentae, and fetal asphyxia. Infants may have intrauterine growth restriction and neurobehavioral deficits characterized by impaired state regulation, impaired auditory information processing, developmental delay, and learning disabilities. At 24 mo of age, they score lower on the mental portion of the Bayley Scales of Infant Development and are twice as likely to have developmental delay. Family disorganization, polysubstance abuse, sexually transmitted infections, and child abuse and neglect may also be present. At 4 yr of age, children exposed prenatally to cocaine demonstrate specific cognitive impairments (visual–spatial and math skills; general knowledge) and are less likely to have an IQ above the normative mean. With a more enriching home environment, IQ scores of cocaine-exposed children are similar to those of nonexposed children.

Treatment

The decision to use drug therapy for neonatal drug withdrawal should be based on the presence of signs of withdrawal. Infants with confirmed drug exposure who do not have signs of withdrawal do not require pharmacologic treatment. Drug withdrawal is a self-limiting process. However, withdrawal from sedative-hypnotic drugs or narcotics can be life-threatening. Indications for drug treatment include seizures, poor feeding, diarrhea, excessive vomiting, inability to sleep, and fever. Several methods to assess severity of the withdrawal are available.

Infants who are undergoing opiate withdrawal require care in a quiet environment with reduction of external stimuli and swaddling. Pharmacologic treatment of heroin and methadone withdrawal requires opiate replacement during the 1st wk or 2 of life (Table 106-2). Methadone is often the drug of choice, but oral or sublingual buprenorphine is an alternate approach. Adjunct treatment with phenobarbital or clonidine is rarely necessary. Methadone withdrawal may require larger amounts of medication for longer periods to control clinical manifestations than are needed for heroin withdrawal. The Modified Finnegan's Neonatal Abstinence Scoring Tool, Lipsitz Neonatal Drug-Withdrawal Scoring System, or other semiobjective scoring tools may be used by clinicians to evaluate withdrawal and help with decisions regarding initiation or adjustment of therapy. The dose and duration of therapy may be adjusted according to the clinical response. Parenteral administration of fluids may be necessary to prevent aspiration or dehydration until the symptoms are brought under control.

Mortality from withdrawal is <5% and may be negligible with early recognition and treatment. The prognosis for normal development is affected by the adverse circumstances of high-risk pregnancy and delivery and by the environment to which the infant is returned after recovery, as well as by the effects of the particular drug on fetal and subsequent neonatal development.

106.1 Maternal Selective Serotonin Reuptake Inhibitors and Neonatal Behavioral Syndromes

Waldemar A. Carlo

Women of childbearing age have a combined incidence of depression and anxiety of approximately 19%. Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine) and, less often, serotonin norepinephrine reuptake inhibitors (venla-

faxine, duloxetine) have been used to treat pregnant women with depression or anxiety disorders. Exposure to these agents during pregnancy may inconsistently produce congenital malformations (see Chapter 96). In addition, poor neonatal adaptation has been noted with the use of many of these agents, but most often with paroxetine and fluoxetine.

It is unclear whether poor neonatal adaptation is a result of serotonin overstimulation **(serotonin syndrome)** or withdrawal **(serotonin discontinuation syndrome).** Indeed, both conditions may occur with different agents. Paroxetine has a short half-life and few if any active metabolites, and is also a potent muscarinic blocking agent. Serum paroxetine levels after birth decline rapidly. Neonatal adaptive symptoms after late pregnancy exposure to paroxetine may be withdrawal with cholinergic overdrive. Symptoms may also be delayed. In contrast, fluoxetine and its active metabolite (nor-fluoxetine) have long half-lives and may produce a serotonin syndrome of acute toxicity. Onset may be at birth or in the 1st 24 hr of life. The cord blood level of fluoxetine is equal to blood level in the mother. All agents cross the placental and blood–brain barriers.

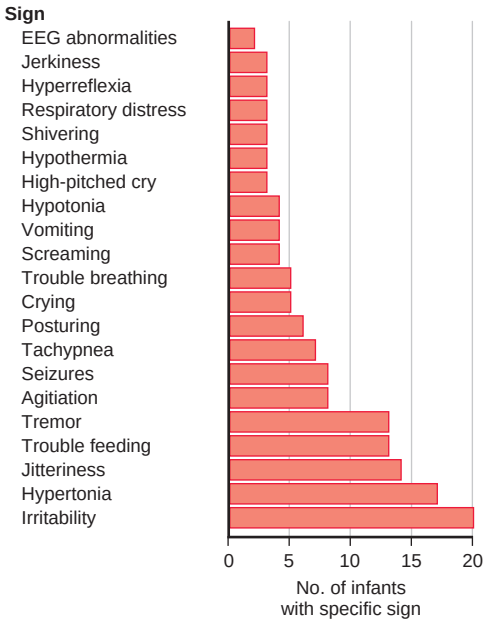

Figure 106-1 Neonatal signs after late in utero exposure to serotonin reuptake inhibitors. Frequencies of specific signs reported to the U.S. Food and Drug Administration (FDA) Adverse Events Reporting System. Ordered by frequency of occurrence (n = 57 infants). EEG, electroencephalographic. *(From Moses-Kolko EL, Bogen D, Perel J, et al: Neonatal signs after late in utero exposure to serotonin reuptake inhibitors,* JAMA *293:2372–2383, 2005.)*

A neonatal behavioral syndrome that has features of both direct serotonin toxicity and withdrawal (cholinergic overdrive) is noted in Figure 106-1 and is characterized by central nervous system (irritability, excess or restless sleep), motor (agitation, tremor, hyperreflexia, rigidity, hypotonia or hypertonia), respiratory (nasal congestion, respiratory distress, tachypnea), gastrointestinal (diarrhea, emesis, poor feeding) and systemic (hypothermia or hyperthermia, hypoglycemia) manifestations. Most infants have only mild symptoms that resolve within 2 wk; a severe syndrome characterized by seizures, dehydration, weight loss, hyperpyrexia, and respiratory failure is present in 1%. No deaths have been reported.

Treatment is directed at the individual manifestations and accompanied by supportive therapies. A method of prevention of neonatal SSRI withdrawal has been proposed that consists of weaning the mother from the SSRI in the 3rd trimester of pregnancy. The advantages of this approach for the fetus must be weighed against the risk for the mother of recurrence of psychiatric symptoms during the last trimester and postpartum period.

106.2 Fetal Alcohol Syndrome

Waldemar A. Carlo

High levels of alcohol ingestion during pregnancy can be damaging to embryonic and fetal development. A specific pattern of malformation identified as *fetal alcohol syndrome* has been documented, and major and minor components of the syndrome are expressed in 1-2 infants/1,000 live births (Table 106-3). Both moderate and high levels of alcohol intake during early pregnancy may result in alterations in

Table 106-3 Fetal Alcohol Syndrome Surveillance Network Case Definition Categories

	PHENOTYPE POSITIVE		
Case Definition Category	**Face**	**Central Nervous System**	**Growth**
Confirmed FAS phenotype with or without maternal alcohol exposure*	Abnormal facial features consistent with FAS as reported by a physician *or* Two of the following: short palpebral fissures, abnormal philtrum, thin upper lip	Frontal-occipital circumference ≤10th percentile at birth or any age *or* Standardized measure of intellectual function ≤1 SD below the mean *or* Standardized measure of developmental delay ≤1 SD below the mean *or* Developmental delay or mental retardation diagnosed by a qualified examiner (e.g., psychologist or physician) *or* Attention deficit disorder diagnosed by a qualified evaluator	Intrauterine weight or height corrected for gestational age ≤10th percentile *or* Postnatal weight or height ≤10th percentile for age *or* Postnatal weight for height ≤10th percentile
Probable FAS phenotype with or without maternal alcohol exposure*	Required; facial features same as above	Must meet either central nervous system or growth criteria as outlined above	

*Documentation in the records of some level of maternal alcohol use during the index pregnancy.
FAS, fetal alcohol syndrome; SD, standard deviation.
From Fetal alcohol syndrome—Alaska, Arizona, Colorado and New York, 1995-1997, MMWR Morb Mortal Wkly Rep *51:433–435, 2002.*

Figure 106-2 **Characteristics of fetal alcohol syndrome.** At birth *(A)* and at 4 yr of age *(B)*. Note the short palpebral fissures; long, smooth philtrum with vermillion border; and hirsutism in the newborn. *(From Jones KL, Smith DW: Recognition of the fetal alcohol syndrome in early infancy,* Lancet *2:999–1001, 1973.)*

growth and morphogenesis of the fetus; the greater the intake, the more severe the signs. The risk of abnormality for infants born to heavy drinkers is twice that for infants born to moderate drinkers; in one study, 32% of infants born to heavy drinkers had congenital anomalies, compared with 9% of those born to abstinent mothers and 14% of those born to moderate drinkers. Additional maternal risk factors associated with fetal alcohol syndrome are advanced maternal age, low socioeconomic status, poor psychological indicators, and binge drinking.

Characteristics of fetal alcohol syndrome include (a) prenatal onset and persistence of growth deficiency for length, weight, and head circumference; (b) facial abnormalities, including short palpebral fissures, epicanthal folds, maxillary hypoplasia, micrognathia, smooth philtrum, and a thin, smooth upper lip (Fig. 106-2); (c) cardiac defects, primarily septal defects; (d) minor joint and limb abnormalities, including some restriction of movement and altered palmar crease patterns; and (e) delay of development and mental deficiency varying from borderline to severe (see Table 106-2). Fetal alcohol syndrome is a common identifiable cause of mental retardation. The severity of dysmorphogenesis may range from severely affected infants with full manifestations of fetal alcohol syndrome to those mildly affected with only a few manifestations.

The detrimental effects may be a consequence of the alcohol itself or to one of its breakdown products. Some evidence suggests that alcohol may impair placental transfer of essential amino acids and zinc, both of which are necessary for protein synthesis, an effect that may account for the intrauterine growth restriction.

Treatment of infants with fetal alcohol syndrome is difficult because no specific therapy exists. These infants may remain hypotonic and tremulous despite sedation, and the prognosis is poor. Counseling with regard to recurrence is important. Prevention is achieved by eliminating alcohol intake after conception.

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Chapter 107

The Endocrine System

Waldemar A. Carlo and Namasivayam Ambalavanan

The endocrinopathies are discussed in detail in Part XXVI.

Pituitary dwarfism is not usually apparent at birth, although male infants with panhypopituitarism may have neonatal hypoglycemia, hyperbilirubinemia, and micropenis. Conversely, constitutional dwarfs usually have length and weight suggestive of prematurity when born after a normal gestational period; otherwise, their physical appearance is normal.

Congenital hypothyroidism is one of the most common preventable causes of mental retardation. Congenital screening followed by thyroid hormone replacement treatment started within 2 wk after birth can normalize cognitive development in children with congenital hypothyroidism. Congenital hypothyroidism occurs in approximately 1/4,000 births (see Chapter 565). Because most infants with congenital hypothyroidism are asymptomatic at birth, all states screen for it. Even though screening is standard in many countries, millions of infants born throughout the world are not screened for congenital hypothyroidism. Thyroid deficiency may also be apparent at birth in genetically determined cretinism or in infants of mothers treated with antithyroid medications or during a pregnancy complicated by maternal hyperthyroidism. Constipation, prolonged jaundice, goiter, lethargy, or poor peripheral circulation as shown by persistently mottled skin or cold extremities should suggest cretinism. Thyroid hormone treatment is aimed to maintain total thyroxine or free thyroxine in the upper half of the normal range during the 1st 3 yr after birth. Early diagnosis and treatment of congenital thyroid hormone deficiency improve intellectual outcome and are facilitated by screening of all newborn infants for this deficiency.

Transient hypothyroxinemia of prematurity is most common in ill and very premature infants. These infants have low thyroxine levels but normal levels of serum thyrotropin and other tests of the pituitary–hypothalamic axis indicating that they are probably chemically euthyroid. Trials of thyroid hormone replacement have reported no difference in developmental outcomes or other morbidities. Current practice is to follow thyroxine levels until they normalize. **Transient hyperthyroidism** may occur at birth in infants of mothers with hyperthyroidism or in infants whose mothers have been receiving thyroid medication.

Transient hypoparathyroidism may manifest as tetany of the newborn (see Chapter 571).

The adrenal glands are subject to numerous disturbances, which may become apparent and require lifesaving treatment during the neonatal period. Acute **adrenal hemorrhage** and failure may occur after breech or other traumatic deliveries or in association with overwhelming infection. Signs of adrenal insufficiency and shock can occur. **Congenital adrenal hyperplasia** is suggested by vomiting, diarrhea, dehydration, hyperkalemia, hyponatremia, shock, ambiguous genitals, or clitoral enlargement. Some infants have ambiguous genitals and hypertension. Because the condition is genetically determined, newborn siblings of patients with the salt-losing variety of adrenocortical hyperplasia should be closely observed for manifestations of adrenal insufficiency. Newborn screening and early diagnosis and therapy for this disorder may prevent severe salt wasting and adverse outcomes. Congenitally hypoplastic adrenal glands may also give rise to adrenal insufficiency during the 1st few wk of life.

Female infants with webbing of the neck, lymphangiectatic edema, hypoplasia of the nipples, cutis laxa, low hairline at the nape of the neck, low-set ears, high-arched palate, deformities of the nails, cubitus valgus, and other anomalies should be suspected of having gonadal dysgenesis.

Transient diabetes mellitus (see Chapter 589) is rare and is encountered only in newborns. It usually manifests as dehydration, loss of weight, or acidosis in infants who are small for gestational age.

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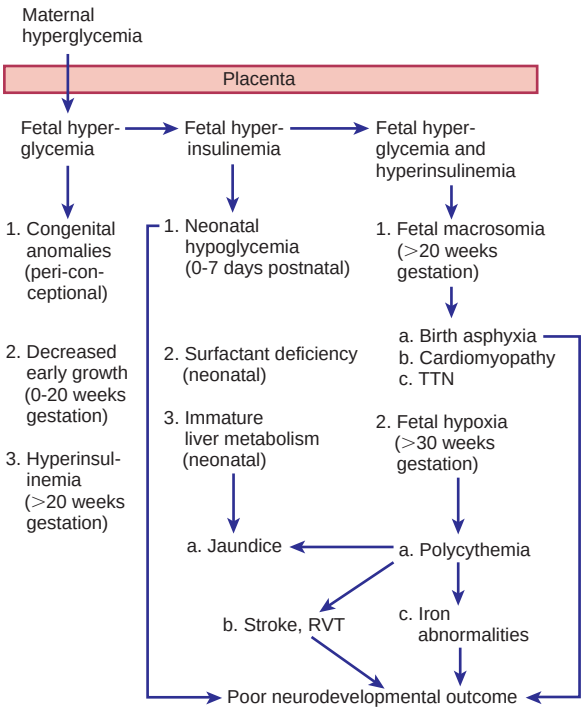

Figure 107-1 The fetal and neonatal events attributable to fetal hyperglycemia *(column 1)*, fetal hyperinsulinemia *(column 2)*, or both in synergy *(column 3)*. Time of risk is denoted in *parentheses*. RVT, renal vein thrombosis; TTN, transient tachypnea of the newborn. *(From Nold JL, Georgieff MK: Infants of diabetic mothers,* Pediatr Clin North Am *51:619-637, 2004.)*

107.1 Infants of Diabetic Mothers

Waldemar A. Carlo

Women with diabetes in pregnancy (type 1, type 2, and gestational) are at increased risk for adverse pregnancy outcomes. Adequate glycemic control before and during pregnancy is crucial to improving outcome.

Diabetic mothers have a high incidence of polyhydramnios, preeclampsia, pyelonephritis, preterm labor, and chronic hypertension; their fetal mortality rate is greater than that of nondiabetic mothers, especially after 32 wk of gestation. Fetal loss throughout pregnancy is associated with poorly controlled maternal diabetes (especially ketoacidosis) and congenital anomalies. Most infants born to diabetic mothers are large for gestational age. If the diabetes is complicated by vascular disease, infants may be growth restricted, especially those born after 37 wk of gestation. The neonatal mortality rate is >5 times that of infants of nondiabetic mothers and is higher at all gestational ages and in every birthweight for gestational age category.

PATHOPHYSIOLOGY

The probable pathogenic sequence is that maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia; fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, and augmented protein synthesis (Fig. 107-1). Related pathologic findings are hypertrophy and hyperplasia of the pancreatic islet β cells, increased weight of the placenta and infant organs except for the brain, myocardial hypertrophy, increased amount of cytoplasm in liver cells, and extramedullary hematopoiesis. Hyperinsulinism and hyperglycemia produce fetal acidosis, which may result in an increased rate of stillbirth. Separation of the placenta at birth suddenly interrupts glucose infusion into the neonate without a proportional effect on the hyperinsulinism, and hypoglycemia and attenuated lipolysis may develop during the 1st few hr after birth.

Hyperinsulinemia has been documented in infants of mothers with gestational diabetes and in those of mothers with insulin-dependent diabetes (diabetic mothers) without insulin antibodies. The former group also has significantly higher fasting plasma insulin levels than normal newborns do despite similar glucose levels; they also respond to glucose with an abnormally prompt elevation in plasma insulin and assimilate a glucose load more rapidly. After arginine administration, they also have an enhanced insulin response and increased disappearance rates of glucose in comparison with normal infants. In contrast, fasting glucose production and utilization rates are diminished in infants of mothers with gestational diabetes. The lower free fatty acid levels in infants of mothers with insulin-dependent diabetes reflect their hyperinsulinemia. With good prenatal diabetic control, the incidence of macrosomia and hypoglycemia has decreased.

Although hyperinsulinism is probably the main cause of hypoglycemia, the diminished epinephrine and glucagon responses that occur may be contributing factors. Congenital anomalies correlate with poor metabolic control during the periconception and organogenesis periods and may be the result of hyperglycemia-induced teratogenesis. Chronic fetal hypoxia, indicated by elevated amniotic fluid erythropoietin values, is associated with increased fetal and neonatal morbidity.

CLINICAL MANIFESTATIONS

Infants of mothers with diabetic and those of mothers with gestational diabetes often bear a surprising resemblance to each other (Fig. 107-2). They tend to be large and plump as a result of increased body fat and enlarged viscera, with puffy, plethoric facies resembling that of patients who have been receiving corticosteroids. These infants may also,

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Figure 107-2 Large, plump, plethoric infant of a mother with gestational diabetes. The baby was born at 38 wk of gestation but weighed 9 lb, 11 oz (4,408 g). Mild respiratory distress was the only symptom other than appearance.

however, be of normal or low birthweight, particularly if they are delivered before term or if their mothers have associated vascular disease.

Hypoglycemia develops in approximately 25-50% of infants of diabetic mothers and 15-25% of infants of mothers with gestational diabetes, but only a small percentage of these infants become symptomatic. The probability that hypoglycemia will develop in such an infant increases, and glucose levels are likely to be lower with higher cord or maternal fasting blood glucose levels. The nadir in an infant's blood glucose concentration is usually reached between 1 and 3 hr; spontaneous recovery may begin by 4-6 hr.

The infants tend to be jittery, tremulous, and hyperexcitable during the 1st 3 days after birth, although hypotonia, lethargy, and poor sucking may also occur. They may have any of the diverse manifestations of hypoglycemia. Early appearance of these signs is more likely to be related to hypoglycemia, and their later appearance to hypocalcemia; these abnormalities may also occur together. Perinatal asphyxia may produce similar signs. Hypomagnesemia may be associated with the hypocalcemia. These manifestations may also occur in the absence of hypoglycemia, hypocalcemia, and asphyxia.

Tachypnea develops in many infants of diabetic mothers during the 1st 2 days after birth and may be a manifestation of hypoglycemia, hypothermia, polycythemia, cardiac failure, transient tachypnea, or cerebral edema from birth trauma or asphyxia. Infants of diabetic mothers have a higher incidence of **respiratory distress syndrome** than do infants of nondiabetic mothers born at comparable gestational age; the greater incidence is possibly related to an antagonistic effect of insulin on stimulation of surfactant synthesis by cortisol.

Cardiomegaly is common (30%), and heart failure occurs in 5-10% of infants of diabetic mothers. Asymmetric septal hypertrophy may occur and may manifest as transient idiopathic hypertrophic subaortic stenosis. Inotropic agents worsen the obstruction and are contraindicated. Congenital heart disease is more common in infants of diabetic mothers. Birth trauma is also a common sequela of fetal macrosomia.

Neurologic development and ossification centers tend to be immature and to correlate with brain size (which is not increased) and gestational age rather than total body weight. In addition, these infants have an increased incidence of hyperbilirubinemia, polycythemia, and renal vein thrombosis; the last should be suspected in the infant with a flank mass, hematuria, and thrombocytopenia.

The incidence of **congenital anomalies** is increased 3-fold in infants of diabetic mothers; cardiac malformations (ventricular or atrial septal defect, transposition of the great vessels, truncus arteriosus, double-outlet right ventricle, tricuspid atresia, coarctation of the aorta) and lumbosacral agenesis are most common. Additional anomalies include neural tube defects, hydronephrosis, renal agenesis and dysplasia, duodenal or anorectal atresia, situs inversus, double ureter, and holoprosencephaly. These infants may also demonstrate abdominal distention caused by a transient delay in development of the left side of the colon, the small left colon syndrome.

TREATMENT

Prophylactic treatment of infants of diabetic mothers should be initiated before birth by means of preconception and frequent prenatal evaluations of all women with diabetes and pregnant women with gestational diabetes, evaluation of fetal maturity, biophysical profile, Doppler velocimetry, and planning of the delivery of these infants in hospitals where expert obstetric and pediatric care is continuously available. Periconception glucose control reduces the risk of anomalies and other adverse outcomes, and glucose control during labor reduces the incidence of neonatal hypoglycemia. Women with type 1 diabetes who have tight glucose control during pregnancy (average daily glucose levels <95 mg/dL) deliver infants with birthweights and anthropomorphic features similar to those of infants of nondiabetic mothers. Treatment of gestational diabetes also reduces complications; dietary advice, glucose monitoring, metformin, and insulin therapy as needed decrease the rate of serious perinatal outcomes (death, shoulder dystocia, bone fracture, or nerve palsy). Women with gestational diabetes may also be treated successfully with glyburide, which may not cross the placenta. In these mothers, the incidence of macrosomia and neonatal hypoglycemia is similar to that in mothers with insulin-treated gestational diabetes.

Regardless of size, infants of diabetic mothers should initially receive close observation and care (Fig. 107-3). Infants should initiate feedings within 1 hr after birth. A screen glucose test should be performed within 30 minutes of the first feed. Transient hypoglycemia is common during the 1st 2-3 hr after birth and may be part of normal adaptation to extrauterine life. The target plasma glucose concentration is ≥45 mg/dL before feeds. Clinicians need to assess the overall metabolic and physiologic status, considering these in the management of hypoglycemia. According to a statement from the American Academy of Pediatrics, treatment is indicated if the plasma glucose is <40 mg/dL and clinical symptoms of hypoglycemia are present. In asymptomatic infants, treatment is indicated if the plasma glucose is <30 mg/dL. Feeding is the initial treatment for hypoglycemia. Gavage feeding with breast milk or formula can be given. Recurrent hypoglycemia can be treated with repeat feedings or intravenous glucose as needed. Infants with persistent glucose levels <25 mg/dL during the 1st 4 hr after birth and <35 mg/dL during 4-24 hr after birth should be treated with intravenous glucose. A dose of 200 mg/kg of dextrose (2 mL/kg of 10% dextrose) should be administered to infants with plasma glucoses below these limits. If question arises about an infant's ability to tolerate oral feeding, a continuous peripheral intravenous infusion at a rate of 4-8 mg/kg/min should be given. Bolus injections of hypertonic glucose should be avoided because they may cause further hyperinsulinemia and potentially produce rebound hypoglycemia.

For treatment of hypocalcemia and hypomagnesemia, see Chapter 106; for respiratory distress syndrome treatment, see Chapter 101.3; for treatment of polycythemia, see Chapter 103.3.

PROGNOSIS

The subsequent incidence of diabetes mellitus in infants of diabetic mothers is higher than that in the general population. Physical development is normal, but oversized infants may be predisposed to childhood obesity that may extend into adult life. Disagreement persists

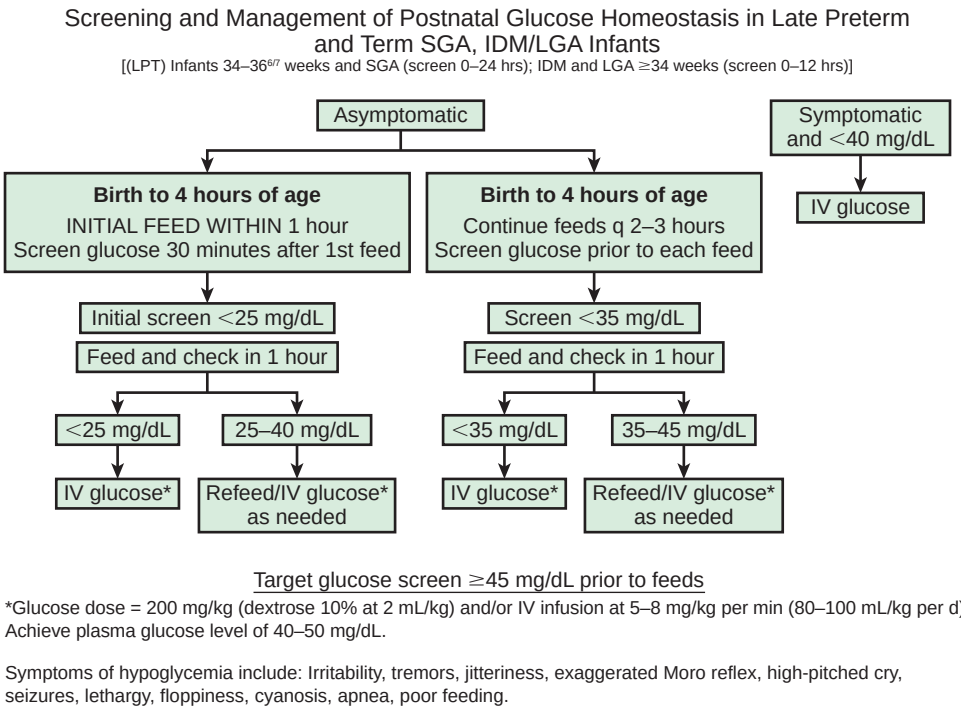

Figure 107-3 Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34-36 wk) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA, screen 0-24 hr; IDM and LGA ≥34 wk, screen 0-12 hr. IV indicates intravenous. *(American Academy of Pediatrics Committee of Fetus and Newborn: Postnatal glucose homeostasis in late-preterm and term infants.* Pediatrics *127:575-579, 2011, Fig. 1, p. 576.)*

about whether these infants have a slightly increased risk of impaired intellectual development unrelated to hypoglycemia; symptomatic hypoglycemia increases the risk, as does maternal ketonuria.

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Chapter 108

Dysmorphology

Anne Slavotinek

Dysmorphology is the study of abnormalities of human form and the mechanisms that cause them. It is estimated that 1 in 40, or 2.5% of newborns, have a recognizable malformation or malformations at birth. In about half of these newborns, a single isolated malformation is found, whereas in the other half, there are multiple malformations. It is estimated that 10% of pediatric hospital admissions involve known genetic conditions, 18% involve congenital defects of unknown etiology, and 40% of surgical admissions are of patients with congenital malformations. Between 20% and 30% of infant deaths and 30-50% of deaths after the neonatal period are a result of congenital abnormalities (http://www.marchofdimes.com/peristats/). In 2001, birth defects accounted for 1 in 5 infant deaths in the United States, with a rate of 137.6 deaths per 100,000 live births, which is higher than other causes, such as preterm/low birthweight (109.5/100,000), sudden infant death syndrome (55.5/100,000), maternal complications of pregnancy (37.3/100,000), and respiratory distress syndrome (25.3/100,000).

CLASSIFICATION OF BIRTH DEFECTS

Congenital birth defects either are isolated, single defects or manifest as multiple anomalies in a single individual. Single primary defects can be classified according to the nature of the presumed cause of the defect as a malformation, dysplasia, deformation, or disruption (Table 108-1, Fig. 108-1), although most are malformations. Malformations and dysplasias both affect intrinsic structure. A **malformation** is a primary structural defect arising from a localized error in morphogenesis and resulting in the abnormal formation of a tissue or organ (Fig. 108-1*A*). **Dysplasia** refers to an abnormal organization of cells into tissues (Fig. 108-1*D*). The distinction of a malformation from a dysplasia may be helpful, but there is much overlap. Deformations and disruptions are secondary effects that result from forces generated extrinsic to the affected tissue or organ. A **deformation** is an alteration in shape or structure of a structure or organ that has differentiated normally (Fig. 108-1*B*). A **disruption** is a structural defect resulting from the destruction of a structure that had formed normally before the insult (Fig. 108-1*C*).

More than 1,000 of the ≈1,750 inherited human disorders with altered morphogenesis display multiple malformations. When several malformations occur in a single individual, they are classified as syndromes, sequences, or associations. A **syndrome** is defined as a pattern of multiple abnormalities that are related by pathophysiology and result from a single, defined etiology. **Sequences** consist of multiple malformations that are caused by a single event that can have many etiologies. An **association** refers to a nonrandom collection of malformations in which there is an unclear or unknown relationship among the malformations such that they do not fit the criteria for a syndrome or sequence.

Malformations and/or Dysplasias

Human malformations and dysplasias are caused by the interactions of genes and environmental factors (Table 108-2; see Fig. 108-1). Some malformations are caused by single-gene defects or abnormalities of multiple genes acting in concert, and the environment causes others. In 1996, it was thought that malformations were caused by monogenic

Figure 108-1 The four major types of problems in morphogenesis: malformation, deformation, disruption, and dysplasia. **A,** An infant with camptomelic dysplasia syndrome, which results in a multiple malformation syndrome caused by a mutation in SOX9. **B,** An infant with oligohydramnios deformation sequence caused by premature rupture of membranes from 17 wk of gestation until birth at 36 wk; the infant was delivered from persistent transverse lie. **C,** A fetus with early amnion rupture sequence with attachment of the placenta to the head and resultant disruption of craniofacial structures with distal limb contractures. **D,** An infant with diastrophic dysplasia caused by inherited autosomal recessive mutations in a sulfate transporter protein. *(From Graham Jr JM:* Smith's recognizable patterns of human deformation, *ed 3, Philadelphia, 2007, Saunders, Fig. 1-1, p. 4.)*

Table 108-1 Mechanisms, Terminology, and Definitions of Dysmorphology

TERMINOLOGY	DEFINITION	EXAMPLE
Malformation sequence	Single, local tissue morphogenesis abnormality that produces a chain of subsequent defects	DiGeorge sequence of primary fourth branchial arch and 3rd and 4th pharyngeal pouch defects that lead to aplasia or hypoplasia of the thymus and parathyroid glands, aortic arch anomalies, and micrognathia
Deformation sequence	Mechanical (uterine) forces that alter structure of intrinsically normal tissue	Oligohydramnios produces deformations by in utero compression of limbs (dislocated hips, equinovarus foot deformity), crumpled ears, dislocated nose, or small thorax
Disruption sequence	In utero tissue destruction after a period of normal morphogenesis	Amnionic membrane rupture sequence, leading to amputation of fingers/toes, tissue fibrosis, and destructive tissue bands
Dysplasia sequence	Poor organization of cells into tissues or organs	Neurocutaneous melanosis sequence with poor migration of melanocyte precursor cells from the neural crest to the periphery, manifesting as melanocytic hamartosis of skin, meninges, and so forth
Malformation syndrome	Appearance of multiple malformations in unrelated tissues without an understandable unifying cause; with enhanced genetic investigation, a single etiology may become identified	Trisomy 21 Teratogens

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, 2004, Elsevier Saunders.*

defects in 7.5% of patients; by chromosomal anomalies in 6%; by multigenic defects in 20%; and by known environmental factors, such as maternal diseases, infections, and teratogens, in 6-7% (Table 108-3); in the remaining 60-70% of patients, malformations were classified as caused by unknown etiologies. A decade later, the percentages were somewhat higher for all categories of known causes of malformations, a change resulting from improved cytogenetic methods for detecting small chromosomal abnormalities as well as techniques for mapping and cloning disease genes. Since the previous edition of this book, it has been discovered that an additional 10-20% of birth defects result from even smaller chromosomal abnormalities detectable by whole genome arrays using comparative genomic hybridization (array CGH) methodology. In spite of these advances, we still do not know the causes for 40-50% of birth defects.

Many developmental abnormalities are caused by mutations in a single gene and display characteristic mendelian patterns of inheritance. The molecular etiology for more than 250 single-gene disorders is known. Affected genes are often part of evolutionarily conserved signal transduction pathways, transcription factors, or regulatory proteins required for key developmental events. Some examples are listed in Table 108-2; they include autosomal recessive spondylocostal dysostosis (SCD) syndrome, the autosomal recessive Smith-Lemli-Opitz syndrome (SLOS), the autosomal dominant Rubinstein-Taybi syndrome, and the X-linked lissencephaly ("smooth brain") syndrome. The SCD syndromes are etiologically heterogeneous and are often caused by mutations in the gene coding for delta-like 3 (*DLL3*), a ligand of the Notch receptors. The Notch/delta pathway is conserved throughout evolution and regulates a number of developmental events. Patients with SCD display a characteristic pattern of abnormal vertebral segmentation associated with a number of other malformations, such as neural tube defects. SLOS (Fig. 108-2) results from mutations in the sterol delta-7-dehydrocholesterol reductase (*DHCR7*) gene, an

Table 108-2 Examples of Malformations with Distinct Causes, Clinical Features, and Pathogenesis

DISORDER	CAUSE/INHERITANCE	CLINICAL FEATURES	PATHOGENESIS
Spondylocostal dysostosis syndromes	Mendelian autosomal recessive	Abnormal vertebral segmentation Neural tube defects	*DLL3* mutations; mutations can also be present in other genes
Rubinstein-Taybi syndrome	Mendelian autosomal recessive	Mental retardation Broad thumbs, toes Hypoplastic maxillae Prominent nose Congenital heart disease	*CBP* mutations or haploinsufficiency
X-linked lissencephaly	Mendelian X-linked	Male: Severe mental retardation Seizures Female: Variable	*DCX* mutation
Aniridia	Autosomal semidominant	Reduced or absent iris	*PAX6* mutations
Waardenburg syndrome	Autosomal semidominant	Deafness White forelock Wide-spaced eyes Pale eye pigment	*PAX3* mutations *MITF* mutations
Holoprosencephaly	Loss of function or heterozygosity	Microcephaly Cyclopia Single central incisor	*SHH* mutations
Velocardiofacial syndrome	Microdeletion 22q11.2	Conotruncal congenital heart disease Cleft palate T-cell defects Facial anomalies	*TBX1* haploinsufficiency/mutations; haploinsufficiency for other genes in the deleted interval
Down syndrome	Chromosomal	Mental retardation Characteristic dysmorphic features Congenital heart disease Increased risk of leukemia Alzheimer disease	50% increase of estimated 250 genes on chromosome 21 Trisomy 21
Neural tube defects	Multifactorial	Meningomyelocele	Defects in folate sensitive enzymes or folic acid uptake
Fetal alcohol syndrome	Teratogenic	Microcephaly Developmental delay Facial abnormalities Behavioral abnormalities	Ethanol toxicity to developing brain
Retinoic acid embryopathy	Teratogenic	Microtia Congenital heart disease	Isotretinoin effects on neural crest and branchial arch development

enzyme important in cholesterol biosynthesis. Patients with SLOS display syndactyly (fusion of the fingers and toes), polydactyly, an upturned (anteverted) nose, ptosis, cryptorchidism, and holoprosencephaly. These mutations link cholesterol biosynthesis pathogenetically to the sonic hedgehog (SHH) pathway, because many of the features of the former disorder are related to defects in SHH, which is post-translationally modified by cholesterol (see Chapter 86). Rubinstein-Taybi syndrome (see Fig. 108-2) results from heterozygous, loss-of-function mutations in the gene coding for a broadly acting transcriptional coactivator called CBP, or CREB-binding protein. The CBP coactivator regulates the transcription of a number of genes, a fact that helps explain why patients with mutations in *CBP* have a wide-ranging phenotype that includes mental retardation, broad thumbs and toes, and congenital heart disease. One of the transcription factors that binds to CBP is *GLI3*, a transcription factor that is part of the SHH pathway (see Fig. 108-2). X-linked lissencephaly—a severe neuronal migration defect that in males causes a smooth brain with reduction or absence of gyri and sulci and in females gives rise to a variable pattern of mental retardation and seizures—is caused by mutations in *DCX*. The DCX protein regulates the activity of dynein motors and moves the nucleus during neuronal migration.

Other malformation syndromes are caused by chromosomal imbalance, multifactorial inheritance, and teratogens (see Tables 108-2 and 108-3). Down syndrome results from an extra dose of part or all of chromosome 21, a small chromosome that contains ≈200 known or predicted genes. It is most commonly caused by trisomy 21, which means that individuals with Down syndrome have an increased dose of as many as 250 genes contained on this chromosome (see Chapter 81.1). Neural tube defects (NTDs) are an example of a disorder that displays multifactorial inheritance in the majority of cases. NTDs and a number of other congenital malformations, such as cleft lip and palate, recur in families, but several genes and environmental factors together contribute to the pathogenesis (see Table 108-2). Many of the genes involved in NTDs are unknown, so one cannot predict with certainty a mode of inheritance or a precise recurrence risk. Empiric risks can be provided on the basis of population studies and the presence of single or multiple relatives with the same malformation. However, an important gene/environment interaction has been identified for NTDs (see Chapter 591.1). Folic acid status is associated with NTDs and can result from a combination of dietary deficiencies and increased utilization during pregnancy as well as from a common variant in the gene for an enzyme in the folate recycling pathway,

Table 108-3 Causes of Congenital Malformations

MONOGENIC (7.5% of major anomalies)
X-linked hydrocephalus
Achondroplasia
Ectodermal dysplasia
Apert syndrome
Treacher Collins syndrome
CHROMOSOMAL (6% of major anomalies)
Trisomy 21, 18, 13
XO, XXY
Deletions 4p–, 5p–, 7q–, 13q–, 18p–, 18q–, 22q–
Prader-Willi syndrome (50% of affected patients have deletion of chromosome 15)
MATERNAL INFECTION (2% of major anomalies)
Intrauterine infections (e.g., herpes simplex virus, cytomegalovirus, varicella-zoster virus, rubella virus, and toxoplasmosis)
MATERNAL ILLNESS (3.5% of major anomalies)
Diabetes mellitus
Phenylketonuria
Hyperthermia
UTERINE ENVIRONMENT (% unknown)
Deformation
Uterine pressure, oligohydramnios: clubfoot, torticollis, congenital hip dislocation, pulmonary hypoplasia, 7th nerve palsy
Disruption
Amniotic bands, congenital amputations, gastroschisis, porencephaly, intestinal atresia
Twinning
ENVIRONMENTAL AGENTS (% unknown)
Polychlorinated biphenyls
Herbicides
Mercury
Alcohol
MEDICATIONS (% unknown)
Thalidomide
Diethylstilbestrol
Phenytoin
Warfarin
Cytotoxic drugs
Paroxetine
Angiotensin-converting enzyme inhibitors
Isotretinoin (vitamin A)
D-Penicillamine
Valproic acid
UNKNOWN ETIOLOGIES
Polygenetic
Associated with infertility (spontaneous or with treatment)
Anencephaly/spina bifida
Cleft lip/palate
Pyloric stenosis
Congenital heart disease
SPORADIC SYNDROME COMPLEXES
VATER (vertebral defects, anal atresia, tracheoesophageal fistula with esophageal atresia, and radial and renal anomalies) syndrome
Pierre Robin syndrome
Prune-belly syndrome
NUTRITIONAL
Low folic acid–neural tube defects

From Behrman RE, Kliegman RM, editors: Nelson's essentials of pediatrics, *ed 4, Philadelphia, 2002, WB Saunders.*

5,10-methylene-tetrahydrofolate reductase, that makes this enzyme less stable. These discoveries led to the recommendation that all women supplement their diets with 400-800 µg of folic acid per day 1 mo before pregnancy and during the 1st 2 mo of pregnancy. This supplementation has resulted in a reduction in the incidence of NTDs by 75%. Several teratogenic causes of birth defects have been described (see Tables 108-2 and 108-3). Ethanol causes a recognizable malformation syndrome called fetal alcohol syndrome (see Chapter 106.2). Children with fetal alcohol syndrome display microcephaly, developmental delay, hyperactivity, and facial dysmorphic features. Ethanol, which is toxic to the developing central nervous system, causes cell death in developing neurons.

Deformations

Most deformations involve the musculoskeletal system (see Figs. 108-1*B* and 108-3). Fetal movement is required for the proper development of the normal musculoskeletal system, and anything that restricts fetal movement can cause a musculoskeletal deformation from intrauterine molding. It is important to recognize that deformations can be caused by problems either intrinsic or extrinsic to the developing fetus. Two major intrinsic causes of deformations are primary neuromuscular disorders and oligohydramnios, or decreased amniotic fluid, which is caused by renal defects. The major extrinsic causes of deformation are those that result in fetal crowding to restrict fetal movement. Examples of such extrinsic causes are oligohydramnios from chronic leakage of amniotic fluid, breech presentation (see Figs. 108-1*B* and 108-4), and abnormal shape of the amniotic cavity. When a fetus is in the breech position, the incidence of deformations is increased 10-fold. The shape of the amniotic cavity has a profound effect on the shape of the fetus and is influenced by many factors, including uterine shape; volume of amniotic fluid; size and shape of the fetus; presence of more than 1 fetus; site of placental implantation; presence of uterine tumors; shape of the abdominal cavity, which is influenced by the pelvis, sacral promontory, and neighboring abdominal organs; and tightness of the abdominal musculature.

It is important to determine whether deformations result from intrinsic or extrinsic causes. Most children with deformations from extrinsic causes are otherwise completely normal, and their prognosis is usually excellent. Correction usually occurs spontaneously. Deformations caused by intrinsic factors, such as multiple joint contractures resulting from central nervous system defects, would have a different prognosis and a far greater significance for the child.

Disruption

Disruption defects are caused by destruction of a previously normally formed part. At least 2 basic mechanisms are known to produce disruption. One involves entanglement followed by tearing apart or amputation of a normally developed structure, usually a digit, arm, or leg, by strands of amnion floating within amniotic fluid **(amniotic bands)** (see Figs. 108-1*C* and 108-5). The second involves interruption of the blood supply to a developing part, which can lead to infarction, necrosis, and/or resorption of structures distal to the insult. If interruption of the blood supply occurs early in gestation, the disruptive defect seen at term usually involves **atresia,** or absence of a particular part. If the infarction occurs later, necrosis is more likely to be present. Genetic factors usually play a minor role in the pathogenesis of disruptions; most are sporadic events in otherwise normal families. The prognosis for a disruptive defect is determined entirely by the extent and location of the tissue loss.

Multiple Anomalies: Syndrome and Sequence

The pattern of multiple anomalies that occurs when a single primary defect in early morphogenesis produces multiple abnormalities through a cascading process of secondary and tertiary errors in morphogenesis is called a **sequence** (see Figs. 108-6 and 108-7). When evaluating a child with multiple anomalies, the physician must differentiate multiple anomalies secondary to a single localized error in morphogenesis (a sequence) from a multiple malformation syndrome. In the former, recurrence risk counseling for the multiple anomalies depends entirely on the risk of recurrence for the single localized malformation. The Pierre-Robin malformation sequence is a pattern of multiple anomalies produced by mandibular hypoplasia. Because the tongue is relatively large for the oral cavity, it drops back (glossoptosis), blocks closure of the posterior palatal shelves, and causes a

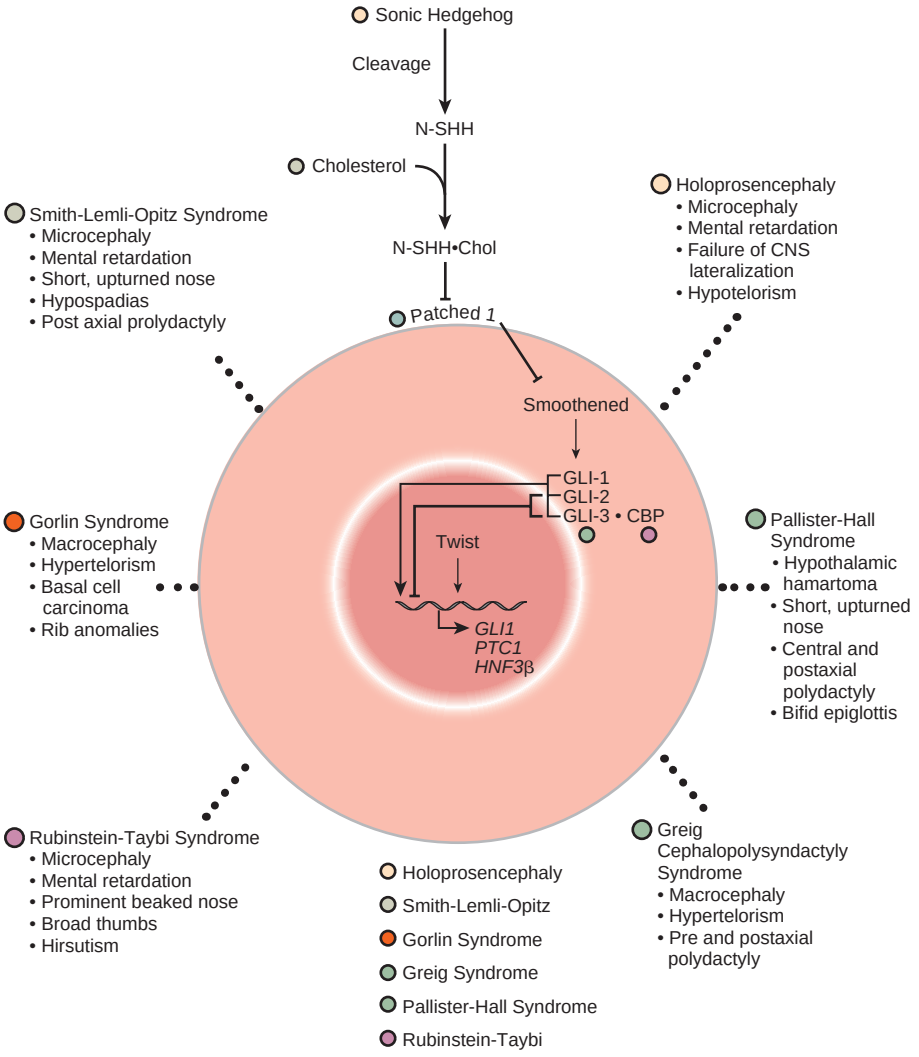

Figure 108-2 Mutations in genes that function together in a genetic developmental pathway commonly have overlapping clinical manifestations. Several components of the sonic hedgehog (SHH) pathway have been identified, and their relationships elucidated (see text for further details). Mutations in several members of this pathway result in phenotypes that have facial dysmorphisms, seen in holoprosencephaly, SLOS, Gorlin syndrome, Greig cephalopolysyndactyly syndrome, Pallister-Hall syndrome, and Rubinstein-Taybi syndrome.

U-shaped cleft palate. There are numerous causes of mandibular hypoplasia, all of which can result in characteristic features of Pierre-Robin sequence.

MOLECULAR MECHANISMS OF MALFORMATIONS

Inborn Errors of Development

The genes mutated in malformation syndromes (as well as genes whose expression is disrupted by environmental agents or teratogens) are part of evolutionarily conserved signal transduction pathways, transcription factors, or regulatory proteins required for key developmental events. We should consider malformations to be inborn errors of development. Consideration of malformations as alterations of important developmental pathways provides a molecular framework for understanding human birth defects.

Sonic Hedgehog Pathway as Model

The SHH pathway is developmentally important during embryogenesis to induce controlled proliferation in a tissue-specific manner; disruption of specific steps in this pathway results in a variety of related developmental disorders and malformations (see Fig. 108-2). Activation of this pathway in the adult leads to abnormal proliferation and cancer. The SHH pathway transduces an external signal in the form of a ligand into changes in gene transcription by binding of the ligand to specific cellular receptors. SHH is a ligand expressed in the embryo in a variety of areas important for development of the brain, face, limbs, and the gut. Sporadic and inherited mutations are found to cause **holoprosencephaly** (see Figs. 108-2 and 108-6), a variably severe midline defect with phenotypes ranging from a single maxillary incisor with hypotelorism to cyclopia. SHH is processed by proteolytic cleavage to an active N-terminal form, which is then further modified by the addition of cholesterol. Defects in cholesterol biosynthesis, in particular the sterol delta-7-dehydrocholesterol reductase gene, result in **SLOS** (see Fig. 108-2). SLOS is also associated with holoprosencephaly. The modified and active form of SHH binds to its transmembrane receptor Patched (PTCH); there are 2 family members: PTCH1 and PTCH2. SHH binding to PTCH inhibits the activity of the transmembrane protein Smoothened (SMOH). SMOH act to suppress downstream targets of the SHH pathway, the GLI family of transcription factors, so inhibition of SMOH by PTCH results in activation of GLI1, GLI2, and GLI3, resulting in alteration of transcription of GLI targets. Somatic inactivating mutations in *PTCH1* and *PTCH2* act as tumor suppressors, whereas activating mutations in SMOH function as oncogenes, particularly in basal cell carcinomas and medulloblastomas. Germline inactivating mutations in *PTCH1* result in **Gorlin syndrome** (see Fig. 108-2), an autosomal dominant disorder characterized by dysmorphic features (short metacarpals, rib defects, broad face, and dental abnormalities), basal cell nevi that undergo malignant transformation, and an increased risk of cancers such as rhabdomyosarcoma and medulloblastoma. *GLI1* amplification has been found in several human tumors, including glioblastoma, osteosarcoma, rhabdomyosarcoma, and B-cell lymphomas; mutations or alterations in *GLI3* have been found in Greig cephalopolysyndactyly syndrome (GCPS), **Pallister-Hall syndrome** (PHS), and postaxial polydactyly type A (and

A/B) and preaxial polydactyly type IV (see Fig. 108-2). GCPS consists of hypertelorism, syndactyly, preaxial polydactyly, and broad thumbs and great toes. PHS is an autosomal dominant disorder characterized by postaxial polydactyly, syndactyly, hypothalamic hamartomas, imperforate anus, and, occasionally, holoprosencephaly. GLI3 binds to CBP, the protein that is haploinsufficient in the **Rubinstein-Taybi syndrome**. Disorders that are caused by mutations in genes that function together in a genetic developmental pathway commonly have overlapping clinical manifestations. These overlapping manifestations result from the expression domains of SHH important for development of the brain, face, limbs, and gut in the embryo. Brain defects are found in holoprosencephaly, SLOS, and PHS. Facial abnormalities are found in holoprosencephaly, Gorlin syndrome, GCPS, and PHS. Limb defects are found in SLOS, Gorlin syndrome, GCPS, PHS, and the polydactyly syndromes. Overexpression or activating mutations of the SHH pathway results in cancer, including basal cell carcinoma, medulloblastoma, glioblastoma, and rhabdomyosarcoma.

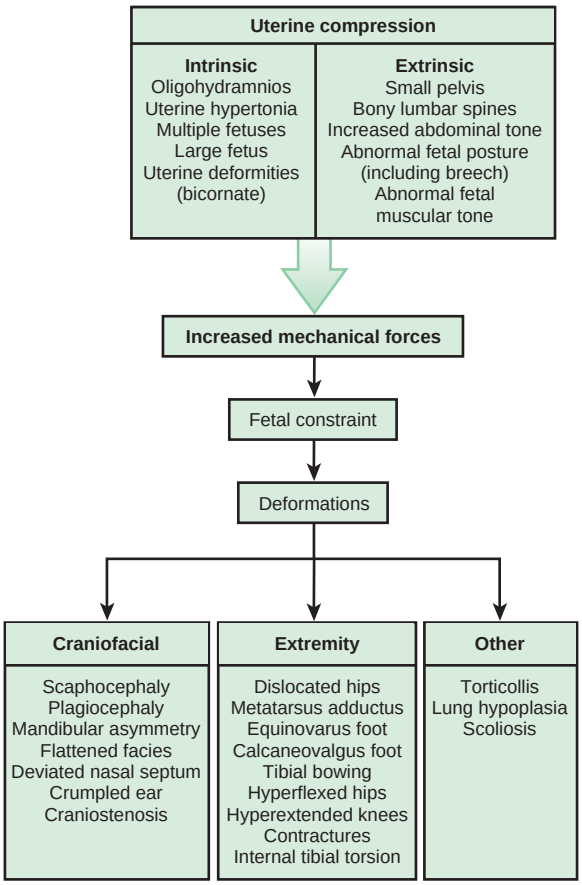

Figure 108-3 Deformation abnormalities resulting from uterine compression. *(From Kliegman RM, Jenson HB, Marcdante KJ, et al, editors:* Nelson essentials of pediatrics, *ed 5, Philadelphia, 2005, Saunders.)*

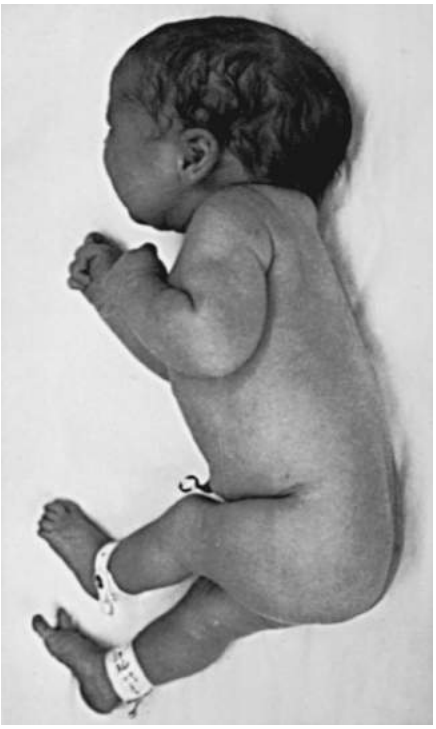

Figure 108-4 Breech deformation sequence.

Figure 108-5 **A,** Amniotic band disruption sequence. **B,** Bands constricting the ankle leading to deformational defects and amputations. *(From Jones KJ:* Smith's recognizable patterns of human malformation, *ed 6, Philadelphia, 2006, Saunders.)*

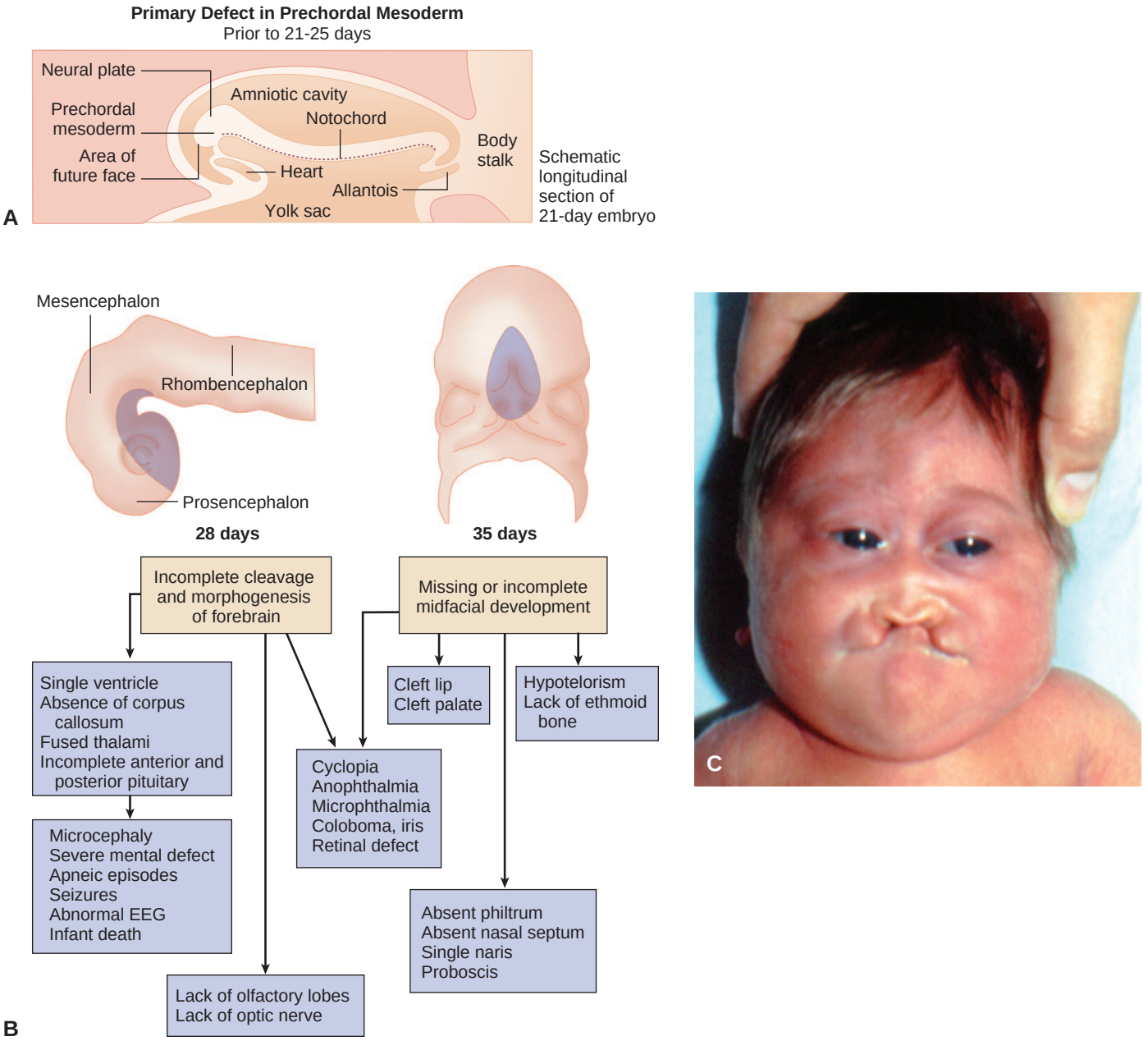

Figure 108-6 Holoprosencephaly sequence. **A,** Schematic longitudinal section of 21-day embryo. **B,** Developmental pathogenesis of the sequence. *C,* Affected individual. *(From Jones KL, Jones MC, Del Campo M, editors:* Smith's recognizable patterns of human malformation, *ed 7, Philadelphia, 2013 Elsevier, Fig. 1, pp. 802-803.)*

The SHH pathway has been shown to interact with the primary cilium, and this interaction is critical to transduce the SHH extracellular signal through to the nuclear machinery. In fact, a host of disorders, including Bardet-Biedl syndrome, oral facial digital syndrome type 1, and Joubert syndrome, are known to be caused by mutations in genes that function in the primary cilium (Table 108-4). These disorders overlap phenotypically with a number of the phenotypes described previously, again demonstrating that perturbations of conserved developmental pathways cause overlapping phenotypes.

Chromosomal Imbalances

It has been recognized for more than 50 yr that genomic imbalances that result from an additional copy of 1 whole human chromosome can result in a characteristic and recognizable syndrome. As previously discussed, an additional copy of chromosome 21 results in Down syndrome (see Chapter 81); loss of 1 of the X chromosomes results in Turner syndrome (see Chapter 81 for discussion of syndromes with whole chromosomal imbalances). With the advent of higher-resolution cytogenetics techniques and standardization of chromosome identification using chromosomal preparations, it became possible to identify subchromosomal deletions and duplications. A number of recurrent deletions and duplications were identified that resulted in characteristic and recognizable syndrome (see Chapter 81, Table 81-12), such as Williams syndrome (deletion of 7q11.23), Miller-Dieker syndrome (deletion of 17p13.3), Smith-Magenis syndrome (deletion of 17p11.2), and velocardiofacial/DiGeorge syndrome (deletion of 22q11.2). Array CGH (or single-nucleotide polymorphism–based genotyping with dosage detection) has made it possible to uncover smaller microdeletions and microduplications associated with various birth defects, mental retardation, and neuropsychiatric disorders. The sensitivity and

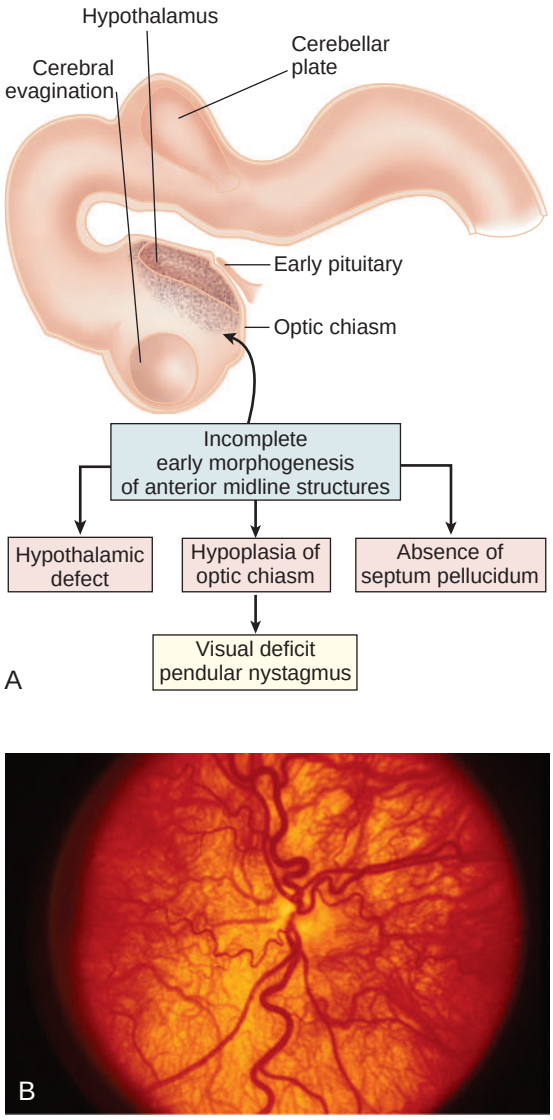

Figure 108-7 Septooptic dysplasia sequence. **A,** Presumed localization of early single defect (stippled area) as shown in sagittal view of 38 day brain. **B,** Photo of retina of 4 yr old patient with the septooptic dysplasia sequence who had reduced vision, pendular nystagmus, and growth deficiency secondary to pituitary growth hormone deficiency. Note the hypoplastic optic nerve heads and aberrant vascular arrangement. *(From Jones KL, Jones MC, Del Campo M, editors:* Smith's recognizable patterns of human malformation, *ed 7, Philadelphia, 2013, Elsevier, Fig. 1, p. 809.)*

specificity of array CGH has made it the technique of choice for the initial evaluation of a child with multiple congenital anomalies and/or mental retardation, although it is important to note that all individuals carry dozens of small microdeletions and microduplications as normal variants. Therefore, it is important to examine any of these findings in children with birth defects with parents and with databases of normal variants detected in individuals without such birth defects. Array CGH is the preferred method for detecting possible genomic abnormalities associated with multiple congenital anomalies and/or mental retardation.

APPROACH TO THE DYSMORPHIC CHILD

One approach to the dysmorphic child is the pattern-recognition approach, which compares the manifestations in the patient against an enormous and memorized (or computerized) knowledge of human pleiotropic disorders. Although this approach can be appropriate for a small number of experienced dysmorphologists, the systematic genetic-mechanism approach can be used by clinicians who are not experts in dysmorphology. By gathering and analyzing these clinical data, the general pediatrician can either diagnose the patient in the straightforward case or initiate a referral process to an appropriate expert.

History

The history for a child with birth defects includes a number of elements that are related to etiologic factors. The first is the pedigree or family history that is necessary to assess the **inheritance pattern,** or lack thereof, of the disorder. For disorders that have simple mendelian inheritance patterns, the recognition of that pattern can be critical to help narrow the differential diagnosis. A number of common birth defects have complex genetic contributions, such as isolated cleft palate and spina bifida. The recognition of a close relative (or the fetus of a close relative) affected with a birth defect that is similar to that of the proband can be quite useful. A 3-generation pedigree is sufficient for this purpose (see Chapter 80).

The perinatal history is an essential component of the history (see Chapter 94.1). It includes the pregnancy history of the mother (useful for recognition of recurrent miscarriages that may be a sign of a familial chromosomal disorder), factors that may relate to deformations or disruptions (oligohydramnios), and maternal exposures to teratogenic drugs or chemicals (methyl mercury, isotretinoin, and ethanol are potential causes of microcephaly). Although recognition of known teratogens is an important part of the history, it is important to know that many more agents are impugned as teratogenic than are confirmed as such. Physicians are encouraged to consult experts in teratology and expert information sources such as Teris (http://depts.washington.edu/~terisweb/teris) to analyze specific potential teratogens.

One final component to the history that is often useful is the natural history of the phenotype. Malformation syndromes caused by chromosomal aneuploidy or aneusomy and single-gene pleiotropic disorders are usually static. Although the patients can experience new complications over time, the phenotype is not progressive. In contrast, disorders that cause dysmorphic features by the mechanism of metabolic perturbations (e.g., Hunter syndrome, Sanfilippo syndrome) are either mild or not apparent at birth and progress relentlessly, causing deterioration of the patient over time.

Physical Examination

The physical examination is essential to the diagnosis of a dysmorphic syndrome. The essential element of the evaluation is objective assessment of the structure of the child. The clinician needs to perform an organized and systematic cataloguing of the size and structure of various body structures. Familiarity with the nomenclature of dysmorphic signs is helpful (Table 108-5). The size and shape of the head is relevant, as many children with Down syndrome have mild microcephaly and brachycephaly (shortened anteroposterior dimension of the skull). Eye position and shape are useful signs for many disorders. There are a number of reference standards with which pediatric physical measurements (e.g., interpupillary distance) can be compared. It is also useful to categorize abnormalities as "major" or "minor" birth defects. The former are those that either cause dysfunction (absence of a digit) or require surgical correction (polydactyly), and the latter those that cause neither significant dysfunction nor require surgical correction (mild cutaneous syndactyly) (Table 108-6 and Fig. 108-8). By cataloging every available physical parameter, the clinician can recognize the diagnosis or at least have enough information for intelligent discussion of the patient with a consultant.

Imaging Studies

Imaging studies can be critical in the diagnosis of a dysmorphic disorder. If short stature or disproportionate stature (long trunk and short limbs) is noted, a full skeletal survey should be performed. The skeletal survey can yield numerous abnormal features that can be used to narrow the differential diagnosis. When there are abnormal neurologic signs or symptoms, central nervous system imaging is indicated. Some

Table 108-4 Childhood Diseases and Syndromes Associated with Motile and Sensory Ciliopathies

PEDIATRIC CILIOPATHY	CLINICAL MANIFESTATIONS	GENE(S)
MOTOR		
Primary ciliary dyskinesia	Chronic bronchitis, rhinosinusitis, otitis media, laterality defects, infertility, CHD	*DNAI1, DNAH5, DNAH11, DNAI2, KTU, TXNDC3, LRRC50, RSPH9, RSPH4A, CCDC40, CCDC39*
SENSORY		
Autosomal recessive polycystic kidney disease	RFD, CHF	*PKHD1*
Nephronophthisis	RFD, interstitial nephritis, CHF, RP	*NPHP1-8, ALMS1, CEP290*
Bardet-Biedl syndrome	Obesity, polydactyly, ID, RP, renal anomalies, anosmia, CHD	*BBS1-12, MKS1, MKS3, CEP290*
Meckel-Gruber syndrome	RFD, polydactyly, ID, CNS anomalies, CHD, cleft lip, cleft palate	*MKS1-6, CC2D2A, CEP290, TMEM216*
Joubert syndrome	CNS anomalies, ID, ataxia, RP, polydactyly, cleft lip, cleft palate	*NPHP1, JBTS1, JBTS3, JBTS4, CORS2, AHI1, CEP290, TMEM216*
Alstrom syndrome	Obesity, RP, DM, hypothyroidism, hypogonadism, skeletal dysplasia, cardiomyopathy, pulmonary fibrosis	*ALMS1*
Orofaciodigital syndrome type 1	Polydactyly, syndactyly, cleft lip, cleft palate, CNS anomalies, ID, RFD	*OFD1*
Ellis van Creveld syndrome	Chondrodystrophy, polydactyly, ectodermal dysplasia, CHD	*EVC, EVC2*
Jeune asphyxiating thoracic dystrophy	Narrow thorax, RFD, RP, dwarfism, polydactyly	*IFT80*
Sensenbrenner syndrome	Dolichocephaly, ectodermal dysplasia, dental dysplasia, narrow thorax, RFD, CHD	*IFT122, IFT43, WDR35*
Short rib-polydactyly syndromes	Narrow thorax, short limb dwarfism, polydactyly, renal dysplasia	*WDR35, DYNC2H1, NEK1*

CHD, congenital heart disease; CHF, congenital hepatic fibrosis; CNS, central nervous system; DM, diabetes mellitus; ID, intellectual disabilities; RFD, renal fibrocystic disease; RP, retinitis pigmentosa.

From Ferkol TW, Leigh MW: Ciliopathies: the central role of cilia in a spectrum of pediatric disorders. J Pediatr *160:366-371, 2012.*

Table 108-5 Definitions of Common Clinical Signs of Dysmorphic Syndromes

SIGN	DEFINITION
Brachycephaly	A condition in which head shape is shortened from front to back along the sagittal plane; the back of the skull and face are flatter than normal
Brachydactyly	A condition of having short digits
Brushfield spots	Speckled white rings about ⅔ of the distance to the periphery of the iris of the eye
Camptodactyly	Permanent flexion of one or more fingers associated with missing inner phalangeal creases indicating lack of finger movement from before 8 wk of gestation
Clinodactyly	A medial or lateral curving of the fingers; usually refers to incurving of the 5th finger
Hypoplastic nail	An unusually small nail on a digit
Low-set ears	This designation is made when the helix meets the cranium at a level below a horizontal plane that is an extension of a line through both inner canthi
Melia	A suffix meaning "limb" (e.g., amelia—missing limb; brachymelia—short limb)
Ocular hypertelorism	Increased distance between the pupils of the 2 eyes, also known as increased interpupillary distance)
Plagiocephaly	A condition in which head shape is asymmetric in the sagittal or coronal plane that can result from asymmetry in suture closure or from asymmetry of brain growth
Posterior parietal hair whorl	A single whorl occurs to the right or left of midline and within 2 cm anterior to the posterior fontanel in 95% of cases. The whorl represents the focal point from which the posterior scalp skin was under growth tension during brain growth between the 10th and 16th wk of fetal development. Aberrant position of the whorl reflects an early defect in brain development
Postaxial polydactyly	Extra finger or toe present on the lateral side of the hand or foot
Preaxial polydactyly	Extra finger or toe present on the medial side of the hand or foot
Prominent lateral palatine ridges	Relative overgrowth of the lateral palatine ridges secondary to a deficit of tongue thrust into the hard palate
Scaphocephaly	A condition in which the head is elongated from front to back in the sagittal plane; most normal skulls are scaphocephalic, Also termed dolichocephaly.
Shawl scrotum	The scrotal skin joins around the superior aspect of the penis and represents a mild deficit in full migration of the labial-scrotal folds
Short palpebral fissures	Decreased horizontal distance of the eyelid folds based on measurement from the inner to the outer canthus
Syndactyly	Incomplete separation of the fingers. It most commonly occurs between the 3rd and 4th fingers and between the 2nd and 3rd toes
Synophrys	Eyebrows that meet in the midline
Telecanthus	Lateral displacement of the inner canthi. The inner canthal distance (ICD) is increased, but the interpupillary distance (IPD) is normal.
Widow's peak	V-shaped midline, downward projection of the scalp hair in the frontal region. It represents an upper forehead intersection of the bilateral fields of periocular hair growth suppression. It usually occurs because the fields are widely spaced, as in ocular hypertelorism

Table 108-6 Minor Anomalies and Phenotype Variants*

CRANIOFACIAL
Large fontanel
Flat or low nasal bridge
Saddle nose, upturned nose
Mild micrognathia
Cutis aplasia of scalp
EYE
Inner epicanthal folds
Telecanthus
Slanting of palpebral fissures
Hypertelorism
Brushfield spots
EAR
Lack of helical fold
Posteriorly rotated pinna
Preauricular with or without auricular skin tags
Small pinna
Auricular (preauricular) pit or sinus
Folding of helix
Darwinian tubercle
Crushed (crumpled) ear
Asymmetric ear sizes
Low-set ears
SKIN
Dimpling over bones
Capillary hemangioma (face, posterior neck)
Dermal melanosis (African Americans, Asians)
Sacral dimple
Pigmented nevi
Redundant skin
Cutis marmorata
HAND
Simian creases
Bridged upper palmar creases
Clinodactyly of 5th digit
Hyperextensibility of thumbs
Single flexion crease of 5th digit (hypoplasia of middle phalanx)
Partial cutaneous syndactyly
Polydactyly
Short, broad thumb
Narrow, hyperconvex nails
Hypoplastic nails
Camptodactyly
Shortened 4th digit
FOOT
Partial syndactyly of 2nd and 3rd toes
Asymmetric toe length
Clinodactyly of 2nd toe
Overlapping toes
Nail hypoplasia
Wide gap between hallux and 2nd toe (wide sandal gap)
Deep plantar crease between hallux and 2nd toe
OTHERS
Mild calcaneovalgus
Hydrocele
Shawl scrotum
Hypospadias
Hypoplasia of labia majora

*Approximately 15% of newborns have 1 minor anomaly, 0.8% have 2 minor anomalies, and 0.5% have 3 minor anomalies. If 2 minor anomalies are present, the probability of an underlying syndrome or a major anomaly (congenital heart disease, renal, central nervous system, limbic) is 5-fold that in the general population. If 3 minor anomalies are present, the probability that there is a major anomaly is 20-30%.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, *ed 2, Philadelphia, Elsevier Saunders, 2004.*

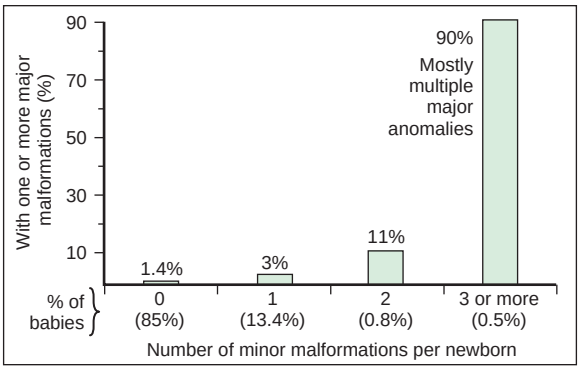

Figure 108-8 Frequency of major malformations in relation to the number of minor anomalies detected in a given newborn baby. *(From Marden PM, Smith DW, McDonald MJ: Congenital anomalies in the newborn infant, including minor variations: a study of 4,412 babies by surface examination for anomalies and buccal smear for sex chromatin.* J Pediatr *64:357, 1964.)*

Table 108-7 Clinical Indications for Chromosome Analysis, or Array CGH*

At least 1 major and 2 minor malformations
At least 2 major malformations
Developmental *or* growth retardation with 2 or more major or minor anomalies

**Note:* These are guidelines, and prudence dictates the use of the chromosome analysis in cases that may not meet these general guidelines. The guidelines are for situations in which such an analysis is strongly recommended.

children with microcephaly will be recognized to have abnormal cortical migration (lissencephaly), a discovery that markedly narrows the differential diagnosis for microcephaly. Other studies, such as echocardiography and renal ultrasonography, can be useful to identify additional major or minor malformations.

Laboratory Studies

The laboratory evaluation of the dysmorphic child is helpful but complex. Cytogenetics with a Giemsa-banded (G-banded) peripheral leukocyte karyotype (or chromosome) analysis was the gold standard and was previously performed in most evaluations of the dysmorphic child (Table 108-7). Array CGH and single-nucleotide polymorphism genotyping **with copy number variation** (dosage detection) are the most sensitive methods for the detection of cytogenomic alterations associated with multiple congenital anomalies. A practical reason for ordering cytogenetic studies early in the diagnostic process is that it typically takes 7-12 days for results.

Molecular testing for mutations that cause pleiotropic developmental anomaly syndromes is available for many disorders. In most cases, however, such testing should not be performed as a screening test, but instead should be ordered thoughtfully after the differential diagnosis has been narrowed. High-throughput genomic DNA sequencing (exome sequencing or whole genome sequencing) are increasingly used as a diagnostic tool.

Historically, dysmorphic and metabolic disorders were considered distinct classes of disease. However, as in the case of the SLOS, metabolic abnormalities of the fetus can cause malformations. A general metabolic screen should be performed unless the differential diagnosis leads the clinician to strongly suspect a non-metabolic disease.

Diagnosis

The examining physician should gather data on the patient's pedigree and perinatal and pediatric (for older children) history and should

have an appreciation for the natural history of the disorder. At this point, the physician has examined the child, identified abnormal physical features, and obtained appropriate imaging studies and preliminary interpretations.

The clinician should now organize the findings by their specificity into potential developmental pathophysiologic processes. The specificity assessment is the simplest. If a child has a patent ductus arteriosus, mild growth retardation, mild microcephaly, and holoprosencephaly (MRI finding of failure to lateralize the forebrain), micropenis, and ptosis, these findings can be prioritized. The patent ductus arteriosus, ptosis, mild growth retardation, and mild microcephaly are nonspecific findings (present in many disorders or often present as isolated features not part of a syndrome), whereas holoprosencephaly and micropenis are present in fewer syndromes and are never normal variants. With this recognition, the clinician can search for disorders that include both holoprosencephaly and micropenis. The search can be performed manually using the features index of a textbook such as *Smith's Recognizable Patterns of Human Malformation* or a computerized database such as the Winter-Baraitser Dysmorphology Database (www.lmdatabases.com/about_lmd.html). Searching for disorders with both findings leads quickly to a modest list of only 21 disorders. One of these is SLOS. The identification of this possible diagnosis prompts the physician to return to the bedside, realize that many of the nonspecific features in the child are common in SLOS, and make a tentative diagnosis of this disorder. Although holoprosencephaly is an uncommon manifestation of SLOS, this manifestation makes sense because of the known pathogenetic link between sonic hedgehog and cholesterol biosynthesis. Because this disorder is caused by mutations in the sterol delta-7-dehydrocholesterol reductase gene and is associated with elevated 7-dehydrocholesterol, the pediatrician can initiate a consultation with the clinical geneticist for suspected SLOS. The consultant can then confirm the diagnosis and begin the process of identifying a laboratory to verify the diagnosis.

Management and Counseling

Management of the affected patient and genetic counseling are essential aspects of the approach to the dysmorphic patient. Children with Down syndrome have a high incidence of hypothyroidism, and children with achondroplasia have a high incidence of cervicomedullary junction constriction. Herein lies one of the many benefits of early and accurate diagnosis, because anticipatory guidance and medical monitoring of patients for syndrome-specific medical risks can prolong and improve their quality of life. When a diagnosis is made, the treating physicians can refer to published information on the natural history and management of particular syndromes through articles, genetics reference texts, online databases and, for more common disorders, general pediatric texts.

The second major benefit of an accurate diagnosis is that it provides data for appropriate recurrence risk estimates. Genetic disorders may have direct effects on only one member of the family, but the diagnosis of the condition has implications for the entire family. One or both parents may be carriers; siblings may be carriers or may wish to know their at-risk status when they reach their reproductive years. Recurrence risk provision is 1 facet of genetic counseling, which should be a component of all evaluations for families affected with birth defects or other heritable disorders (see Chapter 77).

As we understand the underlying pathophysiology of genetic disorders, particularly with respect to the developmental pathways that are disrupted by mutant genes, it will likely be possible to identify potential therapeutic targets amenable to pharmacologic intervention. Once such potential therapies are devised, the precise delineation of the syndrome responsible for the multiple congenital anomalies displayed by an individual will lead to institution of the appropriate intervention for modulating symptoms or even to ameliorate aspects of the phenotype.

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Chapter 109

Infections of the Neonatal Infant

Barbara J. Stoll and Andi L. Shane

109.1 Pathogenesis and Epidemiology

Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. As many as 2% of fetuses are infected in utero, and up to 10% of infants have infections in the 1st mo of life. Neonatal infections are unique in several ways:

1. Infectious agents can be transmitted from the mother to the fetus or newborn infant by diverse modes.
2. The fetus and newborn infant are less capable of responding to infection because of immunologic immaturity. Preterm infants are at particular risk.
3. Coexisting conditions often complicate the diagnosis and management of neonatal infections.
4. The clinical manifestations of newborn infections vary and include subclinical infection, mild to severe manifestations of focal or systemic infection, and, rarely, congenital syndromes resulting from in utero infection. The timing of exposure, inoculum size, immune status, and virulence of the etiologic agent influence the expression of disease.
5. Maternal infection, the source of transplacental fetal infection, is often undiagnosed during pregnancy because the mother was either asymptomatic or had nonspecific signs and symptoms at the time of acute infection.
6. A wide variety of etiologic agents infect the newborn, including bacteria, viruses, fungi, protozoa, and mycoplasmas.

Although survival has increased for immature, very-low birthweight (VLBW) newborns, they remain in the hospital for a long time in an environment that puts them at continuous risk for acquired infections.

Bibliography is available at Expert Consult.

109.2 Modes of Transmission and Pathogenesis

PATHOGENESIS OF INTRAUTERINE INFECTION

Intrauterine infection is a result of clinical or subclinical maternal infection with a variety of agents (cytomegalovirus [CMV], *Treponema pallidum, Toxoplasma gondii,* rubella virus, varicella virus, parvovirus B19) and hematogenous transplacental transmission to the fetus. Transplacental infection may occur at any time during gestation, and signs and symptoms may be present at birth or may be delayed for months or years (Fig. 109-1). Infection may result in early spontaneous abortion, congenital malformation, intrauterine growth restriction, premature birth, stillbirth, acute or delayed disease in the neonatal period, or asymptomatic persistent infection with sequelae later in life. In some cases, no apparent effects are seen in the newborn infant.

The timing of infection during gestation affects the outcome. First-trimester infection may alter embryogenesis, with resulting congenital malformations (congenital rubella) (see Chapter 247). Third-trimester infection often results in active infection at the time of delivery (toxoplasmosis, syphilis) (see Chapters 290 and 218). Infections that occur late in gestation may lead to a delay in clinical manifestations until after birth (syphilis).

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Maternal infection is a necessary prerequisite for transplacental infection. For some etiologic agents (rubella), maternal immunity is effective and antibody is protective for the fetus. For other agents (CMV), maternal antibody may ameliorate the outcome of infection or may have no effect (see Chapter 255). Even without maternal antibody, transplacental transmission of infection to a fetus is variable because the placenta may function as an effective barrier.

PATHOGENESIS OF ASCENDING BACTERIAL INFECTION

In most cases, the fetus or neonate is not exposed to potentially pathogenic bacteria until the membranes rupture and the infant passes through the birth canal and/or enters the extrauterine environment. The human birth canal is colonized with aerobic and anaerobic organisms that may result in ascending amniotic infection and/or colonization of the neonate at birth. Vertical transmission of bacterial agents that infect the amniotic fluid and/or vaginal canal may occur in utero or, more commonly, during labor and/or delivery (Fig. 109-2). **Chorioamnionitis** results from microbial invasion of amniotic fluid, often as a result of prolonged rupture of the chorioamniotic membrane. Amniotic infection may also occur with apparently intact membranes or with a relatively brief duration of membrane rupture. The term *chorioamnionitis* refers to the clinical syndrome of intrauterine infection, which includes maternal fever, with or without local or systemic signs of chorioamnionitis (uterine tenderness, foul-smelling vaginal discharge/amniotic fluid, maternal leukocytosis, maternal and/or fetal tachycardia). Chorioamnionitis may also be asymptomatic, diagnosed only by amniotic fluid analysis or pathologic examination of the placenta. The rate of histologic chorioamnionitis is inversely related to gestational age at birth (Fig. 109-3) and directly related to duration of membrane rupture. Rupture of membranes for longer than 24 hr was once considered prolonged because microscopic evidence of inflammation of the membranes is uniformly present when the duration of rupture exceeds 24 hr. At 18 hr of membrane rupture, however, the incidence of early-onset disease with group B streptococcus (GBS) increases significantly; 18 hr is the appropriate cutoff for increased risk of neonatal infection.

Bacterial colonization does not always result in disease. Factors influencing which colonized infant will experience disease are not well understood but include prematurity, underlying illness, invasive procedures, inoculum size, virulence of the infecting organism, genetic predisposition, the innate immune system, host response, and transplacental maternal antibodies (Fig. 109-4). Aspiration or ingestion of bacteria in amniotic fluid may lead to congenital pneumonia or systemic infection, with manifestations becoming apparent before delivery (fetal distress, tachycardia), at delivery (failure to breathe, respiratory distress, shock), or after a latent period of a few hours (respiratory distress, shock). Aspiration or ingestion of bacteria during the birth process may lead to infection after an interval of 1-2 days.

Resuscitation at birth, particularly if it involves endotracheal intubation, insertion of an umbilical vessel catheter, or both, is associated with an increased risk of bacterial infection. Explanations include the presence of infection at the time of birth or acquisition of infection during the invasive procedures associated with resuscitation.

PATHOGENESIS OF LATE-ONSET POSTNATAL INFECTIONS

After birth, neonates are exposed to infectious agents in the nursery or in the community (including family). Postnatal infections may be

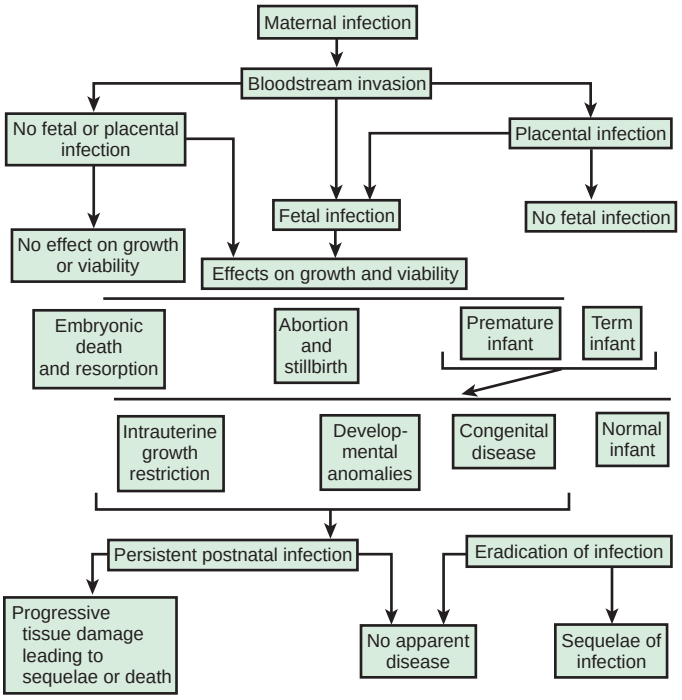

Figure 109-1 Pathogenesis of hematogenous transplacental infections. *(From Klein JO, Remington JS: Current concepts of infections of the fetus and newborn infant. In Remington JS, Klein JO, editors:* Infectious diseases of the fetus and newborn infant, *ed 5, Philadelphia, 2002, WB Saunders.)*

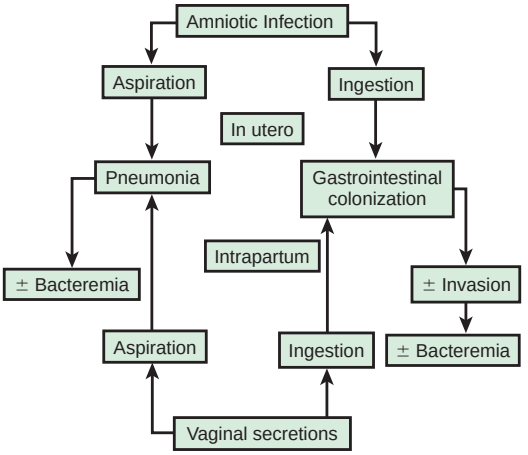

Figure 109-2 Pathways of ascending or intrapartum infection.

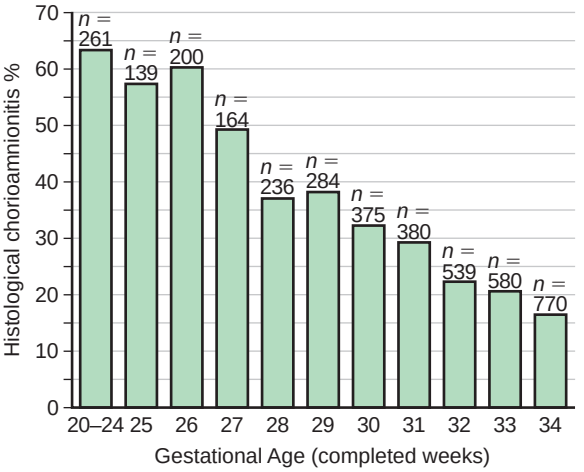

Figure 109-3 Histologic chorioamnionitis in liveborn preterm babies by gestational age (n = 3,928 babies). *(From Lahra MM, Jeffery HE: A fetal response to chorioamnionitis is associated with early survival after preterm birth,* Am J Obstet Gynecol *190:147–151, 2004.)*

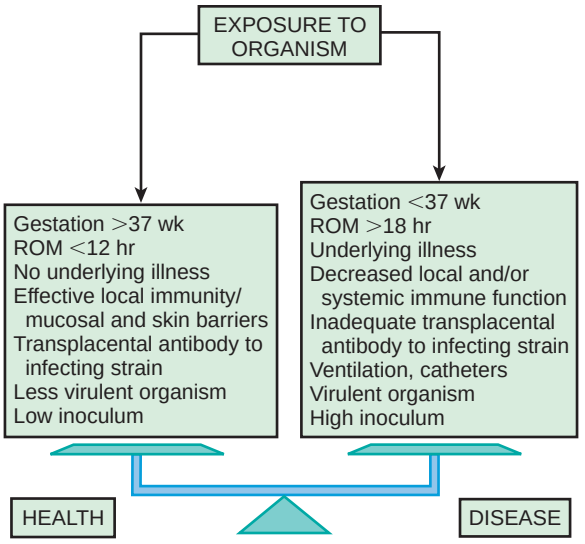

Figure 109-4 Factors influencing the balance between health and disease in neonates exposed to a potential pathogen. ROM, rupture of membranes. *(Adapted from Baker CJ: Group B streptococcal infections,* Clin Perinatol *24:59–70, 1997.)*

transmitted by direct contact with hospital personnel, the mother, or other family members; from breast milk (HIV, CMV); or from inanimate sources such as contaminated equipment. The most common source of postnatal infections in hospitalized newborns is hand contamination of healthcare personnel, underscoring the importance of handwashing.

Most cases of meningitis result from hematogenous dissemination. Less often, meningitis results from contiguous spread as a result of contamination of open neural tube defects, congenital sinus tracts, or penetrating wounds from fetal scalp sampling or internal fetal electrocardiographic monitors. Abscess formation, ventriculitis, septic infarcts, hydrocephalus, and subdural effusions are complications of meningitis that occur more often in newborn infants than in older children.

Bibliography is available at Expert Consult.

109.3 Immunity

During the 1st 3 mo of life, the innate immune system, including phagocytes, natural killer cells, antigen presenting cells, and complement provide defense against pathogens. With advancing age and exposures, the acquired immune system develops and assumes a more prominent role in host defense. Decreased function of neutrophils and low concentrations of immunoglobulins increases the susceptibility of preterm infants to invasive infection. Group B streptococci, *Escherichia coli*, herpes simplex virus (HSV), CMV, varicella-zoster virus (VZV), respiratory syncytial virus (RSV), enteroviruses, and *Candida* species are notable pathogens in the early neonatal period.

IMMUNOGLOBULIN

Immunoglobulin (Ig) G is actively transported across the placenta, with concentrations in a full-term infant comparable to or higher than maternal levels, because of a combination of both acquired and neonatally produced IgG in the third trimester. In premature infants, cord IgG levels are directly proportional to gestational age; at 18-20 wk, IgG levels are <100 mg/dL and reach 400 mg/dL by 30-32 wk of gestation. Levels of maternally derived IgG fall rapidly after birth in a process termed "physiologic hypogammaglobulinemia," with notable implications for premature and small-for-gestational-age neonates, whose IgG levels are often reduced compared with term and appropriate-for-gestational-age neonates. Other classes of immunoglobulins (IgA, IgM, IgD, and IgE) are not transferred across the placenta, therefore elevated cord blood levels of IgA and IgM may be evidence of an intrauterine infection. A predisposition to Gram-negative infections in the neonate may be explained by the inefficiency of neonatally produced IgM to provide opsonins to these organisms. Maternal IgG is an efficient opsonin for Gram-positive organisms but is less so for Gram-negative pathogens.

Term and premature infants are able to mount immune responses to protein antigens including tetanus, diphtheria, hepatitis, and polio but are impaired in their ability to respond to polysaccharide antigens such as *Haemophilus influenzae* type b and group B streptococci. Conjugate vaccines join polysaccharide antigens to immunogenic proteins giving the appearance of a T-cell dependent antigen to the immature neonatal immune system.

COMPLEMENT

A fetus begins to synthesize complement components during weeks 6-14 of gestation; transplacental passage of complement from the maternal circulation does not occur. The complement system mediates bactericidal activity against certain organisms such as *E. coli* and functions as an opsonin with antibody in the phagocytosis of GBS. Full-term newborn infants have slightly diminished classical pathway complement activity and moderately diminished alternative pathway activity. Considerable variability, however, is seen in both the concentration and activity of complement components. Premature infants have lower levels of complement components and less complement activity, and have notably reduced levels of C9, important for Gram-negative bacterial lysis and assembly of the membrane attack complex. These deficiencies contribute to diminished complement-derived chemotactic activity and to a lesser ability to opsonize certain organisms in the absence of antibody.

NEUTROPHILS

Neutrophil Function

Term and late preterm neonates have impaired neutrophil function compared with that of older infants. Quantitative and qualitative deficiencies of the phagocyte system contribute to the newborn's susceptibility to infection. Neutrophil migration (chemotaxis), adhesion, aggregation, and deformability, all of which may be impaired in the neonate, may delay the response to infection. Abnormal expression of cell membrane adhesion molecules (the β_2 integrins and selectins) and abnormalities in the neonatal neutrophil cytoskeleton contribute to impaired chemotaxis. Impairment of the oxidative respiratory burst of neonatal neutrophils is a factor in the increased risk of sepsis, especially in preterm infants. Neutrophil granules contain enzymes; one noted protein is bactericidal/permeability-increasing protein (BPI) that binds to the endotoxin in the cell wall of Gram-negative bacteria. BPI facilitates opsonization and prevents the inflammatory response to endotoxin. BPI activity may be decreased in neonates.

Neutrophil Number

Neutropenia appears to be a better predictor of neonatal sepsis than leukocytosis, although neutropenic ranges differ by gestational age, mode of delivery, altitude of location of birth, and sampling methods. Neonates have a 70-80% reduction in bone marrow neutrophil stores compared to adults and therefore are impaired in their response to infectious and noninfectious stressors. Increasing neutrophil number with granulocyte colony-stimulating factors (G-CSFs) or granulocyte-macrophage colony-stimulating factors (GM-CSFs), cytokines that stimulate myeloid progenitor cells, does not appear to affect clinical outcomes. Band neutrophils constitute less than 15% in normal newborns and may increase in newborns with infection and other stress responses, such as asphyxia.

Natural Killer Cells

Natural killer (NK) cells are a subgroup of lymphocytes that are cytolytic against cells infected with viruses. NK cells also lyse cells coated with antibody in a process called antibody-dependent cell-mediated cytotoxicity. NK cells appear early in gestation and are present in cord

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blood in numbers equivalent to those in adults; neonatal NK cells have an approximately 50% decrease in cytotoxic activity and antibody-dependent cell-mediated cytotoxicity in comparison with NK cells from adults.

CYTOKINES/INFLAMMATORY MEDIATORS

Several adverse outcomes, including brain injury, necrotizing enterocolitis, and bronchopulmonary dysplasia (BPD), may be mediated by an unbalanced cytokine (proinflammatory vs. antiinflammatory) response to infection. The release of tumor necrosis factor-α, interleukin (IL)-1 (IL-1), IL-4, IL-6, IL-8, IL-10, IL-12, platelet-activating factor, and the leukotrienes offers the potential opportunity to facilitate an early laboratory diagnosis of infection.

Functional categorization of T-helper (Th) 1 and Th2 responses is based on cytokine secretion and function. The Th1 response is directed against intracellular organisms and is relatively impaired in neonates, possibly accounting for the predisposition to severe clinical outcomes with infections with intracellular pathogens.

Innate immunity involves nonspecific cellular and humoral responses to an infectious agent without previous exposure. Recognition of pathogens is initiated by soluble components in plasma (including mannose-binding lectin) and by recognition of receptors on monocytes and other cells. Toll-like receptors play an important role in pathogen recognition.

Bibliography is available at Expert Consult.

109.4 Etiology of Fetal and Neonatal Infection

A number of bacterial and nonbacterial (Table 109-1) agents may infect newborns in utero, intrapartum, or postpartum. Intrauterine transplacental infections of significance to the fetus and/or newborn include syphilis, rubella, CMV, toxoplasmosis, parvovirus B19, and varicella. Although HSV, HIV, hepatitis B virus, hepatitis C virus, and tuberculosis (TB) can each result in transplacental infection, the most common mode of transmission for these agents is intrapartum, during labor and delivery with passage through an infected birth canal (HIV, HSV, hepatitis B virus), or postpartum, from contact with an infected mother or caretaker (TB) or with infected breast milk (HIV).

Any microorganism inhabiting the genitourinary or lower gastrointestinal tract may cause intrapartum and postpartum infection. The most common bacteria are GBS and *E. coli*. The more common viruses are CMV, HSV, enteroviruses, and HIV.

Agents that commonly cause **healthcare-associated infections (HAIs)** in the newborn include coagulase-negative staphylococci, Gram-negative bacilli *(E. coli, Klebsiella pneumoniae, Enterobacter, Pseudomonas aeruginosa),* enterococci, *Staphylococcus aureus,* and *Candida.* Viruses contributing to HAIs in the neonate include enteroviruses, CMV, hepatitis A, adenoviruses, influenza, RSV, rhinovirus, parainfluenza, HSV, and rotavirus. Community-acquired pathogens such as *Streptococcus pneumoniae* may also cause infection in newborn infants after discharge from the hospital.

Congenital pneumonia may be caused by CMV, rubella virus, and *T. pallidum* and, less commonly, by the other agents producing transplacental infection (Table 109-2). Microorganisms causing pneumonia acquired during labor and delivery include GBS, Gram-negative enteric aerobes, *Listeria monocytogenes,* genital *Mycoplasma, Chlamydia trachomatis,* CMV, HSV, and *Candida* species.

Bacteria responsible for most cases of nosocomial pneumonia typically include staphylococcal species, Gram-negative enteric aerobes, and occasionally, *Pseudomonas.* Fungi are responsible for an increasing number of systemic infections, usually acquired during prolonged hospitalization of preterm neonates. Respiratory viruses cause isolated cases and outbreaks of nosocomial pneumonia. These viruses, usually endemic during the winter months and acquired from infected hospital staff or visitors to the nursery, include RSV, parainfluenza virus, influenza viruses, and adenovirus. Respiratory viruses are the single most important cause of community-acquired pneumonia and are usually contracted from infected household contacts.

The most common bacterial causes of **neonatal meningitis** are GBS, *E. coli,* and *L. monocytogenes. S. pneumoniae,* other streptococci, nontypable *H. influenzae,* both coagulase-positive and coagulase-negative staphylococci, *Klebsiella, Enterobacter, Pseudomonas, T. pallidum,* and *Mycobacterium tuberculosis* infection involving the central nervous system may also result in meningitis.

Bibliography is available at Expert Consult.

Table 109-1 Nonbacterial Causes of Systemic Neonatal Infections

VIRUSES	MYCOPLASMA
Adenovirus	*Mycoplasma hominis*
CMV	*Ureaplasma urealyticum*
Enteroviruses	**FUNGI**
Parechoviruses	*Candida* species
Hepatitis B virus	*Malassezia* species
HSV	**PROTOZOA**
HIV	Plasmodia
Parvovirus	*Toxoplasma gondii*
Rubella virus	*Trypanosoma cruzi*
VZV	

109.5 Epidemiology of Early- and Late-Onset Neonatal Infections

The terms *early-onset infection* and *late-onset infection* refer to the different ages at onset of infection in the neonatal period. Although these disorders were originally divided arbitrarily into infections occurring before and after 1 wk of life, it is more useful to separate early- and late-onset infections according to peripartum pathogenesis. Early-onset infections are acquired before or during delivery (vertical mother-to-child transmission). Late-onset infections develop after delivery from organisms acquired in the hospital or the community. The age at onset depends on the timing of exposure and virulence of the infecting organism. Very-late-onset infections (onset after 1 mo of

Table 109-2 Etiologic Agents of Neonatal Pneumonia According to Timing of Acquisition

TRANSPLACENTAL	POSTNATAL
CMV	Adenovirus
HSV	*Candida* species*
Mycobacterium Tuberculosis	Coagulase-negative staphylococci
Rubella virus	CMV
Treponema pallidum	Enteric bacteria*
VZV	Enteroviruses
PERINATAL	Influenza viruses A, B
Anaerobic bacteria	Parainfluenza
Chlamydia	*Pseudomonas**
CMV	RSV
Enteric bacteria	*Staphylococcus aureus*
Group B streptococci	*Mycobacterium tuberculosis*
Haemophilus influenzae	
HSV	
Listeria monocytogenes	
Mycoplasma	

*More likely with mechanical ventilation or indwelling catheters, or after abdominal surgery.

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life) may also occur, particularly in VLBW preterm infants or term infants requiring prolonged neonatal intensive care.

The incidence of neonatal bacterial sepsis varies from 1-4/1,000 live births, with geographic variation and changes over time. Studies suggest that term male infants have a higher incidence of sepsis than term females. This sex difference is less clear in preterm low birthweight (LBW) infants. Attack rates of neonatal sepsis increase significantly in LBW infants in the presence of maternal chorioamnionitis, congenital immune defects, mutations of genes involved in the innate immune system, asplenia, galactosemia *(E. coli)*, and malformations leading to high inocula of bacteria (obstructive uropathy).

Data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network documented rates of early-onset sepsis among almost 400,000 live births at Network centers. The overall rate of early-onset sepsis was 0.98 cases per 1,000 live births with rates inversely related to birthweight (401-1500 g birthweight, 10.96/1000; 1501-2500 g birthweight, 1.38/1000; >2500 g birthweight, 0.57/1000) (Table 109-3).

Intrapartum antibiotics are used to reduce vertical transmission of GBS as well as to lessen neonatal morbidity after preterm rupture of membranes. With introduction of selective intrapartum antibiotic prophylaxis to prevent perinatal transmission of GBS, rates of early-onset neonatal GBS infection in the United States declined from 1.7/1,000 live births to 0.25/1,000, according to U.S. Centers for Disease Control and Prevention (CDC) surveillance data. Intrapartum chemoprophylaxis does not reduce the rates of late-onset GBS disease and has no effect on the rates of infection with non-GBS pathogens. Of concern is a possible increase in gram-negative infections (especially *E. coli*) in VLBW and possibly term infants in spite of a reduction in early GBS sepsis by intrapartum antibiotics.

The incidence of meningitis is 0.2-0.4/1,000 live births in newborn infants and is higher in preterm infants. Bacterial meningitis may be associated with sepsis or may occur as a local meningeal infection. *Up to one-third of VLBW infants with late-onset meningitis have negative blood culture results*. The discordance between results of blood and cerebrospinal fluid (CSF) cultures suggests that meningitis may be underdiagnosed among VLBW infants and emphasizes the need for culture of CSF in VLBW infants when late-onset sepsis is suspected and in all infants who have positive blood culture results.

PREMATURITY

The most important neonatal factor predisposing to infection is prematurity or LBW. Preterm LBW infants have a 3- to 10-fold higher incidence of infection than full-term normal birthweight infants. Possible explanations include: (a) maternal genital tract infection is considered to be an important cause of preterm labor, with an increased risk of vertical transmission to the newborn (Fig. 109-5); (b) the frequency of intraamniotic infection is inversely related to gestational age (see Fig. 109-3); (c) premature infants have documented immune dysfunction; and (d) premature infants often require prolonged

Table 109-3 Rates of Early-Onset Sepsis Per 1,000 Live Births: NICHD Neonatal Research Network/CDC Surveillance Study of Early-Onset Sepsis

	BIRTHWEIGHT (g)			
	401-1,500	1,501-2,500	>2,500	All
All	10.96	1.38	0.57	0.98
GBS	2.08	0.38	0.35	0.41
Escherichia coli	5.09	0.54	0.07	0.28

Modified from Stoll BJ, Hansen NI, Sanchez PJ, et al: Early onset neonatal sepsis: the burden of group B streptococcal and E. coli *disease continues,* Pediatrics *127(5):817–826, 2011.*

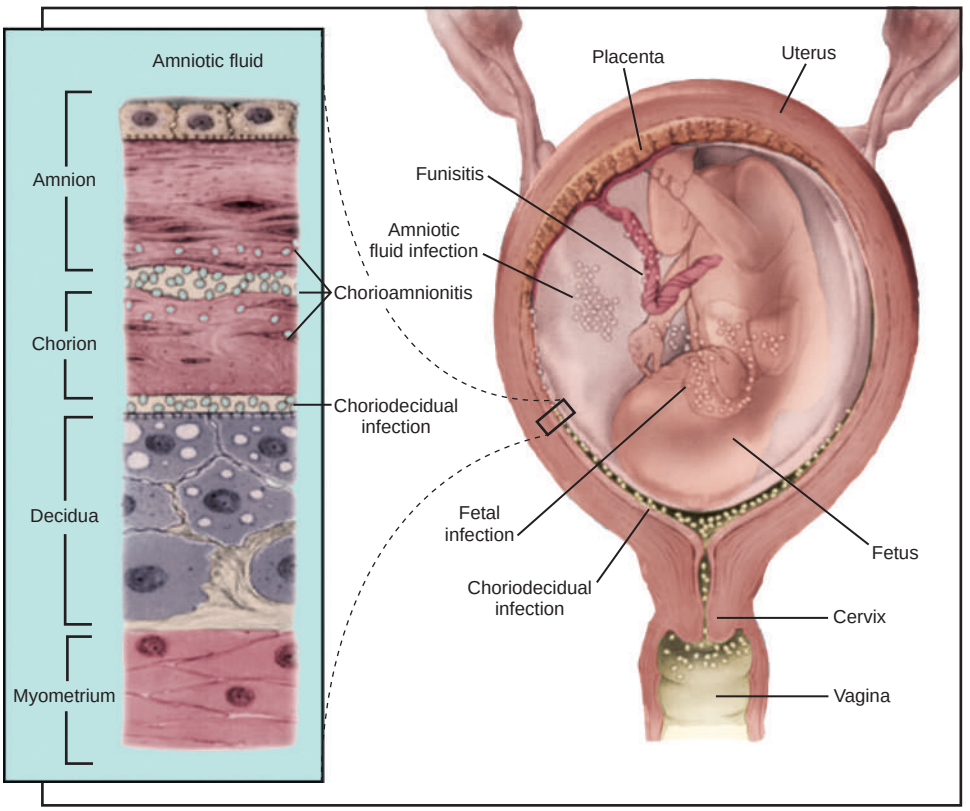

Figure 109-5 Potential sites of bacterial infection within the uterus. *(From Goldenberg RL, Hauth JA, Andrews WW: Intrauterine infection and preterm delivery,* N Engl J Med *342:1500–1507, 2000. Copyright 2000, Massachusetts Medical Society.)*

intravenous access, endotracheal intubation, or other invasive procedures that provide a portal of entry or impair barrier and clearance mechanisms, putting them at continued risk for hospital-acquired infections.

Bibliography is available at Expert Consult.

109.6 Healthcare–Associated Infections (HAI)

HAIs are responsible for significant morbidity and late mortality in hospitalized newborns, with almost 25% of VLBW infants (<1,500 g birthweight) experiencing 1 or more nosocomial infections. The majority of HAIs occur in preterm or term infants who require intensive care. Risk factors for HAIs in these infants include prematurity, low birthweight, invasive procedures, indwelling vascular catheters, parenteral nutrition with lipid emulsions, endotracheal tubes, ventricular shunts, alterations in the skin and/or mucous membrane barriers, frequent use of broad-spectrum antibiotics, and prolonged hospitalization. The most frequent HAIs are bloodstream infections associated with intravascular catheters and ventilator-associated pneumonia. HAIs may also occur in the absence of a catheter or ventilator. Infants receiving intensive care are at risk for community or HAIs during seasonal epidemics (RSV, influenza). Neonatal immunization during the birth hospitalization is the most reliable point of healthcare contact.

Rates of HAIs increase with decreasing birthweight and gestational age. The NICHD Neonatal Research Network has reported rates of 43% for infants weighing 401-750 g; 28% for those weighing 751-1,000 g; 15% for those weighing 1,001-1,250 g; and 7% for those weighing 1,251-1,500 g. It also reports rates of 36% for infants 22-28 wk gestational age (58% at 22 wk; 62% at 23 wk; 55% at 24 wk; 46% at 25 wk; 35% at 26 wk; 27% at 27 wk and 20% at 28 wk). The CDC National Healthcare Safety Network monitors device-associated nosocomial infection rates. Rates are inversely related to birthweight, and in level III neonatal intensive care units (NICUs), they range from 3.7 infections per 1,000 central line days for infants weighing <750 g to 2.0 infections per 1,000 central line days for those weighing >2,500 g. The widespread differences in practice regarding the inclusion of lumbar puncture (LP) in the diagnostic evaluation of an infant with suspected sepsis make it more difficult to determine rates of late-onset meningitis. The mean age at onset of the first episode of late-onset HAI sepsis occurs during 2-3 wk of life, independent of the infecting pathogen. HAIs increase the risk of adverse outcomes, including prolonged hospitalization and mortality.

Various bacterial and fungal agents colonize hospitalized infants, healthcare workers, and visitors. Pathogenic agents can be transmitted by direct contact or indirectly via contaminated equipment, intravenous fluids, medications, blood products, or enteral feedings. Colonization of the infant's skin, umbilicus, and respiratory or gastrointestinal tract with pathogenic agents often precedes the development of infection. Antibiotic use interferes with colonization by normal flora, thereby permitting colonization with more virulent pathogens.

Coagulase-negative staphylococci are the most frequent neonatal HAI. In a cohort of 6,215 VLBW infants in the NICHD Neonatal Research Network, Gram-positive organisms were associated with 70%, Gram-negative with 18%, and fungi with 12% of episodes of late-onset sepsis; coagulase-negative staphylococci, the single most common organism, was isolated in 48% of these infections. The emergence of bacterial pathogens resistant to multiple antibiotics is a growing concern. The emergence of methicillin-resistant *S. aureus,* vancomycin-resistant enterococci, and multidrug-resistant Gram-negative pathogens are particularly alarming. Organisms responsible for neonatal bacterial sepsis and meningitis as well as HAIs fluctuate with antimicrobial pressure.

Viral pathogens including RSV, varicella, influenza, rotavirus, and enteroviruses may be responsible for sporadic infections or for outbreaks in the NICU. Infection prevention policies, including immunization of healthcare providers, visitors, and neonates, when feasible, are essential to prevent and/or contain nursery infection outbreaks. During clusters of infections, outbreaks, or epidemics, investigation of possible reservoirs of infection, modes of transmission, and risk factors is necessary. Identification of colonized infants and nursery personnel may be helpful. Prevention of transmission includes adherence to standard precautions with all patient contact, maintaining a manageable unit census with appropriate nurse : patient ratios, strict compliance with hand hygiene, meticulous neonatal skin care, minimizing the risk of catheter contamination, decreasing the number of venipunctures and heelsticks, reducing the duration of catheter and mechanical ventilation days, encouraging appropriate advancement of enteral feedings, providing education and feedback to nursery personnel, and ongoing monitoring and surveillance of HAIs in the NICU. Evidenced-based care bundles have been developed for many procedures that may predispose a neonate to an HAI. Among those frequently practiced, intravascular central catheter insertion and care practices are frequently bundled.

Hand hygiene remains the most important and effective means of reducing HAIs. Proper hand hygiene with either soap and water or alcohol-based hand sanitizers is essential before and after each patient contact. The use of gloves does not obviate the need for hand hygiene. Skin to skin contact has proven beneficial to the neonate, however ensuring that the contact is with pathogen-free skin is essential. Ongoing education of staff regarding practices that are likely to reduce HAIs and promote active surveillance are important components of infection prevention.

Bibliography is available at Expert Consult.

109.7 Clinical Manifestations of Transplacental Intrauterine Infections

Infection with agents that cross the placenta (CMV, *T. pallidum, T. gondii,* rubella, parvovirus B19) may be asymptomatic at birth or may cause a spectrum of disease ranging from relatively mild symptoms to multisystem involvement with severe and life-threatening complications. For some agents, disease is characterized by chronicity, recurrence, or both, and the agent may cause ongoing injury. Clinical signs and symptoms do not help make a specific etiologic diagnosis but, rather, raise suspicion of an intrauterine infection and help distinguish these infections from acute bacterial infections that occur during labor and delivery. The following signs and symptoms are common to many of these agents (Table 109-4): intrauterine growth restriction, microcephaly or hydrocephalus, intracranial calcifications, chorioretinitis, cataracts, myocarditis, pneumonia, hepatosplenomegaly, direct hyperbilirubinemia, anemia, thrombocytopenia, hydrops fetalis, and skin manifestations. Many of these agents cause late sequelae, even if the infant is asymptomatic at birth. These adverse outcomes include sensorineural hearing loss, visual disturbances (including blindness), seizures, and neurodevelopmental abnormalities.

BACTERIAL SEPSIS

Neonates with bacterial sepsis may have either nonspecific signs and symptoms or focal signs of infection (Table 109-5), including temperature instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory distress, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distention, jaundice, petechiae, purpura, and bleeding. Table 109-6 lists World Health Organization international criteria for bacterial sepsis. The initial manifestation may involve only limited symptomatology and only 1 system, such as apnea alone or tachypnea with retractions, or tachycardia, or the infant may present with an acute catastrophic manifestation with multiorgan dysfunction. Infants should be reevaluated over time to determine whether the symptoms have progressed from mild to severe. Later complications

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Table 109-4 Clinical Manifestations of Transplacental Infections

MANIFESTATION	PATHOGEN
Intrauterine growth restriction	CMV, *Plasmodium*, rubella, toxoplasmosis, *Treponema pallidum*, *Trypanosoma cruzi*, VZV
Congenital anatomic defects:	
Cataracts	Rubella
Cardiac defects	Rubella
Hydrocephalus	HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis
Intracranial calcification	CMV, HIV, toxoplasmosis, *T. cruzi*
Limb hypoplasia	VZV
Microcephaly	CMV, HSV, rubella, toxoplasmosis
Microphthalmos	CMV, rubella, toxoplasmosis
Neonatal organ involvement:	
Anemia	CMV, parvovirus, *Plasmodium*, rubella, toxoplasmosis, *T. cruzi*, *T. pallidum*
Carditis	Coxsackieviruses, rubella, *T. cruzi*
Encephalitis	CMV, enteroviruses, HSV, rubella, toxoplasmosis, *T. cruzi*, *T. pallidum*
Hepatitis	CMV, enteroviruses, HSV
Hepatosplenomegaly	CMV, enteroviruses, HIV, HSV, *Plasmodium*, rubella, *T. cruzi*, *T. pallidum*
Hydrops	Parvovirus, *T. pallidum*, toxoplasmosis
Lymphadenopathy	CMV, HIV, rubella, toxoplasmosis, *T. pallidum*
Osteitis	Rubella, *T. pallidum*
Petechiae, purpura	CMV, enteroviruses, rubella, *T. cruzi*
Pneumonitis	CMV, enteroviruses, HSV, measles, rubella, toxoplasmosis, *T. pallidum*, VZV
Retinitis	CMV, HSV, lymphocytic choriomeningitis virus, rubella, toxoplasmosis, *T. pallidum*, West Nile virus
Rhinitis	Enteroviruses, *T. pallidum*
Skin lesions	Enteroviruses, HSV, measles, rubella, *T. pallidum*, VZV
Thrombocytopenia	CMV, enteroviruses, HIV, HSV, rubella, toxoplasmosis, *T. pallidum*
Late sequelae:	
Convulsions	CMV, enteroviruses, rubella, toxoplasmosis
Deafness	CMV, rubella, toxoplasmosis
Dental/skeletal problems	Rubella, *T. pallidum*
Endocrinopathies	Rubella, toxoplasmosis
Eye pathology	HSV, rubella, toxoplasmosis, *T. cruzi*, *T. pallidum*, VZV
Hepatitis	Hepatitis B
Mental retardation	CMV, HIV, HSV, rubella, toxoplasmosis, *T. cruzi*, VZV
Nephrotic syndrome	*Plasmodium*, *T. pallidum*

of sepsis include respiratory failure, pulmonary hypertension, cardiac failure, shock, renal failure, liver dysfunction, cerebral edema or thrombosis, adrenal hemorrhage and/or insufficiency, bone marrow dysfunction (neutropenia, thrombocytopenia, anemia), and disseminated intravascular coagulopathy (DIC).

A variety of noninfectious conditions can occur together with neonatal infection or can make the diagnosis of infection more difficult. Respiratory distress syndrome (RDS) secondary to surfactant deficiency can coexist with bacterial pneumonia. Because bacterial sepsis can be rapidly progressive, the physician must be alert to the signs and symptoms of possible infection and must initiate diagnostic evaluation and empirical therapy in a timely manner. The

Table 109-5 Initial Signs and Symptoms of Infection in Newborn Infants

GENERAL Fever, temperature instability "Not doing well" Poor feeding Edema	**CARDIOVASCULAR SYSTEM** Pallor; mottling; cold, clammy skin Tachycardia Hypotension Bradycardia
GASTROINTESTINAL SYSTEM Abdominal distention Vomiting Diarrhea Hepatomegaly	**CENTRAL NERVOUS SYSTEM** Irritability, lethargy Tremors, seizures Hyporeflexia, hypotonia Abnormal Moro reflex Irregular respirations Full fontanel High-pitched cry
RESPIRATORY SYSTEM Apnea, dyspnea Tachypnea, retractions Flaring, grunting Cyanosis	**HEMATOLOGIC SYSTEM** Jaundice Splenomegaly Pallor Petechiae, purpura Bleeding
RENAL SYSTEM Oliguria	

Table 109-6 Clinical Criteria for the Diagnosis of Sepsis in the International Setting

Integrated Management of Childhood Illness (IMCI) and WHO Criteria for Severe Infections in Children
NEUROLOGIC: convulsions, drowsy or unconscious, decreased activity, bulging fontanel
RESPIRATORY: respiratory rate >60 breaths/min, grunting, severe chest indrawing, central cyanosis
CARDIAC: poor perfusion, rapid and weak pulse
GASTROINTESTINAL: jaundice, poor feeding, abdominal distention
DERMATOLOGIC: skin pustules, periumbilical erythema or purulence
MUSCULOSKELETAL: edema or erythema overlying bones or joints
OTHER: Temperature >37.7°C (99.9°F; or feels hot) or <35.5°C (95.9°F; or feels cold)

Adapted from World Health Organization: Pocket book of hospital care for children: guidelines for the management of common childhood illnesses *ed 2, 2013:45–69. Available at http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/, accessed July 2013.*

differential diagnosis of many of the signs and symptoms that suggest infection is extensive; noninfectious disorders must also be considered (Table 109-7).

SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

The clinical manifestations of infection depend on the virulence of the infecting organism and the body's inflammatory response. The term *systemic inflammatory response syndrome (SIRS)* is most frequently used to describe this unique process of infection and the subsequent systemic response (see Chapters 70 and 177). In addition to infection, SIRS may result from trauma, hemorrhagic shock, other causes of ischemia, necrotizing enterocolitis, and pancreatitis.

Patients with SIRS have a spectrum of clinical symptoms that represent progressive stages of the pathologic process. In adults, SIRS is defined by the presence of 2 or more of the following: (1) fever or hypothermia, (2) tachycardia, (3) tachypnea, and (4) abnormal white blood cell (WBC) count or an increase in immature forms. In neonates

Table 109-7 Serious Systemic Illness in Newborns: Differential Diagnosis of Neonatal Sepsis

CARDIAC
Congenital: hypoplastic left heart syndrome, other structural disease, persistent pulmonary hypertension of the newborn (PPHN)
Acquired: myocarditis, hypovolemic or cardiogenic shock, PPHN
GASTROINTESTINAL
Necrotizing enterocolitis
Spontaneous gastrointestinal perforation
Structural abnormalities
Hepatic failure (inborn errors of metabolism, neonatal iron storage disease)
HEMATOLOGIC
Neonatal purpura fulminans
Immune-mediated thrombocytopenia
Immune-mediated neutropenia
Severe anemia
Malignancies (congenital leukemia)
Langerhans cell histiocytosis
Hereditary clotting disorders
Familial hemophagocytosis syndrome
METABOLIC
Hypoglycemia
Adrenal disorders: Adrenal hemorrhage, adrenal insufficiency, congenital adrenal hyperplasia
Inborn errors of metabolism: Organic acidurias, lactic acidoses, urea cycle disorders, galactosemia
NEUROLOGIC
Intracranial hemorrhage: spontaneous, caused by child abuse
Hypoxic-ischemic encephalopathy
Neonatal seizures
Infant botulism
RESPIRATORY
Respiratory distress syndrome
Aspiration pneumonia: amniotic fluid, meconium, or gastric contents
Lung hypoplasia
Tracheoesophageal fistula
Transient tachypnea of the newborn

Table 109-8 Definitions of Systemic Inflammatory Respiratory Response Syndrome and Sepsis in Pediatric Patients

SIRS: The systemic inflammatory response to a variety of clinical insults, manifested by 2 or more of the following conditions:
Temperature instability <35°C (95°F) or >38.5°C (101.3°F)
Respiratory dysfunction:
Tachypnea >2 SD above the mean for age
Hypoxemia (PaO_2 <70 mm Hg on room air)
Cardiac dysfunction:
Tachycardia >2 SD above the mean for age
Delayed capillary refill >3 sec
Hypotension >2 SD below the mean for age
Perfusion abnormalities:
Oliguria (urine output <0.5 mL/kg/hr)
Lactic acidosis (elevated plasma lactate and/or arterial pH <7.25)
Altered mental status
Sepsis: The systemic inflammatory response to an infectious process

From Adams-Chapman I, Stoll BJ: Systemic inflammatory response syndrome, Semin Pediatr Infect Dis *12:5–16, 2001.*

and pediatric patients, SIRS manifests as temperature instability, respiratory dysfunction (altered gas exchange, hypoxemia, acute respiratory distress syndrome), cardiac dysfunction (tachycardia, delayed capillary refill, hypotension), and perfusion abnormalities (oliguria, metabolic acidosis) (Table 109-8). Increased vascular permeability results in capillary leak into peripheral tissues and the lungs, with resultant peripheral and pulmonary edema. DIC results in the more severely affected cases. The cascade of escalating tissue injury may lead to multisystem organ failure and death.

Fever

Only approximately 50% of infected newborn infants have a temperature higher than 37.8°C (100°F) (axillary) (see Chapters 176, 177). Fever in newborn infants does not always signify infection; it may be caused by increased ambient temperature, isolette or radiant warmer malfunction, dehydration, central nervous system (CNS) disorders, hyperthyroidism, familial dysautonomia, or ectodermal dysplasia. A single temperature elevation is infrequently associated with infection; fever sustained over 1 hr is more likely to be caused by infection. Most febrile infected infants have additional signs compatible with infection, although a focus of infection is not always apparent. Acute febrile illnesses occurring later in the neonatal period may be caused by urinary tract infection, meningitis, pneumonia, osteomyelitis, or gastroenteritis, in addition to sepsis, thus underscoring the importance of a diagnostic evaluation that includes blood culture, urine culture, LP, and other studies as indicated. Many agents may cause these late infections, including HSV, enteroviruses, RSV, and bacterial pathogens. In premature infants, hypothermia or temperature instability requiring increasing ambient (isolette, warmer) temperatures is more likely to accompany infection.

Rash

Cutaneous manifestations of infection include omphalitis, cellulitis, mastitis, and subcutaneous abscesses. **Ecthyma gangrenosum** is indicative of infection with *Pseudomonas* species. The presence of small salmon-pink papules suggests *L. monocytogenes* infection. A vesicular rash is consistent with herpesvirus infection. The mucocutaneous lesions of *Candida albicans* are discussed elsewhere (see Chapter 234.1). Petechiae and purpura may have an infectious cause. Purple papulonodular lesions are referred to as "blueberry muffin" rash and represent dermal erythropoiesis. Causes include congenital viral infections (CMV, rubella, and parvovirus), congenital neoplastic disease, and Rh hemolytic disease.

Omphalitis

Omphalitis is a neonatal infection resulting from unhygienic care of the umbilical cord, which continues to be a problem, particularly in developing countries. The umbilical stump is colonized by bacteria from the maternal genital tract and the environment (see Chapter 105). The necrotic tissue of the umbilical cord is an excellent medium for bacterial growth. Omphalitis may remain a localized infection or may spread to the abdominal wall, the peritoneum, the umbilical or portal vessels, or the liver. Abdominal wall cellulitis or necrotizing fasciitis, with associated sepsis and a high mortality rate, may develop in infants with omphalitis. Prompt diagnosis and treatment are necessary to avoid serious complications.

Tetanus

See also Chapter 211.

Neonatal tetanus is a serious neonatal infection in developing countries. It results from unclean delivery and unhygienic management of the umbilical cord in an infant born to a mother who has not been immunized against tetanus. The surveillance **case definition** of neonatal tetanus requires the ability of a newborn to suck at birth and for the 1st few days of life, followed by an inability to suck starting between 3 and 10 days of age, difficulty swallowing, spasms, stiffness, seizures, and death. Bronchopneumonia, presumably resulting from aspiration, is a common complication and cause of death. Neonatal tetanus is a preventable disease. It can be prevented by immunizing mothers before or during pregnancy and by ensuring a clean delivery, sterile cutting of the umbilical cord and proper cord care after birth.

Pneumonia

Early signs and symptoms of pneumonia may be nonspecific, including poor feeding, lethargy, irritability, cyanosis, temperature instability, and the overall impression that the infant is not well. Respiratory symptoms of increasing severity are grunting, tachypnea, retractions, flaring of the alae nasi, cyanosis, apnea, and progressive respiratory failure. If the infant is premature, signs of progressive respiratory distress may be superimposed upon RDS or BPD. For infants on mechanical ventilation, the need to increase ventilator support may indicate infection.

Signs of pneumonia on physical examination, such as dullness to percussion, change in breath sounds, and the presence of rales or rhonchi, are very difficult to appreciate in a neonate. Radiographs of the chest may reveal new infiltrates or an effusion, but if the neonate has underlying RDS or BPD, it is very difficult to determine whether the radiographic changes represent a new process or worsening of the underlying disease.

The progression of neonatal pneumonia can be variable. Fulminant infection is most commonly associated with pyogenic organisms such as GBS (see Chapter 184). Onset may occur during the 1st hours or days of life, with the infant often manifesting rapidly progressive circulatory collapse and respiratory failure. With early-onset pneumonia, the clinical course and radiographs of the chest may be indistinguishable from those with severe RDS.

In contrast to the rapid progression of pneumonia caused by pyogenic organisms, an indolent course may be seen in nonbacterial infection. The onset can be preceded by upper respiratory tract symptoms or conjunctivitis. The infant may demonstrate a nonproductive cough, and the degree of respiratory compromise is variable. Fever is usually absent, and radiographic examination of the chest shows focal or diffuse interstitial pneumonitis. Infection is generally caused by *C. trachomatis,* CMV, *Ureaplasma urealyticum,* or 1 of the respiratory viruses. Rhinovirus has been reported to cause severe respiratory compromise in infants, particularly those who are preterm. Although *Pneumocystis (carinii) jiroveci* was implicated in the original description of this syndrome, its etiologic role is now in doubt, except in newborns infected with HIV.

Bibliography is available at Expert Consult.

109.8 Intrapartum and Peripartum Infections

The maternal history provides important information about maternal exposures to infectious diseases, bacterial colonization, immunity (natural and acquired), and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis).

Sexually transmitted infections (STIs) acquired by a pregnant woman are of particular concern to the fetus and newborn because of the potential for intrauterine or perinatal transmission. All pregnant women and their partners should be queried about a history of STIs. Women should also be counseled about the need for timely diagnosis and therapy for infections during pregnancy. The CDC recommends the following screening tests and treatment when indicated:

1. All pregnant women should be offered voluntary and confidential HIV testing at the first prenatal visit, as early in pregnancy as possible. HIV screening should be part of routine prenatal testing, unless the mother declines testing (opt-out screening). For women at high risk of infection during pregnancy (multiple sexual partners or STIs during pregnancy, intravenous drug use, HIV-infected partners), repeat testing in the 3rd trimester is recommended. Rapid HIV screening is indicated for any women who presents in labor with an undocumented HIV status, unless she declines testing.
2. A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit. Repeat screenings early in the 3rd trimester and again at delivery are recommended for women in whom syphilis test results in the 1st trimester were positive and for those at high risk for infection during pregnancy. Infants should not be discharged from the hospital unless the syphilis status of the mother has been determined at least once during pregnancy and preferably again at delivery.
3. Serologic testing for hepatitis B surface antigen (HBsAg) should be performed at the first prenatal visit, even if the woman has been previously vaccinated or tested. Women who were not screened prenatally, those who are at high risk for infection (multiple sexual partners, intravenous drug use, HBsAg-positive sex partner) and those with clinical hepatitis should be retested at the time of delivery.
4. A maternal genital culture for *C. trachomatis* should be performed at the first prenatal visit. Young women (<25 yr) and those at increased risk for infection (new or multiple partners during pregnancy) should be retested during the 3rd trimester.
5. A maternal culture for *Neisseria gonorrhoeae* should be performed at the first prenatal visit. Those at high risk for infection should be retested in the 3rd trimester.
6. All pregnant women at high risk for hepatitis C infection (intravenous drug use, blood transfusion or organ transplantation before 1992) should be screened for hepatitis C antibodies at the first prenatal visit.
7. Evidence does not support routine testing for bacterial vaginosis in pregnancy. For asymptomatic women at high risk for preterm delivery, testing may be considered. Symptomatic women should be tested and treated.
8. The CDC recommends universal screening for rectovaginal GBS colonization of all pregnant women at 35-37 wk gestation, and a screening-based approach to selective intrapartum antibiotic prophylaxis against GBS (Table 109-9 and Figs. 109-6 and 109-7; Chapter 184). Figure 109-8 shows the approach to the infant born after intrapartum prophylaxis.

Suspected Intrauterine Infection

The acronym *TORCH* refers to toxoplasmosis, other agents (syphilis, varicella, parvovirus B19, HIV), rubella, CMV, and HSV. Although the acronym may be helpful in remembering some of the etiologic agents of intrauterine infection, the TORCH battery of serologic tests has a poor diagnostic yield. *Instead, individual diagnostic studies should be selected for each etiologic agent under consideration.* CMV and HSV require culture or polymerase chain reaction (PCR) methods; toxoplasmosis is diagnosed by serologic tests and PCR, whereas syphilis and rubella are diagnosed by serologic methods. Furthermore, reaching a definitive diagnosis of a congenital infection and dating the infection may require assessment of maternal diagnostic testing. Neonatal antibody titers are often difficult to interpret because (1) IgG is acquired from the mother by transplacental passage and (2) determination of neonatal IgM titers to specific pathogens is technically difficult to perform and is not universally available. IgM titers to specific pathogens have high specificity but only moderate sensitivity; they should not be used to preclude infection. Paired maternal and fetal-neonatal IgG titers showing higher newborn IgG levels or rising IgG titers during infancy may be used to diagnose some congenital infections (syphilis). Total cord blood IgM or IgA (neither is actively transported across the placenta to the fetus) and the presence of IgM–rheumatoid factor in neonatal serum are nonspecific tests for intrauterine infection.

If the likelihood of maternal infection with a known teratogenic agent is high, fetal ultrasound examination is recommended. If the examination demonstrates either a physical abnormality or delayed growth for gestational age, examination of a fetal blood sample may be warranted. **Cordocentesis** can provide a sufficient sample for both total and pathogen-specific IgM assays, for PCR, or for culture. The total IgM value is important because the normal fetal IgM level is <5 mg/dL. Any elevation in total IgM may indicate an underlying fetal infection. Specific IgM antibody tests are available for CMV, *T. pallidum,* parvovirus B19, and toxoplasmosis. IgM tests are useful when the

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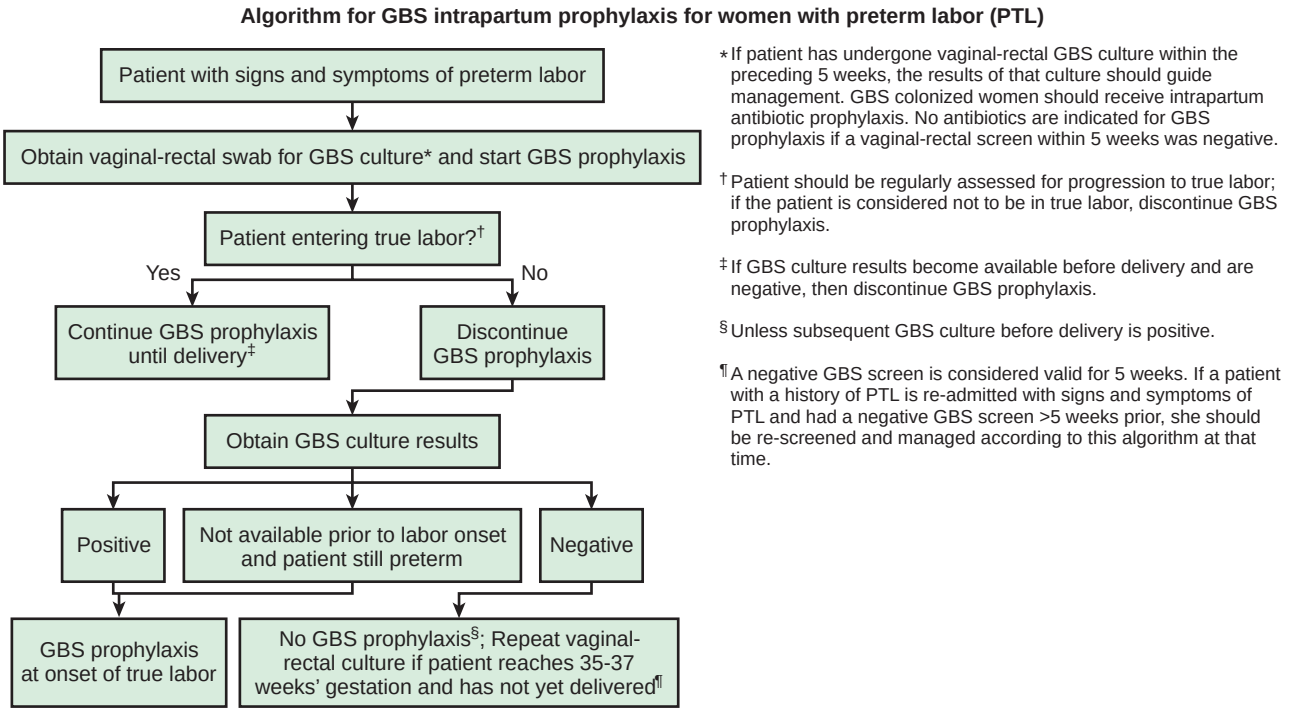


Figure 109-6 Algorithm for GBS intrapartum prophylaxis for women with preterm labor. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*

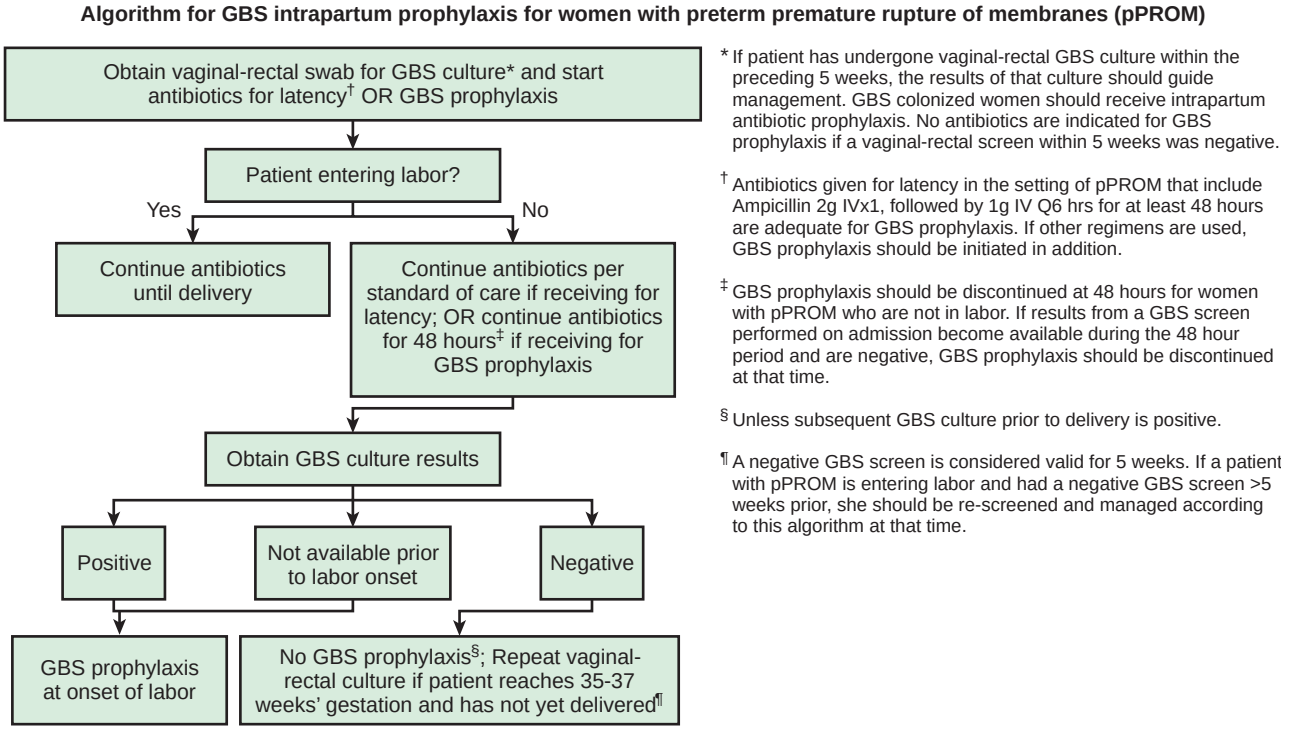
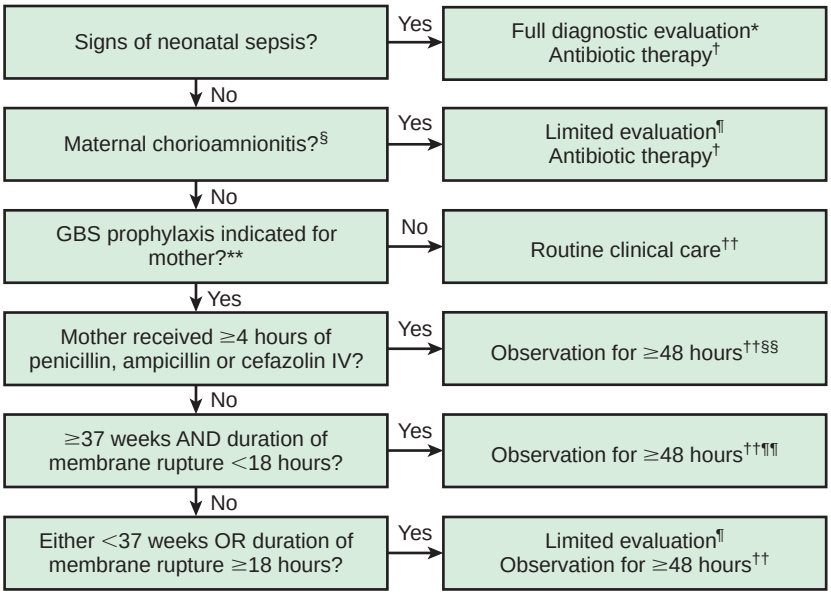


Figure 109-7 Algorithm for GBS intrapartum prophylaxis for women with preterm premature rupture of membranes. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*

results are strongly positive; however a negative pathogen-specific IgM result does not rule out that pathogen as a cause of fetopathy.

If maternal serologic studies point to a specific pathogen, it is sometimes possible to detect the organism in amniotic fluid or fetal blood (culture, PCR). Amniocentesis can be performed and the fluid sent for analysis. The presence of CMV, *Toxoplasma*, or parvovirus in amniotic fluid indicates that the fetus is infected and at high risk, but it does not always mean that the fetus will have severe sequelae. In contrast, HSV and VZV are rarely isolated from amniotic fluid samples. Parvovirus does not grow in the cell cultures commonly available in the virology

Algorithm for secondary prevention of early-onset GBS disease among newborns



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and LP (if patient stable anough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens), and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth), and CBC with differential and platelets (at birth and/or at 6-12 hours of life).

** GBS prophylaxis indicated in one or more of the following: (1) mother GBS positive within preceding 5 weeks, (2) GBS status unknown with one or more intrapartum risk factors including <37 weeks' gestation, ROM ≥18 hours or T ≥100.4°F (38.0°C), (3) GBS bacteriuria during current pregnancy, (4) history of a previous infant with GBS disease.

†† If signs of sepsis develop, a full diagnostic evaluation should be done and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, there is ready access to medical care, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at 6-12 hours of age.

Figure 109-8 Algorithm for secondary prevention of early-onset GBS disease among newborns. *(From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010,* MMWR Recomm Rep *59[RR-10]:1–36, 2010.)*

Table 109-9 Indications for Intrapartum Antibiotic Prophylaxis to Prevent Early-Onset GBS Disease

INTRAPARTUM GBS PROPHYLAXIS INDICATED	INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED
Previous infant with invasive GBS disease	Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy)
GBS bacteriuria during any trimester of the current pregnancy	GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)	Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following: Delivery at <37 weeks' gestation* Amniotic membrane rupture ≥18 hr Intrapartum temperature ≥38.0°C (100.4°F)† Intrapartum NAAT‡ positive for GBS	Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

*Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 109-7 and 109-8.

†If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

‡If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture ≥18 hr, or temperature ≥38.0°C[100.4°F]) is present, then intrapartum antibiotic prophylaxis is indicated.

GBS, group B streptococcus; NAAT, nucleic acid amplification test.

From Verani J, McGee L, Schrag S: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010, MMWR Recomm Rep *59(RR-10):1–36, 2010.*

laboratory. An IgM response is dependent on the timing of the primary infection in relationship to specimen acquisition. When fetal parvovirus infection is suspected, testing of fetal blood or amniotic fluid by PCR is recommended in addition to testing for a specific IgM response in the fetus. PCR may also be used for the diagnosis of toxoplasmosis, CMV, HSV, rubella, and syphilis.

Neonatal infections with CMV, *Toxoplasma,* rubella, HSV, and syphilis present a diagnostic dilemma because (1) their clinical features overlap and may initially be indistinguishable; (2) disease may be unapparent; (3) maternal infection is often asymptomatic; (4) special laboratory studies may be needed; and (5) appropriate management of toxoplasmosis, syphilis, CMV, and HSV, is predicated on an accurate diagnosis. Common shared features that should suggest the diagnosis of an intrauterine infection include intrauterine growth restriction, hematologic involvement (anemia, neutropenia, thrombocytopenia, petechiae, purpura), ocular signs (chorioretinitis, cataracts, keratoconjunctivitis, glaucoma, microphthalmos), CNS involvement (microcephaly, aseptic meningitis, hydrocephaly, intracranial calcifications), other organ system involvement (pneumonia, myocarditis, nephritis, hepatitis with hepatosplenomegaly, jaundice), and nonimmune hydrops. Diagnostic studies in newborns with suspected intrauterine infections should test for each potential etiology individually with acute and convalescent titers. Hepatic dysfunction, with abnormal liver functions tests, may be seen in infants with CMV, HSV, and enteroviral infections. Neonatal HSV disease should be confirmed by PCR identification of HSV from the CSF and blood. Given that approximately 30% of infants infected with HSV present with isolated mucocutaneous manifestations, swabs of any skin lesions, the conjunctiva, and oral and rectal mucosa should also be performed in all infants with suspected HSV disease. Enzyme Linked Virus Inducible System (ELVIS), a simple, 24-hr cell culture test for detecting HSV, compares favorably to standard cell culture sensitivity. HIV PCR testing should be routinely performed on infants with suspected or confirmed congenital infections that may have been cotransmitted with another etiology (HSV, toxoplasmosis). Although exposure cannot be differentiated from infection until 4-6 mo of age, empiric treatment and monitoring may prevent the sequelae of a vertically transmitted HIV infection. Maternal HIV testing is essential to provide guidance regarding breastfeeding practices to the mother of a potentially exposed/infected neonate.

Bibliography is available at Expert Consult.

109.9 Suspected Bacterial or Fungal Infections

Bacterial and fungal infections are diagnosed by isolating the etiologic agent from a normally sterile body site (blood, CSF, urine, joint fluid). Obtaining 2 blood culture specimens by venipuncture from different sites avoids confusion caused by skin contamination and increases the likelihood of bacterial detection. Samples for blood culture should be obtained from an umbilical catheter only at the time of initial insertion. A peripheral venous sample should also be obtained when blood is drawn for culture from central venous catheters or from peripherally inserted central catheters (PICC lines). Although blood cultures are usually the basis for a diagnosis of bacterial infection, the bacteremic phase of the illness may be missed by poor timing of cultures or inadequate blood volume sampled. Low-level bacteremia (<10 colony-forming units/mL) has been observed in some infants from birth to 2 mo of age with positive culture results, however 1-2 mL of blood should increase microorganism recovery in the face of low-colony-count sepsis. Automated blood culture systems (BACTEC, Becton Dickinson; BacT/Alert, Organon Teknika), which continuously monitor blood cultures by checking each bottle every few minutes, result in earlier detection of bacterial growth. After positive signaling in the automated system, the specific pathogen is identified by biochemical tests. PCR technology is emerging for more rapid accurate identification of a number of viral and bacterial agents. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry may assist with early identification of pathogens from blood cultures, optimizing empirical antibiotic therapy in the setting of bloodstream infections. This emerging technique is superior to immunological methods of detection and more rapid than culture, especially of slow-growing organisms.

Documentation of a positive blood culture result is the first diagnostic criterion that must be met for sepsis (Table 109-10). However, some neonates with bacterial infection may have negative blood culture results ("clinical infection" or "clinical sepsis"), and other approaches to identification of etiology are needed. Commonly used diagnostic tests include the total WBC count and differential count and the ratio

Table 109-10 Evaluation of a Newborn for Infection or Sepsis

HISTORY (SPECIFIC RISK FACTORS)
Maternal infection during gestation or at parturition (type and duration of antimicrobial therapy):
Urinary tract infection
Chorioamnionitis
Maternal colonization with group B streptococci, *N. gonorrhoeae,* herpes simplex
Gestational age/birthweight
Multiple birth
Duration of membrane rupture
Complicated delivery
Fetal tachycardia (distress)
Age at onset (in utero, birth, early postnatal, late)
Location at onset (hospital, community)
Medical intervention:
Vascular access
Endotracheal intubation
Parenteral nutrition
Surgery
EVIDENCE OF OTHER DISEASES*
Congenital malformations (heart disease, neural tube defect)
Respiratory tract disease (respiratory distress syndrome, aspiration)
Necrotizing enterocolitis
Metabolic disease, e.g., galactosemia
EVIDENCE OF FOCAL OR SYSTEMIC DISEASE
General appearance, neurologic status
Abnormal vital signs
Organ system disease
Feeding, stools, urine output, extremity movement
LABORATORY STUDIES
Evidence of Infection
Culture from a normally sterile site (blood, CSF, other)
Demonstration of a microorganism in tissue or fluid
Molecular detection (blood, urine, CSF)
Maternal or neonatal serology (syphilis, toxoplasmosis)
Autopsy
Evidence of Inflammation
Leukocytosis, increased immature/total neutrophil count ratio
Acute-phase reactants: C-reactive protein, erythrocyte sedimentation rate
Cytokines: interleukin-6, interleukin-B, tumor necrosis factor
Pleocytosis in CSF or synovial or pleural fluid
Disseminated intravascular coagulation: fibrin degradation products, D-dimer
Evidence of Multiorgan System Disease
Metabolic acidosis: pH, P_{CO_2}
Pulmonary function: P_{O_2}, P_{CO_2}
Renal function: blood urea nitrogen, creatinine
Hepatic injury/function: bilirubin, alanine aminotransferase, aspartate aminotransferase , ammonia, prothrombin time, partial thromboplastin time
Bone marrow function: neutropenia, anemia, thrombocytopenia

*Diseases that increase the risk of infection or may overlap with signs of sepsis

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of immature to total neutrophils. Although both have limitations in sensitivity and specificity, an immature : total neutrophil ratio of ≥0.2 suggests bacterial infection. Neutropenia is more common than neutrophilia in severe neonatal sepsis, but neutropenia also occurs in association with maternal hypertension, preeclampsia, and intrauterine growth restriction. Thrombocytopenia is a nonspecific indicator of infection and in some situations may suggest a fungal etiology. Tests to demonstrate an inflammatory response include determinations of C-reactive protein, procalcitonin, haptoglobin, fibrinogen, proteomic markers in amniotic fluid, inflammatory cytokines (including IL-6, IL-8, and tumor necrosis factor-α), and cell surface markers. Some of these modalities are readily available in clinical laboratories, while others are limited to research settings. Some investigators have attempted to develop and validate "sepsis scores" by incorporating different combinations of inflammatory response parameters and clinical presentation, but a single score has not proven to be consistently reliable.

When the clinical findings suggest an acute infection and the site of infection is unclear, LP with culture of CSF, urine culture, and a chest radiograph should be considered in addition to blood cultures. Urine should be collected by catheterization or suprapubic aspiration to avoid contamination. Urine culture for bacteria can be omitted in suspected early-onset infections because hematogenous spread to the urinary tract is rare in the 1st few days of life. Examination of the buffy coat with Gram or methylene blue stain may demonstrate intracellular pathogens. Demonstration of bacteria and inflammatory cells in Gram-stained gastric aspirates on the 1st day of life may reflect maternal amnionitis, which is a risk factor for early-onset infection. Stains of endotracheal secretions in infants with early-onset pneumonia may demonstrate intracellular bacteria, and cultures may reveal either pathogens or upper respiratory tract flora. However, rapid colonization of the neonatal respiratory tract after intubation may make tracheal aspirates less useful as a diagnostic modality for infection. Careful pathologic and microbiologic examination of the placenta can be helpful in the diagnosis of both chronic and acute intrauterine infections.

Diagnostic evaluation (including blood culture) is indicated for asymptomatic infants born to mothers with chorioamnionitis. The probability of neonatal infection correlates with the degree of prematurity and bacterial contamination of the amniotic fluid. Some experts recommend presumptive treatment with antibiotics, usually ampicillin and gentamicin or cefotaxime. In contrast, all symptomatic infants should be treated with antibiotics, usually ampicillin and gentamicin, or cefotaxime, after blood cultures are obtained. There is controversy over whether a LP is necessary for all term infants with suspected early-onset sepsis. Signs and symptoms of sepsis may be nonspecific and may include temperature instability, decreased responsiveness, respiratory distress, poor feeding, emesis, and diarrhea. Findings commonly observed in older infants with bacterial meningitis including stiff neck, bulging fontanel, convulsions, and opisthotonus, are rare in neonates with bacterial meningitis, making identification of neonatal meningitis from a clinical examination challenging. *If a pathogen is isolated from blood culture or if an infant develops signs and symptoms consistent with sepsis, a LP is indicated.* Some organisms such as GBS may be present only in the CSF and not in the blood at the time of an early onset sepsis evaluation. If the mother has been treated with antibiotics for chorioamnionitis, the newborn's blood culture result may be negative, and the clinician must rely on clinical observation and other laboratory tests (Table 109-11).

PNEUMONIA AND PNEUMONITIS

The **differential diagnosis** of pneumonitis in neonates is broad and includes RDS, meconium aspiration syndrome, persistent pulmonary hypertension, diaphragmatic hernia, transient tachypnea of the newborn, congenital heart disease, and BPD. The diagnosis of infectious pneumonia in a neonate is usually presumptive; microbiologic proof of infection is generally lacking because lung tissue is not easily cultured. CDC definitions of ventilator-associated pneumonia were developed to assist with monitoring of this condition in premature and low birthweight infants. Bacteriologic cultures of tracheal aspirates often reflect upper respiratory tract commensal organisms and usually have no etiologic significance. Culture of fluid obtained by bronchoalveolar lavage in a neonate is unreliable because the small bronchoscopes used in neonates cannot be protected from contamination as they are introduced into the distal airways. Short of tissue obtained by lung biopsy, the only reliable bacteriologic cultures are those performed on specimens obtained from blood or pleural fluid. Unfortunately, blood culture results are usually negative in the presence of a clinical pneumonia, and sufficient pleural fluid for culture is rarely present. Culture of pleural fluid obtained from a chest tube is not considered to be from a sterile site unless the specimen was obtained at the time of thoracostomy.

Cultures of respiratory secretions for *U. urealyticum* and other genital *Mycoplasma* species are of little value because neonates are often colonized with these agents as a result of ingestion of colonized secretions from the maternal genital tract. Neonatal *C. trachomatis* may be manifest by an elevated antichlamydial IgM titer, peripheral eosinophilia and elevated serum immunoglobulin levels as well as identification of the organism from the maternal genital tract. Giemsa-stained smears of conjunctivae or nasopharyngeal mucosa may reveal inclusion bodies confirming the diagnosis. Assessments of neonates for the presence of respiratory viruses by molecular analyses of nasopharyngeal specimens and enteroviruses by molecular analysis of blood and CSF may be beneficial during endemic seasons. Other tests of potential value in evaluating neonates with possible infectious pneumonitis are discussed under diagnosis of infections (see Chapter 109.7).

MENINGITIS

The diagnosis of meningitis is confirmed by examination of CSF and identification of a bacterium, virus, or fungus by culture, antigen, or molecular analysis. The importance of the LP as part of the diagnostic evaluation of the neonate with suspected sepsis has been the subject of debate and clinical practice varies. For term infants with suspected early-onset sepsis, many clinicians routinely obtain blood cultures and a complete blood count, because the etiology of 70-85% of term neonates with bacterial meningitis may be demonstrated by blood culture. Examination and culture of CSF may subsequently be undertaken in term infants with symptoms and/or bacteremia. Many clinicians defer the LP in severely ill infants with suspected early-onset infection because of the fear of respiratory and/or cardiovascular compromise associated with positioning for the procedure. In these situations, blood cultures should be performed and treatment initiated for presumed meningitis until an LP can be safely performed. In some situations, pretreatment with antibiotics makes interpretation of the LP results difficult and some experts would empirically treat the neonate for presumptive meningitis, using higher meningitic doses of antimicrobials and for an extended duration based on the suspected pathogen(s).

Term uninfected infants in the 1st wk of life may have the following CSF findings: protein 84 ± 45 mg/dL, glucose 46 ± 10 mg/dL, and leukocyte count 11 ± 10/mm^3 with the 90th percentile for leukocyte count being 22/mm^3. The proportion of polymorphonuclear leukocytes is 2.2 ± 3.8% with the 90th percentile being 6. A cross-sectional study that included neonates ≤56 days of age (15% premature) during 2005-2007 who underwent LP as part of a sepsis evaluation without an anatomical or procedural reason for CSF pleocytosis, and with a negative enterovirus CSF PCR, noted a significantly higher median CSF WBC count in infants ≤28 days old (3/mm^3, 95th percentile: 19/mm^3) than in infants 29–56 days old (2/mm^3, 95th percentile: 9/mm^3). Elevated CSF protein values and leukocyte counts and hypoglycorrhachia may develop in preterm infants after intraventricular hemorrhage. Many nonpyogenic congenital infections (toxoplasmosis, CMV, HSV, syphilis producing an aseptic meningitis) can also produce alterations in CSF protein values and leukocyte counts.

Gram staining of CSF yields an organism in most neonates with bacterial meningitis. The leukocyte count is usually elevated, with a predominance of neutrophils (>70-90%); the number is often >1,000

Table 109-11 Culture-Based and Non–Culture-Based Diagnostics for Neonatal Sepsis

CATEGORY	PARAMETER	OPTIMAL TIMING, VOLUME OF SPECIMEN, ROUTINE/INVESTIGATIONAL	APPLICABILITY FOR NEONATAL SEPSIS
Culture-based			
Blood	Culture	>1 mL of whole blood ROUTINE*	Gold standard for bacteremia
Cerebrospinal fluid (CSF)	Culture	When clinically feasible ROUTINE	Optimize antimicrobial therapy
Urine	Culture	>72 hr of life ROUTINE	Not useful for EOS; potential benefits for LOS
Tracheal aspirate	Culture	ROUTINE	Usually reflects colonization
Non–culture-based			
Immune function	MHC II TNF-α	INVESTIGATIONAL† INVESTIGATIONAL	Both decreased in chorioamnionitis and sepsis
Neutrophil indices	Neutropenia Absolute neutrophil count Absolute immature neutrophil count	After 12 hr of life Consider GA, delivery mode, altitude, arterial versus venous sampling, time since birth ROUTINE	Neutropenia better predictor for sepsis than leukocytosis
Neutrophil markers	CD64	Elevated for 24 hr after infection Requires 50 μL blood Results within hours INVESTIGATIONAL	Cut points between 2.38–3.62 optimal sensitivity, specificity and NPV for EOS
Platelet count	Thrombocytopenia and thrombocytosis	Late findings; slow to respond ROUTINE	Thrombocytopenia associated with fungal infection
CSF cell count	CSF WBC	Uninfected neonates mean 10 cells/mm^3. Range up to 20 cells/mm^3 ROUTINE	Does not predict culture-proven meningitis
CSF chemistries	CSF protein CSF glucose	Term <100 mg/dL preterm higher; 70–80% of serum glucose ROUTINE	Elevated in fungal meningitis Low glucose specific for bacterial meningitis
Acute phase reactants	CRP Procalcitonin	8–24 hr after infection 2–12 hr after infection ROUTINE/INVESTIGATIONAL	Good NPV Better sensitivity but less specificity than CRP
Sepsis panels/scores		After 24 hr of life INVESTIGATIONAL	Most useful for NPV and discontinuation of antimicrobial therapy

*ROUTINE refers to an assay or parameter that is routinely available and widely used.
†INVESTIGATIONAL refers to an assay or parameter that is undergoing evaluation for clinical use and applicability.
CRP, C-reactive protein; CSF, cerebrospinal fluid; EOS, early-onset sepsis; GA, gestational age; LOS, late-onset sepsis; MHC II, major histocompatibility complex class II; NPV, negative predictive value; TNF, tumor necrosis factor; WBC, white blood cell count.
Shane AL, Stoll BJ. Recent developments and current issues in the epidemiology, diagnosis, and management of bacterial and fungal neonatal sepsis. Am J Perinatol *30(2):131–141, 2013.*

but may be <100 in infants with neutropenia or when the CSF is obtained early in the disease course. Microorganisms are recovered from most patients who have not been pretreated with antibiotics. Bacterial organisms have also been noted microscopically and grown from CSF without an abnormal number of WBCs (<25) or with a normal protein level (<200 mg/dL), thus underscoring the importance of performing a culture and Gram stain on all CSF specimens. Contamination of CSF by bacteremia after traumatic LP may occur rarely. Culture-negative meningitis may be seen with antibiotic pretreatment, a brain abscess, or infection with *Mycobacterium hominis, U. urealyticum, Bacteroides fragilis*, enterovirus, or HSV. Use of PCR has improved the ability to detect pathogens rapidly in CSF, especially enteroviruses and HSV. Head ultrasonography or, more often, CT with contrast enhancement may be helpful in diagnosing ventriculitis and brain abscess.

Bibliography is available at Expert Consult.

109.10 Management

EMPIRIC THERAPY

The optimal course of management of neonates with a suspected bacterial infection is determined by the age of the neonate, the prenatal and postnatal environment, and epidemiology (Table 109-12). Once appropriate culture specimens have been obtained intravenous or, less often, intramuscular antibiotic therapy should be instituted immediately. Although it is preferable to have specimens obtained prior to the initiation of antimicrobial therapy to optimize recovery of bacterial organisms, antimicrobial therapy administration should **not be delayed for specimen collection** in clinically ill neonates. Initial empirical treatment of early-onset bacterial infections should consist of ampicillin and an aminoglycoside (usually gentamicin), or cefotaxime. HAIs acquired in a NICU are more likely to be caused by staphylococci, various Enterobacteriaceae, *Pseudomonas* species, or *Candida* species. Thus, an antistaphylococcal drug (oxacillin or nafcillin for *S. aureus* or, more often, vancomycin for coagulase-negative staphylococci or methicillin-resistant *S. aureus*) should be substituted for ampicillin in a previously hospitalized neonate. A history of recent antimicrobial therapy or the presence of antibiotic-resistant infections in the NICU suggests the need for modification of empiric antimicrobial choices. When the history or the presence of necrotic skin lesions suggests *Pseudomonas* infection, initial therapy should consist of antipseudomonal agent, such as piperacillin, ticarcillin, meropenem, or ceftazidime, and an aminoglycoside. Fungal infections, including candidiasis or aspergillosis, should also be considered when necrotic skin lesions at former sites of adhesive tape are observed. These require immediate surgical intervention as well as antifungal therapy.

Involvement of a pharmacist with expertise in neonatal infections and/or use of a guide containing neonatal dosing by weight and

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Table 109-12 Management and Prevention of Neonatal Sepsis

CONDITION	THERAPY	ADDITIONAL CONSIDERATIONS
Empiric management		
Early-onset sepsis	Ampicillin + aminoglycoside. 10 days for bacteremia; 14 days for GBS and uncomplicated meningitis; extend to 21-28 days for complicated infections.	Consider a third-generation cephalosporin (cefotaxime preferred) or carbapenem for meningitis. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Late-onset sepsis	Vancomycin + aminoglycoside. Duration dependent on pathogen and site.	Alternatives to vancomycin may be considered based on local epidemiology and clinical presentation. Aminoglycoside based regimen preferred to cephalosporin given reduced risk of resistance. Consider cephalosporin if meningitis suspected. Consider a carbapenem if third-generation cephalosporin recently received. Consider amphotericin for fungal etiologies. Tailor therapy to pathogen. Consider discontinuation of therapy if pathogen not isolated.
Nonantimicrobial treatment strategies		
Recombinant G-CSF Recombinant G-MSF	Enhance neutrophil number and function, but no reduction in infection when administered as prophylaxis or improvement in survival when administered as therapy.	Insufficient evidence to support the clinical use of G-CSF or GM-CSF either as treatment or prophylaxis to prevent systemic infections.
IVIG[§]	Augments antibody-dependent cytotoxicity and improves neutrophilic function, *but* no evidence that IVIG in suspected or proven sepsis reduces death.	Insufficient evidence from 10 RCTs or quasi-RCTs to support use in neonates with confirmed or suspected sepsis.
Prevention strategies		
IAP	Administration of penicillin or ampicillin 4 hr prior to parturition.	Successfully reduces rates of EOS caused by GBS. No effect on LOS GBS.
Fluconazole prophylaxis	Administration of weight-based dosing to neonates weighing less than 1,500 g.	Most beneficial in NICUs with high baseline rates of invasive candidiasis.
BLF supplementation with a probiotic, *Lactobacillus rhamnosus* (GG)	BLF is a human milk glycoprotein with a role in innate immune response. LGG enhances the activity of lactoferrin.	BLF supplementation with and without LGG reduced the incidence of 1st LOS in 472 VLBW neonates in large randomized, double-blind RCT. Additional confirmatory studies warranted.

BLF, bovine lactoferrin supplementation; EOS, early-onset sepsis; GBS, group B streptococcus; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IAP, intrapartum antimicrobial prophylaxis; IVIG, intravenous immunoglobulin, LGG, *Lactobacillus rhamnosus* GG; LOS, late-onset sepsis; NICUs, neonatal intensive care unit; RCTs, randomized, controlled trials; VLBW, very low birthweight.

Created with data from Carr R, Modi N, Doré C: G-CSF and GM-CSF for treating or preventing neonatal infections. Cochrane Database Syst Rev *(3):CD003066, 2003; Brocklehurst P, Farrell B, King A, et al; INIS Collaborative Group: Treatment of neonatal sepsis with intravenous immune globulin.* N Engl J Med *365:1201–1211, 2011; Manzoni P, Decembrino L, Stolfi I, et al; Italian Task Force for the Study and Prevention of Neonatal Fungal Infections; Italian Society of Neonatology. Lactoferrin and prevention of late-onset sepsis in the pre-term neonates.* Early Hum Dev *86(Suppl 1):59–61, 2010.*

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gestational age may optimize antimicrobial utilization. Peak and trough measurements of antimicrobials may be useful to ensure therapeutic levels and minimize toxicity if the agent is administered for more than 2-3 days and is indicated for certain infections such as meningitis where CSF penetration and levels must be monitored. Trough measurements may be indicated in infants with compromised kidney or liver function who are receiving potentially nephrotoxic or hepatotoxic agents.

Treatment of newborn infants whose mothers received antibiotics during labor should be individualized. If early-onset sepsis is thought to be likely, treatment of the infant should continue until the infant remains asymptomatic for 24-72 hr and clinical and laboratory evidence of recovery is apparent. Furthermore, in the context of intrapartum antibiotic use, it is important to consider that the organism causing infection may be resistant to the intrapartum therapy, thus influencing selection of empiric antibiotics for the infant. For dosing regimens, see organism-specific chapters in Part XVII of this textbook.

DIRECTED THERAPY

Once the pathogen has been identified and its susceptibility determined, the most appropriate antimicrobial should be administered. For most Gram-negative enteric bacteria, ampicillin and an aminoglycoside or a third-generation cephalosporin (cefotaxime or ceftazidime if *Pseudomonas* coverage is needed) should be used. Enterococci should be treated with both a penicillin-containing antibiotic and an aminoglycoside, if the *Enterococcus* is susceptible to gentamicin. The addition of gentamicin to a penicillin provides synergistic bactericidal and postantibiotic effects. Ampicillin alone is adequate for *L. monocytogenes*, and penicillin suffices for GBS. Clindamycin or metronidazole is appropriate for anaerobic infections; metronidazole is preferred for anaerobic infections that involve the CNS because of its better CNS penetration, compared to clindamycin.

Third-generation cephalosporins, such as cefotaxime, are valuable additions for treating documented neonatal sepsis and meningitis because (1) the minimal inhibitory concentrations of these agents needed for treatment of Gram-negative enteric bacilli are much lower than those of the aminoglycosides, (2) excellent penetration into CSF occurs, and (3) relatively higher doses may be administered with less toxicity. The end result is much higher bactericidal titers in serum and CSF than is achievable with ampicillin-aminoglycoside combinations. However, the *routine* use of third-generation cephalosporins for suspected sepsis in neonates is not optimal without a clear indication for broader spectrum empiric therapy. Routine third-generation cephalosporin use has been linked to the rapid emergence of resistant organisms, *Candida* sepsis, and antibiotic-associated diarrhea in neonates.

ANTIMICROBIAL RESISTANCE

The emergence of antibiotic resistance among pathogens that infect newborns is of great concern. Vancomycin-resistant enterococci and vancomycin-insensitive *S. aureus* are emerging pathogens resulting from the widespread use of vancomycin. Although vancomycin use cannot be avoided in neonatal units where methicillin-resistant *S. aureus* is endemic, its use can be reduced by limiting empirical therapy to patients with a high suspicion of severe infection with coagulase-negative staphylococci (severely ill neonate with an indwelling intravascular catheter) and by discontinuing therapy after 2-3 days when blood culture results are negative. When susceptibility results are available and there is no evidence of CNS or endovascular involvement, clindamycin may be a suitable alternative for therapy of uncomplicated bacteremia and skin and soft tissue infections in a neonate.

BACTEREMIA

If a neonate's condition permits, it is ideal to obtain a repeat blood culture from the site of the positive culture at the time of identification of the organism. This second culture may be helpful, especially in situations where the organism isolated would not be susceptible to the empiric or directed therapy that a neonate is receiving. Therapy for most bloodstream infections should be continued for a total of 7-10 days, or for at least 5-7 days after a clinical response has occurred. The duration of therapy is optimally calculated from the date of first negative culture. If successive blood cultures are notable for the presence of pathogens, the possibility of an infected indwelling catheter, endocarditis, an infected thrombus, an occult abscess, subtherapeutic antibiotic levels, or resistant organisms should be considered. A change in antibiotics, longer duration of therapy, or removal of the catheter may be indicated. Consultation with a pediatric infectious disease specialist may be indicated.

PNEUMONIA

A combination of ampicillin and an aminoglycoside or cefotaxime is appropriate for pneumonia that develops during the 1st 7-10 days of life. Nosocomial pneumonia, which generally manifests in the 2nd wk of life can be treated empirically with ampicillin or vancomycin and an aminoglycoside or a third-generation cephalosporin. *Pseudomonas* pneumonia should be treated with an agent to which the organism is susceptible. Some experts would consider the use of dual therapy for multidrug resistant organisms; however, the benefits of this therapy may vary based on host and pathogen. Pneumonia caused by *C. trachomatis* usually presents between the 1st and 3rd mo of life and is usually treated with oral erythromycin. The effectiveness of erythromycin in treating pneumonia caused by *C. trachomatis* is approximately 80%; in certain clinical situations, a second course of therapy might be required. Data are limited regarding the use of macrolides, such as azithromycin, for neonatal *C. trachomatis* pneumonia, although some practitioners prefer this agent to erythromycin because of the shorter course of azithromycin and the slightly increased risk of pyloric stenosis associated with oral erythromycin in neonates <6 wk of age. *U. urealyticum* infections may be treated with erythromycin.

MENINGITIS

Empiric antimicrobial therapy for bacterial meningitis should include ampicillin in doses used for meningitis, unless staphylococci are likely, in which case vancomycin may be considered. Neonates with shunts may be predisposed to developing meningitis and ventriculitis attributable to resistant Gram-positive organisms. Cefotaxime or gentamicin in meningitic doses are appropriate choices for empiric Gram-negative coverage. Susceptibility testing of Gram-negative organisms is important because resistance to cephalosporins and aminoglycosides is common. Most aminoglycosides administered by parenteral routes do not achieve sufficiently high antibiotic levels in the lumbar CSF or ventricles to inhibit the growth of Gram-negative bacilli. Therefore, some experts recommend a combination of intravenous ampicillin and a third-generation cephalosporin for the treatment of neonatal Gram-negative meningitis. Cephalosporins should not be used as *empirical monotherapy* in neonates <3 mo of age when early or late onset listeriosis is suspected because *L. monocytogenes* is resistant to cephalosporins. Although a rare cause of meningitis in the neonate, enterococci are also resistant to cephalosporins.

Meningitis caused by GBS usually responds clinically within 24-48 hr of antimicrobial therapy. Therapy should be continued for 14-21 days. Gram-negative bacilli may continue to grow from repeated CSF samples for 72-96 hr after the initiation of effective therapy, as a result of the intracellular habitat of many organisms. Treatment of Gram-negative meningitis should be continued for 21 days or for at least 14 days after sterilization of the CSF, whichever is longer. *P. aeruginosa* meningitis should be treated with ceftazidime or meropenem, assuming that the isolate is susceptible. Metronidazole is the treatment of choice for infection caused by *B. fragilis* and other anaerobic organisms. Prolonged antibiotic administration, with or without surgical drainage is indicated for neonatal cerebral abscesses. Imaging is recommended for patients with suspected ventriculitis, hydrocephalus, or cerebral abscess (initial and follow-up assessments) and for those with an unexpectedly complicated course (prolonged coma, focal neurologic deficits, persistent or recurrent fever).

Neonates with suspected neonatal herpes meningoencephalitis should receive intravenous acyclovir; empirical antibacterial therapy may be considered in symptomatic infants with a CSF mononuclear pleocytosis, but this should be discontinued and acyclovir continued if bacterial cultures are negative and a CSF HSV PCR is positive. Supportive care is the current recommended management for severe enteroviral infections such as meningoencephalitis, carditis, and hepatitis. There are currently no Food and Drug Administration-licensed therapies for neonatal enteroviral infections. The effectiveness of intravenous immunoglobulin is unknown. A phase II double-blind, placebo controlled virologic efficacy trial of pleconaril in neonatal enteroviral sepsis syndrome concluded enrollment in 2010 and data analysis is ongoing.

ADJUNCTIVE THERAPIES

Treatment of neonatal infections may be divided into antimicrobial therapy for the suspected or known pathogen and supportive care. Careful attention to respiratory and cardiovascular status is mandatory. Adequate oxygenation of tissues should be maintained; ventilatory support is frequently necessary for respiratory failure caused by sepsis, pneumonia, pulmonary hypertension, or acute respiratory distress syndrome. Refractory hypoxia and shock may require extracorporeal membrane oxygenation, which has reduced mortality rates in full-term infants with respiratory failure. Shock and metabolic acidosis should be identified and managed with fluid resuscitation and inotropic agents as needed. Corticosteroids should be administered only for adrenal insufficiency and in cases of TB meningitis. Fluids, electrolytes, and glucose levels should be monitored carefully with correction of hypovolemia, hyponatremia, hypocalcemia, and hypoglycemia/hyperglycemia. Hyperbilirubinemia should be monitored and treated aggressively with phototherapy and/or exchange transfusion, because the risk of kernicterus increases in the presence of sepsis and meningitis. Seizures should be treated with anticonvulsants. Parenteral nutrition is needed for any infant who cannot sustain enteral feeding.

DIC may complicate neonatal septicemia. Platelet counts, hemoglobin levels, and clotting times should be monitored. DIC is treated by management of the underlying infection, but if bleeding occurs, DIC management may require fresh-frozen plasma, platelet transfusions, or whole blood.

Because neutrophil storage pool depletion has been associated with a poor prognosis, therapies that increase the number or improve the quality of neutrophils have been studied, including granulocyte transfusions, GM-CSF, and G-CSF. The use of G-CSF or GM-CSF abolishes sepsis-induced neutropenia, but none of these therapies has been shown to definitively improve survival.

It is important to remember that nonbacterial infectious agents can produce the syndrome of neonatal sepsis. HSV infection requires immediate specific treatment, as does systemic *Candida* infection. Treatment and other aspects of various nonbacterial infections are discussed in detail in other sections: TB (see Chapter 215), syphilis (see

Chapter 218), genital mycoplasmas (see Chapter 224.2), *C. trachomatis* (see Chapter 226.2), *Candida* (see Chapter 234.1), rubella (see Chapter 250), enteroviruses (see Chapter 250), parvovirus B19 (see Chapter 251), HSV (see Chapter 252), VZV (see Chapter 253), and CMV (see Chapter 255).

Bibliography is available at Expert Consult.

109.11 Complications and Prognosis

Complications of bacteremic infections include endocarditis, septic emboli, abscess formation, septic joints with residual disability, and osteomyelitis and bone destruction. Recurrent bacteremia is rare (<5% of patients). Candidemia may lead to vasculitis, endocarditis, and endophthalmitis, as well as to abscesses in the kidneys, liver, lungs, and brain. Sequelae of sepsis may result from septic shock, DIC, or organ failure.

Mortality rates from the sepsis syndrome depend on the definition of sepsis. In adults, the mortality rate approaches 50%, and the rate in newborn infants is probably at least that high. Reported mortality rates in neonatal sepsis are as low as 10%, because all bacteremic infections are included in the definition. Several studies have documented that the sepsis case fatality rate is highest for Gram-negative and fungal infections.

The case fatality rate for neonatal bacterial meningitis is between 20% and 25%. Many of these patients have associated sepsis. Risk factors for death or for moderate or severe disability include seizure duration >72 hr, coma, need for inotropic agents, and leukopenia. Immediate complications of meningitis include ventriculitis, cerebritis, and brain abscess. Late complications of meningitis occur in 40-50% of survivors and include hearing loss, abnormal behavior, developmental delay, cerebral palsy, focal motor disability, seizure disorders, and hydrocephalus. Advanced imaging (CT, MRI) has demonstrated cerebritis, brain abscess, infarct, subdural effusions, cortical atrophy, and diffuse encephalomalacia in newborns surviving meningitis. A number of these sequelae may be encountered in infants with sepsis but without meningitis, as a result of cerebritis or septic shock. Extremely low birthweight infants (<1,000 g) with sepsis are at increased risk for poor neurodevelopmental and growth outcomes in early childhood.

Bibliography is available at Expert Consult.

109.12 Prevention

MATERNAL STRATEGIES

Maternal immunization protects the mother against vaccine-preventable diseases that can cause intrauterine infections (rubella, hepatitis B, VZV) and may also protect the infant via passive transfer of protective maternal antibodies (tetanus). CMV vaccines are under study. Toxoplasmosis is preventable with appropriate diet and avoidance of exposure to aged cat feces. Malaria during pregnancy can be minimized with chemoprophylaxis and use of insecticide-treated bed nets. Congenital syphilis is preventable by timely diagnosis and appropriate early treatment of infected pregnant women.

Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy during labor, along with rapid delivery of the infant, reduces the risk of early-onset neonatal sepsis. Vertical transmission of GBS and early-onset GBS disease is significantly reduced by selective intrapartum chemoprophylaxis (see Chapter 184). A number of candidate GBS vaccines are currently being studied. Neonatal infection with *Chlamydia* can be prevented by identification and treatment of infected pregnant women (see Chapter 226). Mother-to-child transmission of HIV is significantly reduced by maternal antiretroviral therapy during pregnancy, labor, and delivery, cesarean section delivery prior to rupture of membranes, and antiretroviral treatment of the infant after birth (see Chapter 276).

ANTIFUNGAL PROPHYLAXIS

Prophylactic administration of fluconazole during the 1st 6 wk of life reduces fungal colonization and invasive fungal infection in extremely low birth weight infants—those with birth weights <1000 g. In addition to the individual benefit afforded by prophylaxis for VLBW neonates, fluconazole prophylaxis may have a community impact by decreasing the overall fungal burden of a NICU. Results from more than 14 trials at multiple institutions with 3,100 neonates suggests that fluconazole prophylaxis decreases colonization of the urine, gastrointestinal tract, and integument, without promoting the development of resistance and without adverse effects. Based on an annual United States preterm birth cohort of approximately 30,000 VLBW infants, it has been estimated that fluconazole prophylaxis could prevent approximately 2,000-3,000 cases of invasive candidiasis, approximately 200-300 deaths, and the adverse neurodevelopmental outcomes of invasive candidiasis in approximately 400-500 infants per year. Differing baseline rates of fungal infections, practices related to central venous catheter removal, severity of illness, and practices related to the use of broad-spectra antimicrobials make universal recommendations regarding prophylaxis challenging.

Neonatal practices that may reduce the risks of invasive candidiasis include, limited use of broad spectrum antimicrobials, use of an aminoglycoside instead of a cephalosporin for empiric therapy when meningitis or antimicrobial resistance is not suspected, limitation of postnatal steroid use in VLBW infants, early enteral feeding, and the establishment of the neonatal gut microbiome with human milk feeding

OTHER STRATEGIES FOR PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS

Because of the burden of disease, additional strategies including lactoferrin and probiotic supplementation and the administration of antistaphylococcal monoclonal antibodies have been explored as strategies to prevent HAIs. Although antistaphylococcal monoclonal antibodies have not proven to be of benefit, preliminary data suggest that bovine lactoferrin (BLF) supplementation alone and in combination with probiotics may reduce late onset sepsis. A prospective, multicenter, double-blind, randomized placebo-controlled trial in 11 tertiary care NICUs compared BLF alone or in combination with the probiotic *Lactobacillus rhamnosus* GG (LGG). Over a 9 mo period from 2007-2008, 472 VLBW neonates received placebo, LGG and BLF, or BLF only, daily from birth through 30 days of life or 45 days. Compared with placebo, BLF supplementation with and without LGG reduced the incidence of the first late-onset sepsis episode in VLBW neonates. Further studies of lactoferrin, with and without probiotics, to reduce risk of neonatal sepsis are indicated

ANTIMICROBIAL STEWARDSHIP

Antimicrobial utilization practices in NICUs influence the types of microorganisms responsible for neonatal sepsis and their resistance patterns. The CDC has initiated a campaign to prevent antimicrobial resistance in healthcare settings. This effort is designed to increase clinician awareness and to improve diagnosis and appropriate treatment of infection. The campaign supports involving infectious disease and pharmacy consultants, treating infections with an antimicrobial with the narrowest spectrum and discontinuing therapy when adequate therapy has been administered. Prevention of infections through optimizing infection control and enhanced surveillance are additional components of the campaign.

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Adolescent Medicine

PART XIII

Chapter 110
Adolescent Development

See also Part XVI and Chapters 561 and 562.

110.1 Adolescent Physical and Social Development

Cynthia Holland-Hall and Gale R. Burstein

During the preteen, teenage, and young adult years, young people undergo not only dramatic changes in physical appearance, but also rapid changes in physiologic, psychological, and social functioning. Hormonally driven physiologic changes and ongoing neurologic development occur in the setting of social structures that foster the transition from childhood to adulthood. This period of development comprises *adolescence*, which is divided into 3 phases—early, middle, and late adolescence—each marked by a characteristic set of biologic, cognitive, and psychosocial milestones (Table 110-1). Although individual variations in the timing and pace of development undoubtedly exist, these changes follow a fairly predictable pattern of occurrence. Gender and culture profoundly affect the developmental course, as do physical, social, and environmental influences. Given the interaction of these domains, a biopsychosocial approach is best suited to approach the healthcare of the adolescent.

PHYSICAL DEVELOPMENT

Puberty is the biologic transition from childhood to adulthood. Pubertal changes include the appearance of the secondary sexual characteristics, increase in height, change in body composition, and development of reproductive capacity. Adrenal production of androgen (chiefly **dehydroepiandrosterone sulfate [DHEAS]**) may occur as early as 6 yr of age, with development of underarm odor and faint genital hair (adrenarche). Maturation of the **gonadotropin-releasing hormone** pulse generator is among the earliest neuroendocrine changes associated with the onset of puberty. Under the influence of gonadotropin-releasing hormone, the pituitary gland secretes **luteinizing hormone** and **follicle-stimulating hormone**; initially this occurs in a pulsatile fashion primarily during sleep, but this diurnal variation diminishes throughout puberty. Luteinizing hormone and follicle-stimulating hormone stimulate corresponding increases in gonadal androgens and estrogens. The triggers for these changes are incompletely understood, but may involve the hormone leptin, high concentrations of which are associated with increased body fat and earlier onset of puberty.

Sexual Development

The progression of the development of the secondary sex characteristics may be described using the **sexual maturity rating (SMR) scale (ranging from 1, preadolescence, to 5, sexual maturity)**, or **Tanner stages**. Figures 110-1 and 110-2 depict the physical findings of breast and pubic hair maturation at each SMR. Figures 110-3 and 110-4 depict the typical sequence of pubertal changes in males and females, respectively. The range of normal progress through sexual maturation is wide, and is affected by genetics, the psychosocial environment, nutrition, and overall health status. Environmental exposures may play a role as well.

In males, the first visible sign of puberty and the hallmark of SMR 2 is testicular enlargement, beginning as early as 9.5 yr, followed by the development of pubic hair. This is followed by penile growth during SMR 3. Peak growth occurs when testis volumes reach approximately 9-10 cm^3 during SMR 4. Under the influence of luteinizing hormone and testosterone, the seminiferous tubules, epididymis, seminal vesicles, and prostate enlarge. Sperm may be found in the urine by SMR 3; nocturnal emissions may be noted at this time as well. Some degree of breast tissue growth, typically bilateral, occurs in 40-65% of males during SMR 2-3 as a consequence of a relative excess of estrogenic stimulation. This generally resolves with ongoing maturation.

In females, typically the first visible sign of puberty and the hallmark of SMR 2 is the appearance of breast buds (thelarche), between 8 and 12 yr of age. A significant minority of females develops pubic hair (pubarche) prior to thelarche. Less visible changes include enlargement of the ovaries, uterus, labia, and clitoris, and thickening of the endometrium and vaginal mucosa. A clear vaginal discharge may be present prior to menarche (physiologic leukorrhea). Menses typically begins 2.5 yr after the onset of puberty, during SMR 3-4 (average age: 12.5 yr; normal range: 9-15 yr) (see Fig. 110-4). The timing of menarche is determined largely by genetics; contributing factors likely include adiposity, chronic illness, nutritional status, and the psychosocial environment. Early menstrual cycles often are anovulatory, and therefore somewhat irregular, but typically occur every 21-45 days and include 3-7 days of bleeding.

The onset of puberty and menarche appear to be occurring at earlier ages than previously reported in the United States. Several studies from 1948-1981 identified the average age for the onset of breast development as ranging from 10.6-11.2 yr of age. Multiple reports since 1997 suggest a significantly earlier average age of onset, ranging from 8.9-9.5 yr in African-American females and 10.0-10.4 yr in white females. Nearly 25% of African-American females and 10% of white females initiate breast development by 7 yr of age. There also appears to be a trend toward decreasing ages for the onset of pubic hair development and menarche. Data from the National Health and Nutrition Examination Survey, a nationally representative, longitudinal survey in the United States, show a decline in the average age of menarche of 4.9 mo between the 1960s and 2002. Changes in the timing of menarche *within* ethnic groups, however, were significantly smaller. The larger change seen in the population as a whole may be partially explained by changes in the ethnic makeup of the sample. The reasons for the larger decrease in age for breast development have been postulated to include the epidemic of childhood obesity as well as exposure to estrogen-like environmental toxins (endocrine disruptors), but further research in this area is needed.

Although fewer data are available on changes in the timing of puberty in males, they may be experiencing a similar trend. Although the method of assessing the onset of puberty (i.e., inspection vs. palpation of the testes) varies between studies, it appears that the average age for the onset of genital and pubic hair development may have decreased by 1-2 yr over the past several decades in many industrialized countries. An association of obesity with later onset of puberty in males has been theorized, but has not been consistently demonstrated.

Somatic Growth (See Also Fig. 13-1)

Linear growth acceleration begins in early adolescence for both genders, with 15-20% of adult height accrued during puberty. Females attain a peak height velocity (PHV) of 8-9 cm/yr at SMR 2-3, approximately 6 mo before menarche. Males typically begin their growth

Table 110-1 Milestones in Early, Middle, and Late Adolescent Development

VARIABLE	EARLY ADOLESCENCE	MIDDLE ADOLESCENCE	LATE ADOLESCENCE
Approximate age range	10-13 yr	14-17 yr	18-21 yr
Sexual maturity rating*	1-2	3-5	5
Physical	• Females: Secondary sex characteristics (breast, pubic, axillary hair), start of growth spurt • Males: testicular enlargement, start of genital growth	• Females: peak growth velocity, menarche (if not already attained) • Males: growth spurt, secondary sex characteristics, nocturnal emissions, facial and body hair, voice changes • Change in body composition • Acne	• Physical maturation slows • Increased lean muscle mass in males
Cognitive and moral	• Concrete operations • Egocentricity • Unable to perceive long-term outcome of current decisions • Follow rules to avoid punishment	• Emergence of abstract thought (formal operations) • May perceive future implications, but may not apply in decision making • Strong emotions may drive decision making • Sense of invulnerability • Growing ability to see others' perspectives	• Future-oriented with sense of perspective • Idealism • Able to think things through independently • Improved impulse control • Improved assessment of risk vs. reward • Able to distinguish law from morality
Self-concept/identity formation	• Preoccupied with changing body • Self-consciousness about appearance and attractiveness	• Concern with attractiveness • Increasing introspection	• More stable body image • Attractiveness may still be of concern • Consolidation of identity
Family	• Increased need for privacy • Exploration of dependence/independence boundaries	• Conflicts over control and independence • Struggle for greater autonomy • Increased separation from the parents	• Emotional and physical separation from family • Increased autonomy • Reestablishment of "adult" relationship with parents
Peers	• Same-sex peer affiliations	• Intense peer group involvement • Preoccupation with peer culture • Conformity	• Peer group and values recede in importance
Sexual	• Increased interest in sexual anatomy • Anxieties and questions about pubertal changes • Limited capacity for intimacy	• Testing ability to attract partner • Initiation of relationships and sexual activity • Questions of sexual orientation	• Consolidation of sexual identity • Focus on intimacy and formation of stable relationships • Planning for future and commitment

*See text and Figures 110-1 and 110-2.

acceleration at a later SMR stage, achieve a PHV of 9-10 cm/yr later in the course of puberty (SMR 3-4), and continue their linear growth for approximately 2-3 yr after females have stopped growing (Fig. 110-5). The growth spurt begins distally, with enlargement of the hands and feet, followed by the arms and legs, and finally, the trunk and chest. This growth pattern imparts a characteristic "awkward" appearance to some early adolescents. Body composition changes as well, following the attainment of PHV. Males undergo an increase in lean body mass (sometimes referred to as the "strength spurt"), whereas females develop a higher proportion of body fat. Scoliosis, if present, may progress with rapid axial skeleton growth (see Chapter 679.1). One-half to ⅔ of total body calcium is laid down during puberty. Bone growth precedes increases in bone mineralization and bone density, which may increase the adolescent's risk of fracture during times of rapid growth. Since skeletal growth precedes muscle growth, sprains and strains may be more common during this time as well.

Cardiovascular changes in middle adolescence include increased heart size, higher blood pressure, and increases in blood volume and hematocrit, particularly in males. Coupled with an increase in lung vital capacity, these changes lead to greater aerobic capacity. Androgenic stimulation of sebaceous and apocrine glands may result in acne and body odor. Rapid enlargement of the larynx, pharynx, and lungs leads to changes in vocal quality in males, typically preceded by vocal instability (voice cracking). Elongation of the optic globe often results in myopia (see Chapter 620). Dental changes include jaw growth, loss of the final deciduous teeth, and eruption of the permanent cuspids, premolars, and finally, molars (see Chapter 307). Orthodontic appliances may be needed, secondary to growth exacerbations of bite disturbances. Physiologic changes in sleep patterns and increased sleep requirements occur, causing many adolescents to delay sleep onset at night, with subsequent difficulty awakening for early school start times in the morning (see Chapter 19).

NEUROLOGIC, COGNITIVE, AND MORAL DEVELOPMENT

Cognitive development correlates more closely with chronologic age than pubertal maturation. As children progress through adolescence, they develop and refine their ability to use formal operational thought processes. Abstract, symbolic, and hypothetical thinking replaces the need to manipulate concrete objects. Middle and late adolescents develop the ability to consider multiple options and to assess the long-term consequences of their actions. The capacity for verbal expression is enhanced. Since adolescents' decision-making and subsequent behaviors are the largest determinants of their mortality and morbidity, understanding these cognitive processes is of critical importance.

The belief that major structural brain development is completed in childhood is outdated. It is now clear that neuromaturation continues into the third decade. This maturation is characterized by decreases in gray matter, increases in white matter, and an apparent increase in the efficiency of communication and connectivity between different brain regions. Gray matter volume peaks in the frontal lobes in preadolescence, then decreases. This decrease is a consequence of selective "pruning" of rarely used synaptic connections. Increased white matter volume is believed to reflect increasing myelination and subsequent

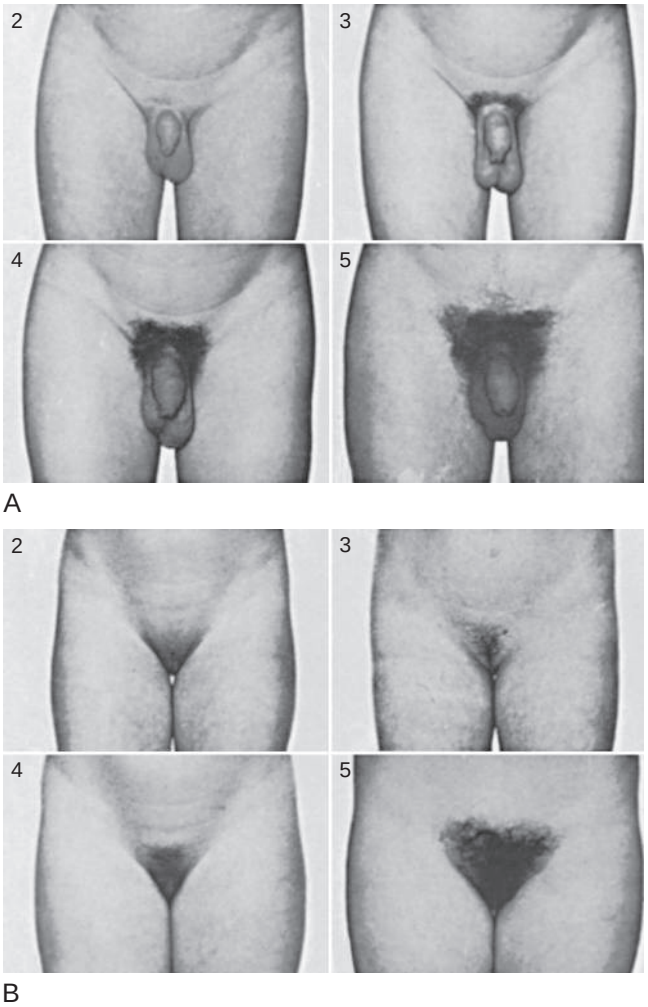

Figure 110-1 Sexual maturity ratings (2-5) of pubic hair changes in adolescent males *(A)* and females *(B)* (see Tables 110-2 and 110-3). *(Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London, London, England.)*

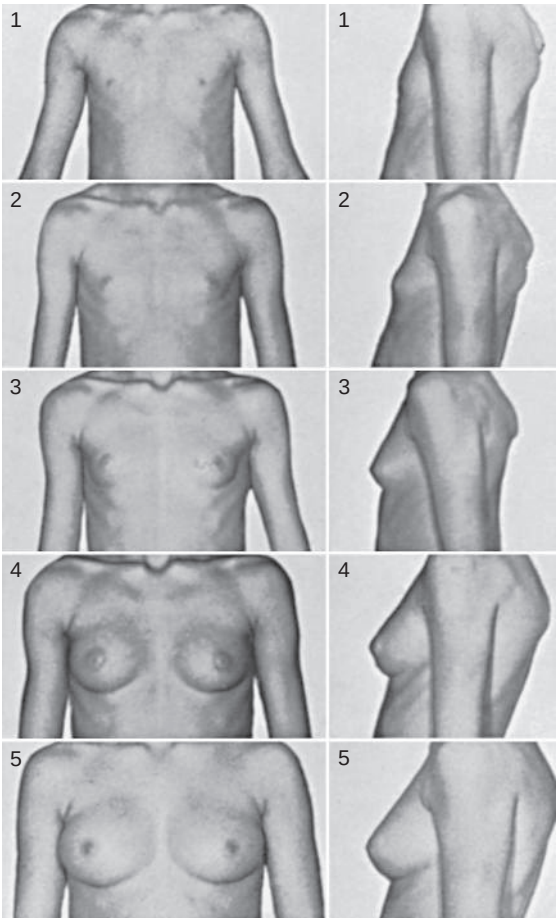

Figure 110-2 Sexual maturity ratings (1-5) of breast changes in adolescent females. *(Courtesy of J.M. Tanner, MD, Institute of Child Health, Department for Growth and Development, University of London, London, England.)*

facilitation of integrated brain activity and more efficient transmission of information between different regions of the brain. These changes are first seen in the posterior cortex (sensory and motor regions), and progress anteriorly (Fig. 110-6). The frontal lobes are among the last areas of the brain to mature, including the prefrontal cortex, the region of the brain associated with executive function: the coordination of complex cognitive processes including impulse control, working memory, the consideration of multiple options and their possible consequences, and the evaluation of risk and reward, among others. (see Chapter 7).

The behavioral correlates of these anatomical changes are speculative; adolescent behaviors may in part be biologically driven and reflect the relative immaturity of the prefrontal cortex and its communication with other regions of the brain. The earlier maturation of the amygdala and other limbic structures, which are involved in the experience of fear and emotion, relative to the frontal executive function systems, which facilitate the regulation and interpretation of those emotional experiences, could explain why adolescents are more likely to make poor decisions in highly emotionally charged situations, relative to mature adults. These so-called "hot cognition" processes may result in the adolescent making a different decision in the context of a strong affective experience than he or she would in a less emotional state ("cool cognition"). These 2 types of cognitive processes may not develop at the same rate; the adolescent may be able to use higher brain structures and functions more effectively when in states of lower

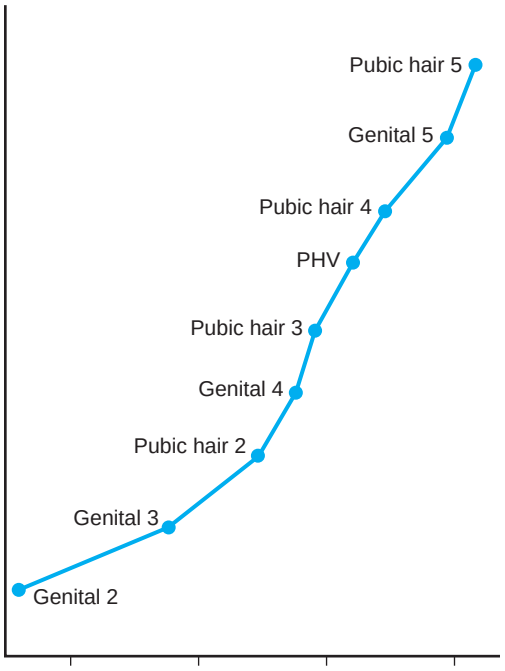

Figure 110-3 Sequence of pubertal events in males. PHV, peak height velocity. *(From Root AW: Endocrinology of puberty,* J Pediatr *83:1, 1973.)*

Table 110-2 Sexual Maturity Rating Stages in Females

SMR STAGE	PUBIC HAIR	BREASTS
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound; diameter of areola increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant, but less than in adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

SMR, sexual maturity rating.
From Tanner JM: Growth at adolescence, *ed 2, Oxford, England, 1962, Blackwell Scientific.*

Table 110-3 Sexual Maturity Rating Stages in Males

SMR STAGE	PUBIC HAIR	PENIS	TESTES
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Minimal change/enlargement	Enlarged scrotum, pink, texture altered
3	Darker, starting to curl, small amount	Lengthens	Larger
4	Resembles adult type, but less quantity; coarse, curly	Larger; glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

SMR, sexual maturity rating.
From Tanner JM: Growth at adolescence, *ed 2, Oxford, England, 1962, Blackwell Scientific.*

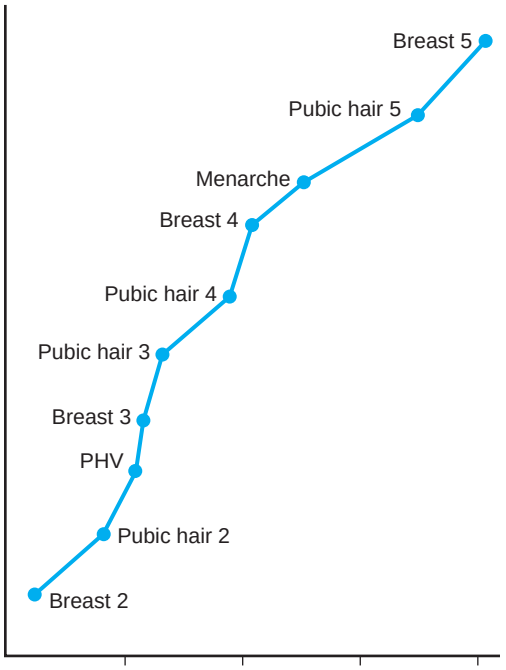

Figure 110-4 Sequence of pubertal events in females. PHV, peak height velocity. *(From Root AW: Endocrinology of puberty,* J Pediatr *83:1, 1973.)*

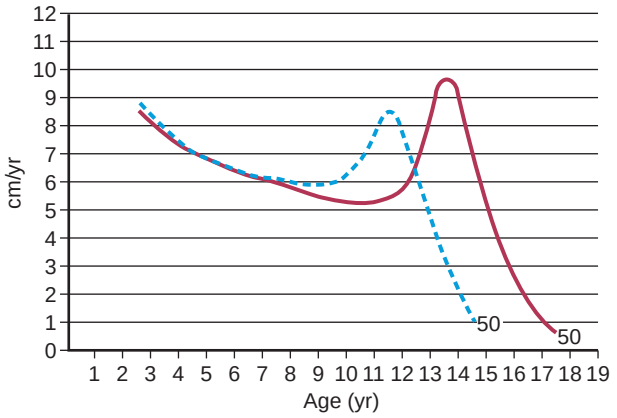

Figure 110-5 Height velocity curves for American males *(solid line)* and females *(dashed line)* who have their peak height velocity at the average age (i.e., average growth tempo). *(From Tanner JM, Davies PSW: Clinical longitudinal standards for height and height velocity for North American children,* J Pediatr *107:317, 1985.)*

emotional arousal. Adolescents' risk taking, desire for immediate gratification, and increased sensation and novelty seeking are similarly believed to result, in part, from this asynchronous brain maturation.

Early adolescents often continue to employ the concrete operational cognitive processes of childhood. Although formal operational cognition is developing, it may be applied inconsistently across different domains. A young adolescent may be able to use abstract thought when completing schoolwork, but not when working through a personal dilemma. Early adolescence also is characterized by egocentricity, the adolescent's belief that they are the center of everyone's attention. Despite being largely imagined, this perception of always being "on stage" can be stressed to the adolescent, who may feel that others are constantly judging or evaluating the adolescent. Early adolescents express a greater need for privacy than they did in childhood, and begin to appreciate the privacy of their own thoughts. With ongoing cognitive development, middle adolescents are more able to consider the needs and feelings of other people. Their creativity and intellectual abilities are enhanced. Perhaps as a result of their increased capacity for abstract thought in combination with a persistent perception of uniqueness, middle adolescents may feel a sense of immortality and immunity to the consequences of risky behaviors. Late adolescents are more future-oriented and able to delay gratification. They can think more independently, consider others' views, and compromise. They have a stronger sense of self, and more stable interests. Under times of

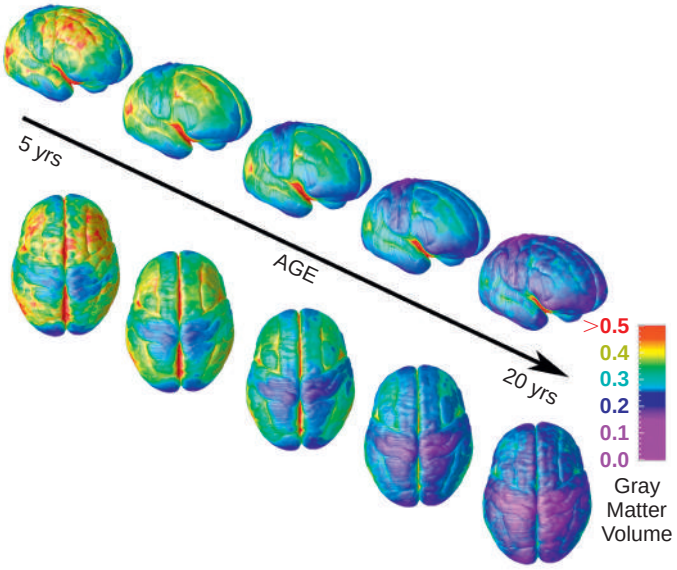

Figure 110-6 Brain Maturation ages 5-20 yr. Constructed from MRI scans of healthy children and teens, figure compresses 15 yr of brain development (ages 5-20) Red = more gray matter, blue = less gray matter. Gray matter wanes in a back-to-front wave as the brain matures and neural connections are pruned. *(Courtesy of Paul Thompson, PhD. UCLA Laboratory of Neuroimaging.)*

stress, adolescents may temporarily revert back to the cognitive processes and coping strategies used at younger ages.

Moral development generally accompanies cognitive development. Preadolescents, concrete and individualistic, follow rules in order to please authority figures and avoid punishment. As they move into early adolescence, they develop a stronger sense of right and wrong, but are likely to perceive these as absolute and unquestionable. Middle and late adolescents may establish a sense of morality driven by their desire to be seen as a good person, to behave in a manner according to their perceived place in society, or by their sense of obligation to care for others. Moral decision making still may be highly subject to emotional context, however. Late adolescents may develop a rational conscience and an independent system of values, though these often are ultimately consistent with parental values. While going through this complex developmental process, religious or political organizations that promote simple answers to complex social or moral questions may hold great appeal to the adolescent.

PSYCHOSOCIAL DEVELOPMENT

In contrast to cognitive development, psychosocial development correlates more strongly with pubertal status and physical maturation than with chronologic age. While cognitive development is more biologically determined, psychosocial development is subject to greater environmental and cultural influences. Indeed, cultural variation can be dramatic. Some late adolescents move immediately from high school into marriage, childbearing, working, and financial independence; others remain dependent on the parents while pursuing their own education for several more years, in a period sometimes referred to as *emerging adulthood*. Psychosocial development also may be nonlinear, with different domains of growth progressing along different timelines. An overriding theme of psychosocial development is the concept of identity formation and consolidation as the adolescent moves away from the nurturing protection of the family, develops an increased affiliation with the peer group(s), and ultimately defines himself or herself as an individual.

Separation from the parents is a hallmark of adolescent development. Early adolescents start to seek out more privacy at home, spending less time with the parents. They begin to reject parental advice and involvement in their decision-making as they explore the boundaries of their dependence on, and independence from, their parents. With evolving cognitive skills, an adolescent has the ability to conceive of an ideal parent, and contrast this ideal with his or her own parents. Adolescents may seek out alternative adult role models, such as teachers, coaches, or parents of friends. Parent–child conflict often peaks during middle adolescence, with disagreements over privileges, independence, and other limits set by the parents. Adolescents may appear intermittently to seek and reject parental acceptance. It is theorized that perhaps the adolescent *needs* to conceive of the parents as "wrong" in order to ameliorate the pain of separating from them. Throughout this time, however, the parents remain a critical source of nurturing and support for the adolescent, and continue to exert significant influence over the adolescent's decision making. Paradoxically, frequent arguments and conflict may coexist with strong emotional bonds and closeness. The late adolescent may reestablish a more "adult–adult" type of relationship with the parents, once again seeking out and considering parental advice and guidance as they enter adulthood.

Increasing importance of the peer group also may buffer the emotional trauma of separating from the parents. Early adolescents tend to socialize largely with same sex peers, both in their individual friendships and larger groups. Females' peer groups tend to be more relationship oriented, whereas males' peer groups are more likely to be centered around a particular activity. In both cases, group cohesion and a sense of belonging become important. Peers become increasingly important in middle adolescence, during which time the adolescent may experiment with being a part of different groups and "try on" different identities. These groups may include both genders. Peer groups may arise from organized activities, such as sports or clubs, or may simply be friendship based. Gang membership is another form of peer acceptance. Conformity with the peers in manners of dress, speech, and behavior is a normal part of this process, and should not necessarily be viewed negatively. Similarly, peer pressure may exist, but its influence over the adolescent's decision making may be positive, negative, or negligible. Acceptance and successful navigation of peer groups during adolescence may give the individual more confidence to move into and out of various social, academic, and professional groups in the future. Late adolescents are less vulnerable to peer group influence, having moved closer to establishing their own stable identity. Their cognitive skills allow them to choose selectively among different peer groups, endorsing and adopting individual values and behaviors that best reflect who they are becoming.

Early adolescents have increased **sexual awareness and interest**, which may manifest as sexual talk and gossip, and often is focused on sexual anatomy. Masturbation and other sexual exploration, sometimes with same-sex peers, are common. The prevalence of other forms of sexual behavior varies by culture; in general, these behaviors are less common in early adolescents. Romantic relationships, if they exist at all, lack emotional depth. Sexual curiosity, experimentation, and activity become more common among middle adolescents. Same-sex attraction is common; sexual orientation may become clear to some adolescents, but still may be evolving in others during this time. Dating behaviors may be seen, but this is culture dependent and may not be a popular construct for all adolescents. Individual relationships often continue to emphasize sexual attraction over emotional intimacy, the latter of which may not be seen until late adolescence. At this time, relationships increasingly involve love and commitment, and demonstrate greater stability.

Body image may affect (and be affected by) adolescents' psychosocial development as well. Early and middle adolescence are commonly the ages at which poor or distorted body image and eating disorders develop. Early adolescents undergo rapid physical changes and may experience uncertainty about whether all of these anatomic and physiologic changes are progressing normally. Reassurance from adults, including their healthcare providers, may be comforting. As puberty comes to an end and these changes slow, the middle adolescent's preoccupation may shift to whether the adolescent is attractive to others. A strong emphasis on physical appearance during this time is normal. Although this focus on physical appearance may continue into adulthood, late adolescence generally is characterized by a shifting balance

toward introspection, with somewhat less emphasis placed on external characteristics.

The **timing of pubertal changes** also can affect psychosocial development and well-being. The progression of pubertal changes in males is generally associated with a positive self-image. Females may initially perceive these changes in their physical appearance more negatively. This appears to be especially true for early-maturing females, some of whom experience greater decreases in self-esteem, engage in more disruptive behaviors, and have more conflict with their parents than do on-time or late-maturing females. Perhaps because they are more comfortable associating with older peers, they are vulnerable to making poor decisions when exposed to high-risk situations, still lacking the cognitive skills to effectively navigate these situations. Early-maturing males tend to have greater self-confidence, social, and academic success, while later-maturing males are at risk for more internalizing behaviors and diminished self-esteem. Many other factors influence how adolescents experience puberty, and supportive peers and adults can have a positive impact on psychosocial development. With successful navigation of these domains, the emerging adult moves into the world with a strong sense of personal identity and their place in society. They are able to work toward a vocation and financial independence, and to manage the responsibilities of adulthood.

IMPLICATIONS FOR PROVIDERS AND PARENTS

Providers can help parents approach their child's adolescent years by reframing some of the "challenges" of adolescence as normal developmental milestones that should be anticipated and accepted. Puberty and emerging sexuality should be approached as positive and health-affirming life changes, rather than focusing discussions only on the negative reproductive risks and outcomes. Even good-natured teasing about bodily changes can be detrimental to the adolescent's self-image. Early-maturing females and late-maturing males should be supported, recognizing their potential increased risk for psychosocial challenges. Emerging positive coping strategies should be promoted in all youth, particularly those with chronic illness or other challenges. Providers need to determine the young adolescents' cognitive development and capacity for abstract thought, and to tailor their communication and counseling style accordingly. Physical examinations should be performed in private with the parent outside the exam room (provided the adolescent is comfortable with this), which also affords the adolescent and provider an opportunity to discuss confidential issues. Reassurance of normal development should be provided.

As adolescents develop more independence and parent–child conflict peaks, providers should remind parents that this is typical, and that arguing does not mean the adolescent does not value the parents' input and perspectives. Although some may rebel initially, most adolescents ultimately adopt a value system very similar to that of their parents. Even if discussions feel ineffective to parents, they should continue to demonstrate and model these values to their child. Similarly, rather than categorically dismissing their child's "negative" interests, such as playing a violent video game, parents should be encouraged to use these opportunities to model critical thinking about the impact of such an activity. Potentially negative peer groups may be approached the same way, while fostering the development of positive peer networks. Authoritative parenting, in which clear and appropriate negotiated limits are set in the context of a caring and mutually respectful parent–child relationship, is most strongly associated with positive psychosocial development. Parental connectedness and close supervision or monitoring of the youth's activities and peer group can be protective against early onset of sexual activity and involvement in other risk-taking behaviors, and can foster positive youth development. Parents should also assume an active role in their adolescent's transition to adulthood to ensure that their child receives appropriate preventive health services.

Parents and providers may each work with adolescents to foster good decision making. In addition to providing adolescents with accurate and complete health information, the adolescent's cognitive ability to use this information in various contexts must be considered. Adolescents may find themselves needing to make important decisions in highly affectively charged situations, in which they may be unable to effectively manage their emotions and use their higher cognitive functions to think through the consequences of their decision. For example, if a romantic couple gets "carried away" in a sexual situation with high emotional arousal, they may make the decision to proceed with unprotected intercourse. By anticipating this situation ahead of time, under conditions of lower emotional arousal, and making a plan for how they will deal with this should it occur, it is possible they may make a different decision (e.g., stick with their prior decision never to have sex without protection), when the time comes. Parents and healthcare providers are in a position to encourage and foster this anticipation and planning under conditions of "cool cognition."

Providers may need to help parents distinguish normal adolescent development and risk-taking behaviors from possible signs of a more serious mental health or conduct problem. Bids for autonomy, such as avoiding family activities, demanding privacy, and increasing argumentativeness, are normal; extreme withdrawal or antagonism may be dysfunctional. Bewilderment and dysphoria at the start of middle school are normal; continued failure to adapt several months later suggests a more serious problem. Although some degree of risk-taking is normal, progressive escalation of risk-taking behaviors is problematic. In general, when the adolescent's behaviors cause significant dysfunction in the domains of home life, academics, or peer relationships, they should be addressed by the parents and healthcare provider, and referral to a mental health provider may be considered. In most cases, parents can be reassured that although adolescence can pose unique challenges, their adolescent, like most adolescents, will come through it to become a successful and happy adult.

Bibliography is available at Expert Consult.

110.2 Sexual Identity Development

Walter O. Bockting

TERMS AND DEFINITIONS

Sex and Sexual Identity

Sex is multifaceted, with at least 9 components: chromosomal sex, gonadal sex, fetal hormonal sex (prenatal hormones produced by the gonads), internal morphologic sex (internal genitalia), external morphologic sex (external genitalia), hypothalamic sex (sex of the brain), sex of assignment and rearing, pubertal hormonal sex, and gender identity and role. *Sexual identity* is a self-perceived identification distilled from any or all aspects of sexuality, and has at least 4 components: sex assigned at birth, gender identity, social sex role, and sexual orientation.

Sex Assigned at Birth

A newborn is assigned a sex before (typically through ultrasound) or at the time of birth based on the external genitalia (natal sex). In case of a *disorder of sex development*, these genitalia may appear ambiguous, and additional components of sex (e.g., chromosomal, gonadal, hormonal sex) are assessed. In consultation with specialists, parents assign the child a sex that they believe is most likely to be consistent with gender identity, which cannot be assessed until later in life (see Chapter 588).

Gender Identity, Gender Role, and Social Sex Role

Gender identity refers to a person's basic sense of being a boy/man, girl/woman, or other gender (e.g., transgender). *Gender role* refers to one's role in society, typically either the male or female role. Gender identity needs to be distinguished from *social sex role* (also referred to as gender expression), which refers to characteristics in personality, appearance, and behavior that are, in a given culture and time, considered masculine or feminine. Gender role is about one's presentation as a boy/man or girl/woman, whereas social sex role is about the masculine and/or

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feminine characteristics one exhibits in a given gender role. Both boys/men, girls/women, and transgender persons can be masculine and/or feminine to varying degrees; gender identity and social sex role are not necessarily congruent. A child or adolescent might be *gender role nonconforming*, that is, a predominantly feminine boy or a predominantly masculine girl.

Sexual Orientation and Behavior

Sexual orientation refers to attractions, behaviors, fantasies, and emotional attachments toward men, women, or both. *Sexual behavior* refers to any sensual activity to pleasure oneself or another person sexually.

Gender Variant and Transgender

Gender variant refers to any gender identity or role that varies from what is typically associated with one's sex assigned at birth. Sometimes the term *gender variant identity* is used to refer to variation in gender identity and in that case is synonymous with transgender. *Transgender* people are a diverse group of individuals who cross or transcend culturally defined categories of gender. They include *transsexuals* (who typically live in the cross-gender role and seek hormonal and/or surgical interventions to modify primary or secondary sex characteristics); *cross-dressers* or *transvestites* (who wear clothing and adopt behaviors associated with the other sex for emotional or sexual gratification and may spend part of the time in the cross-gender role); *drag queens* and *kings* (female and male impersonators); and individuals identifying as *bigender* (both man and woman) or *genderqueer* (gender variant). Transgender individuals may be attracted to men, women, or other transgender persons.

FACTORS THAT INFLUENCE SEXUAL IDENTITY DEVELOPMENT

During prenatal sexual development, a gene located on the Y chromosome (*XRY*) induces the development of testes. The hormones produced by the testes direct sexual differentiation in the male direction resulting in the development of male internal and external genitalia. In the absence of this gene in XX chromosomal females, ovaries develop and sexual differentiation proceeds in the female direction resulting in female internal and external genitalia. These hormones may also play a role in sexual differentiation of the brain. In disorders of sex development, chromosomal and prenatal hormonal sex varies from this typical developmental pattern and may result in ambiguous genitalia at birth.

Gender identity develops early in life and is typically fixed by 2-3 yr of age. Children first learn to identify their own and others' sex (*gender labeling*), then learn that gender is stable over time (*gender constancy*), and finally learn that gender is permanent (*gender consistency*). What determines gender identity remains largely unknown, but it is thought to be an interaction of biologic, environmental, and sociocultural factors.

Some evidence has been found for the impact of biologic and environmental factors on social sex role and gender role behavior, while their impact on gender identity remains less clear. Animal research shows the influence of prenatal hormones on sexual differentiation of the brain. In humans, prenatal exposure to unusually high levels of androgens in girls with congenital adrenal hyperplasia is associated with more masculine gender role behavior, gender variant identity, and same-sex sexual orientation, but cannot account for all of the variance found (see Chapter 576). Research on environmental factors has focused on the influence of sex-typed socialization. Social sex role stereotypes develop early in life. Until later in adolescence, boys and girls are typically socially segregated by gender, reinforcing sex-typed characteristics such as boys' focus on rough-and-tumble play and asserting dominance, and girls focus on verbal communication and creating relationships. Parents, other adults, teachers, peers, and the media serve as gender socializing role models and agents by treating boys and girls differently.

For information on the development of sexual orientation, see Chapter 110.3.

GENDER VARIANCE/GENDER ROLE NONCONFORMITY AMONG CHILDREN AND ADOLESCENTS

Prevalence

Gender variance and gender role nonconformity need to be distinguished from a transgender or a gender variant identity. The former operate on the level of social sex role, whereas the latter is about variation in core gender identity. Gender role nonconformity is more common among girls (7%) than boys (5%), but boys are referred more often than girls for concerns regarding gender identity and role. This is likely a result of parents, teachers, and peers being less tolerant of gender-variant behaviors in boys than in girls.

Gender variance as part of exploring one's gender identity and role is part of normal sexual development. Gender variance in childhood may or may not persist into adolescence. Marked gender variance in adolescence often persists into adulthood. Only a minority of gender-variant children develop an adult transgender identity; most develop a gay or lesbian identity, and some, a heterosexual identity.

Etiology of Gender-Variant Behavior

Prenatal hormones play a role in the development of gender role nonconformity, but cannot completely account for all of the variance. A heritable component of gender-variant behavior exists, but twin studies indicate that genetic factors do not account for all of the variance. Family of origin factors hypothesized to play a role in the development of gender variance lack empirical support. Maternal psychopathology and emotional absence of the father are the only factors shown to be associated with gender variance, yet it is unclear whether these factors are cause or effect.

Stigma, Stigma Management, and Advocacy

Children with gender variance are subject to ostracism and bullying (see Chapter 39.1) from peers, which may negatively impact their psychosocial adjustment and lead to social isolation, loneliness, low self-esteem, depression, suicide, and behavioral problems. To assist children and families, individual stigma management strategies, as well as interventions to change the environment, can be offered. Stigma management might involve consultation with a health professional to provide support and education, normalizing the gender-variant behavior and encouraging the child and family to build on the child's strengths and interests to foster self-esteem. It might also involve making choices about certain preferences (e.g., a boy who likes to wear head bands) to limit these to times and environments that are more accepting. *Most health professionals agree that too much focus on curtailing gender-variant behavior leads to increased shame and undermines the child's self-esteem.*

The health professional and family can also assist the child or adolescent to find others with similar interests (within and beyond the gender-related interests) to strengthen positive peer support. Equally important are interventions in school and society to raise awareness and promote accepting and positive attitudes, take a stand against bullying and abuse, and implement antibullying policies and initiatives. *Gay, lesbian, bisexual, transgender, and straight alliance groups are helpful in providing a haven for gender-variant youth, as well as recognizing them as part of diversity to be respected and embraced within the school system.*

GENDER-VARIANT AND TRANSGENDER IDENTITY AMONG CHILDREN AND ADOLESCENTS

Prevalence

Approximately 1% of parents of 4-11 yr old boys report that their son wished to be of the opposite sex; for girls this percentage is 3.5% for 4-11 yr olds.

Boys are referred by caregivers more often than girls for concerns regarding gender identity. Only a minority of children's gender identity concerns persist into adolescence (20% in 1 study of boys). Persistence of gender identity concerns from adolescence into adulthood is higher; the majority identify as transgender in adulthood and may pursue sex

reassignment. On the basis of adults enrolled in a national sex reassignment program in the Netherlands, the prevalence of transsexual adults is estimated at 1 : 11,900 for male-to-females and 1 : 30,400 for female-to-males. The prevalence of transgender adults in the United Sates is estimated at 1:200.

Etiology of a Gender Variant Identity

The etiology of transgender identity remains unknown. Factors hypothesized to play a role in the development of a transgender identity include environmental and biologic factors. Gender variant children seem to have more trouble than other children with basic cognitive concepts concerning their gender. They may experience emotional distance from their father. Whether these factors are cause or effect remains unclear.

There may be an influence of prenatal and perinatal hormones on sexual differentiation of the brain. Some girls with congenital adrenal hyperplasia develop a male gender identity, yet most do not. The size of the sex-dimorphic central part of the bed nucleus of the stria terminalis in the hypothalamus of male-to-female transgender individuals is smaller than in males and within the range of nontransgender women; the opposite is true for female-to-male transgender individuals. This structure is regulated by hormones in animals, but in humans no evidence yet exists of a direct relationship between prenatal and perinatal hormones and the sexually dimorphic nature of this nucleus.

Clinical Presentation

Children with a gender variant identity may experience 2 sources of stress: internal distress inherent to the incongruence between sex assigned at birth and gender identity (gender dysphoria) or distress associated with social stigma. The first source of distress is reflected in discomfort with the developing primary and secondary sex characteristics and the gender role assigned at birth. The second source of distress relates to feeling different, not fitting in, peer ostracism, and social isolation, and may result in shame, low self-esteem, anxiety, or depression.

Boys with a gender variant identity may at an early age identify as a girl, expect to grow up female, or express the wish to do so. They may experience distress about being a boy and/or having a male body, prefer to urinate in a sitting position, and express a specific dislike of their male genitals and even want to cut off their genitals. They may dress up in girls' clothes as part of playing dress up or in private. Girls may identify as a boy, expect or wish to grow up male. They may experience distress about being a girl and/or having a female body, pretend to have a penis, or expect to grow one. Girls may express a dislike of feminine clothing and hairstyles. In early childhood, children may spontaneously express these concerns, yet depending on the response of the social environment, these feelings may go underground and be kept more private. The distress may intensify by the onset of puberty; the physical changes of puberty are described by many transgender adolescents and adults as traumatic.

Gender variant children and transgender adolescents may struggle with a number of general behavior problems. Both boys and girls have a predominance of internalizing (anxious and depressed) as opposed to externalizing behavioral difficulties. Boys are more prone to anxiety, have more negative emotions and a higher stress response, and are rated lower in self-worth, social competence, and psychological well-being. Gender variant children have more peer relationship difficulties than controls. Both femininity in boys and masculinity in girls are socially stigmatized, although the former seems to carry a higher level of stigma. Boys have been shown to be teased more than girls; teasing for boys increases with age. Poor peer relations is the strongest predictor of behavior problems in both boys and girls.

Transgender adolescents may struggle with a number of adjustment problems as a result of social stigma and lack of access to transgender-specific healthcare. Transgender youth, especially those of ethnic/racial minority groups, are vulnerable to verbal and physical abuse, academic difficulties, school dropout, illicit hormone and silicone use, substance use, difficulty finding employment, homelessness, sex work, forced sex, incarceration, HIV/sexually transmitted infections (STIs), and suicide. Parental support can buffer against psychologic distress, yet many parents react negatively to their child's gender variance, although mothers tend to be more supportive than fathers.

The Diagnosis of Gender Dysphoria: Criteria and Critique

Gender dysphoria (or incongruence) is classified as a mental disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and International Classification of Diseases, which, particularly for children, is controversial (Table 110-4). Critics have argued that the distress children experience is mainly the result of social stigma rather than being inherent to gender variance per se and hence should not be considered a mental disorder. Critics have also expressed concern about children with normal variation in gender role being labeled with a mental disorder perpetuating social stigma, yet there is a tendency of clinicians to underdiagnose rather than overdiagnose children whose gender variance goes beyond behavior and who report gender dysphoria. These children will benefit from the diagnosis to receive early treatment in the form of support, education, advocacy, and, in case of persistent puberty-delaying hormone therapy as a precursor to feminizing or masculinizing hormone therapy.

Transgender Identity Development

A stage model of coming out might be helpful to understand the experience and potential challenges transgender youth might face. In the *pre–coming out* stage, the individual is aware that their gender identity is different from that of most boys and girls. In addition to a gender identity that varies from sex assigned at birth, some of these children are also gender-role nonconforming while others are not. Those who are also gender-role nonconforming cannot hide their transgender identity, are noticed for who they are, and may face teasing, ridicule, abuse, and rejection. They must learn to cope with these challenges at an early age and usually proceed quickly to the next stage of *coming out*. Children who are not visibly gender role nonconforming are able to avoid stigma and rejection by hiding their transgender feelings. They often experience a split between their gender identity cherished in private and expressed in fantasy and a false self-presented outwardly to fit in and meet gendered expectations. These individuals often proceed to coming out later in life.

Coming out involves acknowledging one's transgender identity to self and others (parents, other caregivers, trusted health providers, peers). An open and accepting attitude is essential; rejection can perpetuate stigma and its negative emotional consequences. By accessing transgender community resources, including peer support (either online or offline), the transgender youth can then proceed to the *exploration* stage. This is a time of learning as much as possible about being transgender, getting to know similar others, and experimenting with various options for gender expression. Changes in gender role are carefully considered, as are medical interventions to feminize or masculinize the body to alleviate dysphoria. Successful resolution of this stage is a sense of pride in being transgender and comfort with gender role.

Once gender dysphoria has been alleviated, the individual can proceed with other human development tasks, including dating and relationships in the *intimacy* stage. As a result of social stigma and rejection, transgender individuals may struggle with feeling unlovable. Sexual development has often been compromised by gender and genital dysphoria. Now that greater comfort has been achieved with gender identity and role, dating and sexual intimacy have a greater chance of succeeding. Finally, in the *integration* stage, transgender is no longer the most important signifier of identity but one of several important parts of overall identity.

Interventions and Treatment

Health providers can assist gender variant children, adolescents, and their families by directing them to resources and by helping them to make informed decisions about changes in gender role and the available medical interventions to reduce intense and persistent gender dysphoria. To alleviate socially induced distress, interventions focus on stigma management and stigma reduction. It might be in the child's best interest to set reasonable limits on transgender expression

Table 110-4 Summary of DSM 5 Diagnostic Criteria for Gender Dysphoria

GENDER DYSPHORIA IN CHILDREN (302.6) (F64.2)

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 6 of the following (1 of which must be criterion A1):
   1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
   2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
   3. A strong preferences for cross-gender roles in make-believe play or fantasy play.
   4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
   5. A strong preference for playmates of the other gender.
   6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
   7. A strong dislike of one's sexual anatomy.
   8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

GENDER DYSPHORIA IN ADOLESCENTS OR ADULTS

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 2 of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
   4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

SPECIFY IF WITH A DISORDER OF SEX DEVELOPMENT (E.G., CONGENITAL ADRENAL HYPERPLASIA OR ANDROGEN INSENSITIVITY SYNDROME)

SPECIFY IF POSTTRANSITION: The individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen, namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

Adapted from the American Psychiatric Association, Diagnostic and statistical manual of mental disorders, *ed 5, Washington, DC, 2013, American Psychiatric Publishing.*

contributing to teasing and ridicule. The main goal of these interventions is not to change the child's gender variant behavior but to assist families, schools, and the wider community to create a supportive environment in which the child can thrive and safely explore his or her gender identity and expression. Decisions to change gender roles, particularly in school, are not to be taken lightly and are best carefully anticipated and planned in consultation with parents, child, teachers, school counselor, and other providers involved in the adolescent's care. Medical interventions are available as early as Tanner Stage 2. Such treatment is guided by the Standards of Care set forth by the World Professional Association for Transgender Health. Although some controversy still exists about the appropriateness of early medical intervention, follow up studies of adolescents treated in accordance with these guidelines show it to be effective in alleviating intense and persistent gender dysphoria. Care needs to be taken not to foreclose the child's exploration of identity.

Pediatricians who encounter transgender youth in their practice should be careful not to make assumptions about gender and sexual identity, but rather ask youth how they would describe themselves. This includes asking if they like being a boy or girl, have ever questioned this, or wished they were born the other sex; have a preferred nickname or pronoun (*he* or *she*; if not sure, avoid pronouns); and how they feel about their maturing body and sex characteristics, and what they would change about that if they could. Extra caution should be exercised during physical and genital exams because transgender youth may be particularly uncomfortable with their anatomy. When considering contraceptive options for female-to-males, alternatives to feminizing agents should be explored. For transgender-specific medical interventions, transgender youth should be referred to specialists in the treatment of gender dysphoria (see World Professional Association for Transgender Health, www.wpath.org). For other health concerns, ensure referral to transgender or lesbian, gay, bisexual, transgender (LGBT)-friendly providers, especially in the case of gender segregated treatment facilities. Gender Spectrum (www.genderspectrum.org), Advocates for Youth (www.advocatesforyouth.org), and Parents, Families and Friends of Lesbians and Gays (www.pflag.org) offer excellent support resources for transgender youth and their families.

Bibliography is available at Expert Consult.

110.3 Gay, Lesbian, and Bisexual Adolescents

Stewart L. Adelson and Mark A. Schuster

Understanding a child or adolescent's sexual and emotional development is an essential part of any comprehensive pediatric evaluation. For youth who are or might be gay, lesbian, or bisexual (GLB), such understanding is particularly important. GLB youth as a group have the same health and developmental needs as all youth, and their sexual orientation is a normal variation of human sexuality; however, they encounter distinct developmental challenges and can have additional health and mental health needs related to their orientation and others'

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reaction to it. Their sexual orientation is often different from that expected by family, peers, and society and they must cope with peer rejection, bullying, or family nonacceptance more frequently than most youth. Although the majority of GLB adolescents grow up physically and mentally healthy, they are at increased risk for certain medical and psychological problems as a result of these stresses and the epidemiology of health threats like HIV and other STIs. Pediatric healthcare providers are key in monitoring for such issues, supporting healthy development, and intervening when necessary to prevent or treat the problems for which GLB youth are at risk.

DEFINITIONS

Sexual orientation is the degree of attraction to the people of a particular sex. It encompasses emotional and erotic desires, physiologic arousal, sexual behavior, sexual identity, and social role. As sexuality develops, youth can be oriented entirely toward males, females, or both to various degrees on a continuum. Romantic attraction to the opposite sex is heterosexuality, to the same sex is homosexuality, and to both is bisexuality. **Gay** is a common term for homosexual, in both males and females; **lesbian** refers to homosexual females. Those unsure of their orientation are **curious** or **questioning**. The term **young men who have sex with men** (**MSM**) is sometimes used in the research literature to denote male youth who are engaging in sexual activity with other males, regardless of how they identify themselves.

PREVALENCE OF HOMOSEXUALITY AND BISEXUALITY IN YOUTH

Some junior high and high school students are unsure of their sexual orientation, while others say they are gay, lesbian, or bisexual. Some who do not identify as GLB report same-sex attraction, fantasies, or behavior. Certainty about sexual orientation and identity increases through adolescence with sexual experience. Those who fear nonacceptance may try to suppress or deny their orientation. Consequently, various aspects of orientation—feelings, behavior, and identity—may not be consistent in an individual, and may change during development. Only some youth with homosexual experience identify as "gay," consistent with reluctance about having or revealing a gay identity and underscoring the difference between identity and behavior. Population surveys of youth from 2001-2009 found a median of 2.5% reported that they were "unsure" of their sexual orientation, 1.3% said they were "gay/lesbian," and 3.7% said they were "bisexual." In New York City in 2005-2007, 38.9% of adolescents with only same- or both-sex partners identified as straight.

DEVELOPMENT OF SEXUAL ORIENTATION IN CHILDHOOD AND ADOLESCENCE

See also Chapter 110.2.

Sexual orientation development begins prenatally and continues through childhood and adolescence and into adulthood. Both gender role behavior in childhood and sexual orientation in puberty and adolescence are partly influenced by prenatal genetic and neuroendocrine factors. Sociocultural and psychological factors also influence sexual development. A gay or lesbian sexual orientation is sometimes preceded developmentally by childhood **gender nonconformity**, or variation from population averages in **gender role behavior**. These are activities, interests, styles, and other attributes recognized as masculine or feminine, like toy preferences and preference for opposite-sex playmates. Although childhood gender nonconformity is not experienced by all gay people—and not all gender nonconforming children grow up to be gay—nonconformity is not uncommon (particularly among males) and leads many gay or lesbian people to feel different from peers in childhood, even before sexual desire or identity emerges. When not protected from stigma, gender-nonconforming children may experience ostracism, bullying, or family nonacceptance. These reactions to gender nonconformity can lead to later difficulty integrating a healthy, positive self-image and to long-term mental health problems.

Less frequently, gay or lesbian sexual orientation in adolescence is preceded by childhood *gender incongruity/dysphoria*, a distinct phenomenon in which an individual's gender identity differs from phenotypic sex and assigned gender at birth.

STIGMA, RISK, AND RESILIENCE

Homosexuality has been documented across cultures and historical periods; its meaning and acceptance vary greatly with social context. Gay people are now generally more visible and accepted than previously in the United States; still, youth are often exposed to antihomosexual attitudes. For many GLB youth, revealing their sexual orientation ("coming out") to family, peers, healthcare providers, and others is a significant step. Specific racial/ethnic groups may experience unique developmental stressors; African-American youth report feeling less comfortable than white peers with a gay identity and less comfortable disclosing it.

Some GLB youth experience difficulty coping with stigma. Family nonacceptance, feeling unsafe because of school harassment, and peer bullying related to sexual orientation elevate risk in GLB adolescents for depression, anxiety, substance abuse, suicidal thoughts and attempts, and social problems like truancy, dropping out, running away, and homelessness. Even when not overtly threatened, GLB youth frequently encounter negative attitudes that force them to hide at a developmental period when acceptance holds great significance. Mental health problems, risk taking, or substance use may increase exposure to HIV/STIs. Stigma may also impede access to healthcare in some communities. Thus, along with factors influencing exposure and susceptibility to health threats, stigma partly mediates elevated risk for health and mental health problems in GLB youth.

It is important to reduce stigma against, support acceptance of, and promote resilient coping among GLB youth. Family connectedness and school support and safety are important protective factors against depression, suicidal thoughts and attempts, and substance abuse. GLB antiharassment policies and gay-straight alliances as well as anti-bullying programs increase school safety.

HEALTH AND MENTAL HEALTH

Depression and Suicidality

Rates of suicidality are about 2 or 3 times higher among gay and lesbian youth, and up to 5 times higher among bisexual youth, than among the general population. Family rejection, bullying, and other victimization motivated by homophobia accounts statistically for increased depression and suicidal thoughts and attempts in GLB adolescents. Suicidal thoughts or attempts are highest during the interval following a same-sex sexual experience and prior to self-acceptance as gay.

Sexually Transmitted Infections

The epidemiology of STIs (see Chapter 120), related to specific sexual practices, as well as prevalence of certain STIs in GLB communities, informs recommended counseling, screening, and treatment strategies. Anal intercourse has been shown to be the most efficient route of infection by hepatitis B (see Chapter 358), cytomegalovirus (see Chapter 255), and HIV (see Chapter 276). Oral–anal and digital–anal contact can transmit enteric pathogens, such as hepatitis A. Unprotected oral sex also can lead to oropharyngeal disease in the receptive partner and gonococcal and nongonococcal urethritis in the insertive partner. Certain STIs, particularly ulcerative diseases, such as syphilis (see Chapter 218) and herpes simplex virus infection (see Chapter 252.5), facilitate spread of HIV.

Among U.S. adolescents and young adults, young MSM continue to face the greatest toll of HIV/AIDS for various reasons, including misinformation, noncommunication with partners about risk reduction, potentially false assumptions about partners' serostatus, substance use, and impaired reasoning and judgment. Rates are especially high among black young MSM. Although possible, female-to-female sexual transmission of HIV is inefficient, and females who only engage in same-sex behavior are less likely than other youth to acquire an STI. However, boys and girls who identify as gay or lesbian may engage in sexual activity with partners of the other gender, so counseling and screening for all types of STIs are still relevant.

Substance Abuse

See also Chapter 114.

A subset of GLB youth display increased rates of alcohol and substance use, including more binge drinking and earlier onset and more rapid trajectory of substance use. Problem drinking may be greatest in youth who do not identify as GLB but have same-sex attractions or engage in same-sex sexual behavior. Marijuana and other illicit drug use is more common among bisexual females, but studies have found no increased rates among young gay and bisexual males, and males with bisexual behavior and identity are less likely to drink than young heterosexual males. Smoking is increased among bisexual adolescent females and possibly in adolescent lesbians; studies are conflicting regarding smoking in other GLB adolescent groups.

Obesity and Disordered Eating

See also Chapter 26.

Existing studies suggest certain GLB youth are at risk for disordered eating. Compared with heterosexual girls, lesbian and bisexual girls generally have a more positive body image, although they are more likely to be overweight. In contrast, young gay and bisexual males are more likely to have body image concerns and are more likely to restrict eating or engage in compensatory weight loss strategies. Binge eating may also be more common in GLB youth. Behaviorally bisexual youth may be at greatest risk for disordered eating.

Psychosocial Problems

Academic underachievement, truancy, and dropping out among GLB adolescents are frequently associated with homophobic victimization, harassment, violence, and feeling unsafe at school. Youth who eventually identify as GLB appear to experience higher rates than other youth of child abuse, running away, or being thrown out of their homes. Homosexual young people are overrepresented in homeless and runaway populations across the United States. Life on the streets or in shelters exposes them to drugs and sexual abuse and promotes illegal conduct for survival.

RECOMMENDATIONS FOR CARE

Evaluation

The goal of GLB pediatric care is physical health, social and emotional well-being, and promotion of healthy development. Physicians should provide nonjudgmental care to all adolescents, including those who are GLB or questioning. They should receive the age-appropriate history, examination, and anticipatory guidance recommended for adolescents in general. With some exceptions noted below, the physical examination and laboratory evaluation of GLB and questioning adolescents are the same as for any teenager. However, providers should screen for special potential medical and psychosocial threats to GLB teenagers' health appropriately.

A nonjudgmental healthcare environment, with open communication and a positive relationship with youth and families, is important. In the waiting room, written material about sexual orientation, support groups, and community resources will signal openness to discussing sexuality. Registration forms recognizing the possibility of same-gender parents signal a safe setting (e.g., forms can list parent/guardian #1, parent/guardian #2). Sexual history questions should avoid heterosexual assumptions (e.g., "are you dating someone" instead of "do you have a boyfriend/girlfriend?"). This is important at all ages. Discussing confidentiality and incorporating into each adolescent visit private time with no parent in the room (see Chapter 112) may facilitate discussing sexual orientation, as may use of appropriate health history forms, like the American Medical Association's Guidelines for Adolescent Prevention Services Questionnaire.

Clinicians should remember that any youth might be GLB whether or not they are identified or perceived as such, so clinicians should not presuppose a particular orientation. Competency in conveying sensitivity, acceptance, and respectfulness; effective communication skills; and appropriate attention to privacy and confidentiality (including practices related to billing and record requests; see Chapter 112.1) are fundamental to providing high-quality care. While attuned to youth's' preferences—explicit or implied—for discussing sexual orientation, providers should take the lead tactfully, if necessary, regarding any pressing areas of clinical concern.

Medical and Sexual Health

Sexually transmitted infections (see Chapter 120) pose additional issues specific to GLB youth. Use of latex condoms for anal and oral intercourse should be discussed with boys, and the use of dental dams, cut open latex condoms, or plastic wrap during oral sex should be discussed with girls; the use of latex condoms for sexual appliances are recommended as well. It is important to emphasize that people who have been using alcohol or other drugs are at increased likelihood for engaging in riskier sexual activity. It is important not to assume that a gay boy or lesbian girl who does not identify as bisexual has not had sex with the opposite gender. Lesbians can have an unplanned pregnancy. Similarly, youth who identify as heterosexual and are attracted only to the opposite sex may still have sexual activity with a partner of the same sex.

Although vaccination against hepatitides A and B is recommended for all children, it is particularly recommended that nonvaccinated adolescent males who are having sex or are likely to have sex with males get catchup vaccines. The same recommendation applies to the quadrivalent human papillomavirus vaccine for males. The Centers for Disease Control and Prevention recommends that males who are engaging in sexual activity with males have annual testing for HIV, hepatitis A, hepatitis B, syphilis, urethral gonorrhea and chlamydia (if engaging in insertive oral or anal intercourse), oral gonorrhea (if engaging in receptive oral intercourse), and rectal gonorrhea and chlamydia (if engaging in receptive anal intercourse). For treatment of STIs, see Chapter 120.

Mental Health

Awareness of mental health and social problems is important when caring for GLB youth, as for all youth (see Chapter 111). Clinicians should monitor for depression, suicidality, anxiety, and substance abuse, and know their community's mental health resources. Minor psychosocial problems might be handled by referral to a support group for patients (e.g., Gay, Lesbian & Straight Education Network [GLSEN]) or for parents and others (e.g., Parents, Families, & Friends of Lesbians and Gays [PFLAG]). In some communities, agencies and organizations serving the GLB community can help with social, educational, vocational, housing, and other needs.

Individuals or families who harbor negative attitudes may inquire about mental health treatment to avert or change a homosexual or bisexual orientation. GLB orientation is not an illness, and leading health organizations, including the American Academy of Pediatrics, the American Academy of Family Physicians, the Society for Adolescent Health and Medicine, the American Academy of Child and Adolescent Psychiatry, and the American Medical Association, have concluded that such change is neither possible nor warranted. It is important to distinguish between a GLB orientation, which is not a mental illness, and mental health problems like depression for which GLB youth are at elevated risk. While understanding different families' values, clinicians must recognize the morbidity and mortality associated with stigma and aim to foster physical and emotional health. Individual or family therapy might be indicated for some.

Clinicians should also monitor for specific stressors such as bullying and other homophobic victimization, family nonacceptance, and abuse. Failure to confront harassment constitutes tacit assent.

Anticipatory guidance, referral, and substance abuse treatment should be considered for the subset of GLB youth who use alcohol, drug, or tobacco; some of whom may be using these to manage painful feelings related to conflicts over their sexuality.

Adolescents with serious psychiatric symptoms, such as suicidality, depression, and substance abuse should be referred to mental health specialists with competency in treating GLB adolescents. It is essential to know how to recognize and manage psychiatric emergencies such as suicidal thoughts and attempts (see Chapter 27).

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Chapter 111

The Epidemiology of Adolescent Health Problems

Gale R. Burstein

Adolescence is the first period of life where the major determinants of morbidity and mortality are behavioral rather than congenital or infectious. As adolescents make the transition from childhood to adulthood, they establish behaviors that affect both their current and future health. Adolescence is a time of immense biologic, psychologic, and social change (see Chapter 110). Many of the psychological changes have a biologic substrate in the development and eventual maturation of the central nervous system, particularly the frontal lobe areas responsible for executive functioning (Fig. 111-1). In addition to cognitive development, there are both risk and protective factors for adverse adolescent health behaviors that are dependent on the social environment as well as the mental health of an adolescent (Table 111-1).

Many adolescents continually confront the task of making healthy choices while struggling with impulsivity that can lead to unintentional consequences, such as injuries, sexually transmitted infections, or drug overdoses. Adolescents are also challenged with adopting behaviors that will affect their future adult health, such as eating nutritiously, engaging in physical activity, and choosing not to use tobacco. Environmental factors, such as family, peers, school, community, and religiosity, also contribute to adolescents' health and risk behaviors. The Centers for Disease Control and Prevention (CDC) Youth Risk Behavior Surveillance Survey, a school-based survey of a nationally representative sample of U.S. high school students, demonstrates that youth begin engaging in behaviors that place their health at risk during adolescence (Fig. 111-2).

Although according to the 2012 CDC National Health Interview Survey, a probability sample survey conducted annually, an estimated 81% of 12-17 yr olds report excellent or very good health, 23% missed 3-5 school days in the past year, 9% are uninsured, 6% have no usual place of healthcare, 11% have asthma, 11% have respiratory allergies, 10% have a learning disability, 12% have attention deficit hyperactivity disorder, and 17% take prescription medications routinely. In 2010, the mortality rate among adolescents 15-19 yr of age was 49 deaths per 100,000 population. While varying by gender, the leading causes of death overall among adolescents 15-19 yr of age are (1) unintentional injuries; (2) homicide; and (3) suicide (Table 111-2).

Within the adolescent population, disparities in health occur. Adolescent health outcomes and behaviors vary among populations that can be defined by race or ethnicity, gender, education or income, disability, geographic location (e.g., rural or urban), or sexual orientation. Health disparities result from multiple factors, including poverty, environmental threats, inadequate access to healthcare, individual and behavioral factors, and educational inequalities (Table 111-3).

Table 111-1 Identified Risk and Protective Factors for Adolescent Health Behaviors

BEHAVIOR	RISK FACTORS	PROTECTIVE FACTORS
Smoking	Depression and other mental health problems, alcohol use, disconnectedness from school or family, difficulty talking with parents, minority ethnicity, low school achievement, peer smoking	Family connectedness, perceived healthiness, higher parental expectations, low prevalence of smoking in school
Alcohol and drug misuse	Depression and other mental health problems, low self-esteem, easy family access to alcohol, working outside school, difficulty talking with parents, risk factors for transition from occasional to regular substance misuse (smoking, availability of substances, peer use, other risk behaviors)	Connectedness with school and family, religious affiliation
Teenage pregnancy	Deprivation, city residence, low educational expectations, lack of access to sexual health services, drug and alcohol use	Connectedness with school and family, religious affiliation
Sexually transmitted infections	Mental health problems, substance misuse	Connectedness with school and family, religious affiliation

Adapted from McIntiosh N, Helms P, Smyth R, editors. Fofar and Arneil's textbook of pediatrics, *ed. 6, Edinburgh, 2003, Churchill Livingstone, pp. 1757-1768; and Viner R, Macfarlane A: Health promotion,* BMJ *330:527-529, 2005.*

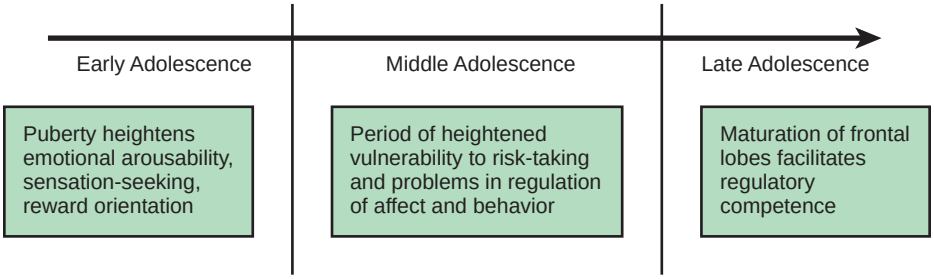

Figure 111-1 It has been speculated that the impact of puberty on arousal and motivation occurs before the maturation of the frontal lobes is complete. This gap may create a period of heightened vulnerability to problems in the regulation of affect and behavior, which might help to explain the increased potential in adolescence for risk taking, recklessness, and the onset of emotional and behavioral problems. *(From Steinberg L: Cognitive and affective development in adolescence,* Trends Cogn Sci *9:69–74, 2005.)*

Table 111-2 Leading Causes of Death Among 15-19 Yr Olds by Gender, United States, 2010*

LEADING CAUSES OF DEATH	MALE	FEMALE
#1	Accidents (unintentional injuries)	Accidents (unintentional injuries)
#2	Assault (homicide)	Intentional self-harm (suicide)
#3	Intentional self-harm (suicide)	Assault (homicide)

*Based on data from Heron M: Deaths: Leading causes for 2009. National vital statistics reports; vol 62. No. 6. Hyattsville, MD, 2013, National Center for Health Statistics.

Table 111-3 Adolescent Health Outcomes by Race/Ethnicity, United States, 2010-2012

OUTCOME	WHITE	BLACK	AI/AN	API	HISPANIC
Deaths*	47.5	70.6	61.5	22.8	41.5
Births§	20.5	43.9	34.9	9.7	46.3
Obese†	11.5	18.2	N/A	N/A	14.1
Asthma†	22.8	26.8	N/A	N/A	20.3
Depressed†	27.2	24.7	N/A	N/A	32.6
Chlamydia*	830.1	4,977.7	2,509.8	313.0***	1,191.0
Gonorrhea*	85.3	1,513.5	324.6	36.5***	139.7
HIV*	2.5	46.3	5.8	2.9***	8.1

*Rates of death in 2010, per 100,000 15-19 year old population by race/ethnicity.
**Rates of infection in 2011 per 100,000 15-19 year old population by race/ethnicity.
***Rates of Asian-only race.
†Percent high school students reporting health outcome.
§Rates of births in 2011 per 1,000 15-19 yr old females by race/ethnicity.
AI/AN, American Indian or Alaska Native; API, Asian or Pacific Islander; HIV, human immunodeficiency virus; N/A, not available.

ACCESS TO HEALTHCARE

Access to healthcare may be limited for adolescents compared to other age groups. Adolescents in the United States make fewer visits to physicians for ambulatory office visits than does any other age group; school-age children and adolescents are more likely than younger children to have unmet health needs and delayed medical care. Adolescents and young adults are less likely to be insured than all other age groups. Young adults 18-24 yr are more likely to be uninsured because until the passage in 2010 of America's Affordable Care Act, many were no longer eligible to receive benefits from their parents' health plans or public insurance programs. In addition, health insurance status differs based on income and race/ethnicity. Adolescents and young adults who are near poor (100-199% federal poverty level) and poor (below 100% federal poverty level) are less likely to have health insurance coverage than those with higher family incomes; and Hispanic and black adolescents and young adults are less likely to have health insurance coverage than their non-Hispanic white and Asian peers. Uninsured children and adolescents are less likely to receive preventive visits and have a regular source of care than the insured, and are more likely to go without treatment of symptoms.

Adolescents who actually receive preventive care may still not have access to time alone with their provider or discuss important confidential health issues, such as sexually transmitted infections, HIV, or pregnancy prevention. Less than half (40%) of adolescents have time alone with their healthcare provider during a preventive healthcare visit; sexually experienced teens report sexual health discussions more often than nonsexually experienced teens, but the frequency is still low at 64% and 33.5% for sexually experienced females and males, respectively.

Table 111-4 Healthy People 2020 Adolescent Health (AH) Objectives

- **AH-1**: Increase the proportion of adolescents who have had a wellness checkup in the past 12 months
- **AH-2**: Increase the proportion of adolescents who participate in extracurricular and out-of-school activities
- **AH-3**: Increase the proportion of adolescents who are connected to a parent or other positive adult caregiver
  - **AH-3.1**: Increase the proportion of adolescents who have an adult in their lives with whom they can talk about serious problems
  - **AH-3.2**: Increase the proportion of parents who attend events and activities in which their adolescents participate
- **AH-4**: (Developmental) Increase the proportion of adolescents and young adults who transition to self-sufficiency from foster care
- **AH-5**: Increase educational achievement of adolescents and young adults
  - **AH-5.1** ***(Leading Health Indicator)***: Increase the proportion of students who graduate with a regular diploma 4 years after starting 9th grade
  - **AH-5.2**: Increase the proportion of students who are served under the Individuals with Disabilities Education Act who graduate high school with a diploma
  - **AH-5.3**: Increase the proportion of students whose reading skills are at or above the proficient achievement level for their grade
  - **AH-5.4**: Increase the proportion of students whose mathematics skills are at or above the proficient achievement level for their grade
  - **AH-5.5**: Increase the proportion of adolescents who consider their school work to be meaningful and important
  - **AH-5.6**: Decrease school absenteeism among adolescents due to illness or injury
- **AH-6**: Increase the proportion of schools with a school breakfast program
- **AH-7**: Reduce the proportion of adolescents who have been offered, sold, or given an illegal drug on school property
- **AH-8**: Increase the proportion of adolescents whose parents consider them to be safe at school
- **AH-9**: (Developmental) Increase the proportion of middle and high schools that prohibit harassment based on a student's sexual orientation or gender identity
- **AH-10**: Decrease the proportion of public schools with a serious violent incident
- **AH-11**: Reduce adolescent and young adult perpetration of, as well as victimization by, crimes
  - **AH-11.1**: Decrease the rate of minor and young adult perpetration of violent crimes
  - **AH-11.2**: Decrease the rate of minor and young adult perpetration of serious property crimes
  - **AH-11.3**: (Developmental) Decrease the percentage of counties and cities reporting youth gang activity
  - **AH-11.4**: (Developmental) Reduce the rate of adolescent and young adult victimization from crimes of violence

From U.S. Department of Health and Human Services: Healthy People 2020, *available at: www.hhs.gov/ash/oah/resources-and-publications/healthy-people-2020.html.*

Under the Patient Protection and Affordable Care Act, healthcare providers will strive to improve the health of their patient population. Healthy People provides science-based, 10-year national objectives for measuring and improving the health of all Americans by establishing benchmarks and monitoring progress over time. The Healthy People 2020 agenda includes 11 adolescent-specific objectives with a goal of improving the healthy development, health, safety, and well-being of adolescents and young adults over the next 10 yr (Table 111-4). This

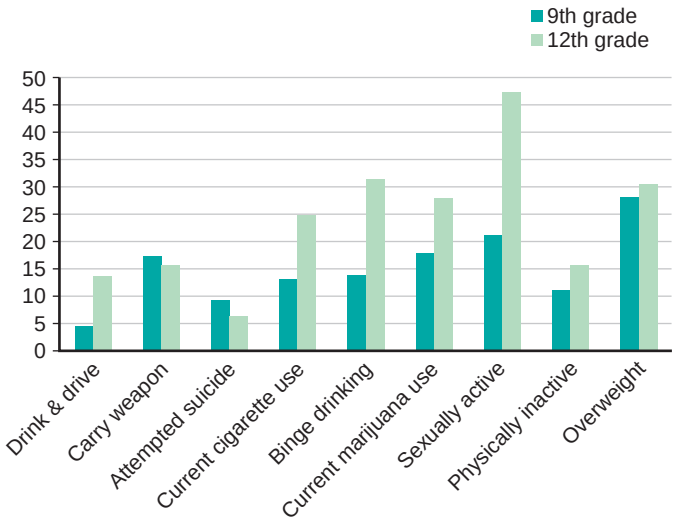

Figure 111-2 Selected health behaviors among 9th and 12th grade high school students. *(Data from Centers for Disease Control and Prevention:* 2011 Youth risk behavior surveillance system. http://www.cdc.gov/healthyyouth/yrbs/index.htm.*)*

science-based initiative is centered around a framework for public health prevention priorities and actions to improve the health status of U.S. youth.

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Chapter 112

Delivery of Healthcare to Adolescents

Gale R. Burstein

Healthcare providers play an important role in nurturing healthy behaviors among adolescents because the leading causes of death and disability among adolescents are preventable. Adolescence provides a unique opportunity to prevent or modify health conditions arising from behaviors that develop in the second decade of life and that can lead to substantial morbidity and mortality, such as trauma, cardiovascular and pulmonary disease, type 2 diabetes, reproductive health disease, and cancer.

Health systems in each community should be in place to ensure comprehensive and high-quality care to adolescents. **Health insurance coverage** that is affordable, continuous, and not subject to exclusion for preexisting conditions, should be available for all adolescents and young adults who have no access to private insurance. **Comprehensive, coordinated benefits** should meet the developmental needs of adolescents, particularly for reproductive, mental health, dental, and substance abuse services. **Safety net providers and programs that provide confidential services,** such as school-based health centers, federally qualified health centers, family planning services, and clinics that treat sexually transmitted infections (STIs) in adolescents and young adults, need to have assured funding for viability and sustainability. **Quality-of-care** data should be collected and analyzed by age so that the performance measures for age-appropriate healthcare needs of adolescents are monitored. **Affordability** is important for access to preventive services. Family involvement should be encouraged, but **confidentiality** and adolescent consent are critically important. **Healthcare providers, trained and experienced** to care for adolescents, should be available in all communities. Healthcare providers should be adequately **compensated** to support the range and intensity of services required to address the developmental and health service needs of adolescents. The creation and dissemination of provider education about adolescent preventive health guidelines have been demonstrated to improve the content of recommended care (Table 112-1). The ease of recognition or expectation that an adolescent's needs can be addressed in a setting relates to the **visibility and flexibility** of sites and services. Staff at sites should be approachable, linguistically capable, and culturally competent. Health services should be **coordinated** to respond to goals for adolescent health at the local, state, and national levels. The coordination should address service financing and delivery in a manner that reduces disparities in care.

Table 112-1 Bright Futures/American Academy of Pediatrics Recommendations for Preventive Healthcare for 11-21 Yr Olds

	PERIODICITY AND INDICATIONS
HISTORY	Annual
MEASUREMENTS	
Body mass index	Annual
Blood pressure	Annual
SENSORY SCREENING	
Vision	At 11, 15, and 18 yr visits or if risk assessment positive
Hearing	If risk assessment positive
DEVELOPMENTAL/BEHAVIORAL ASSESSMENT	
Developmental surveillance	Annual
Psychosocial/behavioral assessment	Annual
Alcohol and drug use assessment	If risk assessment positive
PHYSICAL EXAMINATION	Annual
PROCEDURES	
Immunization*	Annual
Hematocrit or hemoglobin	If risk assessment positive
Tuberculin test	If risk assessment positive
Dyslipidemia screening	If risk assessment positive
STI screening	If sexually active
HIV screening§	Discussed and offer
Cervical dysplasia screening†	Beginning at age 21 yr
ORAL HEALTH	Annual refer to dental home or administer oral health risk assessment
ANTICIPATORY GUIDANCE	Annual‡

*Schedules as per the Advisory Committee on Immunization Practices, published annually at http://www.cdc.gov/vaccines/schedules/hcp/index.html and in the January issue of *Pediatrics*.

†Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

‡Refer to specific guidance by age as listed in *Bright Futures Guidelines*.

§CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. The American Academy of Pediatrics recommends offering routine HIV screening to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends offering routine HIV screening to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

Adapted from Bright Futures and American Academy of Pediatrics Committee on Practice and Ambulatory Medicine. 2014 Recommendations for Pediatric Preventive Health Care. Pediatrics 133:568-570, 2014.

Although most adolescents in the United States have seen a healthcare provider in the past year and report a usual source of healthcare, adolescents are less likely to receive preventive care services. According to the 2011 National Health Interview Survey, an estimated 90% of 12-17 yr old U.S. adolescents had 1 or more contacts with a healthcare professional in the past year, 98% identify a usual source of care at a doctor's office or clinic, and 17% made at least 1 emergency department visit in the past year. Uninsured adolescents are the least likely to receive care. In 2011, an estimated 9% of 12-17 yr olds were without health insurance, 2% had unmet healthcare needs and 4% delayed healthcare because of cost. However, even among adolescents who are fully insured with a usual source of care, most do not receive preventive healthcare. An analysis of claims data from a large Minnesota health plan with approximately 700,000 members found that among patients ages 11-18 yr who were enrolled for at least 4 yr between 1998 and 2007, few received preventive care visits. One-third of adolescents had no preventive care visits from age 13 through 17 yr, and another 40% had only a single such visit. Nonpreventive care visits were more frequent in all age-groups, averaging about 1 per yr at age 11 yr, climbing to about 1.5 per yr at age 17 yr. Among older adolescence, females had both more preventive care and more nonpreventive care visits than did males (Table 112-2).

The Patient Protection and Affordable Care Act (ACA), enacted in March, 2010, has significantly expanded access to both commercial health plans and Medicaid for young adults age 19-26 yr (Fig. 112-1). From June 2010 through June 2012, the proportion of young adults with insurance increased from 65.7% to 73.8%. ACA provisions require that commercial health plans (a) continuing dependent coverage to 26 yr, regardless of the young adults' financial or dependent status, marriage, or educational enrollment; (b) mandate university and college student health plans to enhance consumer protections for students; (c) provide financial assistance for young adults to enroll into health insurance exchanges with incomes ranging from 133% to 399% of the federal poverty level; and offer preventive healthcare services free of any cost sharing, deductibles or copayments. For Medicaid, states must offer enrollment to all adults with incomes less than 133% of the federal poverty level.

The complexity and interaction of physical, cognitive, and psychosocial developmental processes during adolescence require sensitivity and skill on the part of the health professional (see Chapter 110). Health education and promotion, as well as disease prevention, should be the focus of every visit. In 2008, the American Academy of Pediatrics in collaboration with the U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, published the 3rd edition of *Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents*, which offers providers a strategy for delivery of adolescent preventive health services with screening and counseling recommendations for early, middle, and late adolescence (Table 112-3). Bright Futures is rooted in the philosophy of preventive care and reflects the concept of caring for children in a "medical home." These guidelines emphasize effective partnerships with parents and the community to support the adolescent's health and development.

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices currently recommends routine adolescent vaccines for universal administration beginning at the 11-12 yr old visit or as soon as possible, (a) tetanus–diphtheria–acellular pertussis vaccine (Tdap), (b) the meningococcal conjugate vaccine (MCV4), and (c) the human papillomavirus vaccine (see Chapter 172). The Advisory Committee on Immunization Practices recommends annual influenza vaccination and hepatitis A vaccination (HAV) to adolescents and young adults who have not previously received the HAV vaccine series if immunity against HAV is desired or for those at increased risk for infection, such as men who have sex with men, injection drug users, and those with chronic liver disease or clotting factor disorders, or who live in areas that target older children for HAV vaccine.

The time spent on various elements of the screening will vary with the issues that surface during the assessment. For gay and lesbian youth (see Chapter 110.3), emotional and psychologic issues related to their experiences, from fear of disclosure to the trauma of homophobia, may direct the clinician to spend more time assessing emotional and psychologic supports in the young person's environment. For youth with

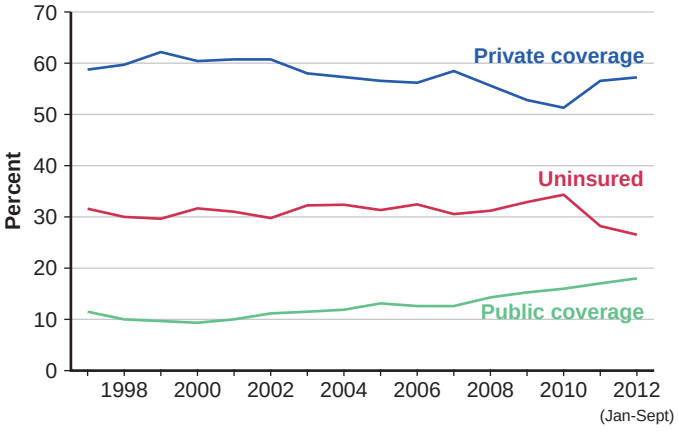

Figure 112-1 Percentage of adults age 19-25 yr with health insurance by coverage type and percentage uninsured at the time of the interview: United States, 1997–September, 2012. Note: Estimates for 2012 are based on data collected in January through September. Data are based on household interviews of a sample of the civilian noninstitutionalized population. *(Data from CDC/NCHS, National Health Interview Survey, 1997-2012, Family Core Component.)*

Table 112-2 Adjusted Mean Number of Preventive and Nonpreventive Care Visits Among Continuously Enrolled Adolescents Between the Ages of 13 and 18 Yr, Health Partners 1998-2007

CHARACTERISTIC	PREVENTIVE CARE VISITS MEAN NUMBER (SD)	*P* VALUE	NONPREVENTIVE CARE VISITS MEAN NUMBER (SD)	*P* VALUE
INSURANCE TYPE				
Commercial	1.070 (0.947)	<0.001	6.829 (6.756)	<0.005
Governmental	1.1781 (1.094)		6.412 (8.009)	
SEX				
Male	1.162 (0.985)	<0.001	7.729 (7.514)	<0.001
Female	0.991 (0.916)		5.918 (5.937)	

Note: Among adolescents with continuous enrollment (>333 days between birthdays) for 4 or more yr. Regression model adjusted mutually for insurance type and sex.

SD: standard deviation.

From Nordin JD, Solberg LI, Parker ED: Adolescent primary care visit patterns. Ann Fam Med *8:511–516, 2010.*

Table 112-3 Adolescent Screening Recommendations

		11-14 YR OLD VISIT	15-17 YR OLD VISIT	18-21 YR OLD VISIT
Universal Screening		**Action**	**Action**	**Action**
Vision (once during each of 3 adolescent age groups)		Snellen test	Snellen test	Snellen test
Dyslipidemia		Lipid screen (once between 9-11 yr)	NA	Lipid screen (once between 18-21 yr)
Selective Screening	**Risk Assessment**	**Action If RA+**	**Action If RA+**	**Action If RA+**
Vision at other ages	+ on risk screening questions	Snellen test	Snellen test	Snellen test
Hearing	+ on risk screening questions	Audiometry	Audiometry	Audiometry
Anemia	+ on risk screening questions	Hemoglobin or hematocrit	Hemoglobin or hematocrit	Hemoglobin or hematocrit
Tuberculosis	+ on risk screening questions	Tuberculin skin test	Tuberculin skin test	Tuberculin skin test
Dyslipidemia	+ on risk screening questions and not previously screened with normal results	Lipid screen	Lipid screen	Lipid screen
STIs	Sexually active	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)	Chlamydia and gonorrhea screen (use tests appropriate for population and clinical setting)
	Sexually active and + on risk screening questions	Syphilis test	Syphilis test	Syphilis test
HIV	Discuss and offer	HIV test*	HIV test*	HIV test*
Pregnancy	Sexually active, without contraception, late menses or amenorrhea	Urine hCG	Urine hCG	Urine hCG (without late or absent menses or heavy or irregular bleeding)
Cervical dysplasia†	NA	NA	NA	Pap smear at age 21 yr
Alcohol or drug use	+ on risk screening questions	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool	Administer alcohol and drug screening tool

*CDC recommends universal, voluntary HIV screening of all sexually active people, beginning at age 13 yr. American Academy of Pediatrics recommends routine HIV screening offered to all adolescents at least once by 16-18 yr of age and to those younger if at risk. U.S. Preventive Services Task Force recommends routine HIV screening offered to all adolescents age 15 yr and older at least once and to those younger if at risk. Patients who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.

†Screening for Cervical Cancer. April 2012. U.S. Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

hCG, human chorionic gonadotropin; NA, not applicable; RA, risk assessment.

Adapted from Hagan JF, Shaw JS, Duncan PM, eds. Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents, *3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2008; and American Academy of Pediatrics, Committee on Practice and Ambulatory Medicine, Bright Futures Periodicity Schedule Workgroup: 2014 recommendations for pediatric preventive health care,* Pediatrics *133(3):568–570, 2014.*

chronic illnesses or special needs, the assessment of at-risk behaviors should not be omitted or deemphasized by assuming they do not experience the "normal" adolescent vulnerabilities.

Bibliography is available at Expert Consult.

112.1 Legal Issues

Gale R. Burstein

The rights of an individual, including those of adolescents, vary widely between nations. In the United States, the right of a minor to consent to treatment without parental knowledge differs between states and is governed by state-specific minor consent laws. Some consent laws are based on a minor's status, such as minors who are emancipated, parents, married, pregnant, in the armed services, or mature. In some states, minors can be considered *emancipated* if they are or have served in the armed services or are living apart from parents and are economically independent through gainful employment. A *mature minor* is a minor who is emotionally and intellectually mature enough to give informed consent and who lives under the supervision of a parent or guardian. Courts have held that if a minor is mature, a physician is not liable for providing beneficial treatment. There is no formal process for recognition of a mature minor. The determination is made by the healthcare provider.

Some minor consent laws are based on services a minor is seeking, such as emergency care, sexual healthcare, substance abuse, or mental healthcare (Table 112-4). All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for STIs. Approximately 25% of states require that minors be a certain age (generally 12-14 yr) before they are allowed to consent for their own care for STIs. No state requires parental consent for STI care or requires that providers notify parents that an adolescent minor child has received STI services, except in limited or unusual circumstances.

Minors' right to consent for contraceptive services varies from state to state. Nearly 50% of states and the District of Columbia explicitly authorize all minors to consent for their own contraceptive services; and 50% of states permit minors to consent for their own contraceptive services under specific circumstances, such as being married, a parent, currently or previously pregnant, over a certain age, or a high school graduate, or per physician's discretion.

A minor's right to consent for mental healthcare and substance abuse treatment services vary by state and age of minor, whether care is medical versus nonmedical (e.g., counseling), and whether care is delivered as an inpatient versus outpatient basis. Minor consent laws often contain provisions regarding confidentiality and disclosure, even when general state consent laws do not have such provisions.

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U.S. Preventive Services Task Force. *Screening for Cervical Cancer*. 2012. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

U.S. Preventive Services Task Force. *Screening for HIV*. http://www.uspreventiveservicestaskforce.org/uspstf/uspshivi.htm.

Table 112-4 Types of Minor Consent Statutes or Rules of Common Law That Allow for the Medical Treatment of a Minor Patient Without Parental Consent

LEGAL EXCEPTIONS TO INFORMED CONSENT REQUIREMENT	MEDICAL CARE SETTING
The "emergency" exception	• The child is suffering from an emergent condition that places his or her life or health in danger • The child's legal guardian is unavailable or unable to provide consent for treatment or transport • Treatment or transport cannot be safely delayed until consent can be obtained • The professional administers only treatment for emergent conditions that pose an immediate threat to the child
The "emancipated minor" exception	• Married • Economically self-supporting and not living at home • Active-duty status in the military • In some states, a minor who is a parent or pregnant • Some states might require a court to declare the emancipation of a minor
The "mature minor" exception	Most states recognize a mature minor, in which a minor, usually ≥14 yr, displays sufficient maturity and intelligence to understand and appreciate the benefits, risks, and alternatives of the proposed treatment and to make a voluntary and reasonable choice on the basis of that information. States vary or whether a judicial determination is required
Exceptions based on specific medical condition (state laws vary)	Minor seeks: • Mental health services • Pregnancy and contraceptive services • Testing or treatment for human immunodeficiency virus infection or acquired immunodeficiency syndrome • Sexually transmitted infection testing and treatment • Drug and alcohol addiction treatment

Data from American Academy of Pediatrics: Consent for emergency medical services for children and adolescents, Pediatrics *128:427–433, 2011.*

The confidentiality of medical information and records of a minor who has consented for his or her own *reproductive healthcare* is governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI or contraceptive services for which minors have given their own consent and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents.

The confidentiality of medical information and records of a minor who has consented for his or her own *healthcare* is also governed by numerous federal and state laws. Laws in some states explicitly protect the confidentiality of STI, contraceptive, or mental health services for which minors have given their own consent and do not allow disclosure of the information without the minor's consent. In other states, laws grant physicians discretion to disclose information to parents. Title X and Medicaid both provide confidentiality protection for family planning services provided to minors with funding from these programs.

Federal regulations issued under the Federal Health Insurance Portability and Accountability Act of 1996, known as the HIPAA Privacy Rule, defer to state and "other applicable laws" with respect to the question of whether parents' have access to information about care for which a minor has given consent. Thus both the state laws that either prohibit or permit disclosure of confidential information and the federal Title X and Medicaid laws that protect the confidentiality of care for adolescents are important under the HIPAA Privacy Rule in determining when confidential information about health services for minors can be disclosed to parents.

Billing for confidential services is complex. Commercial health plans send home an *explanation of benefit* to the primary insured or the primary beneficiary listing services rendered by the provider and reimbursed by the health plan. An explanation of benefit documenting that confidential health services were rendered to their adolescent dependent that is received by a parent may disclose those services. In addition, copayments automatically generated with certain billing codes for office visits and medications can be a barrier for adolescents receiving care, including treatment.

Providers may elect to establish a policy of discussing with their adolescent patients when medical records and other information will be disclosed and developing a mechanism to alert office staff as to what information in the chart is confidential. For legal and other reasons, a chaperone should be present whenever an adolescent female patient is examined by a male physician.

Bibliography is available at Expert Consult.

112.2 Screening Procedures

Gale R. Burstein

INTERVIEWING THE ADOLESCENT

The preparation for a successful interview with an adolescent patient varies based on the history of the relationship with the patient. Patients (and their parents) who are going from preadolescence to adolescence while seeing the same provider, should be guided through the transition. Although the rules for confidentiality are the same for new and continuing patients, the change in the physician-patient relationship, allowing more privacy during the visit and more autonomy in the health process, may be threatening for the parent as well as the adolescent. For new patients, the initial phases of the interview are more challenging given the need to establish rapport rapidly with the patient in order to meet the goals of the encounter. Issues of confidentiality and privacy should be explicitly stated along with the conditions under which that confidentiality may need to be altered, that is, in life- or safety-threatening situations. For new patients, the parents should be interviewed with the adolescent or before the adolescent to ensure that the adolescent does not perceive a breach of confidentiality. The clinician who takes time to listen avoids judgmental statements and the use of street jargon and shows respect for the adolescent's emerging maturity will have an easier time communicating with the adolescent. The use of open-ended questions, rather than closed-ended questions, will further facilitate history taking. (The closed-ended question "Do you get along with your father?" leads to the answer "yes" or "no," in contrast to the question, "What might you like to be different in your relationship with your mother?" which may lead to an answer such as "I would like her to stop always worrying about me.")

The goals of the interview or clinical encounter are to establish an information base, identify problems and issues from the patient's perspective, and identify problems and issues from the perspective of the

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clinician based on knowledge of the health and other issues relevant to the adolescent age group. The adolescent should be given an opportunity to express concerns and the reasons for seeking medical attention. The adolescent as well as the parent should be given an opportunity to express the strengths and successes of the adolescent, in addition to communicating problems.

The effectiveness of an interview can be compromised when the interviewer is distracted by other events or individuals in the office, when there are extreme time limitations obvious to either party, or when there is expressible discomfort with either the patient or the interviewer. The need for an interpreter when a patient is hearing impaired or if the patient and interviewer are not language compatible provides a challenge but not necessarily a barrier under most circumstances (see Chapter 4). Observations during the interview can be useful to the overall assessment of the patient's maturity, presence or absence of depression, and the parent-adolescent relationship. Given the key role of a successful interview in the screening process, adequate training and experience should be sought by clinicians wishing to give comprehensive care to adolescent patients.

PSYCHOSOCIAL ASSESSMENT

A few questions should be asked in order to identify the adolescent who is having difficulty with peer relationships ("Do you have a best friend with whom you can share even the most personal secret?"), self-image ("Is there anything you would like to change about yourself?"), depression ("What do you see yourself doing 5 yr from now?"), school ("How are your grades this year compared with last year?"), personal decisions ("Are you feeling pressured to engage in any behavior for which you do not feel you are ready?"), and an eating disorder ("Do you ever feel that food controls you rather than vice versa?"). Bright Futures materials provide questions and patient encounter forms to structure the assessments that are available at their website (*http://brightfutures.aap.org/index.html*). The **HEADS/SF/FIRST** mnemonic, basic or expanded, can be useful in guiding the interview if encounter forms are not available (Table 112-5). Based on the assessments, appropriate counseling or referrals are recommended for more thorough probing or for in-depth interviewing.

Table 112-5 HEADS/SF/FIRST

Home. Space, privacy, frequent geographic moves, neighborhood.
Education/School. Frequent school changes, repetition of a grade/in each subject, teachers' reports, vocational goals, after-school educational clubs (language, speech, math, etc.), learning disabilities
Abuse. Physical, sexual, emotional, verbal abuse; parental discipline
Drugs. Tobacco, alcohol, marijuana, inhalants, "club drugs," "rave" parties, others. Drug of choice, age at initiation, frequency, mode of intake, rituals, alone or with peers, quit methods, and number of attempts
Safety. Seat belts, helmets, sports safety measures, hazardous activities, driving while intoxicated
Sexuality/Sexual Identity. Reproductive health (use of contraceptives, presence of sexually transmitted infections, feelings, pregnancy)
Family and Friends. Family: Family constellation, genogram, single/married/separated/divorced/blended family, family occupations and shifts; history of addiction in 1st- and 2nd-degree relatives, parental attitude toward alcohol and drugs, parental rules; chronically ill physically or mentally challenged parent. **Friends:** peer cliques and configuration ("preppies," "jocks," "nerds," "computer geeks," cheerleaders), gang or cult affiliation
Image. Height and weight perceptions, body musculature and physique, appearance (including dress, jewelry, tattoos, body piercing as fashion trends or other statement)
Recreation. Sleep, exercise, organized or unstructured sports, recreational activities (television, video games, computer games, Internet and chat rooms, church or community youth group activities [e.g., Boy/Girl Scouts; Big Brother/Sister groups, campus groups]). How many hours per day, days per week involved?
Spirituality and Connectedness. Use HOPE* or FICA† acronym; adherence, rituals, occult practices, community service or involvement
Threats and Violence. Self-harm or harm to others, running away, cruelty to animals, guns, fights, arrests, stealing, fire setting, fights in school

*HOPE, **h**ope or security for the future; **o**rganized religion; **p**ersonal spirituality and practices; **e**ffects on medical care and end of life issues.

†FICA, faith beliefs; importance and influence of faith; community support.

From Dias PJ: Adolescent substance abuse. Assessment in the office, Pediatr Clin North Am *49:269–300, 2002.*

PHYSICAL EXAMINATION

Vision Testing

The pubertal growth spurt may involve the optic globe, resulting in its elongation and myopia in genetically predisposed individuals (see Chapter 621). Vision testing should, therefore, be performed in order to detect this problem before it affects school performance.

Audiometry

Highly amplified music of the kind enjoyed by many adolescents may result in hearing loss (see Chapter 637). A hearing screening is recommended by the Bright Futures guidelines for adolescents who are exposed to loud noises regularly, have had recurring ear infections, or report problems.

Blood Pressure Determination

Criteria for a diagnosis of hypertension are based on age-specific norms that increase with pubertal maturation (see Chapter 445). An individual whose blood pressure exceeds the 95th percentile for his or her age is suspect for having hypertension, regardless of the absolute reading. Those adolescents with blood pressure between the 90th and 95th percentiles should receive appropriate counseling relative to weight and have a follow-up examination in 6 mo. Those with blood pressure above the 90th percentile should have their blood pressure measured on three separate occasions to determine the stability of the elevation before moving forward with an intervention strategy. The technique is important; false-positive results may be obtained if the cuff covers less than two thirds of the upper arm. The patient should be seated, and an average should be taken of the 2nd and 3rd consecutive readings, using the change rather than the disappearance as the diastolic pressure. Most adolescents with elevations of blood pressure have labile hypertension. If the blood pressure is below 2 SD for age, anorexia nervosa and Addison disease should be considered.

Scoliosis

See Chapter 679.

Approximately 5% of male and 10-14% of female adolescents have a mild curvature of the spine. This is 2-4 times the rate in younger children. Scoliosis is typically manifested during the peak of the height velocity curve, at approximately 12 yr in females and 14 yr in males. Curves measuring greater than 10 degrees should be monitored by an orthopedist until growth is complete.

Breast Examination

See Chapters 115 and 551.

Examination of the female adolescent's breasts is performed to detect masses, evaluate progression of sexual maturation, provide reassurance about development, and teach the technique of self-examination with the hope that this practice will continue into the higher risk later years. However, there is disagreement on the justification for promoting this routinely, given the rare instances of malignant breast masses in this age group.

Scrotum Examination

The peak incidence of germ cell tumors of the testes is in late adolescence and early adulthood. Palpation of the testes may have an immediate yield and should serve as a model for instruction of self-examination. Because varicoceles often appear during puberty, the examination also provides an opportunity to explain and reassure the patient about this entity (see Chapter 545).

Pelvic Examination

See Chapter 548.

Laboratory Testing

The increased incidence of iron-deficiency anemia after menarche mandates the performance of a hematocrit annually in females with moderate to heavy menses. The reference standard for this test changes with progression of puberty, as estrogen suppresses erythropoietin (see Chapter 446). Populations with nutritional risk should also have the hematocrit monitored. Androgens have the opposite effect, causing the hematocrit to rise during male puberty; Sexual Maturity Rating 1 males have an average hematocrit of 39%, whereas those who have completed puberty (sexual maturity rating 5; see Chapter 110) have an average value of 43%. Tuberculosis testing on an annual basis is important in adolescents with risk factors, such as an adolescent with HIV, living in the household with someone with HIV, the incarcerated adolescent, or those with other risk factors, because puberty has been shown to activate this disease in those not previously treated. Hepatitis C virus screening should be offered to adolescents who report risk factors, such as injection drug use, received blood products or organ donation before 1992, or long-term hemodialysis.

Sexually active adolescents should undergo screening for STIs as per Centers for Disease Control and Prevention guidelines, regardless of symptoms (see Chapter 120). There are clear indications for chlamydia and gonorrhea screening of females 24 yr old and younger, but less sufficient evidence to support routine screening in young men. Based on feasibility, efficacy, and cost-effectiveness, evidence is insufficient to recommend routine chlamydia screening in all sexually active young men. However, screening of sexually active young males should be considered in clinical settings associated with high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and sexually transmitted disease clinics) and should be offered to young men who have sex with men. HIV screening should be discussed and offered to all adolescents aged 15 yr and older and to younger adolescents who are at increased risk. Routine screening of adolescents who are asymptomatic for certain STIs (e.g., syphilis, trichomoniasis, herpes simplex virus, and human papillomavirus) is not recommended. However, young men who have sex with men and pregnant adolescent females might require more thorough evaluation for all sexually transmitted diseases. Because cervical cancer incidence low and complications from procedures may outweigh benefits of screening adolescent females, cervical cancer screening should not begin until age 21 yr.

Bibliography is available at Expert Consult.

112.3 Transitioning to Adult Care

Cynthia Holland-Hall and Gale R. Burstein

The importance of successfully transitioning the care of adolescents with special healthcare needs (SHCN) from pediatric to adult services has been recognized for over a decade. Successful transition is associated with improved health outcomes and quality of life; poorly managed transition may lead to worsening of chronic disease control. Nonetheless, few pediatric practices incorporate explicit, comprehensive transition services into the care of their patients with SHCN. Barriers to providing transition services include lack of access to appropriate providers of adult primary and subspecialty care, time, and reimbursement by insurance companies. Internists accepting young adult patients with SHCN also perceive a need for better training in congenital and child-onset medical conditions. Families may experience anxiety about leaving trusted pediatric providers, or fear that their child is incapable of assuming care for his or her medical condition. Among the patients themselves, a higher degree of self-efficacy for disease management and independently negotiating the healthcare system, as well as a positive attitude toward transition, lead to a greater perceived readiness to transition their care to an adult model. Medical providers, family members, and adolescent patients therefore each play a critical role in implementing and executing a plan for successful transition.

Table 112-6 Key Elements of the Transition of Health Care Process

- Written Transition Policy to be shared with youth, families, providers, and staff, explaining the process and the responsibilities of all team members
- Transitioning Youth Registry to track the progress of each patient through the transition process
- Longitudinal Readiness Checklists assessing the youth's ability for independence, self-management, and communicating with the adult healthcare system, as well as the family's readiness to assist the patient in achieving these goals
- Written Transition Plan documenting the steps to be conducted to meet the needs identified in the readiness assessment, as well as identifying appropriate adult care resources
- For youth with SHCN, expanded transition services including attention to insurance, entitlements, guardianship, and vocational needs in addition to adult subspecialty care
- Appropriate communication between the pediatric and adult medical home and subspecialists, including a Portable Medical Summary and care plan delivered to the patient and caregivers
- Transfer of care, within the 18- to 21-year age range, to adult providers, to whom pediatric providers continue to serve as a resource until transition is complete

The American Academy of Pediatrics, in conjunction with other key professional societies, has published detailed, comprehensive guidelines for incorporating transition services into the medical home for all adolescents, regardless of the presence or absence of SHCN. These guidelines are based on expert opinion, since the evidence on transition outcomes is limited. Transition encompasses much more than simply the transfer of care to another provider. In fact, many of the elements of transition apply even to family physicians who do not intend to transfer the patient's care, but who still should assist the patient in adapting to an adult model of healthcare delivery. Table 112-6 includes the key elements of healthcare transition. Tools to assist providers with all of these steps are available online from the National healthcare Transition Center (www.gottransition.org).

The process begins with the development of a transition policy and its dissemination to all families of young adolescents, ensuring that families understand that transition planning will be an element of health maintenance and chronic care management visits throughout the adolescent years. By middle adolescence, a transition plan should be developed with the youth and family caregivers, and this plan should be updated at subsequent visits until the patient is ready for implementation of the adult care model in early adulthood. Critical to the transition process is skills training for the adolescent in communication, self-advocacy, and self-care. The ultimate goal is to help all young people maximize their potential as they become young adults.

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Chapter 113

Violent Behavior

Margaret M. Stager

Violence is recognized by the World Health Organization (WHO) as a leading worldwide public health problem. WHO defines violence as "The intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in injury, death, psychologic harm, maldevelopment or deprivation" (see Chapter 39). Youths may be perpetrators, victims, or observers of violence (or any combination of the 3 roles) with varying severity of impact on the individual, family, and larger community. Multiple factors have been identified that may increase the risk of a youth engaging in violence, including poverty, war, substance abuse, mental health disorders, and poor family functioning.

EPIDEMIOLOGY

In 2010, homicide in the United States was the second leading cause of death for 10-24 yr olds totaling 4,828 deaths, which were largely males (86%) killed by a handgun (82.8%). The 2010 homicide rate for teens ages 12-17 yr was 3.0/100,000 youth down 65% from 8.4/100,000 youth in 1993. The WHO reports that other than the United States, where the youth and young adult homicide rate was 11 per 100,000, most countries with homicide rates above 10 per 100,000 are developing nations or countries with rapid socioeconomic changes. The prevalence of behaviors that contribute to violence has not decreased from 1999 to 2011; fighting and weapon carrying remain prevalent among U.S. youth. The rate of homicide by handgun is considerably higher than homicide by other weapon type, suggesting that access to firearms may play a major role in youth injuries and deaths (Fig. 113-1). Gang-related homicides among youths in 5 major U.S. cities are more likely to involve young (15-19 yr) males (80%), racial/ethnic minority (73%), and a firearm (90%) in comparison to nongang homicides. In addition, gang homicides are more likely to occur in public places, in the afternoon/evening hours, and rarely are related to drug trade/use. One quarter of the gang homicides are classified as drive-by shootings.

Violence at schools in the United States remains a significant problem with 32.8% of students reported being in a fight on school property 1 or more times in the preceding 12 mo. The 2011 Youth Risk Behavior Surveillance System reported 16.6% youths overall carried a weapon such as a gun, knife, or club in the last 30 days; 5.4% carried the weapon to school; and 7.4% reported being threatened or injured with a type of weapon on school property. Males are more likely than females to carry a gun or weapon and therefore may need increased monitoring at home and at school. Weapon carrying is highest among white males overall, which may begin as early as 9th grade. Student reports of physical fighting at schools have nearly tripled in the last 4 yr. These violence-related behaviors at school affect the students' perception of safety. More than 5% of students did not go to school on 1 or more days in the preceding 30 days because they felt it was unsafe at school.

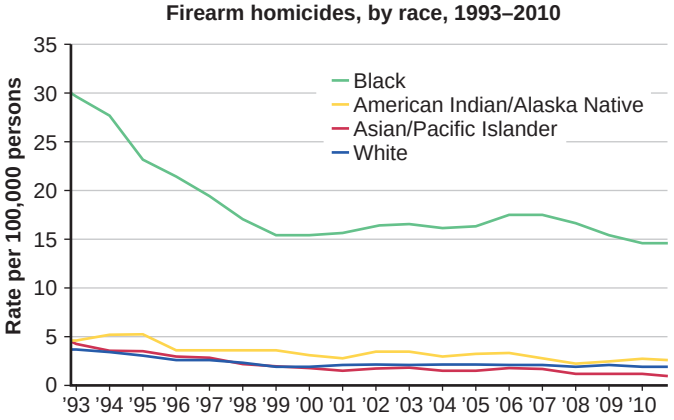

Figure 113-1 Firearm homicides, by race, 1993-2010. *(Data from Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Web-based Injury Statistics Query and Reporting System (WISQARS), 1993–2010. Retrieved March 2013 from* http://www.cdc.gov/ncipc/wisqars.*)*

Dating violence (or intimate partner violence) occurs between 2 people in a close relationship and can be physical (punching, kicking, hitting or shoving), emotional (shaming, bullying, controlling or stalking), or sexual (forcing one's partner to engage in a sexual act when he/she does not consent to it). Incidents of dating violence often occur during the adolescent years with 22.4% of women and 15% of men experiencing some type of partner violence between the ages of 11 and 17 yr. The highest prevalence rates are seen in African-American students and older students. It may start with teasing, name calling, or shaming. It may progress electronically, such as frequent calls, texting, or posting sexual pictures of a partner on social media. Risk factors for being a victim of dating violence includes those who use alcohol, believe dating violence is acceptable, have lack of parental supervision, or have a friend who is in a violent relationship. Most teens do not report the behaviors because they fear retaliation from the partner. Teens who are victims of dating violence are more likely to experience decreased school performance, use drugs and alcohol, have an eating disorder, or experience depression. School-based prevention programs that address attitudes and behaviors linked with dating violence, such as Safe Dates, offer training experiences to change social norms amongst teens. School-based prevention programs initiated at the elementary school level have been found to decrease violent behaviors in students. Increased surveillance of students is warranted both on and around school property to improve student safety.

ETIOLOGY

The WHO places youth violence in a model within the context of 3 larger types of violence: self-inflicted, interpersonal, and collective. **Interpersonal violence** is subdivided into violence largely between family members or partners and includes child abuse. **Community violence** occurs between individuals who are unrelated. **Collective violence** incorporates violence by people who are members of an identified group against another group of individuals with social, political, or economic motivation. The types of violence in this model have behavioral links, in that child abuse victims are more likely to experience violent and aggressive interpersonal behavior as adolescents and adults. Overlapping risk factors exist for the types of violence, such as firearm availability, alcohol use, and socioeconomic inequalities. The benefit to identifying common risk factors for the types of violence lies in the potential for intervening with prevention efforts and gaining positive outcomes for more than one type of violent behavior. The model further acknowledges 4 categories that explore the potential nature of violence as involving physical, sexual, or psychological force, or deprivation.

There may be 2 types of antisocial youth: 1 that is life-course persistent and 1 that is life-course limited. **Adolescent-limited offenders** have no childhood aberrant behaviors and are more likely to commit status offenses such as vandalism, running away, and other behaviors symbolic of their struggle for autonomy from parents. **Life course–persistent offenders** exhibit aberrant behavior in childhood, such as problems with temperament, behavioral development, and cognition; as adolescents they participate in more victim-oriented crimes. The public health model emphasizes the environment and other external influences. A third theoretical model examines violent behaviors across the spectrum occurring within and outside the family and is referred to as the **cycle of violence.** This hypothesis proposes that precursors such as child abuse and neglect, a child witnessing violence, adolescent sexual and physical abuse, and adolescent exposure to violence and

violent assaults predispose youths to outcomes of violent behavior, violent crime, delinquency, violent assaults, suicide, or premature death. An additional common paradigm for high-risk violence behavior poses a balance of risk and protective factors at the individual, family, and community levels.

CLINICAL MANIFESTATIONS

There are several identified risk factors for youth violence, including poverty, association with delinquent peers, poor school performance/low education status, disconnection from adult role models or mentors, prior history of violence or victimization, poor family functioning, childhood abuse, substance abuse, and certain mental health disorders. The most common disorders associated with aggressive behavior in adolescents are mental retardation, learning disabilities, moderately severe language disorders, and mental disorders such as attention-deficit/hyperactivity and mood disturbances. The link between severe mental illness and violent behaviors is strongest for those with cooccurring alcohol or substance abuse or dependence.

Inability to master prosocial skills such as the establishment and maintenance of positive family and peer relations and poor resolution of conflict may put adolescents with these disorders at higher risk of physical violence and other risky behaviors. **Conduct disorder** and **oppositional defiant disorder** are specific psychiatric diagnoses whose definitions are associated with violent behavior (Table 113-1). They occur comorbidly with other disorders, such as attention-deficit/hyperactivity disorder (see Chapter 30), and increase an adolescent's vulnerability for juvenile delinquency, substance use or abuse, sexual promiscuity, adult criminal behavior, incarceration, and antisocial personality disorder. Other cooccurring risk factors for youth violence include use of anabolic steroids, gang tattoos, belief in one's premature death, preteen alcohol use, and placement in a juvenile detention center.

DIAGNOSIS

The assessment of an adolescent at risk or with a history of violent behavior or victimization should be a part of the health maintenance visit of all adolescents. The answers to questions about recent history of involvement in a physical fight, carrying a weapon, or firearms in the household, as well as concerns that the adolescent may have about his or her personal safety may suggest a problem requiring a more in-depth evaluation. The **FISTS** mnemonic provides guidance for structuring the assessment (Table 113-2). The additional factors of physical or sexual abuse, serious problems at school, poor school performance and attendance, multiple incidents of trauma, substance use, and symptoms associated with mental disorders are indications for evaluation by a mental health professional. In a situation of acute trauma, assault victims are not always forthcoming about the circumstances of their injuries for fear of retaliation or police involvement. Stabilization of the injury or the gathering of forensic evidence in sexual assault is the treatment priority; however, once this is achieved, addressing a more comprehensive set of issues surrounding the assault is appropriate.

TREATMENT

In the instance of acute injury secondary to violent assault, the treatment plan should follow standards established by the American Academy of Pediatrics model protocol, which includes, but is not limited to, the stabilization of the injury, evaluation and treatment of the injury, evaluation of the assault circumstance, psychologic evaluation and support, social service evaluation of the circumstance surrounding the assault, and a treatment plan on discharge that is designed to protect the adolescent from subsequent injury episodes and minimize the development of psychologic disability. Victims as well as witnesses of violence are at risk for posttraumatic stress disorder, and future aggressive and/or violent behavior.

Multiple treatment modalities are used simultaneously in managing adolescents with persistent violent and aggressive behavior and range from cognitive-behavioral therapy involving the individual and family to specific family interventions (parent management training, multisystemic treatment) and pharmacotherapy. Treatment of existing comorbid conditions, such as attention-deficit/hyperactivity disorder, depression, and substance abuse, appears to reduce aggressive behavior.

PREVENTION

The WHO recognizes a multifactorial approach to prevention: individual approaches, relationship approaches, community approaches, and societal approaches (Table 113-3). **Individual approaches** concentrate on changing attitudes and behaviors to avoid aggressive and

Table 113-2 FISTS Mnemonic to Assess an Adolescent's Risk of Violence

F: Fighting (How many fights were you in last year? What was the last?)
I: Injuries (Have you ever been injured? Have you ever injured someone else?)
S: Sex (Has your partner hit you? Have you hit your partner? Have you ever been forced to have sex?)
T: Threats (Has someone with a weapon threatened you? What happened? Has anything changed to make you feel safer?)
S: Self-defense (What do you do if someone tries to pick a fight? Have you carried a weapon in self-defense?)

The FISTS mnemonic is adapted with permission from the Association of American Medical Colleges. Alpert EJ, Sege RD, Bradshaw YS. Interpersonal violence and the education of physicians. Acad Med *72:S41–S50, 1997.*

Table 113-1 Oppositional Defiant Disorder, Conduct Disorder, and Juvenile Delinquency

PSYCHIATRIC DISORDER LABELS		
Oppositional Defiant Disorder	**Conduct Disorder**	**Legal Label Juvenile Delinquency**
Recurrent pattern of negativistic, defiant, disobedient, and hostile behavior toward authority figures that has a significant adverse effect on functioning (e.g., social, academic, occupational)	Repetitive and persistent pattern of behavior that violates the basic rights of others or major age-appropriate societal norms or rules	Offenses that are illegal because of age; illegal acts
Examples: losing temper; arguing with adults; defying or refusing to comply with request or rules of adults; annoying behavior; blaming others; and being irritable, spiteful, resentful	Examples: physical fighting, deceitfulness, stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape (even if not adjudicated in the legal system)	Examples: single or multiple instances of being arrested or adjudicated for any of the following: stealing, destruction of property, threatening or causing physical harm to people or animals, driving without a license, prostitution, rape
Diagnosed by a mental health clinician	Diagnosed by a mental health practitioner	Adjudicated in the legal system

From Greydanus DE, Pratt HD, Patel DR, et al: The rebellious adolescent, Pediatr Clin North Am *44:1460, 1997.*

Table 113-3 Public Health Approach to Youth Violence Prevention Model with Examples

	VICTIM (HOST)	PERPETRATOR (VECTOR)	FIREARM (AGENT)	SOCIAL ENVIRONMENT	PHYSICAL ENVIRONMENT
Primary prevention	Conflict resolution Violence anticipatory guidance	Substance abuse treatment Home visiting programs for new and single parents	Handgun and assault weapons ban Firearm registration	Job opportunities Adult-supervised activities	Better lighting Zoning-enforced limits in liquor licenses
Secondary prevention	Medical services Psychologic services	Job training Psychosocial rehabilitation	Handgun locks Public education on risks of ownership	School incident debriefing Safe havens	Increased police presence Graffiti removal
Tertiary prevention	Physical rehabilitation Psychosocial services	Incarceration Educational-psychosocial rehabilitation	Firearm surveillance	Foster care Alternative schools	Urban planning, e.g., decrease population density in public housing and mixture of income levels

From Calhoun AD, Clark-Jones F: Theoretical frameworks: developmental psychopathology, the public health approach to violence, and the cycle of violence, Pediatr Clin North Am *45:287, 1998.*

violent behavior as well as teaching coping strategies and nonviolent conflict resolution for all children as well as youths who have already displayed some violent tendencies. **Relationship approaches** focus more on victims, families, and peer relationships, especially those with the potential to trigger aggressive or violent responses. Solutions include improving skills in coping or problem solving in recent perceived crises, interpersonal conflicts, and close relationships. Family-based programs provide training for parents in areas of effective communication, child development, and solving problems in nonviolent methods. **Community-based approaches** raise public awareness in an effort to stimulate action by community members to reduce violence and protect vulnerable community members. Universal school-based violence prevention programs have been found to be effective in reducing violent and aggressive behaviors. Interventions beginning as early as preschool have been found to have positive outcomes years later. **Societal approaches** include broader advocacy and legislative actions, as well as changing the cultural norm toward violent behaviors. A specific prevention strategy can incorporate several approaches, such as the handgun/firearm prevention recommendations that include gun-lock safety, public education, and legislative advocacy. Other efforts are directed toward establishing a national database to track and define the problem of youth violence. The National Violent Death Reporting System collects and analyzes violent death data from 18 states and aims to improve surveillance of current trends, to share information state to state, to build partnerships among state and community organizations, and to develop and implement prevention and intervention programs. Ultimately, the National Violent Death Reporting System will be expanded to include all 50 states. The CDC characterizes specific successful programs and summarizes program content on its website (www.cdc.gov).

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Chapter 114

Substance Abuse

Margaret M. Stager

Although varying in percentages by nation and culture, a substantial proportion of adolescents will engage in use of a wide range of substances such as alcohol, tobacco, or marijuana. Their reactions to and the consequences of these exposures are influenced by a complex interaction between biologic and psychosocial development, environmental messages, and societal attitudes. Occasional or situational use of certain substances, such as alcohol in the United States, may be viewed as normative given the proportion of youths who report some experience with these substances. Others view the potential for adverse outcomes even with occasional use in immature adolescents, such as motor vehicle crashes and other injuries, sufficient justification to consider any drug use in younger adolescents a considerable risk.

Individuals who initiate drug use at an early age are at a greater risk for becoming addicted than those who try drugs in early adulthood. Drug use in younger, less-experienced adolescents can act as a substitute for developing age-appropriate coping strategies and enhance vulnerability to poor decision making. The first use of the most commonly used drugs occurs before age 18 yr, with 88% of people reporting age of first alcohol use at <21 yr old, the legal drinking age in the United States. Inhalants have been identified as a popular first drug for youth in grade 8. When drug use begins to negatively alter functioning in adolescents at school and at home, and risk-taking behavior is seen, intervention is warranted. Serious drug use is not an isolated phenomenon. It occurs across every segment of the population and is 1 of the most challenging public health problems facing society. The challenge to the clinician is to identify youths at risk for substance abuse and offer early intervention. The challenge to the community and society is to create norms that decrease the likelihood of adverse health outcomes for adolescents and promote and facilitate opportunities for adolescents to choose healthier and safer options. Recognizing those drugs with the greatest *harm*, and at times focusing on *harm reduction* with or without abstinence, is an important modern approach to adolescent substance abuse (Figs. 114-1 and 114-2).

ETIOLOGY

Substance abuse is biopsychosocially determined (Fig. 114-3). Biologic factors, including genetic predisposition, are established contributors. Behaviors such as rebelliousness, poor school performance, delinquency, and criminal activity and personality traits such as low self-esteem, anxiety, and lack of self-control are frequently associated with or predate the onset of drug use. Psychiatric disorders are often comorbidly associated with adolescent substance use. Conduct disorders and antisocial personality disorders are the most common diagnoses coexisting with substance abuse, particularly in males. Teens with depression (see Chapter 26), attention deficit disorder (see Chapter 33), and eating disorders (see Chapter 28) have high rates of substance use. The determinants of adolescent substance use and abuse are explained using a number of theoretical models, with factors at the individual level, the level of significant relationships with others, and the level of the setting or environment. Models include a balance of risk and protective or coping factors contributing to individual differences among adolescents with similar risk factors who escape adverse outcomes.

Risk factors for adolescent *drug use* may differ from those associated with adolescent *drug abuse*. Adolescent *use* is more commonly related to social and peer factors, whereas *abuse* is more often a function of psychological and biologic factors. The likelihood that an otherwise normal adolescent would experiment with drugs may be dependent on the availability of the drug to the adolescent, the perceived positive or otherwise functional value to the adolescent, the perceived risk associated with use, and the presence or absence of restraints as determined by the adolescent's cultural or other important value systems. An abusing adolescent may have genetic or biologic factors coexisting with dependence on a particular drug for coping with day-to-day activities.

Specific historical questions can assist in determining the severity of the drug problem through a rating system (Table 114-1). The type of drug used (marijuana vs. heroin), the circumstances of use (alone or

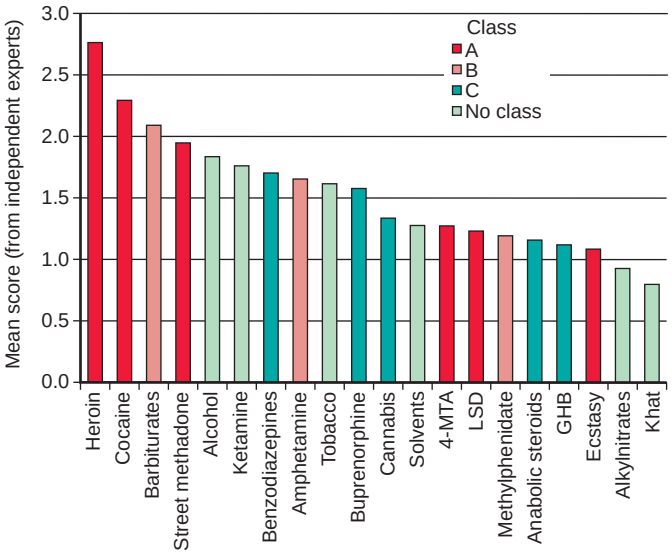

Figure 114-1 Mean harm scores for 20 substances as determined by an expert panel based on 3 criteria: physical harm to user; potential for dependence; and effect on family, community, and society. Classification under the Misuse of Drugs Act, when appropriate, is shown by the color of each bar. Class A drugs are deemed potentially most dangerous; class C least dangerous. *(From Nutt D, King LA, Saulsbury W, et al: Development of a rational scale to access the harm of drugs of potential misuse,* Lancet *369:1047–1053, 2007.)*

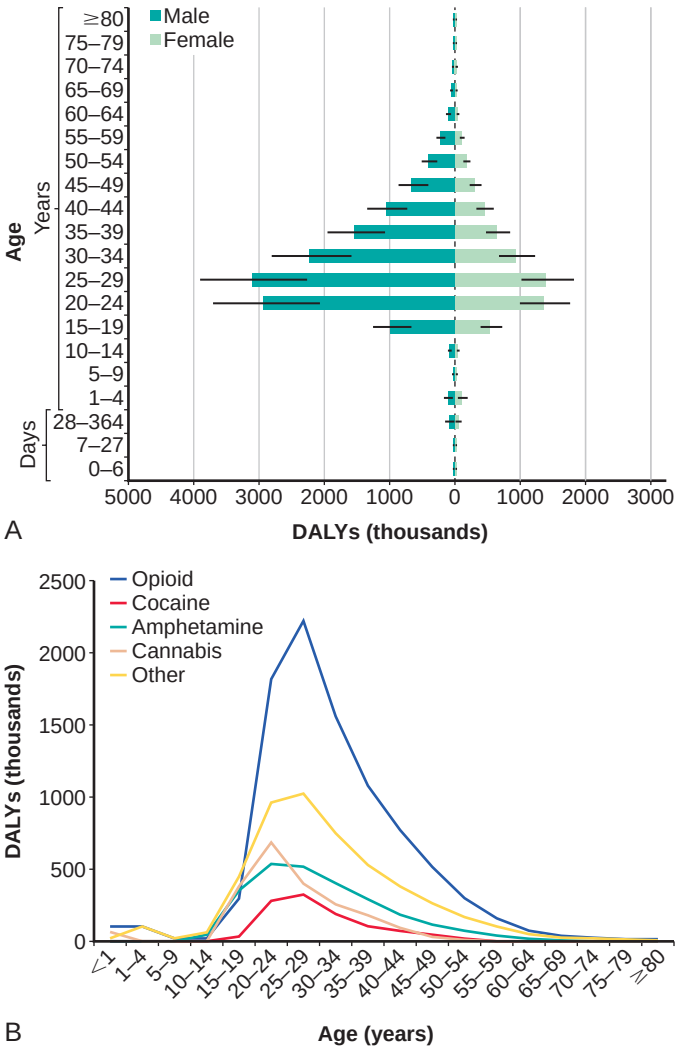

Figure 114-2 Total burden (DALYs) of drug dependence by age and sex in 2010. **A,** DALYs attributable to drug dependence, by age and sex. **B,** DALYs attributable to each type of drug dependence by age. DALYs, disability-adjusted life years. *(From: Degenhardt L, Whitford HA, Ferrari AJ, et al: Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease study 2010.* Lancet *382:1564-1574, 2013, Fig. 2, p. 1569.)*

Table 114-1 Assessing the Seriousness of Adolescent Drug Abuse

VARIABLE	0	+1	+2
Age (yr)	>15	<15	
Sex	Male	Female	
Family history of drug abuse		Yes	
Setting of drug use	In group		Alone
Affect before drug use	Happy	Always poor	Sad
School performance	Good, improving		Recently poor
Use before driving	None		Yes
History of accidents	None		Yes
Time of week	Weekend	Weekdays	
Time of day		After school	Before or during school
Type of drug	Marijuana, beer, wine	Hallucinogens, amphetamines	Whiskey, opiates, cocaine, barbiturates

Total score: 0-3, less worrisome; 3-8, serious; 8-18, very serious.

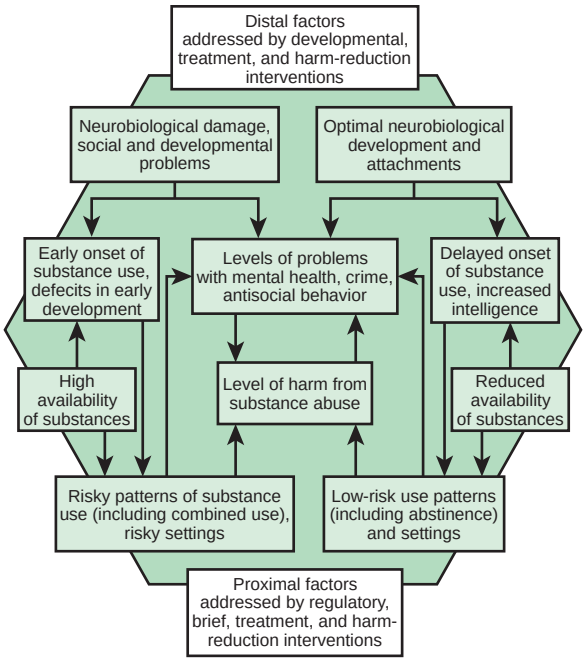

Figure 114-3 Protection and risk model for distal and proximal determinants of risky substance use and related harms. *(From Toumbourou JW, Stockwell T, Neighbors C, et al: Interventions to reduce harm associated with adolescent substance use,* Lancet *369:1391–1401, 2007.)*

Table 114-2 Stages of Adolescent Substance Abuse

STAGE	DESCRIPTION
1	Potential for abuse • Decreased impulse control • Need for immediate gratification • Available drugs, alcohol, inhalants • Need for peer acceptance
2	Experimentation: learning the euphoria • Use of inhalants, tobacco, marijuana, and alcohol with friends • Few, if any, consequences • Use may increase to weekends regularly • Little change in behavior
3	Regular use: seeking the euphoria • Use of other drugs, e.g., stimulants, LSD, sedatives • Behavioral changes and some consequences • Increased frequency of use; use alone • Buying or stealing drugs
4	Regular use: preoccupation with the "high" • Daily use of drugs • Loss of control • Multiple consequences and risk taking • Estrangement from family and "straight" friends
5	Burnout: use of drugs to feel normal • Polysubstance use/cross-addiction • Guilt, withdrawal, shame, remorse, depression • Physical and mental deterioration • Increased risk taking, self-destructive, suicidal

in a group setting), the frequency and timing of use (daily before school vs. rarely on a weekend), the premorbid mental health status (depressed vs. happy), as well as the teenager's general functional status should all be considered in evaluating any youngster found to be abusing a drug. The stage of drug use/abuse should also be considered (Table 114-2). A teen may spend months or years in the experimentation phase trying a variety of illicit substances, including the most common drugs, cigarettes, alcohol, and marijuana. Often it is not until regular use of drugs resulting in negative consequences (problem use) that the teen is identified as having a problem, either by parents, teachers, or a physician. Certain protective factors play a part in buffering the risk factors as well as assisting in anticipating the long-term outcome of experimentation. Having emotionally supportive parents with open communication styles, involvement in organized school activities, having mentors or role models outside of the home, and recognition of the importance of academic achievement are examples of the important protective factors.

EPIDEMIOLOGY

Alcohol, cigarettes, and marijuana are the most commonly reported substances used among U.S. teens (Table 114-3). The prevalence of substance use and associated risky behaviors vary by age, gender, race/ethnicity, and other sociodemographic factors. Younger teenagers tend to report less use of drugs than do older teenagers, with the exception of inhalants (in 2012, 6.0% in 8th grade, 5.1% in 10th grade, 4.7% in 12th grade). Males have higher rates of both licit and illicit drug use than females, with greatest differences seen in their higher rates of frequent use of smokeless tobacco, cigars, and anabolic steroids. In school surveys, drug use rates of Hispanics are between whites and African-Americans, with the exception of 12th grade Hispanics reporting highest rates of cocaine use. African-Americans report less use of drugs across all drug categories (including levels of cigarette use) in comparison to whites and Hispanics. In examining trends in drug use, positive findings are that fewer students reported cigarette, alcohol, or stimulant use than in the previous 3 yr. Marijuana use continues to decline with daily use of marijuana in 2012 as 1.1% in 8th graders, 3.5% in 10th graders, and 6.5% in 12th graders.

Table 114-3 Thirty Day Prevalence Use of Alcohol, Cigarettes, Marijuana, and Inhalants in 8th Graders, 10th Graders, and 12th Graders, 2010 and 2012

	8TH GRADERS (%)	10TH GRADERS (%)	12TH GRADERS (%)
ALCOHOL (ANY USE)			
2010	13.8	28.9	41.2
2012	11.0	27.6	41.5
CIGARETTES (ANY USE)			
2005	7.1	13.6	19.2
2008	4.9	10.8	17.1
SMOKELESS TOBACCO			
2010	4.1	7.5	8.5
2012	2.8	6.4	7.9
MARIJUANA/HASHISH			
2010	8.0	16.7	21.4
2012	6.5	17.0	22.9
INHALANTS			
2010	3.6	2.0	1.4
2012	2.7	1.4	0.9
AMPHETAMINES			
2010	0.5	0.6	0.9
2012	0.5	0.5	1.0

National Institute of Drug Abuse: *2012 Monitoring the Future Study,* www.drugabuse.gov

Prescription drug abuse, or nonmedical use of a prescription drug or an over-the counter (OTC) medicine has gained popularity among teens in the last 3 yr (Table 114-4). In 2012, 14.8% of high school seniors had used a prescription drug or an OTC medicine for nonmedical reasons in the past year. The most commonly used substances were Adderall (7.6%), Vicodin (7.5%), OTC cough medicine (5.6%),

Table 114-4 Commonly Abused Prescription Drugs

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

Commonly Abused Prescription Drugs

Visit NIDA at www.drugabuse.gov

National Institutes of Health
U.S. Department of Health and Human Services

Substances: Category and Name	Examples of *Commercial* and Street Names	DEA Schedule*/How Administered	*Intoxication Effects*/Health Risks
Depressants			
Barbiturates	*Amytal, Nembutal, Seconal, Phenobarbital:* barbs, reds, red birds, phennies, tooies, yellows, yellow jackets	II, III, IV/injected, swallowed	*Sedation/drowsiness, reduced anxiety, feelings of well-being, lowered inhibitions, slurred speech, poor concentration, confusion, dizziness, impaired coordination and memory/*slowed pulse, lowered blood pressure, slowed breathing, tolerance, withdrawal, addiction; increased risk of respiratory distress and death when combined with alcohol
Benzodiazepines	*Ativan, Halcion, Librium, Valium, Xanax, Klonopin:* candy, downers, sleeping pills, tranks	IV/swallowed	
Sleep Medications	*Ambien (zolpidem), Sonata (zaleplon), Lunesta (eszopiclone)*	IV/swallowed	*for barbiturates—euphoria, unusual excitement, fever, irritability/*life-threatening withdrawal in chronic users
Opioids and Morphine Derivatives**			
Codeine	*Empirin with Codeine, Fiorinal with Codeine, Robitussin A-C, Tylenol with Codeine:* Captain Cody, Cody, schoolboy; (with glutethimide: doors & fours, loads, pancakes and syrup)	II, III, IV/injected, swallowed	*Pain relief, euphoria, drowsiness, sedation, weakness, dizziness, nausea, impaired coordination, confusion, dry mouth, itching, sweating, clammy skin, constipation/* slowed or arrested breathing, lowered pulse and blood pressure, tolerance, addiction, unconsciousness, coma, death; risk of death increased when combined with alcohol or other CNS depressants
Morphine	*Roxanol, Duramorph:* M, Miss Emma, monkey, white stuff	II, III/injected, swallowed, smoked	
Methadone	*Methadose, Dolophine:* fizzies, amidone, (with MDMA: chocolate chip cookies)	II/swallowed, injected	*for fentanyl*—80–100 times more potent analgesic than morphine
Fentanyl and analogs	*Actiq, Duragesic, Sublimaze:* Apache, China girl, dance fever, friend, goodfella, jackpot, murder 8, TNT, Tango and Cash	II/injected, smoked, snorted	*for oxycodone*—muscle relaxation/twice as potent analgesic as morphine; high abuse potential
Other Opioid Pain Relievers: Oxycodone HCL Hydrocodone Bitartrate Hydromorphone Oxymorphone Meperidine Propoxyphene	*Tylox, Oxycontin, Percodan, Percocet:* Oxy, O.C., oxycotton, oxycet, hillbilly heroin, percs *Vicodin, Lortab, Lorcet:* vike, Watson-387 *Dilaudid:* juice, smack, D, footballs, dillies *Opana, Numorphan, Numorphone:* biscuits, blue heaven, blues, Mrs. O, octagons, stop signs, O Bomb *Demerol, meperidine hydrochloride:* demmies, pain killer *Darvon, Darvocet*	II, III, IV/chewed, swallowed, snorted, injected, suppositories	*for codeine*—less analgesia, sedation, and respiratory depression than morphine *for methadone*—used to treat opioid addiction and pain; significant overdose risk when used improperly
Stimulants			
Amphetamines	*Biphetamine, Dexedrine, Adderall:* bennies, black beauties, crosses, hearts, LA turnaround, speed, truck drivers, uppers	II/injected, swallowed, smoked, snorted	*Feelings of exhilaration, increased energy, mental alertness/*increased heart rate, blood pressure, and metabolism, reduced appetite, weight loss, nervousness, insomnia, *seizures, heart attack, stroke*
Methylphenidate	*Concerta, Ritalin:* JIF, MPH, R-ball, Skippy, the smart drug, vitamin R	II/injected, swallowed, snorted	*for amphetamines—rapid breathing, tremor, loss of coordination, irritability, anxiousness, restlessness/*delirium, panic, paranoia, hallucinations, impulsive behavior, aggressiveness, tolerance, addiction *for methylphenidate*—increase or decrease in blood pressure, digestive problems, loss of appetite, weight loss
Other Compounds			
Dextromethorphan (DXM)	*Found in some cough and cold medications:* Robotripping, Robo, Triple C	not scheduled/swallowed	*Euphoria, slurred speech/*increased heart rate and blood pressure, dizziness, nausea, vomiting, confusion, paranoia, distorted visual perceptions, impaired motor function

** Schedule I and II drugs have a high potential for abuse. They require greater storage security and have a quota on manufacturing, among other restrictions. Schedule I drugs are available for research only and have no approved medical use. Schedule II drugs are available only by prescription and require a new prescription for each refill. Schedule III and IV drugs are available by prescription, may have five refills in 6 months, and may be ordered orally. Most Schedule V drugs are available over the counter.*

*** Taking drugs by injection can increase the risk of infection through needle contamination with staphylococci, HIV, hepatitis, and other organisms. Injection is a more common practice for opioids, but risks apply to any medication taken by injection.*

Courtesy of the National Institute on Drug Abuse, U.S. Department of Health and Human Services, National Institutes of Health, www.drugabuse.gov.

tranquilizers (5.3%), sedatives (4.5%), and OxyContin (4.3%). Rural adolescents were 26% more likely than urban adolescents to have used prescription drugs nonmedically; use was associated with decreased health status, major depressive episode(s), and other drug (marijuana, cocaine, hallucinogens, and inhalants) and alcohol use. In a large-scale study of 16,209 adolescent exposures to prescription drugs, 52.4% were females, and the mean age was 16.6 yr (SD ± 1.7 yr). The 5 most frequently misused or abused drugs were hydrocodone (32%), amphetamines (18%), oxycodone (15%), methylphenidate (14%), and tramadol (11%). Many of these drugs can be found in the parents' home, some are OTC, while others are purchased from drug dealers at schools and colleges. Teen users of nonmedical opioids use other substances concurrently with the opioid use. Most frequently the teens combine opioids with marijuana, alcohol, cocaine, and tranquilizers putting them at risk for serious complications and overdose.

Anonymous screening of urine sampled from public inner city rest rooms in London demonstrated the presence of various amphetamine derivatives, cocaine, ketamine and cannabis as well as cathinone/cathine metabolites.

CLINICAL MANIFESTATIONS

Although manifestations vary by the specific substance of use, adolescents who use drugs often present in an office setting with no obvious physical findings. Drug use is more frequently detected in adolescents who experience trauma such as motor vehicle crashes, bicycle injuries, or violence. Eliciting appropriate historical information regarding substance use, followed by blood alcohol and urine drug screens, is recommended in emergency settings; while waning in popularity, the illicit substances known as "club drugs" still need to be considered in the differential diagnosis of a teen with an altered sensorium (Table 114-5). An adolescent presenting to an emergency setting with an impaired sensorium should be evaluated for substance use as a part of the differential diagnosis (Table 114-6). Screening for substance use is recommended for patients with psychiatric and behavioral diagnoses. Other clinical manifestations of substance use are associated with the route of use; intravenous drug use is associated with venous "tracks" and needle marks, while nasal mucosal injuries are associated with nasal insufflation of drugs. Seizures can be a direct effect of drugs such as cocaine and amphetamines or an effect of drug withdrawal in the case of barbiturates or tranquilizers.

SCREENING FOR SUBSTANCE ABUSE DISORDERS

In a primary care setting the annual health maintenance examination provides an opportunity for identifying adolescents with substance use or abuse issues. The direct questions as well as the assessment of school performance, family relationships, and peer activities may necessitate a more in-depth interview if there are suggestions of difficulties in those areas. Additionally, there are several self-report screening questionnaires available with varying degrees of standardization, length, and reliability. The **CRAFFT mnemonic** is specifically designed to screen for adolescents' substance use in the primary setting (Table 114-7). Privacy and confidentiality need to be considered when asking the teen about specifics of their substance experimentation or use. Interviewing the parents can provide additional perspective on early warning signs that go unnoticed or disregarded by the teen. Examples of early warning signs of teen substance use are change in mood, appetite, or sleep pattern; decreased interest in school or school performance; loss of weight; secretive behavior about social plans; or valuables such as money or jewelry missing from the home. The use of urine drug screening is recommended when select circumstances are present: (1) psychiatric symptoms to rule out comorbidity or dual diagnoses, (2) significant changes in school performance or other daily behaviors, (3) frequently occurring accidents, (4) frequently occurring episodes of respiratory problems, (5) evaluation of serious motor vehicular or other injuries, and (6) as a monitoring procedure for a recovery program. Table 114-8 demonstrates the types of tests commonly used for detection by substance, along with the approximate retention time between the use and the identification of the substance in the urine. Most initial screening uses an immunoassay method such as the enzyme-multiplied immunoassay technique followed by a confirmatory test using highly sensitive, highly specific gas chromatography–mass spectrometry. The substances that can cause false-positive results should be considered, especially when there is a discrepancy between the physical findings and the urine drug screen result. In 2007 the American of Academy of Pediatrics released guidelines that strongly discourage home-based or school-based testing.

DIAGNOSIS

The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* no longer identifies substance use disorders as those of *abuse* or of *dependence* as was done in previous editions. A substance use disorder is defined by a cluster of cognitive, behavioral, and physiologic symptoms that indicate that an adolescent is using a substance even though there is evidence that the substance is harming the adolescent. Even after detoxification, a substance abuse disorder may leave persisting changes in brain circuits with resulting behavioral changes. There are 11 criteria that describe a pathologic pattern of behaviors related to use of the substance, falling into 4 categories. The **first category** includes the criterion of *impaired control, social impairment, risky use, and pharmacologic criteria.* These criteria describe an individual taking increasing amounts of the substance and one who expresses a persistent desire to cut down substance use with unsuccessful efforts and the increased time, effort, and other resources the teen may be using to obtain the substance. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects and expresses an intense desire for the drug that is most likely to occur in in settings in which the drug had been available, such as a specific type of social situation. The **second cluster** of criterion (5-7) reflects social impairment, including the inability to perform as expected in school, home or at a job, increasing social problems and withdrawing from the individual's family. The **third cluster** of 2 criteria addresses increased risk-involvement associated with use of the substance, and the **final cluster** includes 2 criteria addressing pharmacologic responses (tolerance and/or withdrawal). The total number of criterion present is associated with a determination of a mild, moderate, or severe disorder.

These criteria may have limitations in use with adolescents because of differing patterns of use, developmental implications, and other age-related consequences. Adolescents who meet diagnostic criteria should be referred to a program for substance use disorder treatment unless the primary care physician has additional training in addiction medicine.

COMPLICATIONS

Substance use in adolescence is associated with comorbidities and acts of juvenile delinquency. Youth may engage in other high-risk behaviors such as robbery, burglary, drug dealing, or prostitution for the purpose of acquiring the money necessary to buy drugs or alcohol. Regular use of any drug eventually diminishes judgment and is associated with unprotected sexual activity with its consequences of pregnancy and sexually transmitted infections, including HIV, as well as physical violence and trauma. Drug and alcohol use is closely associated with trauma in the adolescent population. Several studies of adolescent trauma victims have identified cannabinoids and cocaine in blood and urine samples in significant proportions (40%), in addition to the more common identification of alcohol. Any use of injected substances involves the risk of hepatitides B and C viruses as well as HIV (see Chapter 276).

TREATMENT

Adolescent drug abuse is a complex condition requiring a multidisciplinary approach that attends to the needs of the individual, not just drug use. Fundamental principles for treatment include accessibility to treatment; utilizing a multidisciplinary approach; employing individual or group counseling; offering mental health services; monitoring of drug use while in treatment; and understanding that recovery from drug abuse/addiction may involve multiple relapses. For most patients,

Table 114-5 Common Names and Salient Features of Club Drugs Used Recreationally

	MDMA	EPHEDRINE	γ-HYDROXYBUTYRATE	γ-BUTYROLACTONE	1,4-BUTANEDIOL	KETAMINE	FLUNITRAZEPAM	NITRITES	BATH SALTS
Common name	Ecstasy, XTC, E, X, Adam, hug drug, Molly	Herbal Ecstasy, herbal fuel, zest	Liquid Ecstasy, goop soap, Georgia homeboy, grievous bodily harm	Blue nitro, longevity, revivarant, GH revitalizer, gamma G, nitro, insom-X, remforce, firewater, invigorate	Thunder nectar, serenity, pine needle extract, zen, enliven, revitalize plus, lemon drops	K, special K, vitamin K, ket, kat	Roofies, circles, rophies, rib, roche, roaches, forget pill, R2, Mexican valium, roopies ruffies	Poppers, ram, rock hard, thrust, TNT	White lightning, Ivory wave, Cloud 9, Zoom, White rush
Duration of action	4-6 hr	4-6 hr	1.5-3.5 hr	1.5-3.5 hr	1.5-3.5 hr	1-3 hr	6-12 hr	Minutes	2-8 hr.
Elimination half-life	8-9 hr	5-7 hr	27 min	ND	ND	2 hr	9-25 hr	ND	Prolonged
Peak plasma concentration	1-3 hr	2-3 hr	20-60 min*	15-45 min	15-45 min	20 min	1 hr	Seconds	Varies
Physical dependence	No	No	Yes	Yes	Yes	No	Yes	No	Yes
Antidote	No	No	No	No	No	No	Yes	No	Treat with benzodiazepine
DEA schedule	I	None	III	None	None	III	IV	None	I
Detection with routine drug screen	Yes†	Yes†	No	No	No	No‡	No‡	No	In progress
Best detection method (time frame)	GC/MS (4 hr-2 days)	GC/MS (4 hr-2 days)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	GC/MS (1 day)	GC/MS (1-12 hr)	GC/MS (1-12 hr)	GC/MS (1-12 hr)

*Depends on dose.
†Concentrations that are sufficiently high can give positive results for amphetamine because of cross-reactions.
‡Flunitrazepam can give positive results for benzodiazepines; ketamine can give positive results for phencyclidine.
DEA, U.S. Drug Enforcement Agency, currently reviewing possibility of flunitrazepam being placed into schedule of the U.S. Controlled Substance Act; GC/MS, gas chromatography–mass spectroscopy. Duration, half-life, and peak plasma are probably different after high or sequential doses because of nonlinear kinetics; ND, not determined in human beings.
Modified from Ricaurte GA, McCann UD: Recognition and management of complications of new recreational drug use. Lancet *365:2137–2145, 2005.*

Table 114-6 The Most Common Toxic Syndromes

ANTICHOLINERGIC SYNDROMES	
Common signs	Delirium with mumbling speech, tachycardia, dry, flushed skin, dilated pupils, myoclonus, slightly elevated temperature, urinary retention, and decreased bowel sounds. Seizures and dysrhythmias may occur in severe cases.
Common causes	Antihistamines, antiparkinsonian medication, atropine, scopolamine, amantadine, antipsychotic agents, antidepressant agents, antispasmodic agents, mydriatic agents, skeletal muscle relaxants, and many plants (notably jimson weed and Amanita muscaria).
SYMPATHOMIMETIC SYNDROMES	
Common signs	Delusions, paranoia, tachycardia (or bradycardia if the drug is a pure α-adrenergic agonist), hypertension, hyperpyrexia, diaphoresis, piloerection, mydriasis, and hyperreflexia. Seizures, hypotension, and dysrhythmias may occur in severe cases.
Common causes	Cocaine, amphetamine, methamphetamine (and its derivatives 3,4-methylenedioxyamphetamine, 3,4-met hylenedioxymethamphetamine, 3,4-methylenedioxyethamphetamine, and 2,5-dimethoxy-4-bromoamphetamine), and OTC decongestants (phenylpropanolamine, ephedrine, and pseudoephedrine). In caffeine and theophylline overdoses, similar findings, except for the organic psychiatric signs, result from catecholamine release.
OPIATE, SEDATIVE, OR ETHANOL INTOXICATION	
Common signs	Coma, respiratory depression, miosis, hypotension, bradycardia, hypothermia, pulmonary edema, decreased bowel sounds, hyporeflexia, and needle marks. Seizures may occur after overdoses of some narcotics, notably propoxyphene.
Common causes	Narcotics, barbiturates, benzodiazepines, ethchlorvynol, glutethimide, methyprylon, methaqualone, meprobamate, ethanol, clonidine, and guanabenz.
CHOLINERGIC SYNDROMES	
Common signs	Confusion, central nervous system depression, weakness, salivation, lacrimation, urinary and fecal incontinence, gastrointestinal cramping, emesis, diaphoresis, muscle fasciculations, pulmonary edema, miosis, bradycardia or tachycardia, and seizures.
Common causes	Organophosphate and carbamate insecticides, physostigmine, edrophonium, and some mushrooms.

From Kulig K: Initial management of ingestions of toxic substances, N Engl J Med *326:1678, 1992. ©1992 Massachusetts Medical Society. All rights reserved.*

Table 114-7 CRAFFT Mnemonic Tool

- Have you ever ridden in a **C**ar driven by someone (including yourself) who was high or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to **R**elax, feel better about yourself or fit in?
- Do you ever use alcohol or drugs while you are by yourself (**A**lone)?
- Do you ever **F**orget things you did while using alcohol or drugs?
- Do your **F**amily or **F**riends ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into **T**rouble while you were using alcohol or drugs?

From the Center for Adolescent Substance Abuse Research (CeASAR). The CRAFFT Screening Interview. © John R. Knight, MD, Boston Children's Hospital, 2015.

Table 114-8 Urine Screening for Drugs Commonly Abused by Adolescents

DRUG	MAJOR METABOLITE	INITIAL	FIRST CONFIRMATION	SECOND CONFIRMATION	APPROXIMATE RETENTION TIME
Alcohol (blood)	Acetaldehyde	GC	IA		7-10 hr
Alcohol (urine)	Acetaldehyde	GC	IA		10-13 hr
Amphetamines		TLC	IA	GC, GC/MS	48 hr
Barbiturates		IA	TLC	GC, GC/MS	Short-acting (24 hr); long-acting (2-3 wk)
Benzodiazepines		IA	TLC	GC, GC/MS	3 days
Cannabinoids	Carboxy- and hydroxymetabolites	IA	TLC	GC/MS	3-10 days (occasional user); 1-2 mo (chronic user)
Cocaine	Benzoylecgonine	IA	TLC	GC/MS	2-4 days
Methaqualone	Hydroxylated metabolites	TLC	IA	GC/MS	2 wk
Opiates					
Heroin	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Morphine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Codeine	Morphine Glucuronide	IA	TLC	GC, GC/MS	2 days
Phencyclidine		TLC	IA	GC, GC/MS	8 days

GC, gas chromatography; IA, immunoassay; MS, mass spectrometry; TLC, thin-layer chromatography.

Modified from Drugs of abuse—urine screening [physician information sheet]. Los Angeles, Pacific Toxicology. From MacKenzie RG, Kipke MD: Substance use and abuse. In Friedman SB, Fisher M, Schonberg SK, editors: Comprehensive adolescent health care, *St. Louis, 1998, Mosby.*

Table 114-9 Domains of Risk and Protective Factors for Substance Abuse Prevention

RISK FACTORS	DOMAIN	PROTECTIVE FACTORS
Early aggressive behavior	Individual	Self-control
Lack of parental supervision	Family	Parental monitoring
Substance abuse	Peer	Academic competence
Drug availability	School	Anti–drug use policies
Poverty	Community	Strong neighborhood attachment

From National Institute on Drug Abuse: Preventing drug use among children and adolescents. A research based guide for parents, educators, and community leaders. *NIH publication No. 04-4212(B), ed 2, Bethesda, MD, 2003, National Institute on Drug Abuse.*

Table 114-10 Risk Factors for a Teen Developing a Drinking Problem

FAMILY RISK FACTORS
- Low parental supervision
- Poor parent to teen communication
- Family conflicts
- Severe or inconsistent family discipline
- Having a parent with an alcohol or drug problem

INDIVIDUAL RISK FACTORS
- Poor impulse control
- Emotional instability
- Thrill seeking behaviors
- Behavioral problems
- Perceived risk of drinking is low
- Begins drinking before age 14 yr

remaining in treatment for a minimum period of 3 mo will result in a significant improvement.

PROGNOSIS

For adolescent substance abusers who have been referred to a drug treatment program, positive outcomes are directly related to regular attendance in posttreatment groups. For males with learning problems or conduct disorder, outcomes are poorer than for those without such disorders. Peer use patterns and parental use have a major influence on outcome for males. For females, factors such as self-esteem and anxiety are more important influences on outcomes. The chronicity of a substance use disorder makes relapse an issue that must always be kept in mind when managing patients after treatment, and appropriate assistance from a health professional qualified in substance abuse management should be obtained.

PREVENTION

Preventing drug use among children and teens requires prevention efforts aimed at the individual, family, school, and community levels. The National Institute on Drug Abuse (NIDA) has identified essential principles of successful prevention programs. Programs should enhance protective factors (parent support) and reduce risk factors (poor self-control); should address all forms of drug abuse (legal and illegal); should address the specific type(s) of drug abuse within an identified community; and should be culturally competent to improve effectiveness (Table 114-9). The highest risk periods for substance use in children and adolescents are during life transitions such as the move from elementary school to middle school, or from middle school to high school. Prevention programs need to target these emotionally and socially intense times for teens in order to adequately anticipate potential substance use or abuse. Examples of effective research-based drug abuse prevention programs featuring a variety of strategies are listed on the NIDA website (www.drugabuse.gov), and on the Center for Substance Abuse Prevention website (www.prevention.samhsa.gov).

Bibliography is available at Expert Consult.

114.1 Alcohol

Margaret M. Stager

Alcohol is the most popular drug among teens in the United States. By 12th grade, approximately 75% of adolescents in high schools report ever having an alcoholic drink, with 20.5% having their first drink before age 13 yr. Multiple factors can affect a young teen's risk of developing a drinking problem at an early age (Table 114-10). One-third of high school seniors admit to combining drinking behaviors with other risky behaviors, such as driving or taking additional substances. Binge drinking remains especially problematic among the older teens and young adults. Thirty-one percent of high school seniors report having 5 or more drinks in a row in the last 30 days. Higher use is seen in males (23.8%) than in females (19.8%), and whites (24.0%) and Hispanics (24.2%) than in blacks (12.4%). Overall, the prevalence of binge drinking decreased from 2009 (24.2%) to 2011 (21.9%). Teens with binge drinking patterns are more likely to be assaulted, engage in high risk sexual behaviors, have academic problems, and acquire injuries than those teens without binge drinking patterns.

Alcohol contributes to more deaths in young individuals in the United States than all the illicit drugs combined. Among studies of adolescent trauma victims, alcohol is reported to be present in 32-45% of hospital admissions. Motor vehicle crashes are the most frequent type of event associated with alcohol use, but the injuries spanned several types, including self-inflicted wounds.

Alcohol is often mixed with energy drinks (caffeine, taurine, sugars), which can result in a spectrum of alcohol related negative behaviors. Caffeine may counter the sedative effects of alcohol resulting in more alcohol consumption and a perception of not being intoxicated thus leading to risk taking behavior like driving while intoxicated. In addition, aggressive behavior, including sexual assaults and motor vehicle or other injuries has been reported. Both alcohol and caffeine overdoses have also been reported.

PHARMACOLOGY AND PATHOPHYSIOLOGY

Alcohol (ethyl alcohol or ethanol) is rapidly absorbed in the stomach and is transported to the liver and metabolized by 2 pathways. The primary metabolic pathway contributes to the excess synthesis of triglycerides, a phenomenon that is responsible for producing a **fatty liver,** even in those who are well nourished. Engorgement of hepatocytes with fat causes necrosis, triggering an inflammatory process **(alcoholic hepatitis),** which is later followed by fibrosis, the hallmark of **cirrhosis.** Early hepatic involvement may result in elevation in γ-glutamyl transpeptidase and serum glutamic-pyruvic transaminase. The second metabolic pathway, which is utilized at high serum alcohol levels, involves the microsomal enzyme system of the liver, in which the cofactor is reduced nicotinamide-adenine dinucleotide phosphate. The net effect of activation of this pathway is to decrease metabolism of drugs that share this system and to allow for their accumulation, enhanced effect, and possible toxicity.

CLINICAL MANIFESTATIONS

Alcohol acts primarily as a central nervous system depressant. It produces euphoria, grogginess, talkativeness, impaired short-term memory, and an increased pain threshold. Alcohol's ability to produce vasodilation and hypothermia is also centrally mediated. At very high serum levels, respiratory depression occurs. Its inhibitory effect on pituitary antidiuretic hormone release is responsible for its diuretic effect. The gastrointestinal complications of alcohol use can occur from a single large ingestion. The most common is acute erosive **gastritis,** which is manifested by epigastric pain, anorexia, vomiting, and

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Table 114-11 Alcohol Use Disorders Identification Test (AUDIT)

	SCORE (0-4)*
1. How often do you have a drink containing alcohol?	Never (0) to more than 4 per wk (4)
2. How many drinks containing alcohol do you have on a typical day?	One or 2 (0) to more than 10 (4)
3. How often do you have 6 or more drinks on 1 occasion?	Never (0) to daily or almost daily (4)
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) to daily or almost daily (4)
5. How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) to daily or almost daily (4)
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) to daily or almost daily (4)
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) to daily or almost daily (4)
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) to daily or almost daily (4)
9. Have you or someone else been injured as a result of your drinking?	No (0) to yes, during the last year (4)
10. Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested that you should cut down?	No (0) to yes, during the last year (4)

*Score ≥8 = problem drinking.
From Schuckit MA: Alcohol-use disorders, Lancet *373:492–500, 2009, Table 1.*

heme-positive stools. Less commonly, vomiting and midabdominal pain may be caused by acute alcoholic **pancreatitis;** diagnosis is confirmed by the finding of elevated serum amylase and lipase levels.

DIAGNOSIS

Primary care settings provide opportunity to screen teens for alcohol use or problem behaviors. Brief alcohol screening instruments (CRAFFT [see Table 114-7] or AUDIT [Alcohol Use Disorders Identification Test, Table 114-11]) perform well in a clinical setting as techniques to identify alcohol use disorders. A score of ≥8 on the AUDIT questionnaire identifies people who drink excessively and who would benefit from reducing or ceasing drinking (Table 114-11). Teenagers in the early phases of alcohol use exhibit few physical findings. Recent use of alcohol may be reflected in elevated γ-glutamyl transferase and aspartate amino transferase.

In acute care settings, the **alcohol overdose syndrome** should be suspected in any teenager who appears disoriented, lethargic, or comatose. Although the distinctive aroma of alcohol may assist in diagnosis, confirmation by analysis of blood is recommended. At levels >200 mg/dL, the adolescent is at risk of death, and levels >500 mg/dL (median lethal dose) are usually associated with a fatal outcome. When the level of obtundation appears excessive for the reported blood alcohol level, head trauma, hypoglycemia, or ingestion of other drugs should be considered as possible confounding factors.

TREATMENT

The usual mechanism of death from the alcohol overdose syndrome is respiratory depression, and artificial ventilatory support must be provided until the liver can eliminate sufficient amounts of alcohol from the body. In a patient without alcoholism, it generally takes 20 hr to reduce the blood level of alcohol from 400 mg/dL to zero. Dialysis should be considered when the blood level is >400 mg/dL. As a follow-up to acute treatment, referral for treatment of the alcohol use disorder is indicated. Group counseling, individualized counseling, and multifamily educational intervention have been found to be quite effective interventions for teens.

Bibliography is available at Expert Consult.

114.2 Tobacco

Margaret M. Stager

CIGARETTES

The average smoker in the United States starts at age 12 yr, and most are regular smokers by age 14 yr. More than 90% of adolescent smokers become adult smokers. Factors associated with youth tobacco use include exposure to smokers (friends, parents), availability of tobacco, low socioeconomic status, poor school performance, low self-esteem, lack of perceived risk of use, and lack of skills to resist influences to tobacco use.

Current smoking rates among U.S. high school students (as is the case for students in many industrialized nations) have trended downward over the last decade for lifetime cigarette use (from 20.0% to 12.4%) and current frequent cigarette use (from 16.8% to 6.4%). Overall, more whites report current tobacco use (20.3%) than Hispanics (17.5%) or blacks (10.5%). Clove cigarettes (kreteks) and flavored cigarettes (bidis) are popular with younger students. Both types of flavored cigarettes contain tobacco with other additives and deliver more nicotine and other harmful substances because they are unfiltered. Use of cigars and mini-cigars (cigarillos) has not changed in the past 3 yr, with 13.1% of students reporting smoking at least 1 during the 30 days prior to the survey. Cigar/cigarillo use is highest among males (17.8% vs. females 8.0%), and high school seniors (23.9%) versus lower grades (9th grade 12.3%, 10th grade 15.4% and 11th grade 20.4%). Tobacco use is linked to other high-risk behaviors. Teens who smoke are more likely than nonsmokers to use alcohol and engage in unprotected sex, are 8 times more likely to use marijuana, and are 22 times more likely to use cocaine.

Tobacco is used by teens in all regions of the world, although the form of tobacco used differs. In the Americas and Europe, cigarette smoking prevalence is higher than other tobacco use, although cigars and smokeless tobacco are also used; in the Eastern Mediterranean, shisha (flavored tobacco smoked in hookah pipes) is prevalent; in Southeast Asia, smokeless tobacco products are used; in the Western Pacific, betel nut is chewed with tobacco; and pipe, snuff, and rolled tobacco leaves are used in Africa. Cigarette use rates by teens in low- and middle-income nations are increasing.

PHARMACOLOGY

Nicotine, the primary active ingredient in cigarettes, is addictive. Nicotine is absorbed by multiple sites in the body, including the lungs, skin, gastrointestinal tract, and buccal and nasal mucosa. The action of nicotine is mediated through nicotinic acetylcholine receptors located on noncholinergic presynaptic and postsynaptic sites in the brain and causes increased levels of dopamine. Nicotine also stimulates the adrenal glands to release epinephrine, causing an immediate elevation in blood pressure, respiration and heart rate. The average nicotine content of 1 cigarette is 10 mg and the average nicotine intake per cigarette ranges from 1-3 mg. Nicotine, as delivered in cigarette smoke, has a half-life of about 2 hr. **Cotinine** is the major metabolite of nicotine via C-oxidation. It has a biologic half-life of 19-24 hr and can be detected in urine, serum, and saliva.

CLINICAL MANIFESTATIONS

Adverse health effects from regular smoking include an increased prevalence of chronic cough, sputum production, and wheezing.

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Smoking during pregnancy is associated with an average decrease in fetal weight of 200 g; this decrease, added to the already smaller size of infants born to teenagers, increases perinatal morbidity and mortality. Tobacco smoke induces hepatic smooth endoplasmic reticulum enzymes and, as a result, may also influence metabolism of drugs such as phenacetin, theophylline, and imipramine. Withdrawal symptoms can occur when adolescents try to quit. Irritability, decreased concentration, increased appetite, and strong cravings for tobacco are common withdrawal symptoms.

ELECTRONIC CIGARETTES (E-CIGARETTES)

E-cigarettes are electronic nicotine delivery systems that are battery operated, which heat and then vaporize nicotine dissolved in propylene glycol, glycerin, or other solvents. They come in tobacco, mint, cherry, or chocolate flavors, and are highly marketed to adolescents. They have the potential to create nicotine dependency and have not been effective in smoking-cessation programs.

Adverse effects include dry cough, throat irritation, and lipoid pneumonia. Potentially toxic substances have been detected in the vapor (diethylene glycol) as well as carcinogens (nitrosamines). Second-hand exposure is a possibility. These products have been banned in some countries; they are not regulated by the FDA.

SMOKELESS TOBACCO

The 2 forms of smokeless tobacco (SLT) are "chew," a leafy tobacco product sold in pouches, and "snuff," a finely ground tobacco product sold in tins or packets. Users place the SLT along the gum line of the lower jaw whereby the nicotine is absorbed by the mucous membranes. Smokeless tobacco use is largely reported by males in 10th (11.2%) and 12th grades (13.5%) for the 30-day prevalence rates. Snus, is a Swedish tobacco product that is available as a loose powder, or in a small teabag-like sachet. It is placed under the lower lip and unlike American chewing tobacco there is no need to spit. Annual prevalence of Snus use in 2012 was 2.4%, 6.9%, and 7.9% among 8th, 10th, and 12th graders, respectively.

Introduced in 2009, there are several dissolvable SLT products on the market. The Orbs are pellets of ground tobacco that resemble candy and come in various flavors. The Sticks are twin, matchstick-like ground tobacco, and the Strips are flat sheets that quickly dissolve in the mouth. All of these products are small and easily concealed, and therefore can be used throughout the day without detection, especially as there is no need to spit.

Exposure to SLT increases the users risk for oral cancers of the mouth, pharynx, larynx, and esophagus, as well as gum disease and nicotine addiction. Use of SLT among high school boys exceeds 20% in Arkansas, Kentucky, Montana, North Dakota, Oklahoma, South Dakota, Tennessee, Wyoming, and West Virginia (the latter with the highest rate at 25.5%).

TREATMENT

The approach to smoking cessation in adolescents includes the **5 As (Ask, Advise, Assess, Assist, and Arrange)** and use of nicotine replacement therapy in addicted teens who are motivated to quit and are not using SLT. Consensus panels recommend the 5 As, although evidence of efficacy in adolescents is limited. Nicotine patch studies to date in adolescents suggest a positive effect on reducing withdrawal symptoms and that pharmacotherapy should be combined with behavioral therapy to reach higher cessation and lower relapse rates. In a limited number of students, cessation rates of 15% were reported at 3 and 6 mo. Nicotine replacement therapy is also available as a gum, inhaler, nasal spray, lozenge, or microtab (Table 114-12). However, the nicotine patch and nasal spray were found to have numerous side effects in adolescent subjects. Medications such as bupropion are not FDA approved for use in adolescents <18 yr old; some pilot studies in adolescents report cessation efficacy with 150 mg or 300 mg of bupropion daily. Varenicline has successfully been used in adults; however, it now includes a black box warning of neuropsychiatric side effects such as agitation, hostility, depressed mood, and suicidal ideation.

The American Lung Association's Not-On-Tobacco Program (NOT) is a nationally recognized best-practice model for teen smoking cessation. More than 100,000 teens in 48 states have participated in the NOT, which resulted in either quitting (15% on average) or decreased tobacco use. The NOT is a 10 wk, developmentally appropriate, teen-focused, small group program that addresses topics such as stress management, effects of smoking, preparing to quit, dealing with peer pressure, and establishing support networks. The program is available as a train-the-trainer model, including training manuals and student materials (see www.lung.org).

In keeping with teens' high use of cell phones, support for teen smoking cessation is now available as a text-messaging service. Smokefree TXT, a free text messaging service, is offered by the National Cancer Institute and aims to engage teens to quit smoking using daily text messaging on their cell phone. Teens can sign up online (teen.smokefree.gov) or text QUIT to iQUIT (47848). Another cell phone

Table 114-12 Smoking Cessation Pharmacotherapy Available in the United States

THERAPY BRAND	NAME	STRENGTHS	FDA-APPROVED ADULT DOSING	AVAILABILITY*	STUDIED IN ADOLESCENTS	QUIT DATE
NICOTINE REPLACEMENT THERAPY						
Gum‡	Nicorette	2 mg, 4mg	The 0.4-mg strength should be used by patients who smoke 25 or more cigarettes a day; otherwise the 2-mg strength should be used Wk 1-6: 1 piece every 1-2 hr Wk 7-9: 1 piece every 2-4 hr Wk 10-12: 1 piece every 4-8 hr	OTC*	Yes	
Inhaler	Nicotrol Inhaler	4 mg	6-16 cartridges a day for up to 12 wks	Rx	No	
Lozenge	CommitTM, Nicorette mini	2 mg, 4 mg	The 4-mg strength should be used by patients who smoke their first cigarette within 30 minutes of waking; otherwise, the 2-mg strength should be used Wk 1-6: 1 lozenge every 1-2 hr Wk 7-9: 1 lozenge every 2-4 hr Wk 10-12: 1 lozenge every 4-8 hr	OTC	No	Prior to beginning nicotine replacement therapy

Table 114-12 Smoking Cessation Pharmacotherapy Available in the United States—cont'd

THERAPY BRAND	NAME	STRENGTHS	FDA-APPROVED ADULT DOSING	AVAILABILITY*	STUDIED IN ADOLESCENTS	QUIT DATE
Nasal Spray	Nicotrol NS	0.5 mg/spray	1-2 sprays/hr up to a maximum of 80 sprays per day	Rx	Yes	
Transdermal Patch‡	NicoDerm CQ	7, 14, 21 mg/24 hr	For patients who smoke >10 cigarettes daily: Step 1: one 21-mg patch daily for wks 1-6 Step 2: one 14-mg patch daily for wks 7-8 Step 3: one 7-mg patch daily for wks 9-10 For patients who smoke <10 cigarettes daily: begin with the 14-mg patch daily for 6 wks, followed by the 7-mg patch for 2 wks	OTC	Yes	
NONNICOTINE THERAPY						
Bupropion SR‡	Zyban	150-mg sustained release tablets	150 mg by mouth in the morning for 3 days, then increase to 150 mg by mouth twice daily	Rx	Yes	1 wk after starting therapy
Varenicline	Chantix	0.5-, 1-mg tablets	0.5 mg by mouth in the morning for 3 days; increase to 0.5 mg by mouth twice daily for 4 days, then increase to 1 mg by mouth twice daily	Rx	No	

*OTC indicates available over the counter; Rx indicates it is a prescription product.
†None are FDA-approved for use in patients younger than 18 yr.
‡Generics available.
From JP Karpinski, et al: Smoking cessation treatment for adolescents J Pediatr Pharmacol Ther *15(4):249–260, 2010, Table 2.*

application, QuitSTART, is available for teens as an interactive cell phone-based guide that helps them track cravings, monitor moods, offer cessation tips, and follow quit attempts. Both Smokefree TXT and QuitSTART link teens to social media webpages which offer additional information on cessation tools and programs.

Bibliography is available at Expert Consult.

114.3 Marijuana

Margaret M. Stager

Marijuana (THC, "pot," "weed," "hash," "grass"), derived from the *Cannabis sativa* hemp plant, is the most commonly abused illicit drug. The main active chemical, tetrahydrocannabinol (THC), is responsible for its hallucinogenic properties. THC is absorbed rapidly by the nasal or oral routes, producing a peak of subjective effect at 10 min and 1 hr, respectively. Marijuana is generally smoked as a cigarette ("reefer" or "joint") or in a pipe. Although there is much variation in content, each cigarette contains 8-10% THC. Another popular form that is smoked, a "blunt," is a hollowed-out small cigar refilled with marijuana. Hashish is the concentrated THC resin in a sticky black liquid or oil. Although marijuana use by U.S. teens has declined in the last decade, 23.1% of high school students have used marijuana at least once during the previous 30 days, and current marijuana use is highest in black males and seniors. Eight percent of students report having tried marijuana before the age of 13 yr, with a range from 4.3-18.5% across various states, indicating the need for early prevention efforts.

CLINICAL MANIFESTATIONS

In addition to the "desired" effects of elation and euphoria, marijuana may cause impairment of short-term memory, poor performance of tasks requiring divided attention (e.g., those involved in driving), loss of critical judgment, decreased coordination, and distortion of time perception (Table 114-13). Visual hallucinations and perceived body distortions occur rarely, but there may be "flashbacks" or recall of frightening hallucinations experienced under marijuana's influence that usually occur during stress or with fever.

Smoking marijuana for a minimum of 4 days/wk for 6 mo appears to result in dose-related suppression of plasma testosterone levels and spermatogenesis, prompting concern about the potential deleterious effect of smoking marijuana before completion of pubertal growth and development. There is an antiemetic effect of oral THC or smoked marijuana, often followed by appetite stimulation, which is the basis of the drug's use in patients receiving cancer chemotherapy. Although the possibility of teratogenicity has been raised because of findings in animals, there is no evidence of such effects in humans. An **amotivational syndrome** has been described in long-term marijuana users who lose interest in age-appropriate behavior, yet proof of the causative relationship remains equivocal. Chronic use is associated with increased anxiety and depression, learning problems, poor job performance, hyperemesis, and respiratory problems such as pharyngitis, sinusitis, bronchitis, and asthma (see Table 114-13).

The increased THC content of marijuana of 5-15–fold compared to that of the 1970s, is related to the observation of a **withdrawal syndrome,** occurring 24-48 hr after discontinuing the drug. Heavy users experience malaise, irritability, agitation, insomnia, drug craving, shakiness, diaphoresis, night sweats, and gastrointestinal disturbance. The symptoms peak by the 4th day, and they resolve in 10-14 days. Certain drugs may interact with marijuana to potentiate sedation (alcohol, diazepam), potentiate stimulation (cocaine, amphetamines), or be antagonistic (propranolol, phenytoin).

Behavioral interventions, including cognitive-behavioral therapy and motivational incentives, have shown to be effective in treating marijuana dependency.

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Table 114-13 Acute and Chronic Adverse Effects of Cannabis Use

ACUTE ADVERSE EFFECTS • Anxiety and panic, especially in naïve users • Psychotic symptoms (at high doses) • Road crashes if a person drives while intoxicated
CHRONIC ADVERSE EFFECTS • Cannabis dependence syndrome (in around 1 in 10 users) • Chronic bronchitis and impaired respiratory function in regular smokers • Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders • Impaired educational attainment in adolescents who are regular users • Subtle cognitive impairment in those who are daily users for 10 yr or more

From Hall W, Degenhardt L: Adverse health effects of non-medical cannabis use, Lancet *374:1383–1390, 2009.*

SYNTHETIC MARIJUANA

Spice, K2, crazy clown, aroma, black mamba, blaze, dream, and funky monkey are common street names for synthetic marijuana, which is a mixture of herbs or plant materials that have been sprayed with artificial chemicals similar to THC, the psychoactive ingredient in marijuana. One active group of chemicals is the carboxamides, which are not detected by assays to detect THC. In the United States, the chemicals in Spice are designated a schedule I controlled substance by the DEA, thereby making it illegal to sell, buy, or possess them. Nonetheless, synthetic marijuana is the second most common illicit drug used by high school seniors. More than 1 in 10 high school seniors used synthetic marijuana in the last year.

Synthetic marijuana is mainly used by smoking, or mixed with marijuana, or brewed as a tea for drinking. The chemicals in synthetic marijuana affect the same receptors as THC and produce similar effects as seen in marijuana such as relaxation, elevated mood, and altered perception. In addition, sympathomimetic symptoms are quite common and are the cause of significant toxicity. Symptoms of intoxication include vomiting, tachycardia, hypertension, hyperthermia, confusion, extreme anxiety, profuse sweating, agitation, aggression, dysphoria, hallucinations, seizures, rhabdomyolysis, dystonia, unresponsiveness, confusion, and myocardial ischemia. In response to legislation to ban the chemicals in OTC synthetic marijuana products, manufacturers alter and substitute the chemicals in the product, keeping it on the legal market and leaving teens particularly vulnerable to potential health effects.

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114.4 Inhalants

Margaret M. Stager

Inhalants, found in many common household products, comprise a diverse group of volatile substances whose vapors can be inhaled to produce psychoactive effects. The practice of inhalation is popular among younger adolescents and decreases with age. Young adolescents are attracted to these substances because of their rapid action, easy availability, and low cost. Products that are abused as inhalants include volatile solvents (paint thinners, glue), aerosols (spray paint, hair spray), gases (propane tanks, lighter fluid), nitrites ("poppers" or "video head cleaner") and propellants used in whipped cream dispensers. The most popular inhalants among young adolescents are glue, shoe polish, and spray paint. The various products contain a wide range of chemicals with serious adverse health effects (Table 114-14). **Huffing,** the practice of inhaling fumes can be accomplished using a paper bag containing a chemical-soaked cloth, spraying aerosols directly into the nose/mouth, or using a balloon, plastic bag, or soda can filled with fumes. The percentage of adolescents using inhalants has remained stable, with 11.4% of high school students reporting having ever used inhalants in. Eighth and 9th graders report highest use, suggesting targeted prevention strategies are warranted for this age group.

Table 114-14 Hazards of Chemicals Found in Commonly Abused Inhalants

Amyl nitrite, butyl nitrite *("poppers," "video head cleaner")*: sudden sniffing death syndrome, suppressed immunologic function, injury to red blood cells (interfering with oxygen supply to vital tissues)
Benzene *(found in gasoline)*: bone marrow injury, impaired immunologic function, increased risk of leukemia, reproductive system toxicity
Butane, propane *(found in lighter fluid, hair and paint sprays)*: sudden sniffing death syndrome via cardiac effects, serious burn injuries (because of flammability)
Freon *(used as a refrigerant and aerosol propellant)*: sudden sniffing death syndrome, respiratory obstruction and death (from sudden cooling/cold injury to airways), liver damage
Methylene chloride *(found in paint thinners and removers, degreasers)*: reduction of oxygen-carrying of blood, changes to the heart muscle and heartbeat
Nitrous oxide *("laughing gas")*, **hexane**: death from lack of oxygen to the brain, altered perception and motor coordination, loss of sensation, limb spasms, blackouts caused by blood pressure changes, depression of heart muscle functioning
Toluene *(found in gasoline, paint thinners and removers, correction fluid)*: brain damage (loss of brain tissue mass, impaired cognition, gait disturbance, loss of coordination, loss of equilibrium, limb spasms, hearing and vision loss), liver and kidney damage
Trichloroethylene *(found in spot removers, degreasers)*: sudden sniffing death syndrome, cirrhosis of the liver, reproductive complications, hearing and vision damage

CLINICAL MANIFESTATIONS

The major effects of inhalants are psychoactive (Table 114-15). The intoxication lasts only a few minutes, so a typical user will huff repeatedly over an extended period of time (hours) in order to maintain the high. The immediate effects of inhalants are similar to alcohol: euphoria, slurred speech, decreased coordination, and dizziness. Toluene, the main ingredient in model airplane glue and some rubber cements, causes relaxation and pleasant hallucinations for up to 2 hr. Euphoria is followed by violent excitement; coma may result from prolonged or rapid inhalation. Volatile nitrites, such as amyl nitrite, butyl nitrite, and related compounds marketed as room deodorizers, are used as euphoriants, enhancers of musical appreciation, and sexual enhancements among older adolescents and young adults. They may result in headaches, syncope, and lightheadedness; profound hypotension and cutaneous flushing followed by vasoconstriction and tachycardia; transiently inverted T waves and depressed ST segments on electrocardiography; methemoglobinemia; increased bronchial irritation; and increased intraocular pressure.

COMPLICATIONS

Model airplane glue is responsible for a wide range of complications, related to chemical toxicity, to the method of administration (in plastic bags, with resultant suffocation), and to the often dangerous setting in which the inhalation occurs (inner-city roof tops). Common neuromuscular changes reported in chronic inhalant abusers include difficulty coordinating movement, gait disorders, muscle tremors, and spasticity, particularly in the legs (Table 114-16). Chronic use may cause pulmonary hypertension, restrictive lung defects or reduced

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Table 114-15 Stages in Symptom Development After Use of Inhalants

STAGE	SYMPTOMS
1: Excitatory	Euphoria, excitation, exhilaration, dizziness, hallucinations, sneezing, coughing, excess salivation, intolerance to light, nausea and vomiting, flushed skin and bizarre behavior
2: Early CNS depression	Confusion, disorientation, dullness, loss of self-control, ringing or buzzing in the head, blurred or double vision, cramps, headache, insensitivity to pain, and pallor or paleness
3: Medium CNS depression	Drowsiness, muscular uncoordination, slurred speech, depressed reflexes, and nystagmus or rapid involuntary oscillation of the eyeballs
4: Late CNS depression	Unconsciousness that may be accompanied by bizarre dreams, epileptiform seizures, and EEG changes

CNS, central nervous system; EEG, electroencephalogram
From Harris D: Volatile substance abuse, Arch Dis Child Educ Pract Ed *91:ep93-ep100, 2006, Table 1.*

Table 114-16 Documented Clinical Presentations of Volatile Substance Abuse

CLINICAL PRESENTATIONS OF ACUTE AND CHRONIC VOLATILE SUBSTANCE ABUSE	
Ventricular fibrillation	Muscle weakness
Asystolic cardiac arrest	Abdominal pain
Myocardial infarction	Cough
Ataxia	Aspiration pneumonia
Agitation	Chemical pneumonitis
Limb and trunk uncoordination	Coma
Tremor	Visual and auditory hallucinations
Visual loss	Acute delusions
Tinnitus	Nausea and vomiting
Dysarthria	Pulmonary edema
Vertigo	Photophobia
Hyperreflexia	Rash
Acute confusional state	Jaundice
Conjunctivitis	Anorexia
Acute paranoia	Slurred speech
Depression	Diarrhea
Oral and nasal mucosal ulceration	Weight loss
Halitosis	Epistaxis
Convulsions/fits	Rhinitis
Headache	Cerebral edema
Peripheral neuropathy	Visual loss
Methemoglobinemia	Burns
Acute trauma	Renal tubular acidosis

From Harris D: Volatile substance abuse, Arch Dis Child Educ Pract Ed *91:ep93-ep100, 2006, Table 2.*

diffusion capacity, peripheral neuropathy, hematuria, tubular acidosis, and possibly cerebral and cerebellar atrophy. Chronic inhalant abuse has long been linked to widespread brain damage and cognitive abnormalities that can range from mild impairment (poor memory, decreased learning ability) to severe dementia. High-frequency inhalant users were significantly more likely than moderate- and low-frequency users to experience adverse consequences of inhalant intoxication such as behavioral, language, and memory problems. Certain risky behaviors and consequences, such as engaging in unprotected sex or fighting while high on inhalants, were dramatically more common among high-frequency inhalant users than among low-frequency inhalant users. Death in the acute phase may result from cerebral or pulmonary edema or myocardial involvement (Table 114-16).

DIAGNOSIS

Diagnosis of inhalants is difficult because of the ubiquitous nature of the products and decreased parental awareness of their dangers. In the primary care setting, providers need to enquire of parents if they have witnessed any unusual behaviors in their teen; noticed high-risk products in their bedrooms; seen paint on the teen's hands, nose, or mouth; or found paint coated or chemical coated rags. Complete blood counts, coagulation studies, and hepatic and renal function studies may identify the complications. In extreme intoxication, a user may manifest symptoms of restlessness, general muscle weakness, dysarthria, nystagmus, disruptive behavior, and occasionally hallucinations. Toluene is excreted rapidly in the urine as hippuric acid, with the residual detectable in the serum by gas chromatography.

TREATMENT

Treatment is generally supportive and directed toward control of arrhythmia and stabilization of respirations and circulation. Withdrawal symptoms do not usually occur.

Bibliography is available at Expert Consult.

114.5 Hallucinogens

Margaret M. Stager

Several naturally occurring and synthetic substances are used by adolescents for their hallucinogenic properties. They have chemical structures similar to neurotransmitters such as serotonin, yet their exact mechanism of action remains unclear. Lysergic acid diethylamide (LSD) and methylenedioxymethamphetamine (MDMA) (Ecstasy or Molly) are the most commonly reported hallucinogens used.

LYSERGIC ACID DIETHYLAMIDE

LSD (acid, big "d," blotters) is a very potent hallucinogen that is made from lysergic acid found in ergot, a fungus that grows on rye and other grains. Its high potency allows effective doses to be applied to absorbent paper, or it can be taken as a liquid or a tablet. The onset of action can be between 30 and 60 min, and it peaks between 2 and 4 hr. By 10-12 hr, an individual returns to the predrug state. Four percent of U.S. 12th graders report trying LSD at least once.

Clinical Manifestations

The effects of LSD can be divided into 3 categories: somatic (physical effects), perceptual (altered changes in vision and hearing), and psychic effects (changes in sensorium). The common somatic symptoms are dizziness, dilated pupils, nausea, flushing, elevated temperature, and tachycardia. The sensation of synesthesia, or "seeing" smells and "hearing" colors, as well as major distortions of time and self, have been reported with high doses of LSD. Delusional ideation, body distortion, and suspiciousness to the point of toxic psychosis are the more serious of the psychic symptoms. LSD is not considered to be an addictive drug as it does not typically produce drug-seeking behavior.

Treatment

An individual is considered to have a "bad trip" when the sensory experiences causes the user to become terrified or panicked. These episodes should be treated by removing the individual from the aggravating situation and placing him in a quiet room with a calming friend. In situations of extreme agitation or seizures, use of benzodiazepines may be warranted. "Flashbacks" or LSD-induced states after the drug has worn off and tolerance to the effects of the drug are additional complications of its use.

METHYLENEDIOXYMETHAMPHETAMINE

MDMA ("X," Ecstasy, Molly), a phenylisopropylamine hallucinogen, is a synthetic compound similar to hallucinogenic mescaline and the stimulant methamphetamine. Like other hallucinogens, this drug is

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proposed to interact with serotoninergic neurons in the central nervous system (CNS). It is the preferred drug at "raves," all-night dance parties, and is also known as one of the "club drugs" along with γ-hydroxybutyrate (GHB) and ketamine (see Table 114-5). Between 2009 and 2010, past-year use of MDMA increased among both 8th and 10th graders in the US but then declined in both grades. Nationwide, the prevalence of having ever used MDMA was 8.2% of students with highest use reported among males and Hispanics (10.6%). MDMA use increased among high school students from 2009-2011 (8.2%). LSD use remained stable during this time period (2009: 8%; 2011: 8.7%).

Clinical Manifestations

Euphoria, a heightened sensual awareness, and increased psychic and emotional energy are acute effects. Compared to other hallucinogens, MDMA is less likely to produce emotional lability, depersonalization, and disturbances of thought. Nausea, jaw clenching, teeth grinding, and blurred vision are somatic symptoms, whereas anxiety, panic attacks, and psychosis are the adverse psychiatric outcomes. A few deaths have been reported after ingestion of the drug. In high doses, MDMA can interfere with the body's ability to regulate temperature. The resultant hyperthermia in association with vigorous dancing at a "rave" has resulted in severe liver, kidney, and cardiovascular system failure and death. There are no specific treatment regimens recommended for acute toxicity. Chronic MDMA use can lead to changes in brain function, affecting cognitive tasks and memory. These symptoms may occur because of MDMA's effects on neurons that use serotonin as a neurotransmitter. The serotonin system plays an important role in regulating mood, aggression, sexual activity, sleep, and sensitivity to pain. A high rate of dependence has been found among MDMA users. MDMA exposure may be associated with long-term neurotoxicity and damage to serotonin-containing neurons. In nonhuman primates, exposure to MDMA for only 4 days caused damage to serotonin nerve terminals that was evident 6-7 yr later. There are no specific pharmacologic treatments for MDMA addiction. Drug abuse recovery groups are recommended.

PHENCYCLIDINE

Phencyclidine (PCP) (sternyl, angel dust, "hog," "peace pill," "sheets") is an arylcyclohexalamine whose popularity is related, in part, to its ease of synthesis in home laboratories. One of the by-products of home synthesis causes cramps, diarrhea, and hematemesis. It is a "dissociative drug" that produces feelings of detachment from the surrounding environment and self. The drug is thought to potentiate adrenergic effects by inhibiting neuronal reuptake of catecholamines. PCP is available as a tablet, liquid, or powder, which may be used alone or sprinkled on cigarettes ("joints"). The powders and tablets generally contain 2-6 mg of PCP, whereas joints average 1 mg for every 150 mg of tobacco leaves, or approximately 30-50 mg per joint. The prevalence of PCP use (hallucinogenic drug) among U.S. high school students remained stable from 2009 (8.0%) to 2011 (8.7%).

Clinical Manifestations

The clinical manifestations are dose related and produce alterations of perception, behavior, and autonomic functions. Euphoria, nystagmus, ataxia, and emotional lability occur within 2-3 min after smoking 1-5 mg and last for 4-6 hr. At these low doses the user is likely to experience shallow breathing, flushing, generalized numbness of extremities, and loss of motor coordination. Hallucinations may involve bizarre distortions of body image that often precipitate panic reactions. With doses of 5-15 mg, a toxic psychosis may occur, with disorientation, hypersalivation, and abusive language lasting for >1 hr. Hypotension, generalized seizures, and cardiac arrhythmias commonly occur with plasma concentrations from 40-200 mg/dL. Death has been reported during psychotic delirium, from hypertension, hypotension, hypothermia, seizures, and trauma. The coma of PCP may be distinguished from that of the opiates by the absence of respiratory depression; the presence of muscle rigidity, hyperreflexia, and nystagmus; and lack of response to naloxone. PCP psychosis may be difficult to distinguish from schizophrenia. In the absence of a history of use, analysis of urine must be depended on for diagnosis.

Treatment

Management of the PCP-intoxicated patient includes placement in a darkened, quiet room on a floor pad, safe from injury. Acute alcohol intoxication may be present also. For recent oral ingestion, gastric absorption is poor and induction of emesis or gastric lavage is useful. Diazepam, in a dose of 5-10 mg orally or 2-5 mg intravenously, may be helpful if the patient is agitated and not comatose. Rapid excretion of the drug is promoted by acidification of the urine. Supportive therapy of the comatose patient is indicated with particular attention to hydration, which may be compromised by PCP-induced diuresis. Inpatient and/or behavioral treatments can be helpful for chronic PCP users.

Bibliography is available at Expert Consult.

114.6 Cocaine

Margaret M. Stager

Cocaine, an alkaloid extracted from the leaves of the South American *Erythroxylum coca,* is supplied as the hydrochloride salt in crystalline form. With "snorting" it is rapidly absorbed into the bloodstream from the nasal mucosa, detoxified by the liver, and excreted in the urine as benzoylecgonine. Smoking the cocaine alkaloid ("freebasing") involves inhaling the cocaine vapors in pipes, or cigarettes mixed with tobacco or marijuana. Accidental burns are potential complications of this practice. With crack cocaine, the crystallized rock form, the smoker feels "high" in <10 sec. The risk of addiction with this method is higher and more rapidly progressive than from snorting cocaine. Tolerance develops and the user must increase the dose or change the route of administration, or both, to achieve the same effect. To sustain the high, cocaine users repeatedly use cocaine in short periods of time known as "binges." Drug dealers often place cocaine in plastic bags or condoms and swallow these containers during transport. Rupture of a container produces a sympathomimetic crisis (see Table 114-6). Cocaine use among high school students has decreased in the last decade, with 8.5% of 12th graders having tried the drug (any route) at least once. Current cocaine use in last 30 days remains stable at 3% of students.

CLINICAL MANIFESTATIONS

Cocaine is a strong CNS stimulant that increases dopamine levels by preventing reuptake. Cocaine produces euphoria, increased motor activity, decreased fatigability, and mental alertness. Its sympathomimetic properties are responsible for pupillary dilation, tachycardia, hypertension, and hyperthermia. Snorting cocaine chronically results in loss of sense of smell, nosebleeds, and chronic rhinorrhea. Injecting cocaine increases risk for HIV infection. Chronic abusers experience anxiety, irritability, and sometimes paranoid psychosis. Lethal effects are possible, especially when cocaine is used in combination with other drugs, such as heroin, in an injectable form known as a "speedball." Cocaine, when taken with alcohol, is metabolized by the liver to produce cocaethylene, a substance that enhances the euphoria and is associated with a greater risk of sudden death than cocaine alone. Pregnant adolescents who use cocaine place their fetus at risk of premature delivery, complications of low birthweight, and possibly developmental disorders.

TREATMENT

There are no FDA-approved medications for treatment of cocaine addiction. Cognitive-behavioral therapy has been shown to be effective when provided in combination with additional services and social support.

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114.7 Amphetamines

Margaret M. Stager

Methamphetamine, commonly known as "ice," is a nervous system stimulant and schedule II drug with a high potential for abuse. Most of the methamphetamine currently abused is produced in illegal laboratories. It is a white, odorless, bitter tasting powder that is particularly popular among adolescents and young adults because of its potency and ease of absorption. It can be ingested orally, by smoking, needle injection, or absorption across mucous membranes. Amphetamines have multiple CNS effects, among them the release of neurotransmitters and an indirect catecholamine agonist effect. In recent years, there has been a general decline of methamphetamine use among high school students. In the 2012 Monitoring the Future Study, 1.1% of 12th graders report using methamphetamine at least once reflecting a steady decline in use over the last 10 yr.

CLINICAL MANIFESTATIONS

Methamphetamine rapidly increases the release and blocks the reuptake of dopamine, a powerful "feel good" neurotransmitter (Table 114-17). The effects of amphetamines can be dose related. In small amounts amphetamine effects resemble other stimulants: increased physical activity, rapid and/or irregular heart rate, increased blood pressure and decreased appetite. High doses produce slowing of cardiac conduction in the face of ventricular irritability. Hypertensive and hyperpyrexic episodes can occur as seizures (see Table 114-6). Binge effects result in the development of psychotic ideation with the potential for sudden violence. Cerebrovascular damage, psychosis, severe receding of the gums with tooth decay, and infection with HIV and hepatitis B and C can result from long-term use. There is a withdrawal syndrome associated with amphetamine use, with early, intermediate, and late phases (Table 114-17). The early phase is characterized as a "crash" phase with depression, agitation, fatigue, and desire for more of the drug. Loss of physical and mental energy, limited interest in the environment, and anhedonia mark the intermediate phase. In the final phase, drug craving returns, often triggered by particular situations or objects.

TREATMENT

Acute agitation and delusional behaviors can be treated with haloperidol or droperidol. Phenothiazines are contraindicated and may cause a rapid drop in blood pressure or seizure activity. Other supportive treatment consists of a cooling blanket for hyperthermia and treatment of the hypertension and arrhythmias, which may respond to sedation with lorazepam or diazepam. For the chronic user, comprehensive cognitive-behavioral interventions have been shown to effective treatment options.

Bibliography is available at Expert Consult.

114.8 Opiates

Margaret M. Stager

Heroin is a highly addictive synthetic opiate drug made from a naturally occurring substance (morphine) in the opium poppy plant. It is a white or brown powder that can be injected (intravenously or subcutaneously), snorted/sniffed, or smoked. Intravenous injection produces an immediate effect, whereas effects from the subcutaneous route occur in minutes, and from snorting, in 30 minutes. After injection, heroin crosses the blood–brain barrier, is converted to morphine, and binds to opiate receptors. Tolerance develops to the euphoric effect, and the chronic user must use more heroin to achieve the same intense effect. Heroin use among teens peaked in the mid-1990s but is resurgent in some suburban communities, as is the use of prescription opioids found in the home. Nationwide 2.9% of high school students report having tried heroin at least once. Highest use is seen in black males, with a growing prevalence in suburban high school students; ranges vary from 0.8% to 5.3% across large urban, suburban, and rural school districts.

CLINICAL MANIFESTATIONS

The clinical manifestations are determined by the purity of the heroin or its adulterants, combined with the route of administration. The immediate effects include euphoria, diminution in pain, flushing of the skin, and pinpoint pupils (see Table 114-17). An effect on the hypothalamus is suggested by the lowering of body temperature. The most common dermatologic lesions are the "tracks," the hypertrophic linear scars that follow the course of large veins. Smaller, discrete peripheral scars, resembling healed insect bites, may be easily overlooked. The adolescent who injects heroin subcutaneously may have fat necrosis, lipodystrophy, and atrophy over portions of the extremities. Attempts to conceal these stigmata may include amateur tattoos in unusual sites.

Table 114-17 Signs and Symptoms of Intoxication and Withdrawal

	OPIATES	AMPHETAMINES/COCAINE	BENZODIAZEPINES
INTOXICATION			
Behavior	Apathy and sedation; disinhibition; psychomotor retardation; impaired attention and judgment	Euphoria and sensation of increased energy; hypervigilance; grandiosity, aggression, argumentative; labile mood; repetitive stereotyped behaviors; hallucinations, usually with intact orientation; paranoid ideation; interference with personal functioning	Euphoria; apathy and sedation; abusiveness or aggression; labile mood; impaired attention; anterograde amnesia; impaired psychomotor performance; interference with personal functioning
Signs	Drowsiness; slurred speech; pupillary constriction (except anoxia from severe overdose—dilation); decreased level of consciousness	Dilated pupils; tachycardia (occasionally bradycardia, cardiac arrhythmias); hypertension; nausea/vomiting; sweating and chills; evidence of weight loss; dilated pupils; chest pain; convulsions	Unsteady gait; difficulty in standing; slurred speech; nystagmus; decreased level consciousness; erythematous skin lesions or blisters
Overdose	Respiratory depression; hypothermia	Sympathomimetic symptoms	Hypotension; hyperthermia; depression of gag reflex; coma
Withdrawal	Craving to use; lacrimation; yawning; rhinorrhea/sneezing; muscle aches or cramps; abdominal cramps; nausea/vomiting/diarrhoea; sweating; dilated pupils; anorexia; irritability; tremor; piloerection/chills; restlessness; disturbed sleep	Dysphoric mood (sadness/anhedonia); lethargy and fatigue; psychomotor retardation or agitation; craving; increased appetite; insomnia or hypersomnia; bizarre or unpleasant dreams	Tremor of tongue, eyelids, or outstretched hands; nausea or vomiting; tachycardia; postural hypotension; psychomotor agitation; headache; insomnia; malaise or weakness; transient visual, tactile, or auditory hallucinations or illusions; paranoid ideation; grand mal convulsions

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Skin abscesses secondary to unsterile techniques of drug administration are commonly found. There is a loss of libido; the mechanism is unknown. The chronic heroin user may resort to prostitution to support the habit, thus increasing the risk of sexually transmitted diseases (including HIV), pregnancy, and other infectious diseases. Constipation results from decreased smooth muscle propulsive contractions and increased anal sphincter tone. The absence of sterile technique in injection may lead to cerebral microabscesses or endocarditis, usually caused by *Staphylococcus aureus or Pseudomonas aeruginosa.* Abnormal serologic reactions are also common, including false-positive Venereal Disease Research Laboratory and latex fixation tests.

WITHDRAWAL

After a period of ≥8 hr without heroin, the addicted individual undergoes, during a 24-36 hr period, a series of physiologic disturbances referred to collectively as "withdrawal" or the **abstinence syndrome** (see Table 114-17). The earliest sign is yawning, followed by lacrimation, mydriasis, restlessness, insomnia, "goose flesh," cramping of the voluntary musculature, bone pain, hyperactive bowel sounds and diarrhea, tachycardia, and systolic hypertension. Although the administration of methadone is the most common method of detoxification, the addition of buprenorphine, an opiate agonist–antagonist, is available for detoxification and maintenance treatment of heroin and other opiates. Buprenorphine has the advantage of offering less risk of addiction and overdose, and withdrawal effects and can be dispensed in the privacy of a physician's office. Combined with behavioral interventions, it has a greater success rate of detoxification. A combination drug, buprenorphine + naloxone, has been formulated to minimize abuse during detoxification.

OVERDOSE SYNDROME

The overdose syndrome is an acute reaction after the administration of an opiate. It is the leading cause of death among drug users. The clinical signs include stupor or coma, seizures, miotic pupils (unless severe anoxia has occurred), respiratory depression, cyanosis, and pulmonary edema. The differential diagnosis includes CNS trauma, diabetic coma, hepatic (and other) encephalopathy, Reye syndrome, as well as overdose of alcohol, barbiturates, PCP, or methadone. Diagnosis of opiate toxicity is facilitated by intravenous administration of the opiate antagonist naloxone, 0.01 mg/kg (2 mg is a common initial dose for an adolescent), which causes dilation of pupils constricted by the opiate. Diagnosis is confirmed by the finding of morphine in the serum.

TREATMENT

Treatment of acute heroin overdose consists of maintaining adequate oxygenation and continued administration of naloxone, a pure opioid antagonist. It may be given intravenously, intramuscularly, subcutaneously, or through the endotracheal tube. Naloxone has an ultrarapid onset of action (1 min) and a duration of action of 20-60 min. If there is no response, other etiologies for the respiratory depression must be explored. Naloxone may have to be continued for 24 hr if methadone, rather than shorter-acting heroin, has been taken. Admission to the intensive care unit is indicated for patients who require continuous naloxone infusions (rebound coma, respiratory depression), and for those with life-threatening arrhythmias, shock, and seizures.

Bibliography is available at Expert Consult.

114.9 Bath Salts

Margaret M. Stager

Bath salts refers to a group of previously OTC, but now illicit, substances containing 1 or more synthetic chemicals similar to cathinone, an amphetamine-like stimulant found in the Khat plant. The bath salts, marketed under brand names such as Ivory Wave, Cloud Nine, or Vanilla Sky, are sold online or in drug paraphernalia stores as a white or brown crystalline powder and can be ingested, inhaled, or injected. The most current information about teen use of bath salts is derived from the 2012 Monitoring the Future survey of 8th, 10th, and 12th grade students, who use at 0.8%, 0.6%, and 1.3%, respectively. The synthetic cathinones found in bath salts include methylone, mephedrone, and 3,4-methylenedioxypyrovalerone (MDPV) all of which are chemically similar to amphetamines and ecstasy (MDMA). The chemicals in bath salts raise brain dopamine levels causing the user to feel a surge of euphoria, increased sociability and sex drive. In addition, the user may experience a surge in norepinephrine, causing reactions such as an elevated heart rate, chest pain, vasoconstriction, diaphoresis, hyperthermia, dilated pupils, seizures, arrhythmias, and high blood pressure. Users also experience psychiatric symptoms such as aggressive behavior, panic attacks, paranoia, psychosis, delirium, self-mutilation, and hallucinations as a consequence of elevations of serotonin. Intoxication from bath salts may cause excited delirium syndrome, which includes dehydration, rhabdomyolysis, and kidney failure. Treatment of overdose should be directed at specific complications but often includes benzodiazepines or propofol for agitation and other neuropsychiatric manifestations. The synthetic cathinones in bath salts are highly addictive, triggering intense cravings in those who consume them frequently. This may result in dependence, tolerance, and strong withdrawal symptoms as seen in other highly addictive substances. The sale of 2 of the synthetic cathinones, mephedrone and MDPV, is illegal in the United States.

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Chapter 115

The Breast

Cynthia Holland-Hall and Gale R. Burstein

Breast development is often the first visible sign of puberty in the adolescent female. Pediatric practitioners must be able to distinguish normal breast development, including normal variants, from pathologic breast disorders. Visual inspection of the breast tissue should routinely be a component of the young adolescent's general physical examination. Breast development during puberty is described using the Sexual Maturity Rating (SMR) scale, progressing from SMR 1 to SMR 5 as the breast becomes more mature (see Fig. 110-2 in Chapter 110).

FEMALE DISORDERS

See Chapter 551.

MALE DISORDERS

Pubertal gynecomastia (see Chapter 585), occurring in up to 60% of normal adolescent males, has long been attributed to a transient imbalance of estrogen and androgen concentrations. Onset typically is between 10 and 13 yr, peaking at SMR 3-4. This physiologic condition usually regresses within 18-24 mo. Careful physical examination is essential to distinguish between true gynecomastia, characterized by a discreet disc of palpable glandular tissue under the nipple–areolar complex, and pseudogynecomastia, characterized by more diffuse adiposity of the anterior chest wall. Reassurance and continued observation are recommended in most cases; surgery may be indicated in severe or persistent cases. No medical therapies for gynecomastia have been approved for use in adolescents by the U.S. Food and Drug Administration. Small, noncontrolled trials of antiestrogens, such as tamoxifen, appear promising, but more evidence is needed. Conditions associated with nonphysiologic gynecomastia include endocrine disorders, liver disease, neoplasms, chronic disease, and trauma. Although

dozens of medications are implicated as possible causes of gynecomastia, convincing evidence exists only for a few, including several antiandrogens and other exogenous hormones, antiretrovirals, and histamine$_2$-receptor blockers. Calcium channel blockers, certain antipsychotics, and proton pump inhibitors may be causative. Among drugs of abuse, alcohol and anabolic steroids may be associated with gynecomastia, but very little evidence supports an association with marijuana, opiates, or amphetamines.

Other breast pathology in males is uncommon. Benign masses such as neurofibromas, lipomas, and dermoid cysts have been reported in the male breast. Males with Klinefelter syndrome have an elevated risk of breast cancer (see Chapter 583), but this malignancy is otherwise exceedingly rare in adolescents.

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Chapter 116

Menstrual Problems

Gina S. Sucato and Gale R. Burstein

See also Chapter 550.

Menstrual disturbances—including delayed onset, irregularity, heavy flow, and pain—occur in 75% of females during adolescence. Menstrual problems vary in presentation. For adolescents with minor variations from normal (Table 116-1), an explanation of symptoms and reassurance of reproductive health may be all that is needed. Severe dysmenorrhea or prolonged menstrual bleeding can be not only frightening, but a cause of persistent morbidity requiring more aggressive management, potentially including referral to a specialist in adolescent gynecology.

NORMAL MENSTRUATION

The average age of **menarche**, or first menses, varies according to the racial/ethnic background of the population and (possibly) socioeconomic status. There is often a close concordance of the age at menarche between mother and daughter, suggesting that genetic factors are determinants, as well as individual factors such as weight, exercise level, and chronic medical conditions. In the United States, the age of menarche has been relatively stable over the last few decades. The average age at menarche is 12.6 yr for non-Hispanic whites, 12.1 yr for non-Hispanic blacks, and 12.3 yr for Hispanic Americans. Age of menarche has declined in countries and populations experiencing improved nutritional standards and other living conditions. For example, in South Africa, average menarcheal age for blacks has been decreasing at a rate of approximately 0.50 yr/decade compared to an average decline of 0.22 yr/decade for whites.

Menarche typically occurs within 2.5 yr (range: 0.5-3 yr) of the onset of breast budding (thelarche), which is the first sign of puberty in most females. Menarche usually occurs during breast sexual maturity rating (SMR; i.e., Tanner) stage 4. Periods gradually become more regular, and by 3 yr after menarche, 90% of females have an average cycle length of between 21 and 45 days. The older the age at which menarche occurs, the longer it takes for consistently ovulatory cycles to be established. However, for most adolescents, by 5-6 yr after menarche, menstrual cycles are similar to that of adults: between 21 and 35 days long with 75% of cycles being ovulatory.

Table 116-1	Characteristics of Normal Menses*
Cycle length	21-35 days from the 1st day of one period to the 1st day of the next (during 1st 3 yr after menarche can be 21-45 days)
Duration of menses	7 or fewer days
Blood flow	6 or fewer (soaked) pads or tampons per day

*Adolescents with 2 or more cycles outside this range or who skip their period for 3 consecutive mo warrant more thorough evaluation.

MENSTRUAL IRREGULARITIES

In young adolescents, many variations in menstruation are explained by anovulation that results from immaturity of the hypothalamic-pituitary-ovarian axis that governs menstrual cyclicity. However, organic pathology should be considered and excluded in a logical and cost-effective manner. An accurate menstrual history is an important, but often lacking, first step toward a diagnosis. At the time of menarche, all patients should be encouraged to track their periods, something several free smart phone and tablet applications can facilitate.

Previously, a range of terms have been used to describe abnormal menstrual bleeding. These include menorrhagia to indicate regularly occurring bleeding that was excessive in amount or duration, and metrorrhagia to indicate irregular bleeding between periods. Such terms are imprecise, confusing, and not linked to any specific underlying pathology. Abnormal uterine bleeding (AUB) is the preferred term for uterine bleeding that is abnormal in regularity, volume, frequency, or duration. AUB is further specified by adding terms that describe the bleeding as heavy menstrual bleeding, or intermenstrual bleeding. A qualifying letter is added to indicate the etiology of the abnormal bleeding. Of the nine categories of etiologies, the three most relevant to adolescents are ovulatory dysfunction (AUB-O), previously referred to as dysfunctional uterine bleeding, discussed in Chapter 116.2, coagulopathy (AUB-C), and not yet classified (AUB-N).

In addition to a standard medical history noting hospitalizations, chronic illness, and medication use, a complete history for evaluating a patient with menstrual irregularity should include: the timing of pubertal milestones, such as onset of pubic and axillary hair and breast development; a detailed patient menstrual history; age of menarche and overall menstrual pattern of mother and sisters; and a family history of gynecologic problems. The complete review of systems should elicit any changes in headache pattern or vision; the presence of galactorrhea; and any changes in skin, hair, or bowel patterns. Changes in diet, level of exercise, and sports participation are also important factors when generating a differential diagnosis. As with all adolescent visits, the patient should be interviewed alone and the confidential history should assess substance use, consensual sexual activity, forced sexual behavior, abuse, and other psychosocial stressors.

In addition to the basic growth parameters of weight, height, blood pressure, heart rate, and body mass index, a careful review of the patient's growth chart is indicated. Physical exam should document SMR; signs of androgen excess, such as hirsutism or severe acne; and signs suggestive of an eating disorder (see Chapter 28), such as lanugo or knuckle calluses. A careful external genital examination should be performed, but in the absence of sexual activity, an internal pelvic examination is rarely necessary. If being considered for the young adolescent, an internal exam should be performed by someone with expertise in this age group using proper equipment and technique. Trans-abdominal pelvic ultrasound can be a useful adjunct for evaluating anatomic abnormalities in the adolescent.

Bibliography is available at Expert Consult.

116.1 Amenorrhea

Gina S. Sucato and Gale R. Burstein

Amenorrhea, the absence of menstruation, generally requires evaluation if there has been no menstruation within 4 yr of the onset of

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Jones LL, Griffiths PL, Norris SA, et al: Age at menarche and the evidence for a positive secular trend in urban South Africa, *Am J Hum Biol* 21(1):130–132, 2009.

puberty (**primary amenorrhea**), or for the length of 3 previous cycles in a postmenarchal patient (**secondary amenorrhea**). However the following caveats exist: Lack of any pubertal signs by age 13 yr in a girl should prompt evaluation for pubertal delay, and in sexually active patients, or those with other symptoms suggesting pathology, evaluation should be initiated without waiting for 3 missed cycles. The evaluation of a patient presenting with amenorrhea should begin by ascertaining whether she has ever had any previous menstrual bleeding. Some aspects of the evaluation of both primary and secondary amenorrhea are identical; entities that can interrupt the menstrual cycle can also prevent menarche. However, in females with primary amenorrhea consideration must also be given to the possibility of genetic and anatomic conditions.

The differential diagnosis of amenorrhea is broad (Table 116-2) and requires a careful history and physical exam to guide any necessary diagnostic studies. Key to the evaluation is understanding the timing and tempo of the patient's pubertal milestones. Age 15 yr is commonly considered the age at which an evaluation for primary amenorrhea should be undertaken. Evaluation should begin sooner if 4 yr have elapsed since the onset of puberty (breast development in most females). Conversely, expectant management with close follow-up can be considered in a patient whose history, physical (showing some signs of pubertal development), and family history suggest constitutional delay of puberty. When a patient presents with primary amenorrhea, genetic and anatomic conditions are added to the differential diagnosis (Table 116-3).

HISTORY AND PHYSICAL EXAMINATION

Important elements of the history include dietary intake, exercise level, and a thorough review of any ongoing symptoms, including fever, headache, vision changes, chronic respiratory or gastrointestinal complaints, changes in bowel history, galactorrhea, changes in hair or nails, excessive body hair, severe acne, unexplained musculoskeletal complaints, and changes in vaginal discharge (which can disappear in females who are hypoestrogenic for reasons such as poor caloric intake). Any underlying medical conditions and the adequacy of their control should be noted, as well as the presence of any known renal or skeletal anomalies, which can be associated with reproductive system anomalies. Medications, particularly those for psychiatric conditions, should be documented. Family history of menarchal age, eating disorders (see Chapter 28), and **polycystic ovary syndrome (PCOS**; see Chapter 552) should be elicited. A thorough social history is necessary, especially concerning the presence or absence of sexual activity or abuse (see Chapter 40).

Physical examination should begin with careful attention to growth chart trajectories. In addition to a search for undiagnosed systemic disease, clues to an eating disorder, thyroid disease, or hyperandrogenism should be sought. The exam should assess for **body mass index**, orthostatic pulses, blood pressure, abnormal dentition, anosmia or hyposmia (suggestive of Kallmann syndrome; see Chapter 583.2), parotid enlargement, thyroid gland palpation, hepatosplenomegaly or other abdominal mass, lymphadenopathy, presence or absence of breast tissue (by palpation not inspection) and **SMR** (see Chapter 110). Skin exam should note any lanugo, dry or doughy skin, loss of hair from scalp or eyebrows, striae, acanthosis nigricans, or acne. The genital exam should note SMR and appearance of the vagina which should be pink and moist; thin, dry and reddened mucosa suggests estrogen deficiency. The clitoral width should be <1 cm. In the patient with primary amenorrhea, vaginal patency can be assessed painlessly using a slender saline-moist swab (e.g., a urethral swab) and careful avoidance of the hymen. If physical exam assessment of the cervix and uterus is not tolerated, a pelvic ultrasound is advisable in patients with primary amenorrhea.

LABORATORY STUDIES

Diagnostic tests in the patient presenting with amenorrhea should be tailored to her history and physical exam (Table 116-4). However, a urine pregnancy test, serum levels of prolactin, thyroid-stimulating hormone, and follicle-stimulating hormone (FSH) are reasonable to measure in all patients (Fig. 116-1). Elevation of FSH (>30 mIU/mL) in an amenorrheic female suggests ovarian insufficiency, and, if confirmed with repeat testing, should be followed with a pelvic ultrasound, karyotype, and specialist referral.

In patients with signs of androgen excess (e.g., severe acne or hirsutism) or physical stigmata associated with PCOS (rapid pubertal weight gain, acanthosis nigricans) consider measuring levels of 17-hydroxyprogesterone (17-OHP) (morning, in the follicular/preovulatory phase), free and total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione. PCOS affects approximately 5% of premenopausal females; diagnostic criteria for adolescents are controversial but include variations of menstrual irregularity (ranging from amenorrhea to dysfunctional uterine bleeding), polycystic ovarian morphology identified on ultrasound, and physical or biochemical evidence of androgen excess.

With the exceptions of pregnancy, constitutional delay and imperforate hymen, conditions that cause primary amenorrhea limit fertility and diagnosis may cause profound emotional responses in patients and

Table 116-2 Causes of Amenorrhea (Primary or Secondary)

- Pregnancy (regardless of history can cause primary or secondary amenorrhea)
- Functional hypothalamic causes (stress, weight loss, undernutrition, high levels of exercise, energy deficit even at normal weight)
- Female athlete triad (low energy availability, amenorrhea, and low bone density)
- Eating disorders
- Premature ovarian insufficiency (autoimmune, idiopathic, galactosemia, or secondary to radiation or chemotherapy)
- Hypothalamic and/or pituitary damage (e.g., irradiation, tumor, traumatic brain injury, surgery, hemochromatosis, midline central nervous system defects such as septooptic dysplasia, and autoimmune pituitary hypophysitis)
- Thyroid disease (hyper- or hypo-, although the latter usually associated with increased bleeding)
- Prolactinoma
- Systemic disease (e.g., inflammatory bowel disease, cyanotic congenital heart disease, sickle cell disease, cystic fibrosis, celiac disease)
- Hyperandrogenism (polycystic ovary syndrome, nonclassic congenital adrenal hyperplasia, adrenal tumor or dysfunction)
- Drugs and medications (e.g., illicit drugs, atypical antipsychotics, hormones)
- Turner syndrome mosaicism

Table 116-3 Additional Causes of Primary Amenorrhea

- Physiologic/constitutional delay
- Anatomic abnormalities
  - Müllerian agenesis
  - Imperforate hymen
  - Transverse vaginal septum
- Genetic disorders
  - 46 XY disorders of sexual development (e.g., androgen insensitivity syndrome, 5α-reductase deficiency and 17α-hydroxylase deficiency)
  - Mixed gonadal dysgenesis (associated with a number of different chromosome patterns)
  - Turner syndrome (resulting from 45X or a variety of mosaic or other abnormal karyotypes)
  - Genetic hypogonadotropic hypogonadism (e.g., X-linked Kallmann syndrome)

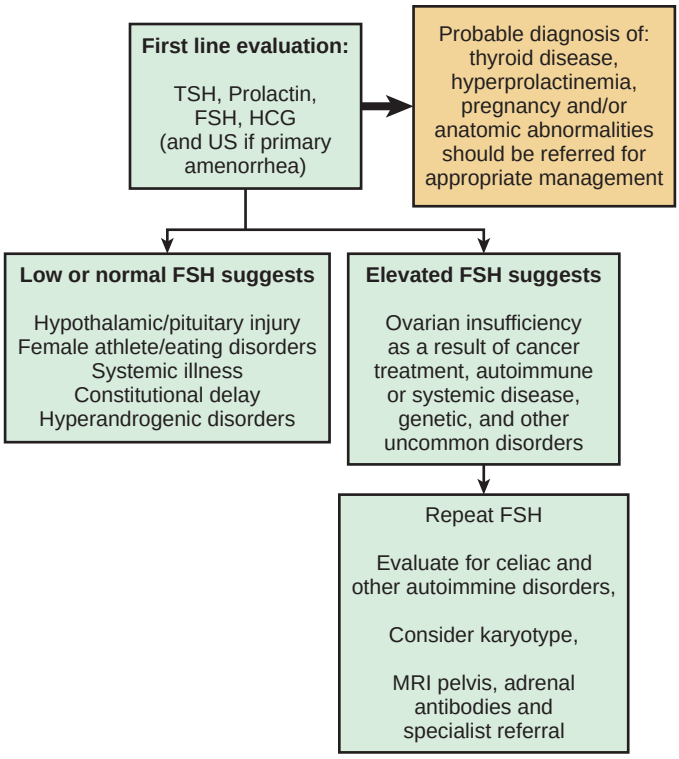

Figure 116-1 Initial diagnostic testing to evaluate amenorrhea

Table 116-4 Laboratory Tests to Evaluate Patients with Abnormal Uterine Bleeding

Complete blood count with platelets
Urine pregnancy test (regardless of history)
Sexually transmitted infections testing
Prothrombin and partial thromboplastin times
Ferritin
von Willebrand factor antigen, ristocetin cofactor, and factor VIII* activities
Liver, kidney, and thyroid function studies
Total and free testosterone†
Pelvic ultrasound (if diagnosis is elusive or anatomic abnormality suspected)

*Any abnormalities should be followed with a ristocetin-induced platelet aggregation and von Willebrand factor multimers. Testing in the 1st 3 days of menses and before any estrogen treatment is started minimizes the chances of false-negative tests. Repeat testing can be warranted in patients for whom there is a high pretest suspicion.

†In patients with signs or symptoms suggestive of PCOS, such as acne, hirsutism, obesity, acanthosis nigricans, and a history of infrequent menses.

families. Thus, before ordering studies to confirm these diagnoses (e.g., karyotype, MRI of reproductive anatomy) the clinician should carefully consider the implications and be prepared to refer to specialists with experience managing the long term treatment of such diagnoses with families.

In patients presumed to have hypothalamic amenorrhea on the basis of a low FSH and prepubertal baseline ultrasensitive assay for luteinizing hormone, and consistent history and physical, MRI of the brain is not necessary in all patients. However, MRI should be considered for patients presenting with a headache history that is a change from baseline; persistent emesis; change in thirst, urination, or vision; elevated prolactin or galactorrhea; or other neurologic symptoms.

TREATMENT

Treatment for amenorrhea varies widely depending upon the underlying cause. Many diagnoses require referral to clinicians in specialties such as endocrinology, adolescent medicine, gynecology, and other surgical subspecialists, and often collaboration with other disciplines such as psychology or nutrition is indicated. For patients with PCOS, the mainstay of treatment is lifestyle modifications and suppression of ovarian androgens (typically with combined oral contraceptive [COC] pills, i.e., estrogen and progestin). Many patients benefit from the addition of metformin and spironolactone as an androgen receptor blocker; all require ongoing monitoring of lipids and periodic screening with an oral glucose tolerance test as a result of the high prevalence of metabolic syndrome in PCOS. For patients with eating disorders or other conditions of energy imbalance that render them hypoestrogenic, normalizing weight and improving nutritional status are the keys to treatment; whether exogenous hormones will adequately protect bone health in these patients is unproven. For females with amenorrhea based on ovarian insufficiency (or absence) exogenous hormones are required for all pubertal development. Experts recommend starting at age 10-12 yr with low-dose transdermal estrogen, progressing to increased doses of estrogen and cyclic progestin, and then continuing maintenance therapy with higher dose combination products such as those found in typical combined hormone contraceptive pills, patches and rings.

For patients with secondary amenorrhea, use of hormones to bring on monthly bleeding (for example with combined hormonal contraception) in the absence of a clear indication (such as PCOS or contraception) is not recommended as doing so will mask the patient's subsequent menstrual pattern. However, in those patients with normal postpubertal estrogen levels progesterone can be useful to periodically (every 4-12 wk) induce shedding of the endometrial lining to avoid build up and subsequent heavy menses. One commonly used regimen is medroxyprogesterone 10 mg daily for the 1st 12 days of the month.

Bibliography is available at Expert Consult.

116.2 Abnormal Uterine Bleeding (AUB)

Gina S. Sucato and Gale R. Burstein

AUB is a broad term used to describe any pattern that is outside what is considered physiologic. Clinicians are encouraged to categorize the abnormal pattern based on the patient's complaint, which will usually be menses that are irregular (AUB/IMB: intermenstrual bleeding) or heavy (AUB/HMB: heavy menstrual bleeding).

IRREGULAR MENSTRUAL BLEEDING

The American Academy of Pediatricians advocates treating menstrual status as a vital sign at routine visits. Although menses are frequently irregular in the early postmenarchal years, further evaluation is necessary when menstrual patterns vary too widely from what is normal for age. Even in the first postmenarchal year, menses should not be less frequent than every 45 days. Menses become increasingly regular with age, and by 3 yr postmenarche are typically 21-35 days long, lasting 3-7 days. An adolescent's personal cycle duration is usually established by age 19 or 20 yr.

Adolescents rarely present with complaints of unusually short or light menses. However, those females, along with those with infrequent menses, should be evaluated similarly to females presenting with secondary amenorrhea. Females whose menses are excessive are much more likely to come to attention for AUB.

In the early postmenarchal years, the most common cause of AUB in adolescents is anovulation because of immaturity of the hypothalamic–pituitary–ovarian axis. In the absence of a midcycle surge of luteinizing hormone to stimulate ovulation, there is no corpus luteum production of progesterone. Without the stabilizing effects of progesterone on the endometrial lining there is increased risk of irregular bleeding. Irregular bleeding because of anovulation, in the absence

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of anatomic, systemic, or endocrinologic disease, is categorized as AUB caused by ovulatory dysfunction (**AUB-O**; previously referred to as dysfunctional uterine bleeding). Although it is the most common cause of abnormal menstrual bleeding in adolescents, AUB-O is a diagnosis of exclusion. In generating a differential diagnosis it is important to remember that most entities that lead to amenorrhea can cause anovulation first, and anovulation is a key risk for heavy irregular bleeding. Table 116-5 lists the causes of AUB.

Breakthrough bleeding while on combined hormonal contraception may occur and is not a reason to discontinue the medication. Compliance, interacting medications (prescribed or over-the-counter: St. John's wort), and smoking may increase the risk of breakthrough bleeding. Unscheduled bleeding is more common with progestin-only contraceptives.

HEAVY AND PROLONGED MENSTRUAL BLEEDING

Irregular bleeding (Table 116-5), particularly that resulting from anovulation, can be long and heavy. However, in patients who have regular, cyclic menses that are long and/or heavy, a hematologic cause should be strongly considered, particularly if menses are heavy from the onset of menarche, or if bleeding is severe enough to warrant hospitalization. In such patients, prevalence estimates for von Willebrand disease (see Chapter 477) and platelet functions disorders (see Chapter 484) range as high as 36% and 44%, respectively. These patients may also report flooding (changing a pad or tampon more than hourly), passing clots larger than an inch in diameter, menses longer than 7 days, a history of hemorrhagic ovarian cysts, excessive bleeding from wounds or postoperatively, and 1st-degree relatives with heavy menses or epistaxis requiring medical treatment.

LABORATORY FINDINGS

Table 116-4 lists laboratory tests to be considered in patients with long heavy bleeding. Females with persistent heavy bleeding despite negative testing should be referred to a hematologist for testing for platelet function disorders, factor deficiencies and other less common disorders. In the initial evaluation, the hemoglobin is the key element as it establishes the **severity of the bleeding: mild** (hemoglobin > 10 g/dL), **moderate** (hemoglobin 8-10 g/dL), or **severe** (hemoglobin < 8 g/dL).

TREATMENT

In **mild** cases, iron supplementation is recommended, and the patient should keep a menstrual calendar to follow the subsequent flow patterns. Nonsteroidal antiinflammatory drugs (e.g., naproxen) are more effective than placebo in treating heavy bleeding and also would help any concurrent dysmenorrhea. Active bleeding typically responds well to cycling with any **COC** (i.e., estrogen and progestin) starting with twice-daily dosing if needed until bleeding stops. Patients with estrogen contraindications can be treated with progestins alone, for example, medroxyprogesterone or norethindrone acetate 10 mg orally per day, either continuously or for 12 days per month. The latter regimen will be followed by monthly bleeding.

Table 116-5 Causes of Irregular Menstrual Bleeding

CAUSES OF AUB	EXAMPLES	FEATURES
Immature hypothalamic–pituitary–ovarian axis (AUB-O)	Patient within 2 yr of menarche; patient more than 2 yr postmenarche but with history of later menarche	Painless, responds to hormonal treatment
Weight changes, disordered eating, or excessive exercise	Anorexia nervosa, bulimia, weight gain or loss of more than 10 pounds from any etiology	Weight loss more commonly results in lighter, less frequent menses
Endocrinologic causes	Thyroid disease, PCOS	Bleeding typically increases with hypothyroidism and decreases with PCOS and hyperthyroidism
Complication of pregnancy	Threatened abortion, postpartum or postabortal endometritis	History of sexual activity and/or pregnancy
Infection	Cervicitis, condyloma, pelvic inflammatory disease	Bleeding usually not heavy, may occur with sexual intercourse
Trauma	Sexual assault, bicycle accidents	History will be evident in patients of menstruating age unless there is cognitive disability
Vaginal foreign body	Toilet paper, broken condoms, tampons	Associated with odor and vaginal discharge, but usually not heavy bleeding
Hematologic causes	von Willebrand disease, platelet function disorder, thrombocytopenia (idiopathic thrombocytopenic purpura, drug induced) hemophilia carriage, clotting factor deficiency, leukemia	Bleeding is heavy and/or long and frequently regular, may present at menarche, may be accompanied by a suggestive family history (hysterectomies or uterine ablation, or cautery for epistaxis) or physical exam (ecchymoses, petechiae)
Medications	Estrogens, progestins, (in pills, patches, rings, injections, implants, and intrauterine devices) androgens, drugs that cause prolactin release (estrogens, phenothiazines, tricyclic antidepressants, metoclopramide), and anticoagulants (heparin, warfarin, aspirin, and nonsteroidal antiinflammatory drugs), and selective serotonin reuptake inhibitors	Affect the hypothalamic–pituitary–ovarian axis, endometrial lining, platelets, or coagulation pathway
Anatomic	Partial obstruction of vagina or uterus causing asynchronous bleeding, cervical or endometrial polyps or myomas, hemangioma, uterine vascular malformation, genital/reproductive tract cancer	Most of these entities are extremely rare, especially reproductive tract cancers
Systemic disease	Celiac disease, rheumatoid arthritis, Ehlers-Danlos syndrome	Accompanied by other signs of the condition

With **moderate** anemia, any of the hormonal regimens above can be used. However, it may be necessary to start with 3-4 COC (or 3-4 doses of medroxyprogesterone 10 mg) per day and taper to daily dosing over the next 2 wk. Patients with ongoing rapid bleeding, syncope or lightheadedness, or hemodynamic instability should be treated in the hospital, as should patients with a hemoglobin of <7-8 g/dL.

Patients with severe anemia should be treated with 1 of the hormone tapers described above, in addition to fluid or blood products as indicated; it is advisable to draw necessary laboratory studies prior to transfusion. Patients with emesis or other significant symptoms may be treated initially with conjugated estrogens 25 mg intravenously every 4-6 hr for 1-2 days. A COC or progestin regimen should be added within the 1st day as progestin is needed to stabilize the endometrial lining and can be used as maintenance therapy after hospital discharge. In the exceptionally rare case of a patient whose bleeding cannot be controlled hormonally, options for gynecologic interventions include intrauterine Foley balloon placement or uterine packing to tamponade the uterus mechanically. Dilation and curettage, performed frequently in adult women, is almost never indicated in adolescents.

Hormonal treatment for AUB should continue for at least 3-6 mo—depending on the patient's age, prior menstrual history, and severity of presentation—before reassessing the need for ongoing therapy. Additional options for maintenance therapy include combined hormonal transdermal patches and vaginal rings, depomedroxyprogesterone acetate 150 mg IM every 3 mo, and placement of a levonorgestrel intrauterine device, depending on the patient's concurrent need for long-term contraception. For those patients who choose to avoid (or augment) hormonal therapy, tranexamic acid 1,300 mg orally 3 times daily can be used for up to the 1st 5 days of menses. This medication, new to the United States, has been available in other countries for years. Nonetheless, published data in young adolescents remain sparse, and the clinical significance of the theoretic increased risk of thrombosis when used in conjunction with hormonal treatment is yet to be determined.

For young women with bleeding disorders, formulation of a long-term treatment plan is best done in collaboration with the patient's hematologist. Females with a known bleeding disorder may be up to 5 times more likely to develop heavy menstrual bleeding. Therefore, it can be helpful while the patient is still premenarchal to proactively put a plan in place in the event of acute heavy menstrual bleeding which can occur with a patient's first menstrual period.

Bibliography is available at Expert Consult.

116.3 Dysmenorrhea

Gina S. Sucato and Gale R. Burstein

Dysmenorrhea, painful uterine cramps that precede and accompany menses, occur in up to 93% of adolescent females based on studies from around the world. Dysmenorrhea is severe enough to interfere with school and other activities in approximately 10% of adolescents in the United States. Yet many adolescents undertreat their symptoms, and fewer still seek medical care for relief.

Dysmenorrhea may be primary or secondary. **Primary dysmenorrhea**, characterized by the absence of any specific pelvic pathologic condition, is by far the more commonly occurring form, accounting for approximately 90% of cases. After ovulation, withdrawal of progesterone results in synthesis of prostaglandins by the endometrium, which stimulate local vasoconstriction, uterine ischemia and pain, and smooth muscle contraction, explaining both uterine and gastrointestinal symptoms. Because of the association with ovulation, primary dysmenorrhea typically presents at least 12 mo after menarche.

Secondary dysmenorrhea results from underlying pathology such as anatomic abnormality, or infection such as pelvic inflammatory disease. However, the most common cause of secondary dysmenorrhea in adolescents is **endometriosis**, a condition in which implants of endometrial tissue are found outside the uterus, most commonly near the fallopian tubes and ovaries. Often there are other family members with endometriosis. Although characteristically there is severe pain at the time of menses, adolescents can present with noncyclic pain as well.

Although primary dysmenorrhea is almost always the cause, a careful history and physical examination is required for adolescents who present with pelvic pain. An internal pelvic exam is not required in females who are not sexually active and whose presentation is consistent with primary dysmenorrhea. Constipation can vary cyclically in many females, especially those with irritable bowel syndrome, and often significantly contributes to the pain. **Mittelschmerz**, brief severe

Table 116-6 Differential Diagnosis of Dysmenorrhea in Adolescents (Red Flags Indicated in Bold)

	PRESENTATION	DIAGNOSIS
Primary	Crampy pelvic pain may be accompanied by: aching/heaviness in lower back and upper thighs, nausea, emesis, diarrhea, headache, mastalgia, fatigue, and dizziness; symptoms begin at or shortly prior to onset of menstrual flow and last 1-3 days	Normal physical exam; internal exam only for sexually active adolescents. Ultrasound can be reserved for those patients with atypical presentations (e.g., onset at menarche) or those whose pain does not respond to NSAIDs and hormonal therapy
Endometriosis and adenomyosis	**Increasingly severe dysmenorrhea despite adequate therapy;** pain exacerbated during menses can occur acyclically as well. (Adenomyosis is the presence of endometrial tissue within the uterine myometrium)	Increased risk in patients with obstructive anomalies and possibly bleeding disorders; however, most teenagers with endometriosis have normal anatomy and bleeding indices; diagnosis is made visually during surgery. *Found in up to 69% of adolescents who underwent laparoscopy for persistent pelvic pain*
Müllerian anomalies with partial outflow obstruction	**Pain begins at or shortly after menarche** and occurs with bleeding; presence of **known renal tract anomaly** (often coexists with müllerian anomaly)	Pelvic ultrasound will demonstrate uterine anomalies (e.g., rudimentary uterine horn); MRI may be required to identify some lesions (e.g., obstructed hemivagina). *Found in 8% of adolescents who underwent laparoscopy for persistent pelvic pain*
Pelvic inflammatory disease	Abrupt onset of dysmenorrhea more severe than baseline in sexually active adolescent; presentation can range from mild discomfort to acute abdomen	Clinical diagnosis made by findings of uterine or adnexal tenderness on bimanual pelvic examination (see Chapter 120); supporting features include dysuria, **vaginal discharge,** fever, and increased white blood cell count
Pregnancy complication	Coincident pain and bleeding may be misdiagnosed as dysmenorrhea	Urine hCG-positive

hCG, human chorionic gonadotropin; NSAIDs, nonsteroidal antiinflammatory drugs.

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Table 116-7 Treatment for Dysmenorrhea

	MEDICATION	REGIMEN	COMMENTS
NSAIDs for up to 5 days)	Ibuprofen, 200 mg	2 tablets PO q 4-6 hr	Over-the-counter
	Naproxen sodium, 275 mg	550 mg loading dose then 275 mg PO q 6 hr	Patients may prefer the equivalent 550 mg PO q 12 hr dosing regimen
	Celecoxib (cyclooxygenase [COX]-2 inhibitor)*	400 mg then 200 mg PO q 12 hr prn pain	Can be used for patients with von Willebrand disease
Hormonal contraception	Combined oral contraceptive pills or vaginal ring	Continuous hormone regimens (as opposed to the standard 21 hormone days followed by 7 placebo days) may offer better relief but increase the risk of intermenstrual bleeding	The data favoring rings and pills over the combined hormone patch for this indication are sparse; treatment can be based on patient preference
	Progestin-only methods	DMPA 150 mg IM or 104 mg SC q 3 mo, levonorgestrel intrauterine device for up to 5 yr, etonogestrel implant for up to 3 yr	DMPA has potential side effects of bone loss and weight gain as well as a higher discontinuation rate than the 2 LARC methods
Gonadotropin-releasing hormone agonist	Depot leuprolide	11.25 mg IM q 3 mo	Consider for patients with presumed endometriosis not responsive to hormonal methods; add-back hormones are recommended to prevent bone loss

*FDA-approved for patients older than 18 yr. Should be used with caution in patient with impaired renal or liver dysfunction, heart failure, a history of gastrointestinal bleeding or ulcer. Full prescribing information can be found at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020998s033,021156s003lbl.pdf.

DMPA, depomedroxyprogesterone acetate; IM, intramuscular; LARC, long-acting reversible contraceptive; NSAIDs, nonsteroidal antiinflammatory drugs.

pain with ovulation, occurs at midcycle and can explain what initially appeared to be noncyclic pelvic pain. Table 116-6 lists the red flags for secondary dysmenorrhea. Ovarian cysts, a frequent concern of families, are usually transient and painless.

Treatment for primary dysmenorrhea is aimed at decreasing levels of prostaglandins, preferably before they are produced. Thus, the mainstay of treatment is with prostaglandin synthetase inhibition by either nonsteroidal antiinflammatory drugs, hormonal contraception, or a gonadotropin-releasing hormone agonist (Table 116-7) beginning at, or preferably the day prior to, menstruation. The high doses of around the clock treatment are rarely needed for more than the 1st 2 days. More data are needed to make specific treatment recommendations regarding exercise, but females should be reassured that participation in usual sports and extracurricular activities is not only permissible but a benchmark of adequate treatment.

For those adolescents whose pain does not respond to optimally dosed nonsteroidal antiinflammatory drugs, or who also require contraception, all of the currently available forms of hormonal contraception will improve dysmenorrhea. A number of trials have investigated adjuvant treatments including heat, aromatherapy, acupressure, acupuncture, transcutaneous nerve stimulation, herbal remedies, yoga, and dietary supplements; however, the mainstay second-line treatment is hormones. The mechanisms are not fully delineated but are presumed to include elimination of progesterone production from the corpus luteum for those methods that prevent ovulation, and decreased prostaglandin production from the diminished endometrial lining. Up to 3 cycles may be required to appreciate the full benefit. Methods and regimens that eliminate a placebo interval may provide better relief. Females whose pain persists despite more than 3 mo of adequate hormonal therapy require further evaluation and treatment.

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116.4 Premenstrual Syndrome and Premenstrual Dysphoric Disorder

Gina S. Sucato and Gale R. Burstein

Premenstrual dysphoric disorder (PMDD) is a depressive disorder that is distinguished from other depressive disorders by its timing. Symptoms of anxiety and depressed mood begin in the luteal phase of the menstrual cycle (i.e., in the second half, after ovulation) and improve within a few days after the onset of menses. PMDD causes significant distress and functional impairment and may be accompanied by physical and behavioral symptoms. PMDD occurs in 2-6% of menstruating females worldwide. Based on a large body of scientific evidence, it has been included in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) V (Table 116-8) as a distinct, treatment-responsive, depressive disorder. It is distinguished from premenstrual syndrome (PMS), which has similar timing and occurs in up to 30% of adolescents, by the severity and consequences of the affective symptoms. Premenstrual symptoms are precipitated by ovulation; symptoms recur in the luteal phase and should disappear at the end of menstruation.

Validated tools to screen for severe PMS and PMDD exist; up to half of females who report PMS do not meet diagnostic criteria when symptoms are rated prospectively. Consequently, use of a menstrual calendar to prospectively document symptoms is necessary, as it is important to distinguish PMDD from anxiety, depression, or another mental health disorder the symptoms of which are exacerbated cyclically but occur throughout the cycle.

Treatment success is gauged by improvement in patient symptoms. In mild cases of PMS, adolescents may have adequate relief following education about the relationship of symptoms to the menstrual cycle and instruction on stress management techniques, including exercise. There is not strong evidence supporting the effectiveness of most COC pills for PMS, particularly in adolescents. However, some experts suggest this treatment option for those patients who also have dysmenorrhea or contraceptive needs.

The treatment option with the most supportive evidence is use of selective serotonin reuptake inhibitors, which are first-line therapy for adult women with severe PMS and PMDD. In contrast to the treatment of depression, selective serotonin reuptake inhibitors can be rapidly effective for PMDD, and thus can be prescribed either continuously or intermittently, beginning at ovulation (or whenever in the luteal phase symptoms begin) and ending when symptoms resolve. Adolescents can be prescribed the standard doses used for adults, for example, fluoxetine 10-20 mg orally daily. Among the many dietary supplements that have been studied, the best evidence is for supplementation with calcium 1,200 mg in 3 divided doses to treat both mood and pain symptoms.

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Table 116-8 Criteria for Premenstrual Dysphoric Disorder

A. In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to *improve* with a few days after the onset of menses, and become *minimal* or absent in the week postmenses.
B. One (or more) of the following symptoms must be present:
   1. Marked affective lability (e.g., mood swings; feeling suddenly sad or tearful, or increased sensitivity to rejection).
   2. Marked irritability or anger or increased interpersonal conflicts.
   3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts.
   4. Marked anxiety, tension, and/or feelings of being keyed up or on edge.
C. One (or more) of the following symptoms must additionally be present, to reach a total of 5 symptoms when combined with symptoms from criterion B above.
   1. Decreased interest in usual activities (e.g., work, school, friends, hobbies).
   2. Subjective difficulty in concentration.
   3. Lethargy, easy fatigability, or marked lack of energy.
   4. Marked change in appetite; overeating; or specific food cravings.
   5. Hypersomnia or insomnia.
   6. A sense of being overwhelmed or out of control.
   7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain.

Note: The symptoms in criteria A-C must have been met for most menstrual cycles that occurred in the preceding year.

D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).
E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).
F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (**Note:** The diagnosis may be made provisionally prior to this confirmation).
G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

From the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Copyright 2013). American Psychiatric Association, pp. 171-172.

Chapter 117

Contraception

Tara Jatlaoui and Gale R. Burstein

The untoward consequences of sexual activity (sexually transmitted infections [STIs; see Chapter 120], and early, unintended pregnancy [see Chapter 118]) all too often are experienced by adolescents. Adolescents often do not seek reproductive healthcare for 6-12 mo after initiating sex; many will become pregnant and/or acquire an STI during this interval. Appropriate counseling and educational interventions with adolescents, including the healthcare provider raising the topic of prevention, can decrease sexual risk behavior; youth who plan sexual initiation (as opposed to "it just happened") are 75% more likely to use contraception at sexual debut.

EPIDEMIOLOGY

Sexual Activity

According to the Youth Risk Behavior Surveillance System 2011, almost half (47.4%) of U.S. high school students had ever had sexual intercourse and one-third reported being currently sexually active (had sexual intercourse with at least 1 person during the 3 mo before the survey).

Although U.S. teens and European teens have similar levels of sexual activity and ages of sexual debut, U.S. teens are less likely to use contraception and less likely to use the most effective methods. Teen pregnancy rates have been declining worldwide as a result of delayed initiation of sexual activity and increased contraceptive use. Despite declines, the U.S. still had the highest 2010 teen birth rate in the Western industrialized world with 34 live births per 1,000 females 15-19 yr old (Fig. 117-1). That is nearly 2 times higher than the 2010 teen birth rate in Ireland, which has the highest rate in Western Europe, and almost 10 times higher than the lowest rate in Switzerland. Of the 750,000 teen pregnancies in the United States in 2008, 31% ended in abortion. More than 80% of these pregnancies are unintended, indicating a remaining unmet need for reliable, effective contraception that teens will consistently use.

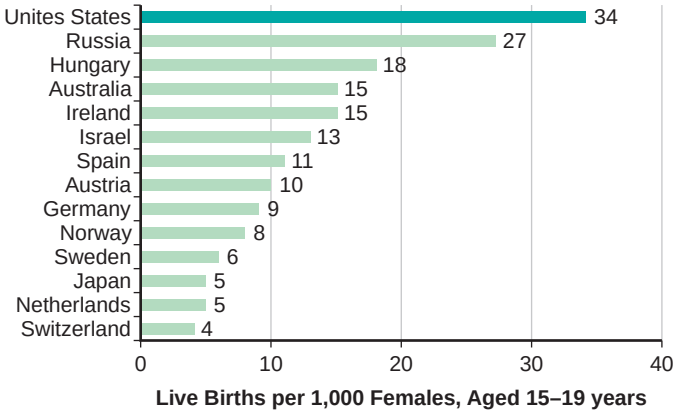

Figure 117-1 Teen birth rates in high income countries. *(From* United Nations Demographic Yearbook 2011, *available at* http://unstats.un.org/unsd/demographic/products/dyb/dyb2011.htm, *and Martin JA, Hamilton BE, Ventura SJ, et al: Births: Final data for 2010. National Vital Statistics Reports; Vol 61, No. 1, Hyattsville, MD: National Center for Vital Statistics, 2012, 1-72.)*

Contraceptive Use

According to the National Survey of Family Growth, 2006-2010, virtually all sexually experienced teens have used some method of contraception in the past. The most commonly used method is the condom, followed by withdrawal and then the pill. Use of contraception at first sex has greatly increased over the last 50 yr and the condom is currently the most common method used at first sex, as reported by more than 75% of males and females. Factors increasing contraception use at first sex include increasing age among teens up to age 17 yr; time in college; and planning their sexual debut (75% more likely to have used contraception than those who did not plan it).

To decrease rates of unintended pregnancy, more teens must use most or moderately effective contraception consistently and correctly.

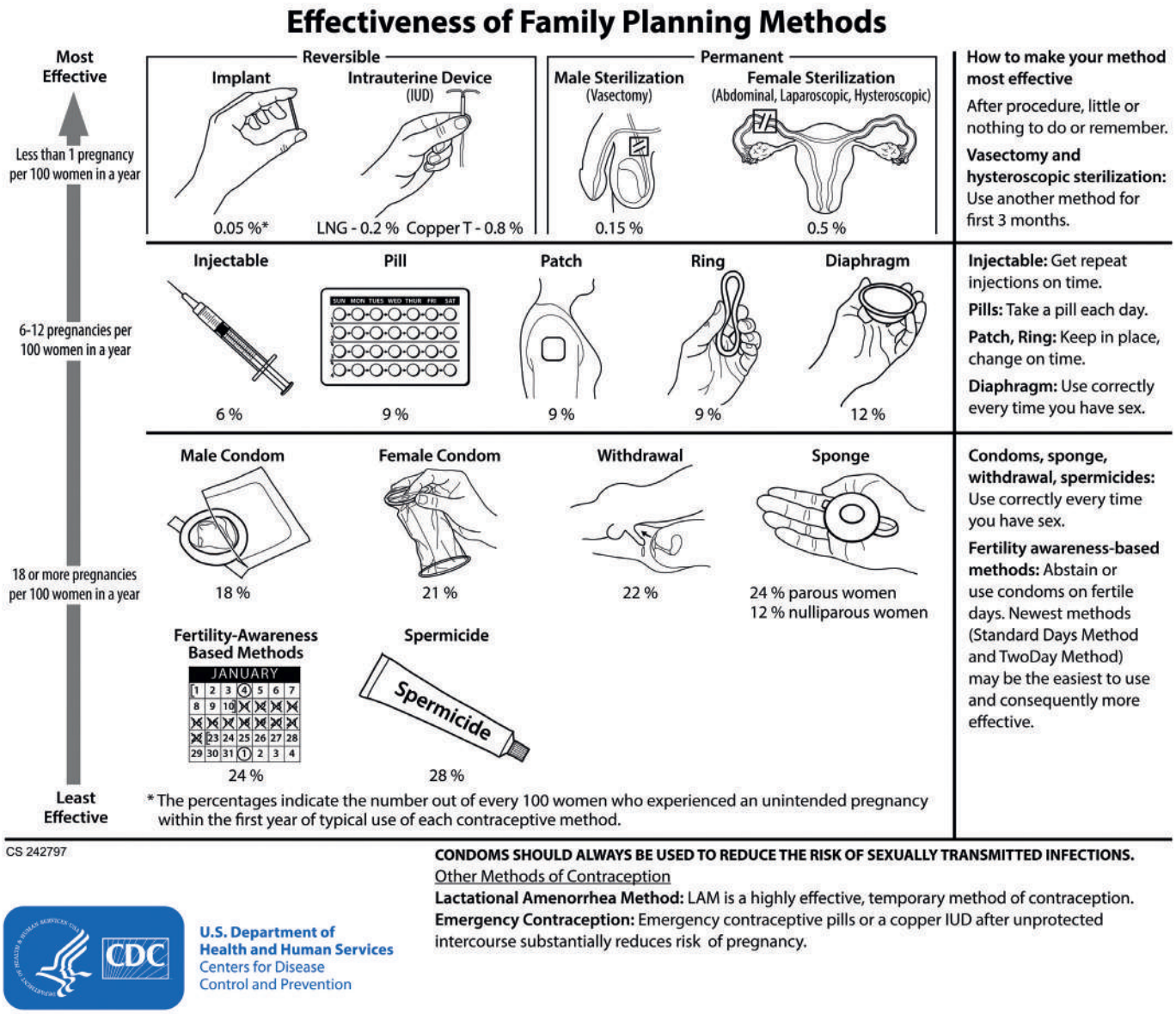

Figure 117-2 Effectiveness of contraceptive methods. *(From Centers for Disease Control and Prevention, Division of Reproductive Health, CS 242797; adapted from World Health Organization.* Comparing typical effectiveness of contraceptive methods. *Geneva, 2007, World Health Organization, and from Trussell J. Contraceptive failure in the United States.* Contraception *83:397–404, 2011.)*

The CDC Effectiveness of Contraceptive Methods Chart illustrates a tiered system of most effective (Tier 1), moderately effective (Tier 2), and least effective (Tier 3) methods (Fig. 117-2). Tier 1 methods include those with failure rates of less than 1 pregnancy per 100 women in a year of typical use. Tier 2 methods have failure rates of 6-12 pregnancies per 100 women in a year of typical use, and Tier 3 methods have failure rates of 18 or more pregnancies per 100 women per year of typical use.

More than half of sexually experienced female teens are currently using most effective or moderately effective contraceptive methods, such as an intrauterine device (IUD) or contraceptive implant, oral contraceptive pills, the contraceptive patch, the vaginal ring, an injectable contraception, or, rarely, sterilization. U.S. teens' use of hormonal methods at last intercourse is less frequent compared to teens in other developed countries: 52% of U.S. teens, 56% of Swedish 18-19 yr olds, 67% of French 15-19 yr olds, 72% of British 16-19 yr olds, and 73% of Canadian 15-19 yr olds use hormonal methods. A higher likelihood of female current contraceptive use is associated with older age at sexual initiation, aspirations for higher academic achievement, acceptance of one's own sexuality, and a positive attitude toward contraception. Condom use should also be encouraged along with effective contraception, preferably Tier 1 or 2, for dual protection against pregnancy and STIs. Only 12% of sexually active female teens who are using a most effective or moderately effective method are using condoms as well.

Contraceptive Counseling

The health screening interview during the adolescent preventive visit offers opportunities to identify and discuss unsafe sexual practices among sexually active adolescents and to identify and reinforce safe sexual behaviors including abstinence (see Chapter 112). Adolescents with medical conditions, either chronic or acute, are particularly vulnerable to having sexual and reproductive health omitted from their visits (see Chapters 42 and 717). Their comorbidities or concurrent medication use may make unintended pregnancy an increased health risk; therefore addressing sexuality and contraceptive issues at visits is imperative.

The goals of counseling with adolescents are to (1) understand adolescent perceptions and misperceptions about pregnancy and use of

contraceptives; (2) help adolescents put unprotected intercourse risk in a personal perspective; (3) educate adolescents regarding the true risks and benefits for the various methods available; and (4) help adolescents choose a safe and effective method that can either be provided on site or be easily obtained by referral. Counseling should include a review of all contraceptive methods available, starting with the most effective methods. The adolescent should be counseled using "**typical use" failure rates,** which reflect the effectiveness of a method for the average person who may not always use the method or use the method correctly (see Fig. 117-2). For example, for oral contraceptive pills, the typical use failure rate is 9% whereas perfect use failure rate is <1%. It is important to ask about use of withdrawal as more than half (58%) of teens have used it for contraception and it has a typical use failure rate of 22%. Abstinence should also be discussed as an option even if teens have engaged in sexual intercourse in the past. Situational abstinence may be the best option if they do not have another method available at a particular time.

Necessary concepts to address while discussing individual methods include how effective the method is, how long the method works, what behaviors are required for correct and consistent use, what side effects may be seen, and what signs or symptoms of complications should prompt a return visit. Reviewing common side effects allows teens to anticipate and cope with any changes with reassurance. Weighing the possibility of certain side effects with the possibility of an unintended pregnancy may also help with the conversation. It is also important to address any specific misperceptions teens may have for certain contraceptives regarding side effects or effectiveness.

Once an adolescent chooses a method, the provider and teen should discuss clear plans on correct and consistent use of the chosen method and strategies for appropriate follow-up (Table 117-1). Providers

Table 117-1 Contraceptive Methods

METHOD	FAILURE RATE (%) Typical Use	FAILURE RATE (%) Perfect Use	DOSING	MECHANISM OF ACTION	POTENTIAL SIDE EFFECTS	ADVANTAGES
HORMONAL CONTRACEPTIVES						
Implant (Implanon or Nexplanon)	0.05	0.05	Insertion of implant into upper arm once every 3 yr	Progestin effects: thickening of cervical mucus, inhibition of ovulation, endometrial atrophy	Rare insertion complications, possible weight gain, uterine bleeding changes including amenorrhea	High efficacy, discreteness, relief of dysmenorrhea, reduced risk of ectopic pregnancy, reversibility, high acceptability and continuation rates; no estrogen
Progestin-releasing IUD (Skyla and Mirena)	0.2	0.2	3 or 5 yr Releases 14 or 20 μg/day levonorgestrel	Progestin effects (see above) and IUD effect of preventing sperm from fertilizing ovum	Breakthrough bleeding in 1st 3-6 mo, then hypo-, or amenorrhea	High efficacy, easy to use, long-acting; no estrogen Decrease in: menstrual blood loss, dysmenorrhea, endometriosis pain, PID risk
Progestin-only injection (Depo-Provera)	6	0.2	3 mo (13 wk) 150 mg depot medroxyprogesterone IM	Progestin effects (see above)	Irregular bleeding or amenorrhea, weight gain, breast tenderness, acne, depression, possible decrease in bone density	No estrogen; decrease in menstrual blood loss, dysmenorrhea, PID risk
The patch	9	0.3	Weekly for 3 wk (off on 4th wk) 20 μg ethinyl estradiol 150 μg norelgestromin released daily	Combined hormonal method: thickens cervical mucus, inhibits ovulation, inhibits sperm's ability to fertilize egg, slows tubal mobility, disrupts ovum transport, induces endometrial atrophy	Breakthrough bleeding, nausea, headaches, breast tenderness, skin site reaction, less effective if patient weighs >90 kg (198 lb)	Similar to OCPs but less-frequent dosing
Vaginal ring (NuvaRing)	9	0.3	Monthly (insert for 3 wk of each mo) Serum levels of 15 μg ethinyl estradiol Releases 150 μg norelgestromin daily	Combined hormonal method (see above)	Vaginal irritation, vaginal discharge, headache	Similar to OCs but less-frequent dosing
Combined Oral Contraceptives (OCPs)	9	0.3	Daily Varies 20-50 μg estrogen Varies 0.15-1 μg progestogen	Combined hormonal method (see above)	Breakthrough bleeding, nausea, headaches, breast tenderness	Decrease in PID risk, ectopic pregnancy risk, menstrual blood loss, dysmenorrhea, acne
Progestin-only pills (POPs)	9	0.3	Daily (within 3-hr period) 0.35 mg norethindrone or 0.075 mg norgestrel	Progestin-only hormonal method: inhibits ovulation, thickens and decreases cervical mucus, atrophies endometrium	Irregular bleeding, breast tenderness, depression	No estrogen; effective after 2 days of use

Continued

Table 117-1 Contraceptive Methods—cont'd

METHOD	FAILURE RATE (%) Typical Use	FAILURE RATE (%) Perfect Use	DOSING	MECHANISM OF ACTION	POTENTIAL SIDE EFFECTS	ADVANTAGES
NONHORMONAL CONTRACEPTIVES						
IUD copper-containing (ParaGard)	0.8	0.6	10 yr 36 × 22 mm, copper wire wound around vertical stem of T	IUD: prevents sperm from fertilizing ova and copper ions may act as spermicide	Heavier menses	Easy to use, long-acting nonhormonal
Male condom	18	2	Every act of intercourse	Barrier method: blocks passage of semen	Latex allergy	Recommended to be used in addition to another contraceptive; only method that decreased STD, HIV risk
Female condom	21	5	Every act of intercourse	Barrier method: lines the vagina fully and perineum partially	Vaginal discomfort, partner penile irritation	Provides some protection against STD, HIV; polyurethane can be used with latex allergy
Spermicides	28	18	Every act of intercourse nonoxynol-9 (in United States). Dose varies by formulation, e.g., gel, suppository, from 52.5-150 mg	Kills sperm by destroying sperm cell membrane	Allergy or sensitivity to ingredients, recurrent urinary tract infections	Recommended to be used in addition to another barrier contraceptive

IUD, intrauterine device; OCs, oral contraceptives; PID, pelvic inflammatory disease; STD, sexually transmitted disease.

From Trussell J: Contraceptive failure in the United States, Contraception *83:397–404, 2011; Hatcher RA, Trussell J, et al, editors:* Contraceptive technology, *New York, 2011, Ardent Media; and As-Sanie S, Gantt A, Rosenthal MS: Pregnancy prevention in adolescents,* Am Fam Physician *70:1517–1524, 2004.*

should help the adolescent consider potential barriers to correct and consistent use (e.g., forgetting to take a pill daily) and develop strategies to deal with each barrier. The provider should assess whether the teen understood the information discussed and may confirm by asking the teen to repeat back key concepts. Chapter 112 discusses confidentiality and consent issues related to contraceptive management.

A pelvic examination is only required for placement of an IUD, unless otherwise indicated. STI screening is appropriate once sexual activity has begun; gonorrhea and chlamydia screening via a self-collected or provider-collected vaginal swab or urine sample is recommended unless symptoms require a pelvic exam. Guidelines from the American Congress of Obstetrics and Gynecology (ACOG) recommend that the first female teen visit to a gynecologist occur between the ages of 13 and 15 yr unless necessary at an earlier age. This visit aims to establish rapport, educate the patient and parents or guardian on healthy sexual development, and provide routine preventive services. Pap test for cervical cancer screening is not recommended until age 21 yr.

Bibliography is available at Expert Consult.

117.1 Long-Acting Reversible Contraception

Tara Jatlaoui and Gale R. Burstein

Long-acting reversible contraception (LARC) includes 2 levonorgestrel IUDs, the Copper IUD and the etonogestrel subdermal implant; LARCs are the only Tier 1 methods that are reversible (see Fig. 117-2). Considered forgettable contraception, LARCs do not require frequent office or pharmacy visits and do not depend on user compliance for effectiveness. In the CHOICE project in St. Louis, more than 9,000 women were give the contraception of their choice at no cost and were followed for 2-3 yr. The failure rates among women who use oral contraceptive pills, transdermal patch or vaginal ring was more than 20 times higher than the failure rate for women using a LARC method according to this study. Acceptance, continuation, and satisfaction in this study were also higher among teens using LARC compared to those using non-LARC methods. The ACOG recommends LARC methods as first-line contraceptives for all females. The US Medical Eligibility Criteria, 2010, supports safe use of both IUDs and implants in this population. Implants are considered category 1 for all ages, and IUDs are considered category 2 for women <20 years old and for nulliparous women (see Table 117-2 for explanation of categories of eligibility).

Table 117-2 Categories of Medical Eligibility Criteria for Contraceptive Use

1 = A condition for which there is no restriction for the use of the contraceptive method.
2 = A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.
3 = A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.
4 = A condition that represents an unacceptable health risk if the contraceptive method is used.

Intrauterine Devices

Intrauterine devices (IUDs) are small, flexible, plastic objects introduced into the uterine cavity through the cervix. They differ in size, shape, and the presence or absence of pharmacologically active substances. In the United States, 3 IUDs are currently available: the Copper T380A and 2 levonorgestrel IUDs. The effectiveness of the copper IUD is enhanced by the copper ions released into the uterine cavity with possible mechanisms including inhibition of sperm transport and prevention of implantation; this IUD is effective for at least 10 yr.

The levonorgestrel IUDs also have various actions, from thickening of cervical mucus and inhibiting sperm survival to suppressing the endometrium; these IUDs are effective for at least 3 and 5 yr. All 3 IUDs have typical use failure rates of less than 1% (see Fig. 117-2).

Common misconceptions of IUDs among healthcare providers are that IUDs cause infections, infertility, and generally are not safe for teens or nulliparous women to use; these misconceptions are a barrier

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to teens accessing these highly effective and acceptable methods. These IUDs does not increase risk of infertility, and the IUD may be inserted safely in teens as well as nulliparous women (see Table 117-2).

Although early studies suggested an increased risk for upper genital tract infection, theoretically as a result of the presence of a foreign body in the cervix, newer work has refuted these earlier concerns. Therefore, clinicians are encouraged to consider use of IUDs in adolescents despite relatively high prevalence rates of STIs in this population. Teens should be screened for gonorrhea and chlamydia at the time of or before IUD placement, although placement should not be delayed if results have not returned and there are no signs of infection. If STI testing returns positive with an IUD in place, the patient may be treated without removing the IUD if she wishes to continue the method.

Implants

There is currently 1 contraceptive implant available in the United States. Originally FDA-approved in 2006, the single rod that releases 60 μg/day of etonogestrel has been updated to a radiopaque rod with a new inserter. This progestin-only method keeps etonogestrel at steady serum levels for 3 yr and primarily works to inhibit ovulation. Similarly to the levonorgestrel IUD, the progestin acts on the uterus to cause an atrophic endometrium and thicken cervical mucus to block sperm penetration; its typical use failure rate is also <1% (see Fig. 117-2). Unlike the IUD, no pelvic exam is required for insertion. A trained provider can quickly place or remove the implant in the upper arm under local anesthesia. Common side effects include amenorrhea, irregular bleeding, or infrequent bleeding, and, less often, prolonged or frequent bleeding. One potential unique complication of this method relates to localized infection and other side effects after implantation, such as bleeding, hematoma, or scarring, and, if inserted too deeply into the muscle, neural damage or migration; however, these events are rare, occurring in <1% of patients. Minor side effects, such as bruising or skin irritation, are more common but tend to resolve without treatment.

Bibliography is available at Expert Consult.

117.2 Other Progestin-Only Methods

Tara Jatlaoui and Gale R. Burstein

Several progestin-only methods are available and include the levonorgestrel IUDs and implant (see Chapter 117.1), as well as an injectable and progestin-only pills. These methods do not contain estrogen and may be useful for teens with contraindications to estrogen (Table 117-3) and are considered generally safe for use in teens (see Table 117-2). Progestins thicken cervical mucus to block sperm entry into the uterine cavity as well as induce an atrophic endometrium leading to either amenorrhea or less menstrual blood loss; the implant and injectable additionally suppress ovulation. Teens should be provided anticipatory counseling regarding bleeding irregularities that may normally occur in the 1st 3-6 mo of hormonal contraception use.

DEPO-PROVERA

An *injectable progestin,* medroxyprogesterone acetate (Depo-Provera, DMPA), is a Tier 2 contraceptive method available as a deep intramuscular injection (150 mg), or as a subcutaneous injection (104 mg) with typical-use failure rates of 6% (see Fig. 117-2). Both preparations must be readministered every 3 mo (13 wk) and act to inhibit ovulation. DMPA is particularly attractive for adolescents who have difficulty with compliance, are intellectually or physically impaired, and are chronically ill or have a condition for which estrogen use is not recommended. After 1 yr of use, 50% of DMPA users develop amenorrhea, which may be an added advantage for teens with heavy menstrual bleeding, dysmenorrhea, anemias, or blood dyscrasias, or for those with impairments that make hygiene difficult. Although concern has been directed toward the potential for loss in bone mineral density in adolescents, thereby potentially increasing their risk for osteoporosis later in life, subsequent studies have found that bone density is recovered after discontinuation of the method and is considered safe for use in this population (see Table 117-2). Healthcare providers may want to consider a contraceptive containing estrogen in teens who are already at high risk for low bone density, such as those on chronic corticosteroids or those with eating disorders (see Chapter 707). Although a black box warning was issued in 2004, the American Academy of Pediatrics and ACOG do not recommend limiting DMPA use to 2 yr for all women and do not recommend routine bone mineral density screening for females using DMPA. There is also concern for weight gain in women using DMPA. A systematic review found 2 studies indicating early weight gain may be predictive of progressive gain over time; thus, those teens gaining weight in the 1st 3-6 mo should consider another method.

Table 117-3 Conditions Classified as U.S. MEC Category 3 and 4 for Combined Hormonal Contraceptive Use

CATEGORY 4
Complicated valvular heart disease
Current breast cancer
Severe decompensated cirrhosis
Deep venous thrombosis/Pulmonary embolism (acute; history, not on anticoagulation or on established therapy for at least 3 mo with higher risk recurrence; major surgery with prolonged immobilization)
Complicated diabetes with nephropathy, retinopathy, neuropathy or other vascular disease or duration of diabetes >20 yr
Migraine with aura
Hypertension (blood pressure above 160/100 mm Hg) or hypertension with vascular disease
Ischemic heart disease (history of or current)
Hepatocellular adenoma
Malignant liver tumor
Peripartum cardiomyopathy (diagnosed <6 mo prior or with moderately or severely impaired cardiac function)
Postpartum <21 days
History of cerebrovascular accident
Systemic lupus erythematosus with positive antiphospholipid antibodies
Thrombogenic mutations
Viral hepatitis (acute or flare)
CATEGORY 3
Past breast cancer with no evidence of disease for 5 yr
Breastfeeding and <1 mo postpartum
Deep venous thrombosis/pulmonary embolism (history of deep venous thrombosis/pulmonary embolism with lower risk recurrence)
Gall bladder disease (current, medically treated)
Migraine without aura (if worsens or first starts while using combined hormonal contraceptives)
History of malabsorptive bariatric surgery
History of cholestasis and past combined oral contraceptive-related
Hypertension (adequately controlled or blood pressure less than 160/100 mm Hg)
Peripartum cardiomyopathy with mild impairment or >6 months
Postpartum 21-42 days with other risk factors for venous thromboembolism
Drug interactions (Ritonavir-boosted protease inhibitors; certain anticonvulsants; rifampin or rifabutin)

From Centers for Disease Control and Prevention: U.S medical eligibility criteria for contraceptive use, 2010, MMWR Recomm Rep *59(RR-4):1–86, 2010.*

PROGESTIN-ONLY PILLS

Progestin-only oral contraceptives are available for the adolescent in whom the use of estrogen is potentially deleterious, such those with active liver disease, replaced cardiac valves, or hypercoagulable states (see Table 117-3). These agents ("mini-pills") are less reliable in inhibiting ovulation, are associated with a typical use failure rate of 9%, and

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are considered Tier 2 or moderately effective contraceptives (see Fig. 117-2). Acceptance by adolescents is limited by the necessity of taking the pill daily and bleeding irregularities, including amenorrhea and breakthrough bleeding. Progestin-only pills are quickly effective after 2 days of initiation in thickening cervical mucus. Effects, however, are short-lived and pill-taking must be punctual, which may be difficult for teens. If a pill is more >3 hr late from normal time, an unintended pregnancy may occur.

Bibliography is available at Expert Consult.

117.3 Combined Hormonal Contraceptives

Tara Jatlaoui and Gale R. Burstein

Combined hormonal contraceptives (CHCs) are methods that include an estrogenic substance in combination with a progestin; methods available in the United States include several formulations of combined oral contraceptives (COCs), a transdermal patch and a vaginal ring. The major mechanism of action of the estrogen-progestin combination is to prevent the surge of luteinizing hormone and, as a result, to inhibit ovulation. Additional effects to the reproductive tract include thickening of the cervical mucus in such a way that prevents sperm penetration and thinning of the endometrial lining, which may decrease menstrual blood loss. Typical use failure rates for all CHCs are the same at 9%.

CHCs are also considered similarly in the U.S. Medical Eligibility Criteria, and recommendations mostly are concerned with estrogen exposure for a given condition or characteristic (see Table 117-3). Thrombophlebitis, hepatic adenomas, myocardial infarction, and carbohydrate intolerance are some of the more serious potential complications of exogenous estrogen use. These disorders are exceedingly rare in adolescents. Even though teenage smokers who use oral contraceptives have more than twice the risk of myocardial infarction, the likelihood of its occurrence is very small, and thus clinically insignificant, compared to the risk of dying from other pregnancy-related complications.

COMBINED ORAL CONTRACEPTIVES

Oral contraceptive pills can be either COCs or progestin-only pills and are commonly referred to as "the pill." The pill is one of the most common contraceptive methods used among women of all ages. To decrease risk of pregnancy and increase continuation, providers are encouraged to provide oral contraceptive pills at the time of patient presentation to start immediately rather than waiting for next menses, as long as the provider is reasonably sure that the patient is not pregnant. Providers are also encouraged to provide up to 13 pill packs at a time, based on evidence that more pill packs given is associated with higher continuation rates. However, most health plans will not cover costs for more than 3 pill packs dispensed at 1 time. Advanced provision of emergency contraceptive pills is also recommended should patients miss pills and have unprotected sex. The effectiveness of COCs is dependent on compliance, and unfortunately adolescents may forget to take a pill each day. Figures 117-3 and 117-4 list the rules for missed pills or following vomiting or diarrhea.

COCs contain 50, 35, 30, 25, or 20 μg of estrogenic substance, typically ethinyl estradiol, and as many as 10 progestins have been available

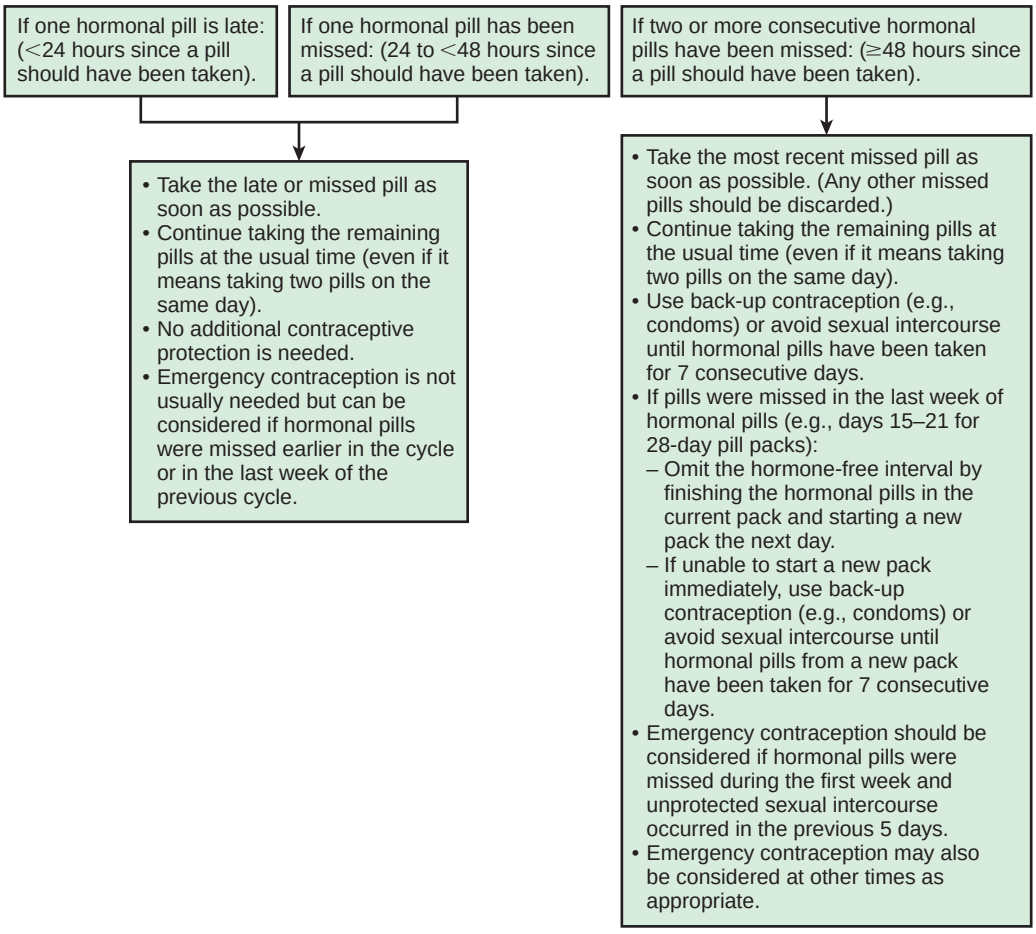

Figure 117-3 Recommended actions after late or missed combined oral contraceptives. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 2, p. 27).*

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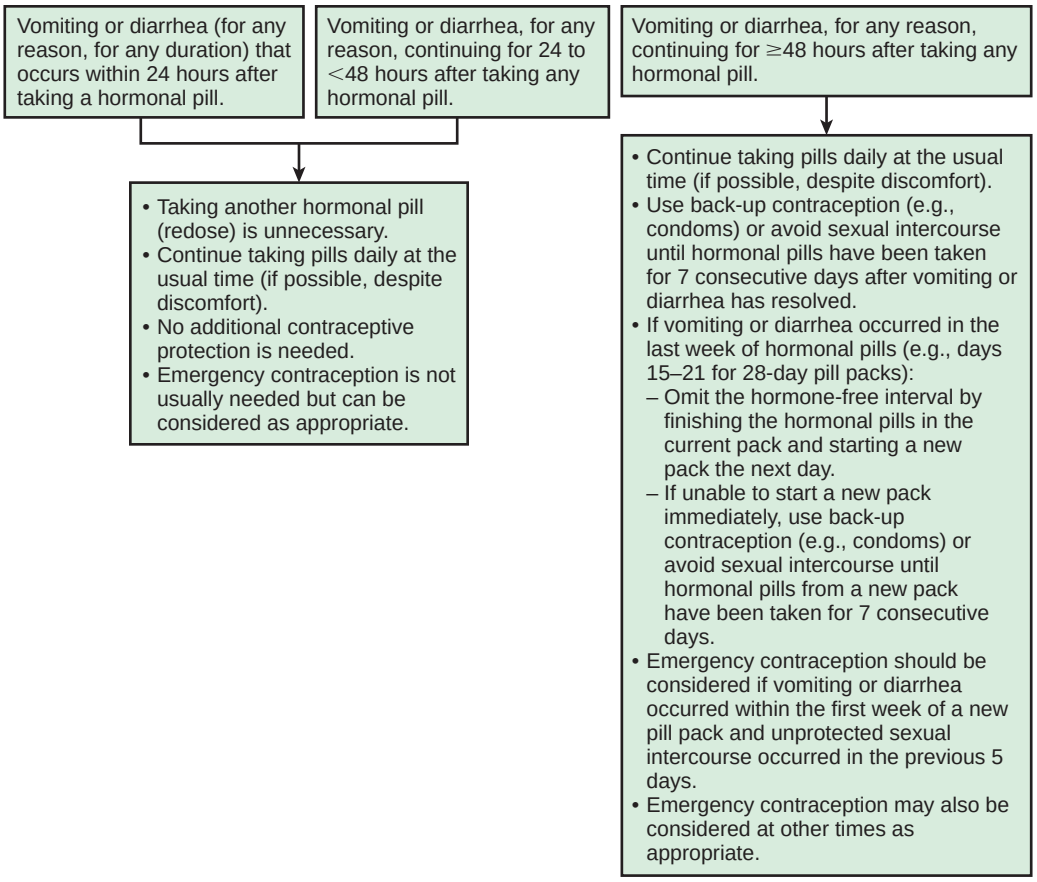

Figure 117-4 Recommended steps after vomiting or diarrhea while using combined oral contraceptives. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 5, p. 30).*

in the United States for combined pills. Multiple preparations are available to help select the formulation with which an individual patient will be satisfied with minimal side effects.

COCs can be packaged as 28-day monophasic pills, which contain the same dose of active pills for 21 or 24 days followed by 7 or 4 days of placebo pills, respectively. Monophasic formulations are also available for extended-cycles of 91 days or 1 yr such that withdrawal bleeding does not occur each month but at the end of each extended cycle. Extended cycling of monophasic COCs for adolescents has some anticipated benefits associated with increased ovarian activity suppression and may decrease failure rates. Other advantages include diminished frequency of hormonal withdrawal (premenstrual) effects including headaches and migraines, mood changes, and heavy monthly bleeding. The most common side effect of extended-cycle oral contraceptive pills is intermenstrual bleeding and/or spotting with the total days of bleeding over the 1st yr of treatment being similar for extended-cycle users and users following a 28-day cycle regimen. The unscheduled bleeding pattern diminishes over time. Multiphasic pill packs contain various levels of estrogen and progestin for 21 active pills and contains 7 placebo pills. Multiphasic formulations are not available for extended cycle use.

The short-term adverse effects of COCs, such as nausea and weight gain, often interfere with compliance in adolescent patients. These effects are usually transient and may be overshadowed by the beneficial effects of a shortened menses and the relief of dysmenorrhea. The inhibition of ovulation or the suppressant effect of estrogens on prostaglandin production by the endometrium makes COCs effective in preventing dysmenorrhea (see Chapter 116). Acne (see Chapter 669) may be worsened by some and improved by other oral contraceptive preparations. The pills with nonandrogenic progestins are particularly effective in reducing acne and hirsutism. Drospirenone, a progestin with antimineralocorticoid activity, has been shown to reduce premenstrual symptomatology, but the potential for hyperkalemia as a side effect eliminates patients with renal, liver, or adrenal diseases and patients on certain medications.

As of 2011, the FDA has concluded that drospirenone-containing oral contraceptives may be associated with a higher risk of blood clots compared to other progestin-containing pills. Although no studies have provided consistent estimates of the comparative risk of blood clots between birth control pills that contain drospirenone and those that do not, nor have studies accounted for patient characteristics that may affect blood clot risk, there has been a 3-fold increased risk of blood clots reported for drospirenone, as compared to products containing levonorgestrel or other progestins. As a result, the FDA is requiring that labeling be revised for the oral contraceptives marketed under the Beyaz, Safyral, Yasmin, and Yaz brands. Despite the risk of blood clots with all oral contraceptives, the risk still remains lower than the risk of developing blood clots during pregnancy or the postpartum period.

TRANSDERMAL PATCH

The *transdermal patch* (Ortho Evra) releases 20 µg ethinyl estradiol and 150 µg norelgestromin daily and is applied to the lower abdomen, buttocks, or upper body. It is worn continuously for 1 wk and changed weekly for a total of 3 wk; then no patch is worn for the fourth wk at which time bleeding occurs (see Table 117-1). It should not be applied to the breast. Limited studies in adolescents suggest higher rates of partial or full detachment compared to adults, with high patient satisfaction and 50-83% continuation rates from 3-18 mo of use (Fig. 117-5). Like other combined hormonal methods, the patch is a Tier 2 or moderately effective contraceptive.

VAGINAL RING

The *vaginal contraceptive ring* (NuvaRing) is a flexible, transparent, colorless vaginal ring that measures about 2.1 inches in diameter and

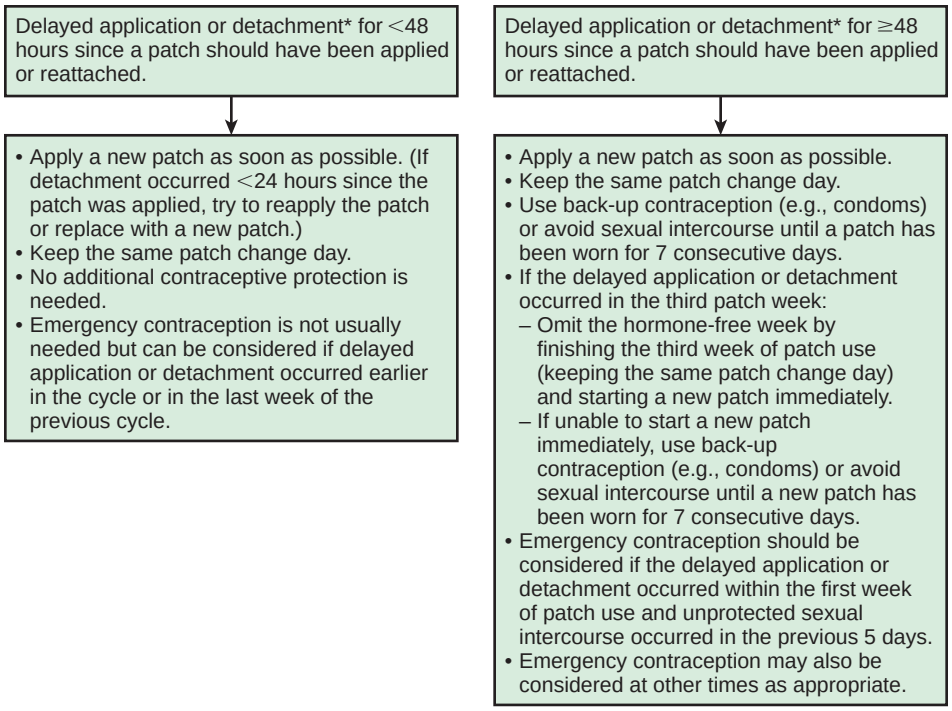

Figure 117-5 Recommended actions after delayed application or detachment with combined hormonal patch. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 3, p. 28).*

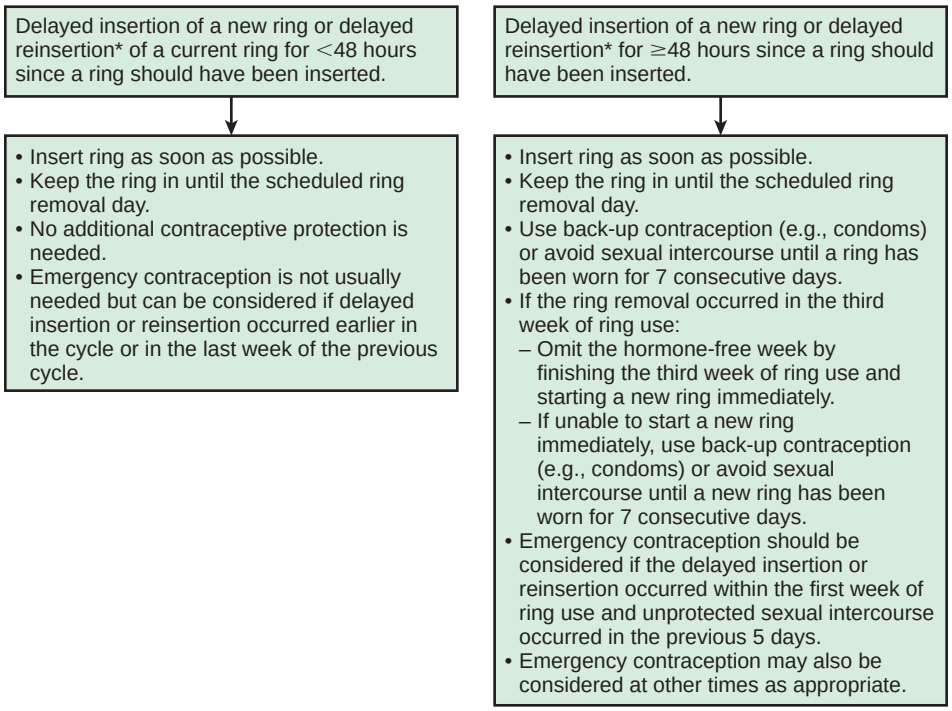

Figure 117-6 Recommended actions after delayed insertion or reinsertion with combined vaginal ring. *(From Centers for Disease Control and Prevention: US Selected Practice Recommendations for Contraceptive Use, 2013,* MMWR Recomm Rep *2013;62(RR-5):1–60, Fig. 4, p. 29).*

is inserted into the vagina by the patient. It releases 15 μg ethinyl estradiol and 120 μg etonogestrel per day and remains in place for 3 wk, during which time these hormones are absorbed. If the ring is accidentally expelled or removed for intercourse, it should be reinserted; however, if it is out of place ≥48 hr, a backup method of contraception should be used (Fig. 117-6). Like other combined hormonal methods, the vaginal ring is a Tier 2 or moderately effective contraceptive.

Contraindications to the use of estrogen-containing methods include those conditions for which CHCs pose an unacceptable health risk (category 4) in the U.S. Medical Eligibility Criteria, 2010 (see Table 117-3): current breast cancer, severe cirrhosis, acute deep venous thrombosis/pulmonary embolism or history of deep venous thrombosis/pulmonary embolism with higher risk for recurrence, major surgery with prolonged immobilization, diabetes with nephropathy, retinopathy or neuropathy, migraines with aura, Stage II hypertension, vascular disease, ischemic heart disease, hepatocellular adenoma or malignant liver tumors, multiple risk factors for cardiovascular disease, peripartum cardiomyopathy, postpartum <21 days, complicated solid organ transplantation, history of cerebrovascular accident, systemic lupus erythematosus with positive antiphospholipid antibodies, thrombogenic mutations and complicated valvular heart disease. The initial history taken before prescribing CHCs should specifically address these risks. The U.S. Medical Eligibility Criteria provides contraceptive safety guidance with more than 1,800 recommendations for more than 120 medical conditions or characteristics (see Table 117-3).

Bibliography is available at Expert Consult.

117.4 Emergency Contraception

Tara Jatlaoui and Gale R. Burstein

Unprotected intercourse at midcycle carries a pregnancy risk of 20-30%. At other times during the cycle, the risk is 2-4%. The risk may be reduced or eliminated by interventions known collectively as emergency contraception (EC) as soon as possible after unprotected intercourse or contraceptive failure with a "window" up to 120 hr. Table 117-4 lists the indications for use of EC. Methods that can be used after unprotected intercourse for EC include the Copper IUD and various emergency contraceptive pills, which include ulipristal acetate, levonorgestrel and COCs following the Yuzpe method. Although the mechanism of action of the Copper IUD as EC is unclear, all emergency contraceptive pills work to delay ovulation and are effective only for intercourse that occurs prior to administration. Initiation of a regular contraceptive method is necessary to prevent pregnancy for any intercourse that occurs for the remainder of the cycle and for future cycles. If pregnancy has already occurred, emergency contraceptive pills will not cause an abortion or have teratogenic effects on the fetus.

Table 117-4 Potential Indications for Use of Emergency Contraception

- Lack of contraceptive use during coitus
- Mechanical failure of male condom (breakage, slippage, or leakage)
- Dislodgment, breakage, or incorrect use of diaphragm, cervical cap, or female condom
- Failure of spermicide tablet or film to melt before intercourse
- Error in practicing withdrawal (coitus interruptus)
- Missed combined oral contraceptives (any 2 consecutive pills)
- Missed progestin-only oral contraceptive (1 or more)
- Expulsion or partial expulsion of an IUD
- Exposure to potential teratogen (such as isotretinoin or thalidomide while not using effective contraception)
- Late injection of injectable contraceptive (>2 wk late of a progestin-only formulation such as depot medroxyprogesterone acetate)*
- 2 or more days late starting new vaginal ring or patch cycle
- Rape

*The usual interval for use of depot medroxyprogesterone acetate as contraception is every 12 wk; the interval for the combined monthly injectable formulation is every 28 to 30 days.

Adapted from Allen RH, Goldberg AB: Emergency contraception: a clinical review, Clin Obstet Gynecol *50:927–936, 2007.*

Teens can access EC information through a ***hotline at 1-888-NOT-2-LATE*** to obtain EC pills over the counter. The American Academy of Pediatrics recommends advance provision of EC pills for teens who are or may become sexually active. A follow-up appointment is also recommended to determine the effectiveness of treatment and to diagnose a possible early pregnancy. The visit also provides an opportunity to counsel the adolescent, explore the situation leading up to the unprotected intercourse or contraceptive failure, test for STIs, offer HIV testing, and initiate continuing contraception when appropriate. Pap smear screening is not initiated until 21 yr of age.

COPPER IUD

The Copper T380A is FDA approved for EC and has been shown to be more than 99% effective if used within 5 days (120 hr) after unprotected sex. The additional benefit of using the Copper IUD for EC is it also provides long-term reversible contraception.

ULIPRISTAL ACETATE

This is the newest formulation available for EC and was FDA approved in 2010 for use up to 120 hr after unprotected sex. It is available only by prescription regardless of age. It has been shown in a few studies to be more effective than levonorgestrel at and beyond 72 hr.

LEVONORGESTREL

In 2009, the FDA approved the emergency contraceptive drug Plan B as an over-the-counter option for women age 17 yr and older. Experience in adolescent women demonstrates more effective use of EC with advance provision and is not associated with more frequent unprotected intercourse or less condom or pill use. Nausea and vomiting are uncommon side effects, and in a recent comparison, levonorgestrel proved more effective at preventing pregnancy than the Yuzpe method.

The **Yuzpe method** has been replaced by the more effective levonorgestrel pills but may be useful for women who already have COCs at home and are in need of EC. For EC, pills consist of COCs totaling 200 μg ethinyl estradiol and 2.0 mg norgestrel or 1.0 mg levonorgestrel. This method is effective in reducing the risk of pregnancy by 75%. The most common side effects are nausea (50%) and vomiting (20%), prompting some clinicians to prescribe or recommend antiemetics along with the oral contraceptives.

Bibliography is available at Expert Consult.

117.5 Dual Protection

Tara Jatlaoui and Gale R. Burstein

Dual protection is the protection against STIs/HIV as well as effective contraception. Although condoms can provide both, providers should encourage more highly effective contraceptive methods along with condoms for each act of intercourse.

CONDOMS

This method prevents sperm from being deposited in the vagina. There are no major side effects associated with the use of a condom. The risk of HIV may have increased the use of condoms among adolescents, with 46.2% of high school students in 1991 reporting using a condom at last sexual intercourse increasing to 60.2% in 2011. The main advantages of condoms are their low price, availability without prescription, little need for advance planning, and, most important for this age

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group, their effectiveness in preventing transmission of STIs, including HIV and human papillomavirus. The typical use failure rate for male condoms is 18%. For most effective dual protection, male latex condoms are recommended as protection against STIs, and should be used with an effective contraceptive method for adolescents such as a LARC. According to the National Survey of Family Growth, only 12% of females used a highly effective method along with a condom in the mo that they were interviewed.

A female condom is available over-the-counter in single-size disposable units. It is a second choice over the male latex condom because of the complexity of properly using the device, its high typical use failure rate of 21%, and the lack of studies in humans demonstrating its effectiveness against STIs. Most adolescents would require intensive education and hands-on practice to use it effectively.

Bibliography is available at Expert Consult.

117.6 Other Barrier Methods

Tara Jatlaoui and Gale R. Burstein

DIAPHRAGM, CERVICAL CAP, AND SPONGE

These methods have few side effects but are much less likely to be used by teenagers. Typical use failure rates exceed 12%. The cervical cap and sponge have lower failure rates in nulliparous women while the diaphragm has similar rates among nulliparous or parous women. Adolescents tend to object to the messiness of the jelly or to the fact that the insertion of a diaphragm may interrupt the spontaneity of sex, or they may express discomfort about touching their genitals.

117.7 Other Methods

Tara Jatlaoui and Gale R. Burstein

SPERMICIDES

A variety of agents containing the spermicide nonoxynol-9 are available as foams, jellies, creams, films, or effervescent vaginal suppositories. They must be placed in the vaginal cavity shortly before intercourse and reinserted before each subsequent ejaculation in order to be effective. Rare side effects consist of contact vaginitis. There has been some concern regarding the vaginal and cervical mucosal damage observed with nonoxynol-9, and the overall impact on HIV transmission is unknown. The finding that nonoxynol-9 is gonococcicidal and spirocheticidal has not been substantiated in randomized clinical trials. Spermicides should be used in combination with other barrier methods as their typical use failure rate alone is 28%.

WITHDRAWAL

The pregnancy risk for use of withdrawal as a contraceptive method is probably underestimated in adolescents, and high typical use failure rate of 22% should be specifically addressed with young adolescents; especially since over half (58%) of teens have used withdrawal for contraception.

FERTILITY AWARENESS–BASED METHODS

These include the standard days method, basal body temperature method, billings method and may also include combinations as well. Since these are based on regular ovulatory cycles, which are less common in teens, these should be used with caution.

LACTATIONAL AMENORRHEA METHOD

The lactational amenorrhea method may be a highly effective temporary contraceptive method if all of the following criteria are met: (a) no return of menses, (b) the infant is <6 mo old, and (c) exclusively breastfeeding.

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Chapter 118

Adolescent Pregnancy

Dianne S. Elfenbein and Marianne E. Felice

EPIDEMIOLOGY

In 1960, the teen birth rate in the United States was recorded as 89.1 births per 1,000 females 15-19 yr of age; by 2011, the rate had decreased to 31.3 births per 1,000 females 15-19 yr of age. Despite increases in the rates in 1990 and 2006, there has been a steady decline over the last half century (Fig. 118-1). The most dramatic decreases have been in African-American and Hispanic adolescents. Pregnancy rates, which include births, miscarriages, stillbirths, and induced abortions, have also decreased since the 1990s. In 1990, the pregnancy rate was 116.9 per 1,000 females age 15-19 yr of age; in 2008, the pregnancy rate was 67.8, indicating that the decline in birthrates was not attributable to an increase in pregnancy terminations. The improvement in U.S. female teen birth rates is attributed to 3 factors: more teens are delaying the onset of sexual intercourse, are using some form of contraception when they begin to have sexual intercourse, and are using long-lasting contraceptive agents such as injections, implants, and intrauterine devices.

In spite of the decrease in female teen births in the last 2 decades, the United States continues to have female teen birth rates markedly higher than those in most other industrialized nations. For comparison, in 2009 the United States birth rate to female teens age 15-19 yr was 37.9 per 1,000 compared to a rate of 22 among all industrialized nations. The Russian Federation reported a rate of 30.2, the UK a rate of 25.0, and Australia a rate of 16.5. Japan's rate was 5.1 births per 1,000 female teens. Among developing countries the estimated rate was 56 and among the least-developed nations, 123. Globally, the estimated rate was 52 births per 1,000 female teens. Globally, teen pregnancy rates declined from 1990 to 2000 but have leveled off since then.

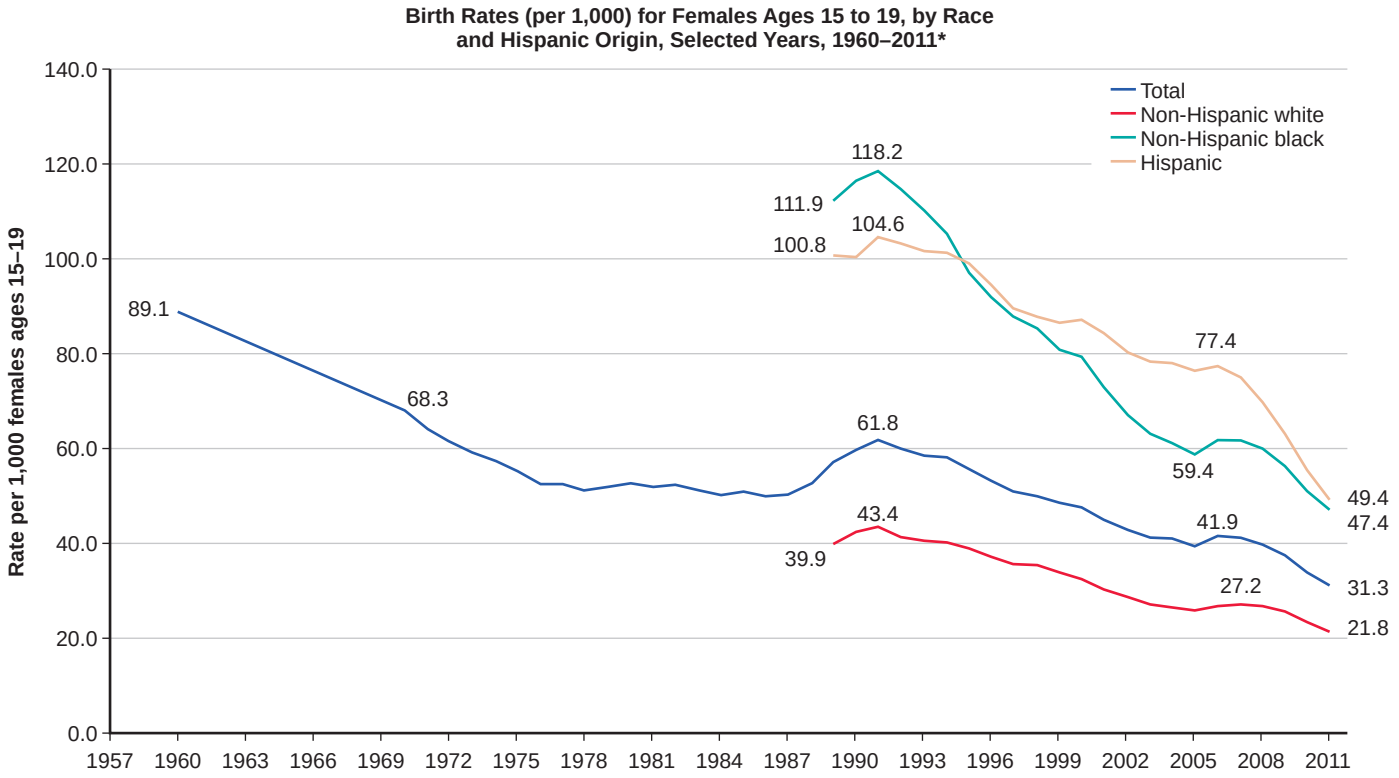
ETIOLOGY

In industrialized countries with policies supporting access to protection against pregnancy and sexually transmitted infections (STIs), older adolescents are more likely to use hormonal contraceptives and condoms, resulting in a lowered risk of unplanned pregnancy. Younger teenagers are likely to be less deliberate and logical about their sexual decisions and their sexual activity is likely to be sporadic or even coercive, contributing to inconsistent contraceptive use and a greater risk of unplanned pregnancy. Better hopes for employment and higher educational goals are associated with lowered probability of childbearing in most groups. In nonindustrialized countries, laws permitting marriage of young and mid-adolescents, poverty, and limited female education are associated with increased adolescent pregnancy rates.

CLINICAL MANIFESTATIONS

Adolescents may experience the traditional symptoms of pregnancy: morning sickness (vomiting, nausea that may also occur any time of the day), swollen tender breasts, weight gain, and amenorrhea. Often the presentation is less classic. Headache, fatigue, abdominal pain, dizziness, and scanty or irregular menses are common presenting complaints.

In the pediatric office, some teens are reluctant to divulge concerns of pregnancy. Denial of sexual activity and menstrual irregularity should not preclude the diagnosis in face of other clinical or historical information. An unanticipated request for a complete checkup or a visit for contraception may uncover a suspected pregnancy. Pregnancy is still the most common diagnosis when an adolescent presents with **secondary amenorrhea.**



*Data for 2011 are preliminary

Figure 118-1 Teen birth rates (births per 1,000 females) in the United States. *(Child Trends, 2013. Teen births. Available at:* http://www.childtrends.org/?indicators=teen-births. *Sources: Data for 1960 from National Center for Health Statistics.* Health, United States, 2001 with urban and rural health chartbook. *Hyattsville, MD, 2001, Table 3; Data for 1970-2011 from Martin JA, Hamilton BE, Ventura JS, et al: Births: final data for 2011. Natl Vital Stat Rep 62(1). Hyattsville, MD: National Center for Health Statistics, 2013.)*

DIAGNOSIS

Table 118-1 provides information regarding the diagnosis of pregnancy.

On physical examination, the findings of an enlarged uterus, cervical cyanosis (**Chadwick sign**), a soft uterus (**Hegar sign**), or a soft cervix (**Goodell sign**) are highly suggestive of an intrauterine pregnancy. A confirmatory pregnancy test is always recommended, either *qualitative* or *quantitative*. Modern **qualitative** urinary detection methods are efficient at detecting pregnancy, whether performed at home or in the office. These tests are based on detection of the beta subunit of human chorionic gonadotropin (hCG). Although claims for nonprescription home pregnancy tests may indicate 98% detection on the day of the first missed menstrual period, sensitivity and accuracy vary considerably. Office or point-of-care tests have increased standardization and generally have increased sensitivity, with the possibility of detecting a pregnancy within 3-4 days after implantation. However, in any menstrual cycle, ovulation may be delayed, and in any pregnancy, the day of implantation may vary considerably, as may rate of production of hCG. This variability, along with variation of urinary concentration, may affect test sensitivity. **Consequently, each negative test should be repeated in 1-4 wk if there is a heightened suspicion of pregnancy.** The most sensitive pregnancy detection test is a serum **quantitative** βhCG radioimmunoassay in which results are reliable within 7 days after fertilization. This more expensive test is used primarily during evaluations for ectopic pregnancy, to detect retained placenta after pregnancy termination, or in the management of a molar pregnancy. It is generally used when serial measurements are necessary in clinical management.

Although not generally used for primary diagnosis of pregnancy, pelvic or vaginal ultrasound can be used to detect and date a pregnancy. Pelvic ultrasound will detect a gestational sac at about 5-6 wk (dated from last menstrual period) and vaginal ultrasound at 4.5-5 wk. This tool may also be used to distinguish diagnostically between intrauterine and ectopic pregnancies.

Table 118-1 Diagnosis of Pregnancy Dated from First Day of Last Menstrual Cycle

CLASSIC SYMPTOMS
Missed menses, breast tenderness, nipple sensitivity, nausea, vomiting, fatigue, abdominal and back pain, weight gain, urinary frequency
Teens may present with unrelated symptoms that enable them to visit the doctor and maintain confidentiality
LABORATORY DIAGNOSIS
Tests for human chorionic gonadotropin in urine or blood may be positive 7-10 days after fertilization, depending on sensitivity
Irregular menses make ovulation/fertilization difficult to predict.
Home pregnancy tests have a high error rate.
PHYSICAL CHANGES
2-3 wk after implantation: cervical softening and cyanosis
8 wk: uterus size of orange
12 wk: uterus size of grapefruit and palpable suprapubically
20 wk: uterus at umbilicus
If physical findings are not consistent with dates, ultrasound will confirm

PREGNANCY COUNSELING AND INITIAL MANAGEMENT

After the diagnosis of pregnancy is made, it is important to begin addressing the psychosocial, as well as the medical, aspects of the pregnancy. The patient's response to the pregnancy should be assessed and her emotional issues addressed. It should not be assumed that the

pregnancy was unintended. Discussion of the patient's options should be initiated. These options include (a) releasing the child to an adoptive family, (b) electively terminating the pregnancy, and (c) raising the child herself with the help of family, father of the baby, friends, and/or other social resources. Options should be presented in a supportive, informative, nonjudgmental fashion; for some young women, they may need to be discussed over several visits. Physicians who are uncomfortable in presenting options to their young patients should refer their patients to a provider who can provide this service expeditiously. Pregnancy terminations implemented early in the pregnancy are generally less risky and less expensive than those initiated later. Other issues that may need discussion are how to inform and involve the patient's parents and the father of the infant; implementing strategies for insuring continuation of the young mother's education; discontinuation of tobacco, alcohol, and illicit drug use; discontinuance and avoidance of any medications that may be considered teratogenic; starting folic acid, calcium, and iron supplements; proper nutrition; and testing for STIs. Especially in younger adolescents, the possibility of **coercive sex** (see Chapter 119) should be considered and appropriate social work/legal referrals made if abuse has occurred, although most pregnancies are not a result of coercive sex. Patients who elect to continue their pregnancies should be referred as soon as possible to an adolescent-friendly obstetric provider.

CHARACTERISTICS OF TEEN PARENTS

Young women who become parents as teenagers often come from economically disadvantaged families. Although birthrates among African-American and Hispanic teens have decreased in the past 2 decades, their rates are more than double those for non-Hispanic whites. Parenting teens frequently have poor school performance prior to becoming pregnant, and they often have a family history of low educational attainment. Learning disabilities are not uncommon. Teen mothers frequently come from single-parent families where their own mother gave birth during adolescence. A large majority (84%) of teen mothers have a baby outside of marriage. They may view pregnancy as having a positive social value and as not interfering with their long-term goals.

Teenage men who become fathers as adolescents also have poorer educational achievement than their age-matched peers. They are more likely than peers to have been involved with illegal activities and with the use of illegal substances. Adult men who father the children of teen mothers are poorer and educationally less advanced than their age-matched peers and tend to be 2-3 yr older than the mother; any combination of age differences may exist. Younger teen mothers are more likely to have a greater age difference between themselves and the father of their child, raising the issue of coercive sex or statutory rape (see Chapter 119).

Male partners have a significant influence on the young woman's decision/desire to become pregnant and to parent her child. Sensitively and appropriately including the male partner in discussions of family planning, contraception, and pregnancy options may be a useful strategy in improving outcomes for all. This can only be successful if the young female patient is willing to have her partner involved in such discussions.

MEDICAL COMPLICATIONS OF MOTHERS AND BABIES

Although pregnant teens are at higher-than-average risk for some complications of pregnancy, most teenagers have pregnancies that are without major medical complications, delivering healthy infants. The miscarriage/stillbirth risk for adolescents is estimated at 15-20%. In the United States, elective pregnancy termination rates peaked from 1985-1988 at 41-46%, decreasing since then to approximately 30% in 2008. As expected, teen mothers have low rates of age-related chronic disease (diabetes or hypertension) that might affect the outcomes of a pregnancy. They also have lower rates of twin pregnancies than older women. They tolerate childbirth well with few operative interventions. However, as compared with 20-39 yr old mothers, teens have higher incidences of low birthweight infants, preterm infants, neonatal deaths, passage of moderate to heavy fetal meconium during parturition, and infant deaths within 1 yr after birth. The highest rates of these poor outcomes occur in the youngest and most economically deprived mothers. Gastroschisis, although very rare, has a markedly higher incidence in infants of teen mothers for reasons that are unclear. Teen mothers also have higher rates of anemia, pregnancy-associated hypertension, and eclampsia, with the youngest teens having rates of pregnancy-associated hypertension higher than the rates of women in their 20s and 30s. The youngest teens also have a higher incidence of poor weight gain (<16 lb) during their pregnancy. This correlates with a decrease in the birth weights of their infants. Poor maternal weight gain also has correlated strongly with teens' late entrance into prenatal care and with inadequate utilization of prenatal care. Sexually active teens have higher rates of STIs than older sexually active women.

Globally, many young women who become pregnant have been exposed to violence or abuse in some form during their lives. There is some evidence that teenage women have the highest rates of **violence** during pregnancy of any group. Violence has been associated with injuries and death as well as preterm births, low birthweight, bleeding, substance abuse, and late entrance into prenatal care. An analysis of the Pregnancy Mortality Surveillance System indicates that in the United States from 1991 to 1999, homicide was the second leading cause of injury-related deaths in pregnant and postpartum women. Women ages 19 yr and younger had the highest pregnancy-related homicide rate (see Chapter 113).

Ectopic pregnancy occurs in 1-2% of conceptions and is more common in women with a previous history of an ectopic pregnancy, pelvic inflammatory disease, prior appendicitis, infertility, in utero exposure to diethylstilbestrol, and possibly the presence of an intrauterine contraceptive device. Most ectopic pregnancies are in the fallopian tube (tubal pregnancy). Manifestations include vaginal spotting after a missed menstrual period that may progress to more intense vaginal bleeding (which may be suggestive of a spontaneous abortion); vaginal bleeding is absent in 10-20%. Abdominal pain is associated with distention of the fallopian tube; tubal rupture results in more intense pain, hemorrhagic shock, and peritonitis. Some women have nonspecific abdominal complaints and are misdiagnosed with gastroenteritis. Cervical motion and adnexal tenderness (and adnexal mass) may be present. Transvaginal sonography (not transabdominal) is the diagnostic test of choice to detect an ectopic pregnancy and reveals an adnexal mass and no uterine pregnancy. Nonetheless, some women will have pregnancy of unknown location by transvaginal sonography; approximately 20% of these will have an ectopic pregnancy. Measurement of sensitive quantitative serum βhCG levels together with transvaginal sonography has value in diagnosing an ectopic pregnancy. If the initial βhCG is above the discriminatory zone (level at which one expects an intrauterine pregnancy) but on transvaginal sonography there is no intrauterine pregnancy, there may be an ectopic pregnancy or an abnormal uterine pregnancy. In addition, if the βhCG is below the discriminatory level (usually <3000 mIU/mL) with no definitive diagnosis by sonography, serial βhCG testing should be performed every 48 hr. In a normal uterine pregnancy, βhCG levels should increase approximately 50% every 48 hr; declining levels may suggest a miscarriage or an ectopic pregnancy. Some would perform a dilation and curettage and check for products of conception or follow serial βhCG levels. If there are no products of conception or if βhCG levels plateau or increase, an ectopic pregnancy is present. Treatment of unstable or advanced patients is usually by laparoscopic surgery or by laparotomy. Because of early detection, many patients remain stable (unruptured). Stable patients with an unruptured ectopic pregnancy may be treated with single-, or more often multiple-, dose methotrexate to induce abortion. Contraindications to methotrexate in a stable patient include size of the ectopic mass (>3.5 cm) and embryonic cardiac motion.

Prematurity and low birthweight increase the perinatal morbidity and mortality for infants of teen mothers. These infants also have higher-than-average rates of sudden infant death syndrome (see Chapter 375), possibly because of less use of the supine sleep position, and are at higher risk of both intentional and unintentional injury (see Chapter 40). One study shows the risk of homicide to be 9-10 times

Table 118-2 2012 American Academy of Pediatrics Clinical Guidelines: Care of Adolescent Parents and Their Children

Create a medical home for adolescent parents and their children	Involve both adolescent mothers and coparenting father Emphasize anticipatory guidance, parenting, and basic child care–giving skills, especially for teen dads
Provide comprehensive, multidisciplinary care	Access community resources such as special Supplemental Nutrition Program for Women, Infants, and Children Provide medical and developmental services to low-income parents and children Facilitate coordination of services
Contraceptive counseling	Emphasize condom use Encourage long-acting contraceptive methods
Encourage breastfeeding	Support breastfeeding in home, work, and school settings
Encourage high school completion	
Assess risk of domestic violence	
Encourage adolescent parenting	Work with other involved adults such as grandparents to encourage developmental growth of adolescent as parent as well as optimize infant developmental outcomes
Adapt counseling to developmental level of adolescent	Utilize school-, home-, and office-based interventions Consider use of support groups
Awareness and monitoring of developmental progression of infant and adolescent parent	Advocate for high-quality community resources for adolescents, including developmental resources, child care, and parenting classes Facilitate access to Head Start and education resources for individuals with disability

Data from Pinzon JL, Jones VF, Committee on Adolescence and Committee on Early Childhood, Care of adolescent parents and their children, Pediatrics 130(6):e1743–1755, 2012.

higher if a child born to a teen mother is not the mother's firstborn as compared with the risk to a firstborn of a woman age 25 yr or older. The perpetrator is often the father, stepfather, or boyfriend of the mother.

After childbirth, **depressive symptoms** may occur in as many as 50% of teenaged mothers. Depression seems to be greater with additional social stressors and with decreased social supports. Support from the infant's father and the teen's mother seems to be especially important in preventing depression. Pediatricians who care for parenting teens should be sensitive to the possibility of depression, as well as to inflicted injury to mother or child; appropriate diagnosis, treatment, and referral to mental health or social agencies should be offered and facilitated.

PSYCHOSOCIAL OUTCOMES/RISKS FOR MOTHER AND CHILD

Educational

Teenage mothers often do poorly in school and drop out prior to becoming pregnant. After childbirth many choose to defer completion of their education for some time. High school graduation or an equivalency degree is generally achieved eventually. Mothers who have given birth as teens generally remain 2 yr behind their age-matched peers in formal educational attainment at least through their 3rd decade. Maternal lack of education limits the income of many of these young families (see Chapter 1).

Substance Use

See also Chapter 114.

Teenagers who abuse drugs, alcohol, and tobacco have higher pregnancy rates than their peers. Most substance-abusing mothers appear to decrease or stop their substance use while pregnant. Use begins to increase again about 6 mo postpartum, complicating the parenting process and the mother's return to school.

Repeat Pregnancy

In the United States, approximately 20% of all births to adolescent mothers (age 15-19 yr) are second order or higher. Prenatal care is begun even later with a second pregnancy, and the second infant is at higher risk of poor outcome than the first birth. Mothers at risk of early repeat pregnancy include those who do not initiate long-acting contraceptives after the index birth, those who do not return to school within 6 mo of the index birth, those who are married or living with the infant's father, and those who are no longer involved with the baby's father and who meet a new boyfriend who wants to have a child. To reduce repeat pregnancy rates in these teens, programs must be tailored for this population, preferably offering comprehensive healthcare for both the young mother and her child (Table 118-2). Healthcare providers should remember to provide positive reinforcement for teen parenting successes (i.e., compliment teen parents when they are doing a good job).

Behavioral, Educational, and Social Outcomes of Children Born to Teen Mothers

Many children born to teen mothers have behavioral problems that may be seen as early as the preschool period. Many drop out of school early (33%), become adolescent parents (25%), or, if male, are incarcerated (16%). Explanations for these poor outcomes include poverty, parental learning difficulties, negative parenting styles of teen parents, maternal depression, parental immaturity, poor parental modeling, social stress, exposure to surrounding violence, and conflicts with grandparents, especially grandmothers. Continued positive paternal involvement throughout the child's life may be somewhat protective against negative outcomes. Many of these poor outcomes appear to be attributable to the socioeconomic/demographic situation in which the teen pregnancy has occurred, not solely to maternal age. Even when socioeconomic status and demographics are controlled, infants of teen mothers have lower achievement scores, lower high school graduation rates, increased risk of teen births themselves, and, at least in Illinois (where records include age of birth mother), a higher probability of abuse and neglect.

Comprehensive programs focused on supporting adolescent mothers and infants utilizing life skills training, medical care, and psychosocial support demonstrate higher employment rates, higher income, and less welfare dependency in adolescents exposed to the programs.

Prevention of Teen Pregnancies

Adolescent pregnancy is a multifaceted problem that requires multifactorial solutions. The provision of contraception and education about fertility risk from the primary care physician is important, but

Table 118-3	Common Components of Most Successful Evidence-Based Programs to Prevent Teen Pregnancy

- Information is provided about the benefits of abstinence.
- Information is provided about contraception for those who are already sexually active.
- Information is provided about the signs and symptoms of STIs and how to prevent STIs.
- Interactive sessions on peer pressure are presented.
- Teenagers are taught communication skills.
- Programs are tailored to meet the needs of specific groups of young people (young men or young women; cultural groups; younger or older teens; etc.).

Adapted from: Suellentrop K: What works 2011-2012: Curriculum-based programs that help prevent teen pregnancy. The National Campaign to Prevent Teen and Unplanned Pregnancy: Washington, DC. http://www.c-hubonline.org/sites/default/files/resources/main/What_Works_0.pdf.

insufficient to address the problem fully. Family and community involvement are essential elements for teen pregnancy prevention. Strategies for primary prevention (preventing first births) are different from the strategies needed for secondary prevention (preventing second or more births). Over the last 30 yr, many models of teen pregnancy prevention programs have been implemented and evaluated. Table 118-3 lists the common components of many successful evidence-based programs.

Abstinence-only sexual education aims to teach adolescents to wait until marriage to initiate sexual activity but, unfortunately, does not mention contraception. Abstinence education is sometimes coupled with "virginity pledges" in which teenagers pledge to remain abstinent until they marry. Other educational programs emphasize HIV and STI prevention and in the process prevent pregnancy, whereas others include both abstinence and contraception in their curricula. Sex education and teaching about contraception do not lead to an increase in sexual activity. Teenagers who participate in programs that have comprehensive sex education components generally have lower rates of pregnancy than those teenagers who have exposure solely to abstinence-only programs or no sex education at all.

In many U.S. communities, programs that engage youth in community service and/or combine sex education and youth development are also successful in deterring pregnancy. Programs vary in their sites of service from schools, to social agencies, to health clinics, to youth organizations, to churches. Programs must be tailored to the cultural background, ethnicity, age group, and gender of the group being targeted for the prevention services.

Secondary prevention programs are fewer in number. In the United States, some communities have tried to "pay" young mothers to not become pregnant again, but these efforts have not always been fruitful. Home visiting by nurses has been successful in some areas, and many communities have developed "Teen Tot" Clinics that provide a "one-stop shopping model" for healthcare for both the teen mother and the baby in the same site at the same time. Both of these latter types of programs have reported some successes.

In the practice setting, the identification of the sexually active adolescent through a confidential clinical interview is a first step in pregnancy prevention. The primary care physician should provide the teenager with factual information in a nonjudgmental manner and then guide the teenager in the decision-making process of choosing a contraceptive (see Chapter 117). The practice setting is an ideal setting to support the teenager who chooses to remain abstinent. When a teenager does become pregnant and requires prenatal care services, healthcare providers should remember that the pregnant teenager is an adolescent who has become pregnant, not a pregnant woman who happens to be an adolescent.

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Chapter 119

Adolescent Rape

Christine E. Barron and Marianne E. Felice

Rape is an act of violence, not an act of sex. Rape is coercive sexual intercourse involving physical force or psychological manipulation of a female or a male. Rape is defined as penetration of any genital, oral, or anal orifice by a part of the assailant's body or any object.

EPIDEMIOLOGY

Exact figures on the incidence of rape are unavailable because many rapes are not reported. Females exceed males as reported rape victims by 8 : 1 to 10 : 1, but male rape may be more underreported than female rape. In the United States, the annual rates of sexual victimization per 1,000 persons were reported in 2010 by the U.S. Department of Justice, National Crime Victimization Survey to be 4.1 for ages 12-17 yr, and 3.7 for ages 18-34 yr. The highest annual rate of sexual victimization has continued to be among 16-19 yr old adolescents. Rape occurs worldwide and is especially prevalent in war and armed conflicts. The World Health Organization estimates that rape and domestic violence are responsible for 5-16% of healthy years of life lost by females of reproductive age.

Female adolescents and young adults account for the highest rates of rape compared to any other age group. The normal developmental growth tasks of adolescence may contribute to this vulnerability in the following ways: (1) the emergence of independence from parents and the establishment of relationships outside the family may expose adolescents to environments with which they are unfamiliar and situations that they are unprepared to handle; (2) dating and becoming comfortable with one's sexuality may result in activities that are unwanted, but the adolescent is too inexperienced to stop the unwanted actions; and (3) young adolescents may be naïve and more trusting than they should be (see Chapter 110). Many teens are computer competent, which gives sexual perpetrators access to unsuspecting vulnerable populations who were previously beyond their reach. Chat rooms and online dating sites represent a major risk for adolescents, resulting in correspondence with individuals unknown to them or protective family members, while simultaneously providing a false sense of security because of remote electronic communications. A determined perpetrator can obtain specific information to identify the adolescent and arrange for a meeting that is primed for sexual victimization.

Some adolescents are at higher risk of being victims of rape than others (Table 119-1).

TYPES OF RAPE

Acquaintance rape (by a person known to the victim) is the most common form of rape for victims 16-24 yr of age. The acquaintance may be a neighbor, classmate, or friend of the family. The victim–assailant relationship may cause conflicting loyalties in families, and the teen's report may be received with disbelief and/or skepticism by the teen's family. Adolescent acquaintance rape differs from adult acquaintance rape because weapons are less-often used, and victims are less likely to sustain physical injuries. Victims of acquaintance rape are also more likely to delay seeking medical care, may never report the crime (males greater than females), and are less likely to proceed with criminal prosecution even after reporting the incident(s).

Date rape (by a person dating the victim) is often drug facilitated and is prevalent in adolescent populations. Date rape drugs are pharmaceuticals administered in a clandestine manner to potential victims. γ-Hydroxybutyric acid (GHB), flunitrazepam (Rohypnol), and ketamine hydrochloride are the leading agents used for these illegal purposes, but may also include alcohol, benzodiazepines, stimulants, barbiturates, opiates, and other drugs (see Chapter 114). The pharmacologic properties of these drugs make them suitable for this use as they have simple modes of administration, are easily concealed

Table 119-1	Adolescents at High Risk of Rape Victimization
MALE AND FEMALE ADOLESCENTS	
Drug and alcohol users	
Runaways	
Those with intellectual disability or developmental delay	
Street youths	
Transgender youth	
Youths with a parental history of sexual abuse	
PRIMARILY FEMALES	
Survivors of prior sexual assault	
Newcomers to a town or college	
PRIMARILY MALES	
Those in institutionalized settings (detention centers, prison)	
Young male homosexuals	

(colorless, odorless, tasteless), have rapid onsets of action with resulting induction of anterograde amnesia, and have rapid eliminations as a result of short half-lives. Detection of these drugs requires a high index of suspicion and medical evaluation within 8-12 hr, prompting specific testing because routine toxicology screening is insufficient.

Date rape victims are often new to a specific environment (college freshman, newcomer to a town) and lack strong social support. Victims may not be assertive in establishing boundaries or limits with their dates and may be intoxicated when the incident takes place. The date rape assailant may engage in more sexual activities than other men his age and often has a history of aggressive behavior toward women. He may interpret passivity as assent and deny the charge of coercion or force; he may also be intoxicated at the time of the assault.

A date rape victim often experiences long-term issues of trust, self-blame, and guilt. She may lose confidence in her judgment concerning men in the future. She is nearly always ashamed of the incident and is less likely to report the rape. She is reluctant to talk about the rape to family, friends, or a counselor and may never heal from the psychological scars that ensue.

Male rape generally refers to same-sex rape of male teens by other males. Specific subgroups of young men are at high risk of being victims of rape (see Table 119-1). Male rape is most prevalent within institutional settings. Male rape that occurs outside of institutional settings typically involves coercion of the male teen by someone considered an authority figure, either male or female. Male rape victims often experience conflicted sexual identity about whether or not they are homosexual. Issues of loss of control and powerlessness are particularly bothersome for male rape victims, and these young men commonly have symptoms of anxiety, depression, sleep disturbance, and suicidal ideation. Males are less likely than females to report rape and less likely to seek professional help.

Gang rape usually occurs when a group of young men rape a solitary female victim. This type of rape may be part of a ritualistic activity or rite of passage for some male group (gangs, college fraternity) or be displaced rage on the part of the assailants.

Female victims of gang rape may find it difficult to return to the environment in which the rape occurred for fear of confrontation with the assailants (college setting or place of employment) and may insist on moving away from the locale entirely.

Statutory rape refers to sexual activity between an adult and an adolescent under the age of legal consent, as defined by individual state law. Statutory rape laws are based on the premise that below a certain age, an individual is not legally capable of giving consent to engage in sexual intercourse. In some states in the United States, statutory rape laws apply to sexual contact or intercourse occurring between a minor and another individual with a specific age difference even when both are minors and both assert that the sexual act was voluntary (an 18 yr old male who has sexual intercourse with a 14 yr old female). The intent of such laws is to protect youths from being victimized, but they may inadvertently lead a teenager to withhold pertinent sexual information from a clinician for fear that her sexual partner will be reported to the law. A clinician must be familiar with the laws of the state or province in which the clinician is practicing medicine.

Stranger rape occurs less frequently within the adolescent population and is most similar to adult rape. Such rapes frequently occur with an abduction, use of weapons, and increased risk of physical injuries. These rapes are more likely to be reported and prosecuted.

CLINICAL MANIFESTATIONS

The adolescent's acute presentation following a rape may vary considerably, from histrionics to near-mute withdrawal. Even if they do not seem to be afraid, most victims are extremely fearful and very anxious about the incident, the rape report, examination, and the entire process including potential repercussions. Because adolescents are between the developmental lines of childhood and adulthood, their responses to rape may have elements of both child and adult behaviors. Many teens, particularly young adolescents, may experience some level of cognitive disorganization.

Adolescents may be reluctant to report rape for a variety of reasons, including self-blame, fear, embarrassment, or in the circumstances of drug-facilitated rape, uncertainty of event details. Adolescent victims, unlike child victims who elicit sympathy and support, are often faced with intense scrutiny regarding their credibility and inappropriately misplaced societal blame for the assault. This view is baseless and should not be used during an evaluation of any teenage victim, including acquaintance rape.

When adolescents do not report a rape, they may present at a future date with symptoms of posttraumatic stress disorder (see Chapters 25 and 39), such as sleep disturbances, nightmares, mood swings, and flashbacks. Other teens may present with psychosomatic complaints or difficulties with schoolwork; all adolescents should be screened for the possibility of sexual abuse at nearly all health examination visits.

INTERVIEW AND PHYSICAL EXAMINATION

Although many teens delay seeking medical care, others present to a medical facility within 72 hr (or up to 96 hr depending on the protocol used) of the rape, at which time forensic evidence collection should be completed. Experienced clinicians with training and knowledge of forensic evidence collection and medical-legal procedures should complete the rape evaluation or supervise the evaluation when possible.

The clinician's responsibilities are to provide support, to obtain the history in a nonjudgmental manner, to conduct a complete examination without retraumatizing the victim, and to collect forensic evidence. The clinician must complete laboratory testing, administer prophylaxis treatment for sexually transmitted infections (STIs) and emergency contraception, arrange for counseling services, and file a report to appropriate authorities. It is not the clinician's responsibility to decide whether a rape has occurred; the legal system will make that determination.

Ideally, a clinician trained in forensic interviewing should obtain the history. In all cases, the history should be obtained by asking *only* open-ended questions to obtain information about: (1) what happened; (2) where did it happen; (3) when did it happen; and (4) who did it. After obtaining a concise history including details of the physical contact that occurred between the victim and the assailant, the clinician should conduct a thorough and complete physical examination and document all injuries. Clinicians should provide sensitive, nonjudgmental support during the entire evaluation, as the adolescent victim has experienced a major trauma and is susceptible to retraumatization during this process. Each component of the evaluation should be explained in detail to the victim, allowing the adolescent as much control as possible, including refusal to complete any part or all of the forensic evidence collection process. It is often useful to permit a trusted supportive person, such as a family member, friend or rape crisis advocate, to be present during the evaluation if that is the adolescent's wish.

The examining clinician should be familiar with the **forensic evidence collection** kit prior to initiating the examination. In the United States, each state's forensic evidence kit is different, but most include

Table 119-2 Laboratory Data for Evaluation of Rape Victims

WITHIN 8-12 HR (IF INDICATED BY HISTORY)
Urine and blood for date rape drugs (GHB, Rohypnol, and ketamine)
Comprehensive toxicology screen (for other classes of drugs)
WITHIN 72 HR (OR UP TO 96 HR DEPENDING ON THE PROTOCOL USED)
Forensic evidence kit
Urinalysis
Pregnancy test
Hepatitis B screen
Syphilis (rapid plasma reagin [RPR], Venereal Disease Research Laboratory [VDRL])
Herpes simplex virus titers (I and II)
HIV
Wet mount for the detection of spermatozoa, *Trichomonas vaginalis*, and bacterial vaginosis
Cultures obtained based on history of physical contact for:
Oropharynx: *Neisseria gonorrhoeae*
Rectal: *N. gonorrhoeae* and *Chlamydia*
Urethral (male): *N. gonorrhoeae* and *Chlamydia*
Endocervical (female): *N. gonorrhoeae* and *Chlamydia*

Table 119-3 Prophylaxis Treatment for Rape Victims

*Neisseria gonorrhoeae**	Ceftriaxone 250 mg IM × 1 dose If positive for gonorrhea, treatment is: Ceftriaxone 20 mg IM × 1 dose **plus** Azithromycin 1 g PO × 1 dose *or* doxycycline 10 mg PO bid × 7 days
*Chlamydia trachomatis**	Azithromycin 1 g PO × 1 dose or Doxycycline 100 mg PO bid × 7 days
Trichomonas vaginalis and bacterial vaginosis*	Metronidazole 2 g PO × 1 dose
HIV†	Combivir 1 tab PO bid × 28 days or Truvada 1 tab PO qd x 28 days
Hepatitis B	Complete immunizations
Human papillomavirus	Complete immunizations
Emergency contraception‡	Ovral 2 tabs (0.05 mg ethinyl estradiol, 0.50 mg norgestrel) and 2nd dose in 12 hr Plan B 1 tab (0.75 mg levonorgestrel) and 2nd dose in 12 hr, or both pills together as 1 dose

*Prophylaxis is recommended for all 3 STIs.

†HIV postexposure prophylaxis is provided for patients with penetration and when the assailant is known to be HIV-positive or at high risk because of a history of incarceration, intravenous drug use, or multiple sexual partners. If provided, follow-up must be arranged.

‡Provided for patients with negative urine pregnancy screen for patients receiving emergency contraception medication other than Plan B. In addition, provide antiemetic (Compazine, Zofran) for patients receiving emergency contraception medication other than Plan B.

some or all of the following components: forensic evidence of semen deposits detected by a fluorescent lamp with a wavelength near 490 nm (many Woods lamps are inadequate); swabs of bite mark impressions to collect genetic markers (DNA, ABO group); swabs of any penetrated orifice; and documentation of acute cutaneous injuries using body diagram charts and/or photographs with visible standard measurements. Areas of restraint should be carefully inspected for injuries; these areas include extremities, neck, and the inner aspect of the oral mucosa where a dentition impression may be seen.

The genital examination of a female rape victim should be undertaken with the patient in the lithotomy position. The genital examination of a male rape victim should be undertaken with the patient in supine position. The clinician's examination should include careful inspection of the entire pelvic, genital, and perianal areas. The clinician should document any acute injuries such as edema, erythema, petechiae, hemorrhage, or tearing. Aqueous solution of toluidine blue (1%), which adheres to nucleated cells, may be used during the acute examination to improve visualization of microtrauma in the perianal area. Additionally, a colposcope may be used to provide magnification and photodocumentation of injuries.

LABORATORY DATA

The forensic evidence kit should be completed when clinically indicated and if the patient is evaluated within 72-92 hr of sexual assault. Table 119-2 lists additional laboratory studies required during initial evaluation. Follow-up evaluations should be scheduled to repeat these laboratory studies.

TREATMENT

Medical treatment includes prophylaxis treatment for STIs (see Chapter 120) and emergency contraception (see Chapter 117). The Centers for Disease Control and Prevention estimates that the risk for acquiring STIs following a sexual assault in adults is 6-12% for *Neisseria gonorrhoeae,* 4-17% for *Chlamydia trachomatis,* and 0.5-3.0% for syphilis. Antimicrobial prophylaxis is recommended for adolescent rape victims because of the risk of acquiring an STI and the risk of pelvic inflammatory disease (Table 119-3). HIV postexposure prophylaxis should be considered and consultation with an infectious disease specialist sought if higher transmission risk factors are identified (e.g., knowing that the perpetrator is HIV-positive, significant mucosal injury of the victim) to prescribe a triple antiretroviral regimen. Clinicians should review the importance for patient's compliance with medical and psychological treatment and follow-up.

At the time of presentation, the clinician should address the need for follow-up care, including psychological counseling. Adolescent victims are at increased risk of posttraumatic stress disorder, depression, self-abusive behaviors, suicidal ideation, delinquency, substance abuse, eating disorders, and sexual revictimization. It is important for the adolescent victim and parents to understand the value of timely counseling services to decrease these potential long-term sequelae. Counseling services should be arranged during the initial evaluation, with follow-up arranged with the primary care physician to improve compliance. Counseling services for family members of the victim may improve their ability to provide appropriate support to the adolescent victim. Caution parents not to use the assault as a validation of their parental guidance, as it will only serve to place blame inappropriately on the adolescent victim.

PREVENTION

Primary prevention may be accomplished through education of preadolescents and adolescents on the issues of rape, healthy relationships, Internet dangers, and drug-facilitated rape. Prevention messages should be targeted to both males and females at high schools and colleges. Particular emphasis on prevention efforts during college orientation is highly recommended. High-risk situations that may increase the likelihood of a sexual assault (use of drugs or alcohol) should be discouraged. **Secondary prevention** includes informing adolescents of the benefits of timely medical evaluations when rape has occurred. Individual clinicians should ask adolescents about past experiences of forced and unwanted sexual behaviors and offer help in dealing with those experiences. The importance of prevention cannot be overstated because adolescents are disproportionately affected by rape and they are particularly vulnerable to long-term consequences.

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Chapter 120

Sexually Transmitted Infections

Gale R. Burstein

Age-specific rates of many sexually transmitted infections (STIs) are highest among sexually experienced adolescents and young adults, after controlling for sexual activity. Although some STI pathogens present as STI syndromes with a specific constellation of symptoms, most are asymptomatic and only detected by a laboratory test. The approach to prevention and control of these infections lies in education, screening, and early diagnosis and treatment.

ETIOLOGY

Any adolescent who has had oral, vaginal, or anal sexual intercourse is at-risk for acquiring an STI. Not all adolescents are at equal risk; physical, behavioral, and social factors contribute to the adolescent's higher risk (Table 120-1). Adolescents who initiate sex at a younger age, youth residing in detention facilities, youth attending sexually transmitted diseases clinics, young men having sex with men, and youth who are injecting-drug users are at higher risk for STIs. Risky behaviors, such as sex with multiple concurrent partners or multiple sequential partners of limited duration, failure to use barrier protection consistently and correctly, and increased biologic susceptibility to infection, also contribute to risk. Although all 50 states and the District of Columbia explicitly allow minors to consent for their own sexual health services, many adolescents encounter multiple obstacles to accessing this care. Adolescents who are victims of sexual assault may not consider themselves "sexually active," given the context of the encounter, and need reassurance, protection, and appropriate intervention when these circumstances are uncovered (see Chapter 119).

EPIDEMIOLOGY

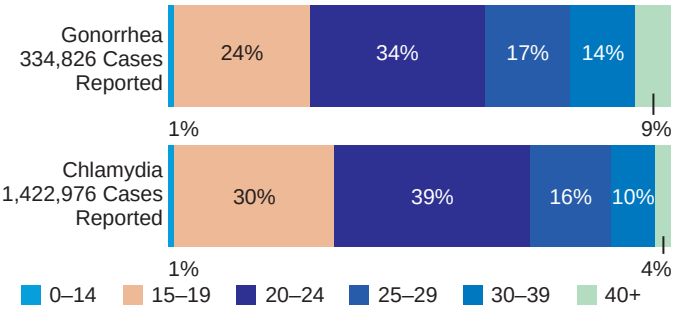
STI prevalence varies by age, gender, and race/ethnicity. In the United States, although adolescents and young adults ages 15-24 yr represent 25% of the sexually experienced population, this age group accounts for nearly 50% of all incident STIs each year. Adolescents and young adults <25 yr of age have the highest reported prevalence of gonorrheal (see Chapter 192) and chlamydial (see Chapter 226) infection; among females and males, rates are highest in the 15-24 yr old age groups (Fig. 120-1). In 2012, females 20-24 yr of age had the highest reported chlamydia rate (3,696 per 100,000 population), followed by females 15-19 yr of age (3,293 per 100,000 population). The reported 2012 chlamydia rate for 15-19 yr old females was more than 4 times higher than for 15-19 yr old males. Chlamydia is common among all races and ethnic groups; Blacks, Native American/Alaska Native, and Hispanic females are disproportionately affected. In 2011, non-Hispanic black females 20-24 yr of age had the highest chlamydia rate of any group (7,863), followed by black females 15-19 yr of age (7,719). Data from the 2007-2008 National Health and Nutrition Examination Survey estimated the prevalence of chlamydia among the U.S. population was highest among African-Americans (Fig. 120-2).

Reported rates of other bacterial STIs are also high among adolescents and young adults. In 2012, 20-24 yr old females had the highest (579 per 100,000 population) and 15-19 yr old females had the second highest gonorrhea rates (521 per 100,000 population) compared to any other age/sex group (see Chapter 192). Following a period of decreasing gonorrhea rates among 20-24 yr old, rates have increased for the past 3 yr. Primary and secondary syphilis rates among 15-19 yr old

Table 120-1 Circumstances Contributing to Adolescents' Susceptibility to Sexually Transmitted Infections

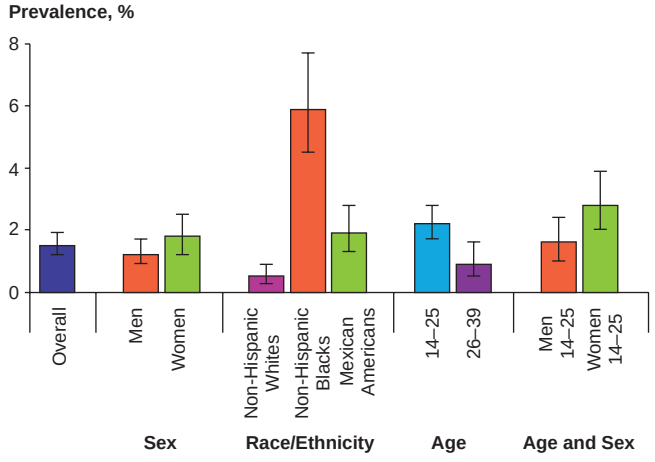
PHYSICAL
Younger age at puberty
Cervical ectopy
Smaller introitus leading to traumatic sex
Asymptomatic nature of sexually transmitted infection
Uncircumcised penis
BEHAVIOR LIMITED BY COGNITIVE STAGE OF DEVELOPMENT
Early adolescence: have not developed ability to think abstractly
Middle adolescence: develop belief of uniqueness and invulnerability
SOCIAL FACTORS
Poverty
Limited access to "adolescent friendly" healthcare services
Adolescent health-seeking behaviors (forgoing care because of confidentiality concerns or denial of health problem)
Sexual abuse and violence
Homelessness
Young adolescent females with older male partners

From Shafii T, Burstein G: An overview of sexually transmitted infections among adolescents, Adolesc Med Clin *15:207, 2004.*



Percentages may not equal 100 because ages were unknown for a small number of cases.

Figure 120-1 Most reported chlamydia and gonorrhea infections occur among 15-24-year-olds. *(Adapted from Centers for Disease Control and Prevention: Reported STD in the United States. http://www.cdc.gov/nchhstp/newsroom/docs/STD-Trends-508.pdf.)*



NOTE: Error bars indicate 95% confidence intervals.

Figure 120-2 Chlamydia–prevalence among persons 14-39 yr of age by sex and survey cycle, National Health and Nutrition Examination Survey, 1999-2008. *(Adapted from Centers for Disease Control and Prevention: Sexually Transmitted Disease Surveillance 2012. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6338a3.htm.)*

females have decreased annually since 2009 from 3.3 cases per 100,000 population to 2.3 per 100,000 population in 2012 (see Chapter 218). Rates among females have been the highest each year in the 20-24 yr age group (3.9 cases per 100,000 population in 2012). Primary and secondary syphilis rates among 15-19 yr old males are much lower than those in older males, although rates among males age 20-24 yr have increased consecutively since 2002, from 5.2 cases per 100,000 males to 23.4 cases in 2011. Males age 20-24 yr also have had the highest rate of primary and secondary syphilis among males of any age group since 2008. Pelvic inflammatory disease (PID) rates are highest in females age 15-24 yr when compared to older women.

Adolescents also suffer from a large burden of viral STIs. Young people in the United States are at persistent risk for HIV infection (see Chapter 278). In 2009, youths age 13-24 yr, who represented 21% of the U.S. population, comprised 7% of persons living with HIV. In 2010, 26% of the estimated 47,500 new HIV infections were among 13-24 yr olds. Of those new infections, 57% were among blacks, 20% among Hispanic/Latinos, and 20% among whites. Nearly 75% of the 12,200 new HIV infections among youths were attributable to male-to-male sexual contact. Only a low percentage of youths have been tested for HIV, and 60% of youths with HIV are unaware of their infection.

The STI with the highest estimated incidence in the United States is human papillomavirus (HPV). The 2003-2006 National Health and Nutrition Examination Survey (NHANES) found a third of females age 14-24 yr old were actively infected with HPV. The highest HPV infection prevalence was among females age 20-24 yr (54%; 95% confidence interval [CI], 46-62%; see Chapter 266). Although HPV infection is common, studies suggest approximately 90% of infections clear within 2 yr.

Herpes simplex virus-2 (HSV-2) is the most prevalent viral STI (see Chapter 252). HSV-2 prevalence rates among adolescents in the United States and young adults appear to be decreasing. The 2005-2008 NHANES estimated that 1.4% (95% CI, 1.0-2.0) of adolescents age 14-19 yr are infected with HSV-2, which is about a 76% decrease observed from the 1988-1994 NHANES and 10.5% (95% CI, 9.0-12.3) of 20-29 yr olds are HSV-2 seropositive, which is a 39% decrease compared to the 1988-1994 NHANES.

Pathogenesis

During puberty, increasing levels of estrogen cause the vaginal epithelium to thicken and cornify and the cellular glycogen content to rise, the latter causing the vaginal pH to fall. These changes increase the resistance of the vaginal epithelium to penetration by certain organisms (including *Neisseria gonorrhoeae*) and increase the susceptibility to others (*Candida albicans* and *Trichomonas;* see Chapter 284). The transformation of the vaginal cells leaves columnar cells on the ectocervix, forming a border of the 2 cell types on the ectocervix, known as the squamocolumnar junction. The appearance is referred to as **ectopy** (Fig. 120-3). With maturation, this tissue involutes. Prior to involution, it represents a unique vulnerability to infection for adolescent females. A 15 yr old sexually active female with endocervical colonization has a 1:8 chance of developing PID compared to the 1:80 chance for a 24 yr old. As a result of these physiologic changes, gonococcal infection becomes primarily cervical and susceptibility to ascending infection is greatest during menses, when the pH is 6.8-7.0. The association of early sexual debut and younger gynecologic age with increased risk of STIs supports this explanation of the pathogenesis of infection in young adolescents.

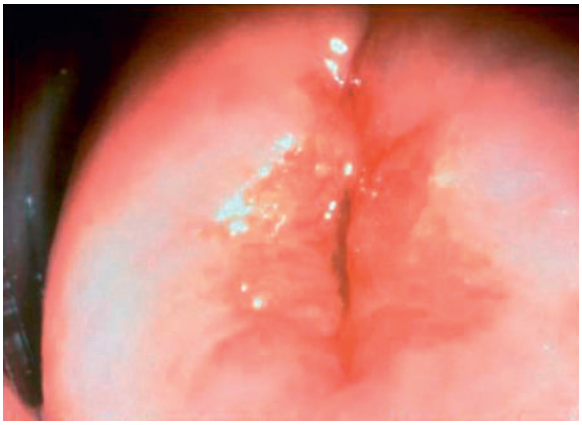


Figure 120-3 Cervical ectopy. *(From the Seattle STD/HIV Prevention Training Center at the University of Washington, Claire E. Stevens.)*

Sexually Transmitted Infection Screening

Early detection and treatment are the primary STI control strategies. Some of the most common STIs in adolescents, including HPV, HSV, chlamydia, and gonorrhea, are usually asymptomatic and if undetected can be spread inadvertently by the infected host. Screening initiatives for chlamydial infections have demonstrated reductions in PID cases by up to 40%. Although federal and professional medical organizations recommend annual chlamydia screening for sexually active females 25 yr and younger, according to the National Center for Quality Assurance, in 2012 approximately 40% of commercially insured and 54% of Medicaid insured 16-20 yr old sexually active females were tested for chlamydia during the previous year. The lack of a dialog about STIs or the provision of STI services at annual preventive service visits to adolescents who are sexually experienced are missed opportunities for screening and education. Comprehensive, confidential, reproductive health services, including STI screening, should be offered to all sexually experienced adolescents (Table 120-2).

Definitions, Etiology, and Clinical Manifestations

STI syndromes are generally characterized by the location of the manifestation (vaginitis) or the type of lesion (genital ulcer). Certain constellations of presenting symptoms suggest the inclusion of a possible STI in the differential diagnosis.

Urethritis

Urethritis is an STI syndrome characterized by inflammation of the urethra, usually caused by an infectious etiology. Urethritis may present with urethral discharge, dysuria, urethral irritation, or meatal pruritus. Urgency, frequency of urination, erythema of the urethral meatus, and urethral pain or burning are less common clinical presentations. Approximately 30-50% of males are asymptomatic but may have signs of discharge on diagnosis. On examination, the classic finding is mucoid or purulent discharge from the urethral meatus (Fig. 120-4). If no discharge is evident on exam, providers may attempt to express discharge by applying gentle pressure to the urethra from the base distally to the meatus 3-4 times. *Chlamydia trachomatis* and *N. gonorrhoeae* are the most commonly identified pathogens. *Mycoplasma genitalium* has been associated with urethritis, but data supporting *Ureaplasma urealyticum* have been inconsistent. *Trichomonas vaginalis* can cause NGU, but the prevalence varies. HSV-1, HSV-2, and Epstein-Barr virus are also potential urethritis pathogens in some cases. Sensitive diagnostic *C. trachomatis* and *N. gonorrhoeae* tests are available for the evaluation of urethritis. However, other pathogens can be considered when NGU is not responsive to treatment, although commercial diagnostic tests are not available for males. Noninfectious causes of urethritis include urethral trauma or foreign body. Unlike in females, urinary tract infections are rare in males who have no genitourinary medical history. In the typical sexually active adolescent male, dysuria and urethral discharge suggest the presence of an STI unless proven otherwise.

Epididymitis

The inflammation of the epididymis in adolescent males is most often associated with an STI, most frequently *C. trachomatis* or *N. gonorrhoeae*. The presentation of unilateral scrotal swelling and tenderness, often accompanied by a hydrocele and palpable swelling of the epididymis, associated with the history of urethral discharge, constitute the presumptive diagnosis of epididymitis. Males who practice insertive

Table 120-2 Routine Laboratory Screening Recommendations for Sexually Transmitted Infections in Sexually Active Adolescents and Young Adults

Chlamydia trachomatis and *Neisseria gonorrhoeae* • Routinely screening for *C. trachomatis* of all sexually active females aged ≤25 yr is recommended annually • Consider screening for C. trachomatis of sexually active adolescent and young adult males annually who have a history of multiple partners in settings with high prevalence rates, such as jails or juvenile corrections facilities, national job training programs, STD clinics, high school clinics, or adolescent clinics • Routinely screening for *N. gonorrhoeae* of all sexually active females age <25 yr is recommended annually • Routinely screen sexually active adolescent and young adult MSM for rectal and urethral chlamydia and gonorrhea annually if they engage in receptive anal or insertive intercourse, respectively, and for routine gonorrhea if they engage in receptive oral sex. More frequent STD screening (i.e., at 3-6 mo intervals) is indicated for MSM who have multiple or anonymous partners or who have sex in conjunction with illicit drug use
HIV • HIV screening should be discussed and offered to all adolescents ≥15 yr in healthcare settings, unless identified at an earlier age with HIV risk factors
SYPHILIS • Syphilis screening should be offered to sexually active adolescents reporting risk factors • The majority of U.S. syphilis cases occurring among young MSM and many early syphilis cases are identified from correctional facilities • Providers should consult with their local health department regarding local syphilis prevalence and associated risk factors that are associated with syphilis acquisition
HEPATITIS C VIRUS • Screening adolescents for hepatitis C virus who report risk factors, i.e., injection drug use, MSM, received blood products or organ donation before 1992, received clotting factor concentrates before 1987, long-term hemodialysis, or high prevalence setting, i.e., correctional facilities or STD clinics

HAV, hepatitis A virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; MSM, men who have sex with men; STD, sexually transmitted diseases.

From Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014, MMWR *http://www.cdc.gov/std/treatment/update.htm*.

Figure 120-4 Gonococcal urethral discharge. *(From the Seattle STD/HIV Prevention Training Center at the University of Washington, Connie Celum and Walter Stamm.)*

anal intercourse are also vulnerable to *Escherichia coli* infection. Testicular torsion, a surgical emergency usually presenting with sudden onset of severe testicular pain, should be considered in the differential diagnosis (see Chapter 545). The evaluation for epididymitis should include obtaining evidence of urethral inflammation by physical exam, Gram stain of urethral secretions, urine leukocyte esterase test, or urine microscopy. A *C. trachomatis* and *N. gonorrhoeae* **nucleic acid amplification test (NAAT)** should be performed.

Vaginitis

Vaginitis is a superficial infection of the vaginal mucosa frequently presenting as a vaginal discharge, with or without vulvar involvement (see Chapter 549). **Bacterial vaginosis, vulvovaginal candidiasis**, and trichomoniasis are the predominant infections associated with vaginal discharge. Bacterial vaginosis is replacement of the normal H_2O_2–producing *Lactobacillus* sp. vaginal flora by an overgrowth of anaerobic microorganisms as well as *Gardnerella vaginalis, Ureaplasma*, and *Mycoplasma*. Although bacterial vaginosis is not categorized as an STI, sexual activity is associated with increased frequency of vaginosis. Vulvovaginal candidiasis, usually caused by *C. albicans*, can trigger vulvar pruritus, pain, swelling, and redness and dysuria. Findings on vaginal exam include vulvar edema, fissures, excoriations, or thick curdy vaginal discharge. Trichomoniasis is caused by the protozoan *T. vaginalis*. Infected females may present with symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation or may be diagnosed by screening an asymptomatic patient. Cervicitis can sometimes cause a vaginal discharge. Laboratory confirmation is recommended because clinical presentations may vary and patients may be infected with more than 1 pathogen.

Cervicitis

The inflammatory process in cervicitis involves the deeper structures in the mucous membrane of the cervix uteri. Vaginal discharge can be a manifestation of cervicitis, however, cervicitis frequently is asymptomatic, Patients also commonly present with complaints of irregular or postcoital bleeding. Two major diagnostic signs characterize cervicitis: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (e.g., swab sign, Fig. 120-5), commonly referred to as mucopurulent cervicitis or cervicitis, and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os signifying friability. Cervical changes associated with cervicitis must be distinguished from cervical ectopy in the younger adolescent to avoid the over diagnosis of inflammation (Fig. 120-6; see Fig. 120-3). The pathogens identified most commonly with cervicitis are *C. trachomatis* and *N. gonorrhoeae,* although no pathogen is identified in the majority of cases. HSV is a less-common pathogen associated with ulcerative and necrotic lesions on the cervix.

Figure 120-5 Mucopurulent cervical discharge positive swab test. *(From Seattle STD/HIV Prevention Training Center at the University of Washington, Claire E. Stevens and Ronald E. Roddy. Available at:* http://www2a.cdc.gov/stdtraining/ready-to-use/pid.htm.*)*

Figure 120-6 Inflamed cervix caused by gonococcal cervicitis. *(From Centers for Disease Control and Prevention:* STD clinical slides. http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm.*)*

Pelvic Inflammatory Disease

PID encompasses a spectrum of inflammatory disorders of the female upper genital tract, including endometritis, salpingitis, tuboovarian abscess, and pelvic peritonitis, usually in combination rather than as separate entities. *N. gonorrhoeae* and *C. trachomatis* predominate as the involved pathogenic organisms in younger adolescents, although PID should be approached as multiorganism etiology, including pathogens such as anaerobes, *G. vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae.* In addition, cytomegalovirus (see Chapter 255), *Mycoplasma hominis*, *U. urealyticum*, and *M. genitalium* (see Chapter 224) may be associated with PID.

PID is difficult to diagnose because of the wide variation in the symptoms and signs. Many females with PID have subtle or mild symptoms resulting in many unrecognized cases. Healthcare providers should consider the possibility of PID in young sexually active females presenting with vaginal discharge and/or abdominal pain.

The clinical diagnosis of PID is based on the presence of at least 1 of the minimal criteria, either cervical motion tenderness, uterine tenderness, or adnexal tenderness, to increase the diagnostic sensitivity and reduce the likelihood of missed or delayed diagnosis. Providers should also consider that adolescents are the population in which PID is typically diagnosed and thus should have a low threshold for initiating empiric treatment. In addition, the majority of females with PID have either mucopurulent cervical discharge or evidence of white blood cell (WBC) on a microscopic evaluation of a vaginal fluid saline preparation. If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be investigated. Specific, but not always practical, criteria for PID include evidence of endometritis on biopsy, transvaginal sonography or MRI evidence of thickened, fluid-filled tubes, or Doppler evidence of tubal hyperemia or laparoscopic evidence of PID.

Genital Ulcer Syndromes

An ulcerative lesion in a mucosal area exposed to sexual contact is the unifying characteristic of infections associated with these syndromes. These lesions are most frequently seen on the penis and vulva, but also occur on oral and rectal mucosa depending on the adolescent's sexual practices. HSV and *Treponema pallidum* (syphilis) are the most common organisms associated with genital ulcer syndromes.

Genital herpes, the most common ulcerative STI among adolescents, is a chronic, lifelong viral infection. Two sexually transmitted HSV types have been identified, HSV-1 and HSV-2. The majority of cases of recurrent genital herpes are caused by HSV-2. However, among young women and men who have sex with men, an increasing proportion of anogenital herpes has been HSV-1. Most HSV-2–infected persons are unaware of their diagnosis because they experience mild or unrecognized infections but continue to shed virus intermittently in the genital tract. Therefore, the majority of genital herpes infections are transmitted by asymptomatic persons who are unaware of their infection.

Although the initial herpetic lesion is a vesicle, by the time the patient presents clinically, the vesicle most often has ruptured spontaneously, leaving a shallow, painful ulcer (Fig. 120-7*A*) although recurrences are generally less intense and painful (Fig. 120-7*B*). Up to 50% of first genital herpes episodes are caused by HSV-1, but recurrences and subclinical shedding are much more frequent for genital HSV-2 infection.

Syphilis is a less common cause of genital ulcers in adolescents than in adults. Lymphogranuloma venereum caused by *C. trachomatis* serovars L1-L3 is uncommon, although outbreaks do occur in men who have sex with men (MSM). In these circumstances, proctitis or proctocolitis is the usual manifestation. HIV is often present in affected men. Unusual infectious causes of genital, anal, or perianal ulcers in the United States and other industrialized countries include chancroid and donovanosis.

Clinical characteristics differentiating the lesions of the most common infections associated with genital ulcers are presented in Table 120-3, along with the required laboratory diagnosis to identify the causative agent accurately. The differential diagnosis includes Behçet disease (see Chapter 161), Crohn disease (see Chapter 336), aphthous ulceration, and **acute genital ulcers** caused by cytomegalovirus (see Chapter 255) or Epstein-Barr virus (see Chapter 254). Acute genital ulcers often follow a flu or mononucleosis-like illness in an immunocompetent female and is unrelated to sexual activity. The lesions are 0.5-2.5 cm in size, bilateral, symmetric, multiple, painful, and necrotic, and are associated with inguinal lymphadenopathy. This primary infection is also associated with fever and malaise. The diagnosis may require Epstein-Barr virus titers, or polymerase chain reaction (PCR) testing. Treatment is supportive care including pain management.

Genital Lesions and Ectoparasites

Lesions that present as outgrowths on the surface of the epithelium and other limited epidermal lesions are included under this categorization of syndromes. HPV can cause genital warts and genital cervical abnormalities that can lead to cancer. Genital HPV types are classified according to their association with cervical cancer. Infections with low-risk types, such as HPV types 6 and 11, can cause benign or low-grade changes in cells of the cervix, genital warts, and recurrent

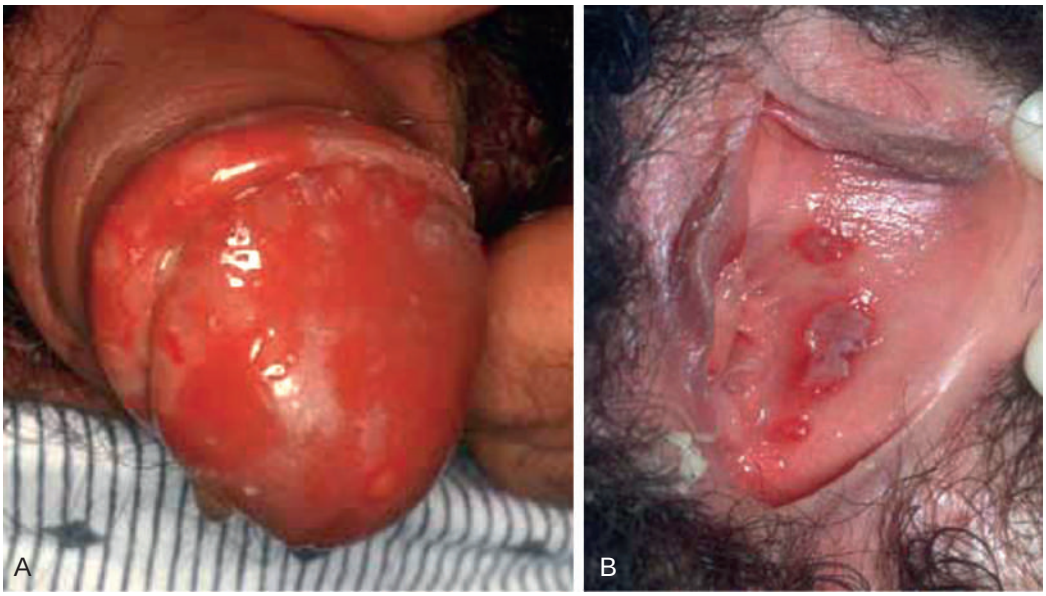


Figure 120-7 *A,* Initial herpes infection showing multiple erosions with polycyclic outlines surrounded by an erythematous halo and associated with intense pain. *B,* Erosions surrounded by an erythematous halo. Clinical signs and symptoms of recurrences are usually less intense than those of initial infection. *(From Martín JM, Villalón G, Jordá E. Update on treatment of genital herpes.* Actas Dermosifiliogr *100:22–32, 2009. Figs 1 & 2.)*

Table 120-3 Signs, Symptoms, and Presumptive and Definitive Diagnoses of Genital Ulcers

SIGNS/SYMPTOMS	HERPES SIMPLEX VIRUS	SYPHILIS (PRIMARY)	CHANCROID
Ulcers	Vesicles rupture to form shallow ulcers	Ulcer with well-demarcated indurated borders and a clean base (chancre)	Unindurated and undermined borders and a purulent base
Painful	Painful	Painless*	Painful
Number of lesions	Usually multiple	Usually single	Multiple
Inguinal lymphadenopathy	First-time infections may cause constitutional symptoms and lymphadenopathy	Usually mild and minimally tender	Unilateral or bilateral painful adenopathy in >50% Inguinal bubo formation and rupture may occur
Clinical suspicion	Typical lesions; positive HSV-2 type-specific serology test	Early syphilis: a typical chancre plus a reactive nontreponemal test (RPR, VDRL) and no history of syphilis or a 4-fold increase in a quantitative nontreponemal test in a person with a history of syphilis; positive treponemal EIA with reactive nontreponemal test (RPR, VDRL) and no prior history of syphilis treatment	Exclusion of other causes of ulcers in the presence of (a) typical ulcers and lymphadenopathy, (b) a typical Gram stain and a history of contact with a high-risk individual (prostitute) or living in an endemic area
Definitive diagnosis	Detection of HSV by culture or PCR from ulcer scraping or aspiration of vesicle fluid	Identification *Treponema pallidum,* from a chancre or lymph node aspirate, on dark-field microscopy	Detection of *Haemophilus ducreyi* by culture

*Primary syphilitic ulcers may be painful if they become coinfected with bacteria or 1 of the other organisms responsible for genital ulcers.

DFA, direct fluorescent antibody; EIA, enzyme immunoassay; HSV, herpes simplex virus; PCR, polymerase chain reaction test: RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

Data from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014, MMWR *http://www.cdc.gov/std/treatment/update.htm.*

respiratory papillomatosis. High-risk HPV types can cause cervical, anal, vulvar, vaginal, and head and neck cancers. High-risk HPV types 16 and 18 are detected in approximately 70% of cervical cancers. Persistent infection increases the risk of cervical cancer. Molluscum contagiosum and condyloma lata associated with secondary syphilis complete the classification of genital lesion syndromes. As a result of the close physical contact during sexual contact, common ectoparasitic infestations of the pubic area occur as pediculosis pubis or the papular lesions of scabies (see Chapter 668).

HIV Disease and Hepatitis B

HIV and hepatitis B present as an asymptomatic, unexpected occurrences in most infected adolescents. High vaccination coverage rates among infants and adolescents have resulted in substantial declines in acute hepatitis B incidence among U.S.-born adolescents. Risk factors identified in the history or routine screening during prenatal care are much more likely to result in suspicion of infection, leading to the appropriate laboratory screening, than are clinical manifestations in this age group (see Chapters 276 and 358).

Diagnosis

Most commonly, adolescents infected with viral and bacterial STI pathogens do not report symptoms suggestive of infection. With the increased use of very sensitive, noninvasive chlamydia and gonorrhea **NAAT**, providers are finding that most genital infections in females as well as many males are asymptomatic. A thorough sexual history is key to identifying adolescents who should be screened for STIs and for identifying those who require a laboratory diagnostic evaluation for a sexually transmitted disease syndrome.

When eliciting a sexual health history, discussions should be appropriate for the patient's developmental level. In addition to questions regarding vaginal or urethral discharge, genital lesions, and lower abdominal pain among females, one should ask about prior treatment of any STI symptoms, including self-treatment using nonprescription medications. **Dyspareunia** is a consistent symptom in adolescents with PID. Providers must ask about oral or anal sexual activity to determine sites for specimen collection.

Urethritis should be objectively documented by evidence of inflammation or infectious etiology. Patient complaint without objective clinical or laboratory evidence does not fulfill diagnostic criteria. Inflammation can be documented by (a) observing urethral mucopurulent discharge, (b) ≥2 WBC per high-power field on microscopic examination Gram stain urethral secretions, (c) urine microscopic findings of ≥10 WBCs per high power field of first-void urine specimen, or (d) a positive urine leucocyte esterase test of a (first-void urine) specimen. Laboratory evaluation is essential to identify the involved pathogens to determine treatment, partner notification, and disease control. *C. trachomatis* and *N. gonorrhoeae* NAATs of a urine specimen are recommended. The presence of Gram-negative intracellular diplococci on microscopy obtained from a male urethral specimen confirms the diagnosis of gonococcal urethritis.

An essential component of the diagnostic evaluation of vaginal, cervical or urethral discharge is a chlamydia and gonorrhea NAAT. NAATs are the most sensitive chlamydia and gonorrhea tests available and are licensed for use with urine, urethral, vaginal, and cervical specimens. Many of the chlamydia NAATs are approved by the Food and Drug Administration (FDA) to test patient-collected vaginal swabs in the clinical setting and liquid cytology specimens. Female vaginal swab specimens and male first-void urine are considered the optimal specimen types. Female urine remains an acceptable chlamydia and gonorrhea NAAT specimen, but may have slightly reduced performance when compared with cervical or vaginal swab specimens. Urine is the recommended specimen for male urethral infection. Gonorrhea and chlamydia NAATs perform well on rectal and oropharyngeal specimens and can be performed by clinical laboratories that have completed the appropriate verification studies to obtain Clinical Laboratory Improvement Amendments (CLIA)-approval, which include most commercial laboratories.

Evaluation of adolescent females with vaginitis includes laboratory data. Traditionally, the cause of vaginal symptoms was determined by pH and microscopic examination of the discharge. However, newer CLIA-waived point-of-care vaginitis tests are available. Using pH paper, an elevated pH (i.e., >4.5) is common with bacterial vaginosis or trichomoniasis. For microscopic exam, a slide can be made with the discharge diluted in 1-2 drops of 0.9% normal saline solution and another slide with discharge diluted in 10% potassium hydroxide (KOH) solution. Examining the saline specimen slide under a microscope may reveal motile or dead *T. vaginalis* or *clue cells* (epithelial cells with borders obscured by small bacteria), which are characteristic of bacterial vaginosis. WBCs without evidence of trichomonads or yeast are usually suggestive of cervicitis. The yeast or pseudohyphae of *Candida* species are more easily identified in the KOH specimen (Fig. 120-8). The

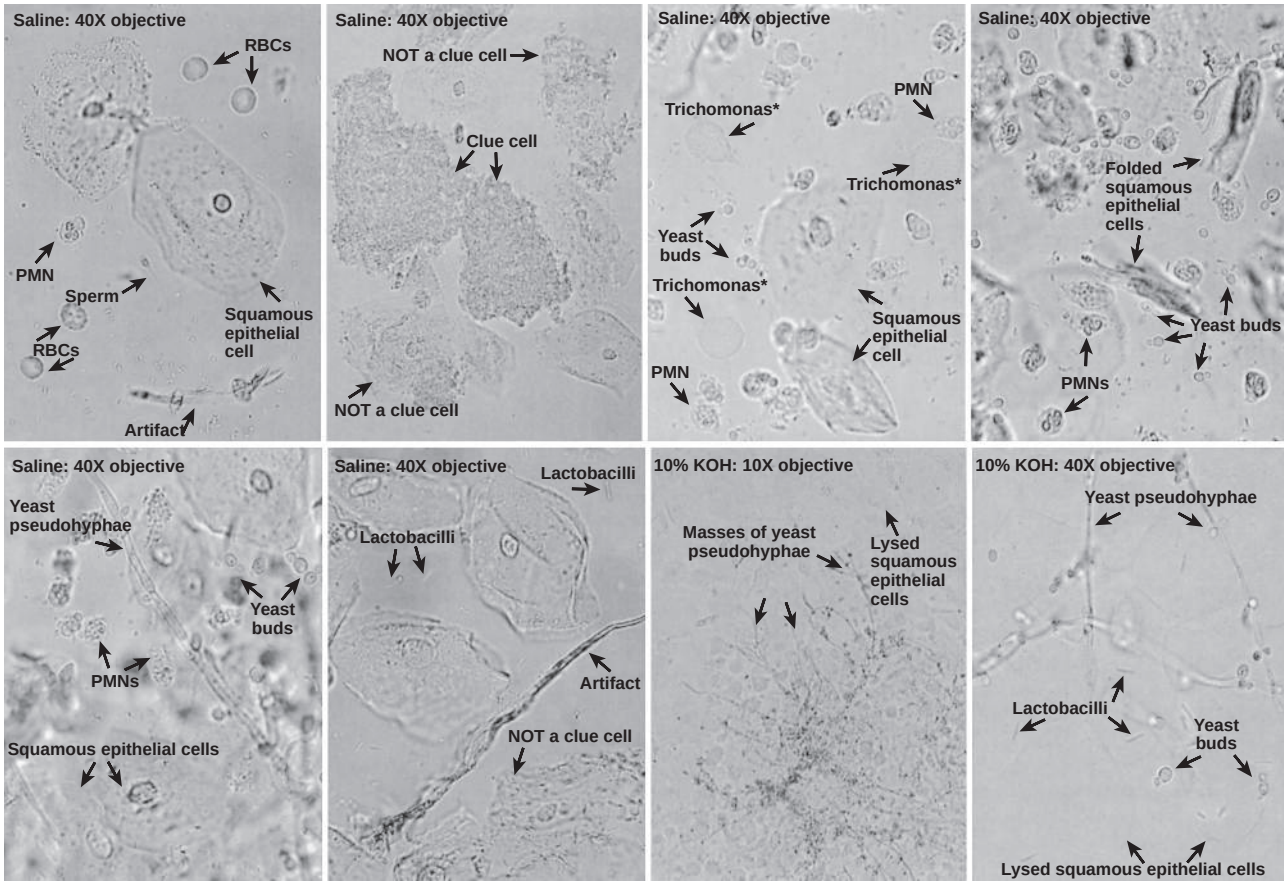


Figure 120-8 Common normal and abnormal microscopic findings during examination of vaginal fluid. KOH, potassium hydroxide solution; PMN, polymorphonuclear leukocyte; RBC, red blood cell. *(From* Adolescent medicine: state of the art reviews, *vol 14, no 2, Philadelphia, 2003, Hanley & Belfus, pp 350–351.)*

sensitivity of microscopy is approximately 50% and requires immediate evaluation of the slide for optimal results. Therefore, lack of findings does not eliminate the possibility of infection. More sensitive, point-of-care vaginitis tests include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Lexington, MA), an immunochromatographic capillary flow dipstick technology that reports an 83% sensitivity; and the OSOM BVBLUE Test (Sekisui Diagnostics, Lexington, MA), which detects elevated vaginal fluid sialidase activity, an enzyme produced by bacterial pathogens associated with bacterial vaginosis including *Gardnerella*, *Bacteroides*, *Prevotella,* and *Mobiluncus*, that reports a 90% sensitivity. Both of these tests are CLIA-waived with results are available within 10 minutes.

Clinical laboratory-based vaginitis tests are also available. The Affirm VPIII (Becton Dickenson, San Jose, CA), a nucleic acid probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *C. albicans*, is a moderate complexity laboratory test, has a sensitivity >83% and a specificity >97%, with results are available within 45 min. Some gonorrhea and chlamydia NAATs also offer an assay for *T. vaginalis* testing of female specimens tested for *N. gonorrhoeae* and *C. trachomatis*, which are considered the gold standard for trichomonas testing.

Objective signs of vulvar inflammation in the absence of vaginal pathogens, along with a minimal amount of discharge, suggest the possibility of mechanical, chemical, allergic, or other noninfectious irritation of the vulva (Table 120-4).

The **definitive diagnosis of PID** is difficult based on clinical findings alone. Clinical diagnosis is imprecise and no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Clinical criteria have a positive predictive value of only 65-90% compared with laparoscopy. Although healthcare providers should maintain a low threshold for the diagnosis of PID, additional criteria to enhance specificity of diagnosis, such as transvaginal ultrasonography, can be considered (Table 120-5).

Cell culture and PCR are the preferred HSV tests. Viral culture sensitivity is low and false negatives do occur as a consequence of intermittent viral shedding. NAATs, including PCR assays for HSV DNA, are more sensitive and increasingly available for diagnosing genital HSV. The Tzanck test is insensitive and nonspecific and should not be relied on.

Accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1). Both laboratory-based and point-of-care tests are available. Because nearly all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. The presence of HSV-1 antibody alone is more difficult to interpret because of the frequency of oral HSV infection acquired during childhood. Type-specific HSV serologic assays might be useful in the following scenarios: (1) recurrent genital symptoms or atypical symptoms with negative HSV cultures; (2) a clinical diagnosis of genital herpes without laboratory confirmation; and (3) a patient with a partner with genital herpes, especially if considering suppressive antiviral therapy to prevent transmission.

For syphilis testing, nontreponemal tests, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL), and treponemal testing, such as fluorescent treponemal antibody absorbed tests, the *T. pallidum* passive particle agglutination (TP-PA) assay, various enzyme and chemiluminescence immunoassays (EIA/CIA) are recommended. However, many clinical laboratories have adopted a reverse sequence of screening in which a treponemal EIA/CIA is performed first, followed by testing of reactive sera with a nontreponemal test (e.g., RPR). A positive treponemal EIA or CIA test can identify both previously treated and untreated or incompletely treated syphilis. False-positive results can occur, particularly among populations with low syphilis prevalence. Persons with a positive treponemal screening test should have a standard nontreponemal test with titer, such as an RPR or VDRL to guide patient management decisions. If EIA/CIA and nontreponemal test (e.g., RPR or VDRL) test results are discordant, the laboratory should perform a different treponemal test to confirm the results of the initial test. Patients with discordant serologic results by EIA/CIA and RPR/VDRL testing whose sera are reactive by TP-PA testing are considered to have past or present syphilis; if sera is TP-PA nonreactive, syphilis is unlikely (Fig. 120-9).

Table 120-4 Pathologic Vaginal Discharge

INFECTIVE DISCHARGE	OTHER REASONS FOR DISCHARGE
COMMON CAUSES *Organisms* *Candida albicans* *Trichomonas vaginalis* *Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium* *Conditions* Bacterial vaginosis Acute pelvic inflammatory disease Postoperative pelvic infection Postabortal sepsis Puerperal sepsis	COMMON CAUSES Retained tampon or condom Chemical irritation Allergic responses Ectropion Endocervical polyp Intrauterine device Atrophic changes
LESS COMMON CAUSES *Ureaplasma urealyticum* Syphilis *Escherichia coli*	LESS COMMON CAUSES Physical trauma Vault granulation tissue Vesicovaginal fistula Rectovaginal fistula Neoplasia Cervicitis

From Mitchell H: Vaginal discharge—causes, diagnosis, and treatment, BMJ *328:1306–1308, 2004.*

Table 120-5 Evaluation for Pelvic Inflammatory Disease

2014 CENTERS FOR DISEASE CONTROL AND PREVENTION DIAGNOSTIC CRITERIA

Minimal Criteria
- Cervical motion tenderness
- *or*
- Uterine tenderness
- *or*
- Adnexal tenderness

Additional Criteria to Enhance Specificity of the Minimal Criteria
- Oral temperature >38.3°C (>101°F)
- Abnormal cervical or vaginal mucopurulent discharge*
- Presence of abundant numbers of white blood cells on saline microscopy of vaginal secretions*
- Elevated ESR or C-reactive protein
- Laboratory documentation of cervical *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection

Most Specific Criteria to Enhance the Specificity of the Minimal Criteria
- Transvaginal sonography or MRI techniques showing thickened, fluid-filled tubes, with or without free pelvic fluid or tuboovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia)
- Endometrial biopsy with histopathologic evidence of endometritis
- Laparoscopic abnormalities consistent with PID

Differential Diagnosis (Partial List)
- GI: appendicitis, constipation, diverticulitis, gastroenteritis, inflammatory bowel disease, irritable bowel syndrome
- GYN: ovarian cyst (intact, ruptured, or torsed), endometriosis, dysmenorrhea, ectopic pregnancy, mittelschmerz, ruptured follicle, septic or threatened abortion, tuboovarian abscess
- Urinary tract: cystitis, pyelonephritis, urethritis, nephrolithiasis

*If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely and alternative causes of pain should be investigated.

ESR, erythrocyte sedimentation rate; GI, gastrointestinal; GYN, gynecologic; WBC, white blood cell.

Adapted from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014, MMWR *http://www.cdc.gov/std/treatment/update.htm*.

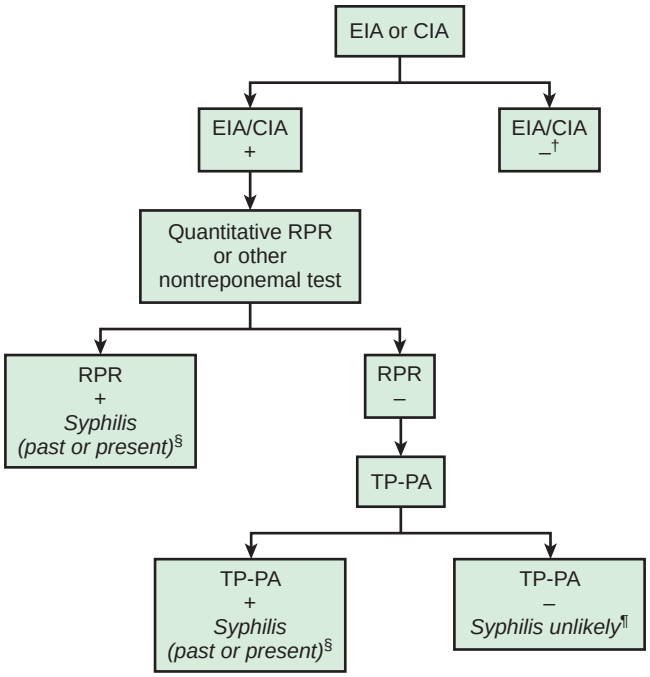


Figure 120-9 **This figure shows the recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation).** The CDC recommends that a specimen with reactive EIA/CIA results be tested reflexively with a quantitative nontreponemal test (e.g., RPR or VDRL). If test results are discordant, the specimen should be tested reflexively using the TP-PA test as a confirmatory treponemal test. EIA/CIA, enzyme immunoassay/chemiluminescence immunoassay; RPR, rapid plasma reagin; TP-PA, *Treponema pallidum* particle agglutination. *Despite these recommendations for reverse sequence screening, CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. §Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC's *STD Treatment Guidelines* (available at http://www.cdc.gov/std/treatment/update.htm). ¶If at risk for syphilis, repeat RPR in several weeks. *(Adapted from CDC: Discordant results from reverse sequence syphilis screening–five laboratories, United States, 2006-2010,* MMWR Morb Mortal Wkly Rep *60:133–137, 2011.)*

HIV screening should be discussed and offered in healthcare settings to all adolescents >15 yr and to younger adolescents with HIV risk factors. Rapid HIV testing with the availability of results in 10-20 min can be useful in settings in which the likelihood of adolescents returning for their results is low. Point-of-care, CLIA-waived tests for whole blood fingerstick and oral fluid specimen testing are available. Clinical studies have demonstrated that the rapid HIV test performance is comparable to those of EIAs. Because some reactive test results may be false-positive, every reactive rapid test must be confirmed.

Treatment

See Part XVII for chapters on the treatment of specific microorganisms and Tables 120-6 to 120-8. Treatment regimens using nonprescription products for candida vaginitis and pediculosis reduce financial and access barriers to rapid treatment for adolescents, but there are potential risks for inappropriate self-treatment and complications from untreated more serious infections that must be considered before using this approach. Minimizing noncompliance with treatment, finding and treating the sexual partners, addressing prevention and contraceptive issues, offering available vaccines to prevent STIs and making every effort to preserve fertility are additional physician responsibilities.

Chlamydia and gonorrhea-infected males and females should be retested approximately 3 mo after treatment, regardless of whether they believe that their sex partners were treated or whenever persons next present for medical care in the 12 mo following initial treatment. Once an infection is diagnosed, partner evaluation, testing, and treatment are recommended for sexual contacts within 60 days of symptoms or diagnosis or the most recent partner if sexual contact was >60 days, even if the partner is asymptomatic. Abstinence is recommended for at least 7 days after both patient and partner are treated. A test for pregnancy should be performed for all females with suspected PID as the test outcome will affect management. Repeat testing 3 mo after treatment is recommended for *Trichomonas* infection.

Diagnosis and therapy are often necessarily carried out within the context of a confidential relationship between the physician and the patient. Therefore, the need to report certain STIs to health department authorities should be clarified at the outset. Health departments are HIPAA-exempt and will not violate confidentiality. The health department's role is to assure that treatment and case finding have been accomplished and that sexual partners have been notified of their STI exposure. **Expedited partner therapy (EPT),** where the patient, preferably, delivers the medication, or a prescription for the medication if medication itself is not possible to the partner for treatment without a

Table 120-6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Chlamydia trachomatis	Azithromycin 1 g orally once *or* Doxycycline 100 mg orally twice daily for 7 days	For pregnancy: Azithromycin 1 g orally once Alternative regimens: Erythromycin base 500 mg orally 4 times a day for 7 days *or* Erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days *or* Levofloxacin 500 mg orally once daily for 7 days *or* Ofloxacin 300 mg orally twice a day for 7 days
Neisseria gonorrhoeae (cervix, urethra, and rectum)	Ceftriaxone 250 mg IM in a single dose *or* Single-dose injectable cephalosporin *plus* Azithromycin 1 g orally once	Alternative if unable to offer IM: Cefixime 400 mg orally in a single dose *plus* Azithromycin 1 g orally once If azithromycin is not available or if patient is allergic to azithromycin, doxycycline 100 mg orally twice daily for 7 days may be substituted for azithromycin as the second antimicrobial Severe cephalosporin allergy: contact infectious disease specialist

Table 120-6 Management Guidelines for Uncomplicated Bacterial STIs in Adolescents and Adults—cont'd

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Neisseria gonorrhoeae (pharynx)	Ceftriaxone 250 mg IM in a single dose *plus* Azithromycin 1 g orally once	No alternative therapy available Patients treated with an alternative regimen should return 14 days after treatment for a test of cure using either culture or NAAT. If the NAAT is positive, every effort should be made to perform a confirmatory culture
Treponema pallidum (primary and secondary syphilis or early latent syphilis, i.e., infection <12 mo)	Benzathine penicillin G 2.4 million units IM in 1 dose	Penicillin allergy: doxycycline 100 mg orally twice daily for 14 days. Limited data suggest ceftriaxone 1-2 g daily either IM or IV for 10-14 days.
Treponema pallidum (late latent syphilis or syphilis of unknown duration)	Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1 wk intervals	Penicillin allergy: doxycycline 100 mg orally twice daily for 28 days with close serologic and clinical follow-up
Haemophilus ducreyi (chancroid: genital ulcers, lymphadenopathy)	Azithromycin 1 g orally in a single dose *or* Ceftriaxone 250 mg IM in a single dose *or* Ciprofloxacin 500 mg orally twice a day for 3 days *or* Erythromycin base 500 mg orally 3 times a day for 7 days	
Chlamydia trachomatis serovars L1, L2, or L3 (lymphogranuloma venereum)	Doxycycline 100 mg orally twice daily for 21 days	Alternative: erythromycin base 500 mg orally 4 times a day for 21 days *or* Azithromycin 1 g orally once a week for 3 wk

IM, intramuscular; IV, intravenous; NAAT, nucleic acid amplification test.

Adapted for Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014 MMWR *http://www.cdc.gov/std/treatment/update.htm*.

Table 120-7 Management Guidelines for Uncomplicated Miscellaneous Sexually Transmitted Infections in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	ALTERNATIVE REGIMENS AND SPECIAL CONSIDERATIONS
Trichomonas vaginalis	Metronidazole 2 g orally in a single dose *or* Tinidazole 2 g orally in a single dose	Metronidazole 500 mg orally twice daily for 7 days
Phthirus pubis (pubic lice)	Permethrin 1% cream rinse applied to affected areas and washed off after 10 min *or* Pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 min Launder clothing and bedding	Malathion 0.5% lotion applied for 8-12 hr and washed off *or* Ivermectin 250 μg/kg PO, repeat in 2 wk
Sarcoptes scabiei (scabies)	Permethrin 5% cream applied to all areas from the neck down, washed off after 8-14 hr or Ivermectin 200 μg/kg orally, repeated in 2 wk Launder clothing and bedding	Lindane (1%) 1 oz of lotion or 30 g of cream in thin layer to all areas of body from neck down; wash off in 8 hr

Adapted from Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2014 MMWR *http://www.cdc.gov/std/treatment/update.htm*.

clinical assessment, is a strategy to reduce further transmission of infection, particularly for male partners of women with gonorrhea and/or chlamydia who are otherwise unlikely to seek care for STI exposure. In randomized trials, EPT has reduced the rates of persistent or recurrent gonorrhea and chlamydia infection. Serious adverse reactions are rare with recommended chlamydia and gonorrhea treatment regimens, such as doxycycline, azithromycin, and cefixime. Transient gastrointestinal side effects are more common but rarely result in severe morbidity. Many states expressly permit EPT or may potentially allow its practice. Resources for information regarding EPT and state laws are available at the Centers for Disease Control and Prevention website (http://www.cdc.gov/std/ept/).

Prevention

Healthcare providers should integrate sexuality education into clinical practice with children from early childhood through adolescence. Providers should counsel adolescents regarding sexual behaviors associated with risk of STI acquisition and should educate using evidence-based prevention strategies, which include a discussion of abstinence and other risk reduction strategies, such as consistent and correct condom use. The U.S. Preventative Task Force recommends high-intensity behavioral counseling to prevent STIs for all sexually active adolescents. The HPV vaccine, either bivalent or quadrivalent, is recommended for 11 and 12 yr old female routine immunization. Catch-up vaccination is recommended for females age 13-26 yr who

Table 120-8 Management Guidelines for Uncomplicated Genital Warts and Genital Herpes in Adolescents and Adults

PATHOGEN	RECOMMENDED REGIMENS	
Human papillomaviruses external genital warts	Patient-applied: Podofilox 0.5% solution or gel self-applied to warts twice daily for 3 consecutive days each wk followed by 4 days of no therapy. May be repeated for up to 4 cycles. *or* Imiquimod 3.75% cream or 5% cream self-applied to warts at bedtime 3 times wkly for up to 16 wk; wash off after 6-10 hr *or* Sinecatechins 15% ointment self-applied 3 times daily for up to 16 wk. Do not wash off after use Provider-administered: Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1-2 wk *or* Trichloroacetic acid (TCA) or bichloracetic acid (BCA) 80-90%. A small amount should be applied only to the warts and allowed to dry, at which time a white "frosting" develops. Can be repeated weekly *or* Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery	
Human papillomaviruses Cervical warts	Refer to specialist for oncologic evaluation	
Human papillomaviruses Vaginal warts	**Cryotherapy** with liquid nitrogen. Avoid cryoprobe use *or* TCA or BCA 80-90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. Can be repeated weekly *or* Surgical removal	
Human papillomaviruses Urethral meatal warts	Cryotherapy with liquid nitrogen *or* Surgical removal	
Human papillomaviruses Anal warts	Cryotherapy with liquid nitrogen *or* TCA or BCA 80-90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. Can be repeated weekly *or* Surgical removal	Warts on the rectal mucosa should be managed in consultation with a specialist. Persons with anal warts should have rectal mucosa inspected by digital examination, standard anoscopy, or high-resolution anoscopy
Herpes simplex virus (genital herpes): First clinical episode	Treat for 7-10 days with 1 of the following: Acyclovir 400 mg orally 3 times daily *or* Acyclovir 200 mg orally 5 times daily *or* Valacyclovir 1 g orally twice daily *or* Famciclovir 250 mg orally 3 times daily	Consider extending treatment if healing is incomplete after 10 days of therapy

Table 120-8	Management Guidelines for Uncomplicated Genital Warts and Genital Herpes in Adolescents and Adults—cont'd	
PATHOGEN	**RECOMMENDED REGIMENS**	
Herpes simplex virus (genital herpes): Episodic therapy for recurrences	Acyclovir 400 mg orally 3 times daily for 5 days *or* Acyclovir 800 mg orally twice daily for 5 days *or* Acyclovir 800 mg orally 3 times daily for 2 days *or* Valacyclovir 500 mg orally twice daily for 3 days *or* Valacyclovir 1,000 mg orally once daily for 5 days *or* Famciclovir 125 mg orally twice daily for 5 days *or* Famciclovir 1,000 mg orally twice daily for 1 day *or* Famciclovir 500 mg orally once then 250 mg twice daily for 2 days	Effective episodic treatment of recurrences requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin
Herpes simplex virus (genital herpes): Suppressive therapy to reduce frequency of recurrences	Acyclovir 400 mg orally twice daily *or* Valacyclovir 500 mg orally once daily or 1 g orally once daily *or* Famciclovir 250 mg orally twice daily	All patients should be counseled regarding suppressive therapy availability, regardless of number of outbreaks per year. Since the frequency of recurrent outbreaks diminishes over time in many patients, providers should periodically discuss the need to continue therapy Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year).

Adapted from Centers for Disease Control and Prevention: STD Treatment Guidelines 2014, MMWR *59 In press.*

have not yet received or completed the vaccine series. The routine use of quadrivalent HPV vaccine is recommended in males age 11 or 12 yr. The CDC's Advisory Committee on Immunization Practices also recommends vaccination with quadrivalent HPV vaccine for males age 13 through 21 yr who have not yet received or completed the vaccine series; males age 22 through 26 yr may be vaccinated.

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Chapter 121

Chronic Fatigue Syndrome

James F. Jones and Hal B. Jenson

Chronic fatigue syndrome (CFS) describes a complex, diverse, and debilitating illness characterized by chronic or intermittent fatigue accompanied by selected symptoms of >3 mo (young children) or >6 mo duration (adolescents or adults). The combination of fatigue and symptoms interferes significantly with usual daily activities and has no apparent medical explanation. The fatigue does not require exertion by the patient, nor does rest relieve it. Post-exertion malaise (i.e., worsening of fatigue and sickness symptoms after mental or physical exertion lasting more than 24 hr) is considered by some to be characteristic of CFS. A definitive causal agent or process has not been identified, although the differential diagnosis includes many infectious and inflammatory diseases. The understanding of this condition is largely from studies among adults and adolescents, with limited descriptions of chronic fatiguing illness among younger children.

This illness was formally defined in 1988 as *chronic fatigue syndrome* because persistent and unexplained fatigue was considered the principal and invariable physical symptom. A variety of names have been used to describe the syndrome (chronic mononucleosis, chronic Epstein-Barr virus infection, myalgic encephalomyelitis, post-infection syndrome, immune dysfunction syndrome), and several case definitions are in use in both clinical and research settings. Some of the more widely used definitions are the 1994 International Research Case Definition (an update of the 1988 version), the Oxford (UK) Guidelines for research, the Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical working case definition, diagnostic and treatments protocols, also commonly referred to as the Canadian Consensus Criteria for CFS/ME (2003), and the 2011 International Consensus Criteria for Myalgic Encephalomyelitis (ME). In 2006, the International Association of Chronic Fatigue Syndrome Pediatric Case Definition Working group developed a case definition specifically for children and adolescents with ME/CFS, utilizing the 3-mo duration of fatigue. In the UK, pediatric practitioners adhere to guidelines in the National Institute for Health and Clinical Excellence (NICE); Chronic fatigue syndrome/Myalgic encephalomyelitis (or encephalopathy); Diagnosis and Management (2007), which includes the 3-mo duration criterion.

The Institute of Medicine (IOM) of the National Academy of Science was commissioned by the Department of Health and Human Services (HHS) to conduct a study to evaluate existing diagnostic criteria and to develop evidence-based diagnostic criteria for use by clinicians. Their recommendations were published in February 2015. The IOM case definition is intended to apply to all ages, and the report includes a special focus on pediatrics. The IOM suggested new diagnostic criteria and a new name, *systemic exertion intolerance disease*, in part to emphasize the post-exertion malaise criterion and bring greater understanding about the illness.

EPIDEMIOLOGY

Between 0.2% and 2.3% of children or adolescents suffer from CFS based on worldwide studies. Most epidemiology studies utilize the 1994 definition. CFS is more prevalent in adolescents than in younger children. The large variation in the CFS prevalence estimates may be

due to variation in study methodology, such as the study population composition (special clinic versus general practice or general population) and data collection procedures (parent/self-reporting vs. clinical evaluation; the choice of case definition and method of applying case definition). Sex/gender distribution differs from that in adults with a more equal distribution in children less than 15 yr of age, while remaining 2- to 3-fold higher in females ages 15-18 yr. Few studies have reported the incidence of CFS among children <10 yr of age, leading to uncertainty in this age group. In adolescents in the Netherlands, the pediatrician-diagnosed incidence of CFS/ME was reported to be 0.01%, while in the UK the incidence was 0.5%.

PATHOGENESIS

Although the cause of CFS is unknown, some patients correlate the onset with a recent episode of a viruslike illness such as infectious mononucleosis (10-12%) (see Chapter 254). A potentially pathophysiologic relationship of CFS to infection is suggested because the sickness or illness behaviors elicited by the nonspecific or innate host responses in infections in general are present in CFS. CFS-like illness after infectious mononucleosis is not predicted by viremia or an altered host response to Epstein-Barr virus infection, but is associated with the severity of the primary infection. There have been a wide variety of other candidate infections associated with postinfection fatigue syndromes, particularly in adults or teenagers older than 16 yr. Efforts continue to determine if infections with these or other agents may produce the illness.

Similarities between CFS symptoms and those experienced by patients with autoimmune and other inflammatory disorders raises the issue of primary perturbations in the immune system in the pathogenesis of CFS. Immunologic alterations (hypogammaglobulinemia or hypergammaglobulinemia, immunoglobulin subclass deficiencies, elevated levels of circulating immune complexes, mild increased helper/suppressor lymphocyte ratios, natural killer cell dysfunction, and monocyte dysfunction) have been reported in adult patients with CFS. These findings have not been consistent among studies. While CFS patients as a group appear to differ from healthy controls, in most studies the laboratory values of the immune parameters are not outside the normal range.

Autonomic nervous system changes are suggested by the orthostatic intolerance experienced by some CFS patients. Orthostatic intolerance (OI) syndromes with circulatory dysfunction including neutrally mediated hypotension, instantaneous orthostatic hypotension, and postural tachycardia syndrome have been observed in some patients with CFS and could contribute to the syndrome. The pathophysiology of these manifestations among adolescents with CFS is unclear, but in postinfection states, they could be associated with failure to replenish mineral and fluid losses that accompany infections or to immune-mediated injury (auto-antibodies directed against the autonomic nervous system).

Because the widespread musculoskeletal pain in CFS is similar to that in fibromyalgia (Chapter 168.3), and fibromyalgia and CFS are often considered overlapping syndromes, they may share similarities in pathogenesis. Fibromyalgia pain is thought to be due to neurochemical imbalances in the central nervous system. Neurochemical changes represent another area for research into the origins of development and persistence of CFS.

A variety of other hypotheses for the biologic basis of this illness are being investigated. These include alterations in energy metabolism (particularly as related to exercise and post-exertion malaise), in sleep, as well as in stress response and the hypothalamic-pituitary-axis. Understanding CFS has proved so challenging because it represents more than one underlying pathophysiology. Current studies are attempting to stratify or subgroup patients to address this possibility.

CLINICAL MANIFESTATIONS

The dominant symptoms expressed by adolescents are similar to those observed in adults and include fatigue and an increased level of illness after physical or mental activity. In younger children, who frequently do not spontaneously describe symptoms, exertion induces behavioral changes manifested by a lack of their usual energy. In adolescents, the fatigue and post-exertional malaise may lead to reduced participation in school activities and time spent with friends. Cognitive problems and difficulties in concentrating are common and are indicated by a decreased ability to keep up with homework and a drop in grades. Sleep complaints include difficulty falling or staying asleep, daytime sleepiness, frequent awakening, and intense and vivid dreaming. While nonrestorative nighttime sleeping is common, diagnosed sleep disorders, such as restless legs or sleep apnea, are not. Myalgias and arthralgias may accompany fatigue and altered sleep. Sore throat and lymph node tenderness occur in some children but may be part of an inciting illness. Adolescents also have increased complaints of headaches, abdominal pain, nausea, and hypersensitivity to touch and noise.

Patients diagnosed with CFS in primary care practices are more likely to report an abrupt onset to their symptoms, often as part of an initial virus-like illness, whereas gradual onset is more common in those identified in population-based studies. School absenteeism is a major problem. In one study two thirds of adolescents missed >2 wk of school over a 6-week observation period and one third required a home tutor. Unlike school phobia, inactivity due to CFS persists on the weekends and during holidays as it does during the school week.

Although fatigue and accompanying symptoms are subjective, the magnitude of impairment of each component can be measured by questionnaires addressing pain and function or, in the case of suspected orthostatic instability, by recording routine or supine/standing heart rate and blood pressure. Fatigue should not be dismissed as a minor ailment. It is generally manifested as lassitude, profound tiredness, intolerance of exertion with easy fatigability, and general malaise.

Abnormal physical examination findings are conspicuously absent, providing reassurance and consternation to both the patient and the physician. The presence of unusual symptoms such as chest palpitations, visual blurring, paresthesias, dry eyes and mouth, diarrhea, cough, night sweats, and rash) should suggest a diagnosis other than CFS. Weight loss, as seen in chronic infections or inflammatory conditions, is uncommon in CFS.

DIAGNOSIS

There are no pathognomonic signs or diagnostic tests for CFS. The diagnosis is clinically defined based on inclusion and exclusion criteria (Fig. 121-1). The diagnostic criteria are applicable to adults and adolescents >11 yr of age because of the current requirement for a self-generated history. The 3- or 6-mo criterion in CFS case definitions does not mean that evaluation and symptom management should wait until that criterion is met before intervention can begin.

CFS is difficult to diagnose in children, who have trouble describing their symptoms and articulating their concerns. Sole reliance on parental history for diagnosis is fraught with confusion because of the inaccuracy of the historical information. A combination of child and parent reports is most effective. It is important to document the child's activity levels and worsening symptoms after physical or mental endeavors. Changes in participation in hobbies and social activities can help identify illness effects on daily activities.

The diagnosis of CFS can be established only after alternative medical and psychiatric causes of fatigue and illness, many of which are treatable, have been excluded. These include any medical condition that may explain the presence of a chronic illness, such as untreated hypothyroidism, respiratory and/or food allergies, sleep apnea, narcolepsy, drug abuse, an adverse effect of medication, or severe obesity. A previously diagnosed medical condition with uncertain resolution that may explain chronic fatigue should be clarified, such as unresolved cases of hepatitis B or C virus infection.

Certain illnesses, for example, fibromyalgia and depression, share similar symptoms with CFS, but are not exclusionary diagnoses. They should be considered in the differential diagnosis in selected cases. There is concern that CFS might be mistaken for readily identifiable psychiatric disorders, but evidence supports differences in clinical

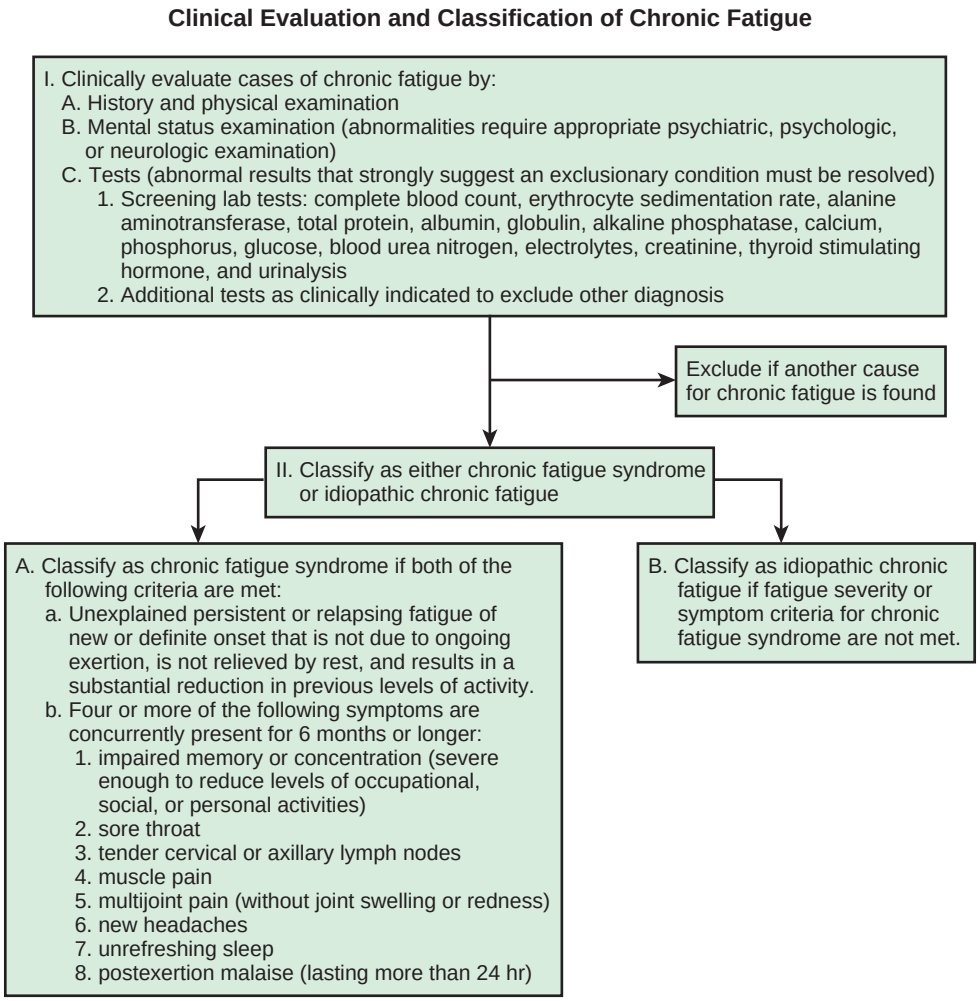

Figure 121-1 The clinical evaluation and classification of unexplained chronic fatigue. The case definition for chronic fatigue syndrome was proposed in 1988 (*Holmes GP, Kaplan JE, Gantz NM, et al. Chronic fatigue syndrome: a working case definition; 108:387–389*), and refined and simplified by an international working group in 1994 *(Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. 1994. Ann Intern Med; 121:953–959).*

presentation between CFS and mood/anxiety disorders. CFS should not be diagnosed in persons with prior diagnoses of a major depressive disorder with psychotic or melancholic features, bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementias of any subtype, anorexia nervosa, bulimia nervosa, or alcohol or other substance abuse within 2 yr before the onset of the chronic fatigue or at any time afterward.

Although evaluation of each patient should be individualized, initial laboratory evaluation should be limited to screening laboratory tests to provide reassurance of the lack of significant medical illnesses (see Fig. 121-1). Further tests should be directed primarily toward excluding treatable diseases that may be suggested by the symptoms or physical findings that are present in specific patients.

MANAGEMENT

Management of CFS is based on relief of the core and most disruptive symptoms in the individual patient (Fig. 121-1). The diagnostic criterion of 3-6 mo duration of illness should not delay evaluation and symptom management, as these may be initiated as soon as the child or adolescent presents with a CFS-like picture. Problems with sleep can be addressed by encouraging patients to adopt good sleep habits using standard sleep hygiene techniques. It may be beneficial to refer the patient to a specialist for identification and treatment of sleep disorders and disturbances. Once pain is found not to be related to specific diseases or illnesses, it is best addressed through nonpharmacologic treatment (see Chapter 62).

One of the nonpharmacologic approaches to pain management, cognitive behavioral therapy (CBT), may also assist patients in coping with CFS. Through explanation and changes in perception of the origins of the illness, CBT may help patients and their families develop coping skills and provide emotional support. Improved methods of coping may allow some improved function while living with the illness. Comorbid psychiatric disorders require appropriate intervention.

While the overall goal is to help CFS patients tolerate activity, children with CFS should avoid physical or mental efforts that result in aggravated CFS symptoms. Return to school should be initiated gradually but systematically to resume normal attendance. Home tutoring may be an interim alternative. Parents can work with teachers and administrators to redefine expectations of activity and performance for children with CFS. Because of the crucial importance of learning socialization skills during childhood and adolescence, even brief periods of attendance during lunch or favorite after-school activities should be encouraged. Complete bed rest and physical inactivity perpetuates immobility and leads to deconditioning. Activities benefit children with certain chronic illnesses in ways other than overcoming deconditioning; however, rapid remobilization usually exacerbates symptoms and should be avoided.

Continued empathy and support by the treating physician are important in maintaining a physician-patient relationship conducive to managing this illness. Careful attention must be directed to the family dynamics to identify and resolve family problems or psychopathology that may be contributing to a child's perceptions of his or her

symptoms. Periodic medical reevaluation is warranted for early detection of other identifiable causes of chronic fatigue and other symptoms, especially with interval development of new symptoms. No data suggest relief of symptoms or cure of CFS by dietary or vitamin supplements.

PROGNOSIS

The clinical course of CFS is highly variable and patients should be informed that their symptoms will likely wax and wane. Children and adolescents with CFS appear to have a more optimistic outcome than adults, typically with an undulating course of gradual but substantial symptomatic improvement, or full recovery, 1-4 yr after diagnosis. Overall, a good functional outcome has been reported in up to 80% of cases. Poor prognostic factors include a gradual onset, increasing school absenteeism, lower socioeconomic status, chronic maternal health problems, and untreated comorbid individual or family psychiatric disorders. Favorable prognostic factors include patient control of their individual rehabilitation program with continued support from health professionals and family members and improvement in orthostatic factors.

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Immunology

PART XIV

Section 1

Evaluation of the Immune System

Chapter 122

Evaluation of Suspected Immunodeficiency

Rebecca H. Buckley

Recurrent infections or fevers in children are among the most frequent clinical dilemmas for primary care physicians. A major reason for the apparent high rate of recurrent infections in children is repeated exposure to common and usually benign infectious agents in childcare and other group settings.

Primary care physicians must have a high index of suspicion if defects of the immune system are to be diagnosed early enough that appropriate treatment can be instituted before irreversible damage develops. Diagnosis is difficult because, until recently, primary immunodeficiency diseases have not been screened for at any time during life anywhere in the world, and most affected do not have abnormal physical features. Screening for severe combined immunodeficiency (SCID; T-cell lymphopenia) is part of the newborn screening programs in 21 states of the United States now; the hope is that it will eventually be performed nationwide. There is also a beginning effort to do this in Europe. Extensive use of antibiotics may mask the classic presentation of many primary immunodeficiency diseases. Evaluation of immune function should be initiated in those rare infants or children who do have clinical manifestations of a specific immune disorder and in all who have a positive family history of early infant death or a known immunodeficiency disorder, unusual, chronic, or recurrent infections such as (1) 1 or more systemic bacterial infections (sepsis, meningitis); (2) 2 or more serious respiratory or documented bacterial infections (cellulitis, abscesses, draining otitis media, pneumonia, lymphadenitis) within 1 yr; (3) serious infections occurring at unusual sites (liver, brain abscess); (4) infections with unusual pathogens *(Pneumocystis jiroveci, Aspergillus, Serratia marcescens, Nocardia, Burkholderia cepacia);* and (5) infections with common childhood pathogens but of unusual severity (Table 122-1). Additional clues to immunodeficiency include failure to thrive with or without chronic diarrhea, persistent infections after receiving live vaccines, and chronic oral or cutaneous moniliasis. Tables 122-2 and 122-3 note certain clinical features that are suggestive of immunodeficiency syndromes.

Children with defects in antibody production, phagocytic cells, or complement proteins have recurrent infections with encapsulated bacteria and may grow and develop normally despite their recurring infections, unless they develop bronchiectasis from repeated lower respiratory tract bacterial infections or persistent enteroviral infections of the central nervous system. Patients with only repeated benign viral infections (with the exception of persistent enterovirus infections) are not as likely to have an immunodeficiency. By contrast, patients with deficiencies in T-cell function usually develop opportunistic infections or serious illnesses from common viral agents early in life, and they fail to thrive (Table 122-4).

The initial evaluation of immunocompetence includes a thorough history, physical examination, and family history (Table 122-5). Most immunologic defects can be excluded at minimal cost with the proper choice of screening tests, which should be broadly informative, reliable, and cost-effective (Table 122-6 and Fig. 122-1). A complete blood count (CBC), manual differential count, and erythrocyte sedimentation rate are among the most cost-effective screening tests. If the erythrocyte sedimentation rate is normal, chronic bacterial or fungal infection is unlikely. If an infant's neutrophil count is persistently elevated in the absence of any signs of infection, a leukocyte adhesion deficiency should be suspected. If the absolute neutrophil count is normal, congenital and acquired neutropenias and leukocyte adhesion defects are excluded. If the absolute lymphocyte count is normal, the patient is not likely to have a severe T-cell defect, because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia. Normal lymphocyte counts are higher in infancy and early childhood than later in life (Fig. 122-2). Knowledge of normal values for absolute lymphocyte counts at various ages in infancy and childhood is crucial in the detection of T-cell defects. At 9 mo of age, an age when infants affected with severe T-cell immunodeficiency are likely to present, the lower limit of normal is 4,500 lymphocytes/mm^3. Absence of Howell-Jolly bodies or pitted erythrocytes by microscopic examination of erythrocytes rules against congenital asplenia. Normal platelet size or count excludes Wiskott-Aldrich syndrome. If newborn screening for T-cell lymphopenia were to be performed on all infants, SCID could be detected at birth, and lifesaving immunologic reconstitution could then be provided to all affected infants shortly after birth and before they become infected.

Patients found to have abnormalities on any screening tests should be characterized as fully as possible before any type of immunologic treatment is begun, unless there is a life-threatening illness (Table 122-7). Some "abnormalities" may prove to be laboratory artifacts and, conversely, an apparently straightforward diagnosis may prove to be a much more complex disorder. For patients with recurrent or unusual bacterial infections, evaluation of T-cell and phagocytic cell functions is indicated even if results of initial screening tests including the CBC and manual differential, immunoglobulin levels, and CH_{50} are normal.

Because of the lack of screening, the true incidence and prevalence of primary immunodeficiency diseases are unknown, although the incidence has been estimated to be 1:10,000 births (Table 122-8). If true, this is higher than some disorders that are part of the newborn metabolic screening program (phenylketonuria is 1:16,000) (see Chapter 85.1). Approximately 80% of the mutated genes causing the more than 220 known primary immunodeficiency diseases have been identified. This is information crucial for genetic counseling and that could eventually be used in neonatal screening. Newborn or early childhood screening would be extremely valuable so that timely initiation of appropriate therapy can be initiated before infections develop; it is likely that many affected patients die before a diagnosis is determined.

B CELLS

Antibody production by B cells is easily evaluated by measuring serum immunoglobulin levels and determining antibody titers to protein and polysaccharide antigens.

A simple screening test for B-cell defects is the measurement of serum immunoglobulin (Ig) A. If the IgA level is normal, selective IgA

Table 122-1 Predisposition to Specific Infections in Humans

PATHOGEN	PRESENTATION	AFFECTED GENE/ CHROMOSOMAL REGION	FUNCTIONAL DEFECT	NOTES
BACTERIA				
Streptococcus pneumoniae	Invasive disease	*IRAK-4, MyD88*	Impaired production of inflammatory cytokines following TLR stimulation	Also susceptible to other pyogenic bacteria such as *Staphylococcus aureus*
Neisseria	Invasive disease	MAC components (C5, C6, C7, C8A, C8B, C8G, C9)	MAC deficiency	
	Invasive disease, poor prognosis	*PFC*	Properdin deficiency	
Mycobacteria	MSMD	*IL12B, IL12RB1, IKBKG*	Impaired IFN-γ response to IL-12, IL-23	Also susceptible to *Salmonella typhi* infections
		IFNGR1, IFNGR2, STAT1	Impaired cellular response to IFN-γ	
Mycobacterium leprae	Leprosy	*PARK2*	Unknown	Possible E3-ubiquitin ligase dysfunction
		LTA	Unknown	
VIRUSES				
Herpes simplex (type 1)	Herpes simplex encephalitis	*UNC93B1, TLR3, STAT1*	Impaired production of type 1 IFNs	STAT1 and NEMO deficiency also predispose to HSV infections, amongst other infections
Epstein-Barr virus	XLP	*SH2DIA*	SAP deficiency	Fulminant infectious mononucleosis, malignant and nonmalignant lymphoproliferative disorders, dysgammaglobulinemia, autoimmunity
		XIAP/BIRC4	XIAP deficiency	
Human papillomaviruses	Epidermodysplasia verruciformis	*EVER1/TMC6*	EVER1 deficiency	Altered neutrophil mobilization, T-cell lymphopenia, recurrent bacterial respiratory infections chronic cutaneous/genital papillomavirus disease
		EVER2/TMC8	EVER2 deficiency	
	WHIM	*CXCR4*	Truncated CXCR4	
PARASITES				
Plasmodium falciparum	Malaria fever episodes	10p15	Unknown	Linkage studies
	Severe malaria	*GNAS*	Unknown	SNP association studies
	Severe malaria	*IFNR1*	Unknown	SNP association studies
Schistosoma mansoni	Intensity of infection	5q311-q33	Unknown	
	Hepatic fibrosis	6q22-q23, *IFNR1*	Unknown	
Leishmania donovani	Visceral leishmaniasis (kala-azar)	22q12, 2q35 *(NRAMP1)*	Unknown	
YEAST				
Candida	APECED, chronic candidiasis	*Aire, STAT1, CARD9*	Unknown	APS-1 chronic candidiasis, chronic hyperthyroidism, Addison disease
Deep dermatophytosis	Tissue invasion	*CARD9*	Unknown	Autosomal recessive

APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MAC, membrane attack complex; MSMD, mendelian susceptibility to mycobacterial disease; NEMO, nuclear factor kappa B essential modulator; SAP, SLAM-associated protein; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis syndrome; XIAP, X-linked inhibitor of apoptosis; XLP, X-linked lymphoproliferative disease.

Modified from Pessach I, Walter J, Notarangelo LD: Recent advances in primary immunodeficiencies: identification of novel genetic defects and unanticipated phenotypes, Pediatr Res *65:3R–12R, 2009.*

deficiency, which is the most common B-cell defect, is excluded, as are most of the permanent types of hypogammaglobulinemia, as IgA is usually very low or absent in those conditions. If IgA is low, IgG and IgM should also be measured. Patients who are receiving corticosteroids or who have protein-losing states (nephrosis, protein-losing enteropathy) often have low serum IgG concentrations but produce antibodies normally. Thus, if immunoglobulins are low, it is crucial before starting intravenous immunoglobulin therapy that antibody titers to specific antigens are measured to determine whether the immunoglobulin levels are low because of inadequate antibody synthesis or due to protein loss. Antibody titers are not interpretable after the patient has received a blood transfusion, fresh-frozen plasma or intravenous immunoglobulin, which contains antibodies from a minimum of 10,000 normal donors.

One useful test for B-cell function is to determine the presence and titer of **isohemagglutinins,** or natural antibodies to type A and B red blood cell polysaccharide antigens. This test measures predominantly IgM antibodies. Isohemagglutinins may be absent normally in the 1st 2 yr of life and are always absent if the patient is blood type AB.

Because most infants and children are immunized with diphtheria-tetanus-pertussis, conjugated *Haemophilus influenzae* type b, and pneumococcal conjugate vaccine, it is often informative to test for specific antibodies to diphtheria, tetanus, *H. influenzae* polyribose phosphate, and pneumococcal antigens. If the titers are low, measurement of antibodies to diphtheria or tetanus toxoids before and 2 wk after a pediatric diphtheria-tetanus-pertussis or diphtheria-tetanus booster is helpful in assessing the capacity to form IgG antibodies to protein antigens. To evaluate a patient's ability to respond to

Table 122-2 Characteristic Clinical Patterns in Some Primary Immunodeficiencies

FEATURES	DIAGNOSIS
IN NEWBORNS AND YOUNG INFANTS (0-6 MO)	
Hypocalcemia, unusual facies and ears, heart disease	DiGeorge anomaly
Delayed umbilical cord detachment, leukocytosis, recurrent infections	Leukocyte adhesion defect
Persistent thrush, failure to thrive, pneumonia, diarrhea	Severe combined immunodeficiency
Bloody stools, draining ears, atopic eczema	Wiskott-Aldrich syndrome
Pneumocystis jiroveci pneumonia, neutropenia, recurrent infections	X-linked hyper-IgM syndrome
IN INFANTS AND YOUNG CHILDREN (6 MO-5 YR)	
Severe progressive infectious mononucleosis	X-linked lymphoproliferative syndrome
Recurrent staphylococcal abscesses, staphylococcal pneumonia with pneumatocele formation, coarse facial features, pruritic dermatitis	Hyper-IgE syndrome
Persistent thrush, nail dystrophy, endocrinopathies	Chronic mucocutaneous candidiasis
Short stature, fine hair, severe varicella	Cartilage hair hypoplasia with short-limbed dwarfism
Oculocutaneous albinism, recurrent infection	Chédiak-Higashi syndrome
Abscesses, suppurative lymphadenopathy, antral outlet obstruction, pneumonia, osteomyelitis	Chronic granulomatous disease
IN OLDER CHILDREN (OLDER THAN 5 YR) AND ADULTS	
Progressive dermatomyositis with chronic enterovirus encephalitis	X-linked agammaglobulinemia
Sinopulmonary infections, neurologic deterioration, telangiectasia	Ataxia-telangiectasia
Recurrent neisserial meningitis	C6, C7, or C8 deficiency
Sinopulmonary infections, splenomegaly, autoimmunity, malabsorption	Common variable immunodeficiency

Ig, immunoglobulin.
Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

Table 122-3 Common Clinical Features of Immunodeficiency

Usually present	Recurrent upper respiratory infections Severe bacterial infections Persistent infections with incomplete or no response to therapy Paucity of lymph nodes and tonsils
Often present	Persistent sinusitis or mastoiditis (*Streptococcus pneumoniae, Haemophilus, Pneumocystis jiroveci, Staphylococcus aureus, Pseudomonas* spp.) Recurrent bronchitis or pneumonia Failure to thrive or growth retardation for infants or children; weight loss for adults Intermittent fever Infection with unusual organisms Skin lesions: rash, seborrhea, pyoderma, necrotic abscesses, alopecia, eczema, telangiectasia Recalcitrant thrush Diarrhea and malabsorption Hearing loss caused by chronic otitis Chronic conjunctivitis Arthralgia or arthritis Bronchiectasis Evidence of autoimmunity, especially autoimmune thrombocytopenia or hemolytic anemia Hematologic abnormalities: aplastic anemia, hemolytic anemia, neutropenia, thrombocytopenia History of prior surgery, biopsy
Occasionally present	Lymphadenopathy Hepatosplenomegaly Severe viral disease (e.g., EBV, CMV, adenovirus, varicella, herpes simplex) Chronic encephalitis Recurrent meningitis Deep infections: cellulitis, osteomyelitis, organ abscesses Chronic gastrointestinal disease, infections, lymphoid hyperplasia, sprue-like syndrome, atypical inflammatory bowel disease Autoimmune disease such as autoimmune thrombocytopenia, hemolytic anemia, rheumatologic disease, alopecia, thyroiditis, pernicious anemia Pyoderma gangrenosum Adverse reaction to vaccines Delayed umbilical cord detachment Chronic stomatitis or peritonitis

EBV, Epstein-Barr virus; CMV, cytomegalovirus.
Modified from Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, WB Saunders, p 1598.*

polysaccharide antigens, anti-pneumococcal antibodies can be measured before and 3 wk after immunization with 23 valent unconjugated pneumococcal polysaccharide vaccine in patients 2-3 yr old or older. Antibodies detected in these tests are of the IgG isotype. These antibody studies can be performed in several different laboratories, but it is important to choose a reliable laboratory and to use the same laboratory for preimmunization and postimmunization titers. In children older than 2 yr of age with low anti-pneumococcal antibody titers after a pneumococcal polysaccharide vaccine immunization, it is useful to boost with conjugate pneumococcal vaccine twice, 1 mo apart, before giving a polysaccharide pneumococcal vaccine 1 mo later and then measuring antibody titers 3 wk later. Patients with significant or permanent B-cell defects do not produce either IgM or IgG antibodies normally. If results of these tests prove to be normal and the immunoglobulins remain low, studies should be performed to evaluate the possible loss of immunoglobulins through the urinary or gastrointestinal tracts (nephrotic syndrome, protein-losing enteropathies, intestinal lymphangiectasia). Very high serum concentrations of 1 or more immunoglobulin classes suggest HIV infection, chronic granulomatous disease, chronic inflammation, or autoimmune lymphoproliferative syndrome.

IgG subclass measurements are seldom helpful in assessing immune function in children with recurrent infections. It is difficult to know the biologic significance of the various mild to moderate deficiencies of IgG subclasses, particularly when completely asymptomatic individuals have been described as totally lacking IgG_1, IgG_2, IgG_4, and/or IgA_1 owing to immunoglobulin heavy-chain gene deletions. Many healthy children have been described as having low levels of IgG_2 but normal responses to polysaccharide antigens when immunized. When children with low IgG_2 subclass levels and histories of

Table 122-4 Characteristic Features of Primary Immunodeficiency

CHARACTERISTIC	PREDOMINANT T-CELL DEFECT	PREDOMINANT B-CELL DEFECT	GRANULOCYTE DEFECT	COMPLEMENT DEFECT
Age at the onset of infection	Early onset, usually 2-6 mo of age	Onset after maternal antibodies diminish, usually after 5-7 mo of age, later childhood to adulthood	Early onset	Onset at any age
Specific pathogens involved	Bacteria: common Gram-positive and Gram-negative bacteria and mycobacteria Viruses: CMV, EBV, adenovirus, parainfluenza 3, varicella, enterovirus Fungi: *Candida* and *Pneumocystis jiroveci*	Bacteria: pneumococci, streptococci, staphylococci, *Haemophilus, Campylobacter, Mycoplasma* Viruses: enterovirus* Fungi and parasites: giardia, cryptosporidia	Bacteria: staphylococci, *Pseudomonas, Serratia, Klebsiella, Salmonella* Fungi and parasites: *Candida, Nocardia, Aspergillus*	Bacteria: pneumococci, *Neisseria*
Affected organs	Extensive mucocutaneous candidiasis, lungs, failure to thrive, protracted diarrhea	Recurrent sinopulmonary infections, chronic gastrointestinal symptoms, malabsorption, arthritis, enteroviral meningoencephalitis*	Skin: abscesses, impetigo, cellulitis Lymph nodes: suppurative adenitis Oral cavity: gingivitis, mouth ulcers Internal organs: abscesses, osteomyelitis	Infections: meningitis, arthritis, septicemia, recurrent sinopulmonary infections
Special features	Graft-vs-host disease caused by maternal engraftment or nonirradiated blood transfusion Postvaccination disseminated BCG or varicella Hypocalcemic tetany in infancy†	Autoimmunity Lymphoreticular malignancy: lymphoma, thymoma Postvaccination paralytic polio	Prolonged attachment of umbilical cord, poor wound healing	Autoimmune disorders: SLE, vasculitis, dermatomyositis, scleroderma, glomerulonephritis, angioedema

*X-linked (Bruton) agammaglobulinemia.
†DiGeorge anomaly.
BCG, Bacille Calmette-Guérin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus.
Modified from Woroniecka M, Ballow M: Office evaluation of children with recurrent infection, Pediatr Clin North Am *47:1211–1224, 2000.*

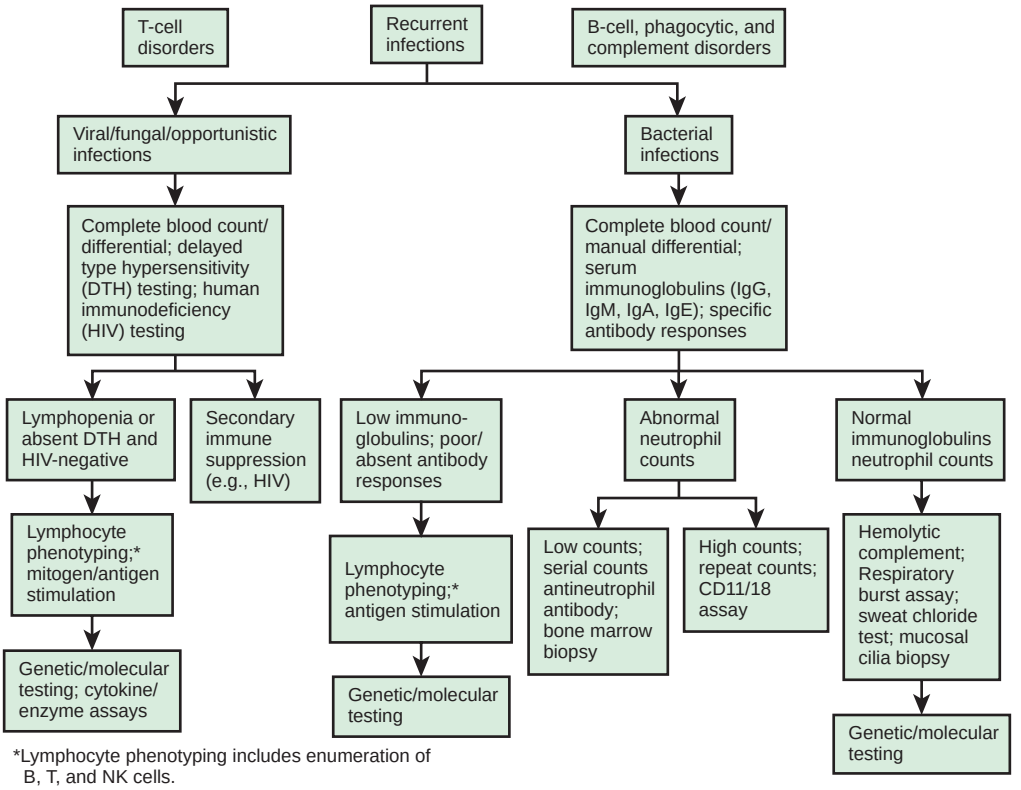

Figure 122-1 A diagnostic testing algorithm for primary immunodeficiency diseases. DTH, delayed-type hypersensitivity. *(From Lindegren ML, Kobrynski L, Rasmussen SA: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders,* MMWR Recomm Rep *53[RR-1]:1–29, 2004.)*

Table 122-5 Special Physical Features Associated with Immunodeficiency Disorders

CLINICAL FEATURES	DISORDERS
DERMATOLOGIC	
Eczema	Wiskott-Aldrich syndrome, IPEX, hyper-IgE syndromes, hypereosinophilia syndromes, IgA deficiency
Sparse and/or hypopigmented hair	Cartilage hair hypoplasia, Chédiak-Higashi syndrome, Griscelli syndrome
Ocular telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Severe dermatitis	Omenn syndrome
Erythroderma	Omenn syndrome, SCID, graft-vs-host disease, Comel-Netherton syndrome
Recurrent abscesses with pulmonary pneumatoceles	Hyper-IgE syndromes
Recurrent organ granulomas or abscesses, lung, liver and rectum especially	Chronic granulomatous disease
Recurrent abscesses or cellulitis	Chronic granulomatous disease, hyper-IgE syndrome, leukocyte adhesion defect
Cutaneous granulomas	Ataxia telangiectasia, SCID, CVID, RAG deficiency
Oral ulcers	Chronic granulomatous disease, severe combined immunodeficiency, congenital neutropenia
Periodontitis, gingivitis, stomatitis	Neutrophil defects
Oral or nail candidiasis	T-cell immune defects, combined defects (SCIDs); mucocutaneous candidiasis; hyper-IgE syndromes; IL-12, -17, -23 deficiencies; *CARD9* deficiency; *STAT1* deficiency
Vitiligo	B-cell defects, mucocutaneous candidiasis
Alopecia	B-cell defects, mucocutaneous candidiasis
Chronic conjunctivitis	B-cell defects
EXTREMITIES	
Clubbing of the nails	Chronic lung disease due to antibody defects
Arthritis	Antibody defects, Wiskott-Aldrich syndrome, hyper-IgM syndrome
ENDOCRINOLOGIC	
Hypoparathyroidism	DiGeorge syndrome, mucocutaneous candidiasis
Endocrinopathies (autoimmune)	Mucocutaneous candidiasis
Diabetes, hypothyroid	IPEX and IPEX-like syndromes
Growth hormone deficiency	X-linked agammaglobulinemia
Gonadal dysgenesis	Mucocutaneous candidiasis
HEMATOLOGIC	
Hemolytic anemia	B- and T-cell immune defects, ALPS
Thrombocytopenia, small platelets	Wiskott-Aldrich syndrome
Neutropenia	Hyper-IgM syndrome, Wiskott-Aldrich variant, chronic granulomatous disease
Immune thrombocytopenia	B-cell immune defects, ALPS
SKELETAL	
Short-limb dwarfism	Short-limb dwarfism with T- and/or B-cell immune defects
Bony dysplasia	ADA deficiency, cartilage hair hypoplasia

ADA, Adenosine deaminase deficiency; AID, activation-induced cytidine deaminase; ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immunodeficiency; GVHD, graft-vs-host disease; Ig, immunoglobulin; IPEX, X-linked immune dysfunction enteropathy polyendocrinopathy; SCID, severe combined immunodeficiency.

From Goldman L, Ausiello D: Cecil textbook of medicine, *ed 22, Philadelphia, 2004, Saunders, p 1599.*

Table 122-6 Initial Screening Immunologic Testing of the Child with Recurrent Infections

COMPLETE BLOOD COUNT, MANUAL DIFFERENTIAL, AND ERYTHROCYTE SEDIMENTATION RATE
Absolute lymphocyte count (normal result [Chapter 727] rules against T-cell defect)
Absolute neutrophil count (normal result [Chapter 727] rules against congenital or acquired neutropenia and [usually] both forms of leukocyte adhesion deficiency, in which elevated counts are present even between infections)
Platelet count (normal result excludes Wiskott-Aldrich syndrome)
Howell-Jolly bodies (absence rules against asplenia)
Erythrocyte sedimentation rate (normal result indicates chronic bacterial or fungal infection unlikely)
SCREENING TESTS FOR B-CELL DEFECTS
Immunoglobulin (Ig) A measurement; if abnormal, IgG and IgM measurement
Isohemagglutinins
Antibody titers to blood group substances, tetanus, diphtheria, *Haemophilus influenzae*, and pneumococcus
SCREENING TESTS FOR T-CELL DEFECTS
Absolute lymphocyte count (normal result indicates T-cell defect unlikely)
Flow cytometry to examine for the presence of naïve T cells (CD3+CD45RA+ cells)
SCREENING TESTS FOR PHAGOCYTIC CELL DEFECTS
Absolute neutrophil count
Respiratory burst assay
SCREENING TEST FOR COMPLEMENT DEFICIENCY
CH_{50}

frequent infections were studied in depth, they were found to have broader immunologic dysfunction, including poor responses to protein antigens, suggesting that they may have been in the process of developing into **common variable immunodeficiency (CVID).** Only when profound antibody deficiencies are detected despite normal levels of immunoglobulins are IgG subclass measurements occasionally helpful. Children who completely lack IgG_2 are usually unable to make antibodies to polysaccharide antigens, although this may also be found among individuals with normal IgG_2. Thus, specific antibody measurements are far more cost-effective than IgG subclass determinations.

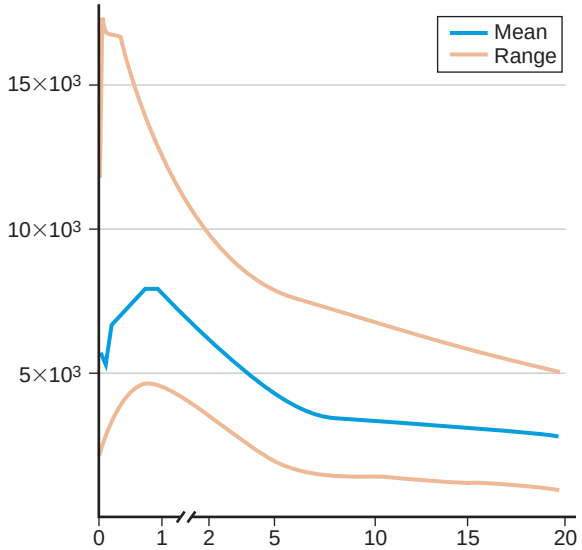

Figure 122-2 Absolute lymphocyte counts in normal individual during maturation. *(Data graphed from Altman PL:* Blood and other body fluids. *Prepared under the auspices of the Committee on Biological Handbooks. Washington, DC, 1961, Federation of American Societies for Experimental Biology.)*

Patients found to be **agammaglobulinemic** should have their blood B cells enumerated by **flow cytometry** using dye-conjugated monoclonal antibodies to B-cell–specific CD antigens (usually CD19 or CD20). Normally, approximately 8-10% of circulating lymphocytes are B cells. B cells are absent in X-linked agammaglobulinemia (XLA) and in several very rare autosomal recessive conditions, but they are present in CVID, IgA deficiency, and hyper-IgM syndromes. This distinction is important, because children with hypogammaglobulinemia from XLA and CVID can have different clinical problems, and the 2 conditions clearly have different inheritance patterns. Patients with XLA have a heightened susceptibility to persistent enteroviral infections, whereas those with CVID have more problems with autoimmune diseases and lymphoid hyperplasia. Molecular testing for XLA and other B-cell defects (see Chapter 124.1) is indicated in cases without a family history to aid genetic counseling.

T CELLS

T cells and T-cell subpopulations can be enumerated by **flow cytometry** using dye-conjugated monoclonal antibodies recognizing CD antigens present on T cells (i.e., CD2, CD3, CD4, and CD8). This is a particularly important test to perform on any infant who is lymphopenic, because $CD3^+$ T cells usually constitute 70% of peripheral lymphocytes. Regardless of molecular type, infants with SCID are unable to produce T cells so are lymphopenic at birth. The flow cytometry for infants suspected of having SCID should also include monoclonal antibodies to naïve (CD45RA) and memory (CD45RO) T cells. In normal infants, more than 95% of the T cells are CD45RA+ (naïve) T cells. If the infant is a SCID, there could be transplacentally transferred maternal T cells detected by flow cytometry, but they would be dominantly CD45RO+ T cells. SCID is a pediatric emergency that can be

Table 122-7 Laboratory Tests in Immunodeficiency

SCREENING TESTS	ADVANCED TESTS	RESEARCH/SPECIAL TESTS
B-CELL DEFICIENCY		
IgG, IgM, IgA, and IgE levels	B-cell enumeration (CD19 or CD20)	Advanced B-cell phenotyping
Isohemagglutinin titers		Biopsies (e.g., lymph nodes)
Ab response to vaccine antigens (e.g., tetanus, diphtheria, pneumococci, *Haemophilus influenzae*)	Ab responses to boosters or to new vaccines	Ab responses to special antigens (e.g., bacteriophage φX174), mutation analysis
T-CELL DEFICIENCY		
Lymphocyte count	T-cell subset enumeration (CD3, CD4, CD8)	Advanced flow cytometry
Chest x-ray examination for thymic size*	Proliferative responses to mitogens, antigens, allogeneic cells	Enzyme assays (e.g., ADA, PNP)
		Thymic imaging
Delayed skin tests (e.g., *Candida*, tetanus toxoid)	HLA typing	Mutation analysis
	Chromosome analysis	T-cell activation studies
		Apoptosis studies
		Biopsies
PHAGOCYTIC DEFICIENCY		
WBC count, morphology	Adhesion molecule assays (e.g., CD11b/CD18, selectin ligand)	Mutation analysis
Respiratory burst assay	Mutation analysis	Enzyme assays (e.g., MPO, G6PD, NADPH oxidase)
COMPLEMENT DEFICIENCY		
CH_{50} activity	AH50, activity	
C3 level	Component assays	
C4 level	Activation assays (e.g., C3a, C4a, C4d, C5a)	

*In infants only.

Ab, antibody; ADA, adenosine deaminase; C, complement; CH, hemolytic complement; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leukocyte antigen; Ig, immunoglobulin; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; PNP, purine nucleoside phosphorylase; WBC, white blood cell; φX, phage antigen.

Modified from Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, Saunders.*

Table 122-8 2003 Modified IUIS Classification of Primary and Secondary Immunodeficiencies

GROUPS AND DISEASES	INHERITANCE
A. PREDOMINANTLY ANTIBODY DEFICIENCIES	
XL agammaglobulinemia	XL
AR agammaglobulinemia	AR
Hyper-IgM syndromes	XL and AR
a. CD40L defect	XL
b. AID defect	AR
c. CD40 defect	AR
d. UNG defect	AR
e. Other hyper-IgM defects	AR
Ig heavy-chain gene deletions	AR
κ Chain deficiency mutations	AR
Selective IgA deficiency	AD
Common variable immunodeficiency	AD
B. SEVERE COMBINED IMMUNODEFICIENCIES	
$T^-B^+NK^-$ SCID	
a. X-linked (γc deficiency)	XL
b. Autosomal recessive (Jak3 deficiency)	AR
$T^-B^+NK^+$ SCID	
a. IL-7 Rα deficiency	AR
b. CD3δ, CD3ε, or CD3ζ deficiencies	AR
c. CD45 deficiency	AR
$T^-B^-NK^+$ SCID	
a. RAG-1/2 deficiency	AR
b. Artemis defect	AR
Omenn Syndrome	
a. RAG-1/2 deficiency	AR
b. IL-7Rα deficiency	AR
c. γc deficiency	XL
Combined Immunodeficiencies	
a. Purine nucleoside phosphorylase deficiency	AR
b CD8 deficiency (ZAP-70 defect)	AR
c. MHC class II deficiency	AR
d. MHC class I deficiency caused by TAP-1/2 mutations	AR
Reticular dysgenesis	AR
C. OTHER CELLULAR IMMUNODEFICIENCIES	
Wiskott-Aldrich syndrome	XL
Ataxia-telangiectasia	AR
DiGeorge anomaly	?
D. DEFECTS OF PHAGOCYTIC FUNCTION	
Chronic Granulomatous Disease	
a. XL	XL
b. AR	AR
1. p22 phox deficiency	
2. p47 phox deficiency	
3. p67 phox deficiency	
Leukocyte adhesion defect 1	AR
Leukocyte adhesion defect 2	AR
Neutrophil G6PD deficiency	XL
Myeloperoxidase deficiency	AR
Secondary granule deficiency	AR
Shwachman syndrome	AR
Severe congenital neutropenia (Kostmann)	AR
Cyclic neutropenia (elastase defect)	AR
Leukocyte mycobacterial defects	AR
IFN-γR1 or R2 deficiency	AR
IFN-γR1 deficiency	AD
IL-12Rβ1 deficiency	AR
IL-12p40 deficiency	AR
STAT1 deficiency	AD
E. IMMUNODEFICIENCIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS	
Fas deficiency	AD
Fas ligand deficiency	
FLICE or caspase 8 deficiency	
Unknown (caspase 3 deficiency)	
F. COMPLEMENT DEFICIENCIES	
C1q deficiency	AR
C1r deficiency	AR
C4 deficiency	AR
C2 deficiency	AR
C3 deficiency	AR
C5 deficiency	AR
C6 deficiency	AR
C7 deficiency	AR
C8α deficiency	AR
C8β deficiency	AR
C9 deficiency	AR
C1 inhibitor	AD
Factor I deficiency	AR
Factor H deficiency	AR
Factor D deficiency	AR
Properdin deficiency	XL
G. IMMUNODEFICIENCY ASSOCIATED WITH OR SECONDARY TO OTHER DISEASES	
Chromosomal Instability or Defective Repair	
Bloom syndrome	
Fanconi anemia	
ICF syndrome	
Nijmegen breakage syndrome	
Seckel syndrome	
Xeroderma pigmentosum	
Chromosomal Defects	
Down syndrome	
Turner syndrome	
Chromosome 18 rings and deletions	
Skeletal Abnormalities	
Short-limbed skeletal dysplasia	
Cartilage-hair hypoplasia	
Immunodeficiency with Generalized Growth Retardation	
Schimke immuno-osseous dysplasia	
Immunodeficiency with absent thumbs	
Dubowitz syndrome	
Growth retardation, facial anomalies, and immunodeficiency	
Progeria (Hutchinson-Gilford syndrome)	
Immunodeficiency with Dermatologic Defects	
Partial albinism	
Dyskeratosis congenita	
Netherton syndrome	
Acrodermatitis enteropathica	
Anhidrotic ectodermal dysplasia	
Papillon-Lefèvre syndrome	
Hereditary Metabolic Defects	
Transcobalamin 2 deficiency	
Methylmalonic acidemia	
Type 1 hereditary orotic aciduria	
Biotin-dependent carboxylase deficiency	
Mannosidosis	
Glycogen storage disease, type 1b	
Chédiak-Higashi syndrome	
Hypercatabolism of Immunoglobulin	
Familial hypercatabolism	
Intestinal lymphangiectasia	
H. OTHER IMMUNODEFICIENCIES	
Hyper-IgE syndromes	AD and AR
Chronic mucocutaneous candidiasis	
Chronic mucocutaneous candidiasis with polyendocrinopathy (APECED)	AR
Hereditary or congenital hyposplenia or asplenia	
Ivemark syndrome	
IPEX syndromes	XL
Ectodermal dysplasia (NEMO defect)	XL

AD, autosomal dominant; ADA, adenosine deaminase; AID, activation-induced cytidine deaminase; APECED, autoimmune, polyendocrinopathy, candidiasis, ectodermal dystrophy; AR, autosomal recessive; caspase, cysteinyl aspartate specific proteinase; FLICE, Fas-associating protein with death domain–like IL-1–converting enzyme; G6PD, glucose 6-phosphate dehydrogenase; ICF, immunodeficiency, centromeric instability, facial anomalies; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy; IUIS, International Union of Immunological Societies; MHC, major histocompatibility complex; NEMO, nuclear factor B essential modulator; SCID, severe combined immunodeficiency; TAP-2, transporter associated with antigen presentation; UNG, uracil-N-glycosylase; XL, X-linked.

Modified from (no authors listed) Primary immunodeficiency diseases. Report of an International Union of Immunological Studies Scientific Committee, Clin Exp Immunol *118:1–28, 1999; Chapel H, Geha R, Rosen F: IUIS PID (Primary Immunodeficiencies) Classification committee: Primary immunodeficiency diseases: an update,* Clin Exp Immunol *132:9–15, 2003; Stiehm ER, Ochs HD, Winkelstein JA:* Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

successfully treated by nonablative stem cell transplantation in more than 92% of cases if diagnosed before serious, untreatable infections develop. Normally, there are roughly twice as many $CD4^+$ (helper) T cells as there are $CD8^+$ (cytotoxic) T cells. Because there are examples of severe immunodeficiency in which phenotypically normal T cells are present, tests of T-cell function are far more informative and cost-effective than enumeration of T-cell subpopulations by flow cytometry. T cells are normally stimulated through their T-cell receptors by antigen present in the groove of major histocompatibility complex molecules. The T-cell receptor can also be stimulated directly with **mitogens** such as phytohemagglutinin, concanavalin A, or pokeweed mitogen. After 3-5 days of incubation with the mitogen, the proliferation of T cells is measured by the incorporation of radiolabeled thymidine into DNA. Other stimulants that can be used to assess T-cell function in the same type of assay include antigens (*Candida,* tetanus toxoid) and allogeneic cells (see Table 122-6).

NATURAL KILLER CELLS

Natural killer (NK) cells can be enumerated by flow cytometry using monoclonal antibodies to NK-specific CD antigens, CD16 and CD56. NK function is assessed by a radiolabeled chromium-release assay, using the cell line K562, which is readily killed by NK cells.

PHAGOCYTIC CELLS

Killing defects of phagocytic cells, which should be suspected if a patient has recurrent staphylococcal abscesses or gram-negative infections, can be evaluated by screening tests measuring the neutrophil respiratory burst after phorbol ester stimulation. The most reliable and useful test of this type is a flow cytometric assessment of the respiratory burst using rhodamine dye. Leukocyte adhesion deficiencies can be easily diagnosed by flow cytometric assays of blood lymphocytes or neutrophils, using monoclonal antibodies to CD18 or CD11 (LAD1) or to CD15 (LAD2).

Phagocytic cell defects can be further defined according to their molecular cause. Mutations in the genes encoding 5 different components of the NADPH pathway have been discovered in various patients with chronic granulomatous disease. It is important to identify the specific molecular type of chronic granulomatous disease to provide appropriate genetic counseling, as 1 type is X linked and the other 4 types are autosomal recessive. Early diagnosis of leukocyte adhesion deficiency is of crucial importance because stem cell transplantation can be lifesaving.

COMPLEMENT

The most effective screening test for complement defects is a CH_{50} assay, which is a bioassay that measures the intactness of the entire complement pathway and yields abnormal results if complement has been consumed from the specimen for any reason. Genetic deficiencies in the complement system are usually characterized by extremely low CH_{50} values. The most common cause of an abnormal CH_{50} result, however, is a delay in or improper transport of the specimen to the laboratory. Specific immunoassays for C3 and C4 are commercially available, but further identification of other complement component deficiencies is usually possible only in research laboratories. Nevertheless, it is extremely important to identify which component is missing, because there are different disease susceptibilities depending on whether there are deficiencies of early or late components (see Chapter 134). Identifying the mode of inheritance is also important for genetic counseling. Properdin deficiency is X linked, but all of the other complement deficiencies are autosomal. Measurement of C4 can be helpful in assessing suspected hereditary angioedema.

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Section 2

The T-, B-, and NK-Cell Systems

Chapter 123

T Lymphocytes, B Lymphocytes, and Natural Killer Cells

Rebecca H. Buckley

Defense against infectious agents is secured through a combination of anatomic physical barriers including the skin, mucous membranes, mucous blanket, and ciliated epithelial cells, as well as the various components of the immune system. The **immune system** of vertebrates integrates 2 fundamental response mechanisms. **Innate (natural) immunity** responds to infection regardless of previous exposure to the agent and includes polymorphonuclear leukocytes, dendritic and mononuclear phagocytic cells, natural killer (NK) cells, various receptors that recognize common pathogen antigens (Toll-like receptors) and the complement system. **Acquired (adaptive) immunity** is a highly specific response that includes T and B lymphocytes. The immune system also helps protect against malignancy and autoimmunity.

LYMPHOPOIESIS IN THE FETUS

Origin of the Lymphoid System

The human immune system arises in the embryo from gut-associated tissue. Pluripotential hematopoietic stem cells first appear in the yolk sac at 2.5-3 wk of gestational age, migrate to the fetal liver at 5 wk of gestation, and later reside in the bone marrow, where they remain throughout life (Fig. 123-1). Lymphoid stem cells develop from such precursor cells and differentiate into T, B, or NK cells, depending on the organs or tissues to which the stem cells traffic. Development of the **primary lymphoid organs**—thymus and bone marrow—begins during the middle of the 1st trimester of gestation and proceeds rapidly. Development of the **secondary lymphoid organs**—spleen, lymph nodes, tonsils, Peyer patches, and lamina propria—soon follows. These organs serve as sites of differentiation of T, B, and NK lymphocytes from stem cells throughout life. Both the initial organogenesis and the continued cell differentiation occur as a consequence of the interaction of a vast array of lymphocytic and microenvironmental cell surface molecules and proteins secreted by the involved cells. The complexity and number of lymphoid cell surface molecules led to the development of an international nomenclature for **clusters of differentiation (CD)** (Table 123-1).

T and B lymphocytes are the only components of the immune system that have antigen-specific recognition capabilities and are responsible for adaptive immunity. NK cells are lymphocytes that are also derived from hematopoietic stem cells and are thought to have a role in host defense against viral infections, tumor surveillance, and immune regulation, but they do not have antigen receptors. Nonantibody proteins synthesized and secreted by T, B, and NK cells, and by the cells with which they interact, act as intercellular mediators and are referred to as **cytokines** or **interleukins (ILs)** (Table 123-2). Cytokines have the ability to act in an autocrine, paracrine, or endocrine manner

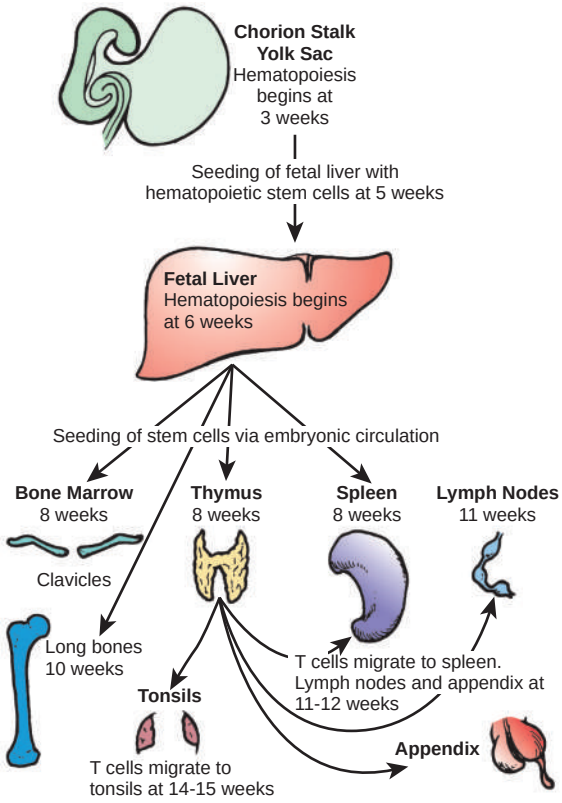

Figure 123-1 Migration patterns of hematopoietic stem cells and mature lymphocytes during human fetal development. *(From Haynes BF, Denning SM: Lymphopoiesis. In Stamatoyannopoulis G, Nienhuis A, Majerus P, editors:* Molecular basis of blood diseases, *ed 2, Philadelphia, 1994, WB Saunders.)*

to promote and facilitate differentiation and proliferation of the cells of the immune system.

T-Cell Development and Differentiation

The primitive thymic rudiment is formed from the ectoderm of the 3rd branchial cleft and endoderm of the 3rd branchial pouch at 4 wk gestation. Beginning at 7-8 wk, the right and left rudiments move caudally and fuse in the midline. Bloodborne T-cell precursors from the fetal liver then begin to colonize the perithymic mesenchyme at 8 wk gestation, and at 8-8.5 wk gestation are found intrathymically. The earliest cells to enter the thymus are found in the subcapsular region and do not express CD3, CD4, CD8, or either type of T-cell receptor. These lymphoid cell precursors are triggered to proliferate and become thymocytes through interactions with the thymic stroma. These cells express CD44 and c-kit (CD117) and slightly later the α chain of the IL-2 receptor. The cells are arrested at this stage until they productively rearrange the β chain locus of the T-cell receptor. The inframe β chain then pairs with the surrogate pre-T α chain and is expressed on the cell surface, which triggers entry into the cell cycle. The presence of small amounts of pre-T α:β on the cell surface in association with CD3 triggers rapid proliferation of these cells, the loss of CD25 and the termination of β-chain gene rearrangement. After cell proliferation ceases, CD4 and CD8 are expressed simultaneously (i.e., they are double-positive thymocytes). Fetal cortical thymocytes are among the most rapidly dividing cells in the body and increase in number by 100,000-fold within 2 wk after stem cells enter the thymus. As these cells proliferate and mature, they migrate deeper into the thymic cortex. The double-positive thymocytes begin efficient rearrangement of the α-chain locus, express low levels of an α:β **T-cell receptor (TCR)** and the associated CD3 complex and are then ready for thymic selection. TCR gene rearrangement begins shortly after colonization of the thymus with stem cells, and the establishment of the T-cell repertoire begins at 8-10 wk of gestation. The mature TCR is a heterodimer of 2 chains, either α and β or γ and δ, that is coexpressed on the cell surface with **CD3,** a complex of 5 polypeptide chains (γ, δ, ε, ζ, η). TCR gene rearrangement occurs by a process in which large, noncontiguous blocks of DNA are spliced together. These segments, known as **V (variable), D (diversity),** and **J (joining),** each have a number of variants. VDJ segments are joined to a constant region of the α gene, and VDJ segments are joined to the β gene to complete the receptor polypeptide genes. Random combinations of the segments account for much of the enormous diversity of TCRs that enables humans to recognize millions of different antigens. TCR gene rearrangement requires the presence of **recombinase activating genes,** *RAG-1* and *RAG-2,* as well as other recombinase components. This process is flawed in both mice and humans with severe combined immunodeficiency (SCID) because of mutations in genes that encode components of the VDJ recombination process. By 9.5-10 wk, more than 95% of thymocytes express CD2, CD4, CD7, CD8, and c (cytoplasmic) CD3, and ≈30% bear the CD1 inner cortical thymocyte antigen. By 10 wk, 25% of thymocytes bear αβ TCRs. Ti αβ T cells gradually increase in number during embryonic life and represent more than 95% of thymocytes postnatally.

As immature cortical thymocytes begin to express TCRs, the processes of positive and negative selection take place. **Positive selection** occurs through the interaction of immature thymocytes, which express low levels of TCR, with major histocompatibility complex (MHC) antigens present on cortical thymic epithelial cells. As a result, thymocytes with TCR capable of interacting with foreign antigens presented on self human leukocyte antigen (HLA) molecules are activated and develop to maturity. Most (>98%) of the cells die by failing to be positively selected or as a consequence of negative selection, but some are selected to mature into CD4 or CD8 single positive cells. Mature thymocytes that survive the selection process either express CD4 and are restricted to interacting with self class II HLA antigens, or express CD8 and are restricted to interacting with self class I HLA antigens when foreign antigens are presented by these MHC molecules. **Negative selection** occurs next in the medulla and is mediated by interaction of the surviving thymocytes, which have much higher levels of TCR expression, with host peptides presented by HLA class I or II antigens present on bone marrow-derived thymic macrophages, dendritic cells, and possibly B cells. This interaction mediates **apoptosis** (programmed cell death) of such autoreactive thymocytes. The thymic medulla contains only mature single-positive T cells that eventually leave the thymus and enter the bloodstream. T-cell functions are acquired concomitantly with the development of single-positive thymocytes, but they are not fully developed until the cells emigrate from the thymus. T cells begin to emigrate from the thymus to the spleen, lymph nodes, and appendix at 11-12 wk of embryonic life, and to the tonsils by 14-15 wk. They leave the thymus via the bloodstream and are distributed throughout the body, with the heaviest concentrations in the paracortical areas of lymph nodes, the periarteriolar areas of the spleen, and the thoracic duct lymph. Recent thymic emigrants coexpress the CD45RA isoforms and CD62L (L-selectin). Rearrangement of the TCR locus during intrathymic T-cell development results in the excision of DNA and the excised elements form circular episomes as a by-product. These **TCR recombination excision circles** can be detected in T cells that are recent thymic emigrants, whereas T cells that develop extrathymically do not contain these episomes. Inability to detect TCR recombination excision circles by real-time polymerase chain reaction of DNA from the dried blood spots collected from infants shortly after birth is the test used for newborn screening for SCID. The homing of lymphocytes to peripheral lymphoid organs is directed by the interaction of a lymphocyte surface adhesion molecule, L-selectin, with carbohydrate moieties on specialized regions of lymphoid organ blood vessels called **high endothelial venules.** By 12 wk gestation, T cells can proliferate in response to plant lectins, such as phytohemagglutinin and concanavalin A, and to allogeneic cells; antigen-binding T cells have been found by 20 wk gestation. **Hassall's corpuscles (bodies),** which are swirls of terminally differentiated medullary epithelial cells, are first seen in the thymic medulla at 16-18 wk of embryonic life.

Table 123-1 CD Classification of Some Lymphocyte Surface Molecules

CD NUMBER	OTHER NAMES	TISSUE/LINEAGE	FUNCTION
CD1	T6	Cortical thymocytes; Langerhans cells	Lipid antigen presentation to TCRγδ cells
CD2	SRBC receptor	T and NK cells	Binds LFA-3 (CD58); alternative pathway of T-cell activation
CD3	T3, Leu 4	T cells	TCR-associated; transduces signals from TCR
CD4	T4, Leu3a	Helper T-cell subset	Receptor for HLA class II antigens; associated with p56 *lck* tyrosine kinase
CD7	3A1, Leu 9	T and NK cells and their precursors	Comitogenic for T lymphocytes
CD8	T8, Leu2a	Cytotoxic T-cell subset; also on 30% of NK cells	Receptor for HLA class I antigens; associated with p56 *lck* tyrosine kinase
CD10	cALLA	B-cell progenitors	Peptide cleavage
CD11a	LFA-1a ∀ chain	T, B, and NK cells	With CD18, ligand for ICAMs 1, 2, and 3
CD11b, c	MAC-1, CR3; CR4	NK cells	With CD18, receptors for C3bi
CD16	FcRIII	NK cells	FcR for IgG
CD19	B4	B cells	Regulates B-cell activation
CD20	B1	B cells	Mediates B-cell activation
CD21	B2	B cells	C3d, also the receptor for EBV; CR2
CD25	IL-2Rα	T, B, and NK cells	Mediates signaling by IL-2
CD34	My10	Stem cells	Binds to L-selectin
CD38	T10	T, B, and NK cells and monocytes	Associates with hyaluronic acid
CD40	CD40	B cells and monocytes	Initiates isotype switching in B cells when ligated
CD44	CD44	Bone marrow stromal and many other cells.	Matrix adhesion molecule
CD45	Leukocyte common antigen, T200	All leukocytes	Tyrosine phosphatase that regulates lymphocyte activation; CD45R0 isoform on memory T cells, CD45RA isoform on naïve T cells
CD56	NCAM; NKH-1	NK cells	Mediates NK homotypic adhesion
CD62L	L-selectin	Marker for recent thymic emigrants. Also found on other leukocytes.	Cell adhesion molecule
CD69	CD69	T cells and NK cells	Early activation marker
CD73	Ecto-5′-nucleotidase	T and B cells	Associates with AMP
CD80	B7.1	B cells	Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor
CD86	B7.2	B cells	Costimulatory with CD28 on T cells to upregulate high affinity IL-2 receptor
CD117	c-kit	Pro-B cells, double-negative thymocytes	Receptor for stem cell factor
CD127	IL-7Rα	T cells	Mediates IL-7 signaling
CD132	Common γ chain (γc)	T, B, and NK cells	Mediates signaling by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21
CD154	CD40 ligand, gp39	Activated $CD4^+$ T cells	Ligates CD40 on B cells and initiates isotype switching
CD278	ICOS	T cells	Interacts with B7-H2

AMP, Adenosine monophosphate; CD, cluster of differentiation; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; ICAM, intracellular adhesion molecule; ICOS, inducible costimulator; Ig, immunoglobulin; IL, interleukin; LFA, lymphocyte function-associated antigen; MAC, membrane attack complex; NCAM, neural cell adhesion molecule; NK, natural killer; SRBC, sheep red blood cell; TCR, T-cell receptor.

B-Cell Development and Differentiation

In parallel with T-cell differentiation, B-cell development begins in the fetal liver before 7 wk of gestation. Fetal liver CD34 stem cells are seeded to the bone marrow of the clavicles by 8 wk of embryonic life and to that of the long bones by 10 wk (see Fig. 123-1). **As B cells differentiate from primitive stem cells, they proceed through stages that are marked by the sequential rearrangement of immunoglobulin gene segments to generate a diverse repertoire of antigen receptors.** The early **pro-B cell** is the first descendent of the pluripotential stem cell committed to B-lineage development and in this stage, the heavy chain locus rearranges first. In the early pro-B cell, D-J rearrangements are made on both chromosomes. In the late pro-B cell, the V segment rearranges to a D-J gene segment, but it is a matter of chance whether the juxtaposed J sequence and the μ constant region sequence downstream can be read in the correct reading frame. There is a roughly 2 in 3 chance that an out-of-frame sequence will occur,

Table 123-2 Functional Classification of Cytokines*

1. Cytokines involved in natural immune responses
   - Type I interferons (IFN-α and IFN-β): inhibit viral replication, inhibit cell proliferation, activate NK cells, and upregulate class I MHC molecule expression
   - TNF-α: mediates host response to Gram-negative bacteria and other infectious agents
   - IL-1α and -1β: mediate host inflammatory response to infectious agents
   - IL-1Ra: a natural antagonist of IL-1, blocks signals delivered by IL-1
   - IL-6: mediates and regulates inflammatory responses
   - Chemokines (IL-8, monocyte chemotactic protein-1 or MCP-1, RANTES, and others): mediate leukocyte chemotaxis and activation
2. Lymphocyte regulatory cytokines
   a. Immunostimulatory or growth-promoting
      - IL-1: costimulates activation of T cells
      - IL-2: growth factor for T, B, NK cells; activates NK and T effector cells
      - IL-4: T- and B-cell growth factor; stimulates IgE production; upregulates classes I and II MHC molecules and FcRεII expression on macrophages; expansion of Th2 subset
      - IL-5: B-cell growth and activation
      - IL-6: growth factor for B cells
      - IL-7: stromal cell factor; growth factor for precursor B and T cells, T-cell homeostatic factor
      - IL-10: growth and differentiation factor for B cells
      - IL-9: growth factor for T cells, B cells, mast cells, eosinophils, neutrophils, endothelial cells
      - IL-12: expansion of Th1 subset; activates effector cells
      - IL-13: growth and differentiating factor for B cells; stimulates IgE production; upregulates Classes I and II MHC molecules and FcRεII expression on macrophages
      - TNF-β: stimulates effector cell function
      - IL-15: regulates NK-cell development and memory cell homeostasis
      - IL-17: promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells.
      - IL-18: induces IFN-γ, GM-CSF, TNF-α in immunocompetent cells
      - IL-21: together with IL-4 regulates IgG and IgE class-switching and Ig synthesis
      - IL-23: autocrine growth factor for Th17 cells
      - IL-27: produced by antigen presenting cells and regulates both T and B cell activity
      - IFN-γ: activates macrophages, NK cells; upregulates classes I and II MHC molecules expression; inhibits IL-4– or IL-13–induced IgE production
   b. Immunosuppressive
      - IL-1Rα: regulates IL-1 activities
      - TGF-β: antagonizes lymphocyte responses
      - IL-10: inhibits activities of Th1 cells
      - IFN-α/β: inhibits production of IFN-γ
3. Hematopoiesis regulating cytokines
   - GM-CSF, G-CSF, M-CSF: colony-stimulating factors
   - Erythropoietin (EPO): differentiation of erythroid precursors
   - IL-3, SCF, c-kit receptor: regulate stem cell development
   - IL-4: mast cell development
   - IL-5: eosinophil differentiation and proliferation
   - IL-6: differentiation of B cells
   - IL-7: differentiation of B and T cells
   - IL-8: promotes cell survival in response to hematopoietic cytokines
   - IL-9: mast-cell growth factor
   - IL-11: elevates platelet count in patients given chemotherapy
   - IL-12: expands and activates resting NK cells
   - IL-15: expands and activates resting NK cells
   - IL-21: limits viability of NK cells
4. Proinflammatory cytokines
   - IL-1, TNF-α, IL-6: participate in the acute-phase response and synergize to mediate inflammation, shock, and death
   - IL-12: stimulates IFN (production by T and NK cells)
   - IL-17: acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and GM-CSF
   - IL-18: induces IFN-γ, GM-CSF, TNF-α; upregulates chemokine receptors
   - IL-23: drives the development of autoreactive IL-17–producing T cells and promotes chronic inflammation
5. Antiinflammatory cytokines
   - IL-4: reduces endotoxin-induced TNF and IL-1 production
   - IL-6: inhibits TNF production
   - IL-10: suppresses lymphocyte functions and downregulates production of proinflammatory cytokines; antiatherogenic
   - IL-11: cytoprotective effect on bowel mucosa, skin and joint inflammation
   - IL-13: downregulates functions of macrophages, suppresses production of proinflammatory cytokines
   - TGF-β: has immunosuppressive effects, inhibits IL-1 and TNF gene expression
   - IL-1Rα: competes with the binding of IL-1 to its cell surface receptors and blocks IL-1R
   - TNFsR: soluble TNF receptor; by binding TNF, blocks interaction of TNF with the target cell

*This is not an exhaustive list.

G-CSF, Granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-1R, interleukin-1 receptor; M-CSF, macrophage colony-stimulating factor; MHC, major histocompatibility complex; MCP-1, monocyte chemotactic protein; NK, natural killer; RANTES, regulated on activation normal t cell expressed and secreted; SCF, stem cell factor; TGF, transforming growth factor; Th1, Th2, Th17, T-helper types 1, 2, and 17; TNF, tumor necrosis factor.

Modified from Whiteside TL: Cytokine measurements and interpretation of cytokine assays in human disease, J Clin Immunol *14:327–339, 1994.*

and only those cells that have productive rearrangements will survive, so a majority of cells are lost. The next stage is the **pre-B cell,** during which immunoglobulin (Ig) light chain genes are rearranged. The **pre-B cell** is distinguished by the expression of cytoplasmic μ heavy chains but no sIgM, because immunoglobulin light chains are not yet produced. The pre-B cells must rearrange the same light chain gene on both chromosomes for a productive rearrangement, so when this does not happen the cells are lost. Fewer cells are lost between the pre-B and immature B cell stages than in the pro-B to pre-B transition. Next is the **immature B-cell** stage, during which the light-chain genes have already been rearranged and sIgM but not sIgD is expressed. The last stage of antigen-independent B-cell development is the **mature or virgin B cell,** which co-expresses both sIgM and sIgD. Pre-B cells can be found in fetal liver at 7 wk gestation, sIgM+ and sIgG+ B cells at between 7 and 11 wk, and sIgD+ and sIgA+ B cells by 12-13 wk. By 14 wk of embryonic life, the percentage of circulating lymphocytes bearing sIgM and sIgD is the same as in cord blood and slightly higher than in the blood of adults.

Antigen-dependent stages of B-cell development are those that develop after the mature or virgin B cell is stimulated by antigen through its antigen receptor (sIg); the outcome is the differentiation of the cell and its progeny into sIg+ memory (CD27) B cells (for that particular antigen) and plasma cells, which synthesize and secrete antibody, which is **antigen-specific immunoglobulin.** Deficiency of activation-induced cytidine deaminase (AICDA) or of uracil DNA glycosylase (UNG), as seen in 2 forms of autosomal recessive hyper IgM, can result in a failure of isotype switching so that only IgM antibodies are formed.

There are 5 **immunoglobulin isotypes**, which are defined by unique heavy-chains: IgM, IgG, IgA, IgD, and IgE. IgG and IgM, the only complement-fixing isotypes, are the most important immunoglobulins in the blood and other internal body fluids for protection against infectious agents. IgM is confined primarily to the intravascular compartment because of its large size, whereas IgG is present in all internal body fluids. IgA is the major protective immunoglobulin of external secretions—in the gastrointestinal, respiratory, and urogenital tracts—but it is also present in the circulation. IgE, present in both internal and external body fluids, has a major role in host defense against parasites. Because of high-affinity IgE receptors on basophils and mast cells, however, IgE is the principal mediator of allergic reactions of the immediate type. The significance of IgD is still not clear. There are also **immunoglobulin subclasses** including 4 subclasses of IgG (IgG_3, IgG_2, IgG_3, and IgG_4) and 2 subclasses of IgA (IgA_1 and IgA_2). These subclasses each have different biologic roles. For example, antipolysaccharide antibody activity is found predominantly in the IgG_2 subclass. Secreted IgM and IgE have been found in abortuses as young as 10 wk, and IgG as early as 11-12 wk. Even though these B-cell developmental stages have been described in the context of B-cell ontogeny in utero, it is important to recognize that the process of B-cell development from pluripotential stem cells goes on throughout postnatal life. Despite the capacity of fetal B lymphocytes to differentiate into immunoglobulin-synthesizing and -secreting cells, plasma cells are not usually found in lymphoid tissues of a fetus until about 20 wk gestation, and then only rarely, because of the sterile environment of the uterus. Peyer patches have been found in significant numbers by the 5th intrauterine mo, and plasma cells have been seen in the lamina propria by 25 wk gestation. Before birth there may be primary follicles in lymph nodes, but secondary follicles are usually not present.

A human fetus begins to receive significant quantities of maternal IgG transplacentally at around 12 wk gestation, and the quantity steadily increases until, at birth, cord serum contains a concentration of IgG comparable to or greater than that of maternal serum. IgG is the only class to cross the placenta to any significant degree. All 4 IgG subclasses cross the placenta, but IgG_2 does so least well. A small amount of IgM (10% of adult levels) and a few nanograms of IgA, IgD, and IgE are normally found in cord serum. Because none of these proteins crosses the placenta, they are presumed to be of fetal origin. These observations raise the possibility that certain antigenic stimuli normally cross the placenta to provoke responses, even in uninfected fetuses. Some atopic infants occasionally have IgE antibodies to antigens, such as egg white, to which they have had no known exposure during postnatal life, suggesting that synthesis of these antibodies could have been induced in the fetus by antigens ingested by the mother.

Natural Killer–Cell Development

NK cell activity is found in human fetal liver cells at 8-11 wk of gestation. NK lymphocytes are also derived from bone marrow precursors. Thymic processing is not necessary for NK-cell development, although NK cells have been found in the thymus. After release from bone marrow, NK cells enter the circulation or migrate to the spleen, with very few NK cells in lymph nodes. In normal individuals, NK cells represent 8-10% of lymphocytes, but the percentages are sometimes slightly lower in cord blood.

Unlike T and B cells, NK cells do not rearrange antigen receptor genes during their development but are defined by their functional capacity to mediate non–antigen-specific cytotoxicity. NK cells have killer inhibitory receptors that recognize certain MHC antigens and inhibit the killing of normal allogeneic cells in 4 specific patterns of reactivity. The genetic loci controlling these receptors are different from MHC alloantigenic loci, and have been mapped to chromosome 19. Virtually all NK cells express CD56, and more than 90% bear CD16 (FcγRIII) on the cell surface. Other CD antigens found on NK cells include CD57 (50-60%), CD7 and CD2 (70-90%), and CD8 (30-40%) (see Table 123-1). Although NK cells share surface antigens with T and myeloid cells, the lineage relationship of NK cells to the latter is still unclear. Some humans with autosomal recessive SCID who have profound deficiencies in T and B cells, have abundant NK cells, whereas those with X-linked and Jak3-deficient SCID have no T or NK cells.

Immune Cell Interactions

Immune cell interaction is of crucial importance to all phases of the adaptive immune response. Unlike the B-cell antigen receptor (Ig), which can recognize native antigen, the TCR can recognize only processed antigenic peptides presented to it by MHC molecules such as **HLA-A, -B, and -C antigens (class I)** and **HLA-DR, -DP, and -DQ antigens (class II)**. The MHC molecules have a groove in their protein structure where peptides fit. Class I MHC molecules are found on most nucleated cells in the body. Class II MHC molecules are found on **antigen-presenting cells (APCs),** which include macrophages, dendritic cells, and B cells. The peptides found in the groove of class I HLA molecules come from proteins normally made in the cell that are degraded and inserted into the groove. The peptides include viral peptides if the cell is infected with a virus. The peptides present in the groove of class II molecules come from exogenous native antigens such as vaccine and bacterial proteins. These proteins are taken up by APCs, degraded, and expressed on the cell surface in the groove of class II HLA molecules. The TCR then interacts with the peptide-bearing HLA molecule and, through its functional and physical link to the CD3 complex of signal-transducing molecules, sends a signal to the T cell to produce cytokines that ultimately result in T-cell activation and proliferation.

Two of the main functions of T cells are to signal B cells to make antibody by producing cytokines and membrane molecules that can serve as ligands for non–antigen-receptor B-cell surface molecules and to kill virally infected cells or tumor cells. For a T cell to perform either of these functions, it first must bind to an APC or to a target cell (the immunologic synapse). For high-affinity binding of T cells to APCs or target cells, several molecules on T cells, in addition to TCRs, bind to molecules on APCs or target cells. The CD4 molecule binds directly to MHC class II molecules on APCs. CD8 on cytotoxic T cells binds the MHC class I molecule on the target cell. Both CD4 and CD8 molecules are directly involved in the regulation of T-cell activation and are physically linked intracellularly to the p56-lck protein tyrosine kinase. The cytoplasmic tail of CD45, the common leukocyte antigen, is a tyrosine phosphatase capable of regulating T-cell signal-transduction events by virtue of the fact that p56-lck is a substrate for CD45 phosphatase activity. Depending on which isoform of CD45 is present on

the T cell (CD45RO on memory T cells, CD45RA on naïve T cells), mechanisms by which CD45 could upregulate or downregulate T-cell triggering have been proposed. Indeed, one form of human SCID is caused by a deficiency of CD45. Lymphocyte function-associated antigen 1 (LFA-1) on the T cell binds a protein called ICAM-1 (intracellular adhesion molecule 1), designated CD54, on APCs. CD2 on T cells binds LFA-3 (CD58) on the APCs. With the adhesion of T cells to APCs (the immunologic synapse), T-helper (Th) cells are stimulated to make interleukins and upregulate cell surface molecules, such as the CD40 ligand (CD154), that provide help for B cells, and cytotoxic T cells are stimulated to kill their targets.

In the **primary antibody response,** native antigen is carried to a lymph node draining the site, taken up by specialized cells called **follicular dendritic cells (FDCs),** and expressed on their surfaces. Virgin B cells bearing sIg specific for that antigen then bind to the antigen on the surfaces of the FDCs. If the affinity of the B-cell sIg antibody for the antigen present on the FDCs is sufficient, and if other signals are provided by activated Th cells, the B cell develops into an antibody-producing plasma cell. If the affinity is not high enough or if T-cell signals are not received, the B cell dies through apoptosis. The signals from activated Th cells include several cytokines (IL-4, IL-5, IL-6, IL-10, IL-13, and IL-21) that they secrete (see Table 123-2) and a surface T-cell molecule, the CD40 ligand or CD154, which, on contact of the activated CD4 positive T cell with the B cell, binds to CD40 on the B-cell surface. CD40 is a type I integral membrane glycoprotein expressed on B cells, monocytes, some carcinomas, and a few other types of cells. It belongs to the tumor necrosis factor/nerve growth factor receptor family. Crosslinking of CD40 on B cells by CD154 on T cells in the presence of certain cytokines causes the B cells to undergo proliferation and to initiate immunoglobulin synthesis. In the primary immune response, only IgM antibody is usually made, and most of it is of relatively low affinity. Some B cells become memory B cells during the primary immune response. These cells switch their immunoglobulin genes so that IgG, IgA, and/or IgE antibodies of higher affinity are formed on a secondary exposure to the same antigen. The **secondary antibody response** occurs when these memory B cells again encounter that antigen. Plasma cells form, just as in the primary response; however, many more cells are rapidly generated, and IgG, IgA, and IgE antibodies are made. In addition, genetic changes in immunoglobulin genes (somatic hypermutation) lead to increased affinity of those antibodies. A lack of somatic hypermutation is seen in deficiency of activation-induced cytidine deaminase (AID) or uracil-N-glycosylase (UNG). The exact pattern of isotype response to antigen in normal individuals varies, depending on the type of antigen and the cytokines present in the microenvironment.

For NK-mediated lysis, binding to the target is of crucial importance. This is best exemplified by persons with leukocyte adhesion deficiency type I (LAD-1) who have mutations in the gene encoding CD18, or the β chain of 3 different adhesion molecules (LFA-1, CR3, and p150,95), and who lack NK function. Thus, binding of NK cells to their targets is facilitated by LFA-1-ICAM interactions. CD56 or NCAM (neural cell adhesion molecule) also mediates homotypic adhesion of NK cells. FcγRIII, or the low-affinity IgG receptor, has a higher affinity for IgG when it is present on NK cells than when it is on neutrophils. FcγRIII also permits NK cells to mediate **antibody-dependent cellular cytotoxicity,** where antibody is bound through its Fc region to the FcγRIII. The antibody-combining portion of the IgG attaches to the target cell, and the NK cell, attached to the target by the Fc portion of the antibody, kills the target cell.

POSTNATAL LYMPHOPOIESIS

T Cells and T-Cell Subsets

Although the percentage of CD3 T cells in cord blood is somewhat less than in the peripheral blood of children and adults, T cells are actually present in higher number because of a higher absolute lymphocyte count in normal infants. An additional distinction is that the ratio of CD4 to CD8 T cells is usually higher (3.5-4:1) in cord blood than in blood of children and adults (1.5-2:1). Virtually all T cells in cord blood bear the CD45RA (naïve) isoform, and a dominance of CD45RA over CD45RO T cells persists during the 1st 2-3 yr of life, after which time the numbers of cells bearing these 2 isoforms gradually equalize. Th cells can be further subdivided according to the cytokines they produce when activated. **Th1 cells** produce IL-2 and IFN-γ, which promote cytotoxic T-cell or delayed hypersensitivity types of responses, whereas **Th2 cells** produce IL-4, IL-5, IL-6, IL-13, and IL-21 (see Table 123-2), which promote B-cell responses and allergic sensitization, and **Th17** cells produce IL-17. Development of Th cells into Th17 cells occurs when IL-6 and transforming growth factor β are present but IL-4 and IL-12 are absent. Th17 cells produce IL-21, which acts in an autocrine manner to activate STAT3, a transcription factor required for their further development as Th17 cells. Th17 cells express the receptor for the cytokine IL-23, stimulation that is required for development of Th17 effector activity. Th17 promotes inflammation by acting on local tissue cells to cause them to produce chemokines, such as IL-8, that recruit neutrophils and other innate effector cells. It is thought that the absence of these cells in the autosomal dominant form of the hyper-IgE syndrome (see Chapter 126) accounts for those patients' infection susceptibility to *Candida*. There are important additional subsets of T cells that have regulatory functions. These include CD25 high + T cells (**Treg cells**), also characterized by the presence of FOXp3 (absent in IPEX syndrome [see Chapter 126]) and considered to be important in the prevention of autoimmune diseases, and T cells that have phenotypic characteristics of NK cells (NKT cells). Cord blood T cells have the capacity to respond normally to **T-cell mitogens** (phytohemagglutinin, concanavalin A, and pokeweed mitogen) and are capable of mounting a normal mixed leukocyte response. Normal newborn infants also have the capacity to develop antigen-specific T-cell responses at birth, as evidenced by vigorous tuberculin reactivity a few wk after bacillus Calmette-Guérin vaccination on day 1 of life. Because patients in the 1st few mo of life may have unrecognized severe T-cell defects, most hospitals now routinely irradiate all blood products given young infants. T-cell defects can readily be detected even at birth by calculating the absolute lymphocyte count because T cells normally constitute 70% of circulating lymphocytes and their absence results in striking lymphopenia (see Fig. 122-2). T-cell lymphopenia also serves as the basis for the currently used newborn screening test for SCID.

B Cells and Immunoglobulins

Newborn infants have increased susceptibility to infections with Gram-negative organisms because IgM antibodies, which are heat-stable opsonins, do not cross the placenta. The level of the heat-labile opsonin, C3b, is also lower in newborn serum than in adults. These factors probably account for impaired phagocytosis of some organisms by newborn polymorphonuclear cells. Maternally transmitted IgG antibodies serve quite adequately as heat-stable opsonins for most Gram-positive bacteria, and IgG antibodies to viruses afford adequate protection against those agents. Because there is a relative deficiency of the IgG_2 subclass, antibodies to capsular polysaccharide antigens may be deficient. Because premature infants have received less maternal IgG by the time of birth than full-term infants, their serum opsonic activity is low for all types of organisms.

B lymphocytes are present in cord blood in slightly higher percentages but considerably higher numbers than in the blood of children and adults, reflecting the higher absolute lymphocyte counts in all normal infants. Cord blood B cells do not synthesize the range of immunoglobulin isotypes made by B cells from children and adults when stimulated with anti-CD40 plus IL-4 or IL-10, producing primarily IgM and at a much reduced quantity.

Neonates begin to synthesize antibodies of the IgM class at an increased rate very soon after birth in response to the immense antigenic stimulation of their new environment. Premature infants appear to be as capable of doing this as do full-term infants. At about 6 days after birth, the serum concentration of IgM rises sharply. This rise continues until adult levels are achieved by ≈1 yr of age. Cord serum from noninfected normal newborns does not contain detectable IgA. Serum IgA is normally first detected at around the 13th day of postnatal life; the level gradually increases during early childhood until adult levels are achieved by 6-7 yr of age. Cord serum contains an IgG

concentration comparable to or greater than that of maternal serum. Maternal IgG gradually disappears during the 1st 6-8 mo of life, while the rate of infant IgG synthesis increases (IgG_1 and IgG_3 faster than IgG_2 and IgG_4 during the 1st yr) until adult concentrations of total IgG are reached and maintained by 7-8 yr of age. IgG_1 and IgG_4 reach adult levels first, followed by IgG_3 at 10 yr and IgG_2 at 12 yr of age. The serum IgG level in infants usually reaches a low point at ≈3-4 mo of postnatal life. The rate of development of IgE generally follows that of IgA. After adult concentrations of each of the 3 major immunoglobulins are reached, these levels remain remarkably constant for a normal individual. The capacity to produce specific antibodies to protein antigens is intact at the time of birth. Normal infants cannot usually produce antibodies to polysaccharide antigens until after 2 yr of age unless the polysaccharide is conjugated to a protein carrier, as is the case for the conjugate *Haemophilus influenzae* type b and *Streptococcus pneumoniae* vaccines.

Natural Killer Cells

The percentage of NK cells in cord blood is usually lower than in the blood of children and adults, but the absolute number of NK cells is approximately the same, owing to the higher lymphocyte count. The capacity of cord blood NK cells to mediate target lysis in either NK-cell assays or antibody-dependent cellular cytotoxicity assays is roughly two-thirds that of adults.

Lymphoid Organ Development

Lymphoid tissue is proportionally small but rather well developed at birth and matures rapidly in the postnatal period. The thymus is largest relative to body size during fetal life and at birth is ordinarily two-thirds of its mature weight, which it attains during the 1st yr of life. It reaches its peak mass, however, just before puberty, and then gradually involutes thereafter. By 1 yr of age, all lymphoid structures are mature histologically. Absolute lymphocyte counts in the peripheral blood also reach a peak during the 1st yr of life (see Fig. 122-2). Peripheral lymphoid tissue increases rapidly in mass during infancy and early childhood. It reaches adult size by approximately 6 yr of age, exceeds those dimensions during the prepubertal years, and then undergoes involution coincident with puberty. The spleen, however, gradually accrues its mass during maturation and does not reach full weight until adulthood. The mean number of Peyer patches at birth is one-half the adult number, and gradually increases until the adult mean number is exceeded during adolescent years.

INHERITANCE OF ABNORMALITIES IN T-, B-, AND NATURAL KILLER–CELL DEVELOPMENT

More than 220 immunodeficiency syndromes have been described (see Table 122-8). Specific molecular defects have been identified in approximately 80% of these diseases. Most are recessive traits, several of which are caused by mutations in genes on the X chromosome and others by mutations on autosomal chromosomes. The molecular bases of 7 X-linked immunodeficiency disorders affecting T, B, and/or NK cells are known (see Chapters 124-126): X-linked immunodeficiency with hyper-IgM, X-linked lymphoproliferative syndrome, XIAD, X-linked agammaglobulinemia, X-linked SCID, the Wiskott-Aldrich syndrome, and nuclear factor kappa B essential modulator (NEMO). A few of the autosomal defects for which the molecular basis is known include (1) combined immunodeficiencies caused by abnormalities of purine salvage pathway enzymes, either adenosine deaminase (encoded by a gene on chromosome 20q13-ter) or purine nucleoside phosphorylase (encoded by a gene on chromosome 14q13.1); (2) combined immunodeficiencies caused by mutations in the gene encoding ZAP-70 (localized to chromosome 2q12), a non-src family protein tyrosine kinase important in T-cell signaling; (3) SCID caused by mutations in the gene on chromosome 19p13.1 encoding Janus kinase 3 (Jak3), the primary signal transducer from the common cytokine receptor γ chain (γc); (4) mutations in genes on chromosome 11 that encode components of the TCR, that is, CD3 γ, δ, and ε; (5) SCID caused by mutations in recombinase activating genes (*RAG1* and *RAG2*); and (6) SCID caused by mutations in the gene on chromosome 5p13 that encodes the α chain of the IL-7 receptor. These are only a few of the conditions for which the mutated genes have been discovered and the number is steadily growing.

PRENATAL DIAGNOSIS AND CARRIER DETECTION

Intrauterine diagnosis of adenosine deaminase and purine nucleoside phosphorylase deficiencies can be established by enzyme analyses on amnion cells (fresh or cultured) obtained before 20 wk gestation. Diagnosis of X-linked or autosomal defects causing SCID, other severe T-cell deficiencies, MHC class I and/or II antigen deficiencies, chronic granulomatous disease, or Wiskott-Aldrich syndrome can be established by direct mutation analysis of cells obtained by chorionic villus sampling or by amniocentesis if the mutation is known in the family or, if not known, by appropriate tests of phenotype or function on small samples of blood obtained by fetoscopy at 18-22 wk of gestation. The same diagnostic procedures can be performed on cord blood, but the only immunodeficiency disorder being routinely screened for is SCID and only 21 states are currently doing this (see Chapter 122). Carriers of any of these conditions can be identified by direct mutation analysis if the family's mutation is known.

Bibliography is available at Expert Consult.

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Chapter 124

Primary Defects of Antibody Production

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Of all of the primary immunodeficiency diseases, those affecting antibody production are most frequent. Selective absence of serum and secretory immunoglobulin (Ig)A is the most common defect, with rates ranging from 1 in 333 to 1 in 18,000 persons among different races and ethnicities. By contrast, agammaglobulinemia is estimated to occur with a frequency of only 1 in 10,000 to 1 in 50,000 persons. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria, predominantly in the upper and lower respiratory tracts; some individuals with selective IgA deficiency or infants with transient hypogammaglobulinemia may have few or no infections. The defective gene products for many primary antibody deficiency disorders have been identified (Table 124-1) and localized (Fig. 124-1). Sometimes the defect is not in the B cell itself but in T cells, which are required for complete B-cell function; some disorders are caused by unknown factors or are secondary to an underlying disease or its treatment (Table 124-2).

X-LINKED AGAMMAGLOBULINEMIA

Patients with X-linked agammaglobulinemia (XLA), or **Bruton agammaglobulinemia,** have a profound defect in B-lymphocyte development resulting in severe hypogammaglobulinemia, an absence of circulating B cells, small to absent tonsils, and no palpable lymph nodes.

Genetics and Pathogenesis

The abnormal gene in XLA maps to q22 on the long arm of the X chromosome and encodes the B-cell protein tyrosine kinase **Btk (Bruton tyrosine kinase).** Btk is a member of the Tec family of cytoplasmic protein tyrosine kinases and is expressed at high levels in all B-lineage cells, including pre-B cells. It appears to be necessary for

Table 124-1 Genetic Basis of Primary Antibody Deficiency Disorders

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1q32	CD21	CVID	Low IgG, low binding of EBV-gp350
2p11	κ Chain	κ Chain deficiency	Absence of immunoglobulins bearing κ chains
2q33	ICOS	ICOS-deficient CVID	Low or absent concentrations of all immunoglobulins
5q13.1	PI3K	B-cell–negative agammaglobulinemia	Low or absent concentrations of all immunoglobulins
6p21.3	Unknown	Selective IgA deficiency; CVID	Low or absent IgA; low concentrations of all immunoglobulins and of switched memory B cells in CVID
11p15.5	CD81	CVID caused by a lack of CD19	Low IgG concentration and poor response to antigens
11q12	CD20	CVID	Low IgG concentration and poor response to polysaccharide antigens
12p13	AID*	Autosomal recessive HIGM type 2	Failure to produce IgG, IgA, and IgE antibodies
12p13	CD27	EBV Lymphoproliferation	Memory B-cell deficiency Hypogammaglobulinemia
12q23-q24.1	UNG	Autosomal recessive HIGM type 5	Failure to produce IgG, IgA, and IgE antibodies
14q32.3	Immunoglobulin heavy chains*	B-cell–negative agammaglobulinemia; in others, selective isotype deficiencies	Absence of antibody production, lack of B cells, in μ heavy-chain mutations; in others, subclasses missing but B cells present
16p11.2	CD19	CD19 deficient CVID	Low or absent concentrations of all immunoglobulins
17p11.2	TACI*	TACI-deficient CVID	Low or absent concentrations of all immunoglobulins
20	CD40*	Autosomal recessive HIGM type 3	Failure to produce IgG, IgA, and IgE antibodies
22q13.1-q13.31	BAFF-R	BAFF-R–deficient CVID	Low or absent concentrations of all immunoglobulins
Xq22	Btk*	XLA or Bruton agammaglobulinemia	Absence of antibody production, lack of B cells
Xq25	SLAM-associated protein (SH2D1A)*	XLP	Lack of anti-EBNA and long-lived T-cell immunity; low immunoglobulins
Xq26	CD154 (CD40 ligand)*	X-linked HIGM type 1	Failure to produce IgG, IgA, and IgE antibodies
Xq28	NEMO	Anhidrotic ectodermal dysplasia with immunodeficiency	Hyper-IgM or -IgG subclass and antipolysaccharide antibody deficiencies

*The gene has been cloned and sequenced.

AID, Activation-induced cytidine deaminase; BAFF-R, B-cell–activating factor of the tumor necrosis factor family receptor; Btk, Bruton tyrosine kinase; CVID, common variable immunodeficiency; EBNA, Epstein-Barr virus nuclear antigen; EBV, Epstein-Barr virus; HIGM, hyper-IgM syndrome; ICOS, inducible costimulatory; NEMO, nuclear factor κB essential modulator; PI3K, phosphatidylinositol 3 kinase; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase; XLA, X-linked agammaglobulinemia; XLP, X-linked lymphoproliferative disease.

pre–B-cell expansion and maturation into surface Ig-expressing B cells, but probably has a role at all stages of B-cell development; it has also been found in cells of the myeloid series. More than 500 different mutations in the human *Btk* gene are recognized; they encompass most parts of the coding portions of the gene. There is not a clear correlation between the location of the mutation and the clinical phenotype. Carriers are detected by mutation analysis, and prenatal diagnosis of affected male fetuses is possible if the mutation is known in the family.

The expression of Btk in cells of myeloid lineage is of interest because boys with XLA often have neutropenia at the height of an acute infection. It is conceivable that Btk is only one of the signaling molecules participating in myeloid maturation and that neutropenia is observed in XLA only when rapid production of such cells is needed. Some pre-B cells are found in the bone marrow; the percentage of peripheral blood B lymphocytes is <1%. The percentage of T cells is increased, ratios of T-cell subsets are normal, and T-cell function is intact. The thymus is normal.

Seven autosomal recessive defects have also been shown to result in **agammaglobulinemia with an absence of circulating B cells** (Table 124-3), including mutations in the genes encoding: (1) the μ heavy chain gene; (2) the Igα and (3) Igβ signaling molecules; (4) B-cell linker adaptor protein (BLNK); (5) the surrogate light chain, λ5/14.1; (6) leucine-rich repeat-containing 8 (LRRC8); and (7) the p85α subunit of phosphatidylinositol-3 kinase.

Clinical Manifestations

Most boys afflicted with XLA remain well during the 1st 6-9 mo of life by virtue of maternally transmitted IgG antibodies. Thereafter, they acquire infections with extracellular pyogenic organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, unless they are given prophylactic antibiotics or immunoglobulin therapy. Infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis. Infections with *Mycoplasma* are also particularly problematic. Chronic fungal infections are seen; *Pneumocystis jiroveci* pneumonia rarely occurs. Viral infections are usually handled normally with the exceptions of hepatitis viruses and enteroviruses. There were several examples of **paralysis** when live polio vaccine was administered to these patients, and chronic, eventually fatal, central nervous system infections with various echoviruses and coxsackieviruses have occurred in a significant number of them. Echovirus-associated **myositis** resembling dermatomyositis has also been observed. These observations suggest a primary role for antibody, particularly secretory IgA, in host defense against enteroviruses. Growth hormone deficiency has also been reported in association with XLA. Neutropenia, responsive to G-CSF, may be present in patients with XLA.

Diagnosis

The diagnosis of XLA should be suspected if **lymphoid hypoplasia** is found on physical examination (minimal or no tonsillar tissue and no

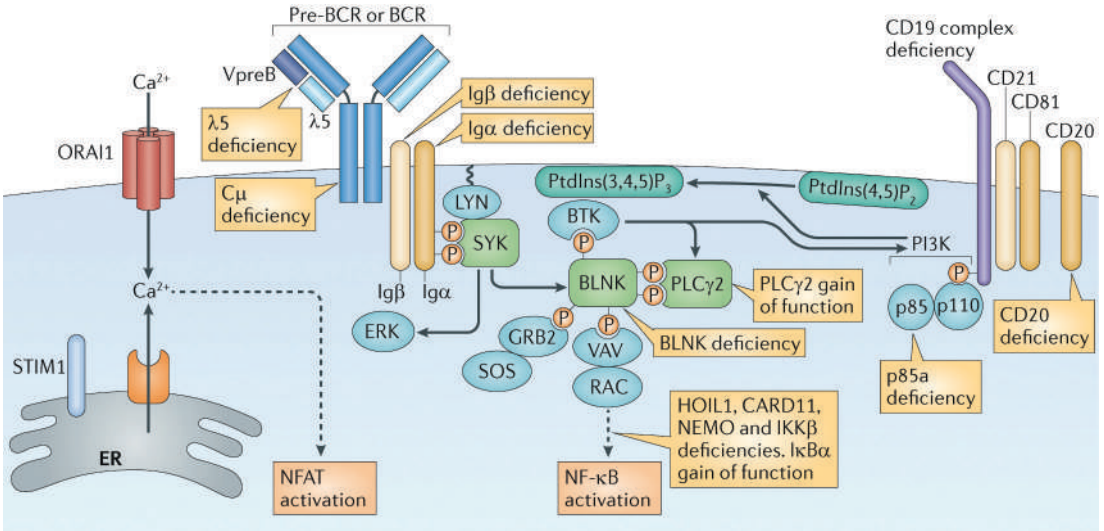

Figure 124-1 The pre-B cell receives proliferation and differentiation signals through the pre–B-cell receptor (BCR) and the coreceptors Igα and Igβ. Signaling from the pre-BCR involves the immunoreceptor tyrosine-based activation motifs (ITAMs) of the coreceptors Igα and Igβ, which scaffold and activate the tyrosine kinase SYK. SYK either activates the extracellular signal-regulated kinase (ERK) pathway or phosphorylates (P) (together with LYN) the adaptor protein B-cell linker (BLNK) and Bruton's tyrosine kinase (BTK), leading to the activation of phospholipase Cγ2 (PLCγ2) and the phosphoinositide-3 kinase (PI3K) pathway. Defects in this pathway affect the pre-BCR (in Cμ or pseudo light-chain λ5), the pre-BCR signal transduction molecules Igα and Igβ, the downstream molecules BTK, BLNK, and PI3K, components of the costimulatory CD19 complex (CD19, CD21, and CD81) and the B-cell marker CD20. The BCR triggers the canonical nuclear factor-κB (NF-κB) pathway through the scaffolding protein CARD11 and activation of the IκB kinase (IKK) complex (comprising IKKα, IKKβ, and NEMO [NF-κB essential modulator]). IKK activation leads to the phosphorylation and degradation of NF-κB inhibitor-α (IκBα) and the subsequent release of the p50-p65 NF-κB heterodimer, which then translocates to the nucleus to regulate gene transcription (not shown). Following antigen binding to antigen receptors (such as the BCR), endoplasmic reticulum Ca^{2+} stores are depleted, STIM1 is activated and ORAI1 Ca^{2+} release-activated Ca^{2+} channels open, resulting in store-operated Ca^{2+} entry. This influx results in activation of the transcription factor NFAT (nuclear factor of activated T cell). The *dashed arrows* indicate downstream signaling events. ER, endoplasmic reticulum; PAD, primary antibody deficiency; PtdIns(4,5)P_2, phosphatidylinositol-4,5-bisphosphate; PtdIns(3,4,5)P_3, phosphatidylinositol-3,4,5-trisphosphate. *(From Durandy A, Kracker S, Fischer A. Primary antibody deficiencies.* Nat Rev Immunol *13:519–533, 2013, Fig. 1, p. 521).*

palpable lymph nodes), and serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits for appropriate age- and race-matched controls usually with total immunoglobulins <100 mg/dL. Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low in this disorder, whereas they are normal in transient hypogammaglobulinemia of infancy. **Flow cytometry** is an important test to demonstrate the **absence of circulating B cells**, which will distinguish this disorder from common variable immunodeficiency, the hyper-IgM syndrome and transient hypogammaglobulinemia of infancy.

COMMON VARIABLE IMMUNODEFICIENCY

Common variable immunodeficiency (CVID) is a syndrome characterized by hypogammaglobulinemia with phenotypically normal B cells. It has also been called **acquired hypogammaglobulinemia** because of a generally later age of onset of infections. CVID patients may appear similar clinically to those with XLA in the types of infections experienced and bacterial etiologic agents involved, except that echovirus meningoencephalitis is rare in patients with CVID (see Table 124-3). In contrast to XLA, the sex distribution in CVID is almost equal, the age at onset is later (although it may be present in infancy), and infections may be less severe.

Genetics and Pathogenesis

Most patients have no identified molecular diagnosis. CVID is a category of primary immunodeficiency disorders that likely consists of several different genetic defects with autosomal recessive or dominant inheritance. Genes known to produce the CVID phenotype when mutated include *ICOS* (inducible costimulator) deficiency, *SH2DIA* (responsible for X-linked lymphoproliferative disease [XLP]), *CD19, CD20, CD21, CD81, BAFF-R* (B-cell–activating factor of the tumor necrosis factor family receptors), *TACI* (transmembrane activator, calcium modulator, and cyclophilin ligand interactor), and 2 genes that encode DNA methyl transferase (DNMT3B and ZBTB24). These mutations in aggregate account for less than 10% of all cases of CVID.

Because CVID occurs in 1st-degree relatives of patients with selective IgA deficiency, and some patients with IgA deficiency later become panhypogammaglobulinemic, a large subtype of CVID may have a common genetic basis with IgA deficiency. The high incidence of abnormal immunoglobulin concentrations, autoantibodies, autoimmune disease, and malignancy in both CVID and IgA deficiency and in other members of those patients' families also suggests a shared hereditary influence. This concept is supported by the discovery of a high incidence of C4-A gene deletions and C2 rare gene alleles in the class III major histocompatibility complex (MHC) region in individuals with either IgA deficiency or CVID, suggesting that a common susceptibility gene is on chromosome 6. Only a few human leukocyte antigen (HLA) haplotypes are shared by individuals affected with IgA deficiency and CVID, with at least 1 of 2 particular haplotypes being present in 77% of those affected. In 1 large family with 13 members, 2 had IgA deficiency and 3 had CVID. All of the immunodeficient patients in the family had at least 1 copy of an MHC haplotype that is abnormally frequent in IgA deficiency and CVID: HLA-DQB1 *0201, HLA-DR3, C4B-Sf, C4A-deleted, G11-15, Bf-0.4, C2a, HSP70-7.5, TNFa-5, HLA-B8, and HLA-A1. In a study of 83 multiply affected families with IgA deficiency and CVID, increased allele sharing at chromosome 6p21 in the proximal part of the MHC was observed in a susceptibility locus now designated as *IGAD1*. More sensitive genetic analysis in 101 multiple-case and 110 single-case families further localized the defect to the *HLADQ/DR* locus. Environmental factors, particularly drugs such as phenytoin, D-penicillamine, gold, and sulfasalazine are suspected to be triggers for disease expression in individuals with the permissive genetic background.

Most cases of CVID are sporadic or follow an autosomal dominant pattern of inheritance. Patients who lack ICOS, a surface protein on

Table 124-2 Other Conditions Associated with Humoral Immunodeficiency

GENETIC DISORDERS	
Monogenic diseases	Ataxia-telangiectasia
	Autosomal forms of severe combined immunodeficiency (SCID)
	Transcobalamin II deficiency and hypogammaglobulinemia
	Wiskott-Aldrich syndrome
	X-linked lymphoproliferative disorder (Epstein-Barr virus [EBV] associated)
	X-linked SCID
Chromosomal anomalies	Chromosome 18q– syndrome
	Monosomy 22
	Trisomy 8
	Trisomy 21
SYSTEMIC DISORDERS	
Malignancy	Chronic lymphocytic leukemia
	Immunodeficiency with thymoma
	T-cell lymphoma
Metabolic or physical loss	Immunodeficiency caused by hypercatabolism of immunoglobulin
	Immunodeficiency caused by excessive loss of immunoglobulins and lymphocytes
ENVIRONMENTAL EXPOSURES	
Drug induced	Antimalarial agents
	Captopril
	Carbamazepine
	Glucocorticoids
	Fenclofenac
	Gold salts
	Imatinib
	Penicillamine
	Phenytoin
	Sulfasalazine
Infectious diseases	Congenital rubella
	Congenital infection with cytomegalovirus
	Congenital infection with *Toxoplasma gondii*
	EBV
	Human immunodeficiency virus

From Schroeder HW, Szymanska-Mroczek E. Primary antibody deficiencies. In Rich RR, Fleisher TA, Shearer, WT, et al, editors: Clinical immunology: principles and practice, *ed 4, St Louis, 2013, WB Saunders.*

activated T cells, have an autosomal recessive pattern of inheritance. Nine such patients from 6 families in the Black Forest of Germany have been found to have identical homozygous large genomic deletions of the *ICOS* gene, suggesting a founder effect. Those who have XLP have an X-linked pattern of inheritance and those with autosomally inherited *TACI* defects may have heterozygous or homozygous mutations.

Despite normal numbers of circulating immunoglobulin-bearing B lymphocytes and the presence of lymphoid cortical follicles, blood B lymphocytes from CVID patients do not differentiate normally into immunoglobulin-producing cells when stimulated with pokeweed mitogen in vitro, even when cocultured with normal T cells. They also have a deficiency of switched memory B cells. B cells from some CVID and some IgA-deficient patients can be stimulated both to switch isotype and to synthesize and secrete some immunoglobulin when stimulated with anti-CD40 and interleukin (IL)-4 or IL-10. T cells and T-cell subsets are usually present in normal percentages, although T-cell function is depressed in some patients.

Clinical Manifestations

The serum immunoglobulin and antibody deficiencies in CVID may be as profound as in XLA. Patients with CVID often have autoantibody formation and normal-sized or enlarged tonsils and lymph nodes; ≈25% of patients have splenomegaly. CVID has also been associated with a sprue-like enteropathy with or without nodular follicular lymphoid hyperplasia of the intestine, thymoma, alopecia areata, hemolytic anemia, gastric atrophy, achlorhydria, thrombocytopenia, and pernicious anemia. Lymphoid interstitial pneumonia, intestinal lung disease, pseudolymphoma, B-cell lymphomas, amyloidosis, and noncaseating sarcoid-like granulomas of the lungs, spleen, skin, and liver also occur. There is a 438-fold increase in lymphomas among affected women in the 5th and 6th decades of life. CVID has been reported to resolve transiently or permanently in patients who acquire HIV infection.

Recurrent or chronic infections include pneumonia, sinusitis, otitis media, and diarrhea (bacterial, giardiasis). Repeated pulmonary infections may produce bronchiectasis. Sepsis and meningitis with encapsulated bacteria occur more frequently than in the general population. There is often a delay in the diagnosis of more than 5 yr between the first infections and a definitive diagnosis.

SELECTIVE IgA DEFICIENCY

An isolated absence or near absence (<10 mg/dL) of serum and secretory IgA is the most common well-defined immunodeficiency disorder, with a disease frequency as high as 0.33% in some populations. This condition can also be and often is associated with ill health.

The basic defect resulting in IgA deficiency is unknown. Phenotypically normal blood B cells are present. IgA deficiency occasionally remits spontaneously or after discontinuation of phenytoin therapy. The occurrence of IgA deficiency in both males and females and in members of successive generations within families suggests autosomal dominant inheritance with variable expressivity. This defect also occurs commonly in pedigrees containing individuals with CVID. Indeed, IgA deficiency may evolve into CVID, and the finding of rare alleles and deletions of MHC class III genes in both conditions suggests that the susceptibility gene common to these 2 conditions may reside in the MHC region on chromosome 6. IgA deficiency is noted in patients treated with the same drugs associated with producing CVID (phenytoin, D-penicillamine, gold, and sulfasalazine), suggesting that environmental factors may trigger this disease in a genetically susceptible person.

Clinical Manifestations

Infections occur predominantly in the respiratory, gastrointestinal, and urogenital tracts. Bacterial agents responsible are the same as in other antibody deficiency syndromes. Intestinal giardiasis is common. Children with IgA deficiency vaccinated intranasally with killed poliovirus produced local IgM and IgG antibodies. Serum concentrations of other immunoglobulins are usually normal in patients with selective IgA deficiency, although IgG_2 (and other) subclass deficiency has been reported, and IgM (usually elevated) may be monomeric.

Patients with IgA deficiency often have IgG antibodies against cow's milk and ruminant serum proteins. These antiruminant antibodies may cause false-positive results in immunoassays for IgA that use goat (but not rabbit) antisera. IgA deficiency is associated with a celiac-like syndrome, which may or may not respond to a gluten-free diet. The incidence of autoantibodies, autoimmune diseases, and malignancy is increased. Serum antibodies to IgA are reported in as many as 44% of patients with selective IgA deficiency. If these antibodies are of the IgE isotype, they can cause severe or fatal anaphylactic reactions after intravenous administration of blood products containing IgA. Only 5-times washed (in 200-mL volumes) normal donor erythrocytes (frozen blood would have this done routinely), or blood products from other IgA-deficient individuals, should be administered to patients with IgA deficiency. Many intravenous immunoglobulin (IVIG) preparations contain sufficient IgA to cause anaphylactic reactions. Administration of IVIG, which is >99% IgG, is not indicated because most IgA-deficient patients make IgG antibodies normally.

IgG SUBCLASS DEFICIENCIES

Some patients have deficiencies of 1 or more of the 4 subclasses of IgG despite normal or elevated total IgG serum concentration. Some

Table 124-3 The Main Phenotypes of Primary Antibody Deficiencies

PHENOTYPE	MAIN CLINICAL FEATURES	MAIN B-CELL BIOLOGIC FEATURES	KNOWN AFFECTED PROTEINS
Pan-agammaglobulinemia (absence of IgM, IgG, and IgA)	Bacterial infections (in the respiratory tract) and enterovirus infections	Absence of CD19*B cells	λ5, BLNK, Btk, Cμ, Igα, Igβ, and PI3K
Variable pan-hypogammaglobulinemia (CVID)	Bacterial infections (in the respiratory tract and gut), autoimmunity, cancer and increased risk of granuloma	Decreased frequency of CD27* memory B cells: defective plasma cells in tissues	CD19, CD20, CD21, CD27, CD81, DNMT3B, ZBTB24, ICOS, SAP, TACI, and BAFF-R
CSR deficiencies (absence or decrease in levels of IgG and IgA)	Bacterial and opportunistic infections	Decreased frequency of CD27* memory B cells	CD40 and CD40L
	Bacterial infections, autoimmunity and lymphadenopathies	Normal frequency of CD27* memory B cells.	AID and UNG
Selective IgA deficiency	Most often asymptomatic	ND	ND
Selective IgM deficiency	Frequent infections with encapsulated bacteria	No IgM antibody production (absence of allohemagglutinins and polysaccharide-specific antibodies)	
Selective IgG_2 and/or IgG_4 deficiency	Frequent bacterial infections, diagnosis after 2 yr of age; sometimes transient in childhood	Defective polysaccharide-specific antibody production	
Selective polysaccharide antibody deficiency	Bacterial infections (after 2 yr of age)	Normal IgG (including IgG_2 and IgG_4) levels	NF-κB pathway proteins (CARD11, HIOL1 and NEMO), Btk, and CD20

AID, Activation-induced cytidine deaminase; BAFF-R, B-cell–activating factor of the tumor necrosis factor family receptor; BLNK, B-cell linker; Btk, Bruton tyrosine kinase; Cμ, constant region-μ; CD40L, CD40 ligand; CSR, class-switch recombination; CVID, common variable immunodeficiency; ICOS, inducible costimulatory; ND, not determined; NEMO, nuclear factor kappa B essential modulator; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3 kinase; SAP, signaling lymphocyte activation molecule (SLAM)-associated protein; TACI, transmembrane activator, calcium modulator, and cyclophilin ligand interactor; UNG, uracil DNA glycosylase.

Modified from Durandy A, Kracker S, Fischer A. Primary antibody deficiencies. Nat Rev Immunol *13:519–533, 2013, Table, p. 524.*

patients with absent or very low concentrations of IgG_2 also have IgA deficiency. Other patients with IgG subclass deficiency have gone on to develop CVID, suggesting that the presence of IgG subclass deficiency may be a marker for more generalized immune dysfunction. The biologic significance of the numerous moderate deficiencies of IgG subclasses that have been reported is difficult to assess, particularly because commercial laboratory measurement of IgG subclasses is problematic. IgG subclass measurement is not cost-effective in evaluating immune function in the child with recurrent infection. The more relevant issue is a patient's capacity to make specific antibodies to protein and polysaccharide antigens, because profound deficiencies of antipolysaccharide antibodies have been noted even in the presence of normal concentrations of IgG_2. IVIG should not be administered to patients with IgG subclass deficiency unless they are shown to have a deficiency of antibodies to a broad array of antigens.

IMMUNOGLOBULIN HEAVY- AND LIGHT-CHAIN DELETIONS

Some completely asymptomatic individuals have been documented to have a total absence of IgG_1, IgG_2, IgG_4, and/or IgA_1 as a result of gene deletions. These abnormalities were discovered fortuitously in 16 individuals, 15 of whom had no history of undue susceptibility to infection, and all of whom produced antibodies of all other isotypes in normal quantities. These patients illustrate the importance of assessing specific antibody formation before deciding to initiate IVIG therapy in IgG subclass-deficient patients.

HYPER-IgM SYNDROME

The hyper-IgM syndrome is genetically heterogeneous and characterized by normal or elevated serum IgM levels associated with low or absent IgG, IgA, and IgE serum levels, indicating a defect in the class-switch recombination (CSR) process. Causative mutations have been identified in 2 genes on the X chromosome, the CD40 ligand (hyper-IgM syndrome type 1 [HIGM1]) and NEMO (nuclear factor κB essential modulator, XHM-ED) genes; and 3 genes on autosomal chromosomes, the activation-induced cytidine deaminase (AID) gene (hyper-IgM type 2 [HIGM2]) on chromosome 12, the uracil DNA glycosylase gene (UNG, hyper-IgM type 5 [HIGM5]), on chromosome 12, and the CD40 gene (hyper-IgM type 3 [HIGM3]) on chromosome 20. Distinctive clinical features permit presumptive recognition of the type of mutation in these patients, thereby aiding proper choice of therapy. All such patients should undergo molecular analysis to ascertain the affected gene for purposes of genetic counseling, carrier detection, and decisions regarding definitive therapy.

X-Linked Hyper-IgM Caused By Mutations in the CD40 Ligand: Hyper-IgM Type 1

HIGM1 is caused by mutations in the gene that encodes the CD40 ligand (CD154, CD40L), which is expressed on activated T-helper cells. Boys with this syndrome have very low serum concentrations of IgG and IgA, with a usually normal or sometimes elevated concentration of polyclonal IgM, may or may not have small tonsils, usually have no palpable lymph nodes, and often have profound **neutropenia.**

Genetics and Pathogenesis

B cells from boys with the CD40 ligand defect are capable of synthesizing not only IgM but also IgA and IgG when cocultured with normal activated T-helper cells, indicating that the B cells are actually normal in this condition and that the defect is in the T cells. The abnormal gene is localized to Xq26, and the gene product, CD154 (CD40L), is the ligand for CD40, which is present on B cells and monocytes. CD154 is upregulated on activated T cells. Mutations in CD154 result in an inability to signal B cells to undergo isotype switching, and thus the B cells produce only IgM. The failure of T cells to interact with B cells through this receptor–ligand pair also causes a failure of upregulation of the B cell and monocyte surface molecules CD80 and CD86 that interact with CD28/CTLA4 on T cells, resulting in failure of "crosstalk" between immune system cells. The failure of interaction of the molecules of those pathways results in a propensity for tolerogenic T-cell signaling and defective recognition of tumor cells. More than 73

distinct point mutations or deletions in the gene encoding CD154 have been identified in 87 unrelated families, giving rise to frame shifts, premature stop codons, and single amino acid substitutions, most of which are clustered in the domain with homology to tumor necrosis factor (TNF), located in the carboxyterminal region.

Clinical Manifestations

Similar to patients with XLA, boys with the CD40 ligand defect become symptomatic during the 1st or 2nd yr of life with recurrent pyogenic infections, including otitis media, sinusitis, pneumonia, and tonsillitis. They have marked susceptibility to *P. jiroveci* pneumonia, and are frequently profoundly neutropenic. Lymph node histology shows only abortive germinal center formation with severe depletion and phenotypic abnormalities of follicular dendritic cells. These patients have normal numbers of circulating B lymphocytes, but a decreased frequency of CD27+ memory B cells. Circulating T cells are also present in normal number and in vitro responses to mitogens are normal, but there is decreased antigen-specific T-cell function. In a study of patients with the CD40 ligand defect, 23.3% had died at a mean age at death of 11.7 yr. In addition to opportunistic infections such as *P. jiroveci* pneumonia, there is an increased incidence of extensive verruca vulgaris lesions, *Cryptosporidium* enteritis, subsequent liver disease, and an increased risk of malignancy. Because of the poor prognosis, the treatment of choice is an HLA-identical hematopoietic stem cell transplant at an early age. Alternative treatment for this condition is monthly infusion of IVIG. In patients with severe neutropenia, the use of granulocyte colony-stimulating factor has been beneficial.

X-Linked Hyper-IgM Caused By Mutations in the Gene Encoding Nuclear Factor κB Essential Modulator; XHM-ED

This syndrome in males is characterized most often clinically as **anhydrotic ectodermal dysplasia with associated immunodeficiency (EDA-ID).** The condition results from missense mutations in the IKBKG gene at position 28q on the X chromosome that encodes **NEMO,** a regulatory protein required for the activation of the transcription factor NF-κB. Germ line loss-of-function mutations cause the X-linked dominant condition incontinentia pigmenti in females and are lethal in male fetuses. Mutations in the coding region of IKBKG are associated with EDA-ID. The immunodeficiency is variable, with most patients showing impaired antibody responses to polysaccharide antigens. Some patients with EDA-ID have hyper-IgM. Pharmacologic inhibitors of NF-κB activation have been shown to downregulate CD154 messenger RNA and protein levels, suggesting the mechanism of hyper-IgM in this condition. The hyper-IgM patients with this defect should be easily recognizable because of the presence of ectodermal dysplasia, although there are some patients with this condition who do not have ectodermal dysplasia.

Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Activation-Induced Cytidine Deaminase: Hyper-IgM Type 2

An autosomal recessive form of hyper-IgM syndrome is caused by mutations in the gene for AID.

Genetics and Pathogenesis

Patients with autosomal recessive hyper-IgM usually have normal numbers of circulating B lymphocytes, but, in contrast to patients with the CD40 ligand defect, B cells from these patients are not able to switch from IgM-secreting to IgG-, IgA-, or IgE-secreting cells, even when cocultured with normal T cells or with monoclonal antibodies to CD40 and a variety of cytokines. When their B cells are cultured in vitro, they spontaneously secrete large amounts of IgM, but this is not further augmented by the addition of cytokines. Thus, in these patients, there is truly an intrinsic B-cell abnormality. The defect in many such patients has been identified as due to mutations in a gene on chromosome 12p13 that encodes AID. AID is a single-stranded DNA deaminase required for somatic hypermutation (SHM) and class-switch recombination (CSR) of immunoglobulin genes. Histologic examination of the enlarged lymph nodes reveals the presence of giant germinal centers (5-10 times larger than normal) filled with highly proliferating B cells. Proliferating B cells coexpress IgM, IgD, and CD38, a phenotype previously described for a small B-cell subset corresponding to germinal center founder cells. These cells are thought to correspond to a transitional stage between follicular mantle and germinal center B cells, at the onset of somatic mutation of the Ig variable region gene and antigen-driven selection. Deficiency of AID results in impaired terminal differentiation of B cells, a failure of CSR, and lack of immunoglobulin gene SHM. They have a normal frequency of CD27+ memory B cells.

Clinical Manifestations

Concentrations of serum IgG, IgA, and IgE are very low in AID deficiency. In contrast to the CD40 ligand defect, however, the serum IgM concentration in patients with AID deficiency is usually markedly elevated and polyclonal. Patients with this form of hyper-IgM have lymphoid hyperplasia, are generally older at age at onset, do not have susceptibility to *P. jiroveci* pneumonia, often do have isohemagglutinins, and are much less likely to have neutropenia unless it occurs on an autoimmune basis. They have a tendency, however, to develop autoimmune and inflammatory disorders including diabetes mellitus, polyarthritis, autoimmune hepatitis, hemolytic anemia, immune thrombocytopenia, Crohn disease, and chronic uveitis. With early diagnosis and monthly infusions of IVIG, as well as good management of infections with antibiotics, patients with AID mutations generally have a more benign course than do boys with the CD40 ligand defect.

Autosomal Recessive Hyper-IgM Caused By Mutations in the Gene for Uracil DNA Glycosylase; Hyper-IgM Type 5

Genetics and Pathogenesis

AID deaminates cytosine into uracil in targeted DNA, which is followed by uracil removal by UNG. Severely impaired CSR was found in 3 hyper-IgM patients reported to have UNG deficiency. Their clinical characteristics were similar to those with AID deficiency, with increased susceptibility to bacterial infections and lymphoid hyperplasia. The patients had a markedly elevated serum IgM and profoundly decreased serum IgG and IgA concentrations. Their B cells had an intrinsic defect in CSR when stimulated with anti-CD40 and IL-4 and constitutively produced high quantities of IgM. They had only a partial defect in SHM, however, and they have a normal frequency of CD27+ memory B cells.

Autosomal Recessive Hyper-IgM Caused By Mutations in CD40: Hyper-IgM Type 3

Five patients with autosomal recessive hyper-IgM from 4 unrelated families failed to express CD40 on their B-cell surfaces and were found to have mutations in the CD40 gene. Clinical manifestations included recurrent sinopulmonary infections, *P. jiroveci* pneumonia and *Cryptosporidium parvum* infections. The patients had very low levels of IgG and IgA and normal or high levels of IgM. More recently, 2 patients were identified with such mutations who did express the CD40 protein on their B cells and monocytes, so mutation analysis was required to make the diagnosis.

Genetics and Pathogenesis

CD40 is a type I integral membrane glycoprotein encoded by a gene on chromosome 20 and belonging to the TNF and nerve growth factor receptor superfamily. It is expressed on B cells, macrophages, dendritic cells, and a few other types of cells. Mutations in the CD40 gene cause an autosomal recessive form of hyper-IgM syndrome that is clinically indistinguishable from HIGM1, resulting from the X-linked CD40 ligand (CD154) defect. In contrast to the CD40 ligand defect, however, the B cells in the autosomal recessive condition are intrinsically abnormal and cannot isotype switch. The T cells are normal except to the extent that they cannot cause upregulation of CD80 and CD86 on B cells and macrophages to interact with CD28/CTLA4 on T cells.

Hyper-IgM Type 4

The defective gene in a 4th autosomal recessive form of hyper-IgM syndrome has not yet been identified, but appears to be in a gene downstream of AID. These patients all have defective CSR with preserved SHM.

X-LINKED LYMPHOPROLIFERATIVE DISEASE

XLP disease, also referred to as **Duncan disease** after the original kindred in which it was described, is an X-linked recessive trait characterized by an inadequate immune response to infection with Epstein-Barr virus (EBV).

Genetics and Pathogenesis

The defective gene in XLP was localized to Xq25, cloned, and the gene product was initially named SAP (for SLAM-associated protein), but is now known officially as SH2D1A. SLAM (signaling lymphocyte activation molecule) is an adhesion molecule that is upregulated on both T and B cells with infection and other stimulation. SH2D1A is highly expressed in thymocytes and peripheral blood T and NK cells, with a prevalent expression on T-helper type 1 cells. Its presence on B lymphocytes is unclear. Thus, although antibody deficiency is frequently present, this is really a T- and natural killer (NK)-cell defect. SH2D1A competes with SHP-2 for binding to SLAM and, as such, is a regulatory molecule. In XLP patients, the absence of SH2D1A can lead to an uncontrolled cytotoxic T-cell immune response to EBV. The SH2D1A protein associates permissively with 2B4 on NK cells; thus, selective impairment of 2B4-mediated NK-cell activation also contributes to the immunopathology of XLP.

XLP type 2 is less common and is caused by a mutation in *XIAP* (X-linked inhibitor of apoptosis protein); disease manifestations are similar to XLP. X-linked immunodeficiency with magnesium defect (XMEN syndrome) is due to a loss of function mutation of the magnesium transporter protein and manifests with chronic EBV infection, EBV lymphoproliferative disorders, and CD4 lymphopenia.

Clinical Manifestations

Affected males are usually healthy until they acquire EBV infection. The mean age of presentation is <5 yr. There are 3 major clinical phenotypes: (1) fulminant, often fatal, infectious mononucleosis (50% of cases); (2) lymphomas, predominantly involving B-lineage cells (25%); and (3) acquired hypogammaglobulinemia (25%). There is a marked impairment in production of antibodies to the EBV nuclear antigen, whereas titers of antibodies to the viral capsid antigen have ranged from absent to markedly elevated. XLP has an unfavorable prognosis; 70% of affected boys die by age 10 yr. Only 2 XLP patients are known to have survived beyond 40 yr of age. Unless there is a family history of XLP, diagnosis prior to the onset of complications is difficult because affected individuals are asymptomatic initially. Using mutation analysis, it is possible to identify affected males within identified kindreds before they develop primary EBV infection. Approximately half of the few patients with XLP given HLA-identical related or unrelated stem cell transplants are surviving without signs of the disease.

Two pedigrees have been reported in which boys in one arm of each pedigree were diagnosed with CVID, whereas those in the other arms had fulminant infectious mononucleosis. The family members with CVID never gave a history of infectious mononucleosis. All affected members of each pedigree had the same distinct SH2D1A mutation, however, despite the different clinical phenotypes. Because the SH2D1A mutation was the same but the phenotype varied in these families, XLP should be considered in all males with a diagnosis of CVID, particularly if there is more than one male family member with this phenotype.

CD27 Deficiency

CD27 deficiency, an autosomal recessive condition, was found to be associated with EBV lymphoproliferation, EBV lymphoma and hypogammaglobulinemia. CD27 is commonly used as marker of memory B cells for the classification of B-cell deficiencies including common variable immune deficiency. It is a member of the TNF receptor family and interacts with CD70 to influence T-, B-, and NK-cell functions. Disturbance of this axis impairs immunity and memory generation against viruses including EBV, influenza, and others.

Bibliography is available at Expert Consult.

124.1 Treatment of B-Cell Defects

Rebecca H. Buckley

Except for the CD40 ligand defect and XLP, for which stem cell transplantation is recommended, judicious use of antibiotics to treat documented infections and regular administration of IVIG are the only effective treatments for primary B-cell disorders. The most common forms of replacement therapy are either intravenous or subcutaneous immunoglobulin (IVIG or SCIG). Broad antibody deficiency should be carefully documented before such therapy is initiated. The rationale for the use of IVIG or SCIG is to provide missing antibodies, not to raise the serum IgG or IgG subclass level. The development of safe and effective immunoglobulin preparations is a major advance in the treatment of patients with severe antibody deficiencies, although it is expensive and there have been national shortages. Almost all commercial preparations are isolated from normal plasma by the Cohn alcohol fractionation method or a modification of it. Cohn fraction II is then further treated to remove aggregated IgG. Additional stabilizing agents such as sugars, glycine, and albumin are added to prevent reaggregation and protect the IgG molecule during lyophilization. The ethanol used in preparation of immunoglobulin inactivates HIV; and an organic solvent/detergent step inactivates hepatitis B and C viruses. Some preparations are also nanofiltered to remove infectious agents. Most commercial lots are produced from plasma pooled from 10,000 to 60,000 donors and therefore contain a broad spectrum of antibodies. Each pool must contain adequate levels of antibody to antigens in various vaccines, such as tetanus and measles. However, there is no standardization based on titers of antibodies to more clinically relevant organisms, such as *S. pneumoniae* and *H. influenzae* type b.

The IVIG and SCIG preparations available in the United States have similar efficacy and safety. Rare transmission of hepatitis C virus has occurred in the past, but the potential transmission of hepatitis C virus has been resolved by additional treatment with an organic solvent/detergent mixture. There has been no documented transmission of HIV by any of these preparations. **IVIG or SCIG at a dose of 400 mg/kg per month** achieves trough IgG levels close to the normal range. Higher doses are indicated in patients with chronic or severe respiratory infections. Systemic reactions may occur, but rarely are these true anaphylactic reactions. Anaphylactic reactions caused by a patient's IgE antibodies to IgA in the IVIG or SCIG preparation may occur in patients with CVID or IgA deficiency. Newly diagnosed patients with CVID should be screened through the American Red Cross for anti-IgA antibodies. If anti-IgA antibodies are detected, IVIG therapy should consist of the one available immunoglobulin preparation containing almost no IgA (Gammagard S/D, Baxter).

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Chapter 125

Primary Defects of Cellular Immunity

Rebecca H. Buckley

In general, patients with defects in T-cell function have infections or other clinical problems that are more severe than in patients with antibody deficiency disorders (see Table 122-4). The defective gene products for some primary T-cell diseases are identified (Table 125-1). These individuals rarely survive beyond infancy or childhood. Transplantation of thymic tissue, or of major histocompatibility complex–compatible sibling or haploidentical (half-matched) parental hematopoietic stem cells, is the treatment of choice for patients with primary T-cell defects (see Chapter 135).

THYMIC HYPOPLASIA (DIGEORGE SYNDROME)

Thymic hypoplasia results from dysmorphogenesis of the 3rd and 4th pharyngeal pouches during early embryogenesis, leading to hypoplasia or aplasia of the thymus and parathyroid glands. Other structures forming at the same age are also frequently affected, resulting in anomalies of the great vessels (right-sided aortic arch), esophageal atresia, bifid uvula, congenital heart disease (conotruncal, atrial, and ventricular septal defects), a short philtrum of the upper lip, hypertelorism, an antimongoloid slant to the eyes, mandibular hypoplasia, and low-set, often notched ears (see Chapters 81 and 108). The diagnosis is often first suggested by hypocalcemic seizures during the neonatal period.

Genetics and Pathogenesis

DiGeorge syndrome occurs in both males and females. Microdeletions of specific DNA sequences from chromosome 22q11.2, the **DiGeorge chromosomal region,** are found in a majority of cases. Several candidate genes have been identified in this region. A T-box transcription family member, *TBX1,* is implicated as an etiology for most of the major signs of DiGeorge syndrome. There appears to be an excess of 22q11.2 deletions of maternal origin. Polymerase chain reaction–based genotyping using microsatellite DNA markers located within the commonly deleted region permits rapid detection of such microdeletions. Conotruncal heart defects and 22q deletions are observed in DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome. The **CATCH 22 syndrome** (*c*ardiac, *a*bnormal facies, *t*hymic hypoplasia, *c*left palate, *h*ypocalcemia) includes the broad clinical spectrum of conditions with 22q11.2 deletions. Other deletions associated with DiGeorge and velocardiofacial syndromes have been identified on chromosome 10p13 (see Chapter 81).

Variable hypoplasia of the thymus and parathyroid glands defines **partial DiGeorge syndrome,** which is more frequent than total aplasia; aplasia is present in <1% of patients with DiGeorge syndrome and defines **complete DiGeorge syndrome.** Slightly less than half of patients with complete DiGeorge syndrome are hemizygous at chromosome 22q11. Approximately 15% are born to diabetic mothers. Another 15% of infants have no identified risk factors. Approximately one-third of infants with complete DiGeorge syndrome have **CHARGE association** (*c*oloboma, *h*eart defect, choanal *a*tresia, growth or developmental *r*etardation, *g*enital hypoplasia, and *e*ar anomalies including deafness). Mutations in the chromodomain helicase DNA binding protein 7 (CHD7) gene on chromosome 8q12.2 are found in approximately 60-65% of individuals with CHARGE syndrome. Concentrations of serum immunoglobulins in DiGeorge syndrome are usually normal, but immunoglobulin (Ig) A may be diminished and IgE elevated. Other laboratory findings vary depending on the degree of thymic dysfunction.

Table 125-1 Genetic Basis of Primary Cellular Immunodeficiency Diseases

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1p35-p34.3	Lck	↓↓ CD4 CD8	Lack of T-cell responses to mitogens or to anti-CD3
2p12	CD8α	↓↓ CD8 deficiency	Lack of cytotoxic T cells
2q12	ZAP-70	CD8 deficiency	Failure of CD4 T cells to respond to usual signals
4p13	RhoH	↓ Naïve CD4+ cells	Low number of recent thymic emigrants, restricted T-cell repertoire
5q31-34	ITK	↓ Naïve CD4+ cells Absence of NKT cells	Poor T-cell responses to mitogens, antigens, and anti-CD3
10p13	Unknown	Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)	Low number of T cells and impaired T-cell function
11q23	CD3γ and ε	CD3 deficiency	Poor T-cell responses to mitogens; lack of cytotoxic T cells; IgG subclass deficiency
14q11.2	TRAC	TCR αβ T-cell deficiency	Poor T-cell responses to mitogens
16p11.2	Coronin-1A	↓↓ CD4 ↓↓ CD8	Poor T-cell response to phytohemagglutinin; impaired antibody responses
20q13.12	MST1/STK4	↓ Naïve T cells Low number of recent thymic emigrants, restricted T-cell repertoire	Poor T-cell responses to mitogens, antigens, and anti-CD3 Decreased switched memory B cells
21q22.3	AIRE	APECED, chronic mucocutaneous candidiasis, parathyroid and adrenal autoimmunity	Poor response to *Candida* antigen; autoimmune responses
22q11.22	?TBX1	Thymic hypoplasia (DiGeorge syndrome, velocardiofacial syndrome)	Low number of T cells and impaired T-cell function

AIRE, Autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis ectodermal dysplasia; Ig, immunoglobulin; ITK, IL-2–inducible tyrosine kinase deficiency; MST1, macrophage-stimulating factor 1; NKT, natural killer T; RhoH, Ras homology family member H; STK4, serine threonine kinase 4; TCR, T-cell receptor; TRAC, T-cell receptor α chain constant region; ZAP-70, zeta-associated protein 70.

Absolute lymphocyte counts are usually only moderately low for age. The CD3 T-cell counts are variably decreased in number, corresponding to the degree of thymic hypoplasia, resulting in an increased percentage of B cells. Lymphocyte responses to mitogen stimulation are absent, reduced, or normal, depending on the degree of thymic deficiency. Thymic tissue, when found, contains Hassall corpuscles, a normal density of thymocytes, and corticomedullary distinction. Lymphoid follicles are usually present, but lymph node paracortical areas and thymus-dependent regions of the spleen show variable degrees of depletion.

Clinical Manifestations

Children with partial thymic hypoplasia may have little trouble with infections and grow normally. Patients with complete DiGeorge syndrome resemble patients with severe combined immunodeficiency in their susceptibility to infections with low-grade or opportunistic pathogens, including fungi, viruses, and *Pneumocystis jiroveci*, and to graft-versus-host disease from nonirradiated blood transfusions. Patients with complete DiGeorge syndrome can develop an atypical phenotype in which oligoclonal T-cell populations appear in the blood associated with rash and lymphadenopathy. These atypical patients appear phenotypically to be similar to patients with **Omenn syndrome** or maternal T lymphocyte engraftment.

It is critical to confirm the diagnosis of complete DiGeorge syndrome in a timely manner because this disease is fatal without treatment. A T-cell count should be obtained on all infants born with primary hypoparathyroidism, CHARGE syndrome, truncus arteriosus, and interrupted aortic arch type B. If a patient has findings consistent with DiGeorge syndrome with or without a rash and lymphadenopathy, the patient should be referred to an immunologist for evaluation.

Treatment

The immune deficiency in the complete DiGeorge syndrome is correctable by cultured unrelated thymic tissue transplants. Some have been given nonirradiated unfractionated bone marrow or peripheral blood transplants from an human leukocyte antigen–identical sibling with subsequent improved immune function because of adoptively transferred donor immunity; however, they have no way of renewing T-cell production because they have no thymus.

DEFECTIVE EXPRESSION OF THE T-CELL RECEPTOR–CD3 COMPLEX

The first type of this disorder was found in 2 brothers in a Spanish family. The proband presented with severe infections and died at 31 mo of age with autoimmune hemolytic anemia and viral pneumonia. His lymphocytes had responded poorly to mitogens and to anti-CD3 in vitro, and could not be stimulated to develop cytotoxic T cells. His antibody responses to protein antigens had been normal, indicating normal T-helper cell function. His 12 yr old brother was healthy but had almost no CD3-bearing T cells and had IgG_2 deficiency similar to his sibling. The defect in this family was caused by mutations in the gene encoding the CD3γ chain (Fig. 125-1).

The second type of this disorder was diagnosed in a 4 yr old French boy who had recurrent *Haemophilus influenzae* pneumonia and otitis media in early life but was later healthy. He had a partial defect in expression of T-cell receptor–CD3 complex, and thus the percentage of CD3 cells was about half-normal, but the level of expression was markedly decreased. The defect was caused by 2 independent CD3ε gene mutations, leading to defective CD3ε chain synthesis. There was a splice site mutation on one allele that did not totally abrogate the normal intron 7 splicing, resulting in partial expression of CD3 on the T cells. Thus, this mutation did not result in failure of T-cell development, whereas mutations in the portions of the gene that encode the extracellular component of CD3ε result in a profound deficiency of circulating mature CD3 T cells.

Two additional unrelated patients from Pakistan were discovered to lack T-cell receptor (TCR)-αβ–positive T cells and were found to have mutations in the TCR α-chain constant (*TRAC*) gene. Clinically they

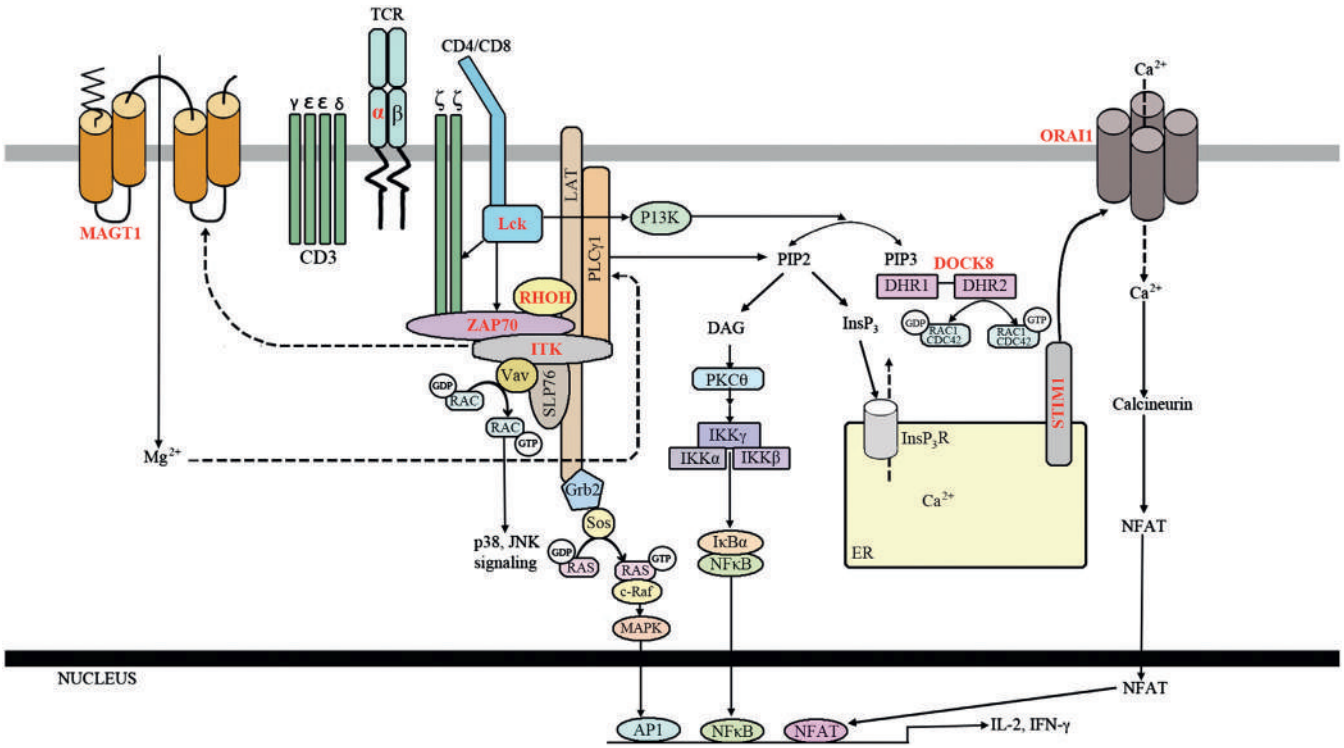

Figure 125-1 Schematic representation of signaling through the T-cell receptor–CD3 complex. Molecules the mutations of which have been associated with partial defect of T-cell development and impaired T-cell function are indicated in *red* and highlighted in *boldface*. *AP1*, Activator protein 1; *DHR*, DOCK-homology region; *Grb2*, growth factor receptor-bound protein 2; *IKK*, IκB kinase; *JNK*, c-Jun N-terminal kinase; *MAPK*, mitogen-activated protein kinase; *NFAT*, nuclear factor of activated T cells; *NFκB*, nuclear factor κB; *PI3K*, phosphoinositide-3 kinase; *PIP3*, phosphatidylinositol (3,4,5)-triphosphate. *(From Notarangelo L: Partial defects of T-cell development associated with poor T-cell function.* J Allergy Clin Immunol *131:1297–1305, 2013, Fig. 1, p. 1299.)*

had increased susceptibility to infections, autoimmunity and profound T cell dysfunction but normal antibody responses. All of their T cells contained TCR gamma delta receptors.

T-CELL ACTIVATION DEFECTS

T-cell activation defects are characterized by the presence of normal or elevated numbers of blood T cells that appear phenotypically normal but fail to proliferate or produce cytokines normally in response to stimulation with mitogens, antigens, or other signals delivered to the TCR, owing to defective signal transduction from the TCR to intracellular metabolic pathways (see Fig. 125-1). These patients have problems similar to those of other T-cell–deficient individuals, and some with severe T-cell activation defects may clinically resemble severe combined immunodeficiency patients. At least 8 new forms of T-cell activation defects have been discovered. The description of only a few of these conditions is included here (see Table 125-1) and DOCK8 deficiency is discussed in Chapter 126.

CD8 LYMPHOCYTOPENIA CAUSED BY MUTATIONS IN THE GENE ENCODING ZETA-ASSOCIATED PROTEIN 70

Patients with this T-cell activation defect present during infancy with severe, recurrent, and often fatal infections. The majority of cases are reported among Mennonites. These patients have normal or elevated numbers of blood B cells and low to elevated serum immunoglobulin concentrations. Their blood lymphocytes exhibit normal expression of the T-cell surface antigens CD3 and CD4, but CD8 cells are almost totally absent. These cells fail to respond normally to mitogens or to allogeneic cells in vitro or to generate cytotoxic T lymphocytes. Natural killer (NK) cell activity is normal. The thymus of 1 patient exhibited normal architecture with normal numbers of CD4:CD8 double-positive thymocytes, but an absence of CD8 single-positive thymocytes. This condition is caused by mutations in the gene encoding **zeta-associated protein 70 (ZAP-70),** a non-src family protein tyrosine kinase important in T-cell signaling that is localized to chromosome 2q12 (see Fig. 125-1). The normal number of CD4:CD8 double-positive T cells results because the thymocytes can use the other member of the same tyrosine kinase family, Syk, to facilitate positive selection. Syk is present at 4-fold higher levels in thymocytes than in peripheral T cells, possibly accounting for the lack of normal responses by the CD4 blood T cells.

Another condition that can result in CD8 deficiency is a mutation in the gene that encodes CD8α. There is a deficiency of cytotoxic T cells in that condition, but the functional immune defect is mild compared to that of ZAP-70 deficiency.

T-Cell Defects Characterized By Epstein-Barr Virus Lymphoproliferation/Lymphoma

In addition to the X-linked lymphoproliferative and X-linked inhibitor of apoptosis protein syndromes and CD27 deficiency characterized primarily as antibody deficiencies (see Chapter 124), there are at least 4 additional primarily T-cell defects that predispose to Epstein-Barr virus (EBV) infections or lymphomas. These include Ras homology family member H (RhoH) deficiency, macrophage-stimulating 1 (MST1)/serine threonine kinase 4 (STK4) deficiency, interleukin (IL)-2–inducible tyrosine kinase (ITK) deficiency and Coronin-1A deficiency (see Table 125-1).

RhoH Deficiency

Two siblings who had a homozygous nonsense mutation in the *RhoH* gene had persistent cutaneous human papillomavirus infections and the older sibling had Burkitt lymphoma. RhoH plays an important role in T-cell activation. Following stimulation of the TCR, RhoH becomes tyrosine phosphorylated and mediates recruitment of ZAP-70 and LCK to the TCR/linker of activation in T cells (LAT) signalosome (see Fig. 125-1). Immunologic findings in the 2 patients included a reduced number of naïve CD4+ T cells and recent thymic emigrants, restricted T-cell diversity and impaired responsiveness of the cells to anti-CD3.

MST1/STK4 Deficiency

Autosomal recessive MST1/STK4 deficiency is associated with recurrent bacterial and viral infections, candidiasis and autoimmunity. The viral infections include warts, molluscum contagiosum, and EBV lymphoproliferative disease. Congenital heart disease and moderate neutropenia have also been reported. Immunologically, there is a severe reduction in naïve T cells, a near absence of recent thymic emigrants, oligoclonal T cells and increased apoptosis of T cells. Thus, MST1/STK4 plays a major role in T-cell development, survival, and migration.

ITK Deficiency

Several patients with EBV lymphoproliferative disease have been described who had mutations in the *ITK* gene. In addition, some also had *P. jiroveci* pneumonia, candidiasis, and BK polyoma infection. The immunologic abnormalities described included marked lymphopenia, a predominance of activated T cells, an absence of NK T cells, and poor T-cell responses to mitogens, antigens and anti-CD3. ITK is a Tec nonreceptor tyrosine kinase expressed in T lymphocytes. The ITK pleckstrin homology domain binds to phosphatidylinositol monophosphates and this binding permits ITK recruitment to the T cell membrane where, upon TCR crosslinking, ITK increases phospholipase Cγ (PLCγ) 1 activation and calcium influx.

Coronin-1a Deficiency

Three siblings from a consanguineous family presented with EBV-associated B-cell lymphoproliferation at an early age (12, 7, and 14 mo) and profound naïve T-cell lymphopenia. In addition, there was impaired development of a diverse T-cell repertoire and near absent invariant NK T cells. They were discovered to have a missense mutation in the gene encoding Coronin-1A that abrogated protein expression. Coronin-1A is a member of a family of proteins that bind F-actin and the Arp2,3 complex; it has an important role in cytoskeletal organization.

LCK DEFICIENCY

A female infant presented at age 15 mo with protracted diarrhea, failure to thrive and recurrent respiratory tract infections. She developed recurring fevers, multiple nodular skin lesions and inflammation of the interphalangeal joints as well as retinal vasculitis and polyserositis. At age 29 mo, she developed a normocytic aregenerative anemia and peripheral thrombocytopenia with antiplatelet autoantibodies. She died from venoocclusive disease shortly after a chemoablated bone marrow transplant. Immunologic investigation revealed CD4 T-cell lymphopenia and low levels of CD4 and CD8 expression on the T-cell surfaces. The T cells present had an oligoclonal T-cell repertoire and exhibited a profound TCR signaling defect. She was found to have a homozygous missense mutation of the *LCK* gene.

Very closely related to this defect is a deficiency of uncoordinated 119 (UNC119), which is a chaperone involved in LCK-mediated signaling. Through LCK, UNC119 regulates T-cell proliferation, differentiation into T effector cells and immunologic synapse formation. A heterozygous dominant-negative missense mutation of the *UNC119* gene was reported in a 32 yr old female with idiopathic CD4 T lymphopenia who had a history of recurrent respiratory infections, shingles, oral herpes infections and persistent fungal infections of the skin and nails. Both LCK deficiency and UNC119 deficiency should be considered when there is idiopathic CD4 T lymphopenia.

CHRONIC MUCOCUTANEOUS CANDIDIASIS

Chronic mucocutaneous candidiasis is a syndrome characterized by impaired immune responsiveness to *Candida.* Some of the known immunodeficiencies that have this complication as a prominent feature include autoimmune polyendocrinopathy syndrome type I (APS1, or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED], described below), homozygous caspase recruitment domain-containing protein 9 *(CARD9)* mutations, both types of hyperimmunoglobulin E syndromes (see Chapter 126), an autosomal recessive deficiency in the IL-17 receptor A (IL-17RA) chain, and an

autosomal dominant deficiency of *STAT1* and of the cytokine IL-17F. IL-17RA deficiency is complete, abolishing cellular responses to IL-17A and IL-17F homo- and heterodimers. By contrast, IL-17F deficiency is partial, with mutant IL-17F–containing homo- and heterodimers displaying impaired, but not abolished, activity.

Although the underlying immune disorders are varied, the clinical presentation of chronic mucocutaneous candidiasis is usually similar. Symptoms can begin in the 1st mo of life or as late as the 2nd decade of life. The disorder is characterized by chronic and severe *Candida* skin and mucous membrane infections. Patients rarely develop systemic *Candida* disease except as noted below. Topical antifungal therapy can provide limited improvement early in the course of the disease, but systemic courses of azoles are usually necessary. The infection usually responds temporarily to treatment but is not eradicated and recurs. Patients with *CARD9* gene mutations have a more severe fungal susceptibility than typical chronic mucocutaneous candidiasis patients. Two described patients with *CARD9* gene mutations had fungal sepsis in addition to chronic mucocutaneous candidiasis; deep tissue dermatophyte infections were also present.

AUTOIMMUNE POLYENDOCRINOPATHY-CANDIDIASIS ECTODERMAL DYSPLASIA

Patients with this syndrome present with chronic mucocutaneous candidiasis and autoimmune polyendocrinopathy, usually producing hypoparathyroidism and Addison disease. Additional features include hypogonadism, chronic active hepatitis, alopecia, vitiligo, pernicious anemia, enamel hypoplasia, type 1diabetes, and Sjögren syndrome. APECED, or APS1, is caused by a mutation in the autoimmune regulator *(AIRE)* gene (see Table 125-1). The gene product, AIRE, is expressed at high levels in purified human thymic medullary stromal cells and is thought to regulate the cell surface expression of tissue-specific proteins such as insulin and thyroglobulin. Expression of these self-proteins allows for the negative selection of autoreactive T cells during their development. Failure of negative selection results in organ-specific autoimmune destruction. The overall significance of AIRE in the establishment and maintenance of T-cell self-tolerance is not well understood.

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Chapter 126

Primary Combined Antibody and Cellular Immunodeficiencies

Rebecca H. Buckley

Patients with combined antibody and cellular defects have severe, frequently opportunistic infections that lead to death in infancy or childhood unless they are provided hematopoietic stem cell transplantation early in life. These are thought to be rare defects, although the true incidences are unknown because until recently there had been no newborn screening for any of these defects. It is possible that many affected children died of infection during infancy without being diagnosed. The causative mutated genes for many combined immunodeficiencies have been identified (Table 126-1). Because life-threatening infections may occur early in infancy, the U.S. Secretary of Health and Human Services recommends that routine screening for severe combined immunodeficiency (SCID) be included in state newborn screening testing. Live, vaccine-derived rotaviral infections have already occurred during the 1st few mo of life in SCID infants, so very early knowledge of this diagnosis could prevent such vaccine-acquired infections. In addition, early identification and subsequent bone marrow transplantation before infections develop result in a very high (92%) survival rate.

126.1 Severe Combined Immunodeficiency

Rebecca H. Buckley

The syndromes of SCID are caused by diverse genetic mutations that lead to absence of all adaptive immune function and, in some, a lack of B cells and natural killer (NK) cells. Patients with this group of disorders have the most severe immunodeficiency.

PATHOGENESIS

SCID results from mutations in any 1 of at least 13 known genes that encode components of the immune system crucial for lymphoid cell development (Table 126-2). All patients with SCID have very small thymuses (<1 g) that usually fail to descend from the neck, contain no thymocytes, and lack corticomedullary distinction or Hassall corpuscles. The thymic epithelium appears histologically normal. Both the follicular and paracortical areas of the spleen are depleted of lymphocytes. Lymph nodes, tonsils, adenoids, and Peyer patches are absent or extremely underdeveloped.

CLINICAL MANIFESTATIONS

Affected infants present within the 1st few mo of life with recurrent or persistent diarrhea, pneumonia, otitis media, sepsis, and cutaneous infections. Growth may appear normal initially, but extreme wasting usually ensues after diarrhea and infections begin. Persistent infections with opportunistic organisms including *Candida albicans, Pneumocystis jiroveci*, parainfluenza 3 virus, adenovirus, respiratory syncytial virus, rotavirus vaccine virus, cytomegalovirus, Epstein-Barr virus (EBV), varicella- zoster virus, measles virus, MMR-V (measles, mumps, rubella, varicella) vaccine virus, or bacillus Calmette-Guérin (BCG) lead to death. Affected infants also lack the ability to reject foreign tissue and are therefore at risk for severe or fatal graft-versus-host disease (GVHD) from T lymphocytes in nonirradiated blood products or in allogeneic stem cell transplants or less severe GVHD from maternal immunocompetent T cells that crossed the placenta while the infant was in utero.

Because all molecular types of SCID lack T cells, the profound T-cell **lymphopenia can be detected on dried blood spots routinely collected from heel sticks shortly after** birth for the purpose of newborn screening by assaying for the presence of T-cell receptor recombination excision circles by real time polymerase chain reaction. T-cell receptor recombination excision circles are absent or extremely low in SCID infants. These infants also have an absence of lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Patients with adenosine deaminase (ADA) deficiency have the lowest absolute lymphocyte counts, usually <500/mm^3, but infants with all molecular types of SCID are lymphopenic because they lack T cells (normally accounting for 70% of circulating lymphocytes). Serum immunoglobulin concentrations are low or absent, and no antibodies are formed after immunizations. Analyses of lymphocyte populations and subpopulations demonstrate distinctive phenotypes for the various genetic forms of SCID (see Table 126-2). T cells are extremely low or absent in all types; when detected, in most cases they are transplacentally derived maternal T cells.

TREATMENT

SCID is a true pediatric emergency. Unless immunologic reconstitution is achieved through stem cell transplantation or gene therapy, death usually occurs during the 1st yr of life and almost invariably before 2 yr of age. If diagnosed at birth or within the 1st 3.5 mo of life, >92% of cases can be treated successfully with human leukocyte antigen (HLA)-identical or T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cell transplantation without the need for pretransplant chemoablation or posttransplant GVHD prophylaxis. ADA-deficient SCID and X-linked SCID have been treated

Table 126-1 Genetic Basis of Combined Immunodeficiency Disorders

CHROMOSOME AND REGION	GENE PRODUCT	DISORDER	FUNCTIONAL DEFICIENCIES
1q	RFX5	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
1q31-q32	CD45	T–B+NK+ SCID	Absence of T- and B-cell functions
3p22.2	Myd88	Toll-receptor innate immune defect	T and B cell functions normal; Failure of activation of nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) by Toll receptor stimuli
5p13	IL-7Rα	T–B+NK+ SCID	Absence of T- and B-cell functions
6p21.3	TAP1, TAP2	MHC class I antigen deficiency	Marked deficiency of CD8 T cells; combined B- and T-cell defects
6q22-q23	IFN-γR1 IFN-γR2 IL-12Rβ_1	Disseminated mycobacterial infections	Failure of macrophages and other cells to produce TNF-α in response to IFN-γ
9p21-p13	Endoribonuclease RNase MRP*	Cartilage-hair hypoplasia	Combined B- and T-cell defects of varying severity
9p24	DOCK8	Autosomal recessive Hyper-IgE syndrome	↓↓ CD4, CD8 and Th17 T cells ↓ Naïve T cells; poor T-cell responses to mitogens; elevated serum IgE levels Decreased switched memory B cells Decreased antibody responses
10p13	Artemis	T–B–NK+ SCID	Absence of T- and B-cell functions
11p13	RAG1 or RAG2	T–B–NK+ SCID	Absence of T- and B-cell functions
11q22.3	ATM, a DNA-dependent kinase	Ataxia-telangiectasia	Selective IgA deficiency; T-cell deficiency
11q23	CD3δ or CD3ζ	T–B+NK+ SCID	Absence of T- and B-cell functions
12q12	IRAK4	Toll-receptor innate immune defect	T- and B-cell functions normal; failure of activation of NF-κB and MAPK by Toll receptor stimuli
13q	RFXAP	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
14q13.1	Purine nucleosidase	PNP deficiency	Severe T-cell deficiency; may have normal immunoglobulins
16p13	CIITA	MHC class II antigen deficiency	Low immunoglobulins, lack of T-cell responses to antigens, CD4 deficiency
17q21.3	STAT3	Autosomal dominant hyper-IgE syndrome	Elevated IgE and IgD, low CD45RO (memory) T cells, no Th17 T cells
19p13.1	Jak3	T–B+NK– SCID	Absence of T-, B-, and NK-cell functions
20q13.11	ADA	T–B–NK– SCID	Absence of T- and B-cell functions
Xp11.4-11.21	WASP	Wiskott-Aldrich syndrome	Thrombocytopenia; poor antibody production to polysaccharides; T-cell deficiency
Xp11.23	FOXP3	Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	Early onset of diarrhea and autoimmune diseases Elevated IgE
Xq13.1	Common γ chain (γc) for several cytokine receptors (including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21)	T–B+NK– SCID	Absence of T-, B-, and NK-cell functions

ADA, Adenosine deaminase; CIITA, class II transactivator; DOCK8, dedicator of cytokinesis 8; FOXP3, forkhead-winged helix transcription factor; IFN-γR1, interferon receptor chain 1; Ig, immunoglobulin; IL, interleukin; IL-7Rα, interleukin 7 receptor α chain; IL-12Rβ_1, interleukin 12 receptor β_1 chain; IFN, interferon; IRAK4, interleukin-1 receptor-associated kinase 4; Jak3, Janus kinase 3; MHC, major histocompatibility complex; Myd88, myeloid differentiation factor 88; NK, natural killer; PNP, purine nucleoside phosphorylase; RAG1 and RAG2, recombinase activating genes 1 and 2; SCID, severe combined immunodeficiency; STAT3, signal transducer and activator of transcription 3; TAP, transporter of antigenic peptide; Th17, T-helper cell type 17; TNF, tumor necrosis factor; WASP, Wiskott-Aldrich syndrome protein.

successfully with somatic gene therapy; although serious adverse events occurred in the case of X-linked SCID. ADA-deficient SCID can also be treated with repeated injections of polyethylene glycol modified bovine ADA (PEG-ADA), although the immune reconstitution achieved is not nearly as good as with stem cell or gene therapy. PEG-ADA should not be started if nonablative stem cell transplantation is contemplated because it will enable the infant to reject the graft.

X-LINKED SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY MUTATIONS IN THE GENE ENCODING THE COMMON CYTOKINE RECEPTOR γ CHAIN

X-linked SCID (X-SCID) is the most common form of SCID in the United States, accounting for 47% of cases (Fig. 126-1). Clinically, immunologically, and histopathologically, affected individuals appear

Table 126-2 Genetic Basis of SCID and SCID Variants

DISEASE	INHERITANCE	PRESUMED PATHOGENESIS	ADDITIONAL FEATURES	TREATMENT
Reticular dysgenesis	AR	Impaired mitochondrial energy metabolism and leukocyte differentiation	Severe neutropenia, deafness. Mutations in adenylate kinase 2	GCSF HSCT
Adenosine deaminase deficiency	AR	Accumulation of toxic purine nucleosides	Neurologic, hepatic, renal, lung, and skeletal and bone marrow abnormalities	HSCT, PEG-ADA, gene therapy
IL-2Rγ deficiency	X-linked	Abnormal signaling through by IL-2 receptor and other receptors containing γc (IL-4, -7, -9, -15, -21)	None	HSCT
Jak3 deficiency	AR	Abnormal signaling downstream of γc	None	HSCT
RAG1 and 2 deficiency	AR	Defective V(D)J recombination	None	HSCT
Artemis deficiency	AR	Defective V(D)J recombination, radiation sensitivity	DCLERE1C gene defects	HSCT
DNA-PK deficiency	AR	Defective V(D)J recombination	None	HSCT
DNA ligase IV deficiency	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bone marrow abnormalities, lymphoid malignancies	HSCT
Cernunnos-XLF	AR	Defective V(D)J recombination, radiation sensitivity	Growth delay, microcephaly, bird-like facies, bone defects	HSCT
CD3δ deficiency	AR	Arrest of thymocytes differentiation at the CD4–CD8– stage	Thymus size may be normal	HSCT
CD3ε deficiency	AR	Arrest of thymocytes differentiation at the CD4–CD8– stage	γ/δ T cells absent	HSCT
CD3ζ deficiency	AR	Abnormal signaling	None	HSCT
IL-7Rα deficiency	AR	Abnormal IL-7R signaling	Thymus absent	HSCT
CD45 deficiency	AR		None	HSCT
Coronin-1A deficiency	AR	Abnormal T-cell egress from thymus and lymph nodes	Normal thymus size. Attention deficit disorder.	HSCT

AR, autosomal recessive; GCSF, granulocyte colony stimulating factor; HSCT, hematopoietic stem cell transplantation; IL, interleukin; Jak3, Janus kinase 3; PEG-ADA, polyethylene glycol-modified adenosine deaminase; RAG1 and RAG2, recombinase activating genes 1 and 2; V(D)J, variable, diversity, joining.

(Modified from Roifman, CM. Grunebaum E. Primary T-cell immunodeficiencies. In Rich RR, Fleisher TA, Shearer WT, et al, editors: Clinical Immunology, *ed 4. Philadelphia, 2013, WB Saunders, Tables 35-1, 35-2, 35-3, 35-4, pp. 440–441).*

similar to those with other forms of SCID except for having uniformly **low percentages of T and NK cells** and an **elevated percentage of B cells** (T–, B+, NK–), a characteristic feature shared only with Janus kinase 3 (Jak3)–deficient SCID. The abnormal gene in X-SCID was mapped to Xq13, cloned, and found to encode the common γ chain (γc) for several cytokine receptors, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21. The shared γc functions both to increase the affinity of the receptor for the respective cytokine and to enable the receptors to mediate intracellular signaling. Incapacitation of the receptors for all of these developmentally crucial cytokines by genetic mutations in γc provides an explanation for the severity of the immunodeficiency in X-SCID. In the 1st 136 patients studied, 95 distinct mutations spanning all 8 IL-2RG exons were identified, most of them consisting of small changes at the level of 1 to a few nucleotides. These mutations resulted in abnormal γc chains in two-thirds of the cases and absent γc protein in the remainder. Carriers can be detected by demonstrating the deleterious mutation in their lymphocytes. Unless donor B or NK cells develop, patients with X-SCID lack B- and NK-cell function after bone marrow transplantation because the abnormal γc persists in those host cells, despite excellent reconstitution of T-cell function by donor-derived T cells.

AUTOSOMAL RECESSIVE SEVERE COMBINED IMMUNODEFICIENCY

This pattern of inheritance of SCID is less common in the United States than in other countries. Mutated genes on autosomal chromosomes have been identified in 12 forms of SCID: ADA deficiency; Jak3 deficiency; IL-7 receptor α chain (IL-7Rα) deficiency; recombinase-activating gene 1 or 2 (RAG1 or RAG2) deficiency; Artemis deficiency; ligase 4 deficiency; DNA–protein kinase catalytic subunit (DNA-PKcs) deficiency; CD3δ, CD3ε, CD3ζ deficiency; and CD45 deficiency (see Fig. 126-1).

Adenosine Deaminase Deficiency

An absence of the enzyme ADA is observed in approximately 15% of patients, the second most common form of SCID, resulting from various point and deletional mutations in the ADA gene on chromosome 20q13-ter. Marked accumulations of adenosine, 2′-deoxyadenosine, and 2′-*O*-methyladenosine lead directly or indirectly to T-cell apoptosis, which causes the immunodeficiency. ADA-deficient patients usually have a much more profound **lymphopenia** than do infants with other types of SCID, with mean absolute lymphocyte counts of <500/mm^3; the absolute numbers of T, B, and NK cells are very low. NK function is normal. After T-cell function is conferred by hematopoietic stem cell transplantation without pretransplant chemotherapy, there is generally excellent B-cell function despite the fact that the B cells are of host origin. This is because ADA deficiency affects primarily T-cell function. Milder forms of ADA deficiency have led to delayed diagnosis of immunodeficiency, even to adulthood. Other **distinguishing features** of ADA-deficient SCID include the presence of rib cage abnormalities similar to a rachitic rosary and numerous skeletal abnormalities of chondroosseous dysplasia, which occur predominantly at the costochondral junctions, at the apophyses of the iliac bones, and in the vertebral bodies where a "bone-in-bone" effect is observed.

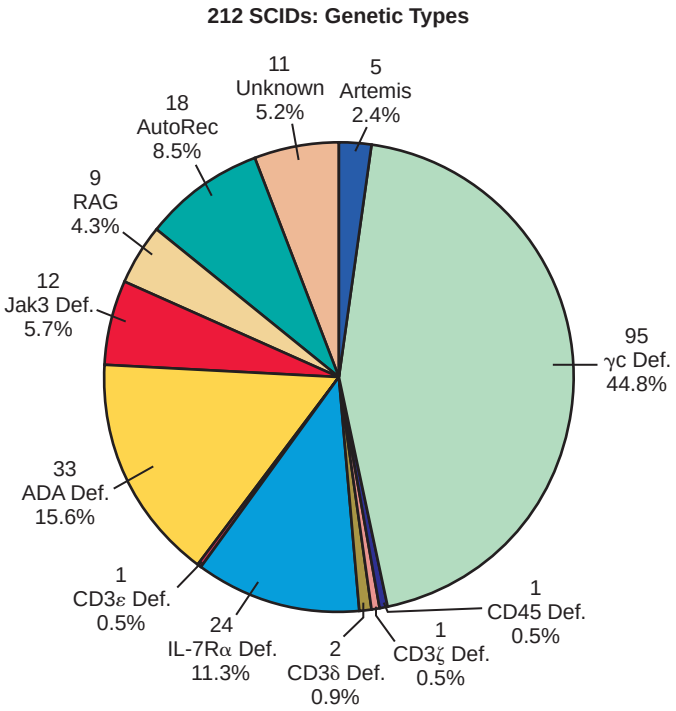

Figure 126-1 Relative frequencies of the different genetic types among 212 patients with severe combined immunodeficiency seen consecutively over 4 decades. *ADA,* adenosine deaminase; *IL-7Rα,* interleukin 7 receptor α chain; *Jak3,* Janus kinase 3; *RAG,* recombinase activating gene.

As with other types of SCID, ADA deficiency can be cured by HLA-identical or haploidentical T-cell–depleted stem cell transplantation without the need for pre- or posttransplant chemotherapy; this remains the treatment of choice. Enzyme replacement therapy should not be initiated if stem cell transplantation is possible because it confers graft-rejection capability. Enzyme replacement provides protective immunity but over time there is a decline of lymphocyte counts and proliferative responses. A number of infants with ADA deficiency have become successfully immune reconstituted by gene therapy in Italy, Great Britain and the United States; in all cases, PEG-ADA was withheld. Spontaneous reversion to normal of a mutation in the ADA gene has also been reported.

Jak3 Deficiency

Patients with this autosomal recessive defect resemble all other types of SCID patients clinically. They have a lymphocyte phenotype similar only to that of patients with X-SCID, with an elevated percentage of B cells and very low or no T and NK cells. Because Jak3 is the only signaling molecule known to be associated with γc, it was a candidate gene for mutations leading to autosomal recessive SCID. Jak3 deficiency accounts for 6% of SCID cases. Even after successful T-cell reconstitution by transplantation of haploidentical stem cells, patients with Jak3-deficient SCID fail to develop NK cells or normal B-cell function owing to the defective function of those host cells that bear abnormal cytokine receptors that share γc.

IL-7Rα Deficiency

Patients with IL-7Rα–deficient SCID have a distinctive lymphocyte phenotype in that, although lacking T cells, they have normal or elevated numbers of both B and NK cells (T–, B+, NK+). This is the **third most common** form of SCID, accounting for 12% of cases in the United States (see Fig. 126-1). In contrast to patients with γc- and Jak3-deficient SCID, the immunologic defect in these patients is completely correctable by T-cell reconstitution alone, because the host B and NK cells appear to be normal.

RAG1 or RAG2 Deficiencies

Infants with these causes of SCID have a different lymphocyte phenotype from those of patients with SCID caused by γc, Jak3, IL-7Rα, or ADA deficiencies in that they lack both B and T lymphocytes and have primarily NK cells in their circulation (T–, B–, NK+). This suggested a problem with their antigen receptor genes, which led to the discovery of mutations in *RAG1* or *RAG2*. Such mutations result in a functional inability to form antigen receptors through genetic recombination. **Omenn syndrome** is an autosomal recessive condition characterized by profound susceptibility to infection and by clonal T-cell infiltration of skin, intestines, liver, and spleen leading to an exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly, and intractable diarrhea. Mutations in the *RAG1* and *RAG2*, as well as rarely in other SCID-causing mutated genes, have been found in patients with this condition. These infants have persistent leukocytosis with marked eosinophilia and lymphocytosis; elevated serum immunoglobulin (Ig) E; low IgG, IgA, and IgM; and low or absent B cells. There is dominance of clonal T-helper (Th)2-like cells, with severely impaired T-cell function as the result of the restricted heterogeneity of the host T-cell repertoire.

Artemis Deficiency

Another cause of SCID is a deficiency of a novel V(D)J (variable, diversity, joining) recombination/DNA repair factor, named Artemis, that belongs to the metallo-β-lactamase superfamily, which is encoded on chromosome 10p by a gene named *DCLRE1C*. Deficiency of Artemis results in an inability to repair DNA after double-stranded cuts by the *RAG1* or *RAG2* gene products in rearranging antigen receptor genes from their germline configuration. Similar to RAG1- and RAG2-deficient SCID, this defect results in failure to develop T and B cells and is, therefore, another form of T–, B–, NK+ SCID, which is called **Athabascan SCID**. There is increased radiation sensitivity of both skin fibroblasts and bone marrow cells of those affected with this type of SCID as well as with DNA-PKcs and ligase 4 deficiencies.

CD45 Deficiency

Another molecular defect causing SCID is a mutation in the gene encoding the common leukocyte surface protein CD45. This hematopoietic cell–specific transmembrane protein tyrosine phosphatase functions to regulate src kinases required for T- and B-cell antigen receptor signal transduction. Three examples of this have been reported. One was found to have a large deletion on 1 CD45 allele and a point mutation causing an alteration of the intervening sequence 13 donor splice site on the other allele. The author has evaluated and treated a third case that was caused by uniparental disomy of chromosome 1 with an inactivating mutation in the gene encoding CD45.

CD3δ, CD3ε, and CD3ζ Deficiencies

Other causes of autosomal recessive SCID are deficiencies of components of the T-cell receptor (CD3δ, CD3ε, and CD3ζ chains). Mutations in the portions of these genes that encode the extracellular components of the proteins result in a profound deficiency of circulating mature CD3 T cells. Thus, CD3δ, CD3ε, and CD3ζ appear to be essential for intrathymic development of T cells. Because only T-cell development is affected in these defects, both B and NK cells are normal. Thus, the lymphocyte phenotype resembles that of SCID infants with IL-7Rα chain deficiency (T–B+NK+).

RETICULAR DYSGENESIS

Reticular dysgenesis was first described in identical twin boys who exhibited a total lack of both lymphocytes and granulocytes in their peripheral blood and bone marrow. The thymus glands weigh <1 g, have no Hassall corpuscles, and have few or no thymocytes. Reticular dysgenesis is considered a variant of SCID. The molecular basis of this autosomal recessive disorder is caused by mutations in the gene encoding adenylate kinase 2. The condition is fatal without definitive therapy and the treatment of choice is a fully myeloablative matched sibling bone marrow transplant. However, such transplants have been successful in only 7 of 17 evaluable patients so transplanted.

126.2 Combined Immunodeficiency

Rebecca H. Buckley

Combined immunodeficiency (CID) is distinguished from SCID by the presence of low but not absent T-cell function. Similar to SCID, CID is a syndrome of diverse genetic causes (see Table 126-1). Patients with CID have recurrent or chronic pulmonary infections, failure to thrive, oral or cutaneous candidiasis, chronic diarrhea, recurrent skin infections, Gram-negative bacterial sepsis, urinary tract infections, and severe varicella in infancy. Although they usually survive longer than infants with SCID, they fail to thrive and die early in life. Neutropenia and eosinophilia are common. Serum immunoglobulins may be normal or elevated for all classes, but selective IgA deficiency, marked elevation of IgE, and elevated IgD levels occur in some cases. Although antibody-forming capacity is impaired in most patients, it is not absent.

Studies of cellular immune function show lymphopenia, profound deficiencies of T cells, and extremely low but not absent lymphocyte proliferative responses to mitogens, antigens, and allogeneic cells in vitro. Peripheral lymphoid tissues demonstrate paracortical lymphocyte depletion. The thymus is very small, with a paucity of thymocytes and usually no Hassall corpuscles. An autosomal recessive pattern of inheritance is common.

PURINE NUCLEOSIDE PHOSPHORYLASE DEFICIENCY

More than 40 patients with CID have been found to have purine nucleoside phosphorylase deficiency. Point mutations identified in the purine nucleoside phosphorylase gene on chromosome 14q13.1 account for these deficiencies. In contrast to ADA deficiency, no characteristic physical or skeletal abnormalities have been noted, but serum and urinary uric acid are usually markedly deficient. Deaths result from generalized vaccinia, varicella, lymphosarcoma, or GVHD mediated by allogeneic T cells in nonirradiated blood or bone marrow. Two-thirds of patients have neurologic abnormalities, one-third of patients have autoimmune diseases, and some have had allergic diseases. Lymphopenia is striking, primarily because of a marked deficiency of T cells; T-cell function is decreased to various degrees. B cell function may be near normal. The proportion of circulating NK cells is increased. Prenatal diagnosis or diagnosis at birth is possible. Bone marrow transplantation is the only successful form of therapy.

CARTILAGE HAIR HYPOPLASIA

Cartilage hair hypoplasia (CHH) is an unusual form of **short-limbed dwarfism** with frequent and severe infections. It occurs predominantly among the Amish, but non-Amish patients have been described.

Genetics and Pathogenesis

CHH is an autosomal recessive condition. Numerous mutations that cosegregate with the CHH phenotype have been identified in the untranslated *RNase MRP* (*RMRP*) gene, which has been mapped to chromosome 9p21-p13 in Amish and Finnish families (see Table 126-1). The RMRP endoribonuclease consists of an RNA molecule bound to several proteins and has at least 2 functions: cleavage of RNA in mitochondrial DNA synthesis and nucleolar cleaving of pre-RNA. Mutations in RMRP cause CHH by disrupting a function of RMRP RNA that affects multiple organ systems. In vitro studies show decreased numbers of T cells and defective T-cell proliferation because of an intrinsic defect related to the G1 phase, resulting in a longer cell cycle for individual cells. NK cells are increased in number and function.

Clinical Manifestations

Clinical features include short, pudgy hands; redundant skin; hyperextensible joints of hands and feet but an inability to extend the elbows completely; and fine, sparse, light hair and eyebrows. Severe and often fatal varicella infections, progressive vaccinia, and vaccine-associated poliomyelitis have been observed. Associated conditions include deficient erythrogenesis, Hirschsprung disease, and an increased risk of malignancies. The bones radiographically show scalloping and sclerotic or cystic changes in the metaphyses and flaring of the costochondral junctions of the ribs. Three patterns of immune dysfunction have emerged: defective antibody-mediated immunity, CID (most common), and SCID. The severity of the immunodeficiency varies; in 1 series, 11 of 77 patients died before age 20 yr, but 2 were still alive at age 76 yr. Stem cell transplantation has resulted in immunologic reconstitution in some CHH patients who had the SCID phenotype.

DEFECTIVE EXPRESSION OF MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS

The 2 main forms of immunodeficiency and abnormalities of expression of the major histocompatibility complex (MHC) are MHC class I (HLA-A, -B, and -C) antigen deficiency and MHC class II (HLA-DR, -DQ, and -DP) antigen deficiency. The associated defects of both B- and T-cell immunity and of HLA expression emphasize the important biologic role for HLA determinants in effective immune cell cooperation.

Major Histocompatibility Complex Class I Antigen Deficiency

Isolated deficiency of MHC class I (HLA-A, -B, and -C) antigens, the **bare lymphocyte syndrome**, is rare. The resulting immunodeficiency is much milder than in SCID, contributing to a later age of presentation. Sera from affected children contain normal quantities of MHC class I antigens and β_2-microglobulin, but MHC class I antigens are not detected on any cells in the body. There is a deficiency of CD8 but not CD4 T cells. Mutations have been found in 2 genes within the MHC locus on chromosome 6 that encode the peptide transporter proteins TAP1 and TAP2. TAP functions to transport antigenic peptides from the cytoplasm across the Golgi apparatus membrane to join the α chain of MHC class I antigens and β_2-microglobulin. All these are then assembled into a MHC class I complex that can then move to the cell surface. If the assembly of the complex cannot be completed because there is no antigenic peptide, the MHC class I complex is destroyed in the cytoplasm.

Major Histocompatibility Complex Class II Antigen Deficiency

Many affected with MHC class II (HLA-DR, -DQ, and -DP) deficiency are of North African descent. Patients present in early infancy with persistent diarrhea that is often associated with cryptosporidiosis and enteroviral infections (e.g., poliovirus, coxsackievirus). They also have an increased frequency of infections with herpesviruses and other viruses, oral candidiasis, bacterial pneumonia, *P. jiroveci* pneumonia, and septicemia. The immunodeficiency is not as severe as in SCID, as evidenced by their failure to develop disseminated infection after BCG vaccination or GVHD from nonirradiated blood transfusions.

Four different molecular defects resulting in impaired expression of MHC class II antigens have been identified (see Table 126-1 and Fig. 124-1). One form is a mutation in the gene on chromosome 1q that encodes a protein called RFX5, a subunit of RFX, which is a multiprotein complex that binds the X box motif of MHC-II promoters. A second form is caused by mutations in a gene on chromosome 13q that encodes a second 36-kD subunit of the RFX complex, called RFX-associated protein (RFXAP). The most common cause of MHC class II defects is a mutation in RFXANK, the gene encoding a 3rd subunit of RFX. In a 4th type, there is a mutation in the gene on chromosome 16p13 that encodes a novel MHC class II transactivator, a non–DNA-binding coactivator that controls the cell-type specificity and inducibility of MHC-II expression. All 4 of these defects cause impairment in the coordinate expression of MHC class II molecules on the surface of B cells and macrophages.

MHC class II–deficient patients have a very low number of CD4 T cells but normal or elevated numbers of CD8 T cells. Lymphopenia is only moderate. The MHC class II antigens HLA-DP, -DQ, and -DR are undetectable on blood B cells and monocytes, even though B cells are present in normal number. Patients are hypogammaglobulinemic owing to impaired antigen-specific responses caused by the absence of these antigen- presenting molecules. In addition, MHC antigen-deficient B cells fail to stimulate allogeneic cells in mixed leukocyte culture. Lymphocyte proliferation studies show normal responses to

mitogens but no response to antigens. The thymus and other lymphoid organs are severely hypoplastic, and the lack of class II molecules results in abnormal thymic selection with circulating CD4 T cells that have altered CDR3 profiles.

IMMUNODEFICIENCY WITH THROMBOCYTOPENIA AND ECZEMA (WISKOTT-ALDRICH SYNDROME)

Wiskott-Aldrich syndrome, an X-linked recessive syndrome, is characterized by atopic dermatitis, thrombocytopenic purpura with normal-appearing megakaryocytes but small defective platelets, and undue susceptibility to infection.

Genetics and Pathogenesis

The abnormal gene, on the proximal arm of the X chromosome at Xp11.22-11.23 near the centromere, encodes a 501 amino acid proline-rich cytoplasmic protein restricted in its expression to hematopoietic cell lineages. The Wiskott-Aldrich syndrome protein (WASP) binds CDC42H2 and rac, members of the Rho family of guanosine triphosphatases. Wiskott-Aldrich syndrome protein appears to control the assembly of actin filaments required for microvesicle formation downstream of protein kinase C and tyrosine kinase signaling. Carriers can be detected by demonstration of the deleterious mutation.

Clinical Manifestations

Patients often have prolonged bleeding from the circumcision site or bloody diarrhea during infancy. The thrombocytopenia is not initially due to antiplatelet antibodies. Atopic dermatitis and recurrent infections usually develop during the 1st yr of life. *Streptococcus pneumoniae* and other bacteria having polysaccharide capsules cause otitis media, pneumonia, meningitis, and sepsis. Later, infections with agents such as *P. jiroveci* and the herpesviruses become more frequent. Survival beyond the teens is rare; infections, bleeding, and EBV-associated malignancies are major causes of death.

Patients with this defect uniformly have an impaired humoral immune response to polysaccharide antigens, as evidenced by absent or markedly diminished isohemagglutinins, and poor or absent antibody responses after immunization with polysaccharide vaccines. IgG_2 subclass concentrations, surprisingly, are normal. Anamnestic responses to protein antigens are poor or absent. There is an accelerated rate of synthesis as well as hypercatabolism of albumin, IgG, IgA, and IgM, resulting in highly variable concentrations of different immunoglobulins, even within the same patient. The predominant immunoglobulin pattern is a low serum level of IgM, elevated IgA and IgE, and a normal or slightly low IgG concentration. Because of their profound antibody deficiencies, these patients should be given monthly infusions of intravenous immunoglobulin (IVIG) regardless of their serum levels of the different immunoglobulin isotypes. Percentages of T cells are moderately reduced, and lymphocyte responses to mitogens are variably depressed.

Treatment

Good supportive care includes appropriate nutrition, routine IVIG, use of killed vaccines, aggressive management of eczema and associated cutaneous infections, platelet transfusion for serious bleeding episodes, splenectomy if a transplant is not going to be done, and high-dose IVIG with systemic steroids for autoimmune complications. Bone marrow or cord blood transplantation is the treatment of choice and is usually curative.

ATAXIA-TELANGIECTASIA

Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.

Genetics and Pathogenesis

The mutated gene responsible for this defect, ataxia-telangiectasia mutation *(ATM)*, was mapped to the long arm of chromosome 11 (11q22-23) and has been cloned. The gene product is a DNA-dependent protein kinase localized predominantly to the nucleus and involved in mitogenic signal transduction, meiotic recombination, and cell-cycle control. Cells from patients, as well as from heterozygous carriers, have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.

In vitro tests of lymphocyte function have generally shown moderately depressed proliferative responses to T- and B-cell mitogens. Percentages of CD3 and CD4 T cells are moderately reduced, with normal or increased percentages of CD8 and elevated numbers of Tiγ/δ T cells. The thymus is very hypoplastic, exhibits poor organization, and lacks Hassall corpuscles.

Clinical Manifestations

The most prominent clinical features are progressive cerebellar ataxia, oculocutaneous telangiectasias, chronic sinopulmonary disease, a high incidence of malignancy, and variable humoral and cellular immunodeficiency. Ataxia typically becomes evident soon after these children begin to walk and progresses until they are confined to a wheelchair, usually by the age of 10-12 yr. The telangiectasias begin to develop at 3-6 yr of age. The most frequent humoral immunologic abnormality is the selective absence of IgA, which occurs in 50-80% of these patients. Hypercatabolism of IgA also occurs. IgE concentrations are usually low, and the IgM may be of the low-molecular-weight variety. IgG_2 or total IgG levels may be decreased, and specific antibody titers may be decreased or normal. Recurrent sinopulmonary infections occur in approximately 80% of these patients. Although common viral infections have not usually resulted in untoward sequelae, fatal varicella has occurred. The malignancies associated with ataxia-telangiectasia are usually of the lymphoreticular type, but adenocarcinomas also occur. Unaffected relatives have an increased incidence of malignancy.

126.3 Defects of Innate Immunity

Rebecca H. Buckley

A number of defects in non–antigen-specific immunity (innate immunity) affect antigen-specific immune responses, as there is interaction between the adaptive and innate immune systems.

INTERFERON-γ RECEPTORS 1 AND 2, IL-12 RECEPTOR β_1, AND IL-12P40 MUTATIONS

Disseminated BCG and other severe nontuberculosis mycobacterial infections (sepsis, osteomyelitis) occur in patients with severe T-cell defects; however, no specific host defect is identified in approximately half of such cases. The first report was a 2.5 mo old Tunisian girl with fatal idiopathic disseminated BCG infection; 4 children from Malta had disseminated atypical mycobacterial infections in the absence of a recognized immunodeficiency. There was consanguinity in all, and all had a functional defect in the upregulation of tumor necrosis factor (TNF) α production by their blood macrophages in response to stimulation with interferon-γ (IFN-γ). All also had a mutation in the gene on chromosome 6q22-q23 that encodes the IFN-γ receptor 1 (IFN-γR1). IFN-γR1 deficiency may be inherited as a complete autosomal recessive (early onset ≈3 yr of age, more episodes, more severe disease, and higher mortality) or partial dominant (onset ≈10 yr of age) disease. Patients with mutations in the IFN-γR2 have also been identified. Related defects were found in other patients who had disseminated mycobacterial infections, who have mutations in either the gene encoding the β_1 chain of the IL-12 receptor (IL-12Rβ_1) or in the gene encoding IL-12p40. IL-12 is a powerful inducer of IFN-γ production by T and NK cells, and the mutated receptor chain gene resulted in unresponsiveness of the cells of these patients to IL-12 and inadequate IFN-γ production. The children deficient in IFN-γR1, IFN-γR2, IL-12Rβ_1, or IL-12p40 appeared not to be susceptible to infection with many agents other than mycobacteria (occasionally *Salmonella*, *Listeria, Histoplasma*). Th1 responses appeared to be normal in these patients, and the susceptibility to mycobacterial infections thus apparently results from an intrinsic impairment of the IFN-γ pathway response to these particular intracellular pathogens, showing that IFN-γ is obligatory for efficient macrophage antimycobacterial activity.

GERMLINE STAT-1 MUTATION

Interferons induce the formation of 2 transcriptional activators: gamma-activating factor (GAF) and interferon-stimulated gamma factor 3 (ISGF3). A natural heterozygous dominant germline *STAT-1* mutation associated with susceptibility to mycobacterial but not viral disease was found in 2 unrelated patients with unexplained mycobacterial disease. This mutation caused a loss of GAF and ISGF3 activation but was dominant for 1 cellular phenotype and recessive for the other. The mutation impaired the nuclear accumulation of GAF, but not of ISGF3, in cells stimulated by interferons, implying that the antimycobacterial but not the antiviral effects of human interferons are mediated by GAF. Two patients were identified with homozygous *STAT-1* mutations; they developed both post–BCG vaccination disseminated disease and lethal viral infections. The mutations in these patients caused a complete lack of STAT-1 and resulted in a lack of formation of both GAF and ISGF3.

IL-1R–ASSOCIATED KINASE 4 DEFICIENCY AND MYELOID DIFFERENTIATION FACTOR 88

Members of IL-1R and the Toll-like receptor superfamily share an intracytoplasmic Toll–IL-1 receptor (TIR) domain, which mediates recruitment of the IL-1R–associated kinase (IRAK) complex via TIR-containing adapter molecules. Three unrelated, otherwise healthy children with recurrent pyogenic infections caused by pneumococci and staphylococci had normal immunocompetence by standard immune studies. They had normal titers of antipneumococcal antibodies. Their blood and fibroblast cells did not activate nuclear factor κB, and mitogen-activated protein kinase and failed to induce downstream cytokines in response to any of the known ligands of TIR-bearing receptors. All were found to have an inherited deficiency of IRAK-4. The TIR-IRAK signaling pathway appears to be crucial for protective immunity against specific bacteria but is redundant against most other microorganisms. There are now more than 50 documented cases of IRAK4 deficiency, and a commonality among cases is susceptibility to pyogenic bacterial infection with pneumococcus and *Pseudomonas*. The pneumococcal infections have the potential to be invasive (even as a presenting feature) and lead to poor clinical outcomes. Severe viral and fungal infections are atypical. The myeloid differentiation factor 88 (MYD88) is an effective phenocopy of IRAK4 deficiency. While discovered later than IRAK4 deficiency, myeloid differentiation factor 88 is an upstream adaptor for IRAK4 and links it to Toll-like receptors, which results in a very similar immunologic defect and clinical syndrome.

NATURAL KILLER CELL DEFICIENCY

NK cells are the major lymphocytes of the innate immune system. NK cells recognize virally infected and malignant cells and mediate their elimination. Individuals with absence or functional deficiencies of NK cells are rare, and they typically have susceptibility to the herpesviruses (including varicella-zoster virus, herpes simplex virus, cytomegalovirus, and EBV) as well as papillomaviruses. A number of gene defects are associated with these isolated abnormalities in NK cells. Autosomal recessive CD16 gene mutations were described in 3 separate families and they altered the first immunoglobulin-like domain of this important NK cell activation receptor. Patients with these mutations have NK cells that are functionally impaired and have clinical susceptibility to herpesviruses. **Autosomal dominant** deficiency of NK cells occurs in individuals with mutations in the GATA2 transcription factor. These patients also have low numbers of monocytes. They have extreme susceptibility to human papilloma virus as well as mycobacteria—the latter presumably from the monocytic defect. **Autosomal recessive** mutations in the MCM4 gene have been identified in a cohort of consanguineous Irish who had growth failure and susceptibility to herpesviruses. These individuals possessed the immature $CD56^{bright}$ minor subset, but lacked the major mature $CD56^{dim}$ subset of NK cells. The reason why MCM4, which encodes a DNA helicase, would interfere with NK cell development remains unclear. Therapeutically, patients should be maintained on antiviral prophylaxis, and allogeneic stem cell transplantation has been successful in certain cases.

HYPER-IGE SYNDROMES

The hyper-IgE syndromes are relatively rare primary immunodeficiency syndromes characterized by recurrent severe staphylococcal abscesses of the skin, lungs, and other sites and markedly elevated levels of serum IgE (Table 126-3). They occur in 2 forms: autosomal dominant and autosomal recessive.

Autosomal Dominant Hyper-IgE Syndrome

This is the most common form in the United States. More than 200 patients with autosomal dominant hyper-IgE syndrome, also known as the Buckley syndrome, have been reported.

Genetics and Pathogenesis

The autosomal dominant hyper-IgE syndrome is caused by heterozygous mutations in the gene encoding STAT-3. These mutations result in a dominant negative effect on the expression of STAT-3 by the other nonmutated gene. It is not clear exactly how the STAT-3 mutation causes all parts of the syndrome, but it is thought that IL-17 deficiency may account in part for the susceptibility to *Candida* infection. IL-17 is a cytokine that acts on monocytes to induce secretion of proinflammatory mediators such as IL-8, TNF, and granulocyte-macrophage colony-stimulating factor.

Clinical Manifestations

The characteristic clinical features of the autosomal dominant form of the hyper-IgE syndrome are staphylococcal abscesses, pneumatoceles, osteopenia, and unusual facial features. There is a history from infancy of recurrent staphylococcal abscesses involving the skin, lungs, joints, viscera and other sites. Persistent pneumatoceles develop as a result of recurrent pneumonia. They often have histories of sinusitis and mastoiditis. *C. albicans* is the second most common pathogen. Allergic respiratory symptoms are usually absent. The pruritic dermatitis that occurs is not typical atopic eczema and does not always persist. The first 2 reported patients were described as having **coarse facial features**, including a prominent forehead, deep-set wide-spaced eyes, a broad nasal bridge, a wide fleshy nasal tip, mild prognathism, facial asymmetry, and hemihypertrophy. In older children, delay in shedding primary teeth, recurrent fractures, and scoliosis occur.

These patients demonstrate an exceptionally high serum IgE concentration; an elevated serum IgD concentration; usually normal concentrations of IgG, IgA, and IgM; pronounced blood and sputum eosinophilia; abnormally low anamnestic antibody responses; and poor antibody and cell-mediated responses to neoantigens. Traditionally, IgE levels >2000 IU/mL confirm the diagnosis. However, IgE levels may fluctuate and even decrease in adults. In neonates and infants with the pruritic pustular dermatosis, IgE levels will be elevated for age and are usually in the 100s. In vitro studies show normal percentages of blood T, B, and NK lymphocytes, except for a decreased percentage of T cells with the memory (CD45RO) phenotype and an absence or deficiency of Th17 T cells. Most patients have normal T-lymphocyte proliferative responses to mitogens but very low or absent responses to antigens or allogeneic cells from family members. Blood, sputum, and histologic sections of lymph nodes, spleen, and lung cysts show striking eosinophilia. Hassall corpuscles and thymic architecture are normal. Phagocytic cell ingestion, metabolism, killing, and total hemolytic complement activity are normal in all patients, and results of chemotaxis studies have been mostly normal.

Autosomal Recessive Hyper-IgE Syndrome

Genetics and Pathogenesis

With the exception of 1 patient who had a mutation in the gene encoding Tyk2, most reported patients with autosomal recessive hyper-IgE syndrome have had mutations in the gene encoding DOCK8, which is on chromosome 9. DOCK8 is a member of the 11-member DOCK protein family. DOCK8 is likely to function as a guanine exchange factor for the Rho-guanosine triphosphatases Cdc42 and Rac1. Guanosine triphosphatase activation induces dynamic filamentous actin rearrangements and lamellipodia formation, leading to cell growth, migration, and adhesion. DOCK8 may be important for the formation

Table 126-3 Hyperimmunoglobulin E Syndromes

	AUTOSOMAL DOMINANT OR SPORADIC (JOB SYNDROME)	AUTOSOMAL RECESSIVE
Gene	*STAT3*	*DOCK8:* less often *TYK2*
INFECTIONS		
Sinopulmonary		
Recurrent bacterial	*S. aureus*, pneumococcus, *H. influenzae*	*S. aureus*, pneumococcus, *H. influenzae*
Pneumatoceles/bronchiectasis	Common	No
Fungal	Aspergillus species	No
Cutaneous		
Abscesses	*S. aureus*	*S. aureus*
Viral	No	HPV, HSV, VZV, MCV
Mucocutaneous candidiasis	Common	Common
ATOPIC DISORDERS		
Newborn eosinophilic pustules	Common	No
Eczema	Common	Common
Asthma	No	Common
Allergies/Anaphylaxis	No	Common
MUSCULOSKELETAL		
Osteopenia, pathologic fractures	Common	No
Scoliosis	Common	No
Retained primary teeth	Common	No
Hyperextensible	Common	No
OTHER FEATURES		
Coarse facies*	Common in adolescent	No
Coronary artery tortuosity/aneurysm	Common	No
UBO on brain MRI	Common	No
Lymphomas	Yes	Higher incidence
Cutaneous malignancy	No	Yes
Mortality	Adulthood	Childhood

*Coarse facies includes broad nose, prominent forehead and chin, deep set eyes
HPV, human papillomavirus; HSV, herpes simplex virus; MCV, molluscum virus; UBO, unidentified bright objects of cerebral cortex on T_2 MRI; VZV, varicella-zoster virus.

of the immunologic synapse that leads to T-cell activation, proliferation, and differentiation. Of the 33 patients reported, 25 were from Turkey, 2 each were from Mexico and Iran, and 1 each was from Lebanon, Oman, Italy, and Ireland. Autosomal recessive hyper-IgE syndrome may rarely be due to mutations in phosphoglucomutase 3 (PGM3 deficiency).

Clinical Manifestations

Unlike those with the autosomal dominant form of this syndrome, a large majority of patients with autosomal recessive hyper-IgE have severe atopic dermatitis, asthma, food allergies, and anaphylaxis. They also have recurrent skin viral infections, including severe herpes simplex, herpes zoster, molluscum contagiosum, and papillomavirus skin infections (see Table 126-3). In addition, patients can have abscesses, mucocutaneous candidiasis, upper respiratory infections, and pneumonia. Neurologic problems, including strokes, meningitis, and aneurysms, are prominent. Malignancies are also more common than in the autosomal dominant form. Patients with the autosomal recessive hyper-IgE syndrome do not have pneumatoceles, a history of fractures, unusual facial features, or delayed shedding of the baby teeth, as seen with the autosomal dominant form of the hyper-IgE syndrome (see Table 126-3).

Most patients with autosomal recessive hyper-IgE have elevated serum IgE levels, low serum IgM levels, and variable IgG antibody responses. They also have eosinophilia and lymphopenia, low T-cell numbers and impaired T-cell function. Their immunologic phenotype is that of a CID.

Treatment

The most effective **therapy** for the autosomal dominant hyper-IgE syndrome is long-term administration of therapeutic doses of a penicillinase-resistant antistaphylococcal antibiotic, adding other agents as required for specific infections. IVIG should be administered to antibody-deficient patients, and appropriate thoracic surgery should be provided for superinfected pneumatoceles or those persisting beyond 6 mo. Bone marrow transplantation has been variably successful in this condition. The prognosis in the autosomal recessive form of the hyper-IgE syndrome is much poorer than in the autosomal dominant form, and most patients die early (see Table 126-3). The treatment of choice for the autosomal recessive form is allogeneic bone marrow transplantation.

126.4 Treatment of Cellular or Combined Immunodeficiency

Rebecca H. Buckley

Good supportive care, including prevention and treatment of infections, is critical while patients await more definitive therapy (Table 126-4). Having knowledge of the pathogens causing disease with specific immune defects is also useful (see Table 126-4).

Transplantation of MHC-compatible sibling or rigorously T-cell–depleted haploidentical (half-matched) parental hematopoietic stem cells is the treatment of choice for patients with fatal T-cell or combined T- and B-cell defects. The major risk to the recipient from transplants of bone marrow or peripheral blood stem cells is GVHD from donor T cells. Patients with less severe forms of cellular immunodeficiency, including some forms of CID, Wiskott-Aldrich syndrome, cytokine deficiency, and MHC antigen deficiency, reject even HLA-identical marrow grafts unless chemoablative treatment is given before transplantation. Several patients with these conditions have been treated successfully with hematopoietic stem cell transplantation after conditioning.

More than 90% of patients with primary immunodeficiency transplanted with HLA-identical related marrow will survive with immune reconstitution. T-cell–depleted haploidentical-related marrow transplants in patients with primary immunodeficiency have had their greatest success in patients with SCID, who do not require

Table 126-4 Infection in the Host Compromised by B- and T-Cell Immunodeficiency Syndromes

IMMUNODEFICIENCY SYNDROME	OPPORTUNISTIC ORGANISMS ISOLATED MOST FREQUENTLY	APPROACH TO TREATMENT OF INFECTIONS	PREVENTION OF INFECTIONS
B-cell immunodeficiencies	Encapsulated bacteria (*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*, and *Neisseria meningitidis*), *Pseudomonas aeruginosa, Campylobacter* sp., enteroviruses, rotaviruses, *Giardia lamblia, Cryptosporidium* sp., *Pneumocystis jiroveci, Ureaplasma urealyticum*, and *Mycoplasma pneumoniae*	1. IVIG 200-800 mg/kg 2. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 3. Incision and drainage if abscess present 4. Antibiotic selection on the basis of sensitivity data	1. Maintenance IVIG for patients with quantitative and qualitative defects in IgG metabolism (400-800 mg/kg q 3-5 wk) 2. In chronic recurrent respiratory disease, vigorous attention to postural drainage 3. In selected cases (recurrent or chronic pulmonary or middle ear), prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole
T-cell immunodeficiencies	Encapsulated bacteria (*S. pneumoniae, H. influenzae, S. aureus*), facultative intracellular bacteria (*Mycobacterium tuberculosis*, other *Mycobacterium* sp., and *Listeria monocytogenes*); *Escherichia coli; P. aeruginosa; Enterobacter* sp.; *Klebsiella* sp.; *Serratia marcescens; Salmonella* sp.; *Nocardia* sp.; viruses (cytomegalovirus, herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, rotaviruses, adenoviruses, enteroviruses, respiratory syncytial virus, measles virus, vaccinia virus, and parainfluenza viruses); protozoa (*Toxoplasma gondii* and *Cryptosporidium* sp.); and fungi (*Candida* sp., *Cryptococcus neoformans, Histoplasma capsulatum*, and *P. jiroveci*)	1. Vigorous attempt to obtain specimens for culture before antimicrobial therapy 2. Incision and drainage if abscess present 3. Antibiotic selection on the basis of sensitivity data 4. Early antiviral treatment for herpes simplex, cytomegalovirus, and varicella-zoster viral infections 5. Topical and nonadsorbable antimicrobial agents frequently are useful	1. Prophylactic administration of trimethoprim-sulfamethoxazole for prevention of *P. jiroveci* pneumonia 2. Oral nonadsorbable antimicrobial agents to lower concentration of gut flora 3. No live virus vaccines or bacillus Calmette-Guérin vaccine 4. Careful tuberculosis screening

IVIG, intravenous immunoglobulin.
From Stiehm ER, Ochs HD, Winkelstein JA: Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders.*

pretransplant conditioning or GVHD prophylaxis. Of patients with SCID, 92% have survived after T-cell–depleted parental marrow is given soon after birth when the infant is healthy without pretransplant chemotherapy or posttransplant GVHD prophylaxis. Currently, bone marrow transplantation remains the most important and effective therapy for SCID. Early in 2000, there was remarkable success with gene therapy in X-SCID. Unfortunately, leukemic-like clonal T cells or lymphomas developed in 5 of 20 children so treated as a result of insertional mutagenesis, which led to a cessation of those trials. By contrast, in ADA-deficient SCID, there has been outstanding success without insertional oncogenesis. More recently, gene therapy has been successful in the Wiskott-Aldrich syndrome but unfortunately with the problem of insertional mutagenesis.

126.5 Immune Dysregulation with Autoimmunity or Lymphoproliferation

Rebecca H. Buckley

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

Autoimmune lymphoproliferative syndrome (ALPS), also known as Canale-Smith syndrome, is a disorder of abnormal lymphocyte apoptosis leading to polyclonal populations of T cells (double-negative T cells), which express CD3 and α/β antigen receptors but do not have CD4 or CD8 coreceptors (CD3 + T cell receptor α/β^+ $CD4^-$ $CD8^-$). These T cells respond poorly to antigens or mitogens and do not produce growth or survival factors (IL-2). The genetic deficit in most patients is a germline or somatic mutation in the Fas gene, which produces a cell-surface receptor of the TNF receptor superfamily (TNFRSF6), which, when stimulated by its ligand, will produce programmed cell death (Table 126-5). Persistent survival of these lymphocytes leads to immune dysregulation and autoimmunity. ALPS is also caused by other genes in the Fas pathway (*FASLG* and *CASP10*). In addition, ALPS-like disorders are associated with other mutations; RAS-associated autoimmune lymphoproliferative disorder (RALD), CASPASE-8 deficiency syndrome (CEDS), Fas-associated protein with death domain deficiency (FADD), and protein kinase C delta deficiency (PRKCD). These disorders have varying degrees of immune deficiency, autoimmunity and lymphoproliferation.

Clinical Manifestations

ALPS is characterized by autoimmunity, chronic persistent or recurrent lymphadenopathy, splenomegaly, hepatomegaly (in 50%), and hypergammaglobulinemia (IgG, IgA). Many patients present in the 1st yr of life, and most are symptomatic by yr 5. Lymphadenopathy can be striking (Fig. 126-2). Splenomegaly may produce hypersplenism with cytopenias. Autoimmunity also produces anemia (Coombs-positive hemolytic anemia) or thrombocytopenia or a mild neutropenia. The lymphoproliferative process (lymphadenopathy, splenomegaly) may regress over time, but autoimmunity does not and is characterized by frequent exacerbations and recurrences. Other autoimmune features include urticaria, uveitis, glomerulonephritis, hepatitis, vasculitis, glomerulonephritis, vasculitis, panniculitis, arthritis, and central nervous system involvement (seizures, headaches, encephalopathy).

Malignancies are also more common in patients with ALPS and include Hodgkin and non-Hodgkin lymphomas and solid-tissue tumors of thyroid, skin, heart, or lung. ALPS is one cause of Evan syndrome (immune thrombocytopenia and immune hemolytic anemia).

Diagnosis

Laboratory abnormalities depend on the lymphoproliferative organ response (hypersplenism) or the degree of autoimmunity (anemia, thrombocytopenia). There may be lymphocytosis or lymphopenia. Table 126-5 lists the criteria for the diagnosis. Flow cytometry helps identify the lymphocyte type (see Fig. 126-2). Functional genetic analysis for the *TNFRSF6* gene often reveals a heterozygous mutation.

Table 126-5 Diagnostic Criteria for Autoimmune Lymphoproliferative Syndrome

REQUIRED
1. Chronic nonmalignant lymphoproliferation (>6 mo lymphadenopathy and/or splenomegaly)
2. Elevated peripheral blood double-negative T cells

ACCESSORY
Primary
Defective in vitro Fas-mediated apoptosis (in 2 separate assays)
Somatic or germline mutation in ALPS causative gene (FAS, FASL, CASP10)
Secondary
1. Elevated biomarkers (Any of following)
   a. Plasma soluble FASL >200 pg/mL
   b. Plasma IL-10 >20 pg/mL
   c. Plasma or serum vitamin B_{12} >1500 ng/L
   d. Plasma IL-18 >500 pg/mL
2. Immunohistochemical findings consistent with ALPS as determined by experienced histopathologist
3. Autoimmune cytopenias and polyclonal hypergammaglobulinemia
4. Family history of ALPS or nonmalignant lymphoproliferation

DIAGNOSIS
Definitive: Required plus 1 primary accessory criterion
Probable: Required plus 1 secondary accessory criterion
Of note, probable and definitive ALPS should be treated the same in the clinic

Modified from Teachey DT: New advances in the diagnosis and treatment of autoimmune lymphoproliferative syndrome. Curr Opin Pediatr *24:1–8, 2013, Table 2, p. 4.*

Treatment

Lymphoproliferative manifestations have been managed with corticosteroids and immunosuppressive agents (Cytoxan [cyclophosphamide], methotrexate, azathioprine); once weaned, the manifestation recurs. Hypersplenism may require splenectomy. Malignancies can be treated with the usual protocols used in patients unaffected by ALPS. Stem cell transplantation is another possible option in treating the autoimmune manifestations of ALPS.

IMMUNE-DYSREGULATION, POLYENDOCRINOPATHY, ENTEROPATHY, X-LINKED SYNDROME

This immune dysregulation syndrome is characterized by onset within the 1st few wk or mo of life with watery diarrhea (autoimmune enteropathy), an eczematous rash (erythroderma in neonates), insulin-dependent diabetes mellitus, hyperthyroidism or more often hypothyroidism, severe allergies, and other autoimmune disorders (Coombs-positive hemolytic anemia, thrombocytopenia, neutropenia). Psoriasiform or ichthyosiform rashes and alopecia have also been reported,

Immune-dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is caused by a mutation in the *FOXP3* gene, which encodes a forkhead-winged helix transcription factor *(scurfin)* involved in the function and development of CD4+CD25+ regulatory T cells. The absence of regulatory cells may predispose to abnormal activation of effector T cells. Dominant gain of function mutations in *STAT1* and other gene mutations (Table 126-6) produces an IPEX-like syndrome.

Clinical Manifestations

Watery diarrhea with intestinal villous atrophy leads to failure to thrive in most patients. Cutaneous lesions (usually eczema) and

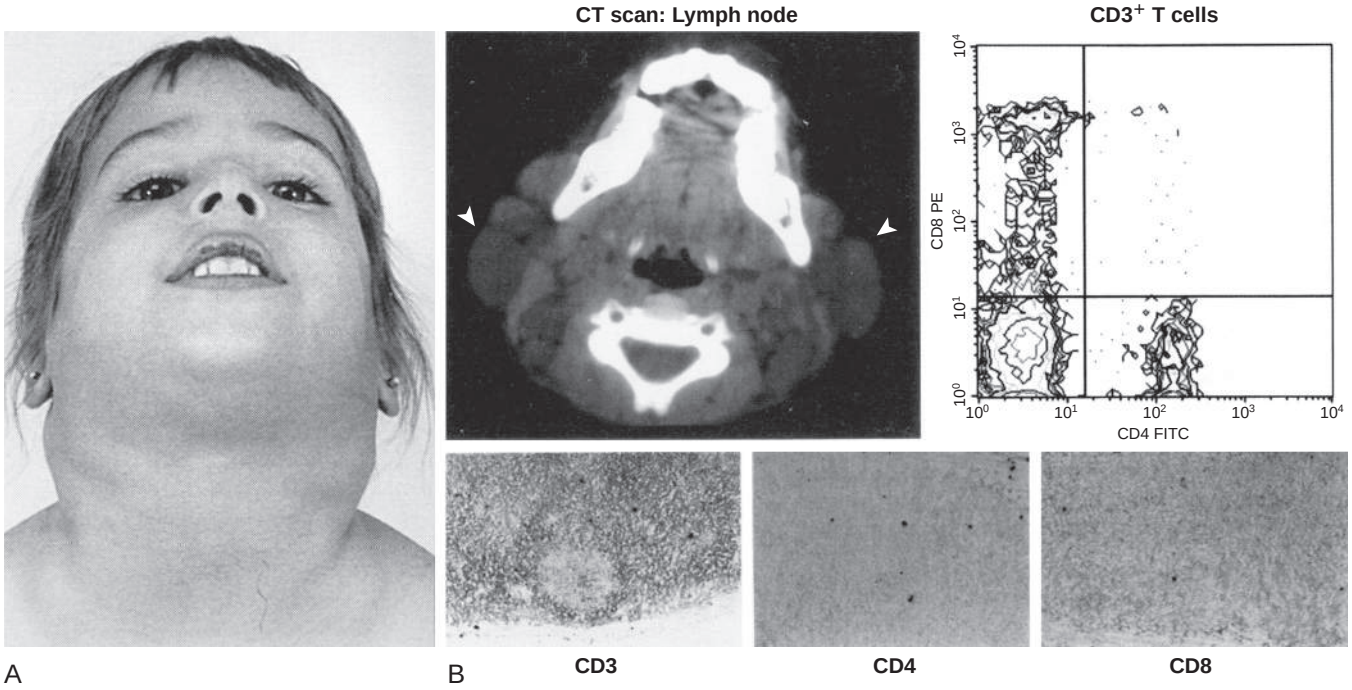

Figure 126-2 Clinical, radiographic, immunologic, and histologic characteristics of the autoimmune lymphoproliferative syndrome. **A,** Front view of the National Institutes of Health patient. **B,** *Top middle*, a CT scan of the neck is shown demonstrating enlarged preauricular, cervical, and occipital lymph nodes. *Arrowheads* denote the most prominent lymph nodes. The *top right* panels show the flow-cytometric analysis of peripheral blood T cells from a patient with autoimmune lymphoproliferative syndrome (ALPS), with CD8 expression on the vertical axis and CD4 on the horizontal axis. The *lower left quadrant* contains CD4-CD8 (double-negative) T cells, which are usually present at <1% of T cells expressing the αβ T-cell receptor. The *bottom panels* show CD3, CD4, and CD8 staining on serial sections of a lymph node biopsy specimen from a patient with ALPS and also shows that large numbers of DNCD3+ CD4-CD8 (double-negative) T cells are present in the interfollicular areas of the lymph node. *(Adapted from Siegel RM, Fleisher TA: The role of Fas and related death receptors in autoimmune and other disease states,* J Allergy Clin Immunol *103:729–738, 1999.)*

Table 126-6 Clinical and Laboratory Features of IPEX and IPEX-Like Disorders

	IPEX	CD25	STAT5B	STAT1	ITCH
AUTOIMMUNITY					
Eczema	+++	+++	++	++	++
Enteropathy	+++	+++	++	++	++
Endocrinopathy	+++	++	+	++	++
Allergic disease	+++	+	+	++	++
Cytopenias	++	++	++	–	
Lung disease	+	++	+++	+	+++
INFECTIONS					
Yeast	–	++	–	+++	–
Herpes virus	–	+++ (EBV/CMV)	++ (VZV)	++	–
Bacterial	+/–	++	++	++	+
Associated features	None	None	Growth failure	Vascular anomalies	Dysmorphic growth failure
Serum immunoglobulins	Elevated	Elevated or normal	Elevated or normal	Low, normal, or high	Elevated
Serum IgE	Elevated	Normal or elevated	Normal or elevated	Normal or mildly elevated	Elevated
CD25 expression	Normal	Absent	Normal or low	Normal	Not tested
CD4+CD45RO	Elevated	Elevated	Elevated	Normal or high	Not tested
FOXP3 expression	Absent or normal	Normal or low	Normal or low	Normal	Not tested
IGF-1, IGFBP-3	Normal	Normal	Low	Normal	Not tested
Prolactin	Normal	Normal	Elevated	Normal	Not tested

CMV, cytomegalovirus; EBV, Epstein Barr Virus; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor–binding protein 3; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked; VZV, varicella zoster virus; ITCH, ubiquitin ligase deficiency.

From: Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X–linked (IPEX) and IPEX–related disorders: an evolving web of heritable autoimmune diseases. Curr Opin Pediatr *25:708–715, 2013, Table 1, p. 709.*

insulin-dependent diabetes begin in infancy. Lymphadenopathy and splenomegaly are also present. Serious bacterial infections (meningitis, sepsis, pneumonia, osteomyelitis) may be related to neutropenia, malnutrition, or immune dysregulation. Laboratory features reflect the associated autoimmune diseases, dehydration, and malnutrition. In addition, serum IgE levels are elevated with normal levels of IgM, IgG, and IgA. The diagnosis is made clinically and by mutational analysis of the *FOXP3* gene.

Treatment

Inhibition of T-cell activation by cyclosporine, tacrolimus, or sirolimus with steroids is the treatment of choice, along with the specific care of the endocrinopathy and other manifestations of autoimmunity. Stem cell transplantation is the only possibility for curing IPEX. Overall, the combination of the risks for serious bacterial infection in the untreated condition and the risks of immunosuppression and bone marrow transplantation gives IPEX a poor prognosis. Untreated, most die by 2 yr of age.

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Section 3

The Phagocytic System

Chapter 127

Neutrophils

Thomas D. Coates

THE PHAGOCYTIC INFLAMMATORY RESPONSE

The phagocyte system includes both granulocytes (neutrophils, eosinophils, and basophils) and mononuclear phagocytes (monocytes and tissue macrophages). Neutrophils and mononuclear phagocytes share primary functions, including the defining properties of large particle ingestion and microbial killing. Phagocytes participate primarily in the innate immune response but also help initiate acquired immunity. Mononuclear phagocytes, including tissue macrophages and circulating monocytes, are discussed in Chapter 128.

Neutrophils provide the rapid effector arm of the innate immune system. They circulate in the bloodstream for only about 6 hr (Table 127-1), but upon encountering specific chemotactic signals, they adhere to the vascular endothelium and transmigrate into tissues, where they ingest and kill microbes and release chemotactic signals to recruit more neutrophils and to attract dendritic cells and other initiators of the acquired immune response.

HEMATOPOIESIS

The hematopoietic progenitor system can be envisioned as a continuum of functional compartments with the most primitive compartment composed of very rare **pluripotential stem cells**, which have high self-renewal capacity and give rise to more mature stem cells, including cells that are committed to either lymphoid or myeloid development (Fig. 127-1). Common lymphoid progenitor cells give rise to

Table 127-1 Neutrophil and Monocyte Kinetics

NEUTROPHILS	
Average time in mitosis (myeloblast to myelocyte)	7-9 days
Average time in postmitosis and storage (metamyelocyte to neutrophil)	3-7 days
Average half-life in the circulation	6 hr
Average total body pool	6.5×10^8 cells/kg
Average circulating pool	3.2×10^8 cells/kg
Average marginating pool	3.3×10^8 cells/kg
Average daily turnover rate	1.8×10^8 cells/kg
MONONUCLEAR PHAGOCYTES	
Average time in mitosis	30-48 hr
Average half-life in the circulation	36-104 hr
Average circulating pool (monocytes)	1.8×10^7 cells/kg
Average daily turnover rate	1.8×10^9 cells/kg
Average survival in tissues (macrophages)	Months

From Boxer LA: Function of neutrophils and mononuclear phagocytes. In Bennett JC, Plum F, editors: Cecil textbook of internal medicine, *ed 20, Philadelphia, 1996, WB Saunders.*

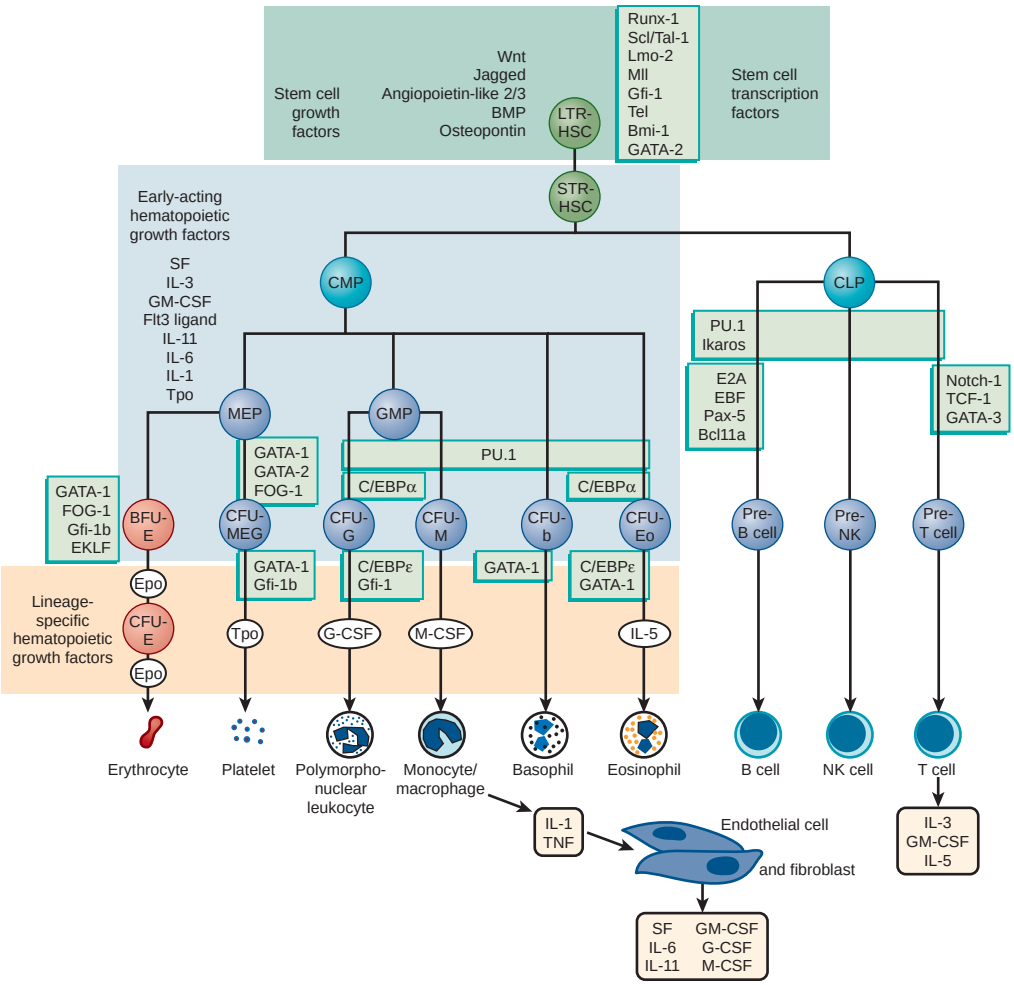

Figure 127-1 Major cytokine sources and actions and transcription factor requirements. Cells of the bone marrow microenvironment such as macrophages, endothelial cells, and reticular fibroblastoid cells, produce macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interleukin (IL)-6, and probably stem cell factor (SCF) after induction with endotoxin (macrophage) or IL-1/tumor necrosis factor (TNF) (endothelial cells and fibroblasts). T-cells produce IL-3, GM-CSF, and IL-5 in response to antigenic and IL-1 stimulation. These cytokines have overlapping actions during hematopoietic differentiation, as indicated, and for all lineages optimal development requires a combination of early- and late-acting factors. Transcription factors important for survival or self-renewal of stem cells are shown at the top *(light green panel)* and stages of hematopoiesis blocked after the depletion of indicated transcription factors for multipotent and committed progenitors are shown in light green boxes throughout. *CFU-E*, erythroid colony-forming unit; *CFU-E/b/M*, erythrocyte, basophil, and megakaryocyte colony-forming unit; *CFU-Eo*, eosinophil colony-forming unit; *CFU-G*, granulocyte colony-forming unit; *CFU-M*, macrophage colony-forming unit; *MSC*, myeloid stem cells; *NK*, natural killer; *PSC*, pluripotent stem cells. *(From Nathan DG, Orkin SH, Ginsburg D, et al, editors:* Nathan and Oski's hematology of infancy and childhood*, ed 7, Philadelphia, 2009, WB Saunders.)*

T- and B-cell precursors and their mature progeny (see Chapter 123). Common myeloid progenitor cells eventually give rise to committed single-lineage progenitors of the recognizable precursors through a random process of lineage restriction in a stepwise process (see Chapter 446). The capacity of lineage-specific committed progenitors to proliferate and differentiate in response to demand provides the hematopoietic system with a remarkable range of response to changing requirements for mature blood cell production.

The proliferation, differentiation, and survival of immature hematopoietic progenitor cells are governed by hematopoietic growth factors, a family of glycoproteins (see Chapter 446). Besides regulating proliferation and differentiation of progenitors, these factors influence the survival and function of mature blood cells. During granulopoiesis and monopoiesis, multiple cytokines regulate the cells at each stage of differentiation from pluripotent stem cells to non-dividing terminally differentiated cells (monocytes, neutrophils, eosinophils, and basophils). As cells mature, they lose receptors for most cytokines, especially those that influence early cell development; however, they retain receptors for cytokines that affect their mobilization and function, such as granulocyte colony-stimulating factor and macrophage colony–stimulating factor. Mature phagocytes also express receptors for chemokines, which help direct the cells to sites of inflammation. Chemokine receptors such as CXCR4 and its ligand SDF-1 play a key role in retention of developing myeloid cells within bone marrow.

NEUTROPHIL MATURATION AND KINETICS

The process of intramedullary granulocyte maturation involves changes in nuclear configuration and accumulation of specific intracytoplasmic granules. The bone marrow microenvironment supports the normal steady-state renewal of peripheral blood neutrophils through the generation of growth and differentiation factors by stromal cells. Growth factors such as granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor not only stimulate cell division, but also induce the expression of transcription factors that regulate the biosynthesis of functional components of the neutrophil, such as granule proteins. The transcription factor PU.1 is essential for myelopoiesis, both as a positive regulatory element and as a suppressor of GATA-1, a transcription factor that directs nonmyeloid differentiation. Other transcription factors, such as Runx1 (AML1), c-myb, CDP, C/EBPα, C/EBPγ, and MEF, are expressed in the myeloblast and promyelocyte, and some of these are required for azurophil granule protein expression. As cells enter the myelocyte stage, RUNX1 and

myb are downregulated, whereas PU.1 and C/EBPε expression rises to initiate terminal differentiation.

Granulocytes survive for only 6-12 hr in the circulation, and therefore daily production of 2×10^4 granulocytes/μL of blood is required to maintain a level of circulating granulocytes of 5×10^3/μL (see Table 127-1). The relatively small peripheral blood pool includes the rapidly interchanging circulating and marginating pools; the latter provides entrance into the tissue phase, where neutrophils may survive for hours or days. The circulating pool is fed and buffered by a much larger marrow population of mature neutrophils and myeloid precursors, representing the marrow reserve and proliferating pools, respectively. Proliferation of myeloid cells, encompassing approximately 5 mitotic divisions, takes place only during the 1st 3 stages of neutrophil development, in myeloblasts, promyelocytes, and myelocytes. After the myelocyte stage, the cells terminally differentiate into nondividing, maturing metamyelocytes, bands, and neutrophils.

Neutrophil maturation is associated with nuclear condensation and lobulation and with the sequential production of characteristic granule populations. A myeloblast is a relatively undifferentiated cell with a large oval nucleus, a sizeable nucleolus, and a deficiency of granules. Promyelocytes acquire peroxidase-positive azurophilic (primary) granules, and then myelocytes and metamyelocytes acquire specific (secondary) granules; tertiary granules and secretory vesicles develop in the final stage of neutrophil maturation.

NEUTROPHIL FUNCTION

Neutrophil responses are initiated as circulating neutrophils flowing through the postcapillary venules detect low levels of chemokines and other chemotactic substances released from a site of infection. The sequence of events as the neutrophil moves from circulating in the blood to the encounter and destruction of bacteria is carefully orchestrated by a series of biochemical events, defects of which are associated with genetic disorders of neutrophil function (Fig. 127-2). In fact, these disorders of neutrophil function lead to our understanding of the cell biology of phagocyte function. A subset of circulating neutrophils loosely adheres to the endothelium through low-affinity receptors called selectins and rolls along the endothelium forming the marginated pool. Soluble effectors of inflammation trigger subtle changes in surface adhesion molecules on endothelial cells at the site of infection. The rolling of neutrophils allows more intense exposure of neutrophils to activating factors such as tumor necrosis factor or interleukin-1 (Fig. 127-2). Exposure of neutrophils ti these same activating factors induces

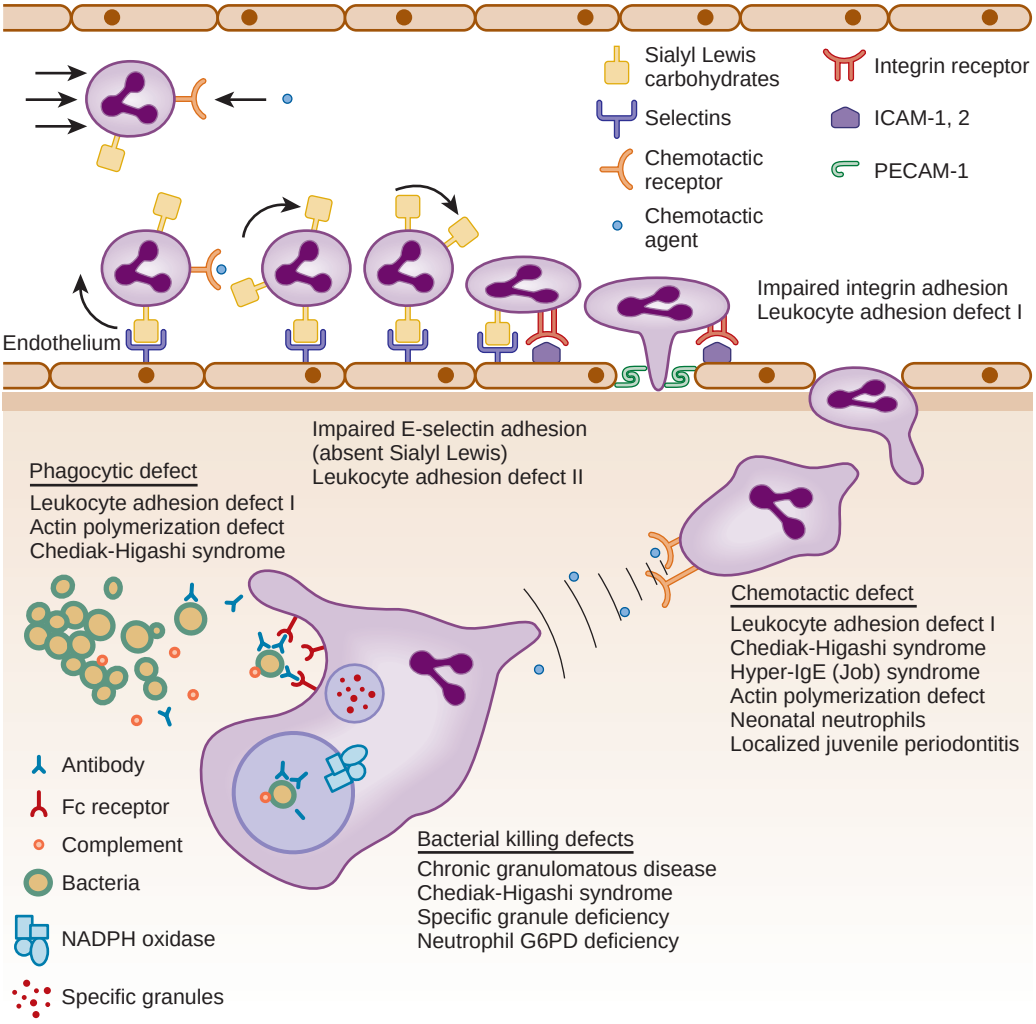

Figure 127-2 The neutrophil-mediated inflammatory response and associated neutrophil dysfunction syndromes. Circulating neutrophils loosely attach to endothelium via selectins and roll along the vessel wall until they arrive at the site of infection. Inflammatory monokines, interleukin 1 (IL-1), and tumor necrosis factor (TNF), activate endothelial cells to express E- and P-selectins. E- and P-selectins serve as counter receptors for neutrophils sialyl Lewis X and Lewis X to cause low-avidity neutrophil rolling. Activated endothelial cells express ICAM-1, which serves as a counter-receptor for neutrophil β_2 integrin molecules, leading to high-avidity leukocyte spreading and the start of transendothelial migration at the infection site. Neutrophils invade through the vascular basement membrane with the release of proteases and reactive oxidative intermediates, causing local destruction of surrounding tissue at sites of high concentrations of chemotactic factors and migrate to the site of infection where they ingest and kill the bacteria. *(Modified from Kyono W, Coates TD: A practical approach to neutrophil disorders.* Pediatr Clin North Am *49:929, 2002.)*

qualitative and quantitative changes in the family of β_2-integrin adhesion receptors (the CD11/CD18 group of surface molecules), leading to tight adhesion between neutrophils and endothelial cells at the site of inflammation and ultimately to transmigration of the neutrophil into the tissue.

Once through the endothelium, the neutrophil senses the gradient of chemokines or other chemoattractants and migrates to sites of infection. Neutrophil migration is a complex process involving rounds of receptor engagement, signal transduction, and remodeling of the actin-microfilaments composing in part the cytoskeleton. Actin polymerization–depolymerization occurs in approximately 8 sec cycles and drives cyclic extension and retraction of the actin-rich lamella at the front of the neutrophil. Receptors at the leading edge of the lamella detect the gradient of attractant and follow microorganisms, ingest and destroy them. When the neutrophil reaches the site of infection, it recognizes pathogens by means of Fc immunoglobulin and complement receptors, Toll-like receptors, fibronectin receptors, and other adhesion molecules.

The neutrophil ingests microbes that are coated by **opsonins**, serum proteins such as immunoglobulin and complement component C3. The pathogens are engulfed into a closed vacuole, the **phagosome** (Fig. 127-3) where 2 cellular responses essential for optimal microbicidal activity occur concomitantly: degranulation and activation of nicotinamide-adenine dinucleotide phosphate (NADPH)–dependent oxidase. Fusion of neutrophil granule membranes with the phagosome membrane delivers potent antimicrobial proteins and small peptides into the phagosome.

Assembly and activation of NADPH oxidase at the phagosome membrane as well (see Fig. 127-3) generating large amounts of superoxide (O_2^-) from molecular oxygen that, in turn, decomposes to produce hydrogen peroxide (H_2O_2) and singlet oxygen. **Myeloperoxidase,** a major azurophil granule component, catalyzes the reaction of H_2O_2 with ubiquitously present chloride ions to create hypochlorous acid (HOCl) in the phagosome. Hypochlorous acid is essentially Clorox bleach. H_2O_2 and HOCl are potent microbicidal agents that break down and clear pathogens from sites of infection.

In addition, neutrophils secrete a wide variety of cytokines and chemokines that recruit more neutrophils to fight the infection, attract monocytes and macrophages that possess both microbicidal and scavenger functions, and promote antigen presentation to help initiate the adaptive immune response. Also, the reactive oxidants can inactivate chemotactic factors and may serve to terminate the process of neutrophil influx, thereby attenuating the inflammatory process. Finally, the release of reactive oxygen species, granule proteins, and cytokines can also damage local tissues, leading to the classic signs of inflammation or to more permanent impairment of tissue integrity and function.

Bibliography is available at Expert Consult.

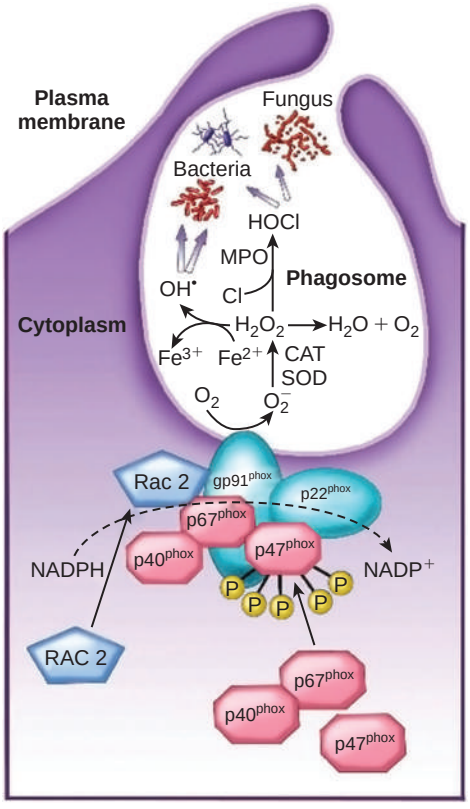

Figure 127-3 Nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase components and activation. On activation of phagocytic cells, the 3 cytosolic components *(red)* of the NADPH oxidase ($p67^{phox}$, $p47^{phox}$, and $p40^{phox}$), plus the small guanosine triphosphatase (GTPase) protein Rac2, are translocated to the membrane of the phagocytic vacuole. The $p47^{phox}$ subunit binds to the flavocytochrome$_{b558}$ membrane component *(blue-green)* of the NADPH oxidase ($gp91^{phox}$ plus $p22^{phox}$). The NADPH oxidase catalyses the formation of superoxide by transferring an electron from NADPH to molecular oxygen (O_2), thereby forming the superoxide free radical. The unstable superoxide anion is converted to hydrogen peroxide, either spontaneously or by superoxide dismutase (SOD). Hydrogen peroxide can follow different metabolic pathways into more potent reactive oxidants (such as OH• or HOCl) or degradation to $H_2O + O_2$. *(Modified from Stiehm ER, Ochs HD, Winkelstein JA:* Immunologic disorders in infants and children, *ed 5, Philadelphia, 2004, WB Saunders, p 622.)*

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Chapter 128

Monocytes, Macrophages, and Dendritic Cells

Richard B. Johnston Jr.

Mononuclear phagocytes (monocytes, macrophages) are distributed across all body tissues and play a central role in maintaining homeostasis. They are essential for innate host defense against infection, tissue repair and remodeling, and the antigen-specific adaptive immune response. No human has been identified as having congenital absence of this cell line, probably because macrophages are required to remove primitive tissues during fetal development as new tissues develop to replace them. Monocytes and tissue macrophages in their several forms (Table 128-1) have variable morphology and surface markers and different transcriptional profiles but common functions, particularly phagocytosis. **Dendritic cells** (DCs) are specialized derivatives of this system that develop from myeloid–lymphoid cell precursors.

DEVELOPMENT

Monocytes develop more rapidly during bone marrow hematopoiesis and remain longer in the circulation than do neutrophils (see Table 127-1). The first recognizable monocyte precursor is the monoblast, followed by the promonocyte with cytoplasmic granules and an indented nucleus, and, finally, the fully developed monocyte with cytoplasm filled with granules containing hydrolytic enzymes. The transition from monoblast to mature circulating monocyte requires about 6 days.

Two major subsets of human blood monocytes can be identified on the basis of surface antigens: CD14++ CD16–, originally termed

Table 128-1	Principal Sites of Macrophages in Tissues
Liver (Kupffer cells)	
Lung (interstitial and alveolar macrophages)	
Connective tissue, adipose tissue, and interstitium of major organs and skin	
Serosal cavities (pleural and peritoneal macrophages)	
Synovial membrane (type A synoviocytes)	
Bone (osteoclasts)	
Brain and retina (microglial cells)	
Spleen, lymph nodes, bone marrow	
Intestinal wall	
Breast milk	
Placenta	
Granulomas (multinucleated giant cells)	

"classical monocytes" because they constitute 90-95% of total monocytes, and the more mature CD14+ CD16+ "proinflammatory" monocytes, which produce more proinflammatory tumor necrosis factor-α (TNF-α) and less immunosuppressive interleukin (IL)-10 in response to microbial stimuli. Monocytes of either subset migrate into tissues in response to localized inflammation or, apparently, randomly in the absence of inflammation.

Most organ macrophages probably arise from macrophage progenitors that develop in the embryo before hematopoiesis occurs. Exceptions are macrophage populations in the skin and intestines and at sites of active inflammation, which appear to derive commonly from blood monocytes.

Whether tissue macrophages originate from blood monocytes or in the embryo, organ-specific factors must influence differentiation of the precursor cells and endow each tissue macrophage type with its characteristic features. Monocytes or embryonic progenitors in the liver become **Kupffer cells** that bridge the sinusoids separating adjacent plates of hepatocytes. Those at the lung airway surface become large ellipsoid **alveolar macrophages,** and those in the bone become **osteoclasts.** All macrophages have at least 3 major functions in common: phagocytosis, presentation of antigens to lymphocytes, and enhancement or suppression of the immune response through release of a variety of potent hormone-like factors termed cytokines. At sites of inflammation, monocytes and macrophages can fuse to form multinucleated giant cells; these cells maintain the antimicrobial functions of macrophages.

ACTIVATION

The most important step in the maturation of tissue macrophages is the conversion from a resting to a more functionally active cell, a process driven primarily by certain cytokines and microbial products. **Macrophage activation** is a generic term, with the functional characteristics of an activated macrophage population varying with the cytokine or other stimulus (microbial, chemical) to which the population has been exposed.

Classical activation refers to a response to infection that is driven by specifically activated T-helper (Th) type 1 (Th1)–type lymphocytes and natural killer cells through their release of interferon-γ (IFN-γ). TNF-α secreted by activated macrophages amplifies their activation, as does bacterial cell wall protein or endotoxin through Toll-like receptors. **Alternative activation** is driven by Th2–type lymphocytes through release of IL-4 and IL-13, cytokines that regulate antibody responses, allergy, and resistance to parasites. Alternatively activated macrophages may have particular functional advantages, such as in wound healing and immunoregulation. In the traditional context of host defense, the term *activated macrophage* indicates that the "classically activated" cell has an enhanced capacity to kill microorganisms or tumor cells. These macrophages are larger, with more pseudopods and pronounced ruffling of the plasma membrane, and they exhibit accelerated activity of many functions (Table 128-2). Considering the variety of macrophage activities essential to the maintenance of homeostasis, it seems likely that so-called classically and alternatively activated macrophages are examples of a continuum of physiologic functions expressed by these long-lived cells in response to the specific task at hand.

Table 128-2	Upregulated Functions in Macrophages Activated in Response to Infection
Microbicidal and tumoricidal activity	
Phagocytosis (of most particles) and pinocytosis	
Phagocytosis-associated respiratory burst (O_2^-, H_2O_2)	
Generation of nitric oxide	
Chemotaxis	
Glucose transport and metabolism	
Membrane expression of MHC, CD40, TNF receptor	
Antigen presentation	
Secretion	
Complement components	
Lysozyme, acid hydrolases, and cytolytic proteinases	
Collagenase	
Plasminogen activator	
Interleukins, including IL-1, IL-12, and IL-15	
TNF-α	
Interferons, including IFN-α and IFN-β	
Antimicrobial peptides (cathelicidin, defensins)	
Angiogenic factors	

H_2O_2, hydrogen peroxide; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; O_2^-, superoxide anion; TNF, tumor necrosis factor.

Classical macrophage activation is accomplished during infection with intracellular pathogens (e.g., mycobacteria, *Listeria*) through crosstalk between Th1 lymphocytes and antigen-presenting macrophages mediated by the engagement of a series of ligands and receptors on the 2 cell types, including CD40 on macrophages and CD40 ligand on Th cells, and through secretion of cytokines. Macrophages encountering microorganisms release IL-12, which stimulates T cells to release IFN-γ. These interactions constitute the basis of cell-mediated immunity. IFN-γ is an especially important macrophage-activating cytokine; it is currently used as a therapeutic agent.

FUNCTIONAL ACTIVITIES

Numerous functions are upregulated when the macrophage is activated in response to infection (see Table 128-2). Obviously important are the ingestion and killing of intracellular pathogens such as mycobacteria, *Listeria, Leishmania, Toxoplasma,* and some fungi; however, splenic and hepatic macrophages also clear extracellular pathogens such as pneumococci from the bloodstream. Killing of the ingested organisms depends heavily on products of the respiratory burst (e.g., hydrogen peroxide) and on nitric oxide, and release of these metabolites is enhanced in activated macrophages.

The activity of mononuclear phagocytes against cancers in humans is less-well understood. This activity may involve more than the phagocytic process. Macrophages may kill tumor cells by means of secreted products, including lysosomal enzymes, nitric oxide, oxygen metabolites, cytolytic proteinases, and TNF-α. Proteolytic enzymes and cytocidal factors present on the surface membrane of monocytes may have a role in tumor rejection. In contrast, tumor-associated macrophages also appear to stimulate growth of certain tumors through secretion of growth and angiogenic factors.

The capacity to undergo diapedesis across the endothelial wall of blood vessels and to migrate to sites of microbial invasion is essential to monocyte function. Chemotactic factors for monocytes include complement products and chemokines derived from neutrophils, lymphocytes, and other cell types. Phagocytosis of the invading organisms can then occur, influenced by the presence of opsonins for the invader (antibody, complement, mannose-binding and surfactant proteins), the inherent surface properties of the microorganism, and the state of activation of the macrophage.

Monocytes migrating to intestinal mucosa are modified by stromal factors so that they lose innate receptors for microbial products such

as endotoxin, and they do not effectively produce proinflammatory cytokines. They retain, however, the capacity to ingest and kill microbes. They have been modified during evolution to allow the absence of inflammation typical of normal intestinal mucosa in spite of its constant exposure to huge numbers of microbes and their inflammatory by-products.

Macrophages play an essential role in the disposal of damaged and dying cells, helping resolve the inflammatory response and heal wounds. Brain microglia demonstrate these functions particularly well. In conditions such as stroke, neurodegenerative disease, and tumor invasion, these cells can become activated, surround damaged and dead cells, and clear cellular debris. Macrophages lining the sinusoids of the spleen are especially important in ingesting aged or autoantibody-coated erythrocytes or platelets; splenectomy is used to manage autoimmune cytopenias. Macrophages in inflammatory sites can recognize changes in phosphatidylserine on the membrane of neutrophils undergoing apoptosis, and these can be removed before they become necrotic and spill their toxic contents into the tissue. Macrophages also remove the extracellular traps exuded by inflammatory neutrophils, thus reducing the risk of autoimmunity. Macrophages can be identified early in fetal development, where they function to remove debris as one maturing embryonic tissue replaces another. They are also important in removing immune complexes, protein fragments, and inorganic particles such as elements of cigarette smoke that enter the alveoli.

Macrophages are integrally involved in the induction and expression of adaptive immune responses, including antibody formation and cell-mediated immunity. This involvement depends on their capacity to break down foreign material in phagocytic and pinocytic vesicles and then present individual antigens on their surface as peptides or polysaccharides bound to class II major histocompatibility complex (MHC) molecules. B lymphocytes and, most effectively, DCs can also present antigens to T cells for the specific immune response. Expression of MHC class II molecules is increased in activated macrophages, and antigen presentation is more effective.

The heightened capacity of activated macrophages to synthesize and release various hydrolytic enzymes and microbicidal materials (see Table 128-2) probably plays a part in their increased killing capacity, although not every macrophage product is secreted in increased amounts when the cell is activated. The macrophage is an extraordinarily active secretory cell. It has been shown to secrete more than 100 distinct substances, including cytokines, growth factors, and sterol hormones, placing it in a class with the hepatocyte. Because of the profound effect of some of these secretory products on other cells and the large number and widespread distribution of macrophages, this network of cells can be viewed as an important endocrine organ. IL-1 illustrates this point well. Microbes and microbial products, burns, ischemia–reperfusion, and other causes of inflammation or tissue damage stimulate the release of IL-1, mainly by monocytes, macrophages, and epithelial cells. In turn, IL-1 elicits fever, sleep, and release of IL-6, which induces production of acute-phase proteins.

As traumatic damage and infection subside, the macrophage population shifts toward playing an essential role in tissue repair and healing through removal of apoptotic cells and secretion of IL-10, transforming growth factor-β, lipoxins, and omega-3 fatty acid–derived resolvins, protectins, and maresins (macrophage mediators in resolving inflammation).

DENDRITIC CELLS

DCs are derived from both myeloid and lymphoid bone marrow progenitors. They are specialized to capture, process, and present antigens to T cells to generate adaptive immunity or tolerance to self-antigens. Human monocytes can be induced to differentiate into DCs in some circumstances, particularly inflammation. DCs express retractable dendritic (branched) extensions and potent endocytic capacity but are a heterogeneous population from the standpoint of location, surface markers, level of antigen-presenting activity, and function. There are 2 major functional types of DCs, *conventional DCs,* which include Langerhans cells in the epithelial surfaces of skin and mucosa, and dermal or interstitial DCs in subepithelial skin and interstitia of solid organs; and *plasmacytoid DCs*, sentinels for viral infection and principal source of antiviral IFN-α and IFN-β.

DCs migrating from the bloodstream enter skin, epithelial surfaces, and lymphoid organs where, as immature cells, they internalize self- and foreign-antigens. Microbial products, cytokines, or molecules exposed in damaged tissue ("danger signals" or "alarmins") induce DC maturation, with upregulation of cytokine receptors and MHC class II and costimulatory molecules. Stimulated DCs in the periphery migrate to lymphoid organs where they continue to mature. They function there as the most potent cells that present antigens to T lymphocytes and induce their proliferation, activities that are central to the antigen-specific adaptive immune response. Macrophage IL-10 acts to suppress DC maturation during resolution of inflammation.

DCs from cancer patients have been used in an attempt to control their cancer. The patient's DCs are amplified and matured from blood monocytes or marrow progenitor cells by cytokines, exposed to antigens from the patient's tumor, then injected into the patient as a "vaccine" against the cancer.

ABNORMALITIES OF MONOCYTE-MACROPHAGE OR DENDRITIC CELL FUNCTION

Mononuclear phagocytes, as well as neutrophils, from patients with **chronic granulomatous disease** exhibit a profound defect of phagocytic killing (see Chapter 130). The inability of affected macrophages to kill ingested organisms leads to abscess formation and characteristic granulomas at sites of macrophage accumulation beneath the skin and in the liver, lungs, spleen, and lymph nodes. IFN-γ is currently used for preventing infection in patients with chronic granulomatous disease and for treating the decreased bone resorption of **congenital osteopetrosis**, which is caused by decreased function of osteoclasts. Genetic deficiency of the CD11/CD18 complex of membrane adherence glycoproteins **(leukocyte adhesion defect-1),** which includes a receptor for opsonic complement component 3, results in impaired phagocytosis by monocytes (see Chapter 130).

The monocyte–macrophage system is prominently involved in **lipid storage diseases** called sphingolipidoses (see Chapter 86.3). In these conditions, the expression in macrophages of a systemic enzymatic defect permits the accumulation of cell debris that is normally cleared. Resistance to infection can be impaired, at least partly because of impairment in macrophage function. **Gaucher disease** is the prototype for these disorders. In this condition, the enzyme glucocerebrosidase functions abnormally, thus allowing accumulation of glucocerebroside from cell membranes in Gaucher cells throughout the body. In all locations, the Gaucher cell is an altered macrophage. These patients can be treated with infusions of the normal enzyme modified to expose mannose residues, which bind to mannose receptors on macrophages.

The cytokine IL-12 is a powerful inducer of IFN-γ production by T cells and natural killer cells. Individuals with inherited deficiency in macrophage receptors for IFN-γ or lymphocyte receptors for IL-12, or in IL-12 itself, suffer a severe, profound, and selective susceptibility to infection by nontuberculous mycobacteria such as *Mycobacterium avium* complex or bacillus Calmette-Guérin (see Chapter 126). About half of these patients have had disseminated *Salmonella* infection. These abnormalities are now grouped as **defects in the IFN-γ–IL-12 axis**.

Monocyte–macrophage function has been shown to be partially abnormal in various clinical conditions. Cultured mononuclear phagocytes of newborns are more readily infected than adult cells by HIV-1 and measles virus. Macrophages from newborns release less granulocyte colony-stimulating factor and IL-6 in culture, and this deficiency is accentuated in cells from preterm infants. This finding supports the observations that levels of granulocyte colony-stimulating factor are significantly decreased in blood from newborns, and that the marrow granulocyte storage pool is diminished in infants, particularly preterm infants. Mononuclear cells from newborns produce less IFN-γ and IL-12 than do adult cells, and macrophages cultured from cord blood are not activated normally by IFN-γ. This combination of deficiencies

would be expected to blunt the newborn's response to infection by viruses, fungi, and certain bacteria such as *Listeria*.

There are 2 disorders in which macrophage activation is pathologically excessive. **Familial and acquired hemophagocytic lymphohistiocytosis** is characterized by uncontrolled activation of T cells and macrophages, with resultant fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, marked elevation of serum proinflammatory cytokines, and macrophage hemophagocytosis (see Chapter 507). Up to 5% of children with systemic onset juvenile rheumatoid arthritis develop an acute severe complication termed **macrophage activation syndrome,** with persistent fever (rather than typical febrile spikes), hepatosplenomegaly, pancytopenia, macrophage hemophagocytosis, and coagulopathy, which can progress to disseminated intravascular coagulation and death if not recognized (see Chapter 155).

Two genetic autoinflammatory diseases result from dysregulation of the mononuclear phagocyte–produced proinflammatory cytokine IL-1. In **neonatal onset multisystem inflammatory disorder** monocytes overproduce IL-1**.** In **deficiency of the IL-1-receptor antagonist**, normal activity levels of IL-1 go unopposed. In both conditions patients present in the 1st few days or weeks of life with pustular or urticarial rash, bony overgrowth, sterile osteomyelitis, elevated sedimentation rate, and other evidence of systemic inflammation. The recombinant IL-1-receptor antagonist anakinra is effective treatment for both these disorders.

The term *histiocyte* was originally used to describe cells thought to be macrophages in fixed tissue preparations. Histiocytosis X represents a malignancy-like overgrowth of Langerhans-type DCs (see Chapter 507). Thus, the term **Langerhans cell histiocytosis** better describes this disorder, because histiocyte is a histologic term and not cell specific.

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Chapter 129

Eosinophils

Brian P. Vickery

Eosinophils are distinguished from other leukocytes by their morphology, constituent products, and association with specific diseases. Eosinophils are nondividing fully differentiated cells with a diameter of ≈8 μm and a bilobed nucleus. They differentiate from stem cell precursors in the bone marrow under the control of T-cell–derived interleukin (IL)-3, granulocyte-macrophage colony-stimulating factor, and, especially, IL-5. Their characteristic membrane-bound specific granules stain reddish brown with eosin and consist of a crystalline core made up of major basic protein (MBP) surrounded by a matrix containing the eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin. These basic proteins are cytotoxic for the larval stages of helminthic parasites and are also thought to contribute to much of the inflammation associated with chronic allergic diseases such as asthma (see Chapter 144).

Both eosinophil MBP and eosinophil cationic protein are also present in large quantities in the airways of patients who have died of asthma and are thought to inflict epithelial cell damage leading to airway hyperresponsiveness. Eosinophil granule contents also contribute to Loeffler endocarditis associated with hypereosinophilic syndrome. MBP has the potential to activate other proinflammatory cells, including mast cells, basophils, neutrophils, and platelets. Eosinophils have the capacity to generate large amounts of the lipid mediators platelet-activating factor and leukotriene C_4, both of which can cause vasoconstriction, smooth muscle contraction, and mucus hypersecretion. Eosinophils are a source of a number of proinflammatory cytokines, including IL-1, IL-3, IL-4, IL-5, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor; they can also function as antigen-presenting cells. Thus, eosinophils have considerable potential to initiate and sustain inflammatory response of the innate and acquired immune systems.

Eosinophil migration from the vasculature into the extracellular tissue is mediated by the binding of leukocyte adhesion receptors to their ligands or counterstructures on the postcapillary endothelium. Similar to neutrophils (see Fig. 127-2), transmigration begins as the eosinophil selectin receptor binds to the endothelial carbohydrate ligand in loose association, which promotes eosinophils rolling along the endothelial surface until they encounter a priming stimulus such as a chemotactic mediator. Eosinophils then establish a high-affinity bond between integrin receptors and their corresponding immunoglobulin-like ligand. Unlike neutrophils, which become flattened before transmigrating between the tight junctions of the endothelial cells, eosinophils can use unique integrins, known as VLA-4, to bind to vascular cell adhesion molecule-1, which enhances eosinophil adhesion and transmigration through endothelium. Eosinophils are recruited to tissues in inflammatory states by the chemokine **eotaxin.** These unique pathways account for selective accumulation of eosinophils in allergic and inflammatory disorders. Eosinophils normally dwell primarily in tissues, especially tissues with an epithelial interface with the environment, including the respiratory, gastrointestinal, and lower genitourinary tracts. The life span of eosinophils may extend for weeks within tissues.

IL-5 selectively enhances eosinophil production, adhesion to endothelial cells, and function. Considerable evidence shows that IL-5 has a pivotal role in promoting eosinophil accumulation. It is the predominant cytokine in allergen-induced pulmonary late-phase reaction, and antibodies against IL-5 block eosinophil infiltration into the lungs in animal models associated with airway hyperresponsiveness following allergen challenge. Eosinophils also bear unique receptors for several chemokines, including RANTES (regulated upon activation, normal T-cell expressed and secreted), eotaxin, and monocyte chemotactic proteins 3 and 4. These chemokines appear to be key mediators in the induction of tissue eosinophilia.

DISEASES ASSOCIATED WITH EOSINOPHILIA

The **absolute eosinophil count** (AEC) is used to quantify eosinophilia. Calculated as the white blood cell count/μL × percent of eosinophils, it is usually <450 cells/μL and varies diurnally, with eosinophil numbers higher in the early morning and diminishing as endogenous glucocorticoid levels rise.

Many diseases with allergic, infectious, hematologic, autoimmune, or idiopathic origins are associated with moderate (AEC 1,500-5,000 cells/μL) or severe (AEC >5,000 cells/μL) eosinophilia in peripheral blood (Table 129-1). These disorders may range from mild and transient to chronic and life-threatening, and, importantly, blood eosinophil numbers do not always reflect the extent of eosinophil involvement in disease-affected tissues. Because prolonged eosinophilia is associated with end-organ damage, especially involving the heart, patients with persistently elevated AECs should undergo a thorough evaluation to search for an underlying cause.

Allergic Diseases

Allergy is the most common cause of eosinophilia in children in the United States. Patients with allergic asthma commonly have eosinophils in the blood, sputum, and/or lung tissue. Hypersensitivity drug reactions can elicit eosinophilia, and when associated with organ dysfunction (e.g., DRESS [drug rash with eosinophilia and systemic symptoms]), these reactions can be serious (see Chapter 152). If a drug is suspected of triggering eosinophilia, biochemical evidence of organ dysfunction should be sought and if found, the drug should be discontinued. Various skin diseases have also been associated with eosinophilia, including atopic dermatitis/eczema, pemphigus, urticaria, and toxic epidermal necrolysis.

Table 129-1 Causes of Eosinophilia

ALLERGIC DISORDERS
Allergic rhinitis
Asthma
Acute and chronic urticaria
Pemphigoid
Hypersensitivity drug reactions (drug rash with eosinophilia and systemic symptoms [DRESS])
Eosinophilic gastrointestinal disorders
Interstitial nephritis
INFECTIOUS DISEASES
Tissue-Invasive Helminth Infections
Trichinosis
Toxocariasis
Strongyloidosis
Ascariasis
Filariasis
Schistosomiasis
Echinococcosis
Pneumocystis carinii
Toxoplasmosis
Scarlet fever
Amebiasis
Malaria
Bronchopulmonary aspergillosis
Coccidioidomycosis
Scabies
MALIGNANT DISORDERS
Brain tumors
Hodgkin disease and T-cell lymphoma
Acute myelogenous leukemia
Myeloproliferative disorders
Eosinophilic leukemia
GASTROINTESTINAL DISORDERS
Inflammatory bowel disease
Peritoneal dialysis
Chronic active hepatitis
Eosinophilic gastrointestinal disorders:
• Eosinophilic esophagitis
• Eosinophilic gastroenteritis
• Eosinophilic colitis
RHEUMATOLOGIC DISEASE
Rheumatoid arthritis
Eosinophilic fasciitis
Scleroderma
IMMUNODEFICIENCY DISEASE
Hyperimmunoglobulin E syndromes
Wiskott-Aldrich syndrome
Graft-versus-host disease
Omenn syndrome
Severe congenital neutropenia
Hypersensitivity pneumonia
MISCELLANEOUS
Thrombocytopenia with absent radii
Churg-Strauss syndrome (eosinophilic granulomatosis with vasculitis)
Vasculitis
Adrenal insufficiency
Postirradiation of abdomen
Histiocytosis with cutaneous involvement
Hypereosinophilic syndromes
Autoimmune lymphoproliferative syndromes (ALPS)
Immune dysregulation, polyendocrinopathy, X-linked (IPEX)

Eosinophilic gastrointestinal diseases are important emerging allergic causes of eosinophilia in tissue and, in some cases, peripheral blood (see Chapter 337). In these conditions, eosinophils are inappropriately recruited to esophagus, stomach, and/or intestine, where they induce tissue inflammation and clinical symptoms such as dysphagia, food aversion, abdominal pain, vomiting, and diarrhea. Treatment options include allergen elimination diets and swallowed topical corticosteroids.

Infectious Diseases

Eosinophilia is often associated with invasive infection with multicellular helminthic parasites, which are the most common cause in developing countries. Table 129-1 includes examples of specific organisms. The level of eosinophilia tends to parallel the magnitude and extent of tissue invasion, especially by larvae such as visceral larva migrans (see Chapter 298). Eosinophilia often *does not* occur in established parasitic infections that are well contained within tissues or are solely intraluminal in the gastrointestinal tract, such as *Giardia lamblia* and *Enterobius vermicularis* infection.

In evaluating patients with unexplained eosinophilia, the dietary history and geographic or travel history may indicate potential exposures to helminthic parasites. It is frequently necessary to examine the stool for ova and larvae at least 3 times. Additionally, the diagnostic parasite stages of many of the helminthic parasites that cause eosinophilia never appear in feces. Thus, normal results of stool examinations do not absolutely preclude a helminthic cause of eosinophilia; diagnostic blood tests or tissue biopsy may be needed. *Toxocara* causes **visceral larva migrans** usually in toddlers with pica (see Chapter 298). Most young children are asymptomatic, but some develop fever, pneumonitis, hepatomegaly, and hypergammaglobulinemia accompanied by severe eosinophilia. Isohemagglutinins are frequently elevated. Serology can establish the diagnosis.

Two fungal diseases may be associated with eosinophilia: aspergillosis in the form of **allergic bronchopulmonary aspergillosis** (see Chapter 237.1) and coccidioidomycosis (see Chapter 240) following primary infection, especially in conjunction with erythema nodosum. HIV can also be associated with peripheral eosinophilia.

Hypereosinophilic Syndrome

The idiopathic hypereosinophilic syndrome is a heterogeneous group of disorders characterized by sustained overproduction of eosinophils. The 3 diagnostic criteria for this disorder are (1) AEC >1,500 cells/μL persisting for 6 mo or longer or at least on 2 occasions or with evidence of tissue eosinophilia; (2) absence of another diagnosis to explain the eosinophilia; and (3) signs and symptoms of organ involvement. The clinical signs and symptoms of hypereosinophilic syndrome can be heterogeneous because of the diversity of potential organ (pulmonary, cutaneous, neurologic, serosal, gastrointestinal) involvement. Loeffler endocarditis, one of the most serious and life-threatening complications, can cause heart failure from endomyocardial thrombosis and fibrosis. Eosinophilic leukemia, a clonal myeloproliferative variant, may be distinguished from idiopathic hypereosinophilic syndrome by demonstrating a clonal interstitial deletion on chromosome 4q12 that fuses the platelet-derived growth factor receptor-α (PDGFRA) and FIP1-like-1 (FIP1L1) genes; this disorder is treated with imatinib mesylate, which helps target the fusion oncoprotein (Fig. 129-1).

Therapy is aimed at suppressing eosinophilia and is initiated with corticosteroids. Imatinib mesylate, a tyrosine kinase inhibitor, may be effective in FIP1L1-PDGFRA–negative patients. Hydroxyurea may be beneficial in patients unresponsive to corticosteroids. Specific anti–IL-5 monoclonal antibodies (mepolizumab) target this cytokine, which has a central role in eosinophil differentiation, mobilization and activity. With therapy, the eosinophil count declines and corticosteroid doses may be reduced. For patients with prominent organ involvement who fail to respond to therapy, the mortality is ≈75% after 3 yr.

Miscellaneous Diseases

Eosinophilia is observed in many patients with primary immunodeficiency syndromes, especially hyperimmunoglobulin E syndrome (see Chapters 122 and 126), Wiskott-Aldrich syndrome, and Omenn syndrome. Eosinophilia is also frequently present in the syndrome of thrombocytopenia with absent radii and in familial

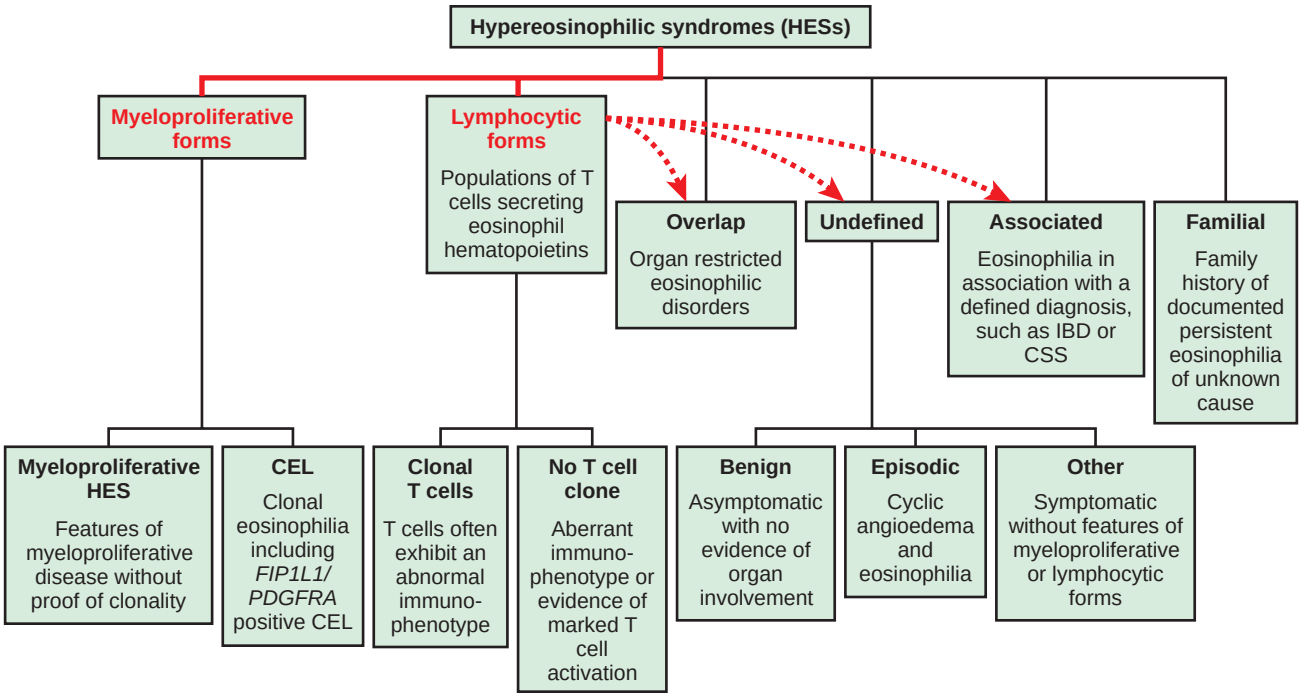

Figure 129-1 **Revised classification of hypereosinophilic syndromes.** Changes from the previous classification are indicated in *red*. *Dashed arrows* identify hypereosinophilic syndrome (HES) forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin–producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. *IBD,* Inflammatory bowel disease. *(From Simon HU, Rothenberg ME, Bocher BS, et al: Refining the definition of hypereosinophilic syndrome.* J Allergy Clin Immunol *126:45–49, 2010, Fig. 1, p. 47.)*

reticuloendotheliosis with eosinophilia. Eosinophilia can be found in patients with Hodgkin disease, as well as in acute lymphoid and myeloid leukemia. Other considerations include gastrointestinal disorders such as ulcerative colitis, Crohn disease during symptomatic phases, chronic hepatitis, Churg-Strauss vasculitis, and adrenal insufficiency.

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Chapter 130

Disorders of Phagocyte Function

Thomas D. Coates

Neutrophils are the first-line of defense against microbial invasion. They arrive at the site of inflammation during the critical 2-4 hr after microbial invasion to contain the infection and prevent hematogenous dissemination. This well-orchestrated process is one of the most interesting stories in modern cell biology. In fact, much of our knowledge about neutrophil function derives from studies done in patients with genetic errors in neutrophil function. These critical functions and their associated disorders are depicted in Figure 127-2. Children with phagocytic dysfunction present at a young age with recurrent infections that are often involve unusual organisms and are poorly responsive to treatment.

Primary defects of phagocytic function comprise fewer than 20% of immunodeficiencies and there is significant overlap in the presenting signs and symptoms between phagocytic disorders and lymphocyte and humeral disorders. Children with phagocytic defects present with deep tissue infection, pneumonia, adenitis, or osteomyelitis rather than blood stream infections (Tables 130-1 and 130-2, and Fig. 130-1). A few clinical features point to phagocyte defects rather than other immunodeficiencies, but correct diagnosis relies on highly specialized laboratory tests.

Chemotaxis, the direct migration of cells into sites of infection, involves a complex series of events (see Chapter 127). Disorders of adhesion or granule abnormalities can have intermediate or profound motility defects and the propensity to infections is related to a combination of these functional deficits. However, studies of a Tongan family with recessively inherited neutrophil actin dysfunction tell us that a pure severe chemotactic defect can result in fatal recurrent infection. Defective in vitro chemotaxis of neutrophils can be detected in children having various clinical conditions. However, unless chemotaxis is essentially absent, it is difficult to establish whether frequent infections arise from a primary chemotactic abnormality or occur as secondary medical complications of the underlying disorder. For example, dental infection with *Capnocytophaga* is associated with a clear neutrophil motility defect that resolves when the infection is eliminated.

Motility defects present with significant skin and mucosal infections. They can also have tender cutaneous nodular lesions that characteristically do not contain any neutrophils. In fact, presence of a true abscess makes the diagnosis of a significant chemotactic defect less likely.

Laboratory tests of chemotaxis are biologic assays and have high variability except in the most experienced of hands. The assays must be done on freshly obtained blood and are affected by many factors related to blood sampling itself. It is best to assay other features of the suspected disorder, such as surface marker expression, to establish a specific diagnosis.

LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency 1 (LAD-1), 2 (LAD-2), and 3 (LAD-3) are rare autosomal recessive disorders of leukocyte function. LAD-1 affects about 1 per 10 million individuals and is characterized by

Table 130-1 Infections and WBC Defects: Features That Can Be Seen in Phagocyte Disorders

SEVERE INFECTIONS		RECURRENT INFECTIONS		SPECIFIC INFECTIONS		UNUSUALLY LOCATED INFECTIONS	
TYPE OF INFECTION	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSIDER	MICROORGANISM	DIAGNOSIS TO CONSIDER	SITE OF INFECTION	DIAGNOSIS TO CONSIDER
Cellulitis	Neutropenia, LAD CGD, HIES	Cutaneous	Neutropenia, CGD, LAD, HIES	*Staphylococcus epidermidis*	Neutropenia, LAD	Umbilical cord	LAD
Colitis	Neutropenia, CGD	Gums	LAD, neutrophil motility disorders	*Serratia marcescens, Nocardia, Burkholderia cepacia*	CGD	Liver abscess	CGD
Osteomyelitis	CGD, MSMD pathway defects	Upper and lower respiratory tract	Neutropenia, HIES, functional neutrophil disorders	*Aspergillus*	Neutropenia, CGD, HIES	Gums	LAD, neutrophil motility disorders
		Gastrointestinal tract	CGD, MSMD pathway defects (salmonella)	Nontuberculous mycobacteria, BCG	MSMD pathway defects, SCID, CGD		
		Lymph nodes	CGD, MSMD pathway defects (mycobacteria)	*Candida*	Neutropenia, CGD, MPO		
		Osteomyelitis	CGD, MSMD				

BCG, bacille Calmette-Guérin; CGD, chronic granulomatous disease; HIES, hyperimmunoglobulin E syndrome; LAD, leukocyte adhesion deficiency; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency.

From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-1, p. 134.*

Table 130-2 Clinical Disorders of Neutrophil Function

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DEGRANULATION ABNORMALITIES			
Chédiak-Higashi syndrome	Autosomal recessive; disordered coalescence of lysosomal granules; responsible gene is *CHSI/LYST*, which encodes a protein hypothesized to regulate granule fusion	Decreased neutrophil chemotaxis, degranulation, and bactericidal activity; platelet storage pool defect; impaired NK function, failure to disperse melanosomes	Neutropenia; recurrent pyogenic infections, propensity to develop marked hepatosplenomegaly as a manifestation of the hemophagocytic syndrome
Specific granule deficiency	Autosomal recessive; functional loss of myeloid transcription factor arising from a mutation or arising from reduced expression of *Gfi-1* or *C/EBPε*, which regulates specific granule formation	Impaired chemotaxis and bactericidal activity; bilobed nuclei in neutrophils; defensins, gelatinase, collagenase, vitamin B_{12}–binding protein, and lactoferrin	Recurrent deep-seated abscesses
ADHESION ABNORMALITIES			
Leukocyte adhesion deficiency 1	Autosomal recessive; absence of CD11/CD18 surface adhesive glycoproteins (β_2 integrins) on leukocyte membranes most commonly arising from failure to express CD18 messenger RNA	Decreased binding of C3bi to neutrophils and impaired adhesion to ICAM1 and ICAM2	Neutrophilia; recurrent bacterial infection associated with a lack of pus formation
Leukocyte adhesion deficiency 2	Autosomal recessive; loss of fucosylation of ligands for selectins and other glycol-conjugates arising from mutations of the GDP-fucose transporter	Decreased adhesion to activated endothelium expressing ELAM	Neutrophilia; recurrent bacterial infection without pus
Leukocyte adhesion deficiency 3 (LAD-1 variant syndrome)	Autosomal recessive; impaired integrin function arising from mutations of *FERMT3* which encodes kindlin-3 in hematopoietic cells; kindlin-3 binds to β-integrin and thereby transmits integrin activation	Impaired neutrophil adhesion and platelet activation	Neutrophilia; recurrent infections, bleeding tendency

Continued

Table 130-2 Clinical Disorders of Neutrophil Function—cont'd

DISORDER	ETIOLOGY	IMPAIRED FUNCTION	CLINICAL CONSEQUENCE
DISORDERS OF CELL MOTILITY			
Enhanced motile responses; FMF	Autosomal recessive gene responsible for FMF on chromosome 16 which encodes for a protein called pyrin; pyrin regulates caspase-1 and thereby IL-1β secretion; mutated pyrin may lead to heightened sensitivity to endotoxin, excessive IL-1β production, and impaired monocyte apoptosis	Excessive accumulation of neutrophils at inflamed sites, which may be the result of excessive IL-1β production	Recurrent fever, peritonitis, pleuritis, arthritis, and amyloidosis
DEPRESSED MOTILE RESPONSES			
Defects in the generation of chemotactic signals	IgG deficiencies; C3 and properdin deficiency can arise from genetic or acquired abnormalities; mannose-binding protein deficiency predominantly in neonates	Deficiency of serum chemotaxis and opsonic activities	Recurrent pyogenic infections
Intrinsic defects of the neutrophil, e.g., LAD, Chédiak-Higashi syndrome, specific granule deficiency, neutrophil actin dysfunction, neonatal neutrophils	In the neonatal neutrophil there is diminished ability to express β_2 integrins, and there is a qualitative impairment in β_2-integrin function	Diminished chemotaxis	Propensity to develop pyogenic infections
Direct inhibition of neutrophil mobility, e.g., drugs	Ethanol, glucocorticoids, cyclic AMP	Impaired locomotion and ingestion; impaired adherence	Possible cause for frequent infections; neutrophilia seen with epinephrine arises from cyclic AMP release from endothelium
Immune complexes	Bind to Fc receptors on neutrophils in patients with rheumatoid arthritis, systemic lupus erythematosus, and other inflammatory states	Impaired chemotaxis	Recurrent pyogenic infections
Hyper-IgE syndrome	Autosomal dominant; responsible gene is *Stat3*	Impaired chemotaxis at times; impaired regulation of cytokine production	Recurrent skin and sinopulmonary infections, eczema, mucocutaneous candidiasis, eosinophilia, retained primary teeth, minimal trauma fractures, scoliosis, and characteristic facies
Hyper-IgE syndrome–AR	Autosomal recessive; more than 1 gene likely contributes to its etiology	High IgE levels, impaired lymphocyte activation to staphylococcal antigens	Recurrent pneumonia without pneumatoceles sepsis, enzyme, boils, mucocutaneous candidiasis, neurologic symptoms, eosinophilia
MICROBICIDAL ACTIVITY			
Chronic granulomatous disease	X-linked and autosomal recessive; failure to express functional $gp91^{phox}$ in the phagocyte membrane in $p22^{phox}$ (AR). Other AR forms of CGD arise from failure to express protein $p47^{phox}$ or $p67^{phox}$	Failure to activate neutrophil respiratory burst leading to failure to kill catalase-positive microbes	Recurrent pyogenic infections with catalase-positive microorganisms
G6PD deficiency	Less than 5% of normal activity of G6PD	Failure to activate NADPH-dependent oxidase, and hemolytic anemia	Infections with catalase-positive microorganisms
Myeloperoxidase deficiency	Autosomal recessive; failure to process modified precursor protein arising from missense mutation	H_2O_2-dependent antimicrobial activity not potentiated by myeloperoxidase	None
Rac2 deficiency	Autosomal dominant; dominant negative inhibition by mutant protein of Rac2-mediated functions	Failure of membrane receptor–mediated O_2^- generation and chemotaxis	Neutrophilia, recurrent bacterial infections
Deficiencies of glutathione reductase and glutathione synthetase	AR; failure to detoxify H_2O_2	Excessive formation of H_2O_2	Minimal problems with recurrent pyogenic infections

AMP, adenosine monophosphate; AR, autosomal recessive; C, complement; CD, cluster of differentiation; CGD, chronic granulomatous disease; ELAM, endothelial-leukocyte adhesion molecule; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GDP, guanosine diphosphate; ICAM, intracellular adhesion molecule; Ig, immunoglobulin; IL-1, interleukin-1; LAD, leukocyte adhesion deficiency; NADPH, nicotinamide adenine dinucleotide phosphate; NK, natural killer.

Modified from Curnutte JT, Boxer LA: Clinically significant phagocytic cell defects. In Remington JS, Swartz MN, editors: Current clinical topics in infectious disease, *ed 6, New York, 1985, McGraw-Hill, p 144.*

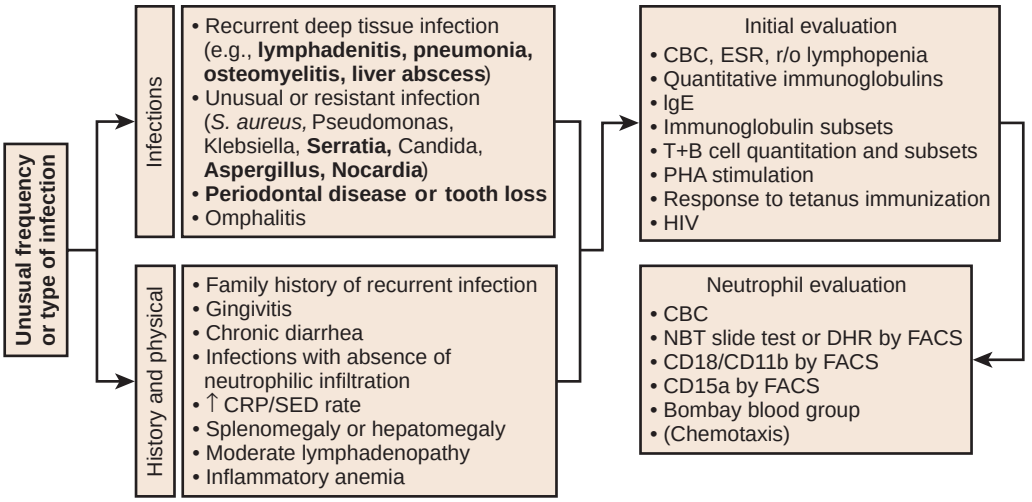

Figure 130-1 Algorithm for clinical evaluation of patients with recurrent infections. Shown are the evaluations that can be done in a routine clinical laboratory. The CBC can detect marked leukocytosis in LAD and giant granules of Chédiak-Higashi may be seen on the smear. Chemotaxis and all other neutrophil functions assays require highly specialized research laboratories. *CBC*, complete blood count; *CD*, cluster of differentiation; *CRP*, C-reactive protein; *DHR*, dihydrorhodamine; *ESR*, erythrocyte sedimentation rate; *HIV*, human immunodeficiency virus; *Ig*, immunoglobulin; *NBT*, nitro blue tetrazolium. *(Modified from Dinauer, MC, Coates TD, Disorders of neutrophil function. In Hoffman R, Benz EJ, Silberstein LE, Helsop H, Weitz J, Anastasi J, editors:* Hematology: basic principles and practice, *ed 6, Philadelphia, 2012, WB Saunders, pp. 655–674.)*

Table 130-3 Leukocyte Adhesion Deficiency Syndromes

LEUKOCYTE ADHESION DEFICIENCY (LAD)	TYPE 1 (LAD1)	TYPE 2 (LAD2 OR CDG-IIC)	TYPE 3 (LAD3)	E-SELECTIN DEFICIENCY	RAC2 DEFICIENCY
OMIM	116920	266265	612840	131210	602049
Inheritance pattern	Autosomal recessive	Autosomal recessive	Autosomal recessive	Unknown	Autosomal dominant
Affected protein(s)	Integrin β_2 common chain (CD18)	Fucosylated proteins (e.g., sialyl-Lewis^x, CD15s)	Kindlin 3	Endothelial E-selectin expression	Rac2
Neutrophil function affected	Chemotaxis, tight adherence	Rolling, tethering	Chemotaxis, adhesion, superoxide production	Rolling, tethering	Chemotaxis, superoxide production
Delayed umbilical cord separation	Yes (severe phenotype only)	Yes	Yes	Yes	Yes
Leukocytosis/ neutrophilia	Yes	Yes	Yes	No (mild neutropenia)	Yes

OMIM, Online Mendelian Inheritance in Man.
From Leung DYM: Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Table 12-4, p. 139.*

recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia (Table 130-3). The neutrophils have significant defects in adhesion, motility, and ability to phagocytose bacteria.

Genetics and Pathogenesis

LAD-1 results from mutations of the gene on chromosome 21q22.3 encoding CD18, the 95-kDa β_2-leukocyte transmembrane integrin subunit. Normal neutrophils express 4 heterodimeric adhesion molecules: LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18, also known as CR3 or iC3b receptor), p150,95 (CD11c/CD18), and α_1 β_2 (CD11d/CD18). These 4 transmembrane adhesion molecules are composed of unique extracellular α_1 encoded on chromosome 16, and share a common β_2 subunit (CD18) that links them to the membrane and connects them to intracellular signal transduction machinery. This group of leukocyte integrins is responsible for the tight adhesion of neutrophils to the endothelial cell surface, egress from the circulation, and adhesion to iC3b-coated microorganisms, which promotes phagocytosis and particulate activation of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Some mutations of CD11/CD18 allow a low level of assembly and activity of integrin molecules, resulting in retention of some neutrophil integrin adhesion function and a moderate phenotype.

Because of their inability to adhere firmly to intercellular adhesion molecules 1 (ICAM-1) and 2 (ICAM-2) expressed on inflamed endothelial cells (see Chapter 127), neutrophils cannot transmigrate through the vessel wall and move to the site infection. Furthermore, neutrophils that do arrive at inflammatory sites fail to recognize microorganisms opsonized with complement fragment iC3b, an important stable opsonin formed by the cleavage of C3b. Hence, other neutrophil functions such as degranulation and oxidative metabolism normally triggered by iC3b binding are also markedly compromised in LAD-1 neutrophils, resulting in impaired phagocytic function and high risk for serious and recurrent bacterial infections.

Monocyte function is also impaired, with poor fibrinogen-binding function, an activity that is promoted by the CD11/CD18 complex. Consequently, such cells are unable to participate effectively in wound healing.

Children with **LAD-2** share the clinical features of LAD-1 but have normal CD11/CD18 integrins. Features unique to LAD-2 include neurologic defects, cranial facial dysmorphism, and absence of the erythrocyte ABO blood group antigen (Bombay phenotype). LAD-2 (also known as congenital disorder of glycosylation IIc) derives from mutations in the gene encoding a specific GDP-L-fucose transporter of the Golgi apparatus. This abnormality prevents the incorporation of fucose into various cell surface glycoproteins, including the carbohydrate structure sialyl Lewis X that is critical for low-affinity rolling adhesion of neutrophils to vascular endothelium. This is an important initial step necessary for subsequent integrin-mediated activation, spreading, and transendothelial migration. Infections in LAD-2 are milder than that in LAD-1.

LAD-3 is characterized by a Glanzmann thrombasthenia-like bleeding disorder, delayed separation of the umbilical cord, and serious skin and soft-tissue infections similar to that seen in LAD-1, and failure of leukocytes to undergo β_2- and β_1-integrin–mediated adhesion and migration. Mutations in *KINDLIN3* affect integrin activation.

Clinical Manifestations

Patients with the severe clinical form of LAD-1 express <0.3% of the normal amount of the β_2-integrin molecules, whereas patients with the moderate phenotype may express 2-7% of the normal amount. Children with severe forms of LAD present in infancy with recurrent, indolent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa. Significant neutrophilic leukocytosis, often >25,0000/mm^3, is a prominent feature. They may have a history of delayed separation of the umbilical cord, usually with associated infection of the cord stump. The presence of significant omphalitis is an important feature that distinguishes these rare patients from the 10% of healthy infants can have cord separation at age 3 wk or later. Skin infection may progress to large chronic ulcers with polymicrobial infection, including anaerobic organisms (Fig. 130-2). The ulcers heal slowly, need months of antibiotic treatment, and often require plastic surgery grafting. Severe gingivitis can lead to early loss of primary and secondary teeth (Fig. 130-3). Infected areas characteristically have very little neutrophilic infiltration.

The pathogens infecting patients with LAD-1 are similar to those affecting patients with severe neutropenia (see Chapter 131) and include *Staphylococcus aureus* and enteric Gram-negative organisms such as *Escherichia coli.* These patients are also susceptible to opportunistic infection by fungi such as *Candida* and *Aspergillus.* Typical signs of inflammation, such as swelling, erythema, and warmth, may be absent. Pus does not form, and few neutrophils are identified microscopically in biopsy specimens of infected tissues. Despite the paucity of neutrophils within the affected tissue, the circulating neutrophil count during infection typically exceeds 30,000/μL and can surpass 100,000/μL. During intervals between infections, the peripheral blood neutrophil count may chronically exceed 12,000/μL. LAD-1 genotypes with only moderate, rather than absent, amounts of functional integrins at the surface of the neutrophil, significantly have reduced severity and frequency of infections compared to children with the severe form, although gingival disease is still a prominent feature.

Laboratory Findings

The diagnosis of LAD-1 is established most readily by **flow cytometric** measurements of surface CD11b/CD18 in stimulated and unstimulated neutrophils. Neutrophil and monocyte adherence, aggregation, chemotaxis, and iC3b-mediated phagocytosis demonstrate striking abnormalities. However, these assays are not clinically available. Delayed-type hypersensitivity reactions are normal, and most individuals have normal specific antibody synthesis. However, some patients have impaired T-lymphocyte–dependent antibody responses. The diagnosis of LAD-2 is established by flow cytometric measurement of sialyl Lewis X (CD15) on neutrophils. It is important to note that the flow cytometric assays are not done the same as the more common lymphocyte subset analysis and require specialized approaches to detect levels of surface expression, especially to detect milder phenotypes.

Treatment

Treatment of LAD-1 depends on the phenotype as determined by the level of expression of functional CD11/CD18 integrins. Early **allogeneic hematopoietic stem cell transplantation (HSCT)** is the treatment of choice for severe LAD-1 (and LAD-3). Other treatment is largely supportive. Patients can be maintained on prophylactic trimethoprim-sulfamethoxazole and should have close surveillance for early identification of infections and initiation of empirical treatment with broad-spectrum antibiotics. Specific determination of the etiologic agent by culture or biopsy is important because of the prolonged antibiotic treatment required in the absence of neutrophil function.

Some LAD-2 patients have responded to fucose supplementation, which induced a rapid reduction in the circulating leukocyte count and appearance of the sialyl Lewis X molecules accompanied by marked improvement in leukocyte adhesion.

Prognosis

The severity of infectious complications correlates with the degree of β_2-integrin deficiency. Patients with severe deficiency may die in infancy, and those surviving infancy have a susceptibility to severe life-threatening systemic infections. Patients with moderate deficiency have infrequent life-threatening infections and relatively long survival.

Figure 130-2 Skin infection of a patient with leukocyte adhesion deficiency type 1. Failure to form pus, inability to demarcate the fibrotic skin debris, and limited inflammation. Enterococcus gallinarium was cultured from the wound. *(From Rich RR:* Clinical immunology principles and practices, *ed 4, Philadelphia, 2013, WB Saunders, Fig. 21-3, p. 273).*

Figure 130-3 Oral pathology in a patient with leukocyte adhesion deficiency type 1. Gingivitis and severe periodontitis are hallmarks of LAD 1. *(From Rich RR:* Clinical immunology principles and practices, *ed 4, Philadelphia, 2013, WB Saunders, Fig. 21-2, p. 273.)*

CHÉDIAK-HIGASHI SYNDROME

Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by increased susceptibility to infection caused by defective degranulation of neutrophils, a mild bleeding diathesis, partial oculocutaneous albinism, progressive peripheral neuropathy, and a tendency to develop a life-threatening form of hemophagocytic lymphohistiocytosis (see Chapter 507). CHS is caused by a fundamental defect in granule morphogenesis that results in abnormally large granules in multiple tissues. Pigmentary dilution involving the hair, skin, and ocular fundi results from pathologic aggregation of melanosomes. Neurologic deficits are associated with a failure of decussation of the optic and auditory nerves. Patients exhibit an increased susceptibility to infection that can be explained only in part by defects in neutrophil function. The patients have progressive neutropenia as well abnormalities in natural killer (NK) function, again related to granule dysfunction.

Genetics and Pathogenesis

LYST (for lysosomal traffic regulator), the gene mutated in CHS, is located at chromosome 1q2-q44. The LYST/CHS protein is thought to regulate vesicle transport by mediating protein–protein interaction and protein–membrane associations. Loss of function may lead to indiscriminate interactions with lysosomal surface proteins, yielding giant granules through uncontrolled fusion of lysosomes with each other.

Almost all cells of patients with CHS show some oversized and dysmorphic lysosomes, storage granules, or related vesicular structures. Melanosomes are oversized, and delivery to the keratinocytes and hair follicles is compromised, resulting in hair shafts devoid of pigment granules. This abnormality in melanosomes leads to the macroscopic impression of hair and skin that is lighter than expected from parental coloration. The same abnormality in melanocytes leads to the partial ocular albinism associated with light sensitivity.

Beginning early in neutrophil development, spontaneous fusion of giant primary granules with each other or with cytoplasmic membrane components results in huge secondary lysosomes with reduced contents of hydrolytic enzymes, including proteinases, elastase, and cathepsin G. This deficiency of proteolytic enzymes may be responsible for the impaired killing of microorganisms by CHS neutrophils.

Clinical Manifestations

Patients with CHS have light skin and silvery hair and frequently complain of solar sensitivity and photophobia that is associated with rotary nystagmus. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous membranes, skin, and respiratory tract. Affected children are susceptible to Gram-positive bacteria, Gram-negative bacteria, and fungi, with *S. aureus* being the most common offending organism. The **neuropathy** may be sensory or motor in type, and ataxia may be a prominent feature. Neuropathy often begins in the teenage years and becomes the most prominent problem.

Patients with CHS have prolonged bleeding times with normal platelet counts, resulting from impaired platelet aggregation associated with a deficiency of the dense granules containing adenosine diphosphate and serotonin.

The most life-threatening complication of CHS is the development of an accelerated phase characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes. The onset of the accelerated phase, which can occur at any age, is now recognized to be a genetic form of **hemophagocytic lymphohistiocytosis.** This occurs in 85% of patients and usually results in death.

Laboratory Findings

The diagnosis of CHS is established by finding large inclusions in all nucleated blood cells. These can be seen on Wright-stained blood films and are accentuated by a peroxidase stain. Because of impaired egress from the bone marrow, cells containing the large inclusions may be missed on peripheral blood smear but readily identified on bone marrow examination. The patients have progressive neutropenia and abnormal platelet, neutrophil, and NK function.

Treatment

High-dose ascorbic acid (200 mg/day for infants, 2,000 mg/day for adults) may improve the clinical status of some children in the stable phase. Although controversy surrounds the efficacy of ascorbic acid, given the safety of the vitamin, it is reasonable to administer ascorbic acid to all patients.

The only curative therapy to prevent the accelerated phase is **HSCT.** Normal stem cells reconstitute hematopoietic and immunologic function, correct the NK cell deficiency, and prevent conversion to the accelerated phase, but cannot correct or prevent the neuropathy. If the patient is in the accelerated phase with active hemophagocytic lymphohistiocytosis, HSCT often fails to prevent death.

MYELOPEROXIDASE DEFICIENCY

Myeloperoxidase (MPO) deficiency is an autosomal recessive disorder of oxidative metabolism and is one of the most common inherited disorders of phagocytes, occurring at a frequency approaching 1 per 2,000 individuals. MPO is a green heme protein located in the azurophilic lysosomes of neutrophils and monocytes and is the basis for the greenish tinge to pus accumulated at a site of infection.

Clinical Manifestations

MPO deficiency is usually clinically silent. Rarely, patients may have disseminated candidiasis, usually in conjunction with diabetes mellitus. Acquired partial MPO deficiency can develop in acute myelogenous leukemia and in myelodysplastic syndromes.

Laboratory Findings

Deficiency of neutrophil and monocyte MPO can be identified by histochemical analysis. Severe MPO deficiency can cause the dihydrorhodamine (DHR) flow cytometric assay for chronic granulomatous disease to be falsely positive. Unlike chronic granulomatous disease (CGD), eosinophils in severe MPO deficiency will still reduce DHR and yield a normal reaction.

Treatment

There is no specific therapy. Aggressive treatment with antifungal agents should be provided for candidal infections. The prognosis is usually excellent.

CHRONIC GRANULOMATOUS DISEASE

CGD is characterized by neutrophils and monocytes capable of normal chemotaxis, ingestion, and degranulation, but unable to kill **catalase-positive microorganisms** because of a defect in the generation of microbicidal oxygen metabolites. CGD is a rare disease with an incidence of 4-5 per 1 million individuals; it is caused by 4 genes, 1 X-linked and 3 autosomal recessive in inheritance.

Genetics and Pathogenesis

Activation of the phagocyte NADPH oxidase requires stimulation of the neutrophils and involves assembly from cytoplasmic and integral membrane subunits (see Fig. 127-3). Oxidase activation initiates with phosphorylation of a cationic cytoplasmic protein, $p47^{phox}$ (47-kDa phagocyte oxidase protein). Phosphorylated $p47^{phox}$, together with 2 other cytoplasmic components of the oxidase, $p67^{phox}$ and the low-molecular-weight guanosine triphosphatase Rac2, translocates to the membrane where they combine with the cytoplasmic domains of the transmembrane flavocytochrome b_{558} to form the active oxidase complex (see Fig. 127-3). The flavocytochrome is a heterodimer composed of $p22^{phox}$ and highly glycosylated $gp91^{phox}$. The $gp91^{phox}$ glycoprotein catalyzes electron transport through its NADPH-binding, flavin-binding, and heme-binding domains.. Defects in any of these NADPH oxidase components can lead to CGD.

Approximately 65% of patients with CGD are males who inherit their disorder as a result of mutations in *CYBB*, an X-chromosome gene encoding $gp91^{phox}$. Approximately 35% of patients inherit CGD in an autosomal recessive fashion resulting from mutations in the *NCF1* gene on chromosome 7, encoding $p47^{phox}$. Defects in the genes

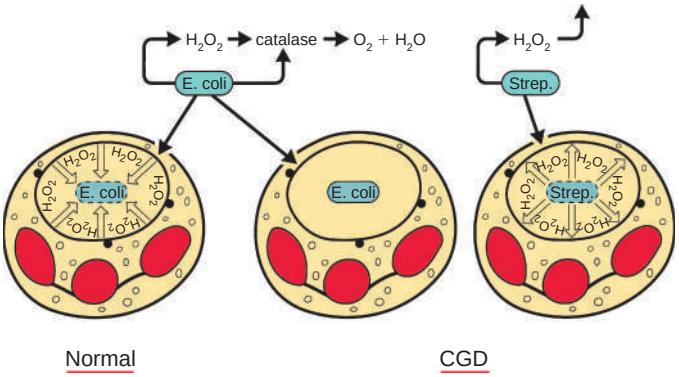

Figure 130-4 The pathogenesis of chronic granulomatous disease (CGD). The manner in which the metabolic deficiency of the CGD neutrophil predisposes the host to infection is shown schematically. Normal neutrophils stimulate hydrogen peroxide in the phagosome containing ingested *Escherichia coli*. Myeloperoxidase is delivered to the phagosome by degranulation, as indicated by the *closed circles*. In this setting, hydrogen peroxide acts as a substrate for myeloperoxidase to oxidize halide to hypochlorous acid and chloramines that kill the microbes. The quantity of hydrogen peroxide produced by the normal neutrophil is sufficient to exceed the capacity of catalase, a hydrogen peroxide-catabolizing enzyme of many aerobic microorganisms, including *Staphylococcus aureus*, most Gram-negative enteric bacteria, *Candida albicans*, and *Aspergillus*. When organisms such as *E. coli* gain entry into CGD neutrophils, they are not exposed to hydrogen peroxide because the neutrophils do not produce it, and the hydrogen peroxide generated by microorganisms themselves is destroyed by their own catalase. When CGD neutrophils ingest streptococci, which lack catalase, the organisms generate enough hydrogen peroxide to result in a microbicidal effect. As indicated *(middle)*, catalase-positive microbes such as *E. coli* can survive within the phagosome of the CGD neutrophil. *(Modified from Boxer LA: Quantitative abnormalities of granulocytes. In Beutler E, Lichtman MA, Coller BS, et al, editors:* Williams hematology, *ed 6, New York, 2001, McGraw-Hill, p. 845.)*

encoding p67^{phox} (*NCF2* on chromosome 1) and p22^{phox} (*CYBA* on chromosome 16) are inherited in an autosomal recessive manner and account for approximately 5% of cases of CGD.

The CGD phagocytic vacuoles lack microbicidal reactive oxygen species and remain acidic, so bacteria are not killed or digested properly (Fig. 130-4). Hematoxylin-and-eosin–stained sections from patients' tissues show multiple granulomas that give CGD its descriptive name.

Clinical Manifestations

Although the clinical presentation is variable, several features suggest the diagnosis of CGD. Any patient with recurrent pneumonia, lymphadenitis, hepatic or subcutaneous or other abscesses, osteomyelitis at multiple sites, a family history of recurrent infections, or any infection with an unusual catalase-positive organism requires evaluation. Other clinical features include chronic colitis or enteritis, gastric outlet or ureteral obstruction from granulomas, or blood stream infection caused by *Salmonella*, *Burkholderia cepacia*, or *Candida*.

The onset of clinical signs and symptoms usually occurs in early infancy, though a few patients with very rare subtypes have presented later in life. The attack rate and severity of infections are exceedingly variable thought the infection incidence does decrease in the second decade coincident with maturation of the lymphocyte and humoral immunity. The most common pathogen is *S. aureus*, although any catalase-positive microorganism may be involved. Other organisms frequently causing infections include *Serratia marcescens*, *B. cepacia*, *Aspergillus*, *Candida albicans*, *Nocardia*, and *Salmonella*. There may also be increased susceptibility to mycobacterium, including the bacillus Calmette-Guérin vaccine. Pneumonia, lymphadenitis, osteomyelitis, and skin infections are the most common illnesses encountered. Bacteremia or fungemia occurs but is much less common than focal infections and usually only occurs when local infections have been inappropriately treated for long periods of time. Patients may suffer from the sequelae of chronic infection, including anemia of chronic disease, poor growth, lymphadenopathy, hepatosplenomegaly, chronic purulent dermatitis, restrictive lung disease, gingivitis, hydronephrosis, esophageal dysmotility, and pyloric outlet narrowing. Perirectal abscesses and recurrent skin infections, including folliculitis, cutaneous granulomas, and discoid lupus erythematosus also suggest the possibility of CGD. **Granuloma formation** and inflammatory processes are a hallmark of CGD and may be the presenting symptoms that prompt testing for CGD if they cause pyloric outlet obstruction, bladder outlet or ureter obstruction, or rectal fistulas and granulomatous colitis simulating Crohn disease. More than 80% of CGD patients have positive serology for Crohn disease. Persistent fever especially with splenomegaly and cytopenia warrants an evaluation for secondary macrophage activation syndrome. This has been seen in CGD and may require treatment with steroids and discontinuation of interferon-γ treatment.

Laboratory Findings

The diagnosis is most often made by performing **flow cytometry** using dihydrorhodamine 123 (DHR) to measure oxidant production through its increased fluorescence when oxidized by H_2O_2. The nitroblue tetrazolium dye test is frequently cited in the literature but is now only rarely used clinically. The X-linked carrier state is usually easily diagnosed in the mother by DHR fluorescence by presence of a bimodal response to stimulation. It is important to test the mother as some extremely Lyonized carriers with <5% positive cells may have chronic clinical problems as well. Ideally, at least the first patient in a kindred should have DNA analysis to facilitate prenatal diagnosis and for genetic counseling purposes.

A few individuals have been described with apparent CGD caused by severe glucose-6-phosphate dehydrogenase deficiency, leading to insufficient NADPH substrate for the phagocyte oxidase. The erythrocytes of these patients also lack the enzyme, leading to chronic hemolysis.

Treatment

HSCT is the only known **cure** for CGD, although gene therapy has been transiently successful in a few patients and is the topic of active research. We strongly recommend HSCT transplant for all patients with CGD if a suitable sibling or unrelated donor can be identified. The long-term outcome for survival late into adulthood is not good even in the hands of experienced CGD clinicians.

Patients with CGD should be given daily oral trimethoprim-sulfamethoxazole as it reduces the number of bacterial infection. A placebo-controlled study found that **interferon-γ** 50 μg/m^2 3 times/wk significantly reduces the number of hospitalizations and serious infections, although the mechanism of action is unclear. **Itraconazole** (200 mg/day for patients weighing >50 kg and 100 mg/day for patients weighing <50 kg and 5 yr of age or younger) administered prophylactically reduces the frequency of fungal infections.

Management of infection is dramatically different than in normal children. CGD patients are always at risk for deep-seated, indolent bacterial infections that can become widespread if not treated properly. They also develop the same kinds of infections that occur in normal children so determination of the appropriate treatment can be difficult. The erythrocyte sedimentation rate (ESR) can be quite helpful. If the child does not have a deep-seated infection, the ESR will be normal or will normalize within several days with standard management. However, if it does not, a search for deep tissues is warranted, as is consideration of empiric antibiotics. Cultures should be obtained, but are usually negative. Because all neutrophil functions in CGD except killing are normal, there is often an exuberant inflammatory reaction to a very small number of organisms. Thus, blood cultures and direct cultures of biopsy samples are usually negative unless there are a lot of organisms. Most abscesses require surgical drainage for therapeutic

and diagnostic purposes. Prolonged use of antibiotics is required even for common bacterial infections. A simple pneumonia may require 6-8 wk of parenteral antibiotics. Infections should be treated for at least 1 wk past normalization of the sedimentation rate to prevent recurrence. Severe pneumonias can be cleared completely but may require many months of parenteral antibiotics. Especially because cultures are often not helpful, we support an "antibiotic sensitivity by sedimentation rate response" approach to treatment. The ESR rates are often in the 40-80 mm/hr or more range with severe infection and will drop monotonically over a week or so after starting antibacterial drugs. It is important to check the ESR daily or every other day as there is moderate variability in this test and changes in treatment need to be based on trends rather than individual values. If there is a clear downward trend over 3-6 days, we continue with antibacterials alone. If this is not the case, parenteral voriconazole should be added to cover *Aspergillus*. Failure of the ESR to come down suggests another antimicrobial approach needs to be tried. Because of the rarity of this disorder, it is critical to seek counsel from someone with significant direct experience with management of several CGD patients. Granulocyte transfusions have been used but it is not clear that they are very helpful. The ESR should be regularly monitored in well patients and whenever they appear ill. A high ESR itself is usually not enough to trigger treatment. However, in the presence of symptoms, one should search for sources at least by contrast CT of the sinus, chest, and abdomen. If the patient is unstable or has very high fevers, *B. cepacia* should be considered and empirically covered. This organism can cause septic shock quickly, unlike the usual smoldering infections seen in CGD. We treat with antibiotics until the ESR is normal and radiographic evidence of infection has been cleared, if possible. The overall incidence of infection decreases in the second decade of life as nonneutrophil immunity matures, but increased risk of infection is lifelong.

Corticosteroids may be useful for the treatment of children with antral and urethral obstruction or severe granulomatous colitis. They can also be helpful in pneumonia to shrink granulomas in the lung and promote drainage. We favor short (4-6 days) pulses of 1-2 mg/kg prednisone with rapid taper to avoid long-term side effects and risk of fungus. Pulses can be repeated if clinical effect has not been achieved.

Genetic Counseling

Identifying a patient's specific genetic subgroup by DNA analysis is useful primarily for genetic counseling and prenatal diagnosis. In X-linked CGD, all possibly affected females should be tested by DHR to exclude carrier state. Counseling is best done by a physician who has direct knowledge of the clinical manifestations of CGD.

Prognosis

The overall mortality rate for CGD is about 2 patient deaths/yr per 100 cases, with the highest mortality among young children. The development of effective infection prophylactic regimens, close surveillance for signs of infections, and aggressive surgical and medical interventions has improved the prognosis.

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Chapter 131

Leukopenia

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Leukopenia refers to an abnormally low number of white blood cells (WBCs) in the circulating blood secondary to a paucity of lymphocytes, granulocytes or both. Because there are marked developmental changes in normal values for WBC counts during childhood (see Chapter 727), normal ranges must be considered in the context of age. For newborns, the mean WBC count at birth is high, followed by a rapid fall beginning at 12 hr through the 1st wk of life. Thereafter, values are stable until 1 yr of age, after which a slow steady decline in the WBC count continues throughout childhood until adult values are reached during adolescence. Evaluation of patients with leukopenia begins with a thorough history, physical examination, and at least 1 confirmatory complete blood count with differential. Further evaluation then depends upon whether the leukopenia represents a decreased number of neutrophils, lymphocytes, or both cell populations (Table 131-1). Treatment depends upon the etiology and clinical manifestations of the leukopenia.

NEUTROPENIA

Neutropenia is defined as a decrease in the absolute number of circulating segmented neutrophils and bands in the peripheral blood. The **absolute neutrophil count (ANC)** is determined by multiplying the total WBC count by the percentage of segmented neutrophils plus bands. Normal neutrophil counts must be stratified for age and race. Neutrophils predominate at birth but rapidly decrease in the 1st few days of life. During infancy, neutrophils constitute 20-30% of circulating leukocyte populations. Near equal numbers of neutrophils and lymphocytes are found in the peripheral circulation at 5 yr of age, and the characteristic 70% predominance of neutrophils that occurs in adulthood is usually attained during puberty. For white children older than 12 mo of age, the lower limit of normal for the ANC is 1,500/μL; for black children older than 12 mo of age the lower limit of normal is 1,200/μL. The relatively lower limit of normal in blacks likely reflects the prevalence of the Duffy negative (Fy–/–) blood group, which is selectively enriched in populations in the malarial belt of Africa and is associated with ANCs 200-600/μL less than those who are Duffy positive.

Neutropenia may be characterized as **mild neutropenia,** with an ANC of 1,000-1,500/μL; **moderate neutropenia,** with an ANC of 500-1,000/μL; or **severe neutropenia,** with an ANC <500/μL. ANC <200 is also termed *agranulocytosis*. This stratification aids in predicting the risk of pyogenic infection in patients who have neutropenia as a resulting from disorders of bone marrow production as only patients with severe neutropenia have a significantly increased susceptibility to life-threatening infections. Neutropenia associated with monocytopenia, lymphocytopenia, or hypogammaglobulinemia increases the risk for infection compared to isolated neutropenia. *Patients with neutropenia caused by increased destruction (e.g., autoimmune) may tolerate very low ANCs without increased frequency of infection.*

Acute neutropenia evolves over a few days and is often a result of rapid neutrophil use and/or compromised neutrophil production. **Chronic neutropenia** by definition lasts longer than 3 mo and arises from reduced production, increased destruction or excessive splenic sequestration of neutrophils. The etiology of neutropenia can be classified as either an acquired disorder or extrinsic insult (Table 131-2), or, more rarely, an inherited, intrinsic defect (Table 131-3).

Clinical Manifestations of Neutropenia

Individuals with neutrophil counts <500/μL are at substantial risk for developing infections, primarily from their endogenous flora as well as from nosocomial organisms. However, some patients with isolated chronic neutropenia may not experience many serious infections, probably because the remainder of the immune system remains intact or because neutrophil delivery to tissues is preserved, as in autoimmune neutropenias. In contrast, children whose neutropenia is secondary to acquired disorders of production such as with cytotoxic therapy, immunosuppressive drugs, or radiation therapy are likely to develop serious bacterial infections because many arms of the immune system are markedly compromised. Neutropenia associated with additional monocytopenia or lymphocytopenia, is more highly associated with serious infection than neutropenia alone. The integrity of skin and mucous membranes, the vascular supply to tissues, and nutritional status also influence the risk of infection.

The most common **clinical presentation of profound neutropenia** includes fever, aphthous stomatitis, and gingivitis. Infections

Table 131-1 Diagnostic Approach for Patients with Leukopenia

EVALUATION	ASSOCIATED CLINICAL DIAGNOSES
INITIAL EVALUATION	
• History of acute or chronic leukopenia	
• General medical history	Congenital syndromes (Shwachman-Diamond, Wiskott-Aldrich, Fanconi anemia, dyskeratosis congenita, glycogen storage disease type Ib, disorders of vesicular transport)
• Physical examination: stomatitis, gingivitis, dental defects, congenital anomalies	
• Spleen size	Hypersplenism
• History of drug exposure	Drug-associated neutropenia
• Complete blood count with differential and reticulocyte counts	Neutropenia, aplastic anemia, autoimmune cytopenias
IF ANC <1,000/μL	
Evaluation of Acute Onset Neutropenia	
• Repeat blood counts in 3-4 weeks	Transient myelosuppression (e.g., viral)
• Serology and cultures for infectious agents	Active or chronic infection with viruses (e.g., EBV, CMV), bacteria, mycobacteria, rickettsia
• Discontinue drug(s) associated with neutropenia	Drug-associated neutropenia
• Test for antineutrophil antibodies	Autoimmune neutropenia
• Measure quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Neutropenia associated with disorders of immune function
IF ANC <500/μL ON 3 SEPARATE TESTS	
• Bone marrow aspiration and biopsy, with cytogenetics	Severe congenital neutropenia, Shwachman-Diamond syndrome, myelokathexis; chronic benign or idiopathic neutropenia
• Glucocorticoid stimulation test	Chronic benign or idiopathic neutropenia, some autoimmune neutropenias
• Serial CBCs (3/wk for 6 wk)	Cyclic neutropenia
• Exocrine pancreatic function	Shwachman-Diamond syndrome
• Skeletal radiographs	Shwachman-Diamond syndrome, cartilage-hair hypoplasia, Fanconi anemia
IF ALC <1000/μL	
• Repeat blood counts in 3-4 weeks	Transient leukopenia (e.g., viral)
IF ALC <1000/μL ON 3 SEPARATE TESTS	
• HIV-1 antibody or RNA test	HIV-1 infection, AIDS
• Quantitative immunoglobulins (G, A, and M), lymphocyte subsets	Congenital or acquired disorders of immune function
IF THERE IS PANCYTOPENIA	
• Bone marrow aspiration and biopsy	Bone marrow replacement by malignancy, fibrosis, granulomata, storage cells; aplastic anemia
• Bone marrow cytogenetics	Myelodysplasia, leukemia
• Vitamin B_{12} and folate levels	Vitamin deficiencies

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CBC, complete blood count; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

commonly associated with neutropenia include cellulitis, furunculosis, perirectal inflammation, colitis, sinusitis, and otitis media, as well as more serious infections such as pneumonia, deep tissue abscess, and sepsis. The most common pathogens causing infections in neutropenic patients are *Staphylococcus aureus* and Gram-negative bacteria. Isolated neutropenia does not heighten a patient's susceptibility to parasitic or viral infections or to bacterial meningitis. The usual signs and symptoms of local infection and inflammation such as exudate, fluctuance, and regional lymphadenopathy may be diminished in the absence of neutrophils because of the inability to form pus, but patients with agranulocytosis still experience fever and feel pain at sites of inflammation.

Laboratory Findings

Isolated absolute neutropenia has a limited number of causes (Tables 131-2 through 131-5). The duration and severity of the neutropenia greatly influence the extent of laboratory evaluation. Patients with chronic neutropenia since infancy and a history of recurrent fevers and chronic gingivitis should have WBC counts and differential counts determined 3 times/wk for 6-8 wk to evaluate the periodicity suggestive of **cyclic neutropenia**. Bone marrow aspiration and biopsy should be performed on select patients to assess cellularity and myeloid maturation. Additional marrow studies such as cytogenetic analysis and special stains for detecting leukemia and other malignant disorders should be obtained for patients with suspected intrinsic defects in the myeloid progenitors and for patients with suspected malignancy. If malignancy is not a concern, assessing the ANC before and 4-6 hr after a single dose of glucocorticosteroid (usually prednisone 1-2 mg/kg) measures mobilization of the bone marrow reserve pool of mature neutrophils; an increase in the ANC to a normal or only moderately low level indicates "chronic benign" or idiopathic neutropenia, and may render bone marrow examination unnecessary. Selection of further laboratory tests is determined by the duration and severity of the neutropenia and the associated findings on physical examination (see Table 131-1).

Acquired Neutropenia

Infection-Related Neutropenia. Transient neutropenia often accompanies or follows viral infections (see Table 131-4) and is the most frequent cause of neutropenia in childhood. Viruses commonly causing acute neutropenia include influenzas A and B, adenovirus, respiratory syncytial virus, enteroviruses, human herpes virus 6, measles, rubella, and varicella. Parvovirus B19 and hepatitides A and B may also cause neutropenia, but are more commonly associated with pure red cell aplasia or multiple cytopenias, respectively. Viral-associated acute neutropenia often occurs during the 1st 24-48 hr of illness and usually persists for 3-8 days, which generally corresponds to the period of viremia. The neutropenia is related to virus-induced redistribution of neutrophils from the circulating to the marginating pool. In addition, neutrophil sequestration may occur after virus-induced tissue damage or splenomegaly. Significant neutropenia also may be associated with severe bacterial, protozoal, rickettsial, and fungal infections (see Table 131-4). Bacterial sepsis is a particularly serious cause of neutropenia, especially among younger infants and

Table 131-2 Causes of Neutropenia Extrinsic to Marrow Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Infection	Viruses, bacteria, protozoa, rickettsia, fungi	Clinical features and laboratory findings of the infectious agent
Drug-induced	Phenothiazines, sulfonamides, anticonvulsants, penicillins, aminopyrine	Usually none; occasional hypersensitivity reaction (fever, lymphadenopathy, rash, hepatitis, nephritis, pneumonitis, aplastic anemia) or antineutrophil antibody
Immune neutropenia	Alloimmune, autoimmune	Myeloid hyperplasia with left shift in bone marrow (may appear to be "arrest" at metamyelocyte or band stage)
Reticuloendothelial sequestration	Hypersplenism	Anemia, thrombocytopenia
Bone marrow replacement	Malignancy (leukemia, lymphoma, metastatic solid tumor, etc.)	Anemia, thrombocytopenia, malignant cells in bone marrow
Cancer chemotherapy or radiation therapy	Suppression of myeloid cell production	Anemia, thrombocytopenia, bone marrow hypoplasia

Table 131-3 Acquired Disorders of Myeloid Cells

CAUSE	ETIOLOGIC FACTORS/AGENTS	ASSOCIATED FINDINGS
Aplastic anemia	Stem cell destruction and depletion	Pancytopenia
Vitamin B_{12} or folate deficiency	Malnutrition; congenital deficiency of B_{12} absorption, transport, and storage; vitamin avoidance	Megaloblastic anemia, hypersegmented neutrophils
Acute leukemia, chronic myelogenous leukemia	Bone marrow replacement with malignant cells	Pancytopenia, leukocytosis
Myelodysplasia	Dysplastic maturation of stem cells	Bone marrow hypoplasia with megaloblastoid red cell precursors, thrombocytopenia
Prematurity with birth weight <2 kg	Impaired regulation of myeloid proliferation and reduced size of postmitotic pool	Maternal preeclampsia
Chronic idiopathic neutropenia	Impaired myeloid proliferation and/or maturation	None
Paroxysmal nocturnal hemoglobinuria	Acquired stem cell defect secondary to mutation of *PIG-A* gene	Pancytopenia, thrombosis

Table 131-4 Infections Associated with Neutropenia

Viral	Cytomegalovirus, dengue, Epstein-Barr virus, hepatitis viruses, HIV, influenza, measles, parvovirus B19, rubella, varicella
Bacterial	*Anaplasma* (formerly *Ehrlichia*) *phagocytophilum*, brucella, paratyphoid, pertussis, tuberculosis (disseminated), tularemia, typhoid; any form of sepsis
Fungal	Histoplasmosis (disseminated)
Protozoan	Malaria, leishmaniasis (kala-azar)
Rickettsial	Psittacosis, Rocky Mountain spotted fever, typhus, rickettsialpox

Table 131-5 Forms of Drug-Induced Neutropenia

	IMMUNOLOGIC	TOXIC	HYPERSENSITIVITY
Paradigm drugs	Aminopyrine, propylthiouracil, penicillins	Phenothiazines, clozapine	Phenytoin, phenobarbital
Time to onset	Days to weeks	Weeks to months	Weeks to months
Clinical appearance	Acute, often explosive symptoms	Often asymptomatic or insidious onset	May be associated with fever, rash, nephritis, pneumonitis, or aplastic anemia
Rechallenge	Prompt recurrence with small test dose	Latent period; high doses required	Latent period; high doses required
Laboratory findings	Antineutrophil antibody may be positive; bone marrow myeloid hyperplasia	Bone marrow myeloid hypoplasia	Bone marrow myeloid hypoplasia

children. Premature neonates are especially prone to exhausting their marrow reserve and rapidly succumbing to bacterial sepsis.

Chronic neutropenia often accompanies infection with Epstein-Barr virus, cytomegalovirus, or HIV. The neutropenia associated with AIDS probably arises from a combination of viral bone marrow suppression, antibody-mediated destruction of neutrophils, and effects of antiretroviral or other drugs.

Drug-Induced Neutropenia. Drugs constitute a common cause of neutropenia (see Table 131-5). The incidence of drug-induced neutropenia increases dramatically with age; only 10% of cases occur among children and young adults. The majority of cases occur among adults older than age 65 yr, likely reflecting the more frequent use of multiple medications in that age group. Almost any drug can cause neutropenia. The most common offending drug classes are antimicrobial agents, antithyroid drugs, antipsychotics, antipyretics, and antirheumatics. Drug-induced neutropenia has several underlying mechanisms—immune-mediated, toxic, idiosyncratic, hypersensitivity, idiopathic—that are distinct from the severe neutropenia that predictably occurs after administration of antineoplastic drugs or radiotherapy.

Drug-induced neutropenia from immune mechanisms usually develops abruptly, is accompanied by fever, and lasts for about 1 wk after the discontinuation of the drug. The process likely arises from effects of drugs, such as propylthiouracil or penicillin, that act as haptens to stimulate antibody formation, or drugs, such as quinine, that induce immune complex formation. Other drugs, including the antipsychotic drugs such as the phenothiazines, can cause neutropenia when given in toxic amounts, but some individuals, such as those with preexisting neutropenia, may be susceptible to levels at the high end of the usual therapeutic range. Late-onset neutropenia can occur after rituximab therapy. Idiosyncratic reactions, for example to chloramphenicol, are unpredictable with regard to dose or duration of use. Hypersensitivity reactions are rare and may involve arene oxide metabolites of aromatic anticonvulsants. Fever, rash, lymphadenopathy, hepatitis, nephritis, pneumonitis, and aplastic anemia are often associated with hypersensitivity-induced neutropenia. Acute hypersensitivity reactions such as those caused by phenytoin or phenobarbital may last for only a few days if the offending drug is discontinued. Chronic hypersensitivity may last for months to years.

Once neutropenia occurs, the most effective therapeutic measure is withdrawal of nonessential drugs, particularly drugs most commonly associated with neutropenia. Usually the neutropenia will resolve soon after withdrawal of the offending drug. If the neutropenia fails to improve with drug withdrawal and the patient is symptomatic with infection or stomatitis, subcutaneous administration of recombinant human granulocyte colony-stimulating factor (filgrastim) 5 μg/kg/day should be considered. Drug-induced neutropenia may be asymptomatic and noted only as an incidental finding or because of regular monitoring of WBC counts during drug therapy. For patients who are asymptomatic, continuation of the suspected offending drug depends on the relative risks of neutropenia vs discontinuation of a possibly essential drug. If the drug is continued, blood counts should be monitored for possible progression to agranulocytosis.

Neutropenia commonly and predictably follows the use of anticancer drugs or radiation therapy, especially radiation therapy directed at the pelvis or vertebrae, secondary to cytotoxic effects on rapidly replicating myeloid precursors. A decline in the WBC count typically occurs 7-10 days after administration of the anticancer drug and may persist for 1-2 wk. The neutropenia accompanying malignancy or following cancer chemotherapy is frequently associated with compromised cellular immunity and barrier compromise secondary to central venous lines and mucositis, thereby predisposing patients to a much greater risk of infection (see Chapter 178) than found in disorders associated with isolated neutropenia. Patients with chemotherapy/radiation-related neutropenia and fever must be treated aggressively with broad-spectrum antibiotics.

Nutrition-Related Neutropenia. Poor nutrition can contribute to neutropenia. Ineffective myelopoiesis may result in neutropenia caused by acquired dietary vitamin B_{12} or folic acid deficiency. In addition, megaloblastic pancytopenia also can result from extended use of antibiotics such as trimethoprim-sulfamethoxazole, which inhibit folic acid metabolism, and from the use of phenytoin, which may impair folate absorption in the small intestine, or from surgical resection of the small intestine. Neutropenia also occurs with starvation and marasmus in infants, with anorexia nervosa, and occasionally among patients receiving prolonged parenteral nutrition without vitamin supplementation.

Immune-Mediated Neutropenia. Immune-mediated neutropenia is usually associated with the presence of circulating antineutrophil antibodies, which may mediate neutrophil destruction by complement-mediated lysis or splenic phagocytosis of opsonized neutrophils, or by accelerated apoptosis of mature neutrophils or myeloid precursors.

Alloimmune neonatal neutropenia occurs after transplacental transfer of maternal alloantibodies directed against antigens on the infant's neutrophils, analogous to Rh hemolytic disease. Prenatal sensitization induces maternal IgG antibodies to neutrophil antigens on fetal cells. The neutropenia is often severe and infants may present within the 1st 2 wk of life with skin or umbilical infections, fever, and pneumonia caused by the usual microbes that cause neonatal disease. By 7 wk of age, the neutrophil count usually returns to normal, reflecting the decay of maternal antibodies in the infant's circulation. **Treatment** consists of supportive care and appropriate antibiotics for clinical infections, plus filgrastim for severe infections without neutrophil recovery.

Mothers with autoimmune disease may give birth to infants who develop transient neutropenia, known as **neonatal passive autoimmune neutropenia**. The duration of the neutropenia depends on the time required for the infant to clear the maternally transferred circulating immunoglobulin G antibody. It persists in most cases for a few weeks to a few months. Neonates almost always remain asymptomatic.

Autoimmune neutropenia (AIN) of infancy is a benign condition with an annual incidence of approximately 1 per 100,000 among children between infancy and 10 yr of age. Patients usually have severe neutropenia on presentation, with ANC <500/μL, but the total WBC count is generally within normal limits. Monocytosis or eosinophilia may occur but does not impact the low rate of infection. The median age of presentation is 8-11 mo with a range of 2-54 mo. There is a slight female predominance. The diagnosis is often evident when a blood count incidentally reveals neutropenia in a child with a minor infection. Occasionally, children may present with more severe infections, including abscesses, pneumonia, or sepsis. The diagnosis may be established by the presence of antineutrophil antibodies in serum; however, the test has frequent false-negative and false-positive results, so the absence of detectable antibody does not exclude the diagnosis and a positive result does not exclude other conditions. The diagnosis may also be based clinically on a benign course and normal or hyperplastic myeloid maturation in the bone marrow. There is considerable overlap between AIN of infancy and "chronic benign neutropenia."

Treatment is not generally necessary because the disease is only rarely associated with severe infection and usually remits spontaneously. Low-dose filgrastim may be useful for severe infections, to promote wound healing following surgery, or to avert emergency room visits or hospitalizations for febrile illnesses. Longitudinal studies of infants with AIN demonstrate median durations of disease ranging from 7-30 mo. Affected children generally have no evidence or risk of other autoimmune diseases.

AIN in older children can occur as an isolated process, as a manifestation of other autoimmune diseases, or as a secondary complication of infection, drugs or malignancy. In primary AIN, low circulating neutrophil counts are the only hematologic finding, and associated diseases or other factors that cause neutropenia are absent. Secondary AIN associated with immune dysregulation or other factors is more commonly identified in older children and is less likely to spontaneously remit. AIN is distinguished from other forms of neutropenia by the demonstration of antineutrophil antibodies (with caveats discussed above) and myeloid hyperplasia on bone marrow examination. The

most common antineutrophil antibody targets are human neutrophil antigens 1a, 1b, and 2.

Treatment of AIN relies on management of any underlying disorders. In addition, judicious use of appropriate antibiotics for bacterial infections, and regular dental hygiene is generally beneficial. Infections tend to be less frequent in AIN than with the corresponding degree of neutropenia from other causes, probably because tissue delivery of neutrophils is greater than that in conditions resulting from impaired production. Prophylactic antibiotics may be helpful for the management of recurrent minor infections. For patients with serious or recurrent infections, filgrastim is generally effective at raising the ANC and preventing infection. Very low doses (<1-2 μg/kg/day) are usually effective, and administration of standard doses can lead to severe bone pain as a consequence of marrow expansion.

Neutropenia Secondary to Bone Marrow Replacement. Various acquired bone marrow disorders lead to neutropenia, usually accompanied by anemia and thrombocytopenia. Hematologic malignancies, including leukemia, lymphoma, and metastatic solid tumors suppress myelopoiesis by infiltrating the bone marrow with tumor cells. Neutropenia may also accompany aplastic anemia, myelodysplastic disorders or preleukemic syndromes, which are characterized by multiple cytopenias and often macrocytosis. Treatment requires management of the underlying disease.

Neutropenia Secondary to Reticuloendothelial Sequestration. Splenic enlargement resulting from intrinsic splenic disease (storage disease), portal hypertension, or systemic causes of splenic hyperplasia (inflammation or neoplasia) can lead to neutropenia. Most often the neutropenia is mild to moderate and is accompanied by corresponding degrees of thrombocytopenia and anemia. The reduced neutrophil survival corresponds to the size of the spleen, and the extent of the neutropenia is inversely proportional to bone marrow compensatory mechanisms. Usually the neutropenia may be corrected by successfully treating the underlying disease. In selected cases, splenectomy may be necessary to restore the neutrophil count to normal, but results in increased risk of infections by encapsulated bacterial organisms. Patients undergoing splenectomy should receive appropriate presplenectomy immunizations and may benefit from antibiotic prophylaxis postsplenectomy to help mitigate the risk of sepsis. Splenectomy should be avoided in patients with common variable immunodeficiency, autoimmune lymphoproliferative disease and other immunodeficiency syndromes because of the higher risk of sepsis.

Inherited Neutropenia

Intrinsic disorders of proliferation or maturation of myeloid precursor cells are rare. Table 131-6 presents a classification based on genetics and molecular mechanisms; selected disorders are discussed below.

Primary Disorders of Granulocytopoiesis. **Cyclic neutropenia** is a rare autosomal dominant congenital granulopoietic disorder occurring with an estimated incidence of 0.5-1 cases per 1 million population. The disorder is characterized by regular, periodic oscillations, with the ANC ranging from normal to <200/μL, mirrored by reciprocal cycling of monocytes. Cyclic neutropenia is sometimes termed *cyclic hematopoiesis* because of the secondary cycling of other blood cells, such as platelets and reticulocytes. The mean oscillatory period of the cycle is 21 days (± 4 days). During the neutropenic nadir, many patients suffer from malaise, fever, oral and genital ulcers, gingivitis, periodontitis, or pharyngitis, and occasionally lymph node enlargement. More serious infections may occasionally occur, including pneumonia, mastoiditis, and intestinal perforation with peritonitis leading to life-threatening clostridial sepsis. Prior to the availability of filgrastim, approximately 10% of patients developed fatal clostridial or Gram-negative infections. Cyclic neutropenia arises from a regulatory abnormality involving early hematopoietic precursor cells and is almost invariably associated with mutations in the neutrophil elastase gene, *ELANE*, that lead to accelerated apoptosis as a result of abnormal protein folding. Many patients experience abatement of symptoms with age. The cycles tend to become less noticeable in older patients, and the hematologic picture often begins to resemble that of chronic idiopathic neutropenia.

Cyclic neutropenia is diagnosed by obtaining blood counts 3 times/wk for 6-8 wk. The requirement for repeated blood counts is necessary because some of the elastase mutations overlap with those in patients who have **severe congenital neutropenia**. Demonstrating oscillation or a lack thereof in the blood counts helps to identify the patients risk for progression to myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), a risk that is only associated with severe congenital neutropenia. The diagnosis can be confirmed with genetic studies demonstrating a mutation in the *ELANE* gene. Affected patients with neutrophil nadirs <200/μL are treated with filgrastim and their cycle of profound neutropenia changes from a 21-day period with at least 3-5 days of profound neutropenia to a 9-11 day interval with 1 day of less-profound neutropenia. The dose needed to maintain nadirs >500/μL is usually 2-4 μg/kg/day administered daily or every other day.

Severe congenital neutropenia (SCN) is a rare, genetically heterogeneous, congenital granulopoietic disorder with an estimated incidence of 1-2 cases per 1 million population. The disorder is characterized by an arrest in myeloid maturation at the promyelocyte stage in the bone marrow, resulting in ANCs consistently <200/μL and may occur sporadically, with autosomal dominant or recessive inheritance. The **dominant** form is caused most often by mutations in the *ELANE* gene, which accounts for 60-80% of SCN cases, while **recessive** forms arise from mutations in *HAX1* (the form also known as **Kostmann disease**) or *G6PC3* (encoding a myeloid-specific isoform of glucose-6-phosphatase). *HAX1* mutations may be associated with neurologic deficits, and *G6PC3* with heart defects, urogenital abnormalities, and venous angiectasia. In addition to severe neutropenia, peripheral blood counts generally show monocytosis and many also exhibit eosinophilia; chronic inflammation may lead to secondary anemia and thrombocytosis. Patients who have SCN experience frequent episodes of fever, skin infections (including omphalitis), oral ulcers, gingivitis, pneumonia and perirectal abscesses, typically appearing in the 1st few mo of life. Infections often disseminate to the blood, meninges and peritoneum, and are usually caused by *S. aureus*, *Escherichia coli,* and *Pseudomonas* species. Prior to the current era of filgrastim therapy, most patients died of infectious complications within the 1st 1-2 yr of life despite prophylactic antibiotics.

More than 95% of SCN patients respond to filgrastim treatment with an increase in the ANC and a decrease in infections. Doses required to achieve an ANC >1000/uL vary greatly. A starting dose of filgrastim 5 μg/kg/day is recommended; the dose should be gradually increased, if necessary, as high as 100 μg/kg/day to attain an ANC of 1,000-2,000/μL. The 5% of patients who do not respond to filgrastim or who require high doses (>8 μg/kg/day) should be considered for hematopoietic stem cell transplantation. Besides infections, patients with SCN are at risk for developing MDS associated with monosomy 7 and AML. For this reason, regular monitoring with blood counts and yearly bone marrow surveillance, including karyotyping and fluorescence in situ hybridization, should be performed on all SCN patients. Although clonal cytogenetic abnormalities may spontaneously remit, their appearance should be considered a strong indication for hematopoietic stem cell transplantation, which is much more likely to be successful prior to progression to MDS/AML.

Disorders of Molecular Processing. Shwachman-Diamond syndrome (SDS) is an autosomal recessive disorder classically characterized by neutropenia, pancreatic insufficiency, and short stature with skeletal abnormalities. SDS is caused by proapoptotic mutations of the *SBDS* gene, which encodes a protein that plays a role in ribosome biogenesis and RNA processing. The initial symptoms are usually steatorrhea and failure to thrive because of malabsorption, which usually develops by 4 mo of age, although the gastrointestinal symptoms may be subtle in some patients and go unrecognized. Patients have also been reported to have respiratory problems with frequent otitis media, pneumonia and eczema. Virtually all patients with SDS have neutropenia, with the ANC periodically <1000/μL. Some children have defects in chemotaxis or in the number or function of B, T, and natural killer (NK) cells that may contribute to the increased susceptibility to pyogenic infection. The diagnosis of SDS is based on clinical

Table 131-6 Intrinsic Disorders of Myeloid Precursor Cells

SYNDROME	INHERITANCE *(GENE)*	CLINICAL FEATURES (INCLUDING STATIC NEUTROPENIA UNLESS OTHERWISE NOTED)
PRIMARY DISORDERS OF MYELOPOIESIS		
Cyclic neutropenia	AD *(ELANE)*	Periodic oscillation (21-day cycles) in ANC
Severe congenital neutropenia	AD (primarily *ELANE*, also *GFI* and others)	Risk of MDS/AML
	AR *(G6PC3, HAX1)* (*HAX1* = Kostmann syndrome)	*G6PC3:* cardiac and urogenital anomalies, venous angiectasias; *HAX1:* neurologic abnormalities, risk of MDS/AML
	XL *(WAS)*	Neutropenic variant of Wiskott-Aldrich syndrome
DISORDERS OF MOLECULAR PROCESSING		
Shwachman-Diamond syndrome	Ribosomal defect: AR *(SBDS)*	Pancreatic insufficiency, metaphysical dysostosis, bone marrow failure, MDS/AML
Dyskeratosis congenita	Telomerase defects: XL *(DKC1)*, AD *(TERC)*, AR *(TERT)*	Nail dystrophy, leukoplakia, abnormal and carious teeth, lacey reticulated hyperpigmentation of the skin, bone marrow failure
DISORDERS OF VESICULAR TRAFFICKING		
Chédiak-Higashi syndrome	AR *(LYST)*	Partial albinism, giant granules in myeloid cells, platelet storage pool defect, impaired natural killer cell function, HLH
Griscelli syndrome, type II	AR *(RAB27a)*	Partial albinism, impaired natural killer cell function, neurological impairment, HLH
Cohen syndrome	AR *(COH1)*	Partial albinism, pigmentary retinopathy, developmental delay, facial dysmorphism
Hermansky-Pudlak syndrome, type II	AR *(AP3P1)*	Cyclic neutropenia, partial albinism, HLH
p14 deficiency	Probable AR *(MAPBPIP)*	Partial albinism, decreased B and T cells
VPS45 defects	AR *(VPS45)*	neutrophil dysfunction, bone marrow fibrosis, nephromegaly
DISORDERS OF METABOLISM		
Glycogen storage disease, type 1b	AR *(G6PT1)*	Hepatic enlargement, growth retardation, impaired neutrophil motility
Barth syndrome	XL *(TAZ1)*	Episodic neutropenia, dilated cardiomyopathy, methylglutaconic aciduria
Pearson syndrome	Mitochondrial (DNA deletions)	Episodic neutropenia, pancytopenia; defects in exocrine pancreas, liver, and kidneys
NEUTROPENIA IN DISORDERS OF IMMUNE FUNCTION		
Common variable immunodeficiency	Familial, sporadic *(TNFRSF13B)*	Hypogammaglobulinemia, other immune system defects
IgA deficiency	Unknown (Unknown or *TNFRSF13B*)	Decreased IgA
Severe combined immunodeficiency	AR, XL (multiple loci)	Absent humoral and cellular immune function
Hyper-IgM syndrome	XL *(HIGM1)*	Absent IgG, elevated IgM, autoimmune cytopenias
WHIM syndrome	AD *(CXCR4)*	Warts, hypogammaglobulinemia, infections, myelokathexis
Cartilage-hair hypoplasia	AR *(RMKP)*	Lymphopenia, short-limbed dwarfism, metaphyseal chondrodysplasia, fine sparse hair
Schimke immunoosseous dysplasia	Probable AR *(SMARCAL1)*	Lymphopenia, pancytopenia, spondyloepiphyseal dysplasia, growth retardation, renal failure
X-linked agammaglobulinemia	BTK	Agammaglobulinemia, neutropenia in ~25%

AD, autosomal dominant; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; AR, autosomal recessive; HLH, hemophagocytic lymphohistiocytosis; Ig, immunoglobulin; MDS, myelodysplasia; XL, X-linked, BTK, Briton tyrosine kinase.

phenotype; approximately 90% of patients have mutations identified in the *SBDS* gene. SDS may progress to bone marrow hypoplasia or to MDS/AML; cytogenetic abnormalities, particularly isochromosome i(7q) and del(20q), often precede conversion to MDS, so bone marrow monitoring is warranted. Treatment includes pancreatic enzyme replacement, plus filgrastim in patients with severe neutropenia.

Dyskeratosis congenita, a disorder of telomerase activity, most often presents as bone marrow failure rather than isolated neutropenia. The classical phenotype also includes nail dystrophy, leukoplakia, malformed teeth, and reticulated hyperpigmentation of the skin, although many patients, particularly young ones, do not exhibit these clinical features.

Vesicular Trafficking Disorders. This group of very rare **primary immunodeficiency syndromes** (see Table 131-6) derives from autosomal recessive defects in the biogenesis or trafficking of lysosomes and related endosomal organelles. As a result, the syndromes share phenotypic characteristics including defects in melanosomes contributing to partial albinism, abnormal platelet function, and immunologic defects involving not only neutrophil number, but also the function of neutrophils, B lymphocytes, NK cells, and cytotoxic T lymphocytes. The syndromes share a high risk of hemophagocytic lymphohistiocytosis (HLH) as a result of defects in T and NK cells.

Chédiak-Higashi syndrome, best known for the characteristic giant cytoplasmic granules in neutrophils, monocytes, and lymphocytes, is a disorder of subcellular vesicular dysfunction caused by mutations in the *LYST* gene, with resultant giant granules in all granule-bearing cells. Patients have increased susceptibility to infections, mild bleeding diathesis, progressive peripheral neuropathy, and predisposition to life-threatening HLH. The only curative treatment is hematopoietic stem cell transplantation.

Griscelli syndrome type II also features neutropenia, partial albinism, and a high risk of HLH, but peripheral blood granulocytes do not show giant granules. Patients often have hypogammaglobulinemia. The disorder is caused by mutations in *RAB27a*, which encodes a small guanosine triphosphatase that regulates granule secretory pathways. The only curative treatment is hematopoietic stem cell transplantation.

Disorders of Metabolism. Recurrent infections with neutropenia are a distinctive feature of **glycogen storage disease (GSD)**

type Ib. As in classic von Gierke disease (GSDIa), glycogen storage in GSDIb causes massive hepatomegaly and severe growth retardation (see Chapter 87.1). Mutations in glucose-6-phosphate transporter 1, *G6PT1*, inhibit glucose transport in GSDIb, resulting in both defective neutrophil motility and increased apoptosis associated with neutropenia and recurrent bacterial infections. **Treatment** with filgrastim can correct the neutropenia but does not correct the underlying functional neutrophil defects.

Neutropenia in Disorders of Immune Dysfunction. Congenital immunologic disorders that have severe neutropenia as a clinical feature include X-linked agammaglobulinemia, common variable immunodeficiency, the severe combined immunodeficiencies, autoimmune lymphoproliferative syndrome, hyperimmunoglobulin M syndrome, WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, and a number of even rarer immunodeficiency disorders (see Table 131-6).

Unclassified Neutropenic Disorders. Chronic benign neutropenia of childhood represents a common group of disorders characterized by mild to moderate neutropenia that does not lead to an increased risk of pyogenic infections. Spontaneous remissions are often reported, although these may represent misdiagnosis of AIN of infancy, in which remissions occur commonly during childhood. Chronic benign neutropenia may be sporadic or inherited in either a dominant or recessive form. Because of the relatively low risk of serious infection, patients usually do not require any form of therapy.

Idiopathic chronic neutropenia is characterized by the onset of neutropenia after 2 yr of age, with no identifiable etiology. Patients with an ANC persistently <500/μL may be afflicted with recurrent pyogenic infections involving the skin, mucous membranes, lungs, and lymph nodes. Bone marrow examination reveals variable patterns of myeloid formation with arrest generally occurring between the myelocyte and band forms. The diagnosis overlaps with chronic benign and AINs.

Treatment

The management of acquired transient neutropenia associated with malignancies, myelosuppressive chemotherapy, or immunosuppressive chemotherapy differs from that of congenital or chronic forms of neutropenia. In the former situation, infections sometimes are heralded only by fever, and sepsis is a major cause of death. Early recognition and treatment of infections may be lifesaving (see Chapter 178). Therapy of severe chronic neutropenia is dictated by the clinical manifestations. Patients with benign neutropenia and no evidence of repeated bacterial infections or chronic gingivitis require no specific therapy. Superficial infections in children with mild to moderate neutropenia may be treated with appropriate oral antibiotics. In patients who have invasive or life-threatening infections, broad-spectrum intravenous antibiotics should be started promptly.

Subcutaneously administered filgrastim can provide effective treatment of severe chronic neutropenia including SCN, chronic symptomatic idiopathic neutropenia, and cyclic neutropenia. Treatment leads to dramatic increases in neutrophil counts, resulting in marked attenuation of infection and inflammation. Doses range from 2-5 μg/kg/day for cyclic, idiopathic, and autoimmune neutropenias, to 10-100 μg/kg/day for SCN. The long-term effects of filgrastim therapy include a propensity for the development of moderate splenomegaly, thrombocytopenia, and, rarely, vasculitis; only patients with SCN are at risk for MDS/AML.

Patients with SCN or SDS who develop MDS or AML respond only to hematopoietic stem cell transplantation; chemotherapy is ineffective. Hematopoietic stem cell transplantation is also the treatment of choice for aplastic anemia or HLH.

LYMPHOPENIA

The definition of **lymphopenia,** like neutropenia, is age-dependent and can be from acquired or inherited causes. **The absolute lymphocyte count (ALC)** is determined by multiplying the total WBC count by the percentage of total lymphocytes. For children younger than 12 mo old, lymphopenia is defined as an ALC <3,000 cells/μL. For older children and adults, an ALC <1,000 cells/μL is considered lymphopenia. In isolation, mild to moderate lymphopenia is generally a benign condition often detected only in the evaluation of other illnesses. However, severe lymphopenia can result in serious, life-threatening illness. Lymphocyte subpopulations can be measured by flow cytometry, which uses the pattern of lymphocyte antigen expression to quantitate and classify T, B, and NK cells.

Table 131-7 Causes of Lymphocytopenia

ACQUIRED	
Infectious diseases	AIDS, hepatitis, influenza, sepsis, tuberculosis, typhoid
Iatrogenic	Corticosteroids, cytotoxic chemotherapy, high-dose PUVA, immunosuppressive therapy, radiation, thoracic duct drainage
Systemic diseases	Hodgkin disease, lupus erythematosus, myasthenia gravis, protein-losing enteropathy, renal failure sarcoidosis
Other	Aplastic anemia, dietary deficiencies, thermal injury
INHERITED	
Aplasia of lymphopoietic stem cells	Cartilage-hair hypoplasia, ataxia-telangiectasia, SCID, thymoma, Wiskott-Aldrich syndrome

PUVA, psoralen and ultraviolet A irradiation; SCID, severe combined immunodeficiency.

Acquired Lymphopenia

Acute lymphopenia is most often a consequence of infection and/or is iatrogenic from lymphocyte-toxic medications and treatments (Table 131-7). Microbial causes include viruses (e.g., respiratory syncytial virus, cytomegalovirus, influenza, measles, and hepatitis) bacterial infections (e.g., tuberculosis, typhoid fever, histoplasmosis, and brucellosis) and malaria. The mechanisms behind infection-associated lymphopenia are not fully elucidated but probably include lymphocyte redistribution and accelerated apoptosis. Corticosteroids are a common cause of medication-induced lymphopenia, as are lymphocyte-specific immunosuppressive agents (e.g., antilymphocyte globulin, alemtuzumab, and rituximab) chemotherapy drugs, and radiation. In most cases, infectious and iatrogenic causes of acute lymphopenia are reversible, although full lymphocyte recovery from chemotherapy and lymphocyte-specific immunosuppressive agents may take several months to years. Prolonged lymphopenia (Table 131-7) may be caused by recurrent infection; persistent infections, mostly notably HIV; malnutrition; mechanical loss of lymphocytes through protein-losing enteropathy or thoracic duct leaks; or systemic diseases such as lupus erythematosus, rheumatoid arthritis, sarcoidosis, renal failure, lymphoma, and aplastic anemia.

Inherited Lymphopenia

Primary immunodeficiencies and bone marrow failure syndromes are the main cause of inherited lymphopenia in children (see Table 131-7). Primary immunodeficiency may result in a severe quantitative defect, as in X-linked agammaglobulinemia and severe combined immunodeficiency (SCID), or a qualitative or progressive defect as in Wiskott-Aldrich syndrome and common variable immunodeficiency. X-linked agammaglobulinemia is characterized by a near absence of mature B cells because of a mutation in *BTK* that results in a dysfunctional tyrosine kinase. SCIDs are a genetically heterogenous group of disorders characterized by abnormalities of thymopoiesis and T-cell maturation. Newborn screening for severe T-cell deficiency, via analysis of T-cell receptor excision circles from dried blood spot Guthrie cards, is available in many states to aid in the rapid identification and treatment of infants with SCID and other T-cell disorders. Quantitative defects in lymphocytes can also be appreciated in select forms of inherited bone marrow failure such as reticular dysgenesis, SCN secondary to *GFI1* mutation, and dyskeratosis congenita.

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Chapter 132

Leukocytosis

Kelly J. Walkovich and Peter E. Newburger

Leukocytosis is an elevation in the total leukocyte or white blood cell (WBC) count that is 2 SD above the mean count for a particular age (see Chapter 727). To evaluate the patient with leukocytosis, it is critical to determine which class of WBC is elevated in conjunction with the duration and extent of the leukocytosis. For discussion of WBC elevation caused by immature leukocytes in acute and chronic leukemias, see Chapter 495.

A WBC count exceeding 50,000/μL is termed a **leukemoid reaction** because of the similarity to some features of leukemia. Leukemoid reactions are usually neutrophilic, and unlike true leukemia, show only small proportions of immature myeloid cells, consisting primarily of band forms, occasional metamyelocytes, and progressively rarer myelocytes, promyelocytes, and blasts. The process is most frequently associated with septicemia and severe bacterial infections, including shigellosis, salmonellosis, and meningococcemia.

A proportion of immature neutrophil cells >5%, termed a **left shift**, indicates rapid release of cells from the bone marrow, consisting primarily of band forms, which usually constitute 1-5% of circulating neutrophilic cells, or metamyelocytes and myelocytes, which are not usually found in the peripheral circulation. Higher degrees of left shift with more immature neutrophil precursors are indicative of serious bacterial infections and may be a dire sign of depletion of the bone marrow reserve pool of neutrophils. Marked left shift may occasionally be encountered with trauma, burns, surgery, acute hemolysis, or hemorrhage.

NEUTROPHILIA

Neutrophilia is an increase in the total number of blood neutrophils that is 2 SD above the mean count for age (see Chapter 727). Elevated absolute neutrophil counts represent disturbances of the normal equilibrium involving bone marrow neutrophil production, movement out of the marrow compartments into the circulation, and neutrophil destruction. Neutrophilia may arise either alone or in combination with enhanced mobilization into the **circulating pool** from either the bone marrow storage compartment or the peripheral blood **marginating pool,** by impaired neutrophil egress into tissues, or by expansion of the circulating neutrophil pool secondary to increased granulocytopoiesis. Myelocytes are not released to the blood except under extreme circumstances.

Acute Acquired Neutrophilia

Neutrophilia is usually an acquired, secondary finding associated with inflammation, infection, injury, or stress (Table 132-1). Acute or chronic bacterial infections, trauma, and surgery are among the most common causes encountered in clinical practice. Neutrophilia may also be associated with heatstroke, burns, diabetic ketoacidosis, or any other acute stress. Drugs commonly associated with neutrophilia include epinephrine, corticosteroids, and recombinant growth factors such as recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim) and recombinant human granulocyte-macrophage colony-stimulating factor.

Epinephrine causes release into the circulation of a sequestered pool of neutrophils that normally marginate along the vascular endothelium. Corticosteroids accelerate the release of neutrophils and bands from a large storage pool within the bone marrow and impair the migration of neutrophils from the circulation into tissues. Acute neutrophilia in response to inflammation and infections occurs because of release of neutrophils from the marrow storage pool. The postmitotic marrow neutrophil pools are approximately 10 times the size of the blood neutrophil pool, and about half of these cells are bands and segmented neutrophils. In neutrophil production disorders, such as those associated with malignancies and cancer chemotherapy, the size of this pool may be reduced and the capacity to develop neutrophilia remains impaired. Exposure of blood to foreign substances such as hemodialysis membrane activates the complement system and causes transient neutropenia followed by neutrophilia because of release of bone marrow neutrophils. G-CSF and granulocyte-macrophage colony-stimulating factor cause acute and chronic neutrophilia by mobilizing cells from the marrow reserves and by stimulating neutrophil production.

Table 132-1 Causes of Neutrophilia

TYPE	CAUSE	EXAMPLE
Acute acquired	Bacterial infections	
	Surgery	
	Acute stress	Burns, diabetic ketoacidosis, heat stroke, postneutropenia rebound, exercise
	Drugs	Corticosteroids, epinephrine, hematopoietic growth factors, lithium
Chronic acquired	Chronic inflammation	Inflammatory bowel disease, rheumatoid arthritis, vasculitis
	Persistent infection	Tuberculosis
	Persistent stress	Chronic blood loss, hypoxia, sickle cell and other chronic hemolytic anemias
	Drugs	Corticosteroids, lithium; rarely ranitidine, quinidine
	Other	Postsplenectomy, tumors, Hodgkin disease
Lifelong	Congenital asplenia	
	Hereditary disorders	Familial cold urticaria, hereditary neutrophilia, leukocyte adhesion deficiencies, periodic fever syndromes

Chronic Acquired Neutrophilia

Chronic acquired neutrophilia is usually associated with continued stimulation of neutrophil production resulting from persistent inflammatory reactions or chronic infections (e.g., tuberculosis), vasculitis, postsplenectomy states, Hodgkin disease, chronic myelogenous leukemia, chronic blood loss, sickle cell disease, some chronic hemolytic anemias, and prolonged administration of corticosteroids (see Table 132-1). Chronic neutrophilia can arise after expansion of cell production secondary to stimulation of cell divisions within the mitotic precursor pool, which consists of promyelocytes and myelocytes. Subsequently, the size of the postmitotic pool increases. These changes lead to an increase in the marrow reserve pool, which can be readily mobilized for release of neutrophils into the circulation. The neutrophil production rate can increase greatly in response to exogenously administered hemopoietic growth factors, such as G-CSF, with a maximum response taking at least 1 wk to develop.

Lifelong Neutrophilia

Congenital or acquired asplenia is associated with lifelong neutrophilia. Uncommon genetic disorders that present with neutrophilia include leukocyte function disorders such as leukocyte adhesion deficiency and Rac2 mutation (see Chapter 124), and systemic disorders such as familial cold urticarial, periodic fever syndromes, and familial myeloproliferative disease (see Table 132-1). Two kindreds have been reported with autosomal dominant hereditary neutrophilia, with 1 caused by an activating mutation in the G-CSF receptor gene that leads to an increased proliferation of neutrophil precursors and a heightened risk of myelodysplastic syndrome.

Table 132-2 Causes of Monocytosis	
CAUSE	**EXAMPLE**
Infections	
Bacterial infections	Brucellosis, subacute bacterial endocarditis, syphilis, tuberculosis typhoid
Nonbacterial infections	Fungal infections, kala-azar, malaria, Rocky Mountain spotted fever, typhus
Hematologic disorders	Congenital and acquired neutropenias, hemolytic anemias
Malignant disorders	Acute myelogenous leukemia, chronic myelogenous leukemia, juvenile myelomonocytic leukemia, Hodgkin disease, non-Hodgkin lymphomas, preleukemia
Chronic inflammatory diseases	Inflammatory bowel disease, polyarteritis nodosa, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus
Miscellaneous	Cirrhosis, drug reaction, postsplenectomy, recovery from bone marrow suppression

Evaluation of persistent neutrophilia requires a careful history, physical examination, and laboratory studies to search for infectious, inflammatory, and neoplastic conditions. The leukocyte alkaline phosphatase score of circulating neutrophils can differentiate chronic myelogenous leukemia, in which the level is uniformly near zero, from reactive or secondary neutrophilia, which feature normal to elevated levels.

MONOCYTOSIS

The average absolute blood monocyte count varies with age, which must be considered in the assessment of monocytosis. Given the role of monocytes in antigen presentation and cytokine secretion and as effectors of ingestion of invading organisms, it is not surprising that many clinical disorders give rise to monocytosis (Table 132-2). Most commonly, monocytosis occurs in patients recovering from myelosuppressive chemotherapy and is a harbinger of the return of the neutrophil count to normal. Monocytosis is occasionally a sign of an acute bacterial, viral, protozoal, or rickettsial infection, and may also occur in some forms of chronic neutropenia and postsplenectomy states. Chronic inflammatory conditions can stimulate sustained monocytosis, as can preleukemia, chronic myelogenous leukemia, lymphomas, and occasionally Hodgkin disease.

Lymphocytosis

The most common cause of lymphocytosis is an acute viral illness, as part of the normal T-cell response to the infection. In infectious mononucleosis, the B cells are infected with the Epstein-Barr virus and the T cells react to the viral antigens present in the B cells, resulting in **atypical lymphocytes** with characteristic large, vacuolated morphology. Other viral infections classically associated with lymphocytosis are cytomegalovirus and viral hepatitis. Chronic bacterial infections such as tuberculosis and brucellosis may lead to a sustained lymphocytosis. Pertussis is accompanied by marked lymphocytosis in approximately 25% of infants infected before 6 mo of age. Thyrotoxicosis and Addison disease are endocrine disorders associated with lymphocytosis. Persistent or pronounced lymphocytosis suggests acute lymphocytic leukemia.

Basophilia

Basophilia is defined as an absolute basophil count >120 cells/μL. Basophilia is a nonspecific sign of a wide variety of disorders and is usually of limited diagnostic importance. Basophilia is most often present in hypersensitivity reactions and frequently accompanies the leukocytosis of chronic myeloid leukemia.

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Section 4

The Complement System

Chapter 133

The Complement System

Richard B. Johnston Jr.

Complement (C) was originally defined as the nonspecific, heat-labile complementary principal required with specific antibody to lyse bacteria. The 1st 4 components were numbered in the order of their discovery and are termed the classical pathway. Unfortunately, the components fix to the immune complex in a different order, C1423. Beyond this confusing start, complement is a logical, exquisitely balanced, and highly influential system that is fundamental to the clinical expression of host defense and inflammation. In addition, it is evolutionarily ancient, and as it coevolved with other physiologic systems, it developed the capacity to perform functions beyond just host defense. Among these, it promotes phagocytic removal of dying body cells, molecular debris, and synapses during brain formation. But it can also cause harm and has been implicated in more than 30 illnesses.

The complement system, an essential component of innate immunity, is broadly conceptualized as the **classical, lectin,** and **alternative pathways,** which interact and depend on each other for their full activity; the **membrane attack complex (C5b6789),** formed from activity of any pathway; cell membrane **receptors** that bind complement components or fragments to mediate complement activity; and a large array of serum and membrane regulatory proteins (Table 133-1,

Table 133-1 Constituents of the Complement System

SERUM COMPONENTS THAT ARE THE CORE OF THE COMPLEMENT SYSTEM Classical pathway: C1q, C1r, C1s, C4, C2, C3 Alternative pathway: Factor B, Factor D Lectin pathway: Mannose-binding lectin (MBL), ficolins 1/2/3, MBL-associated serine proteases (MASPs) 1/2/3 Membrane attack complex: C5, C6, C7, C8, C9 Regulatory protein, enhancing: properdin Regulatory proteins, downregulating: C1 inhibitor (C1 INH), C4-binding protein (C4-bp), factor H, factor I, vitronectin, clusterin, carboxypeptidase N (anaphylatoxin inactivator)
MEMBRANE REGULATORY PROTEINS CR1 (CD35), membrane cofactor protein (MCP; CD46), decay-accelerating factor (DAF, CD55), CD59 (membrane inhibitor of reactive lysis; protectin)
MEMBRANE RECEPTORS CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), CR4 (CD11c/CD18), C3a receptor, C5a receptor, C1q receptors, complement receptor of the immunoglobulin superfamily (CRIg)

Fig. 133-1). The circulating components and regulators together comprise approximately 15% of the globulin fraction and 4% of the total proteins in serum. The normal concentrations of serum complement components vary by age (see Chapter 727); newborn infants have mild to moderate deficiencies of all components.

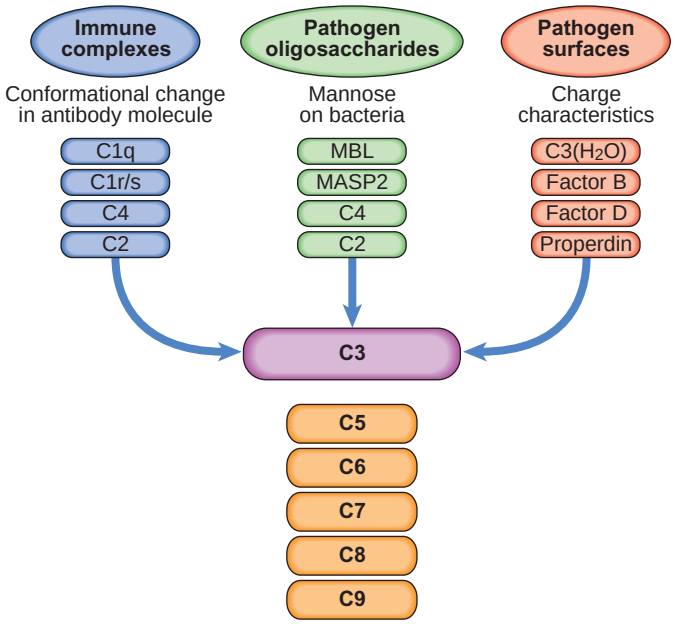

Figure 133-1 The complement cascade. The classical pathway is activated primarily by antibody while the mannose-binding lectin and alternative pathways are activated directly by pathogens. In each case, the activation arm leads to cleavage of C3. *(From Leung DYM, editor:* Pediatric allergy principles and practice, *ed 2, Philadelphia, 2010, WB Saunders, Fig. 11-1, p. 121.)*

After C1423, complement nomenclature is logical and consists of only a few rules. Fragments of components resulting from cleavage by other components acting as enzymes are assigned lowercase letters (a, b, c, d, e); with the exception of C2 fragments, the smaller piece that is released into surrounding fluids is assigned the lowercase letter *a,* and the major part of the molecule, bound to other components or to some part of the immune complex, is assigned letter *b*—for example, C3a and C3b. Components of the alternative pathway, B and D, have been assigned uppercase letters, as have the control proteins I and H, which downregulate both pathways. C3, and especially its major fragment C3b, is a component of both the classical and alternative pathways.

Complement is a system of interacting proteins. The biologic functions of the system depend on the interactions of individual components, which occur in sequential, cascade fashion. Activation of each component, except the 1st, depends on activation of the prior component or components in the sequence. Interaction occurs along 3 pathways (Fig. 133-2): the **classical pathway,** in the order antigen–antibody–C142356789; the **lectin** (carbohydrate-binding) **pathway**, in the order microbial carbohydrate–lectin (mannose-binding lectin [MBL] or ficolin)–MBL-associated serine protease–C42356789; and the **alternative pathway,** in the order activator–C3bBD–C356789. Antibody accelerates the rate of activation of the alternative pathway, but activation can occur on appropriate surfaces in the absence of antibody. The classical and the alternative pathways interact with each other through the ability of both to activate C3.

Activation of the early-acting components of complement (C1423) results in the generation of a series of active enzymes, C1, C42, and C423, on the surface of the immune complex or underlying cell. These enzymes cleave and activate the next component in the sequence. In contrast, the interaction among C5b, C6, C7, C8, and C9 is nonenzymatic and depends on changes in molecular configuration.

CLASSICAL AND LECTIN PATHWAYS

The classical pathway sequence begins with fixation of C1, by way of C1q, to the Fc, non–antigen-binding part of the antibody molecule after antigen–antibody interaction. The C1 tricomplex changes

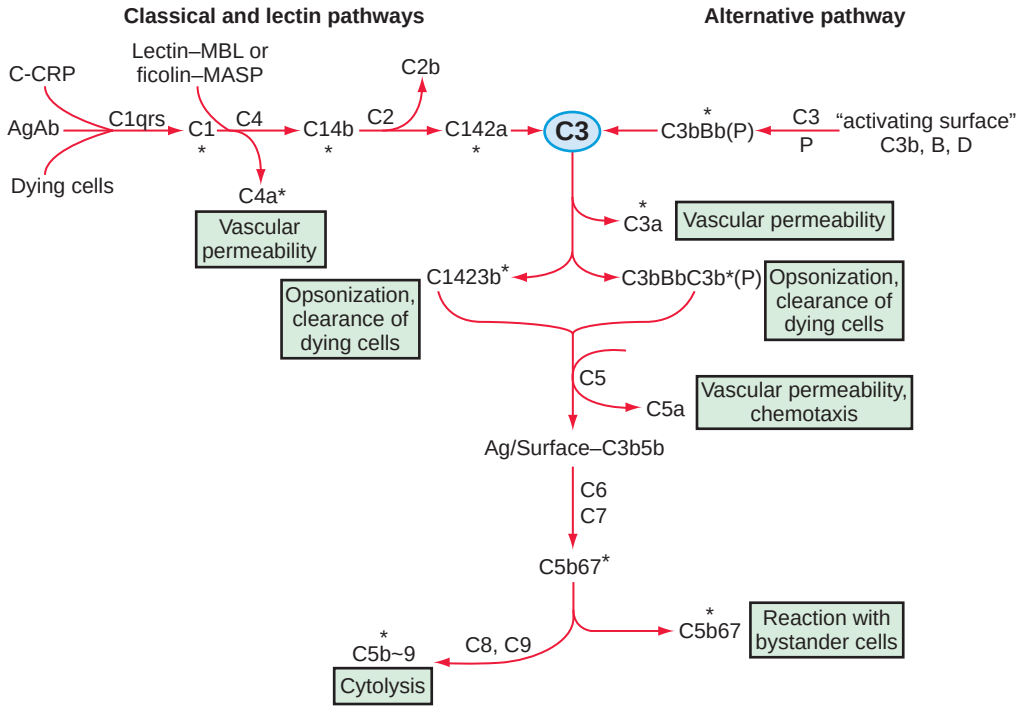

Figure 133-2 Sequence of activation of the components of the classical and lectin pathways of complement and interaction with the alternative pathway. Activation of C3 is the essential target. Functional activities generated during activation are enclosed in boxes. The multiple sites at which inhibitory regulator proteins (not shown) act are indicated by *asterisks,* emphasizing the delicate balance between action and control in this system that is essential for host defense yet capable of profound damage to host tissues. *Ab,* antibody (immunoglobulin G or M class); *Ag,* antigen (bacterium, virus, tumor or tissue cell); *B, D, I, P,* factors B, D, I, and properdin; *C-CRP,* carbohydrate–carbohydrate-reactive protein; *C4-bp,* C4-binding protein; *MASP,* MBL-associated serine protease; *MBL,* mannose-binding lectin.

configuration and the C1s subcomponent becomes an active enzyme, "C1 esterase." Certain bacteria, *Mycoplasma,* RNA viruses, and the lipid A component of bacterial endotoxin can activate C1q directly and trigger the full complement cascade.

As part of the innate immune response, broadly reactive "natural" antibodies and C-reactive protein, which reacts with carbohydrate from microorganisms and with dying cells, can substitute for specific antibody in the fixation of C1q and initiate reaction of the entire sequence. Endogenous agents, including uric acid crystals, amyloid deposits, DNA, and components of damaged cells such as apoptotic blebs and mitochondrial membranes, can activate C1q directly. But in this case, the ligand–C1q complex interacts strongly with the inhibitors C4-binding protein and factor H, allowing some C3-mediated opsonization and phagocytosis, but limiting the full inflammatory response typically triggered by microbes. C1q synthesized in the brain and retina enables the complement-dependent pruning of synapses that is essential for normal nervous system development.

There are 4 recognition molecules in the lectin pathway: MBL and ficolins 1, 2, and 3. MBL is the prototype of the collectin family of carbohydrate-binding proteins (lectins) that are believed to play an important part in innate, nonspecific immunity; its structure is homologous to that of C1q. These lectins, in association with MBL-associated serine proteases 1, 2, and 3 (MASPs 1/2/3), can bind to mannose, lipoteichoic acid, and other carbohydrates on the surface of bacteria, fungi, parasites, and viruses. MASPs then function there like C1s to cleave C4 and C2 and activate the complement cascade. The peptide C4a has weak "anaphylatoxin" activity and reacts with mast cells to release the chemical mediators of immediate hypersensitivity, including histamine. C3a and C5a, released later in the sequence, are potent anaphylatoxins, and C5a is also an important chemotactic factor. Fixation of C4b to the complex permits it to adhere to neutrophils, macrophages, B cells, dendritic cells, and erythrocytes. MASP-2 can activate clotting by generating thrombin from prothrombin, which could prevent microbial spread.

Cleavage of C3 and generation of C3b is the next step in the sequence. The serum concentration of C3 is the highest of any component, and its activation is the most crucial step in terms of biologic activity. Cleavage of C3 can be achieved through the **C3 convertase** of the classical pathway, C142, or of the alternative pathway, C3bBb. Once C3b is fixed to a complex or dead or dying host cell, it can bind to cells with receptors for C3b (complement receptor 1 [CR1]), including B lymphocytes, erythrocytes, and phagocytic cells (neutrophils, monocytes, and macrophages). Efficient **phagocytosis** of most microorganisms in vitro, especially by neutrophils, requires binding of C3 to the microbe. The severe pyogenic infections that commonly occur in C3-deficient patients indicate that phagocytosis in vivo is also inefficient without C3. The biologic activity of C3b is controlled by cleavage by **factor I** to iC3b, which promotes phagocytosis on binding to the **iC3b receptor (CR3)** on phagocytes. Further degradation of iC3b by factor I and proteases yields C3dg, then C3d; C3d binds to CR2 on B lymphocytes and thereby serves as a costimulator of antigen-induced B-cell activation.

ALTERNATIVE PATHWAY

The alternative pathway can be activated by C3b generated through classical pathway activity or proteases from neutrophils or the clotting system. It can also be activated by a form of C3 created by low-grade, spontaneous reaction of native C3 with a molecule of water, a "tick-over" that occurs constantly in plasma. Once formed, C3b or the hydrolyzed C3 can bind to any nearby cell or to factor B. Factor B attached to C3b in the plasma or on a surface can be cleaved to Bb by the protease factor D. The complex C3bBb becomes an efficient C3 convertase, which generates more C3b through an amplification loop. Properdin can bind to C3bBb, increasing stability of the enzyme and protecting it from inactivation by factors I and H, which modulate the loop and the pathway.

Certain "activating surfaces" promote alternative pathway activation if C3b is fixed to them, including bacterial teichoic acid or endotoxin, virally infected cells, antigen–immunoglobulin A complexes, and cardiopulmonary bypass and renal dialysis membranes. These surfaces act by protecting the C3bBb enzyme from the control otherwise exercised by factors I and H. Rabbit red blood cell membrane is such a surface, which serves as the basis for an assay of serum alternative pathway activity. Sialic acid on the surface of microorganisms or cells prevents formation of an effective alternative pathway C3 convertase by promoting activity of factors I and H. Nevertheless, significant activation of C3 can occur through the alternative pathway, and the resultant biologic activities are qualitatively the same as those achieved through activation by C142 (see Fig. 133-2).

MEMBRANE ATTACK COMPLEX

The sequence leading to cytolysis begins with the attachment of C5b to the C5-activating enzyme from the classical pathway, C4b2a3b, or from the alternative pathway, C3bBb3b. C6 is bound to C5b without being cleaved, stabilizing the activated C5b fragment. The C5b6 complex then dissociates from C423 and reacts with C7. C5b67 complexes must attach promptly to the membrane of the parent or a bystander cell, or they lose their activity. Next, C8 binds, and the C5b678 complex then promotes the addition of multiple C9 molecules. The C9 polymer of at least 3-6 molecules forms a transmembrane channel, and lysis ensues.

CONTROL MECHANISMS

Without control mechanisms acting at multiple points, there would be no effective complement system, and unbridled consumption of components would generate severe, potentially lethal damage to the host. At the 1st step, C1 inhibitor (C1 INH) inhibits C1r and C1s enzymatic activity and, thus, the cleavage of C4 and C2. C1 INH also inhibits MASP-2, factors XIa and XIIa of the clotting system, and kallikrein of the contact system. Activated C2 has a short half-life, and this relative instability limits the effective life of C42 and C423. The alternative pathway enzyme that activates C3, C3bBb, also has a short half-life, though it can be prolonged by the binding of properdin (P) to the enzyme complex. P can also bind directly to microbes and promote assembly of the alternative pathway C3 convertase.

Serum contains the enzyme carboxypeptidase N, which cleaves the N-terminus arginine from C4a, C3a, and C5a, thereby limiting their biologic activity. Factor I inactivates C4b and C3b; factor H accelerates inactivation of C3b by factor I; and an analogous factor, C4-binding protein (C4-bp), accelerates C4b cleavage by factor I, thus limiting assembly of the C3 convertase. Three protein constituents of cell membranes, CR1, membrane cofactor protein (MCP), and decay-accelerating factor (DAF), promote the disruption of C3 and C5 convertases assembled on those membranes. Another cell membrane-associated protein, CD59, can bind C8 or both C8 and C9 and thereby interfere with insertion of the membrane attack complex (C5b6789). The serum proteins vitronectin and clusterin can inhibit attachment of the C5b67 complex to cell membranes, bind C8 or C9 in a full membrane attack complex, or otherwise interfere with the formation or insertion of this complex. Vitronectin also promotes macrophage uptake of dying neutrophils. The genes for the regulatory proteins factor H, C4-bp, MCP, DAF, CR1, and CR2 are clustered on chromosome 1.

PARTICIPATION IN HOST DEFENSE

Neutralization of virus by antibody can be enhanced with C1 and C4 and further enhanced by the additional fixation of C3b through the classical or alternative pathway. Complement may, therefore, be particularly important in the early phases of a viral infection when antibody is limited. Antibody and the full complement sequence can also eliminate infectivity of at least some viruses by the production of typical complement "holes," as seen by electron microscopy. Fixation of C1q can opsonize (promote phagocytosis) through binding to the C1q receptor.

C4a, C3a, and C5a can bind to mast cells and thereby trigger release of histamine and other mediators, leading to vasodilation and the swelling and redness of inflammation. C5a can enhance macrophage phagocytosis of C3b-opsonized particles and induce macrophages to release the cytokines tumor necrosis factor and interleukin 1. C5a is a major chemotactic factor for neutrophils, monocytes, and eosinophils, which can efficiently phagocytize microorganisms opsonized with C3b

or cleaved C3b (iC3b). Further inactivation of cell-bound C3b by cleavage to C3d and C3dg removes its opsonizing activity, but it can still bind to B cells. Fixation of C3b to a target cell can enhance its lysis by natural killer cells or macrophages.

Insoluble immune complexes can be solubilized if they bind C3b, apparently because C3b disrupts the orderly antigen-antibody lattice. Binding C3b to a complex also allows it to adhere to C3 receptors (CR1) on red blood cells, which then transport the complexes to hepatic and splenic macrophages for removal. This phenomenon may at least partially explain the immune complex disease found in patients who lack C1, C4, C2, or C3.

The complement system serves to link the innate and adaptive immune systems. C4b or C3b coupled to immune complexes promotes their binding to antigen-presenting macrophages, dendritic cells, and B cells. Coupling of antigen to C3d allows binding to CR2 on B cells, which markedly reduces the amount of antigen needed to trigger an antibody response.

Neutralization of endotoxin in vitro and protection from its lethal effects in experimental animals require C1 INH and later-acting components of complement, at least through C6. Finally, activation of the entire complement sequence can result in lysis of virus-infected cells, tumor cells, and most types of microorganisms. Bactericidal activity of complement has not appeared to be important to host defense, except for the occurrence of *Neisseria* infections in patients lacking later-acting components of complement (see Chapter 134).

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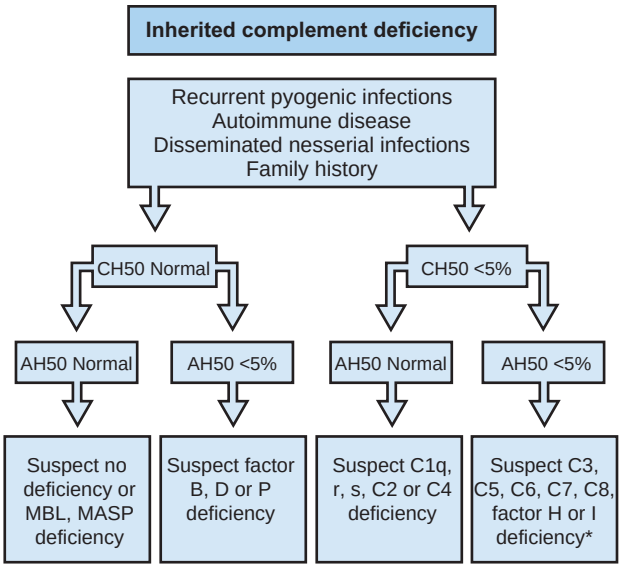

Figure 134-1 Flow chart for the evaluation of inherited complement deficiencies using hemolytic screening assays for the classical (CH_{50}) and alternative pathways (AH_{50}). For each assay, the entire activation pathway including the membrane attack complex (MAC) is required for lysis. *(Modified from Rich RR, Fleisher TA, Shearer WT, et al, editors,* Clinical immunology: principles and practice, *ed 4, Philadelphia, 2012, WB Saunders, Fig. 20-8, p. 262.)*

Chapter 134

Disorders of the Complement System

134.1 Evaluation of the Complement System

Richard B. Johnston Jr.

Testing for **total hemolytic complement activity (CH_{50})** effectively screens for most of the common diseases of the complement system. A normal result in this assay depends on the ability of all 11 components of the classical pathway and membrane attack complex to interact and lyse antibody-coated sheep erythrocytes. The dilution of serum that lyses 50% of the cells determines the end point. In **congenital deficiencies** of C1 through C8, the CH_{50} value is 0 or close to 0; in C9 deficiency, the value is approximately half-normal. Values in the acquired deficiencies vary with the type and severity of the underlying disorder. This assay does not detect deficiency of mannose-binding lectin (MBL), factors D or B of the alternative pathway, or properdin (Fig. 134-1). Deficiency of factors I or H permits consumption of C3, with partial reduction in the CH_{50} value. When clotted blood or serum sits at room temperature or warms, CH_{50} activity begins to decline, which leads to values that are falsely low but not zero. It is important to separate the serum and freeze it at –70°C (–94°F) by no more than 1 hr after blood draw.

In **hereditary angioedema,** depression of C4 and C2 during an attack significantly reduces the CH_{50}. Typically, C4 is low and C3 normal or slightly decreased. Concentrations of C1 inhibitor protein will be normal in 15% of cases; but C1 acts as an esterase, and the diagnosis can be established by showing increased capacity of patients' sera to hydrolyze synthetic esters.

A decrease in serum concentration of both C4 and C3 suggests activation of the **classical pathway** by immune complexes. Decreased C3 and normal C4 levels suggest activation of the **alternative pathway.** This difference is particularly useful in distinguishing nephritis secondary to immune complex deposition from that caused by NeF (nephritic factor). In the latter condition and in deficiency of factor I or H, factor B is consumed and C3 serum concentration is low. Alternative pathway activity can be measured with a relatively simple and reproducible hemolytic assay that depends on the capacity of rabbit erythrocytes to serve as both an activating (permissive) surface and a target of alternative pathway activity. This assay (**AP_{50}**) detects deficiency of properdin, factor D, and factor B. Immunochemical methods can be used to quantify individual components of all 3 pathways, guided by results of the screening hemolytic assays. It is possible to analyze the genes encoding most of the components.

A defect of complement function should be considered in any patient with recurrent angioedema, autoimmune disease (especially systemic lupus erythematosus [SLE]), chronic nephritis, hemolytic-uremic syndrome, or partial lipodystrophy, or with recurrent pyogenic infections, disseminated meningococcal or gonococcal infection, or a second episode of bacteremia at any age. A previously well adolescent or young adult with meningococcal meningitis caused by an uncommon serotype (not A, B, or C) should undergo screening for a late-component or alternative pathway deficiency with CH_{50} and AP_{50} assays.

Bibliography is available at Expert Consult.

134.2 Genetic Deficiencies of Complement Components

Richard B. Johnston Jr.

Congenital deficiencies of all 11 components of the classical-membrane attack pathway and of factor D and properdin of the alternative pathway are described in Table 134-1. All of the components of the

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Table 134-1 Genetic Deficiencies of Plasma Complement Components and Associated Clinical Findings

DEFICIENT COMPONENT	INFECTION*			AUTOIMMUNE/IMMUNE COMPLEX DISEASE*		
	VERY COMMON	COMMON	OCCASIONAL	VERY COMMON	COMMON	OCCASIONAL
CLASSICAL PATHWAY						
C1q			Pneumococcal B/M, other pyogenic	SLE	GN	DV/DLE
C1r, C1s, C1rs		Other pyogenic	Pneumococcal B/M, DGI	SLE	Other AD	GN
C4		Other pyogenic		SLE	GN, other AD	
C2		Other pyogenic, pneumococcal B/M, meningococcal M			SLE, GN, DV/DLE, other AD	
C3	Other pyogenic	Pneumococcal B/M, meningococcal M			GN, DV/DLE	SLE, other AD
C5	Meningococcal M	DGI	Other pyogenic			SLE, GN
C6	Meningococcal M	DGI	Other pyogenic			SLE, GN, other AD
C7	Meningococcal M		DGI, other pyogenic		SLE, other AD	
C8	Meningococcal M	DGI	Other pyogenic			SLE, GN
C9		Meningococcal M				
LECTIN PATHWAY						
MBL			Other pyogenic, fungal, HIV			SLE
MASP-2			Pneumococcal pneumonia			SLE
Ficolin-3			Other pyogenic			
ALTERNATIVE PATHWAY						
Factor D	DGI, meningococcal M, other pyogenic					
CONTROL PROTEINS						
C1 INH	Hereditary angioedema†					SLE
Factor I	Other pyogenic, meningococcal M	Pneumococcal B/M				
Factor H		Meningococcal B/M	Other pyogenic		GN, aHUS	SLE
Properdin		Meningococcal M	Pneumococcal B/M, other pyogenic		DV/DLE	
C4-binding protein						Other AD

*A finding was reported as "very common" if it occurred in 50% or more of reported cases, "common" if reported in approximately 5-50% of cases, and "occasional" if present in 1 or 2 cases or <5% of the more frequent deficiencies.

†Hereditary angioedema is not typically associated with infection or autoimmunity.

aHUS, atypical hemolytic-uremic syndrome; B/M, bacteremia and/or meningitis; DGI, disseminated gonococcal infection; DV/DLE, dermal vasculitis or typical discoid lupus erythematosus; GN, glomerulonephritis in various forms, often membranoproliferative; HIV, human immunodeficiency virus; M, meningitis; MASP, MBL-associated serine protease; MBL, mannose-binding lectin; other AD, autoimmune disease (almost all possible diagnoses have been reported); other pyogenic, serious deep or systemic infection caused by, or typically caused by, a pyogenic bacterium (abscess, osteomyelitis, pneumonia, bacteremia other than pneumococcal, meningitis other than meningococcal or pneumococcal, cellulitis, myopericarditis, and peritonitis); SLE, typical systemic lupus erythematosus or an SLE-like syndrome without characteristic serologic findings.

Data from Figueroa JE, Densen P: Infectious diseases associated with complement deficiencies, Clin Microbiol Rev *4:359–395, 1991; Ross SC, Densen P: Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency,* Medicine (Baltimore) *63:243–273, 1984; and other cases and series reported to date.*

classical and alternative pathways except properdin are inherited as autosomal recessive codominant traits. Each parent transmits a gene that codes for synthesis of half the serum level of the component. Deficiency results from inheritance of 1 null gene from each parent; the hemizygous parents typically have low normal CH_{50} levels and no consequences of the partial deficiency. Properdin deficiency is transmitted as an X-linked trait.

Most patients with primary **C1q deficiency** have SLE; some have an SLE-like syndrome without typical SLE serology, a chronic rash with underlying vasculitis, or membranoproliferative glomerulonephritis (MPGN). Some C1q-deficient children have serious infections, including septicemia and meningitis. Individuals with **C1r, C1s, combined C1r/C1s, C4, C2,** or **C3 deficiency** also have a high incidence of autoimmune syndromes (see Table 134-1), especially SLE or an SLE-like syndrome without an elevated antinuclear antibody level.

C4 is encoded by 2 genes, *C4A* and *C4B*. **C4 deficiency** represents absence of both gene products. Complete deficiency of only C4A, present in approximately 1% of the population, also predisposes to SLE, although C4 levels are only partially reduced. Patients with only C4B deficiency may be predisposed to infection. A few patients with **C5, C6, C7,** or **C8 deficiency** have SLE, but recurrent meningococcal infections are much more likely to be the major problem.

There are at least 2 possible reasons for the concurrence of complement component deficiencies, especially C1, C4, C2, or C3 deficiency, and autoimmune–immune complex diseases. First, deposition of C3 on autoimmune complexes facilitates their removal from the circulation through binding to complement receptor 1 (CR1) on erythrocytes and transport to the spleen and liver. Second, the early components, particularly C1q and C3, expedite the clearance of necrotic and apoptotic cells, which are sources of autoantigens.

Individuals with **C2 deficiency** carry the risk of life-threatening septicemic illnesses, most commonly caused by pneumococci. However, most have not had problems with increased susceptibility to infection, presumably because of the protective function of the alternative pathway. The genes for C2, factor B, and C4 are situated close to each other on chromosome 6, and a partial depression of factor B levels can occur in conjunction with C2 deficiency. Persons with a deficiency of both proteins may be at particular risk.

Because C3 can be activated by C142 or by the alternative pathway, a defect in the function of either pathway can be compensated for, at least to some extent. Without C3, however, opsonization of bacteria is inefficient, and the chemotactic fragment from C5 (C5a) is not generated. Some organisms must be well opsonized in order to be cleared, and genetic **C3 deficiency** has been associated with recurrent, severe pyogenic infections caused by pneumococci, *Haemophilus influenzae*, and meningococci.

More than half of the individuals reported to have congenital **C5, C6, C7,** or **C8 deficiency** have had meningococcal meningitis or extragenital gonococcal infection. Patients with **C9 deficiency**, which is most often reported in individuals of Japanese descent, retain about one-third normal CH_{50} titers; some of these patients have also had *Neisseria* disease. In studies of patients 10 yr of age and older with systemic meningococcal disease, 3-15% have had a genetic deficiency of C5, C6, C7, C8, C9, or properdin. Among patients with infections caused by the uncommon *Neisseria meningitidis* serogroups (X, Y, Z, W135, 29E, or nongroupable; not A, B, or C), 33-45% have an underlying complement deficiency. It is not clear why patients with a deficiency of 1 of the late-acting components suffer a particular predisposition to *Neisseria* infections. It may be that serum bacteriolysis is uniquely important in defense against this organism. Many persons with such a deficiency have no significant illness.

A few individuals have been identified with **deficiency of factor D** of the alternative pathway, all with recurrent infections, most often neisserial. Hemolytic complement activity and C3 levels in their serum were normal, but alternative pathway activity was markedly deficient or absent.

Mutations in the structural gene encoding MBL or polymorphisms in the promoter region of the gene result in pronounced interindividual variation in the level of circulating MBL. More than 90% of individuals with **MBL deficiency** do not express a predisposition to infection. Those with a very low level of MBL have a predisposition to recurrent respiratory infections in infancy and to serious pyogenic and fungal infections if there is another underlying defect of host defense. MBL-associated serine protease (**MASP)-2 deficiency** has been reported with SLE-like symptoms and recurrent pneumococcal pneumonia. Homozygous **ficolin-3 deficiency** is associated with repeated pneumonia since early childhood, cerebral abscesses, and bronchiectasis.

Bibliography is available at Expert Consult.

134.3 Deficiencies of Plasma, Membrane, or Serosal Complement Control Proteins

Richard B. Johnston Jr.

Congenital deficiencies of 5 plasma complement control proteins have been described (see Table 134-1). **Factor I deficiency** was reported originally as a deficiency of C3 resulting from hypercatabolism. The first patient described had suffered a series of severe pyogenic infections similar to those associated with agammaglobulinemia or congenital deficiency of C3. Factor I is an essential regulator of both pathways. Its deficiency permits prolonged existence of C3b as a part of the C3 convertase of the alternative pathway, C3bBb. This results in constant activation of the alternative pathway and cleavage of more C3 to C3b, in circular fashion. Intravenous infusion of plasma or purified factor I induced a prompt rise in serum C3 concentration in the patient and a return to normal of in vitro C3-dependent functions such as opsonization.

The effects of **factor H deficiency** are like those of factor I deficiency because factor H also assists in dismantling the alternative pathway C3 convertase. A trigger event such as infection initiates uninhibited continuous activation of the alternative pathway, which consumes C3, factor B, total hemolytic activity, and alternative pathway activity. Patients have sustained systemic infections due to pyogenic bacteria, particularly *N. meningitidis.* Many have had glomerulonephritis or atypical hemolytic uremic syndrome (aHUS) (see Chapter 518). Mutations in genes encoding membrane cofactor protein (MCP; CD46), factors I or B, C3, or the endothelial antiinflammatory protein thrombomodulin, or autoantibodies to factors H or B, also are associated with aHUS. The majority of patients with factor H deficiency and aHUS, typically younger than 2 yr of age, develop end-stage renal disease or die. The few patients thus far reported as having **C4-binding protein deficiency** have approximately 25% of the normal levels of the protein and no typical disease presentation, although 1 had angioedema and Behçet disease.

Persons with **properdin deficiency** have a striking predisposition to *N. meningitidis* meningitis. All reported patients have been male. The predisposition to infection in these patients demonstrates clearly the need for the alternative pathway in defense against bacterial infection. Serum hemolytic complement activity is normal in these patients, and if the patient has specific antibacterial antibody from immunization or prior exposure, the need for the alternative pathway and properdin is greatly reduced. Several patients have had dermal vasculitis or discoid lupus.

Hereditary angioedema occurs in persons unable to synthesize normal levels of active C1 inhibitor (C1 INH). In 85% of affected families, the patient has markedly reduced concentrations of inhibitor, averaging 30% of normal; the other 15% have normal or elevated concentrations of an immunologically cross-reacting but nonfunctional protein. Both forms of the disease are transmitted as autosomal dominant traits. C1 INH suppresses the complement proteases C1rs and MASP-2 and the activated proteases of the contact and fibrinolysis systems. In doing so, C1 INH is consumed as a "suicide inhibitor." In the absence of full C1 INH function, activation of any of these proteases tips the balance toward the protease. This activation leads to uncontrolled C1 and kallikrein activity with breakdown of C4 and C2 and release of bradykinin, which interacts with vascular endothelial cells to cause vasodilation, which produces localized, nonpitting edema. The biochemical triggers that induce attacks of angioedema in these patients are not well understood.

Swelling of the affected part progresses rapidly, without urticaria, itching, discoloration, or redness and often without severe pain. Swelling of the intestinal wall, however, can lead to intense abdominal cramping, sometimes with vomiting or diarrhea. Concomitant subcutaneous edema is often absent, and patients have undergone abdominal surgery or psychiatric examination before the true diagnosis was established. Laryngeal edema can be fatal. Attacks last 2-3 days and then gradually abate. They may occur at sites of trauma, especially dental, after vigorous exercise, or with menses, fever, or emotional stress. Attacks begin in the 1st 5 yr of life in almost half of patients, but are usually not severe until late childhood or adolescence. **Acquired C1 INH deficiency** can occur in association with B-cell cancer or autoantibody to C1 INH. SLE and glomerulonephritis have been reported in patients with the congenital disease.

Three of the membrane complement control proteins—CR1, MCP (CD46), and decay-accelerating factor (DAF)—prevent the formation of the full C3-cleaving enzyme, C3bBb, which is triggered by C3b deposition. CD59 (membrane inhibitor of reactive lysis) prevents the full development of the membrane attack complex that creates the "hole." **Paroxysmal nocturnal hemoglobinuria** (PNH) is a hemolytic anemia that occurs when DAF and CD59 are not expressed on the erythrocyte surface. The condition is acquired as a somatic mutation in a hematopoietic stem cell of the *PIG-A* gene on the X chromosome. The product of this gene is required for normal synthesis of a

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glycosyl-phosphatidylinositol molecule that anchors about 20 proteins to cell membranes, including DAF and CD59. One patient with **genetic isolated CD59 deficiency** had a mild PNH-like disease in spite of normal expression of membrane DAF. In contrast, **genetic isolated DAF deficiency** has not resulted in hemolytic anemia.

Bibliography is available at Expert Consult.

134.4 Secondary Disorders of Complement

Richard B. Johnston Jr.

Partial deficiency of C1q has occurred in patients with severe combined immunodeficiency disease or hypogammaglobulinemia, apparently secondary to the deficiency of immunoglobulin (Ig) G, which normally binds reversibly to C1q and prevents its rapid catabolism.

Chronic MPGN can be caused by NeF, an IgG autoantibody to the C3-cleaving enzyme of the alternative pathway, C3bBb, which protects the enzyme from inactivation and promotes over activation of the alternative pathway. The result is increased consumption of C3 and decreased concentration of serum C3. Pyogenic infections, including meningitis, may occur if the serum C3 level drops to <10% of normal. This disorder has been found in children and adults with **partial lipodystrophy**. Adipocytes are the main source of factor D and synthesize C3 and factor B; exposure to NeF induces their lysis. An IgG NeF that binds to and inhibits the breakup of C42, the classical pathway C3 convertase, has been described in acute postinfectious nephritis and in SLE. The consumption of C3 that characterizes poststreptococcal nephritis and SLE could be caused by this factor, by complement activation by immune complexes, or by both.

Newborn infants have mild to moderate reductions in all plasma components of the complement system. Opsonization and generation of chemotactic activity in serum from full-term newborns can be markedly deficient through either the classical or alternative pathway. Complement activity is even lower in preterm infants. Patients with severe chronic cirrhosis of the liver, hepatic failure, malnutrition, or anorexia nervosa can have significant deficiency of complement components and functional activity. Synthesis of components is depressed in these conditions, and serum from some patients with malnutrition also contains immune complexes that could accelerate depletion.

Patients with **sickle cell disease** have normal activity of the classical pathway, but some have defective function of the alternative pathway in opsonization of pneumococci, in bacteriolysis and opsonization of *Salmonella,* and in lysis of rabbit erythrocytes. Deoxygenation of erythrocytes from patients with sickle cell disease alters their membranes to increase exposure of phospholipids that can activate the alternative pathway and consume its components. This activation is accentuated during painful crisis. Children with nephrotic syndrome may have decreased serum levels of factors B and D and subnormal serum opsonizing activity.

Immune complexes initiated by microorganisms or their by-products can induce complement consumption. Activation occurs primarily through fixation of C1 and initiation of the classical pathway. Formation of immune complexes and consumption of complement have been demonstrated in lepromatous leprosy, bacterial endocarditis, infected ventriculojugular shunts, malaria, infectious mononucleosis, dengue hemorrhagic fever, and acute hepatitis B. Nephritis or arthritis can develop as a result of deposition of immune complexes and activation of complement in these infections. In SLE, immune complexes activate C142, and C3 is deposited at sites of tissue damage, including kidneys and skin; depressed synthesis of C3 is also noted. The syndrome of recurrent urticaria, angioedema, eosinophilia, and hypocomplementemia secondary to activation of the classical pathway may be due to autoantibody to C1q and circulating immune complexes. Circulating immune complexes and decreased C3 have been reported in some patients with dermatitis herpetiformis, celiac disease, primary biliary cirrhosis, and Reye syndrome.

Circulating bacterial products in sepsis or tissue factors released after severe trauma can initiate activation of the classical and alternative pathways, leading to increased serum levels of C3a, C5a, and C5b-9 and systemic inflammatory response syndrome and multiple organ failure. C5a and its receptors, particularly on neutrophils, appear to be central to the pathogenesis of systemic inflammatory response syndrome. Intravenous injection of iodinated roentgenographic contrast medium can trigger a rapid and significant activation of the alternative pathway, which may explain the occasional reactions that occur in patients undergoing this procedure.

Burns can induce massive activation of the complement system, especially the alternative pathway, within a few hours after injury. Resulting generation of C3a and C5a stimulates neutrophils and induces their sequestration in the lungs, leading to shock lung. Cardiopulmonary bypass, extracorporeal membrane oxygenation, plasma exchange, or hemodialysis using cellophane membranes may be associated with a similar syndrome as a result of activation of plasma complement, with release of C3a and C5a. In patients with erythropoietic protoporphyria or porphyria cutanea tarda, exposure of the skin to light of certain wavelengths activates complement, generating chemotactic activity. This chemotactic activity leads to lysis of capillary endothelial cells, mast cell degranulation, and the appearance of neutrophils in the dermis.

Some tumor cells can avoid complement-mediated lysis by overexpressing DAF, MCP, CD59, CR1, or factor H, or by secreting proteases that cleave tumor-bound C3b. Microorganisms have evolved similar evasive mechanisms; for example, HIV-1 particles budding from infected cells acquire the membrane proteins DAF and CD59, and staphylococci can produce multiple complement inhibitors.

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134.5 Treatment of Complement Disorders

Richard B. Johnston Jr.

No specific therapy is available at present for genetic deficiencies of the components of the classical, alternative, and lectin complement pathways. Much can be done, however, to protect patients with any of these disorders from serious complications; and specific treatment is available for 3 disorders caused by control-protein deficiencies, hereditary angioedema, aHUS, and PNH.

Management of hereditary angioedema starts with avoidance of precipitating factors, usually trauma. Infusion of C1 INH concentrate (nanofiltered C1-esterase inhibitor), an inhibitor of kallikrein (ecallantide) that blocks bradykinin production, and an antagonist of the bradykinin receptor (icatibant) are approved in the United States for use in adolescents and adults for long-term prophylaxis, preparation for surgery or dental procedures, or treatment of acute attacks. The synthetic androgen oxandrolone increases the level of functional C1 INH severalfold and is approved for cautious use in children. Antihistamines, adrenalin, and corticosteroids have no effect. Eculizumab, a humanized monoclonal antibody to C5, is an effective treatment for PNH and aHUS.

Effective supportive management is available for other primary diseases of the complement system, and identification of a specific defect in the complement system can have an important impact on management. Concern for the associated complications such as autoimmune disease and infection should encourage vigorous diagnostic efforts and earlier institution of therapy. Individuals with SLE and a complement defect generally respond as well to therapy as do those without complement deficiency. With the onset of unexplained fever, cultures should be obtained and antibiotic therapy instituted more quickly and with less stringent indications than in a normal child. The parent or patient should be given letters describing any predisposition to systemic bacterial infection or autoimmune disease associated with the patient's deficiency, along with the recommended approach to management, for possible use by school, camp, or emergency room physicians. The

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patient and close household contacts should be immunized against *H. influenzae, Streptococcus pneumoniae,* and *N. meningitidis*. High titers of specific antibody might opsonize effectively without the full complement system, and immunization of household members could reduce the risk of exposing patients to these particularly threatening pathogens. Repeat immunization of patients is advisable since complement deficiency can be associated with a blunted or shorter-lived antibody response than normal.

Considering the many conditions in which complement is a central mediator of disease, there is an intensive effort to develop therapeutic complement inhibitors. These include soluble CR1 and inhibitors of C5 convertase and C3a and C5a binding. Heparin, which inhibits both classical and alternative pathways, has been used to prevent "post-pump syndrome."

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Section 5

Hematopoietic Stem Cell Transplantation

Chapter 135

Principles and Clinical Indications of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Thousands of children have received an infusion of either **allogeneic** (from a donor) or **autologous** (from the same individual) hematopoietic stem cells to cure both malignant and nonmalignant disorders. **Autologous** transplantation is employed as a rescue strategy after delivering otherwise lethal doses of radiotherapy and chemotherapy in children with hematologic malignancies such as relapsed lymphoma or selected solid tumors (e.g., neuroblastoma, brain tumors). **Allogeneic** transplantation is used to treat children with genetic diseases of blood cells, such as thalassemia and primary immunodeficiency diseases, as well as hematologic malignancies, such as leukemia and myelodysplastic syndromes. Since 1968 and for many years, bone marrow has represented the only source of hematopoietic progenitors employed. Growth factor (granulocyte colony-stimulating factor)–mobilized peripheral blood hematopoietic stem cells and umbilical cord blood hematopoietic progenitors have been more recently introduced in the clinical practice to perform hematopoietic stem cell transplantation (HSCT).

An human leukocyte antigen (HLA)–matched sibling was once the only type of donor employed. Today, matched unrelated volunteers, full-haplotype mismatched family members, and unrelated cord blood donors have been largely employed to transplant patients lacking an HLA-identical relative.

Protocols for allogeneic HSCT consist of 2 parts: the preparative regimen and transplantation itself. During the **preparative conditioning regimen,** chemotherapy, often associated with irradiation, is administered to destroy the patient's hematopoietic system and to suppress the immune system, especially T cells, so that graft rejection is prevented. In patients with malignancies, the preparative regimen also serves to significantly reduce the tumor burden. The patient then receives an intravenous infusion of hematopoietic cells from the donor. Less-aggressive conditioning regimens, known as reduced intensity conditioning regimens, are also used in pediatric patients. These regimens are mainly immune-suppressive and aim at inducing a state of reduced immune competence of the recipient permitting to avoid the rejection of donor cells.

The immunology of HSCT is distinct from that of other types of transplant because, in addition to stem cells, the graft contains mature blood cells of donor origin, including T cells, B cells, natural killer cells, and dendritic cells. These cells repopulate the recipient's lymphohematopoietic system and give rise to a new immune system, which helps eliminate residual leukemia cells that survive the conditioning regimen. This effect is known as the **graft-versus-leukemia (GVL) effect.**

The donor immune system exerts its T-cell–mediated GVL effect through alloreactions directed against not shared recipient histocompatibility antigens displayed on recipient leukemia cells. Because some of these histocompatibility antigens are also displayed on tissues, however, T-cell–mediated alloreactions may ensue. Specifically, donor alloreactive cytotoxic CD8+ effector T cells may attack recipient tissues—in particular, the skin, gastrointestinal tract, and liver—causing acute graft-versus-host disease (GVHD), a condition of varying severity, that, in some cases, can be life-threatening or even fatal (see Chapter 137). Although the main benefit for allogeneic HSCT recipients with leukemia derives from the GVL effect displayed by immune-competent cells, disease recurrence remains the main cause of treatment failure. The risk of failing to eradicate leukemia is influenced by many variables, including disease phase, molecular lesions of tumor cells, and disparity for major or minor histocompatibility antigens in the donor/recipient pairs. Strategies for rescuing patients experiencing disease recurrence are mainly based on either second transplantation or infusion of donor leukocytes. To overcome the hurdle of tumor elusion caused by HLA-loss on malignant cells, the use of non-HLA–restricted chimeric antigen receptors (CARs) has been envisaged. This therapeutic strategy is based on genetic reprogramming of T cells through artificial immune receptors that reproducibly and efficiently redirect the antigen specificity of polyclonal T lymphocytes toward target antigens expressed by leukemic cells. When expressed by T cells, CARs mediate antigen recognition and tumor cytolysis in an major histocompatibility complex (MHC)–unrestricted fashion, and can target any molecule (protein, carbohydrate, or glycolipid) expressed on the surface of tumor cells, thus bypassing one of the major tumor escape mechanisms based on the down regulation of MHC molecules. CARs are composed of an extracellular specific antigen-binding moiety, obtained from the variable regions of a monoclonal antibody, linked together to form a single-chain antibody (scFv), and of an intracellular signaling component derived from the ζ chain of the T-cell–receptor–CD3 complex. The addition to the CAR gene construct of costimulation signals and cytokines promoting T-cell expansion and/or survival improves the antitumor efficiency of the engineered T cells and their survival in the tumor milieu. Gamma retrovirus and lentiviruses are usually used to transduce CARs into T lymphocytes to be employed in the clinical setting. These vectors have been shown to efficiently infect T lymphocytes, integrate into the host genome and produce robust expression of the gene in human T cells and their progeny.

The success of allogeneic HSCT is undermined by diversity between donors and recipients in major and minor histocompatibility antigens. MHC molecules, the HLA-A, HLA-B, and HLA-C MHC class I molecules, present peptides to CD8+ T cells, while the HLA-DR, HLA-DQ, and HLA-DP MHC class II molecules present peptides to CD4+ T cells. There are hundreds of variant forms of each class I and class II molecule, and even small differences can elicit alloreactive T-cell

responses that mediate graft rejection and/or GVHD. Disparities for HLA-A, -B, -C, or -DRB1 alleles in the donor–recipient pair are independent risk factors for both acute and chronic GVHD.

Minor histocompatibility antigens derive from differences between the HLA-matched recipient and donor in peptides that are presented by the same HLA allotype. They are a result of polymorphisms of non-HLA proteins, of differences in the level of expression of proteins, or of genetic differences between males and females. An example of the latter is represented by the H-Y antigens encoded by the Y chromosome, which can stimulate GVHD when a female donor is employed to transplant an HLA-identical male recipient. Thus, from this evidence, it is clear that GVHD may occur even when the donor and recipient are HLA identical.

The optimal donor for any patient undergoing HSCT is an HLA-identical sibling. Because polymorphic HLA genes are closely linked and usually constitute a single genetic locus, any pair of siblings has a 25% chance of being HLA identical. Thus, also in view of the limited family size in the developed countries, less than 25-30% of patients in need of an allograft can receive their transplant from an HLA-identical sibling. This percentage is even lower in patients with inherited disorders.

HEMATOPOIETIC STEM CELL TRANSPLANTATION FROM AN HLA-IDENTICAL SIBLING DONOR

Allogeneic HSCT from an HLA-compatible sibling is the treatment of choice for children with hematological malignancies and congenital diseases (Table 135-1). Best results are achieved in patients with congenital or acquired non-malignant disorders because the risk of disease recurrence is low and the cumulative transplantation-related mortality is lower than in children receiving transplants for hematologic malignancies.

ACUTE LYMPHOBLASTIC LEUKEMIA

Allogeneic HSCT is used for pediatric patients with acute lymphoblastic leukemia (ALL), either in the first complete remission when a child is considered to be at high risk of leukemia recurrence (such as, e.g., those carrying poor-risk cytogenetic characteristics or with high levels of minimal residual disease), or in second or further complete remission after previous marrow relapse. ALL is the most common indication for HSCT in childhood. Several patient-, donor-, disease-, and transplant-related variables may influence the outcome of patients with ALL given an allogeneic HSCT. The long-term probabilities of event-free survival for patients with ALL transplanted in the 1st or 2nd complete remission is 60–70% and 40-60%, respectively. Inferior results are obtained in patients receiving transplants in more advanced disease phases. The use of radiotherapy, total body irradiation, during the preparative regimen offers an advantage in terms of better event-free survival compared to a regimen consisting of cytotoxic drugs alone (Fig. 135-1), but it can induce more long-term side effects. Less-intensive GVHD prophylaxis is also associated with a better outcome. Bone marrow is still the preferred source of stem cells to be employed for transplantation.

ACUTE MYELOID LEUKEMIA

Allogeneic HSCT from an HLA-identical sibling is largely employed as postremission treatment of pediatric patients with acute myeloid leukemia (AML). In fact, many studies show that children with AML in 1st complete remission who are given allogeneic HSCT as consolidation therapy have a better probability of event-free survival than those treated with either chemotherapy alone or with autologous transplantation. Results obtained in patients given HSCT from an HLA-identical sibling after either a total body irradiation–containing or a chemotherapy-based preparative regimen are similar, the probability of event-free survival being in the order of 70%. Children with acute promyelocytic leukemia in molecular remission at the end of treatment with chemotherapy and all-*trans*-retinoic acid, or with AML and either translocation t(8;21) or inversion of chromosome 16 (inv16) are no longer considered eligible for allogeneic HSCT in 1st complete remission in view of their excellent prognosis with alternative treatments. Studies suggest restricting the use of HSCT to those patients with poor molecular lesions, such as FLT3-internal tandem duplication, or mixed lineage leukemia abnormalities, or with high levels of minimal residual disease at time the end of induction therapy. Approximately 40% of pediatric patients with AML in the second complete remission can be rescued by an allograft from an HLA-identical sibling.

Table 135-1 Indications for Allogeneic Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia

First complete remission for patients at very high risk of relapse
- Translocation t(9;22) or t(4;11)
- Early thymocyte precursor phenotype
- Nonresponder after 1 wk of corticosteroid therapy and
  - T-immunophenotype or
  - >100,000 cells/μL at diagnosis
- Not in remission at the end of the induction phase
- Marked hypodiploidy (<43 chromosomes)
- High levels of minimal residual disease at the end of induction therapy

Second complete remission

Third or later complete remission
- Acute myeloid leukemia in 1st complete remission or in advanced disease phase
- Philadelphia chromosome–positive chronic myeloid leukemia
- Myelodysplastic syndromes
- Hodgkin and non-Hodgkin lymphomas
- Selected solid tumors
  - Metastatic neuroblastoma
  - Rhabdomyosarcoma refractory to conventional treatment
  - Very-high-risk Ewing sarcoma
- Severe acquired aplastic anemia
- Fanconi anemia
- Congenital dyskeratosis
- Diamond-Blackfan anemia
- Thalassemia major
- Sickle cell disease
- Variants of severe combined immunodeficiency
- Hyperimmunoglobulin M syndrome
- Leukocyte adhesion deficiency
- Omenn syndrome
- Wiskott-Aldrich syndrome
- Chédiak-Higashi syndrome
- Kostmann syndrome (infantile malignant agranulocytosis), chronic granulomatous disease and other severe neutrophil defects
- X-linked lymphoproliferative disease (Duncan syndrome)
- Hemophagocytic lymphohistiocytosis
- Selected severe variants of platelet function disorders (e.g., Glanzmann thromboasthenia, or congenital amegakaryocytic thrombocytopenia)
- Selected types of mucopolysaccharidosis (Hurler disease) or other liposomal/peroxisomal disorders (Krabbe disease, adrenoleukodystrophy)
- Infantile malignant osteopetrosis
- Life-threatening cytopenia unresponsive to conventional treatments

CHRONIC MYELOGENOUS LEUKEMIA

For many yr, allogeneic HSCT has been considered to be the only proven curative treatment for children with Philadelphia-positive (Ph+) chronic myelogenous leukemia. Leukemia-free survival of chronic myelogenous leukemia patients after an allograft is 45-80%, the phase of disease (chronic phase, accelerated phase, blast crisis), recipient age, type of donor employed (either related or unrelated), and time interval between diagnosis and HSCT being the main factors influencing the outcome. The best results are obtained in children transplanted during the chronic phase from an HLA-identical sibling within 1 year from diagnosis. Treatment with the specific BCR-ABL tyrosine protein kinase inhibitors (imatinib mesylate, dasatinib,

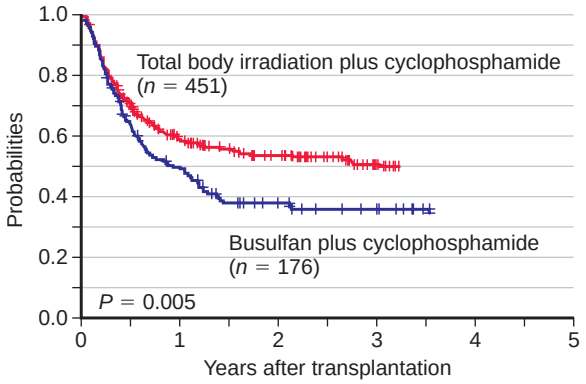

Figure 135-1 Cumulative probability of leukemia-free survival after HLA-identical sibling bone marrow transplantation for childhood acute lymphoblastic leukemia, by pretransplantation conditioning regimen of total body irradiation (TBI) plus cyclophosphamide (CY) *(upper line)* or busulfan (Bu) plus cyclophosphamide *(lower line)*. There was superior survival with the TBI plus cyclophosphamide regimen. *(From Davies S, Ramsay NK, Klein JP, et al: Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia.* J Clin Oncol *18:340–347, 2000.)*

nilotinib), targeting the enzymatic activity of the BCR-ABL fusion protein, could modify the natural history of the disease and, thus, the indications for transplantation. Infusion of donor leukocytes can re-induce a state of complete remission in a large proportion of patients experiencing leukemia relapse.

JUVENILE MYELOMONOCYTIC LEUKEMIA

This is a rare hematopoietic malignancy of early childhood, representing 2–3% of all pediatric leukemias. Juvenile myelomonocytic leukemia (JMML) is characterized by hepatosplenomegaly and organ infiltration, with excessive proliferation of cells of monocytic and granulocytic lineages. Hypersensitivity to granulocyte-macrophage colony-stimulating factor and pathologic activation of the RAS-RAF-MAP (mitogen-activated protein) kinase signaling pathway play an important role in the pathophysiology. JMML usually runs an aggressive clinical course, with a median duration of survival for untreated children of <12 mo from diagnosis. Rare patients with *CBL-1* or *N-RAS* mutations can survive for years without an allograft. HSCT is able to cure approximately 50-60% of patients with JMML. Patients who receive a transplant from an unrelated donor have comparable outcome to those given HSCT from an HLA-compatible related donor. Cord blood transplantation represents a suitable alternative option for those patients with either a related or an unrelated donor. Leukemia recurrence is the main cause of treatment failure in children with JMML after HSCT, the relapse rate being as high as 40-50%. Because children with JMML frequently have massive spleen enlargement, splenectomy has been performed before transplantation. Spleen size at the time of HSCT and splenectomy before HSCT do not appear to affect the post-transplantation outcome. Although donor leukocyte infusion is not useful to rescue patients experiencing disease recurrence, a second allograft can induce sustained remission in approximately one-third of children with JMML relapsing after a 1st HSCT.

MYELODYSPLASTIC SYNDROMES OTHER THAN JUVENILE MYELOMONOCYTIC LEUKEMIA

Myelodysplastic syndromes are a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis leading to peripheral blood cytopenia and a propensity to evolve toward AML. HSCT is the treatment of choice for children with refractory anemia with excess of blasts (RAEB) and for those with RAEB in transformation (RAEB-t). The probability of survival without evidence of disease for these children is 60% if the donor is an HLA-identical sibling, whereas that of patients transplanted from an alternative donor is slightly lower. It is still unclear whether patients with myelodysplastic syndromes and a blast percentage >20% benefit from pretransplantation chemotherapy. HSCT from an HLA-identical sibling is also the preferred treatment for all children with refractory cytopenia. Transplantation from an alternative donor is also employed in children with refractory cytopenia associated with monosomy 7, complex karyotype, life-threatening infections, profound neutropenia, or transfusion-dependency. For children with refractory cytopenia, the probability of event-free survival after HSCT may be as high as 80%, disease recurrence being rarely observed. This observation has provided the rationale for testing reduced-intensity regimens in these patients.

NON-HODGKIN LYMPHOMA AND HODGKIN DISEASE

Childhood non-Hodgkin lymphoma (NHL) and Hodgkin disease (HD) are quite responsive to conventional chemoradiotherapy, but some of these patients are at high risk for relapse. HSCT can cure a proportion of patients with relapsed NHL and HD and should be offered early after relapse, while the disease is still sensitive to therapy. If an HLA-identical sibling is available, allogeneic transplantation should be offered to patients with NHL to take advantage of the GVL effect. Patients with sensitive disease and limited tumor burden have favorable outcomes, with event-free survival rates of 50-60%. Studies also suggest that patients with HD can benefit from a GVL effect when given an allograft.

ACQUIRED APLASTIC ANEMIA

HSCT from an HLA-identical sibling is the treatment of choice for children with the severe form of acquired aplastic anemia, defined as 2 of the following: platelet count <20,000/mm^3, absolute neutrophil count <500/mm^3, or reticulocyte count <1% when anemia is present, together with hypoplastic bone marrow (<20% total cellularity). The probability of survival with sustained donor engraftment for these patients is <85-90%, younger patients having even better outcomes. Every child diagnosed with severe acquired aplastic anemia should undergo HLA-typing as early as possible in order to identify a suitable HLA-compatible family donor. Graft rejection represents the most important cause of treatment failure. Blood transfusion should be avoided whenever possible because sensitization to blood products increases the likelihood of graft rejection. GVHD prophylaxis combining cyclosporine and short-term methotrexate is associated with a better outcome as compared to cyclosporine alone (Fig. 135-2). Some studies suggest that the addition of antithymocyte globulin to the classical conditioning regimen consisting of cyclophosphamide (200 mg/kg) can reduce the risk of graft rejection, particularly in patients with previous heavy sensitization to blood products. The use of granulocyte colony-stimulating factor mobilized peripheral blood progenitors has provided inferior results with respect to the infusion of bone marrow cells, since it is associated with an increased risk of chronic GVHD.

CONSTITUTIONAL APLASTIC ANEMIA

Fanconi anemia and **dyskeratosis congenita** are genetic disorders associated with a high risk of developing pancytopenia. Fanconi anemia is an autosomal recessive disease characterized by spontaneous chromosomal fragility, which is increased after exposure of peripheral blood lymphocytes to DNA crosslinking agents, including clastogenic compounds, such as diepoxybutane, mitomycin C, and melphalan. Patients with Fanconi anemia, besides being at risk of pancytopenia, show a high propensity to develop clonal disorders of hematopoiesis, such as myelodysplastic syndromes and AML. HSCT can rescue aplastic anemia and prevent the occurrence of clonal hematopoietic disorders. In view of their defects in DNA repair mechanisms, which are responsible for the chromosomal fragility, Fanconi anemia patients have an exquisite sensitivity to alkylating agents. Thus, they must be prepared for the allograft with reduced doses of cyclophosphamide. Many patients were once successfully transplanted after receiving low-dose cyclophosphamide and thoracoabdominal irradiation. However, the use of this regimen is associated with an increased incidence of

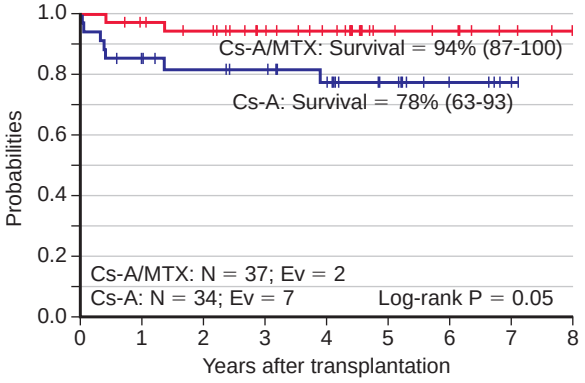

Figure 135-2 Cumulative probability of survival after HLA-identical sibling bone marrow transplantation (BMT) for aplastic anemia, by graft-versus-hostvs disease (GVHD) prophylaxis with cyclosporin alone *(dotted line)* or cyclosporine plus methotrexate *(continuous line)*. GVHD prophylaxis combining cyclosporin and short-term methotrexate is associated with superior outcome compared to cyclosporin alone. *EV*, number of events occurring in each arm of randomization; *N*, number of patients in each arm of randomization. *(From Locatelli F, Bruno B, Zecca M, et al: Cyclosporin A and short-term methotrexate versus cyclosporin A as graft versus host disease prophylaxis I patients with severe aplastic anemia given allogeneic bone marrow transplantation from an HLA-identical sibling: results of a GITMO/EMBT randomized trial.* Blood *96:1690–1697, 2000.)*

Figure 135-3 Kaplan-Meier estimates of survival and thalassemia-free survival and cumulative incidences of rejection and nonrejection mortality for 33 thalassemic patients younger than 17 yr of age. Survival was 93%, with incidence of recurrent thalassemia after transplantation of 8%. *(From Sodani P, Gaziev D, Polchi P, et al: New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years.* Blood *104:1201–1203, 2004.)*

posttransplantation head and neck cancers. Either reduced doses of cyclophosphamide alone or low-dose cyclophosphamide with fludarabine are currently employed for preparing Fanconi anemia patients to the allograft. Using these regimens, the success rate of HSCT from an HLA-identical sibling is on the order of 70-80%. Results of unrelated donor allograft have markedly improved over time and rival with those obtained using an HLA-identical sibling donor.

Allogeneic HSCT remains the only potentially curative approach for severe bone marrow failure associated with dyskeratosis congenita, a rare congenital syndrome characterized also by atrophy and reticular pigmentation of the skin, nail dystrophy, and leukoplakia of mucous membranes. Results of allograft in these patients have been relatively poor, due to occurrence of both early and late complications, reflecting increased sensitivity of endothelial cells to radiotherapy and alkylating agents.

THALASSEMIA

Conventional treatment (i.e., regular blood transfusion and iron-chelation therapy) has dramatically improved both the survival and quality of life of patients with thalassemia, changing a previously fatal disease with early death to a chronic, slowly progressive disease compatible with prolonged survival. However, HSCT remains the only curative treatment for patients with thalassemia. In patients with thalassemia, the risk of dying from transplant-related complications is primarily dependent on patient age, iron overload, and concomitant hepatic viral infections. Adults, especially when affected by chronic active hepatitis, have a poorer outcome than children. Among children, 3 classes of risk have been identified on the basis of 3 parameters, namely regularity of previous iron chelation, liver enlargement, and presence of portal fibrosis. In pediatric patients without liver disease who have received regular iron chelation (class 1 patients), the probability of survival with transfusion independence is >90%, whereas for patients with low compliance with iron chelation and signs of severe liver damage (class 3 patients), the probability of survival is 60% (Fig. 135-3). As in other nonmalignant disorders the most effective pharmacologic combinations (such as that including cyclosporine and methotrexate) should be employed to prevent GVHD. The outcome of patients transplanted from an unrelated donor has been reported to be similar to that of HLA-identical sibling recipients.

SICKLE CELL DISEASE

Disease severity varies greatly among patients with sickle cell disease, with 5-20% of the overall population suffering significant morbidity from vasoocclusive crises and pulmonary, renal, or neurologic damage. Despite the fact that hydroxyurea, an agent favoring the synthesis of fetal hemoglobin, reduces the frequency and severity of vasoocclusive crises and improves the quality of life for patients with sickle cell disease, allogeneic HSCT is the only curative treatment for this disease. Although HSCT can cure homozygous hemoglobin S disease, selecting appropriate candidates for transplantation is difficult. Patients with sickle cell disease may survive for decades, but some patients have a poor quality of life, with repeated hospitalizations for painful vasoocclusive crises and central nervous system infarcts. The main **indications for** performing HSCT in patients with sickle cell disease are history of strokes, magnetic resonance imaging of central nervous system lesions associated with impaired neuropsychologic function, failure to respond to hydroxyurea as shown by recurrent acute chest syndrome, and/or recurrent vasoocclusive crises and/or severe anemia and/or osteonecrosis. The results of HSCT are best when performed in children with an HLA-identical sibling, with a probability of cure of 80-90%. The use of antithymocyte globulin during the preparative regimen improves patient outcome, dramatically reducing the risk of graft failure.

IMMUNODEFICIENCY DISORDERS

HSCT is the **treatment of choice** for children affected by severe combined immunodeficiency, as well as for other inherited immunodeficiencies, including Wiskott-Aldrich Syndrome, leukocyte adhesion deficiency, and chronic granulomatous disease (see also Table 135-1 for details), among others. With an HLA-identical sibling, the probability of survival approaches 100%, with less-favorable results for patients transplanted from an HLA–partially matched relative. Some children with severe combined immunodeficiency, mainly those without residual natural killer activity or maternal T-cell engraftment, may be transplanted without receiving any preparative regimen, the donor lymphoid cells usually being the only elements that engraft. Sustained donor engraftment is more difficult to achieve in children with Omenn syndrome, hemophagocytic lymphohistiocytosis, or leukocyte adhesion deficiency. Life-threatening opportunistic fungal and viral infections occurring before the allograft adversely affect the patient's outcome after HSCT. Patients with the most severe immunodeficiencies must be transplanted as early as possible.

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Chapter 136

Hematopoietic Stem Cell Transplantation from Alternative Sources and Donors

Andrea Velardi and Franco Locatelli

Two-thirds of patients who need allogeneic hematopoietic stem cell transplantation (HSCT) do not have an available human leukocyte antigen (HLA)-identical sibling. Alternative donor/sources of hematopoietic stem cells are being increasingly used and include: matched unrelated donors, unrelated umbilical cord blood (UCB), and HLA-haploidentical relatives. Each of these 3 options has advantages and limitations, but rather than being considered competing alternatives, they should be regarded as complementary strategies to be chosen after a careful evaluation of the relative risks and benefits in the patient's best interest. The choice of the donor will depend on various factors related to urgency of transplantation, patient-, disease-, transplant-related factors and center experience. Physician preference is expected to influence this choice as well.

UNRELATED DONOR TRANSPLANTS

One of the most widely used strategies for children who need an allograft and do not have an available HLA-identical sibling is to identify an unrelated HLA-matched donor in a registry. Today, worldwide international registries include more than 20 million HLA-typed volunteer donors. HLA-A, -B, -C class I loci, and the DRB1 class II locus are the HLA loci most influencing outcome after HSCT from an unrelated volunteer. The roles played by other class II loci (namely, DQB1 and DP1 loci) on patient outcome remain controversial.

Data on serologic typing of HLA classes IA and IB loci are available for all donors, and there is information on DRB1 typing for approximately one-third of donors. Although in the past serologic (low-resolution) typing was used for HLA-A and -B loci, currently, the unrelated donors are selected using high-resolution (allelic) molecular typing of loci HLA-A, -B, -C, and -DRB1. The chance of finding an HLA-matched donor depends on the frequency of the HLA phenotype, which is closely linked to the ethnic origin of the registry donors and ranges from 60-70% for white patients to <10% for persons of other ethnic groups (Hispanic, black, etc).

Identifying a suitable unrelated donor is a complicated and lengthy process, the median time elapsing from the start of search to transplantation being 3-4 mo. During this period, a patient with acute leukemia may relapse and require further therapy, accumulating organ toxicity that unfavorably affects outcome. Moreover, for various different reasons, a relevant proportion of donors (sometimes reaching 10-20%) are either no longer available or refuse donation. Despite these limitations, many thousands of matched unrelated donor transplantations have been performed.

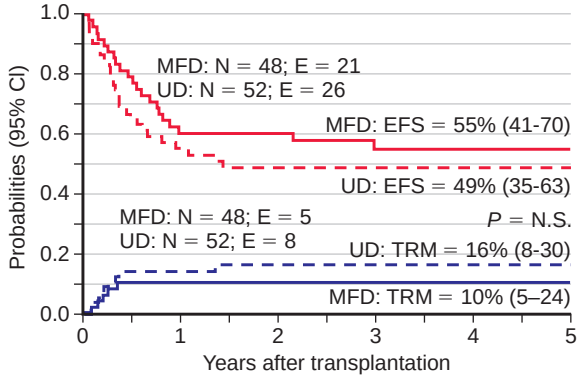
Initially, HLA polymorphism and the intrinsic limitations of conventional (i.e., serologic) HLA-typing techniques unfavorably affected the accuracy of matching, thus increasing rejection rates and the incidence of acute and chronic graft-versus-host disease (GVHD). Consequently, because the event-free survival of recipients of an unrelated donor allograft was worse than that observed when the donor was a compatible sibling transplant, there is no consensus on the use of unrelated donor transplants for nonmalignant diseases, such as thalassemia or primary immune deficiency syndromes other than severe combined immunodeficiency (SCID). DNA-based (i.e., high-resolution molecular) techniques for HLA typing have revealed an impressive number of new alleles within antigens that were previously defined by serology only. Matching by high-resolution DNA typing reduces the risk of immune complications, namely graft rejection and GVHD, but also the chance of finding a suitable donor. Nevertheless, the advent of both high-resolution molecular HLA classes I and II loci-typing coupled with progress in the prophylaxis and treatment of GVHD has resulted in a reduction of transplantation-related mortality and improvement of outcome. Indeed, outcomes from a fully matched unrelated volunteer donor are now similar to those of HSCT from an HLA-identical sibling, as indicated by results of unrelated donor transplantation in children with acute lymphoblastic leukemia in second complete remission, juvenile myelomonocytic leukemia, or thalassemia (Fig. 136-1).

Although a single locus disparity in patients with leukemia does not markedly affect the probability of event-free survival as the increased risk of toxic death may be compensated for by a reduction in the relapse rate, in patients with nonmalignant disorders optimal results are obtained only when a donor matched at the allelic level with the recipient is selected. In general, a single HLA disparity in the donor–recipient pair, irrespective of whether antigenic or allelic in nature, predicts a greater risk of nonleukemia mortality; multiple allelic disparities at different HLA loci have an additive detrimental effect and are associated with an even worse outcome. To reduce the risk of acute GVHD, **ex vivo T-cell depletion of the graft** has been employed, but has not significantly affected patient outcome, which is similar to that of patients given an unmanipulated graft and pharmacologic prophylaxis for GVHD.

The analyses on the outcome of unrelated donor HSCT include only patients who are transplanted; these numbers do not take into account patients for whom a donor is not found. For patients who urgently need a transplant, the time required to identify a suitable donor from a potential panel, establish eligibility, and harvest the cells may lead to relapse and failure to transplant. For patients who do not have a matched donor or who urgently need a transplant, attention has focused on unrelated cord blood and HLA-haploidentical, mismatched family donors.

UMBILICAL CORD BLOOD TRANSPLANTS

UCB transplantation (UCBT) is a viable option for children who need allogeneic HSCT. To date, several hundred children have been cured



No. of cases at risk:

MFD	48	28	25	19	14	9
UD	52	26	20	16	9	4

Figure 136-1 Kaplan-Meier estimates of event-free survival *(EFS) (upper lines)* and transplantation-related mortality *(TRM) (lower lines)* according to the type of donor used, matched family donor *(MFD)* or unrelated donor *(UD)*. Matched family donor was superior (55% EFS and 10% TRM) compared to unrelated donor (49% EFS and 16% TRM). *(From Locatelli F, Nöllke P, Zecca M, et al: Hematopoietic stem cell transplantation [HSCT] in children with juvenile myelomonocytic leukemia [JMML]: results of the EWOG-MDS/EBMT trial.* Blood *105:410–419, 2005.)*

through transplantation of either related or unrelated UCB units. UCBT offers the advantages of absence of risks to donors, reduced risk of transmitting infections, and, for transplants from unrelated donors, immediate availability of cryopreserved cells, the median time elapsing from start of search to transplantation being only 3-4 wk. In comparison to bone marrow transplantation (BMT), the advantages of UCBT are also represented by lower incidence and severity of GVHD, easier procurement and prompter availability of cord blood cells, and the possibility of using donors showing HLA disparities with the recipient. Despite these advantages, the large experience gained over the last 2 decades has clearly demonstrated that UCBT patients may be exposed to an increased risk of early fatal complications, mainly because of a lower engraftment rate of donor hematopoiesis, delayed kinetics of neutrophil recovery, and lack of adoptive transfer of pathogen-specific memory T-cells. In fact, transfer of donor-derived, memory T cells significantly contributes to early immunologic reconstitution of children after unmanipulated allogeneic bone marrow or peripheral blood stem cell transplantation.

Concerning the issues of engraftment and hematopoietic recovery, it has been unquestionably shown that an inverse correlation between the number of nucleated cord blood cells infused per kilogram recipient body weight and the risk of dying for transplantation-related causes exists. In particular, engraftment is a major concern when the nucleated cells are $<2.5 \times 10^7$/kg of recipient body weight. As a cord blood unit usually contains between 1×10^9 and 1.8×10^9 cells, it is not surprising that UCB transplantation has been less frequently employed for adolescents or adults with body weight >40 kg. Indeed, it can be estimated that only 30% of the UCB units available in the bank inventory could suffice for a 75 kg patient according to the recommended threshold cell dose (namely more than 2.5×10^7 total nucleated cells/kg recipient body weight before thawing the unit). In view of these findings, it is not surprising that efforts have been focused on approaches capable of increasing the number of UCB cells to be transplanted. Selection of the richest cord blood units, infusion of 2 units in the same recipient (i.e., double UCBT), and transplantation of ex vivo expanded progenitors have contributed to improve the results of UCBT, opening new scenarios for a wider application of the procedure. In particular, double UCBT is largely employed as it was demonstrated to be effective in adults, significantly increasing the engraftment rate, as compared to single-unit UCBT. In the majority of double UCBT, the 2 UCB units are partially HLA-matched with the recipient, as well as with each other, and sustained hematopoiesis after double UCBT is usually derived from a single donor. This technique is of interest to pediatricians for extending the applicability of UCBT also to adolescents or to patients with a body weight exceeding 40-50 kg.

Direct intrabone transplantation of UCB cells is also a feasible and safe approach, able to overcome the problem of graft failure, even when low numbers of HLA-mismatched cord-blood cells are transplanted, and to guarantee prompt platelet recovery.

Despite the low incidence of acute and chronic GVHD observed after UCB transplantation, the risk of recurrence of leukemia is not increased. The long-term results of UCB transplants are similar to those after transplantation from other sources of hematopoietic stem cells. In particular, several published reports have compared the outcome of UCBT and BMT from unrelated donors in children with hematologic malignancies. Recipients of UCBT were transplanted from donors with greater HLA-disparities, received 1-log fewer nucleated cells, had delayed neutrophil and platelet recovery, and showed reduced incidence of GVHD as compared to children given BMT. Nevertheless, both the relapse rate and the overall survival probability did not differ in unrelated UCBT or BMT pediatric recipients. The outcome of patients receiving a fully matched UCB unit is reported to be even better than that of patients who receive a transplant from an HLA-identical, unrelated volunteer. Thus, today, there is no doubt that, in the absence of an HLA-identical family donor, unrelated UCBT can be considered a suitable option for children with malignant and nonmalignant disorders. Results of UCBT have been of particular interest in children with Hurler syndrome or Krabbe disease transplanted with cord blood cells from an unrelated donor, as well as in children with hemoglobinopathies given a related UCB transplantation. It has to be emphasized that the lower risk of GVHD associated with UCBT is of particular importance in patients affected by nonmalignant disorders.

Approximately 5% of patients receiving UCB transplantation develop an autoimmune disorder. These disorders include autoimmune hemolytic anemia, autoimmune thrombocytopenia, Evans syndrome, and immune neutropenia. Less frequently, patients have developed Graves disease, glomerulonephritis, rheumatoid arthritis, or thyroiditis. Treatment for these post-UCB transplant-related autoimmune diseases has included steroids, rituximab, and cyclosporine, with only varying degrees of success.

HAPLOIDENTICAL TRANSPLANTS

HSCT from an HLA-haploidentical (haplo-HSCT) donor offers an immediate source of hematopoietic stem cells to almost all leukemia patients who fail to find a matched donor, whether related or unrelated, or a suitable cord blood unit. Indeed, almost all children have at least 1 haploidentical–3 loci mismatched family member who is promptly available as donor. Moreover, the few patients who reject the haploidentical transplant have the advantage of another immediately available donor within the family.

Efficient T-cell depletion of the graft has been demonstrated to prevent acute and chronic GVHD even when using haploidentical parental bone marrow differing at the 3 major HLA loci. The benefits of T-cell depletion were first demonstrated in transplantation of children with SCID. More than 300 transplants in SCID patients using haploidentical donors have been performed worldwide, with a high rate of long-term partial or complete immune reconstitution.

As patients with acute leukemia have a high chance of rejecting a haploidentical bone marrow graft, a "megadose" of granulocyte colony-stimulating factor–mobilized peripheral blood stem cells has been demonstrated to be crucial for overcoming the barrier of HLA incompatibility in the donor–recipient pair and for eluding residual antidonor cytotoxic T-lymphocyte precursor activity in the recipient. Indeed, in leukemia patients, the combination of high-intensity immune-suppressive/myeloablative conditioning regimens with the infusion of great numbers of highly purified, peripheral blood CD34+ cells has been demonstrated capable to (1) guarantee the successful and sustained engraftment of donor haematopoiesis across the HLA barrier, and (2) guarantee a very low incidence of grades II-IV acute GVHD without the need for any posttransplantation immune suppression as prophylaxis. The physical elimination of mature T cells from the graft, necessary for preventing GVHD occurrence in a context of great immune genetic disparity, leads to the consequence that recipients cannot benefit from the adoptive transfer of donor memory T lymphocytes that, through their peripheral expansion, are the main factor responsible for protection from infections in the 1st few mo after transplantation. A state of profound immune deficiency lasts for at least 4-6 mo after transplantation in haplo-HSCT recipients. Sophisticated strategies of adoptive infusions of T-cell lines or clones specific for the most common and life-threatening pathogens (namely Epstein-Barr virus, human cytomegalovirus, *Aspergillus*, and adenovirus) have been envisaged and successfully tested in a few pilot trials to protect the recipients in the early posttransplantation period. Selective approaches of graft manipulation have also been developed. In particular, promising results have been obtained through a negative depletion of T lymphocytes carrying the α/β chains of the T-cell receptor. B-lymphocytes are also depleted to prevent the occurrence of Epstein-Barr virus–related lymphoproliferative disease. Through this approach the patient can benefit from the adoptive transfer of committed hematopoietic progenitors, mature natural killer (NK) cells and γ/δ+ T cells, which can confer a protection against life-threatening infections.

The outcomes of haplo-HSCT have been more extensively reported in adults than in children. The reported probability of survival at 3-4 yr after a haplo-HSCT in children with acute leukemia ranged from 18-48%. Survival was influenced by many factors, the most important being the state of remission at time of transplantation, with poorer outcomes in children with myeloid leukemias than in those with lymphoid leukemia. It has been reported that in haplotype mismatched

parent-to-child HSCT, patients with acute leukemia grafted from the mother had reduced relapse rates as compared with recipients of paternal grafts, translating into better event-free survival.

For many years the absence of the T-cell mediated graft-versus-leukemia (GVL) effect has been considered rendering the recipients of a T-cell depleted allograft more susceptible to leukemia relapse. However, it has been demonstrated that a GVL effect displayed by donor NK cells can compensate for this lack of T-specific alloreactivity when an HLA-disparate NK alloreactive relative is employed as a donor.

DONOR VERSUS RECIPIENT NATURAL KILLER–CELL ALLOREACTIVITY

Donor vs recipient NK-cell alloreactivity is a biologic phenomenon that is unique to the mismatched transplant. It derives from a mismatch between donor NK clones, carrying specific inhibitory receptors for self–major histocompatibility complex (MHC) class I molecules, and MHC class I ligands on recipient cells. NK cells are primed to kill by several activating receptors, which play an important role in the NK cell-mediated GVL effect. Human NK cells discriminate allelic forms of MHC molecules via **killer cell immunoglobulin-like receptors (KIRs),** which are clonally distributed with each cell in the repertoire bearing at least 1 receptor that is specific for self-MHC class I molecules. Because NK cells coexpress inhibitory receptors for self-MHC class I molecules, autologous cells are not killed. When faced with mismatched allogeneic targets, NK cells sense the missing expression of self–class I alleles and mediate alloreactions. In mismatched transplants, there are many donor recipient pairs in which the donor NK inhibitory cells do not recognize the recipient's class I alleles as self. Consequently, the donor NK cells are not blocked and are activated to lyse the recipient's lymphohematopoietic cells.

Haplo-HSCT trials demonstrate that MHC class I mismatches, which generate an alloreactive NK cell response in the graft-versus-host direction, eradicate leukemia cells, improve engraftment, and protect from T-cell–mediated GVHD. Lack of an NK-alloreactive donor is the strongest independent risk factor for leukemia relapse after adjustment for disease status at transplantation. The potential for donor vs recipient NK cell alloreactivity, which can be predicted by standard HLA typing, is recommended when selecting the donor of choice from among the mismatched family members.

The chance of finding a "perfect mismatch" NK-alloreactive donors in the family is on the order of 50%. From a practical point of view, first, the transplantation candidate is HLA typed. Candidates expressing class I alleles belonging to the 3 class I groups recognized by KIRs (HLA-C group 1, HLA-C group 2, and HLA-Bw4 alleles) will block all NK cells from every donor and belong to the one-third of the population that is resistant to alloreactive NK killing. Patients who express only 1 or 2 of these allele groups may find NK-alloreactive donors.

Donor HLA typing identifies family members who do not express the class I group(s) expressed by the patient and, therefore, have the potential for NK alloreactivity. Not all inhibitory KIRs are present in 100% of the population. KIR2DL2/3, the receptor for HLA-C group 1, is present in all persons; KIR2DL1, the receptor for HLA-C group 2, is present in 97% of persons; and KIR3DL1, the receptor for HLA-Bw4 alleles, is present in ≈90%. Donor KIR genotyping ensures that the donor expresses the relevant NK cells.

In HLA-Bw4 mismatches, even when the KIR3DL1 gene is present, NK repertoire studies show alloreactive NK cells in approximately two-thirds of individuals. This may be because they occur in highly variable frequencies or because allelic KIR3DL1 variants may not allow receptor expression at the cell membrane. Therefore, for HLA-Bw4 mismatches, direct assessment of the donor NK repertoire is necessary.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Autologous transplantation, using the patient's own stored marrow, is associated with a low risk of life-threatening transplant-related complications, although the main cause of failure is disease recurrence resulting from a lack of the immune-mediated GVL effect. Bone marrow was once the only source of stem cells employed in patients given an autograft; in the past few years, the vast majority of patients treated with autologous HSCT receive hematopoietic progenitors mobilized in peripheral blood by either cytokines alone (mainly granulocyte colony-stimulating factor) or by cytokines plus cytotoxic agents. A CXCR4 antagonist (plerixafor) can be extremely effective in mobilizing hematopoietic progenitors in the periphery. When compared to bone marrow, the use of peripheral blood progenitors is associated with a faster hematopoietic recovery and a comparable outcome. A major concern in patients with malignancies given autologous HSCT is represented by the risk of reinfusing malignant cells with the graft; tumor progenitors contained in the graft can contribute to recurrence of the original malignant disease. This observation has provided the rational for **tumor purging** using elaborated strategies aimed at reducing or eliminating tumor contamination of the graft.

Table 136-1 Indications to Autologous Hematopoietic Stem Cell Transplantation for Pediatric Diseases

- Acute lymphoblastic leukemia after an isolated extramedullary relapse
- Relapsed Hodgkin or non-Hodgkin lymphoma
- Stage IV or relapsed neuroblastoma
- High-risk, relapsed, or resistant brain tumors
- Stage IV Ewing sarcoma
- Life-threatening autoimmune diseases resistant to conventional treatments

Autologous HSCT is employed primarily to prevent relapse in patients with acute myelogenous leukemia (AML) who achieve complete remission after induction therapy, and also for selected children with relapsed lymphomas and selected solid tumors (Table 136-1).

Randomized studies have not shown an advantage in terms of event-free survival for patients with AML in the 1st complete remission given an autologous HSCT as compared to those treated with chemotherapy alone. The probability of event-free survival for children with AML in the 1st complete remission given autologous HSCT is reported to range from 40-60%. Ex vivo purging of bone marrow cells with mafosfamide has been shown to reduce the risk of disease recurrence in children with AML in the 1st complete remission given an autologous transplantation.

Patients with sensitive lymphomas and little tumor burden have favorable outcomes after autologous HSCT, with disease-free survival rates of 50-60%, whereas high-risk patients with bulky tumor or poorly responsive disease have a dismal outcome, with survival rates of 10-20%.

Some studies suggest that, as compared to conventional chemotherapy and radiotherapy, autologous HSCT may offer an advantage in terms of event-free survival to children with acute lymphoblastic leukemia in the second complete remission after an isolated extramedullary relapse (i.e., central nervous system, testicular relapse).

Autologous HSCT in patients with high-risk neuroblastoma is associated with a better outcome compared to conventional chemotherapy. In these patients, posttransplantation infusion of a monoclonal antibody directed against a molecule (GD2) expressed on the surface of neuroblastoma cells confers a protection against the risk of tumor recurrence.

For children with brain tumors at high risk of relapse, or resistant to conventional chemotherapy and irradiation, the dose-limiting toxicity for intensifying therapy is myelosuppression, thus providing a role for stem cell rescue. Several studies provide encouraging results for patients with different histologic types of brain tumors treated with autologous HSCT.

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Chapter 137

Graft-Versus-Host Disease, Rejection, and Venoocclusive Disease

Andrea Velardi and Franco Locatelli

The major cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (HSCT) is graft-versus-host disease (GVHD), which is caused by engraftment of immunocompetent donor T lymphocytes in an immunologically compromised host which show histocompatibility differences with the donor. These differences between the donor and the host may result in donor T-cell activation against either recipient major histocompatibility complex antigens or minor histocompatibility antigens. GVHD is usually subdivided in 2 forms: acute GVHD, which occurs within 3 mo after transplantation, and chronic GVHD, which, although related, is a different disease, occurring later and displaying some clinical and pathologic features that resemble those observed in selected autoimmune disorders (systemic sclerosis, Sjögren syndrome, etc.).

ACUTE GRAFT-VERSUS-HOST DISEASE

Acute GVHD is caused by the alloreactive, donor-derived T cells contained in the graft, which attack nonshared recipient's antigens on target tissues. A three-step process generates the clinical syndrome. First, conditioning-induced tissue damage activates recipient antigen-presenting cells, which present recipient alloantigens to the donor T cells transferred with the graft and secrete cytokines, such as interleukin 12, favoring the polarization of T-cell response in the type 1 direction. Second, in response to recipient antigens, donor T cells become activated, proliferate, expand, and generate cytokines such as tumor necrosis factor-α, interleukin (IL)-2, and interferon-γ. In the third step of the process, these cytokines cause tissue damage and promote differentiation of cytotoxic CD8+ T cells, which, together with macrophages, in turn, kill recipient cells and further disrupt tissues.

Acute GVHD usually develops from 2-8 wk posttransplantation. The primary **manifestations** are an erythematous maculopapular rash, persistent anorexia, vomiting and/or diarrhea, and liver disease with increased serum levels of bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (Table 137-1). Diagnosis may benefit from skin, liver, or gastrointestinal biopsy for confirmation. Endothelial damage and lymphocytic infiltrates are seen in all affected organs. The epidermis and hair follicles of the skin are damaged, the hepatic small bile ducts show segmental disruption, and there is destruction of the crypts and mucosal ulceration of the gastrointestinal tract. Grade I acute GVHD (skin rash alone) has a favorable prognosis and often does not require treatment (Fig. 137-1). Grade II GVHD is a moderately severe multiorgan disease requiring immunosuppressive therapy. Grade III GVHD is a severe multiorgan disease, and grade IV GVHD is a life-threatening, often fatal condition. The standard **pharmacologic prophylaxis** of GVHD after an unmanipulated allograft relies mainly on posttransplant administration of immunosuppressive drugs, such as cyclosporine or tacrolimus or combinations of either with methotrexate or prednisone, anti–T-cell antibodies, mycophenolate mofetil, and other immunosuppressive agents. Infusion of cyclophosphamide on days +3 and +5 after transplantation has been proposed as a strategy to delete alloreactive donor T lymphocytes that become activated, and thus cycling, after exposure to recipient antigens. Pretransplantation infusion of either antithymocyte globulin or monoclonal antibodies such as alemtuzumab is largely used to modulate alloreactivity of donor T cells, in particular in patients given the allograft from either an unrelated donor or a partially matched relative. An alternative approach, which has been widely used in clinical practice, is the removal of T lymphocytes from the graft (T-cell depletion). Any form of GVHD prophylaxis in itself may impair posttransplantation immunologic reconstitution, increasing the risk of infection-related deaths. T-cell depletion of the graft is also associated with an increased risk of leukemia recurrence in patients transplanted from an human leukocyte antigen (HLA)-identical sibling or an unrelated volunteer.

Despite prophylaxis, significant acute GVHD develops in ≈30% of recipients of HSCT from matched siblings and in as many as 60% of HSCT recipients from unrelated donors. The risk of acute GVHD is increased by factors such as diagnosis of malignant disease, older donor and recipient ages, and, in patients given an unmanipulated allograft, GVHD prophylaxis including only 1 drug. However, the most important risk factor for acute GVHD is the present of disparities for HLA-molecules in the donor–recipient pair. Acute GVHD is usually initially treated with glucocorticoids; approximately 40-50% of patients show a complete response to steroids. The risk of transplantation-related mortality is much higher in patients who do not respond to

Table 137-1 Clinical Staging and Grading of Graft-Versus-Host Disease

STAGE	SKIN	LIVER	INTESTINAL TRACT
+	Maculopapular rash <25% of body surface	Bilirubin 2-3 mg/dL	>500 mL diarrhea/day
++	Maculopapular rash 25%–50% of body surface	Bilirubin 3-6 mg/dL	>1,000 mL diarrhea/day
+++	Generalized erythroderma	Bilirubin 6-15 mg/dL	>1,500 mL diarrhea/day
++++	Generalized erythroderma with bullous formation and desquamation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus

GVHD GRADE	SKIN STAGE	LIVER STAGE	INTESTINAL TRACT STAGE	DECREASE IN CLINICAL PERFORMANCE
I	+ to ++	0	0	None
II	+ to +++	+	+	Mild
III	++ to +++	++ to ++++	++ to +++	Marked
IV	++ to ++++	++ to ++++	++ to ++++	Extreme

Adapted from Thomas ED, Storb R, Clift RA, et al: Bone marrow transplantation [in 2 parts]. N Engl J Med *292:832–843, 895–902, 1975.*

Figure 137-1 Acute graft-versus-host disease of the skin with ear, arm, shoulder, and trunk involvement. See also color plates. *(Courtesy of Evan Farmer, MD.)*

steroids than in those showing a complete response. Mofetil mycophenolate, extracorporeal photopheresis, pentostatin, or monoclonal antibodies targeting either molecules expressed on T cells or cytokines released during the inflammatory cascade, which underlies the physiopathology of GVHD, have been used in patients with steroid-resistant acute GVHD. There are no clear data showing the superiority of one of these approaches over the others. Promising results in children with steroid-resistant acute GVHD have been obtained using mesenchymal stromal cells, which are able to blunt the inflammatory response associated with acute GVHD.

CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic GVHD develops or persists >3 mo posttransplantation and is the most frequent late complication of allogeneic HSCT with an incidence of ≈25% in pediatric patients. Chronic GVHD is the major cause of nonrelapse mortality and morbidity in long-term HSCT survivors. Acute GVHD is recognized as the most important factor predicting the development of the chronic form of the disease. The use of matched unrelated volunteers as donors, and of peripheral blood as the stem cell source, has increased the incidence and severity of chronic GVHD. Other factors that predict occurrence of chronic GVHD include older donor and recipient ages, female donor for male recipient, diagnosis of malignancy, and use of total-body irradiation as part of the preparative regimen.

Chronic GVHD is a disorder of immune regulation characterized by autoantibody production, increased collagen deposition and fibrosis, and clinical symptoms similar to those seen in patients with autoimmune diseases. The predominant cytokines involved in the pathophysiology of chronic GVHD are usually type II cytokines such as IL-4, IL-5, and IL-13. IL-4 and IL-5 contribute to eosinophilia, B-cell hyperactivity with elevated immunoglobulin (Ig) M, IgG, and IgE titers. Associated monoclonal gammopathies indicate clonal dysregulation. Chronic GVHD is dependent on the development and persistence of donor T cells that are not tolerant to the recipient. Maturation of transplanted stem cells within a damaged thymus could lead to errors in negative selection and production of cells that have not been tolerized to recipient antigens and are, therefore, autoreactive or, more accurately, **recipient reactive.** This ongoing immune reactivity results in clinical features resembling a systemic autoimmune disease with lichenoid and sclerodermatous skin lesions, malar rash, sicca syndrome, arthritis, joint contractures, obliterative bronchiolitis, and bile duct degeneration with cholestasis.

Patients with chronic GVHD involving only the skin and liver have a favorable course (Fig. 137-2). Extensive multiorgan disease may be associated with a very poor quality of life, recurrent infections associated with prolonged immunosuppressive regimens to control GVHD, and a high mortality rate. Morbidity and mortality are highest in patients with a **progressive onset** of chronic GVHD that directly

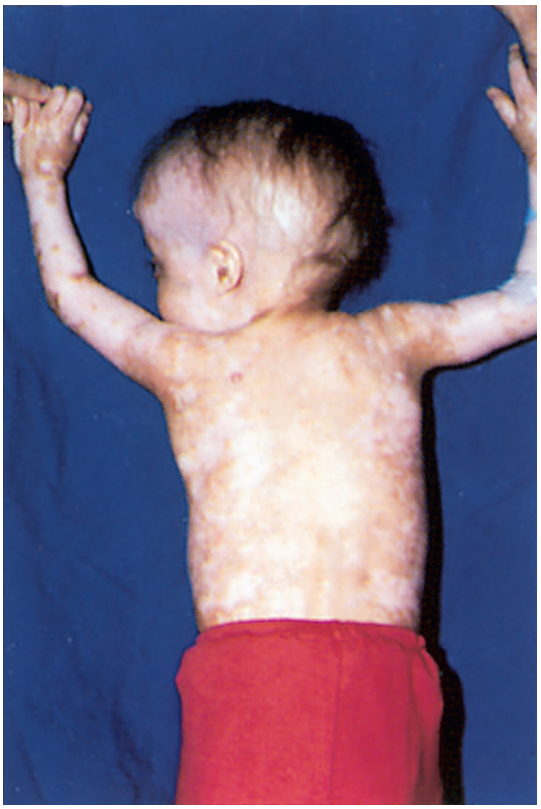

Figure 137-2 Chronic graft-versus-host disease of the skin with sclerodermoid changes. *(Courtesy of Evan Farmer, MD.)*

follows acute GVHD, intermediate in those with a **quiescent onset** after resolution of acute GVHD, and lowest in patients with **de novo onset** in the absence of acute GVHD. Single-agent prednisone is standard treatment at present, although other agents, including extracorporeal photopheresis, mofetil mycophenolate, anti-CD20 monoclonal antibody, and pentostatin, have been employed with variable success. Treatment with imatinib mesylate, which inhibits the synthesis of collagen, has been shown to be effective in patients with chronic GVHD and sclerotic features. As a consequence of prolonged immunosuppression, patients with chronic GVHD are particularly susceptible to infections and should receive appropriate antibiotic prophylaxis, including trimethoprim-sulfamethoxazole. Chronic GVHD resolves in most pediatric patients but may require 1-3 yr of immunosuppressive therapy before the drugs can be withdrawn without the disease recurring. Chronic GVHD promotes also the development of secondary neoplasms, in particular in patients with Fanconi anemia.

Graft failure is a serious complication exposing patients to a high risk of fatal infection. **Primary graft failure** is defined as failure to achieve a neutrophil count of 0.2×10^9/L by 21 days posttransplantation. **Secondary graft failure** is loss of peripheral blood counts following initial transient engraftment of donor cells. Causes of graft failure after autologous and allogeneic transplantation include transplantation of an inadequate stem cell dose (more frequently observed in children given cord blood transplantation), and viral infections such as with cytomegalovirus or human herpesvirus type 6, which are often associated with activation of recipient macrophages. Graft failure after allogeneic transplantation, however, is mainly caused by immunologically mediated rejection of the graft by residual recipient-type T cells that survive the conditioning regimen. **Diagnosis** of graft failure resulting from immunologic mechanisms is based on examination of peripheral blood and marrow aspirate and biopsy, along with molecular analysis of chimerism status. Persistence of lymphocytes of host origin in allogeneic transplant recipients with graft failure indicates immunologic

rejection. The risk of immune-mediated graft rejection is higher in patients given HLA-disparate, T-cell–depleted grafts, reduced-intensity conditioning regimens, and transplantation of low numbers of stem cells, and in recipients who are sensitized toward HLA antigens or, less frequently, minor histocompatibility antigens. Allosensitization develops as a consequence of preceding blood product transfusions and is observed particularly in recipients with aplastic anemia, sickle cell disease, and thalassemia. In HSCT for nonmalignant diseases, such as mucopolysaccharidoses, graft failure is also facilitated by the absence of previous treatment with cytotoxic and immunosuppressive drugs. In thalassemia, graft failure is promoted by expansion of recipient hematopoietic cells. GVHD prophylaxis with methotrexate, an antimetabolite, and antiinfective prophylaxis with trimethoprim-sulfamethoxazole or ganciclovir may also delay engraftment.

Treatment of graft failure usually requires removing all potentially myelotoxic agents from the treatment regimen and attempting a short trial of hematopoietic growth factors, such as granulocyte colony-stimulating factor. A second transplant, usually preceded by a highly immune-suppressive regimen, is frequently employed to rescue patients experiencing graft failure. High-intensity regimens are generally tolerated poorly if administered within 100 days from a 1st transplant because of cumulative toxicities.

VENOOCCLUSIVE DISEASE

Hepatic venoocclusive disease, also known as sinusoidal obstruction syndrome, presents with hepatomegaly, right upper quadrant tenderness, jaundice, and weight gain from fluid retention and ascites. Onset is usually within 30 days of transplantation, with an incidence of approximately 15%, depending on the intensity of the conditioning protocol. Risk factors include young age, prior hepatic disease (fibrosis, cirrhosis), abdominal radiation, repeated transplantations, neuroblastoma, osteopetrosis and familial hemophagocytic lymphohistiocytosis. The severe form of venoocclusive disease has a high mortality rate; treatment results for severe disease are poor.

Prophylaxis has traditionally used heparin and ursodeoxycholic acid; however, only defibrotide has demonstrated some efficacy in preventing venoocclusive disease. Defibrotide is a combination of porcine oligodeoxyribonucleotides that reduces procoagulant activity and enhances fibrinolytic properties of endothelial cells.

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Chapter 138

Infectious Complications of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Hematopoietic stem cell transplantation (HSCT) recipients experience a transient but profound state of immune deficiency. Immediately after transplantation, because neutrophils are absent or markedly reduced, patients are particularly susceptible to bacterial and fungal infections. Consequently, most centers start prophylactic antibiotic or antifungal treatment during the conditioning regimen. Despite these prophylactic measures, most patients will develop fever and signs of infection in the early posttransplantation period. The common pathogens include enteric bacteria and fungi such as *Candida* and *Aspergillus.* An indwelling central venous line, routinely employed in all children given HSCT, is a significant risk factor for bacterial and fungal infections, staphylococcal species and *Candida* being the most frequent pathogens in catheter-related infections (see Chapter 178). Emergence of multidrug resistant strains of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* has become a serious problem, being associated with a high case : fatality ratio.

HSCT recipients remain at increased risk of developing severe infections even after the neutrophil count has normalized, because T-cell number and function remain below normal for months after transplantation. Unrelated donor transplant recipients are at increased risk of developing graft-versus-host disease (GVHD), which is itself an additional risk factor for fungal and viral opportunistic infections, as are the associated immunosuppressive treatments. After cord blood transplantation, infections are the consequence of both the slow neutrophil engraftment and donor T-cell naïveté. In haploidentical transplantation, the increased risk of infection observed in the 1st 4-6 mo after the allograft is the consequence of T-cell depletion of the graft. Indeed, patients given this type of transplantation, as well as those receiving cord blood transplantation, cannot benefit from the adoptive transfer of donor-derived, antigen-experienced T cells.

Among HSCT recipients, invasive aspergillosis, cytomegalovirus (CMV) infection, disseminated adenovirus infections, and Epstein-Barr virus (EBV)–related lymphoproliferative disorders represent peculiar, life-threatening complications that significantly affect patient's outcome.

Invasive **aspergillosis** remains a significant cause of infectious morbidity and mortality in HSCT recipients. Despite prompt and aggressive administration of potent antifungal agents, proven cases of aspergillosis remain difficult to treat, with case-fatality rates of 80-90%. The annual incidence of invasive aspergillosis has risen with use of stem cells from alternative sources. The incidence is 7.3% in recipients of an human leukocyte antigen (HLA)-matched related donor transplant and 10.5% in patients given the allograft from either an HLA-mismatched family donor or an unrelated donor volunteer. Most cases of aspergillosis are diagnosed from 40-180 days after HSCT, with 30% diagnosed <40 days before and 17% more than 6 mo after transplantation. The risk of developing aspergillosis is mainly influenced by the duration of neutropenia, GVHD occurrence, use of corticosteroid therapy, posttransplant CMV infection, viral respiratory tract infections, advanced disease status, older age, and T-cell depletion of the graft. Patients with a previous history of invasive aspergillosis are at particular risk.

Aspergillus infection often originates from the upper airway mucosa. Early lesions in the nose should be sought in patients with neutropenia who have fever and minimal epistaxis. Rapid extension into the adjacent paranasal sinuses, orbit, or face is usual, with or without the appearance of lung lesions. In the lung, invasive aspergillosis generally presents as an acute, rapidly progressive, densely consolidated pulmonary infiltrate. Infection progresses by direct extension across tissue and by hematogenous dissemination to brain and other organs. The earliest CT finding is one or more small pulmonary nodules. As a nodule enlarges, the dense central core of infarcted tissue becomes surrounded by edema or hemorrhage, forming a hazy rim, the **halo sign.** This rim disappears in a few days as the dense core enlarges. In neutropenic patients, when bone marrow function recovers, the infarcted central core cavitates, creating the **crescent sign.** Repeated positivity for serum galactomannan represents a useful biomarker for confirming/suspecting a diagnosis of invasive aspergillosis. Antifungal prophylaxis includes isolation of the patient in a laminar air flow or positive pressure room. Liposomal amphotericin B, azole compounds (itraconazole, voriconazole, posaconazole) and echinocandins (caspofungin, micafungin, anidulafungin) are useful for both preventing and treating the fungal infection. Voriconazole represents the treatment of choice for patients with invasive pulmonary and brain aspergillosis. However, often, aspergillosis does not respond satisfactorily to antifungal agents alone, and patients remain at risk until T-cell counts and function recover. This observation provides the rationale

for developing strategies to accelerate the recovery of pathogen-specific immune responses.

CMV infection remains the most common and potentially severe viral complication in patients given allogeneic HSCT. Seropositivity for CMV is an independent risk factor for mortality, even in recipients of matched sibling or unrelated donor transplants. CMV is itself immunosuppressive, as it impairs dendritic cell and T-lymphocyte function. Moreover, ganciclovir, the most frequently used anti-CMV agent, may cause leukopenia and T-cell immune suppression.

The period of maximal risk for CMV infection is 1-4 mo after transplantation. Until CMV-specific T-cell responses develop months after transplant, CMV infection may result in a variety of syndromes including fever, leukopenia, thrombocytopenia, hepatitis, pneumonitis, retinitis, esophagitis, gastritis, and colitis. CMV pneumonia, the most life-threatening complication related to viral infection, has been reported to occur in up to 15-20% of bone marrow transplant recipients, with a case fatality rate of 85%. The risk is greatest between 5 and 13 wk after transplantation. Risk factors include T-cell depletion of the graft, donor seronegative status together with recipient seropositive status, acute GVHD, and patient older age.

Tachypnea, hypoxia, and unproductive cough signals respiratory involvement. Chest x-ray often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly. The differential diagnosis includes infection with *Pneumocystis jiroveci* or other viral, bacterial, or fungal pathogens, pulmonary hemorrhage, and injury secondary to irradiation or to treatment with cytotoxic drugs. Gastrointestinal CMV involvement may lead to ulcers of the esophagus, stomach, small intestine, and colon that may result in bleeding or perforation.

Fatal CMV infections are often associated with persistent viremia and multiorgan involvement. In the 1980s, antiviral treatment was deferred until overt clinical symptoms of CMV infection developed, which led to a high incidence of fatal events. CMV disease has largely been **prevented** through prophylaxis and a preemptive approach. Prophylaxis is based on administration of antiviral drugs to all transplanted patients for a median duration of 3 mo after transplantation. The major drawbacks of this approach refer to drug toxicity, occurrence of late CMV disease, mainly pneumonia, after withdrawal of prophylaxis, treatment of patients who do not need antiviral therapy as they would not have reactivated CMV infection, and low cost-effectiveness. Preemptive, or presymptomatic, therapy aims at treating only patients who experience CMV reactivation and, thus, are at risk of developing overt disease; it starts only upon detection of CMV in blood by any assay. The most widely used assay is CMV detection of CMV DNA in blood, which have been used to decide inception of treatment when it either becomes positive or reaches a predetermined threshold. Although in the past treatment usually started after this assay became positive, nowadays therapy is usually initiated when a certain viral load is reached. Moreover, quantification of CMV DNA in blood provides a reliable approach for deciding interruption of treatment. The major drawback of this strategy is the need of serial monitoring that is required for the period in which patients are at risk of developing CMV disease. In this regard, approaches to reliably prove the restoration of virus-specific immunity have been developed. Generally, ganciclovir, or less frequently foscarnet, is usually used for prophylaxis and preemptive treatment of CMV infection. Treatment is usually discontinued when repeated negative controls have been obtained.

Disseminated adenovirus infection is a life-threatening complication of HSCT recipients. Clinical manifestations include fever, hepatitis, enteritis, meningoencephalitis, and pneumonia. Young children are at particular risk of developing this complication. Diagnosis is based on the demonstration of high levels of adenovirus DNA in blood or on recovery of virus in tissue biopsies. Pharmacologic treatment of adenovirus infections is based on the use of cidofovir, which has significant renal toxicity and sometimes is unable to control viral replication. Recovery of immune system function is associated with a greater chance to survive adenovirus disseminated infection.

EBV-related **lymphoproliferative** disease (EBV-LPD) is a major complication in HSCT and solid-organ transplantation. In patients given HSCT, selective procedures of T-cell-depletion–sparing B lymphocytes, as well as the use of HLA partially matched family and unrelated donors, are risk factors for the development of EBV-LPD. These disorders usually present in the 1st 4-6 mo after transplantation as high-grade diffuse large-cell B-cell lymphomas, which are oligoclonal or monoclonal, express the full array of EBV antigens, and are of donor origin. High levels of EBV-DNA in blood and in vitro spontaneous growth of EBV-lymphoblastoid cell lines predict development of EBV-LPD.

In immunocompromised hosts, EBV-LPD originates from a deficiency of virus-specific cytotoxic T lymphocytes (CTLs), which control outgrowth of EBV-infected B cells. This finding provided the rationale for developing strategies of adoptive cell therapy to restore EBV-specific immune competence. Unselected donor leukocyte infusion, the first attempt at EBV-directed adoptive immunotherapy in humans, can induce EBV-LPD remission but exposes patients to a high risk of developing clinically relevant GVHD and is not suitable for patients transplanted from an HLA-mismatched donor. A safer approach is infusion of in vitro generated EBV-specific CTL lines of donor origin containing both CD8+ and CD4+ T lymphocytes. These CTL lines prevent lymphoproliferative disorders in patients considered at high risk, such as patients given T-cell depleted HSCT from HLA-disparate donors, and cure clinically overt LPD. Infusion of EBV-specific CTLs from third-party donors sharing HLA-class I molecules with the recipient can be also useful. In recent years, use of monoclonal antibodies directed against CD20, a molecule expressed on B cells, has significantly contributed to reduce the incidence and severity of EBV-related LPD, although it can be associated with the emergence of neoplasms in which cells are CD19+ but CD20 negative, thus rendering patients no longer susceptible to the treatment with the monoclonal antibody.

Chapter 139

Late Effects of Hematopoietic Stem Cell Transplantation

Andrea Velardi and Franco Locatelli

Many children given hematopoietic stem cell transplantation (HSCT) become long-term survivors. Besides chronic graft-versus-host disease (GVHD), long-term complications that may develop in pediatric transplant recipients include impaired growth, neuroendocrine dysfunction, delayed puberty, infertility, second malignancies, cataracts and other ocular complications, leukoencephalopathy, and cardiac and pulmonary dysfunction.

Children given HSCT before puberty may develop **growth impairment,** precluding achievement of the genetic target for adult height. The decrease in growth velocity is similar for boys and girls and is more frequently observed in patients given total-body irradiation (TBI) as part of the preparative regimen. Fractionation of irradiation has a less-adverse impact on height than does single-dose TBI, whereas the use of craniospinal radiotherapy before transplantation plays a synergistic detrimental role with TBI in favoring growth impairment. A study of 175 children younger than 6 yr of age, 6-12 yr of age, or 12-15 yr of age receiving TBI-based regimens and not treated with growth hormone reported a mean final adult height of 3.49, 1.92, and 0.37 SD below average, respectively. Chronic GVHD and its treatment with corticosteroids may also contribute to growth impairment. Serial studies of children given a busulfan-based preparative regimen indicate busulfan

has much less impact on growth but produces the same gonadal failure as TBI-based regimens. Preparative regimens using only cyclophosphamide for children transplanted for aplastic anemia have little, if any, detrimental effect on growth and development.

Growth impairment of patients given TBI is mainly a result of direct damage of cartilage plates and to the effect of TBI on the hypothalamic–pituitary axis, which leads to an inappropriately low production of growth hormone (GH). GH deficiency is susceptible to at least partial correction through administration of hormonal replacement therapy. Annual growth evaluation should be performed in all children after HSCT. Children showing a decreased growth velocity should be further investigated through evaluation of bone age and secretion of GH in response to pharmacologic stimulus. Current studies are aimed at identifying children with GH deficiencies at an earlier age and administering hormonal replacement therapy. Initial concerns about potential risks of favoring disease recurrence or promoting development of second malignancies in GH substitute therapy have not been confirmed and GH replacement therapy is widely employed.

The use of TBI during the preparative regimen involves the thyroid gland in the irradiation field and may result in **hypothyroidism.** Some children who have received single-dose TBI develop either compensated (28-56%) or overt (9-13%) hypothyroidism. The use of fractionated TBI reduces the incidence of both compensated (10-14%) and overt (<5%) hypothyroidism. Children younger than 7 yr old at the time of allograft are at greater risk of developing hypothyroidism. Chemotherapy-only preparative regimens have far fewer adverse effects on normal thyroid function. The site of injury by irradiation is at the level of the thyroid gland rather than at the pituitary or hypothalamus. Therapy with thyroxine is very effective for overt hypothyroidism, but treatment of compensated hypothyroidism is more controversial, although there is evidence that hormonal replacement therapy may reduce the risk of thyroid carcinoma through a suppression of thyroid-stimulating hormone. Despite treatment of hypothyroidism, the incidence of thyroid carcinoma is not negligible. An annual echo of the thyroid gland is indicated for timely identification of nodules in the thyroid gland suspected to be of neoplastic origin. When a nodule with echo characteristics suggestive for a carcinoma is identified, a needle biopsy is indicated to clarify the histologic nature of the nodule. The cumulative incidence of hypothyroidism increases over time, underscoring the importance of annual thyroid function studies.

Gonadal hormones are essential for normal pubertal growth, as well as for development of secondary sexual characteristics. A significant proportion of patients receiving TBI-containing preparative regimens show **delayed development of secondary sexual characteristics,** resulting from primary ovarian or testicular failure. Laboratory evaluation of these patients reveals elevated follicle-stimulating hormone and luteinizing hormone levels with depressed estradiol and testosterone serum levels. These patients benefit from careful follow-up with evaluation of annual Tanner scores and endocrine function. Supplementation of gonadal hormones is useful for primary gonadal failure and is administered with GH to promote pubertal growth. The incidence of sex hormone deficiency is lower in patients given a busulfan-based regimen, while infertility during adulthood is a common problem of these children, as well as of those prepared to the allograft with TBI. The use of reduced-intensity regimens can have the advantage of sparing fertility in a large proportion of patients.

The overall risk of developing a **secondary form of cancer** is significantly higher after HSCT than in the general population. Although few studies have specifically analyzed pediatric patients, available evidence indicates that the cumulative incidence of second malignancies shows a slight, but continuous, tendency to increase over time. Several types of secondary tumors have been identified in patients given HSCT. The most frequently diagnosed neoplasms are thyroid carcinoma, brain tumors, and epithelial cancers. Young age, male gender, use of TBI during the preparative regimen, chronic GVHD, and an intrinsic genetic predisposition to develop cancer (Fanconi anemia) have been reported to be risk factors for development of secondary malignancies after HSCT.

Cataracts mainly occur in children given a radiotherapy-based preparative regimen. The incidence of cataracts is particularly high if TBI is delivered as a single-fraction (800-1,000 cGy). The introduction of fractionated TBI has led to a marked reduction of this complication to ≈10-20% of patients, one-third of whom require surgical intervention. Corticosteroids, frequently employed for treating GVHD, also promote development of cataracts. A dry eye syndrome, or keratoconjunctivitis sicca, may also affect HSCT recipients. It is often related to chronic GVHD and postradiotherapy fibrosis of the lacrimal gland and is treated with artificial tears and lubricants.

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Allergic Disorders

PART XV

Chapter 140

Allergy and the Immunologic Basis of Atopic Disease

Cezmi A. Akdis and Scott H. Sicherer

Allergic or atopic patients have an altered state of reactivity to common environmental and food antigens that do not cause clinical reactions in unaffected people. Patients with clinical allergy usually produce immunoglobulin (Ig) E antibodies to the antigens that trigger their illness. The term *allergy* represents the clinical expression of IgE-mediated allergic diseases that have a familial predisposition and that manifest as hyperresponsiveness in target organs such as the lung, skin, gastrointestinal tract, and nose. There has been a significant increase in the prevalence of allergic diseases during the last few decades. This increase is attributed to changes in environmental factors (exposure to tobacco smoke, air pollution, indoor and outdoor allergens, respiratory viruses, obesity and perhaps a decline in certain infectious diseases [hygiene hypothesis]).

KEY ELEMENTS OF ALLERGIC DISEASES

Allergens

Allergens are almost always proteins, but not all proteins are allergens. For a protein antigen to display allergenic activity, it must induce IgE production, which must lead to a type 1 hypersensitivity response upon subsequent exposure to the same protein. Biochemical properties of the allergen, stimulating factors of the innate immune response around the allergen substances at the time of exposure, stability of the allergen in the tissues, digestive system, skin, or mucosa, and the dose and time of stay in lymphatic organs during the interaction with the immune system are all factors that may cause an antigen to become an allergen. This is distinguished from general antigen responses, which induce a state of immune responsiveness without associated IgE production.

Most allergens are proteins of 10-70 kDa molecular weight; molecules <10 kDa do not bridge adjacent IgE antibody molecules on the surfaces of mast cells or basophils; most molecules >70 kDa do not pass through mucosal surfaces, a feature needed to reach antigen-presenting cells (APCs) for stimulation of the immune system. Allergens frequently contain proteases, which promote barrier dysfunction and increase allergen penetration into host tissues. Low-molecular-weight moieties, such as drugs, can become allergens by reacting with serum proteins or cell membrane proteins to be recognized by the immune system. Carbohydrate structures can also be allergens and are most relevant with the increasing use of biologics in clinical practice; patients with cetuximab-induced anaphylaxis have IgE antibodies specific for galactose-α-1,3-galactose (see Chapter 151).

T Cells

Everyone is exposed to potential allergens. Atopic individuals respond to allergen exposure with rapid expansion of **T-helper type 2 (Th2)** cells that secrete cytokines, such as interleukin (IL)-4, IL-5, and IL-13, favoring IgE synthesis and eosinophilia. Allergen-specific IgE antibodies associated with atopic response are detectable by serum testing or positive immediate reactions to allergen extracts on prick skin testing (see Chapter 141). The Th2 cytokines IL-4 and IL-13 play a key role in immunoglobulin isotype switching to IgE (Fig. 140-1). IL-5 and IL-9 are important in differentiation and development of eosinophils. The combination of IL-3, IL-4, and IL-9 contributes to mast cell activation. Th2 cytokines are important effector molecules in the pathogenesis of asthma and allergic diseases; acute allergic reactions are characterized by infiltration of Th2 cells into affected tissues. In addition, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) contribute to Th2 response and eosinophilia.

A fraction of the immune response to allergen results in proliferation of **T helper type 1 (Th1)** cells. Th1 cells are typically involved in the eradication of intracellular organisms, such as mycobacteria, because of the ability of Th1 cytokines to activate phagocytes and promote the production of opsonizing and complement-fixing antibodies. The Th1 component of allergen-specific immune response contributes to chronicity and the effector phase in allergic disease. Activation and apoptosis of epithelial cells induced by Th1 cell–secreted interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and Fas ligand constitute an essential pathogenetic event for the formation of eczematous lesions in atopic dermatitis and bronchial epithelial cell shedding in asthma.

Chronic lesions of allergic reactions are characterized by infiltration of Th1 and **Th17 cells**. This is important because Th1 cytokines such as IFN-γ can potentiate the function of allergic inflammatory effector cells such as eosinophils and thereby contribute to disease severity. Th17 and Th22 cells link the immune response to tissue inflammation; IL-17A and IL-17F and IL-22 are their respective prototype cytokines. Although both T-helper cell subsets play roles in immune defense to extracellular bacteria, IL-17 augments inflammation, whereas IL-22 plays a tissue-protective role. Cytokines in the IL-17 family act on multiple cell types, including epithelial cells and APCs, to cause the release of chemokines, antimicrobial peptides, and proinflammatory cytokines to enhance inflammation and antimicrobial responses. In addition, recently identified Th9 cells produce IL-9, but not other typical Th1, Th2, and Th17 cytokines, and constitute a distinct population of effector T cells that promotes tissue inflammation. Figure 140-2 depicts the complex cytokine cascades involving Th1, Th2, Th9, Th17 and Th22 cells.

T-regulatory (Treg) cells are a subset of T cells thought to play a critical role in expression of allergic and autoimmune diseases. These cells have the ability to suppress effector T cells of either the Th1 or Th2 phenotypes (Fig. 140-3). Treg cells express $CD4^+CD25^+$ surface molecules and immunosuppressive cytokines such as IL-10 and transforming growth factor-β (TGF-β_1). The forkhead box/winged-helix transcription factor gene *FOXP3* is expressed specifically by $CD4^+CD25^+$ Treg cells and programs their development and function. Adoptive transfer of Treg cells inhibits the development of airway eosinophilia and protects against airway hyperreactivity in animal models of asthma. T-cell response to allergens in healthy individuals shows a wide range, from no detectable response to involvement of active peripheral tolerance mechanisms mediated by different subsets of Treg cells. Individuals who are not allergic even though they are exposed to high doses of allergens, such as beekeepers and cat owners, show a detectable allergen-specific IgG4 response accompanied by IL-10–producing Treg cells. It is thought that $CD4^+CD25^+$ Treg cells play an important role in mitigating the allergic immune response and that the lack of such cells may predispose to the development of allergic diseases. Patients with mutations in the human *FOXP3* gene lack $CD4^+CD25^+$ Treg cells and develop severe immune dysregulation, with polyendocrinopathy, food allergy, and high serum IgE levels (XLAAD/

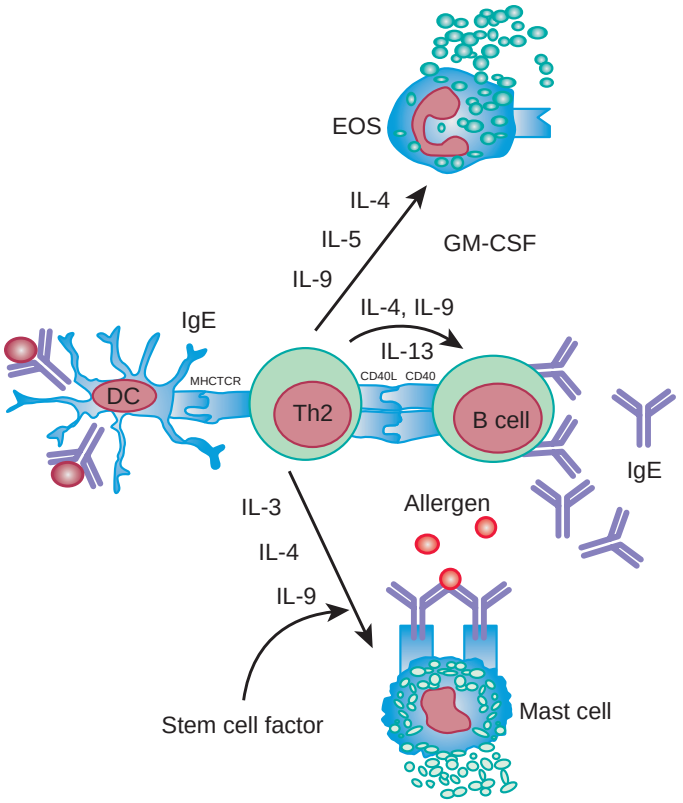

Figure 140-1 **Role of Th2 cytokines in allergic cascade.** DC, dendritic cell; EOS, eosinophil; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; Th2, T-helper type 2 cell.

IPEX disease) (see Chapter 126). In addition to Treg cells, IL-10 secreting and allergen-specific Breg cells that increase during allergen-specific immunotherapy, and may play a role in allergen tolerance were recently demonstrated.

Antigen-Presenting Cells

Dendritic cells, Langerhans cells, monocytes, and macrophages have the ability to present allergens to T cells and thereby modulate allergic inflammation by controlling the type of T-cell development. APCs are a heterogeneous group of cells that share the property of antigen presentation in the context of the major histocompatibility complex (MHC) and are found primarily in lymphoid organs and the skin. Dendritic cells (DCs) and Langerhans cells are unique in their ability to prime naïve T cells and are responsible for the primary immune response, or the **sensitization phase** of allergy. Monocytes and macrophages are thought to contribute to activating memory T-cell responses upon reexposure to allergen, which characterizes the **elicitation phase** of allergy.

Peripheral DCs residing in sites such as the skin, intestinal lamina propria, and lung are relatively immature. These immature DCs take up antigens in tissues and then migrate to the T-cell areas in locally draining lymph nodes. The DCs undergo phenotypic and functional changes during migration, characterized by increased expression of MHC class I, MHC class II, and costimulatory molecules that react with CD28 expressed on T cells. In the lymph nodes, they directly present processed antigens to resting T cells to induce their proliferation and differentiation.

Mature DCs have been designated as myeloid DC or plasmacytoid DC on the basis of their ability to favor Th1 or Th2 differentiation, respectively. The critical factor for polarization to Th1 cells is the level of IL-12 produced by myeloid DC. By contrast, plasmacytoid DC have low levels of IL-12. Plasmacytoid DC particularly play a role in antiviral immunity by rapid production of high amounts of interferon

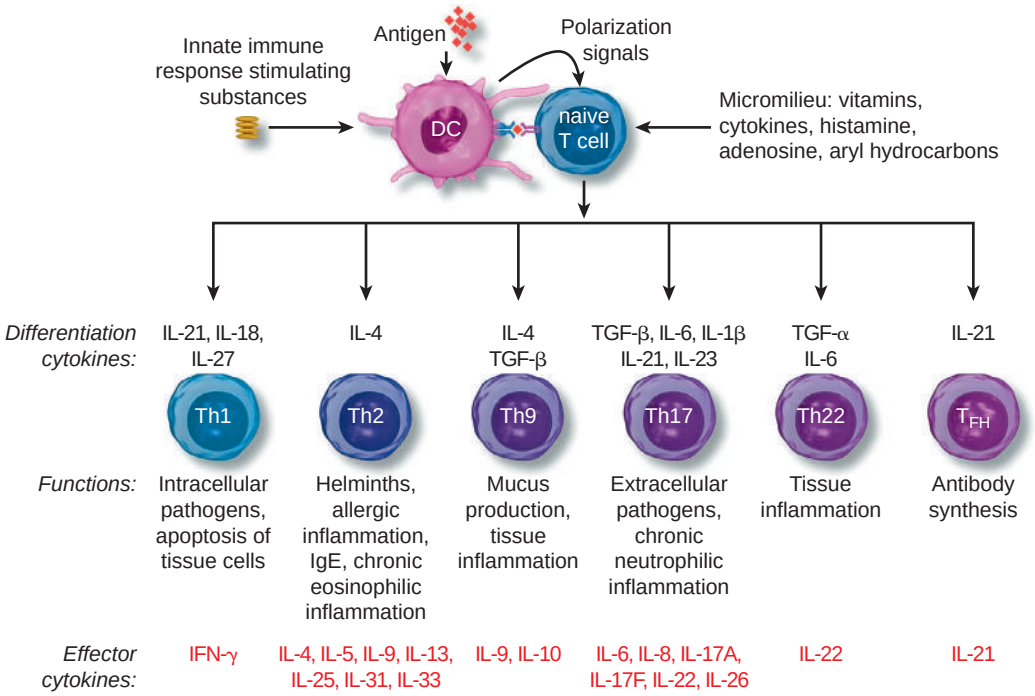

Figure 140-2 **Effector T-cell subsets.** Following antigen presentation by dendritic cells (DCs), naïve T cells differentiate into Th1, Th2, Th9, Th17, Th22, and follicular helper TFH effector subsets. Their differentiation requires cytokines and other cofactors that are released from dendritic cells and also expressed in the micromilieu. T-cell activation in the presence of interleukin-4 (IL-4) enhances differentiation and clonal expansion of Th2 cells, perpetuating the allergic response. IFN-γ, interferon-γ; TGF-β, transforming growth factor-β. *(From Akdis M, Palomares O, van de Veen W, van Splunter M, Akdis CA. TH17 and TH22 cells: a confusion of antimicrobial response with tissue inflammation versus protection,* J Allergy Clin Immunol *129:1438–1449, 2012.)*

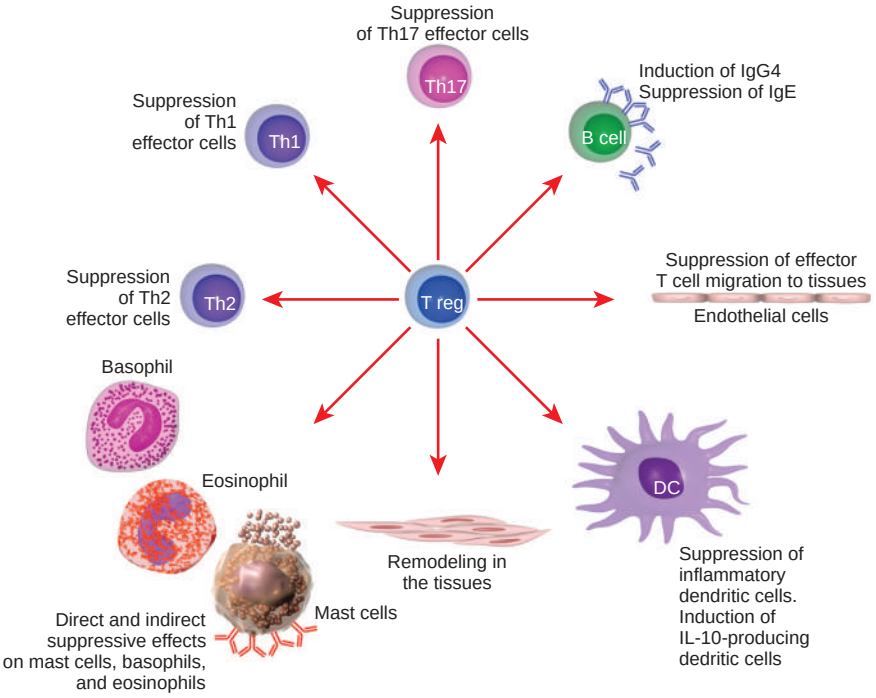

Figure 140-3 **FoxP3⁺, CD4⁺, CD25⁺, and Tr1 cells contribute to the control of allergen-specific immune responses in several major ways:** Suppression of dendritic cells that support the generation of effector T-cells; suppression of Th1, Th2, and Th17 cells; suppression of allergen-specific IgE, and induction of IgG_4 and/or IgA; suppression of mast cells, basophils, and eosinophils; interaction with resident tissue cells and remodeling, and suppression of effector T-cell migration to tissues. IL-10, interleukin 10. *(From Akdis CA, Akdis M: Mechanisms and treatment of allergic disease in the big picture of regulatory T cells,* J Allergy Clin Immunol *123:735–746, 2009.)*

(IFN)-α and also help B cells for antibody production. There is considerable interest in the role of TSLP, which is overexpressed in the mucosal surfaces and skin of atopic individuals. TSLP enhances Th2 cell differentiation by inducing expression of OX40L on immature myeloid DCs in the absence of IL-12 production.

Presence of allergen-specific IgE on the cell surfaces of APCs is a unique feature of atopy. Importantly, the formation of high-affinity IgE receptor I (FcεRI)/IgE/allergen complexes on APC cell surfaces markedly facilitates allergen uptake and presentation. The clinical importance of this phenomenon is supported by the observation that FcεRI-positive Langerhans cells bearing IgE molecules are a prerequisite for skin-applied, aeroallergen provocation of eczematous lesions in patients with atopic dermatitis. The role of the low-affinity IgE receptor II (FcεRII, CD23) on monocytes-macrophages is less clear, although it appears that under certain conditions it can also facilitate antigen capture. Cross-linking of FcεRII, as well as FcεRI, on monocytes-macrophages leads to the release of inflammatory mediators. There is a critical role for DCs in induction of oral tolerance; tolerogenic DCs are compartmentalized within the mucosa and present antigen through a mechanism designed to produce a Th1/Treg–suppressive response that ablates allergen-specific T cells.

Immunoglobulin E and its Receptors

The acute allergic response depends on IgE and its ability to bind selectively to the α chain of the high-affinity FcεRI or the low-affinity FcεRII (CD23). Cross-linking of receptor-bound IgE molecules by allergen initiates a complex intracellular signaling cascade followed by the release of various mediators of allergic inflammation from mast cells and basophils. The FcεRI molecule is also found on the surface of antigen-presenting DCs (e.g., Langerhans cells), but differs from the structure found on mast cells/basophils in that the FcεRI molecule found on DCs lacks the β chain. CD23 is found on B cells, eosinophils, platelets, and DCs. Cross-linking and FcεRI aggregation on mast cells and basophils can also lead to anaphylaxis (see Chapter 149). Differential expression of tyrosine kinases responsible for positive and negative regulation of mast cell/basophil degranulation are thought to be responsible for this aberrant allergic response.

The induction of IgE synthesis requires 2 major signals. The first signal (signal 1) initiates IL-4 or IL-13 activation of germline transcription at the ε Ig locus, which dictates isotype specificity. The second signal (signal 2) involves the engagement of CD40 on B cells by CD40 ligand expressed on T cells. This engagement results in activation of the recombination machinery, resulting in DNA switch recombination. Interactions between several costimulatory molecule pairs (CD28 and B7; lymphocyte function–associated antigen-1 and intercellular adhesion molecule-1; CD2 and CD58) can further amplify signal 1 and signal 2 to enhance IgE synthesis. Factors that inhibit IgE synthesis include Th1-type cytokines (IL-12, IFN-α, IFN-γ) and microbial DNA containing CpG (cytosine-phosphate-guanine) repeats.

Eosinophils

Allergic diseases are characterized by peripheral blood and tissue eosinophilia. Eosinophils participate in both innate and adaptive immune responses and, like mast cells, contain dense intracellular granules that are sources of inflammatory proteins. These granule proteins include major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Eosinophil granule proteins damage epithelial cells, induce airway hyperresponsiveness, and cause degranulation of basophils and mast cells. Major basic protein released from eosinophils can bind to an acidic moiety on the M2 muscarinic receptor and block its function, thereby leading to increased acetylcholine levels and the development of increased airway hyperreactivity. Eosinophils are also a rich source of prostaglandins and leukotrienes; in particular, cysteinyl leukotriene C4 contracts airway smooth muscle and increases vascular permeability. Other secretory products of eosinophils include cytokines (IL-4, IL-5, TNF-α), proteolytic enzymes, and reactive oxygen intermediates, all of which significantly enhance allergic tissue inflammation.

Several cytokines regulate the function of eosinophils in allergic disease. Eosinophils develop and mature in the bone marrow from myeloid precursor cells activated by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Allergen exposure of allergic patients causes resident hematopoietic CD34 cells to express the IL-5 receptor. The IL-5 receptor activation induces eosinophil maturation, causing eosinophils to synthesize granule proteins, prolonging their survival, potentiating degranulation of eosinophils, and stimulating release of eosinophils from the bone marrow. GM-CSF also enhances proliferation, cell survival, cytokine production, and degranulation of eosinophils. Certain chemokines, such as RANTES (regulated upon activation, normal T-cell expressed and secreted),

macrophage inflammatory protein-1α (MIP-1α), and eotaxins, are important for recruiting eosinophils into local allergic tissue inflammatory reactions. Eotaxins mobilize IL-5–dependent eosinophil colony–forming progenitor cells from the bone marrow. These progenitors are rapidly cleared from the blood and either return to the bone marrow or are recruited to inflamed tissue sites.

Mast Cells

Mast cells are derived from CD34 hematopoietic progenitor cells that arise in bone marrow. Upon entering the circulation, they travel to peripheral tissue, where they undergo tissue-specific maturation. Mast cell development and survival relies on interactions between the tyrosine kinase receptor c-kit expressed on the surface of mast cells and the fibroblast-derived c-kit ligand stem cell factor. Unlike mature basophils, mature mast cells do not typically circulate in the blood. They are, instead, widely distributed throughout connective tissues, where they often lie adjacent to blood vessels and beneath epithelial surfaces that are exposed to the external environment, such as the respiratory tract, gastrointestinal tract, and skin. So placed, mast cells are positioned anatomically to participate in allergic reactions. At least 2 subpopulations of human mast cells are recognized: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells with tryptase are the predominant type found in the lung and small intestinal mucosa, whereas mast cells with both tryptase and chymase are the predominant type found in skin, the gastrointestinal submucosa, and blood vessels.

Mast cells contain, or produce on appropriate stimulation, a diverse array of mediators that have different effects on allergic inflammation and organ function. They include preformed granule-associated mediators (histamine, serine proteases, proteoglycans) and membrane-derived lipid, cytokine, and chemokine mediators arising from de novo synthesis and release. The most important mast cell-derived lipid mediators are the cyclooxygenase and lipoxygenase metabolites of arachidonic acid, which have potent inflammatory activities. The major cyclooxygenase product of mast cells is prostaglandin D_2, and the major lipoxygenase products are the sulfidopeptide leukotrienes (LTs): LTC_4 and its peptidolytic derivatives LTD_4 and LTE_4. Mast cells also can produce cytokines that promote Th2-type responses (IL-4, IL-13, GM-CSF) and inflammation (TNF-α, IL-6), and regulate tissue remodeling (TGF, vascular endothelial cell growth factor). Immunologic activation of mast cells and basophils typically begins with cross-linkage of IgE bound to the FcεRI with multivalent allergen. Mast cell surface FcεRI is increased by IL-4 and IgE. Surface levels of FcεRI decrease in subjects receiving treatment with anti-IgE antibody that lowers serum IgE, which is of potential therapeutic interest.

MECHANISMS OF ALLERGIC TISSUE INFLAMMATION

IgE-mediated immune responses can be classified chronologically according to 3 reaction patterns. The **early-phase response** is the immediate response after allergen is introduced into target organs. This response is characterized by mast cell degranulation and release of preformed mediators, occurring within an immediate time frame of between 1 and 30 min after allergen exposure and resolving within 1-3 hr. Acute reactions are associated with increased local vascular permeability, which leads to leakage of plasma proteins, tissue swelling, and increased blood flow, as well as itching, sneezing, wheezing, and acute abdominal cramps in the skin, nose, lung, and gastrointestinal tract, respectively, depending on the targeted organ.

A second, **late-phase response** can occur within hours of allergen exposure, reaching a maximum at 6-12 hr and resolving by 24 hr. Late-phase responses are characterized in the skin by edema, redness, and induration; in the nose by sustained nasal blockage; and in the lung by airway obstruction and persistent wheezing. In general, late-phase responses are associated with early infiltration of neutrophils and eosinophils followed by basophils, monocytes, macrophages, and Th2-type cells. Recruitment of inflammatory cells from the circulation requires increased expression of adhesion molecules on their cell surfaces and expression of their ligand on endothelial cells, which are under the control of cytokines. Several hours after allergen exposure, TNF-α released by activated mast cells induces the vascular endothelial expression of cell adhesion molecules, and this change leads to transendothelial migration of various inflammatory cells. Preferential accumulation of eosinophils occurs through interactions between selective adhesion molecules on the eosinophil cell surface (e.g., $\alpha_4\beta_1$ integrin or very late antigen-4); vascular cell adhesion molecule-1 surface expression can be enhanced by IL-4 and IL-13 on endothelial cells.

Chemokines are chemotactic cytokines that play a central role in tissue-directed migration of inflammatory cells. RANTES, MIP-1α, monocyte chemotactic protein (MCP)-3, and MCP-4 are chemoattractants for eosinophils and mononuclear cells, whereas eotaxins are relatively selective for eosinophils. These chemoattractants have been detected in epithelium, macrophages, lymphocytes, and eosinophils at sites of late-phase responses and allergic tissue inflammation. Blockade of these chemokines leads to significant reduction in tissue-directed migration of allergic effector cells.

In the third reaction pattern, **chronic allergic disease,** tissue inflammation can persist for days to years. Several factors contribute to persistent tissue inflammation, including recurrent exposure to allergens and microbial agents. The repeated stimulation of allergic effector cells such as mast cells, basophils, eosinophils, and Th2 cells contributes to unresolved inflammatory conditions. Additionally, Th2-type cytokines (IL-3, IL-5, GM-CSF) secreted during allergic reactions can prolong survival of allergic effector cells by delaying apoptosis. Local differentiation of tissue-infiltrating eosinophil precursors induced by IL-5 results in self-generation of eosinophils, further sustaining damage of local tissue. Tissue remodeling leading to irreversible changes in target organs is also a feature of chronic allergic disease. In asthma, **remodeling** involves thickening of the airway walls and submucosal tissue, as well as smooth muscle hypertrophy and hyperplasia, which are associated with a decline in lung function. This is an unexpected role for eosinophils in airway remodeling as well as chronic inflammation. In atopic dermatitis, lichenification is an obvious manifestation of skin remodeling.

Th2 cytokines can not only maintain allergic inflammation but also influence tissue remodeling by activating resident cells in target organs; IL-4, IL-9, and IL-13 induce mucus hypersecretion and metaplasia of mucus cells; IL-4 and IL-13 stimulate fibroblast growth and synthesis of extracellular matrix proteins; and IL-5 and IL-9 increase subepithelial fibrosis. TGF-β produced by eosinophils and fibroblasts can enhance subepithelial fibrosis. IL-11 expressed by eosinophils and epithelial cells also contributes to subepithelial fibrosis, in addition to enhancing deposition of collagen and the accumulation of fibroblasts. Additional interleukins released from epithelial cells and DCs, such as IL-25, IL-31, and IL-33, also contribute to the Th2 and eosinophilic inflammation in the affected tissues. The resulting tissue injury amplifies further epithelial injury through proinflammatory cytokine release, extracellular matrix deposition in target organs, and angiogenesis. Genetic predisposition to aberrant injury-repair responses may contribute to chronicity of illness. Once the allergic immune response is established, it can be self-perpetuating and can lead to chronic disease in genetically predisposed individuals. The subsequent infiltration of Th1 cells and Th17 cells enhances the inflammatory potential of allergic effector cells and contributes to chronic tissue inflammatory responses through the release of proinflammatory cytokines and chemokines. In addition, an autoimmune response might be playing a causative role in allergic inflammation resulting from possible mechanisms through IgE autoantibodies, IgG autoantibodies, and Th1 cell and Th17 cell autoreactivity.

GENETIC BASIS OF ATOPY

Allergic diseases are complex genetic conditions susceptible to environmental triggers. Several major groups of genes are associated with allergic diseases: genes that regulate systemic expression of atopy (increased IgE synthesis, eosinophilia, mast cell responses) that are commonly expressed among various allergic diseases, genes that control barrier function in specific target organs (e.g., the skin in atopic

dermatitis, the lung in asthma, the gastrointestinal tract in food allergy), and genes encoding pattern-recognition receptors of the innate immune system that engage microbial pathogens and influence adaptive immune responses. Once allergic responses have been initiated, a genetic predisposition to chronic allergic inflammation and aberrant injury-repair responses contribute to tissue remodeling and persistent disease.

Atopic diseases have a strong familial predisposition, with approximately 60% heritability found in twin studies of asthma and atopic dermatitis. The 5q23-35 region comprises several genes implicated in allergic disease pathogenesis, including genes coding for Th2 cytokines (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF). Among these, *IL4* is a well-studied potential candidate gene. A nucleotide change at position 589 of the *IL4* promoter region is associated with the formation of a unique binding site for NF-AT (**n**uclear **f**actor for **a**ctivated **T** cells) transcription factor, increased IL-4 gene transcription, higher NF-AT binding affinity, and increased IgE production. Similarly, *IL13* coding region variants have been associated with asthma and atopic dermatitis. An association between atopy and a gain-of-function polymorphism on chromosome 16, which codes for the α subunit of the IL-4R, has been found. This finding is consistent with the important role of IL-4, IL-13, and their receptors in the immunopathogenesis of allergic diseases.

Genome-wide searches have also linked atopy to chromosome region 11q13. The gene encoding the β subunit of FcεRI-β has been proposed to be the candidate gene in this region. The β subunit gene modifies the FcεRI activity on mast cells, and several genetic variants of FcεRI-β are associated with asthma and atopic dermatitis. Chromosome 6 contains genes coding for human leukocyte antigen class I and class II molecules, which regulate the specificity and intensity of the immune responses to specific allergens. IgE responses to specific allergens, such as ragweed antigen Amb a V and mite allergen *Der p* I, have been linked to specific MHC class II loci. TNF-α, a key cytokine that contributes to the influx of inflammatory cells, is also located on chromosome 6. TNF-α polymorphisms are associated with asthma.

Barrier dysfunction has a key role in the pathogenesis of allergic diseases. Genetic linkage studies of atopic dermatitis have demonstrated the importance of chromosome 1q21, which contains a cluster of genes involved in epidermal differentiation. Filaggrin is a protein that is essential in the formation of the stratum corneum. Null mutations of the filaggrin gene are strongly associated with early onset and severe atopic dermatitis. Mutations in the gene encoding the serine protease inhibitor SPINK5 has been shown to cause **Netherton disease**, a single-gene disorder associated with erythroderma, food allergy, and high serum IgE levels. A common polymorphism in SPINK5 (in particular, Glu420Lys) increases the risk of developing atopic dermatitis and asthma. SPINK5 is expressed in the outer epidermis and is thought to be critical to neutralizing the proteolytic activity of *Staphylococcus aureus* and common allergens such as *Der p* I, which use these proteases to penetrate the skin to induce allergic responses. Barrier dysfunction is involved in other allergic diseases, such as asthma and rhinosinusitis, but likely involves other barrier genes, such as those encoding gap junctions.

Candidate genes associated with asthma susceptibility have been identified by positional cloning: *GPRA* (G-protein coupled receptor for asthma susceptibility on chromosome 7p14), *ADAM-33* (a disintegrin and metalloproteinase 33 on chromosome 20p), and *DPP10* (dipeptidyl peptidase 10 on chromosome 2q14). The functions of these genes do not fit into classical pathways of atopy and therefore provide new insights into asthma pathogenesis. *GPRA* encodes a G-protein coupled receptor, with isoforms expressed in bronchial epithelial cells and smooth muscle in asthmatic persons, suggesting an important role for these tissues in asthma. *ADAM-33* is expressed in bronchial smooth muscle and has been linked to bronchial hyperresponsiveness. *DPP10* encodes a dipeptidyl dipeptidase that can remove the terminal 2 peptides from certain proinflammatory chemokines, a change that may modulate allergic inflammation.

Pattern-recognition receptors of the innate immune system, which are expressed by epithelial cells and DCs, are associated with disease susceptibility. These receptors recognize specific microbial components. Polymorphisms in CD14 (engages endotoxin), Toll-like receptor 2 (which engages *S. aureus*), and T-cell immunoglobulin domain and mucin domain (which engage hepatitis A virus) correlate with asthma and/or atopic dermatitis susceptibility. Dysregulation of these frontline immune defense systems would permit abnormal response to common environmental allergens.

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Chapter 141

Diagnosis of Allergic Disease

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ALLERGY HISTORY

Obtaining a complete history from the allergic patient involves eliciting a description of all symptoms along with their timing and duration, exposure to common allergens, and responses to previous therapies. Because patients often suffer from more than 1 allergic disease, the presence or absence of other allergic diseases, including allergic rhinoconjunctivitis, asthma, food allergy, eosinophilic esophagitis, atopic dermatitis, and drug allergy should be determined. A family history of allergic disease is common and is one of the most important factors predisposing a child to the development of allergies. The risk of allergic disease in a child approaches 50% when 1 parent is allergic and 66% when both parents are allergic, with maternal history of atopy having a greater effect than paternal history.

Several characteristic behaviors are often seen in allergic children. Because of nasal pruritus and rhinorrhea, children with allergic rhinitis often perform the **allergic salute** by rubbing their nose upward with the palm of their hand. This repeated maneuver may give rise to the **nasal crease,** a horizontal wrinkle over the bridge of the nose. Characteristic vigorous **grinding** of the eyes with the thumb and side of the fist is frequently observed in children with allergic conjunctivitis. The **allergic cluck** is produced when the tongue is placed against the roof of the mouth to form a seal and withdrawn rapidly in an effort to scratch the palate. The presence of other symptoms, such as fever, unilateral nasal obstruction, and purulent nasal discharge, suggests other diagnoses.

The timing of onset and the progression of symptoms are relevant. The onset of recurrent or persistent nasal symptoms coinciding with placement in a daycare center might suggest recurrent infection rather than allergy. When patients present with a history of episodic acute symptoms, it is important to review the setting in which symptoms occur as well as the activities and exposures that immediately precede their onset. Symptoms associated with lawn mowing suggest allergy to grass pollen or fungi, whereas if symptoms occur in homes with pets, animal dander sensitivity is an obvious consideration. Reproducible reactions after ingestion of a specific food raise the possibility of food allergy. When symptoms wax and wane but evolve gradually and are more chronic in duration, a closer look at whether the timing and progression of symptoms correlate with exposure to a seasonal aeroallergen is warranted.

Aeroallergens, such as pollens and fungal spores, the concentrations of which in outdoor air fluctuate seasonally, are prominent causes of allergic disease. Correlating symptoms with seasonal pollination patterns of geographically relevant plants and trees along with information provided by local pollen counts can aid in identifying the allergen. Throughout most of the United States, trees pollinate in the early spring, grasses pollinate in the late spring and early summer, and

weeds pollinate in late summer through the fall. The presence of fungal spores in the atmosphere follows a seasonal pattern in the northern United States with spore counts rising with the onset of warmer weather and peaking in late summer months, only to recede again with the first frost through the winter. In warmer regions of the southern United States, fungal spores and grass pollens may cause symptoms on a perennial basis.

Rather than experiencing seasonal symptoms, some patients suffer allergic symptoms year-round. In these patients, sensitization to perennial allergens usually found indoors, such as dust mites, animal dander, cockroaches, and fungi, warrants consideration. Species of certain fungi, such as *Aspergillus* and *Penicillium,* are found indoors whereas *Alternaria* is found in both indoor and outdoor environments. Cockroach allergens are often problematic in inner city environments. Patients sensitive to perennial allergens often also become sensitized to seasonal allergens and experience baseline symptoms year-round with worsening during the pollen seasons.

The age of the patient is an important consideration in identifying potential allergens. Infants and young children are first sensitized to allergens that are in their environment on a continuous basis, such as dust mites, animal dander, and fungi. Sensitization to seasonal allergens usually takes several seasons of exposure to develop and is thus unlikely to be a significant trigger of symptoms in infants and toddlers.

Food allergies are more common in infants and young children, resulting primarily in cutaneous, gastrointestinal, and, less frequently, respiratory symptoms. Symptoms of immediate or immunoglobulin (Ig) E-mediated hypersensitivity food reactions develop within minutes to 2 hr after ingestion of the offending food. Symptoms of non–IgE-mediated food allergies are often delayed or chronic (see Chapter 151).

Complete information from previous evaluations and prior treatments for allergic disease should be reviewed, including impact of changes in local environment (e.g., home vs. school), response to medications, elimination diets, and duration and impact of allergen immunotherapy (if applicable). Improvement in symptoms with medications or avoidance strategies used to treat allergic disease provides additional evidence for an allergic process.

A thorough environmental survey should be performed, focusing on potential sources of allergen and/or irritant exposure, particularly when respiratory symptoms (upper and/or lower) are reported. The age and type of the dwelling, how it is heated and cooled, the use of humidifiers or air filtration units, and any history of water damage should be noted. Forced air heating may stir up dust mite, fungi, and animal allergens. The irritant effects of wood-burning stoves, fireplaces, and kerosene heaters may provoke respiratory symptoms. Increased humidity or water damage in the home is often associated with greater exposure to dust mites and fungi. Carpeting serves as a reservoir for dust mites, fungi, and animal dander. The number of domestic pets and their movements about the house should be ascertained. Special attention should be focused on the bedroom, where a child spends a significant proportion of time. The age and type of bedding, the number of stuffed animals, type of window treatments, and the accessibility of pets to the room should be reviewed. The number of smokers in the home and where they smoke is useful information. Activities that might result in exposure to allergens or respiratory irritants such as paint fumes, cleansers, sawdust, or glues should be identified. Similar information should be obtained in regard to other environments where the child spends large portions of time, such as a relative's home or school setting.

PHYSICAL EXAMINATION

In patients with **asthma,** spirometry should be performed. If respiratory distress is observed, pulse oximetry should be performed.

The child presenting with a chief complaint of rhinitis or rhinoconjunctivitis should be observed for mouth breathing, paroxysms of sneezing, sniffing/snorting, throat clearing, and rubbing of the nose and eyes (representing pruritus). Infants should be observed during feeding for nasal obstruction severe enough to interfere with feeding or for more obvious signs of aspiration or gastroesophageal reflux. The frequency and nature of coughing that occurs during the interview and any positional increase in coughing or wheezing should be noted. Children with asthma should be observed for congested or wet cough, tachypnea at rest, retractions, and audible wheezes, which may worsen with crying. Patients with atopic dermatitis should be monitored for repetitive scratching and the extent of skin involvement.

Because children with severe asthma as well as those receiving chronic or frequent oral corticosteroids may suffer growth suppression, an accurate height should be plotted at regular intervals. However, long-term follow-up studies suggest that use of inhaled glucocorticoids in prepubertal children is associated with a small initial decrease in attained height (~1 cm) that may persist as a reduction in adult height that is not progressive or cumulative. Poor weight gain in a child with chronic chest symptoms should prompt consideration of cystic fibrosis. Anthropometric measures are also important to monitor in those on restricted diets because of multiple food allergies or eosinophilic esophagitis. Blood pressure should be measured to evaluate for steroid-induced hypertension. The patient with acute asthma may present with **pulsus paradoxus,** defined as a drop in systolic blood pressure during inspiration >10 mm Hg. Moderate to severe airways obstruction is indicated by a decrease of >20 mm Hg. An increased heart rate may be the result of an asthma flare or the use of a β-agonist or decongestant. Fever is not caused by allergy alone and should prompt consideration of an infectious process, which may exacerbate asthma.

Parents are often concerned about blue-gray to purple discolorations beneath their child's lower eyelids, which can be attributed to venous stasis and are referred to as **allergic shiners.** They are found in up to 60% of allergic patients and almost 40% of patients *without* allergic disease. Thus, "shiners" may suggest, but are not diagnostic of, allergic disease. In contrast, the **Dennie-Morgan folds** (Dennie lines) are a feature of atopic dermatitis. These are prominent infraorbital skin folds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin.

In patients with **allergic conjunctivitis,** involvement of the eyes is bilateral. Examination of the conjunctiva reveals varying degrees of lacrimation, conjunctival injection, and edema. In severe cases, periorbital edema involving primarily the lower eyelids or **chemosis** (conjunctival edema that is gelatinous in appearance) may be observed. The classic discharge associated with allergic conjunctivitis is usually described as "stringy" or "ropy." In children with vernal conjunctivitis, a more severe, chronic phenotype, examination of the tarsal conjunctiva may reveal cobblestoning. **Keratoconus,** or protrusion of the cornea, may occur in patients with vernal conjunctivitis or periorbital atopic dermatitis as a result of repeated trauma produced by persistent rubbing of the eyes. Children treated with high-dose or chronic corticosteroids are at risk for development of posterior subcapsular cataracts.

The external ear should be examined for eczematous changes in patients with atopic dermatitis, including the postauricular area and base of the earlobe. Because otitis media with effusion is common in children with allergic rhinitis, pneumatic otoscopy should be performed to evaluate for the presence of fluid in the middle ear and to exclude infection.

Examination of the nose in allergic patients may reveal the presence of a nasal crease. Nasal patency should be assessed, and the nose examined for structural abnormalities affecting nasal airflow, such as septal deviation, turbinate hypertrophy, and nasal polyps. Decrease or absence of the sense of smell should raise concern about chronic sinusitis or nasal polyps. Nasal polyps in children should raise concerns of cystic fibrosis. The nasal mucosa in allergic rhinitis is classically described as pale to purple in comparison with the beefy red mucosa of patients with nonallergic rhinitis. Allergic nasal secretions are typically thin and clear. Purulent secretions suggest another cause of rhinitis. The frontal and maxillary sinuses should be palpated to identify tenderness to pressure that might be associated with acute sinusitis.

Examination of the lips may reveal cheilitis caused by drying of the lips from continuous mouth breathing or repeated licking of the lips in an attempt to replenish moisture and relieve discomfort (**lip licker's dermatitis**). Tonsillar and adenoidal hypertrophy along with a history of impressive snoring raises the possibility of obstructive

sleep apnea. The posterior pharynx should be examined for the presence of postnasal drip and posterior pharyngeal lymphoid hyperplasia ("cobblestoning").

Chest findings in asthmatic children vary significantly and may depend on disease duration, severity, and activity. In a child with well-controlled asthma, the chest should appear entirely normal on examination between asthma exacerbations. Examination of the same child during an acute episode of asthma may reveal hyperinflation, tachypnea, use of accessory muscles, wheezing, and decreased air exchange with a prolonged expiratory time. Tachycardia may be caused by the asthma exacerbation or accompanied by jitteriness after treatment with β-agonists. Decreased airflow or rhonchi and wheezes over the right chest may be noted in children with mucus plugging and right middle lobe atelectasis. The presence of cyanosis indicates severe respiratory compromise. Unilateral wheezing after an episode of coughing and choking in a small child without a history of previous respiratory illness suggests **aspiration of a foreign body.** Wheezing limited to the larynx in association with inspiratory stridor may be seen in older children and adolescents with **vocal cord dysfunction.** Digital clubbing is rarely seen in patients with uncomplicated asthma and should prompt further evaluation to rule out other potential chronic diagnoses, such as cystic fibrosis.

The skin of the allergic patient should be examined for evidence of urticaria/angioedema or atopic dermatitis. **Xerosis,** or dry skin, is the most common skin abnormality of allergic children. **Keratosis pilaris**, often found on facial cheeks and extensor surfaces of the upper arms and thighs, is a benign condition characterized by skin-colored or slightly pink papules caused by keratin plugs lodged in the openings of hair follicles. Examination of the skin of the palms and soles may reveal thickened skin and exaggerated palmar and plantar creases (hyperlinearity) in children with moderate-to-severe atopic dermatitis.

DIAGNOSTIC TESTING

In Vitro Tests

Allergic diseases are often associated with increased numbers of eosinophils circulating in the peripheral blood and invading the tissues and secretions of target organs. Eosinophilia, defined as the presence of >500 eosinophils/μL in peripheral blood, is the most common hematologic abnormality of allergic patients. Seasonal increases in the number of circulating eosinophils may be observed in sensitized patients after exposure to allergens such as tree, grass, and weed pollens. The number of circulating eosinophils can be suppressed by certain infections and systemic corticosteroids. In certain pathologic conditions, such as drug reactions, eosinophilic pneumonias, and eosinophilic esophagitis, significantly increased numbers of eosinophils may be present in the target organ in the absence of peripheral blood eosinophilia. Increased numbers of eosinophils are observed in a wide variety of disorders in addition to allergy (Table 141-1; see Chapter 129). Eosinophil counts >1500 without an identifiable etiology should suggest 1 of the 2 hypereosinophilic syndromes (Table 141-1; see Chapter 129).

Nasal and bronchial secretions may be examined for the presence of eosinophils. The presence of eosinophils in the sputum of asthmatic patients is classic. An increased number of eosinophils in a smear of nasal mucus with Hansel stain is a more sensitive indicator of nasal allergies than peripheral blood eosinophilia and can aid in distinguishing allergic rhinitis from other causes of rhinitis. An elevated IgE value is often found in the serum of allergic patients, because IgE is the primary antibody associated with immediate hypersensitivity reactions. IgE values are measured in international units (IU), with 1 IU equal to 2.4 ng of IgE. Maternal IgE (unlike IgG) does not cross the placenta. Serum IgE levels gradually rise over the first years of life to peak in the teen years and decrease steadily thereafter. Additional factors, such as genetic influences, race, gender, certain diseases, and exposure to cigarette smoke and allergens, also affect serum IgE levels. Total serum IgE levels may increase 2- to 4-fold during and immediately after the pollen season and then gradually decline until the next pollen season. Comparison of total IgE levels among patients with allergic diseases reveals that those with atopic dermatitis tend to have the highest levels while patients with allergic asthma generally have higher levels than those with allergic rhinitis. Although average total IgE levels are higher in populations of allergic patients than in comparable populations without allergic disease, the overlap in levels is such

Table 141-1 Differential Diagnosis of Childhood Eosinophilia

PHYSIOLOGIC
Prematurity
Infants receiving hyperalimentation
Hereditary
INFECTIOUS
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis)
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*)
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis)
Mycobacterial (tuberculosis, leprosy)
Viral (HIV-1, HTLV-1, hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus)
PULMONARY
Allergic (rhinitis, asthma)
Churg-Strauss syndrome
Loeffler syndrome
Hypersensitivity pneumonitis
Eosinophilic pneumonia (chronic, acute)
Pulmonary interstitial eosinophilia
DERMATOLOGIC
Atopic dermatitis
Pemphigus
Dermatitis herpetiformis
Infantile eosinophilic pustular folliculitis
Eosinophilic fasciitis (Schulman syndrome)
Eosinophilic cellulitis (Wells syndrome)
Kimura disease (angiolymphoid hyperplasia with eosinophilia)
HEMATOLOGIC/ONCOLOGIC
Neoplasm (lung, gastrointestinal, uterine)
Leukemia/lymphoma
Myelofibrosis
Myeloproliferative (FIP1L1-PDGFRA–positive) hypereosinophilic syndrome
Lymphatic hypereosinophilic syndrome
Systemic mastocytosis
IMMUNOLOGIC
T-cell immunodeficiencies
Hyperimmunoglobulin E (Job) syndrome
Wiskott-Aldrich syndrome
Graft-versus-host disease
Drug hypersensitivity
Postirradiation
Postsplenectomy
ENDOCRINE
Addison disease
Hypopituitarism
CARDIOVASCULAR
Loeffler disease (fibroplastic endocarditis)
Congenital heart disease
Hypersensitivity vasculitis
Eosinophilic myocarditis
GASTROINTESTINAL
Benign proctocolitis
Inflammatory bowel disease
Eosinophilic gastrointestinal diseases (EGID)

FIP1L1-PDGFRA, FIP1-like 1–platelet-derived growth factor receptor α.

that the diagnostic value of a total IgE level is poor. Approximately one-half of patients with allergic disease have total IgE levels in the normal range. However, measurement of total IgE is indicated when the diagnosis of **allergic bronchopulmonary aspergillosis** is suspected because total serum IgE concentration >1,000 ng/mL is a criterion for diagnosis of this disorder (see Chapter 237.1). Total serum IgE may also be elevated in several nonallergic diseases (Table 141-2; see Chapter 126).

The presence of IgE specific for a particular allergen can be documented in vivo by skin testing or in vitro by the measurement of **allergen-specific IgE (sIgE)** levels in the serum (Table 141-3). The first test for documenting the presence of sIgE was called the radioallergosorbent test because it used a radiolabeled anti-IgE antibody. The radioallergosorbent test has been replaced by an improved generation of automated enzymatic sIgE immunoassays. These assays use solid-phase supports to which allergens of an individual allergen extract are bound. A small amount of the patient's serum is incubated with the allergen-coated support. The allergen-coated support bound to the patient's sIgE is then incubated with enzyme-conjugated antihuman IgE. Incubation of this sIgE–antihuman IgE complex with a fluorescent substrate of the conjugated enzyme results in the generation of fluorescence that is proportional to the amount of sIgE in the serum sample. The amount of sIgE in the serum sample is calculated by interpolation from a standard calibration curve and reported in arbitrary mass units (kilo-IU of allergen-specific antibody per unit volume of sample [kU_A/L]). Laboratory reports may specify classes, counts, or units, but quantification of results in kU_A/L is most useful. There are 3 commercial detection systems approved by the U.S. Food and Drug Administration that have excellent performance characteristics, but the individual systems do not measure sIgE antibodies with comparable efficiencies and thus are not interchangeable. **Component testing** refers to emerging diagnostic tests where sIgE is measured to specific proteins that comprise allergens (e.g., Ara h 2 from peanut or Bet v 1 from birch pollen), rather than to a mixture of the allergens extracted from the source. Testing sIgE to component allergens may add additional diagnostic value by differentiating immune responses that are directed toward clinically relevant allergenic proteins.

Table 141-2 Nonallergic Diseases Associated with Increased Serum IgE Concentrations

PARASITIC INFESTATIONS
Ascariasis
Capillariasis
Echinococcosis
Fascioliasis
Filariasis
Hookworm
Onchocerciasis
Malaria
Paragonimiasis
Schistosomiasis
Strongyloidiasis
Trichinosis
Visceral larva migrans
INFECTIONS
Allergic bronchopulmonary aspergillosis
Candidiasis, systemic
Coccidioidomycosis
Cytomegalovirus mononucleosis
Human immunodeficiency virus type 1 infections
Infectious mononucleosis (Epstein-Barr virus)
Leprosy
Pertussis
Viral respiratory infections
IMMUNODEFICIENCY
Autosomal dominant hyperimmunoglobulin E syndrome (*STAT3* mutations)
Autosomal recessive hyperimmunoglobulin E syndrome (*DOCK8, TYK2* mutations)
IgA deficiency, selective
Nezelof syndrome (cellular immunodeficiency with immunoglobulins)
Thymic hypoplasia (DiGeorge anomaly)
Wiskott-Aldrich syndrome
NEOPLASTIC DISEASES
Hodgkin disease
IgE myeloma
Bronchial carcinoma
OTHER DISEASES AND DISORDERS
Alopecia areata
Bone marrow transplantation
Burns
Cystic fibrosis
Dermatitis, chronic acral
Erythema nodosum, streptococcal infection
Guillain-Barré syndrome
Kawasaki disease
Liver disease
Medications
Nephritis, drug-induced interstitial
Nephrotic syndrome
Pemphigus, bullous
Polyarteritis nodosa, infantile
Primary pulmonary hemosiderosis
Rheumatoid arthritis

In Vivo Tests

Allergen skin testing is the primary in vivo procedure for the diagnosis of allergic disease. Mast cells with sIgE antibodies attached to high-affinity receptors on their surfaces reside in the skin of allergic patients. The introduction of minute amounts of an allergen into the skin of the sensitized patient results in cross-linking of IgE antibodies on the mast cell surface, thereby triggering local mast cell activation. Once activated, these mast cells release a variety of preformed and newly generated mediators that act on surrounding tissues. Histamine is the mediator most responsible for the immediate wheal and flare reactions observed in skin testing. Examination of the site of a positive skin test result reveals a pruritic wheal surrounded by erythema. The time course of these reactions is rapid in onset, reaching a peak within 10-20 min and usually resolving over the next 30 min.

Skin testing is performed using the **prick/puncture technique.** With this technique, a small drop of allergen is applied to the skin surface, and a tiny amount is introduced into the epidermis by lightly pricking or puncturing the outer layer of skin through the drop of extract with a small needle or other device. When the **skin prick test**

Table 141-3 Determination of Specific IgE by Skin Testing Versus In Vitro Testing

VARIABLE	SKIN TEST*	sIgE ASSAY
Risk of allergic reaction	Yes (especially ID)	No
Relative sensitivity	High	High
Affected by antihistamines	Yes	No
Affected by corticosteroids	Usually not	No
Affected by extensive dermatitis or dermographism	Yes	No
Broad selection of antigens	Fewer	Yes
Immediate results	Yes	No
Expensive	No	Yes
Lability of allergens	Yes	No
Results evident to patient	Yes	No

*Skin testing may be the prick test or intradermal (ID) injection.

(SPT) result is negative but the history suggestive, selective skin testing (for vaccines, venom, drugs, and aeroallergens) using the **intradermal technique** may be performed. This technique involves using a 26-gauge needle to inject 0.01-0.02 mL of an allergen extract diluted 1,000- to 100-fold into the dermis of the arm. Intradermal skin tests are *not recommended for use with food allergens* because of the risk of triggering anaphylaxis. Irritant rather than allergic reactions can occur with intradermal skin testing if higher concentrations of extracts are used. Although skin prick testing is less sensitive than intradermal skin testing, positive SPT results tend to correlate better with clinical symptoms.

The number of skin tests performed should be individualized, with the allergens suggested by the history taken into account. A positive and negative control SPT, using histamine and saline, respectively, is performed with each set of skin tests. A negative control is necessary to assess for dermatographism, in which reactions are caused merely by applying pressure to overly sensitive skin. A positive control is necessary to establish the presence of a cutaneous response to histamine. Medications with antihistaminic properties in addition to adrenergic agents such as ephedrine and epinephrine suppress skin test responses and should be avoided for appropriate intervals (≈5 half-lives) prior to skin testing. Prolonged courses of systemic corticosteroids may suppress cutaneous reactivity by decreasing the number of tissue mast cells as well as their ability to release mediators.

Whether identified via serologic or skin testing, detection of sIgE denotes a sensitized state (i.e., atopy or a tendency toward development of allergic disease) but is not equivalent to a clinically relevant allergic diagnosis. *Many children with positive tests have no clinical symptoms upon exposure to the allergen*. Increasingly strong tests (higher serum sIgE results or larger SPT wheal sizes) generally correlate with increasing likelihood of clinical reactivity (but not severity). The limitations of these test modalities underscore the need for the clinician to obtain a detailed medical history that can guide the selection and interpretation of test results. Large panels of indiscriminately performed screening tests may, therefore, provide misleading information.

Both serum sIgE tests and SPT are sensitive and have similar diagnostic properties. The benefits of the serologic immunoassays are that performance is not limited by presence of skin disease (i.e., active atopic dermatitis) or medication use (i.e., antihistamines). Advantages of skin testing are that they provide rapid results to the patient/family during the clinic visit, do not require venipuncture, and are less costly.

Under certain circumstances, **provocation testing** is performed to examine the association between allergen exposure and the development of symptoms. The bronchial provocation test most frequently performed clinically is the methacholine challenge, which causes potent bronchoconstriction of asthmatic but not of normal airways. **Methacholine challenge testing** is performed to document the presence and degree of bronchial hyperreactivity in a patient in whom asthma is suspected. After baseline spirometry values are obtained, increasing concentrations of nebulized methacholine are inhaled until a drop occurs in lung function, specifically a 20% decrease in FEV_1 (forced expiratory volume in the first second of expiration), or the patient is able to tolerate the inhalation of a set concentration of methacholine, typically 25 mg/mL.

Oral **food challenges** are performed to determine whether a specific food causes symptoms or whether a suspected food can be added to the diet. Food challenges are performed for those foods incriminated by the history and results of skin tests and/or immunoassays for sIgE. These challenges may be performed in an open, single-blind, double-blind, or double-blind placebo-controlled fashion and involve the ingestion of gradually increasing amounts of the suspected food at set time intervals until the patient either experiences a reaction or tolerates a normal portion (i.e., 1 serving size) of the food openly. Because of the potential for significant allergic reactions, these challenges should be performed only in an appropriately equipped facility with personnel experienced in the performance of food challenges and the treatment of anaphylaxis, including cardiopulmonary resuscitation.

Upper gastrointestinal **endoscopy** is required to confirm the diagnosis of eosinophilic esophagitis. One or more biopsy specimens from the proximal and distal esophagus must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (high power field) (peak value) is considered a minimum threshold for the diagnosis.

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Chapter 142

Principles of Treatment of Allergic Disease

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The basic principles of the treatment of allergic disease include the avoidance of exposure to allergens and irritants that trigger symptoms and the pharmacologic management of symptoms caused by unavoidable acute and chronic allergen exposures. In selected patients, allergen immunotherapy may be considered.

ENVIRONMENTAL CONTROL MEASURES

Children spend the majority of their time in indoor environments, including the home. In an effort to save energy, houses and buildings have been built more tightly and with more insulation with limited air exchange. These factors have led to an increase in indoor humidity and higher concentrations of allergens and irritants. Examination of indoor environments suggests that house dust mite, cat, and cockroach allergens are the most common significant triggers of allergic disease in these settings; exposures to allergens from other pets, pests, mold, and respiratory irritants such as cigarette smoke are also a problem.

More than 30,000 species of mites have been identified, but the term *dust mites* usually refers to the pyroglyphid mites *Dermatophagoides pteronyssinus, Dermatophagoides farinae,* and *Euroglyphus maynei,* which are the major sources of allergen in house dust. Respiration and water vapor exchange occur through the skin of dust mites, rendering them sensitive to humidity and temperature extremes. The regular use of humidifiers promotes dust mite survival. Mites do not survive with relative humidity <50%. They feed on animal and human skin scales and other debris, which is why they exist in large numbers in mattresses and bedding, carpet, and upholstered furniture. They may also be found in flour and mixes for baked goods. Anaphylaxis has been reported following the ingestion of baked goods, such as waffles and pancakes, prepared with flour infested with dust mites ("pancake syndrome"). Dust mite fecal pellets are a major source of allergens. They consist of partially digested food combined with digestive enzymes encased in a permeable membrane, which keeps the fecal pellets intact. These fecal pellets have been likened to pollen grains, given their similarities in size (10-40 μm), the amount of allergen they contain, and their ability to release allergens rapidly on contact with moist mucous membranes. Mites can persist in imported furnishings for at least 2 yr; mite allergens have been shown to remain stable under domestic conditions for periods of at least 4 yr. Dust mite allergens become airborne during normal household activities; a vigorous disturbance, such as vacuuming without a vacuum bag, shaking a bed sheet, or a pillow fight, can launch significant amounts of dust mite allergens into the air. Once airborne, dust mite allergen particles settle out of the air relatively rapidly because of their size and weight. Nonetheless, dust mite allergen exposure likely occurs during sleep on mite-infested pillows and mattresses and during normal household activities when dust mite concentrations in the home are high. Levels of dust mite allergens as

Table 142-1 Environmental Control of Allergen Exposure

ALLERGEN	CONTROL MEASURES
Dust mites	Encase bedding in airtight, allergen-impermeable covers Wash bedding weekly in water at temperatures >54.4°C (130°F) Remove wall-to-wall carpeting Replace curtains with blinds Remove upholstered furniture Reduce indoor humidity Minimize bedroom and living room clutter
Animal dander	Avoid furred pets Keep animals out of patient's bedroom
Cockroaches	Control available food and water sources Keep kitchen/bathroom surfaces dry and free of standing water Seal cracks in walls Use professional extermination services; safe pesticide should be used in baits
Mold	Repair moisture-prone areas Avoid high humidity in patient's bedroom Use high-efficiency particulate air (HEPA) filters in living areas Repair water leaks Replace carpets with hardwood floors Regularly check basements, attics, and crawl spaces for standing water and mold
Pollen	Keep automobile and house windows closed Control timing of outdoor exposure Restrict camping, hiking, and leaf raking Drive in an air-conditioned automobile Air-condition the home Install portable HEPA filters

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2010, Mosby, p. 297.*

low as 2 μg/g of house dust can lead to sensitization, whereas levels of 10 μg/g of house dust are associated with symptoms.

Appropriate environmental control measures can significantly reduce exposure to dust mite allergens (Table 142-1). Major emphasis should be placed on reducing exposure to dust mite allergens in the bedroom and living areas in which the child spends a large amount of time. Encasements impermeable to dust mite allergens should be placed on all pillows, the mattress, and the box spring. Dust should be removed from the surfaces of these covers and the bed frame by vacuuming weekly. The sheets and mattress pad should be washed weekly in hot water at a temperature of >54.4°C (130°F). Minimizing the number of items in the room that collect dust, such as books, drapes, toys, stuffed animals, and any clutter, is recommended. Major reservoirs of dust mite allergen that are often more difficult to deal with include the carpet and upholstered furniture, which should be vacuumed weekly with an efficient double-thickness-bagged vacuum cleaner. The actual benefit of applying acaricides or denaturing agents to carpets and upholstered furniture remains unclear, and the amount of effort required may be more than most families are willing to invest. If possible, carpet removal, at least in the bedroom, may prove a better choice for eliminating a large reservoir of dust mite allergen. Other measures for dust mite allergen control include maintaining the indoor relative humidity at <50% and keeping the air conditioning set at the lowest level during the warmer months.

In many countries, more than half of the households have pets, the most common of which are cats and dogs. The major sources of allergens from cats, dogs, and horses are hair, dander, and saliva, whereas the major source of allergens from rodents is urine. Studies of airborne cat allergen have shown that a significant portion is found on small particles. As much as 30% of airborne cat allergen may reside on particles <5 μm. Particles this small may not be adequately filtered by the nose and could potentially be deposited in the airways. Their small size enables these particles to remain airborne for longer periods and to be suspended repeatedly by air currents from heating and ventilation systems or just by walking across the carpet or sitting in an upholstered chair. **Fel d 1,** the major cat allergen, is a highly charged protein that readily sticks to a variety of surfaces, including walls, carpeting, and upholstered furniture. Owing to this adhesiveness, cat allergens bind to the cat owner's clothing and are routinely transported to public buildings, including schools, where they have been measured in moderately high amounts. From these sites, significant amounts of cat allergen can subsequently be carried into homes without cats. Analysis of house dust from homes with cats reveals levels of Fel d 1 ranging from 8 μg to 1.5 mg/g of house dust. Levels of Fel d 1 in homes without cats vary from 0.2 to 80 μg/g of house dust. Sensitization to cat allergen is associated with levels ranging from 1 to 8 μg/g of house dust. Carpets, upholstered furniture, and bedding serve as reservoirs of cat allergens, resulting in the persistence of significant amounts in the home for months after a cat has been removed. Complete avoidance of cat allergen is virtually impossible, although significant reduction in exposure to cat allergens is achievable.

Removing the pet from the home is obviously the most effective means of reducing exposure to animal allergens, although it has been demonstrated that without other interventions, such as removing carpeting and upholstered furniture and wiping down walls, it takes 6 mo or more for the levels of cat allergen to drop to a level found in houses without a cat. As a result, cat owners who remove their pets from their homes should be informed not to expect immediate results. Unfortunately, advice to remove a pet from the home or keep it outdoors is often ignored. In contrast to dust mite allergens, cat allergen is light and remains suspended in the air for long periods. As a result, **air cleaners with high-efficiency particulate air (HEPA) filters** are helpful in reducing the amount of airborne cat allergen. Other suggested methods include washing the cat regularly and maintaining a cat allergen–free bedroom from which the cat is excluded and where mattress covers and air-filtering devices are used. The cat should also be restricted from other living areas where the sensitized child spends large amounts of time, such as the family room and other play areas (see Table 142-1). Regular vacuuming with a HEPA-filtered and double-thickness bag vacuum cleaner is also encouraged. Similar measures are suggested for the control of exposure to other animal allergens, although whether these measures reduce exposure to levels resulting in clinical improvement as demonstrated by decreased symptoms, improved peak flows, or decreases in bronchial hyperreactivity remains to be documented by appropriately controlled studies.

Infestation of the home by insects and other pests, such as mice and rats, is another potential source of significant indoor allergen exposure. Studies have identified exposure to cockroach allergens as a major risk factor for the development of asthma in inner-city children. Once sensitized, inner-city cockroach-sensitive asthmatic children with continued exposure to high levels of cockroach allergens in their bedrooms are at higher risk for urgent care visits and hospitalization than are inner-city asthmatic children who are not allergic to cockroaches. Recommended methods to decrease cockroach allergen exposure include reducing cockroaches' access to the home by sealing cracks in the flooring and walls and removing sources of food and water by repairing leaky pipes, putting away food in sealed containers, and frequent cleaning (see Table 142-1). Regular extermination using baits or chemical treatment of infested areas is also advised.

Efforts to improve indoor air quality should also encompass reducing exposure to respiratory irritants. Passive exposure to environmental tobacco smoke worsens asthma and increases nasal symptoms in patients with allergic nasal disease. Smoking cessation should be repeatedly encouraged, and smoking indoors should never be permitted. The use of wood-burning stoves, fireplaces, and kerosene heaters should also be discouraged.

Although exposure to pollens and molds occurs primarily outdoors, these allergens are detectable indoors during the warmer months,

when their indoor levels often reflect their prevalence in the outdoor environment. During the winter, when the outdoor levels of other molds are lowest, the indoor molds *Aspergillus* and *Penicillium* are the most prevalent. Molds are often found in damp basements and thrive in conditions associated with increased moisture in the home, such as water leaks, flooding, and increased humidity promoted by the excessive use of humidifiers or swamp coolers. Exposure to indoor mold allergens can be reduced by maintaining the indoor relative humidity at <50%, removing contaminated carpets, and wiping down washable surfaces prone to fungal growth, such as shower stalls, shower curtains, sinks, drip trays, and garbage pails, with the use of solutions of detergent and 5% bleach (see Table 142-1). Dehumidifiers should be placed in damp basements. Standing water at any site in the home should be eliminated, and the cause addressed. Removing all items from the home that are prone to mold contamination is also encouraged. Keeping the windows and doors closed and using air conditioning to filter outdoor air can keep both indoor pollen and mold levels to a minimum during the warmer months, when outdoor levels of these allergens are at their peak. The use of window or attic fans is to be avoided. Laundry should be dried in a dryer rather than on a clothesline. Measures to avoid pollens and mold spores when out of the house include closing the windows and using the air conditioner when traveling in the car, avoiding moldy vegetation, and wearing a mask when these materials cannot be avoided. Outdoor activities during periods of high pollen counts should be kept to a minimum. Pollen travels best on warm, dry, breezy days but counts are lowest during chilly, wet periods. Someone other than the sensitized patient should mow the lawn and rake leaves. Hand washing after outdoor play is suggested to avoid transferring pollens from the hands to the eyes and nose. At the end of the day, showering and shampooing are suggested to avoid contamination of the bed with allergens.

PHARMACOLOGIC THERAPY

Adrenergic Agents

Adrenergic agents exert their effects through the stimulation of cell surface α- and β-adrenergic receptors in a variety of target tissues. In general, α-adrenergic receptor stimulation results in excitatory responses such as vasoconstriction, whereas β-adrenergic stimulation leads to inhibitory responses such as bronchodilation. The α-adrenergic receptors have been classified into α_1- and α_2-adrenergic receptors. There are 3 subtypes of α_1-adrenergic receptors and 3 subtypes of α_2-adrenergic receptors. The β-adrenergic receptors are further divided into 3 subtypes: β_1, β_2, and β_3. Each of these adrenergic receptors exhibits a distinctive tissue distribution. The physiologic response in a given tissue to the administration of an adrenergic agent depends on the specific receptor-binding characteristics of the drug as well as the numbers and distribution of the various types of adrenergic receptors in the tissue. Epinephrine remains the drug of choice for the treatment of anaphylaxis because of its combined α- and β-adrenergic effects. Epinephrine autoinjectors are prescribed for ease of administration and are available in 2 dosages: 0.15 mg for children who weigh <30 kg, and 0.30 mg for children who weigh ≥30 kg, according to manufacturer recommendations. Consider prescribing the 0.15 mg dose for children who weigh ≥25 kg to avoid under-dosing.

The α-adrenergic agents are effective in the treatment of allergic nasal disease because of their decongestant effects (see Tables 143-4 and 143-5). In the nose, stimulation of α_1-adrenergic receptors on postcapillary venules and of α_2-adrenergic receptors on precapillary arterioles leads to vasoconstriction, resulting in a reduction in nasal congestion. The oral decongestants currently in clinical use include pseudoephedrine and phenylephrine. These medications are available individually or in combination with antihistamines in liquid and tablet forms, including sustained-release preparations. Pseudoephedrine is rapidly and thoroughly absorbed, whereas phenylephrine, the less effective of the 2 drugs, is incompletely absorbed, resulting in a significantly lower bioavailability of ≈38%. Peak plasma concentrations of these drugs are reached between 30 min and 2 hr of administration, but the decongestant effect has not been directly correlated to the plasma concentration. Pseudoephedrine is excreted essentially unchanged by the kidney. The use of oral decongestants should be avoided in patients <6 yr of age and in patients with hypertension, coronary artery disease, glaucoma, or metabolic disorders, such as diabetes and hyperthyroidism. Reported **adverse effects** of oral decongestants include excitability, headache, nervousness, palpitations, tachycardia, arrhythmias, hypertension, nausea, vomiting, and urinary retention. Decongestants available as topical nasal sprays include phenylephrine, oxymetazoline, naphthazoline, tetrahydrozoline, and xylometazoline. Given their efficacy and rapid onset of action, the potential for excessive use of topical nasal decongestants resulting in rebound nasal congestion (rhinitis medicamentosa) is high and patients should be carefully counseled to prevent dependency on the product. Thus, limiting the use of these sprays to 2-3 days is generally recommended.

Drugs that stimulate β-adrenergic receptors have been used for years in the treatment of asthma because of their potent bronchodilator effects (see Table 144-16). The subclassification of β-adrenergic receptors into β_1 and β_2 subtypes led to the development of drugs selective for the β_2-adrenergic receptor, such as albuterol, levalbuterol, and pirbuterol, that have the advantage of producing significant bronchodilation with less cardiac stimulation. *The long-acting inhaled β_2-adrenergic agonists (LABAs) salmeterol and formoterol,* with a 12-hr duration of action, are approved for use in children ≥4 yr of age. LABAs are not recommended for the treatment of acute asthma exacerbations because of their relatively slow onset of action. Concern about an increased risk of asthma-related adverse events is why LABAs are not recommended as monotherapy for the long-term control of persistent asthma, but are promoted as best used in conjunction with an inhaled steroid. Dry powder inhaled and metered-dose inhaler preparations combining a *LABA with an inhaled corticosteroid have had significant impact on treatment of moderate persistent asthma.* In addition to their bronchodilating effects, β_2-adrenergic agonists have been reported to improve mucociliary clearance, decrease microvascular permeability, inhibit cholinergic nerve transmission, and reduce mediator release in mast cells, basophils, and eosinophils. Although β-adrenergic agonists can be delivered orally, by inhalation, or by injection, the inhaled route is preferred because of the rapid onset of action and fewer adverse effects. Reported **adverse effects** of β-adrenergic agents include tremor, palpitations, tachycardia, arrhythmias, central nervous system stimulation, hyperglycemia, hypokalemia, hypomagnesemia, and a transient increase in hypoxia, which is attributed to an increase in perfusion to inadequately ventilated areas of the asthmatic lung.

Anticholinergic Agents

Anticholinergic drugs inhibit vagally mediated reflexes by antagonizing the action of acetylcholine at muscarinic receptors. Of the available anticholinergic agents, **ipratropium bromide** is the most commonly used. It is a quaternary amine that is poorly absorbed across mucosal surfaces and does not readily cross the blood–brain barrier. As a bronchodilator, it has a slower onset of action than short-acting inhaled β_2-agonists and takes longer to reach maximal effect, making it less effective as a rescue medication. There is increasing support, particularly in children, for combination therapy using ipratropium bromide and β-agonist therapy in more severe asthma exacerbations. Multiple doses of combined therapy can decrease risk of hospitalization in children by 25%. Ipratropium is available by prescription as a metered-dose inhaler delivering 17 μg/spray and as a 0.02% nebulized solution (500 μg/2.5 mL).

Ipratropium given as a nasal spray (0.03-0.06%) is effective in the reduction of rhinorrhea resulting from perennial nonallergic rhinitis, the common cold, and vasomotor rhinitis. The use of ipratropium is suboptimal in the treatment of moderate to severe allergic rhinitis because it does not alter other common allergic nasal symptoms, such as sneezing, nasal congestion, and pruritus. Nasal dryness and epistaxis are occasionally encountered with use of the nasal spray.

Antihistamines

The release of histamine and its effects on surrounding tissues is central to the development of symptoms classically associated with the allergic response. Histamine exerts its effects through binding with 1 of its 4

receptors, as H_1-, H_2-, H_3-, or H_4-receptor. Histamine effects triggered through H_1-receptor binding are those most relevant to allergic inflammation, and include pain, pruritus, vasodilation, increased vascular permeability, smooth muscle contraction, mucus production, and the stimulation of parasympathetic nerve endings and reflexes. The antimuscarinic effect of some of the early H_1-type antihistamines may be explained by the reported 45% homology of the H_1-receptor with the human muscarinic receptor. The H_1-type antihistamines prevent the effects of H_1-receptor activation through reversible, competitive inhibition of histamine by binding to the H_1-receptor. Antihistamines work best in preventing rather than reversing the actions of histamine and are most effective when given at doses and dosing intervals resulting in the persistent saturation of target organ tissue histamine receptors.

The H_1-type antihistamines are traditionally divided into 6 classes on the basis of differences in their chemical structures (Tables 142-2 and 143-3). These antihistamines are further divided into first-generation antihistamines, which, because of their lipophilicity, cross the blood–brain barrier to exert effects on the central nervous system, and second-generation antihistamines, which exert minimal, if any, central nervous system effects because of their inability to cross the blood-brain barrier owing to their size, charge, and lipophilicity. The sedative effects and cognitive impairment associated with the use of first-generation antihistamines are well documented. Thus, a primary advantage of second-generation antihistamines is that they are nonsedating or much less sedating than first-generation antihistamines. Although fexofenadine is considered the least sedating of the available nonprescription antihistamines (0% occupation of central nervous system H_1-receptors), cetirizine has the most potential for sedation (26-30%). Both first- and second-generation antihistamines are available in oral preparations. Many first-generation and second-generation antihistamines are available in nonprescription form, including diphenhydramine, loratadine, fexofenadine, and cetirizine. Other antihistamines require a prescription, such as hydroxyzine and cyproheptadine. Antihistamines available as an intranasal spray are azelastine and olopatadine, the latter also functioning as a mast cell stabilizer. The benefit of this form of administration is the potential for a rapid onset of action, within 15 min. Azelastine, which is systemically absorbed and can cross the blood–brain barrier, has the potential for central nervous system effects in some patients and is not currently approved for use in children <12 yr of age. Patients often experience a bitter metallic taste in their mouths when using azelastine, which is a common reason for nonadherence.

Orally administered antihistamines are well absorbed and reach peak serum concentrations within ~2 hr. High tissue concentrations of antihistamines are usually achieved, likely accounting for the sustained suppression of wheal and flare reactions even after serum levels have significantly declined. Most antihistamines are metabolized by the hepatic cytochrome P450 enzyme system. Elimination of antihistamines may be reduced in patients with hepatic impairment or by the simultaneous ingestion of inhibitors of this pathway, such as erythromycin and other macrolide antibiotics, ciprofloxacin, ketoconazole, itraconazole, and certain antidepressants, such as nefazodone and fluvoxamine. Some antihistamines, such as hydroxyzine and loratadine, are converted to clinically active metabolites. Clearance of fexofenadine and cetirizine is reduced in patients with impaired renal function. Cetirizine clearance is also reduced in patients with hepatic dysfunction. Fruit juices (apple, orange, grapefruit) are organic anion transporter inhibitors and interfere with the absorption of fexofenadine: juices should be avoided 4 hr before or 1-2 hr after taking fexofenadine.

The efficacy of antihistamines in the treatment of seasonal and perennial allergic rhinoconjunctivitis is well documented (see Chapter 143). Compared with other medications in regard to the relief of allergic nasal symptoms, antihistamines are more effective than cromolyn sodium, but significantly less effective than intranasal corticosteroids. Improvement in symptom relief in patients with allergic rhinitis has been reported when an antihistamine is given in combination with a decongestant or with an intranasal steroid. Numerous formulations combining antihistamines and decongestants are available. Antihistamines have also been shown to be beneficial in the treatment of acute and chronic urticaria/angioedema. With regard to asthma, a significant clinical effect of antihistamines at conventional doses is difficult to document, other than the possible improvement offered by better control of allergic nasal symptoms.

Second-generation antihistamines are preferable over first-generation antihistamines for the treatment of allergic disease in children because of negligible sedative and anticholinergic effects without a sacrifice in efficacy. Most second-generation antihistamines are effective with convenient once-daily dosing, which may improve therapy adherence. The widespread availability of first-generation antihistamines and their lower cost account for their continued use. The **adverse effects** most often encountered with second-generation agents include the performance impairment and anticholinergic effects noted with first-generation antihistamines although generally to a lesser degree. The anticholinergic adverse effects encountered may include drying of the mouth and eyes, urinary retention, constipation, excitation, nervousness, palpitations, and tachycardia. Prolongation of the QT interval and ventricular tachycardia (torsades de pointes) has been noted in older no longer available second-generation antihistamines; current antihistamines are not associated with concerning cardiac effects.

Table 142-2 Classification of Antihistamines (H_1-Antagonists)

CLASS	EXAMPLES
ETHYLENEDIAMINES	
First-generation	Antazoline, pyrilamine, tripelennamine
TYPE II ETHANOLAMINES	
First-generation	Carbinoxamine, clemastine, diphenhydramine
TYPE III ALKYLAMINES	
First-generation	Brompheniramine, chlorpheniramine, triprolidine
Second-generation	Acrivastine
TYPE IV PIPERAZINES	
First-generation	Cyclizine, hydroxyzine, meclizine
Second-generation	Cetirizine, levocetirizine
TYPE V PIPERIDINES	
First-generation	Azatadine, cyproheptadine, ketotifen
Second-generation	Fexofenadine, loratadine, desloratadine
TYPE VI PHENOTHIAZINES	
First-generation	Methdilazine, promethazine

Chromones

Cromolyn sodium and nedocromil sodium are the 2 chromones used to treat allergic disorders. Neither cromolyn nor nedocromil is absorbed well orally, with only 1% of the swallowed dose absorbed. These drugs must be applied topically to the mucosal surface of the target organ to be effective. Both drugs inhibit mast cell degranulation and mediator release. They suppress the activation of a variety of cells, such as eosinophils, neutrophils, macrophages, and epithelial cells. They also suppress the activity of afferent C-type sensory nerve fibers of the nonadrenergic, noncholinergic nervous system. Both drugs inhibit the intracellular increase in free calcium after mast cell activation and phosphorylate a mast cell protein resembling moesin, which is thought to be involved in terminating mediator release.

Cromolyn and nedocromil prevent early- and late-phase allergic responses when administered before allergen exposure. They block allergen-induced increases in bronchial hyperresponsiveness, as well as seasonal increases in nonspecific bronchial hyperresponsiveness. With prolonged use, both drugs are capable of reducing bronchial hyperresponsiveness. These drugs have no bronchodilator properties but can inhibit the bronchoconstrictive effects of a variety of stimuli, such as allergen challenge, exercise, hyperventilation with cold air,

ultrasonically nebulized distilled water, and exposure to atmospheric and industrial pollutants.

Cromolyn and nedocromil are used as alternative, but not preferred, therapy for the treatment of mild persistent asthma. Because of their lack of bronchodilator properties, neither drug is useful for the treatment of acute asthma, although both may be used as preventive treatment before vigorous exercise or unavoidable known allergen exposure. Nedocromil is the more potent of the two, but no formulation of nedocromil is currently available for asthma in the United States. Cromolyn is available for the treatment of asthma by prescription as a 1% solution (20 mg/2 mL) for nebulization. The suggested dose for the treatment of asthma is 20 mg of cromolyn 2-4 times/24 hr by nebulization. In numerous studies, cromolyn has been found useful in the treatment of allergic rhinitis and allergic conjunctivitis. Preparations for the nasal and ocular administration of cromolyn are available without a prescription. The suggested dose for the treatment of allergic rhinitis is one spray in each nostril 3 to 4 times daily of a nasal spray containing 5.2 mg of cromolyn per spray (see Table 143-5). For the treatment of allergic conjunctivitis, the suggested dose is 1 drop in each eye 4-6 times a day of a 4% ophthalmic solution. A 2% solution of nedocromil is available by prescription for the treatment of allergic conjunctivitis at a suggested dose of 1-2 drops in each eye twice daily.

The safety of these drugs, even with prolonged administration, is well documented. Because of their favorable safety profile, the chromones are often chosen for use during pregnancy.

Glucocorticoids

Glucocorticoids are widely used in the treatment of allergic disorders because of their potent antiinflammatory properties. The diverse antiinflammatory actions of glucocorticoids are mediated via the glucocorticoid receptor, which is present in all inflammatory effector cells, as well as by direct inhibition of cytokines and mediators. Glucocorticoids are administered topically in ophthalmic preparations, nasal sprays, creams and ointments, metered-dose inhalers, and as a solution for nebulization. Systemic administration is accomplished orally or parenterally. The proper use and efficacy of glucocorticoids in the treatment of allergic disease along with the adverse effects associated with their use are presented in discussions of individual allergic diseases (see Chapters 142-152).

Leukotriene-Modifying Agents

Drugs that alter the leukotriene pathway exert their clinical effects either by inhibiting leukotriene production or by blocking receptor binding. These agents possess mild antiinflammatory properties and exhibit bronchodilator effects. In addition to inhibiting the early- and late-phase allergic responses to inhaled allergen, they diminish bronchoconstriction induced by exercise and exposure to allergen, aspirin, and cold air. Leukotriene-modifying agents have some use in the treatment of asthma (see Chapter 144) and are modestly effective in the treatment of allergic rhinitis (see Chapter 143).

Theophylline

Because of its bronchodilating effects, theophylline (1,3-dimethylxanthine) had been used for yr for the treatment of acute and chronic asthma. The bronchodilator effect of theophylline is likely caused by its action as a phosphodiesterase inhibitor, whereas its ability to antagonize adenosine receptors may play a role in other effects, such as the attenuation of diaphragmatic muscle fatigue and diminishing adenosine-enhanced mast cell mediator release. Theophylline inhibits the immediate- and late-phase pulmonary responses to allergen challenge and exhibits modest protective effects. The therapeutic and toxic effects of theophylline are related to the serum concentration, with the incidence of toxic effects significantly increasing as the serum levels approach and exceed 20 μg/mL. A variety of conditions and medications are capable of increasing or decreasing theophylline metabolism. The **toxic effects** of theophylline, ranging from mild nausea, insomnia, irritability, tremors, and headache to cardiac arrhythmias, seizures, and death, necessitate the routine monitoring of theophylline serum levels. Because of the introduction of other effective therapies for the treatment of acute and chronic asthma, the need to monitor drug serum levels routinely, and the potential for significant toxicity, the role of theophylline in the treatment of asthma has contracted significantly (see Chapter 144).

Lodoxamide Tromethamine

A mast cell stabilizer, lodoxamide tromethamine is more effective than topical cromolyn sodium in alleviating signs and symptoms of allergic ocular disease (see Chapter 147). It is used in children >2 yr of age for vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis. Occasional adverse effects have included transient burning or stinging after instillation.

Combination Mast Cell Stabilizer and Antihistamine

Olopatadine, epinastine, and ketotifen are examples of combination mast cell stabilizers and H_1-receptor antagonists effective in relieving signs and symptoms of allergic conjunctivitis after topical instillation, although all H_1-antihistamines likely have some mast cell stabilizing activity. Dosing is typically twice per day, except of olopatadine, which is dosed once daily.

Antiimmunoglobulin E

Monoclonal antiimmunoglobulin E antibodies (anti-IgE) bind to circulating IgE at a site that prevents its subsequent attachment to the high-affinity receptors for IgE on the mast cell surface. The parenteral administration of anti-IgE reduces free serum IgE concentrations, inhibits skin test responses in allergic patients, suppresses early- and late-phase responses to allergens, and decreases sputum eosinophilia in asthmatic persons. Anti-IgE has a beneficial effect in the treatment of patients with asthma, allergic rhinitis, and urticaria. An anti-IgE preparation **(omalizumab)** is available for the treatment of children ≥12 yr of age with documented allergen-induced asthma that is inadequately controlled by inhaled corticosteroids. Although this agent is usually well tolerated, local reactions at the injection site and rare episodes of anaphylaxis have been reported. Anti-IgE may also be beneficial in the treatment of other allergic disorders, such as anaphylaxis and food allergy, but more studies are needed. One monoclonal antibody preparation of anti-IgE used in the treatment of adults with peanut allergy resulted in a significant increase in the symptom threshold dose of peanuts. The cost of anti-IgE therapy and need for regular injections requires careful patient selection, special consideration being given to those patients with persistent symptoms despite aggressive pharmacotherapy, significant adverse effects of current therapy, and more than 1 allergic disorder.

Nasal Saline Irrigation

Irrigation with nasal saline can improve symptoms for those with mild allergic rhinitis. Nasal saline irrigation can be used alone or before topical medication. Squeeze bottle kits for this purpose are available over the counter, and typically about 200 mL are irrigated through the nares. Patients may make their own irrigation solutions or buy commercially-prepared solutions. Patients should use boiled or distilled water, as cases of sinus infection with amoebas found in tap water have been reported.

New Therapies

Recombinant soluble interleukin (IL)-4 receptor antagonists exert their effects by binding to and inactivating IL-4 before it can attach to its cell surface receptor. Although initial studies of an inhaled soluble IL-4 receptor in patients with moderate asthma requiring inhaled corticosteroids suggested a beneficial clinical effect, subsequent clinical studies of the effects of anti–IL-4 drugs in the treatment of asthma revealed these therapies to be safe, but clinical efficacy was lacking. Clinical trials of humanized monoclonal anti–IL-5 antibodies administered by injection to asthmatic patients revealed a decrease in circulating eosinophils and sputum eosinophilia, but a lesser reduction of eosinophils from the bronchial submucosa, and this effect was

unaccompanied by a reduction in methacholine reactivity or a suppression of the early- or late-phase response to allergen.

The use of cytokines with antiinflammatory effects in the treatment of allergic disorders is under investigation. Unfortunately, initial studies have not demonstrated a beneficial effect of IL-10 or interferons in the treatment of asthma. Although studies have documented that IL-12 administration is associated with a decrease in eosinophil accumulation in response to allergen challenge, inhibition of early- and late-phase responses to allergen and decreases in bronchial hyperreactivity have not been observed. In addition, the high incidence of significant adverse effects encountered with IL-12 administration limits its potential as a viable therapeutic option.

ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy involves administering gradually increasing doses of allergens to a person with allergic disease for the purpose of reducing or eliminating the patient's adverse clinical response to subsequent natural exposure to those allergens. When properly administered to an appropriate candidate, allergen immunotherapy is a safe, effective form of therapy capable not only of reducing or preventing symptoms but also of potentially altering the natural history of the disease by minimizing disease duration and preventing disease progression. Conventional allergen immunotherapy is given subcutaneously under the direction of an experienced allergist. Sublingual immunotherapy (SLIT) is widely used in Europe for aeroallergens but is not yet FDA-approved in the United States. Sublingual and oral immunotherapy (OIT) for foods are being investigated and are also not FDA-approved.

Indications and Contraindications

Allergen immunotherapy is reserved for patients with an allergic disease demonstrated to respond to this form of therapy, such as seasonal or perennial allergic rhinoconjunctivitis, asthma triggered by allergen exposures, and insect venom sensitivity. Proof of the efficacy of conventional allergen immunotherapy for the treatment of food allergy, atopic dermatitis, latex allergy, and acute or chronic urticaria is lacking; consequently, conventional allergen immunotherapy is not recommended for the treatment of these disorders. Before allergen immunotherapy is considered, sensitivity of the patient to the allergens to be administered should be documented by a positive skin test result or an in vitro test revealing an increased serum level of allergen-specific IgE. The clinical relevance of these allergens should be supported by a history of symptoms upon known exposure or a timing of symptoms that correlates well with suspected allergen exposure, such as the presence of allergic nasal and ocular symptoms throughout the late summer and fall in a child with a positive ragweed skin test response. The duration and severity of the patient's symptoms, as well as the patient's preferences, should warrant the expense, effort, and risk associated with the administration of allergen immunotherapy. The presence of disabling symptoms in spite of a trial of allergen avoidance and appropriate medications at a suitable dose should be documented. Venom immunotherapy (VIT) is indicated in children <16 yr of age who have experienced respiratory or cardiovascular symptoms following a sting. For those ≥16 yr, VIT is indicated for any systemic reaction, including those limited to skin but not contiguous from the site of the sting (see Chapter 146).

Other factors that may affect the decision to institute allergen immunotherapy include quality-of-life issues, such as the amount of school missed or medical resource utilization, the age of the patient, and other logistical factors. With the exception of VIT, few data for the efficacy of allergen immunotherapy in children <5 yr of age are available. Allergen immunotherapy is not recommended for children <5 yr of age because of their increased risk of systemic reactions, the special expertise required to treat anaphylaxis in this age group, their potential inability to communicate clearly with the physician in the event of an allergic reaction, and their age-related potential for emotional distress with frequent injections. Other important logistic factors include the willingness of the patient to comply with a schedule of frequent injections over the course of several yr, cost considerations, and the availability of an appropriate medically supervised setting for administering allergen immunotherapy.

Allergen immunotherapy is **contraindicated** in children undergoing β-blocker therapy as well as those with certain immunologic or autoimmune disorders, allergic bronchopulmonary aspergillosis, hypersensitivity pneumonitis, severe psychiatric disturbance, or a medical condition that would impair the ability to survive an allergic reaction. Pregnancy is a contraindication to the initiation of allergen immunotherapy or dosing increases, although a pregnant adolescent can continue to receive her usual maintenance dose. Patients with unstable asthma should not be started on allergen immunotherapy because of their increased risk for anaphylaxis. Allergen immunotherapy is not used for the treatment of allergic bronchopulmonary aspergillosis or hypersensitivity pneumonitis because it has no benefit. Children receiving β-blockers and angiotensin-converting enzyme-inhibitors are not ideal candidates for allergen immunotherapy because of an increased intensity of allergic reactions and a poor response of conventional therapy to these reactions with β-blocker therapy. Allergen immunotherapy is usually avoided in patients with autoimmune disorders because of the theoretical concern for stimulation of the immune system (formation of antigen–antibody complexes), which might result in disease activation.

Allergen Extracts

The potency of the aqueous extracts used in allergen immunotherapy is affected by numerous factors. Allergens from weed and grass pollens are more easily extracted in aqueous solutions and, as a result, are more potent than extracts obtained from other sources, such as molds, tree pollens, and dust mites. Owing to their complexity, allergen extracts from mold allergens are more variable than extracts from pollen allergens. Refrigeration and appropriate handling of allergen extracts used in allergen immunotherapy are important because degradation of many allergen extracts, such as those from tree, grass, weed pollens, and dust mites, may occur at higher temperatures. Dilute extracts are more susceptible to loss of potency resulting from adherence of allergen to the glass vial than are more concentrated extracts. To combat this effect, preservatives such as 0.03% human serum albumin or 10-50% glycerin may be added to dilute allergen extracts. Some allergen extracts, such as those from cockroaches, dust mites, and molds, contain proteases capable of degrading other allergens in the extract. It is often recommended that these allergens not be mixed with those from tree, grass, and weed pollens. Insect venoms are never mixed with other allergens. When available, the use of standardized allergen extracts is preferred to ensure consistency in dosing and to avoid the variability in allergen content encountered with nonstandardized allergen extracts.

Allergen Extract Administration

The goal of allergen immunotherapy is to increase gradually the dose of allergen extract administered until the injection of an "optimal" maintenance dose containing 4-12 μg of each major allergen in the extract is reached. The mixture of allergen extracts administered during the course of allergen immunotherapy is individually formulated for each patient on the basis of the patient's documented sensitivities. Although various dosing schedules are used, initial injections are most often given at 5-10–day intervals year-round. Schedules of allergen administration are selected according to the sensitivity of the patient to the allergens in the extract. The most sensitive patients are advanced to a maintenance dose more gradually. Doses of allergen immunotherapy are increased according to a set schedule, although the reaction to the previous injection is also taken into account. A systemic reaction to the previous dose would result in a significant reduction in the next dose, whereas reducing the dose solely on the basis of a large local reaction does not reduce the rate of systemic reactions. Usually 5-6 mo of weekly injections is required to reach the maintenance dose, although it may take longer in highly sensitive patients. Unique schedules for the administration of insect venoms, which differ from those for the administration of other allergens (see Chapter 146), are used. Once the maintenance dose is reached and well tolerated, the interval between injections is increased to a few weeks

or a month. Because allergen extracts gradually lose potency, the first dose from a fresh replacement vial of maintenance allergen extract is reduced by 25-75% and is then increased in increments weekly until the usual maintenance dose is reached. The recommended length for a course of allergen immunotherapy is 3-5 yr. Insect VIT may be continued indefinitely in patients with a history of life-threatening anaphylaxis. Patients who have not shown improvement after 1 year of receiving maintenance doses of an appropriate allergen extract are unlikely to benefit, and allergen immunotherapy should be discontinued. Most patients enjoy a sustained improvement after allergen immunotherapy whereas others experience a gradual return of symptoms. Those who experience a relapse would be expected to respond upon resuming immunotherapy.

Rush immunotherapy is the administration of multiple injections either in a single day or over several days in an attempt to reach maintenance dose more rapidly. The risk of adverse reactions, including systemic reactions, is higher than with traditional allergen immunotherapy schedules. Patients to undergo rush immunotherapy are often pretreated with antihistamines and corticosteroids. Children are at even greater risk for adverse reactions with rush immunotherapy; thus the benefits and risks should be fully considered. Preadministration of omalizumab (anti-IgE therapy) reduces the incidence of systemic reactions associated with the use of this form of immunotherapy.

Although allergen immunotherapy is regarded as safe, the potential for anaphylaxis always exists when patients are injected with extracts containing allergens to which they are sensitized. Allergen immunotherapy should be offered in only medical settings where a physician with access to emergency equipment and medications required for the treatment of anaphylaxis is available (see Chapter 149). Allergen injections should never be given at home or by untrained personnel. The patient should remain in the office for 30 min after the injection because most reactions to allergen immunotherapy begin within this time frame. Fatal anaphylaxis triggered by allergen immunotherapy, although rare, is estimated to occur at an incidence of 1 per 2 million injections. The risk of an adverse reaction is increased by dosage errors and the use of rush immunotherapy schedules. Particular caution is warranted when injections from a new vial are given. Patients with exquisite sensitivity or unstable asthma and those experiencing exacerbations of allergic rhinitis or asthma are also at increased risk for adverse reactions to allergen immunotherapy. Precautions to reduce significant adverse reactions include using standardized extracts, having extract vials personalized for each patient, allowing only trained personnel to administer injections, paying careful attention to detail when giving injections, ensuring beforehand that the patient is medically stable, having appropriate medications and equipment available, and requiring the patient to remain in the office for 30 min after each injection. Checking peak flow or spirometry before an injection is advisable for some asthmatic patients. It is also prudent to advise patients to carry self-injectable epinephrine for 24 hr following each injection. While uncommon, delayed systemic reactions have been reported following immunotherapy injections.

Other approaches to immunotherapy are under investigation; they include chemical or genetic manipulation of the allergen and linking of the principle allergenic moiety of a relevant allergen to a highly active adjuvant, such as an immunostimulatory sequence mimicking patterns of bacterial DNA.

Local nasal immunotherapy is administered by having the patient spray allergen solutions into the nose at scheduled intervals. Although symptom amelioration has been noted, a lack of a significant systemic immunologic response has decreased interest in pursuing this form of therapy. SLIT involves the sublingual administration of high-dose allergen, which is then swallowed. SLIT is now FDA-approved for a limited number of pollens, and its use is expected to increase given its favorable safety profile and convenience of administration.

Efficacy

The positive impact of allergen immunotherapy on seasonal or perennial allergic rhinitis or rhinoconjunctivitis is well documented. In regard to the treatment of allergic rhinitis, birch, mountain cedar, grass, ragweed, and *Cladosporium* are allergens for which allergen immunotherapy has been effective. Effectiveness of allergen immunotherapy with other allergens commonly used for the treatment of allergic rhinitis is inconclusive. Most of the controlled trials examining the effects of allergen immunotherapy on seasonal or perennial allergic asthma also report favorable results. A meta-analysis of 20 trials examining the effects of allergen immunotherapy on allergic asthma revealed a significant increase in the odds for improvement after treatment along with fewer symptoms, improved pulmonary functions, less need for medication, and a reduction in bronchial hyperreactivity. The most convincing data for the benefit of allergen immunotherapy in the treatment of allergic asthma are available for birch, mountain cedar, grass, ragweed, and dust mite with less conclusive but suggestive data available for *Cladosporium, Alternaria,* and cat allergens. Studies examining the effects of allergen immunotherapy in the treatment of patients with allergic rhinitis and allergic asthma have documented increases in circulating allergen-specific IgG and decreases in allergen-specific IgE after treatment. Reductions in sensitivity to administered allergens have been demonstrated in nasal and bronchial challenges. These studies have often shown that the late-phase response after allergen challenge is ablated or significantly reduced. The protective benefit as well as the safety of VIT in patients with sensitivity to *Hymenoptera* venoms has also been well documented in several large studies. The efficacy of allergen immunotherapy for the treatment of urticaria and latex allergy has not been documented. Dust mite allergen immunotherapy may be helpful in patients with atopic dermatitis. Studies using OIT, involving the oral administration of gradually increasing doses of a food allergen under close medical observation followed by a prolonged maintenance phase of daily fixed-dose food allergen administration at home, has been shown to desensitize patients but has not yet proven to induce tolerance. Although still under investigation, OIT and perhaps SLIT are promising therapeutic approaches to the treatment of food allergy in the future.

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Chapter 143

Allergic Rhinitis

Henry Milgrom and Scott H. Sicherer

Allergic rhinitis (AR) is an inflammatory disorder of the nasal mucosa marked by nasal congestion, rhinorrhea, and itching, often accompanied by sneezing and conjunctival inflammation. Its recognition as a major chronic respiratory disease of children rests largely on its high prevalence, detrimental effects on quality of life and school performance, and comorbidities. Children with AR often have related conjunctivitis, sinusitis, otitis media, serous otitis, hypertrophic tonsils and adenoids, and eczema. Childhood AR is associated with a 3-fold increase in risk for asthma at an older age. Over the past 50 yr an upsurge in AR has been observed throughout the world, particularly in areas where its prevalence previously had been low. In prosperous societies, 20-40% of children suffer from AR. The symptoms may appear in infancy; with the diagnosis generally established by the time the child reaches age 6 yr. The prevalence peaks late in childhood.

Risk factors include family history of atopy and serum immunoglobulin (Ig) E higher than 100 IU/mL before age 6 yr. Early life exposures and/or their absence have a profound influence on the development of the allergic phenotype. The risk increases in children whose mothers smoke heavily, even before delivery and especially before the infants are 1 yr old, and those with heavy exposure to indoor allergens. A critical period exists early in infancy when the genetically susceptible individual is at greatest risk of sensitization. Delivery by

cesarean section is associated with AR and atopy in children with a parental history of asthma or allergies. This association may be explained by the lack of exposure to maternal vaginal/fecal flora during delivery. Children between 2 and 3 yr old who have elevated anticockroach and antimouse IgE are at increased risk of wheezing, AR, and atopic dermatitis. The occurrence of 3 or more episodes of rhinorrhea in the first year of life is associated with AR at age 7 yr. Intriguingly, the exposure to dogs, cats, and endotoxin early in childhood protects against the development of atopy. Prolonged breastfeeding is beneficial, but it does not need to be exclusive There is also a decreased risk of asthma, AR, and atopic sensitization with early introduction to wheat, rye, oats, barley, fish and eggs.

ETIOLOGY AND CLASSIFICATION

Two factors necessary for expression of AR are sensitivity to an allergen and the presence of the allergen in the environment. AR classification as **seasonal** or **perennial** is giving way to the designations **intermittent** and **persistent.** The 2 sets of terms are based on different suppositions, but inhalant allergens are the main cause of all forms of AR irrespective of terminology. AR may also be categorized as **mild-intermittent, moderate-severe intermittent, mild-persistent,** and **moderate-severe persistent** (Fig. 143-1). The symptoms of intermittent AR occur on <4 days per week or for <4 consecutive weeks. In persistent AR symptoms occur on >4 days per week and/or for >4 consecutive weeks. The symptoms are considered mild when they are not troublesome, the sleep is normal, there is no impairment in daily activities, and no incapacity at work or school. Severe symptoms result in sleep disturbance, and impairment in daily activities and school (Fig. 143-1).

In temperate climates, airborne pollen responsible for exacerbation of intermittent AR appear in distinct phases: trees pollinate in the spring, grasses in the early summer, and weeds in the late summer. In temperate climates, mold spores persist outdoors only in the summer, but in warm climates throughout the year. Symptoms of intermittent AR typically cease with the appearance of frost. Knowledge of the time of occurrence of symptoms, of the regional patterns of pollination and mold sporulation, and of the patient's specific IgE is necessary for the recognition of the cause of intermittent AR. Persistent AR is most often associated with the indoor allergens: house dust mites, animal danders, mice, and cockroaches. Cat and dog allergies are of major importance in the United States. The allergens from saliva and sebaceous secretions may remain airborne for a prolonged time. The ubiquitous major cat allergen, Fel d 1, may be carried on cat owners' clothing into such "cat-free" settings as schools and hospitals.

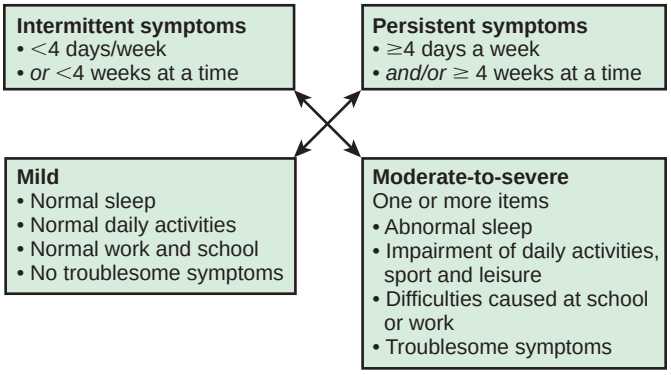

Figure 143-1 ARIA classification of allergic rhinitis. Every box can be subclassified further into seasonal or perennial on the basis of timing of symptoms or when causative and allergen therapeutic factors are considered. For example, a UK patient with grass pollen allergy might have moderate-to-severe persistent seasonal rhinitis in June and July and be suitable for specific allergen immunotherapy. *(From Scadding GK, Durham SR, Mirakian R, et al: BASCI guidelines for the management of allergic and non-allergic rhinitis.* Clin Exp Allergy *38:19-42, 2008 [Fig 2, p. 22].)*

PATHOGENESIS

The exposure of an atopic host to an allergen leads to specific IgE production. The clinical reactions on reexposure to the allergen have been designated as early-phase and late-phase allergic responses. Bridging of the IgE molecules on the surface of mast cells by allergen initiates early-phase allergic response, characterized by degranulation of mast cells and release of preformed and newly generated inflammatory mediators including histamine, prostaglandin 2, and the cysteinyl leukotrienes. Late-phase allergic response appears 4-8 hr following allergen exposure. Inflammatory cells, including basophils, eosinophils, neutrophils, mast cells, and mononuclear cells, infiltrate the nasal mucosa. Eosinophils release proinflammatory mediators, including cysteinyl leukotrienes, cationic proteins, eosinophil peroxidase, and major basic protein, and serve as a source of interleukin (IL)-3, IL-5, granulocyte-macrophage colony-stimulating factor, and IL-13. Repeated intranasal introduction of allergens causes "priming"—a more brisk response even with a lesser provocation. Over the course of an allergy season a multifold increase in submucosal mast cells takes place. These cells, once thought to have a role exclusively in the early-phase allergic response, have an important function in sustaining chronic allergic disease. Allergens, autoantigens, and components of superimposed infectious agents activate the immune system.

CLINICAL MANIFESTATIONS

Symptoms of AR may be ignored or mistakenly attributed to a respiratory infection. Older children blow their noses, but younger children tend to sniff and snort. Nasal itching brings on grimacing, twitching, and picking of the nose that may result in epistaxis. Children with AR often perform the allergic salute, an upward rubbing of the nose with an open palm or extended index finger. This maneuver relieves itching and briefly unblocks the nasal airway. It also gives rise to the nasal crease, a horizontal skin fold over the bridge of the nose. The diagnosis of AR is based on symptoms in the absence of an upper respiratory tract infection and structural abnormalities. Typical complaints include intermittent nasal congestion, itching, sneezing, clear rhinorrhea, and conjunctival irritation. Symptoms increase with greater exposure to the responsible allergen. The patients may lose their sense of smell and taste. Some experience headaches, wheezing, and coughing. Nasal congestion is often more severe at night, causing mouth breathing and snoring, interfering with sleep, and arousing irritability.

Signs on physical exam include abnormalities of facial development, dental malocclusion, and the "allergic gape" or continuous open-mouth breathing, chapped lips, "allergic shiners" (dark circles under the eyes), and the transverse nasal crease. Conjunctival edema, itching, tearing, and hyperemia are frequent findings. A nasal exam performed with a source of light and a speculum may reveal clear nasal secretions; edematous, boggy, and bluish mucus membranes with little or no erythema; and swollen turbinates that may block the nasal airway. It may be necessary to use a topical decongestant to perform an adequate examination. Thick, purulent nasal secretions indicate the presence of infection.

DIFFERENTIAL DIAGNOSIS

Evaluation of AR calls for a thorough history, including details of the patient's environment and diet and family history of allergic conditions such as eczema, asthma, and AR, physical examination, and laboratory evaluation. The history and laboratory findings provide clues to the provoking factors. Symptoms that include sneezing, rhinorrhea, nasal itching, and congestion and the laboratory findings of elevated IgE, specific IgE antibodies, and positive allergy skin test results typify AR. Intermittent AR differs from persistent AR by history and skin test results. Nonallergic rhinitides cause sporadic symptoms. Their causes are often unknown. Nonallergic inflammatory rhinitis with eosinophils imitates AR in presentation and response to treatment, but without elevated IgE antibodies. Vasomotor rhinitis is characterized by excessive responsiveness of the nasal mucosa to physical stimuli. Other nonallergic conditions, such as infectious rhinitis; structural problems, including nasal polyps and septal deviation; rhinitis medicamentosa (caused by the overuse of topical vasoconstrictors); hormonal rhinitis

Table 143-1 Causes of Nonallergic Rhinitis

Structural/mechanical factors:
- Deviated septum/septal wall anomalies
- Hypertrophic turbinates
- Adenoidal hypertrophy
- Foreign bodies

Nasal tumors:
- Benign
- Malignant
- Choanal atresia

Infectious:
- Acute
- Chronic

Inflammatory/immunologic:
- Granulomatosis with polyangiitis
- Sarcoidosis
- Midline granuloma
- Systemic lupus erythematosus
- Sjögren syndrome
- Nasal polyposis

Physiologic:
- Ciliary dyskinesia syndrome
- Atrophic rhinitis

Hormonally induced:
- Hypothyroidism
- Pregnancy
- Oral contraceptives
- Menstrual cycle
- Exercise
- Atrophic

Drug induced:
- Rhinitis medicamentosa
- Oral contraceptives
- Antihypertensive therapy
- Aspirin
- Nonsteroidal antiinflammatory drugs

Reflex induced:
- Gustatory rhinitis
- Chemical or irritant induced
- Posture reflexes
- Nasal cycle
- Environmental factors:
- Odors
- Temperature
- Weather/barometric pressure
- Occupational
- Nonallergic rhinitis with eosinophilia syndrome
- Perennial nonallergic rhinitis (vasomotor rhinitis)
- Emotional factors

From Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2003, Mosby, p. 290.*

associated with pregnancy or hypothyroidism; neoplasms; vasculitides; and granulomatous disorders may mimic AR (Table 143-1, Fig. 143-2). Occupational risks for rhinitis include exposure to allergens (grain dust, insects, latex, enzymes) and irritants (wood dust, paint, solvents, smoke, cold air).

COMPLICATIONS

AR is frequently associated with complications and comorbid conditions. Children with AR experience frustration over their appearance. Allergic conjunctivitis, characterized by itching, redness and swelling of the conjunctivae, has been reported in at least 20% of the population and in more the 70% of patients with AR, most frequently in older children and young adults. The 2 conditions share pathophysiologic mechanisms and epidemiologic characteristics (see Chapter 147). Chronic sinusitis is a common complication of AR, sometimes associated with purulent infection, but most patients have negative bacterial cultures despite marked mucosal thickening, and sinus opacification. The inflammatory process is characterized by marked eosinophilia. Allergens, possibly fungal, are the inciting agents. The sinusitis of triad asthma (asthma, sinusitis with nasal polyposis, and aspirin sensitivity) often responds poorly to therapy. Patients who undergo repeated endoscopic surgery derive diminishing benefit with each successive procedure.

Rhinitis that coexists with asthma may be taken too lightly or completely overlooked. Up to 78% of patients with asthma have AR, and 38% of patients with AR have asthma. Aggravation of AR coincides with exacerbation of asthma, and treatment of nasal inflammation reduces bronchospasm, asthma-related emergency department visits, and hospitalizations. Postnasal drip associated with AR commonly causes persistent or recurrent cough. Eustachian tube obstruction and middle ear effusion are frequent complications. Chronic allergic inflammation causes hypertrophy of adenoids and tonsils that may be associated with eustachian tube obstruction, serous effusion, otitis media, and obstructive sleep apnea. AR is linked to snoring in children. The association between rhinitis and sleep abnormalities and subsequent daytime fatigue is well documented.

The Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) is suitable for children 6-12 yr old, and the Adolescent Rhinoconjunctivitis Quality of Life Questionnaire (ARQLQ) is appropriate for patients 12-17 yr of age. Children with rhinitis have anxiety and physical, social, and emotional issues that affect learning and the ability to integrate with peers. The disorder contributes to headaches and fatigue, limits daily activities, and interferes with sleep. There is evidence of impaired cognitive functioning and learning that may be exacerbated by the adverse effects of sedating medications. Rhinitis is an important cause of lost school attendance, resulting in more than 2 million days of absence in the United States annually.

LABORATORY FINDINGS

Epicutaneous skin tests provide the best method for detection of allergen-specific IgE (positive predictive value of 48.7% for the epidemiologic diagnosis of AR). They are inexpensive and sensitive, and the risks and discomfort are minimal. Responses to seasonal respiratory allergens are rare before 2 seasons of exposure, and children <1 yr seldom display positive skin test responses to these allergens. To avoid false-negative results, montelukast should be withheld for 1 day, most sedating antihistamine preparations for 3-4 days, and nonsedating antihistamines for 5-7 days. Serum immunoassays for specific IgE to allergens provide a suitable alternative (positive predictive value 43.5%) for patients with dermatographism or extensive dermatitis, those taking medications that interfere with mast cell degranulation, others at high risk for anaphylaxis, and some who cannot cooperate with the procedure. Presence of eosinophils in nasal smear supports the diagnosis of AR, and of neutrophils infectious rhinitis. Eosinophilia and measurements of total serum IgE concentrations have relatively low sensitivity.

TREATMENT

Safe and effective prevention and/or relief of symptoms are the current goals of treatment. Specific measures to limit indoor allergen exposure may reduce the risk of sensitization and symptoms of allergic respiratory disease. Sealing the patient's mattress, pillow, and covers in allergen-proof encasings reduces the exposure to mite allergen. Bed linen and blankets should be washed every week in hot water (>54.4°C [130°F]). The only effective measure for avoiding animal allergens in the home is the removal of the pet. Avoidance of pollen and outdoor molds can be accomplished by staying in a controlled environment. Air conditioning allows for keeping windows and doors closed, reducing the pollen exposure. High-efficiency particulate air filters lower the counts of airborne mold spores.

Oral antihistamines help reduce sneezing, rhinorrhea and ocular symptoms. Administered as needed they provide acceptable treatment for mild-intermittent disease. Antihistamines have been classified as first generation (relatively sedating) or second generation (relatively nonsedating). Antihistamines usually are administered by mouth, but they are also available for topical ophthalmic and intranasal use. Both first- and second-generation antihistamines are available as nonprescription drugs. Second-generation antihistamines are preferred

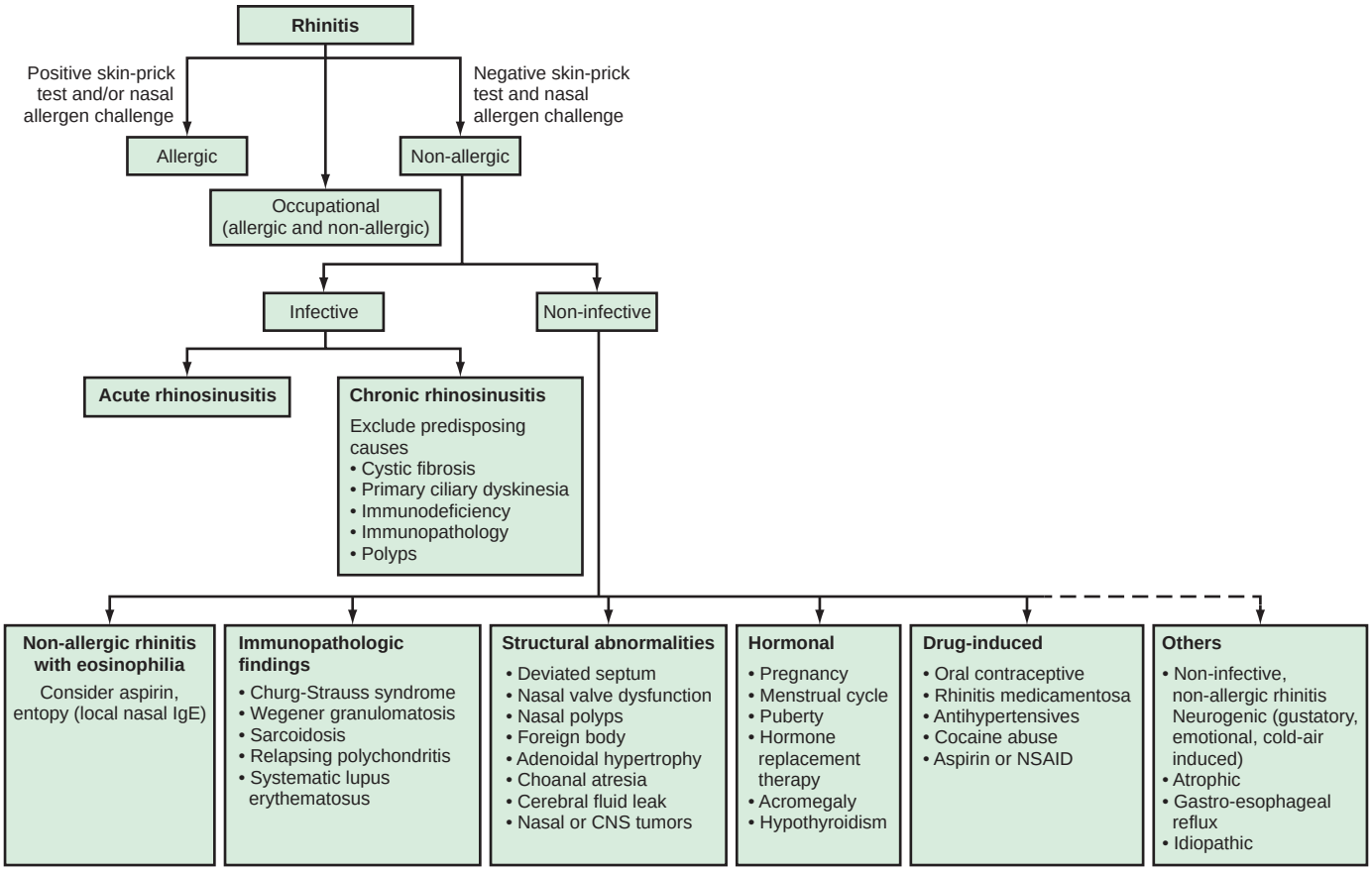

Figure 143-2 Diagnostic algorithm for rhinitis. Nasal allergen challenge is a research procedure and is not undertaken routinely. Causes likely to be seen in children are highlighted in italics. NSAID, nonsteroidal antiinflammatory drug. *(From Greiner AN, Hellings PW, Rotiroti G, Scadding GK: Allergic rhinitis. Lancet 378:2112-2120, 2011 [Fig. 3, p. 2116].)*

because they cause less sedation. Preparations containing pseudoephedrine, typically in combination with other agents, are used for relief of nasal and sinus congestion and pressure and other symptoms such as rhinorrhea, sneezing, lacrimation, itching eyes, oronasopharyngeal itching, and cough. Pseudoephedrine is available without prescription (generally in fixed combination with other agents such as first-generation antihistamines: brompheniramine, chlorpheniramine, triprolidine; second-generation antihistamines: desloratadine, fexofenadine, loratadine; antipyretics: acetaminophen, ibuprofen; antitussives: guaifenesin, dextromethorphan; anticholinergic: methscopolamine). Pseudoephedrine is an oral vasoconstrictor disfavored for causing irritability and insomnia and for its association with infant mortality. Because younger children (2-3 yr of age) are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations have voluntarily revised their product labeling to warn against the use of preparations containing pseudoephedrine for children younger than 4 yr. Pseudoephedrine is misused as a starting material for the synthesis of methamphetamine and methcathinone. Oral agents for treatment of AR are shown in Tables 143-2, 143-3, and 143-4.

The anticholinergic nasal spray ipratropium bromide is effective for the treatment of serous rhinorrhea (Table 143-5). Intranasal decongestants (oxymetazoline and phenylephrine) should be used for less than 5 days, not to be repeated more than once a month in order to avoid rebound nasal congestion. Sodium cromoglycate (available as nonprescription drug) is effective but requires frequent administration, q4h. Leukotriene-modifying agents have a modest effect on rhinorrhea and nasal blockage (see Chapter 144 for additional indications and side effects). Nasal saline irrigation is a good adjunctive option with all other treatments of AR. Patients with more persistent, severe symptoms require intranasal corticosteroids, the most effective therapy for AR, a treatment that may be beneficial also for concomitant allergic conjunctivitis (Table 143-6). These agents reduce the symptoms of AR with eosinophilic inflammation, but not those of rhinitis associated with neutrophils or free of inflammation. Beclomethasone, triamcinolone, and flunisolide are absorbed from the gastrointestinal tract, as well as from the respiratory tract; budesonide, fluticasone, mometasone, and ciclesonide offer greater topical activity with lower systemic exposure. More severely affected patients may benefit from simultaneous treatment with oral antihistamines and intranasal corticosteroids.

Allergy immunotherapy is an effective treatment for AR and allergic conjunctivitis. In addition to reducing symptoms, it may change the course of allergic disease and induce allergen-specific immune tolerance. Immunotherapy administered by subcutaneous injection should be considered for children in whom IgE-mediated allergic symptoms cannot be adequately controlled by avoidance and medication, especially in the presence of comorbid conditions. Sublingual immunotherapy has been used successfully in Europe and South America. Sublingual immunotherapy is considered investigational in the United States, and there are no extracts for sublingual administration licensed by the FDA. Omalizumab (anti-IgE antibody) given subcutaneously has a dose-dependent effect on seasonal AR; its role compared with standard therapy has yet to be determined.

Typically, treatment of AR with oral antihistamines and inhaled corticosteroids provides sufficient relief for most cases of coexisting allergic conjunctivitis. If it fails, additional therapies directed primarily to allergic conjunctivitis may be added (see Chapter 147). Intranasal corticosteroids are of some value for the treatment of ocular symptoms, but ophthalmic corticosteroids remain the most potent pharmacologic agents for ocular allergy. They carry the risk of adverse effects, such as delayed wound healing, secondary infection, elevated intraocular

Table 143-2 Oral Allergic Rhinitis Treatments (Prescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
SECOND-GENERATION ANTIHISTAMINES			
Desloratadine			
Clarinex Reditabs*	2.5 mg, 5 mg	Orally disintegrating tablet	Children 6-11 mo of age: 1 mg once daily
Clarinex Tablets	5 mg	Tabs	Children 12 mo-5 yr of age: 1.25 mg once daily
Clarinex Syrup	0.5 mg/mL	Syrup	Children 6-11 yr of age: 2.5 mg once daily Adults and adolescents ≥12 yr of age: 5 mg once daily
Levocetirizine dihydrochloride			
Xyzal Oral Solution	0.5 mg/mL	Solution	6 mo-5 yr: max 1.25 mg once daily in the P.M. 6-11 yr: max 2.5 mg once daily in the P.M.
LEUKOTRIENE ANTAGONIST			
Montelukast			
Singulair	10 mg	Tablets	6 mo-5 yr: 4 mg daily
Singulair Chewables*	4 mg, 5 mg	Chewable tablets	6-14 yr: 5 mg daily
Singulair Oral Granules	4 mg/packet	Oral granules	>14 yr: 10 mg daily

*Contains phenylalanine.
Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19. Philadelphia, 2012 Mosby.*

Table 143-3 Oral Allergic Rhinitis Treatments (Nonprescription, Examples)

GENERIC/BRAND	STRENGTH	FORMULATIONS	DOSING
FIRST-GENERATION H_1 ANTAGONISTS			
Chlorpheniramine maleate			
Chlor-Trimeton	4 mg	Tablets	2-5 yr: 1 mg every 4-6 hr (maximum 6 mg/day)
Chlor-Trimeton Syrup	2 mg/5 mL	Syrup	6-11 yr: 2 mg every 4-6 hr (maximum 12 mg/day) >12 yr 4 mg every 4-6 hr (maximum 24 mg/day)
SECOND-GENERATION H_1 ANTAGONISTS			
Cetirizine			
Children's Zyrtec Allergy Syrup	1 mg/mL	Syrup	6-12 mo: 2.5 mg once daily
Children's Zyrtec Chewable	5 mg, 10 mg	Chewable tablets	12-23 mo: initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily
Zyrtec tablets	5 mg, 10 mg	Tablets	2-5 yr: 2.5 mg/day; may be increased to a maximum of 5 mg/day given either as a single dose or divided into 2 doses
Zyrtec Liquid Gels	10 mg	Liquid-filled gels	≥6 yr: 5-10 mg/day as a single dose or divided into 2 doses
Fexofenadine HCl			
Children's Allegra	30 mg	Tablet	
Children's Allegra ODT*	30 mg	Orally disintegrating tablets	6 mo-<2 yr: 15 mg (2.5 mL) every 12 hr
Children's Allegra Oral Suspension	30 mg/5 mL	Suspension	>2-11 yr: 30 mg every 12 hr
Allegra	Tabs 30, 60, 180 mg	Tablet	>12 yr-adult: 60 mg every 12 hr; 180 mg once daily
Loratadine			
Alavert ODT*	10 mg	Orally disintegrating tablets	2-5 yr: 5 mg once daily.
	10 mg	Tablets	>6 yr: 10 mg once daily or 5 mg twice daily
	10 mg	Liquid-filled caps	
	5 mg	Chewable tablets	
	1 mg/mL	Syrup	

*Contains phenylalanine.
Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-4 Combined Antihistamine + Sympathomimetic (Examples)

GENERIC	STRENGTH	FORMULATIONS	DOSING
Chlorpheniramine maleate Phenylephrine HCl Sudafed Sinus & Allergy	4 mg 10 mg	Tablets	>12 yr: 1 tablet every 4 hr not to exceed 6 tablets per day
Cetirizine + pseudoephedrine Zyrtec-D 12 hour	5 mg cetirizine + 120 mg pseudoephedrine	Extended release tablet	>12 yr: 1 tablet every 12 hr

Dosing recommendations taken in part from Arcara K, Tschudy M for the Johns Hopkins Hospital: The Harriet Lane Handbook, *ed 19, Philadelphia, 2012, Mosby.*

Table 143-5 Miscellaneous Intranasal Sprays

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Ipratropium bromide: Atrovent nasal spray (0.06%)	*I:* Symptomatic relief of rhinorrhea *M:* Anticholinergic Colds (symptomatic relief of rhinorrhea): 5-12 yr: 2 sprays in each nostril 3 times/day ≥12 yr and adults: 2 sprays in each nostril 3-4 times/day	Atrovent inhalation aerosol is contraindicated in patients with hypersensitivity to soy lecithin Safety and efficacy of use beyond 4 days in patients with the common cold have not been established *Adverse effects:* Epistaxis, nasal dryness, nausea
Azelastine: Astelin	*I:* Treatment of rhinorrhea, sneezing, and nasal pruritus *M:* Antagonism of histamine H_1-receptor 6-12 yr: 1 spray bid >12 yr: 1-2 sprays bid	May cause drowsiness *Adverse effects:* Headache, somnolence, bitter taste
Cromolyn sodium: NasalCrom	*I:* AR. *M:* Inhibition of mast cell degranulation >2 yr: 1 spray tid-qid; max ×6 /day	Not effective immediately; requires frequent administration
Oxymetazoline: Afrin, Nostrilla	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic agonist, vasoconstricting agent 0.05% solution: instill 2-3 sprays into each nostril twice daily; therapy should not exceed 3 days	Excessive dosage may cause profound central nervous system (CNS) depression Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month Use with caution in patients with hyperthyroidism, heart disease, hypertension, and diabetes *Adverse effects:* Hypertension, palpitations, reflex bradycardia, nervousness, dizziness, insomnia, headache, CNS depression, convulsions, hallucinations, nausea, vomiting, mydriasis, elevated intraocular pressure, blurred vision
Phenylephrine: Neo-Synephrine	*I:* Symptomatic relief of nasal mucosal congestion *M:* Adrenergic, vasoconstricting agent 2-6 yr: 1 drop every 2-4 hr of 0.125% solution as needed. *Note:* Therapy should not exceed 3 continuous days 6-12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% solution as needed. *Note:* Therapy should not exceed 3 continuous days >12 yr: 1-2 sprays or 1-2 drops every 4 hr of 0.25% to 0.5% solution as needed; 1% solution may be used in adults with extreme nasal congestion. *Note:* Therapy should not exceed 3 continuous days	Use in excess of 3 days may result in severe rebound nasal congestion Do not repeat more than once a month 0.16% and 0.125% solutions are not commercially available *Adverse effects:* Reflex bradycardia, excitability, headache, anxiety, and dizziness

Table 143-6 Intranasal Inhaled Corticosteroids

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Beclomethasone: Beconase AQ (42 μg/spray) Qnasl (80 μg/spray)	*I:* AR *M:* Antiinflammatory, immune modulator 6-12 yr: 1 spray in each nostril bid; may increase if needed to 2 sprays in each nostril bid >12 yr: 1 or 2 sprays in each nostril bid	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flunisolide	6-14 yr: 1 spray each nostril 3 times daily *or* 2 sprays in each nostril twice daily; not to exceed 4 sprays/day in each nostril ≥15 yr: 2 sprays each nostril twice daily (morning and evening); may increase to 2 sprays 3 times daily; maximum dose: 8 sprays/day in each nostril (400 μg/day)	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth

Continued

Table 143-6 Intranasal Inhaled Corticosteroids—cont'd

DRUG	INDICATIONS (I), MECHANISM(s) OF ACTION (M), AND DOSING	COMMENTS, CAUTIONS, ADVERSE EVENTS, AND MONITORING
Triamcinolone	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril
Nasacort AQ (55 μg/spray)	2-6 yr; 1 spray in each nostril qd 6-12 yr: 1-2 sprays in each nostril qd ≥12 yr: 2 sprays in each nostril qd	*Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Fluticasone propionate (available as a generic preparation):	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril Ritonavir significantly increases fluticasone serum concentrations and may result in systemic corticosteroid effects Use fluticasone with caution in patients receiving ketoconazole or other potent cytochrome P450 3A4 isoenzyme inhibitor *Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Flonase (50 μg/spray)	≥4 yr: 1-2 sprays in each nostril qd	
Fluticasone furoate: Veramyst (27.5 μg/spray)	2-12 yr: Initial dose: 1 spray (27.5 μg/spray) per nostril once daily (55 μg/day) Patients who do not show adequate response may use 2 sprays per nostril once daily (110 μg/day) Once symptoms are controlled, dosage may be reduced to 55 μg once daily Total daily dosage should not exceed 2 sprays in each nostril (110 μg)/day ≥12 yr and adolescents: Initial dose: 2 sprays (27.5 μg/spray) per nostril once daily (110 μg/day) Once symptoms are controlled, dosage may be reduced to 1 spray per nostril once daily (55 μg/day) Total daily dosage should not exceed 2 sprays in each nostril (110 μg)/day	
Mometasone:	*I:* AR *M:* Antiinflammatory, immune modulator	Mometasone and its major metabolites are undetectable in plasma after nasal administration of recommended doses Preventive treatment of seasonal AR should begin 2-4 wk prior to pollen season Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril
Nasonex (50 μg/spray)	2-12 yr: 1 spray in each nostril qd >12 yr: 2 sprays in each nostril qd	*Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Budesonide:	*I:* AR *M:* Antiinflammatory, immune modulator	Shake container before use; blow nose; occlude 1 nostril, administer dose to the other nostril
Rhinocort Aqua (32 μg/spray)	6-12 yr: 2 sprays in each nostril qd >12 yr: up to 4 sprays in each nostril qd (maximum dose)	*Adverse effects:* Burning and irritation of nasal mucosa, epistaxis Monitor growth
Ciclesonide:	*I:* AR *M:* Antiinflammatory, immune modulator	Prior to initial use, gently shake, then prime the pump by actuating 8 times
Omnaris Zetonna (50 μg/spray)	2-12 yr: 1-2 sprays in each nostril qd >12 yr: 2 sprays in each nostril qd	If the product is not used for 4 consecutive days, gently shake and reprime with 1 spray or until a fine mist appears
Azelastine/fluticasone (137 μg azelastine/50 μg fluticasone) Dymista	>12 yr: 1 spray in each nostril bid	Shake bottle gently before using. Blow nose to clear nostrils. Keep head tilted downward when spraying. Insert applicator tip ¼ to ½ inch into nostril, keeping bottle upright, and close off the other nostril. Breathe in through nose. While inhaling, press pump to release spray

pressure, and formation of cataracts. These agents are only suited for the treatment of allergic conjunctivitis that does not respond to the medications discussed above. Sound practice calls for the assistance of an ophthalmologist.

PROGNOSIS

Therapy with nonsedating antihistamines and topical corticosteroids, when taken faithfully, significantly improves health-related quality-of-life measures in patients. The reported rates of remission among children are between 10% and 23%. Pharmacotherapy that will target cells and cytokines involved in inflammation and treat allergy as a systemic process is on the horizon, and more selective targeting of drugs based on the development of specific biomarkers and genetic profiling may soon be realized.

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Chapter 144

Childhood Asthma

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Asthma is a chronic inflammatory condition of the lung airways resulting in episodic airflow obstruction. This chronic inflammation heightens the twitchiness of the airways—airways hyperresponsiveness (AHR)—to provocative exposures. Asthma management is aimed at reducing airways inflammation by minimizing proinflammatory environmental exposures, using daily controller antiinflammatory medications, and controlling comorbid conditions that can worsen asthma. Less inflammation typically leads to better asthma control, with fewer exacerbations and decreased need for quick-reliever asthma medications. Nevertheless, exacerbations can still occur. Early intervention with systemic corticosteroids greatly reduces the severity of such episodes. Advances in asthma management and, especially, pharmacotherapy enable all but the uncommon child with difficult asthma to live normally.

ETIOLOGY

Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated (Fig. 144-1). In the susceptible host, immune responses to common airways exposures (e.g., respiratory viruses, allergens, tobacco smoke, air pollutants) can stimulate prolonged, pathogenic inflammation and aberrant repair of injured airways tissues. Lung dysfunction (AHR, reduced airflow) and airway remodeling develop. These pathogenic processes in the growing lung during early life adversely affect airways growth and differentiation, leading to altered airways at mature ages. Once asthma has developed, ongoing inflammatory exposures appear to worsen it, driving disease persistence and increasing the risk of severe exacerbations.

Genetics

To date, more than 100 genetic loci have been linked to asthma, although relatively few have consistently been linked to asthma in different study cohorts. Replicating variants include genetic loci containing proallergic, proinflammatory genes. Because epigenetic marks are heritable, are responsive to environmental exposures, and can result in rapid and persistent changes in gene expression it is conceivable that epigenetic modification of genes play a role in the transmission of asthma.

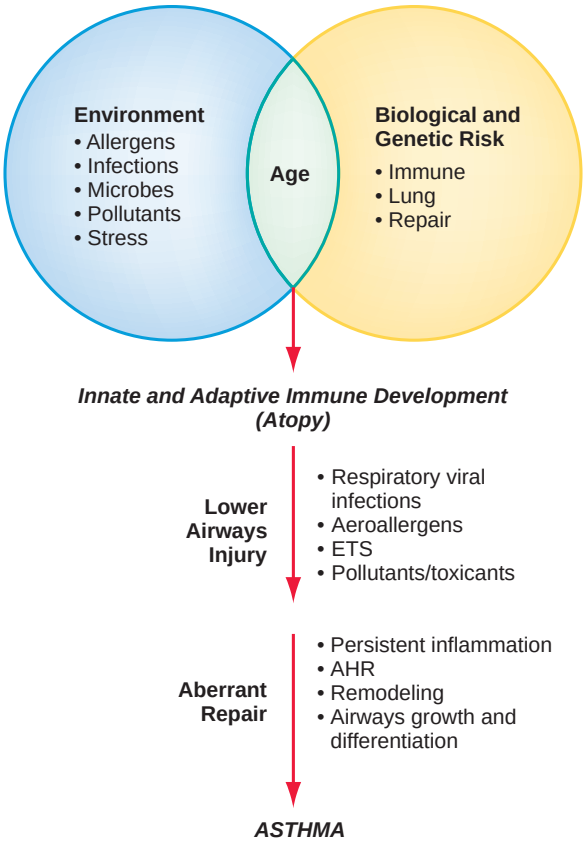

Figure 144-1 Etiology and pathogenesis of asthma. A combination of environmental and genetic factors in early life shape how the immune system develops and responds to ubiquitous environmental exposures. Respiratory microbes, inhaled allergens, and toxins that can injure the lower airways target the disease process to the lungs. Aberrant immune and repair responses to airways injury underlie persistent disease. AHR, airways hyperresponsiveness; ETS, environmental tobacco smoke.

Environment

Recurrent wheezing episodes in early childhood are associated with common respiratory viruses, especially common cold rhinoviruses, and also respiratory syncytial virus, influenza virus, adenovirus, parainfluenza virus, and human metapneumovirus. This association implies that host features affecting immunologic host defense, inflammation, and the extent of airways injury from ubiquitous viral pathogens underlie susceptibility to recurrent wheezing in *early* childhood. Other airways exposures can also exacerbate ongoing airways inflammation, increase disease severity, and drive asthma persistence. Home allergen exposures in sensitized individuals can initiate airways inflammation and hypersensitivity to other irritant exposures, and are strongly linked to disease severity and persistence. Consequently, eliminating the offending allergen(s) can lead to resolution of asthma symptoms and can sometimes cure asthma. Environmental tobacco smoke and common air pollutants can aggravate airways inflammation and increase asthma severity. Cold, dry air, hyperventilation from physical play or exercise, and strong odors can trigger bronchoconstriction. Although many exposures that trigger and aggravate asthma are well recognized, the causal environmental features underlying the development of host susceptibilities to the various common airway exposures are not well defined.

EPIDEMIOLOGY

Asthma is a common chronic disease, causing considerable morbidity. In 2011, more than 10 million children (14% of U.S. children) had ever been diagnosed with asthma, with 70% of this group reporting current asthma. Male gender and living in poverty are demographic risk factors for having childhood asthma in the U.S. Fifteen percent of boys

compared to 13% of girls have had asthma; and 18% of all children living in poor families (incomes less than $25,000 per year), compared to 12% of children in families not classified as poor, have had asthma.

Childhood asthma is among the most common causes of childhood emergency department visits, hospitalizations, and missed school days. In the United States in 2006, childhood asthma accounted for 593,000 emergency department visits, 155,000 hospitalizations, and 167 deaths. A disparity in asthma outcomes links high rates of asthma hospitalization and death with poverty, ethnic minorities, and urban living. In the past 2 decades, black children have had 2-7 times more emergency department visits, hospitalizations, and deaths as a result of asthma than nonblack children. Although current asthma prevalence is higher in black than in nonblack U.S. children (in 2011, 16.5% vs 8.1% for white and 9.8% for Latino children), prevalence differences cannot fully account for this disparity in asthma outcomes.

Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in our management and pharmacopeia to treat asthma. Numerous studies conducted in different countries have reported an increase in asthma prevalence of approximately 50% per decade. Globally, childhood asthma prevalence varies widely in different locales. A study of childhood asthma prevalence in 233 centers in 97 countries (International Study of Asthma and Allergies in Childhood, Phase 3) found a wide range in the prevalence of current wheeze in 6-7 yr (2.4-37.6%) and 13-14 yr old children (0.8-32.6%). Asthma prevalence correlated well with reported allergic rhinoconjunctivitis and atopic eczema prevalence. Childhood asthma seems more prevalent in modern metropolitan locales and more affluent nations, and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities with domestic animals are less likely to experience asthma and allergy.

Approximately 80% of all asthmatic patients report disease onset prior to 6 yr of age. However, of all young children who experience recurrent wheezing, only a minority go on to have persistent asthma in later childhood. Early childhood risk factors for persistent asthma have been identified (Table 144-1) and have been described as major (parent asthma, eczema, inhalant allergen sensitization) and minor (allergic rhinitis, wheezing apart from colds, ≥4% peripheral blood eosinophils, food allergen sensitization) risk factors. Allergy in young children with recurrent cough and/or wheeze is the strongest identifiable factor for the persistence of childhood asthma.

Types of Childhood Asthma

There are 2 common types of childhood asthma based on different natural courses: (1) **recurrent wheezing** in *early* childhood, primarily triggered by common respiratory viral infections, usually resolves during the preschool/lower school years; and (2) **chronic asthma** associated with allergy that persists into later childhood and often adulthood (Table 144-2). School-age children with mild-moderate persistent asthma generally improve as teenagers, with some (~40%) developing intermittent disease. Milder disease is more likely to remit. Inhaled corticosteroid controller therapy for children with persistent asthma does not alter the likelihood of outgrowing asthma in later childhood; however, because children with asthma generally improve with age, their need for controller therapy subsequently lessens and often resolves. Progressive decline in lung function can be a feature of severe, persistent disease.

Asthma is also classified by disease severity (e.g., intermittent or persistent [mild, moderate, or severe]) or control (e.g., well, not well, or very poorly controlled), especially for asthma management purposes. Because most children with asthma can be well controlled with conventional management guidelines, children with asthma can also be characterized according to treatment response and medication requirements as being: (1) easy-to-treat: well controlled with low

Table 144-1 Early Childhood Risk Factors for Persistent Asthma

Parental asthma
Allergy:
• Atopic dermatitis (eczema)
• Allergic rhinitis
• Food allergy
• Inhalant allergen sensitization
• Food allergen sensitization
Severe lower respiratory tract infection:
• Pneumonia
• Bronchiolitis requiring hospitalization
Wheezing apart from colds
Male gender
Low birthweight
Environmental tobacco smoke exposure
Reduced lung function at birth

Table 144-2 Asthma Patterns in Childhood, Based on Natural History and Asthma Management

TRANSIENT NONATOPIC WHEEZING
Common in early preschool years
Recurrent cough/wheeze, primarily triggered by common respiratory viral infections
Usually resolves during the preschool and lower school years, without increased risk for asthma in later life
Reduced airflow at birth, suggestive of relatively narrow airways. AHR near birth. Improves by school age
PERSISTENT ATOPY-ASSOCIATED ASTHMA
Begins in early preschool years
Associated with atopy in early preschool years:
• Clinical (e.g., atopic dermatitis in infancy, allergic rhinitis, food allergy)
• Biologic (e.g., early inhalant allergen sensitization, increased serum immunoglobulin E, increased blood eosinophils)
• Highest risk for persistence into later childhood and adulthood
Lung function abnormalities:
• Those with onset before 3 yr of age acquire reduced airflow by school age
• Those with later onset of symptoms, or with later onset of allergen sensitization, are less likely to experience airflow limitation in childhood
ASTHMA WITH DECLINING LUNG FUNCTION
Children with asthma with progressive increase in airflow limitation
Associated with hyperinflation in childhood, male gender
ASTHMA MANAGEMENT TYPES
(From national and international asthma management guidelines)
SEVERITY CLASSIFICATION*
• Intrinsic disease severity while not on asthma medications
Intermittent
Persistent:
• Mild
• Moderate
• Severe
CONTROL CLASSIFICATION*
• Clinical assessment while asthma being managed and treated
Well controlled
Not well controlled
Very poorly controlled
MANAGEMENT PATTERNS
• **Easy-to-treat:** well controlled with low levels of daily controller therapy
• **Difficult-to-treat:** well controlled with multiple and/or high levels of controller therapies
• **Exacerbators:** despite being well controlled, continue to have severe exacerbations
• **Refractory:** continue to have poorly controlled asthma despite multiple and high levels of controller therapies

*From National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): *Guideline for the diagnosis and management of asthma.* NIH Publication No. 07-4051. Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

AHR, airways hyperresponsiveness.

levels of controller therapy; (2) difficult-to-treat: well controlled with multiple and/or high levels of controller therapies; (3) exacerbators: despite being well controlled, continue to have severe exacerbations; and (4) refractory asthma: continue to have poorly controlled asthma despite multiple and high levels of controller therapies (Table 144-2). Different airways pathologic processes, causing airways inflammation, AHR, and airways congestion and blockage, are believed to underlie these different types of asthma.

PATHOGENESIS

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumen; bronchoconstriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular inflammatory infiltrate and exudates distinguished by eosinophils, but also including other inflammatory cell types (neutrophils, monocytes, lymphocytes, mast cells, basophils), can fill and obstruct the airways and induce epithelial damage and desquamation into the airways lumen. Helper T lymphocytes and other immune cells that produce proallergic, proinflammatory cytokines (interleukin [IL]-4, IL-5, IL-13), and chemokines (eotaxins) mediate this inflammatory process. Pathogenic immune responses and inflammation may also result from a breach in normal immune regulatory processes (such as regulatory T lymphocytes that produce IL-10 and transforming growth factor-β) that dampen effector immunity and inflammation when they are no longer needed. Hypersensitivity or susceptibility to a variety of provocative exposures or triggers (Table 144-3) can lead to airways inflammation, AHR, edema, basement membrane thickening, subepithelial collagen deposition, smooth muscle and mucous gland hypertrophy, and mucus hypersecretion—all processes that contribute to airflow obstruction.

Table 144-3 Asthma Triggers

Common viral infections of the respiratory tract Aeroallergens in sensitized asthmatic patients
INDOOR ALLERGENS • Animal dander • Dust mites • Cockroaches • Molds
SEASONAL AEROALLERGENS • Pollens (trees, grasses, weeds) • Seasonal molds
AIR POLLUTANTS • Environmental tobacco smoke • Ozone • Nitrogen dioxide • Sulfur dioxide • Particulate matter • Wood- or coal-burning smoke • Mycotoxins • Endotoxin • Dust
STRONG OR NOXIOUS ODORS OR FUMES • Perfumes, hairsprays • Cleaning agents
OCCUPATIONAL EXPOSURES • Farm and barn exposures • Formaldehydes, cedar, paint fumes Cold dry air Exercise Crying, laughter, hyperventilation
COMORBID CONDITIONS • Rhinitis • Sinusitis • Gastroesophageal reflux
DRUGS • Aspirin and other nonsteroidal antiinflammatory drugs • β-Blocking agents • Sulfiting agents • Tartrazine

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Intermittent dry coughing and expiratory wheezing are the most common chronic symptoms of asthma. Older children and adults report associated shortness of breath and chest congestion and tightness; younger children are more likely to report intermittent, nonfocal chest pain. Respiratory symptoms can be worse at night, associated with sleep, especially during prolonged exacerbations triggered by respiratory infections or inhalant allergens. Daytime symptoms, often linked with physical activities (exercise-induced) or play, are reported with greatest frequency in children. Other asthma symptoms in children can be subtle and nonspecific, including self-imposed limitation of physical activities, general fatigue (possibly resulting from sleep disturbance), and difficulty keeping up with peers in physical activities. Asking about previous experience with asthma medications (bronchodilators) may provide a history of symptomatic improvement with treatment that supports the diagnosis of asthma. Lack of improvement with bronchodilator and corticosteroid therapy is inconsistent with underlying asthma and should prompt more vigorous consideration of asthma-masquerading conditions.

Asthma symptoms can be triggered by numerous common events or exposures: physical exertion and hyperventilation (laughing), cold or dry air, and airways irritants (see Table 144-3). Exposures that induce airways inflammation, such as infections with common respiratory pathogens (rhinovirus, respiratory syncytial virus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, *Mycoplasma pneumoniae, Chlamydia pneumoniae*), and inhaled allergens in sensitized children, also increase AHR to dry cold air and irritant exposures. An environmental history is essential for optimal asthma management (see Chapter 141).

The presence of risk factors, such as a history of other allergic conditions (allergic rhinitis, allergic conjunctivitis, atopic dermatitis, food allergies), parental asthma, and/or symptoms apart from colds, supports the diagnosis of asthma. During routine clinic visits, children with asthma commonly present without abnormal signs, emphasizing the importance of the medical history in diagnosing asthma. Some may exhibit a dry, persistent cough. The chest findings are often normal. Deeper breaths can sometimes elicit otherwise undetectable wheezing. In clinic, quick resolution (within 10 min) or convincing improvement in symptoms and signs of asthma with administration of a short-acting inhaled β-agonist (SABA; e.g., albuterol) is supportive of the diagnosis of asthma.

During asthma exacerbations, expiratory wheezing and a prolonged exhalation phase can usually be appreciated by auscultation. Decreased breath sounds in some of the lung fields, commonly the right lower posterior lobe, are consistent with regional hypoventilation caused by airways obstruction. Rhonchi and crackles (or rales) can sometimes be heard, resulting from excess mucus production and inflammatory exudate in the airways. The combination of segmental crackles and poor breath sounds can indicate lung segmental atelectasis that is difficult to distinguish from bronchial pneumonia and can complicate acute asthma management. In severe exacerbations, the greater extent of airways obstruction causes labored breathing and respiratory distress, which manifests as inspiratory and expiratory wheezing, increased prolongation of exhalation, poor air entry, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In extremis, airflow may be so limited that wheezing cannot be heard (Table 144-4).

DIFFERENTIAL DIAGNOSIS

Many childhood respiratory conditions can present with symptoms and signs similar to those of asthma (Table 144-5). Besides asthma, other common causes of chronic, intermittent coughing include gastroesophageal reflux (GER) and rhinosinusitis. Both GER and chronic sinusitis can be challenging to diagnose in children. Often, GER is clinically silent in children, and children with chronic sinusitis do not report sinusitis-specific symptoms, such as localized sinus pressure and

Table 144-4 Formal Evaluation of Asthma Exacerbation Severity in the Urgent or Emergency Care Setting*

	MILD	MODERATE	SEVERE	SUBSET: RESPIRATORY ARREST IMMINENT
SYMPTOMS				
Breathlessness	While walking	While at rest (infant—softer, shorter cry, difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
SIGNS				
Respiratory rate†	Increased	Increased	Often >30 breaths/min	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/min)‡	<100	100-120	>120	Bradycardia
Pulsus paradoxus	Absent <10 mm Hg	May be present 10-25 mm Hg	Often present >25 mm Hg (adult) 20-40 mm Hg (child)	Absence suggests respiratory muscle fatigue
FUNCTIONAL ASSESSMENT				
Peak expiratory flow (value predicted or personal best)	≥70%	Approx. 40-69% or response lasts <2 hr	<40%	<25%§
Pa_{O_2} (breathing air)	Normal (test not usually necessary)	≥60 mm Hg (test not usually necessary)	<60 mm Hg; possible cyanosis	
and/or				
P_{CO_2}	<42 mm Hg (test not usually necessary)	<42 mm Hg (test not usually necessary)	≥42 mm Hg; possible respiratory failure	
Sa_{O_2} (breathing air) at sea level	>95% (test not usually necessary)	90-95% (test not usually necessary)	<90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents			

*Notes:
- The presence of several parameters, but not necessarily all, indicates the general classification of the exacerbation.
- Many of these parameters have not been systematically studied, especially as they correlate with each other. Thus, they serve only as general guides.
- The emotional impact of asthma symptoms on the patient and family is variable but must be recognized and addressed and can affect approaches to treatment and follow-up.

†Normal breathing rates in awake children by age: <2 mo, <60 breaths/min; 2-12 mo, <50 breaths/min; 1-5 yr, <40 breaths/min; 6-8 yr, <30 breaths/min.
‡Normal pulse rates in children by age: 2-12 mo, <160 beats/min; 1-2 yr, <120 beats/min; 2-8 yr, <110 beats/min.
§Peak expiratory flow testing may not be needed in very severe attacks.
Modified from EPR–3. Expert panel report 3: guidelines for the diagnosis and management of asthma, *NIH Publication No. 07-4051, Bethesda, MD, 2007, U.S. Department of Health and Human Services; National Institutes of Health, National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program.* http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

tenderness. In addition, both GER and rhinosinusitis are often comorbid with childhood asthma and, if not specifically treated, may make asthma difficult to manage.

In early life, chronic coughing and wheezing can indicate recurrent aspiration, tracheobronchomalacia, a congenital anatomic abnormality of the airways, foreign-body aspiration, cystic fibrosis, or bronchopulmonary dysplasia.

In older children and adolescents, vocal cord dysfunction (VCD) can manifest as intermittent daytime wheezing (Table 144-6). In this condition, the vocal cords involuntarily close inappropriately during inspiration and sometimes exhalation, producing shortness of breath, coughing, throat tightness, and often audible laryngeal wheezing and/or stridor. In most cases of VCD, spirometric lung function testing reveals "truncated" and inconsistent inspiratory and expiratory flow-volume loops, a pattern that differs from the reproducible pattern of airflow limitation in asthma that improves with bronchodilators. VCD can coexist with asthma. Flexible rhinolaryngoscopy in the patient with symptomatic VCD can reveal paradoxical vocal cord movements with anatomically normal vocal cords. This condition can be well managed with specialized speech therapy training in the relaxation and control of vocal cord movement. Furthermore, treatment of underlying causes of vocal cord irritability (e.g., high GER/aspiration, allergic rhinitis, rhinosinusitis, asthma) can improve VCD. During acute VCD exacerbations, in addition to relaxation breathing techniques in conjunction with inhalation of heliox (a mixture of 70% helium and 30% oxygen) can relieve vocal cord spasm and VCD symptoms.

Exercise-induced laryngeal obstruction must be considered in children with a presumptive diagnosis of exercise-induced asthma. The diagnosis is confirmed by continuous video laryngoscopy during exercise.

In some locales, hypersensitivity pneumonitis (farming communities, homes of bird owners), pulmonary parasitic infestations (rural areas of developing countries), or tuberculosis may be common causes of chronic coughing and/or wheezing. Rare asthma-masquerading conditions in childhood include bronchiolitis obliterans, interstitial lung diseases, primary ciliary dyskinesias, humoral immune deficiencies, allergic bronchopulmonary mycoses, congestive heart failure, mass lesions in or compressing the larynx, trachea, or bronchi, and coughing and/or wheezing that is an adverse effect of medication. *Chronic pulmonary diseases often produce clubbing, but clubbing is a very unusual finding in childhood asthma.*

LABORATORY FINDINGS

Lung function tests can help to confirm the diagnosis of asthma and to determine disease severity.

Pulmonary Function Testing

Forced expiratory airflow measures are helpful in diagnosing and monitoring asthma and in assessing efficacy of therapy. Lung function testing is particularly helpful in children with asthma who are poor perceivers of airflow obstruction or when physical signs of asthma do not occur until airflow obstruction is severe.

Table 144-5 Differential Diagnosis of Childhood Asthma

UPPER RESPIRATORY TRACT CONDITIONS
Allergic rhinitis*
Chronic rhinitis*
Sinusitis*
Adenoidal or tonsillar hypertrophy
Nasal foreign body
MIDDLE RESPIRATORY TRACT CONDITIONS
Laryngotracheobronchomalacia*
Laryngotracheobronchitis (e.g., pertussis)*
Laryngeal web, cyst, or stenosis
Exercise-induced laryngeal obstruction
Vocal cord dysfunction*
Vocal cord paralysis
Tracheoesophageal fistula
Vascular ring, sling, or external mass compressing on the airway (e.g., tumor)
Foreign body aspiration*
Chronic bronchitis from environmental tobacco smoke exposure*
Toxic inhalations
LOWER RESPIRATORY TRACT CONDITIONS
Bronchopulmonary dysplasia (chronic lung disease of preterm infants)
Viral bronchiolitis*
Gastroesophageal reflux*
Causes of bronchiectasis:
Cystic fibrosis
Immune deficiency
Allergic bronchopulmonary mycoses (e.g., aspergillosis)
Chronic aspiration
Immotile cilia syndrome, primary ciliary dyskinesia
Bronchiolitis obliterans
Interstitial lung diseases
Hypersensitivity pneumonitis
Pulmonary eosinophilia, Churg-Strauss vasculitis
Pulmonary hemosiderosis
Tuberculosis
Pneumonia
Pulmonary edema (e.g., congestive heart failure)
Medications associated with chronic cough:
Acetylcholinesterase inhibitors
β-Adrenergic antagonists
Angiotensin-converting enzyme inhibitors

*More common asthma masqueraders.

Table 144-6 Similarities and Differences Between Vocal Cord Dysfunction and Asthma

VOCAL CORD DYSFUNCTION	ASTHMA
Extrathoracic	Intrathoracic
Rare (?never) hypoxemia	+ Hypoxemia
No hypercapnia/acidosis	+ Hypercapnia/acidosis
Normal expiratory spirometry	Reduced expiratory flow
Abnormal inspiratory loop (in some)	Normal inspiratory loop
Start/stop abruptly; few symptoms between episodes	Persistent symptoms
Frequent emergency department/office visits	Frequent emergency department/office visits
Multiple medications	Multiple medications

From Noyes BE, Kemp JS: Vocal cord dysfunction in children. Paediat Respir Rev *8:155–163, 2007 (Table 2, p. 159).*

Table 144-7 Lung Function Abnormalities in Asthma

Spirometry (in clinic):
- Airflow limitation:
- Low FEV_1 (relative to percentage of predicted norms)
- FEV_1:FVC ratio <0.80

Bronchodilator response (to inhaled β-agonist):
- Improvement in FEV_1 ≥12% and ≥200 mL*

Exercise challenge:
- Worsening in FEV_1 ≥15%*

Daily peak flow or FEV_1 monitoring: day to day and/or A.M.-to-P.M. variation ≥20%*

*Main criteria consistent with asthma.
FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Many asthma guidelines promote spirometric measures of airflow and lung volumes during forced expiratory maneuvers as standard for asthma assessment. **Spirometry** is a helpful objective measure of airflow limitation (Fig. 144-2). Spirometry is an essential assessment tool in children who are at risk for severe asthma exacerbations and those who have poor perception of asthma symptoms. Knowledgeable personnel are needed to perform and interpret findings of spirometry tests. Valid spirometric measures depend on a patient's ability to properly perform a full, forceful, and prolonged expiratory maneuver, usually feasible in children >6 yr of age (with some younger exceptions). Reproducible spirometric efforts are an indicator of test validity; i.e., the **FEV_1** (forced expiratory volume in 1 sec) should be reproducible within 5% on 3 measurements, and the *highest* value taken as the reported measure effort of the 3 is used. This standard utilization of the highest of 3 reproducible efforts is indicative of the effort dependence of reliable spirometric testing.

In asthma, airways blockage results in reduced airflow with forced exhalation (see Fig. 144-2). Because asthmatic patients typically have hyperinflated lungs, FEV_1 can be simply adjusted for full expiratory lung volume—the forced vital capacity (FVC)—with an FEV_1:FVC ratio. Generally, an FEV_1:FVC ratio <0.80 indicates significant airflow obstruction (Table 144-7). Normative values for FEV_1 have been determined for children on the basis of height, gender, and ethnicity. Abnormally low FEV_1 as a percentage of predicted norms is 1 of 6 criteria used to determine asthma severity and control in asthma management guidelines sponsored by the U.S. National Institutes of Health (NIH) and the Global Initiative for Asthma (GINA).

Such measures of airflow alone are not diagnostic of asthma, because numerous other conditions can cause airflow reduction. Bronchodilator response to an inhaled β-agonist (e.g., albuterol) is greater in asthmatic patients than nonasthmatic persons; an improvement in FEV_1 ≥12% or >200 mL is consistent with asthma. Bronchoprovocation challenges can be helpful in diagnosing asthma and optimizing asthma management. Asthmatic airways are hyperresponsive and therefore more sensitive to inhaled methacholine, mannitol, and cold or dry air. The degree of AHR to these exposures correlates to some extent with asthma severity and airways inflammation. Although bronchoprovocation challenges are carefully dosed and monitored in an investigational setting, their use is rarely practical in general practice. Exercise challenges (aerobic exertion or "running" for 6-8 min) can help to identify children with exercise-induced bronchospasm. Although the airflow response of nonasthmatic persons to exercise is to increase functional lung volumes and improve FEV_1 slightly (5-10%), exercise often provokes airflow obstruction in persons with inadequately treated asthma. Accordingly, in asthmatic patients, FEV_1 typically decreases during or after exercise by >15% (see Table 144-7). The onset of exercise-induced bronchospasm is usually within 15 min after a vigorous exercise challenge and can spontaneously resolve within 30-60 min. Studies of exercise challenges in school-age children typically identify an additional 5-10% with exercise-induced bronchospasm and previously unrecognized asthma. There are 2 caveats regarding exercise challenges: first,

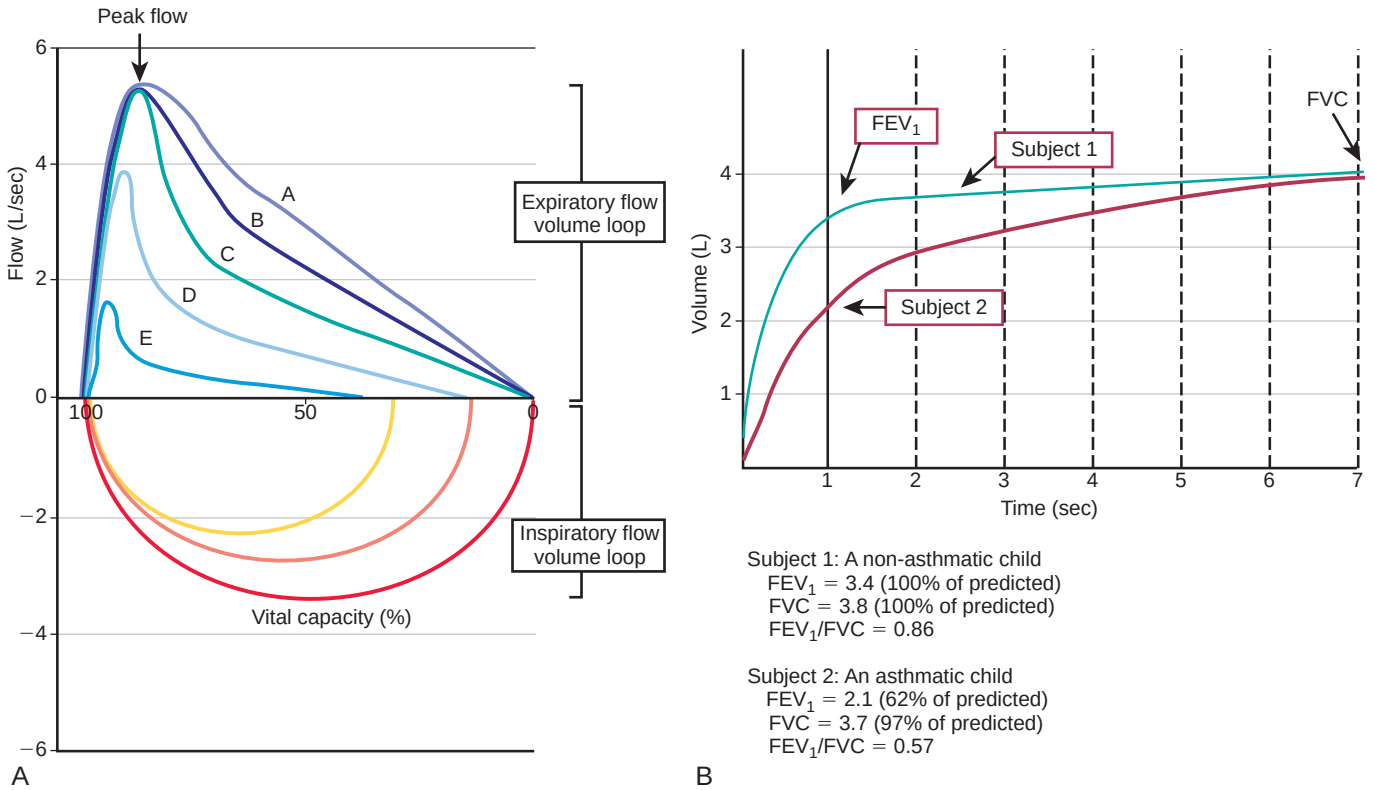

Figure 144-2 Spirometry. *A,* Spirometric flow-volume loops. A is an expiratory flow-volume loop of a nonasthmatic person without airflow limitation. B through E are expiratory flow-volume loops in asthmatic patients with increasing degrees of airflow limitation (B is mild; E is severe). Note the "scooped" or concave appearance of the asthmatic expiratory flow-volume loops; with increasing obstruction, there is greater "scooping." *B,* Spirometric volume-time curves. Subject 1 is a nonasthmatic person; subject 2 is an asthmatic patient. Note how the FEV_1 and FVC lung volumes are obtained. The FEV_1 is the volume of air exhaled in the 1st sec of a forced expiratory effort. The FVC is the total volume of air exhaled during a forced expiratory effort, or forced vital capacity. Note that subject 2's FEV_1 and FEV_1:FVC ratio are smaller than subject 1's, demonstrating airflow limitation. Also, subject 2's FVC is very close to what is expected.

treadmill challenges in the clinic are not completely reliable and can miss exertional asthma that can be demonstrated on the playing field; and second, exercise challenges can induce severe exacerbations in at-risk patients. Careful patient selection for exercise challenges and preparedness for severe asthma exacerbations are required.

Measuring **exhaled nitric oxide** (FE_{NO}), a marker of airway inflammation in allergy-associated asthma, may possibly help adjust antiinflammatory management and confirm the diagnosis of asthma.

Peak expiratory flow (PEF) monitoring devices provide simple and inexpensive home-use tools to measure airflow and can be helpful in a number of circumstances (Fig. 144-3). Similarly to spirometry in clinics, poor perceivers of asthma can benefit by monitoring PEFs at home to assess their airflow as an indicator of asthma control or problems. PEF devices vary in the ability to detect airflow obstruction: they are generally less sensitive and reliable than spirometry to detect airflow obstruction such that, in some patients, PEF values decline only when airflow obstruction is severe. Therefore, PEF monitoring should be started by measuring morning and evening PEFs (best of 3 attempts) for several weeks for patients to practice the technique, to determine diurnal variation and a "personal best," and to correlate PEF values with symptoms (and ideally spirometry). Diurnal variation in PEF >20% is consistent with asthma (see Fig. 144-3 and Table 144-7).

Radiology

The findings of chest radiographs (posteroanterior and lateral views) in children with asthma often appear to be normal, aside from subtle and nonspecific findings of hyperinflation (e.g., flattening of the diaphragms) and peribronchial thickening (Fig. 144-4). Chest radiographs can help identify abnormalities that are hallmarks of asthma masqueraders (aspiration pneumonitis, hyperlucent lung fields in bronchiolitis obliterans) and complications during asthma exacerbations (atelectasis, pneumomediastinum, pneumothorax). Some lung abnormalities can be better appreciated with high-resolution, thin-section chest CT scans. Bronchiectasis, which is sometimes difficult to appreciate on chest radiograph but is clearly seen on CT scan, implicates an asthma masquerader such as cystic fibrosis, allergic bronchopulmonary mycoses (aspergillosis), ciliary dyskinesias, or immune deficiencies.

Other tests, such as allergy testing to assess sensitization to inhalant allergens, help with the management and prognosis of asthma. In a comprehensive U.S. study of 5-12 yr old asthmatic children (Childhood Asthma Management Program [CAMP]), 88% of the subjects had inhalant allergen sensitization according to results of allergy prick skin testing.

TREATMENT

The NIH-sponsored *National Asthma Education and Prevention Program's Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma 2007* is available online (www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm). Similar guidelines *From the Global Strategy for Asthma Management and Prevention,* GINA 2012, are also available online (www.ginaasthma.org). The key components to optimal asthma management are specified (Fig. 144-5). **Management** of asthma should have the following components: (1) assessment and monitoring of disease activity; (2) education to enhance patient and family knowledge and skills for self-management; (3) identification and management of precipitating factors and comorbid conditions that worsen asthma; and (4) appropriate selection of medications to address the patient's needs. The long-term goal of asthma management is attainment of optimal asthma control.

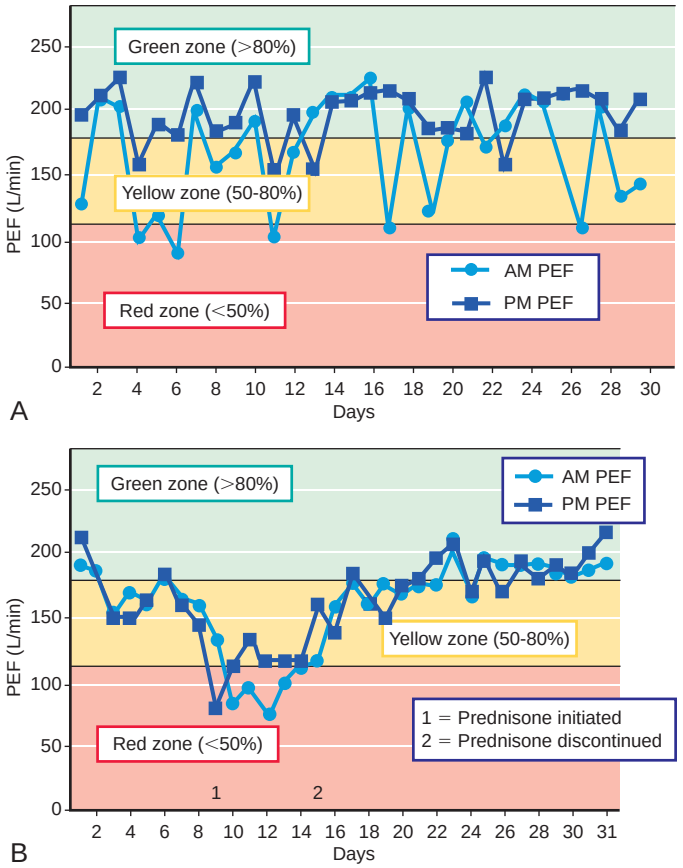

Figure 144-3 An example of the role of peak flow monitoring in childhood asthma. *A,* PEFs performed and recorded twice daily, in the morning (A.M.) and evening (P.M.), over 1 mo in an asthmatic child. This child's "personal best" PEF value is 220 L/min; therefore, the green zone (>80-100% of best) is 175-220 L/min; the yellow zone (50-80%) is 110-175 L/min; and the red zone (<50%) is <110 L/min. Note that this child's P.M. PEF values are almost always in the green zone, whereas his A.M. PEFs are often in the yellow or red zone. This pattern illustrates the typical diurnal A.M.-to-P.M. variation of inadequately controlled asthma. *B,* PEFs performed twice daily, in the morning (A.M.) and evening (P.M.), over 1 mo in an asthmatic child in whom an asthma exacerbation developed from a viral respiratory tract infection. Note that the child's PEF values were initially in the green zone. A viral respiratory tract infection led to asthma worsening, with a decline in PEF to the yellow zone that continued to worsen until PEF values were in the red zone. At that point, a 4-day prednisone course was administered, followed by improvement in PEF back to the green zone.

Component 1: Regular Assessment and Monitoring

Regular assessment and monitoring are based on the concepts of asthma severity, asthma control, and responsiveness to therapy. **Asthma severity** is the intrinsic intensity of disease, and assessment is generally most accurate in patients not receiving controller therapy. Hence, assessing asthma severity directs the initial level of therapy. The 2 general categories are **intermittent** asthma and **persistent** asthma, the latter being further subdivided into **mild, moderate,** and **severe.** In contrast, **asthma control** refers to the degree to which symptoms, ongoing functional impairments, and risk of adverse events are minimized, and goals of therapy are met. In children receiving controller therapy, assessment of asthma control is important in adjusting therapy and is categorized in 3 levels: well-controlled, not well-controlled, and very poorly controlled. **Responsiveness to therapy** is the ease or difficulty with which asthma control is attained by treatment.

Classification of asthma severity and control is based on the domains of **impairment** and **risk.** These domains may not correlate with each other and may respond differently to treatment. In some children with asthma, day-to-day impairment is well controlled, but the risk of severe exacerbations remains. The NIH guidelines have distinct criteria for 3 childhood age groups—0-4 yr, 5-11 yr, and ≥12 yr—for the evaluation of both severity (Table 144-8) and control (Table 144-9). The level of asthma severity or control is based on the most severe impairment or risk category. In assessing asthma severity, **impairment** consists of an assessment of the patient's recent symptom frequency (daytime and nighttime, with subtle differences in numeric cutoffs between the 3 age groups), SABA usage for quick relief, ability to engage in normal or desired activities, and airflow compromise evaluated by spirometry in children 5 yr and older. **Risk** refers to the likelihood of developing severe asthma exacerbations. Of note, in the absence of frequent symptoms, persistent asthma should be considered, and therefore long-term controller therapy should be initiated for infants or children who have risk factors for asthma (see earlier) and 4 or more episodes of wheezing over the past year that lasted longer than 1 day and affected sleep, or 2 or more exacerbations in 6 mo requiring systemic corticosteroids.

Asthma management can be optimized through regular clinic visits every 2-6 wk until good asthma control is achieved. For children already on controller medication therapy, management is tailored to the child's level of control. The NIH guidelines provide tables for evaluating asthma control for the 3 age groups (see Table 144-9). In evaluation of asthma control, as in severity assessment, impairment includes an assessment of the patient's symptom frequency (daytime and nighttime), SABA usage for quick relief, ability to engage in normal or desired activities, and, for older children, airflow measurements. Furthermore, with respect to risk assessment, besides considering severity and frequency of exacerbations requiring systemic corticosteroids, tracking of lung growth in older children and monitoring adverse effects of medications is also warranted. The degree of impairment and presence of risk are used to determine the patient's level of asthma control as well-controlled, not well-controlled, or very poorly controlled. Children with *well-controlled asthma* have daytime symptoms ≤2 days/wk and need a rescue bronchodilator ≤2 days/wk; an FEV_1 of >80% of predicted (and an FEV_1:FVC ratio >80% for children 5-11 yr of age); no interference with normal activity; and <2 exacerbations in the past year. The impairment criteria vary slightly depending on age group: there are different thresholds in the frequency of nighttime awakenings; addition of FEV_1:FVC ratio criteria for children 5-11 yr old and addition of validated impairment questionnaires (e.g., Asthma Control Test [ACT] for ages ≥12 yr, Childhood ACT for ages 4-11 yr). Children whose status does not meet all of the criteria defining well-controlled asthma are determined to have either not-well-controlled or very poorly controlled asthma, which is determined by the single criterion with the poorest rating.

Two to 4 asthma checkups per year are recommended for reassessing and maintaining good asthma control. Lung function testing (spirometry) is recommended at least annually and more often if asthma is poorly perceived, inadequately controlled and/or lung function is abnormally low. PEF monitoring at home can be helpful in the assessment of asthmatic children with poor symptom perception, other causes of chronic coughing in addition to asthma, moderate to severe asthma, or a history of severe asthma exacerbations. PEF monitoring is feasible in children as young as 4 yr who are able to master this skill. Use of a **stoplight zone system** tailored to each child's "personal best" PEF values can optimize effectiveness and interest (see Fig 144-3): The green zone (80-100% of personal best) indicates good control; the yellow zone (50-80%) indicates less-than-optimal control and necessitates increased awareness and treatment; the red zone (<50%) indicates poor control and greater likelihood of an exacerbation, requiring immediate intervention. In actuality, these ranges are approximate and may need to be adjusted for many asthmatic children by raising the ranges that indicate inadequate control (in the yellow zone, 70-90%). Once-daily PEF monitoring is preferable in the morning when peak flows are typically lower.

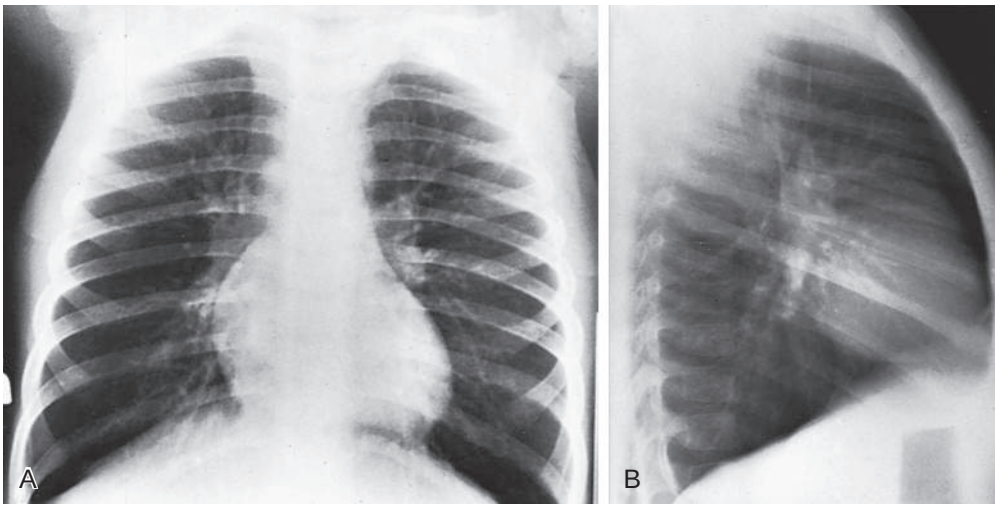

Figure 144-4 A 4-year-old boy with asthma. Frontal *(A)* and lateral *(B)* radiographs show pulmonary hyperinflation and minimal peribronchial thickening. No asthmatic complication is apparent.

Recurrent/chronic cough, wheeze, dyspnea

Diagnosis
- Symptoms
- Exacerbations
- Risk factors (Tables 144-1, -2)
- Triggers (Table 144-3)
- Lung function (Figs. 144-2, -3; Table 144-7)
- Differential dx. (Table 144-5)

Asthma

Management

• *Assessment and monitoring*	• Assess severity (Table 144-8) • Monitor control (Table 144-9) • Med adverse effects (Table 144-15)
• *Education*	• Key elements (Table 144-10)
• *Contol environmental factors and co-morbid conditions*	• Environmental controls (Table 144-11) • Co-morbidities (Table 144-11)
• *Medications*	• Long-term controllers (Tables 144-12 to 144-14) • Quick relievers (Table 144-12)
• *Exacerbations*	• Management (Table 144-16) • High-risk features (Table 144-17) • Home action plan

Optimal goal: Well-controlled asthma

• *Reduce impairment*	• Prevent chronic symptoms • Prevent sleep disturbance • Infrequent SABA need • Maintain (near) normal lung function • Maintain normal activity
• *Reduce risk*	• Prevent exacerbations • Minimize ER visits/hospitalizations • Prevent reduced lung growth • No (minimal) adverse effects of therapy

Figure 144-5 The key elements to optimal asthma management. SABA, short-acting β-agonist.

Component 2: Patient Education

Specific educational elements in the clinical care of children with asthma are believed to make an important difference in home management and in adherence of families to an optimal plan of care and eventually impacting patient outcomes (Table 144-10). Every visit presents an important opportunity to educate the child and family, allowing them to become knowledgeable partners in asthma management, because optimal management depends on their daily assessments and implementation of any management plan. Effective communications take into account sociocultural and ethnic factors of children and their families, provide an open forum for concerns about asthma and its treatment to be raised and addressed, and include patients and families as active participants in the development of treatment goals and selection of medications. Self-management skills should be reevaluated regularly (e.g., inhaler medication technique).

During initial patient visits, a basic understanding of the pathogenesis of asthma (chronic inflammation and AHR underlying a clinically intermittent presentation) can help children with asthma and their parents understand the importance of recommendations aimed at reducing airways inflammation to achieve and maintain good asthma control. It is helpful to specify the expectations of good asthma control resulting from optimal asthma management (see Fig. 144-5). Addressing concerns about potential adverse effects of asthma pharmacotherapeutic agents, especially their risks relative to their benefits, is essential in achieving long-term adherence with asthma pharmacotherapy and environmental control measures.

Children with asthma and their families, particularly patients with moderate or severe persistent or poorly controlled asthma and patients who have had severe exacerbations, benefit from a written asthma management plan. This plan has 2 main components: (1) a daily "routine" management plan describing regular asthma medication use and other measures to keep asthma under good control; and (2) an action plan to manage worsening asthma, describing indicators of impending exacerbations, identifying what medications to take, and specifying when and how to contact the regular physician and/or obtain urgent/emergency medical care.

Regular follow-up visits are recommended to help to maintain optimal asthma control. In addition to determining disease control level and revising daily and exacerbation management plans accordingly, follow-up visits are important teaching opportunities to encourage open communication of concerns with asthma management recommendations (e.g., daily administration of controller medications). Reassessing patients' and parents' understanding of the role of different medications in asthma management and control, and their technique in using inhaled medications, can be insightful and can help guide teaching to improve adherence to a management plan that might not have been adequately or properly implemented.

ADHERENCE

Asthma is a chronic condition that is usually best managed with daily controller medication. However, symptoms wax and wane, severe exacerbations are infrequent, and when asthma is asymptomatic, a natural tendency is to reduce or discontinue daily controller therapies. As such, adherence to a daily controller regimen is commonly suboptimal;

Table 144-8 Assessing Asthma Severity and Initiating Treatment for Patients Who Are Not Currently Taking Long-Term Control Medications*

	CLASSIFICATION OF ASTHMA SEVERITY			
		PERSISTENT		
	Intermittent	Mild	Moderate	Severe
COMPONENTS OF SEVERITY				
Impairment				
Daytime symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Nighttime awakenings:				
Age 0-4 yr	0	1-2×/mo	3-4×/mo	>1×/wk
Age ≥5 yr	≤2×/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
Short-acting β_2-agonist use for symptoms (not for prevention of exercise-induced bronchospasm)	≤2 days/wk	>2 days/wk but not daily, and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Extreme limitation
Lung function:				
FEV_1 % predicted, age ≥5 yr	Normal FEV_1 between exacerbations >80% predicted	≥80% predicted	60-80% predicted	<60% predicted
FEV_1:FVC ratio†:				
Age 5-11 yr	>85%	>80%	75-80%	<75%
Age ≥12 yr	Normal	Normal	Reduced 5%	Reduced >5%
Risk				
Exacerbations requiring systemic corticosteroids:				
Age 0-4 yr	0-1/yr (see notes)	≥2 exacerbations in 6 mo requiring systemic corticosteroids **or** ≥4 wheezing episodes/yr lasting >1 day *and* risk factors for persistent asthma		
Age ≥ 5 yr	0-1/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)	≥2/yr (see notes)
Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.				
RECOMMENDED STEP FOR INITIATING THERAPY				
All ages	Step 1	Step 2		
Age 0-4 yr			Step 3	Step 3
Age 5-11 yr			Step 3, medium-dose ICS option	Step 3, medium-dose ICS option **or** Step 4
Age ≥12 yr			Consider a short course of systemic corticosteroids	Consider a short course of systemic corticosteroids
In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly. If no clear benefit is observed within 4-6 wk, consider adjusting therapy or alternative diagnoses.				

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether a patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 mo, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

†Normal FEV_1:FVC: 8-19 yr, 85%; 20-39 yr, 80%.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; ICS, inhaled corticosteroids.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

inhaled corticosteroids (ICSs) are underused 60% of the time. In one study, children with asthma who required an oral corticosteroid course for an asthma exacerbation had used their daily controller ICS 15% of the time. Misconceptions about controller medication time to onset, efficacy, and safety often underlie poor adherence and can be addressed by asking about such concerns at each visit.

Component 3: Control of Factors Contributing to Asthma Severity

Controllable factors that can worsen asthma can be generally grouped as (1) environmental exposures and (2) comorbid conditions (Table 144-11).

Eliminating and Reducing Problematic Environmental Exposures

The majority of children with asthma have an allergic component to their disease; steps should be taken to investigate and minimize allergen exposures in sensitized asthmatic patients. The medical history should address potential allergen triggers (see below), but often patients have chronic symptoms and cannot identify potential triggers. Therefore, allergy testing should be considered for at least those with persistent asthma. For asthmatic patients who are allergic to allergens in their homes, reducing or eliminating these home allergen exposures can decrease asthma symptoms, medication requirements, AHR, severe exacerbations, and disease persistence. Common home allergen

Table 144-9 Assessing Asthma Control and Adjusting Therapy in Children*

	CLASSIFICATION OF ASTHMA CONTROL		
	Well-Controlled	**Not Well-Controlled**	**Very Poorly Controlled**
COMPONENTS OF CONTROL			
Impairment			
Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
Nighttime awakenings:			
Age 0-4 yr	≤1×/mo	>1×/mo	>1×/wk
Age 5-11 yr	≤1×/mo	≥2×/mo	≥2×/wk
Age ≥12 yr	≤2×/mo	1-3×/wk	≥4×/wk
Short-acting β_2-agonist use for symptoms (not for exercise-induced bronchospasm pretreatment)	≤2 days/wk	>2 days/wk	Several times per day
Interference with normal activity	None	Some limitation	Extremely limited
Lung function:			
Age 5-11 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
FEV_1/FVC:	>80%	75-80%	<75%
Age ≥ 12 yr:			
FEV_1 (% predicted or peak flow)	>80% predicted or personal best	60-80% predicted or personal best	<60% predicted or personal best
Validated questionnaires†:			
Age ≥ 12 yr:			
ATAQ	0	1-2	3-4
ACQ	≤0.75	≤1.5	N/A
ACT	≥20	16-19	≤15
Risk			
Exacerbations requiring systemic corticosteroids:			
Age 0-4 yr	0-1/yr	2-3/yr	>3/yr
Age ≥5 yr	0-1/yr	≥2/yr (see notes)	
Consider severity and interval since last exacerbation.			
Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Reduction in lung growth *or* progressive loss of lung function	Evaluation requires long-term follow-up care.		
RECOMMENDED ACTION FOR TREATMENT			
	Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well-controlled for at least 3 mo.	Step up‡ (1 step) and reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.	Consider short course of oral corticosteroids. Step up§ (1-2 steps) and reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative options.

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

†Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain) and definition of minimal important difference (MID) for each:
- ATAQ, Asthma Therapy Assessment Questionnaire; MID = 1.0
- ACQ, Asthma Control Questionnaire; MID = 0.5
- ACT, Asthma Control Test; MID not determined

‡ACQ values of 0.76-1.40 are indeterminate regarding well-controlled asthma.

§Before step-up therapy: (a) review adherence to medications, inhaler technique, and environmental control; (b) if alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

Table 144-10 Key Elements of Productive Clinic Visits for Asthma

Specify goals of asthma management
Explain basic facts about asthma:
- Contrast normal vs asthmatic airways
- Link airways inflammation, "twitchiness," and bronchoconstriction
- Long-term-control and quick-relief medications
- Address concerns about potential adverse effects of asthma pharmacotherapy

Teach, demonstrate, and have patient show proper technique for:
- Inhaled medication use (spacer use with metered-dose inhaler)
- Peak flow measures

Investigate and manage factors that contribute to asthma severity:
- Environmental exposures
- Comorbid conditions

Create written 2-part asthma management plan:
- Daily management
- Action plan for asthma exacerbations

Regular follow-up visits:
- Twice yearly (more often if asthma not well-controlled)
- Monitor lung function annually

Table 144-11 Control of Factors Contributing to Asthma Severity

ELIMINATE OR REDUCE PROBLEMATIC ENVIRONMENTAL EXPOSURES:
Environmental tobacco smoke elimination or reduction in home and automobiles
Allergen exposure elimination or reduction in sensitized asthmatic patients:
- Animal danders: pets (cats, dogs, rodents, birds)
- Pests (mice, rats)
- Dust mites
- Cockroaches
- Molds

Other airway irritants:
- Wood- or coal-burning smoke
- Strong chemical odors and perfumes (e.g., household cleaners)
- Dusts

TREAT COMORBID CONDITIONS:
- Rhinitis
- Sinusitis
- Gastroesophageal reflux

exposures include furred or feathered animals as pets (cats, dogs, rodents, birds) or as pests (mice, rats), and occult indoor allergens, such as dust mites, cockroaches, and molds. Although some sensitized children may report an increase in asthma symptoms on exposure to the allergen source, improvement from allergen avoidance may not become apparent without a sustained period of days to weeks away from the offending exposure. Tobacco, wood and coal smoke, dusts, strong odors, and noxious air pollutants can all aggravate asthma. These airways irritants should be eliminated from or reduced in the homes and automobiles used by children with asthma. School classrooms and daycare settings can also be sites of environmental exposures that worsen asthma. Eliminating or minimizing these exposures (e.g., furred or feathered pets in classrooms of sensitized children with asthma) can reduce asthma symptoms, disease severity, and the amount of medication needed to achieve good asthma control. Annual influenza vaccination continues to be recommended for all children with asthma, although influenza is not responsible for the large majority of virus-induced asthma exacerbations experienced by children.

Aspirin-exacerbated respiratory disease, formerly called aspirin-induced asthma, is also associated with chronic eosinophilic rhinitis and nasal polyposis. Inhibition of cyclooxygenase by aspirin and other nonsteroidal antiinflammatory drugs (including cyclooxygenase [COX]-2 inhibiting agents) is thought to be the primary mechanism, which leads to exacerbations of disease, predominantly in patients with moderate to severe persistent asthma. Acetaminophen, a weak COX-1 inhibitor, is safe in low doses, but may produce symptoms if high doses are taken. The incidence is between 5% and 10% of predominantly adolescents with asthma; it is rare in children <10 yr of age. Following ingestion of the drug, symptoms may appear between 30 and 120 min and include profuse rhinorrhea, nasal congestion, and tearing, accompanied by bronchospasm. Vocal cord spasm and an anaphylactic-like reaction are rare complications. Aspirin and related drugs should be avoided in these patients; an alternative approach is aspirin desensitization by an allergist.

Treating Comorbid Conditions

Rhinitis, sinusitis, and GER often accompany asthma and worsen disease severity. They can also mimic asthma symptoms and lead to misclassification of asthma severity and control. Indeed, these conditions with asthma are the most common causes of chronic coughing. Effective management of these comorbid conditions may improve asthma symptoms and disease severity, such that less asthma medication is needed to achieve good asthma control.

GER is observed in 43% of children with persistent asthma. GER may worsen asthma through 2 postulated mechanisms: (1) aspiration of refluxed gastric contents (micro- or macro-aspiration); and (2) vagally mediated reflex bronchospasm. Occult GER should be suspected in individuals with difficult-to-control asthma, especially patients who have prominent asthma symptoms while eating or sleeping (in a horizontal position) or who prop themselves up in bed to reduce nocturnal symptoms. GER can be demonstrated by reflux of barium into the esophagus during a barium swallow procedure or by esophageal probe monitoring. Because radiographic studies lack sufficient sensitivity and specificity, extended esophageal monitoring is the method of choice for diagnosing GER. If significant GER is noted, reflux precautions should be instituted (no food 2 hr before bedtime, head of the bed elevated 6 in, avoidance of caffeinated foods and beverages) and medications such as proton pump inhibitors (omeprazole, lansoprazole) or H_2-receptor antagonists (cimetidine, ranitidine) administered for 8-12 wk. Proton pump inhibition did not improve asthma control in a study of children with persistent, poorly controlled asthma and GER.

Rhinitis is usually comorbid with asthma, detected in ≈90% of children with asthma. Rhinitis can be seasonal and/or perennial, with allergic and nonallergic components. Rhinitis complicates and worsens asthma via numerous direct and indirect mechanisms. Nasal breathing may improve asthma and reduce exercise-induced bronchospasm by humidifying and warming inspired air and filtering out allergens and irritants that can trigger asthma and worsen airway inflammation. Reduction of nasal congestion and obstruction can help the nose to perform these humidifying, warming, and filtering functions. In asthmatic patients, improvement in rhinitis is also associated with improvement in AHR, lower airways inflammation, asthma symptoms, and asthma medication use. Optimal rhinitis management in children is similar to asthma management in regard to the importance of interventions to reduce nasal inflammation (see Chapter 143).

Radiographic evidence for **sinus disease** is common in patients with asthma. There is usually significant improvement in asthma control in patients diagnosed and treated for sinus disease. A coronal, "screening" or "limited" CT scan of the sinuses is the gold standard test for sinus disease and can be helpful if recurrent sinusitis has been suspected and repeatedly treated without such evidence. In comparison, sinus X-rays are inaccurate. If the patient with asthma has clinical and radiographic evidence for sinusitis, topical therapy to include nasal saline irrigations, intranasal corticosteroids, and a 2-3–wk course of antibiotics should be considered.

Component 4: Principles of Asthma Pharmacotherapy

The current version of NIH asthma guidelines (2007) provides treatment recommendations that vary by age groups and are based on current evidence (Table 144-12). The goals of therapy are to achieve a well-controlled state by reducing the components of both impairment (e.g., preventing chronic and troublesome symptoms, allowing infrequent need of quick-reliever medications, maintaining "normal" lung function, maintaining normal activity levels including physical activity and school attendance, meeting families' expectations and satisfaction

Table 144-12 Stepwise Approach for Managing Asthma in Children*

AGE	THERAPY†	INTERMITTENT ASTHMA	PERSISTENT ASTHMA: DAILY MEDICATION				
			STEP DOWN if possible (and asthma is well controlled at least 3 months)		ASSESS CONTROL	STEP UP if needed (first check inhaler technique, adherence, environmental control, and comorbid condition)	
		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
0-4 yr	Preferred	SABA prn	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA	High-dose ICS + *either* LABA *or* LTRA *and* Oral corticosteroid
	Alternative		Cromolyn or montelukast				
5-11 yr	Preferred	SABA prn	Low-dose ICS	*Either* low-dose ICS ± LABA, LTRA, or theophylline *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA *and* Oral corticosteroid
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline		Medium-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline	High-dose ICS + *either* LTRA *or* Theophylline *and* Oral corticosteroid
≥12 yr	Preferred	SABA prn	Low-dose ICS	Low-dose ICS + LABA *or* Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA *and* Consider omalizumab for patients with allergies	High-dose ICS + LABA + oral corticosteroid *and* Consider omalizumab for patients with allergies
	Alternative		Cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS + LTRA, theophylline, or zileuton	Medium-dose ICS + LTRA, theophylline, or zileuton		

Each step: Patient education, environmental control, and management of comorbidities.
Age ≥5 yr: Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.
QUICK-RELIEF MEDICATION FOR ALL PATIENTS
SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-min intervals as needed. Short course of oral systemic corticosteroids may be needed.
Caution: Use of SABA >2 days/wk for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.
For ages 0-4 yr: With viral respiratory infection: SABA q4-6h up to 24 hr (longer with physician consult). Consider short course of systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.

*Notes:
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children age 0-4 yr are limited. The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.
- Zileuton is less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function.

†Alphabetical order is used when more than 1 treatment option is listed within *either* preferred or alternative therapy.
ICS, inhaled corticosteroid; LABA, inhaled long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; prn, as needed; SABA, inhaled short-acting β_2-agonist.
Adapted from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): Guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

with asthma care) and risk (e.g., preventing recurrent exacerbations, reduced lung growth, and medications' adverse effects). The recommendations for initial therapy are based on assessment of asthma severity. For patients who are already using controller therapy, modification of treatment is based on assessment of asthma control and responsiveness to therapy. A major objective of this approach is to identify and treat all "persistent" and inadequately controlled asthma with antiinflammatory controller medication. Daily controller therapy is not recommended for children with "intermittent asthma." *Management of intermittent asthma is simply the use of a SABA as needed for symptoms and for pretreatment in those with exercise-induced bronchospasm (Step 1 therapy; see Table 144-12).*

The preferred treatment for all patients with persistent asthma is daily ICS therapy, as monotherapy or in combination with adjunctive therapy. The type(s) and amount(s) of daily controller medications to be used are determined by the asthma severity and control rating. Alternative medications for Step 2 therapy include a leukotriene receptor antagonist (montelukast), nonsteroidal antiinflammatory agents (cromolyn and nedocromil), and theophylline (for youths). For young children (≤4 yr) with moderate or severe persistent asthma, medium-dose ICS monotherapy is recommended (Step 3); combination therapy is recommended only as a Step 4 treatment for uncontrolled asthma.

Along with medium-dose ICSs, combination therapy with an ICS plus any of the following adjunctive therapies (depending on age group) is recommended as Steps 3 and 4 treatment for moderate persistent asthma, or as step-up therapy for uncontrolled persistent asthma: long-acting inhaled β_2-agonists (LABAs), leukotriene-modifying agents, chromones, and theophylline. In a study of children with uncontrolled asthma while on low-dose ICS, the addition of LABA provided more improvement than either adding a leukotriene receptor antagonist (LTRA) or increasing ICS dosage. However, some children had a good response to ICS or LTRA, justifying them as step-up controller therapy options.

Children with severe persistent asthma (treatment Steps 5 and 6) should receive high-dose ICS and LABA. Long-term administration of oral corticosteroids as controller therapy can be effective, but is rarely needed with the availability of potent ICS and LABA combination formulations in single devices. In addition, omalizumab can be used in children ≥12 yr old with severe allergic asthma. A rescue course of systemic corticosteroids may be necessary at any step. For children age ≥5 yr with allergic asthma requiring Steps 2-4 care, allergen immunotherapy can be considered.

"Step-Up, Step-Down" Approach

The NIH guidelines emphasize initiating higher-level controller therapy at the outset to establish prompt control, with measures to "step down" therapy once good asthma control is achieved. Initially, airflow limitation and the pathology of asthma may limit the delivery and efficacy of ICS such that stepping up to higher doses and/or combination therapy may be needed to gain asthma control. Furthermore, ICS requires weeks to months of daily administration for optimal efficacy to occur. Combination pharmacotherapy can achieve relatively immediate improvement while also providing daily ICS to improve long-term control and reduce exacerbation risk.

Asthma therapy can be stepped down after good asthma control has been achieved and ICS has had time to achieve optimal efficacy. By determining the lowest number or dose of daily controller medications that can maintain good control, the potential for medication adverse effects is reduced. If a child has had well-controlled asthma for at least 3 mo, the guidelines suggest decreasing the dose or number of the child's controller medication(s) to establish the minimum required medications to maintain well-controlled asthma. Regular follow-up is still emphasized because the variability of asthma's course is well recognized. In contrast, if a child has not-well-controlled asthma, the therapy level should be increased by 1 step and close monitoring is recommended. For a child with very poorly controlled asthma, the recommendations are that treatment go up 2 steps and/or a short course of oral corticosteroid therapy be given, with evaluation within 2 wk. As step-up therapy is being considered at any point, it is important to check inhaler technique and adherence, implement environmental control measures, and identify and treat comorbid conditions.

Referral to Asthma Specialist

Referral to an asthma specialist for consultation or co-management is recommended if there are difficulties in achieving or maintaining control. For children younger than 4 yr, referral is recommended for moderate persistent asthma or if the patient requires at least Step 3 care, and should be considered if the patient requires Step 2 care. For children 5 yr of age and older, consultation with a specialist is recommended if the patient requires Step 4 care or higher, and should be considered if Step 3 is required. Referral is also recommended if allergen immunotherapy or anti–immunoglobulin (Ig) E therapy is being considered.

Long-Term Controller Medications

All levels of persistent asthma should be treated with daily medications to improve long-term control (see Table 144-12). Such medications include ICSs, LABAs, leukotriene modifiers, nonsteroidal antiinflammatory agents, and sustained-release theophylline. An anti-IgE preparation, omalizumab (Xolair), is approved by the FDA for use as an add-on therapy in children ≥12 yr who have moderate to severe allergic asthma that is difficult to control. Corticosteroids are the most potent and most effective medications used to treat both the acute (administered systemically) and chronic (administered by inhalation) manifestations of asthma. They are available in inhaled, oral, and parenteral forms (Tables 144-13 and 144-14).

Inhaled Corticosteroids

The NIH guidelines recommend daily ICS therapy as the treatment of choice for all patients with persistent asthma (see Table 144-12). ICS therapy improves lung function as well as reduces asthma symptoms, AHR, and use of "rescue" medications; most importantly, it reduces urgent care visits, hospitalizations, and prednisone use for asthma exacerbations by approximately 50%. ICS therapy may lower the risk of death attributable to asthma. It can achieve all of the goals of asthma management and, as a result, is viewed as first-line treatment for persistent asthma.

Six ICSs are approved for use in children by the FDA, and the NIH guidelines provide an equivalence classification (see Table 144-14), although direct comparisons of efficacy and safety outcomes in children are lacking. ICSs are available in metered-dose inhalers (MDIs), in dry powder inhalers (DPIs), or in suspension for nebulization. Fluticasone propionate, mometasone furoate, ciclesonide, and, to a lesser extent, budesonide are considered "second-generation" ICSs, in that they have greater antiinflammatory potency and diminished systemic bioavailability for potential adverse effects, owing to extensive first-pass hepatic metabolism. The selection of the initial ICS dose is based on the determination of disease severity. A fraction of the initial ICS dose is often sufficient to maintain good control after this goal has been achieved.

Although ICS therapy has been widely used in adults with persistent asthma, its application in children has lagged because of concerns about the potential for adverse effects with long-term use. Generally, clinically significant adverse effects that occur with long-term systemic corticosteroid therapy have not been seen or have only very rarely been reported in children receiving ICSs in recommended doses. The risk of adverse effects from ICS therapy is related to the dose and frequency with which ICSs are given (Table 144-15). High doses (≥1,000 μg/day in children) and frequent administration (4 times/day) are more likely to have local and systemic adverse effects. Children who receive maintenance therapy with higher ICS doses are also likely to require systemic corticosteroid courses for asthma exacerbations, further increasing the risk of corticosteroid adverse effects.

The most commonly encountered **adverse effects** of ICSs are local: oral candidiasis (thrush) and dysphonia (hoarse voice). Thrush results from propellant-induced mucosal irritation and local immunosuppression. Dysphonia occurs from vocal cord myopathy. These effects are

Table 144-13 Usual Dosages for Long-Term Control Medications

Medication	AGE 0-4 yr	5-11 yr	≥12 yr
INHALED CORTICOSTEROIDS (see Table 144-13)			
Methylprednisolone: 2, 4, 8, 16, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL, 15 mg/5 mL Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/mL, 5 mg/5 mL	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 30 mg/day for 3-10 days	• 0.25-2 mg/kg daily in single dose in A.M. or qod as needed for control • Short-course "burst": 1-2 mg/kg/day; maximum 60 mg/day for 3-10 days	• 7.5-60 mg daily in a single dose in A.M. or qod as needed for control • Short-course "burst" to achieve control: 40-60 mg/day as single or 2 divided doses for 3-10 days
Fluticasone/salmeterol: DPI: 100, 250, or 500 mg/50 mg HFA: 45 μg/21 μg, 115 μg/21 μg, 230 μg/21 μg	NA	1 inhalation bid; dose depends on level of severity or control	1 inhalation bid; dose depends on level of severity or control 2 inhalations bid; dose depends on level of severity or control
Budesonide/formoterol: HFA: 80 μg/4.5 μg, 160 μg/4.5 μg	NA		2 inhalations bid; dose depends on level of severity or control
Mometasone/formoterol HFA: 100 μg/5 μg, 200 μg/5 μg			2 inhalations bid; dose depends on level of severity or control
Cromolyn: Nebulizer 20 mg/ampule	1 ampule qid; NA <2 yr of age	1 ampule qid	1 ampule qid
Leukotriene receptor antagonists: Montelukast: 4 or 5 mg chewable tablet 4 mg granule packets 10 mg tablet	4 mg qhs (1-5 yr of age)	5 mg qhs (6-14 yr)	10 mg qhs
Zafirlukast: 10- or 20-mg tablet	NA	10 mg bid (7-11 yr)	40 mg daily (20 mg tablet bid)
5-Lipoxygenase inhibitor: Zileuton CR: 600-mg tablet	NA	NA	1,200 mg twice daily (give 2 tablets bid)
Theophylline: Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual max: • <1 yr of age: 0.2 (age in wk) + 5 = mg/kg/day • >1 yr of age: 16 mg/kg/day	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	Starting dose 10 mg/kg/day up to 300 mg maximum; usual maximum 800 mg/day
Immunomodulators: Omalizumab (anti-IgE): Subcutaneous injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	NA	NA	150-375 mg SC q 2-4 wk, depending on body weight and pretreatment serum IgE level

bid, Twice a day; DPI, dry powder inhaler; HFA, hydrofluoroalkane Ig, immunoglobulin; MDI, metered-dose inhaler; q, every; qhs, every night; qid, 4 times a day; qod, every other day; SC, subcutaneous.

dose-dependent and are most common in individuals receiving high-dose ICS and/or oral corticosteroid therapy. The incidence of these local effects can be greatly minimized by using a spacer with an MDI ICS, because spacers reduce oropharyngeal deposition of the drug and propellant. Mouth rinsing using a "swish and spit" technique after ICS use is also recommended.

The potential for growth suppression and osteoporosis with long-term ICS use has been a concern. In the long-term, prospective NIH-sponsored CAMP study of children with mild to moderate asthma, after ≈4.3 yr of ICS therapy and 5 yr after the trial, there was a significant 1.7 cm decrease in height in girls, but not in boys. There was also a slight dose-dependent effect of ICS therapy on bone mineral accretion in boys, but not girls. A greater effect on bone mineral accretion was observed with increasing numbers of courses of oral corticosteroid burst therapy for asthma, as well as an increase in risk for osteopenia, again limited to boys. Although this study cannot predict a significant effect of ICS therapy in childhood on osteoporosis in later adulthood, improved asthma control with ICS therapy may result in a need for fewer courses of oral corticosteroid burst therapy over time. These findings were with use of budesonide at doses of about 400 μg/day; higher ICS doses, especially of agents with increased potency, have a greater potential for adverse effects. Hence, corticosteroid adverse effects screening and osteoporosis prevention measures are recommended for patients receiving higher ICS doses, as these patients are also likely to require systemic courses for exacerbations (see Table 144-15).

Systemic Corticosteroids

ICS therapy has allowed the large majority of children with asthma to maintain good disease control without maintenance oral corticosteroid therapy. Oral corticosteroids are used primarily to treat asthma exacerbations and, rarely, in patients with severe disease who remain symptomatic despite optimal use of other asthma medications. In these severely asthmatic patients, every attempt should be made to exclude any comorbid conditions and to keep the oral corticosteroid dose at ≤20 mg qod. Doses exceeding this amount are associated with numerous adverse effects (see Chapter 577). To determine the need for continued oral corticosteroid therapy, tapering of the oral corticosteroid

Table 144-14 Estimated Comparative Inhaled Corticosteroid Doses

	LOW DAILY DOSE BY AGE			MEDIUM DAILY DOSE BY AGE			HIGH DAILY DOSE BY AGE		
Drug	**0-4 yr**	**5-11 yr**	**≥12 yr**	**0-4 yr**	**5-11 yr**	**≥12 yr**	**0-4 yr**	**5-11 yr**	**≥12 yr**
Beclomethasone HFA, 40 or 80 μg/puff	NA	80-160 μg	80-240 μg	NA	>160-320 μg	>240-480 μg	NA	>320 μg	>480 μg
Budesonide DPI 90, 180, or 200 μg/inhalation	NA	180-400 μg	180-600 μg	NA	>400-800 μg	>600-1200 μg	NA	>800 μg	>1200 μg
Budesonide inhaled suspension for nebulization, 0.25, 0.5, and 1.0 mg dose	0.25-0.5 mg	0.5 mg	NA	>0.5-1.0 mg	1.0 mg	NA	>1.0 mg	2.0 mg	NA
Flunisolide, 250 μg/puff	NA	500-750 μg	500-1000 μg	NA	1000-1250 μg	>1000-2000 μg	NA	>1250 μg	>2000 μg
Flunisolide HFA, 80 μg/puff	NA	160 μg	320 μg	NA	320 μg	>320-640 μg	NA	≥640 μg	>640 μg
Fluticasone HFA/MDI: 44, 110, or 220 μg/puff	176 μg	88-176 μg	88-264 μg	>176-352 μg	>176-352 μg	>264-440 μg	>352 μg	>352 μg	>440 μg
Fluticasone DPI, 50, 100, or 250 μg/inhalation	NA	100-200 μg	100-300 μg	NA	>200-400 μg	>300-500 μg	NA	>400 μg	>500 μg
Mometasone DPI, 110 μg and 220 μg/inhalation	NA	NA	220 μg	NA	NA	440 μg	NA	NA	>440 μg
Triamcinolone acetonide, 75 μg/puff	NA	300-600 μg	300-750 μg	NA	>600-900 μg	>750-1500 μg	NA	>900 μg	>1500 μg

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; NA, not approved and no data available for this age group.

Adapted, from the National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3): guidelines for the diagnosis and management of asthma—summary report 2007, J Allergy Clin Immunol *120(Suppl):S94–S138, 2007.*

Table 144-15 Risk Assessment for Corticosteroid Adverse Effects

	CONDITIONS	RECOMMENDATIONS
Low risk	(≤1 risk factor*) Low- to medium-dose ICS (see Table 144-11)	• Monitor blood pressure and weight with each physician visit • Measure height annually (stadiometry); monitor periodically for declining growth rate and pubertal developmental delay • Encourage regular physical exercise • Ensure adequate dietary calcium and vitamin D with additional supplements for daily calcium if needed • Avoid smoking and alcohol • Ensure TSH status if patient has history of thyroid abnormality
Medium risk	(If >1 risk factor,* consider evaluating as high risk) High-dose ICS (see Table 144-11) At least 4 courses oral corticosteroid/yr	As above, plus: • Yearly ophthalmologic evaluations to monitor for cataracts or glaucoma • Baseline bone densitometry (DEXA scan) • Consider patient at increased risk for adrenal insufficiency, especially with physiologic stressors (e.g., surgery, accident, significant illness)
High risk	Chronic systemic corticosteroids (>7.5 mg daily or equivalent for >1 mo) ≥ 7 oral corticosteroid burst treatments/year Very-high-dose ICS (e.g., fluticasone propionate ≥800 μg/day)	As above, plus: • DEXA scan: if DEXA Z score ≤1.0, recommend close monitoring (every 12 mo) • Consider referral to a bone or endocrine specialist • Bone age assessment • Complete blood count • Serum calcium, phosphorus, alkaline phosphatase determinations • Urine calcium and creatinine measurements • Measurements of testosterone in males, estradiol in amenorrheic premenopausal women, vitamin D (25-OH and 1,25-OH vitamin D), parathyroid hormone, and osteocalcin • Urine telopeptides for those receiving long-term systemic or frequent oral corticosteroid treatment • Assume adrenal insufficiency for physiologic stressors (e.g., surgery, accident, significant illness)

*Risk factors for osteoporosis: Presence of other chronic illness(es), medications (corticosteroids, anticonvulsants, heparin, diuretics), low body weight, family history of osteoporosis, significant fracture history disproportionate to trauma, recurrent falls, impaired vision, low dietary calcium and vitamin D intake, and lifestyle factors (decreased physical activity, smoking, and alcohol intake).

DEXA, dual-energy x-ray absorptiometry; ICS, inhaled corticosteroid; TSH, thyroid-stimulating hormone.

dose (over several weeks to months) should be considered, with close monitoring of the patient's symptoms and lung function.

When administered orally, prednisone, prednisolone, and methylprednisolone are rapidly and completely absorbed, with peak plasma concentrations occurring within 1-2 hr. Prednisone is an inactive prodrug that requires biotransformation via first-pass hepatic metabolism to prednisolone, its active form. Corticosteroids are metabolized in the liver into inactive compounds, with the rate of metabolism influenced by drug interactions and disease states. Anticonvulsants (phenytoin, phenobarbital, carbamazepine) increase the metabolism of prednisolone, methylprednisolone, and dexamethasone, with methylprednisolone most significantly affected. Rifampin also enhances the clearance of corticosteroids and can result in diminished therapeutic effect. Other medications (ketoconazole, oral contraceptives) can significantly delay corticosteroid metabolism. Macrolide antibiotics (erythromycin, clarithromycin, troleandomycin) delay the clearance of only methylprednisolone.

Children who require long-term oral corticosteroid therapy are at risk for development of associated adverse effects over time. Essentially all major organ systems can be adversely affected by long-term oral corticosteroid therapy (see Chapter 577). Some of these effects occur immediately (metabolic effects). Others can develop insidiously over several months to years (growth suppression, osteoporosis, cataracts). Most adverse effects occur in a cumulative dose- and duration-dependent manner. Children who require routine or frequent short courses of oral corticosteroids, especially with concurrent high-dose ICSs, should receive corticosteroid adverse effects screening (see Table 144-15) and osteoporosis preventive measures (see Chapter 707).

Long-Acting Inhaled β-Agonists

LABAs (salmeterol, formoterol) are considered to be daily controller medications, *not intended* for use as rescue medication for acute asthma symptoms or exacerbations, nor as monotherapy for persistent asthma. Controller formulations that combine an ICS with a LABA (fluticasone/salmeterol, budesonide/formoterol, mometasone/formoterol) are available and recommended, in lieu of separate inhaler delivery devices. Salmeterol has a prolonged onset of action, with maximal bronchodilation approximately 1 hr after administration, whereas formoterol has an onset of action within 5-10 min. Both medications have a prolonged duration of effect, at least 12 hr. Given their long duration of action, they are well suited for patients with nocturnal asthma and for individuals who require frequent SABA use during the day to prevent exercise-induced bronchospasm. Their major role is as an add-on agent in patients whose asthma is suboptimally controlled with ICS therapy alone. For those patients, the addition of a LABA to ICS therapy is superior to doubling the dose of ICS, especially on day and nocturnal symptoms. Of note, the FDA requires all LABA-containing medications to be labeled with a warning of an increase in severe asthma episodes associated with these agents. Some studies have reported a higher number of asthma-related deaths among patients receiving LABA therapy in addition to their usual asthma care than in patients not receiving LABAs. This notice reinforces the appropriate use of LABAs in the management of asthma. Specifically, *LABA products should not be initiated as first-line or sole asthma therapy without the concomitant use of an ICS,* used with worsening wheezing, or used for acute control of bronchospasm. LABAs should be stopped once asthma control is achieved, and the asthma should be maintained with the use of an asthma controller agent (ICS). Fixed-dose preparations (with an ICS) are recommended to ensure compliance with these guidelines.

Leukotriene-Modifying Agents

Leukotrienes are potent proinflammatory mediators that can induce bronchospasm, mucus secretion, and airways edema. Two classes of leukotriene modifiers have been developed: inhibitors of leukotriene synthesis and LTRAs. Zileuton, the only leukotriene synthesis inhibitor, is not approved for use in children <12 yr of age. Because zileuton can result in elevated liver function enzyme values in 2-4% of patients, and interacts with medications metabolized via the cytochrome P450 system, it is rarely prescribed for children with asthma.

LTRAs have bronchodilator and targeted antiinflammatory properties and reduce exercise-, aspirin-, and allergen-induced bronchoconstriction. *LTRAs are recommended as alternative treatment for mild persistent asthma and as add-on medication with ICS for moderate persistent asthma.* Two LTRAs are FDA-approved for use in children: montelukast and zafirlukast. Both medications improve asthma symptoms, decrease the need for rescue β-agonist use, and improve lung function. Montelukast is FDA-approved for use in children ≥1 yr of age and is administered once daily. Zafirlukast is FDA-approved for use in children ≥5 yr of age and is administered twice daily. Although incompletely studied in children with asthma, LTRAs appear to be less effective than ICSs in patients with mild persistent asthma. In general, ICSs improve lung function by 5-15%, whereas LTRAs improve lung function by 2-7.5%. LTRAs are not thought to have significant adverse effects, although case reports described a Churg-Strauss–like vasculitis (pulmonary infiltrates, eosinophilia, cardiomyopathy) in adults with corticosteroid-dependent asthma treated with LTRAs. It remains to be determined whether these patients have a primary eosinophilic vasculitis masquerading as asthma, which was "unmasked" as the oral corticosteroid dose was tapered, or whether the disease is a very rare adverse effect of LTRA. Montelukast has rarely been associated with mood changes and suicidality.

Nonsteroidal Antiinflammatory Agents

Cromolyn and nedocromil are nonsteroidal antiinflammatory agents that can inhibit allergen-induced asthmatic responses and reduce exercise-induced bronchospasm. Both drugs are considered alternative antiinflammatory drugs for children with mild persistent asthma. Although largely devoid of adverse effects, these medications must be administered frequently (2-4 times/day) and are not nearly as effective daily controller medications as ICSs and leukotriene-modifying agents. Because they inhibit exercise-induced bronchospasm, they can be used in place of SABAs, especially in children who develop unwanted adverse effects with β-agonist therapy (tremor and elevated heart rate). Cromolyn and nedocromil can also be used in addition to a SABA in a combination pretreatment for exercise-induced bronchospasm in patients who continue to experience symptoms with use of SABA pretreatment alone. Nedocromil has been taken off the market and cromolyn is only available in a solution for nebulization.

Theophylline

In addition to its bronchodilator effects, theophylline has antiinflammatory properties as a phosphodiesterase inhibitor, although the extent of its clinical relevance has not been clearly established. When used long-term, theophylline can reduce asthma symptoms and the need for rescue SABA use. Although it is considered an alternative monotherapy controller agent for older children and adults with mild persistent asthma, it is no longer considered a first-line agent for young children, in whom there is significant variability in the absorption and metabolism of different theophylline preparations, necessitating frequent dose monitoring (drug blood levels) and adjustments. Because theophylline may have some corticosteroid-sparing effects in individuals with oral corticosteroid–dependent asthma, it is still sometimes used in this group of asthmatic children. Theophylline has a narrow therapeutic window; therefore, when it is used, serum theophylline levels need to be routinely monitored, especially if the patient has a viral illness associated with a fever or is started on a medication known to delay theophylline clearance, such as a macrolide antibiotic, cimetidine, an oral antifungal agent, an oral contraceptive, a leukotriene synthesis inhibitor, or ciprofloxacin. Theophylline overdosage and elevated theophylline levels have been associated with headaches, vomiting, cardiac arrhythmias, seizures, and death.

Anti–Immunoglobulin E (Omalizumab)

Omalizumab is a humanized monoclonal antibody that binds IgE, thereby preventing its binding to the high-affinity IgE receptor and blocking IgE-mediated allergic responses and inflammation. Because it is unable to bind IgE that is already bound to high-affinity IgE

receptors, the risk of anaphylaxis via direct IgE cross linking by the drug is circumvented. It is FDA-approved for patients >12 yr old with moderate to severe asthma, documented hypersensitivity to a perennial aeroallergen, and inadequate disease control with inhaled and/or oral corticosteroids. Omalizumab is given every 2-4 wk subcutaneously, the dosage based on body weight and serum IgE levels. Asthmatic patients receiving omalizumab have fewer asthma exacerbations and symptoms while able to reduce their ICS and/or oral corticosteroid doses. This agent is generally well tolerated, although local injection site reactions can occur. Hypersensitivity reactions (including anaphylaxis) and malignancies have been very rarely associated with omalizumab use. The FDA requires packaging of omalizumab to contain a black box warning of potentially serious and life-threatening anaphylactic reactions with omalizumab treatment. On the basis of reports from approximately 39,500 patients, anaphylaxis following omalizumab treatment occurred in at least 0.1% of treated people. Although most of these reactions occurred within 2 hr of omalizumab injection, there are reports of serious delayed reactions 2-24 hr or even longer after injections. Anaphylaxis occurred after any omalizumab dose (including the first dose). Omalizumab-treated patients should be observed in the facility for an extended period after the drug is given, and medical providers who administer the injection should be prepared to manage life-threatening anaphylactic reactions. Patients who receive omalizumab should be fully informed about the signs and symptoms of anaphylaxis, their chance of development of delayed anaphylaxis following each injection, and how to treat it, including the use of autoinjectable epinephrine.

Mepolizumab, an anti–IL-5 antibody, has been shown to improve asthma control, reduce prednisone dose and lower sputum and blood eosinophil events in adults with prednisone-dependent asthma who also had sputum eosinophils. Dupilumab, an anti–IL-4 receptor antibody and another monoclonal antibody against IL-13, have also shown promise in adult studies.

Quick-Reliever Medications

Quick-reliever or "rescue" medications (SABAs, inhaled anticholinergics, and short-course systemic corticosteroids) are used in the management of acute asthma symptoms (Table 144-16).

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)

RISK ASSESSMENT ON ADMISSION		
Focused history	• Onset of current exacerbation • Frequency and severity of daytime and nighttime symptoms and activity limitation • Frequency of rescue bronchodilator use • Current medications and allergies • Potential triggers • History of systemic steroid courses, emergency department visits, hospitalization, intubation, or life-threatening episodes	
Clinical assessment	• Physical examination findings: vital signs, breathlessness, air movement, use of accessory muscles, retractions, anxiety level, alteration in mental status • Pulse oximetry • Lung function (defer in patients with moderate to severe distress or history of labile disease)	
Risk factors for asthma morbidity and death	See Table 144-17	
TREATMENT		
Drug and Trade Name	**Mechanisms of Action and Dosing**	**Cautions and Adverse Effects**
Oxygen (mask or nasal cannula)	Treats hypoxia	• Monitor pulse oximetry to maintain O_2 saturation >92% • Cardiorespiratory monitoring
Inhaled short-acting β-agonists:	Bronchodilator	• During exacerbations, frequent or continuous doses can cause pulmonary vasodilation, $\dot{V}/\dot{Q}$ mismatch, and hypoxemia • Adverse effects: palpitations, tachycardia, arrhythmias, tremor, hypoxemia
Albuterol nebulizer solution (5 mg/mL concentrate; 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	Nebulizer: 0.15 mg/kg (minimum: 2.5 mg) as often as every 20 min for 3 doses as needed, then 0.15-0.3 mg/kg up to 10 mg every 1-4 hr as needed, or up to 0.5 mg/kg/hr by continuous nebulization	• Nebulizer: when giving concentrated forms, dilute with saline to 3 mL total nebulized volume
Albuterol MDI (90 μg/puff)	2-8 puffs up to every 20 min for 3 doses as needed, then every 1-4 hr as needed	• For MDI: use spacer/holding chamber
Levalbuterol (Xopenex) nebulizer solution (1.25 mg/0.5 mL concentrate; 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)	0.075 mg/kg (minimum: 1.25 mg) every 20 min for 3 doses, then 0.075-0.15 mg/kg up to 5 mg every 1-4 hr as needed, or 0.25 mg/kg/hr by continuous nebulization	• Levalbuterol 0.63 mg is equivalent to 1.25 mg of standard albuterol for both efficacy and side effects
Systemic corticosteroids:	Antiinflammatory	• If patient has been exposed to chickenpox or measles, consider passive immunoglobulin prophylaxis; also, risk of complications with herpes simplex and tuberculosis • For daily dosing, 8 A.M. administration minimizes adrenal suppression • Children may benefit from dosage tapering if course exceeds 7 days • Adverse effects monitoring: Frequent therapy bursts risk numerous corticosteroid adverse effects (see Chapter 578); see Table 144-15 for adverse effects screening recommendations

Continued

Table 144-16 Management of Asthma Exacerbation (Status Asthmaticus)—cont'd

Prednisone: 1, 2.5, 5, 10, 20, 50 mg tablets Methylprednisolone (Medrol): 2, 4, 8, 16, 24, 32 mg tablets Prednisolone: 5 mg tablets; 5 mg/5 mL and 15 mg/5 mL solution	0.5-1 mg/kg every 6-12 hr for 48 hr, then 1-2 mg/kg/day bid (maximum: 60 mg/day)	
Depo-Medrol (IM); Solu-Medrol (IV)	Short-course "burst" for exacerbation: 1-2 mg/kg/day qd or bid for 3-7 days	
Anticholinergics:	Mucolytic/bronchodilator	• Should not be used as first-line therapy; added to β_2-agonist therapy
Ipratropium:		
Atrovent (nebulizer solution 0.5 mg/2.5 mL; MDI 18 μg/inhalation)	Nebulizer: 0.5 mg q6-8h (tid-qid) as needed MDI: 2 puffs qid	
Ipratropium with albuterol:		
DuoNeb nebulizer solution (0.5 mg ipratropium + 2.5 mg albuterol/3 mL vial)	1 vial by nebulizer qid	• Nebulizer: may mix ipratropium with albuterol
Injectable sympathomimetic epinephrine:	Bronchodilator	• For extreme circumstances (e.g., impending respiratory failure despite high-dose inhaled SABA, respiratory failure)
Adrenalin 1 mg/mL (1:1000) EpiPen autoinjection device (0.3 mg; EpiPen Jr 0.15 mg)	SC or IM: 0.01 mg/kg (max dose 0.5 mg); may repeat after 15-30 min	
Terbutaline:		• Terbutaline is β-agonist–selective relative to epinephrine • Monitoring with continuous infusion: cardiorespiratory monitor, pulse oximetry, blood pressure, serum potassium • Adverse effects: tremor, tachycardia, palpitations, arrhythmia, hypertension, headaches, nervousness, nausea, vomiting, hypoxemia
Brethine 1 mg/mL	Continuous IV infusion (terbutaline only): 2-10 μg/kg loading dose, followed by 0.1-0.4 μg/kg/min Titrate in 0.1-0.2 μg/kg/min increments every 30 min, depending on clinical response	
RISK ASSESSMENT FOR DISCHARGE		
Medical stability	Discharge to home if there has been sustained improvement in symptoms and bronchodilator treatments are at least 3 hr apart, physical findings are normal, PEF >70% of predicted or personal best, and oxygen saturation >92% when breathing room air	
Home supervision	Capability to administer intervention and to observe and respond appropriately to clinical deterioration	
Asthma education	See Table 144-9	

IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow; SABA, short-acting β-agonist; SC, subcutaneous; $\dot{V}/\dot{Q}$, ventilation–perfusion.

Short-Acting Inhaled β-Agonists

Given their rapid onset of action, effectiveness, and 4-6 hr duration of action, SABAs (albuterol, levalbuterol, terbutaline, pirbuterol) are the drugs of choice for acute asthma symptoms ("rescue" medication) and for preventing exercise-induced bronchospasm. β-Agonists cause bronchodilation by inducing airway smooth muscle relaxation, reducing vascular permeability and airways edema, and improving mucociliary clearance. Levalbuterol, or the r-isomer of albuterol, is associated with less tachycardia and tremor, which can be bothersome to some asthmatic patients. Overuse of β-agonists is associated with an increased risk of death or near-death episodes from asthma. This is a major concern for some patients with asthma who rely on the frequent use of SABAs as a "quick fix" for their asthma, rather than using controller medications in a preventive manner. It is helpful to monitor the frequency of SABA use, in that use of at least 1 MDI/mo or at least 3 MDIs/year (200 inhalations/MDI) indicates inadequate asthma control and necessitates improving other aspects of asthma therapy and management.

Anticholinergic Agents

As bronchodilators, the anticholinergic agents (ipratropium bromide) are less potent than the β-agonists. Inhaled ipratropium is used primarily in the treatment of acute severe asthma. When used in combination with albuterol, ipratropium can improve lung function and reduce the rate of hospitalization in children who present to the emergency department with acute asthma. Ipratropium is the anticholinergic formulation of choice for children because it has few central nervous system adverse effects and it is available in both MDI and nebulizer formulations. Although widely used in children with asthma exacerbations of all ages, it is approved by the FDA for use in children >12 yr of age. A long-acting inhaled anticholinergic agent, tiotropium, is gaining interest as a potential add-on controller therapy (i.e., in addition to ICS with or without LABA) for adults with asthma.

Delivery Devices and Inhalation Technique

Inhaled medications are delivered in aerosolized form in a MDI, as a DPI formulation, or in a suspension or solution form delivered via a

nebulizer. In the past, MDIs, which require coordination and use of a spacer device, have dominated the market. MDIs are now using hydrofluoroalkane propellant for its ozone-friendly properties, rather than chlorofluorocarbon. Spacer devices, recommended for the administration of all MDI medications, are simple and inexpensive tools that: (1) decrease the coordination required to use MDIs, especially in young children; (2) improve the delivery of inhaled drug to the lower airways; and (3) minimize the risk of propellant-mediated adverse effects (thrush). Optimal inhalation technique for each puff of MDI-delivered medication is a slow (5 sec) inhalation, then a 5-10 sec breathhold. No waiting time between puffs of medication is needed. Young, preschool-age children cannot perform this inhalation technique. MDI medications can also be delivered with a spacer and mask, using a different technique: Each puff is administered with regular breathing for about 30 sec or 5-10 breaths, a tight seal must be maintained, and talking, coughing, or crying will blow the medication out of the spacer. This technique will not deliver as much medication per puff as the optimal MDI technique used by older children and adults.

DPI devices (e.g., Diskus, Flexhaler Autohaler, Twisthaler, Aerolizer) are popular because of their simplicity of use, albeit adequate inspiratory flow is needed. They are breath-actuated (the drug comes out only as it is breathed in) and spacers are not needed. Mouth rinsing is recommended after ICS use to rinse out ICS deposited on the oral mucosa and reduce the swallowed ICS and the risk of thrush.

Nebulizers have been the mainstay of aerosol treatment for infants and young children. An advantage of using nebulizers is the simple technique required of relaxed breathing. The preferential nasal breathing, small airways, low tidal volume, and high respiratory rate of infants markedly increase the difficulty of inhaled drug therapy targeting the lung airways. Disadvantages of nebulizers include need for a power source, inconvenience in that treatments take about 5 min, expense, and potential for bacterial contamination.

Asthma Exacerbations and Their Management

Asthma exacerbations are acute or subacute episodes of progressively worsening symptoms and airflow obstruction. Airflow obstruction during exacerbations can become extensive, resulting in life-threatening respiratory insufficiency. Often, asthma exacerbations worsen during sleep (between midnight and 8 A.M.), when airways inflammation and hyperresponsiveness are at their peak. Importantly, SABAs, which are first-line therapy for asthma symptoms and exacerbations, increase pulmonary blood flow through obstructed, unoxygenated areas of the lungs with increasing dosage and frequency. When airways obstruction is not resolved with SABA use, ventilation–perfusion mismatching can cause significant hypoxemia, which can perpetuate bronchoconstriction and further worsen the condition. Severe, progressive asthma exacerbations need to be managed in a medical setting, with administration of supplemental oxygen as first-line therapy and close monitoring for potential worsening. Complications that can occur during severe exacerbations include atelectasis and air leaks in the chest (pneumomediastinum, pneumothorax).

A severe exacerbation of asthma that does not improve with standard therapy is termed **status asthmaticus.** Immediate management of an asthma exacerbation involves a rapid evaluation of the severity of obstruction and assessment of risk for further clinical deterioration (see Tables 144-15 and 144-16). For most patients, exacerbations improve with frequent bronchodilator treatments and a course of systemic (oral or intravenous) corticosteroid. However, the optimal management of a child with an asthma exacerbation should include a more comprehensive assessment of the events leading up to the exacerbation and the underlying disease severity. Indeed, the frequency and severity of asthma exacerbations help define the severity of a patient's asthma. Whereas most children who experience life-threatening asthma episodes have moderate to severe asthma by other criteria, some children with asthma appear to have mild disease except when they suffer severe, even near-fatal exacerbations. The biologic, environmental, economic, and psychosocial risk factors associated with asthma morbidity and death can further guide this assessment (Table 144-17).

Table 144-17 Risk Factors for Asthma Morbidity and Mortality

BIOLOGIC
Previous severe asthma exacerbation (intensive care unit admission, intubation for asthma)
Sudden asphyxia episodes (respiratory failure, arrest)
Two or more hospitalizations for asthma in past year
Three or more emergency department visits for asthma in past year
Increasing and large diurnal variation in peak flows
Use of >2 canisters of short-acting β-agonists per month
Poor response to systemic corticosteroid therapy
Male gender
Low birthweight
Nonwhite (especially black) ethnicity
Sensitivity to *Alternaria*
ENVIRONMENTAL
Allergen exposure
Environmental tobacco smoke exposure
Air pollution exposure
Urban environment
ECONOMIC AND PSYCHOSOCIAL
Poverty
Crowding
Mother <20 yr old
Mother with less than high school education
Inadequate medical care:
Inaccessible
Unaffordable
No regular medical care (only emergency)
Lack of written asthma action plan
No care sought for chronic asthma symptoms
Delay in care of asthma exacerbations
Inadequate hospital care for asthma exacerbation
Psychopathology in the parent or child
Poor perception of asthma symptoms or severity
Alcohol or substance abuse

Asthma exacerbations characteristically vary among individuals but tend to be similar in the same patient. Severe asthma exacerbations, resulting in respiratory distress, hypoxia, hospitalization, and/or respiratory failure, are the best predictors of future life-threatening exacerbations or a fatal asthma episode. In addition to distinguishing such high-risk children, some experience exacerbations that come on over days, with airflow obstruction resulting from progressive inflammation, epithelial sloughing, and cast impaction of small airways. When such a process is extreme, respiratory failure as a result of fatigue can ensue, necessitating mechanical ventilation for numerous days. In contrast, some children experience abrupt-onset exacerbations that may result from extreme AHR and physiologic susceptibility to airways closure. Such exacerbations, when extreme, are asphyxial in nature, often occur outside medical settings, are initially associated with very high arterial partial pressure of carbon dioxide (P_{CO_2}) levels, and tend to require only brief periods of supportive ventilation. Recognizing the characteristic differences in asthma exacerbations is important for optimizing their early management.

Home Management of Asthma Exacerbations

Families of all children with asthma should have a **written action plan** to guide their recognition and management of exacerbations, along with the necessary medications and tools to manage them. Early recognition of asthma exacerbations in order to intensify treatment early can often prevent further worsening and keep exacerbations from becoming severe. A written home action plan can reduce the risk of asthma death by 70%. The NIH guidelines recommend immediate treatment with "rescue" medication (inhaled SABA, up to 3 treatments in 1 hr). A good response is characterized by resolution of symptoms within 1 hr, no further symptoms over the next 4 hr, and improvement in PEF value to at least 80% of personal best. The child's physician

should be contacted for follow-up, especially if bronchodilators are required repeatedly over the next 24-48 hr. If the child has an incomplete response to initial treatment with rescue medication (persistent symptoms and/or a PEF value <80% of personal best), a short course of oral corticosteroid therapy (prednisone 1-2 mg/kg/day [not to exceed 60 mg/day] for 4 days), in addition to inhaled β-agonist therapy, should be instituted. The physician should also be contacted for further instructions. Immediate medical attention should be sought for severe exacerbations, persistent signs of respiratory distress, lack of expected response or sustained improvement after initial treatment, further deterioration, or high-risk factors for asthma morbidity or mortality (previous history of severe exacerbations). For patients with severe asthma and/or a history of life-threatening episodes, especially if abrupt-onset in nature, providing an epinephrine autoinjector and, possibly, portable oxygen at home should be considered. Use of either of these extreme measures for home management of asthma exacerbations would be an indication to call 911 for emergency support services.

Emergency Department Management of Asthma Exacerbations

In the emergency department, the primary goals of asthma management include correction of hypoxemia, rapid improvement of airflow obstruction, and prevention of progression or recurrence of symptoms. Interventions are based on clinical severity on arrival, response to initial therapy, and presence of risk factors that are associated with asthma morbidity and mortality (see Table 144-17). Indications of a severe exacerbation include breathlessness, dyspnea, retractions, accessory muscle use, tachypnea or labored breathing, cyanosis, mental status changes, a silent chest with poor air exchange, and severe airflow limitation (PEF or FEV_1 value <50% of personal best or predicted values). Initial treatment includes supplemental oxygen, inhaled β-agonist therapy every 20 min for 1 hr, and, if necessary, systemic corticosteroids given either orally or intravenously (see Table 144-16). Inhaled ipratropium may be added to the β-agonist treatment if no significant response is seen with the first inhaled β-agonist treatment. An intramuscular injection of epinephrine or other β-agonist may be administered in severe cases. Oxygen should be administered and continued for at least 20 min after SABA administration to compensate for possible ventilation-perfusion abnormalities caused by SABAs.

Close monitoring of clinical status, hydration, and oxygenation are essential elements of immediate management. A poor response to intensified treatment in the 1st hr suggests that the exacerbation will not remit quickly. The patient may be discharged to home if there is sustained improvement in symptoms, normal physical findings, PEF >70% of predicted or personal best, an oxygen saturation >92% while the patient is breathing room air for 4 hr. Discharge medications include administration of an inhaled β-agonist up to every 3-4 hr plus a 3-7 day course of an oral corticosteroid. Optimizing controller therapy before discharge is also recommended. The addition of ICS to a course of oral corticosteroid in the emergency department setting reduces the risk of exacerbation recurrence over the subsequent month.

Hospital Management of Asthma Exacerbations

For patients with moderate to severe exacerbations that do not adequately improve within 1-2 hr of intensive treatment, observation and/or admission to the hospital, at least overnight, is likely to be needed. Other indications for hospital admission include high-risk features for asthma morbidity or death (see Table 144-17). Admission to an intensive care unit is indicated for patients with severe respiratory distress, poor response to therapy, and concern for potential respiratory failure and arrest.

Supplemental oxygen, frequent or continuous administration of an inhaled bronchodilator, and systemic corticosteroid therapy are the conventional interventions for children admitted to the hospital for status asthmaticus (see Table 144-16). Supplemental oxygen is administered because many children hospitalized with acute asthma have or eventually have hypoxemia, especially at night and with increasing SABA administration. SABAs can be delivered frequently (every 20 min to 1 hr) or continuously (at 5-15 mg/hr). When administered continuously, significant systemic absorption of β-agonist occurs and, as a result, continuous nebulization can obviate the need for intravenous β-agonist therapy. Adverse effects of frequently administered β-agonist therapy include tremor, irritability, tachycardia, and hypokalemia. Patients requiring frequent or continuous nebulized β-agonist therapy should have ongoing cardiac monitoring. Because frequent β-agonist therapy can cause ventilation–perfusion mismatch and hypoxemia, oximetry is also indicated. Inhaled ipratropium bromide is often added to albuterol every 6 hr if patients do not show a remarkable improvement, although there is little evidence to support its use in hospitalized children receiving aggressive inhaled β-agonist therapy and systemic corticosteroids. In addition to its potential to provide a synergistic effect with a β-agonist agent in relieving severe bronchospasm, ipratropium bromide may be beneficial in patients who have mucous hypersecretion or are receiving β-blockers.

Short-course systemic corticosteroid therapy is recommended for use in moderate to severe asthma exacerbations to hasten recovery and prevent recurrence of symptoms. Corticosteroids are effective as single doses administered in the emergency department, short courses in the clinic setting, and both oral and intravenous formulations in hospitalized children. Studies in children hospitalized with acute asthma have found corticosteroids administered orally to be as effective as intravenous corticosteroids. Accordingly, oral corticosteroid therapy can often be used, although children with sustained respiratory distress who are unable to tolerate oral preparations or liquids are obvious candidates for intravenous corticosteroid therapy.

Patients with persistent severe dyspnea and high-flow oxygen requirements require additional evaluations, such as complete blood cell counts, measurements of arterial blood gases and serum electrolytes, and chest radiograph, to monitor for respiratory insufficiency, comorbidities, infection, and/or dehydration. Hydration status monitoring is especially important in infants and young children, whose increased respiratory rate (insensible losses) and decreased oral intake put them at higher risk for dehydration. Further complicating this situation is the association of increased antidiuretic hormone secretion with status asthmaticus. Administration of fluids at or slightly below maintenance fluid requirements is recommended. Chest physical therapy, incentive spirometry, and mucolytics are **not** recommended during the early acute period of asthma exacerbations as they can trigger severe bronchoconstriction.

Despite intensive therapy, some asthmatic children remain critically ill and at risk for respiratory failure, intubation, and mechanical ventilation. Complications (air leaks) related to asthma exacerbations increase with intubation and assisted ventilation; every effort should be made to relieve bronchospasm and prevent respiratory failure. Several therapies, including parenterally administered epinephrine, β-agonists, methylxanthines, magnesium sulfate (25-75 mg/kg, maximum dose 2.5 g, given intravenously over 20 min), and inhaled heliox (helium and oxygen mixture) have demonstrated some benefit as adjunctive therapies in patients with severe status asthmaticus. Administration of either methylxanthine or magnesium sulfate requires monitoring of serum levels and cardiovascular status. Parenteral (subcutaneous, intramuscular, or intravenous) epinephrine or terbutaline sulfate may be effective in patients with life-threatening obstruction that is not responding to high doses of inhaled β-agonists, because in such patients, inhaled medication may not reach the lower airway.

Rarely, a severe asthma exacerbation in a child results in respiratory failure, and intubation and mechanical ventilation become necessary. Mechanical ventilation in severe asthma exacerbations requires the careful balance of enough pressure to overcome airways obstruction while reducing hyperinflation, air trapping, and the likelihood of barotrauma (pneumothorax, pneumomediastinum) (see Chapter 411). To minimize the likelihood of such complications, mechanical ventilation should be anticipated, and asthmatic children at risk for the development of respiratory failure should be managed in a pediatric ICU. Elective tracheal intubation with rapid-induction sedatives and paralytic agents is safer than emergency intubation. Mechanical ventilation aims to achieve adequate oxygenation while tolerating mild to

moderate hypercapnia (P_{CO_2} 50-70 mm Hg) to minimize barotrauma. Volume-cycled ventilators, using short inspiratory and long expiratory times, 10-15 mL/kg tidal volume, 8-15 breaths/min, peak pressures <60 cm H_2O, and without positive end-expiratory pressure are starting mechanical ventilation parameters that can achieve these goals. As measures to relieve mucous plugs, chest percussion and airways lavage are not recommended because they can induce further bronchospasm. One must consider the nature of asthma exacerbations leading to respiratory failure; those of rapid or abrupt onset tend to resolve quickly (hours to 2 days), whereas those that progress gradually to respiratory failure can require days to weeks of mechanical ventilation. Such prolonged cases are further complicated by muscle atrophy and, when combined with corticosteroid-induced myopathy, can lead to severe muscle weakness requiring prolonged rehabilitation. This myopathy should not be confused with the rare occurrence of an asthma-associated flaccid paralysis (Hopkins syndrome), which is of unknown etiology but prolongs the intensive care stay.

In children, management of severe exacerbations in medical centers is usually successful, even when extreme measures are required. Consequently, asthma deaths in children rarely occur in medical centers; most occur at home or in community settings before lifesaving medical care can be administered. This point highlights the importance of home and community management of asthma exacerbations, early intervention measures to keep exacerbations from becoming severe, and steps to reduce asthma severity. A follow-up appointment within 1-2 wk of a child's discharge from the hospital after resolution of an asthma exacerbation should be used to monitor clinical improvement and to reinforce key educational elements, including action plans and controller medications.

Special Management Circumstances

Management of Infants and Young Children. Recurrent wheezing episodes in preschool-age children are very common, occurring in as much as one-third of this population. Of them, most improve and even become asymptomatic during the prepubescent school-age years, whereas others have lifelong persistent asthma. All require management of their recurrent wheezing problems (see Tables 144-5, 144-7, and 144-12). The updated NIH guidelines recommend risk assessment to identify preschool-age children who are likely to have persistent asthma. One implication of this recommendation is that these at-risk children may be candidates for conventional asthma management, including daily controller therapy and early intervention with exacerbations (see Tables 144-8, 144-9, and 144-12). Nebulized budesonide and montelukast appear to be more effective than cromolyn. For young children with a history of moderate to severe exacerbations, nebulized budesonide is FDA approved, and its use as a controller medication could prevent subsequent exacerbations.

Using aerosol therapy in infants and young children with asthma presents unique challenges. There are 2 delivery systems for inhaled medications for this age group, the nebulizer and the MDI with spacer/holding chamber and face mask. Multiple studies demonstrate the effectiveness of both nebulized albuterol in acute episodes and nebulized budesonide in the treatment of recurrent wheezing in infants and young children. In such young children, inhaled medications administered via MDI with spacer and face mask may be acceptable, although perhaps not preferred owing to limited published information and lack of FDA approval for children <4 yr of age.

Asthma Management in Pregnancy. The goals of asthma management during pregnancy should include prevention of exacerbations and control of chronic symptoms through the use of medications that pose minimal risk to the mother and fetus because most drugs cross the placenta. It is considered safer for pregnant asthmatic women to be treated with controller medications than it is to have uncontrolled symptoms and severe exacerbations. Albuterol is the preferred SABA for use during pregnancy. There is reassuring efficacy and safety data from prospective cohort studies supporting ICS use in pregnant women with asthma. Budesonide is currently the preferred ICS for pregnant women, attaining an FDA Pregnancy Category B rating because of substantial reassuring safety data. Nonmedication approaches to improve asthma control are encouraged. A multidisciplinary approach with monthly evaluations (including pulmonary function tests when not contraindicated) and ongoing consultation with the obstetrician and asthma specialist is recommended. Frequent fetal and maternal surveillance is especially important for adolescents with suboptimal asthma control, those with moderate to severe asthma, and those with a recent exacerbation.

Asthma Management During Surgery. Patients with asthma are at risk from disease-related complications from surgery, such as bronchoconstriction and asthma exacerbation, atelectasis, impaired coughing, respiratory infection, and latex exposure, that may induce asthma complications in patients with latex allergy. All patients with asthma should be evaluated before surgery, and those who are inadequately controlled should allow time for intensified treatment in order to improve asthma stability before surgery if possible. A systemic corticosteroid course may be indicated for the patient who is having symptoms and/or FEV_1 or PEF values <80% of the patient's personal best. In addition, patients who have received >2 wk of systemic corticosteroid and/or moderate- to high-dose ICS therapy may be at risk for intraoperative adrenal insufficiency. For these patients, anesthesia services should be alerted to provide "stress" replacement doses of systemic corticosteroid for the surgical procedure and possibly the postoperative period if needed.

PROGNOSIS

Recurrent coughing and wheezing occurs in 35% of preschool-age children. Of these, approximately one-third continue to have persistent asthma into later childhood, and approximately two-thirds improve on their own through their teen years. Asthma severity by the ages of 7-10 yr is predictive of asthma persistence in adulthood. Children with moderate to severe asthma and with lower lung function measures are likely to have persistent asthma as adults. Children with milder asthma and normal lung function are likely to improve over time, with some becoming periodically asthmatic (disease-free for months to years); however, complete remission for 5 yr in childhood is uncommon.

PREVENTION

Although chronic airways inflammation may result in pathologic remodeling of lung airways, conventional anti-inflammatory interventions—the cornerstone of asthma control—do not help children outgrow their asthma. Although controller medications reduce asthma morbidities, most children with moderate to severe asthma continue to have symptoms into young adulthood. Investigations into the environmental and lifestyle factors responsible for the lower prevalence of childhood asthma in rural areas and farming communities suggest that early immunomodulatory intervention might prevent asthma development. A *hygiene hypothesis* purports that naturally occurring microbial exposures in early life might drive early immune development away from allergic sensitization, persistent airways inflammation, and remodeling. If these natural microbial exposures truly have an asthma-protective effect, without significant adverse health consequences, then these findings may foster new strategies for asthma prevention.

Several nonpharmacotherapeutic measures with numerous positive health attributes—avoidance of environmental tobacco smoke (beginning prenatally), prolonged breastfeeding (>4 mo), an active lifestyle, and a healthy diet—might reduce the likelihood of asthma development. Immunizations are currently not considered to increase the likelihood of development of asthma; therefore, all standard childhood immunizations are recommended for children with asthma, including varicella and annual influenza vaccines.

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Chapter 145

Atopic Dermatitis (Atopic Eczema)

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Atopic dermatitis (AD), or eczema, is the most common chronic relapsing skin disease seen in infancy and childhood. It affects 10-30% of children worldwide and frequently occurs in families with other atopic diseases, such as asthma, allergic rhinitis, and food allergy. Infants with AD are predisposed to development of allergic rhinitis and/or asthma later in childhood, a process called "the atopic march."

ETIOLOGY

AD is a complex genetic disorder that results in a defective skin barrier, reduced skin innate immune responses, and exaggerated T-cell responses to environmental allergens and microbes that lead to chronic skin inflammation.

PATHOLOGY

Acute AD skin lesions are characterized by **spongiosis,** or marked intercellular edema, of the epidermis. In AD, dendritic antigen-presenting cells in the epidermis, such as Langerhans cells, exhibit surface-bound immunoglobulin (Ig) E molecules. These antigen-presenting cells play an important role in cutaneous allergen presentation to T-helper type 2 (Th2) cells (see Chapter 140). There is a marked perivenular T-cell infiltrate with occasional monocyte-macrophages in acute AD lesions. Mast cells are found in normal numbers but in different stages of degranulation. Chronic, lichenified AD is characterized by a hyperplastic epidermis with hyperkeratosis, and minimal spongiosis. There are predominantly IgE-bearing Langerhans cells in the epidermis, and macrophages in the dermal mononuclear cell infiltrate. Mast cell and eosinophil numbers are increased, contributing to skin inflammation.

PATHOGENESIS

Two forms of AD have been identified. **Atopic eczema** is associated with IgE-mediated sensitization (at onset or during the course of eczema) and occurs in 70-80% of patients with AD. **Nonatopic eczema** is not associated with IgE-mediated sensitization and is seen in 20-30% of patients with AD. Both forms of AD are associated with eosinophilia. In atopic eczema, circulating T cells expressing the skin homing receptor **cutaneous lymphocyte-associated antigen** produce increased levels of Th2 cytokines, including interleukin (IL)-4 and IL-13, which induce isotype switching to IgE synthesis. Another cytokine, IL-5, plays an important role in eosinophil development and survival. Nonatopic eczema is associated with lower IL-4 and IL-13 production than is atopic eczema.

Compared with the skin of healthy subjects, both unaffected skin and acute skin lesions of patients with AD have an increased number of cells expressing IL-4 and IL-13. Chronic AD skin lesions, by contrast, have significantly fewer cells that express IL-4 and IL-13, but increased numbers of cells that express IL-5, granulocyte-macrophage colony-stimulating factor, IL-12, and interferon (IFN)-γ than acute AD lesions. Chronic AD is characterized by a shift from a Th2-dominant to a Th1-dominant profile. The infiltration of IL-22–expressing T cells correlates with severity of AD, blocks keratinocyte differentiation, and induces epidermal hyperplasia.

The development of AD skin lesions is orchestrated by local tissue expression of proinflammatory cytokines and chemokines, which play a central role in defining the nature of the inflammatory infiltrate in AD. The chemotactic protein, CCL27, is highly upregulated in AD and preferentially attracts cutaneous lymphocyte-associated antigen-positive T cells to the skin. Other C-C chemokines, RANTES (regulated on activation, normal T-cell expressed and secreted), monocyte chemotactic protein-4, and eotaxin are increased in AD skin lesions, resulting in chemotaxis of eosinophils, macrophages, and Th2 lymphocytes expressing their receptor (CCR3).

In healthy people, the skin acts as a protective barrier against external irritants, moisture loss, and infection. Proper function of the skin depends on adequate moisture and lipid content, functional immune responses, and structural integrity. **Severely dry skin is a hallmark of AD.** This results from compromise of the epidermal barrier, which leads to excess transepidermal water loss, allergen penetration, and microbial colonization. **Filaggrin**, a structural protein in the epidermis, and its breakdown products are critical to skin barrier function. Genetic mutations in the filaggrin gene family have been identified in up to 50% of patients with severe AD. Cytokines found in allergic inflammation, such as IL-4, IL-13, IL-22, IL-25, and tumor necrosis factor, can also reduce filaggrin expression. AD patients thereby have increased risk of bacterial, viral, and fungal infection related to impairment of innate immunity, including a loss of barrier function and impaired generation of antimicrobial peptides.

CLINICAL MANIFESTATIONS

AD typically begins in infancy. Approximately 50% of patients experience symptoms in the 1st yr of life, and an additional 30% are diagnosed between 1 and 5 yr of age. Intense **pruritus**, especially at night, and **cutaneous reactivity** are the cardinal features of AD. Scratching and excoriation cause increased skin inflammation that contributes to the development of more pronounced eczematous skin lesions. Foods (cow milk, egg, peanut, tree nuts, soy, wheat, fish, shellfish), aeroallergens (pollen, grass, animal dander, dust mites), infection (staphylococcus, herpes simplex, molluscum), reduced humidity, excessive sweating, and irritants (wool, acrylic, soaps, toiletries, fragrances, detergents) can exacerbate (trigger) pruritus and scratching.

Acute AD skin lesions are intensely pruritic with erythematous papules (Figs. 145-1 and 145-2). Subacute dermatitis manifests as erythematous, excoriated, scaling papules. In contrast, chronic AD is characterized by **lichenification** (Fig. 145-3), or thickening of the skin with accentuated surface markings, and **fibrotic papules.** In chronic AD, all

Figure 145-1 Atopic dermatitis, typical cheek involvement. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 242.)*

Figure 145-2 Crusted lesions of atopic dermatitis on the face. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 242.)*

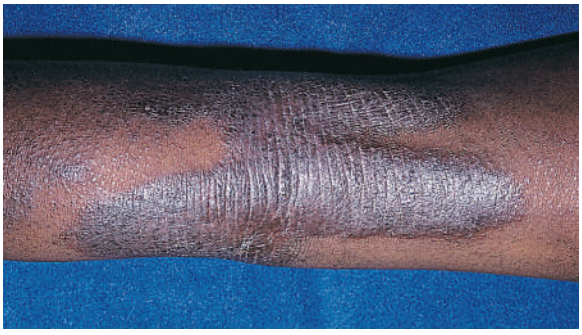

Figure 145-3 Lichenification of the popliteal fossa from chronic rubbing of the skin in atopic dermatitis. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 2, St. Louis, 1996, Mosby, p. 33.)*

3 types of skin reactions may coexist in the same individual. Most patients with AD have dry, lackluster skin irrespective of their stage of illness. Skin reaction pattern and distribution vary with the patient's age and disease activity. AD is generally more acute in infancy and involves the face, scalp, and extensor surfaces of the extremities. The diaper area is usually spared. Older children and children with chronic AD have lichenification and localization of the rash to the flexural folds of the extremities. AD often goes into remission as the patient grows older, leaving an adolescent or adult with skin prone to itching and inflammation when exposed to exogenous irritants.

LABORATORY FINDINGS

There are no specific laboratory tests to diagnose AD. Many patients have peripheral blood eosinophilia and increased serum IgE levels. Serum IgE measurement or prick skin testing can identify the allergens to which patients are sensitized. The diagnosis of clinical allergy to these allergens requires confirmation by history and environmental challenges.

Table 145-1 Clinical Features of Atopic Dermatitis

MAJOR FEATURES
Pruritus
Facial and extensor eczema in infants and children
Flexural eczema in adolescents
Chronic or relapsing dermatitis
Personal or family history of atopic disease
ASSOCIATED FEATURES
Xerosis
Cutaneous infections (*Staphylococcus aureus*, group A streptococcus, herpes simplex, coxsackievirus, vaccinia, molluscum, warts)
Nonspecific dermatitis of the hands or feet
Ichthyosis, palmar hyperlinearity, keratosis pilaris
Nipple eczema
White dermatographism and delayed blanch response
Anterior subcapsular cataracts, keratoconus
Elevated serum immunoglobulin E levels
Positive results of immediate-type allergy skin tests
Early age at onset
Dennie lines (Dennie-Morgan infraorbital folds)
Facial erythema or pallor
Course influenced by environmental and/or emotional factors

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

AD is diagnosed on the basis of 3 major features: pruritus, an eczematous dermatitis that fits into a typical presentation, and a chronic or chronically relapsing course (Table 145-1). Associated features, such as a family history of asthma, hay fever, elevated IgE, and immediate skin test reactivity, are variably present.

Many inflammatory skin diseases, immunodeficiencies, skin malignancies, genetic disorders, infectious diseases, and infestations share symptoms with AD and should be considered and excluded before a diagnosis of AD is established (Table 145-2). Severe combined immunodeficiency syndrome (see Chapter 126.1) should be considered for infants presenting in the 1st yr of life with diarrhea, failure to thrive, generalized scaling rash, and recurrent cutaneous and/or systemic infection. Histiocytosis (see Chapter 507) should be excluded in any infant with AD and failure to thrive. Wiskott-Aldrich syndrome (see Chapter 126.2), an X-linked recessive disorder associated with thrombocytopenia, immune defects, and recurrent severe bacterial infections, is characterized by a rash almost indistinguishable from that in AD. One of the hyper-IgE syndromes (see Chapter 126.2) is characterized by markedly elevated serum IgE values, recurrent deep-seated bacterial infections, chronic dermatitis, and refractory dermatophytosis. Many of these patients have disease as a result of autosomal dominant STAT3 mutations. In contrast, some patients with hyper-IgE syndrome present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance. These patients may have a Dock 8 (Dedicator of cytokinesis 8) mutation. This diagnosis should be considered in young children with severe eczema, food allergy, and disseminated skin viral infections.

Adolescents who present with an eczematous dermatitis but no history of childhood eczema, respiratory allergy, or atopic family history may have allergic **contact dermatitis** (see Chapter 655.1). A contact allergen may be the problem in any patient whose AD does not respond to appropriate therapy. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. Topical glucocorticoid contact allergy has been reported in patients with chronic dermatitis on topical corticosteroid therapy. Eczematous dermatitis has also been reported with HIV infection as well as with a variety of infestations such as scabies. Other conditions that can be confused with AD include psoriasis, ichthyoses, and seborrheic dermatitis.

Table 145-2 Differential Diagnosis of Atopic Dermatitis

CONGENITAL DISORDERS
Netherton syndrome
Familial keratosis pilaris
CHRONIC DERMATOSES
Seborrheic dermatitis
Contact dermatitis (allergic or irritant)
Nummular eczema
Psoriasis
Ichthyoses
INFECTIONS AND INFESTATIONS
Scabies
HIV-associated dermatitis
Dermatophytosis
Insect bites
Onchocerciasis
MALIGNANCIES
Cutaneous T-cell lymphoma (mycosis fungoides/Sézary syndrome)
Letterer-Siwe disease (Langerhans cell histiocytosis)
AUTOIMMUNE DISORDERS
Dermatitis herpetiformis
Pemphigus foliaceus
Graft-versus-host disease
Dermatomyositis
IMMUNODEFICIENCIES
Wiskott-Aldrich syndrome
Severe combined immunodeficiency syndrome
Hyperimmunoglobulin E syndromes (autosomal dominant and recessive types)
Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome
METABOLIC DISORDERS
Zinc deficiency
Pyridoxine (vitamin B_6) and niacin
Multiple carboxylase deficiency
Phenylketonuria

Modified from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *St. Louis, 2003, Mosby, p. 562.*

TREATMENT

The treatment of AD requires a systematic, multifaceted approach that incorporates skin hydration, topical anti-inflammatory therapy, identification and elimination of flare factors (Table 145-3), and, if necessary, systemic therapy. Assessment of the severity also helps direct therapy (Table 145-4).

Cutaneous Hydration

Because patients with AD have impaired skin barrier function from reduced lipid levels, they present with diffuse, abnormally dry skin, or **xerosis.** *Moisturizers are first-line therapy.* Lukewarm soaking baths for 15-20 min followed by the application of an occlusive emollient to retain moisture provide symptomatic relief. Hydrophilic ointments of varying degrees of viscosity can be used according to the patient's preference. Occlusive ointments are sometimes not well tolerated because of interference with the function of the eccrine sweat ducts and may induce the development of folliculitis. In these cases, less occlusive agents should be used. Several prescription (classified as a medical device) "therapeutic moisturizers/barrier creams" are available, containing components such as ceramides and filaggrin acid metabolites intended to improve skin barrier function. There are little data demonstrating their efficacy over standard emollients.

Hydration by baths or wet dressings promotes transepidermal penetration of topical glucocorticoids. Dressings may also serve as effective barriers against persistent scratching, in turn promoting healing of excoriated lesions. Wet dressings are recommended for use on severely affected or chronically involved areas of dermatitis refractory to skin care. It is critical that wet dressing therapy be followed by topical emollient application to avoid potential drying and fissuring from the therapy. Wet dressing therapy can be complicated by maceration and secondary infection and should be closely monitored by a physician.

Topical Corticosteroids

Topical corticosteroids are the cornerstone of antiinflammatory treatment for acute exacerbations of AD. Patients should be carefully instructed on their use of topical glucocorticoids in order to avoid potential adverse effects. There are 7 classes of topical glucocorticoids, ranked according to their potency as determined by vasoconstrictor assays (Table 145-5). Because of their potential adverse effects, the

Table 145-3 List of Aggravating Factors and Counselling for AD Patients

Clothing: avoid skin contact with irritating fibers (wool, large-fiber textiles); do not use tight and too warm clothing to avoid excessive sweating. New nonirritating clothing designed for AD children is being evaluated
Tobacco: avoid exposure
Cool temperature in bedroom and avoid too many bed covers
Increase emollient use with cold weather
Avoid exposure to herpes sores; urgent visit if flare of unusual aspect
Vaccines: normal schedule in noninvolved skin, including egg-allergic patients (see text)
Sun exposure: no specific restriction. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in altitude or at beach resorts
Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool
Food allergens
Maintain breast feeding until 4 mo if possible
Otherwise normal diet, unless an allergy work-up has proven the need to exclude a specific food
Indoor aeroallergens
House dust mites
Use adequate ventilation of housing; keep the rooms well aerated even in winter
Avoid wall-to-wall carpeting
Remove dust with a wet sponge
Vacuum floors and upholstery with an adequately filtered cleaner once a week
Avoid soft toys in bed (cradle), except washable ones
Wash bed sheets at a temperature higher than 55° every 10 days
Use bed and pillow encasings made of Gore-Tex or similar material
Furred pets: advise to avoid. If allergy is demonstrated, be firm on avoidance measures, such as pet removal
Pollen: close windows during peak pollen season on warm and dry weather and restrict, if possible, stays outdoors. Windows may be open at night and early in the morning or during rainy weather. Avoid exposure to risk situations (lawn mowing). Use pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen

From Darsow U, Wollenberg A, Simon D, et al: ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. J Eur Acad Dermatol Venereol *24:317–328, 2010 (Table 2, p. 321).*

Table 145-4 Categorization of Physical Severity of Atopic Eczema

Clear—Normal skin, with no evidence of atopic eczema
Mild—Areas of dry skin, infrequent itching (with or without small areas of redness)
Moderate—Areas of dry skin, frequent itching, redness (with or without excoriation and localized skin thickening)
Severe—Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation)

From Lewis-Jones S, Mugglestone MA; Guideline Development Group: Management of atopic eczema in children aged up to 12 years: summary of NICE guidance, BMJ *335:1263–1264, 2007.*

Table 145-5 Selected Topical Corticosteroid Preparations*

GROUP 1
Clobetasol propionate (Temovate) 0.05% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% ointment/lotion/gel
Fluocinonide (Vanos) 0.1% cream
GROUP 2
Mometasone furoate (Elocon) 0.1% ointment
Halcinonide (Halog) 0.1% cream
Fluocinonide (Lidex) 0.05% ointment/cream
Desoximetasone (Topicort) 0.25% ointment/cream
Betamethasone dipropionate (Diprolene) 0.05% cream
GROUP 3
Fluticasone propionate (Cutivate) 0.005% ointment
Halcinonide (Halog) 0.1% ointment
Betamethasone valerate (Valisone) 0.1% ointment
GROUP 4
Mometasone furoate (Elocon) 0.1% cream
Triamcinolone acetonide (Kenalog) 0.1% ointment/cream
Fluocinolone acetonide (Synalar) 0.025% ointment
GROUP 5
Fluocinolone acetonide (Synalar) 0.025% cream
Hydrocortisone valerate (Westcort) 0.2% ointment
GROUP 6
Desonide (DesOwen) 05% ointment/cream/lotion
Alclometasone dipropionate (Aclovate) 0.05% ointment/cream
GROUP 7
Hydrocortisone (Hytone) 2.5% , 1%, 0.5% ointment/cream/lotion

*Representative corticosteroids are listed by group from 1 (superpotent) through 7 (least potent).

Adapted from Stoughton RB: Vasoconstrictor assay-specific applications. In Malbach HI, Surber C, editors: Topical corticosteroids, *Basel, Switzerland, 1992, Karger, pp. 42–53.*

ultrahigh-potency glucocorticoids should not be used on the face or intertriginous areas and should be used only for very short periods on the trunk and extremities. Mid-potency glucocorticoids can be used for longer periods to treat chronic AD involving the trunk and extremities. Long-term control can be maintained with twice-weekly applications of topical fluticasone or mometasone to areas that have healed but are prone to relapse, once control of AD is achieved after a daily regimen of topical corticosteroids. Compared with creams, ointments have a greater potential to occlude the epidermis, resulting in enhanced systemic absorption. Adverse effects of topical glucocorticoids can be divided into local adverse effects and systemic adverse effects, the latter of which result from suppression of the hypothalamic–pituitary–adrenal axis. Local adverse effects include the development of striae and skin atrophy. Systemic adverse effects are related to the potency of the topical corticosteroid, site of application, occlusiveness of the preparation, percentage of the body surface area covered, and length of use. The potential for adrenal suppression from potent topical corticosteroids is greatest in infants and young children with severe AD requiring intensive therapy.

Topical Calcineurin Inhibitors

The nonsteroidal topical calcineurin inhibitors are effective in reducing AD skin inflammation. Pimecrolimus cream 1% (Elidel) is indicated for mild to moderate AD. Tacrolimus ointment 0.1% and 0.03% (Protopic) is indicated for moderate to severe AD. Both are approved for short-term or intermittent long-term treatment of AD in patients ≥2 yr whose disease is unresponsive to or who are intolerant of other conventional therapies or for whom these therapies are inadvisable owing to potential risks. Topical calcineurin inhibitors may be better than topical corticosteroids in the treatment of patients whose AD is poorly responsive to topical steroids, of patients with steroid phobia, and of patients with face and neck dermatitis, in which ineffective, low-potency topical corticosteroids are usually used because of fears of steroid-induced skin atrophy.

Tar Preparations

Coal tar preparations have antipruritic and antiinflammatory effects on the skin; however, the antiinflammatory effects are usually not as pronounced as those of topical glucocorticoids or calcineurin inhibitors. Tar preparations are useful in reducing the potency of topical glucocorticoids required in long-term maintenance therapy of AD. Tar shampoos can be particularly beneficial for scalp dermatitis. Adverse effects associated with tar preparations include skin irritation, folliculitis, and photosensitivity.

Antihistamines

Systemic antihistamines act primarily by blocking the histamine H_1 receptors in the dermis, thereby reducing histamine-induced pruritus. Histamine is only one of many mediators that induce pruritus of the skin, so patients may derive minimal benefit from antihistaminic therapy. Because pruritus is usually worse at night, sedating antihistamines (hydroxyzine, diphenhydramine) may offer an advantage with their soporific side effects when used at bedtime. Doxepin hydrochloride has both tricyclic antidepressant and H_1- and H_2-receptor blocking effects. Short-term use of a sedative to allow adequate rest may be appropriate in cases of severe nocturnal pruritus. Studies of newer nonsedating antihistamines have shown variable effectiveness in controlling pruritus in AD, although they may be useful in the small subset of patients with AD and concomitant urticaria.

Systemic Corticosteroids

Systemic corticosteroids are rarely indicated in the treatment of chronic AD. The dramatic clinical improvement that may occur with systemic corticosteroids is frequently associated with a severe rebound flare of AD after therapy discontinuation. Short courses of oral corticosteroids may be appropriate for an acute exacerbation of AD while other treatment measures are being instituted in parallel. If a short course of oral corticosteroids is given, it is important to taper the dosage and begin intensified skin care, particularly with topical corticosteroids and frequent bathing followed by application of emollients, to prevent rebound flaring of AD.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug that acts primarily on T cells by suppressing cytokine gene transcription. Cyclosporine forms a complex with an intracellular protein, cyclophilin, and this complex, in turn, inhibits calcineurin, a phosphatase required for

activation of NFAT (nuclear factor of activated T cells), a transcription factor necessary for cytokine gene transcription. Cyclosporine (5 mg/kg/day) for short-term and long-term (1 yr) use has been beneficial for children with severe, refractory AD. Possible adverse effects include renal impairment and hypertension.

Antimetabolites

Mycophenolate mofetil is a purine biosynthesis inhibitor used as an immunosuppressant in organ transplantation that has been used for treatment of refractory AD. Aside from immunosuppression, herpes simplex retinitis and dose-related bone marrow suppression have been reported with its use. Of note, not all patients benefit from treatment. Therefore, the medication should be discontinued if the disease does not respond within 4-8 wk. Methotrexate is an antimetabolite with potent inhibitory effects on inflammatory cytokine synthesis and cell chemotaxis. Methotrexate has been used for patients with recalcitrant AD. In AD, dosing is more frequent than the weekly dosing used for psoriasis. Azathioprine is a purine analog with antiinflammatory and antiproliferative effects that has been used for severe AD. Myelosuppression is a significant adverse effect, and thiopurine methyl transferase levels may identify individuals at risk for it. Before any of these drugs is used, patients should be referred to an AD specialist who is familiar with treatment of severe AD to weigh relative benefits of alternative therapies.

Phototherapy

Natural sunlight is often beneficial to patients with AD as long as sunburn and excessive sweating are avoided. Many phototherapy modalities are effective for AD, including ultraviolet A-1, ultraviolet B, narrow-band ultraviolet B, and psoralen plus ultraviolet A. Phototherapy is generally reserved for patients in whom standard treatments fail. Maintenance treatments are usually required for phototherapy to be effective. Short-term adverse effects with phototherapy include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include predisposition to cutaneous malignancies.

Unproven Therapies

Other therapies that may be considered in patients with refractory AD are as follows.

Interferon-γ

IFN-γ is known to suppress Th2-cell function. Several studies, including a multicenter, double-blind, placebo-controlled trial and several open trials, have demonstrated that treatment with recombinant human IFN-γ results in clinical improvement of AD. Reduction in clinical severity of AD correlated with the ability of IFN-γ to decrease total circulating eosinophil counts. Influenza-like symptoms are commonly observed side effects during the treatment course.

Omalizumab

Treatment of patients who have severe AD and elevated serum IgE values with monoclonal anti-IgE may be considered in those with allergen-induced flares of AD. However, there have been no published double-blind, placebo-controlled trials of its use. Most reports have been case studies and show inconsistent responses to anti-IgE.

Allergen Immunotherapy

In contrast to its acceptance for treatment of allergic rhinitis and extrinsic asthma, immunotherapy with aeroallergens in the treatment of AD is controversial. There are reports of both disease exacerbation and improvement. Studies suggest specific immunotherapy in patients with AD sensitized to dust mite allergen showed improvement in severity of skin disease, as well as reduction in topical steroid use.

Probiotics

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG has been shown to reduce the incidence of AD in at-risk children during the first 2 yr of life. The treatment response has been found to be more pronounced in patients with positive skin prick test results and elevated IgE values. Other studies have not demonstrated a benefit.

Chinese Herbal Medications

Several placebo-controlled clinical trials have suggested that patients with severe AD may benefit from treatment with traditional Chinese herbal therapy. The subjects had significantly reduced skin disease and decreased pruritus. The beneficial response of Chinese herbal therapy is often temporary, and effectiveness may wear off despite continued treatment. The possibility of hepatic toxicity, cardiac side effects, or idiosyncratic reactions remains a concern. The specific ingredients of the herbs also remain to be elucidated, and some preparations have been found to be contaminated with corticosteroids. At present, Chinese herbal therapy for AD is considered investigational.

Vitamin D

Vitamin D deficiency often accompanies severe AD. Vitamin D enhances skin barrier function, reduces corticosteroid requirements to control inflammation and augments skin antimicrobial function. Several small clinical studies suggest vitamin D can enhance antimicrobial peptide expression in the skin and reduce severity of skin disease especially in patients with low baseline vitamin D, for example, during the wintertime when exacerbation of AD often occurs. Patients with AD might benefit from supplementation with vitamin D, particularly if they have a documented low level or low vitamin D intake.

AVOIDING TRIGGERS

It is essential to identify and eliminate triggering factors, both during the period of acute symptoms and on a long-term basis to prevent recurrences (see Table 145-3).

Irritants

Patients with AD have a low threshold response to irritants that trigger their itch-scratch cycle. Soaps or detergents, chemicals, smoke, abrasive clothing, and exposure to extremes of temperature and humidity are common triggers. Patients with AD should use soaps with minimal defatting properties and a neutral pH. New clothing should be laundered before wearing to decrease levels of formaldehyde and other chemicals. Residual laundry detergent in clothing may trigger the itch-scratch cycle; using a liquid rather than powder detergent and adding a second rinse cycle facilitates removal of the detergent.

Every attempt should be made to allow children with AD to be as normally active as possible. A sport such as swimming may be better tolerated than others that involve intense perspiration, physical contact, or heavy clothing and equipment. Rinsing off chlorine immediately and lubricating the skin after swimming are important. Although ultraviolet light may be beneficial to some patients with AD, high sun protection factor sunscreens should be used to avoid sunburn.

Foods

Food allergy is comorbid in approximately 40% of infants and young children with moderate to severe AD (see Chapter 151). Undiagnosed food allergies in patients with AD may induce eczematous dermatitis in some patients and urticarial reactions, wheezing, or nasal congestion in others. Increased severity of AD symptoms and younger age correlate directly with the presence of food allergy. Removal of food allergens from the diet leads to significant clinical improvement but requires a great deal of education, because most common allergens (egg, milk, peanut, wheat, soy) contaminate many foods and are difficult to avoid.

Potential allergens can be identified by a careful history and performing selective skin prick tests or in vitro blood testing for allergen-specific IgE. Negative skin and blood test results for allergen-specific IgE have a high predictive value for excluding suspected allergens. Positive results of skin or blood tests using foods often do not correlate with clinical symptoms and should be confirmed with controlled food challenges and elimination diets. Extensive elimination diets, which can be nutritionally deficient, are rarely required. Even with multiple

positive skin test results, the majority of patients react to fewer than 3 foods under controlled challenge conditions.

Aeroallergens

In older children, AD flares can occur after intranasal or epicutaneous exposure to aeroallergens such as fungi, animal dander, grass, and ragweed pollen. Avoiding aeroallergens, particularly dust mites, can result in clinical improvement of AD. Avoidance measures for dust mite–allergic patients include using dust mite–proof encasings on pillows, mattresses, and box springs; washing bedding in hot water weekly; removing bedroom carpeting; and decreasing indoor humidity levels with air conditioning.

Infections

Patients with AD have increased susceptibility to bacterial, viral, and fungal skin infections. Antistaphylococcal antibiotics are very helpful for treating patients who are heavily colonized or infected with *Staphylococcus aureus.* Erythromycin and azithromycin are usually beneficial for patients who are not colonized with a resistant *S. aureus* strain; a first-generation cephalosporin (cephalexin) is recommended for macrolide-resistant *S. aureus*. Topical mupirocin is useful in the treatment of localized impetiginous lesions, with systemic antibiotics for widespread infections. Cytokine-mediated skin inflammation contributes to skin colonization with *S. aureus;* this fact indicates the importance of combining effective anti-inflammatory therapy with antibiotics for treating moderate to severe AD to avoid the need for repeated courses of antibiotics, which can lead to the emergence of antibiotic-resistant strains of *S. aureus.* Dilute bleach baths (½ cup of bleach in 40 gallons of water) twice weekly may be also considered to reduce *S. aureus* colonization. In one randomized trial the group who received the bleach baths plus intranasal mupirocin (5 days/mo) had significantly decreased severity of AD at 1 and 3 mo compared with placebo. Patients rinse off after the soaking. Further studies are needed to validate this technique.

Herpes simplex virus (HSV) can provoke recurrent dermatitis and may be misdiagnosed as *S. aureus* infection. The presence of punched-out erosions, vesicles, and infected skin lesions that fail to respond to oral antibiotics suggests HSV infection, which can be diagnosed by a Giemsa-stained Tzanck smear of cells scraped from the vesicle base or by viral polymerase chain reaction or culture. Topical corticosteroids should be temporarily discontinued if HSV infection is suspected. Reports of life-threatening dissemination of HSV infections in patients with AD who have widespread disease mandate antiviral treatment. Persons with AD are also susceptible to **eczema vaccinatum,** which is similar in appearance to eczema herpeticum and historically follows smallpox (vaccinia virus) vaccination. Cutaneous warts and molluscum contagiosum are additional viral infections affecting children with AD.

Dermatophyte infections also can contribute to exacerbation of AD. Patients with AD have been found to have a greater susceptibility to *Trichophyton rubrum* fungal infections than nonatopic control subjects. There has been particular interest in the role of *Malassezia furfur* (formerly known as *Pityrosporum ovale*) in AD because it is a lipophilic yeast commonly present in the seborrheic areas of the skin. IgE antibodies against *M. furfur* have been found in patients with head and neck dermatitis. A reduction of AD severity has been observed in those patients after treatment with antifungal agents.

COMPLICATIONS

Exfoliative dermatitis may develop in patients with extensive skin involvement. It is associated with generalized redness, scaling, weeping, crusting, systemic toxicity, lymphadenopathy, and fever, and is usually caused by superinfection (e.g., with toxin-producing *S. aureus* or HSV infection) or inappropriate therapy. In some cases, the withdrawal of systemic glucocorticoids used to control severe AD precipitates exfoliative erythroderma.

Eyelid dermatitis and chronic blepharitis may result in visual impairment from corneal scarring. **Atopic keratoconjunctivitis** is usually bilateral and can have disabling symptoms that include itching, burning, tearing, and copious mucoid discharge. Vernal conjunctivitis is associated with papillary hypertrophy or cobblestoning of the upper eyelid conjunctiva. It typically occurs in younger patients and has a marked seasonal incidence with spring exacerbations. **Keratoconus** is a conical deformity of the cornea believed to result from chronic rubbing of the eyes in patients with AD. Cataracts may be a primary manifestation of AD or from extensive use of systemic and topical glucocorticoids, particularly around the eyes.

PROGNOSIS

AD generally tends to be more severe and persistent in young children, particularly if they have null mutations in their filaggrin genes. Periods of remission occur more frequently as patients grow older. Spontaneous resolution of AD has been reported to occur after age 5 yr in 40-60% of patients affected during infancy, particularly for mild disease. Earlier studies suggested that approximately 84% of children outgrow their AD by adolescence; however, later studies reported that AD resolves in approximately 20% of children monitored from infancy until adolescence and becomes less severe in 65%. Of those adolescents treated for mild dermatitis, >50% may experience a relapse of disease as adults, which frequently manifests as hand dermatitis, especially if daily activities require repeated hand wetting. Predictive factors of a poor prognosis for AD include widespread AD in childhood, filaggrin gene null mutations, concomitant allergic rhinitis and asthma, family history of AD in parents or siblings, early age at onset of AD, being an only child, and very high serum IgE levels.

PREVENTION

Breastfeeding or a feeding with a hypoallergenic hydrolyzed formula may be beneficial. Probiotics and prebiotics may also reduce the incidence or severity of AD, but this approach is unproven. If an infant with AD is diagnosed with food allergy, the breast feeding mother may need to eliminate the implicated food allergen from her diet. Identification and elimination of triggering factors is the mainstay for prevention of flares as well as for the long-term treatment of AD.

Emollient therapy applied to the whole body for the first few months of life may enhance the cutaneous barrier and reduce the risk of eczema.

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Chapter 146

Insect Allergy

Julie Wang and Scott H. Sicherer

Allergic responses to stinging or, more rarely, biting insects vary from localized cutaneous reactions to systemic anaphylaxis. Allergic reactions that are caused by inhalation of airborne particles of insect origin result in acute and chronic respiratory symptoms of seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

ETIOLOGY

Most reactions to stinging and biting insects, such as those induced by wasps, mosquitoes, flies, and fleas, are limited to a primary lesion isolated to the area of the sting or bite and do not represent an allergic response. Occasionally, insect stings or bites induce pronounced localized reactions or systemic reactions that may be based on immediate or delayed hypersensitivity reactions. Systemic allergic responses to insects are attributed most typically to immunoglobulin (Ig) E antibody–mediated responses, which are caused primarily by stings from venomous insects of the order Hymenoptera and more rarely from ticks, spiders, scorpions, and *Triatoma* (kissing bug). Members of the order Hymenoptera include apids (honeybee, bumblebee), vespids

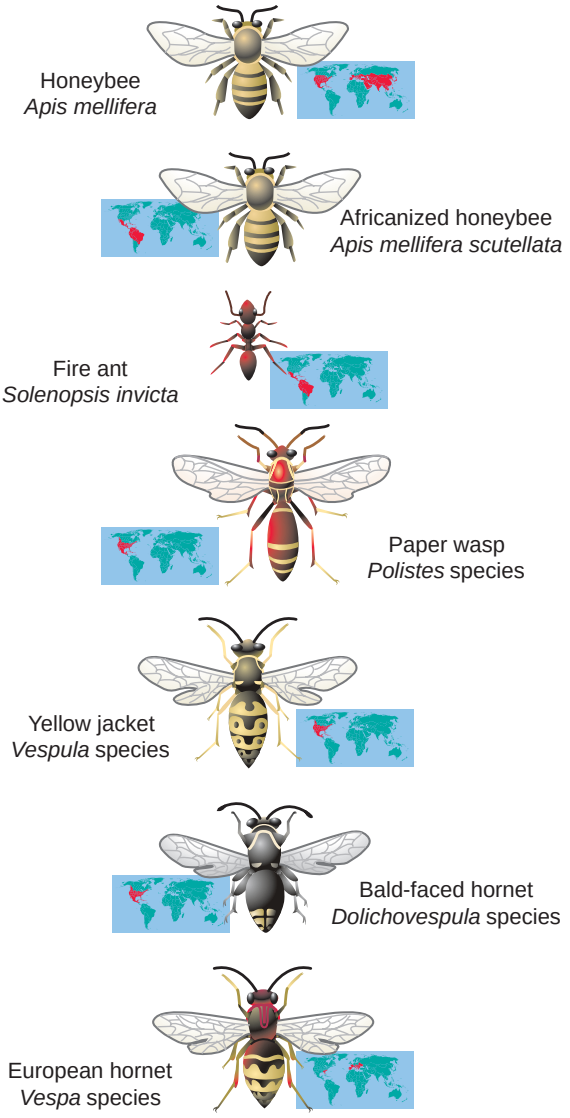

Figure 146-1 Species of Hymenoptera and their geographical distribution. *(From Freeman TM: Hypersensitivity to Hymenoptera stings,* N Engl J Med *351:1978–1984, 2004.)*

(yellow jacket, wasp, hornet), and formicids (fire and harvester ants) (Fig. 146-1). Among winged stinging insects, yellow jackets are the most notorious for stinging because they are aggressive and ground dwelling, and they linger near activities involving food. Hornets nest in trees, whereas wasps build honeycomb nests in dark areas such as under porches; both are aggressive if disturbed. Honeybees are less aggressive, nest in tree hollows, and, unlike the stings of other flying Hymenoptera, honeybee stings almost always leave a barbed stinger with venom sac.

In the United States, fire ants are found increasingly in the Southeast, living in large mounds of soil. When disturbed, the ants attack in large numbers, anchor themselves to the skin by their mandibles, and sting multiple times in a circular pattern. Sterile pseudopustules form at the sting sites. Systemic reactions to stinging insects occur in 0.4-0.8% of children and 3% of adults and account for approximately 40 deaths each year in the United States.

Although reactions to insect bites are common, IgE-mediated reactions are infrequently reported and anaphylaxis is rare. The *Triatoma* (kissing bug) bite causes an erythematous plaque that is painless. Mosquito bites generally result in local reactions that are pruritic. Large local reactions to mosquito bites can occur in some young children; this is known as Skeeter syndrome, and is often misdiagnosed as cellulitis. The tabanid species (horsefly, deerfly), commonly found in rural and suburban areas, are large flies that induce painful bites.

IgE antibody–mediated allergic responses to airborne particulate matter carrying insect emanations contribute to seasonal and perennial symptoms affecting the upper and lower airways. Seasonal allergy is attributed to exposures to a variety of insects, particularly aquatic insects such as the caddis fly and midge, or lake fly, at a time when larvae pupate and adult flies are airborne. Perennial allergy is attributed to sensitization to insects such as cockroaches and ladybugs, as well as house dust mite, which is phylogenetically related to spiders rather than insects and has 8 rather than 6 legs.

PATHOGENESIS

Hymenoptera venoms contain numerous components with toxic and pharmacologic activity and with allergenic potential. These constituents include vasoactive substances such as histamine, acetylcholine, and kinins; enzymes such as phospholipase and hyaluronidase; apamin; melittin; and formic acid. The majority of patients who experience systemic reactions after Hymenoptera stings have IgE-mediated sensitivity to antigenic substances in the venom. Some venom allergens are homologous among members of the Hymenoptera order; others are family specific. There is substantial cross-reactivity among vespid venoms, but these venom allergies are distinct from honeybee venom allergies.

Localized skin responses to biting insects are caused primarily by vasoactive or irritant materials derived from insect saliva, and rarely occur from IgE-associated responses. Systemic IgE-mediated allergic reactions to salivary proteins of biting insects such as mosquitoes are reported but uncommon.

A variety of proteins derived from insects can become airborne and induce IgE-mediated respiratory responses, causing inhalant allergies. The primary allergen from the caddis fly is a hemocyanin-like protein, and that from the midge fly is derived from hemoglobin. Allergens from the cockroach are the best studied and are derived from cockroach saliva, secretions, fecal material, and debris from skin casts.

CLINICAL MANIFESTATIONS

Clinical reactions to stinging venomous insects are categorized as local, large local, generalized cutaneous, systemic, toxic, and delayed/late. Simple **local reactions** involve limited swelling and pain, and generally last <24 hr. **Large local reactions** develop over hours and days, involve swelling of extensive areas (>10 cm) that are contiguous with the sting site, and may last for days. **Generalized cutaneous reactions** typically progress within minutes and include cutaneous symptoms of urticaria, angioedema, and pruritus beyond the site of the sting. **Systemic reactions** are identical to anaphylaxis from other triggers and may include symptoms of generalized urticaria, laryngeal edema, bronchospasm, and hypotension. Stings from a large number of insects at once may result in **toxic reactions** of fever, malaise, emesis, and nausea owing to the chemical properties of the venom in large doses. Serum sickness, nephrotic syndrome, vasculitis, neuritis, or encephalopathy may occur as **delayed/late reactions** to stinging insects.

Insect bites are usually urticarial but may be papular or vesicular. Papular urticaria affecting the lower extremities in children is usually caused by multiple bites. Occasionally, individuals have large local reactions. IgE antibody–associated immediate- and late-phase allergic responses to mosquito bites sometimes mimic cellulitis.

Inhalant allergy caused by insects results in clinical disease similar to that induced by other inhalant allergens such as pollens. Depending on individual sensitivity and exposure, reactions may result in seasonal or perennial rhinitis, conjunctivitis, and/or asthma.

DIAGNOSIS

The diagnosis of allergy from stinging and biting insects is generally evident from the history of exposure, typical symptoms, and physical findings. The diagnosis of Hymenoptera allergy rests in part on the identification of venom-specific IgE by prick skin testing or in vitro testing. The primary reasons to pursue testing are to confirm reactivity when venom immunotherapy (VIT) is being considered or when it is clinically necessary to confirm venom hypersensitivity as a cause of a reaction. Venoms of 5 Hymenoptera (honeybee, yellow jacket, yellow

hornet, white-faced hornet, and wasp), as well as the jack jumper ant in Australia and whole-body extract of fire ant, are available for skin testing. Although skin tests are considered to be the most sensitive modality for detection of venom-specific IgE, additional evaluation with an in vitro serum assay for venom-specific IgE is recommended if skin test results are negative in the presence of a convincing history of a severe systemic reaction. With in vitro tests, there is a 20% incidence of both false-positive and false-negative results, so it is not appropriate to exclude venom hypersensitivity based on this test alone. If initial skin prick and in vitro test results are negative in the context of a convincing history of a severe reaction, repeat testing is recommended before concluding that allergy is unlikely. Skin tests are usually accurate within 1 wk of a sting reaction, but occasionally a refractory period is observed that warrants retesting after 4-6 wk if the initial results are negative. If repeat skin prick and in vitro results are still negative despite a convincing history, occult mast cell disorders should be considered and a baseline serum tryptase should be measured. As many as 40% of skin test–positive subjects may not experience anaphylaxis on sting challenge, so testing without an appropriate clinical history is potentially misleading.

The diagnosis of inhalant insect allergy may be evident from a history of typical symptoms. A chronic respiratory symptom during long-term exposure, as may occur with cockroach allergy, is less amenable to identification by history alone. Skin prick or in vitro immunoassay tests for specific IgE to the insect are used to confirm inhalant insect allergy. Allergy tests may be particularly warranted for potential cockroach allergy in patients with persistent asthma and known cockroach exposure.

TREATMENT

For local cutaneous reactions caused by insect stings and bites, treatment with cold compresses, topical medications to relieve itching, and, occasionally, the use of a systemic antihistamine and oral analgesic are appropriate. Stingers should be removed promptly by scraping, with caution not to squeeze the venom sac because doing so could inject more venom. Sting sites rarely become infected, possibly owing to the antibacterial actions of venom constituents. Vesicles left by fire ant stings that are scratched open should be cleansed to prevent secondary infection.

Anaphylactic reactions after a Hymenoptera sting are treated exactly like anaphylaxis from any cause; epinephrine is the drug of choice. Adjunctive treatment includes antihistamines, corticosteroids, intravenous fluids, oxygen, and transport to the emergency room. (see Chapter 149). Referral to an allergist-immunologist should be considered for patients who have experienced a generalized cutaneous or systemic reaction to an insect sting, need education about avoidance and emergency treatment, may be candidates for VIT, or have a condition that may complicate management of anaphylaxis (e.g., use of β-blockers).

Venom Immunotherapy

Hymenoptera VIT is highly effective (95-97%) in decreasing the risk for severe anaphylaxis. The selection of patients for VIT depends on several factors (Table 146-1). Individuals with local reactions regardless of age are not at increased risk for severe systemic reactions on a subsequent sting and are not candidates for VIT. The risk of a systemic reaction for those who experienced a large local reaction is no more than 5-10%; testing or VIT is usually not recommended, and prescription of self- injectable epinephrine is considered optional but usually not necessary. There is growing evidence that VIT can reduce the size and duration of large, local reactions, and therefore VIT may be considered for those with frequent or unavoidable large, local reactions. *Those who experience severe systemic reactions, such as airway involvement or hypotension, and have specific IgE to venom allergens should receive immunotherapy.* Immunotherapy against winged Hymenoptera is not usually indicated for children ≤16 yr of age in whom stings have caused only generalized urticaria or angioedema, because their risk for a systemic reaction after a subsequent sting is approximately 10%. If a systemic reaction does occur, it is likely to be isolated skin reactions, with <5% risk of a more severe reaction and <1% risk of life-threatening anaphylaxis. The risk could be reduced to 1% after treatment with VIT, so it is an option to consider if multiple future stings are anticipated. *Immunotherapy against Hymenoptera is indicated in those ≥17 yr of age who have specific IgE to venom allergens and a history of generalized urticaria or a systemic reaction,* because their risk for future systemic reactions is 30-60%. VIT is usually not indicated if there is no evidence of IgE to venom.

The incidence of adverse effects in the course of treatment is not trivial in adults, as 50% experience large local reactions and about 10% experience systemic reactions. The incidence of both local and systemic reactions is much lower in children. Patients treated with honeybee venom are at higher risk for systemic reactions to VIT than those receiving treatment with vespid venom. Individuals with mast cell disorders are at increased risk for severe anaphylaxis and more frequent systemic reactions with VIT.

It is uncertain how long immunotherapy with Hymenoptera venom should continue. In general, a 3-5 year treatment duration is recommended because >80% of adults who have received 5 yr of therapy tolerate challenge stings without systemic reactions for 5-10 yr after completion of treatment. Long-term responses to treatment are even better for children. Follow-up over a mean of 18 yr of children with moderate to severe insect sting reactions who received VIT for a mean treatment period of 3-5 yr and were stung again showed a reaction rate of only 5%; untreated children experienced a reaction rate of 32%. Whereas duration of therapy with VIT may be individualized, it is clear that a significant number of untreated children retain their allergy. Lifelong treatment may be considered for those who have had severe life-threatening anaphylaxis with insect stings, those with honeybee allergy, and those with occupational exposures to Hymenoptera. Lifelong VIT should also be considered for those with mast cell disorders as these individuals have a higher rate of failure of VIT and relapse when VIT is discontinued.

Less is known about the natural history of fire ant hypersensitivity and efficacy of immunotherapy for this allergy. The criteria for starting immunotherapy are similar to those for hypersensitivities to other Hymenoptera, but there is stronger consideration to treat children ≤16 yr of age with VIT if they have experienced only generalized

Table 146-1 Indications for Venom Immunotherapy Against Winged Hymenoptera

SYMPTOMS	AGE	SKIN TEST/IN VITRO TEST	RISK OF SYSTEMIC REACTION IF UNTREATED*	VIT RECOMMENDED
Large local reaction	Any	Usually not indicated	5-10%	Usually not indicated
Generalized cutaneous reaction	≤16 yr	Usually not indicated	10%	Usually not indicated
	≥17 yr	Positive result	20%	Yes
		Negative result	—	No
Systemic reaction	Any	Positive result	Child: 40% Adult: 30-60%	Yes
		Negative result	—	Usually no

*Risks generally decrease after 10 yr.

urticaria. Only whole-body fire ant extract is commercially available for diagnostic skin testing and immunotherapy.

Inhalant Allergy

The symptoms of inhalant allergy caused by insects are managed as for other causes of seasonal or perennial rhinitis (see Chapter 143), conjunctivitis (see Chapter 147), and asthma (see Chapter 144).

PREVENTION

Avoidance of stings and bites is essential. To reduce the risk of stings, sensitized individuals should avoid attractants such as perfumes and bright-colored clothing outdoors, wear gloves when gardening, and wear long pants and shoes with socks when walking in the grass or through fields. Typical insect repellents do not guard against Hymenoptera. Nests of these insects should be removed if they are close to the home.

Individuals who have had generalized cutaneous or systemic reactions to Hymenoptera stings should have immediate access to **self-injectable epinephrine.** Adults responsible for allergic children, and older patients who can self-treat, must be carefully taught the indications for and technique of administration of this medication. Particular attention is necessary for children in out-of-home daycare centers, at school, or attending camps, to ensure that an emergency action plan is in place. The individual at risk for anaphylaxis from an insect sting should also wear an identification bracelet indicating the allergy.

Avoidance of the insect is the preferred management of inhalant allergy. This can prove difficult, particularly, for instance, for those living in multiple-dwelling apartments, where eradication of cockroaches is problematic. Immunotherapy for dust mites is effective and should be considered in conjunction with avoidance measures. In contrast, there is limited data regarding the efficacy of cockroach immunotherapy.

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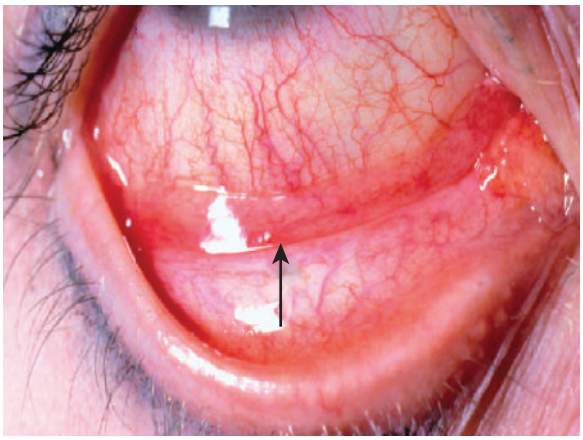

Figure 147-1 **Allergic conjunctivitis.** Arrow indicates area of chemosis in the conjunctivitis. *(From Adkinson NF Jr, Bochner BS, Busse WW, et al, editors:* Middleton's allergy principles and practice, *ed 7, vol 2, Philadelphia, Elsevier, 2009, p. 1121.)*

Chapter 147

Ocular Allergies

Mark Boguniewicz, Christine B. Cho, and Scott H. Sicherer

The eye is a common target of allergic disorders because of its marked vascularity and direct contact with allergens in the environment. The conjunctiva is the most immunologically active tissue of the external eye. Ocular allergies can occur as isolated target organ disease or more commonly in conjunction with nasal allergies. Ocular symptoms can significantly affect quality of life.

CLINICAL MANIFESTATIONS

There are a few distinct entities that constitute allergic eye disease, all of which have bilateral involvement. Sensitization is necessary for all of these except for giant papillary conjunctivitis. Vernal keratoconjunctivitis and atopic keratoconjunctivitis are potentially sight-threatening.

Allergic Conjunctivitis

Allergic conjunctivitis is the most common hypersensitivity response of the eye, affecting approximately 25% of the general population and 30% of children with atopy. It is caused by direct exposure of the mucosal surfaces of the eye to environmental allergens. Patients complain of variable ocular itching, rather than pain, with increased tearing. Clinical signs include bilateral injected conjunctivae with vascular congestion that may progress to chemosis, or conjunctival swelling, and a watery discharge (Fig. 147-1). Allergic conjunctivitis occurs in a seasonal or, less commonly, perennial form. **Seasonal allergic conjunctivitis** is typically associated with allergic rhinitis (see Chapter 143) and is most commonly triggered by pollens. Major pollen groups in the temperate zones include trees (late winter to early spring), grasses (late spring to early summer), and weeds (late summer to early fall), but seasons can vary significantly in different parts of the country. Mold spores can also cause seasonal allergy symptoms, principally in the summer and fall. Seasonal allergy symptoms may be aggravated by coincident exposure to perennial allergens. **Perennial allergic conjunctivitis** is triggered by allergens such as animal danders or dust mites that are present throughout the year. Symptoms are usually less severe than with seasonal allergic conjunctivitis. Because pollens and soil molds may be present intermittently by season, and exposure to allergens such as furred animals may be perennial, classification as intermittent (symptoms present <4 days/wk or for <4 wk) and persistent (symptoms present >4 days/wk and for >4 wk) has been proposed.

Vernal Keratoconjunctivitis

Vernal keratoconjunctivitis is a severe bilateral chronic inflammatory process of the upper tarsal conjunctival surface that occurs in a limbal or palpebral form. It may threaten eyesight if there is corneal involvement. Although vernal keratoconjunctivitis is not immunoglobulin E mediated, it occurs most frequently in children with seasonal allergies, asthma, or atopic dermatitis. Vernal keratoconjunctivitis affects boys twice as often as girls and is more common in persons of Asian and African descent. It affects primarily children in temperate areas, with exacerbations in the spring and summer. Symptoms include severe ocular itching exacerbated by exposure to irritants, light, or perspiration. In addition, patients may complain of severe photophobia, foreign-body sensation, and lacrimation. Giant papillae occur predominantly on the upper tarsal plate and are typically described as **cobblestoning** (Fig. 147-2). Other signs include a stringy or thick, ropey discharge, cobblestone papillae, transient yellow-white points in the limbus (Trantas dots) and conjunctiva (Horner points), corneal "shield" ulcers, and Dennie lines (Dennie-Morgan folds), which are prominent symmetric skinfolds that extend in an arc from the inner canthus beneath and parallel to the lower lid margin. Children with vernal keratoconjunctivitis have measurably longer eyelashes, which may represent a reaction to ocular inflammation.

Atopic Keratoconjunctivitis

Atopic keratoconjunctivitis is a **chronic** inflammatory ocular disorder most commonly involving the lower tarsal conjunctiva. It may threaten eyesight if there is corneal involvement. Almost all patients have **atopic dermatitis,** and a significant number have asthma. Atopic

keratoconjunctivitis rarely presents before late adolescence. Symptoms include severe bilateral ocular itching, burning, photophobia, and tearing with a mucoid discharge that are much more severe than in allergic conjunctivitis and persist throughout the year. The bulbar conjunctiva is injected and chemotic; cataracts may occur. Trantas dots or giant papillae may also be present. Eyelid eczema can extend to the periorbital skin and cheeks with erythema and thick, dry scaling. Secondary staphylococcal blepharitis is common because of eyelid induration and maceration.

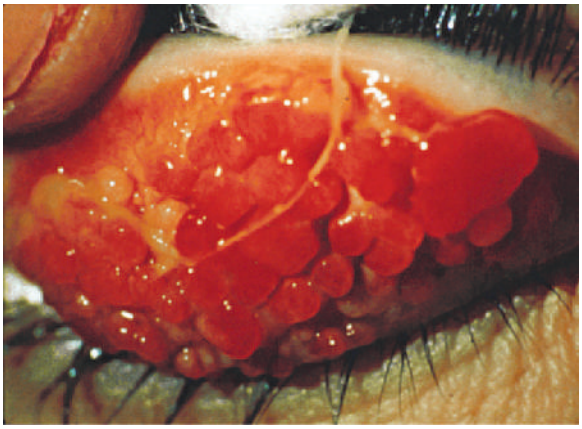

Figure 147-2 **Vernal keratoconjunctivitis.** Cobblestone papillae and ropey discharge are seen on the underside (tarsal conjunctiva) of the upper eyelid. *(From Adkinson NF Jr, Bochner BS, Busse WW, et al, editors:* Middleton's allergy principles and practice, *ed 7, vol 2, Philadelphia, Mosby/Elsevier, 2009, p. 1124.)*

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis has been linked to chronic exposure to foreign bodies, such as contact lenses, both hard and soft, ocular prostheses, and sutures. Symptoms and signs include mild bilateral ocular itching, tearing, a foreign-body sensation, and excessive ocular discomfort with mild mucoid discharge with white or clear exudate on awakening, which may become thick and stringy. Trantas dots, limbal infiltration, bulbar conjunctival hyperemia, and edema may develop.

Contact Allergy

Contact allergy typically involves the eyelids but can also involve the conjunctivae. It is being recognized more frequently in association with increased exposure to topical medications, contact lens solutions, and preservatives.

DIAGNOSIS

Nonallergic conjunctivitis can be viral, bacterial, or chlamydial in origin. It is typically unilateral but can be bilateral with symptoms initially developing in 1 eye (see Chapter 626). Symptoms include stinging or burning rather than itching and often a foreign-body sensation. Ocular discharge can be watery, mucoid, or purulent. Masqueraders of ocular allergy also include nasolacrimal duct obstruction, foreign body, blepharoconjunctivitis, dry eye, uveitis, and trauma.

TREATMENT

Primary treatment of ocular allergies includes avoidance of allergens, cold compresses, and lubrication. Secondary treatment regimens include the use of oral or topical antihistamines and, if necessary, topical decongestants, mast cell stabilizers, and antiinflammatory agents (Table 147-1). Drugs with dual antihistamine and mast cell blocking activities provide the most advantageous approach in treating allergic conjunctivitis, with both fast-acting symptomatic relief and

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis

DRUG AND TRADE NAMES	MECHANISM OF ACTION AND DOSING	CAUTIONS AND ADVERSE EVENTS
Azelastine hydrochloride 0.05% Optivar	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% Emadine	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% Livostin	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate	Antihistamine/vasoconstrictor	Avoid prolonged use (>3-4 days) to avoid rebound symptoms. Not for use with contact lenses.
0.3%/Naphazoline hydrochloride 0.025% Naphcon-A, Opcon-A	Children >6 yr: 1-2 gtt qid	
Cromolyn sodium 4% Crolom, Opticrom	Mast cell stabilizer Children >4 yr 1-2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% Alomide	Mast cell stabilizer Children ≥2 yr: 1-2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% Alocril	Mast cell stabilizer Children ≥3 yr 1-2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% Alamast	Mast cell stabilizer Children >3 yr: 1-2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% Elestat	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid	Contact lenses should be removed prior to use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.

Continued

Table 147-1 Topical Ophthalmic Medications for Allergic Conjunctivitis—cont'd		
DRUG AND TRADE NAMES	**MECHANISM OF ACTION AND DOSING**	**CAUTIONS AND ADVERSE EVENTS**
Ketotifen fumarate 0.025% Zaditor	Antihistamine/mast cell stabilizer Children ≥3 yr 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2% Patanol Pataday	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart) 1 gtt q day	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Alcaftadine, 0.25% Lastacaft	Antihistamine/mast cell stabilizer Children > 2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Bepotastine besilate 1.5% Bepreve	Antihistamine/mast cell stabilizer Children >2 yr: 1 gtt bid q8-12 hr	Contact lenses should be removed prior to application, may be inserted after 10 minutes. Not for the treatment of contact lens irritation.
Ketorolac tromethamine 0.5% Acular	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period of time, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight-threatening. Do not use while wearing contact lenses.
Fluorometholone 0.1%, 0.25% suspension (0.1%, 0.25%) and ointment (0.1%) FML, FML Forte, Flarex	Fluorinated corticosteroid Children ≥2 yr, 1 gtt into conjunctival sac of affected eye(s) bid-qid. During initial 24–48 hr, dosage may be increased to 1 gtt q 4 hr. Ointment (approximately 1.3 cm in length) into the conjunctival sac of affected eye(s) 1–3 times daily. May be applied q 4 hr during initial 24–48 hr of therapy	If improvement does not occur after 2 days, patient should be reevaluated. Patient should remove soft contact lenses prior to administering (contains benzalkonium chloride) and delay reinsertion of lenses for ≥15 minutes after administration. Close monitoring for development of glaucoma and cataracts.

NSAID, nonsteroidal antiinflammatory drug.

disease-modifying action. Children often complain of stinging or burning with use of topical ophthalmic preparations and usually prefer oral antihistamines for allergic conjunctivitis. It is important not to contaminate topical ocular medications by allowing the applicator tip to contact the eye or eyelid. Using refrigerated medications may decrease some of the discomfort associated with their use. Topical decongestants act as vasoconstrictors, reducing erythema, vascular congestion, and eyelid edema, but do not diminish the allergic response. Adverse effects of topical vasoconstrictors include burning or stinging and rebound hyperemia or conjunctivitis medicamentosa with chronic use. Combined use of an antihistamine and a vasoconstrictive agent is more effective than use of either agent alone. Use of topical nasal corticosteroids for allergic rhinoconjunctivitis decreases ocular symptoms, presumably through a naso-ocular reflex.

Tertiary treatment of ocular allergy includes topical or, rarely, oral corticosteroids and should be conducted in conjunction with an ophthalmologist. Local administration of topical corticosteroids may be associated with increased intraocular pressure, viral infections, and cataract formation. Other immunomodulatory medications, such as topical tacrolimus or topical cyclosporine are used as steroid-sparing agents by ophthalmologists. Allergen immunotherapy can be very effective in seasonal and perennial allergic conjunctivitis, especially when associated with rhinitis, and can decrease the need for oral or topical medications to control allergy symptoms.

Because vernal conjunctivitis and atopic keratoconjunctivitis can be associated with visual morbidity, if these diagnoses are suspected, the patient should be referred to an ophthalmologist.

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Chapter 148

Urticaria (Hives) and Angioedema

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Urticaria and angioedema affect 20% of individuals at some point in their lives. Episodes of hives that last for <6 wk are considered acute, whereas those that occur on most days of the week for >6 wks are designated chronic. The distinction is important, because the causes and mechanisms of urticaria formation and the therapeutic approaches are different in each instance.

ETIOLOGY AND PATHOGENESIS

Acute urticaria and angioedema are often caused by an allergic immunoglobulin (Ig) E–mediated reaction (Table 148-1). This form of urticaria is a self-limited process that occurs when an allergen activates mast cells in the skin. Common causes of acute generalized urticaria include foods, drugs (particularly antibiotics), and stinging insect venoms. If an allergen (latex, animal dander) penetrates the skin locally, hives often can develop at the site of exposure. Acute urticaria can also result from non–IgE-mediated stimulation of mast cells,

Table 148-1 Etiology of Acute Urticaria

Foods	Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, strawberries (direct mast cell degranulation)
Medications	Suspect all medications, even nonprescription or homeopathic
Insect stings	Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)
Infections	Bacterial (streptococcal pharyngitis, *Mycoplasma*, sinusitis); viral (hepatitis, mononucleosis [Epstein-Barr virus], coxsackieviruses A and B); parasitic *(Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella);* fungal (dermatophytes, *Candida*)
Contact allergy	Latex, pollen, animal saliva, nettle plants, caterpillars
Transfusion reactions	Blood, blood products, or IV immunoglobulin administration

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: Allergy in primary care, *Philadelphia, 2000, WB Saunders, p. 232.*

Table 148-2 Etiology of Chronic Urticaria

Idiopathic/autoimmune	Approximately 30% of chronic urticaria cases are physical urticaria and 60-70% are idiopathic. Of the idiopathic cases approximately 35-40% have anti-IgE or anti-FcεRI (high-affinity IgE receptor α chain) autoantibodies (autoimmune chronic urticaria)
Physical	Dermatographism Cholinergic urticaria Cold urticaria Delayed pressure urticaria Solar urticaria Vibratory urticaria Aquagenic urticaria
Autoimmune diseases	Systemic lupus erythematosus Juvenile idiopathic arthritis Thyroid (Graves, Hashimoto) Celiac disease Inflammatory bowel disease Leukocytoclastic vasculitis
Autoinflammatory/ periodic fever syndromes	NOMID (neonatal onset multisystem inflammatory disease) Muckle-Wells syndrome Familial cold autoinflammatory syndrome Cold urticarial, immunodeficiency, autoimmunity as a result of *PLCG2* deficiency
Neoplastic	Lymphoma Mastocytosis Leukemia
Angioedema	Hereditary angioedema (autosomal dominant inherited deficiency of C1-esterase inhibitor) Acquired angioedema Angiotensin-converting enzyme inhibitors

From Lasley MV, Kennedy MS, Altman LC: Urticaria and angioedema. In Altman LC, Becker JW, Williams PV, editors: Allergy in primary care, *Philadelphia, 2000, WB Saunders, p. 234.*

caused by radiocontrast agents, viral agents (including hepatitis B and Epstein-Barr virus), opiates, and nonsteroidal antiinflammatory agents. The diagnosis of chronic urticaria is established when lesions occur on most days of the week for >6 wk and are not physical urticaria or recurrent acute urticaria with repeated exposures to a specific agent (Table 148-2). In about half the cases, chronic urticaria is accompanied by angioedema. Rarely, angioedema occurs without urticaria. Angioedema without urticaria is often a result of allergy, but recurrent angioedema raises a question about other diagnoses.

A typical hive is an erythematous, pruritic raised wheal that blanches with pressure, is transient, and resolves without residual lesions, unless the area was intensely scratched. In contrast, urticaria associated with serum sickness reactions, systemic lupus erythematosus or other vasculitides, in which a skin biopsy reveals a small-vessel vasculitis, often have distinguishing clinical features. Lesions that burn more than itch, last >24 hr, do not blanch, blister, heal with scarring, or are associated with bleeding into the skin (purpura) suggest urticarial vasculitis. Atypical aspects of the gross appearance of the hives or associated symptoms should heighten concern that the urticaria or angioedema may be the manifestation of a systemic disease process.

PHYSICAL URTICARIA

Physically induced urticaria and angioedema share the common property of being induced by an environmental stimulus, such as a change in temperature or direct stimulation of the skin with pressure, stroking, vibration, or light (Table 148-3).

Cold-Dependent Disorders

Cold urticaria is characterized by the development of localized pruritus, erythema, and urticaria/angioedema after exposure to a cold stimulus. Total-body exposure as seen with swimming in cold water can cause massive release of vasoactive mediators, resulting in hypotension, loss of consciousness and even death if not promptly treated. The diagnosis is confirmed by challenge testing for an isomorphic cold reaction by holding an ice cube in place on the patient's skin for 4 min. In patients with cold urticaria, an urticarial lesion develops about 10 minutes after removal of the ice cube and upon rewarming of the chilled skin. Cold urticaria can be associated with the presence of **cryoproteins,** such as cold agglutinins, cryoglobulins, cryofibrinogen, and the Donath-Landsteiner antibody seen in secondary syphilis (paroxysmal cold hemoglobinuria). In patients with cryoglobulins, the isolated proteins appear to transfer cold sensitivity and activate the complement cascade upon in vitro incubation with normal plasma. The term **idiopathic cold urticaria** generally applies to patients without abnormal circulating plasma proteins such as cryoglobulins. Cold urticaria has also been reported after viral infections. Cold urticaria must be distinguished from the **familial cold autoinflammatory syndrome** (see "Diagnosis," later).

Cholinergic Urticaria

Cholinergic urticaria is characterized by the onset of small punctate pruritic wheals surrounded by a prominent erythematous flare associated with exercise, hot showers, and sweating. Once the patient cools down, the rash usually subsides in 30-60 min. Occasionally, symptoms of more generalized cholinergic stimulation, such as lacrimation, wheezing, salivation, and syncope, are observed. These symptoms are mediated by cholinergic nerve fibers that innervate the musculature via parasympathetic neurons and innervate the sweat glands by cholinergic fibers that travel with the sympathetic nerves. Elevated plasma histamine values parallel the onset of urticaria triggered by changes in body temperature.

Dermatographism

The ability to write on skin, termed dermatographism (also called dermographism or urticaria factitia), may occur as an isolated

Table 148-3 Diagnostic Testing for Urticaria and Angioedema

DIAGNOSIS	DIAGNOSTIC TESTING
Food and drug reactions	Elimination of offending agent, skin testing, and challenge with suspected foods
Autoimmune urticaria	Autologous serum skin test; antithyroid antibodies; antibodies against the high-affinity IgE receptor
Thyroiditis	Thyroid-stimulating hormone; antithyroid antibodies
Infections	Appropriate cultures or serology
Collagen vascular diseases and cutaneous vasculitis	Skin biopsy, CH_{50}, C1q, C4, C3, factor B, immunofluorescence of tissues, antinuclear antibodies, cryoglobulins
Malignancy with angioedema	CH_{50}, C1q, C4, C1-INH determinations
Cold urticaria	Ice cube test
Solar urticaria	Exposure to defined wavelengths of light, red blood cell protoporphyrin, fecal protoporphyrin, and coproporphyrin
Dermatographism	Stroking with narrow object (e.g., tongue blade, fingernail)
Pressure urticaria	Application of pressure for defined time and intensity
Vibratory urticaria	Vibration for 4 min
Aquagenic urticaria	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermographism
Hereditary angioedema	C4, C2, CH_{50}, C1-INH testing by protein and function
Familial cold urticaria	Challenge by cold exposure, measurement of temperature, white blood cell count, erythrocyte sedimentation rate, and skin biopsy
C3b inactivator deficiency	C3, factor B, C3b inactivator determinations
Chronic idiopathic urticaria	Skin biopsy, immunofluorescence (negative result), autologous skin test

disorder or may accompany chronic urticaria or other physical urticaria, such as cholinergic and cold urticaria. It can be diagnosed by observing the skin after stroking it with a tongue depressor. In patients with dermatographism, a linear response occurs secondary to reflex vasoconstriction, followed by pruritus, erythema, and a linear flare caused by secondary dilation of the vessel and the extravasation of plasma.

Pressure-Induced Urticaria and Angioedema

Pressure-induced urticaria differs from most types of urticaria or angioedema in that symptoms typically occur 4-6 hr after pressure has been applied. The disorder is clinically heterogeneous. Some patients may complain of swelling secondary to pressure with normal-appearing skin (no urticaria), so the term *angioedema* is more appropriate. Other lesions are predominantly urticarial and may or may not be associated with significant swelling. When urticaria is present, an infiltrative skin lesion is seen, characterized by a perivascular mononuclear cell infiltrate and dermal edema similar to that seen in chronic idiopathic urticaria. Symptoms occur at sites of tight clothing; foot swelling is common after walking; and buttock swelling may be prominent after sitting for a few hours. This condition can coexist with chronic idiopathic urticaria or can occur separately. The diagnosis is confirmed by challenge testing in which pressure is applied perpendicular to the skin. This is often done with a sling attached to a 10 lb weight that is placed over the patient's arm for 20 min.

Solar Urticaria

Solar urticaria is a rare disorder in which urticaria develops within minutes of direct sun exposure. Typically, pruritus occurs first, in approximately 30 sec, followed by edema confined to the light-exposed area and surrounded by a prominent erythematous zone. The lesions usually disappear within 1-3 hr after cessation of sun exposure. When large areas of the body are exposed, systemic symptoms may occur, including hypotension and wheezing. Solar urticaria has been classified into 6 types, depending on (1) the wavelength of light that induces skin lesions and (2) the ability or inability to transfer the disorder passively with serum IgE. The rare inborn error of metabolism, **erythropoietic protoporphyria,** can be confused with solar urticaria because of the development of itching and burning of exposed skin immediately after sun exposure. In erythropoietic protoporphyria, fluorescence of ultraviolet-irradiated red blood cells can be demonstrated and protoporphyrins are found in the urine.

Aquagenic Urticaria

Patients with aquagenic urticaria demonstrate small wheals after contact with water, regardless of its temperature, and are thereby distinguishable from patients with cold urticaria or cholinergic urticaria. Direct application of a compress of water to the skin is used to test for the presence of aquagenic urticaria. In some of these patients, chlorine or other trace contaminants are responsible for the reaction.

CHRONIC IDIOPATHIC URTICARIA AND ANGIOEDEMA

A common disorder of unknown origin, chronic idiopathic urticaria and angioedema is often associated with normal routine laboratory values and no evidence of systemic disease. Chronic urticaria does not appear to result from an allergic reaction. It differs from allergen-induced skin reactions and from physically induced urticaria in that histologic studies reveal a cellular infiltrate predominantly around small venules. Skin examination reveals infiltrative hives with palpably elevated borders, sometimes varying greatly in size and/or shape but generally being rounded.

Biopsy of the typical lesion reveals non-necrotizing, perivascular, mononuclear cellular infiltration. Many types of histopathologic processes can occur in the skin and manifest as urticaria. Patients with **hypocomplementemia** and **cutaneous vasculitis** can have urticaria and/or angioedema. Biopsy of these lesions in patients with urticaria, arthralgias, myalgias, and an elevated erythrocyte sedimentation rate (ESR) as manifestations of necrotizing venulitis can reveal fibrinoid necrosis with a predominantly neutrophilic infiltrate. Yet the urticarial lesions may be clinically indistinguishable from those seen in the more typical, nonvasculitic cases.

There is an increased association of chronic urticaria with the presence of antithyroid antibodies. Affected patients generally have antibodies to thyroglobulin or a microsomally derived antigen (peroxidase) even if they are euthyroid. The incidence of elevated thyroid antibodies in patients with chronic urticaria is ≈12%, compared with 3-6% in the general population. Although some patients show clinical reduction of the urticaria with thyroid replacement therapy, others do not. The role of thyroid autoantibodies in chronic urticaria is uncertain. It has been proposed that their presence may reflect a tendency of the patient to develop autoantibodies, but that they may not play a direct role in chronic urticaria. Of patients with chronic urticaria, 35-40% have a positive **autologous serum skin test** result: If serum from these patients is intradermally injected into their skin, a significant wheal and flare reaction develops. Such patients frequently have a complement-activating IgG antibody directed against the α subunit of the IgE receptor that can crosslink the IgE receptor (α subunit) and degranulate mast cells and basophils. An additional 5-10% of patients

with chronic urticaria have anti-IgE antibodies rather than an anti–IgE receptor antibody. These patients, classified as having autoimmune urticaria, tend to have a more severe clinical course than patients without evidence of autoantibodies, but the difference is not dramatic.

DIAGNOSIS

The diagnosis of both acute and chronic urticaria is primarily clinical and requires that the physician be aware of the various forms of urticaria.

Urticaria is transient, pruritic, erythematous, raised wheals, with flat tops and edema that may become tense and painful. The lesions may coalesce and form polycyclic, serpiginous, or annular lesions (Figs. 148-1 and 148-2). Individual lesions usually last 20 min to 3 hr, and rarely more than 24 hr. The lesions often disappear only to reappear at another site. **Angioedema** involves the deeper subcutaneous tissues in locations such as the eyelids, lips, tongue, genitals, dorsum of the hands or feet, or wall of the gastrointestinal (GI) tract.

Drugs and foods are the most common causes of acute urticaria. Allergy skin testing for foods can be helpful in sorting out causes of acute urticaria, especially when supported by historical evidence. The role of an offending food can then be proven by elimination and careful challenge in a controlled setting. In the absence of information implicating an ingestant cause, skin testing for foods and implementation of elimination diets are generally not useful for either acute or chronic urticaria. Patients with delayed urticaria 3-6 hr after a meal consisting of mammalian meat should be evaluated for IgE to galactose-alpha-1,3-galactose ("alpha-gal"), a carbohydrate moiety. Alpha-gal has been identified as a trigger in this circumstance, with sensitization apparently linked to tick bites in specific geographic regions, such as the mid-Atlantic area of the United States. Skin testing for aeroallergens is not indicated unless there is a concern about contact urticaria (animal dander or grass pollen). Dermatographism is frequent in patients with urticaria and can complicate allergy skin testing by causing false-positive reactions, but this distinction is usually discernable.

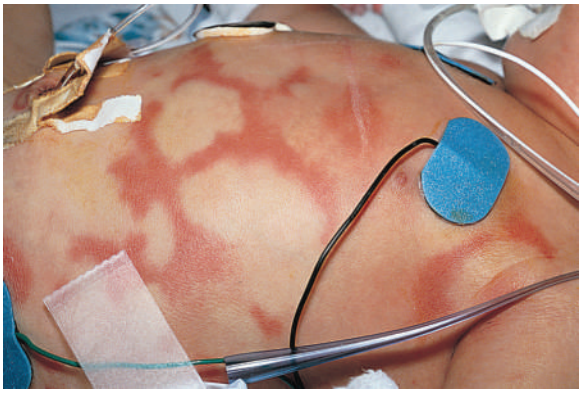

Figure 148-1 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 300.)*

Figure 148-2 Annular urticaria of unknown etiology. *(From Eichenfield LF, Friedan IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 301.)*

An exogenous cause of chronic urticaria is rarely identified, reflecting the wide variety of allergens with which we come in contact. Autoimmune diseases are rare causes of chronic urticarial or angioedema. An autologous serum skin test may be useful in establishing the diagnosis of autoimmune urticaria. In vitro testing for serum-derived activity that activates basophils involves detection of the expression of the surface marker CD63 or CD203c by donor basophils after incubation with patient serum. The clinical applicability and significance of these tests remains debated. The **differential diagnosis** of chronic urticaria includes cutaneous or systemic mastocytosis, complement-mediated mast cell degranulation as may occur with the presence of circulating immune complexes, malignancies, mixed connective tissue diseases, and cutaneous blistering disorders (e.g., bullous pemphigoid; see Table 148-2). In general, laboratory testing should be limited to a complete blood cell count with differential, ESR determination, urinalysis, thyroid autoantibody testing, and liver function tests. Further studies are warranted if the patient has fever, arthralgias, or elevated ESR (see Table 148-3). Testing for antibodies directed at the high affinity IgE receptor may be warranted in patients with intractable urticaria. Hereditary angioedema, a potentially life-threatening form of angioedema usually associated with deficient C1 inhibitor activity, is the most important familial form of angioedema (see Chapter 134.3), but is not associated with typical urticaria. In patients with eosinophilia, stools should be obtained for ova and parasite testing, because infection with helminthic parasites has been associated with urticaria. A syndrome of episodic angioedema/urticaria and fever with associated eosinophilia has been described in both adults and children. In contrast to other hypereosinophilic syndromes, this entity has a benign course.

Skin biopsy for diagnosis of possible **urticarial vasculitis** is recommended for urticarial lesions that persist at the same location for >24 hr, those with pigmented or purpuric components, and those that burn more than itch. Collagen vascular diseases such as systemic lupus may manifest urticarial vasculitis as a presenting feature. The skin biopsy in urticarial vasculitis typically shows endothelial cell swelling of postcapillary venules with necrosis of the vessel wall, perivenular neutrophil infiltrate, diapedesis of red blood cells, and fibrin deposition associated with deposition of immune complexes.

Mastocytosis is characterized by mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, and skin. Clinical effects of mast cell activation are common, including pruritus, flushing, urtication, abdominal pain, nausea, and vomiting. The diagnosis is confirmed by a bone marrow biopsy showing increased numbers of spindle-shaped mast cells that express CD2 and CD25. **Urticaria pigmentosa** is the most common skin manifestation of mastocytosis and may occur as an isolated skin finding. It appears as small, yellow-tan to reddish brown macules or raised papules that urticate on scratching **(Darier sign).** This sign can be masked by antihistamines. The diagnosis is confirmed by a skin biopsy that shows increased numbers of dermal mast cells.

Physical urticaria should be considered in any patient with chronic urticaria and a suggestive history (see Table 148-3). Papular urticaria commonly occurs in small children, generally on the extremities. It manifests as grouped or linear, highly pruritic wheals or papules mainly on exposed skin at the sites of insect bites.

Exercise-induced anaphylaxis manifests as varying combinations of pruritus, urticaria, angioedema, wheezing, laryngeal obstruction, or hypotension after exercise (see Chapter 149). Cholinergic urticaria is differentiated by positive results of heat challenge tests and the rare occurrence of anaphylactic shock. The combination of ingestion of various food allergens (shrimp, celery, or wheat) and postprandial exercise has been associated with urticaria/angioedema and

anaphylaxis. In patients with this combination disorder, food or exercise alone does not produce the reaction.

Muckle-Wells syndrome and **familial cold autoinflammatory syndrome** are rare, dominantly inherited conditions associated with recurrent urticaria-like lesions. Muckle-Wells syndrome is characterized by arthritis and joint pain that usually appears in adolescence. It is associated with progressive nerve deafness, recurrent fever, elevated ESR, hypergammaglobulinemia, renal amyloidosis, and a poor prognosis. Familial cold autoinflammatory syndrome is characterized by a cold-induced rash that has urticarial features but is rarely pruritic. Cold exposure leads to additional symptoms such as conjunctivitis, sweating, headache, and nausea. Patient longevity is usually normal.

TREATMENT

Acute urticaria is a self-limited illness requiring little treatment other than antihistamines and avoidance of any identified trigger. Hydroxyzine and diphenhydramine are sedating but are effective and commonly used for treatment of urticaria. Loratadine, fexofenadine, and cetirizine are also effective and are preferable because of reduced frequency of drowsiness and longer duration of action (Table 148-4). Epinephrine 1:1,000, 0.01 mL/kg (maximum: 0.3 mL) intramuscularly usually provides rapid relief of acute, severe urticaria/angioedema but is seldom required. A short course of oral corticosteroids should be given only for very severe episodes of urticaria and angioedema that are unresponsive to antihistamines.

The best treatment of physical urticaria is avoidance of the stimulus. Antihistamines are also helpful. Cyproheptadine in divided doses is the drug of choice for cold-induced urticaria. Treatment of dermatographism consists of local skin care and antihistamines; for severe symptoms, high doses may be needed. The initial objective of therapy is to decrease pruritus so that the stimulation for scratching is diminished. A combination of antihistamines, sunscreens, and avoidance of sunlight is helpful for most patients.

Chronic urticaria only rarely responds favorably to dietary manipulation. Removal of recognized urticarial aggravators such as salicylates and β-blockers should be considered. The mainstay of therapy is the use of nonsedating or low-sedating H_1 antihistamines. In those patients not showing response to standard doses, pushing the H_1 blockade with higher than the usual recommended doses of these agents is a common next approach. The 3-drug combination of H_1 and H_2 antihistamine combined with a leukotriene receptor antagonist (montelukast) is helpful for many patients. If hives persist after maximal H_1- and/or H_2-receptor blockade has been achieved, a brief course of oral corticosteroids may be considered, but long-term steroid use is best avoided. Treatment with cyclosporine 4-6 mg/kg/day has been effective in some adults with chronic urticaria but its use is limited by hypertension and/or nephrotoxicity. Immunomodulatory agents such as omalizumab (anti-IgE antibody) that have been used with success in cases of chronic urticarial that are refractory to other therapies, but are not approved for the treatment of this condition by the FDA. These include omalizumab (anti-IgE), cyclosporine, hydroxychloroquine, sulfasalazine, colchicine, dapsone, mycophenolate, intravenous immunoglobulin, and plasmapheresis.

Table 148-4 Treatment of Urticaria and Angioedema

CLASS/DRUG	DOSE	FREQUENCY
ANTIHISTAMINES, TYPE H_1 (SECOND GENERATION)		
Fexofenadine	6-11 yr: 30 mg >12 yr: 60 mg	bid
	Adult: 180 mg	Once daily
Loratadine	2-5 yr: 5 mg >6 yr: 10 mg	Once daily
Desloratadine	6-11 mo: 1 mg 12 mo-5 yr: 1.25 mg 6-11 yr: 2.5 mg >12 yr: 5 mg	Once daily
Cetirizine	6-23 mo: 2.5 mg 2-6 yr: 2.5-5mg >6 yr: 5-10 mg	Once daily
Levocetirizine	6 mo-5 yr: 1.25 mg 6-11 yr: 2.5 mg >12 yr: 5 mg	Once daily Once daily Once daily
ANTIHISTAMINES, TYPE H_2		
Cimetidine	Infants: 10-20 mg/kg/day Children: 20-40 mg/kg/day	Divided q6-12h
Ranitidine	1 mo-16 yr: 5-10 mg/kg/day	Divided q12h
Famotidine	3-12 mo: 1 mg/kg/day 1-16 yr: 1-2 mg/kg/day	Divided q12h
LEUKOTRIENE PATHWAY MODIFIERS		
Montelukast	12 mo-5 yr: 4 mg 6-14 yr: 5 mg >14 yr: 10 mg	Once daily
Zafirlukast	5-11 yr: 10 mg	bid
IMMUNOMODULATORY DRUGS		
Cyclosporine	4-6 mg/kg/day	Once daily*
Sulfasalazine	>6 yr: 30 mg/kg/day	Divided q6h†
Intravenous immunoglobulin (IVIG)	400 mg/kg/day	5 consecutive days

*Monitor blood pressure and serum creatinine, potassium, and magnesium levels monthly.

†Monitor complete blood count and liver function tests at baseline, every 2 wk for 3 mo, and then every 1-3 mo.

HEREDITARY ANGIOEDEMA

Hereditary angioedema (HAE) (types 1 and 2) is an inherited autosomal dominant disease caused by low functional levels of the plasma protein C1 inhibitor (C1-INH) (see Chapter 134). Patients typically report episodic attacks of angioedema or deep localized swelling, most commonly on a hand or foot, that begin during childhood and become much more severe during adolescence. Cutaneous nonpitting and nonpruritic edema not associated with urticaria is the most common symptom. The swelling usually becomes more severe over about 1.5 days and then resolves over about the same period. In some patients attacks are preceded by the development of a rash, that is erythema marginatum, that is erythematous, not raised, and not pruritic. The second major symptom complex noted by patients is attacks of severe abdominal pain caused by edema of the mucosa of any portion of the GI tract. The intensity of the pain can approximate that of an acute abdomen, often resulting in unnecessary surgery. Either constipation or diarrhea during these attacks can be noted. The GI edema generally follows the same time course to resolution as the cutaneous attacks, and often does not occur at the same time as the peripheral edema. Patients usually have a prodrome, a tightness or tingling in the area that will swell, lasting most frequently for several hours, followed by the development of angioedema.

Laryngeal edema, the most feared complication of HAE, can cause complete respiratory obstruction. Although life-threatening attacks are infrequent, more than half of patients with HAE experience laryngeal involvement at some time during their lives. Dental work with the injection of procaine HCL (Novocain) into the gums is a common precipitant, but laryngeal edema can be spontaneous. The clinical condition may deteriorate rapidly, progressing through mild discomfort to complete airway obstruction over a period of hours. Soft-tissue edema can be readily seen when the disease involves the throat and uvula. If this edema progresses to difficulty swallowing secretions or a change in the tone of the voice, the patient may require emergency intubation or even tracheostomy to ensure an adequate airway. Other presentations are less common. These patients typically do not respond well to treatment with epinephrine, antihistamines, or glucocorticoids.

In most cases the cause of the attack is unknown, but in some patients trauma or emotional stress clearly precipitates attacks. Drugs like angiotensin-converting enzyme inhibitors that inhibit the degradation of bradykinin make the disease strikingly worse, and estrogens also make attacks more severe. In some females menstruation also regularly induces attacks. The frequency of attacks varies greatly among

affected individuals and at different times in the same individual. Some individuals experience weekly episodes, whereas others may go years between attacks. Episodes can start at any age.

C1-INH is a member of the serpin family of proteases, similar to α-antitrypsin, antithrombin III, and angiotensinogen. These proteins stoichiometrically inactivate their target proteases by forming stable, 1 : 1 complexes with the protein to be inhibited. Synthesized primarily by hepatocytes, C1-INH is also synthesized by monocytes. The regulation of the protein production is not completely understood, but it is believed that androgens may stimulate C1-INH synthesis, because patients with the disorder respond clinically to androgen therapy with raised serum levels of C1-INH. C1-INH deficiency is an autosomal dominant disease, with as many as 25% of patients giving no family history. Because all C1-INH–deficient patients are heterozygous for this gene defect, it is believed that half the normal level of C1-INH is not sufficient to prevent attacks.

Although named for its action on the first component of complement (C1 esterase), C1-INH also inhibits components of the fibrinolytic, clotting, and kinin pathways. Specifically, C1-INH inactivates plasmin-activated Hageman factor (factor XII), activated factor XI, plasma thromboplastin antecedent, and kallikrein. Within the complement system, C1-INH blocks the activation of C1 and the rest of the classic complement pathway by binding to C1r and C1s. Without adequate C1-INH, unchecked activation of C1 causes cleavage of C4 and C2, the following proteins in the complement cascade. Levels of C3 are normal. The major factor responsible for the edema formation is now known to be bradykinin, an important nonapeptide mediator that can induce leakage of postcapillary venules. Bradykinin is derived from cleavage of the circulating protein high molecular weight kininogen by the plasma enzyme kallikrein.

Two genetic types of C1-INH deficiency are described that result in essentially the same phenotypic expression. The C1-INH gene is located on chromosome 11 in the p11-q13 region. The inheritance is autosomal dominant with incomplete penetrance. Persons inheriting the abnormal gene can have a clinical spectrum ranging from asymptomatic to severely affected. Type 1 HAE is the most common form, accounting for approximately 85% of cases. Synthesis of C1-INH is blocked at the site of the faulty allele or the protein is not secreted normally because of faulty protein processing, but secretion occurs at the normal allele. The result is secretion of the normal protein, yielding quantitative serum concentrations of C1-INH that are approximately 20-40% of normal. Type 2 HAE accounts for approximately 15% of cases. Mutations of one of the amino acids near the active site of the inhibitor lead to synthesis of nonfunctional C1-INH protein and again less than half of the normal functioning protein. Patients with type 2 HAE have either normal or increased concentrations of the protein and low values in assays of C1-INH function.

A clinical syndrome resembling HAE and termed type 3 HAE has been described that affects mostly women and has a tendency to cause fewer abdominal attacks and more upper airway attacks. In this condition, no abnormalities of complement or of C1-INH have been described. Approximately 20% of affected patients have been found to have a gain-of-function abnormality of clotting factor XII, but the fundamental cause is still unknown.

The FDA has approved purified C1-INH for prophylaxis to prevent attacks. Androgens like the gonadotropin inhibitor danazol were previously used to prevent attacks. Weak androgens have many side affects that preclude their use in some patients. Their use in children is problematic because of the possibility of premature closure of the epiphyses, and these agents are not used in pregnant women. The fibrinolysis inhibitor ε-aminocaproic acid is also effective in preventing attacks and has been used in children, but its use was attended by the development of severe fatigue and muscle weakness over time.

In 2008, the FDA approved, for adolescents and older, the use of purified C1-INH (Cinryze), prepared from human plasma given intravenously for prophylaxis of this disease following clinical trials. The half-life of this plasma protein is relatively short, on the order of 40 hr, and the approved regimen is 1,000 units given twice a week. In 2009, a similar purified C1-inhibitor product, Berinert, used as 20 units/kg intravenously, was approved for the treatment of acute attacks. A recombinant C1-INH product has been approved for treatment of acute attacks in Europe, but is not currently approved for treatment in the United States. In 2009, a kallikrein inhibitor, ecallantide, given subcutaneously, was approved by the FDA for acute treatment in patients age 16 yr and older. This 60 amino acid peptide causes anaphylaxis in the rare patient, and is approved to be given only by medical personnel. In 2010, a bradykinin type 2 receptor antagonist, icatibant was approved for acute treatment in patients age 18 yr and older. All treatments are most effective when given early in an attack, and begin to have noticeable effect after about 1-4 hr after treatment.

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Chapter 149

Anaphylaxis

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Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. Anaphylaxis in children, particularly infants, is underdiagnosed. Anaphylaxis occurs when there is a sudden release of potent biologically active mediators from mast cells and basophils, leading to cutaneous (urticaria, angioedema, flushing), respiratory (bronchospasm, laryngeal edema), cardiovascular (hypotension, dysrhythmias, myocardial ischemia), and gastrointestinal (nausea, colicky abdominal pain, vomiting, diarrhea) symptoms (Table 149-1).

ETIOLOGY

The most common causes of anaphylaxis in children are different for hospital and community settings. Anaphylaxis occurring in the hospital results primarily from allergic reactions to medications and latex. Food allergy is the most common cause of anaphylaxis occurring outside the hospital, accounting for about half of the anaphylactic reactions reported in pediatric surveys from the United States, Italy, and South Australia (Table 149-2). Peanut allergy is an important cause of food-induced anaphylaxis, accounting for the majority of fatal and near-fatal reactions. In the hospital, latex is a particular problem for children undergoing multiple operations, such as patients with spina bifida and urologic disorders, and has prompted many hospitals to switch to latex-free products. Patients with latex allergy may also experience food-allergic reactions from homologous proteins in foods such as bananas, kiwi, avocado, chestnut, and passion fruit. Anaphylaxis to galactose-α-1,3-galactose has been reported 3-6 hr after eating meat.

EPIDEMIOLOGY

The overall annual incidence of anaphylaxis in the United States is estimated at 50 cases/100,000 persons/yr, totaling >150,000 cases/yr, with the highest rate for the pediatric age group (0-19 yr) at 70/100,000 persons/yr. An Australian parental survey found that 0.59% of children 3-17 yr of age had experienced at least 1 anaphylactic event. Having asthma and the severity of asthma are important anaphylaxis risk factors (Table 149-3).

PATHOGENESIS

Principal pathologic features in fatal anaphylaxis include acute bronchial obstruction with pulmonary hyperinflation, pulmonary edema, intraalveolar hemorrhaging, visceral congestion, laryngeal edema, and urticaria and angioedema. Acute hypotension is attributed to vasomotor dilation and/or cardiac dysrhythmias.

Most cases of anaphylaxis are believed to be the result of activation of mast cells and basophils via cell-bound allergen-specific

Table 149-1 Symptoms and Signs of Anaphylaxis in Infants

ANAPHYLAXIS SYMPTOMS THAT INFANTS CANNOT DESCRIBE	ANAPHYLAXIS SIGNS THAT MAY BE DIFFICULT TO INTERPRET/UNHELPFUL IN INFANTS, AND WHY	ANAPHYLAXIS SIGNS IN INFANTS
GENERAL Feeling of warmth, weakness, anxiety, apprehension, impending doom	Nonspecific behavioral changes such as persistent crying, fussing, irritability, fright, suddenly becoming quiet	
SKIN/MUCUS MEMBRANES Itching of lips, tongue, palate, uvula, ears, throat, nose, eyes, etc.; mouth-tingling or metallic taste	Flushing (may also occur with fever, hyperthermia, or crying spells)	Rapid onset of hives (potentially difficult to discern in infants with acute atopic dermatitis; scratching and excoriations will be absent in young infants); angioedema (face, tongue, oropharynx)
RESPIRATORY Nasal congestion, throat tightness; chest tightness; shortness of breath	Hoarseness, dysphonia (common after a crying spell); drooling or increased secretions (common in infants)	Rapid onset of coughing, choking, stridor, wheezing, dyspnea, apnea, cyanosis
GASTROINTESTINAL Dysphagia, nausea, abdominal pain/cramping	Spitting up/regurgitation (common after feeds), loose stools (normal in infants, especially if breastfed); colicky abdominal pain	Sudden, profuse vomiting
CARDIOVASCULAR Feeling faint, presyncope, dizziness, confusion, blurred vision, difficulty in hearing	Hypotension (need appropriate-size blood pressure cuff; low systolic blood pressure for children is defined as <70 mm Hg from 1 mo to 1 yr, and less than (70 mm Hg + [2 × age in yr]) from 1-10 yr; tachycardia, defined as >140 beats/min from 3 mo to 2 yr, inclusive; loss of bowel and bladder control (ubiquitous in infants)	Weak pulse, arrhythmia, diaphoresis/sweating, collapse/unconsciousness
CENTRAL NERVOUS SYSTEM Headache	Drowsiness, somnolence (common in infants after feeds)	Rapid onset of unresponsiveness, lethargy, or hypotonia; seizures

Adapted from Simons FER. Anaphylaxis in infants: can recognition and management be improved? J Allergy Clin Immunol *120:537–540, 2007.*

Table 149-2 Anaphylaxis Triggers in the Community*

ALLERGEN TRIGGERS (IgE-DEPENDENT IMMUNOLOGIC MECHANISM)*
Foods (e.g., peanut, tree nuts, shellfish, fish, milk, egg, wheat, soy, sesame, meat [galactose-α-1,3-galactose])
Food additives (e.g., spices, colorants, vegetable gums, and contaminants)
Stinging insects: Hymenoptera species (e.g., bees, yellow jackets, wasps, hornets, and fire ants)
Medications (e.g., β-lactam antibiotics, ibuprofen)
Biologic agents (e.g., monoclonal antibodies [infliximab, omalizumab] and allergens [challenge tests, specific immunotherapy])
Natural rubber latex
Vaccines
Inhalants (rare) (e.g., horse or hamster dander, grass pollen)
Previously unrecognized allergens (foods, venoms, biting insect saliva, medications, biologic agents)
OTHER IMMUNE MECHANISMS (IGE INDEPENDENT)
IgG mediated (infliximab, high-molecular-weight dextrans)
Immune aggregates (IVIG)
Drugs (aspirin, NSAID, opiates, contrast material, ethylene oxide/dialysis tubing)
Complement activation
Physical factors (e.g., exercise†, cold, heat, sunlight/ultraviolet radiation)
Ethanol
Idiopathic*

*In the pediatric population, some anaphylaxis triggers, such as hormones (progesterone), seminal fluid, and occupational allergens, are uncommon, as is idiopathic anaphylaxis.

†Exercise with or without a cotrigger, such as a food or medication, cold air, or cold water.

IVIG, intravenous immunoglobulin; NSAID, nonsteroidal antiinflammatory drug.

Adapted from Leung DYM, Sampson HA, Geha RS, et al: Pediatric allergy principles and practice, *New York, 2010, Elsevier, p. 652.*

Table 149-3 Patient Risk Factors for Anaphylaxis

AGE-RELATED FACTORS
Infants: anaphylaxis can be hard to recognize, especially if the first episode; patients cannot describe symptoms
Adolescents and young adults: increased risk taking behaviors such as failure to avoid known triggers and to carry an epinephrine autoinjector consistently
Pregnancy: risk of iatrogenic anaphylaxis—for example, from β lactam antibiotics to prevent neonatal group B streptococcal infection, agents used perioperatively during caesarean sections, and natural rubber latex
Older people: increased risk of death because of concomitant disease and drugs
CONCOMITANT DISEASES
Asthma and other chronic respiratory diseases
Cardiovascular diseases
Mastocytosis
Allergic rhinitis and eczema*
Depression, cognitive dysfunction, substance misuse
DRUGS
β-Adrenergic blockers†
Angiotensin-converting enzyme (ACE) inhibitors†
Sedatives, antidepressants, narcotics, recreational drugs, and alcohol may decrease the patient's ability to recognize triggers and symptoms
COFACTORS THAT AMPLIFY ANAPHYLAXIS
Exercise: anaphylaxis associated with exercise may be food dependent or food independent; nonsteroidal antiinflammatory drugs and other listed cofactors may also be relevant
Acute infection such as an upper respiratory tract infection
Fever
Emotional stress
Disruption of routine—for example, travel and jet lag
Premenstrual status in women and girls

*Atopic diseases are a risk factor for anaphylaxis triggered by food, latex, and exercise, but not for anaphylaxis triggered by most drugs or by insect stings

†Patients taking β-adrenergic blockers or ACE inhibitors seem to be at increased risk for severe anaphylaxis. In addition, those taking β-adrenergic blockers may not respond optimally to epinephrine treatment and may need glucagon, a polypeptide with non–catecholamine-dependent inotropic and chronotropic cardiac effects, atropine for persistent bradycardia, or ipratropium for persistent bronchospasm.

Modified from Simons FER, Sheikh A: Anaphylaxis: the acute episode and beyond. BMJ *2013;346:f602 (Box 2, p. 32).*

Table 149-4 Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any *1* of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin and/or mucosal tissue (e.g., *generalized* hives, pruritus or flushing, swollen lips/tongue/uvula) *AND AT LEAST 1 OF THE FOLLOWING:*
   a. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced peak PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a **likely** allergen for that patient* (minutes to several hours):
   a. Involvement of the skin/mucosal tissue (e.g., *generalized* hives, itch/flush, swollen lips/tongue/uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. *Persistent* gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP following exposure to ***known** allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP
   b. Adults: systolic BP <90 mm Hg or >30% drop from patient's baseline

BP, blood pressure; PEF, peak expiratory flow.

Modified from Sampson HA, Muñoz-Furlong A, Campbell RL, et al: Second symposium on the definition and management of anaphylaxis: summary report. Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, J Allergy Clin Immunol *117:391–397, 2006.*

immunoglobulin (Ig) E molecules. Patients initially must be exposed to the responsible allergen to generate allergen-specific antibodies. In many cases, the child and the parent are unaware of the initial exposure, which may be from passage of food proteins in maternal breast milk or skin exposures. When the child is reexposed to the sensitizing allergen, mast cells and basophils, and possibly other cells, such as macrophages, release a variety of mediators (histamine, tryptase) and cytokines that can produce allergic symptoms in any or all target organs. Clinical anaphylaxis may also be caused by mechanisms other than IgE-mediated reactions, including direct release of mediators from mast cells by medications and physical factors (morphine, exercise, cold), disturbances of leukotriene metabolism (aspirin and nonsteroidal antiinflammatory drugs), immune aggregates and complement activation (blood products), probable complement activation (radiocontrast dyes, dialysis membranes), and IgG-mediated reactions (high-molecular-weight dextran, chimeric or humanized monoclonal antibodies) (see Table 149-2).

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The onset of symptoms may vary depending on the cause of the reaction. Reactions from ingested allergens (foods, medications) are delayed in onset (minutes to 2 hr) compared with those from injected allergens (insect sting, medications) and tend to have more gastrointestinal symptoms. Initial symptoms may include any of the following constellation of symptoms: pruritus about the mouth and face; a sensation of warmth, weakness, and apprehension (sense of doom); flushing, urticaria and angioedema, oral or cutaneous pruritus, tightness in the throat, dry staccato cough and hoarseness, periocular pruritus, nasal congestion, sneezing, dyspnea, deep cough and wheezing; nausea, abdominal cramping, and vomiting, especially with ingested allergens; uterine contractions (manifesting as lower back pain); and faintness and loss of consciousness in severe cases. Some degree of obstructive laryngeal edema is typically encountered with severe reactions. Cutaneous symptoms may be absent in up to 20% of cases, and the acute onset of severe bronchospasm in a previously well asthmatic person should suggest the diagnosis of anaphylaxis. Sudden collapse in the absence of cutaneous symptoms should also raise suspicion of vasovagal collapse, myocardial infarction, aspiration, pulmonary embolism, or seizure disorder. Laryngeal edema, especially with abdominal pain, may also be a result of hereditary angioedema (see Chapter 148). Symptoms in infants may not be easy to identify (see Table 149-1).

LABORATORY FINDINGS

Laboratory studies may indicate the presence of IgE antibodies to a suspected causative agent, but this result is not definitive. Plasma histamine is elevated for a brief period but is unstable and difficult to measure in a clinical setting. **Plasma tryptase** is more stable and remains elevated for several hours but often is not elevated, especially in food-induced anaphylactic reactions.

DIAGNOSIS

A National Institutes of Health–sponsored expert panel has recommended an approach to the diagnosis of anaphylaxis (Table 149-4). The differential diagnosis includes other forms of shock (hemorrhagic, cardiogenic, septic), vasopressor reactions including flush syndromes such as carcinoid syndrome, excess histamine syndromes (systemic mastocytosis), ingestion of monosodium glutamate, scombroidosis, and hereditary angioedema. In addition, panic attack, vocal cord dysfunction, pheochromocytoma, and red man syndrome (caused by vancomycin) should be considered.

TREATMENT

Anaphylaxis is a medical emergency requiring aggressive management with **intramuscular (first line)** *or intravenous* ***epinephrine***, intramuscular or intravenous H_1 and H_2 antihistamine antagonists, oxygen, intravenous fluids, inhaled β-agonists, and corticosteroids (Table 149-5, Fig. 149-1). The initial assessment should ensure an adequate airway with effective respiration, circulation, and perfusion. Epinephrine is the most important medication, and there should be no delay in its administration. Epinephrine should be given by the intramuscular route to the lateral thigh (1:1000 dilution, 0.01 mg/kg; max 0.5 mg). For children ≥12 yr, many recommend the 0.5 mg intramuscular dose. The intramuscular dose can be repeated 2 or 3 times at intervals of 5-15 min if an intravenous continuous epinephrine infusion has not yet been started and symptoms persist. The 1:10,000 dilution of epinephrine should be used for intravenous administration. If IV access is not readily available, then epinephrine can be administered via the endotracheal or intraosseous routes. Anaphylaxis refractory to repeated doses of epinephrine has anecdotally been treated with glucagon or methylene blue. The patient should be placed in a supine position and lower extremities elevated when there is concern for hemodynamic compromise. Fluids are also important in patients with shock. Other drugs (antihistamines, glucocorticosteroids) have a secondary role in the management of anaphylaxis. Patients may experience **biphasic anaphylaxis,** which occurs when anaphylactic symptoms recur after apparent resolution. The mechanism of this phenomenon is unknown, but it appears to be more common when therapy is initiated late and symptoms at presentation are more severe. It does not appear to be affected by the administration of corticosteroids during the initial therapy. More than 90% of biphasic responses occur within 4 hr, so patients should be observed for at least 4 hr before being discharged from the emergency department. Referrals should be made to appropriate specialists for further evaluation and follow-up.

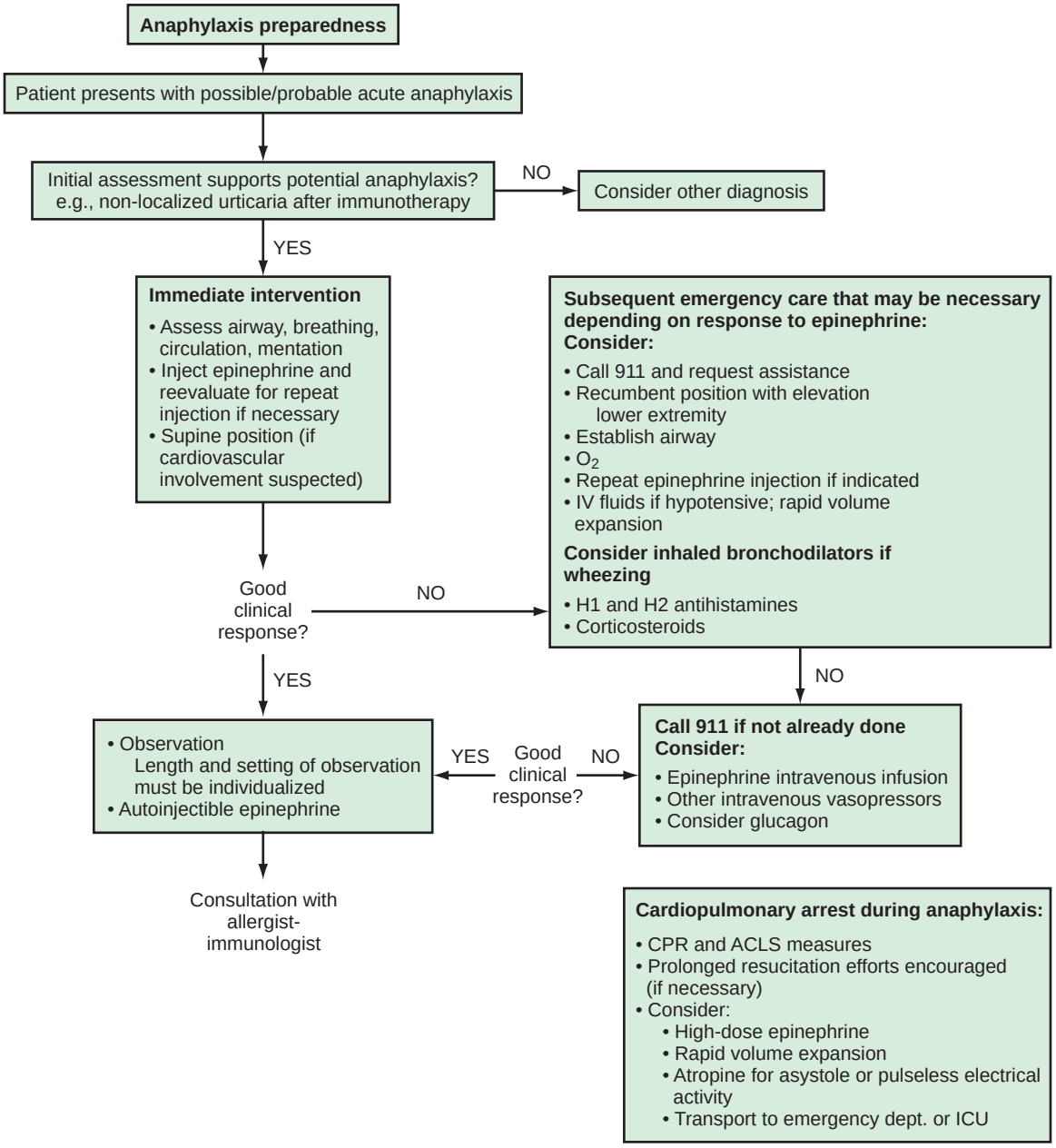

Figure 149-1 Algorithm for the treatment of anaphylactic event in the outpatient setting. IV, Intravenous. *(From Lieberman P, Nicklas RA, Oppenheimer J, et al: The diagnosis and management of anaphylaxis practice parameter: 2010 update,* J Allergy Clin Immunol *126:477–480 e471–442, 2010 [Fig. E2].)*

Table 149-5 Management of a Patient with Anaphylaxis

TREATMENT	MECHANISM(S) OF EFFECT	DOSAGE(S)	COMMENTS; ADVERSE REACTIONS
PATIENT EMERGENCY MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Weight 8-25 kg: Adrenaclick, Auvi-Q, EpiPen Jr (0.15 mg) IM Weight >25 kg: Adrenaclick, Auvi-Q, EpiPen (0.3 mg) IM	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO or IM	Hypotension, tachycardia, somnolence, and paradoxical excitement
Transport **to an Emergency Facility**			
EMERGENCY PERSONNEL MANAGEMENT (DEPENDENT ON SEVERITY OF SYMPTOMS)			
Epinephrine (adrenaline)	α_1, β_1, β_2 adrenergic effects	0.01 mg/kg up to 0.5 mg IM in lateral thigh Epinephrine autoinjector: 0.15 mg for 8-25kg, 0.3 mg for >25 kg 0.01 mL/kg/dose of 1:1,000 solution up to 0.5 mL IM May repeat every 10-15 min For severe hypotension: 0.01 mL/kg/dose of 1:10,000 slow IV push	Tachycardia, hypertension, nervousness, headache, nausea, irritability, and tremor
Supplemental oxygen and airway management			
Volume expanders			
Crystalloids (normal saline or Ringer lactate)		30 mL/kg in 1st hr	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Colloids (hydroxyethyl starch)		10 mL/kg rapidly followed by slow infusion	Rate titrated against blood pressure response If tolerated, place patient supine with legs raised
Antihistamines			
Cetirizine (liquid)	Antihistamine (competitive of H_1 receptor)	Cetirizine liquid–5 mg/5 mL 0.25 mg/kg up to 10 mg PO	Hypotension, tachycardia, and somnolence
Alt: diphenhydramine	Antihistamine (competitive of H_1 receptor)	1.25 mg/kg up to 50 mg PO, IM, or IV	Hypotension, tachycardia, somnolence, and paradoxical excitement
Ranitidine	Antihistamine (competitive of H_2 receptor)	1 mg/kg up to 50 mg IV Should be administered slowly	Headache, mental confusion
Alt: cimetidine	Antihistamine (competitive of H_2 receptor	4 mg/kg up to 200 mg IV Should be administered slowly	Headache, mental confusion
Corticosteroids			
Methylprednisolone	Antiinflammatory	Solu-Medrol (IV) 1-2 mg/kg up to 125 mg IV Depo-Medrol (IM) 1 mg/kg up to 80 mg IM	Hypertension, edema, nervousness, and agitation
Prednisone	Antiinflammatory	1 mg/kg up to 75 mg PO	Hypertension, edema, nervousness, and agitation
Nebulized albuterol	β-Agonist	(0.83 mg/mL [3 mL]) via mask with O_2	Palpitations, nervousness, central nervous system stimulation, tachycardia; use to supplement epinephrine when bronchospasm appears unresponsive; may repeat
POSTEMERGENCY MANAGEMENT			
Antihistamine		Cetirizine (5-10 mg qd) or loratadine (5-10 mg qd) for 3 days	
Corticosteroids		*Optional:* Oral prednisone (1 mg/kg up to 75 mg) daily for 3 days	
Preventive treatment			
Prescription for epinephrine autoinjector and antihistamine			
Provide written plan outlining patient emergency management (may download form from http://www.foodallergy.org)			
Follow-up evaluation to determine/confirm etiology			
Immunotherapy for insect sting allergy			
Patient education			
Instruction on avoidance of causative agent			
Information on recognizing early signs of anaphylaxis			
Stress early treatment of allergic symptoms to avoid systemic anaphylaxis			
Encourage wearing medical identification jewelry			

IM, intramuscularly; IV, intravenously; PO, by mouth.

PREVENTION

For patients experiencing anaphylactic reactions, the triggering agent should be avoided and education regarding early recognition of anaphylactic symptoms and administration of emergency medications should be provided. Patients with food allergies must be educated in allergen avoidance, including active reading of food ingredient labels and knowledge of potential contamination and high-risk situations. Any child with food allergy and a history of asthma, peanut, tree nut, fish or shellfish allergy, or a previous anaphylactic reaction should be given an epinephrine autoinjector (Adrenaclick, Auvi-Q, EpiPen), liquid cetirizine (or alternatively, diphenhydramine), and a written emergency plan in case of accidental ingestion. A form can be downloaded from Food Allergy Research & Education at http://www.foodallergy.org.

In cases of food-associated exercise-induced anaphylaxis, children must not exercise within 2-3 hr of ingesting the triggering food and, like children with exercise-induced anaphylaxis, should exercise with a friend, learn to recognize the early signs of anaphylaxis (sensation of warmth and facial pruritus), stop exercising, and seek help immediately if symptoms develop. Children experiencing a systemic anaphylactic reaction including respiratory symptoms to an insect sting should be evaluated and treated with immunotherapy, which is more than 90% protective. Reactions to medications can be reduced and minimized by using oral medications in preference to injected forms and avoidance of cross-reacting medications. Low osmolarity radiocontrast dyes and pretreatment can be used in patients in whom previous reactions are suspected. The use of nonlatex gloves and materials should be used in children undergoing multiple operations. Any child who is at risk for anaphylaxis should receive emergency medications (including epinephrine autoinjector), education on identification of signs and symptoms of anaphylaxis and proper administration of medications, and a written emergency plan in case of accidental exposure, and encouraged to wear medical identification jewelry.

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Chapter 150

Serum Sickness

Anna Nowak-Węgrzyn and Scott H. Sicherer

Serum sickness is a systemic, immune complex–mediated hypersensitivity vasculitis classically attributed to the therapeutic administration of foreign serum proteins or other medications (Table 150-1).

ETIOLOGY

Immune complexes involving heterologous (animal) serum proteins and complement activation are important pathogenic mechanisms in serum sickness. Antibody therapies derived from the horse or sheep are available for treatment of envenomation by the black widow spider and a variety of snakes, for treatment of botulism, and for immunosuppression (antithymocyte globulin). The availability of alternative medical therapies, modified or bioengineered antibodies, and biologics of human origin have supplanted the use of nonhuman antisera, reducing the risk of serum sickness. A *serum sickness–like reaction* may be attributed to drug allergy, triggered by antibiotics (particularly cefaclor). In contrast to a true serum sickness, serum sickness–like reactions do not exhibit the immune complexes, hypocomplementemia, vasculitis, and renal lesions that are seen in serum sickness reactions.

PATHOGENESIS

Serum sickness is a classic example of a type III hypersensitivity reaction caused by antigen–antibody complexes. In the rabbit model using bovine serum albumin as the antigen, symptoms develop with the appearance of antibody against the injected antigen. As free antigen concentration falls and antibody production increases over days, antigen–antibody complexes of various sizes develop in a manner analogous to a precipitin curve. Whereas small complexes usually circulate harmlessly and large complexes are cleared by the reticuloendothelial system, intermediate-sized complexes that develop at the point of slight antigen excess may deposit in blood vessel walls and tissues. There the immune microprecipitates induce vascular (leukocytoclastic vasculitis with immune complex deposition) and tissue damage through activation of complement and granulocytes.

Complement activation (C3a, C5a) promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. The processes of immune complex deposition and of neutrophil accumulation may be facilitated by increased vascular permeability, owing to the release of vasoactive amines from tissue mast cells. Mast cells may be activated by binding of antigen to immunoglobulin (Ig) E or through contact with anaphylatoxins (C3a). Tissue injury results from the liberation of proteolytic enzymes and oxygen radicals from the neutrophils.

CLINICAL MANIFESTATIONS

The symptoms of serum sickness generally begin 7-12 days after injection of the foreign material, but may appear as late as 3 wk afterward. The onset of symptoms may be accelerated if there has been earlier exposure or previous allergic reaction to the same antigen. A few days before the onset of generalized symptoms, the site of injection may become edematous and erythematous. Symptoms usually include fever, malaise, and rashes. Urticaria and morbilliform rashes are the predominant types of skin eruptions. In a prospective study of serum sickness induced by administration of equine antithymocyte globulin, an initial rash was noted in most patients. It began as a thin serpiginous band of erythema along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. In most patients, the band of erythema was replaced

Table 150-1 Proteins and Medications that Cause Serum Sickness*

PROTEINS FROM OTHER SPECIES
Antithymocyte globulin
Antitetanus toxoid
Antivenin (Crotalidae) polyvalent (horse serum based)
Crotalidae polyvalent immune Fab (ovine serum based)
Antirabies globulin
Infliximab
Rituximab
Etanercept
Anti-HIV antibodies ([PE]HRG214)
Hymenoptera stings
Streptokinase
DRUGS
Antibiotics
Cefaclor
Penicillins
Trimethoprim sulfate
Minocycline
Meropenem
Neurologic
Bupropion
Carbamazepine
Phenytoin
Sulfonamides
Barbiturates

*Based on review of most current literature. Other medications that are not listed are also cited to cause serum sickness.

HIV, human immunodeficiency virus.

From Aceves SS, Serum Sickness IN Burg FD, Ingelfinger JR, Polin RA, Gershon AA, editors, Current Pediatric Therapy, *ed 18, Philadelphia, Elsevier, 2006, Chapter 20, Table 1, p. 1138.*

by petechiae or purpura, presumably because of low platelet counts or local damage to small blood vessels. Additional symptoms include edema, myalgia, lymphadenopathy, symmetric arthralgia or arthritis involving multiple joints, and gastrointestinal complaints, including pain, nausea, diarrhea, and melena. Symptoms typically resolve within 2 wk of removal of the offending agent, although in unusual cases, symptoms can persist for as long as 2-3 mo.

Carditis, glomerulonephritis, Guillain-Barré syndrome, and peripheral neuritis are rare complications. Serum sickness–like reactions from drugs are characterized by fever, pruritus, urticaria, and arthralgias that usually begin 1-3 wk after drug exposure. The urticarial skin eruption becomes increasingly erythematous as the reaction progresses and can evolve into dusky centers with round plaques.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of serum sickness and serum sickness-like reactions includes viral illnesses with exanthems, hypersensitivity vasculitis, Kawasaki disease, acute rheumatic fever, acute meningococcal or gonococcal infection, endocarditis, systemic onset juvenile idiopathic arthritis (Still disease), Lyme disease, hepatitis and other types of drug reactions (see Chapter 152).

DIAGNOSIS

In most cases, the diagnosis of serum sickness is made clinically based upon the characteristic pattern of acute or subacute onset of a rash, fever, and severe arthralgia and myalgia disproportionate to the degree of swelling, occurring after exposure to a potential culprit.

The patients who appear moderately or severely ill, or who are not taking a medication that can be readily identified as the culprit, should be evaluated with the following laboratory tests:

- Complete blood count and differential; thrombocytopenia is often present.
- Erythrocyte sedimentation rate and C-reactive protein; erythrocyte sedimentation rate is usually elevated.
- Urinalysis; mild proteinuria, hemoglobinuria, and microscopic hematuria may be seen.
- Serum chemistries, including blood urea nitrogen, creatinine, and liver function tests.
- Complement studies, including CH50, C3, and C4; serum complement levels (C3 and C4) are generally decreased and reach a nadir at about day 10. C3a anaphylatoxin may be increased.
- Testing for specific infectious diseases, if indicated by the history or physical examination.
- Appropriate viral or bacterial cultures if an infection is suspected.

Skin biopsies are not usually necessary for confirming the diagnosis, because the findings are variable and not specific for serum sickness. Direct immunofluorescence studies of skin lesions often reveal immune deposits of IgM, IgA, IgE, or C3.

TREATMENT

There are no evidence-based guidelines or controlled trials upon which to base therapy recommendations. Treatment is primarily supportive, consisting of discontinuation of the offending agent, antihistamines for pruritus, and nonsteroidal antiinflammatory agents and analgesics for low-grade fever and mild arthralgia. When the symptoms are especially severe, for example, fever >38.5°C (101.3°F), severe arthralgia or myalgia, or renal dysfunction, systemic corticosteroids can be used. Prednisone (1-2 mg/kg/day, max 60 mg/day) for 1-2 wk is usually sufficient. Once the offending agent is discontinued and depending on its half-life, symptoms resolve spontaneously in 1-4 wk. Symptoms lasting longer suggest another diagnosis.

PREVENTION

The primary mode of prevention of serum sickness is to seek alternative therapies. In some cases, non–animal-derived formulations may be available (human-derived botulinum immune globulin). Other alternatives are partially digested antibodies of animal origin and engineered (humanized) antibodies. The potential of these therapies to elicit serum sickness–like disease appears low. When only animal-derived antitoxin/antivenom is available, skin tests should be performed before administration of serum, but this procedure indicates the risk only of anaphylaxis, not of serum sickness. For patients who have evidence of anaphylactic sensitivity to horse serum, a risk-to-benefit assessment must be made to determine the need to proceed with treatment. If needed, the serum can usually be successfully administered by a process of rapid desensitization using protocols of gradual administration outlined by the manufacturers. Serum sickness is not prevented by desensitization or by pretreatment with corticosteroids.

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Chapter 151

Food Allergy and Adverse Reactions to Foods

Anna Nowak-Węgrzyn, Hugh A. Sampson, and Scott H. Sicherer

Adverse reactions to foods consist of any untoward reaction following the ingestion of a food or food additive and are classically divided into **food intolerances** (e.g., **lactose intolerance**), which are adverse physiologic responses, and **food allergies,** which are adverse immunologic responses and can be immunoglobulin (Ig) E-mediated or non–IgE-mediated (Tables 151-1 to 151-3). Like other atopic disorders, food allergies appear to have increased over the past 3 decades, primarily in countries with a Western lifestyle. Worldwide, estimates of food allergy prevalence range from 1-10%; in the United States, food allergies affect an estimated 3.5% of the U.S. population. Up to 6% of children experience food allergic reactions in the 1st 3 yr of life, including approximately 2.5% with cow's milk allergy, 1.5% with egg allergy, and 1% with peanut allergy. Peanut allergy prevalence tripled over the past decade. Most children "outgrow" milk and egg allergies, with approximately 50% doing so by school-age. In contrast, approximately 80-90% of children with peanut, nut, or seafood allergy retains their allergy for life.

PATHOGENESIS

Food intolerances are the result of a variety of mechanisms, whereas food allergy is predominantly caused by IgE-mediated and/or cell-mediated mechanisms. In susceptible individuals exposed to certain allergens, food-specific IgE antibodies are formed that bind to Fcε receptors on mast cells, basophils, macrophages, and dendritic cells. When food allergens penetrate mucosal barriers and reach cell-bound IgE antibodies, mediators are released that induce vasodilation, smooth muscle contraction, and mucus secretion, which result in symptoms of immediate hypersensitivity (allergy). Activated mast cells and macrophages may release several cytokines that attract and activate other cells, such as eosinophils and lymphocytes, leading to prolonged inflammation. Symptoms elicited during acute IgE-mediated reactions can affect the **skin** (urticaria, angioedema, flushing), **gastrointestinal tract** (oral pruritus, angioedema, nausea, abdominal pain, vomiting, diarrhea), **respiratory tract** (nasal congestion, rhinorrhea, nasal pruritus, sneezing, laryngeal edema, dyspnea, wheezing), and **cardiovascular system** (dysrhythmias, hypotension, loss of consciousness). In the other major form of food allergies, lymphocytes, primarily food allergen–specific T cells, secrete excessive amounts of various

Table 151-1 Adverse Food Reactions

FOOD INTOLERANCE (NON–IMMUNE SYSTEM-MEDIATED, NONTOXIC, NONINFECTIOUS)
Host factors
Enzyme deficiencies—lactase (primary or secondary), sucrase/isomaltase, hereditary fructose intolerance, galactosemia
Gastrointestinal disorders—inflammatory bowel disease, irritable bowel syndrome, pseudoobstruction, colic
Idiosyncratic reactions—caffeine in soft drinks ("hyperactivity")
Psychologic—food phobias, obsessive/compulsive disorder
Migraines (rare)
Food factors (toxic or infectious or pharmacologic)
Infectious organisms—*Escherichia coli, Staphylococcus aureus, Clostridium perfringens, Shigella,* botulism, *Salmonella, Yersinia, Campylobacter*
Toxins—histamine (scombroid poisoning), saxitoxin (shellfish)
Pharmacologic agents—caffeine, theobromine (chocolate, tea), tryptamine (tomatoes), tyramine (cheese), benzoic acid in citrus fruits (perioral flare)
Contaminants—heavy metals, pesticides, antibiotics

FOOD ALLERGY
IgE-mediated
Cutaneous—urticaria, angioedema, morbilliform rashes, flushing, contact urticarial
Gastrointestinal—oral allergy syndrome, gastrointestinal anaphylaxis
Respiratory—acute rhinoconjunctivitis, bronchospasm
Generalized—anaphylactic shock, exercise induced anaphylaxis
Mixed IgE- and non–IgE-mediated
Cutaneous—atopic dermatitis, contact dermatitis
Gastrointestinal—allergic eosinophilic esophagitis and gastroenteritis
Respiratory—asthma
Non–IgE-mediated
Cutaneous—contact dermatitis, dermatitis herpetiformis (celiac disease)
Gastrointestinal—food protein–induced enterocolitis, proctocolitis, and enteropathy syndromes, celiac disease, food protein induced enteropathy
Respiratory—food-induced pulmonary hemosiderosis (Heiner syndrome)
Unclassified

IgE, immunoglobulin E.

Table 151-2 Differential Diagnosis of Adverse Food Reactions

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)
Structural abnormalities (pyloric stenosis, Hirschsprung disease, reflux)
Enzyme deficiencies (primary or secondary):
Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase
Galactosemia
Malignancy with obstruction
Other: pancreatic insufficiency (cystic fibrosis), peptic disease

CONTAMINANTS AND ADDITIVES
Flavorings and preservatives—rarely cause symptoms:
Sodium metabisulfite, monosodium glutamate, nitrites
Dyes and colorings—very rarely cause symptoms (urticaria, eczema):
Tartrazine
Toxins:
Bacterial, fungal (aflatoxin), fish-related (scombroid, ciguatera)
Infectious organisms:
Bacteria (*Salmonella, Escherichia coli, Shigella*)
Virus (rotavirus, enterovirus)
Parasites (*Giardia, Akis simplex* [in fish])
Accidental contaminants:
Heavy metals, pesticides
Pharmacologic agents:
Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese)

PSYCHOLOGIC REACTIONS
Food phobias

Table 151-3 Natural History of Food Allergy and Cross-Reactivity Between Common Food Allergies

FOOD	USUAL AGE AT ONSET OF ALLERGY	CROSS REACTIVITY	USUAL AGE AT RESOLUTION
Hen's egg white	0-1 yr	Other avian eggs	7 yr (75% of cases resolve)*
Cow's milk	0-1 yr	Goat's milk, sheep's milk, buffalo milk	5 yr (76% of cases resolve)*
Peanuts	1-2 yr	Other legumes, peas, lentils; coreactivity with tree nuts	Persistent (20% of cases resolve)
Tree nuts	1-2 yr; in adults, onset occurs after cross reactivity to birch pollen	Other tree nuts; coreactivity with peanuts	Persistent (9% of cases resolve)
Fish	Late childhood and adulthood	Other fish (low cross-reactivity with tuna and swordfish)	Persistent†
Shellfish	Adulthood (in 60% of patients with this allergy)	Other shellfish	Persistent
Wheat*	6-24 mo	Other grains containing gluten (rye, barley)	5 yr (80% of cases resolve)
Soybeans*	6-24 mo	Other legumes	2 yr (67% of cases resolve)
Kiwi	Any age	Banana, avocado, latex	Unknown
Apples, carrots, and peaches§	Late childhood and adulthood	Birch pollen, other fruits, nuts	Unknown

*Recent studies suggest that resolution may occur at a later age, especially in children with multiple food allergies and lifetime peak food-specific IgE >50 kU_A/L.
†Fish allergy that is acquired in childhood can resolve.
§Allergy to fresh apples, carrots, and peaches (**oral allergy syndrome**) is commonly caused by heat-labile proteins. Fresh fruit causes oral pruritus, but cooked fruit is tolerated. There is generally no risk of anaphylaxis, although in rare cases, allergies to cross-reactive lipid transfer protein can cause anaphylaxis after ingestion of fruits (e.g., peach) and vegetables.
Modified from Lack G: Food allergy, N Engl J Med *359:1252–1260, 2008, Table 1.*

cytokines that lead to a "delayed," more chronic inflammatory process affecting the **skin** (pruritus, erythematous rash), **gastrointestinal tract** (failure to thrive, early satiety, abdominal pain, vomiting, diarrhea), or **respiratory tract** (food-induced pulmonary hemosiderosis). Mixed IgE and cellular responses to food allergens can also lead to chronic disorders such as atopic dermatitis, asthma, and allergic eosinophilic esophagitis and gastroenteritis.

Children in whom IgE-mediated food allergies develop may be sensitized by food allergens penetrating the gastrointestinal barrier, referred to as **class 1 food allergens,** or by food allergens that are partially homologous to plant pollens penetrating the respiratory tract, referred to as **class 2 food allergens.** Any food may serve as a class 1 food allergen, but **egg, milk, peanuts, tree nuts, fish, soy, and wheat** account for 90% of food allergies during childhood. Many of the major allergenic proteins of these foods have been characterized. There is variable but significant cross-reactivity with other proteins within an individual food group. Exposure and sensitization to these proteins often occur very early in life. Virtually all milk allergies develop by 12 mo of age and all egg allergies by 18 mo of age, and the median age of first peanut allergic reactions is 14 mo, Because allergic reactions to these high-risk allergens occur in infancy, it was once thought that avoidance of these foods and delayed introduction to the diet would prevent allergy. Indeed, the opposite is probably true and delayed introduction of these foods actually increases the risk of allergy. Current recommendations are to introduce egg, peanut products, fish, wheat, and other allergenic foods after 4-6 mo of exclusive breast feeding (Table 151-4).

Class 2 food allergens are typically vegetable, fruit or nut proteins that are partially homologous with pollen proteins (see Table 151-3). With the development of seasonal allergic rhinitis from birch, grass, or ragweed pollens, subsequent ingestion of certain uncooked fruits or vegetables provokes the **oral allergy syndrome.** Intermittent ingestion of allergenic foods may lead to acute symptoms such as urticaria or anaphylaxis, whereas prolonged exposure may lead to chronic disorders such as atopic dermatitis and asthma. Cell-mediated sensitivity typically develops to class 1allergens.

CLINICAL MANIFESTATIONS

From a clinical and diagnostic standpoint, it is most useful to subdivide food hypersensitivity disorders according to the predominant target organ (Table 151-5) and immune mechanism (see Table 151-1).

Gastrointestinal Manifestations

Gastrointestinal food allergies are often the first form of allergy to affect infants and young children and typically manifest as irritability, vomiting or "spitting-up," diarrhea, and poor weight gain. Cell-mediated hypersensitivities without IgE involvement predominate, making standard allergy tests such as prick skin tests and in vitro tests for food-specific IgE antibodies of little diagnostic value.

Food protein–induced enterocolitis syndrome (FPIES) typically manifests in the first several months of life as irritability, intermittent vomiting and protracted diarrhea, and may result in dehydration (Table 151-6). Vomiting generally occurs 1-3 hr after feeding, and continued exposure may result in abdominal distention, bloody diarrhea, anemia, and failure to thrive. Symptoms are most commonly provoked by cow's milk or soy protein–based formulas. A similar enterocolitis syndrome occurs in older infants and children from rice, oat, wheat, egg, peanut, nut, chicken, turkey, or fish. Hypotension occurs in approximately 15% of cases after allergen ingestion and may initially be thought to be caused by sepsis. FPIES usually resolves by age 3 yr.

Food protein-induced proctocolitis presents in the first few mo of life as blood-streaked stools in otherwise healthy infants (see Table 151-6). Approximately 60% of cases occur among breastfed infants, with the remainder largely among infants fed cow's milk or soy

Table 151-4 Prevention of Food Allergy

Exclusive breast feeding for 4-6 mo
Introduce solid (complementary) foods after 4-6 mo of exclusive breast feeding
Introduce low-risk complementary foods 1 at a time
Introduce potentially highly allergenic foods (fish, eggs, peanut products, milk, wheat) soon after the lower-risk foods (no need to avoid or delay)
Don't avoid allergenic foods during pregnancy or nursing
Soy-based formulas do not prevent allergic disease

Table 151-5 Symptoms of Food-Induced Allergic Reactions

TARGET ORGAN	IMMEDIATE SYMPTOMS	DELAYED SYMPTOMS
Cutaneous	Erythema Pruritus Urticaria Morbilliform eruption Angioedema	Erythema Flushing Pruritus Morbilliform eruption Angioedema Eczematous rash
Ocular	Pruritus Conjunctival erythema Tearing Periorbital edema	Pruritus Conjunctival erythema Tearing Periorbital edema
Upper respiratory	Nasal congestion Pruritus Rhinorrhea Sneezing Laryngeal edema Hoarseness Dry staccato cough	
Lower respiratory	Cough Chest tightness Dyspnea Wheezing Intercostal retractions Accessory muscle use	Cough, dyspnea, and wheezing
GI (oral)	Angioedema of the lips, tongue, or palate Oral pruritus Tongue swelling	
GI (lower)	Nausea Colicky abdominal pain Reflux Vomiting Diarrhea	Nausea Abdominal pain Reflux Vomiting Diarrhea Hematochezia Irritability and food refusal with weight loss (young children)
Cardiovascular	Tachycardia (occasionally bradycardia in anaphylaxis) Hypotension Dizziness Fainting Loss of consciousness	
Miscellaneous	Uterine contractions Sense of "impending doom"	

Note: This table is presented as Table IV in the Guidelines.
GI, gastrointestinal.
From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table IV, p. S19).*

Table 151-6 Food Protein-Induced Gastrointestinal Syndromes

	FPIES	PROCTOCOLITIS	ENTEROPATHY	EOSINOPHILIC GASTROENTEROPATHIES*
Age at onset	1 day–1 year	1 day–6 months	Dependent of age of exposure to antigen, cow's milk and soy up to 2 yr	Infant to adolescent
Food proteins implicated				
Most common	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy	Cow's milk, soy, egg white, wheat, peanut
Less common	Rice, chicken, turkey, fish, pea	Egg, corn, chocolate	Wheat, egg	Meats, corn, rice, fruits, vegetables, fish
Multiple food hypersensitivities	>50% both cow's milk and soy	40% both cow's milk and soy	Rare	Common
Feeding at the time of onset	Formula	>50% exclusive breast feeding	Formula	Formula
Atopic background				
Family history of atopy	40-70%	25%	Unknown	~50% (often history of eosinophilic esophagitis)
Personal history of atopy	30%	22%	22%	~50%
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Laboratory findings				
Anemia	Moderate	Mild	Moderate	Mild-moderate
Hypoalbuminemia	Acute	Rare	Moderate	Mild-severe
Methemoglobinemia	May be present	No	No	No
Allergy evaluation				
Food prick skin test	Negative†	Negative	Negative	Positive in ~50%
Serum food allergen IgE	Negative†	Negative	Negative	Positive in ~50%
Total IgE	Normal	Negative	Normal	Normal to elevated
Peripheral blood eosinophilia	No	Occasional	No	Present in <50%
Biopsy findings				
Colitis	Prominent	Focal	No	May be present
Lymph nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; also neutrophilic infiltrates, papillary elongation and basal zone hyperplasia
Food challenge	Vomiting in 2-4 hr; diarrhea in 5-8 hr	Rectal bleeding in 6-72 hr	Vomiting, diarrhea, or both in 40-72 hr	Vomiting and diarrhea in hours to days
Treatment	Protein elimination, 80% respond to casein hydrolysate and symptoms clear in 3-10 days; rechallenge in 1.5-2 yr	Protein elimination, symptoms clear in 3 days with casein hydrolysate, resume/continue breastfeeding on maternal antigen-restricted diet	Protein elimination, symptoms clear in 1-3 wk, rechallenge and biopsy in 1-2 yr	Protein elimination, good response to casein hydrolysate, excellent response to elemental diet, symptoms clear within 2-3 wk, excellent acute response to steroids; rechallenge and biopsy in 1-2 yr
Natural history	Cow's milk: 60% resolved by 2 yr Soy: 25% resolved by 2 yr	Resolved by 9-12 months	Most cases resolve in 2-3 yr	Typically a prolonged, relapsing course
Reintroduction of the food	Inpatient food challenge	At home, gradually advancing from 1 oz to full feedings over 2 weeks	Home, gradually advancing	Home, gradually advancing

*Eosinophilic gastroenteropathies encompass esophagitis, gastritis, gastroenterocolitis.
†If positive, may be a risk factor for persistent disease.
FPIES, food protein-induced enterocolitis syndrome.
From Nowak-Wegrzyn A, Muraro A: Food protein-induced enterocolitis syndrome. Curr Opin Allergy Immunol *9:371-377, 2009 (Table 1, p. 372).*

protein–based formula. Blood loss is typically modest, but can occasionally produce anemia.

Food protein–induced enteropathy often manifests in the first several months of life as diarrhea, often with steatorrhea and poor weight gain (see Table 151-6). Symptoms include protracted diarrhea, vomiting in up to 65% of cases, failure to thrive, abdominal distention, early satiety, and malabsorption. Anemia, edema, and hypoproteinemia occur occasionally. **Cow's milk sensitivity** is the most common cause of this food protein–induced enteropathy in young infants, but it has also been associated with sensitivity to soy, egg, wheat, rice, chicken, and fish in older children. **Celiac disease,** the most severe form of protein-induced enteropathy, occurs in about 1 : 100 of the U.S. population, although it may be "silent" in many patients (see Chapter 338.2). The full-blown form is characterized by extensive loss of absorptive villi and hyperplasia of the crypts, leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence, and weight loss or failure to thrive. Oral ulcers and other extraintestinal symptoms secondary to malabsorption may occur. Genetically susceptible individuals (HLA-DQ2 or HLA-DQ8) demonstrate a cell-mediated response to tissue transglutaminase deamidated gliadin (a fraction of gluten), which is found in wheat, rye, and barley.

Eosinophilic esophagitis (EoE) may appear from infancy through adolescence, more frequently in boys (see Chapter 324). In young children, it is primarily cell mediated and manifests as chronic gastroesophageal reflux, intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional reflux medications. EoE is a clinicopathologic diagnosis. The diagnosis is confirmed when 15 eosinophils per high-power field are seen on esophageal biopsy during treatment with proton pump inhibitors. **Eosinophilic gastroenteritis** occurs at any age and causes symptoms similar to those of EoE as well as prominent weight loss or failure to thrive, both of which are the hallmarks of this disorder. More than 50% of patients with this disorder are atopic, however food-induced IgE-mediated reactions have been implicated only in a minority of patients. Generalized edema secondary to hypoalbuminemia may occur in some infants with marked protein-losing enteropathy.

Oral allergy syndrome (pollen-associated food allergy syndrome) is an IgE-mediated hypersensitivity that occurs in many older children with birch and ragweed pollen-induced allergic rhinitis. Symptoms are usually confined to the oropharynx and consist of the rapid onset of oral pruritus, tingling and angioedema of the lips, tongue, palate, and throat, and occasionally a sensation of pruritus in the ears and tightness in the throat. Symptoms are generally short lived and are caused by local mast cell activation following contact with fresh fruit and vegetable proteins that cross-react with birch pollen (apple, carrot, potato, celery, hazel nuts, kiwi, cherry, pear), grass pollen (potato, tomato, watermelon, kiwi), and ragweed pollen (banana, melons such as watermelon and cantaloupe).

Acute gastrointestinal allergy generally manifests as acute abdominal pain and vomiting that accompany IgE-mediated allergic symptoms in other target organs.

Skin Manifestations

Cutaneous food allergies are also common in infants and young children.

Atopic dermatitis is a form of eczema that generally begins in early infancy and is characterized by pruritus, a chronically relapsing course, and association with asthma and allergic rhinitis (see Chapter 145. Although not often apparent from history, at least 30% of children with moderate to severe atopic dermatitis have food allergies. The younger the child and the more severe the eczema, the more likely food allergy is playing a pathogenic role in the disorder.

Acute urticaria and angioedema are among the most common symptoms of food allergic reactions (see Chapter 148). The onset of symptoms may be very rapid, within minutes after ingestion of the responsible allergen. Symptoms result from activation of IgE-bearing mast cells by food allergens that are absorbed and circulated rapidly throughout the body. Foods most commonly incriminated in children include egg, milk, peanuts, and nuts, although reactions to various seeds (sesame, poppy) and fruits (kiwi) are becoming more common. Chronic urticaria and angioedema are rarely caused by food allergies.

Perioral dermatitis is often a contact dermatitis caused by substances in toothpaste, gums, lipstick, to medications. **Perioral flushing** is often noted in infants fed citrus fruits and may be caused by benzoic acid in the food. It may also occur during nursing. In both situations, it is benign. Flushing may also be caused by auriculotemporal nerve (Frey) syndrome (familial, forceps delivery), which resolves spontaneously.

Respiratory Manifestations

Respiratory food allergies are uncommon as isolated symptoms. Although many parents believe that nasal congestion in infants is often caused by milk allergy, studies show this not to be the case. **Food-induced rhinoconjunctivitis** symptoms typically accompany allergic symptoms in other target organs, such as skin, and consist of typical allergic rhinitis symptoms (periocular pruritus and tearing, nasal congestion and pruritus, sneezing, rhinorrhea). Wheezing occurs in approximately 25% of IgE-mediated food allergic reactions, but only approximately 10% of asthmatic patients have food-induced respiratory symptoms.

Anaphylaxis

Anaphylaxis is defined as a serious, multisystem allergic reaction that is rapid in onset and potentially fatal. Food allergic reactions are the single most common cause of anaphylaxis seen in hospital emergency departments in the United States. In addition to the rapid onset of cutaneous, respiratory, and gastrointestinal symptoms, patients may demonstrate cardiovascular symptoms, including hypotension, vascular collapse, and cardiac dysrhythmias, which are presumably caused by massive mast cell–mediator release. **Food-associated exercise-induced anaphylaxis** occurs more frequently among teenage athletes, especially females (see Chapter 149).

DIAGNOSIS

A thorough medical history is necessary to determine whether a patient's symptomatology represents an adverse reaction (see Table 151-2), whether the adverse food reaction is an intolerance or food allergic reaction, and if the latter, whether it is likely to be an IgE-mediated or a cell-mediated response (Fig. 151-1). The following facts should be established: (1) the food suspected of provoking the reaction and the quantity ingested, (2) the interval between ingestion and the development of symptoms, (3) the types of symptoms elicited by the ingestion, (4) whether ingesting the suspected food produced similar symptoms on other occasions, (5) whether other inciting factors, such as exercise, are necessary, and (6) the interval from the last reaction to the food.

Prick skin tests and in vitro laboratory tests are useful for demonstrating IgE sensitization, defined as presence of food-specific IgE antibodies. Many fruits and vegetables require prick-prick skin testing with fresh produce because labile proteins are destroyed during commercial preparation. A negative skin test result virtually excludes an IgE-mediated form of food allergy. Conversely, the majority of children with positive skin test responses to a food do not react when the food is ingested, so more definitive tests, such as quantitative IgE tests or food elimination and challenge, are often necessary to establish a diagnosis of food allergy. Serum food-specific IgE levels ≥15 kU_A/L for milk (≥5 kU_A/L for children ≤1 yr), ≥7 kU_A/L for egg (≥2 kU_A/L for children <2 yr), and ≥14 kU_A/L for peanut are associated with a >95% likelihood of clinical reactivity to these foods in children with suspected reactivity. In the absence of a clear history of reactivity to a food and evidence of food-specific IgE antibodies, definitive studies must be performed before recommendations are made for avoidance or the use of highly restrictive diets that may be nutritionally deficient, logistically impractical, disruptive to the family, expensive, and a potential source of future feeding disorders. IgE-mediated food allergic reactions are generally very food specific, so the use of broad exclusionary diets, such as avoidance of all legumes, cereal grains, or animal products, is not warranted (Tables 151-3 and 151-7).

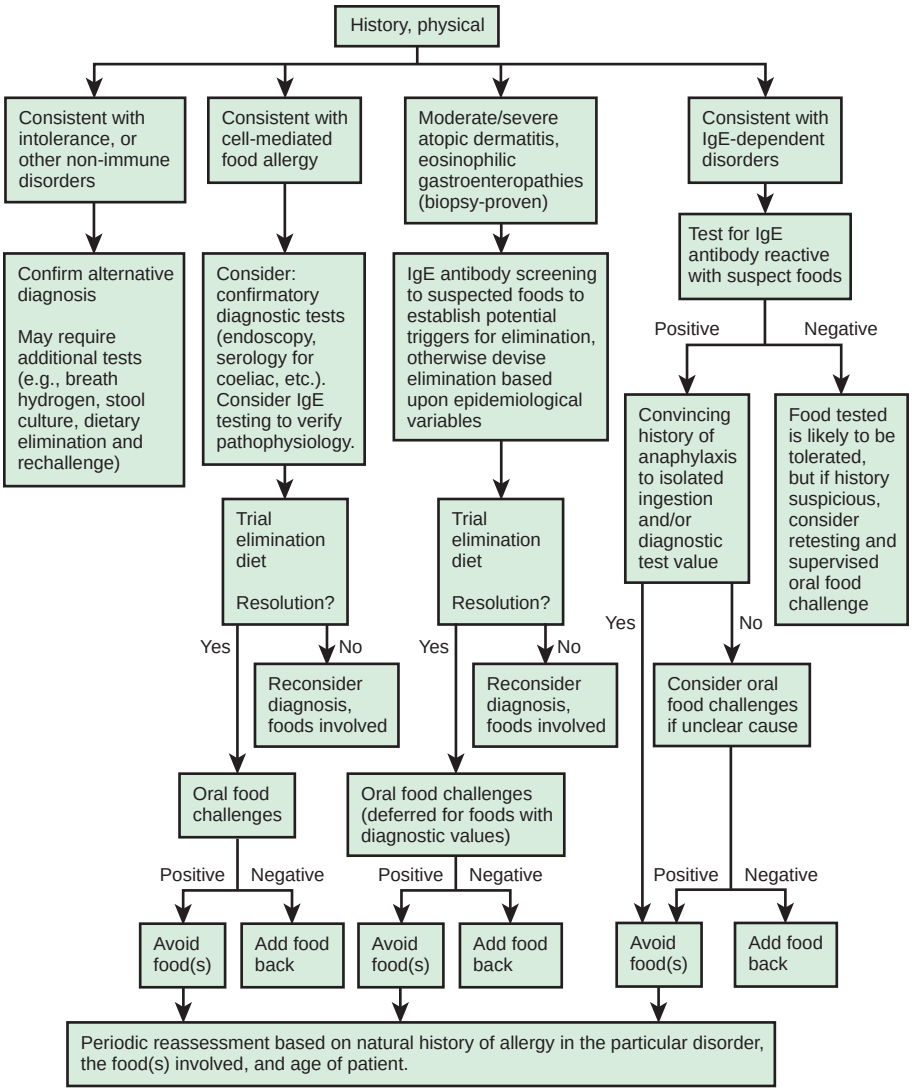

Figure 151-1 General scheme for diagnosis of food allergy. *(From Sicherer SH: Food allergy,* Lancet *360:701–710, 2002.)*

Table 151-7 Clinical Implications of Cross-Reactive Proteins in IgE-Mediated Allergy

FOOD FAMILY	RISK OF ALLERGY TO ≥1 MEMBER (%; APPROXIMATE)	FEATURE(S)
Legumes	5	Main causes of reactions are peanut, soybean, lentil, lupine, and garbanzo (chickpea)
Tree nuts (e.g., almond, cashew, hazelnut, walnut, brazil)	35	Reactions are often severe
Fish	50	Reactions can be severe
Shellfish	75	Reactions can be severe
Grains	20	
Mammalian milks	90	Cow's milk is highly cross reactive with goat's or sheep's milk (92%) but not with mare's milk (4%)
Rosaceae (pitted fruits)	55	Risk of reactions to more than three related foods is very low (<10%), symptoms are usually mild (oral allergy syndrome)
Latex-food	35	For individuals allergic to latex, banana, kiwi, fig, chestnut, and avocado are the main causes of reactions
Food-latex	11	Individuals allergic to banana, kiwi, fig, chestnut, and avocado may be at an increased risk of reactions to latex

Modified from Sicherer SH: Food allergy, Lancet *360:701–710, 2002.*

Table 151-8	ACIP and AAP Red Book Recommendations for Administering Vaccines to Patients with Egg Allergy	
VACCINE	**ACIP**	**AAP RED BOOK**
MMR/MMRV	May be used	May be used
Influenza	Receive with some precautions*	Receive with some precautions*
Rabies	Use caution	No specific recommendation
Yellow fever	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)	Contraindicated, but desensitization protocols may be followed to administer vaccine if necessary (citing PI)

AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices.

From Boyce JA, Assa'ad A, Burks AW, et al: Guideline for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel, J Allergy Clin Immunol *126(6):S1–S58, 2010 (Table V, p S31).*

*In 2012, recommendations changed to suggest those with mild egg allergy receive the inactivated influenza vaccine in the primary care setting with a 30 minute observation and preparedness to treat anaphylaxis. Those with severe egg allergy are referred to an allergist.

There are no laboratory studies to help identify foods responsible for cell-mediated reactions. Consequently, **elimination diets followed by food challenges** are the only way to establish the diagnosis. Allergists experienced in dealing with food allergic reactions and able to treat anaphylaxis should perform food challenges. Before a food challenge is initiated, the suspected food should be eliminated from the diet for 10-14 days for IgE-mediated food allergy and up to 8 wk for some cell-mediated disorders, such as EoE. Some children with cell-mediated reactions to cow's milk do not tolerate hydrolysate formulas and must receive amino acid–derived formulas. If symptoms remain unchanged despite appropriate elimination diets, it is unlikely that food allergy is responsible for the child's disorder.

TREATMENT

Appropriate identification and elimination of foods responsible for food hypersensitivity reactions are the only validated treatments for food allergies. Complete elimination of common foods (milk, egg, soy, wheat, rice, chicken, fish, peanut, nuts) is very difficult because of their widespread use in a variety of processed foods. The lay organization Food Allergy Research and Education (FARE, www.foodallergy.org) provides excellent information to help parents deal with both the practical and emotional issues surrounding these diets. Validated educational materials are also available through the Consortium of Food Allergy Research (www.cofargroup.org). Children with asthma and IgE-mediated food allergy, peanut or nut allergy, or a history of a previous severe reaction should be given self-injectable epinephrine and a written emergency plan in case of accidental ingestion (see Chapter 149). Because many food allergies are outgrown, children should be reevaluated periodically by an allergist to determine whether they have lost their clinical reactivity. A number of clinical trials are beginning to evaluate the efficacy of oral, sublingual, and epicutaneous (patch) immunotherapy for the treatment of IgE-mediated food allergies (milk, egg, peanut). Combining oral immunotherapy with anti-IgE treatment (omalizumab) may be even more effective than oral immunotherapy alone. Furthermore, extensively heated milk or egg in baked products are tolerated by the majority of milk and egg allergic children. Regular ingestion of baked products with milk and egg appears to accelerate resolution of milk and egg allergy. Management of egg-allergic children who require immunizations is noted in Table 151-8.

PREVENTION

There is no consensus as to whether food allergies can be prevented. At present there is insufficient evidence to support the practice of restricting the maternal diet during pregnancy or breastfeeding or of delaying introduction of various allergenic foods to infants from atopic families (see Table 151-4). Exclusive breastfeeding for the first 4-6 mo of life may reduce allergic disorders in the first few years of life in infants at high risk for development of allergic disease. Potentially allergenic foods (eggs, milk, wheat, soy, peanut and tree nut products, fish) should be introduced after this period of exclusive breastfeeding and may prevent the development of allergies later in life. Use of partially hydrolyzed whey formulas may be beneficial if breast feeding cannot be continued for 4-6 mo or after weaning, especially to prevent eczema in high risk families, but his approach remains controversial. Probiotic supplements may also reduce the incidence and severity of eczema. Because some *skin preparations* contain peanut oil, which may sensitize young infants, especially those with cutaneous inflammation, such preparations should be avoided.

Bibliography is available at Expert Consult.

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Chapter 152

Adverse Reactions to Drugs

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Adverse drug reactions can be divided into predictable (type A) and unpredictable reactions (type B). **Predictable drug reactions,** including drug toxicity, drug interactions, and adverse effects, are dose dependent, can be related to known pharmacologic actions of the drug, and occur in patients without any unique susceptibility. **Unpredictable drug reactions** are dose independent, often are not related to the pharmacologic actions of the drug, and occur in patients who are genetically predisposed. These include idiosyncratic reactions, allergic (hypersensitivity) reactions, and pseudoallergic reactions. Allergic reactions require prior sensitization, manifest as signs or symptoms characteristic of an underlying allergic mechanism such as anaphylaxis or urticaria, and occur in genetically susceptible individuals. They can occur at doses significantly below the therapeutic range. **Pseudoallergic reactions** resemble allergic reactions but are caused by non–immunoglobulin (Ig) E-mediated release of mediators from mast cells and basophils. Drug-independent cross-reactive antigens can induce sensitization manifesting as drug allergy. Patients with cetuximab-induced anaphylaxis have IgE antibodies in pretreatment samples specific for galactose-α-1,3-galactose. Galactose-α-1,3-galactose is present on the antigen-binding portion of the cetuximab heavy chain and is similar to structures in the ABO blood group.

Table 152-1 Heterogeneity of Drug-Induced Allergic Reactions

ORGAN-SPECIFIC REACTIONS	CLINICAL FEATURES	EXAMPLES OF CAUSATIVE AGENTS
CUTANEOUS		
Exanthems	Diffuse fine macules and papules evolve over days after drug initiation Delayed-type hypersensitivity	Allopurinol, aminopenicillins, cephalosporins, antiepileptic agents, and antibacterial sulfonamides
Urticaria, angioedema	Onset within minutes of drug initiation Potential for anaphylaxis Often IgE mediated	IgE mediated: β-lactam antibiotics Bradykinin mediated: ACEI
Fixed drug eruption	Hyperpigmented plaques Recur at same skin or mucosal site	Tetracycline, NSAIDs, and carbamazepine
Pustules	Acneiform Acute generalized eczematous pustulosis (AGEP)	Acneiform: corticosteroids, sirolimus AGEP: antibiotics, calcium-channel blockers
Bullous	Tense blisters Flaccid blisters	Furosemide, vancomycin Captopril, penicillamine
SJS	Fever, erosive stomatitis, ocular involvement, purpuric macules on face and trunk with <10% epidermal detachment	Antibacterial sulfonamides, anticonvulsants, oxicam NSAIDs, and allopurinol
TEN	Similar features as SJS but >30% epidermal detachment Mortality as high as 50%	Same as SJS
Cutaneous lupus	Erythematous/scaly plaques in photodistribution	Hydrochlorothiazide, calcium-channel blockers, ACEIs
Hematologic	Hemolytic anemia, thrombocytopenia, granulocytopenia	Penicillin, quinine, sulfonamides
Hepatic	Hepatitis, cholestatic jaundice	Para-aminosalicylic acid, sulfonamides, phenothiazines
Pulmonary	Pneumonitis, fibrosis	Nitrofurantoin, bleomycin, methotrexate
Renal	Interstitial nephritis, membranous glomerulonephritis	Penicillin, sulfonamides, gold, penicillamine, allopurinol
MULTIORGAN REACTIONS		
Anaphylaxis	Urticaria/angioedema, bronchospasm, gastrointestinal symptoms, hypotension IgE- and non–IgE-dependent reactions	β-Lactam antibiotics, monoclonal antibodies
DRESS	Cutaneous eruption, fever, eosinophilia, hepatic dysfunction, lymphadenopathy	Anticonvulsants, sulfonamides, minocycline, allopurinol
Serum sickness	Urticaria, arthralgias, fever	Heterologous antibodies, infliximab
Systemic lupus erythematosus	Arthralgias, myalgias, fever, malaise	Hydralazine, procainamide, isoniazid
Vasculitis	Cutaneous or visceral vasculitis	Hydralazine, penicillamine, propylthiouracil

ACEI, angiotensin-converting enzyme inhibitor; DRESS, drug rash with eosinophilia and systemic symptoms; NSAID, nonsteroidal antiinflammatory drug (NSAID); SJS, Stevens-Johnson syndrome.

From Khan DA, Solensky R: Drug allergy, J Allergy Clin Immunol *125:S126–S137, 2010 (Table 1, p. S127).*

EPIDEMIOLOGY

The incidence of adverse drug reactions in the general as well as pediatric populations remains unknown, although data from hospitalized patients show it to be 6.7%, with a 0.32% incidence of fatal adverse drug reactions. Databases such as the FDA MedWatch program (http://www.fda.gov/medwatch/index.html) likely suffer from underreporting. Cutaneous reactions are the most common form of adverse drug reactions, with ampicillin, amoxicillin, penicillin, and trimethoprim-sulfamethoxazole being the most commonly implicated drugs (Tables 152-1 and 152-2). Although the majority of adverse drug reactions do not appear to be allergic in nature, 6-10% can be attributed to an allergic or immunologic mechanism. Importantly, given the high probability of recurrence of allergic reactions, these reactions should be preventable, and information technology–based interventions may be especially useful to reduce risk of reexposure.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Immunologically mediated adverse drug reactions have been classified according to the **Gell and Coombs classification:** immediate hypersensitivity reactions (type I), cytotoxic antibody reactions (type II), immune complex reactions (type III), and delayed-type hypersensitivity reactions (type IV). Immediate hypersensitivity reactions occur when a drug or drug metabolite interacts with preformed drug-specific IgE antibodies that are bound to the surfaces of tissue mast cells and/or circulating basophils. The cross-linking of adjacent receptor-bound IgE by antigen causes the release of preformed and newly synthesized mediators, such as histamine and leukotrienes, that contribute to the clinical development of urticaria, bronchospasm, or anaphylaxis. Cytotoxic reactions involve IgG or IgM antibodies that recognize drug antigen on the cell membrane. In the presence of serum complement, the antibody-coated cell is either cleared by the monocyte–macrophage system or is destroyed. Examples are drug-induced hemolytic anemia and thrombocytopenia. Immune complex reactions are caused by soluble complexes of drug or metabolite in slight antigen excess with IgG or IgM antibodies. The immune complex is deposited in blood vessel walls and causes injury by activating the complement cascade, as seen in serum sickness. Clinical manifestations include fever, urticaria, rash, lymphadenopathy, and arthralgias. Symptoms typically appear 1-3 wk after the last dose of an offending drug and subside when the drug and/or its metabolite is cleared from the body. Delayed-type hypersensitivity reactions are mediated by drug-specific T lymphocytes. Sensitization usually occurs via the topical route of administration, resulting in allergic contact dermatitis. Commonly implicated drugs include neomycin and local anesthetics in topical formulations.

Certain adverse drug reactions, including drug fever and the morbilliform rash seen with use of ampicillin or amoxicillin in the setting of Epstein-Barr virus infection, are not easily classified. Studies point to the role of T cells and eosinophils in delayed maculopapular reactions to a number of antibiotics. The mechanisms of T-cell–mediated drug hypersensitivity are not well understood. A novel hypothesis, the p-i concept, suggests pharmacologic interactions of drugs with immune receptors as another class of drug hypersensitivity. In T-cell–mediated

Table 152-2 Serious Non–IgE-Mediated Drug Eruptions

DIAGNOSIS	MUCOSAL LESIONS	TYPICAL SKIN LESIONS	PRODROMAL SIGNS AND SYMPTOMS	DRUG ASSOCIATED (%)	DRUGS MOST OFTEN IMPLICATED	TYPICAL TIME TO ONSET (wk)	ALTERNATIVE CAUSES NOT RELATED TO DRUGS
Drug hypersensitivity syndrome (DHS) or drug rash with eosinophilia and systemic symptoms (DRESS) syndrome	Infrequent	Severe exanthematous rash (could become edematous, pustular, purpuric), exfoliative dermatitis	30-50% involve fever, lymphadenopathy, hepatitis, nephritis, carditis, eosinophilia, atypical lymphocytes	≥90	Phenytoin, carbamazepine, phenobarbital, sulfonamides, allopurinol, minocycline, nitrofurantoin, terbinafine, vancomycin, dapsone, abacavir, nevirapine, nonsteroidal antiinflammatory drugs (NSAIDs)	1-6	Cutaneous lymphoma
Stevens-Johnson syndrome (SJS)	Erosions at ≥2 sites	Crops of lesions on skin, conjunctivae, mouth, and genitalia; detachment of ≤10% of body surface area	High fever, sore throat, rhinorrhea, cough	48-64	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs	1-3	
Toxic epidermal necrolysis (TEN)	Erosions at ≥2 sites	Lesions similar to those with SJS; confluent epidermis separates readily with lateral pressure; detachment of ≥30% of body surface area	Fever, headache, sore throat; nearly all cases involve fever, "acute skin failure," leukopenia, lesions of the respiratory and/or gastrointestinal tracts	43-65	Sulfonamides, phenytoin, carbamazepine, barbiturates, allopurinol, aminopenicillins, NSAIDs	1-3	Exanthematous stage of Kawasaki disease; staphylococcal scalded-skin syndrome

Revised from Segal AR, Doherty KM, Leggott J, et al: Cutaneous reactions to drugs in children, Pediatrics *120:e1082–e1096, 2007.*

allergic drug reactions, the specificity of the T-cell receptor that is stimulated by the drug may be directed to a cross-reactive major histocompatibility complex–peptide compound. This information suggests that even poorly reactive native drugs are capable of transmitting a stimulatory signal via the T-cell receptor, which activates T cells and results in proliferation, cytokine production, and cytotoxicity. Previous contact with the causative drug is not obligatory, and an immune mechanism should be considered as the cause of hypersensitivity, even in reactions that occur with first exposure. Such reactions have been described for radiocontrast media and neuromuscular blocking agents.

Drug Metabolism and Adverse Reactions

Most drugs and their metabolites are not immunologically detectable until they have become covalently attached to a macromolecule. This multivalent hapten–protein complex forms a new immunogenic epitope that can elicit T- and B-lymphocyte responses. The penicillins and related β-lactam antibiotics are highly reactive with proteins and can directly haptenate protein carriers, possibly accounting for the frequency of immune-mediated hypersensitivity reactions with this class of antibiotics.

Incomplete or delayed metabolism of some drugs can give rise to toxic metabolites. Hydroxylamine, a reactive metabolite produced by cytochrome P450 oxidative metabolism, may mediate adverse reactions to sulfonamides. Patients who are slow acetylators appear to be at increased risk (see Chapter 59). In addition, cutaneous reactions in patients with AIDS treated with trimethoprim-sulfamethoxazole, rifampin, or other drugs may be a result of glutathione deficiency resulting in toxic metabolites. Serum sickness–like reactions in which immune complexes have not been documented, which occur most commonly with cefaclor, may result from an inherited propensity for hepatic biotransformation of drugs into toxic or immunogenic metabolites.

Risk Factors for Hypersensitivity Reactions

Risk factors for adverse drug reactions include prior exposure, previous reactions, age (20-49 yr), route of administration (parenteral or topical), dose (high), and dosing schedule (intermittent), as well as genetic predisposition (slow acetylators). Atopy does not appear to predispose patients to allergic reactions to low-molecular-weight compounds, but atopic patients in whom an allergic reaction develops have a significantly increased risk of serious reaction. Atopic patients also appear to be at greater risk for pseudoallergic reactions induced by radiocontrast media. Pharmacogenomics has an important role in identifying individuals at risk for certain drug reactions (see Chapter 59).

DIAGNOSIS

An accurate medical history is an important first step in evaluating a patient with a possible adverse drug reaction. Suspected drugs need to be identified along with dosages, route of administration, previous exposures, and dates of administration. In addition, underlying hepatic or renal disease may influence drug metabolism. A detailed description of past reactions may yield clues to the nature of the adverse drug reaction. The propensity for a particular drug to cause the suspected reaction can be checked with information in *Physicians' Desk Reference, Drug Eruption Reference Manual,* or directly from the drug manufacturer. It is important to remember, however, that the history may be unreliable, and many patients are inappropriately labeled as being drug allergic. This label can result in inappropriate withholding of a needed drug or class of drugs. In addition, relying solely on the history can lead to overuse of drugs reserved for special indications, such as vancomycin in patients in whom penicillin allergy is suspected. Approximately 90% of patients with a clinical history of penicillin allergy do not have evidence of penicillin-specific IgE antibodies on testing.

Skin testing is the most rapid and sensitive method of demonstrating the presence of *IgE antibodies* to a specific allergen. It can be performed with high-molecular-weight compounds, such as foreign antisera, hormones, enzymes, and toxoids. Reliable skin testing can also be performed with penicillin, but not with most other antibiotics. Most immunologically mediated adverse drug reactions are caused by metabolites rather than by parent compounds, and the metabolites for most drugs other than penicillin have not been defined. In addition, many metabolites are unstable or must combine with larger proteins to be useful for diagnosis. Testing with nonstandardized reagents requires caution in interpretation of both positive and negative results, because some drugs can induce nonspecific irritant reactions. Whereas a wheal-and-flare reaction is suggestive of drug-specific IgE antibodies, a negative skin test result does not exclude the presence of such antibodies because the relevant immunogen may not have been used as the testing reagent.

A positive skin test response to the major or minor determinants of penicillin has a 60% positive predictive value for an immediate hypersensitivity reaction to penicillin. In patients in whom skin test responses to the major and minor determinants of penicillin are negative, 97-99% (depending on the reagents used) tolerate the drug without an immediate reaction. At present, the major determinant of penicillin testing reagent PrePen (benzylpenicilloyl-polylysine) in the United States is available, but the minor determinant mixture has not been approved by the FDA as a testing reagent. Limited studies utilizing serum tests for IgE to β-lactams suggest high specificity (97-100%) but low sensitivity (29-68%). The positive and negative predictive values of skin testing for antibiotics other than penicillin are not well established. Nevertheless, positive immediate hypersensitivity skin test responses to nonirritant concentrations of nonpenicillin antibiotics may be interpreted as a presumptive risk of an immediate reaction to such agents.

Results of direct and indirect Coombs tests are often positive in drug-induced hemolytic anemia. Assays for specific IgG and IgM have been shown to correlate with a drug reaction in immune cytopenia, but, in most other reactions, such assays are not diagnostic. In general, many more patients express humoral or T-cell immune responses to drug determinants than express clinical disease. Serum tryptase is elevated with systemic mast cell degranulation and can be seen with drug-associated mast cell activation, although it is not pathognomonic for drug hypersensitivity, and nonelevated tryptase values can be seen in well-defined anaphylaxis.

TREATMENT

Specific **desensitization,** *which involves the progressive administration of an allergen to render effector cells less reactive, is reserved for patients with IgE antibodies to a particular drug for whom an alternative drug is not available or appropriate.* Specific protocols for many different drugs have been developed. Desensitization should be performed in a hospital setting, usually in consultation with an allergist and with resuscitation equipment available at all times. Although mild complications, such as pruritus and rash, are fairly common and often respond to adjustments in the drug dose or dosing intervals and medications to relieve symptoms, more severe systemic reactions can occur. Oral desensitization may be less likely to induce anaphylaxis than parenteral administration. Pretreatment with antihistamines or corticosteroids is not usually recommended. It is important to recognize that desensitization to a drug is effective only while the drug continues to be administered and that after a period of interruption or discontinuation, hypersensitivity can recur.

Graded challenges based on the administration of a drug in an incremental fashion until a therapeutic dose is achieved can be attempted with drugs causing non–IgE-mediated reactions, including trimethoprim-sulfamethoxazole. Graded challenges in aspirin- or nonsteroidal antiinflammatory drug (NSAID)–intolerant patients, particularly those with respiratory reactions, can also be performed. Patients with severe non–IgE-mediated hypersensitivity reactions should not receive the predisposing agents even in the small amounts used for skin testing (see Table 152-2).

β-Lactam Hypersensitivity

Penicillin is a frequent cause of anaphylaxis and is responsible for the majority of all drug-mediated anaphylactic deaths in the United States.

Although IgE-mediated reactions may occur after administration of penicillin by any route, parenteral administration is more likely to cause anaphylaxis. If a patient requires penicillin and has a previous history suggestive of penicillin allergy, it is necessary to perform skin tests on the patient for the presence of penicillin-specific IgE, ideally with both the major and minor determinants of penicillin. Skin tests for minor determinants of penicillin are important because approximately 20% of patients with documented anaphylaxis do not demonstrate skin reactivity to the major determinant. The major determinant is commercially available (Pre-Pen). The minor determinant mixture is currently not licensed and is synthesized as a nonstandardized testing reagent at select academic centers. Penicillin G is often used as a substitute for the minor determinant mixture, and may have negative predictive value similar to testing with major and minor determinants. Patients should be referred to an allergist capable of performing appropriate testing. If the skin test response is positive to either major or minor determinants of penicillin, the patient should receive an alternative non–cross-reacting antibiotic. If administration of penicillin is deemed necessary, desensitization can be performed by an allergist in an appropriate medical setting. Skin testing for penicillin-specific IgE is not predictive for delayed-onset cutaneous, bullous, or immune complex reactions. In addition, penicillin skin testing does not appear to resensitize the patient.

Other β-lactam antibiotics, including semisynthetic penicillins, cephalosporins, carbacephems, and carbapenems, share the β-lactam ring structure. Patients with late-onset morbilliform rashes with amoxicillin are not considered to be at risk for IgE-mediated reactions to penicillin and do not require skin testing before penicillin administration. Many patients with Epstein-Barr virus infections treated with ampicillin or amoxicillin can experience a nonpruritic rash. Similar reactions occur in patients who receive allopurinol as treatment for elevated uric acid or have chronic lymphocytic leukemia. If the rash to ampicillin or amoxicillin is urticarial or systemic or the history is unclear, the patient should undergo penicillin skin testing if a penicillin is needed. There have been reports of antibodies specific for semisynthetic penicillin side chains in the absence of β-lactam ring–specific antibodies, although the clinical significance of such side chain–specific antibodies is unclear.

Varying degrees of in vitro cross-reactivity have been documented between cephalosporins and penicillins. Although the risk of allergic reactions to cephalosporins in patients with positive skin test responses to penicillin appears to be low (<2%), anaphylactic reactions have occurred after administration of cephalosporins in patients with a history of penicillin anaphylaxis. If a patient has a history of penicillin allergy and requires a cephalosporin, skin testing for major and minor determinants of penicillin should preferably be performed to determine whether the patient has penicillin-specific IgE antibodies. If skin test results are negative, the patient can receive a cephalosporin with no greater risk than found in the general population. If skin test results are positive for penicillin, recommendations may include: administration of an alternative antibiotic; cautious graded challenge with appropriate monitoring, with the recognition that there is a 2% chance of inducing an anaphylactic reaction; and desensitization to the required cephalosporin. Cross-reactivity is most likely when the cephalosporin shares the same side chain as the penicillin (Table 152-3).

Conversely, patients who require penicillin and have a history of an IgE-mediated reaction to a cephalosporin should also undergo penicillin skin testing. Patients with a negative result can receive penicillin. Patients with a positive result should either receive an alternative medication or undergo desensitization to penicillin. In patients with a history of allergic reaction to one cephalosporin who require another cephalosporin, skin testing with the required cephalosporin can be performed, with the recognition that the negative predictive value of such testing is unknown. If the skin test response to the cephalosporin is positive, the significance of the test should be checked further in control subjects to determine whether the positive response is IgE mediated or an irritant response. The drug can then be administered by graded challenge or desensitization.

Carbapenems (imipenem, meropenem) represent another class of β-lactam antibiotics with a bicyclic nucleus that demonstrate a high degree of cross-reactivity with penicillins, although prospective studies suggest incidence of cross-reactivity on skin testing of approximately 1%. In contrast to β-lactam antibiotics, monobactams (aztreonam) have a monocyclic ring structure. Aztreonam-specific antibodies have been shown to be predominantly side chain–specific; data suggest that aztreonam can be safely administered to most penicillin-allergic subjects. On the other hand, administration of aztreonam to a patient with ceftazidime allergy may be associated with increased risk of allergic reaction owing to similarity of side chains.

Sulfonamides

The most common type of reaction to sulfonamides is a maculopapular eruption often associated with fever that occurs after 7-12 days of therapy. Immediate reactions, including anaphylaxis, as well as other immunologic reactions, have also been suggested. Hypersensitivity reactions to sulfonamides occur with much greater frequency in HIV-infected individuals. For patients in whom maculopapular rashes develop after sulfonamide administration, both graded challenge and desensitization protocols have been shown to be effective. These regimens should not be used in individuals with a history of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Hypersensitivity reactions to sulfasalazine used for treatment of inflammatory bowel disease appear to result from the sulfapyridine moiety. Slow desensitization over ≈1 mo permits tolerance of the drug in many patients. In addition, oral and enema forms of 5-aminosalicylic acid, thought to be the pharmacologically active agent in sulfasalazine, are effective alternative therapies.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Blistering mucocutaneous disorders induced by drugs encompass a spectrum of reactions, including SJS and TEN (see Chapters 654.2 and 654.3). Epidermal detachment of <10% is suggestive of SJS, 30% detachment suggests TEN, and 10-30% detachment suggests overlap of the 2 syndromes. The features of SJS include confluent purpuric macules on face and trunk and severe, explosive mucosal erosions, usually at more than 1 mucosal surface, accompanied by fever and constitutional symptoms. Ocular involvement may be particularly severe, and the liver, kidneys, and lungs may also be involved. TEN, which appears to be related to keratinocyte apoptosis, manifests as

Table 152-3 Groups of β-Lactam Antibiotics That Share Identical R1-Group Side Chains*

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine Cephaloglycin Loracarbef	Cefditoren Ceftizoxime Cefmenoxime			

*Each column represents a group with identical R1 side chains.

From Solensky R, Khan DA: Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol *105:273e1–273e78, 2010 (Table 16, p. 273e49).*

widespread areas of confluent erythema followed by epidermal necrosis and detachment with severe mucosal involvement. The risk of infection and mortality are high. Skin biopsy differentiates subepidermal cleavage characteristic of TEN from intraepidermal cleavage characteristic of the scalded-skin syndrome induced by staphylococcal toxins. TEN must be treated in a burn unit. Corticosteroids are contraindicated because they can significantly increase the risk of infection. High intravenous doses of immunoglobulin have been shown to be beneficial in patients with TEN, likely because of inhibition of Fas-mediated keratinocyte cell death by naturally occurring Fas-blocking antibodies in the intravenous immunoglobulin preparation.

Hypersensitivity to Antiretroviral Agents

A growing number of adverse drug reactions have been observed with antiretroviral agents, including reverse transcriptase inhibitors, protease inhibitors, and fusion inhibitors. Hypersensitivity to abacavir is a well-recognized, multiorgan, potentially life-threatening reaction that occurs in HIV-infected children. The reaction is independent of dose, with onset generally within 9-11 days of initiation of drug therapy. Rechallenge can be accompanied by significant hypotension and potential mortality (rate of 0.03%), and thus hypersensitivity to abacavir is an absolute contraindication for any subsequent use. Prophylaxis with prednisolone does not appear to prevent hypersensitivity reactions to abacavir. Importantly, genetic susceptibility appears to be conferred by the HLA-B*5701 allele, with a positive predictive value of >70% and a negative predictive value of 95-98%. Genetic screening would be cost-effective in white populations but not in populations of African or Asian descent, in which HLA-B*5701 allele frequency is <1%.

Chemotherapeutic Agents

Hypersensitivity reactions to chemotherapeutic drugs have been described, including to monoclonal antibodies. Rapid desensitization to a variety of unrelated agents, including carboplatin, paclitaxel, and rituximab, can be safely achieved in a 12-step protocol. Of note, this approach appears to be successful in both IgE-mediated and non–IgE-mediated reactions.

Biologics

An increasing number of biologic agents have become available for the treatment of autoimmune, allergic, cardiovascular, infectious, and neoplastic diseases. Their use may be associated with a variety of adverse reactions, including hypersensitivity reactions. Given the occurrence of anaphylaxis, including cases with delayed onset and protracted progression in spontaneous postmarketing adverse event reports, the FDA issued a boxed warning regarding risk of anaphylaxis and need for patient monitoring with use of omalizumab (see Chapter 144).

Vaccines

Measles-mumps-rubella vaccine has been shown to be safe in egg-allergic patients (although rare reactions to gelatin or neomycin can occur). The ovalbumin content in influenza vaccine is generally low and the majority of egg-allergic patients tolerate the vaccine. Skin testing with the influenza vaccine is not recommended for egg-allergic patients, but may be helpful if allergy to the vaccine itself is suspected. Egg-allergic patients should be given the injectable, not the live intranasal vaccine and be observed for 30 min after vaccination, in a setting prepared to treat anaphylaxis. For those with egg-allergic reactions resulting in more than urticaria, administration by an allergist is recommended.

Perioperative Agents

Anaphylactoid (non–IgE-mediated anaphylaxis) reactions occurring during general anesthesia may be caused by induction agents (thiopental) or muscle-relaxing agents (succinylcholine, pancuronium). Quaternary ammonium muscle relaxants (succinylcholine) can act as bivalent antigens in IgE-mediated reactions. Negative skin test results do not necessarily predict that a drug will be tolerated. Latex allergy should always be considered in the differential diagnosis of a perioperative reaction.

Local Anesthetics

Adverse drug reactions associated with local anesthetic agents are primarily toxic reactions resulting from rapid drug absorption, inadvertent intravenous injection, or overdose. Local anesthetics are classified as esters of benzoic acid (group I) or amides (group II). Group I includes benzocaine and procaine; group II includes lidocaine, bupivacaine, and mepivacaine. In suspected local anesthetic allergy, skin testing followed by a graded challenge can be performed or an anesthetic agent from a different group can be used.

Insulin

Insulin use has been associated with a spectrum of adverse drug reactions, including local and systemic IgE-mediated reactions, hemolytic anemia, serum sickness reactions, and delayed-type hypersensitivity. In general, human insulin is less allergenic than porcine insulin, which is less allergenic than bovine insulin, but for individual patients, porcine or bovine insulin may be the least allergenic. Patients treated with nonhuman insulin have had systemic reactions to recombinant human insulin even on the first exposure. More than 50% of patients who receive insulin develop antibodies against the insulin preparation, although there may not be any clinical manifestations. Local cutaneous reactions usually do not require treatment and resolve with continued insulin administration, possibly owing to IgG-blocking antibodies. More severe local reactions can be treated with antihistamines or by splitting the insulin dose between separate administration sites. Local reactions to the protamine component of neutral protamine Hagedorn insulin may be avoided by switching to Lente insulin. Immediate-type reactions to insulin, including urticaria and anaphylactic shock, are unusual and almost always occur after reinstitution of insulin therapy in sensitized patients. Insulin therapy should not be interrupted if a systemic reaction to insulin occurs and continued insulin therapy is essential. Skin testing may identify a less-antigenic insulin preparation. The dose following a systemic reaction is usually reduced to one-third, and successive doses are increased in 2-5 unit increments until the dose resulting in glucose control is attained. Insulin skin testing and desensitization are required if insulin treatment is subsequently interrupted for more than 24-48 hr. Immunologic resistance usually occurs when high titers of predominantly IgG antibodies to insulin develop. A rare form of insulin resistance caused by circulating antibodies to tissue insulin receptors is associated with acanthosis nigricans and lipodystrophy. Coexisting insulin allergy may be present in up to a third of patients with insulin resistance. Approximately half of affected patients benefit from substitution with a less-reactive insulin preparation, based on skin testing.

Drug-Induced Hypersensitivity Syndrome

Drug-induced hypersensitivity syndrome, also referred to as DRESS (drug rash with eosinophilia and systemic symptoms) syndrome, is a potentially life-threatening syndrome that has been described primarily with anticonvulsants, although many other medications have been implicated (see Tables 152-1 and 152-2). It is characterized by fever, maculopapular rash, facial edema, eosinophilia, generalized lymphadenopathy, and potentially life-threatening damage of 1 or more organs, usually renal or hepatic. Onset is delayed, usually weeks after initiation of the medication. It has been associated with reactivation of human herpesvirus 6. *Treatment is withdrawal of the medication, systemic steroids, and supportive care, but symptoms can worsen or persist for weeks to months after the drug has been discontinued.*

Red Man Syndrome

Red man syndrome is caused by nonspecific histamine release and is most commonly described with administration of intravenous vancomycin. It can be prevented by slowing the vancomycin infusion rate or by preadministration of H_1-blockers.

Radiocontrast Media

Anaphylactoid reactions to radiocontrast media or dye can occur after intravascular administration and during myelograms or retrograde pyelograms. No single pathogenic mechanism has been defined, but it

is likely that mast cell activation accounts for the majority of these reactions. Complement activation has also been described. There is no evidence that sensitivity to seafood or iodine predisposes to radiocontrast media reactions. Predictive tests are not available. Patients who have atopic profiles, who are using β-blockers, and who have had prior anaphylactoid reactions are at increased risk. Other diagnostic alternatives should be considered, or patients can be given low-osmolality radiocontrast media with a pretreatment regimen including oral prednisone, diphenhydramine, and albuterol, with or without cimetidine or ranitidine.

Narcotic Analgesics

Opiates such as morphine and related narcotics can induce direct mast cell degranulation. Patients may experience generalized pruritus, urticaria, and occasionally, wheezing. If there is a suggestive history and analgesia is required, a nonnarcotic medication should be considered. If this intervention does not control pain, graded challenge with an alternative opiate is an option.

Aspirin and Nonsteroidal Antiinflammatory Drugs

Aspirin and NSAIDs can cause anaphylactoid reactions or urticaria and/or angioedema in children, and, rarely, asthma with or without rhinoconjunctivitis in adolescents. There is no skin or in vitro test to identify patients who may react to aspirin or other NSAIDs. Once aspirin or NSAID intolerance has been established, options include avoidance and pharmacologic desensitization and subsequent continued treatment with aspirin or NSAIDs, if indicated. A number of studies suggest that cyclooxygenase-2 inhibitors are tolerated by the majority of patients with NSAID-induced adverse reactions.

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Rheumatic Diseases of Childhood

PART XVI

Chapter 153

Evaluation of Suspected Rheumatic Disease

C. Egla Rabinovich

Rheumatic diseases are defined by the constellation of results of the physical examination, autoimmune marker and other serologic tests, tissue pathology, and imaging. Defined diagnostic criteria exist for most rheumatic diseases. Recognition of clinical patterns remains essential for diagnosis because there is no single diagnostic test and results may be positive in the absence of disease. Further complicating the diagnosis, children sometimes present with partial criteria that evolve over time or with features of more than one rheumatic disease (**overlap syndromes**). The primary mimics of rheumatic diseases are infection and malignancy but also include metabolic, orthopedic, and chronic pain conditions. Exclusion of possible mimicking disorders is essential before initiation of treatment for a presumptive diagnosis, especially corticosteroids. After careful evaluation has excluded nonrheumatic causes, referral to a pediatric rheumatologist for confirmation of the diagnosis and treatment should be considered.

SYMPTOMS SUGGESTIVE OF RHEUMATIC DISEASE

There are no classic symptoms of a rheumatic disease, but common symptoms include joint pain, fever, fatigue, and rash. Presenting signs and symptoms help direct the evaluation and limit unnecessary testing. Once a differential diagnosis is developed on the basis of history and physical findings, a directed assessment assists in determining the diagnosis.

Arthralgias are common in childhood and are a frequent reason for referral to pediatric rheumatologists. Arthralgias without physical findings for arthritis suggest infection, malignancy, orthopedic conditions, benign syndromes, or pain syndromes such as fibromyalgia (Table 153-1). Although rheumatic diseases may manifest as arthralgias, arthritis is a stronger predictor of the presence of rheumatic disease and a reason for referral to a pediatric rheumatologist. The timing of joint pain along with associated symptoms including poor sleep and interference with normal activities provides important clues. Poor sleep, debilitating generalized joint pain that worsens with activity, school absences, and normal physical and laboratory findings in an adolescent suggest a **pain syndrome** (e.g., fibromyalgia). If arthralgia is accompanied by a history of dry skin, hair loss, fatigue, growth disturbance, and/or cold intolerance, testing for **thyroid disease** is merited. Nighttime awakenings because of severe pain along with decreased platelet count or white blood cell count or, alternatively, a very high white blood cell count, may lead to the diagnosis of malignancy, especially marrow-occupying lesions such as **acute lymphocytic leukemia** and **neuroblastoma**. Pain with physical activity suggests a mechanical problem such as an overuse syndrome or orthopedic condition. An adolescent girl presenting with knee pain aggravated by walking up stairs and on patellar distraction likely has **patellofemoral syndrome**. Children ages 3 to 10 yr who have a history of episodic pain that occurs at night after increased daytime physical activity that is relieved by rubbing, but who have no limp or complaints in the morning, likely have **growing pains**. There is often a positive family history for growing pains, which may aid in this diagnosis. Intermittent pain in a child, especially a girl age 3 to 10 yr, that is increased with activity and is associated with hyperextensible joints on exam is likely **benign hypermobility syndrome**. Many febrile illnesses cause arthralgias that improve when the temperature normalizes, and arthralgias are part of the diagnostic criteria for **acute rheumatic fever** (ARF; see Chapter 183.1).

Arthralgia may also be a presenting symptom of pediatric **systemic lupus erythematosus** (**SLE**) and chronic childhood arthritis such as **juvenile idiopathic arthritis (JIA).** Interestingly, many children with JIA do not complain of joint symptoms at presentation. Other symptoms more suggestive of arthritis include morning stiffness, joint swelling, limited range of motion, pain with joint motion, gait disturbance, fever, and fatigue and/or stiffness after physical inactivity (gelling phenomenon). A diagnosis of chronic juvenile arthritis cannot be made without the finding of arthritis on physical examination (see Chapters 155 and 156), and there are no laboratory tests diagnostic of juvenile rheumatoid arthritis or any other chronic inflammatory arthritis in childhood.

Fatigue is a nonspecific symptom that may point to the presence of a rheumatic disease but is also common in nonrheumatic causes such as viral infections, pain syndromes, depression, and malignancy. Fatigue, rather than the specific complaints of muscle weakness, is a common presenting complaint in **juvenile dermatomyositis (JDM)**. It is also commonly present in SLE, vasculitis, and the chronic childhood arthritides. Overwhelming fatigue with inability to attend school is more suggestive of chronic fatigue syndrome, pediatric fibromyalgia, or other amplified pain syndrome.

SIGNS SUGGESTIVE OF RHEUMATIC DISEASE

A complete physical examination is mandated in any child in whom a rheumatic disease is suspected, because many rheumatic diseases have associated subtle physical findings that will further refine the differential diagnosis. In addition, many rheumatic diseases have multisystem effects, and a stepped assessment should focus on delineating the extent of organ system involvement (e.g., skin, joints, muscle, hepatic, renal, cardiopulmonary).

Presence of a photosensitive malar rash that spares the nasolabial folds is suggestive of SLE (Table 153-2; see Fig. 158-1*A*), especially in an adolescent girl. Diffuse facial rash is more indicative of JDM. A hyperkeratotic rash on the face or around the ears of an adolescent African-American girl may represent discoid lupus (see Fig. 158-1*D*). A palpable purpuric rash on the extensor surfaces of the lower extremities points to **Henoch-Schönlein purpura** (see Fig. 167-1*A*). Less localized purpuric rashes and petechiae are present in systemic vasculitis or blood dyscrasias including coagulopathies. Nonblanching erythematous papules on the palms are seen in vasculitis and SLE. Gottron papules (see Fig. 159-2) and heliotrope rashes (see Fig. 159-1) along with erythematous rashes on the elbows and knees are pathognomonic of JDM. Dilated capillary loops in the nail beds (periungual telangiectasias; see Fig. 159-3) are common in JDM, scleroderma, and secondary Raynaud phenomenon. An evanescent macular rash associated with fever is part of the diagnostic criteria for systemic onset arthritis (see Fig. 155-12). Sun sensitivity or photosensitive rashes are indicative of SLE or JDM but can also be caused by antibiotics.

Mouth ulcers are part of the diagnostic criteria for SLE and Behçet disease (see Fig. 158-1*D*); painless nasal ulcers and erythematous macules on the hard palate are also common in SLE. Cartilage loss in the nose, causing a saddle nose deformity, is classically present in granulomatosis with polyangiitis (formally Wegener granulomatosis; see Fig. 167-4) but is also seen in relapsing polychondritis and syphilis.

Table 153-1 Symptoms Suggestive of Rheumatic Disease

SYMPTOM	RHEUMATIC DISEASE(S)	POSSIBLE NONRHEUMATIC DISEASES CAUSING SIMILAR SYMPTOMS
Fevers	Systemic JIA, SLE, vasculitis, acute rheumatic fever, sarcoidosis, MCTD	Malignancies, infections and post-infectious syndromes, inflammatory bowel disease, periodic fever (autoinflammatory) syndromes, Kawasaki disease, HSP
Arthralgias	JIA, SLE, rheumatic fever, JDM, vasculitis, scleroderma, sarcoidosis	Hypothyroidism, trauma, endocarditis, other infections, pain syndromes, growing pains, malignancies, overuse syndromes
Weakness	JDM, myositis secondary to SLE, MCTD, and deep localized scleroderma	Muscular dystrophies, metabolic and other myopathies, hypothyroidism
Chest pain	Juvenile rheumatoid arthritis, SLE (with associated pericarditis or costochondritis)	Costochondritis (isolated), rib fracture, viral pericarditis, panic attack, hyperventilation
Back pain	Enthesitis related arthritis, juvenile ankylosing spondylitis	Vertebral compression fracture, diskitis, intraspinal tumor, spondylolysis, spondylolisthesis, bone marrow–occupying malignancy, pain syndromes, osteomyelitis, muscle spasm, injury
Fatigue	SLE, JDM, MCTD, vasculitis, JIA	Pain syndromes, chronic infections, chronic fatigue syndrome, depression

HSP, Henoch-Schönlein purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus.

Table 153-2 Signs Suggestive of Rheumatic Disease

SIGN	RHEUMATIC DISEASES	COMMENTS	NONRHEUMATIC CAUSES
Malar rash	SLE, JDM	SLE classically spares nasolabial folds	Sunburn, parvovirus B19 (fifth disease), Kawasaki disease
Oral ulcers	SLE, Behçet disease	Behçet disease also associated with genital ulcers	HSV infection, PFAPA syndrome
Purpuric rash	Vasculitis, e.g., ANCA-associated vasculitis, HSP	HSP typically starts as small lesions on lower extremities and buttocks that coalesce	Meningococcemia, thrombocytopenia, clotting disorders
Gottron papules	JDM	Look for associated heliotrope rash, periungual telangiectasias	Psoriasis, eczema
Arthritis	Juvenile idiopathic arthritis, SLE, vasculitis, HSP, MCTD, scleroderma, acute rheumatic fever, reactive arthritis	Chronic joint swelling (>6 wk) required for diagnosis of chronic arthritis of childhood; MCTD associated with diffuse puffiness of hands	Postviral arthritis, reactive arthritis, trauma, infection, Lyme disease, Kawasaki disease, malignancy, overuse syndromes

ANCA, antineutrophilic cytoplasmic antibody; HSP, Henoch-Schönlein purpura; HSV, herpes simplex virus; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PFAPA, periodic fever, aphthous stomatitis, pharyngitis and adenitis; SLE, systemic lupus erythematosus.

Alopecia can be associated with SLE but is also found in localized scleroderma (see Fig. 160-4) and JDM. **Raynaud phenomenon** may be a primary benign idiopathic disorder or can be a presenting complaint in the child with scleroderma, lupus, mixed connective tissue disease (MCTD), or an overlap syndrome. Diffuse lymphadenopathy is present in many rheumatic diseases, including SLE, polyarticular JIA, and systemic JIA. Irregular pupils may represent the insidious and unrecognized onset of uveitis associated with juvenile arthritis. Erythematous conjunctiva may be a result of uveitis or episcleritis associated with juvenile rheumatoid arthritis, SLE, sarcoidosis, spondyloarthropathies, or vasculitis.

A pericardial rub and orthopnea are suggestive of pericarditis, often seen in systemic JIA, SLE, and sarcoid. Coronary artery dilation is strongly suggestive of Kawasaki disease but may also be a finding in systemic arthritis and other forms of systemic vasculitis. Interstitial lung disease, suggested by dyspnea on exertion or the finding of basilar rales with decreased carbon monoxide diffusion capacity, occurs in SLE, MCTD, and systemic sclerosis. Signs consistent with pulmonary hemorrhage points to Wegener granulomatosis, microscopic angiitis, or SLE. Pulmonary vascular aneurysms are indicative of Behçet disease.

Arthritis is defined by the presence of intraarticular swelling or 2 or more of the following findings on joint examination: pain on motion, loss of motion, erythema, and heat. Arthritis is present in all of the chronic childhood arthritis syndromes, along with SLE, JDM, vasculitis, Behçet disease, sarcoidosis, Kawasaki disease, and Henoch-Schönlein purpura. Nonrheumatic causes of arthritis include malignancy, infections such as septic arthritis, Lyme disease, osteomyelitis, viral infections (such as rubella, hepatitis B, parvovirus B19), and postinfectious etiologies such as Epstein-Barr virus, ARF, and reactive arthritis. ARF typically involves a migratory (lasting hours to days), painful arthritis. Pain on palpation of long bones is suggestive of malignancy. Specific muscle testing for weakness should be performed in a child presenting with fatigue or difficulty with daily tasks, as both of these symptoms may be manifestations of muscle inflammation.

LABORATORY TESTING

There are no specific screening tests for rheumatologic disease. Once a differential diagnosis is determined, appropriate testing can be performed (Tables 153-3 and 153-4). Initial studies are generally performed in standard local laboratories. Screening for specific autoantibodies can be performed in commercial laboratories, but confirmation of results in a tertiary care center immunology laboratory is often necessary.

One essential laboratory test for rheumatic disease assessment is the complete blood count, as it yields many diagnostic clues. Elevated white blood cell count is compatible with malignancy, infection, systemic JIA, and vasculitis. Leukopenia can be caused by postinfectious, especially viral, etiologies, SLE, or malignancy. Lymphopenia is more specific for SLE than is leukopenia. Platelets are acute-phase reactants and are therefore elevated with inflammatory markers. Exceptions are a bone marrow–occupying malignancy, such as leukemia or neuroblastoma, SLE, and early Kawasaki disease. Anemia is nonspecific and may

Table 153-3 Autoantibody Specificity and Disease Associations

ANTIBODY	DISEASE	PREVALENCE (%)	SPECIFICITY
Antinuclear antibody (ANA)	SLE, juvenile rheumatoid arthritis, dermatomyositis, scleroderma, psoriatic arthritis, MCTD	—	Associated with increased risk of uveitis in JIA and psoriatic arthritis Up to 30% of children testing positive for ANAs have no underlying rheumatic disease
Double-stranded DNA (dsDNA)	SLE	60-70	High specificity for SLE; associated with lupus nephritis
Smith (Sm)	SLE	20-30	Highly specific for SLE; associated with lupus nephritis
Smooth muscle (Sm)	Autoimmune hepatitis	—	—
Pm-Scl (polymyositis-scleroderma)	Sclerodermatomyositis	—	—
SSA (Ro)	SLE, Sjögren syndrome	25-30	Associated with neonatal lupus syndrome, subacute cutaneous lupus, thrombocytopenia
SSB (La)	SLE, Sjögren syndrome	25-30	Usually coexists with anti-SSA antibody
Ribonuclease protein (RNP)	MCTD, SLE	30-40	Suggestive of MCTD unless meets criteria for SLE
Histone	Drug-induced lupus, SLE	—	—
Centromere	Limited cutaneous systemic sclerosis	70	Nonspecific for systemic sclerosis
Topoisomerase I (Scl-70)	Systemic sclerosis	—	Rare in childhood
Antineutrophil cytoplasmic antibodies (ANCAs)	Vasculitis	—	—
Cytoplasmic (cANCAs)/ PR3-ANCA		—	cANCAs associated with granulomatosis with polyangiitis (Wegener), cystic fibrosis
Perinuclear (pANCAs)/ MPO-ANCA		—	pANCAs associated with microscopic polyangiitis, polyarteritis nodosa, SLE, inflammatory bowel disease, cystic fibrosis, primary sclerosing cholangitis, Henoch-Schönlein purpura, Kawasaki disease, Churg-Strauss syndrome
Anticitrullinated protein (ACPA) also called anti-cyclic citrullinated protein (anti-CCP)	RF positive JIA	50-90	Specific for JIA (RF+), may be positive before RF

MCTD, mixed connective tissue disease; MPO-ANCA, antimyeloperoxidase; PR3-ANCA, antiproteinase 3; RF, rheumatoid factor; SLE, systemic lupus erythematosus.
Modified from Aggerwal A: Clinical application of tests used in rheumatology, Indian J Pediatr *69:889–892, 2002.*

be caused by any chronic illness, but hemolytic anemia (positive Coombs test result) may point to SLE or MCTD. Rheumatoid factor is present in less than 10% of children with JIA and thus has poor sensitivity as a diagnostic tool; it may be elevated by infections such as endocarditis, tuberculosis, syphilis, viral infections (parvovirus B19, hepatitides B and C, mycoplasma) as well as primary biliary cirrhosis and malignancies. In a child with chronic arthritis, rheumatoid factor serves as a prognostic indicator.

Inflammatory markers (erythrocyte sedimentation rate, C-reactive protein level) are nonspecific and are elevated in infections and malignancies as well as rheumatic diseases. Their levels may also be normal in rheumatic diseases such as arthritis, scleroderma, and dermatomyositis. Inflammatory marker measurements are more useful in rheumatic diseases for following response to treatment than as diagnostic tests. Muscle enzymes include aspartate aminotransferase, alanine aminotransferase, creatinine phosphokinase, aldolase, and lactate dehydrogenase, any of which may be elevated in JDM as well as in other diseases causing muscle breakdown. Muscle-building supplements, medications, and extreme physical activity may also cause muscle breakdown and enzyme elevations. Aspartate aminotransferase, alanine aminotransferase, and aldolase are also elevated secondary to liver disease, and a γ-glutamyltransferase measurement may help differentiate whether the source is muscle or liver.

The use of an antinuclear antibody (ANA) measurement as a screening test is not recommended, as it has low specificity. A positive ANA test result may be induced by infection, especially Epstein-Barr virus infection, endocarditis, and parvovirus B19 infection. The ANA test result is also positive in up to 30% of normal children and the level of ANA is increased in those with a 1st-degree relative with a known rheumatic disease. In the majority of children with a positive ANA test result without signs of a rheumatic disease on initial evaluation, autoimmune disease does not develop disease over time, so this finding does not necessitate referral to a pediatric rheumatologist. A positive ANA test result is found in many rheumatic diseases, including JIA, in which it serves as a predictor of the risk for inflammatory eye disease. Once a positive ANA test result is discovered in a child, the need for specific autoantibody testing is directed by the presence of clinical signs and symptoms (see Table 153-3).

IMAGING STUDIES

Plain radiographs are useful in evaluation of arthralgias and arthritis, as they offer reassurance in benign pain syndromes and their findings are often abnormal in malignancies, osteomyelitis, and long-standing chronic juvenile arthritis. Radionucleotide bone scans help localize areas of abnormality in the patient with diffuse pains caused by osteomyelitis, neuroblastoma, chronic multifocal osteomyelitis, and systemic arthritis. MRI findings are abnormal in inflammatory myositis and suggest the optimal site for biopsy. MRI is more sensitive than plain radiographs in detecting the presence of early erosive arthritis and demonstrates increased joint fluid, synovial enhancement, and sequela of trauma with internal joint derangement. Cardiopulmonary evaluation is suggested for diseases commonly affecting the heart and

Table 153-4 Evaluation Based on Suspected Diagnosis

SUSPECTED RHEUMATIC DISEASE(S)	INITIAL EVALUATION	FURTHER EVALUATION	SUBSPECIALTY EVALUATION
SLE, MCTD	CBC, ESR, ANA, ALT, AST, CPK, creatinine, albumin, total protein, urinalysis, BP, thyroid profile	If ANA test result is positive: anti–SSA (Ro), anti–SSB (La), anti-Smith, and anti-RNP Abs; anti-dsDNA Ab, C3, C4, Coombs, spot urine protein/creatinine ratio, CXR	Antiphospholipid Abs, lupus anticoagulant, anti–β_2-glycoprotein, echocardiogram; consider renal biopsy, PFTs, bronchoscopy with lavage, HRCT of chest; consider lung biopsy
JDM	CBC, CPK, ALT, AST, LDH, aldolase, ANA; check gag reflex	Consider MRI of muscle	Consider electromyography and possible muscle biopsy, PFTs, swallowing study, serum neopterin
JIA	CBC, ESR, creatinine, ALT, AST, consider anti–streptolysin O/anti–DNAase B for streptococcus-induced arthritis, Epstein-Barr virus titers, Lyme titer, parvovirus B19 titer, plain radiograph of joints	Consider Ab titers to unusual infectious agents, purified protein derivative, RF, ANA, HLA-B27, anti-CCP	MRI
Granulomatosis with polyangiitis (Wegener granulomatosis)	CBC, ANCA, AST, ALT, albumin, creatinine, ESR, urinalysis, CXR, BP	Spot urine protein/creatinine ratio, anti–myeloperoxidase and anti–proteinase-3 Abs, PFTs	Bronchoscopy with lavage, HRCT chest; consider lung and kidney biopsies
Sarcoidosis	CBC, electrolytes, AST, ALT, albumin, creatinine, calcium, phosphorous, ACE, BP	CXR, PFTs	Consider testing for Blau syndrome in infants (see Chapter 159); HRCT of chest; consider renal and lung biopsy
Localized scleroderma	Skin biopsy, CBC, ESR		Serum immunoglobulin G, ANA, RF, single-stranded DNA Ab, antihistone Ab, CPK
Systemic scleroderma	ANA, CBC, ESR, BP, AST, ALT, CPK, creatinine, CXR	Anti-Scl70, PFTs	HRCT of chest, echocardiogram, upper gastrointestinal radiography series

Ab, antibody; ACE, angiotensin-converting enzyme (normally elevated in childhood; interpret with caution); ALT, alanine aminotransferase; ANA, antinuclear antibody; anti-dsDNA Ab, anti–double stranded DNA antibody; AST, aspartate aminotransferase; BP, blood pressure; CBCD, complete blood count with differential; CCP, cyclic citrullinated protein; CPK, creatine phosphokinase; CXR, chest radiograph; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; HRCT, high-resolution CT; LDH, lactate dehydrogenase; PFTs, pulmonary function tests; RF, rheumatoid factor.

lung, including SLE, systemic scleroderma, MCTD, JDM, and sarcoid, as clinical manifestations may be subtle. This evaluation, which may include echocardiogram, pulmonary function tests, and high-resolution CT of the lungs along with consideration of bronchoalveolar lavage, is generally performed by a pediatric rheumatologist to whom the patient is referred (see Table 153-4).

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Chapter 154

Treatment of Rheumatic Diseases

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Nonpharmacologic as well as pharmacologic interventions are often necessary to meet the desired goals of disease management. Optimal disease management requires family-centered care delivered by a multidisciplinary team of healthcare professionals providing medical, psychological, social, and school support. Rheumatologic conditions most often follow a course marked by flares and periods of remission, although some children have unremitting disease. The goals of treatment are to control disease, relieve discomfort, avoid or limit drug toxicity, prevent or reduce organ damage, and maximize the physical function and quality of life of affected children. Nonpharmacologic therapy is an important adjunct to medical management of rheumatic diseases. A key predictor of long-term outcome consists of early recognition and referral to a rheumatology team experienced in the specialized care of children with rheumatic diseases. Significant differences in outcome are seen 10 yr after disease onset in patients with juvenile idiopathic arthritis (JIA) depending on whether referral to a pediatric rheumatology center was accomplished within 6 mo of onset.

PEDIATRIC RHEUMATOLOGY TEAMS AND PRIMARY CARE PHYSICIANS

The **multidisciplinary pediatric rheumatology team** (Table 154-1) offers coordinated services for children and their families. General principles of treatment include: early recognition of signs and symptoms of rheumatic disease with timely referral to rheumatology for prompt initiation of treatment; monitoring for disease complications and adverse effects of treatment; coordination of subspecialty care and rehabilitation services with communication of clinical information; and child- and family-centered chronic illness care, including self-management support, alliance with community resources, partnership with schools, resources for dealing with the financial burdens of disease, and connection with advocacy groups. Planning for transition to adult care providers needs to start in adolescence. Central to effective care is partnership with the primary care provider, who helps coordinate care, monitor compliance with treatment plans, ensure appropriate immunization, monitor for medication toxicities, and

Table 154-1 Multidisciplinary Treatment of Rheumatic Diseases in Childhood

Accurate diagnosis and education of family	Pediatric rheumatologist Pediatrician Nurse: • Disease-related education • Medication administration (injection teaching) • Safety monitoring Social worker: • Facilitation of school services • Resource identification (community, government, financial, advocacy groups, vocational rehabilitation)
Physical medicine and rehabilitation	Physical therapy: • Addressing deficits in joint or muscle mobility, limb length discrepancies, gait abnormalities, weakness Occupational therapy: • Splinting to reduce joint contractures/deformities and lessen stress on joints; adaptive devices for activities of daily living
Consultant team	Ophthalmology: • Eye screening for uveitis (see Table 155-4) • Screening for medication-related ocular toxicity (hydroxychloroquine, glucocorticoids) Nephrology Orthopedics Dermatology Gastroenterology
Physical and psychosocial growth and development	Nutrition: • Addressing undernourishment from systemic illness, obesity/overnourishment from glucocorticoids School integration: • Individualized Educational Plan (IEP) or 504 plan Peer group relationships Individual and/or family counseling
Coordination of care	Involvement of patient and family as active team members Communication among healthcare providers Involvement of school (school nurse) and community (social worker) resources

identify disease exacerbations and concomitant infections. Communication between the primary care provider and subspecialty team permits timely intervention when needed.

THERAPEUTICS

A key principle of pharmacologic management of rheumatic diseases is that early disease control, striving for induction of remission, leads to less tissue and organ damage with improved short- and long-term outcomes. Medications are chosen from broad therapeutic classes on the basis of diagnosis, disease severity, anthropometrics, and adverse effect profile. Many drug therapies used do not have U.S. Food and Drug Administration (FDA) indications for pediatric rheumatic diseases given the relative rarity of these conditions. The evidence base may be limited to case series, uncontrolled studies, or extrapolation from use in adults. The exception is JIA, for which there is a growing body of randomized control trial evidence, particularly for newer therapeutics. Therapeutic agents used for treatment of childhood rheumatic diseases (Table 154-2) have various mechanisms of action, but all suppress inflammation. **Both biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) directly affect the immune system**. DMARDs should be prescribed by specialists. Live vaccines are contraindicated in patients taking immunosuppressive glucocorticoids or DMARDs. A negative test result for tuberculosis (purified protein derivative and/or QuantiFERON-TB Gold) should be verified and the patient's immunization status updated, if possible, before such treatment is initiated. Killed vaccines are not contraindicated, and annual injectable influenza vaccine is recommended.

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are prescribed to decrease both the pain and acute and chronic inflammation associated with arthritis, pleuritis, pericarditis, uveitis, and cutaneous vasculitis, but they are not disease modifying. NSAID antiinflammatory effects require regular administration at adequate doses based on weight (mg/kg) or body surface area (mg/m^2), for longer periods than needed for analgesia alone. The mean time to achieve antiinflammatory effect in JIA is 4-6 wk of consistent administration. NSAIDs work primarily by inhibiting the enzyme **cyclooxygenase (COX),** which is critical in the production of **prostaglandins,** a family of substances that promote inflammation. Two types of COX receptors have been demonstrated; **selective COX-2 inhibitors** (such as celecoxib and meloxicam) inhibit receptors responsible for promoting inflammation with potential for fewer gastrointestinal (GI) adverse effects. Clinical trials in children with JIA found celecoxib and meloxicam to be similar, in effectiveness and tolerability, to the nonselective NSAID naproxen.

The most frequent adverse effects of NSAIDs in children are nausea, decreased appetite, and abdominal pain. Gastritis or ulceration occurs less frequently in children. Less-common adverse effects, occurring in ≤5% of children undergoing long-term NSAID therapy, include mood change, concentration difficulty that can simulate attention deficit disorder, sleepiness, irritability, headache, tinnitus, alopecia, anemia, elevated liver enzyme values, proteinuria, and hematuria. Certain agents (indomethacin) have a higher risk of toxicity than others (ibuprofen); naproxen has an intermediate risk. These NSAID-associated adverse effects reverse quickly once the medication is stopped. Additional rare NSAID-specific adverse reactions may also occur. Aseptic meningitis has been associated with ibuprofen, primarily in patients with lupus. Naproxen is more likely than other NSAIDs to cause a unique skin reaction called **pseudoporphyria,** which is characterized by small hypopigmented depressed scars occurring in areas of minor skin trauma, such as fingernail scratches. Pseudoporphyria is more likely to occur in fair-skinned individuals and on sun-exposed areas. If pseudoporphyria develops, the inciting NSAID should be discontinued because scars can persist for years or be permanent. NSAIDs should be used cautiously in patients with dermatomyositis or systemic vasculitis because of an increased frequency of GI ulceration with these disorders. *Salicylates have been supplanted by other NSAIDs owing to the relative frequency of salicylate hepatotoxicity and the association with Reye syndrome.*

The response to NSAIDs varies greatly among individual patients, but overall, 40-60% of children with JIA experience improvement in their arthritis with NSAID therapy. Patients may try several different NSAIDs for 6-wk trials before finding one that demonstrates clinical benefit. NSAIDs with longer half-lives or sustained-release formulations allow for once- or twice-daily dosing and improve compliance. Laboratory monitoring for toxicity includes a complete blood count (CBC), serum creatinine, liver function tests (LFTs), and urinalysis every 6-12 mo, though guidelines for frequency of testing are not established.

Nonbiologic Disease-Modifying Antirheumatic Drugs

Methotrexate

Methotrexate (MTX), an antimetabolite, is a cornerstone of therapy in pediatric rheumatology because of its sustained effectiveness and relative low toxicity over prolonged periods of treatment. The mechanism of action low-dose MTX in arthritis is complex but is believed

Table 154-2 Therapeutics for Childhood Rheumatic Diseases*

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Nonsteroidal antiinflammatory drugs (NSAIDs)‡	Etodolac[a]	PO once-daily dose: 20-30 kg: 400 mg 31-45 kg: 600 mg 46-60 kg: 800 mg >60 kg: 1,000 mg	JIA Spondyloarthropathy Pain Serositis Cutaneous vasculitis Uveitis	GI intolerance (abdominal pain, nausea), gastritis, hepatitis, tinnitus, anemia, pseudoporphyria, aseptic meningitis, headache, renal disease	CBC, LFTs, BUN/creatinine, urinalysis at baseline, then every 6-12 mo
	Ibuprofen[a]	40 mg/kg/day PO divided 3 times daily Max 2400 mg per day			
	Naproxen[a]	15 mg/kg/day PO in 2 divided doses Maximum 1,000 mg per day			
	Celecoxib[a]	10-25 kg: 50 mg PO twice daily >25 kg: 100 mg PO twice daily			
	Meloxicam[a]	0.125 mg/kg, maximum 7.5 mg, PO once daily			
Disease modifying antirheumatic drugs (DMARDs)	Methotrexate[a]	10-20 mg/m^2/wk (0.35-0.65 mg/kg/wk) PO 20-30 mg/m^2/wk (0.65-1 mg/kg/wk) SC; higher doses better absorbed by SC injection	JIA Uveitis	GI intolerance (nausea, vomiting), hepatitis, myelosuppression, mucositis, teratogenesis, lymphoma, interstitial pneumonitis	CBC, LFTs at baseline, monthly × 3, then every 8-12 wk
	Leflunomide	PO once daily: 10 to <20 kg: 10 mg 20-40 kg: 15 mg >40 kg: 20 mg	JIA	hepatitis, hepatic necrosis, cytopenias, mucositis, teratogenesis, peripheral neuropathy	CBC, LFTs, at baseline, monthly × 6, then every 8-12 wk
	Hydroxychloroquine	5-6 mg/kg PO once daily; do not exceed 6.5 mg/kg/daily Maximum dose 400 mg daily	SLE JDMS Antiphospholipid antibody syndrome	Retinal toxicity, GI intolerance, rash, skin discoloration, anemia, cytopenias, myopathy, CNS stimulation, death (overdose)	Ophthalmologic screening every 6-12 mo
	Sulfasalazine[a]	30-50 mg/kg/day divided in twice-daily doses Adult maximum 3 g/day	Spondyloarthropathy, JIA	GI intolerance, rash, hypersensitivity reactions, Stevens-Johnson syndrome, cytopenias, hepatitis, headache	CBC, LFTs, BUN/creatinine, urinalysis at baseline, every other wk × 3 mo, monthly × 3, then every 3 mo
Tumor necrosis factor α (TNF-α) antagonists	Adalimumab[a]	SC once every other wk: 15 to <30 kg: 20 mg ≥30 kg: 40 mg	JIA, spondyloarthropathy, psoriatic arthritis, uveitis	Injection site reaction, infection, rash, cytopenias, lupus-like syndrome, potential increased malignancy risk	TB test; anti-dsDNA, CBC
	Etanercept[a]	0.8 mg/kg SC once weekly (maximum 50 mg/dose) or 0.4 mg/kg SC twice weekly (maximum 25 mg/dose)	JIA	Injection site reactions, infections, rash, demyelinating disorders, cytopenias, potential increased malignancy risk	TB test; CBC
	Infliximab	5-10 mg/kg IV q4-8wk	JIA Spondyloarthropathy Uveitis Sarcoidosis	Infusion reactions, hepatitis, potential increased malignancy risk	TB test; anti-dsDNA, LFTs

*Consult a clinical pharmacology reference for current dosing and monitoring guidelines, and complete list of known adverse effects.

Continued

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Modulate T-cell activation	Abatacept[a]	IV every 2 wk × 3 doses, then monthly for ≥6 yr of age: <75 kg: 10 mg/kg 75-100 kg: 750 mg >100 kg: 1,000 mg	JIA	Infection, headache, potential increased malignancy risk	
Anti-CD20 (B cell) antibody	Rituximab	575 mg/m^2, maximum 1,000 mg, IV on days 1 and 15	SLE	Infusion reactions, lymphopenia, reactivation hepatitis B, rash, serum sickness, arthritis, PML	CBC, BMP; consider monitoring quantitative IgG
Anti-BLyS antibody	Belimumab[e]	10 mg/kg IV every 2 wk × 3 doses, then every 4 wk	SLE	Infusion reactions, infection, depression	
Interleukin 1 antagonist	Anakinra	1-2 mg/kg/daily Adult maximum 100 mg	Systemic JIA CAPS	Injection site reactions, infection	CBC
	Canakinumab[b]	Given SC every 8 wk (CAPS) every 4 wk (Systemic JIA): 15-40 kg: 2 mg/kg (up to 3 mg/kg if needed) >40 kg: 150 mg	CAPS Systemic JIA	Injection site reaction, infection, diarrhea, nausea, vertigo, headache	
Interleukin-6 antagonist	Tocilizumab[a]	≥2 yr and ≥30 kg, 8 mg/kg/dose every 2 wk; ≥2 yr and ≤30 kg, 12 mg/kg/dose every 2 wk	Systemic JIA	Infusion reactions, elevated LFTs, elevated lipids, thrombocytopenia, infections	CBC, LFTs, platelet count, serum lipid profile
Intravenous immunoglobulin	IVIG[c]	1,000-2,000 mg/kg IV infusion For JDMS, give monthly	Kawasaki disease JDMS SLE	Infusion reaction, aseptic meningitis, renal failure	Serum creatinine, BUN, IgG level
Cytotoxic	Cyclophosphamide	0.5-1 g/m^2 IV (maximum 1.5 g) monthly for 6-mo induction, then every 2-3 mo Oral regimen: 1-2 mg/kg/daily; maximum 150 mg/daily	SLE Vasculitis JDMS Pulmonary hemorrhage	Nausea, vomiting, myelosuppression, mucositis, hyponatremia, alopecia, hemorrhagic cystitis, gonadal failure, teratogenesis, secondary malignancy	CBC
Immunosuppressive	Mycophenolate mofetil	Oral suspension: maximum 1,200 mg/m^2/day PO (up to 2 g/day) divided twice daily Capsules: maximum 1,500 mg/day PO for BSA 1.25-1.5 m^2, 2 g/day PO for BSA >1.5 m^2 divided twice daily	SLE Uveitis	GI intolerance (diarrhea, nausea, vomiting), renal impairment, neutropenia, teratogenesis, secondary malignancy, PML	CBC, BMP

Table 154-2 Therapeutics for Childhood Rheumatic Diseases—cont'd

CLASSIFICATION	THERAPEUTIC†	DOSE	INDICATION†	ADVERSE REACTIONS	MONITORING
Glucocorticoids	Prednisone[a,d-f]	0.05-2 mg/kg/day PO given in 1-4 divided doses; maximum varies by individual (80 mg/daily) Adverse effects are dose dependent; lowest effective dose should be used	SLE JDMS Vasculitis JIA Uveitis Sarcoidosis	Cushing syndrome, osteoporosis, increased appetite, weight gain, striae, hypertension, adrenal suppression, hyperglycemia, infection, avascular necrosis	Blood glucose, potassium Blood pressure
	Methylprednisolone[a,d-g]	0.5-1.7 mg/kg/day or 5-25 mg/m^2/day IM/IV in divided doses q6-12h For severe manifestations: 30 mg/kg/dose (maximum 1 g) daily for 1-5 days	SLE JDMS Vasculitis Sarcoidosis Localized scleroderma		
	Intraarticular	Dose varies by joint and formulation	JIA	Subcutaneous atrophy, skin hypopigmentation, calcification, infection	
	Prednisolone ophthalmic suspension	1-2 drops into eye up to every hr while awake Needs monitoring by ophthalmologist	Uveitis	Ocular hypertension, glaucoma, nerve damage, cataract, infection	Ophthalmologic exam

Blys, B-lymphocyte stimulator; BMP, basic metabolic panel; BSA, body surface area; BUN, blood urea nitrogen; CAPS, cryopyrin-associated periodic syndrome; CBC, complete blood count; CNS, central nervous system; dsDNA, double-stranded DNA; GI, gastrointestinal; Ig, immunoglobulin; IM, intramuscular(ly); IV, intravenous(ly); IVIG, intravenous immunoglobulin; JDMS, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; LFTs, liver function tests; PML, progressive multifocal leukoencephalopathy; PO, by mouth; SC, subcutaneous(ly); SLE, systemic lupus erythematosus; TB, tuberculosis.

†Therapeutics used in practice may not have a FDA-approved indication. Individual therapeutics annotated with FDA-approved indication as follows: a, JIA; b, CAPS; c, Kawasaki disease; d, sarcoidosis; e, SLE; f, uveitis; g, dermatomyositis.

‡Many more products available in this class.

to result from the inhibition of folate-dependent processes by MTX polyglutamates, primarily their effect on the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leading to an increase of extracellular adenosine and consequently, cyclic adenosine monophosphate, which inhibits the production of proinflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-1β and their downstream effects on lymphocyte activation and proliferation.

MTX has a central role in the treatment of arthritis, especially in children with polyarticular JIA. The response to oral MTX (10 mg/m^2 once a week) is better than the response to placebo (63% vs. 36%). Children who show no response to standard doses of MTX often do show response to higher doses (15 or 30 mg/m^2/wk). Subcutaneous administration of MTX is similar in absorption and pharmacokinetic properties to intramuscular injection, with less pain. MTX is commonly used in treatment of juvenile dermatomyositis as a steroid-sparing agent, with efficacy in 70% of patients. It has also been used successfully at a dosage of 10-20 mg/m^2/wk in patients with systemic lupus erythematosus (SLE) to treat arthritis, serositis, and rash.

Because of the lower dose used in treating rheumatic diseases, MTX is well tolerated by children with toxicity being milder and qualitatively different from that observed with treatment of neoplasms. In 8 published studies including 288 patients with JIA taking MTX, adverse effects included elevated liver enzyme values (15%), GI toxicity (13%), stomatitis (3%), headache (1-2%), and leukopenia, interstitial pneumonitis, rash, and alopecia (<1%). Hepatotoxicity observed among adults with rheumatoid arthritis treated with MTX has raised concern about similar problems in children. Analysis of liver biopsy specimens in children with JIA undergoing long-term MTX treatment has revealed occasional mild fibrosis and no evidence of even moderate liver damage. Children receiving MTX should be counseled to avoid alcohol, smoking, and pregnancy. *Folic acid* 1 mg daily is given as an adjunct to minimize adverse effects. Lymphoproliferative disorders have been reported in adults treated with MTX, primarily in association with Epstein-Barr virus infection. Regression of lymphoma may follow withdrawal of MTX.

Monitoring laboratory tests for MTX toxicity include CBC and LFTs at regular intervals, initially every 4 wk for the 1st 3 mo of treatment, then every 8-12 wk, with more frequent intervals after dosing adjustments or in response to abnormal values.

Hydroxychloroquine

Hydroxychloroquine sulfate is an antimalarial drug important in the treatment of SLE and dermatomyositis, particularly cutaneous manifestations of disease and to reduce lupus flares. It is not indicated to treat JIA because of lack of efficacy. The most significant potential adverse effect is retinal toxicity, which occurs rarely but results in irreversible color blindness or loss of central vision. Complete ophthalmologic examinations, including assessment of peripheral vision and color fields, are conducted at baseline and every 6-12 mo to screen for retinal toxicity. Retinal toxicity is rare (1/5,000 patients) and is associated with weight-based dosing exceeding 6.5 mg/kg/day; therefore, recommended dosing is <6.5 mg/kg/day not to exceed 400 mg/day. Other potential adverse effects include rash, skin discoloration, gastric irritation, bone marrow suppression, central nervous system stimulation, and myositis.

Leflunomide

Leflunomide is a DMARD approved for treatment of rheumatoid arthritis that offers an alternative to MTX for treatment of JIA. MTX outperformed leflunomide for treatment of JIA in a randomized trial (at 16 wk, 89% of patients receiving MTX achieved a 30% response rate vs. 68% of those receiving leflunomide), although both drugs were effective. Dosing is oral, once daily, and weight based: 10 mg for children 10 to <20 kg, 15 mg for children 20-40 kg, and 20 mg for children >40 kg. Adverse reactions include paresthesias and peripheral neuropathy, GI intolerance, elevated liver transaminases and hepatic failure, cytopenias, alopecia, and teratogenesis. Leflunomide has a long half-life, and in cases in which discontinuation of the agent is required, a drug elimination protocol with *cholestyramine* may be indicated. Avoidance of pregnancy is essential. Monitoring laboratory tests include CBC, LFTs, every 4 wk for the 1st 6 mo of treatment, then every 8-12 wk.

Sulfasalazine

Sulfasalazine is used to treat children with polyarticular JIA oligoarticular JIA, and the peripheral arthritis and enthesitis associated with juvenile ankylosing spondylitis. In JIA, sulfasalazine 50 mg/kg/day (adult maximum: 3,000 mg/day) achieves greater improvement in joint inflammation, global assessment parameters, and laboratory parameters than placebo. More than 30% of sulfasalazine-treated patients withdraw from the treatment because of adverse effects, primarily GI irritation and skin rashes. Sulfasalazine is associated with severe systemic hypersensitivity reactions, including Stevens-Johnson syndrome. Sulfasalazine is generally considered contraindicated in children with active systemic JIA because of increased hypersensitivity reactions. Sulfasalazine should not be used in patients with sulfa or salicylate hypersensitivity or porphyria.

Monitoring laboratory tests for sulfasalazine toxicity include CBC, LFTs, serum creatinine/blood urea nitrogen (BUN), and urinalysis, every other week for the 1st 3 mo of treatment, monthly for 3 mo, every 3 mo for 1 yr, then every 6 mo.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug approved by the FDA for organ transplant rejection. In rheumatology, MMF is used primarily for treatment of lupus, uveitis, and autoimmune skin manifestations. In adult clinical trials, MMF was noninferior to cyclophosphamide for induction therapy of lupus nephritis, with a potential for less-adverse effects (infection, gonadal toxicity). Dosing is based on body surface area: 600 mg/m^2 orally twice daily, with maximum dosage limits varying by formulation and body surface area. The most common adverse reaction is GI intolerance. Infections, cytopenias, and secondary malignancies are among other adverse reactions reported.

Glucocorticoids

Glucocorticoids are given through oral, intravenous, ocular, topical, and intraarticular administration as part of treatment of rheumatic disease. Oral steroids are foundational treatment for moderate to severe lupus, dermatomyositis, and most forms of vasculitis; their long-term use is associated with a long list of well-described, dose-dependent complications, including linear growth suppression, Cushingoid features, osteoporosis, avascular necrosis, hypertension, impaired glucose tolerance, mood disturbance, and increased infection risk. Glucocorticoids should be tapered to the lowest effective dose over time, and DMARDs introduced as **steroid-sparing agents.**

Intravenous steroids have been used to treat severe, acute manifestations of systemic rheumatic diseases such as SLE, dermatomyositis, and vasculitis. The intravenous route allows for higher doses to obtain an immediate, profound antiinflammatory effect. **Methylprednisolone,** 10-30 mg/kg/dose up to a maximum of 1 g, given over 1 hr daily for 1-5 days, is the intravenous preparation of choice. Although generally associated with fewer adverse effects than oral steroids, intravenously administered steroids are associated with significant and occasionally life-threatening toxicities, such as cardiac arrhythmia, acute hypertension, hypotension, hyperglycemia, shock, pancreatitis, and avascular necrosis.

Ocular steroids are prescribed by ophthalmologists as ophthalmologic drops or injections into the soft tissue surrounding the globe (sub–Tenon capsule injection) for active uveitis. Long-term ocular steroid use leads to cataract formation and glaucoma. Current ophthalmologic management has significantly decreased the frequency of blindness as a complication of JIA-associated uveitis.

Intraarticular steroids are being used with increasing frequency as initial therapy for children with oligoarticular JIA or as bridge therapy while awaiting efficacy of a DMARD in polyarticular disease. Most patients have significant clinical improvement within 3 days. Duration of response depends on steroid preparation used, joint affected, and arthritis subtype, with the anticipated response rate to knee injection being between 60% and 80% at 6 mo. Intraarticular administration may result in subcutaneous atrophy and hypopigmentation of the skin at the injection site, as well as subcutaneous calcifications along the needle track.

Biologic Agents

Biologic agents are proteins that have been engineered to target and modulate specific components of the immune system with the goal of decreasing the inflammatory response. Antibodies have been developed to target specific cytokines such as IL-1 and IL-6 or to interfere with specific immune cell function through depletion of B cells or suppression of T-cell activation (Table 154-3). The availability of these agents has dramatically increased the therapeutic options for treating rheumatic disease recalcitrant to nonbiologic therapies and they are, in some instances, becoming first-line interventions. A primary concern regarding biologic therapy is that when use is combined with other immunosuppressants, risk of malignancy may be increased.

Tumor Necrosis Factor-α Antagonists

Currently, 2 TNF antagonists have an FDA indication for treatment of children with moderate to severe polyarticular JIA (etanercept and adalimumab). *Etanercept* is a genetically engineered fusion protein consisting of 2 identical chains of the recombinant extracellular TNF receptor monomer fused with the Fc domain of human immunoglobulin G_1. Etanercept binds both TNF-α and lymphotoxin-α (formerly

Table 154-3 Summary of Biologic Therapies Studied in Juvenile Idiopathic Arthritis and Their Method of Action

DRUG	METHOD OF ACTION
Etanercept	Soluble TNF p75 receptor fusion protein that binds to and inactivates TNF-α
Infliximab	Chimeric human/mouse monoclonal antibody that binds to soluble TNF-α and its membrane-bound precursor, neutralizing its action
Adalimumab	A humanized IgG_1 monoclonal antibody that binds to TNF-α
Abatacept	Soluble, fully human fusion protein of the extracellular domain of (CTLA-4, linked to a modified Fc portion of the human IgG_1. It acts as a costimulatory signal inhibitor by binding competitively to CD80 or CD86, where it selectively inhibits T-cell activation
Tocilizumab	A humanized anti–human IL-6 receptor monoclonal antibody
Anakinra	An IL-1 receptor antagonist (IL-1RA)

CTLA, cytotoxic T lymphocyte–associated antigen; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.

From Beresford MW, Baildam EM: New advances in the management of juvenile idiopathic arthritis—2: the era of biologicals, Arch Dis Child Educ Pract Ed *94:151–156, 2009.*

called TNF-β) and inhibits their activity. Three fourths of children with active polyarticular JIA that fails to respond to MTX demonstrate response to etanercept after 3 mo of therapy. Dosing is 0.8 mg/kg subcutaneous weekly (maximum 50 mg/dose) or 0.4 mg/kg subcutaneously twice a week (maximum 25 mg/dose). Adalimumab is a fully human anti-TNF monoclonal antibody used alone or in combination with MTX. In a placebo-controlled withdrawal-design study, children continuing to receive adalimumab were less likely to experience disease flares (43% vs. 71%) even if they were also taking MTX (37% vs. 65%). Adalimumab is administered subcutaneously every other week at a dose of 20 mg for children weighing 15-30 kg and 40 mg for those weighing >30 kg.

Infliximab, a chimeric mouse-human monoclonal antibody, was tested in a randomized controlled clinical trial for use in JIA but did not achieve study end points. However, it is FDA approved for pediatric inflammatory bowel disease and has been used "off label" for treatment of polyarticular JIA, uveitis, Behçet syndrome, and sarcoidosis. Two additional anti-TNF agents—*golimumab*, a human monoclonal antibody against TNF, and *certolizumab pegol*, a pegylated humanized antibody against TNF—have been approved by the FDA for rheumatoid arthritis in adults and are currently in pediatric trials.

The most common adverse reactions are injection-site reactions that diminish over time. TNF blockade is associated with an increased frequency of serious systemic infections, including sepsis, dissemination of latent tuberculosis, and invasive fungal infections in endemic areas. TNF blockade should not be initiated in subjects with history of chronic or frequent recurrent infections. Tuberculosis should be tested for prior to initiation of therapy with TNF antagonists. If test results are positive, antitubercular treatment must be administered before anti-TNF treatment can be started. There is a theoretically increased risk of malignancy with TNF-α antagonists, and there have been reports of development of lupus-like syndromes, leukocytoclastic vasculitis, interstitial lung disease, demyelinating syndromes, antibody formation to the drug, rashes, cytopenias, anaphylaxis, serum sickness, and other reactions. The benefit : risk profile appears favorable after a decade of experience with this therapeutic class; the safety of longer-term suppression of TNF function is unknown.

Modulator of T-Cell Activation

Abatacept is a selective inhibitor of T-cell costimulation resulting in T-cell anergy. It is FDA approved for treatment of moderate to severe polyarticular JIA. In a double-blind, randomized controlled withdrawal trial in children whose disease had not responded to DMARDs, 53% of placebo-treated patients, compared with 20% of abatacept-treated patients, experienced disease flares during the double-blind withdrawal period. The frequency of adverse events did not differ between the groups. Abatacept is administered IV every other week for 3 doses (<75 kg: 10 mg/kg/dose; 75-100 kg: 750 mg/dose; >100 kg: 1,000 mg/dose; maximum 1,000 mg/dose at 0, 2, and 4 wk) and then monthly thereafter.

B-Cell Depletion

Rituximab is a chimeric monoclonal antibody to the antigen CD20, a transmembrane protein on the surface of B-cell precursors and mature B lymphocytes. This antibody induces B-cell apoptosis and causes depletion of circulating and tissue-based B cells. Antibody production is not completely abrogated as plasma cells are not removed. Rituximab is licensed for treatment of B-cell non-Hodgkin lymphoma and is FDA approved for use in adult rheumatoid arthritis and idiopathic thrombocytopenic purpura but does not have a pediatric indication. Rituximab may also have a role in treatment of SLE, particularly its hematologic manifestations. Adverse events include serious infusion reactions, cytopenias, hepatitis B virus reactivation, hypogammaglobulinemia, infections, serum sickness, vasculitis, and a rare but fatal side effect, progressive multifocal leukoencephalopathy. Resistance to rituximab may develop over time in patients being treated for lymphoma.

Belimumab is a human monoclonal antibody to B-lymphocyte stimulator that negatively affects B-cell proliferation, differentiation, and long-term survival. It was FDA-approved in March 2011 for treatment of SLE in adults and studies of long-term safety and efficacy are ongoing. Currently, belimumab is not FDA approved for use in pediatric SLE.

Interleukin-1 Antagonists

Anakinra, a recombinant form of the human IL-1 receptor antagonist, competitively inhibits binding of IL-1α and IL-1β to the natural receptor, interrupting the cytokine proinflammatory cascade. Anakinra has been approved for rheumatoid arthritis in adults. In meta-analyses of treatments for rheumatoid arthritis, anakinra was outperformed by TNF-α antagonists but has a special niche in pediatric rheumatology for treatment of systemic JIA (SoJIA) and other autoinflammatory syndromes, such as cryopyrin-associated periodic syndromes. The medication is dosed subcutaneously, 1-2 mg/kg, once daily. An IL-1β monoclonal antibody, *canakinumab* is FDA approved for use in cryopyrin-associated periodic syndromes dosed subcutaneously every 8 wk and SoJIA dosed subcutaneously every 4 wk. Adverse reactions include significant injection site reactions and increased bacterial infections.

Interleukin-6 Receptor Antagonist

Tocilizumab, is an anti-IL-6 receptor antibody binding to both soluble as well as membrane-associated receptors. Tocilizumab has FDA approval for treatment of SoJIA and polyarticular JIA. Adverse reactions include transaminase and lipid elevations. Tocilizumab is given as an IV infusion every 2 (SoJIA) to 4 (polyarticular JIA) wk.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is thought to be beneficial in various clinical conditions. IVIG significantly improves the short- and long-term natural history of Kawasaki disease. Open studies have supported benefit for juvenile dermatomyositis, lupus-associated thrombocytopenia, and polyarticular JIA. IVIG is given as 1-2 g/kg/dose, administered once monthly. It has been occasionally associated with severe systemic allergic–like reactions and post-infusion aseptic meningitis (headache, stiff neck).

Cytotoxics

Cyclophosphamide

Cyclophosphamide requires metabolic conversion in the liver to its active metabolites, which alkylate the guanine in DNA, leading to immunosuppression by the inhibition of the S2 phase of mitosis. The subsequent decrease in numbers of T and B lymphocytes results in diminished humoral and cellular immune responses. Cyclophosphamide infusions (500-1,000 mg/m^2) given monthly for 6 mo, and then every 3 mo for 12-18 mo, have been shown to reduce the frequency of renal failure in patients with lupus and diffuse proliferative glomerulonephritis. Open trials suggest efficacy in severe central nervous system lupus. Oral cyclophosphamide (1-2 mg/kg/day) is effective as induction treatment of severe antineutrophilic cytoplasmic antibody-associated vasculitis and other forms of systemic vasculitis as well as interstitial lung disease or pulmonary hemorrhage associated with rheumatic disease. Cyclophosphamide is a potent cytotoxic drug associated with significant toxicities. Potential short-term adverse effects include nausea, vomiting, anorexia, alopecia, mucositis, hemorrhagic cystitis, and bone marrow suppression. Long-term complications include an increased risk for sterility and cancer, especially leukemia, lymphoma, and bladder cancer. Thirty percent to 40% of adult women with lupus treated with intravenous cyclophosphamide become infertile; the risk of ovarian failure appears to be significantly lower in adolescent and premenarchal girls. Ovarian suppression with an inhibitor of gonadotropin-releasing hormone to preserve fertility is currently being studied.

Other Drugs

Azathioprine is sometimes used to treat antineutrophilic cytoplasmic antibody-associated vasculitis following induction therapy or to treat SLE. *Cyclosporine* has been used occasionally in the treatment of dermatomyositis on the basis of uncontrolled studies and is helpful in the

treatment of macrophage activation syndrome complicating SoJIA (see Chapter 155). There are case reports describing the successful use of *thalidomide*, or its analog *lenalidomide,* as treatment for SoJIA, inflammatory skin disorders, and Behçet disease. Several drugs commonly used in the past to treat arthritis are no longer part of standard treatment, including salicylates, gold compounds, and D-penicillamine.

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Chapter 155

Juvenile Idiopathic Arthritis

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Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and one of the more common chronic illnesses of childhood. JIA represents a heterogeneous group of disorders all sharing the clinical manifestation of arthritis. The etiology and pathogenesis of JIA are largely unknown, and the genetic component is complex, making clear distinction among various subtypes difficult. As a result, several classification schemas exist, each with its own limitations. The former classification scheme of the American College of Rheumatology uses the term *juvenile rheumatoid arthritis* and categorizes the disease into 3 onset types (Table 155-1). Attempting to standardize nomenclature, The International League of Associations for Rheumatology (ILAR) proposed a different classification using the term **JIA** (Table 155-2), inclusive of all subtypes of chronic juvenile arthritis. We refer to the ILAR classification criteria; see Chapter 156 for enthesitis-related arthritis (ERA) and psoriatic JIA (Tables 155-3 and 155-4).

EPIDEMIOLOGY

The worldwide incidence of JIA ranges from 0.8-22.6/100,000 children per year, with prevalence ranges from 7-401/100,000. These wide-ranging numbers reflect population differences, particularly environmental exposure and immunogenetic susceptibility, along with variations in diagnostic criteria, difficulty in case ascertainment, and lack of population-based data. It is estimated that 300,000 children in the United States have arthritis, including 100,000 with a form of JIA. Oligoarthritis is the most common subtype (40-50%), followed by polyarthritis (25-30%) and systemic JIA (5-15%) (see Table 155-4). There is no sex predominance in systemic JIA (sJIA), but more girls than boys are affected in both oligoarticular (3 : 1) and polyarticular (5 : 1) JIA. The peak age at onset is between 2 and 4 yr for oligoarticular disease. Age of onset has a bimodal distribution in polyarthritis, with peaks at 2-4 yr and 10-14 yr. sJIA occurs throughout childhood with a peak between 1 and 5 yr.

Table 155-1 Criteria for the Classification of Juvenile Rheumatoid Arthritis

- Age at onset: <16 yr
- Arthritis (swelling or effusion, or the presence of 2 or more of the following signs: limitation of range of motion, tenderness or pain on motion, increased heat) in ≥1 joint
- Duration of disease: ≥6 wk
- Onset type defined by type of articular involvement in the 1st 6 mo after onset:
  - Polyarthritis: ≥5 inflamed joints
  - Oligoarthritis: ≤4 inflamed joints
  - Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
- Exclusion of other forms of juvenile arthritis

Modified from Cassidy JT, Levison JE, Bass JC, et al: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis, Arthritis Rheum *29:174–181, 1986.*

ETIOLOGY

The etiology and pathogenesis of JIA are not completely understood, though both immunogenetic susceptibility and an external trigger are considered necessary. JIA is a complex genetic trait in which multiple genes may affect disease susceptibility. Variants in major histocompatibility complex (MHC) class I and class II regions have indisputably been associated with different JIA subtypes. Non-HLA candidate loci are also associated with JIA, including polymorphisms in the genes encoding protein tyrosine phosphatase nonreceptor 22 (PTPN22), tumor necrosis factor (TNF)-α, macrophage inhibitory factor, interleukin (IL)-6, and IL-1α. There is evidence that the IL-6 gene confers susceptibility to sJIA, with increased transmission of the −174G allele in patients older than 5 yr. Possible nongenetic triggers include bacterial and viral infections, enhanced immune responses to bacterial or mycobacterial heat shock proteins, abnormal reproductive hormone levels, and joint trauma.

PATHOGENESIS

JIA is an autoimmune disease associated with alterations in both humoral and cell-mediated immunity. T lymphocytes have a central role, releasing proinflammatory cytokines favoring a type 1 helper T-lymphocyte response. Studies of T-cell receptor expression confirm recruitment of T lymphocytes specific for synovial non–self antigens. B-cell activation, immune complex formation, and complement activation also promote inflammation. Inheritance of specific cytokine alleles may predispose to upregulation of inflammatory networks, resulting in systemic disease or more severe articular disease.

sJIA is characterized by dysregulation of the innate immune system with a lack of autoreactive T cells and autoantibodies. It therefore may be more accurately classified as an **autoinflammatory disorder**, more like familial Mediterranean fever, than the other subtypes of JIA. This theory is also supported by work demonstrating similar expression patterns of a phagocytic protein (S100A12) in sJIA and familial Mediterranean fever, as well as the same marked responsiveness to IL-1 inhibitors.

All these immunologic abnormalities cause inflammatory synovitis, characterized pathologically by villous hypertrophy and hyperplasia with hyperemia and edema of the synovial tissue. Vascular endothelial hyperplasia is prominent and is characterized by infiltration of mononuclear and plasma cells with a predominance of T lymphocytes (Fig. 155-1). Advanced and uncontrolled disease leads to pannus formation and progressive erosion of articular cartilage and contiguous bone (Figs. 155-2 and 155-3).

CLINICAL MANIFESTATIONS

Arthritis must be present to make a diagnosis of any JIA subtype. Arthritis is defined by intraarticular swelling or the presence of 2 or more of the following signs: limitation in range of motion, tenderness or pain on motion, and warmth. Initial symptoms may be subtle or acute and often include morning stiffness with a limp or gelling after inactivity. Easy fatigability and poor sleep quality may be associated. Involved joints are often swollen, warm to touch, and painful on movement or palpation with reduced range of motion, but usually are not erythematous. Arthritis in large joints, especially knees, initially accelerates linear growth and causes the affected limb to be longer, resulting in a discrepancy in limb lengths. Continued inflammation stimulates rapid and premature closure of the growth plate, resulting in shortened bones.

Table 155-2 International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis (JIA)

CATEGORY	DEFINITION	EXCLUSIONS
Systemic	Arthritis in ≥1 joint with, or preceded by, fever of at least 2 wk in duration that is documented to be daily ("quotidian"*) for at least 3 days and accompanied by ≥1 of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly or splenomegaly or both 4. Serositis†	a. Psoriasis or a history of psoriasis in the patient or a 1st-degree relative b. Arthritis in an HLA-B27–positive boy beginning after the 6th birthday c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis, or a history of one of these disorders in a 1st-degree relative d. Presence of immunoglobulin M RF on at least 2 occasions at least 3 mo apart
Oligoarthritis	Arthritis affecting 1-4 joints during the 1st 6 mo of disease. Two subcategories are recognized: 1. Persistent oligoarthritis—affecting ≤4 joints throughout the disease course 2. Extended oligoarthritis—affecting >4 joints after the 1st 6 mo of disease	a, b, c, d (above) plus e. Presence of systemic JIA in the patient
Polyarthritis (RF-negative)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; a test for RF is negative	a, b, c, d, e
Polyarthritis (RF-positive)	Arthritis affecting ≥5 joints during the 1st 6 mo of disease; ≥2 tests for RF at least 3 mo apart during the 1st 6 mo of disease are positive	a, b, c, e
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis‡ 2. Nail pitting§ and onycholysis 3. Psoriasis in a 1st-degree relative	b, c, d, e
Enthesitis-related arthritis	Arthritis and enthesitis,‖ or arthritis or enthesitis with at least 2 of the following: 1. Presence of or a history of sacroiliac joint tenderness or inflammatory lumbosacral pain or both¶ 2. Presence of HLA-B27 antigen 3. Onset of arthritis in a male >6 yr old 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter syndrome, or acute anterior uveitis in a 1st-degree relative	a, d, e
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥2 of the above categories.	

RF, rheumatoid factor.
**Quotidian fever* is defined as a fever that rises to 39°C (102.2°F) once a day and returns to 37°C (98.6°F) between fever peaks.
†*Serositis* refers to pericarditis, pleuritis, or peritonitis, or some combination of the 3.
‡*Dactylitis* is swelling of ≥1 digits, usually in an asymmetric distribution, that extends beyond the joint margin.
§A minimum of 2 pits on any 1 or more nails at any time.
‖*Enthesitis* is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
¶*Inflammatory lumbosacral pain* refers to lumbosacral pain at rest with morning stiffness that improves on movement.
From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

Table 155-3 Characteristics of the American College of Rheumatology (ACR) and International League of Associations for Rheumatology (ILAR) Classifications of Childhood Chronic Arthritis

PARAMETER	ACR (1977)	ILAR (1997)
Term	Juvenile rheumatoid arthritis (JRA)	Juvenile idiopathic arthritis (JIA)
Minimum duration	≥6 wk	≥6 wk
Age at onset	<16 yr	<16 yr
≤4 joints in 1st 6 mo after presentation	• Pauciarticular	• Oligoarthritis: a. Persistent: <4 joints for course of disease b. Extended: >4 joints after 6 mo
>4 joints in 1st 6 mo after presentation	• Polyarticular	• Polyarthritis rheumatoid factor–negative • Polyarthritis rheumatoid factor–positive
Fever, rash, arthritis	• Systemic-onset	• Systemic
Other categories included	Exclusion of other forms	• Psoriatic arthritis • Enthesitis-related arthritis • Undifferentiated: a. Fits no other category b. Fits more than 1 category
Inclusion of psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis	No (see Chapter 156)	Yes

Table 155-4 Overview of the Main Features of the Subtypes of Juvenile Idiopathic Arthritis

INTERNATIONAL LEAGUE OF ASSOCIATIONS FOR RHEUMATOLOGY SUBTYPE	PEAK AGE OF ONSET (Yr)	FEMALE:MALE RATIO	PERCENTAGE OF ALL JIA CASES	ARTHRITIS PATTERN	EXTRAARTICULAR FEATURES	LABORATORY INVESTIGATIONS	NOTES ON THERAPY
Systemic arthritis	1-5	1:1	5-15	Polyarticular, often affecting knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; WBC ↑↑; ESR ↑↑; CRP ↑↑; ferritin ↑; platelets ↑↑ (normal or ↓ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1 or IL-6 inhibitors in resistant cases or as first-line therapy
Oligoarthritis	2-4	3:1	40-50 (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in ≈30% of cases	ANA positive in ≈60%; other test results usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intraarticular steroids; MTX occasionally required
Polyarthritis: RF-negative	2-4 and 10-14	3:1 and 10:1	20-35	Symmetric or asymmetric; small and large joints; cervical spine; temporomandibular joint	Uveitis in ≈10%	ANA positive in 40%; RF negative; ESR ↑ or ↑↑; CRP ↑/normal; mild anemia	Standard therapy with MTX and NSAIDs; then, if nonresponsive, anti-TNF agents or other biologics, including abatacept, indicated as first-line therapy
RF-positive	9-12	9:1	<10	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	2-4 and 9-11	2:1	5-10	Asymmetric arthritis of small or medium-sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑/normal; mild anemia	NSAIDs and intraarticular steroids; MTX, anti-TNF agents
Enthesitis-related arthritis	9-12	1:7	5-10	Predominantly lower limb joints affected; sometimes axial skeleton (but less than in adult, ankylosing spondylitis)	Acute anterior uveitis; association with reactive arthritis and inflammatory bowel disease	80% of patients positive for HLA-B27	NSAIDs and intra-articular steroids; consider sulfasalazine as alternative to MTX; anti-TNF agents

ANA, antinuclear antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MTX, methotrexate; NSAID, nonsteroidal antiinflammatory drug; RF, rheumatoid factor; TNF, tumor necrosis factor; WBC, white blood cell count.

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, Philadelphia, 2009, Saunders.*

Figure 155-1 Synovial biopsy specimen from a 10 yr old child with oligoarticular juvenile idiopathic arthritis. There is a dense infiltration of lymphocytes and plasma cells in the synovium.

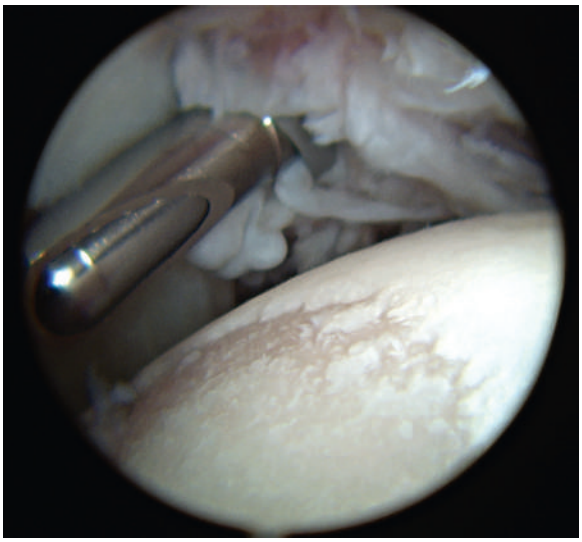

Figure 155-2 Arthroscopy in the shoulder of a child with juvenile idiopathic arthritis showing pannus formation and cartilage erosions. *(Courtesy of Dr. Alison Toth.)*

Figure 155-3 MRI with gadolinium of a 10 yr old child with juvenile idiopathic arthritis (same patient as in Fig. 155-1). The dense white signal in the synovium near the distal femur, proximal tibia, and patella reflects inflammation. MRI of the knee is useful to exclude ligamentous injury, chondromalacia of the patella, and tumor.

Figure 155-4 Oligoarticular juvenile idiopathic arthritis with swelling and flexion contracture of the right knee.

Oligoarthritis is defined as involving ≤4 joints within the 1st 6 mo of disease onset, and often only a single joint is involved (see Table 155-4). It predominantly affects the large joints of the lower extremities, such as the knees and ankles (Fig. 155-4). Isolated involvement of upper extremity large joints is less common. Those in whom disease never develops in more than 4 joints are regarded as having **persistent oligoarticular JIA**, whereas evolution of disease in more than 4 joints after 6 mo changes the classification to **extended oligoarticular JIA** and is associated with a worse prognosis. Isolated involvement of the hip is *almost never* a presenting sign and suggests ERA (see Chapter 156) or a nonrheumatic cause. The presence of a positive antinuclear antibody (ANA) confers increased risk for asymptomatic anterior uveitis, requiring periodic slit-lamp examination (Table 155-5). ANA positivity may also be correlated with younger age at disease onset, female sex, asymmetric arthritis, and lower number of involved joints over time.

Polyarthritis is characterized by inflammation of ≥5 joints in both upper and lower extremities (Figs. 155-5 and 155-6). Rheumatoid factor (RF)–positive polyarthritis resembles the characteristic symmetric presentation of adult rheumatoid arthritis. **Rheumatoid nodules** on the extensor surfaces of the elbows, spine, and over the Achilles tendons, although unusual, are associated with a more severe course and almost exclusively occur in RF-positive individuals (Fig. 155-7). **Micrognathia** reflects chronic temporomandibular joint disease

Table 155-5 Frequency of Ophthalmologic Examination in Patients with Juvenile Idiopathic Arthritis

TYPE	ANTINUCLEAR ANTIBODY TEST RESULT	AGE AT ONSET (Yr)	DURATION OF DISEASE (Yr)	RISK CATEGORY	EYE EXAMINATION FREQUENCY (Mo)
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	–	≤6	≤4	Moderate	6
	–	≤6	>4	Low	12
	–	>6	NA	Low	12
Systemic disease	NA	NA	NA	Low	12

From Cassidy J, Kivlin J, Lindsley C, et al: Section on Rheumatology; Section on Ophthalmology: Ophthalmologic examinations in children with juvenile rheumatoid arthritis, Pediatrics *117:1843–1845, 2006.*

Figure 155-5 Hands and wrists of a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor–negative. Notice the symmetric involvement of the wrists, metacarpophalangeal joints, and proximal and distal interphalangeal joints. In this photograph, there is cream with occlusive dressing on the patient's right hand in preparation for placement of an intravenous line for administration of a biologic agent.

(Fig. 155-8). Cervical spine involvement (Fig. 155-9), manifesting as decreased neck extension, occurs with a risk of atlantoaxial subluxation and neurologic sequelae. Hip disease may be subtle, with findings of decreased or painful range of motion on exam (Fig. 155-10).

sJIA is characterized by arthritis, fever, rash, and prominent visceral involvement, including hepatosplenomegaly, lymphadenopathy, and serositis (pericarditis). The characteristic fever, defined as spiking temperatures to ≥39°C (102.2°F), occurs on a daily or twice-daily basis for at least 2 wk, with a rapid return to normal or subnormal temperatures (Fig. 155-11). The fever is often present in the evening and is frequently accompanied by a characteristic faint, erythematous, macular rash. The evanescent **salmon-colored lesions,** classic for sJIA, are linear or circular and are most commonly distributed over the trunk and proximal extremities (Fig. 155-12). The classic rash is nonpruritic and migratory with lesions lasting <1 hr. **Koebner phenomenon,** a cutaneous hypersensitivity in which classic lesions are brought on by superficial trauma, is often present. Heat can also evoke rash. Fever, rash, hepatosplenomegaly, and lymphadenopathy are present in >70% of affected children. Without arthritis, the differential diagnosis includes the episodic fever syndromes, infection, and malignancy. Some children initially present with only systemic features, and evolve over time, but definitive diagnosis requires presence of arthritis. Arthritis may affect any number of joints, but the course is classically polyarticular, may be very destructive, and can include hip, cervical spine, and temporomandibular joint involvement.

Macrophage activation syndrome (MAS) is a rare but potentially fatal complication of sJIA that can occur at any time (onset, medication change, active or remission) during the disease course. It is also referred to as secondary hemophagocytic syndrome or hemophagocytic lymphohistiocytosis (HLH) (see Chapter 507). There is increasing evidence that sJIA/MAS and HLH share similar functional defects in granule-dependent cytotoxic lymphocyte activity. MAS classically manifests as acute onset of high spiking fevers, lymphadenopathy, hepatosplenomegaly, and encephalopathy. Laboratory evaluation shows thrombocytopenia and leukopenia with elevated liver enzymes, lactate dehydrogenase, ferritin, and triglycerides. Patients may have purpura and mucosal bleeding, as well as elevated fibrin split product values and prolonged prothrombin and partial prothromboplastin times. The erythrocyte sedimentation rate (ESR) falls because of hypofibrinogenemia and hepatic dysfunction, a feature useful in distinguishing MAS from a flare of systemic disease (Table 155-6). Although finalized diagnostic criteria for MAS do not currently exist, the features that were decided by an international consensus panel as the most important indicators of MAS include a falling platelet count, extreme hyperferritinemia, evidence of macrophage hemophagocytosis in the bone marrow, increased liver enzymes, falling leukocyte count, persistent, continuous fever ≥38°C (100.4°F), falling ESR, hypofibrinogenemia, and hypertriglyceridemia. *A relative change in laboratory values is likely more relevant in making an early diagnosis than are absolute normal values.* The diagnosis is suggested by clinical criteria and is confirmed by bone marrow biopsy demonstrating hemophagocytosis (Table 155-6). Emergency treatment with high-dose intravenous methylprednisolone, cyclosporine, or anakinra may be effective. Severe cases may require therapy similar to that for primary HLH (see Chapter 507).

Bone mineral metabolism and skeletal maturation are adversely affected in children with JIA, regardless of subtype. Children with JIA have decreased bone mass (osteopenia), which appears to be associated with increased disease activity. Increased levels of cytokines such as TNF-α and IL-6, both key regulators in bone metabolism, have deleterious effects on bone within the joint as well as systemically in the axial and appendicular bones. Abnormalities of skeletal maturation become most prominent during the pubertal growth spurt.

DIAGNOSIS

JIA is a clinical diagnosis without any diagnostic laboratory tests. The meticulous clinical exclusion of other diseases and many mimics is therefore essential. Laboratory studies, including tests for ANA and RF, are only supportive or prognostic, and their results may be normal in patients with JIA (see Tables 155-1 to 155-4).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for arthritis is broad and a careful, thorough investigation for other underlying etiology is imperative (Table 155-7). History, physical exam, laboratory tests, and radiography may help exclude other possible causes. Arthritis can be a presenting manifestation for any of the multisystem rheumatic diseases of childhood, including systemic lupus erythematosus (see Chapter 158), juvenile dermatomyositis (see Chapter 159), sarcoidosis (see Chapter 165), and

Figure 155-6 Progression of joint destruction in a girl with polyarticular juvenile idiopathic arthritis, rheumatoid factor–positive, despite doses of corticosteroids sufficient to suppress symptoms in the interval between the radiographs shown in **A** and **B. A,** Radiograph of the hand at onset. **B,** Radiograph taken 4 yr later, showing a loss of articular cartilage and destructive changes in the distal and proximal interphalangeal and metacarpophalangeal joints as well as destruction and fusion of wrist bones.

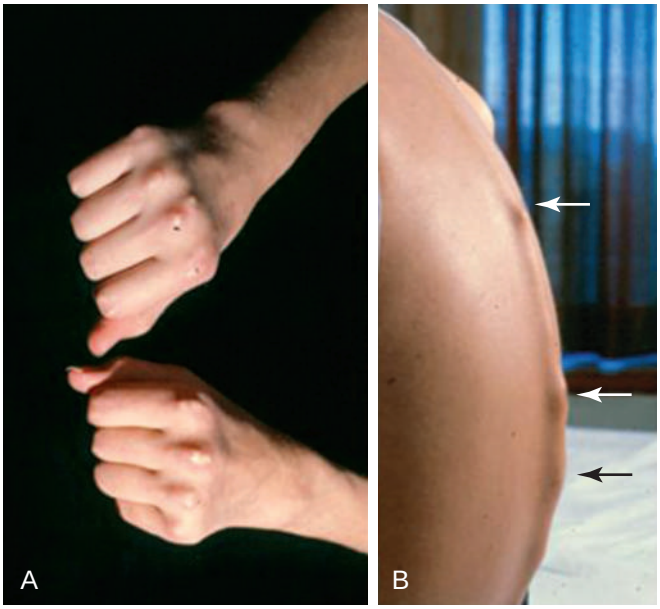

Figure 155-7 Rheumatoid nodules overlying bony prominences in an adolescent with rheumatoid factor–positive polyarthritis. *(From Rosenberg AM, Oen KG: Polyarthritis. In Cassiday JT, Petty RE, Laxer RM, et al, editors:* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders Elsevier,* Fig. 15-5, *p. 257.)*

Figure 155-8 CT scan of the temporomandibular joint of a patient with juvenile idiopathic arthritis exhibiting destruction on the right.

the vasculitic syndromes (see Chapter 167). In scleroderma (see Chapter 160), limited range of motion as a consequence of sclerotic skin overlying a joint may be confused with sequelae from chronic inflammatory arthritis. **Acute rheumatic fever** is characterized by exquisite joint pain and tenderness, a remittent fever, and a migratory polyarthritis. **Autoimmune hepatitis** can also be associated with an acute arthritis.

Many infections are associated with arthritis, and a recent history of infectious symptoms may help make a distinction. Viruses, including parvovirus B19, rubella, Epstein-Barr virus, hepatitis B virus, and HIV,

Figure 155-9 Radiograph of the cervical spine of a patient with active juvenile idiopathic arthritis, showing fusion of the neural arch between joints C2 and C3, narrowing and erosion of the remaining neural arch joints, obliteration of the apophyseal space, and loss of the normal lordosis.

Figure 155-10 Severe hip disease in a 13 yr old boy with active systemic juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The patient had received corticosteroids systemically for 9 yr.

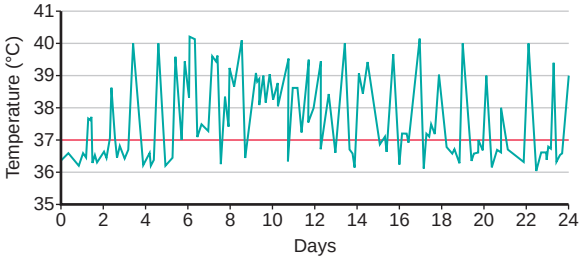

Figure 155-11 High-spiking intermittent fever in a 3 yr old patient with systemic juvenile idiopathic arthritis. *(From Ravelli A, Martini A: Juvenile idiopathic arthritis,* Lancet *369:767–778, 2007.)*

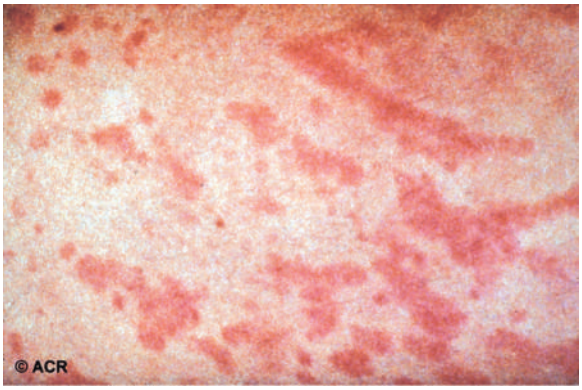

Figure 155-12 The rash of systemic juvenile idiopathic arthritis. The rash is salmon-colored, macular, and nonpruritic. Individual lesions are transient and occur in crops over the trunk and extremities. *(Reprinted from the American College of Rheumatology:* Clinical slide collection on the rheumatic diseases, *Atlanta, copyright 1991, 1995, 1997, ACR. Used with permission of the American College of Rheumatology.)*

Table 155-6 Main Clinical, Laboratory, and Pathologic Features of Macrophage Activation Syndrome

LABORATORY CRITERIA
1. Cytopenias
2. Abnormal liver function tests
3. Coagulopathy (hypofibrinogenemia)
4. Decreased erythrocyte sedimentation rate
5. Hypertriglyceridemia
6. Hyponatremia
7. Hypoalbuminemia
8. Hyperferritinemia
9. Elevated sCD25 and sCD163
CLINICAL CRITERIA
1. Nonremitting fever
2. Hepatomegaly
3. Splenomegaly
4. Lymphadenopathy
5. Hemorrhages
6. Central nervous system dysfunction (headache, seizures, lethargy, coma, disorientation)
HISTOPATHOLOGIC CRITERIA
1. Macrophage hemophagocytosis in the bone marrow aspirate
2. Increased CD163 staining of the bone marrow

From Ravelli A, Grom A, Behrens E, Cron R: Macrophage activation syndrome as part of systemic juvenile idiopathic arthritis: diagnosis, genetics, pathophysiology and treatment, Genes Immun *13:289–298, 2012.*

can induce a transient arthritis. Arthritis may follow enteric infections (see Chapter 157). **Lyme disease** (see Chapter 222) should be considered in children with oligoarthritis living in or visiting endemic areas. Although a history of tick exposure, preceding flu-like illness, and subsequent rash should be sought, they are not always present. Monoarticular arthritis unresponsive to antiinflammatory treatment may be the result of chronic mycobacterial or other infection such as *Kingella kingae*, and the diagnosis is established by synovial fluid analysis or biopsy. Acute onset of fever and a painful, erythematous, hot joint suggests septic arthritis. Isolated hip pain with limited motion raises the possibility of suppurative arthritis (see Chapter 685), osteomyelitis (see Chapter 684), toxic synovitis, Legg-Calvé-Perthes disease, slipped capital femoral epiphysis, and chondrolysis of the hip (see Chapter 678).

Lower-extremity arthritis and tenderness over insertion of ligaments and tendons, especially in a boy, raises the possibility of ERA (see Chapter 156). **Psoriatic arthritis** can manifest as limited joint involvement in an unusual distribution (e.g., small joints of the hand and

Table 155-7 Conditions Causing Arthritis or Extremity Pain

RHEUMATIC AND INFLAMMATORY DISEASES Juvenile idiopathic arthritis Systemic lupus erythematosus Juvenile dermatomyositis Polyarteritis nodosa Scleroderma Sjögren syndrome Behçet disease Overlap syndromes Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis Sarcoidosis Kawasaki syndrome Henoch-Schönlein purpura Chronic recurrent multifocal osteomyelitis	BONE AND CARTILAGE DISORDERS Trauma Patellofemoral syndrome Hypermobility syndrome Osteochondritis dissecans Avascular necrosis (including Legg-Calvé-Perthes disease) Hypertrophic osteoarthropathy Slipped capital femoral epiphysis Osteolysis Benign bone tumors (including osteoid osteoma) Histiocytosis Rickets
SERONEGATIVE SPONDYLOARTHROPATHIES Juvenile ankylosing spondylitis Inflammatory bowel disease Psoriatic arthritis Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions	NEUROPATHIC DISORDERS Peripheral neuropathies Carpal tunnel syndrome Charcot joints
INFECTIOUS ILLNESSES Bacterial arthritis (septic arthritis, *Staphylococcus aureus, Kingella kingae*, pneumococcus, gonococcus, *Haemophilus influenzae*) Lyme disease Viral illness (parvovirus, rubella, mumps, Epstein-Barr virus, hepatitis B, Chikungunya virus) Fungal arthritis Mycobacterial infection Spirochetal infection Endocarditis	NEOPLASTIC DISORDERS Leukemia Neuroblastoma Lymphoma Bone tumors (osteosarcoma, Ewing sarcoma) Histiocytic syndromes Synovial tumors
REACTIVE ARTHRITIS Acute rheumatic fever Reactive arthritis (postinfectious caused by *Shigella, Salmonella, Yersinia, Chlamydia*, or meningococcus) Serum sickness Toxic synovitis of the hip Postimmunization	HEMATOLOGIC DISORDERS Hemophilia Hemoglobinopathies (including sickle cell disease)
IMMUNODEFICIENCIES Hypogammaglobulinemia Immunoglobulin A deficiency Human immunodeficiency virus	MISCELLANEOUS DISORDERS Autoinflammatory diseases Recurrent multifocal osteomyelitis Pigmented villonodular synovitis Plant-thorn synovitis (foreign-body arthritis) Myositis ossificans Eosinophilic fasciitis Tendinitis (overuse injury) Raynaud phenomenon
CONGENITAL AND METABOLIC DISORDERS Gout Pseudogout Mucopolysaccharidoses Thyroid disease (hypothyroidism, hyperthyroidism) Hyperparathyroidism Vitamin C deficiency (scurvy) Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome) Fabry disease Farber disease Amyloidosis (familial Mediterranean fever)	PAIN SYNDROMES Fibromyalgia Growing pains Depression (with somatization) Reflex sympathetic dystrophy Regional myofascial pain syndromes

ankle) years prior to onset of cutaneous disease. **Inflammatory bowel disease** may manifest as oligoarthritis, usually affecting joints in the lower extremities, as well as gastrointestinal symptoms, elevations in ESR, and microcytic anemia.

Many conditions present solely with arthralgias (i.e., joint pain). Hypermobility may cause joint pain, especially in the lower extremities. Growing pains should be suspected in a child between the ages of 4-12 yr complaining of leg pain in the evenings with normal investigative studies and no morning symptoms. Nocturnal pain also alerts to the possibility of a malignancy. An adolescent with missed school days may suggest a diagnosis of fibromyalgia (see Chapter 168).

Children with **leukemia** or **neuroblastoma** may have joint or bone pain resulting from malignant infiltration of the bone, synovium, or, more often, the bone marrow, sometimes mo before demonstrating lymphoblasts on peripheral blood smear. Physical examination may reveal no tenderness, a deeper pain with palpation of the bone, or pain out of proportion to exam findings. Malignant pain often awakens the child from sleep and may cause cytopenias. Because platelets are an acute-phase reactant, a high ESR with leukopenia and a low normal platelet count may also be a clue to underlying leukemia. In addition, the characteristic quotidian fever of sJIA is absent in malignancy. Bone marrow examination is necessary for diagnosis. Some diseases, such as cystic fibrosis, diabetes mellitus, and the glycogen storage diseases, have associated arthropathies (see Chapter 169). Swelling that extends beyond the joint can be a sign of lymphedema or Henoch-Schönlein purpura (see Chapter 515). A peripheral arthritis indistinguishable from JIA occurs in the humoral immunodeficiencies (see Chapter 124), such as common variable immunodeficiency and

X-linked agammaglobulinemia. Skeletal dysplasias associated with a degenerative arthropathy are diagnosed from their characteristic radiologic abnormalities.

Systemic onset of JIA often presents as an fever of unknown origin (see Chapter 177). Important considerations in the differential diagnosis include infections (endocarditis, brucellosis, cat scratch disease, Q fever, mononucleosis), autoinflammatory disease (see Chapter 163) malignancy (leukemia, lymphoma, neuroblastoma) and HLH (see Chapter 507.2).

LABORATORY FINDINGS

Hematologic abnormalities often reflect the degree of systemic or articular inflammation, with elevated white blood cell and platelet counts and a microcytic anemia. Inflammation may also cause elevations in ESR and C-reactive protein, although it is not unusual for both to be normal in children with JIA.

Elevated ANA titers are present in 40-85% of children with oligoarticular or polyarticular JIA, but are rare with sJIA. ANA seropositivity is associated with increased risk of **chronic uveitis** in JIA. Approximately 5-15% of patients with polyarticular JIA are seropositive for RF. Anti–cyclic citrullinated peptide antibody, like RF, is a marker of more aggressive disease. Both ANA and RF seropositivity can occur in association with transient events, such as viral infection.

Children with sJIA usually have striking elevations in inflammatory markers and white blood cell and platelet counts. Hemoglobin levels are low, typically in the range of 7-10 g/dL, with indices consistent with anemia of chronic disease. The ESR is usually high, except in MAS. Although immunoglobulin levels tend to be high, ANA and RF are uncommon. **Ferritin values** are typically elevated and can be markedly increased in MAS (>10,000 ng/mL). In the setting of MAS, all cell lines have the potential to decline precipitously owing to the consumptive process. A low or normal white blood cell count and/or platelet count in a child with active sJIA should raise concerns for MAS.

Early radiographic changes of arthritis include soft tissue swelling, periarticular osteopenia, and periosteal new-bone apposition around affected joints (Fig. 155-13). Continued active disease may lead to subchondral erosions, loss of cartilage, with varying degrees of bony destruction, and fusion. Characteristic radiographic changes in cervical spine, most frequently in the neural arch joints at C2-C3 (see Fig. 155-9) may progress to atlantoaxial subluxation. MRI is more sensitive than radiography to detect early changes (Fig. 155-14).

TREATMENT

The goals of treatment are to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. All children with JIA need individualized treatment plans, and management is tailored according to disease subtype and severity, presence of poor

Figure 155-13 Early (6 mo duration) radiographic changes of juvenile idiopathic arthritis. Soft-tissue swelling and periosteal new bone formation appear adjacent to the 2nd and 4th proximal interphalangeal joints.

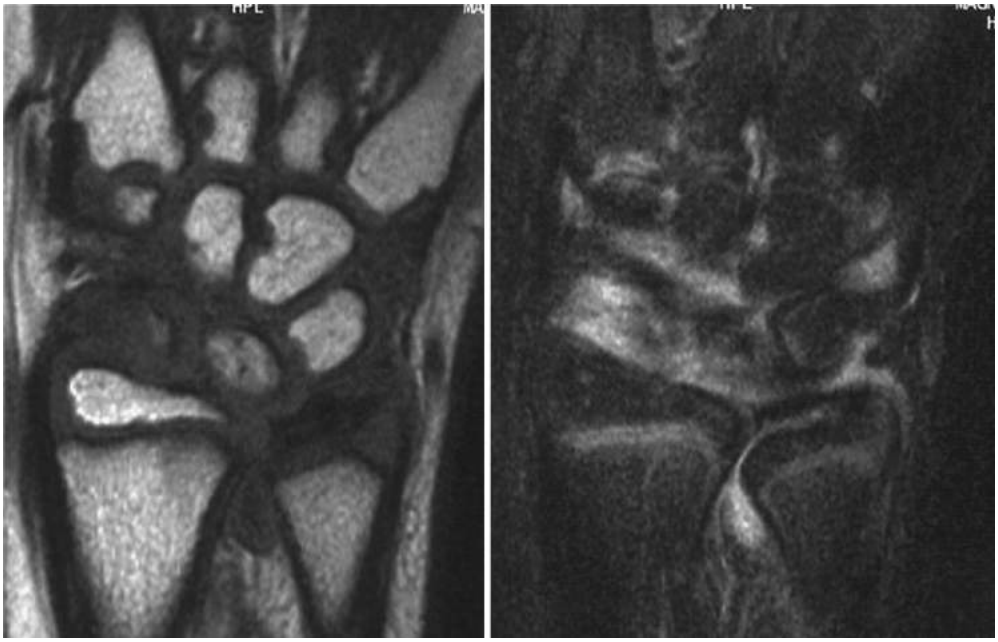

Figure 155-14 MRI of the wrist in a child with wrist arthritis. Image on the *left* shows multiple erosions of carpal bones. Image on the *right*, obtained after administration of gadolinium contrast agent, reveals uptake consistent with active synovitis.

Table 155-8 Pharmacologic Treatment of Juvenile Idiopathic Arthritis (JIA)

TYPICAL MEDICATIONS	TYPICAL DOSES	JIA SUBTYPE	SIDE EFFECT(S)
NONSTEROIDAL ANTIINFLAMMATORY DRUGS			
Naproxen	15 mg/kg/day PO divided bid (maximum dose 500 mg bid)	Polyarthritis Systemic Oligoarthritis	Gastritis, renal and hepatic toxicity, pseudoporphyria
Ibuprofen	40 mg/kg/day PO divided tid (maximum dose 800 mg tid)	Same as above	Same as above
Meloxicam	0.125 mg/kg PO once daily (maximum dose 15 mg daily)	Same as above	Same as above
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS			
Methotrexate	0.5-1 mg/kg PO or SC weekly (maximum dose 25 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Nausea, vomiting, oral ulcerations, hepatic toxicity, blood count dyscrasias, immunosuppression, teratogenicity
Sulfasalazine	Initial 12.5 mg/kg PO daily; increase by 10 mg/kg/day Maintenance: 40-50 mg/kg divided bid (maximum dose 2 g/day)	Polyarthritis	GI upset, allergic reaction, pancytopenia, renal and hepatic toxicity, Stevens-Johnson syndrome
Leflunomide*	10-20 mg PO daily	Polyarthritis	GI upset, hepatic toxicity, allergic rash, alopecia (reversible), teratogenicity (needs washout with cholestyramine)
BIOLOGIC AGENTS			
Anti–Tumor Necrosis Factor-α			
Etanercept	0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/wk)	Polyarthritis Systemic Persistent or extended oligoarthritis	Immunosuppressant, concern for malignancy, demyelinating disease, lupus-like reaction, injection site reaction
Infliximab*	3-10 mg/kg IV q4-8wk	Same as above	Same as above, infusion reaction
Adalimumab	<30 kg: 20 mg SC every other week >30 kg: 40 mg SC every other week	Same as above	Same as above
Anticytotoxic T-Lymphocyte–Associated Antigen-4 Immunoglobulin			
Abatacept	<75 kg: 10 mg/kg/dose IV q4wk 75-100 kg: 750 mg/dose IV q4wk >100 kg: 1,000 mg/dose IV q4wk	Polyarthritis	Immunosuppressant, concern for malignancy, infusion reaction
Anti-CD20			
Rituximab*	750 mg/m2 IV 2 wk × 2 (maximum dose 1,000 mg)	Polyarthritis	Immunosuppressant, infusion reaction, progressive multifocal encephalopathy
Interleukin-1 Inhibitors			
Anakinra*	1-2 mg/kg SC daily (maximum dose 100 mg/day)	Systemic	Immunosuppressant, GI upset, injection site reaction
Canakinumab	15-40 kg: 2 mg/kg/dose SC q8wk >40 kg: 150 mg SC q8wk	Systemic	Immunosuppressant, headache, GI upset, injection site reaction
Rilonacept*	2.2 mg/kg/dose SC weekly (maximum dose 160 mg)	Systemic	Immunosuppressant, allergic reaction, dyslipidemia, injection site reaction
Interleukin-6 Receptor Antagonist			
Tocilizumab	<30 kg: 12 mg/kg/dose q2wk >30 kg: 8 mg/kg/dose q2wk (maximum dose 800 mg)	Systemic Polyarthritis	Immunosuppressant, hepatic toxicity, dyslipidemia, cytopenias, GI upset, infusion reaction

bid, Twice daily; GI, gastrointestinal; IV, intravenous; PO, oral; SC, subcutaneous; tid, 3 times daily.
*Not indicated by the U.S. Food and Drug Administration for use in JIA.

prognostic indicators, and response to medications. Disease management also requires monitoring for potential medication toxicities (see Chapter 154).

Children with oligoarthritis often show partial response to nonsteroidal antiinflammatory drugs (NSAIDs), with improvement in inflammation and pain (Table 155-8). Those who have no or partial response after 4-6 wk of treatment with NSAIDs or who have functional limitations, such as joint contracture or leg-length discrepancy, benefit from injection of intraarticular corticosteroids. Triamcinolone hexacetonide is a long-lasting preparation that provides a prolonged response. A minority of patients with oligoarthritis show no response to NSAIDs and injections, and therefore require treatment with disease-modifying antirheumatic drugs (DMARDs), methotrexate, and, if no response, TNF inhibitors.

NSAIDs alone rarely induce remission in children with polyarthritis or sJIA. Methotrexate is the oldest and least toxic of the DMARDs available for adjunctive therapy. It may take 6-12 wk to see the effects of methotrexate. Failure of methotrexate monotherapy warrants the addition of a biologic DMARD. Biologic medications that inhibit proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, demonstrated excellent disease control. TNF-α antagonists (e.g., etanercept, adalimumab) are used to treat children with an inadequate response to methotrexate, with poor prognostic factors, or with severe disease onset. Early aggressive therapy with a combination of methotrexate and a TNF-α antagonist may result in earlier achievement of clinically inactive disease.

TNF inhibition is not as effective for the systemic symptoms found in sJIA. When systemic symptoms dominate systemic steroids are started followed by the initiation of IL-1 or IL-6 antagonist therapy, which often induces a dramatic and rapid response. Patients with severe disease activity may go directly to anakinra. Canakinumab, an IL-1β inhibitor, and tocilizumab, an IL-6 receptor antagonist, are

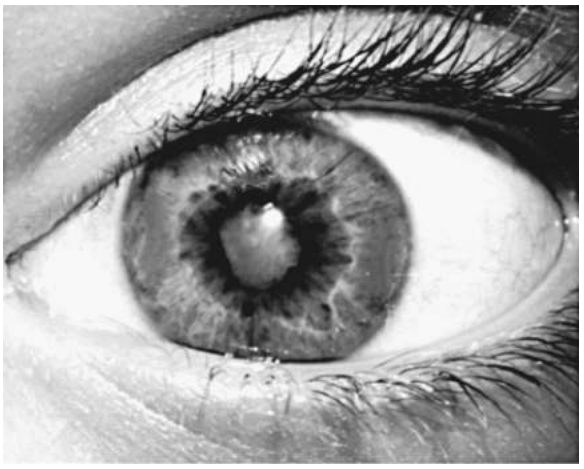

Figure 155-15 Chronic anterior uveitis, or iridocyclitis, of juvenile idiopathic arthritis. Extensive posterior synechiae have resulted in a small, irregular pupil. A well-developed cataract and early band keratopathy can be seen at the medial and lateral margins of the cornea.

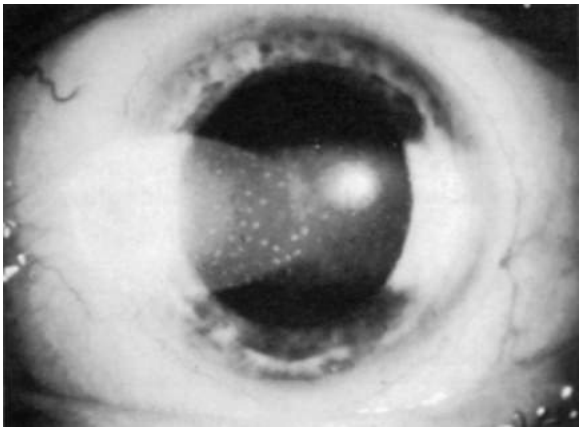

Figure 155-16 A slit-lamp examination shows "flare" in the fluid of the anterior chamber (caused by increased protein content) and keratic precipitates on the posterior surface of the cornea, representing small collections of inflammatory cells. *(Courtesy of Dr. H.J. Kaplan. From Petty RE, Rosenbaum JT: Uveitis in juvenile idiopathic arthritis. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Fig. 20-3, p. 309.)*

FDA-approved treatments for sJIA in children older than 2 yr. Standardized consensus treatment plans have been published to guide therapy for sJIA. These outline 4 treatment plans based on glucocorticoids, methotrexate, anakinra, or tocilizumab with optional glucocorticoid use in the latter 3 plans as clinically indicated.

With the advent of newer DMARDs, the use of systemic corticosteroids can often be avoided or minimized. Systemic steroids are recommended only for management of severe systemic illness, for **bridge therapy** during the wait for therapeutic response to a DMARD, and for control of uveitis. Steroids impose risks of severe toxicities, including Cushing syndrome, growth retardation, and osteopenia, and they do not prevent joint destruction.

Oral Janus kinase (JAK) inhibitors (tofacitinib, ruxolitinib) inhibit JAK signaling pathways involved in immune activation and inflammation. Tofacitinib is FDA approved for adults with rheumatoid arthritis.

Management of JIA must include periodic slit-lamp ophthalmologic examinations to monitor for asymptomatic uveitis (see Table 155-5; Figs. 155-15 and 155-16). Optimal treatment of uveitis requires collaboration between the ophthalmologist and rheumatologist. Initial management of uveitis may include mydriatics and corticosteroids used topically, systemically, or through periocular injection. DMARDs allow for a decrease in exposure to steroids, and methotrexate and antibodies to TNF-α (adalimumab and infliximab) are effective in treating severe uveitis.

Dietary evaluation and counseling to ensure appropriate calcium, vitamin D, protein, and caloric intake are important for children with JIA. Physical therapy and occupational therapy are invaluable adjuncts to any treatment program. A social worker and nurse clinician can be important resources for families, to recognize stresses imposed by a chronic illness, to identify appropriate community resources, and to aid compliance with the treatment protocol.

PROGNOSIS

Although the course of JIA in an individual child is unpredictable, some prognostic generalizations can be made on the basis of disease type and course. Studies analyzing management of JIA in the pre-TNF-α era indicate that up to 50% of patients with JIA have active disease persisting into early adulthood, often with severe limitations of physical function.

Children with persistent oligoarticular disease fare well, with a majority achieving disease remission. Those with extended oligoarticular disease have a poorer prognosis. Children with oligoarthritis, particularly girls who are ANA-positive and with onset of arthritis earlier than 6 yr of age, are at greatest risk for development of chronic uveitis. There is no association between the activity or severity of arthritis and uveitis. Persistent, uncontrolled anterior uveitis (see Fig. 155-15) can cause posterior synechiae, cataracts, glaucoma, and band keratopathy, with resultant blindness. Morbidity can be averted with early diagnosis and implementation of systemic therapy.

The child with polyarticular JIA often has a more prolonged course of active joint inflammation and requires early and aggressive therapy. Predictors of severe and persistent disease include young age at onset, RF seropositivity or rheumatoid nodules, the presence of anti–cyclic citrullinated peptide antibodies, and large numbers of affected joints. Disease involving the hip and hand and wrist is also associated with a poorer prognosis and may lead to significant functional impairment.

sJIA is often the most difficult to control in terms of both articular inflammation and systemic manifestations. Poorer prognosis is related to polyarticular distribution of arthritis, fever lasting >3 mo, and increased inflammatory markers, such as platelet count and ESR, for >6 mo. IL-1 and IL-6 inhibitors, have changed the management and improved the outcomes for children with severe and prolonged systemic disease.

Orthopedic complications include leg length discrepancy and flexion contractures, particularly of the knees, hips, and wrists. Discrepancies in leg length can be managed with a shoe lift on the shorter side to prevent secondary scoliosis. Joint contractures require aggressive medical control of arthritis, often in conjunction with intraarticular corticosteroid injections, appropriate splinting, and stretching of the affected tendons. Popliteal cysts may require no treatment if they are small or respond to intraarticular corticosteroid injection in the anterior knee.

Psychosocial adaptation may be affected by JIA. Studies indicate that, compared with control subjects, a significant number of children with JIA have problems with lifetime adjustment and employment. Disability not directly associated with arthritis may continue into young adulthood in as many as 20% of patients, together with continuing chronic pain syndromes at a similar frequency. Psychological complications, including problems with school attendance and socialization, may respond to counseling by mental health professionals.

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Chapter 156

Ankylosing Spondylitis and Other Spondyloarthritides

Pamela F. Weiss and Robert A. Colbert

The diseases collectively referred to as **spondyloarthritides** include ankylosing spondylitis (AS), arthritis associated with inflammatory bowel disease (IBD) and psoriasis, and reactive arthritis following gastrointestinal or genitourinary infections (Tables 156-1 and 156-2). Many children with spondyloarthritis are classified in the juvenile idiopathic arthritis (JIA) category of **enthesitis-related arthritis (ERA). Children and adolescents with spondyloarthritis, who may not meet ERA criteria, include arthritis associated with psoriasis or IBD, juvenile AS (JAS), and reactive arthritis.**

EPIDEMIOLOGY

JIA is diagnosed in 90 per 100,000 children in the United States every year (see Chapter 155). ERA accounts for 10-20% of JIA, and has a mean age of onset of 12 yr. Unlike other JIA categories, males are affected more often than females, accounting for 60% of ERA cases. AS occurs in 0.2-0.5% of adults, with approximately 15% of cases beginning in childhood. These disorders can be familial, largely as a result of the influence of HLA-B27, which is found in 90% of JAS and 50% of ERA compared to 7% of healthy individuals. Approximately 20% of children with ERA have a family history of HLA-B27–associated disease, such as reactive arthritis, AS, or IBD with sacroiliitis.

ETIOLOGY AND PATHOGENESIS

Spondyloarthritides are complex diseases in which susceptibility is largely genetically determined. HLA-B27 is responsible for 23.3% of AS heritability, with genes encoding the interleukin (IL)-23 receptor (*IL23R*), ERAP1 (endoplasmic reticulum aminopeptidase-1), IL-12p40 (*IL12B*), and others having important roles, but together accounting for only approximately 2% of heritability. Infection with certain gastrointestinal or genital pathogens can trigger reactive arthritis (see Chapter 157 and Table 156-2); environmental triggers for other forms of spondyloarthritis have not been identified. Unusual properties of HLA-B27, such as its tendency to misfold and form unusual cell surface structures, may have a role. Inflamed joints and entheses in spondyloarthritides contain T cells, B cells, macrophages, osteoclasts, proliferating fibroblasts and osteoblasts. Bone loss and osteoproliferation in and around vertebral bodies and facet joints in long-standing AS contribute to significant morbidity.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical manifestations that help distinguish spondyloarthritis from other forms of juvenile arthritis include arthritis of the axial skeleton (sacroiliac joints) and hips, enthesitis (inflammation at the site of tendon, ligament, or joint capsule attachment to bone), symptomatic eye inflammation (acute anterior uveitis), and gastrointestinal inflammation (even in the absence of IBD) (see Table 156-1).

Enthesitis-Related Arthritis

Children have ERA if they have *either* arthritis and enthesitis *or* arthritis or enthesitis, with at least 2 of the following characteristics: (1) sacroiliac joint tenderness or inflammatory lumbosacral pain, (2) the presence of HLA-B27, (3) onset of arthritis in a male older than 6 yr,

Table 156-2 Etiologic Microorganisms of Reactive Arthritis

PROBABLE	POSSIBLE
Chlamydia trachomatis	*Neisseria gonorrhoeae*
Shigella flexneri	*Mycoplasma fermentans*
Salmonella enteritidis	*Mycoplasma genitalium*
Salmonella typhimurium	*Ureaplasma urealyticum*
Yersinia enterocolitica	*Escherichia coli*
Yersinia pseudotuberculosis	*Cryptosporidium*
Campylobacter jejuni	*Entamoeba histolytica*
	Giardia lamblia
	Brucella abortus
	Clostridium difficile
	Streptococcus pyogenes
	Chlamydia pneumoniae
	Chlamydia psittaci

From Kim PS, Klausmeier TL, Orr DP: Reactive arthritis: a review. J Adolesc Health *44:309–315, 2009, Table 2, p. 311.*

Table 156-1 Overlapping Characteristics of the Spondyloarthritides

CHARACTERISTIC	JUVENILE ANKYLOSING SPONDYLITIS	JUVENILE PSORIATIC ARTHRITIS	INFLAMMATORY BOWEL DISEASE	REACTIVE ARTHRITIS
Enthesitis	+++	+	+	++
Axial arthritis	+++	++	++	+
Peripheral arthritis	+++	+++	+++	+++
HLA-B27 positive	+++	+	+++	+++
Antinuclear antibody positive	–	++	–	–
Rheumatoid factor positive	–	–	–	–
Systemic disease:				
Eyes	+	+	+	+
Skin	–	+++	+	+
Mucous membranes	–	–	+	+
Gastrointestinal tract	–	–	++++	+++

Frequency of characteristics: –, absent; +, <25%; ++, 25-50%; +++, 50-75%, ++++, 75% or more.
From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

(4) acute anterior uveitis, and (5) a family history of an HLA-B27–associated disease (ERA, sacroiliitis with IBD, reactive arthritis, or acute anterior uveitis) in a 1st-degree relative. Patients with psoriasis (or a family history of psoriasis in a 1st-degree relative), a positive rheumatoid factor test result, or systemic arthritis are excluded from this group. During the 1st 6 mo of disease the arthritis is typically asymmetric and involves 4 or fewer joints. The most frequently affected joints are the knees, ankles, and hips. Inflammation of the small joints of the foot, or tarsitis, is highly suggestive of ERA. Enthesitis is typically symmetric and most commonly affects the lower limbs. Up to 40% of children develop clinical or radiographic evidence of sacroiliac joint arthritis as part of their disease. When the sacroiliac or other axial joints are involved, children may experience inflammatory back pain (Table 156-3) and alternating buttock pain. Patients may also experience pain with palpation of the lower back or with pelvic compression. Untreated sacroiliitis may evolve into AS, but risk factors for progression are unclear.

Psoriatic Arthritis

Psoriatic arthritis accounts for approximately 10% of JIA. Common clinical features of psoriatic arthritis are nail pitting (Fig. 156-1), onycholysis, and dactylitis (sausage-like swelling of the fingers or toes).

Children have psoriatic arthritis if they have arthritis and psoriasis *or* arthritis and at least 2 of the following: (1) dactylitis, (2) nail pitting or onycholysis, or (3) psoriasis in a 1st-degree relative. The presence of psoriasis aids in diagnosis but is not required. Disease onset peaks during the preschool and early adolescent years. Children with onset during the preschool years are more often female, antinuclear antibody–positive, and at risk for asymptomatic ocular inflammation.

Table 156-3	Symptoms Characteristic of Inflammatory Back Pain
Pain at night with morning stiffness (and improvement upon arising)	
No improvement with rest	
Improvement with exercise	
Insidious onset	
Good response to nonsteroidal antiinflammatory drugs	

Disease onset during adolescence is equally common among males and females. In the majority of children, the arthritis is asymmetric and affects 4 or fewer joints at presentation. Large (knees and ankles) and small (fingers and toes) joints may be involved. Although distal interphalangeal joint involvement is uncommon, it is highly suggestive of the diagnosis. Enthesitis is detectable in 20-60% of patients and seems to be more frequent in those who present at an older age. Axial (sacroiliac) and root (hip) joints may be affected in up to 30% of children; the risk of axial arthritis is highest in those who are HLA-B27–positive.

Juvenile Ankylosing Spondylitis

JAS frequently begins with oligoarthritis and enthesitis. The arthritis occurs predominantly in the lower extremities and often involves the hips. In comparison to adult-onset AS, axial disease and inflammatory back pain are less frequent at disease onset, while enthesitis and peripheral arthritis are more common. AS is diagnosed according to the modified NY criteria if there is sufficient radiographic evidence of sacroiliitis (sacroiliitis of grade 2 or greater bilaterally or at least grade 3 unilaterally) and if the patient meets at least one clinical criterion involving inflammatory back pain, limitation of motion in the lumbar spine (Fig. 156-2), or limitation of chest expansion. JAS is present if the patient is <16 yr old. Juvenile *onset* AS is frequently used to describe adult AS when the symptoms began before 16 yr of age, but full criteria were not met until later.

To fulfill the modified New York criteria for AS, patients must have radiographic changes in the sacroiliac joints as well as clinical sequelae of axial disease. Because radiographic sacroiliitis can take many years to develop in adults and even longer in children, and clinical sequelae may lag further behind, criteria to identify pre-radiographic axial spondyloarthritis have been developed by the Assessment of SpondyloArthritis International Society. To meet criteria for axial spondyloarthritis patients must have at least 3 mo of back pain and sacroiliitis on imaging (acute inflammation on MRI or definite radiographic sacroiliitis by the New York criteria) plus 1 feature of spondyloarthritis (i.e., inflammatory back pain, arthritis, enthesitis [heel], uveitis, dactylitis, psoriasis, Crohn disease/ulcerative colitis, good response to nonsteroidal antiinflammatory drugs [NSAIDs], family history for spondyloarthritis, HLA-B27, or elevated C-reactive protein). Alternatively, patients can fulfill axial spondyloarthritis criteria if

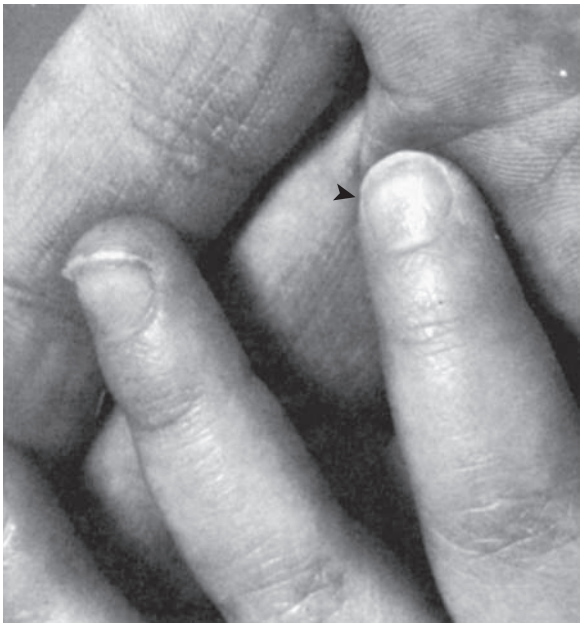

Figure 156-1 Nail pitting *(arrowhead)* and "sausage digit" (dactylitis) of the left index finger of a girl with juvenile psoriatic arthritis. *(From Petty RE, Malleson P: Spondyloarthropathies of childhood,* Pediatr Clin North Am *33:1079–1096, 1986.)*

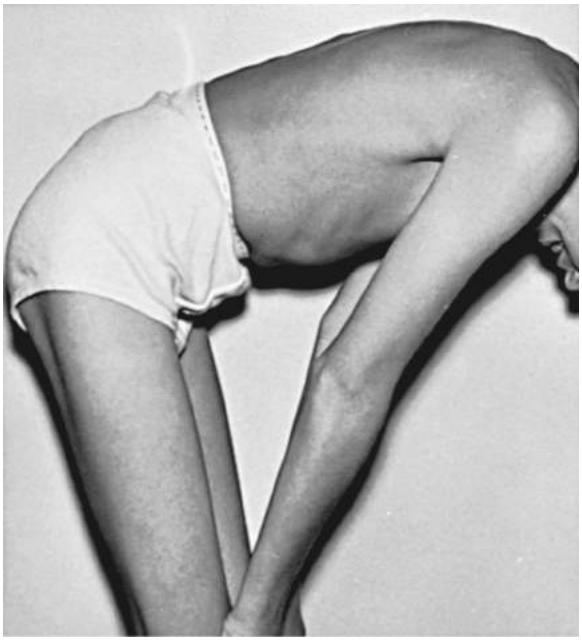

Figure 156-2 Loss of lumbodorsal spine mobility in a boy with ankylosing spondylitis. The lower spine remains straight when the patient bends forward.

they are HLA-B27–positive and have at least 2 features of spondyloarthritis. These criteria have not been validated in the pediatric population but may be useful as a guide to evaluating preradiographic spondyloarthritis.

Arthritis with Inflammatory Bowel Disease

The presence of erythema nodosum, pyoderma gangrenosum, fever, weight loss, or anorexia in a child with chronic arthritis should raise suspicion of IBD. Two patterns of arthritis complicate IBD. Polyarthritis affecting large and small joints is most common and often reflects the activity of the intestinal inflammation. Less frequently, arthritis of the axial skeleton, including the sacroiliac joints, occurs, resulting in AS. As with psoriatic arthritis, the presence of HLA-B27 is a risk factor for the development of axial disease. The severity of axial involvement is independent of the activity of the gastrointestinal inflammation.

LABORATORY FINDINGS

Laboratory evidence of systemic inflammation with elevation of the erythrocyte sedimentation rate and/or C-reactive protein value is variable in most spondyloarthritides and may or may not be present at the onset of disease. Rheumatoid factor and antinuclear antibodies are absent, except in patients with psoriatic arthritis, of which as many as 50% are antinuclear antibody–positive. HLA-B27 is present in ≈90% of children with JAS, compared with ≈7% of healthy individuals but is less frequent in ERA and other types of spondyloarthritis.

Imaging

Conventional radiographs detect chronic bony changes and damage but not active inflammation. Early radiographic changes in the sacroiliac joints include indistinct margins and erosions that can result in joint space widening. Sclerosis typically starts on the iliac side of the joint (Fig. 156-3). Peripheral joints may exhibit periarticular osteoporosis, with loss of sharp cortical margins in areas of enthesitis, which may eventually show erosions or bony spurs (enthesophytes). Squaring of the corners of the vertebral bodies and syndesmophyte formation resulting in the classic "bamboo spine" characteristic of advanced AS is rare in early disease, particularly in childhood. CT, like radiographs, can detect chronic bony changes but not active inflammation and has the disadvantage of more radiation exposure. The **gold standard** for early visualization of sacroiliitis is evidence of bone marrow edema adjacent to the joint on **MRI** with short T1 inversion recovery (STIR) sequences. Gadolinium does not add value to the study if STIR is used. MRI will reveal abnormalities before the plain radiograph. Whole body MRI is also used to evaluate the axial skeleton in adults with early disease as it can detect vertebral lesions in addition to sacroiliac changes.

Figure 156-3 Well-developed sacroiliitis in a boy with ankylosing spondylitis. Both sacroiliac joints show extensive sclerosis, erosion of joint margins, and apparent widening of the joint space.

DIFFERENTIAL DIAGNOSIS

The onset of arthritis following a recent history of diarrhea or symptoms of urethritis or conjunctivitis may suggest reactive arthritis (see Chapter 157). Lower back pain can be caused by suppurative arthritis of the sacroiliac joint, osteomyelitis of the pelvis or spine, osteoid osteoma of the posterior elements of the spine, pelvic muscle pyomyositis, or malignancies. In addition, mechanical conditions such as spondylolysis, spondylolisthesis, and Scheuermann disease should be considered. Back pain secondary to fibromyalgia usually affects the soft tissues of the upper back in a symmetric pattern and is associated with well-localized tender points and sleep disturbance (see Chapter 168.1). Legg-Calvé-Perthes disease (avascular necrosis of the femoral head), slipped capital femoral epiphysis, and chondrolysis may also manifest as pain over the inguinal ligament and loss of internal rotation of the hip joint, but without other features of spondyloarthritis, such as involvement of other entheses and/or joints. Radiography or MRI is critical for distinguishing these conditions.

TREATMENT

The goals of therapy are to control inflammation, minimize pain, preserve function, and prevent **ankylosis** (fusion of adjacent bones) using a combination of antiinflammatory medications, physical therapy, and education. Treatment regimens for spondyloarthritis include monotherapy or combination therapy with NSAIDs, disease-modifying antirheumatic drugs, or biologic agents. NSAIDs, such as naproxen (15-20 mg/kg/day), are frequently used initially and may reduce structural damage (syndesmophyte formation and growth) if used continually. With relatively mild disease, intraarticular corticosteroids (e.g., triamcinolone hexacetonide) may also help to control peripheral joint inflammation. However, for moderate disease and JAS, it is typically necessary to add a second-line agent. Disease-modifying antirheumatic drugs such as sulfasalazine (up to 50 mg/kg/day; maximum 3 g/day) or methotrexate (10 mg/m^2) may be beneficial for peripheral arthritis, but these medications have not been shown to improve axial disease in adults. Tumor necrosis factor-α inhibitors (e.g., etanercept, infliximab, adalimumab) have been efficacious in reducing symptoms and improving function in adults with AS, and there is evidence that similar responses are seen in children. It remains unclear whether tumor necrosis factor inhibitors have an impact on structural damage in established AS, underscoring the need for earlier recognition and better therapies.

Physical therapy and low-impact exercise should be included in the treatment program for all children with spondyloarthritis. Exercise to maintain range of motion in the back, thorax, and affected joints should be instituted early in the disease course. Custom-fitted insoles are particularly useful in management of painful entheses around the feet, and the use of pillows to position the lower extremities while the child is in bed can be helpful.

PROGNOSIS

Observational studies suggest that ongoing disease activity for greater than 5 yr in juvenile spondyloarthritis predicts disability. Disease remission occurs in less than 20% of children with spondyloarthritis 5 yr after diagnosis. Factors associated with disease progression include tarsitis, HLA-B27 positivity, hip arthritis within the 1st 6 mo, and disease onset after age 8. Important questions, such as which patients with ERA will go on to have JAS/AS, have yet to be addressed. Outcomes for JAS compared with adult-onset AS suggest that hip disease requiring replacement is more common in children but axial disease is more severe in adults.

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Chapter 157

Reactive and Postinfectious Arthritis

Pamela F. Weiss and Robert A. Colbert

In addition to causing arthritis by means of direct microbial infection (i.e., septic arthritis; see Chapter 685), infection can lead to the generation and deposition of immune complexes as well as antibody or T cell–mediated cross-reactivity with self. Microbes may influence the immune response in ways that indirectly affect susceptibility to immune-mediated inflammatory diseases such as systemic lupus erythematosus, inflammatory bowel disease, juvenile idiopathic arthritis, and spondyloarthritis. **Reactive and postinfectious arthritis** are defined as joint inflammation caused by a sterile inflammatory reaction following a recent infection. We use *reactive arthritis* to refer to arthritis that occurs following enteropathic or urogenital infections and *postinfectious arthritis* to describe arthritis that occurs after infectious illnesses not classically considered in the reactive arthritis group, such as infection with group A streptococcus or viruses. In some cases, nonviable components of the initiating organism have been demonstrated in affected joints, and the presence of viable, yet nonculturable, bacteria within the joint remains an area of investigation.

The course of **reactive arthritis** is variable and may remit or progress to a chronic spondyloarthritis including ankylosing spondylitis (see Chapter 156). In **postinfectious arthritis**, the pain or joint swelling is usually transient, lasting less than 6 wk, and does not necessarily share the typical spondyloarthritis pattern of joint involvement. The distinction between postinfectious arthritis and reactive arthritis is not always clear, either clinically or in terms of pathophysiology.

PATHOGENESIS

Reactive arthritis typically follows enteric infection with *Salmonella* sp., *Shigella flexneri, Yersinia enterocolitica, Campylobacter jejuni*, or genitourinary tract infection with *Chlamydia trachomatis*. *Escherichia coli* and *Clostridium difficile* are also causative enteric agents, although less common (see Table 156-2 in Chapter 156). Although similar in some respects to reactive arthritis, acute rheumatic fever caused by group A streptococcus (see Chapters 183.1 and 438), arthritis associated with infective endocarditis (see Chapter 437), and the tenosynovitis associated with *Neisseria gonorrhoeae* are considered in later chapters.

Approximately 75% of patients with reactive arthritis are HLA-B27–positive. Incomplete elimination of bacteria and bacterial products, such as DNA, has been proposed as a factor in reactive arthritis. A relationship with clinical characteristics of specific infectious disorders is not present. In postinfectious arthritis, several viruses (rubella, varicella-zoster, herpes simplex, cytomegalovirus) have been isolated from the joints of patients. Antigens from other viruses (e.g., hepatitis B, adenovirus) have been identified in immune complexes from joint tissue.

Patients with reactive arthritis who are HLA-B27–positive have an increased frequency of acute and symptomatic uveitis and other extraarticular features. In addition, HLA-B27 is a risk factor for persistent gastrointestinal inflammation following enteric infections, even after resolution of the initial infection, and significantly increases the risk that the individual will develop chronic spondyloarthritis. Nevertheless, reactive arthritis also occurs in HLA-B27–negative patients, emphasizing the importance of other genes in disease susceptibility.

CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS

Symptoms of reactive arthritis begin approximately 2-4 wk following infection. The classic triad of arthritis, urethritis, and conjunctivitis is relatively uncommon in children. The arthritis is typically oligoarticular, with a predilection for lower extremities. Dactylitis may occur, and enthesitis (Fig. 157-1) is common (affects as many as 90% of patients; see Chapter 156). Cutaneous manifestations can occur and may include circinate balanitis, ulcerative vulvitis, oral lesions, erythema nodosum, and keratoderma blennorrhagica, which is similar in appearance to pustular psoriasis (Fig. 157-2). Systemic symptoms may include fever, malaise, and fatigue. Early in the disease course, markers of inflammation—erythrocyte sedimentation rate, C-reactive protein, and platelets—may be markedly elevated. The clinical manifestations may last for weeks to months.

Familiarity with other causes of postinfectious arthritis is vital when a diagnosis of reactive arthritis is being considered. Numerous viruses are associated with postinfectious arthritis (Table 157-1) and may result in particular patterns of joint involvement. Rubella and hepatitis B virus typically affect the small joints, whereas mumps and varicella often involve large joints, especially the knees. The **hepatitis B arthritis–dermatitis syndrome** is characterized by urticarial rash and a symmetric migratory polyarthritis resembling that of serum sickness. Rubella-associated arthropathy may follow natural rubella infection and, infrequently, rubella immunization. It typically occurs in young women, with an increased frequency with advancing age, and is uncommon in preadolescent children and in males. Arthralgia of the knees and hands usually begins within 7 days of onset of the rash or 10-28 days after immunization. Parvovirus B19, which is responsible

Figure 157-1 Enthesitis—swelling of the posterior aspect of the left heel and lateral aspect of the ankle. *(Courtesy of Nora Singer, Case Western Reserve University and Rainbow Babies' Hospital.)*

Figure 157-2 Keratoderma blennorrhagica. *(Courtesy of Dr. M.F. Rein and The Centers for Disease Control and Prevention Public Health Image Library, 1976. Image #6950.)*

Table 157-1 Viruses Associated with Arthritis

TOGAVIRUSES	ADENOVIRUSES Adenovirus 7
RUBIVIRUS Rubella	HERPESVIRUSES Epstein-Barr Cytomegalovirus Varicella-zoster Herpes simplex
ALPHAVIRUSES Ross River Chikungunya O'nyong-nyong Mayaro Sindbis Ockelbo Pogosta	PARAMYXOVIRUSES Mumps
	HEPADNAVIRUS Hepatitis B
ORTHOPOXVIRUSES Variola virus (smallpox) Vaccinia virus Parvoviruses	ENTEROVIRUSES Echovirus Coxsackievirus B

Adapted from Cassidy JT, Petty RE: Infectious arthritis and osteomyelitis. In Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Saunders.*

for erythema infectiosum (fifth disease), can cause arthralgia, symmetric joint swelling, and morning stiffness, particularly in adult women and less frequently in children. Arthritis occurs occasionally during cytomegalovirus infection and may occur during varicella infections but is rare after Epstein-Barr virus infection. Varicella may also be complicated by suppurative arthritis, usually secondary to group A streptococcus infection. HIV is associated with an arthritis that resembles psoriatic arthritis more than juvenile idiopathic arthritis (see Chapter 155).

Poststreptococcal arthritis is a postinfectious arthritis that may follow infection with either group A or group G streptococcus. It is typically oligoarticular, affecting lower extremity joints, and mild symptoms can persist for months. Poststreptococcal arthritis differs from rheumatic fever, which typically manifests with painful migratory polyarthritis of brief duration. Because valvular lesions have occasionally been documented by echocardiography after the acute illness, some clinicians consider poststreptococcal arthritis to be an incomplete form of acute rheumatic fever (see Chapter 183.1). Certain HLA-DRB1 types may predispose children to development of either poststreptococcal arthritis (HLA-DRB1*01) or acute rheumatic fever (HLA-DRB1*16).

Transient synovitis (toxic synovitis), another form of postinfectious arthritis, typically affects the hip, often after an upper respiratory tract infection (see Chapter 678.2). Boys from 3-10 yr of age are most commonly affected and have acute onset of severe pain in the hip (groin), with referred pain to the thigh or knee, lasting approximately 1 wk. The erythrocyte sedimentation rate and white blood cell count are usually normal. Radiologic or ultrasound examination may confirm widening of the joint space secondary to an effusion. Aspiration of joint fluid is often necessary to exclude septic arthritis and typically results in dramatic clinical improvement. The trigger is presumed to be viral, although responsible microbes have not been identified.

Nonsuppurative arthritis has been reported in children, usually adolescent boys, in association with **severe truncal acne**. Patients often have fever and persistent infection of the pustular lesions. **Pyogenic (sterile) arthritis, pyoderma gangrenosum and acne (cystic)** syndrome, an autosomal dominant disorder caused by a mutation in the *PSTPIP1* gene, is a difficult-to-treat but rare autoinflammatory disorder that has responded to anakinra or anti–tumor necrosis factor antibody therapy in a few patients. Recurrent episodes of erosive arthritis begin in childhood, while cystic acne and the painful ulcerating lesions of pyoderma gangrenosum begin during adolescence. Recurrent episodes may also be associated with a sterile myopathy and may last for several months.

Infective endocarditis can be associated with arthralgia, arthritis, or signs suggestive of vasculitis, such as Osler nodes, Janeway lesions, and Roth spots. Postinfectious arthritis, perhaps because of immune complexes, also occurs in children with *N. gonorrhoeae, Neisseria meningitidis, Haemophilus influenzae* type b, and *Mycoplasma pneumoniae* infections.

DIAGNOSIS

A recent genitourinary or gastrointestinal infection may suggest the diagnosis of reactive arthritis, but there is no diagnostic test. A complete blood count, acute phase reactants, complete metabolic panel, and urinalysis may be helpful to exclude other etiologies. Although stool or urogenital tract cultures can be performed in an attempt to isolate the triggering organism, the offending agent is not typically found at the time arthritis presents. Imaging findings are nonspecific or normal. Documenting previous streptococcal infection with antibody testing (anti-streptolysin O and anti-DNAse B) may help to diagnose postinfectious arthritis. Serum sickness associated with the antibiotic treatment of preceding infection must be excluded.

Because the preceding infection can be remote or mild and often not recalled by the patient, it is also important to rule out other causes of arthritis. Acute and painful arthritis affecting a single joint suggests septic arthritis, mandating joint aspiration; osteomyelitis may cause pain and an effusion in an adjacent joint but is more often associated with focal bone pain and tenderness at the site of infection. Arthritis affecting a single joint, particularly the knee, may also be secondary to Lyme in endemic areas. The diagnosis of postinfectious arthritis is often established by exclusion, and after the arthritis has resolved. Arthritis associated with gastrointestinal symptoms or abnormal liver function test results may be triggered by infectious or autoimmune hepatitis. Arthritis or spondyloarthritis may occur in children with inflammatory bowel disease, such as Crohn disease or ulcerative colitis (see Chapter 336). When 2 or more blood cell lines are low or progressively decrease in a child with arthritis, parvovirus infection, macrophage activation (hemophagocytic) syndrome, and leukemia should be strongly considered. Persistent arthritis (>6 wk) suggests the possibility of a chronic rheumatic disease, including juvenile idiopathic arthritis (see Chapters 155 and 156) and systemic lupus erythematosus (see Chapter 158).

TREATMENT

Specific treatment is unnecessary for most cases of reactive or postinfectious arthritis. Nonsteroidal antiinflammatory agents are often needed for management of pain and functional limitation. Unless ongoing *Chlamydia* infection is suspected, attempts to treat the offending organism are not warranted. If swelling or arthralgia recurs, further evaluation may be necessary to exclude active infection or evolving rheumatic disease. Intraarticular steroid injections may be utilized for refractory or severely involved joints once acute infection has been ruled out. Systemic steroids or disease-modifying anti-rheumatic drugs are rarely indicated but may be considered for chronic disease. Participation in physical activity should be encouraged, and physical therapy may be needed to maintain normal function and prevent muscle atrophy. For postinfectious arthritis due to streptococcal disease, current recommendations include penicillin prophylaxis for at least 1 yr. Long-term prophylaxis is often recommended, but the duration is controversial and may need to be individualized.

COMPLICATIONS AND PROGNOSIS

Postinfectious arthritis following viral infections usually resolves without complications unless it is associated with involvement of other organs, such as encephalomyelitis. Children with reactive arthritis after enteric infections occasionally experience inflammatory bowel disease months to years after onset. Both uveitis and carditis have been reported in children diagnosed with reactive arthritis. Reactive arthritis, especially after bacterial enteric infection or genitourinary tract infection with *C. trachomatis,* has the potential for evolving to chronic arthritis, particularly spondyloarthritis (see Chapter 156). The presence of HLA-B27 or significant systemic features increases the risk of chronic disease.

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Chapter 158

Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multisystem inflammation and the presence of circulating autoantibodies directed against self-antigens. SLE occurs in both children and adults, disproportionately affecting females of reproductive age. Although nearly every organ may be affected, most commonly involved are the skin, joints, kidneys, blood-forming cells, blood vessels, and the central nervous system. Compared with adults, children and adolescents with SLE have more severe disease and more widespread organ involvement.

ETIOLOGY

The pathogenesis of SLE remains largely unelucidated, but several factors likely influence risk and severity of disease, including genetics, hormonal milieu, and environmental exposures.

A genetic predisposition to SLE is suggested by the association with **specific genetic abnormalities,** including congenital deficiencies of C1q, C2, and C4, as well as several polymorphisms (e.g., interferon regulatory factor 5 and protein tyrosine phosphatase N22), and familial clustering of SLE or other autoimmune disease. In addition, certain human leukocyte antigen (HLA) types (including HLA-B8, HLA-DR2, and HLA-DR3) occur with increased frequency in patients with SLE. Although SLE clearly has a genetic component, its occurrence is sporadic in families and its concordance is incomplete (estimated at 2-5% among dizygotic twins and 25-60% among monozygotic twins), suggesting that multiple genes are involved and that epigenetic and nongenetic factors are also important in disease expression.

Because SLE preferentially affects females, especially during their reproductive years, it is suspected that hormonal factors are important in pathogenesis. Of individuals with SLE, 90% are female, making gender the strongest risk factor for SLE. Estrogens are likely to play a role in SLE, and both in vitro and animal model studies suggest that estrogen exposure promotes B-cell autoreactivity. Estrogen-containing oral contraceptives do not appear to induce flares in quiescent SLE, though the risk of flares may be increased in postmenopausal women receiving hormone replacement.

Environmental exposures that may trigger the development of SLE remain largely unknown; certain viral infections (including Epstein-Barr virus) may play a role in susceptible individuals, and ultraviolet light exposure is known to aggravate SLE disease activity. Environmental influences also may induce epigenetic modifications to DNA, which increase the risk of SLE and drug-induced lupus; in mouse models, drugs such as procainamide and hydralazine can promote lymphocyte hypomethylation causing a lupus-like syndrome.

EPIDEMIOLOGY

The reported prevalence of SLE in children and adolescents (1-6/100,000) is lower than that in adults (20-70/100,000). Prevalence of SLE is highest among African-Americans, Asians, Hispanics, Native Americans, and Pacific Islanders for both adult and pediatric populations. SLE predominantly affects females, with reported 2-5:1 ratio prior to puberty, 9:1 ratio during reproductive years, and return to near prepubertal ratios in the postmenopausal period. Childhood SLE is rare before 5 yr of age and is usually diagnosed in adolescence, with a median age at diagnosis of 11-12 yr. Up to 20% of all individuals with SLE are diagnosed prior to age 16 yr.

PATHOLOGY

Histologic features most suggestive of SLE include findings in the kidney and skin, especially the discoid rash. Renal manifestations of SLE are classified histologically according to the criteria of the International Society of Nephrology (see Chapter 514). The finding of diffuse proliferative glomerulonephritis (class IV) significantly increases risk for renal morbidity. Renal biopsies are helpful to establish the diagnosis of SLE and to stage disease. Immune complexes are commonly found with "full house" deposition of immunoglobulin and complement. The characteristic **discoid rash** depicted in Figure 158-1*D* is characterized on biopsy by hyperkeratosis, follicular plugging, and infiltration of mononuclear cells into the dermal-epidermal junction. The histopathology of photosensitive rashes can be nonspecific, but immunofluorescence examination of both affected and nonaffected skin may reveal deposition of immune complexes within the dermal–epidermal junction. This finding is called the **lupus band test**, which is specific for SLE.

PATHOGENESIS

A hallmark of SLE is the generation of **autoantibodies** directed against self-antigens, particularly nucleic acids. These intracellular antigens are ubiquitously expressed but are usually inaccessible and cloistered within the cell. During cell necrosis or **apoptosis**, the antigens are released. SLE skin cells are highly susceptible to damage from ultraviolet light, and the resulting cell death leads to release of cell contents, including nucleic antigens. Individuals with SLE may have markedly increased levels of apoptosis or significantly impaired ability to clear cell debris, causing prolonged exposure to nucleic antigens in the bloodstream and increased opportunity for recognition by immune cells, leading to B cell autoantibody production. Circulating autoantibodies form immune complexes and deposit in tissues, leading to local complement activation, initiation of a proinflammatory cascade, and,

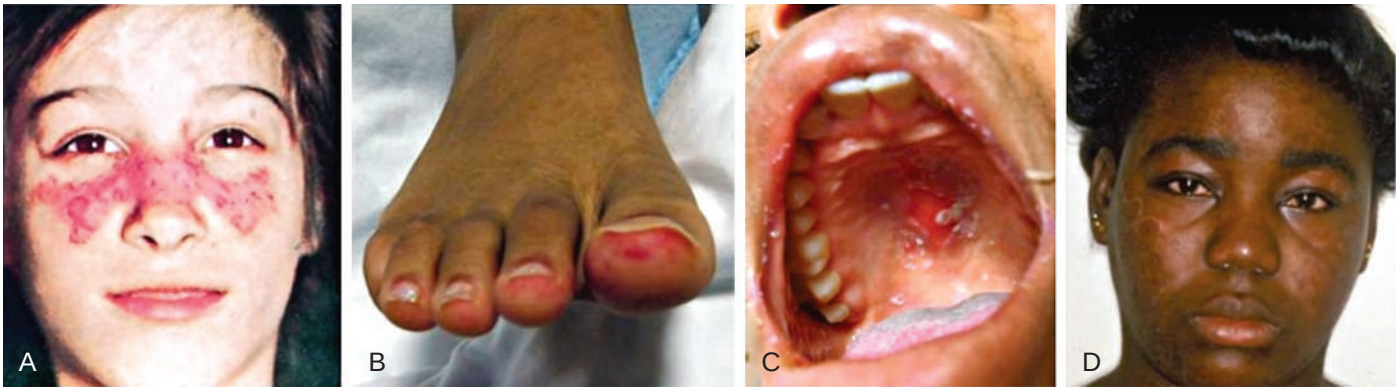

Figure 158-1 Mucocutaneous manifestations of SLE. **A,** Malar rash; **B,** vasculitic rash on toes; **C,** oral mucosal ulcers; **D,** discoid rash in malar distribution.

ultimately, tissue damage. Antibodies to double-stranded DNA can form immune complexes, deposit in glomeruli, and initiate inflammation leading to glomerulonephritis. However, many individuals with SLE have circulating antibodies to double-stranded DNA yet do not have nephritis, suggesting that autoantibodies are not the only pathway leading to end organ damage in SLE.

Both the innate and adaptive arms of the immune system have been implicated in the dysregulation of the immune system seen in SLE. High levels of interferon-α production by plasmacytoid dendritic cells promote expression of other proinflammatory cytokines and chemokines, maturation of monocytes into myeloid dendritic cells, promotion of autoreactive B and T cells, and loss of self-tolerance. Many, but not all, patients with SLE exhibit this cytokine profile, known as the **type I interferon signature.** Other cytokines with increased expression in SLE include interleukin (IL)-1, IL-2, IL-6, IL-10, IL-12, IL-17, IL-21, interferon-γ, B-lymphocyte stimulator (BLyS), and anti–tumor necrosis factor-α.

Both B and T cells demonstrate functional impairments in SLE. In active SLE, B-cell populations have impaired tolerance and increased autoreactivity, enhancing B cells' ability to produce autoantibodies following exposure to self-antigen. In addition, cytokines such as BLyS may promote abnormal B-cell number and function. T-cell abnormalities in SLE include increased numbers of memory T cells and decreased number and function of T-regulatory cells. SLE T cells display aberrant signaling and increased autoreactivity. As a result, they are resistant to attrition by normal apoptosis pathways.

CLINICAL MANIFESTATIONS

Any organ system can be involved in SLE, so the potential clinical manifestations are myriad (Table 158-1). The presentation of SLE in childhood or adolescence differs from that in adults. The most common presenting complaints of children with SLE include fever, fatigue, hematologic abnormalities, arthralgia, and arthritis. Arthritis is usually present in the 1st yr of diagnosis, may be asymptomatic (morning stiffness, painless swelling) but is often a symmetric polyarthritis affecting large and small joints. Tenosynovitis is often present, but radiologic joint changes are very rare. Pediatric lupus may develop in patients previously diagnosed with polyarticular or systemic juvenile idiopathic arthritis (see Chapter 155).

Renal disease in SLE is often asymptomatic, underscoring the need for careful monitoring of blood pressure and urinalyses; in adolescents, SLE often presents with nephrotic syndrome and/or renal failure with the predominant symptoms being edema, fatigue, changes in urine color, and nausea/vomiting. Because SLE symptoms and findings may develop serially over several years and not be present at one time, the diagnosis may require longitudinal follow up. SLE is often characterized by periods of flare and disease quiescence or may follow a more smoldering disease course. The neuropsychiatric complications of SLE may occur with or without apparently active SLE, posing a particularly difficult diagnostic challenge in adolescents, who are already at high risk for mood disorders (Fig. 158-2). Long-term complications of SLE and its therapy, including accelerated atherosclerosis and osteoporosis, become clinically evident in young to middle adulthood. SLE is a disease that evolves over time in each affected individual, and new manifestations may arise even many years after diagnosis.

DIAGNOSIS

The diagnosis of SLE requires a comprehensive clinical and laboratory assessment revealing characteristic multisystem disease and excluding other etiologies, including infection and malignancy. Presence of 4 of the 11 **American College of Rheumatology (ACR) 1997 Revised Classification Criteria for SLE** (Table 158-2) simultaneously or cumulatively over time establishes the diagnosis of SLE. Of note, although a positive antinuclear antibody (ANA) test result is not required for the diagnosis of SLE, ANA-negative lupus is extremely rare. Although ANA is very sensitive for SLE (95-99%), it is not very specific (~50%). Antibodies against double-stranded DNA and anti-Smith are specific for SLE (~98%) but not as sensitive (40-65%). Hypocomplementemia, although common in SLE, is not represented among the ACR classification criteria; hypocomplementemia has been added to **updated criteria validated by the Systemic Lupus International Collaborating Clinics (SLICC) in 2012** (Table 158-3). Other differences in the SLICC criteria include addition of nonscarring alopecia, additional cutaneous and neurologic manifestations of lupus, and a positive direct Coombs test in the absence of hemolytic anemia.

Table 158-1 Potential Clinical Manifestations of Systemic Lupus Erythematosus

TARGET ORGAN	POTENTIAL CLINICAL MANIFESTATIONS
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, tendonitis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid (annular) rash, photosensitive rash, cutaneous vasculitis (petechiae, palpable purpura, digit ulcers, gangrene, urticaria), livedo reticularis, periungual capillary abnormalities, Raynaud phenomenon, alopecia, oral and nasal ulcers, panniculitis, chilblains, alopecia
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, migraines, pseudotumor, peripheral neuropathy (mononeuritis multiplex) , chorea, optic neuritis, cranial nerve palsies, acute confusional states, dural sinus thrombosis
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy, peritonitis
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema, dry eyes, optic neuritis

DIFFERENTIAL DIAGNOSIS

Multiorgan disease is the hallmark of SLE, and given its wide array of potential clinical manifestations, SLE is in the differential diagnosis of many clinical scenarios, including unexplained fevers, joint pain, arthritis, rash, cytopenias, neurologic or cardiopulmonary abnormalities, nephritis, and nephrotic syndrome. For patients ultimately diagnosed with pediatric SLE, the initial differential diagnosis often includes infections (sepsis, Epstein-Barr virus, parvovirus B19, endocarditis), malignancies (leukemia and lymphoma), poststreptococcal glomerulonephritis, other rheumatologic conditions (systemic onset juvenile idiopathic arthritis, vasculitides), and drug-induced lupus.

Drug-induced lupus refers to the presence of SLE manifestations triggered by exposure to specific medications, including minocycline, many anticonvulsants, sulfonamides, antiarrhythmic agents, and other drugs (Table 158-4). In individuals prone to SLE, these agents may act as a trigger for true SLE. In others, these agents provoke a reversible lupus-like syndrome. Unlike SLE, drug-induced lupus affects males and females equally. A genetic predisposition toward slow drug acetylation may increase the risk of drug-induced lupus. Circulating antihistone

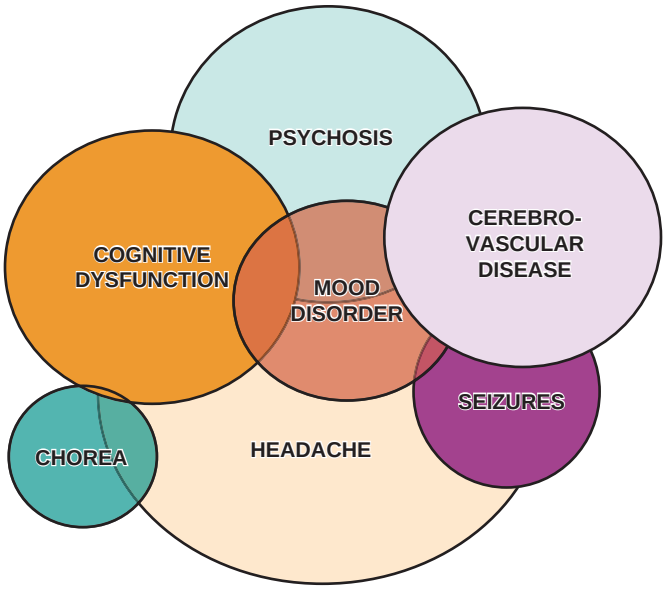

Figure 158-2 **Overlapping neuropsychiatric symptoms in pediatric SLE.** Patients with pediatric SLE most commonly have more than 1 neuropsychiatric symptom—in particular for seizures. *(From Silverman E, Eddy A: Systemic lupus erythematosus. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders/Elsevier,* Fig. 21-17, *p. 329.)*

Table 158-2 American College of Rheumatology 1997 Revised Classification Criteria for Systemic Lupus Erythematosus*

Malar rash
Discoid rash
Photosensitivity
Oral or nasal ulcers
Arthritis
Nonerosive, ≥2 joints
Serositis
Pleuritis, pericarditis or peritonitis
Renal manifestations†
Consistent renal biopsy
Persistent proteinuria or renal casts
Seizure or psychosis
Hematologic manifestations†
Hemolytic anemia
Leukopenia (<4,000 leukocytes/mm^3)
Lymphopenia (<1,500 leukocytes/mm^3)
Thrombocytopenia (<100,000 thrombocytes/mm^3)
Immunologic abnormalities†
Positive anti–double-stranded or anti-Smith antibody
False-positive rapid plasma regain test result, positive lupus anticoagulant test result, or elevated anticardiolipin immunoglobulin (Ig) G or IgM antibody
Positive antinuclear antibody test result

*The presence of 4 of 11 criteria establishes the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

†Each of these criteria counts as a single criterion whether 1 or more definitions are satisfied.

Adapted from Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum *40:1725, 1997.*

Table 158-3 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria for Systemic Lupus Erythematosus*

CLINICAL CRITERIA	IMMUNOLOGIC CRITERIA
Acute cutaneous lupus	Positive antinuclear antibody
Malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash, or subacute cutaneous lupus	Positive double-stranded DNA antibody
Chronic cutaneous lupus	Positive anti-Smith antibody
Classic discoid rash, lupus panniculitis, mucosal lupus, lupus erythematous tumidus, chilblains lupus, discoid lupus/lichen planus overlap	Antiphospholipid antibody positivity
Oral or nasal ulcers	Positive lupus anticoagulant, false-positive test for rapid plasma regain, medium to high titer anticardiolipin antibody level (IgA, IgG, IgM), or positive anti–B_2-glycoprotein I antibody (IgA, IgG, IgM)
Nonscarring alopecia	Low complement
Synovitis (≥2 joints)	Low C3, C4, or Ch50 level
Serositis	Positive direct Coombs test (in the absence of hemolytic anemia)
Pleurisy or pericardial pain ≥1 day, pleural effusion or rub, pericardial effusion or rub, ECG evidence of pericarditis	
Renal	
Presence of red blood cell casts or urine protein/creatinine ratio representing >500 mg protein/24 hours	
Neurologic	
Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, or acute confusional state	
Hemolytic anemia	
Leukopenia (<4,000/mm^3) or lymphopenia (<1,000/mm^3)	
Thrombocytopenia (<100,000/mm^3)	

*The presence of 4 criteria (including at least 1 clinical and 1 immunologic criterion) establishes the diagnosis of SLE. Biopsy-proven lupus nephritis with positive ANA or anti–double-stranded DNA also satisfies the diagnosis of SLE. These criteria were developed for classification in clinical trials and not for clinical diagnosis.

Adapted from Petri M: Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus, Arthritis Rheum *64(8):2677–2686, 2012.*

Table 158-4 Medications Associated with Drug-Induced Lupus

DEFINITE ASSOCIATION Minocycline, procainamide, hydralazine, isoniazid, penicillamine, diltiazem, interferon-α, methyldopa, chlorpromazine, etanercept, infliximab, adalimumab
PROBABLE ASSOCIATION Phenytoin, ethosuximide, carbamazepine, sulfasalazine, amiodarone, quinidine, rifampin, nitrofurantoin, beta blockers, lithium, captopril, interferon-γ, hydrochlorothiazide, glyburide, docetaxel, penicillin, tetracycline, statins, gold, valproate, griseofulvin, gemfibrozil, propylthiouracil

antibodies are often present in drug-induced SLE; these antibodies are only detected in up to 20% of individuals with SLE. Hepatitis, which is rare in SLE, is more common in drug-induced lupus. Individuals with drug-induced lupus are less likely to demonstrate antibodies to double-stranded DNA, hypocomplementemia, and significant renal or neurologic disease. In contrast to SLE, manifestations of drug-induced lupus typically resolve after withdrawal of the offending medication; however, complete recovery may take several months to years.

LABORATORY FINDINGS

A positive ANA test result is present in 95-99% of individuals with SLE. This test has poor specificity for SLE, as up to 20% of healthy individuals also have a positive ANA test result, making the ANA a poor screening test for SLE. ANA titers are not reflective of disease activity; therefore, repeating ANA titers is not helpful in disease management. Antibodies to double-stranded DNA are more specific for SLE, and in some individuals, anti–double-stranded DNA levels correlate with disease activity, particularly those with significant nephritis. Anti-Smith antibody, although found specifically in patients with SLE, does not correlate with disease activity. Serum levels of total hemolytic complement (CH_{50}), C3, and C4 are typically decreased in active disease and often improve with treatment; although hypocomplementemia is not included in the ACR classification criteria, it has been added to 2012 SLICC criteria, along with direct Coombs positivity. Table 158-5 lists autoantibodies found in SLE along with their clinical associations. Hypergammaglobulinemia is a common but nonspecific finding. Inflammatory markers, particularly erythrocyte sedimentation rate, are often elevated in active disease. C-reactive protein (CRP) correlates less well with disease activity and acutely elevated CRP values may reflect infection, while chronic mild elevation of CRP may indicate increased cardiovascular risk.

Antiphospholipid antibodies, which increase clotting risk, can be found in up to 66% of children and adolescents with SLE. Antiphospholipid antibodies can be detected by several means, and laboratory features that point to the presence of these antibodies include the presence of anticardiolipin antibodies, prolonged phospholipid-dependent coagulation test results (partial thromboplastin time, dilute Russell viper-venom time), and a circulating **lupus anticoagulant** (which confirms that a prolonged partial thromboplastin time is not corrected with mixing studies). When an arterial or venous clotting event occurs in the presence of an antiphospholipid antibody, **antiphospholipid antibody syndrome** is diagnosed. Antiphospholipid antibody syndrome can occur in the context of SLE or independent of SLE (see Chapter 479).

TREATMENT

Treatment of SLE is tailored to the individual and is based on specific disease manifestations and medication tolerability. For all patients, sunscreen and avoidance of prolonged direct sun exposure and other ultraviolet light may help control disease and should be reinforced at every visit with the patient. Hydroxychloroquine (5-7 mg/kg/day up to 400 mg/day) is recommended for all individuals with SLE if tolerated. In addition to treating mild SLE manifestations such as rash and mild arthritis, hydroxychloroquine prevents SLE flares, improves lipid profiles, and may have a beneficial impact on mortality and renal outcomes. Potential toxicities include retinal pigmentation and color vision impairment; therefore, ophthalmology exams every 6-12 mo are recommended for patients taking hydroxychloroquine. Nonsteroidal antiinflammatory agents can be useful for management of arthralgias and arthritis; it is important to keep in mind their potential hepatic, renal, and cardiovascular toxicities.

Table 158-5 Autoantibodies Commonly Associated with Systemic Lupus Erythematosus (SLE)

ANTIBODY	CLINICAL ASSOCIATION
Anti–double-stranded DNA	Correlates with disease activity, especially nephritis, in some with SLE
Anti-Smith antibody	Specific for the diagnosis of SLE
Antiribonucleoprotein antibody	Increased risk for Raynaud phenomenon and pulmonary hypertension High titer may suggest diagnosis of mixed connective tissue disorder
Anti-Ro antibody (anti-SSA antibody) Anti-La antibody (anti-SSB antibody)	Associated with sicca syndrome May suggest diagnosis of Sjögren syndrome Increased risk of neonatal lupus in offspring (congenital heart block) May be associated with cutaneous and pulmonary manifestations of SLE May be associated with isolated discoid lupus
Antiphospholipid antibodies (including anticardiolipin antibodies)	Increased risk for venous and arterial thrombotic events
Antihistone antibodies	Present in a majority of patients with drug-induced lupus May be present in SLE

Corticosteroids are a mainstay for treatment of significant manifestations of SLE and work quickly to improve acute deterioration; side effects often limit patient compliance, especially in adolescence, and potential toxicities are worrisome. It is important to limit dose and length of exposure to corticosteroids whenever possible. Potential consequences of corticosteroid therapy include growth disturbance, weight gain, striae, acne, hyperglycemia, hypertension, cataracts, avascular necrosis, and osteoporosis. The optimal dosing of corticosteroids in children and adolescents with SLE remains unknown; severe disease is often treated with high doses of intravenous methylprednisolone (e.g., 30 mg/kg/day for 3 days, followed by weekly pulses) or high doses of oral prednisone (1-2 mg/kg/day). As disease manifestations improve, corticosteroid dosages are gradually tapered over months. It often becomes necessary to introduce steroid-sparing immunosuppressive medications in order to limit cumulative steroid exposure.

Steroid-sparing immunosuppressive agents often used in the treatment of pediatric SLE include methotrexate, leflunomide, azathioprine, mycophenolate mofetil, cyclophosphamide, and belimumab. Methotrexate, leflunomide, and azathioprine are often used to treat persistent moderate disease, including arthritis, significant cutaneous or hematologic involvement, and pleural disease. Intravenous or oral cyclophosphamide is reserved for the most severe, potentially life-threatening SLE manifestations, such as renal, neurologic, and cardiopulmonary disease. Although cyclophosphamide is highly effective in controlling disease, the potential toxicities are significant, including cytopenias, infection, hemorrhagic cystitis, premature gonadal failure, and increased risk of future malignancy. Attention to adequate hydration can attenuate the risk of hemorrhagic cystitis. Fortunately, young girls are at much lower risk of gonadal failure than older women, and the use of gonadotropin-releasing hormone agonists, such as leuprolide acetate, may help prevent gonadal failure. Clinical trial data on the

use of rituximab in SLE with treatment-resistant glomerulonephritis has been largely disappointing, but results from the LUNAR study suggest there may be benefit for subpopulations of SLE patients. The FDA has approved the use of belimumab (a monoclonal antibody against BLyS, also called B-cell activating factor); when added to standard SLE therapy, belimumab improves multiple markers of disease severity. BLyS levels are elevated in SLE and relate to disease activity. Treatment reduces the number of SLE flares and decreases the dose of prednisone. Side effects include fever, nausea, and diarrhea.

The Childhood Arthritis Rheumatology Research Alliance has developed a consensus treatment plan induction therapy of newly-diagnosed proliferative lupus nephritis that is specific to the pediatric SLE population; these guidelines advise 6 mo of therapy with either cyclophosphamide or mycophenolate mofetil, used in combination with a standardized glucocorticoid regimen. For patients who fail to achieve a partial response in 6 mo it is appropriate to switch agents. Consensus statements for maintenance therapy of lupus nephritis recommend use of mycophenolate mofetil, every 3 mo IV cyclophosphamide or azathioprine for 12 mo after completing induction therapy.

Given the lifelong nature of SLE, optimal care of children and adolescents with this disease also involves preventive practices. Owing to the enhanced risk of atherosclerosis in SLE, attention to cholesterol levels, smoking status, body mass index, blood pressure, and other traditional cardiovascular risk factors is warranted. Even though the Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) study failed to support placing all children with SLE on a statin, ad hoc analyses suggest that statins may be considered for primary prevention of atherosclerotic disease in certain clinical circumstances, particularly pubertal patients with an elevated CRP. For all SLE patients, adequate intake of calcium and vitamin D is necessary to prevent future osteoporosis. Infections commonly complicate SLE, so routine immunization is recommended, as well as annual influenza vaccination and administration of the 23-valent pneumococcal vaccine. Prompt attention to febrile episodes should include an evaluation for serious infections. It should be remembered that pregnancy can worsen SLE, and obstetric complications are more common in SLE. In addition, many of the medications used to treat SLE are teratogenic. As a consequence, it is important to counsel adolescent girls about these risks and appropriate contraceptive options. SLE patients with antiphospholipid antibody syndrome are treated with long-term anticoagulation to prevent thrombotic events.

COMPLICATIONS

Within the 1st several yr of diagnosis, the most common causes of death in individuals with SLE include infection and complications of glomerulonephritis and neuropsychiatric disease (Table 158-6). Over the long-term, the most common causes of mortality also include complications of atherosclerosis and malignancy. The increased risk of premature atherosclerosis in SLE is not explained by traditional risk factors and is partly a result of the chronic immune dysregulation and inflammation associated with SLE. Increased malignancy rates may be caused by immune dysregulation as well as exposure to medications with carcinogenic potential.

Table 158-6 Morbidity in Childhood Lupus

Renal	Hypertension, dialysis, transplantation
Central nervous system	Organic brain syndrome, seizures, psychosis, neurocognitive dysfunction
Cardiovascular	Atherosclerosis, myocardial infarction, cardiomyopathy, valvular disease
Immune	Recurrent infection, functional asplenia, malignancy
Musculoskeletal	Osteopenia, compression fractures, avascular necrosis
Ocular	Cataracts, glaucoma, retinal detachment, blindness
Endocrine	Diabetes, obesity, growth failure, infertility, fetal wastage

From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders.*

PROGNOSIS

The severity of disease in pediatric SLE is notably worse than the typical course for most adult-onset SLE. However, owing to advances in the diagnosis and treatment of SLE, survival has improved dramatically over the past 50 yr. Currently, the 5 yr survival rate for pediatric SLE is ~95%, though the 10 yr survival rate remains ~80-90%. Given their long burden of disease, children and adolescents with SLE face a high risk of future morbidity and mortality from the disease and its complications, especially atherosclerosis and malignancy (see Table 158-6). Given the complex and chronic nature of SLE, it is optimal for children and adolescents with SLE to be treated by pediatric rheumatologists in a multidisciplinary clinic.

Bibliography is available at Expert Consult.

158.1 Neonatal Lupus

Deborah Friedman, Rebecca E. Sadun, Stacy P. Ardoin, and Laura E. Schanberg

Neonatal lupus, an entity distinct from SLE, is one of the few rheumatic disorders manifesting in the neonate. Clinical manifestations of neonatal lupus include a characteristic annular or macular rash typically affecting the face (especially the periorbital area), trunk, and scalp (Fig. 158-3). The rash typically appears within the 1st 6 wk of life after exposure to ultraviolet light and lasts 3-4 mo; however, it can be present at birth. Infants may also have cytopenias and hepatitis, but the most feared complication is congenital heart block. Conduction system abnormalities range from prolongation of the PR interval to complete heart block, with development of progressive

Figure 158-3 Neonatal lupus syndrome. Typical rash, often photosensitive with a malar distribution, appearing as annular plaques with erythema and scaling. *(Reproduced, with written parental permission, from Pain C, Beresford MW: Neonatal lupus syndrome,* Paediatr Child Health *17:223–227, 2007.)*

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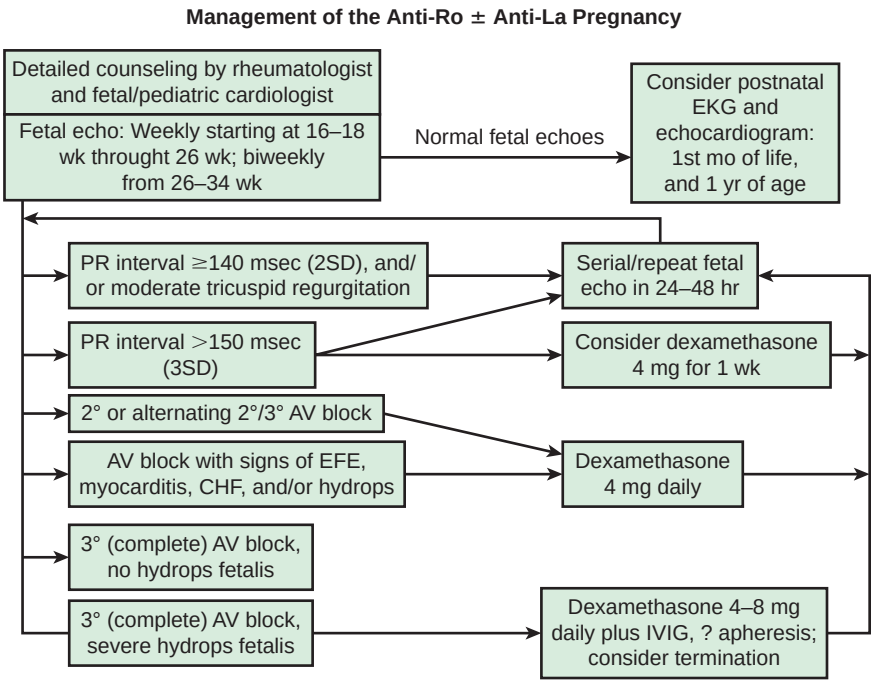

Figure 158-4 **Algorithm for the management of the anti-Ro ± anti-La pregnancy.** All such pregnancies should include counseling and serial fetal echocardiograms.

cardiomyopathy in the most severe cases. The noncardiac manifestations of neonatal lupus are usually reversible, whereas congenital heart block is permanent. Conduction system abnormalities can be detected in utero by fetal echocardiogram beginning at 16 wk of gestational age.

Neonatal lupus results from the passive transfer of maternal immunoglobulin G autoantibodies to the fetus. The vast majority of neonatal lupus cases are associated with maternal anti-Ro (also known as SSA) and anti-La antibodies (also known as SSB). Despite the clear association with maternal autoantibodies, their presence alone is not sufficient to cause disease, as ~2% of offspring born to mothers with anti-Ro and anti-La antibodies experience congenital heart block.

In vitro studies suggest that during cardiac development, Ro and La antigens may be exposed on the surface of cardiac cells in the proximity of the atrioventricular node, making the antigens accessible to maternal autoantibodies. Binding incites a local immune response, resulting in fibrosis within the conduction system as well as more extensive disease in fatal cases. In the skin, exposure to ultraviolet light results in cell damage and the subsequent exposure of Ro and La antigens, inducing a similar local inflammatory response that produces the characteristic rash.

Although the scant clinical trial data have been mixed, fluorinated corticosteroids (dexamethasone or betamethasone), intravenous immunoglobulin, plasmapheresis, hydroxychloroquine, and terbutaline (combined with steroids) have been used in pregnant women with anti-Ro or anti-La antibodies to prevent occurrence or progression of fetal cardiac abnormalities, including congenital heart block, endocardial fibroelastosis, and hydrops fetalis. Most encouraging are retrospective cohort studies suggesting maternal treatment with hydroxychloroquine may provide effective prophylaxis against congenital heart block. The mechanisms of action probably involve changes in acidification of endosomes and their interaction with Toll-like receptors. All clinical data on the use of hydroxychloroquine in pregnancy points to safety, and there are ongoing prospective clinical studies examining efficacy in the prevention of neonatal lupus syndrome in pregnant women known to be anti-Ro and/or anti-La positive.

Fluorinated corticosteroids seem to improve cases of hydrops. Significant conduction system abnormalities after birth are treated with cardiac pacing and occasionally intravenous immunoglobulin and steroids, while severe cardiomyopathy may require cardiac transplantation. Transient, noncardiac manifestations are conservatively managed, with topical steroids used occasionally to treat the rash.

Because maternal autoantibodies gain access to the fetus via the placenta at the 16th wk of gestation, all pregnant women with circulating anti-Ro or anti-La antibody (or those with a history of offspring with neonatal lupus or congenital heart block) are monitored by a pediatric cardiologist with regular fetal electrocardiography from 16 wk of gestation until delivery. If fetal bradycardia is found unexpectedly during in utero monitoring, screening for maternal anti-Ro and anti-La antibodies is warranted.

In contrast to SLE, neonatal lupus is not characterized by ongoing immune dysregulation, although infants with neonatal lupus may be at some increased risk for development of future autoimmune disease. A mother who has borne a child with congenital heart block caused by neonatal lupus has an approximately 17% risk of recurrence with future pregnancies. With cardiac pacing, children with conduction system disease in the absence of cardiomyopathy have an excellent prognosis. If the conduction defect is not addressed, affected children are at risk for exercise intolerance, arrhythmias, and death. A proposed management algorithm is presented in Figure 158-4.

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Chapter 159

Juvenile Dermatomyositis

Angela Byun Robinson and Ann M. Reed

Juvenile dermatomyositis (JDM) is the most common inflammatory myositis in children, distinguished by proximal muscle weakness and a characteristic rash. Inflammatory cell infiltrates result in vascular inflammation, the underlying pathology in this disorder.

ETIOLOGY

Evidence suggests that the etiology of JDM is multifactorial, based on genetic predisposition and an unknown environmental trigger. Human

leukocyte antigen (HLA) alleles such as B8, DRB1*0301, DQA1*0501, and DQA1*0301 are associated with increased susceptibility to JDM in selected populations. Maternal microchimerism may play a part in the etiology of JDM by causing graft-versus-host disease or autoimmune phenomena. Persistent maternal cells have been found in blood and tissue samples of children with JDM. An increased number of these maternal cells are positive for HLA-DQA1*0501, which may assist with transfer or persistence of chimeric cells. Specific cytokine polymorphisms in tumor necrosis factor-α promoter and variable number tandem repeats of the interleukin-1 receptor antagonist may increase genetic susceptibility. These polymorphisms are common in the general population. A history of infection in the 3 mo prior to disease onset is commonly reported; multiple studies have failed to produce a causative organism. Constitutional signs and upper respiratory symptoms predominate, but one-third of patients report preceding gastrointestinal (GI) symptoms. Group A streptococcus, upper respiratory infections, GI infections, coxsackievirus B, toxoplasma, enteroviruses, parvovirus B19, and multiple other organisms have been postulated as possible pathogens in the etiology of JDM. Despite these concerns, results of serum antibody testing and polymerase chain reaction amplification of the blood and muscle tissue for multiple infectious diseases have not been revealing. Environmental factors may also play a contributing role, with geographic and seasonal clustering reported; however, no clear theory of etiology has emerged.

EPIDEMIOLOGY

The incidence of JDM is approximately 3 cases/1 million children/yr without racial predilection. Peak age of onset is between 4 and 10 yr. There is a second peak of dermatomyositis onset in late adulthood (45-64 yr), but adult-onset dermatomyositis appears to be a distinctly separate entity in prognosis and etiology. In the United States, the ratio of girls to boys with JDM is 2:1. Multiple cases of myositis in a single family are rare, but familial autoimmune disease may be increased in families with children who have JDM than in families of healthy children. Reports of seasonal association have not been confirmed, although clusters of cases may occur.

PATHOGENESIS

Interferon upregulates genes critical in immunoregulation and major histocompatibility complex (MHC) class I expression, activates natural killer cells, and supports dendritic cell maturation. Upregulation of gene products controlled by type I interferons occurs in patients with dermatomyositis, potentially correlating with disease activity and holding promise as clinical biomarkers.

It appears that children with genetic susceptibility to JDM (HLA-DQA1*0501, HLA-DRB*0301) may have prolonged exposure to maternal chimeric cells and/or an unknown environmental trigger. Once triggered, an inflammatory cascade with type I interferon response leads to upregulation of MHC class I expression and maturation of dendritic cells. Overexpression of MHC class I upregulates adhesion molecules, which influence migration of lymphocytes, leading to inflammatory infiltration of muscle. In an autoregulatory feedback loop, muscle inflammation increases the type I interferon response, regenerating the cycle of inflammation. Cells involved in the inflammatory cascade include natural killer cells (CD56), T-cell subsets (CD4, CD8, Th17), monocytes/macrophages (CD14), and plasmacytoid dendritic cells. Neopterin, interferon-inducible protein 10, monocyte chemoattractant protein, myxovirus resistance protein, and von Willebrand factor products, as well as other markers of vascular inflammation may be elevated in patients with JDM who have active inflammation.

Table 159-1 Diagnostic Criteria for Juvenile Dermatomyositis

Classic rash	Heliotrope rash of the eyelids Gottron papules
Plus 3 of the following:	
Weakness	Symmetric Proximal
Muscle enzyme elevation (≥1)	Creatine kinase Aspartate aminotransferase Lactate dehydrogenase Aldolase
Electromyographic changes	Short, small polyphasic motor unit potentials Fibrillations Positive sharp waves Insertional irritability Bizarre, high-frequency repetitive discharges
Muscle biopsy	Necrosis Inflammation

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Table 159-2 Clinical Features of Juvenile Dermatomyositis During the Course of the Disease

FEATURE	%
Muscle weakness	90-100
Dysphagia or dysphonia	13-40
Muscle atrophy	10
Muscle pain and tenderness	30-83
Skin lesions	85-100
Heliotrope rash of eyelids	66-83
Gottron papules	57-91
Erythematous rash of malar/facial area	42-100
Periungual capillary changes	80
Photosensitive rash	5-42
Ulcerations	22-30
Calcinosis	12-30
Lipodystrophy	11-14
Raynaud phenomenon	2-15
Arthritis and arthralgia	22-58
Joint contractures	26-27
Fever	16-46
Gastrointestinal signs and symptoms	8-22
Restrictive pulmonary disease	4-32
Interstitial lung disease	1-7
Cardiac involvement	0-3

From Rider LG, Lindsley CB, Cassidy JT: Juvenile dermatomyositis. In Cassidy JT, Petty RE, Laxer RM, et al, editors, Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Table 24-20, p. 410.*

CLINICAL MANIFESTATIONS

Children with JDM present with either rash, insidious onset of weakness, or both. Fevers, dysphagia or dysphonia, arthritis, muscle tenderness, and fatigue are also commonly reported at diagnosis (Tables 159-1 and 159-2).

Rash develops as the first symptom in 50% of cases and appears concomitant with weakness only 25% of the time. Children often exhibit extreme photosensitivity to ultraviolet light exposure with generalized erythema in sun-exposed areas. If seen over the chest and neck, this erythema is known as the **"shawl sign."** Erythema is also commonly seen over the knees and elbows. The characteristic **heliotrope rash** (Fig. 159-1) is a blue-violet discoloration of the eyelids that may be associated with periorbital edema. Facial erythema crossing the

nasolabial folds is also common, in contrast to the malar rash without nasolabial involvement typical of systemic lupus erythematosus. Classic **Gottron papules** (Fig. 159-2) are bright pink or pale, shiny, thickened or atrophic plaques over the proximal interphalangeal joints and distal interphalangeal joints and occasionally on the knees, elbows, small joints of the toes, and ankle malleoli. The rash of JDM is sometimes mistaken for eczema or psoriasis. Rarely, a thickened erythematous and scaly rash develops in children over the palms (known as **mechanic's hands)** and soles along the flexor tendons, which is associated with anti–Jo-1 antibodies.

Evidence of small vessel inflammation is often visible in the nailfolds and gums as individual capillary loops that are thickened, tortuous, or absent (Fig. 159-3). Telangiectasias may be visible to the naked eye but are more easily visualized under capillaroscopy or with use of a magnifier such as an ophthalmoscope. Severe vascular inflammation causes cutaneous ulcers on toes, fingers, axillae, or epicanthal folds.

Weakness associated with JDM is often insidious and difficult to differentiate from fatigue at onset. It is typically symmetric, affecting proximal muscles such as the neck flexors, shoulder girdle, and hip flexors. Parents may report difficulty climbing stairs, combing hair, and getting out of bed. Examination reveals inability to perform a sit-up, head lag in a child after infancy, and **Gower sign** (use of hands on thighs to stand from a sitting position). Patients with JDM may roll to the side rather than sit straight up from lying to compensate for truncal weakness. Approximately half of children exhibit muscle tenderness as a result of muscle inflammation.

Esophageal and respiratory muscles are also affected, resulting in aspiration or respiratory failure. It is essential to assess for dysphonia or nasal speech, palatal elevation with gag, dysphagia, and gastroesophageal reflux by means of history, physical exam, and swallow study, if symptoms are present. Respiratory muscle weakness can be a medical emergency and lead to respiratory failure. Children with respiratory muscle weakness do not manifest typical symptoms of impending respiratory failure with increased work of breathing, instead demonstrating hypercarbia rather than hypoxemia.

Lipodystrophy and **calcinosis** (Fig. 159-4) are thought to be associated with long-standing or undertreated disease. Dystrophic deposition of calcium phosphate, hydroxyapatite, or fluoroapatite crystals occurs in subcutaneous plaques or nodules, resulting in painful ulceration of the skin with extrusion of crystals or calcific liquid. Calcinosis is reported in up to 40% of children with JDM, but the prevalence is thought to be lower in children who are treated early and aggressively. In rare instances, an "exoskeleton" of calcium deposition forms, greatly limiting mobility. Lipodystrophy results in progressive loss of subcutaneous and visceral fat, typically over the face and upper body, and may be associated with a metabolic syndrome similar to polycystic ovarian syndrome with insulin resistance, hirsutism, acanthosis,

Figure 159-1 The facial rash of juvenile dermatomyositis. There is erythema over the bridge of the nose and malar areas with violaceous (heliotropic) discolorations of the upper eyelids.

Figure 159-2 The rash of juvenile dermatomyositis. The skin over the metacarpal and proximal interphalangeal joints may be hypertrophic and pale red (Gottron papules).

Figure 159-3 Nailfold capillary pattern in rheumatic disease. **A,** Normal nailfold capillary pattern in a healthy child with a homogeneous distribution and uniform appearance of capillary loops. **B,** The nailfold capillary pattern in a child with juvenile dermatomyositis shows dropout of capillary end loops, resulting in a wide band of avascularity. Dilated, tortuous capillaries can also be seen. **C,** Severe periungual telangiectasias may be seen without microscopy.

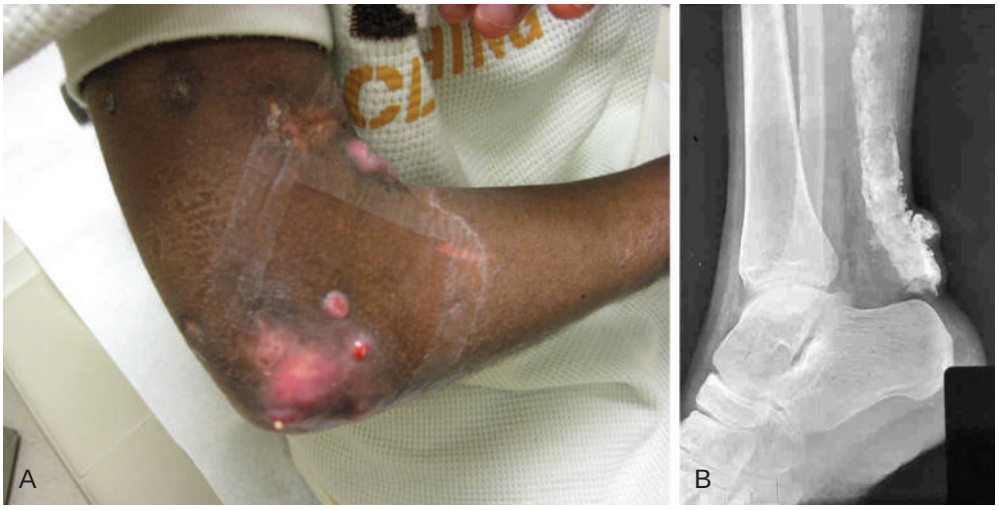

Figure 159-4 Rash and calcifications in dermatomyositis. **A,** Skin effects of calcification. **B,** Radiographic evidence of calcification.

hypertriglyceridemia, and abnormal glucose tolerance. Lipodystrophy may be generalized or localized.

Rarely, vasculitis of the GI tract develops in children with severe JDM, with crampy abdominal pain, pancreatitis, GI bleeding, and potential for intestinal perforation or infarction. Involvement of the cardiac muscle with pericarditis, myocarditis, and conduction defects has been reported. An association with malignancy at disease onset is observed in adults with dermatomyositis but very rarely in children.

DIAGNOSIS

Diagnosis of dermatomyositis requires the presence of characteristic rash as well as at least three signs of muscle inflammation and weakness (see Table 159-1). Diagnostic criteria developed in 1975 predate the use of MRI and have not been validated in children. Diagnosis is often delayed because of the insidious nature of disease onset.

Electromyography shows signs of myopathy (increased insertional activity, fibrillations, and sharp waves) as well as muscle fiber necrosis (decreased action potential amplitude and duration). Nerve conduction studies are typically normal unless severe muscle necrosis and atrophy are present. It is important that electromyography (EMG) be performed in a center with experience in pediatric EMG and its interpretation. Muscle biopsy is typically indicated when diagnosis is in doubt or for grading disease severity. Biopsy of involved muscle reveals focal necrosis and phagocytosis of muscle fibers, fiber regeneration, endomysial proliferation, inflammatory cell infiltrates and vasculitis, and tubuloreticular inclusion bodies within endothelial cells. Findings of lymphoid structures and vasculopathy may portend more severe disease.

Some children present with classic rash but no apparent muscle weakness or inflammation; this variation is called **amyopathic JDM or dermatomyositis sine myositis**. It is unclear whether these children have isolated skin disease or mild undetected muscle inflammation, risking progression to more severe muscle involvement with long-term sequelae such as calcinosis and lipodystrophy if untreated.

Differential diagnosis depends on the presenting symptoms. If the presenting complaint is solely weakness without rash or atypical disease, other causes of myopathy should be considered, including polymyositis, infection-related myositis (influenza A and B, coxsackievirus B, and other viral illnesses), muscular dystrophies (Duchenne and Becker as well as others), myasthenia gravis, Guillain-Barré syndrome, endocrinopathies (hyperthyroidism, hypothyroidism, Cushing syndrome, Addison disease, parathyroid disorders), mitochondrial myopathies, and metabolic disorders (glycogen and lipid storage diseases). Infections associated with prominent muscular symptoms include trichinosis, *Bartonella* infection, toxoplasmosis, and staphylococcal pyomyositis. Blunt trauma and crush injuries may lead to transient rhabdomyolysis with myoglobinuria. Myositis in children may also be associated with vaccinations, drugs, growth hormone, and graft-versus-host disease. The rash of JDM may be confused with eczema, dyshidrosis, psoriasis, malar rash from systemic lupus erythematosus, capillary telangiectasias from Raynaud phenomenon, and other rheumatic diseases. Muscle inflammation is also seen in children with systemic lupus erythematosus, juvenile idiopathic arthritis, mixed connective tissue disease, inflammatory bowel disease, and antineutrophil cytoplasmic antibody–positive vasculitides. Table 159-3 compares other juvenile inflammatory myositis disorders.

LABORATORY FINDINGS

Elevated serum levels of **muscle-derived enzymes** (creatine kinase, aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) reflect muscle inflammation. Not all enzyme levels rise with inflammation in a specific individual; alanine aminotransferase is most commonly elevated on initial presentation, whereas the creatine kinase level may be normal. The erythrocyte sedimentation rate is often normal, and the rheumatoid factor test result is typically negative. There may be anemia consistent with chronic disease. Antinuclear antibody is present in >80% of children with JDM. Results of tests for antibodies to SSA, SSB, Sm, ribonucleoprotein, and double-stranded DNA are generally negative. Antibodies to Pm/Scl identify a small, distinct subgroup of myopathies with a protracted disease course, often complicated by pulmonary interstitial fibrosis and/or cardiac involvement. Similar to what is seen in adults, the presence of myositis-specific autoantibodies in JDM such as anti–Jo-1, anti–Mi-2, anti-p155/140, anti-NXP2, and other myositis-specific autoantibodies help define distinct clinical subsets and may predict the development of complications, although differences remain in certain aspects such as malignancy between adults and children.

Radiographic studies aid both diagnosis and medical management. MRI using T2-weighted images and fat suppression (Fig. 159-5) identifies active sites of disease, reducing sampling error and increasing the sensitivity of muscle biopsy and EMG, results of which are nondiagnostic in 20% of instances if the procedures are not directed by MRI. Extensive rash and abnormal MRI findings may be found despite normal serum levels of muscle-derived enzymes. Muscle biopsy often demonstrates evidence of disease activity and chronicity that is not suspected from the levels of the serum enzymes alone.

A contrast swallow study may document palatal dysfunction and risk of aspiration. Pulmonary function testing detects a restrictive defect consistent with respiratory weakness and reduced diffusion capacity of carbon monoxide from alveolar fibrosis associated with other connective tissue diseases. Serial measurement of vital capacity or negative inspiratory force can document changes in respiratory weakness, especially in an inpatient setting. Calcinosis is seen easily on radiographs, along the fascial planes and within muscles.

Table 159-3 Phenotypic Characteristics of the Clinical Subgroups of Juvenile Myositis*

CHARACTERISTIC	JDM	JPM	JCTM
Demographics			
Median age at diagnosis (yr)	Youngest (7.4 yr)	Oldest (12.1 yr)	Intermediate (10.2 yr)
Race	Predominantly white (71.2%)	Black (39.4%)	Black or other (49.0%)
Severity at onset	Mild or moderate severity	**Severe or very severe onset**	Mild or moderate severity
Median delay to diagnosis (mo)	4 mo	3.5 mo	Longer delay (7 mo)
Clinical features	Gottron papules Heliotrope rash **Periungual capillary abnormalities** **Malar rash** *Photosensitivity* *Linear extensor erythema*† Cuticular overgrowth Mucous membrane involvement "V-sign" and "shawl-sign" rashes Skin ulcerations Dyspnea on exertion	*Weight loss* Falling episodes Raynaud phenomenon Abnormal PFT Dyspnea on exertion Cardiac abnormalities on EKG or ECHO	Gottron papules Heliotrope rash **Malar rash** **Raynaud phenomenon** **Interstitial lung disease** **Arthralgia** *Linear extensor erythema*† *Mucous membrane involvement* *Arthritis* *Photosensitivity* *Sclerodactyly* *Periungual capillary abnormalities*† Cuticular overgrowth Abdominal pain, GI bleeding Dyspnea on exertion Weight loss
Autoantibodies	Intermediate ANA titer (median, 1:320) *Anti-p155/140*† Anti-MJ Anti-Mi-2	Intermediate ANA titer (median, 1:320) Anti-SRP Anti-aminoacyl-tRNA synthetase (anti–Jo-1)	Highest ANA titer (median, 1:1280) **Anti-U1-RNP** Anti-PM-Sc1 Anti-Ro Anti-SM Anti-La All other U-RNP autoantibodies
Laboratory features	*Lowest CK level (median, 829 U/L)*	**Highest CK level (median, 5027 U/L)** Highest levels of aldolase and ALT	Intermediate CK level (median 1208 U/L)
Outcome	Low mortality (2.4%) Calcinosis (34.0%)	Medium mortality (6.3%) **Frequently hospitalized (71.9%)** Wheelchair use	Highest mortality (14.6%)

ALT, alanine aminotransferase; ANA, antinuclear antibody; CK, creatine kinase; ECHO, echocardiogram; EKG, electrocardiogram; GI, gastrointestinal; JCTM, juvenile myositis overlapping with another autoimmune or connective tissue disease; JDM, juvenile dermatomyositis; JPM, juvenile polymyositis; PFT, pulmonary function test; tRNA, transfer RNA.

*Bold indicates significant in logistic regression; *italics* indicates top variables entered in pruned-down random forest models. Other variables included in this table were significant in univariable analysis to $p \leq 0.01$.

†Removed from logistic regression analyses because variable was either 100% or 0% in 1 of the compared subgroups. Gottron papules and heliotrope rash, which were part of the definition of cases of dermatomyositis, were not entered into multivariable analyses.

Modified from Shah M, Mamyrova G, Targoff IN, et al: The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore) *92:25–41, 2013, Table 9, p. 36.*

TREATMENT

The aid of an experienced pediatric rheumatologist is invaluable in outlining an appropriate course of treatment for a child with JDM. Prior to the advent of corticosteroids, one-third of patients spontaneously improved, one-third had a chronic, lingering course, and one-third died from the disease. Corticosteroids have altered the course of disease, lowering morbidity and mortality. Methotrexate decreases the length of treatment with corticosteroids, thereby reducing morbidity from steroid toxicity. Intravenous gammaglobulin is frequently used as an adjunct for treatment of severe disease.

Corticosteroids are still the mainstay of treatment. In a clinically stable child without debilitating weakness, oral prednisone at 2 mg/kg/day (maximum 60 mg daily) is usually started. Children with GI involvement have decreased absorption of oral steroids and require intravenous administration. In more-severe cases with respiratory or oropharyngeal weakness, high-dose pulse methylprednisolone is used (30 mg/kg/day for 3 days, maximum dose 1 g/day) with ongoing weekly or monthly IV dosing along with daily oral corticosteroids as needed. Corticosteroid dosage is slowly tapered over a period of 12 mo, after indicators of inflammation (muscle enzymes) normalize and strength improves.

Weekly oral, intravenous, or subcutaneous methotrexate (the lesser of 1 mg/kg or 15 mg/m^2, maximum 40 mg) is commonly used as a steroid-sparing agent in JDM. The concomitant use of methotrexate halves the cumulative dosage of steroids needed for disease control. Risks of methotrexate include immunosuppression, blood count dyscrasias, chemical hepatitis, pulmonary toxicity, nausea/vomiting, and teratogenicity. Folic acid is typically given with methotrexate starting at a dose of 1 mg daily to reduce toxicity and side effects of folate inhibition (oral ulcers, nausea, and anemia). Children who are taking immunosuppressive medications such as methotrexate should avoid live-virus vaccination, although inactivated influenza vaccination is recommended yearly.

Hydroxychloroquine has little toxicity risk and is used as a secondary disease-modifying agent to reduce rash and maintain remission. Typically, it is administered at doses between 4 and 6 mg/kg/day orally

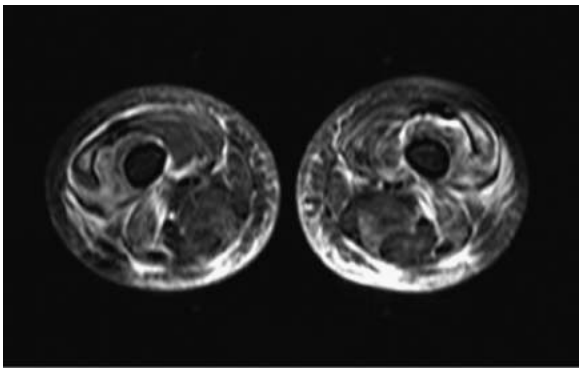

Figure 159-5 MRI using T2-weighting and fat suppression of the proximal muscle of the lower extremities of a child with juvenile dermatomyositis with normal muscle enzyme levels. There is focal inflammatory myopathy. The bright areas reflect the inflammatory response in involved muscle. The darker areas are more normal. Identification of involved areas by MRI directs the location of the muscle biopsy or electromyography.

in either tablet or liquid form. Ophthalmologic follow-up 1-2 times per year to monitor for rare retinal toxicity is recommended. Other side effects include hemolysis in patients with glucose-6-phosphate deficiency, GI intolerance, and skin/hair discoloration.

The use of rituximab in a trial of steroid-dependent patients with resistant inflammatory myopathies, including JDM, did not meet the primary study end point showing a difference in time to improvement between subjects given rituximab at baseline or at 8 wk, but overall, 83% of all subjects met the definition of improvement in the trial. Reports of the use of other biologic agents are based on case reports with mixed results.

Other medications for severe unresponsive disease include intravenous immunoglobulin, mycophenolate mofetil, cyclosporine, and cyclophosphamide. Children with pharyngeal weakness may need nasogastric or gastrostomy feedings to avoid aspiration, whereas those with GI vasculitis require full bowel rest. Rarely, children with severe respiratory weakness require ventilator therapy and even tracheostomy until the respiratory weakness improves.

Physical therapy and occupational therapy are integral parts of the treatment program, initially for passive stretching early in the disease course and then for direct reconditioning of muscles to regain strength and range of motion. Therapy may improve strength muscle measures and cardiovascular fitness. Bed rest is not indicated, because weight bearing improves bone density and prevents contractures. Social work and psychology services may facilitate adjustment to the frustration of physical impairment in a previously active child and aid with sleep disturbances associated with rheumatic disease.

All children with JDM should avoid sun exposure and apply high sun protection factor sunscreen daily, even in winter and on cloudy days. Vitamin D and calcium supplements are indicated for all children undergoing long-term corticosteroid therapy, in an attempt to reduce osteopenia and osteoporosis from medication.

COMPLICATIONS

Most complications from JDM are related to prolonged and severe weakness, including muscle atrophy, to cutaneous calcifications and scarring or atrophy, and to lipodystrophy. Secondary complications from medical treatments are also common. Children with acute and severe weakness are at risk for aspiration pneumonia and respiratory failure and occasionally require nasogastric feeding and mechanical ventilation until weakness improves. Crampy abdominal pain and occult GI bleeding may indicate bowel wall vasculitis and lead to ischemia, GI bleeding, and perforation if not treated with complete bowel rest and aggressive treatment for the underlying inflammation. Surgery should be avoided if possible, because the GI vasculitis is diffuse and not easily amenable to surgical intervention. Contrast-enhanced CT may show dilation or thickening of the bowel wall, intraluminal air, or evidence of bowel necrosis. Cardiac involvement by JDM is rare but includes arrhythmias.

Pathologic calcifications may be related to severity of disease and prolonged delay to treatment and potentially to genetic polymorphisms of tumor necrosis factor -α-308. Calcium deposits tend to form in subcutaneous tissue and along muscle. Some ulcerate through the skin and drain a soft calcific liquid, and others manifest as hard nodules along extensor surfaces or embedded along muscle. Draining lesions serve as a nidus for cellulitis or osteomyelitis. Nodules cause skin inflammation that may mimic cellulitis. Spontaneous regression of calcium deposits may occur, but there is no evidence-based recommendation for treatment of calcinosis.

Lipodystrophy manifests in 10-40% of patients with JDM and can be difficult to recognize. Fat atrophy may be generalized, partial, or local. Lipodystrophy has been associated with insulin resistance, acanthosis nigricans, dyslipidemia, hypertension, and menstrual irregularity, similar to features seen in polycystic ovarian disease or metabolic syndrome.

Children receiving prolonged corticosteroid therapy are prone to complications such as cessation of linear growth, weight gain, hirsutism, adrenal suppression, immunosuppression, striae, cushingoid fat deposition, mood changes, osteoporosis, cataracts, avascular necrosis, and steroid myopathy. Families should be counseled on the effects of corticosteroids and advised to use medical alert identification and to consult a nutritionist regarding a low-salt, low-fat diet with adequate vitamin D and calcium supplementation.

PROGNOSIS

The mortality rate in JDM has decreased since the advent of corticosteroids, from 33% to currently approximately 1%; little is known about the long-term consequences of persistent vascular inflammation. The period of active symptoms has decreased from about 3.5 yr to <1.5 yr with more aggressive immunosuppressive therapy; the vascular, skin, and muscle symptoms of children with JDM generally respond well to therapy. At 7 yr of follow-up, 75% of patients have little to no residual disability, but 25% continue to have chronic weakness and 40% have chronic rash. Up to one-third may need long-term medications to control their disease. Children with JDM appear able to repair inflammatory damage to vasculature and muscle.

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Chapter 160

Scleroderma and Raynaud Phenomenon

Heather A. Van Mater and C. Egla Rabinovich

Juvenile scleroderma encompasses a range of conditions unified by the presence of fibrosis of the skin. Juvenile scleroderma is divided into 2 major categories, **juvenile localized scleroderma** (**JLS**, also known as **morphea**), which is largely limited to the skin, and juvenile **systemic sclerosis** (**JSSc**), with multisystem organ involvement. Localized disease is the predominant type seen in pediatric populations (>95%), but systemic sclerosis is associated with mortality and severe morbidity.

ETIOLOGY AND PATHOGENESIS

The etiology of scleroderma is unknown, but the mechanism of disease appears to be a combination of a vasculopathy, autoimmunity, immune activation, and fibrosis. Triggers, including trauma, infection, and, possibly, subclinical graft-versus-host reaction from persistent maternal cells (microchimerism), injure vascular endothelial cells, resulting in increased expression of adhesion molecules. These molecules entrap platelets and inflammatory cells, resulting in vascular changes with manifestations such as Raynaud phenomenon and pulmonary hypertension. Inflammatory cells infiltrate the area of initial vascular damage, causing further vascular damage and resulting in thickened artery walls and reduction in capillary numbers. Macrophages and other inflammatory cells then migrate into affected tissues and secrete cytokines that induce fibroblasts to reproduce and synthesize excessive amounts of collagen, resulting in fibrosis and subsequent lipoatrophy, dermal fibrosis, with loss of sweat glands and hair follicles. In late stages, the entire dermis may be replaced by compact collagen fibers.

Autoimmunity is believed to be a key process in the pathogenesis of both localized and systemic scleroderma, given the high percentage of affected children with autoantibodies. Children with localized disease often have a positive antinuclear antibody (ANA) test result (42%), and 47% of this subgroup have antihistone antibodies. Children with JSSc have higher rates of ANA positivity (80.7%) and may have anti-Scl 70 antibody (34%, antitopoisomerase I). The relationship between specific autoantibodies and the various forms of scleroderma is not well understood, and all antibody test results may be negative, especially in JLS.

CLASSIFICATION

Localized scleroderma is distinct from systemic scleroderma and rarely progresses to systemic disease. Within the category of JLS there are several subtypes that are differentiated by both the distribution of the lesions and the depth of involvement (Table 160-1). Up to 15% of children have a combination of 2 or more subtypes.

EPIDEMIOLOGY

Juvenile scleroderma is rare, with an estimated prevalence of 1/100,000. Localized scleroderma is far more common than SSc in children, by a 10:1 ratio, with **linear scleroderma** being the most common subtype. LS is predominantly a pediatric condition, with 65% of patients diagnosed before age 18 yr. After age 8 yr the female:male ratio for both LS and SSc is approximately 3:1, whereas in patients younger than 8 yr there is no sex predilection.

CLINICAL MANIFESTATIONS

Localized Scleroderma

The onset of scleroderma is generally insidious, and manifestations vary according to disease subtype. The initial skin manifestations of localized disease usually include erythema or a bluish hue seen around an area of waxy induration; subtle erythema may be the only presenting sign (Fig. 160-1). Edema and erythema are followed by indurated, hypopigmented or hyperpigmented, atrophic lesions (Fig. 160-2). **LS** varies in size from a few centimeters to the entire length of the extremity, with varying depth. Patients sometimes present with arthralgias, synovitis, or flexion contractures (Fig. 160-3). Children also experience limb length discrepancies as a result of growth impairment caused by involvement of muscle and bone. Children with **en coup de sabre** (Fig. 160-4) may have symptoms unique to central nervous system involvement, such as seizures, hemifacial atrophy, ipsilateral uveitis, and learning/behavioral changes.

Up to 25% of children with LS have extracutaneous manifestations, most commonly arthritis (47%) and neurologic symptoms (17%) associated with en coup de sabre.

Systemic Scleroderma

SSc also has an insidious onset with a prolonged course characterized by periods of remission and exacerbation, ending in either remission or, more commonly, chronic disability and death.

The skin manifestations of SSc include an early phase of edema that spreads proximally from the dorsum of the hands and fingers and includes the face. An eventual decrease in edema is followed by induration and fibrosis of skin, ultimately resulting in loss of subcutaneous fat, sweat glands, and hair follicles. Later, atrophic skin becomes shiny and waxy in appearance. As lesions spread proximally, flexion contractures develop at the elbows, hips, and knees associated with secondary muscle weakness and atrophy. In the face, this process results in a small oral stoma with decreased mouth aperture. Skin ulceration over pressure points, such as the elbows, may be associated with subcutaneous calcifications. Severe Raynaud phenomenon causes ulceration of the fingertips with subsequent loss of tissue pulp and tapered fingers (**sclerodactyly**) (Fig. 160-5). Resorption of the distal tufts of the distal phalanges may occur (**acroosteolysis**). Hyperpigmented postinflammatory changes surrounded by atrophic depigmentation gives a

Table 160-1 Classification of Pediatric Scleroderma (Morphea)

LOCALIZED SCLERODERMA
Plaque Morphea
Confined to dermis, occasionally superficial panniculus
Well-circumscribed circular area of induration, often a central waxy, ivory-colored area surrounded by a violaceous halo; unilateral
Generalized Morphea
Involves dermis primarily, occasionally panniculus
Defined as confluence of individual morphea plaques or lesions in 3 or more anatomic sites; more likely to be bilateral
Bullous Morphea
Bullous lesions that can occur with any of the subtypes of morphea
Linear Scleroderma
Linear lesions can extend through the dermis, subcutaneous tissue, and muscle to underlying bone; more likely unilateral
Limbs/trunk:
One or more linear streaks of the extremities or trunk
Flexion contracture occurs when lesion extends over a joint; limb length discrepancies
En coup de sabre:
Involves the scalp and/or face; lesions can extend into the central nervous system, resulting in neurologic sequelae, most commonly seizures and headaches
Parry Romberg syndrome:
Hemifacial atrophy without a clearly definable en coup de sabre lesion; can also have neurologic involvement
Deep Morphea
Involves deeper layers, including panniculus, fascia, and muscle; more likely to be bilateral
Subcutaneous morphea:
Primarily involves the panniculus or subcutaneous tissue
Plaques are hyperpigmented and symmetric
Eosinophilic fasciitis:
Fasciitis with marked blood eosinophilia
Fascia is the primary site of involvement; typically involves extremities
Classic description is "peau d'orange" or orange peel texture, but early disease manifests as edema (see Fig. 160-2)
Morphea profunda:
Deep lesion extending to fascia and sometimes muscle, but may be limited to a single plaque, often on trunk
Disabling pansclerotic morphea of childhood:
Generalized full-thickness involvement of skin on the trunk, face and extremities, sparing finger tips and toes
SYSTEMIC SCLEROSIS
Diffuse
Most common type in childhood
Symmetric thickening and hardening of the skin (sclerosis) with fibrous and degenerative changes of viscera
Limited
Rare in childhood
Previously known as CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) syndrome

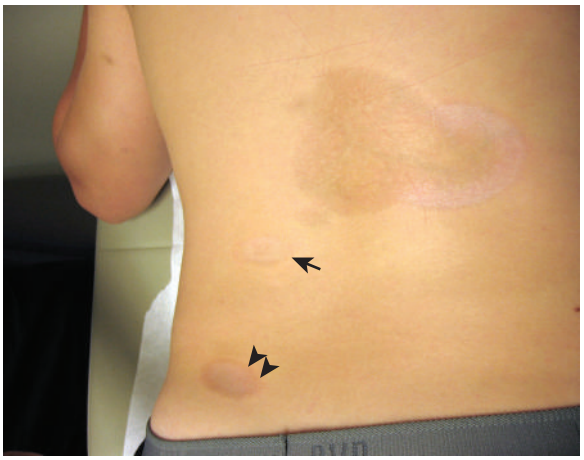

Figure 160-1 Boy with generalized morphea. Note the active circular lesion *(arrowheads)* with a surrounding rim of erythema. The largest lesion has areas of postinflammatory hyperpigmentation and depression with an area of erythema on the right. The small lesion *(arrow)* demonstrates depression caused by lipoatrophy.

Figure 160-2 Inactive linear scleroderma demonstrating hyperpigmented lesion with areas of normal skin (skip lesions).

Figure 160-3 Child with untreated linear scleroderma resulting in knee contracture, immobility of ankle, chronic skin breakdown of scar on the lateral knee, and areas of hypopigmentation and hyperpigmentation. The affected leg is 1 cm shorter.

Figure 160-4 Child with en coup de sabre lesion on scalp extending down to forehead. Prior to treatment the skin on the scalp was bound down with chronic skin breakdown. Note the area of hypopigmentation extending down the forehead *(arrows)*.

Figure 160-5 Sclerodactyly and finger ulcerations in a patient with systemic sclerosis who is poorly compliant with treatment.

salt-and-pepper appearance to skin. Over a period of years, remodeling of lesions sometimes results in focal improvement in skin thickening.

Pulmonary disease is the most common visceral manifestation of SSc and includes both arterial and interstitial involvement (alveolitis). Symptoms range from asymptomatic disease to exercise intolerance, dyspnea at rest, and right-sided heart failure. **Pulmonary arterial hypertension** is a poor prognostic sign, developing either as a consequence of lung disease or independently as part of the vasculopathy. Clinical manifestations of pulmonary arterial hypertension in children appear late in the course, are subtle, and include cough and dyspnea on exertion. Pulmonary evaluation should include pulmonary function testing, bronchioalveolar lavage, and high-resolution chest CT. Pulmonary function tests reveal decreased vital capacity and decreased diffusion of carbon monoxide capacity, while neutrophilia and/or eosinophilia on bronchioalveolar lavage suggest active alveolitis. Chest CT is much more sensitive than chest radiographs, which are often normal, showing typical basilar ground-glass abnormalities, reticular linear opacities, nodules, honeycombing, and mediastinal adenopathy.

Other organ systems include gastrointestinal tract disease, which is seen in 25% of children with the disease. Common manifestations include esophageal and intestinal dysmotility resulting in dysphagia, reflux, dyspepsia, gastroparesis, bacterial overgrowth, dilated bowel loops and pseudoobstruction, and dental caries, as well as malabsorption and failure to thrive. Renal arterial disease can cause chronic or severe episodic hypertension; unlike adult disease, renal crisis is rare. Cardiac fibrosis is associated with arrhythmias, ventricular hypertrophy, and decreased cardiac function. Mortality from JSSc is most commonly a result of cardiopulmonary disease.

Raynaud Phenomenon

Raynaud phenomenon (RP) is the most frequent initial symptom in pediatric systemic sclerosis, present in 70% of affected children months to years before other manifestations. RP refers to the classic triphasic sequence of blanching, cyanosis, and erythema of the digits induced

Table 160-2 Classification of Raynaud Phenomenon

Isolated Raynaud phenomenon
Occupational Raynaud phenomenon:
Cold injury
Vibrating tools
Polyvinyl chloride exposure
Secondary Raynaud phenomenon:
Systemic sclerosis
Mixed connective tissue disease
Sjögren syndrome
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Rheumatoid arthritis
Arteritis
Antiphospholipid antibody syndrome
Primary biliary cirrhosis
Carpal tunnel syndrome
Cryoglobulinemia
Leukemia
Vasospastic disorders (migraine, Prinzmetal angina)
Infection:
Hepatitis B and C (cryoglobulinemia)
Cytomegalovirus (?)
Obstructive vascular disease:
Thromboangiitis obliterans
Thoracic outlet syndrome (cervical rib)
Metabolic syndrome:
Hypothyroid
Carcinoid syndrome
Drug-induced:
Antimigraine medications
β-Blocker
Bleomycin
Interferons
Ergotamine derivatives

From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelley's textbook of rheumatology, *ed 8, vol II, Philadelphia, 2009, Saunders/Elsevier.*

by cold exposure and/or emotional stress. RP is most commonly independent of an underlying rheumatic disease (**Raynaud disease**), but it can be a consequence of rheumatic diseases such as scleroderma, systemic lupus erythematosus, and mixed connective tissue disease (Table 160-2). The color changes are brought about by (1) initial arterial vasoconstriction, resulting in hypoperfusion and pallor (blanching), (2) venous stasis (cyanosis), and (3) reflex vasodilation caused by the factors released from the ischemic phase (erythema). The color change is classically reproduced by immersing the hands in iced water and reversed by warming. During the blanching phase, there is inadequate tissue perfusion in the affected area, associated with pain and paresthesias and resulting in ischemic damage only when associated with a rheumatic disease. The blanching usually affects the distal fingers, but may also involve thumbs, toes, ears, and tip of the nose. The affected area is usually well demarcated and uniformly white. Digital ulcers associated with RP are indicative of underlying rheumatic disease.

Raynaud disease often begins in adolescence and is characterized by symmetric occurrence, the absence of tissue necrosis and gangrene, and the lack of manifestations of an underlying rheumatic disease. Children have normal nail-fold capillaries (absence of periungual telangiectasias). RP should be distinguished from **acrocyanosis** and **chilblains.** Acrocyanosis is a vasospastic disorder resulting in cool, painless, bluish discoloration in the hands and sometimes feet despite normal tissue perfusion. It may be exacerbated by stimulant medications used to treat attention deficit disorder. Chilblains is a condition with episodic color changes and the development of nodules related to severe cold exposure and spasm-induced vessel and tissue damage; this condition has been associated with systemic lupus erythematosus.

Table 160-3 Provisional Criteria for the Classification of Juvenile Systemic Sclerosis (SSc)

MAJOR CRITERION (REQUIRED)*
Proximal skin sclerosis/induration of the skin proximal to metacarpophalangeal or metatarsophalangeal joints
MINOR CRITERIA (AT LEAST 2 REQUIRED)
Cutaneous: sclerodactyly
Peripheral vascular: Raynaud phenomenon, nailfold capillary abnormalities (telangiectasias), digital tip ulcers
Gastrointestinal: dysphagia, gastroesophageal reflux
Cardiac: Arrhythmias, heart failure
Renal: Renal crisis, new-onset arterial hypertension
Respiratory: pulmonary fibrosis (high-resolution computed tomography/radiography), decreased diffusing capacity for carbon monoxide, pulmonary arterial hypertension
Neurologic: neuropathy, carpal tunnel syndrome
Musculoskeletal: tendon friction rubs, arthritis, myositis
Serologic: antinuclear antibodies—SSc-selective autoantibodies (anticentromere, antitopoisomerase I [Scl-70], antifibrillarin, anti-PM/Scl, antifibrillin or anti-RNA polymerase I or III

*Diagnosis requires at least 1 major and at least 2 minor criteria.

From Zulian F, Woo P, Athreya BH, et al: The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Rheum *57:203–212, 2007.*

DIAGNOSIS

The diagnosis of localized scleroderma is based on the distribution and depth of characteristic lesions. Biopsy is helpful to confirm the diagnosis. The diagnosis of JSSc requires proximal sclerosis/induration of the skin as well as the presence of 2 of 20 minor criteria (Table 160-3).

DIFFERENTIAL DIAGNOSIS

The most important condition to differentiate from JLS is JSSc. Contractures and synovitis from juvenile arthritis can be differentiated from those due to linear scleroderma by the absence of skin changes. Other conditions to consider include chemically induced scleroderma-like disease, **diabetic cheiroarthropathy**, **pseudoscleroderma**, and **scleredema**. Pseudoscleroderma is composed of a group of unrelated diseases characterized by patchy or diffuse cutaneous fibrosis without the other manifestations of scleroderma. These include phenylketonuria, syndromes of premature aging, and localized idiopathic fibrosis. **Scleredema** is a transient, self-limited disease of both children and adults that has sudden onset after a febrile illness (especially streptococcal infections) and is characterized by patchy sclerodermatous lesions on the neck and shoulders and extending to the face, trunk, and arms.

LABORATORY FINDINGS

There are no laboratory studies diagnostic of either localized or systemic scleroderma. Although the results of complete blood counts, serum chemistry analyses, and urinalysis are normal, children may have elevated erythrocyte sedimentation rate, eosinophilia, or hypergammaglobulinemia, all of which normalize with treatment. Elevations of muscle enzymes, particularly aldolase, can be seen with muscle involvement. Patients with JSSc may have anemia, leukocytosis, and eosinophilia and autoantibodies (ANA, anti-Scl 70). Imaging studies delineate the affected area and can be used to follow disease progression. MRI is useful in en coup de sabre and Parry Romberg syndrome for determination of central nervous system or orbital involvement. Infrared thermography utilizes the temperature variation between areas of active and inactive cutaneous disease to help differentiate active disease from damage. The role of ultrasound to look at lesion activity is evolving. High-resolution CT, pulmonary function tests, echocardiography, and manometry are useful tools for diagnosing and monitoring visceral involvement in JSSc.

TREATMENT

Treatment for scleroderma varies according to the subtype and severity. Superficial morphea may benefit from topical corticosteroids or ultraviolet therapy. For lesions involving deeper structures, systemic therapy is recommended. A combination of methotrexate and corticosteroids is effective in treating JLS by preventing lesion extension and resulting in significant skin softening and improved range of motion of affected joints. The treatment plan for JLS and includes: (1) weekly subcutaneous methotrexate given at 1/mg/kg weekly (maximum dose: 25 mg); (2) weekly methotrexate as in (1) plus either 3 mo of high-dose intravenous corticosteroids (30 mg/kg, maximum dose: 1,000 mg) for 3 consecutive days a month *or* weekly corticosteroids at the same dose for 3 mo; (3) high daily oral corticosteroids (2 mg/kg/day, maximum: 60 mg) with a slow taper over 48 wk. Mycophenolate mofetil is a second-line agent for recalcitrant disease. Physical and occupational therapy are important adjuncts to pharmacologic treatment. Eosinophilic fasciitis often responds well to corticosteroids and methotrexate.

Treatments for JSSc target specific disease manifestations. RP is treated with cold avoidance with pharmacologic interventions are reserved for severe disease. Calcium channel blockers (nifedipine 30-60 mg of sustained-release form daily, amlodipine 2.5-10 mg daily) are the most common pharmacologic interventions. Additional potential therapies for RP include losartan, prazosin, bosentan, and sildenafil. Angiotensin-converting enzyme inhibitors (captopril, enalapril) are recommended for hypertension associated with renal disease. Methotrexate or mycophenolate mofetil may be beneficial for skin manifestations. Cyclophosphamide and mycophenolate mofetil are used to treat pulmonary alveolitis and prevent fibrosis. Corticosteroids should be used cautiously in systemic sclerosis because of an association with renal crisis. Adults with systemic sclerosis have been successfully treated with high-dose cyclophosphamide, antithymocyte globulin and autologous stem cell transplantation.

The treatment of RP begins with avoiding cold stimuli, use of hand and foot warmers, and avoiding carrying bags by their handles (impairs circulation). Nifedipine (10-20 mg tid adult dose) reduces but does not eliminate the number and severity of episodes. Side effects include headache, flushing, and hypotension. Topical nitrates may result in digital vasodilation and may reduce the severity of an episode.

PROGNOSIS

Localized scleroderma is generally self-limited, with initial inflammatory stage followed by a period of stabilization and then softening for an average disease duration of 3-5 yr; however there are reports of active disease lasting up to 20 yr. Prolonged disease activity is associated primarily with linear and deep disease subtypes. Localized scleroderma, especially linear and deep subtypes, can result in significant morbidity, disfigurement, and disability as a result of joint contractures, muscle atrophy, limb shortening, facial asymmetry, and hyper- and hypopigmentation. Death from a **en coup de sabre** lesion with progressive neurologic decline has been reported.

JSSc has a more variable prognosis. Although many children have a slow, insidious course, others demonstrate a rapidly progressive form with early organ failure and death. Skin manifestations reportedly soften years after disease onset. Overall, the prognosis of JSSc is better than that of the adult form, with 5-, 10-, and 15-year survival rates, respectively, in children of 89%, 80-87%, and 74-87%. The most common cause of death is heart failure caused by myocardial and pulmonary fibrosis.

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Chapter 161

Behçet Disease

Seza Özen

Behçet disease (BD) is classified as a primary *variable vessel vasculitis*, emphasizing the involvement of any size and type (arterial, venous) of vessel. BD is also recognized as an autoinflammatory disease. Originally described with recurrent oral ulcerations, uveitis and skin abnormalities, the spectrum is much broader.

EPIDEMIOLOGY

BD has a high prevalence in countries along the *Silk Road,* extending from Japan to the eastern Mediterranean. It is increasingly recognized among people of European ancestry. BD has a prevalence of 5-7 per 100,000 adults, which makes it more frequent than the other vasculitides such as granulomatosis polyangiitis (Wegener disease). The increased disease recognition might have had a role in the rising prevalences as well as the immigrations of the 20th century. Prevalence in children is probably not more than 10% of the adult counterparts in eastern Mediterranean countries. In children, boys and girls are equally affected. Family history of BD is present in approximately 20% of the cases. Onset in children is 8-12 yr of age; newborns of affected mothers have demonstrated symptoms of BD.

ETIOLOGY AND PATHOGENESIS

BD is a polygenic autoinflammatory disorder. Genetic contribution to BD is evident through the well-known association with HLA-B5101, the familial cases, the sibling and twin recurrence rate, the specific frequency of the disease among people along the *Silk Road*, evidence for genetic anticipation and the genome wide analysis studies that support the genetic contribution in the pathogenesis. Genome wide analysis studies among Turkish and Japanese BD patients confirm the marked association with HLA-B5101. Other significant associations include interleukin (IL)-10 and IL-23R/IL-12RB2 genes. Other possible susceptibility loci in a Turkish cohort demonstrate associations in STAT4 (a transcription factor in a signaling pathway related to cytokines such as IL-12, type I interferons, and IL-23), and ERAP1 (an endoplasmic reticulum–expressed aminopeptidase that functions in processing of peptides onto major histocompatibility complex class I).

The autoinflammatory nature of the disease is suggested by the episodic nature of the disease, the prominent innate immune system activation, the absence of identifiable autoantibodies and the co-association with the *MEFV* (Mediterranean fever) gene. An infectious agent may be responsible for inducing the aberrant innate immune system attacks in the genetically predisposed host. A number of infectious agents have been implicated and include streptococci, herpes simplex virus type 1, and parvovirus B19.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

The course of BD is characterized by exacerbations and remissions. There is also marked heterogeneity in disease manifestation (Table 161-1).

The mean age of the first symptom is between 8 and 12 yr. The most frequent initial symptom is a painful **oral ulcer** (Fig. 161-1). The oral ulcers are often recurrent, may be single or multiple, range from 2-10 mm, and may be in any location in the oral cavity. They are often very painful. The oral ulcers last 3-10 days and heal without scarring. In contrast, the genital ulcers heal with scars. Genital scars are noted in 60% of the patients, usually occur after puberty, and are seen on the labia, scrotum, penis, or the anal area.

Another key feature of BD that has significant morbidity is bilateral eye involvement seen in 30-60% of pediatric patients. The main symptoms of **anterior uveitis** are blurred vision, redness, periorbital or

global pain, and photophobia. Although it is often in the form of panuveitis, anterior uveitis may be seen in females. Uveitis in general is more common in males. Vitreitis and retinal vasculitis are the most prominent features of posterior involvement. Complications of uveitis include blindness (unusual with treatment), glaucoma, and cataracts. Retinal vasculitis, retinal detachment, and retrobulbar neuritis (optic neuritis) are less-common eye manifestations of BD.

The **skin lesions** of BD range from erythema nodosum, papulopustular acneiform lesions, folliculitis, purpura, and ulcers. **Pathergy** is also a skin feature that is a pustular reaction occurring 24-48 hr after a sterile needle puncture or saline injection; it is not pathognomonic of BD.

Table 161-1 Criteria of the International Study Group for the Diagnosis of Behçet disease

CRITERION	DESCRIPTION
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulceration recurring at least 3 times in one 12 mo period, observed by physician or patient
Plus 2 of the following:	
Recurrent genital ulcers	Aphthous ulceration or scarring observed by physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, cells in vitreous on slit-lamp examination, or retinal vasculitis observed by an ophthalmologist
Skin lesions	Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions, or acneiform nodules observed by physician in postadolescent patient not on corticosteroid treatment
Pathergy	Skin reaction to a needle prick observed by physician at 24-48 hr

From International Study Group for Behçet's Disease: Criteria for diagnosis of Behçet's disease, Lancet *335:1070–1080,1990.*

Figure 161-1 Oral aphthous lesion in a girl with Behçet disease. *(From Ozen S, Petty RE: Behçet disease. In Cassidy JT, Petty RE, Laxer RM, et al, editors,* Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Saunders, Fig. 36-1, p. 554.)*

The **vasculitis** of BD involves both arterial or venous thrombosis and aneurysm formation or occlusions or stenosis in arteries of any size. In children deep venous thrombosis of the lower limbs is the most frequent vasculitic feature. If the hepatic vein is thrombosed Budd-Chiari syndrome may occur. Pulmonary aneurysms are the most severe feature of pediatric BD, associated with the highest mortality. Coronary artery aneurysms may confuse BD with Kawasaki disease. Microvascular involvement may be noted in the nail bed capillaries.

Central nervous system (CNS) manifestations in children include meningoencephalitis (headache, meningismus, cerebrospinal fluid pleocytosis), encephalomyelitis, pseudotumor cerebri, dural sinus thrombosis, and organic psychiatric disorders (psychosis, depression, dementia). Dural sinus thrombosis is the most common CNS manifestation in children.

Gastrointestinal involvement manifests with abdominal pain, diarrhea, and intestinal ulcerations, most often in the ileocecal region. Gastrointestinal BD may be difficult to distinguish from inflammatory bowel disease. Oligoarticular **arthritis/arthralgia** is present in more than 50% of the patients and can be recurrent, but is nondeforming. Other rare manifestations include orchitis, renal vasculitis, glomerulonephritis, or amyloidosis and cardiac involvement.

DIAGNOSIS

The International Study Group criteria are most widely used and require the presence of oral ulcers (at least 3 times per year) along with 2 other major features, including genital ulcers, a positive pathergy test, uveitis, and the characteristic skin lesions (see Table 161-1). If only 1 of the criteria is present along with oral ulcerations, the term *incomplete* or *partial Behçet disease* is applied. There are no specific laboratory tests. Acute-phase reactants are often mildly elevated. The diagnosis relies on the constellation of symptoms and excluding other causes.

TREATMENT AND PROGNOSIS

Azathioprine is highly recommended to treat inflammatory eye disease. For oral and genital ulcers topical treatment is recommended (sucralfate, steroids). Colchicine is recommended for erythema nodosum or arthritis in males and females and for genital ulcers in females. There is no evidence-based treatment for gastrointestinal disease, but thalidomide, sulfasalazine, steroids, azathioprine and anti–tumor necrosis factor (TNF) agents have been recommended. For CNS disease and vasculitis, steroids, azathioprine, cyclophosphamide, interferon alpha, and in unresponsive CNS disease anti-TNF agents are suggested. There is no consensus about the benefit of anticoagulation in the management of vein thrombosis in BD.

In patients without major organ involvement, colchicine significantly improves oral and genital ulcers, skin features, and disease activity. In pediatric patients with vascular involvement with venous thrombosis, steroids and azathioprine have been used, whereas those with pulmonary arterial or cardiac involvement are initially treated with cyclophosphamide; follow-up of at least 18 mo demonstrated that those treated are free of vascular relapses. Patients treated with anti-TNF drugs have had persistent responses in 90%, 89%, 100%, and 91% of patients with resistant mucocutaneous, ocular, gastrointestinal, and central nervous system involvement, respectively.

Mortality in children with BD is low except for the pulmonary aneurysms. However, BD is a chronic disease associated with significant morbidity. Early diagnosis and effective treatment improves the outcome of BD.

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Chapter 162

Sjögren Syndrome

C. Egla Rabinovich

Sjögren syndrome is a chronic, inflammatory, autoimmune disease characterized by progressive lymphocytic and plasma cell infiltration of the exocrine glands, especially salivary and lacrimal, with potential for systemic manifestations. It is rare in children and predominantly affects middle-age women with classic symptoms of dry eyes (**keratoconjunctivitis sicca**) and dry mouth (**xerostomia**).

EPIDEMIOLOGY

Sjögren syndrome typically manifests at 35-45 yr of age, with 90% of cases among women, but it is underrecognized in children as symptoms often start in childhood. The mean age at diagnosis in children is 9-10 yr; 75% are girls. The disease can occur as an isolated disorder, referred to as *primary Sjögren syndrome (sicca complex)*, or as a *secondary Sjögren syndrome* in association with other rheumatic disorders such as systemic lupus erythematosus, scleroderma, or mixed connective tissue disease, and usually precedes the associated autoimmune disease by years.

ETIOLOGY AND PATHOGENESIS

The etiology of Sjögren syndrome is complex and includes genetic predisposition and possibly an infectious trigger. Lymphocytes and plasma cells infiltrate salivary glands, forming distinct periductal and periacinar foci that become confluent and may replace epithelial structure. Several genes regulating apoptosis influence the chronicity of lymphocytic infiltration.

CLINICAL MANIFESTATIONS

International classification criteria have been developed for the diagnosis of Sjögren syndrome in adult patients, but these criteria apply poorly to children. Although diagnostic criteria in children have been proposed, they have not been validated (Table 162-1). Recurrent parotid gland enlargement and parotitis are the most common manifestations in children (>70%), whereas sicca syndrome (dry mouth, painful mucosa, sensitivity to spicy foods, halitosis, widespread dental caries) predominate in adults. In a cross sectional study of children with Sjögren syndrome, manifestations included recurrent parotitis (72%), sicca symptoms (38%), polyarthritis (18%), vulvovaginitis (12%), hepatitis (10%), Raynaud phenomenon (10%), fever (8%), renal tubular acidosis (9%), lymphadenopathy (8%), and central nervous system involvement (5%).

Subjective symptoms of xerostomia complaints are relatively rare in juvenile cases, perhaps indicating that Sjögren syndrome is a slowly progressive disease; however increased dental caries is seen clinically in children. Serologic markers (antinuclear antibodies, and antibodies to Ro [SSA] and SSB [La]) and articular manifestations are significantly more frequent in adults. Frequencies of the finding of antinuclear antibodies and SSA and SSB antibodies in children are reported to be 78%, 75%, and 65%, respectively, with rheumatoid factor present in 67%. Additional clinical manifestations from a variety of organ involvement patterns include a decreased sense of smell, hoarseness, chronic otitis media, leukocytoclastic vasculitis (purpura), and internal organ exocrine disease involving the lungs (diffuse interstitial lymphocytosis), pancreas, hepatobiliary system, gastrointestinal tract, kidneys (renal tubular acidosis), musculoskeletal (arthritis and arthralgia), hematologic (cytopenias), peripheral nervous system (sensory and autonomic neuropathy), and central nervous system (optic neuritis, transverse myelitis, meningoencephalitis).

Table 162-1 Proposed Criteria for Pediatric Sjögren Syndrome

I. CLINICAL SYMPTOMS
   1. Oral: recurrent parotitis or enlargement of parotid gland, dry mouth (xerostomia)
   2. Ocular: dry eyes (xerophthalmia) recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
   3. Other mucosal: recurrent vaginitis
   4. Systemic: fever, non-inflammatory arthralgias, hypokalemic paralysis, abdominal pain

II. IMMUNOLOGIC ABNORMALITIES: presence of at least 1 of the following antibodies: anti-SSA, anti-SSB, high titer antinuclear antibody, rheumatoid factor

III. OTHER ABNORMALITIES OR INVESTIGATIONS
   1. Biochemical: elevated serum amylase
   2. Hematologic: leukopenia, high sedimentation rate
   3. Immunologic: polyclonal hyperimmunoglobulinemia
   4. Renal: renal tubular acidosis
   5. Histologic proof of lymphocytic infiltration of salivary glands or other organs (i.e., liver)
   6. Objective documentation of ocular dryness (Bengal red staining or Schirmer test)
   7. Positive findings of parotid gland scintigraphy

IV. Exclusion of all other autoimmune diseases

Diagnosis requires ≥4 criteria.

From Bartunkova J. Primary Sjögren syndrome in children and adolescents: proposal for diagnostic criteria, Clin Exp Rheumatol *17:381–386, 1999.*

Non–exocrine disease manifestations of Sjögren syndrome may be related to inflammatory vascular disease (in skin, muscle and joints, serosal surfaces, and peripheral and central nervous systems), noninflammatory vascular disease (Raynaud phenomenon), mediator-induced disease (hematologic cytopenias, fatigue, and fever), and autoimmune endocrinopathy (thyroiditis).

DIAGNOSIS

Clinical presentation of recurrent parotitis and or recurrent parotid gland swelling in a child or adolescent is characteristic and should raise the suspicion for this disorder. The diagnosis is based on clinical features supported by biopsy of salivary or parotid glands demonstrating foci of lymphocytic infiltration, the current gold standard for diagnosis. Children are more likely to have normal minor salivary gland but abnormal parotid gland biopsies. Supporting laboratory abnormalities include cryoglobulinemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, positive rheumatoid factor, and detection of SSA and SSB antibodies. Anti–β-fodrin autoantibodies, directed against an apoptotic cleavage product of α-fodrin, are a useful diagnostic marker for juvenile Sjögren syndrome. The **Schirmer test** detects abnormal tear production (≤5 mm of wetting of filter paper strip in 5 min) and **Rose-Bengal staining** detects damaged ocular epithelial conjunctival and corneal cells. Imaging studies, including MRI, technetium ^{99m}Tc scintigraphy, and sialography, are useful in the diagnostic evaluation for Sjögren syndrome (Fig. 162-1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Sjögren syndrome in children includes **juvenile recurrent parotitis**, characterized by intermittent unilateral parotid swelling typically lasting only a few days. It is frequently associated with fever and may undergo remission with puberty. Unlike in Sjögren syndrome, there is a male predominance, it is seen in the younger children (3-6 yr of age), and there is a lack of focal lymphocytic infiltrates on biopsy. Other conditions in the differential diagnosis include eating disorders, infectious parotitis (mumps, streptococcal and staphylococcal infections, Epstein-Barr virus, cytomegalovirus, HIV, parainfluenza, influenza enterovirus) and local trauma to the buccal mucosa. Rarely, polycystic parotid disease, tumors, and sarcoidosis may present with recurrent parotid swelling. In these conditions,

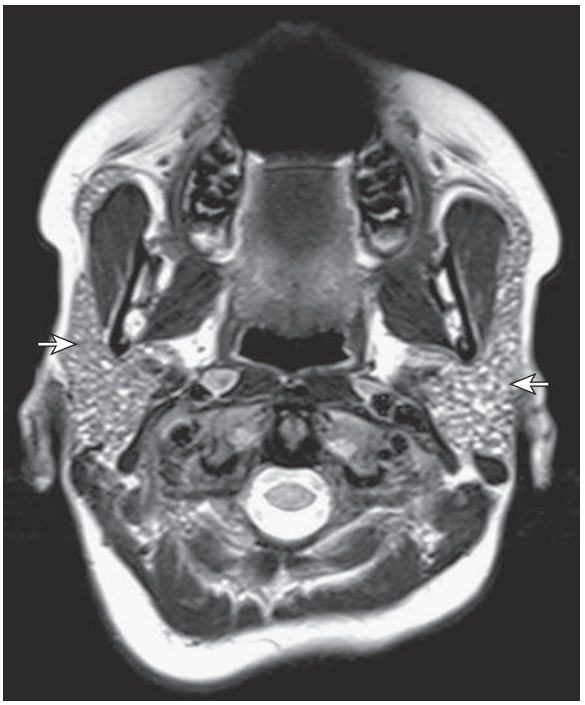

Figure 162-1 T2-weighted MRI of child with Sjögren syndrome showing parotitis *(arrows)*.

sicca complex, rash, arthralgia, and antinuclear antibodies are usually absent.

TREATMENT

Symptomatic treatment of Sjögren syndrome includes the use of artificial tears, massage of the parotids, oral lozenges, and fluids to limit the damaging effects of decreased secretions. Corticosteroids, nonsteroidal antiinflammatory drugs, and hydroxychloroquine are among the more commonly used agents for treatment, with reports of methotrexate and etanercept used for treatment of arthritis. Stronger immunosuppressive agents, such as cyclosporine and cyclophosphamide, are reserved for severe functional disorders and life-threatening complications.

COMPLICATIONS AND PROGNOSIS

The symptoms of Sjögren syndrome develop and progress slowly. Diminished salivary flow typically remains constant for years. Because monoclonal B-lymphocyte disease originates chiefly from lymphocytic foci within salivary glands or from parenchymal internal organs, there is increased risk for mucosa-associated lymphoid tissue lymphoma. Maternal Sjögren syndrome can be an antecedent to the neonatal lupus syndrome (see Chapter 158.1).

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Chapter 163

Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases

Amanda K. Ombrello and Daniel L. Kastner

The hereditary periodic fever syndromes are a group of monogenic diseases that present with recurrent bouts of fever and associated pleural and/or peritoneal inflammation, arthritis, and various types of skin rash. They are subsumed among a larger group of disorders, the systemic autoinflammatory diseases, that were first recognized for their seemingly unprovoked episodes of inflammation, without the high-titer autoantibodies or antigen-specific T cells commonly seen in autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis. Whereas the autoimmune diseases are disorders of the adaptive immune system, with its lymphocyte effector cells and receptors that somatically rearrange and mutate, the autoinflammatory diseases largely represent disorders of the phylogenetically more primitive innate immune system, mediated by myeloid effector cells and germline-encoded receptors. The autoinflammatory diseases can cause an intense acute phase response with elevation of the erythrocyte sedimentation rate, C-reactive protein, and serum amyloid A, in some cases leading to amyloid A (AA) amyloidosis (see Chapter 164).

The hereditary periodic fever syndromes include 2 illnesses with an autosomal recessive mode of inheritance, familial Mediterranean fever (FMF; MIM249100) and the hyperimmunoglobulinemia D with periodic fever syndrome (HIDS; MIM260920). Hereditary periodic fever syndromes with an autosomal dominant mode of inheritance include the tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS; MIM191190) and a spectrum of disorders known as the cryopyrin-associated periodic syndromes (CAPSs), or cryopyrinopathies. From mildest to most severe, CAPS includes the familial cold autoinflammatory syndrome (FCAS1; MIM120100), Muckle-Wells syndrome (MWS; MIM191100), and neonatal-onset multisystem inflammatory disease (NOMID; MIM607115) (also known as chronic infantile neurologic cutaneous and articular syndrome, or CINCA) (Table 163-1).

There are a number of other mendelian autoinflammatory diseases that present in childhood and are not considered hereditary periodic fever syndromes. These include the syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA; MIM604416), deficiency of the interleukin 1 (IL-1) receptor antagonist (DIRA; MIM612852), Blau syndrome (also known as early-onset sarcoidosis; MIM186580), chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE; MIM256040), autoinflammation with phospholipase $C\gamma_2$-associated antibody deficiency and immune dysregulation (APLAID; MIM614878), and deficiency of adenosine deaminase-2 (DADA2) (Table 163-2). Other disorders include congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD) due to biallelic mutations of the *TRNT1* gene as well as disease produced by mutations in the phospholipase $C\gamma_2$ gene (cold-induced urticaria, granulomatous rash, bronchiolitis, enterocolitis, eye inflammation) or by mutations in the cat-eye syndrome chromosome region, candidate 1 (*CECR1*) causing fever, stroke, rash, and vasculitis. An interferonopathy due to upregulation of *TMEM173* that encodes STING (stimulation of

Table 163-1 Differential Diagnosis of Familial Autoinflammatory Syndromes

	FAMILIAL MEDITERRANEAN FEVER (FMF)	Mevalonate Kinase Deficiency (MKD)		TUMOR NECROSIS FACTOR RECEPTOR–ASSOCIATED PERIODIC SYNDROME (TRAPS)	Cryopyrin-Associated Periodic Syndrome (CAPS)			DEFICIENCY OF IL-1 RECEPTOR ANTAGONIST (DIRA)
		HYPERIMMUNOGLOBULIN D SYNDROME (HIDS)	MEVALONIC ACIDURIA		FAMILIAL COLD AUTOINFLAMMATORY SYNDROME (FCAS)	MUCKLE-WELLS SYNDROME (MWS)	CHRONIC INFANTILE NEUROLOGIC CUTANEOUS AND ARTICULAR SYNDROME (CINCA)	
Mode of Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
Age at Onset (yr)	<20	<1	<1	<20	<1	<20	<1	Birth, <4 wk
Duration of attack (days)*	<2	4-6	4-5	>14	<2	1-2	?	Continuous
Cutaneous Involvement	Erysipelas-like erythema	Maculopapular rash	Morbilliform rash	Migratory rash, overlying area of myalgia	Cold-induced urticaria-like lesions	Urticaria-like rash	Urticaria-like lesions	Generalized pustulosis
Musculoskeletal Involvement	Monoarthritis common	Arthralgia, occasional oligoarthritis	Arthralgia common	Severe myalgia common; occasional frank monoarthritis	Arthralgia common; occasional mild myalgia	Lancing limb pain, arthralgia common; arthritis can occur	Epiphyseal bone formation	Sterile pustulous osteomyelitis
Abdominal Involvement	Sterile peritonitis common	Splenomegaly, severe pain common	Splenomegaly, pain may occur	Severe pain common	None	May occur	Hepatosplenomegaly	
Eye Involvement	Uncommon	Uncommon	Uncommon	Conjunctivitis and periorbital edema common	Conjunctivitis	Conjunctivitis; sometimes optic nerve elevation	Papilledema with possible loss of vision, uveitis	
Distinguishing Clinical Symptoms	Erysipelas-like erythema	Prominent cervical lymphadenopathy	Dysmorphic features, neurologic symptoms	Migratory nature of myalgia and rash, periorbital edema	Cold-induced urticaria-like lesions	Sensorineural hearing loss	Chronic aseptic meningitis, sensorineural hearing loss, arthropathy	
Gene Involved	*MEFV*	*MVK*	*MVK*	*TNFRSF1A*	*CIAS1 = NLRP3*	*CIAS1 = NLRP3*	*CIAS1 = NRLP3*	*IL-1RN*
Protein Involved	Pyrin (marenostrin)	Mevalonate kinase	Mevalonate kinase	Type 1 tumor necrosis factor receptor	Cryopyrin	Cryopyrin	Cryopyrin	IL-1RA

Note: For details on Blau syndrome, DIRA, and pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, see text.

*Duration may vary; this is a typical duration.

Modified from Hull KM, Shoham N, Chae JJ, et al: The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations, Curr Opin Rheumatol *15:61–69, 2003.*

Table 163-2 Clinical Grouping of Autoinflammatory Diseases by Fever and Skin Manifestations

1. Nonspecific maculopapular rashes with recurrent episodic fever and abdominal pain (the classic "periodic fever syndromes")
   Recurrent fever attacks of short duration (typically <7 days)
   - FMF: familial Mediterranean fever
   - HIDS: mevalonate kinase deficiency/hyperimmunoglobulinemia D with periodic fever syndrome

   Recurrent fever attacks of longer duration (typically >7 days)
   - TRAPS: TNF receptor-associated periodic fever syndrome
2. Neutrophilic urticaria (the cryopyrinopathies)
   Recurrent fever attacks of short duration (typically <24 hr)
   - CAPS/FCAS: familial cold autoinflammatory syndrome
   - CAPS/MWS: Muckle-Wells syndrome

   Continuous low-grade fever
   - CAPS/NOMID: neonatal onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular syndrome (CINCA)
3. Granulomatous skin lesions and minimal or low-grade fever attacks
   - Blau syndrome/early-onset sarcoidosis (pediatric granulomatous arthritis)
4. Pustular skin rashes and episodic fever
   With inflammatory bone disease
   - DIRA: deficiency of interleukin-1 receptor agonist
   - Majeed syndrome

   With pyogenic arthritis
   - PAPA: pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

   With inflammatory bowel disease
   - Early-onset inflammatory bowel disease

   Without other organ involvement
   - DITRA: deficiency of interleukin-36-receptor antagonist
   - CAMPS: CARD14-mediated psoriasis
5. Atypical neutrophilic dermatosis with histiocytic-like infiltrate
   - PRAAS: proteasome associated autoinflammatory syndromes
6. Syndromes with autoinflammation and immunodeficiency
   - PLAID: PLCγ_2-associated antibody deficiency and immune dysregulation
   - APLAID: autoinflammation and PLCγ_2-associated antibody deficiency and immune dysregulation
   - HOIL-1 deficiency

From Almeida de Jesus A, Goldbach-Mansky R: Monogenic autoinflammatory diseases: concept and clinical manifestations. Clin Immunol *147:155-174, 2013, Table 1.*

interferon genes) produces infantile onset of neutrophilic rash, increased acute-phase reactants, fever, interstitial lung disease, paratracheal adenopathy, and facial nodules.

There are also a number of autoinflammatory disorders with a complex mode of inheritance. These include the syndrome of periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) and chronic recurrent multifocal osteomyelitis (CRMO; MIM259680) (Table 163-3). Other genetically complex disorders that are sometimes considered autoinflammatory are covered elsewhere in this volume: systemic-onset juvenile idiopathic arthritis (see Chapter 155), Behçet disease (see Chapter 161), and Crohn disease (see Chapter 336). Distinguishing one disorder from the others may be difficult; Tables 163-4 and 163-5 and Figures 163-1 and 163-2 can be helpful to this end.

FAMILIAL MEDITERRANEAN FEVER

FMF is a recessively inherited autoinflammatory disease usually characterized by recurrent 1-3 day self-limited episodes of fever, serositis, mono- or pauciarticular arthritis, or an erysipeloid rash, sometimes complicated by AA amyloidosis.

Etiology

FMF is caused by mutations in *MEFV*, a 10 exon gene located on the short arm of chromosome 16 encoding a 781 amino acid protein denoted pyrin (from the Greek for fever). Pyrin is expressed in granulocytes, monocytes, and dendritic cells, and in peritoneal, synovial, and dermal fibroblasts. The N-terminal ~90 amino acids of pyrin are the prototype for a motif (the PYRIN domain) that mediates protein-protein interactions and is found in more than 20 different human proteins that regulate inflammation and apoptosis. Through PYRIN-domain interactions, pyrin can activate caspase-1, the enzyme that converts the 31 kDa pro–IL-1β molecule into the biologically active 17 kDa IL-1β, which is a major mediator of fever and inflammation.

Many of the FMF-associated mutations in pyrin are found at the C-terminal B30.2 domain of pyrin, encoded by exon 10 of *MEFV*. More than 50 such FMF mutations are listed in an online database (http://fmf.igh.cnrs.fr/ISSAID/infevers/), nearly all of which are missense substitutions. Homozygosity for the M694V mutation may be associated with an earlier age of onset, arthritis, and an increased risk of amyloidosis. The substitution of glutamine for glutamic acid at residue 148 (E148Q), is considered to be either a mild mutation or a functional polymorphism in the pyrin protein. The combined frequencies of FMF mutations among several Mediterranean populations are extraordinarily high (up to 1:3), suggesting the possibility of a heterozygote advantage. It is also noteworthy that there is a small percentage of patients of typical ethnicity and the clinical findings of FMF who have no demonstrable *MEFV* mutations, suggesting the possibility of a second FMF locus.

Epidemiology

FMF occurs primarily among ethnic groups of Mediterranean ancestry, most commonly Jews, Turks, Armenians, Arabs, and Italians. Owing to a higher frequency of the M694V mutation, FMF is more severe and more readily recognized in the Sephardic (North African) than the Ashkenazi (East European) Jewish population. Nevertheless, due to demographics, most Jewish FMF patients in the US are of Ashkenazi ancestry. With the advent of genetic testing, mutation-positive FMF has been documented worldwide, although at lower frequency than in the Mediterranean basin and Middle East. Most patients present with symptoms in childhood, with 90% of patients presenting prior to the age of 20 yr.

Pathogenesis

It appears that FMF mutations lead to a gain-of-function and IL-1β–dependent inflammation, with a gene-dosage effect. These results may explain why many heterozygous carriers of FMF mutations have biochemical evidence of inflammation, why as many as 30% of symptomatic FMF patients have only 1 demonstrable *MEFV* mutation, and why IL-1 inhibitors have a therapeutic effect in FMF.

Table 163-3 Autoinflammatory Bone Disorders

	CRMO	Majeed Syndrome	DIRA	Cherubism	cmo and lupo Mice
Ethnicity	Worldwide, but mostly European	Arabic	European, Puerto Rican, Arabic	Worldwide	Occurs in various backgrounds
Fever	Uncommon	Common	Uncommon	No	Not assessed
Sites of osseous involvement	Metaphyses of long bones > vertebrae, clavicle, sternum, pelvis, others	Similar to CRMO	Anterior rib ends, metaphyses of long bones, vertebrae, others	Mandible > maxilla Rarely ribs	Vertebrae hind > forefeet
Extraosseous manifestations	PPP, psoriasis, IBD, others	Dyserythropoietic anemia, Sweet syndrome, HSM, growth failure	Generalized pustulosis, nail changes, lung disease, vasculitis	Cervical lymphadenopathy	Dermatitis, extramedullary hematopoiesis, splenomegaly
Family history of inflammatory disorders	Psoriasis, PPP, arthritis, IBD, others	Psoriasis in some obligate carriers	No known associations	No known associations	Heterozygotes normal
Inheritance	Not clear	Autosomal recessive	Autosomal recessive	Autosomal dominant; incomplete penetrance	Autosomal recessive
Gene defect	Unknown	*LPIN2*	*IL1RN*	*SH3BP2* ≫ *PTPN11*	*Pstpip2*
Protein name	?	Lipin2	IL-1Ra	SH3BP2	PSTPIP2 (a.k.a. MAYP)
Protein function	?	Fat metabolism: (PAP enzyme activity), ↑ message to oxidative stress, ? role in mitosis	Antagonist of IL-1 receptor	↑ Myeloid cell response to M-CSF and RANKL, ↑ TNF-α expression in macrophages	Macrophage proliferation, macrophage recruitment to sites of inflammation, cytoskeletal function
Cytokine abnormalities	↑ serum TNF-α	Not tested	↑ IL-1α, IL-1β, MIP-1α, TNF-α, IL-8, IL-6 ex vivo monocyte assay; skin reveals ↑ IL-17 staining	↑ serum TNF-α in mouse model	cmo: ↑serum IL-6, MIP-1α, TNF-α, CSF-1, IP-10 Lupo: ↑ serum MIP-1α, IL-4, RANTES, TGF-β

CRMO, chronic recurrent multifocal osteomyelitis; CSF, colony-stimulating factor; DIRA, deficiency of interleukin-1 receptor antagonist; HSM, hepatosplenomegaly; IBD, inflammatory bowel disease; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IP-10, interferon-inducible protein-10; M-CSF, macrophage–colony-stimulating factor; MIP-1α, macrophage inflammatory protein-1α; PAP, phosphatidate phosphatase; PPP, palmer-plantar pustulosis; PSTPIP2, proline-serine-threonine phosphatase interacting protein; RANKL, receptor activator of nuclear factor-κB ligand; RANTES, regulated upon activation, normal T-cell expressed and secreted; SH3BP2, SH3 binding protein 2; TGF, transforming growth factor; TNF-α, tumor necrosis factor α.

From Ferguson PJ, Laxer RM: Autoinflammatory bone disorders. In Cassidy JT, Petty RE, Laxer RM, et al, editors: Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2010, Saunders, Table 44-2.*

Clinical Manifestations

Clinical features of FMF may include fever, serositis presenting as pleuritic chest pain or severe abdominal pain, arthritis, and rash. The pleural pain is typically unilateral, whereas the abdominal pain can be generalized or localized to 1 quadrant, similar to other forms of peritonitis. FMF-associated arthritis occurs primarily in the large joints, may be accompanied by large, neutrophil-rich effusions, and is usually nonerosive and nondestructive. The hallmark cutaneous finding is an erysipeloid erythematous rash that overlies the ankle or dorsum of the foot (Fig. 163-3). Other clinical findings include scrotal pain caused by inflammation of the tunica vaginalis testis, febrile myalgia, exercise-induced myalgia (particularly common in children), and an association with various forms of vasculitis, including Henoch-Schönlein purpura in as many as 5% of pediatric patients. FMF episodes may be triggered by stress, menses, or infections. Between flares, patients are generally symptom-free but may have persistent elevation of their inflammatory markers. The attack frequency can vary from weekly to 1-2 flares/year.

Diagnosis

The diagnosis of FMF can often be made clinically, paying special attention to the duration and recurrence of episodes, documentation of fever, the characteristic serositis, synovitis, or erysipeloid rash, responsiveness to daily colchicine prophylaxis, and the absence of other causative factors. The differential diagnosis includes other hereditary periodic fever syndromes, and, depending on the specific circumstances, may include PFAPA, systemic-onset juvenile idiopathic arthritis (Still disease), cyclic hematopoiesis, gynecologic disorders (when abdominal pain predominates), porphyria, hereditary angioedema, septic arthritis, and the crystalline arthritides.

Genetic testing can be used as adjunctive evidence in ambiguous cases, and in circumstances in which the clinician has little experience with FMF or related conditions. Although FMF is often regarded as a recessively inherited disorder, with the attendant expectation that patients will have 2 mutations in *trans*, it should be noted that in some series as many as 30–50% of patients with typical FMF, responsive to colchicine, have only a single demonstrable mutation, and a small percentage have no identifiable *MEFV* mutation. The interpretation of genetic testing may be further complicated by the presence of complex alleles in which 2 mutations may be found in *cis* (usually an exon 10 mutation with E148Q in exon 2).

Treatment

Prophylactic daily oral colchicine decreases the frequency, duration, and intensity of FMF flares. This regimen also prevents the development of systemic AA amyloidosis. Colchicine is generally well-tolerated and safe in children, with the most common side effects being diarrhea and other gastrointestinal complaints. Some patients develop lactose intolerance while taking colchicine. Gastrointestinal side effects can be minimized by initiating therapy at a low dose (for young children, 0.3 mg/day) and slowly titrating upward. A dose-related transaminitis may also be observed; bone marrow suppression is rarely seen at the dosages prescribed for FMF. Pediatric patients may require doses of colchicine similar to those needed in adults (1-2 mg/day), reflecting the fact that children metabolize the drug more rapidly than adults. It is not always possible to find a tolerated dose of colchicine at which all

Table 163-4 Clues That May Assist in the Diagnosis of Autoinflammatory Syndromes

AGE OF ONSET	
At birth	NOMID, DIRA, FCAS
Infancy and 1st yr of life	HIDS, FCAS, NLRP12
Toddler	PFAPA
Late childhood	PAPA
Most common of autoinflammatory syndromes to have onset in adulthood	TRAPS, DITRA
Variable (mostly in childhood)	All others
ETHNICITY AND GEOGRAPHY	
Armenians, Turks, Italian, Sephardic Jews	FMF
Arabs	FMF, DITRA (Arab Tunisian)
Dutch, French, German, Western Europe	HIDS, MWS, NLRP12
United States	FCAS
Can occur in blacks (West Africa origin)	TRAPS
Eastern Canada, Puerto Rico	DIRA
Worldwide	All others
TRIGGERS	
Vaccines	HIDS
Cold exposure	FCAS, NLRP12
Stress, menses	FMF, TRAPS, MWS, PAPA, DITRA
Minor trauma	PAPA, MWS, TRAPS, HIDS
Exercise	FMF, TRAPS
Pregnancy	DITRA
Infections	All, especially DITRA
ATTACK DURATION	
<24 h	FCAS, FMF
1–3 d	FMF, MWS, DITRA (fever)
3–7 d	HIDS, PFAPA
>7 d	TRAPS, PAPA
Almost always "in attack"	NOMID, DIRA
INTERVAL BETWEEN ATTACKS	
3–6 wk	PFAPA, HIDS
>6 wk	TRAPS
Mostly unpredictable	All others
Truly periodic	PFAPA, cyclic neutropenia
USEFUL LABORATORY TESTS	
Acute-phase reactants must be normal between attacks	PFAPA
Urine mevalonic acid in attack	HIDS
IgD > 100 mg/dL	HIDS
Proteinuria (amyloidosis)	FMF, TRAPS, MWS, NOMID
RESPONSE TO THERAPY	
Corticosteroid dramatic	PFAPA
Corticosteroid partial	TRAPS, FCAS, MWS, NOMID, PAPA*
Colchicine	FMF, PFAPA (30% effective)
Cimetidine	PFAPA (30% effective)
Etanercept	TRAPS, FMF arthritis
Anti–IL-1 dramatic	DIRA (anakinra), FCAS, MWS, NOMID, PFAPA
Anti–IL-1 mostly	TRAPS, FMF
Anti–IL-1 partial	HIDS, PAPA

DIRA, deficiency of the IL-1 receptor antagonist; DITRA, deficiency of the IL-36 receptor antagonist (generalized pustular psoriasis); FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome; IL, interleukin; MWS, Muckle-Wells syndrome; NLRP, nucleotide oligomerization domain–like receptor family, pyrin domain; NOMID, neonatal-onset multisystem inflammatory disorder; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, acne syndrome; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, adenitis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.

*For intraarticular steroids.

From Hashkes PJ, Toker O: Autoinflammatory syndromes. Pediatr Clin North Am *59:447–470, 2012, Table 2.*

Table 163-5 Differential Diagnosis of Periodic Fever

1 Hereditary (see Table 163-1)
2 Nonhereditary
  a Infectious
    i Hidden infectious focus (e.g., aortoenteric fistula, Caroli disease)
    ii Recurrent reinfection (e.g., chronic meningococcemia, host defense defect)
    iii Specific infection (e.g., Whipple disease, malaria)
  b Noninfectious inflammatory disorder, e.g.:
    i Adult-onset Still disease
    ii Juvenile chronic rheumatoid arthritis
    iii Periodic fever, aphthous stomatitis, pharyngitis, and adenitis
    iv Schnitzler syndrome
    v Behçet syndrome
    vi Crohn disease
    vii Sarcoidosis
    viii Extrinsic alveolitis
    ix Humidifier lung, polymer fume fever
  c Neoplastic
    i Lymphoma (e.g., Hodgkin disease, angioimmunoblastic lymphoma)
    ii Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma)
  d Vascular (e.g., recurrent pulmonary embolism)
  e Hypothalamic
  f Psychogenic periodic fever
  g Factitious or fraudulent

From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors: Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Table 97-2.*

symptoms are suppressed, but approximately 90% of patients have a marked improvement in disease-related symptoms. Colchicine is generally continued during pregnancy and lactation.

A small percentage of FMF patients are either unresponsive to or intolerant of therapeutic doses of colchicine. Based on the role of pyrin in IL-1β activation, a randomized placebo-controlled trial demonstrated the safety and effectiveness of rilonacept, an IL-1 inhibitor, in FMF, and there are case reports of the effectiveness of anakinra, a recombinant IL-1 receptor antagonist.

Complications and Prognosis

Amyloidosis is the most serious complication of FMF, and in its absence FMF patients may live a normal life span. Amyloidosis may develop when serum AA, an acute-phase reactant found at extremely high levels in the blood during FMF attacks, is cleaved to produce a 76 amino acid fragment that misfolds and deposits ectopically, most commonly in the kidneys, gastrointestinal tract, spleen, lungs, testes, thyroid, and adrenals. Rarely, cardiac amyloidosis may develop; macroglossia and amyloid neuropathy are generally not seen with the amyloidosis of FMF. The most common presenting sign of AA amyloidosis is proteinuria. The diagnosis is then usually confirmed by rectal or renal biopsy. There are a small number of case reports, mostly from the Middle East, in which amyloidosis may actually precede overt FMF attacks, presumably because of subclinical inflammation.

Risk factors for the development of amyloidosis in FMF include homozygosity for the M694V *MEFV* mutation, polymorphisms of the *serum AA* gene (encoding AA), noncompliance with colchicine treatment, male gender, and a positive family history of AA amyloid. For reasons that are unclear, country of origin is also a major risk factor for amyloidosis in FMF, with patients raised in the Middle East having a much higher risk than genotypically identical patients raised in the West. Aggressive lifelong suppression of the acute phase reactants should be the goal in patients with FMF amyloidosis, and there are documented cases in which this may result in resorption of amyloid deposits. The natural history of untreated amyloidosis in FMF is the inexorable progression to renal failure, often within 3–5 yr.

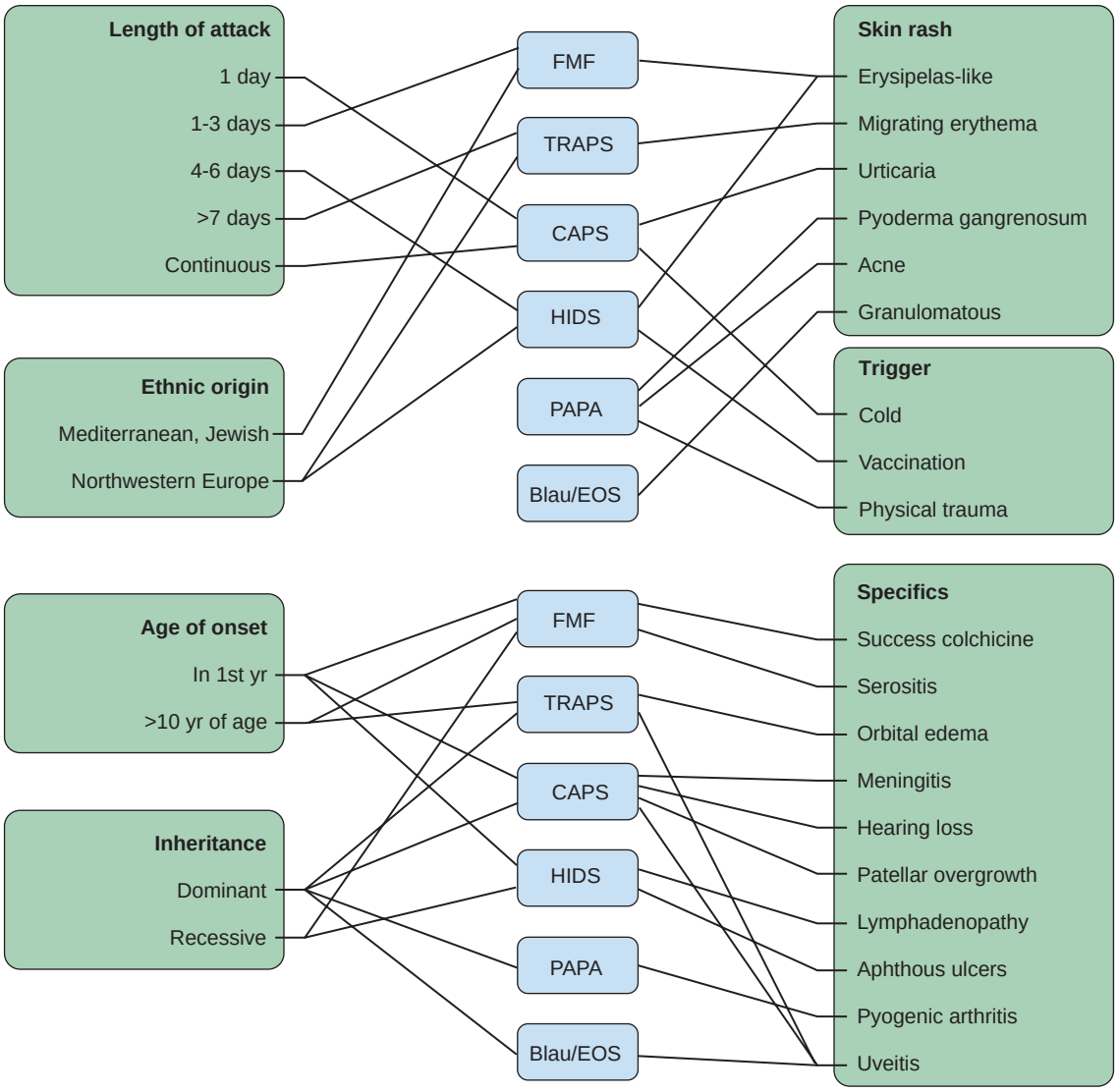

Figure 163-1 **Differential diagnosis of the familial autoinflammatory syndromes.** First exclude other, more common causes of fever and inflammation in the patient. When a familial autoinflammatory syndrome seems likely, check the clinical characteristics found in the patient on the *right* and *left* of the diagram, and assign 1 point to each syndrome that is linked to these characteristics by a line (1 characteristic could lead to or point to more than 1 syndrome). The final combined score assigns a rank for the likelihood of the disorders in this patient and offers help in deciding on the correct subsequent diagnostic tests. This algorithm is not evidence based but is solely derived from expert opinion. CAPS, cryopyrin-associated periodic syndrome; EOS, early-onset sarcoidosis; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; PAPA, pyogenic sterile arthritis, pyoderma gangrenosum, and acne; TRAPS, tumor necrosis factor receptor–associated periodic syndrome. *(From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-2.)*

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME

HIDS, also known as **mevalonate kinase deficiency**, was initially described in a cohort of Dutch patients and occurs primarily in patients of Northern European descent. HIDS is recessively inherited and caused by mutations of *MVK*, a gene located on the long arm of chromosome 12 that encodes mevalonate kinase (MK). HIDS-associated mutations are distributed throughout the MK protein, but the 2 most common mutations are the substitution of isoleucine for valine at residue 377 (V377I), a variant that is quite common in the Dutch population, and the substitution of threonine for isoleucine at residue 268 (I268T).

MK is expressed in multiple tissues, and catalyzes the conversion of mevalonic acid to 5-phosphomevalonic acid in the biosynthesis of cholesterol and nonsterol isoprenoids. Patients with HIDS-associated mutations have markedly reduced, but not absent, MK enzymatic activity. HIDS patients usually have low-normal serum cholesterol levels, but the deficiency of isoprenoids may cause increased IL-1β production by aberrant activation of the small guanosine triphosphatase Rac1. Temperature elevation may further exacerbate this process by more complete inhibition of MK activity, leading to a possible positive feedback loop. Complete genetic deficiency of MK results in a more severe phenotype known as mevalonic aciduria (see Chapter 85).

The clinical features of HIDS generally appear within the 1st 6 mo of life. Febrile attacks last between 3 and 7 days with abdominal pain that is often accompanied by diarrhea, nausea, and vomiting. Other clinical manifestations include cervical lymphadenopathy, diffuse macular rash, aphthous ulcers, headaches, and occasional splenomegaly (Figs. 163-4 to 163-6). Arthritis/arthralgia can be present in an oligoarticular or polyarticular pattern. Inflammatory disease–like illness and Kawasaki disease–like presentation have also been reported. Attacks are often precipitated by intercurrent illness, immunizations, and surgery. Families frequently recount flares around the time of birthdays, holidays, and family vacations. Patients with mevalonic

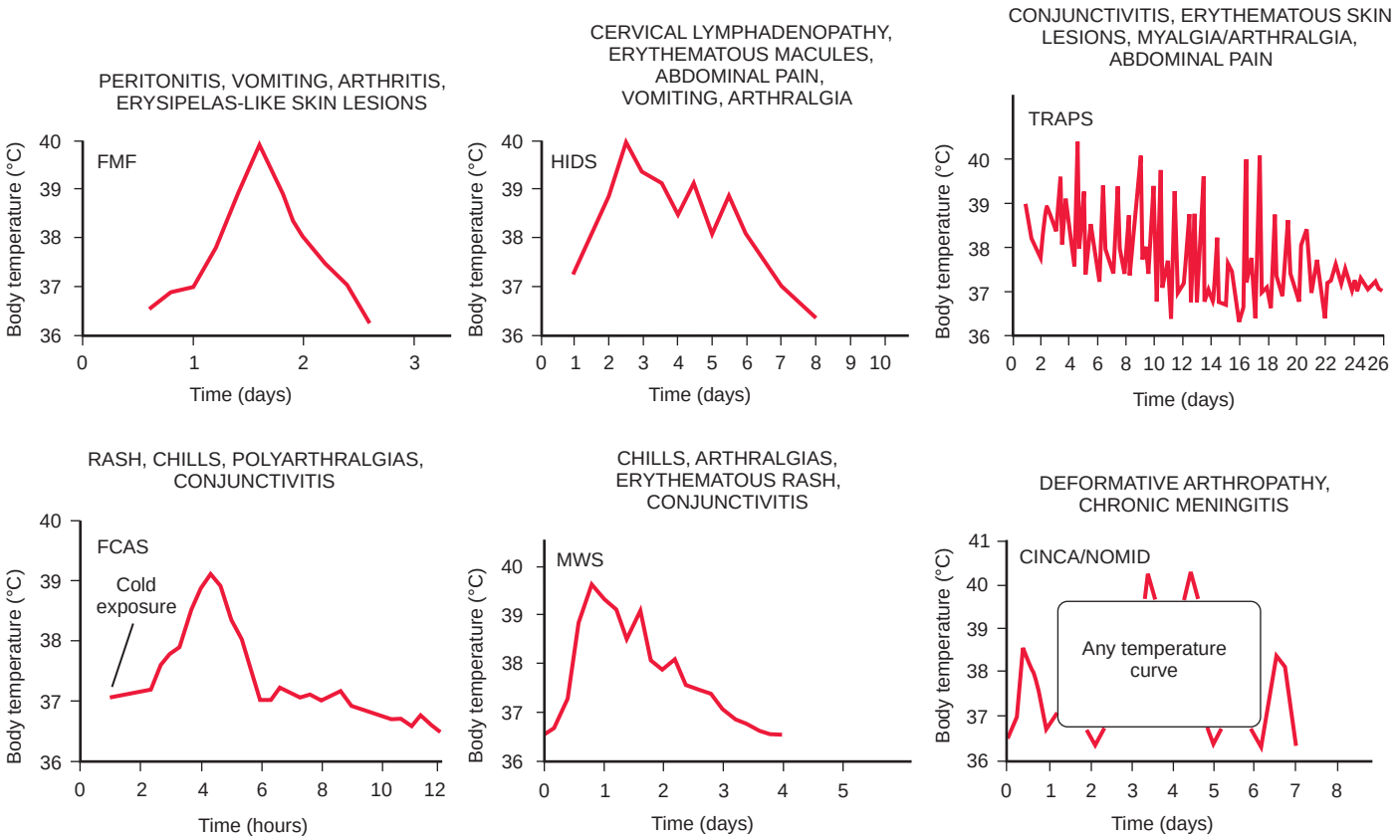

Figure 163-2 Characteristic patterns of body temperature during inflammatory attacks in the familial autoinflammatory syndromes. Interindividual variability for each syndrome is considerable, and even for the individual patient, the fever pattern may vary greatly from episode to episode. Note the different time scales on the x-axes. CINCA/NOMID, chronic infantile neurologic cutaneous and articular syndrome/neonatal-onset multisystemic inflammatory disease; FCAS, familial cold autoinflammatory syndrome; HIDS, hyper-IgD syndrome; MWS, Muckle-Wells syndrome; TRAPS, tumor necrosis factor receptor–associated periodic syndrome. *(From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-1.)*

Figure 163-3 Characteristic erysipeloid erythema associated with familial Mediterranean fever. This rash appears during a flare and overlies the ankle or dorsum of the foot.

Figure 163-4 Polymorphic rash on the hands, arms, and legs of a patient with hyperimmunoglobulinemia D syndrome (HIDS). *(From Takada K, Aksentijevich I, Mahadevan V, et al. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome.* Arthritis Rheum *48:2646, 2003.)*

aciduria present with severe mental retardation, ataxia, myopathy, cataracts, and failure to thrive (see Chapter 85).

The diagnosis of HIDS may be confirmed either by the presence of 2 mutations in *MVK* (approximately 10% of patients with seemingly typical disease have only a single identifiable mutation) and/or elevated levels of mevalonate in the urine during acute attacks. The eponymous elevation in serum IgD levels is not universally present, especially in young children, and is thought to be an epiphenomenon. Conversely, serum IgD levels may be increased in other autoinflammatory diseases as well as some chronic infections. During attacks, leukocytosis and increased serum levels of acute-phase reactants and proinflammatory cytokines are commonly present.

The symptoms of HIDS may persist for years but tend to become less prominent in adulthood. Patients with HIDS usually have a normal life span. Unlike FMF and TRAPS, the incidence of AA amyloidosis is quite low. Standards for the treatment of HIDS are evolving. Very few

Figure 163-5 Petechiae on the leg of a hyper-IgD syndrome patient during a febrile attack. *(From Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-7.)*

Figure 163-6 Aphthous ulceration detected on the tongue of a patient with hyper-IgD syndrome. *(Courtesy Dr. K. Antila, North Carelian Central Hospital, Joensuu, Finland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-8.)*

patients respond to colchicine; milder disease may respond to nonsteroidal antiinflammatory drugs. Corticosteroids are of limited utility. Small trials of both etanercept and either intermittent or daily anakinra in HIDS are promising.

THE TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME

Like FMF and HIDS, TRAPS is characterized by recurrent fevers and localized inflammation, but it is inherited in an autosomal dominant fashion and has a number of distinguishing clinical and immunologic features. TRAPS was first recognized in patients of Irish descent and denoted *familial Hibernian fever* to draw a contrast with FMF, but the current nomenclature was proposed when mutations in *TNFRSF1A* were discovered not only in the original Irish family, but in families from a number of other ethnic backgrounds. *TNFRSF1A* is located on the short arm of chromosome 12, and encodes the 55 kDa receptor (denoted p55, TNFR1, or CD120a) for TNF that is widely expressed on a number of cell types. A second 75 kDa receptor largely restricted to leukocytes is encoded on chromosome 1.

TRAPS was originally defined as an autoinflammatory disorder resulting from *TNFRSF1A* mutations, and thus genetic testing is required to make the diagnosis. To date, more than 90 disease-associated *TNFRSF1A* mutations are listed on the online *Infevers* database, as well as a smaller number of variants of unknown significance. Nearly all of the TRAPS-associated mutations in are in the extracellular domain of the TNFR1 protein, with about one-third involving the substitution of another amino acid for a highly conserved cysteine residue, thus disrupting disulfide bonds and leading to protein misfolding. A number of other missense mutations not involving cysteine residues have been shown to have a similar effect on TNFR1 protein folding. Misfolded TNFR1 aggregates intracellularly and leads to constitutive signaling through mitogen-activated protein kinases, resulting in the release of proinflammatory cytokines such as IL-1β and TNF-α. The substitution of glutamine for arginine at residue 92 (R92Q) and the substitution of leucine for proline at residue 46 (P46L) are seen in greater than 1% of the white and African-American populations, respectively. These variants do not lead to the same biochemical or signaling abnormalities seen with more-severe TRAPS mutations, and, like E148Q in FMF, there is debate as to whether they are mild mutations or functional polymorphisms.

Patients with TRAPS typically present within the 1st decade of life. Flares can occur with variable frequency but the duration is often substantially longer when compared to FMF or HIDS flares. The febrile episodes of TRAPS last at least 3 days and can persist for weeks at a time. As in FMF, there may be pleural and/or peritoneal involvement. At times patients present with signs of an acute abdomen; on exploration such patients have sterile peritonitis, sometimes with adhesions from previous episodes. Patients may also have nausea and frequently report constipation at the onset of flares that progresses to diarrhea by the conclusion. Ocular signs include periorbital edema and conjunctivitis. TRAPS patients may also experience severe myalgia and on imaging the muscle groups may have focal areas of edema. There are a number of rashes that can be seen in TRAPS patients, but the most common is an erythematous macular rash that on biopsy contains superficial and deep perivascular infiltrates of mononuclear cells. Patients often report that the rash migrates distally on a limb during its course with an underlying myalgia and can resemble cellulitis. Other rashes include erythematous annular patches as well as a serpiginous rash (Fig. 163-7). Approximately 10-15% of patients with TRAPS may develop AA amyloidosis; the presence of cysteine mutations and a positive family history are risk factors for this complication. If amyloidosis does not develop, TRAPS patients have a normal life expectancy.

Colchicine is generally not effective in TRAPS. For relatively mild disease, nonsteroidal anti-inflammatory agents may suffice. For more severe disease with infrequent attacks, corticosteroids at the time of an attack may be effective, but it is not unusual for steroid requirements to increase over time. Because some patients with TRAPS exhibit a defect in activation-induced TNF receptor shedding, and have diminished levels of immune modulatory soluble TNFR in the blood, etanercept, the soluble p75 TNFR:Fc fusion protein has been studied in this disorder. Etanercept is often effective in reducing the severity and frequency of flares, but longitudinal follow-up of TRAPS patients treated with etanercept indicates waning efficacy with time. Of note, treatment of TRAPS with anti-TNF monoclonal antibodies has sometimes led to a paradoxical worsening of disease. Experience with both anakinra, a recombinant IL-1 receptor antagonist, and canakinumab, a monoclonal anti–IL-1β antibody, has been favorable in TRAPS patients.

Figure 163-7 Cutaneous manifestations of tumor necrosis factor receptor-associated periodic syndrome. **A,** Right flank of a patient with the T50M mutation. **B,** Serpiginous rash involving the face, neck, torso, and upper extremities of a child with the C30S mutation. **C,** Erythematous, macular patches with crusting on the flexor surface of the right arm of a patient with the T50M mutation. *(From Hull KM, Drewe, Aksentijevich I, et al: The TNF receptor-associated periodic syndrome [TRAPS]: emerging concepts of an autoinflammatory syndrome,* Medicine (Baltimore) *81:349–368, 2002.)*

CRYOPYRIN-ASSOCIATED PERIODIC FEVER SYNDROMES

CAPS represents a spectrum of clinical disorders, including FCAS, MWS, and NOMID/CINCA. Although 3 separate clinical diagnoses have been defined, it should be emphasized that the cryopyrinopathies are really a continuum, and that patients may present with overlap syndromes that do not fit neatly into a single diagnosis. This spectrum of illness is caused by mutations in *NLRP3* (formerly known as *CIAS1*), located on the long arm of chromosome 1, which encodes a protein variously denoted cryopyrin or NLRP3. More than 100 disease-associated *NLRP3* mutations have been enumerated on the *Infevers* online database. Advances in next-generation sequencing have also permitted the identification of symptomatic individuals with somatic *NLRP3* mosaicism.

NLRP3 is a PYRIN domain-containing protein that is strongly expressed in myeloid cells, and to a lesser degree in other tissues. It is a part of a macromolecular complex termed the NLRP3 inflammasome that activates pro–IL-1β to its mature form in response to a variety of endogenous danger-associated molecular patterns and pathogen-associated molecular patterns. Patients with cryopyrinopathies have gain-of-function mutations in *NLRP3* that result in constitutive or easily-triggered activation of the NLRP3 inflammasome.

The cryopyrinopathies are characterized by recurrent fevers and an urticaria-like rash that develops early in infancy (Fig. 163-8). Histopathologic examination reveals a perivascular neutrophilic infiltrate without the mast cells or mast cell degranulation seen with true urticaria. In patients with FCAS, febrile attacks generally begin 1-3 hr after generalized cold exposure. FCAS patients also experience polyarthralgia of the hands, knees, and ankles, and conjunctivitis may also develop during attacks. FCAS episodes are self-limited and generally resolve within 24 hr. AA amyloidosis rarely occurs in FCAS.

In contrast to FCAS, the febrile episodes of MWS are not cold-induced, but are characterized by the same urticarial rash seen in FCAS (Fig. 163-9). Many MWS patients also develop progressive sensorineural hearing loss, and, untreated, approximately 30% of MWS patients develop AA amyloidosis. NOMID patients present in the neonatal

Figure 163-8 Urticarial rash. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

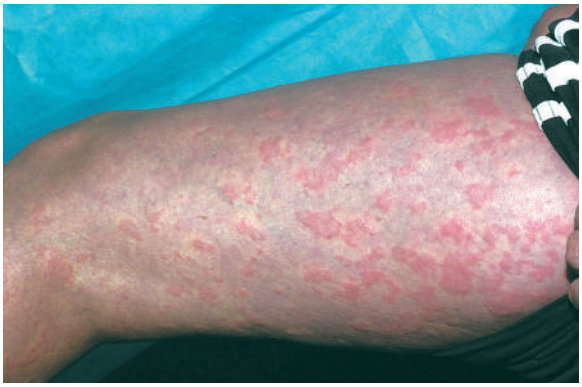

Figure 163-9 Urticarial skin rash in a patient with Muckle-Wells syndrome. *(Courtesy Dr. D. L. Kastner, National Institutes of Health, Bethesda, Maryland; from Simon A, van der Meer JWM, Drenth JPH: Familial autoinflammatory syndromes. In Firestein GS, Budd RC, Gabriel SE, et al, editors:* Kelley's textbook of rheumatology, *ed 9, Philadelphia, 2012, Saunders, Fig. 97-14.)*

Figure 163-10 A 3 yr old girl with neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous and articular (CINCA) disease. Note the markedly deformed hands, rash, frontal bossing, and large head. *(From Padeh S: Periodic fever syndromes,* Pediatr Clin North Am *52:577–560, 2005.)*

period with a diffuse, urticarial rash, daily fevers, and dysmorphic features. Significant joint deformities, particularly of the knees, may develop because of bony overgrowth of the epiphyses of the long bones (Figs. 163-10 and 163-11). NOMID patients also develop chronic aseptic meningitis, leading to increased intracranial pressure, optic disc edema, visual impairment, progressive sensorineural hearing loss, and intellectual disability (Fig. 163-12). Because of the severe disabilities associated with untreated NOMID, this disorder appeared to be sporadic before *NLRP3* mutations were identified in these patients.

Figure 163-11 Metaphyseal bone overgrowth. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Targeted therapy with anakinra, a recombinant IL-1 receptor antagonist, has been life-changing for NOMID patients, not only controlling fever and rash, but also preventing end-organ damage. Anakinra was FDA-approved for NOMID. Rilonacept, a soluble IL-1 receptor decoy, and canakinumab, a long-acting, fully humanized IgG_1 anti–IL-1β monoclonal antibody, are effective in both FCAS and MWS, and are FDA-approved for both conditions. Aggressive IL-1 blockade has resulted in attenuation of amyloidosis in the cryopyrinopathies.

OTHER MENDELIAN AUTOINFLAMMATORY DISEASES

The Syndrome of Pyogenic Arthritis with Pyoderma Gangrenosum and Acne

PAPA syndrome is a rare autosomal dominant disorder caused by mutations in *PSTPIP1*, a gene located on chromosome 15 that encodes the cytoskeletal proline serine threonine phosphatase-interacting (PSTPIP) protein. The PSTPIP1 protein interacts with a number of immunologically important molecules, including CD2, the Wiskott-Aldrich syndrome protein (WASP), and pyrin. PAPA-associated PSTPIP1 mutations markedly increase its affinity to pyrin and cause increased IL-1β production.

Clinical manifestations of PAPA syndrome include recurrent episodes of sterile, pyogenic arthritis that leads to erosions and joint destruction, and appears to develop spontaneously or after minor trauma. The onset of arthritis is often in early childhood. Cutaneous manifestations tend to develop in adolescence, at which time patients are prone to developing severe cystic acne. Additionally, PAPA patients commonly develop ulcerating pyoderma gangrenosum lesions (Fig. 163-13), and some develop pathergy reactions.

The treatment of PAPA syndrome may involve the use of corticosteroids, IL-1 antagonists, and TNF inhibitors, sometimes in combination. The joint manifestations of PAPA appear to respond to IL-1

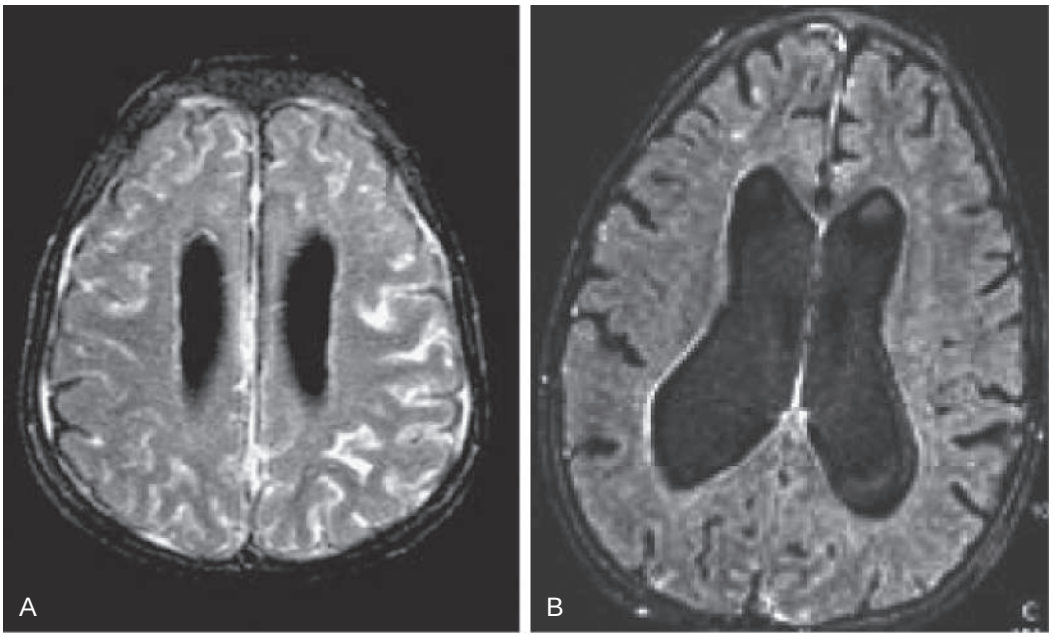

Figure 163-12 **A,** Leptomeningeal enhancement; **B,** hydrocephalus and cerebral atrophy. Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Figure 163-13 Pyoderma gangrenosum lesions in a patient with PAPA syndrome and the A230T mutation in *PSTPIP1.* Note the diffuse scarring indicative of prior lesions on his upper back.

blockade, whereas the cutaneous manifestations seem to respond more favorably to TNF blockade. Local measures, such as joint aspiration and drainage and intensive wound care, are also important in the care of PAPA patients, as is pain management for cutaneous disease. Caution should be taken when prescribing sulfonamides because some PAPA patients develop pancytopenia.

Deficiency of the Interleukin-1 Receptor Antagonist

DIRA is an autosomal recessive autoinflammatory disease that is distinct from the cryopyrinopathies. DIRA is characterized by systemic inflammation and a neutrophilic pustulosis, sterile multifocal osteomyelitis, widening of the anterior ends of the ribs, periostitis, osteopenia, and usually a neonatal onset (Figs. 163-14 and 163-15). Although fever is not a prominent clinical feature, patients do have markedly elevated acute-phase reactants. DIRA is caused by loss-of-function mutations in *IL1RN*, encoding the IL-1 receptor antagonist. The treatment of choice is anakinra, a recombinant form of the protein these patients lack.

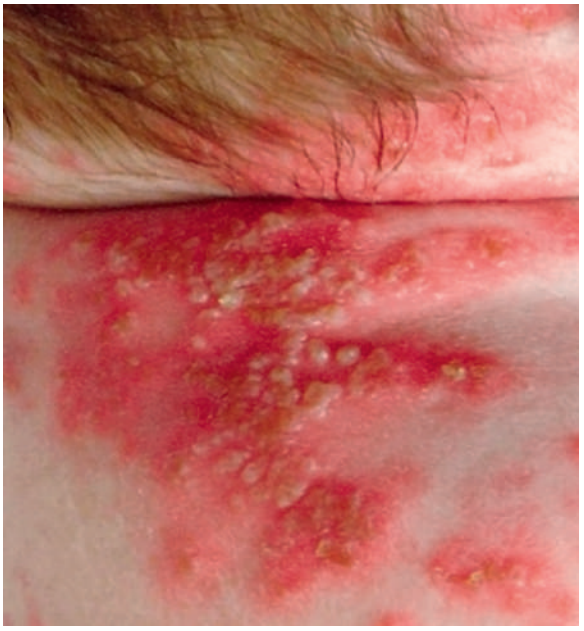

Figure 163-14 **Pustular rash.** Inflammatory clinical manifestations and organ damage in the IL-1–mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

Blau Syndrome

Blau syndrome is a rare autosomal dominant disorder that manifests as early-onset granulomatous arthritis, uveitis, and rash. The arthritis may affect the ankles and wrists, and may lead to flexion contractures of the fingers and toes (camptodactyly)**. Early-onset sarcoidosis** presents with a similar clinical picture, sometimes with visceral involvement, and both conditions are caused by mutations in *CARD15/*

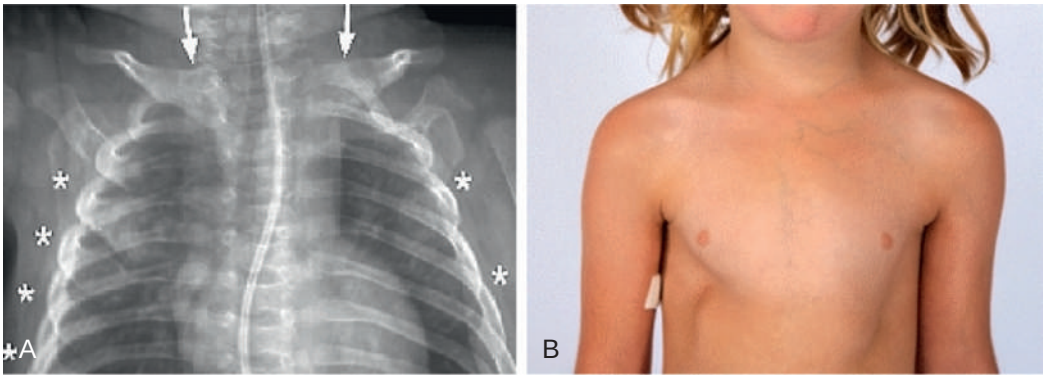

Figure 163-15 **A,** Widening of multiple ribs (*) and clavicles *(arrows)* in DIRA osteomyelitis; **B,** chest deformity. Inflammatory clinical manifestations and organ damage in the IL-1-mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA). *(From Jesus AA, Goldbach-Mansky R: IL-1 blockade in autoinflammatory syndromes.* Annu Rev Med *65:223–244, 2014, Fig. 2.)*

NOD2 on chromosome 16. The protein encoded by this gene, variously denoted caspase recruitment domain protein 15 or nucleotide-binding oligomerization domain 2 protein, is an intracellular sensor of bacterial products in dendritic cells, myelomonocytic cells, and Paneth cells. Mutations in the NACHT oligomerization domain of this protein cause Blau syndrome/early-onset sarcoidosis, while variants primarily in the leucine-rich repeat domain of this protein are associated with susceptibility to Crohn disease. Corticosteroids have been the mainstay of therapy for Blau syndrome. There are a number of case reports of the beneficial effects of TNF inhibitors, in Blau syndrome.

Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature

CANDLE is an autosomal recessive disease resulting from mutations in *PSMB8.* This gene encodes the β5i subunit of the immunoproteasome, a macromolecular complex that degrades proteins in immune cells for presentation on major histocompatibility complex class I molecules. Disease-associated mutations result in a loss of function. Patients present in the 1st yr of life with recurrent fevers, violaceous swollen eyelids, purpuric skin lesions with a mixed mononuclear and neutrophilic infiltrate, arthralgia, delayed physical development, and anemia. Acute-phase reactants are also elevated in these patients and, over time, they develop progressive lipodystrophy. On gene expression profiling, CANDLE patients have a robust interferon signature. There is no established treatment for CANDLE, although the interferon pathway may represent a therapeutic target. Two other disorders, **Nakajo-Nishimura syndrome** and the **syndrome of joint contractures, muscular atrophy, microcytic anemia, and panniculitis-induced lipodystrophy**, are clinically similar to CANDLE and are also caused by mutations in *PSMB8.*

Autoinflammation with Phospholipase $C\gamma_2$-Associated Antibody Deficiency and Immune Dysregulation

APLAID is a dominantly-inherited disorder characterized by recurrent blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies, and mild immunodeficiency. It is caused by gain-of-function mutations in *PLCG2,* leading to increased signaling through the phospholipase $C\gamma_2$ pathway in immune cells. To date there is no established therapy for APLAID.

Deficiency of Adenosine Deaminase 2

DADA2 is an autoinflammatory disorder caused by loss-of-function mutations in *CECR1*, encoding adenosine deaminase 2, characterized by recurrent fevers and a spectrum of vascular manifestations that includes livedo racemosa, early-onset ischemic lacunar strokes, and polyarteritis nodosa. Patients may also present with hepatosplenomegaly and a mild immunodeficiency. ADA2 is a protein produced primarily by monocytes and macrophages, which appear to act as a growth factor both for endothelial cells and for the antiinflammatory M2 subset of macrophages. Patients experience a vicious circle of vasculopathy and inflammation. Although there is no established therapy, there is anecdotal evidence supporting the use of etanercept.

GENETICALLY COMPLEX AUTOINFLAMMATORY DISEASES

Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis

PFAPA is the most common recurrent fever syndrome in children. It usually presents between the ages of 2 and 5 yr with recurring episodes of fever, malaise, exudative-appearing tonsillitis with negative throat cultures, cervical lymphadenopathy, oral aphthae, and, less commonly, headache, abdominal pain, and arthralgia. The episodes last 4-6 days, regardless of antipyretic or antibiotic treatment, and often occur with clock-like regularity on 3-6 wk cycles. Findings during the episodes may include mild hepatosplenomegaly, mild leukocytosis, and elevated acute-phase reactants. Both the frequency and the intensity of the episodes diminish with increasing age.

The etiology and pathogenesis of PFAPA remain unknown. The majority of patients show dramatic response to a single oral dose of prednisone (0.6-2.0 mg/kg), although this approach does not prevent recurrence and may actually shorten the interval between flares. Cimetidine given at doses of 20-40 mg/kg/day is effective at preventing recurrences in approximately one-third of cases. Complete resolution has also been reported after tonsillectomy in some but not all patients. A pilot study of anakinra (1 mg/kg subcutaneously) given for 1-2 days at the onset of symptoms showed promising results.

Chronic Recurrent Multifocal Osteomyelitis

CRMO is a form of inflammatory bone disease most commonly seen in children (see Table 163-3). Histologically and radiologically, CRMO is virtually indistinguishable from infectious osteomyelitis. Patients typically present with bone pain and may also have fever, soft-tissue swelling, and elevated acute-phase reactants. Cultures are sterile. The etiology of sporadic CRMO is unknown. Rarely CRMO can occur with congenital dyserythropoietic anemia (Majeed syndrome), caused by mutations in *LPIN2.* CRMO has also been seen in association with inflammatory bowel disease and inflammatory skin disease such as palmoplantar pustulosis. There is evidence for reduced production of the antiinflammatory cytokine IL-10 in CRMO. Initial therapy includes nonsteroidal antiinflammatory medications. Second-line treatments include corticosteroids, TNF inhibitors, and bisphosphonates.

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Chapter 164

Amyloidosis

Karyl S. Barron and Amanda Ombrello

Amyloidosis comprises a group of diseases characterized by extracellular deposition of insoluble, fibrous amyloid proteins in various body tissues.

ETIOLOGY

Amyloidosis is a disease caused by protein misfolding. These misfolded proteins infiltrate, aggregate, and form insoluble fibrils that can affect the normal function of a number of vital organs.

In the amyloidosis nomenclature, there is a distinction made between amyloidosis that develops from mutations in the *amyloid fibril protein itself* versus amyloidosis associated with genetic mutation in nonamyloid proteins. The former are referred to as hereditary amyloidoses; examples include mutations in the genes for transthyretin and apolipoprotein A, both of which are uncommon in children. This is in contrast to amyloid A (AA) amyloidosis, which develops in patients with chronic inflammatory states. It is estimated that, worldwide, approximately 45% of all amyloid cases are AA amyloidosis. In the past, chronic infectious diseases such as tuberculosis, malaria, leprosy, and chronic osteomyelitis accounted for most cases of AA amyloidosis. With effective treatment for these infections, other causes of AA have become more common. A number of chronic inflammatory rheumatic diseases such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis, as well as hereditary autoinflammatory diseases, have an increased risk for the development of AA amyloidosis. AA amyloidosis has also been associated with granulomatous diseases such as sarcoidosis, cystic fibrosis, Crohn disease, malignancies such as mesothelioma and Hodgkin diseases, intravenous drug abuse, and other infections, such as bronchiectasis and HIV. Approximately 6% of AA amyloidosis cases have no identified disease association. AL amyloidosis (formally known as idiopathic amyloidosis or myeloma-associated amyloidosis) is extremely rare in children, occurring in middle-aged or older individuals.

EPIDEMIOLOGY

Only AA amyloidosis affects children in appreciable numbers. The factors that determine the risk for amyloidosis as a complication of inflammation are not clear, because many individuals with long-standing inflammatory disease do not demonstrate tissue amyloid deposition, while some children with relatively recent onset of disease may develop amyloid. In developed countries, prior to the initiation of therapy with disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents, RA was the most common inflammatory disease associated with AA amyloidosis. Patients who had a long history of poorly controlled severe disease with extraarticular manifestations were the most at risk for developing amyloidosis and the median time from first symptoms of their rheumatic condition to the diagnosis of amyloidosis was 212 mo. The full effect of DMARD and biologic therapy in RA-associated amyloidosis has yet to be fully appreciated, but studies are showing a sustained decline in the number of new cases.

JIA is another rheumatic disease that is associated with the development of AA amyloidosis with the highest prevalence in patients with systemic JIA followed by those with polyarticular disease (see Chapter 155). In the pre-DMARD and biologic era, the prevalence of AA amyloidosis in JIA patients ranged from 1-10%. Higher prevalence was seen in Northern European patients, especially Polish patients who had a prevalence of 10.6%; lower prevalence was observed in North America. The reasons for this discrepancy are not completely understood although it is speculated that selection bias, genetic background, and tendency toward more early aggressive therapy in North Americans may have played a role.

The **hereditary autoinflammatory diseases** define a group of illnesses that are characterized by attacks of seemingly unprovoked recurrent inflammation without significant levels of either autoantibodies or antigen-specific T cells, which are typically found in patients with autoimmune diseases (see Chapter 163). Whereas autoimmune diseases such as systemic lupus erythematosus and RA result from a derangement in the adaptive immune system, the autoinflammatory syndromes are a result of malfunctions in the innate immune system. The inflammatory attacks are mediated by cells of the innate immune system (neutrophils and macrophages). Although seemingly unprovoked, these attacks are often initiated by stress, immunization, or trauma, suggesting that gene–environment interactions play an important role in pathogenesis. Although there is some variability among the autoinflammatory diseases, common findings include fevers, cutaneous rashes, arthritis, serositis, and ocular involvement. The inflammatory attacks are accompanied by intense acute phase responses (erythrocyte sedimentation rate and C-reactive protein) and high levels of serum amyloid A (SAA). Amyloidosis AA is associated with some but not all the hereditary autoinflammatory diseases.

Familial Mediterranean fever (FMF) is the most common of the mendelian autoinflammatory diseases and is seen most frequently in the Armenian, Arab, Turkish, and Sephardi Jewish populations. FMF is an autosomal recessive disease that results from mutations in the *MEFV* gene, which encodes the pyrin/marenostrin protein. *MEFV* mutations affecting the M680 and M694 amino acid residues are associated with early onset of FMF, severe disease, and an increased risk of AA amyloidosis. Patients residing in Armenia, Turkey, and Arabian countries have an increased risk of developing AA amyloidosis compared to patients with the same mutations of *MEFV* living in North America.

Tumor necrosis factor receptor associated periodic syndrome (TRAPS) is associated with mutations in the *TNFRSF1A* gene, which encode the 55 kDa tumor necrosis factor (TNF) receptor protein (TNFR1). It is estimated that 14-25% of patients with TRAPS develop AA amyloidosis. Patients with mutations in *TNFRSF1A* that affect cysteine residues have the highest risk of developing AA amyloidosis. It is thought that these cysteine residues participate in assembly of disulfide bonds important for TNFR1 folding and disruption of these bonds affects protein folding.

Mutations in the *NLRP3* gene (also known as *CIAS1*, **cold-induced autoinflammatory syndrome 1)** cause 3 clinically distinct diseases: familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID) that is also known as chronic infantile neurologic cutaneous and articular (CINCA) syndrome. Mutations in *NLRP3* are inherited in an autosomal dominant fashion or as *de novo* mutations in patients with the most severe disease. Familial cold autoinflammatory syndrome is generally the least severe of the cryopyrinopathies and is rarely associated with AA amyloidosis. MWS presents with fevers, myalgias, arthralgias, urticarial-like rash, and progressive sensorineural hearing loss. AA amyloidosis is quite common in MWS, affecting up to one-third of the patients. NOMID/CINCA is the most severe cryopyrinopathy. Historically 20% of patients died before reaching adulthood but with current therapies, many are living longer lives. There have been NOMID patients who develop AA amyloidosis as they get older, although cases are not as frequent as those with MWS, possibly due to a shortened life span in these patients.

Hyper IgD syndrome (HIDS) is another autoinflammatory disease that presents in early childhood with chills, high fevers, abdominal pain, lymphadenopathy, and occasional rash. HIDS is an autosomal recessive disease that involves loss of function mutations in the *MVK* gene that encodes the mevalonate kinase enzyme. Inflammatory markers, including SAA, are high during attacks and may remain elevated in the intercurrent period. AA amyloidosis is rare in HIDS but has been reported.

Although seen less frequently than in the hereditary periodic fever syndromes, the risk of AA amyloidosis has been well established in patients with Crohn disease. It is estimated that AA amyloidosis occurs in approximately 1% of patients in the United States and up to 3% in Northern European patients. Conversely, AA amyloidosis presenting

in patients with ulcerative colitis is extremely rare, with estimated prevalence of 0.07%. The patients have a long-standing history of aggressive, poorly controlled disease; however there are reports of amyloidosis in patients with well-controlled inflammatory markers.

PATHOGENESIS

The deposition of AA amyloid fibrils is a result of a prolonged inflammatory state that leads to misfolding of the AA amyloid protein and deposition into tissues. The precursor protein of the fibrils in AA amyloidosis is an apolipoprotein called SAA. SAA is produced in the liver in response to proinflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-α and can increase more than 1,000-fold during inflammation. It has been speculated that SAA has a role as a chemoattractant and in lipid metabolism. Supporting this theory is the finding that amyloid deposition occurs initially in organs that are major sites of lipid and cholesterol metabolism such as the kidney, liver, and spleen.

Under normal circumstances SAA is secreted by the liver and completely degraded by macrophages. The secreted SAA protein is 104 amino acids in length and is primarily secreted in an α-helix structure. For reasons not completely understood, patients with AA amyloidosis have a flaw resulting in incomplete degradation and accumulation of intermediate SAA products. In these patients, SAA is transferred to the lysosome where the c-terminal portion of the SAA protein is cleaved, allowing the remaining protein to fold into a β-pleated sheet configuration. Deposited amyloid contains only 66-76 amino acids compared to the 104 in secreted SAA. These cleaved fragments polymerize and form fibrils that are deposited in the extracellular space and bind proteoglycans and other proteins such as serum amyloid P. These fibrils then become resistant to proteolysis and deposit in organ tissues.

CLINICAL MANIFESTATIONS

Although organ involvement may vary, AA amyloidosis most commonly affects the kidneys; 90% of patients have some degree of renal involvement. Unexplained proteinuria may be the presenting feature in some patients. Nephrotic syndrome and renal failure may develop if the underlying inflammatory condition is not controlled or if diagnosis is delayed. Median survival after diagnosis has been reported to be 133 mo; patients with higher SAA levels had significantly higher risk of death than those with lower SAA levels. Gastrointestinal involvement is seen in approximately 20% of patients and usually manifests as chronic diarrhea, gastrointestinal bleeding, abdominal pain, and malabsorption, whereas testes are frequently involved (87%). Relatively uncommon findings associated with AA amyloidosis include anemia, amyloid goiter, hepatomegaly, splenomegaly, adrenal involvement, and pulmonary involvement. Tissues, such as the heart, tongue, and skin, are rarely involved.

DIAGNOSIS

The diagnosis of amyloidosis is established by biopsy demonstrating amyloid fibril proteins in affected tissues. The tissues most commonly tested include kidney, rectum, abdominal fat pad, and gingiva. Amyloid deposits are composed of seemingly homogeneous eosinophilic material that stains with Congo red dye and demonstrates the pathognomonic "apple-green birefringence" in polarized light. Amyloid can also be recognized with routine hematoxylin and eosin staining and electron microscopy.

LABORATORY FINDINGS

Patients with AA amyloidosis usually show elevated acute-phase reactants and high levels of immunoglobulins. Specific laboratory testing is possible only for AL amyloidosis, and most patients with this form of amyloidosis show increased plasma cells in the bone marrow and serum or urine monoclonal immunoglobulin (Ig) or free light chain. A biopsy showing amyloid deposition along with a monoclonal serum protein distinguishes AL amyloidosis from monoclonal gammopathy of uncertain significance, which is common in older adults.

TREATMENT

There is no established therapy to AA amyloidosis and, thus, the primary means of treatment of AA amyloidosis is aggressive management of the underlying inflammatory or infectious disease, which decreases levels of SAA protein. As newer therapies have been developed to treat the underlying condition, there is emerging evidence that the incidence of AA amyloidosis is decreasing. Colchicine is effective not only in controlling the attacks of FMF but also in preventing the development of amyloidosis associated with FMF. Children with FMF who are homozygous for the M694V mutation in the *MEFV* gene are at greater risk for development of amyloidosis and should be monitored closely.

Unlike AA amyloidosis associated with FMF, AA amyloidosis associated with other autoinflammatory diseases (including TRAPS, cryopyrin-associated periodic syndrome, and HIDS) and chronic rheumatic diseases (JIA, RA, and ankylosing spondylitis) do not respond to colchicine. Although AA amyloidosis associated with JIA may respond to chlorambucil, this drug is associated with chromosome breakage and a risk of subsequent malignancy.

Increasing use of biologic medicines against proinflammatory cytokines to treat RA, JIA, spondyloarthropathies, and the hereditary autoinflammatory diseases seems to impact risk factors for the development of AA amyloidosis. The class of medications referred to as the anti–TNF-α drugs have been paramount in the management of RA and other autoimmune disease. In both autoimmune and autoinflammatory conditions with accompanying AA amyloidosis, there are reports documenting the effectiveness of anti-TNF agents in blunting the progression of amyloidosis. Adverse effects of anti-TNF medications include reactivation of tuberculosis and hepatitis B, thus careful screening should be performed before instituting therapy. Additionally, the development of various antibodies, autoantibodies, and autoimmune disease has been noted in patients taking anti-TNF agents. Extreme caution should be used in prescribing anti-TNF agents to patients with a history of heart failure or demyelinating disease, as use can cause exacerbations in their underlying cardiac and neurologic diseases.

The IL-1 pathway is the target of multiple biologic medications used in autoimmune and autoinflammatory diseases. The 3 available IL-1 antagonists are anakinra (IL-1 receptor antagonist), rilonacept (soluble IL-1 receptor decoy), and canakinumab (long-acting fully humanized IgG_1 anti–IL-1β monoclonal antibody). The various IL-1 inhibitors have been successful at slowing the progression of AA amyloidosis, and in some cases treatment results in regression of amyloid associated proteinuria.

Tocilizumab, an anti–IL-6 receptor antibody, has been shown to attenuate experimental AA amyloid and to reverse AA amyloidosis complicating JIA and RA. Eprodisate disodium is currently in international trial in patients with AA amyloidosis–associated nephropathy. By binding the amyloidogenic precursor proteins, eprodisate disodium attempts to prevent the deposition of amyloid in organ, hence preserving renal function.

COMPLICATIONS AND PROGNOSIS

End-stage renal failure is the underlying cause of death in 40-60% of patients with amyloidosis, with a median survival time from diagnosis of 2-10 yr. According to a large-scale study of 374 patients with AA amyloidosis, the factors associated with a poor prognosis include older age, a lower albumin serum level, end-stage renal disease at baseline, and prolonged serum elevation of SAA. An elevated SAA value was the most powerful risk factor for end-stage renal disease and death from AA amyloidosis.

PREVENTION

The primary means of preventing AA amyloidosis is treatment of the underlying inflammatory or infectious disease, resulting in decreases in the level of SAA protein and the risk of amyloid deposition. Although the period of latency between the onset of inflammation (of the underlying disease) and the initial clinical signs of AA amyloidosis may vary and is often prolonged, progression of the amyloid depositions can be rapid.

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Chapter 165

Sarcoidosis

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Sarcoidosis is a rare multisystem granulomatous disease of unknown etiology. The name is derived from a Greek word meaning "flesh-like condition," in reference to the characteristic skin lesions. There appear to be 2 age-dependent distinct patterns of disease among children with sarcoidosis. The clinical features in older children are similar to those in adults (pediatric onset adult sarcoidosis), with frequent systemic features (fever, weight loss, malaise), pulmonary involvement and lymphadenopathy. In contrast, early-onset sarcoidosis manifesting in children <4 yr of age is characterized by the triad of rash, uveitis, and polyarthritis.

ETIOLOGY

The etiology of sarcoidosis remains obscure but likely results from exposure of a genetically susceptible individual to 1 or more unidentified antigens. This exposure initiates an exaggerated immunologic response that ultimately leads to the formation of granulomas. The human major histocompatibility complex is located on chromosome 6, and specific human leukocyte antigen class I and class II alleles are associated with disease phenotype. Genetic polymorphisms involving various cytokines and chemokines may also have a role in development of sarcoidosis. Familial clustering supports the contribution of genetic factors to sarcoidosis susceptibility. Environmental and occupational exposures are also associated with disease risk. There are positive associations between sarcoidosis and agricultural employment, occupational exposure to insecticides, and moldy environments typically associated with microbial bioaerosols.

Blau syndrome is an autosomal dominant, familial form of sarcoidosis and is typified by the early onset of granulomatous inflammation involving the skin, eyes, and joints. Missense mutations in the *CARD15/NOD2* gene on chromosome 16 have been found in affected family members and appear to be associated with development of sarcoidosis. The 2 most common amino acid substitutions are R334W (arginine to glutamine) and R334Q (arginine to tryptophan). Similar genetic mutations also have been found in individuals with a sporadic **early-onset sarcoidosis (EOS)** (rash, uveitis, arthritis), suggesting that this nonfamilial form and Blau syndrome are genetically and phenotypically identical (see Chapter 163).

EPIDEMIOLOGY

A nationwide patient registry of childhood sarcoidosis in Denmark estimated the annual incidence to be 0.22-0.27 per 100,000 children. The incidence increases with age, and peak onset occurs at 20-39 yr. The most common age of reported childhood cases is 13-15 yr. Annual incidence is about 11 per 100,000 in adult white Americans and is 3 times higher in African-Americans. There is no clear sex predominance in childhood sarcoidosis. Within the United States, the majority of childhood sarcoidosis cases are reported in the Southeastern and South Central states.

An international registry and Spanish cohort of Blau syndrome and EOS reported the mean age of disease onset as 30 mo and 36 mo, respectively. All but 3 of these young patients presented before 5 yr of age. There does not appear to be a sex preference in either condition.

PATHOLOGY AND PATHOGENESIS

Noncaseating, epithelioid granulomatous lesions are a cardinal feature of sarcoidosis. Activated macrophages, epithelioid cells, and multinucleated giant cells as well as CD4+ T lymphocytes accumulate and become tightly packed in the center of the granuloma. The causative agent that initiates this inflammatory process is not known. The periphery of the granuloma contains a loose collection of monocytes, CD4+ and CD8+ T lymphocytes, and fibroblasts. The interaction between the macrophages and CD4+ T lymphocytes is important in the formation and maintenance of the granuloma. The activated macrophages secrete high levels of tumor necrosis factor-α (TNF-α) and other proinflammatory mediators. The CD4+ T lymphocytes differentiate into type 1 helper T cells and release interleukin (IL)-2 and interferon-γ, promoting proliferation of lymphocytes. Granulomas may heal or resolve with complete preservation of the parenchyma. In approximately 20% of the lesions, the fibroblasts in the periphery proliferate and produce fibrotic scar tissue, leading to significant and irreversible organ dysfunction.

The sarcoid macrophage is able to produce and secrete 1,25-$(OH)_2$-vitamin D or calcitriol, an active form of vitamin D typically produced in the kidneys. The hormone's natural functions are to increase intestinal absorption of calcium and bone resorption and to decrease renal excretion of calcium and phosphate. An excess of calcitriol may result in hypercalcemia and hypercalciuria in patients with sarcoidosis.

CLINICAL MANIFESTATIONS

Sarcoidosis is a multisystem disease, and granulomatous lesions may occur in any organ of the body. The clinical manifestations depend on the extent and degree of granulomatous inflammation and are extremely variable. Children may present with nonspecific symptoms, such as fever, weight loss, and general malaise. In adults and older children, pulmonary involvement is most frequent, with infiltration of the thoracic lymph nodes and lung parenchyma. Isolated bilateral hilar adenopathy (Fig. 165-1) on chest radiograph is the most common finding, but parenchymal infiltrates and miliary nodules may also be seen (Fig. 165-2). Patients with lung involvement are commonly found to have restrictive changes on pulmonary function testing. Symptoms of pulmonary disease are seldom severe and generally consist of a dry, persistent cough.

Extrathoracic lymphadenopathy and infiltration of the liver, spleen, and bone marrow also occur often. Infiltration of the liver and spleen typically leads to isolated hepatomegaly and splenomegaly, respectively, but actual organ dysfunction is rare. Cutaneous disease, such as plaques, nodules, erythema nodosum in acute disease, or lupus pernio in chronic sarcoidosis, appears in one quarter of cases and is usually present at onset. Red-brown to purple maculopapular lesions < 1 cm

Figure 165-1 Chest radiograph demonstrating a stage I disease with enlarged mediastinal and hilar lymph nodes. *(From Iannuzzi M: Sarcoidosis. In Goldman L, Schafer AI, editors,* Goldman's Cecil medicine, *ed 24, Philadelphia, 2012, Saunders, Fig. 95-1, p. 582.)*

Figure 165-2 Chest radiograph of a 10 yr old girl with sarcoidosis showing widely disseminated peribronchial infiltrates, multiple small nodular densities, hyperaeration of the lungs, and hilar lymphadenopathy.

Figure 165-3 Sarcoidosis nodules on the face. *(From Shah BR, Laude TA:* Atlas of pediatric clinical diagnosis, *Philadelphia, 2000, Saunders.)*

on the face, neck, upper back, and extremities are the most common skin finding (Fig. 165-3). Ocular involvement is frequent and has variable manifestations, including anterior or posterior uveitis, conjunctival granulomas, eyelid inflammation, and orbital or lacrimal gland infiltration. The arthritis in sarcoidosis can be confused with juvenile idiopathic arthritis. Central nervous system (CNS) involvement is rare in early childhood but may manifest as seizures, cranial nerve involvement, intracranial mass lesions, and hypothalamic dysfunction. Kidney disease also occurs infrequently in children but typically manifests as renal insufficiency, proteinuria, transient pyuria, or microscopic hematuria as a result of either early monocellular infiltration or granuloma formation in kidney tissue. Only a small fraction of children have hypercalcemia or hypercalciuria, which is therefore an infrequent cause of kidney disease. Sarcoid granulomas can also infiltrate the heart and lead to cardiac arrhythmias and, rarely, sudden death. Other rare sites of disease involvement include blood vessels of any size, the gastrointestinal tract, parotid gland, muscles, bones, and testes.

In contrast to the variable clinical presentation of sarcoidosis in older children, Blau syndrome and EOS (NOD2-associated sarcoidosis) classically manifest as the triad of uveitis, arthritis, and rash. Pulmonary disease and lymphadenopathy are less common. The arthritis is polyarticular and symmetric, with large boggy effusions. Large and small joints are involved; tenosynovitis is an associated finding. Joints are stiff and moderately tender. The rash may wax and wane and is diffuse (mostly truncal), erythematous or tan, macular–papular, and often desquamates at times being confused with eczema or ichthyosis vulgaris. Tender subcutaneous nodules resembling erythema nodosum may be seen on the legs. Noncaseating granulomas are demonstrated with biopsy of the skin or joint synovium.

Granulomatous iridocyclitis and posterior uveitis may progress to panuveitis, which has a high risk for vision loss. Iris nodules, photophobia, erythema, cataracts, or glaucoma may be present or develop over time.

Patients with NOD2 mutations in particular display this more restricted phenotype but may also have visceral disease, whereas those without a NOD2 mutation often show extended manifestations, including fever, hepatosplenomegaly, lymphadenopathy, and lung, kidney, and CNS involvement.

Infantile onset panniculitis with uveitis and systemic granulomatosis is an uncommon manifestation of sarcoidosis. Sarcoidosis has also been reported in adults treated with type 1 interferons for hepatitis or multiple sclerosis.

LABORATORY FINDINGS

There is no single standard laboratory test diagnostic of sarcoidosis. Anemia, leukopenia, and eosinophilia may be seen. Other nonspecific findings include hypergammaglobulinemia and elevations in acute-phase reactants, including erythrocyte sedimentation rate and C-reactive protein value. Hypercalcemia and/or hypercalciuria occur in only a small proportion of children with sarcoidosis. Angiotensin-converting enzyme (ACE) is produced by the epithelioid cells of the granuloma, and its serum value may be elevated, but this finding lacks diagnostic sensitivity and specificity. ACE levels are estimated to be elevated in more than 50% of children with sarcoidosis. In addition, ACE values may be difficult to interpret because reference values for serum ACE are age dependent. Fluorodeoxyglucose F18 positron emission tomography can help identify nonpulmonary sites for a diagnostic biopsy.

DIAGNOSIS

Definitive diagnosis ultimately requires demonstration of the characteristic noncaseating granulomatous lesions in a biopsy specimen (usually taken from the most readily available affected organ) and exclusion of other known causes of granulomatous inflammation. Skin and transbronchial lung biopsies have higher yield, greater specificity, and fewer associated adverse events than biopsy of mediastinal lymph nodes or liver. Additional diagnostic testing should include chest radiography, pulmonary function testing with measurement of diffusion capacity, hepatic enzyme measurements, and renal function assessment. Ophthalmologic slit-lamp examination is essential, as ocular findings are frequent in sarcoidosis and vision loss is a sequela of untreated disease.

Bronchoalveolar lavage may be used to assess for disease activity, and the fluid typically reveals an excess of lymphocytes with an increased CD4+:CD8+ ratio of 2-13:1. In addition to flexible bronchoscopy with transbronchial biopsy, endosonographic guided intrathoracic node aspiration has been valuable in obtaining tissue to assess for noncaseating granulomas.

DIFFERENTIAL DIAGNOSIS

Because of its protean manifestations, the differential diagnosis of sarcoidosis is extremely broad and depends largely on the initial clinical manifestations. **Granulomatous infections**, including tuberculosis, cryptococcosis, pulmonary mycoses (histoplasmosis, blastomycosis, coccidioidomycosis), brucellosis, tularemia, and toxoplasmosis, must be excluded. Other causes of granulomatous inflammation are

granulomatosis with polyangiitis (formerly Wegener granulomatosis), hypersensitivity pneumonia, chronic berylliosis, and other occupational exposures to metals. Immunodeficiencies that may manifest with granulomatous lesions include common variable immunodeficiency, selective immunoglobulin A deficiency, chronic granulomatous disease, ataxia telangiectasia, and severe combined immunodeficiency. Granulomas of the lung, skin or lymph nodes have been reported in patients treated with anti-TNF agents. Lymphoma should be ruled out in cases of hilar or other lymphadenopathy. Sarcoid arthritis may mimic juvenile idiopathic arthritis. Evaluation for endocrine disorders is needed in the setting of hypercalcemia or hypercalciuria.

TREATMENT

Treatment should be based on disease severity as well as the number and type of organs involved. Corticosteroids are the mainstay of treatment for most acute and chronic disease manifestations. The optimal dose and duration of corticosteroid therapy in children have not been established. Induction treatment typically begins with oral prednisone or prednisolone (1-2 mg/kg/day up to 40 mg daily) for 8-12 wk until manifestations improve. Corticosteroid dosage is then gradually decreased over 6-12 mo to the minimal effective maintenance dose (e.g., 5-10 mg/day) that controls symptoms, or discontinued if symptoms resolve. Methotrexate or leflunomide may be effective as a corticosteroid-sparing agent. On the basis of the role of TNF-α in the formation of granulomas, there is rationale for use of TNF-α antagonists. Results of small clinical trials showed modest effects with infliximab and adalimumab treatment of selected disease manifestations (CNS, lupus pernio, pulmonary, ocular), whereas etanercept does not appear to be particularly effective. Other therapeutics used for sarcoidosis manifestations include topical corticosteroids (eye), inhaled corticosteroids (lung), azathioprine (CNS), cyclophosphamide (cardiac, CNS), hydroxychloroquine (skin), mycophenolate mofetil (CNS, skin), thalidomide or its analogs (skin), and nonsteroidal antiinflammatory drugs (joints).

With regard to treatment of EOS, there are also few case reports on the successful use of thalidomide and infliximab. Findings of elevated IL-1 levels and response to human IL-1 receptor antagonist (anakinra) in EOS, however, have been inconsistent.

PROGNOSIS

The prognosis of childhood sarcoidosis is not well defined. The disease may be self-limited with complete recovery or may persist with a progressive or relapsing course. Outcome is worse in the setting of multiorgan or CNS involvement. Most children requiring treatment experience considerable improvement with corticosteroids, though a significant number have morbid sequelae, mainly involving the lungs and eyes. Children with EOS have a poorer prognosis and generally experience a more chronic, progressive disease course. The greatest morbidity is associated with ocular involvement, including cataract formation, development of synechiae, and loss of visual acuity or blindness; long-term systemic treatment may be required for the eye disease. Progressive polyarthritis may result in joint destruction. The overall mortality rate in childhood sarcoidosis is low.

Serial pulmonary function tests and chest radiographs are useful in following the course of lung involvement. Monitoring for other organ involvement should also include electrocardiogram with consideration of an echocardiogram, urinalysis, renal function tests, and measurements of hepatic enzymes and serum calcium. Other potential indicators of disease activity include inflammatory markers and serum ACE, although changes in ACE level do not always correlate with other indicators of disease status. Given the frequency of asymptomatic eye disease and the ocular morbidity associated with pediatric sarcoidosis, all patients should have an ophthalmologic examination at presentation with monitoring at regular intervals, perhaps every 3-6 mo as recommended in children with juvenile idiopathic arthritis.

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Chapter 166

Kawasaki Disease

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Kawasaki disease (KD), formerly known as **mucocutaneous lymph node syndrome** and **infantile polyarteritis nodosa,** is an acute febrile illness of childhood seen worldwide with the highest incidence occurring in Asian children. KD is a vasculitis with a predilection for the coronary arteries. Approximately 20-25% of untreated children develop coronary artery abnormalities (CAA) including aneurysms, whereas <5% of children treated with intravenous gammaglobulin (IVIG) develop CAA. Nonetheless, KD is the leading cause of acquired heart disease in children in most developed countries, including the United States and Japan.

ETIOLOGY

The cause of KD remains unknown, but certain epidemiologic and clinical features support an infectious origin. These features include the young age group affected, epidemics with wave-like geographic spread of illness, the self-limited nature of the acute febrile illness, and the clinical features of fever, rash, enanthem, conjunctival injection, and cervical lymphadenopathy. Further evidence of an infectious trigger includes the infrequent occurrence of the illness in infants younger than 3 mo, likely the result of maternal antibodies, and the rarity of cases in adults, likely the result of prior exposures with subsequent immunity. However, there are features that are not consistent with an infectious origin. For example, it is unusual to have multiple cases present at the same time within a family or daycare center. Furthermore, no single infectious etiologic agent has been successfully identified, despite a comprehensive search.

A genetic role in the pathogenesis of KD seems likely, as evidenced by the higher risk of KD in Asian children regardless of country of residence, and in siblings and children of individuals with a history of KD. Furthermore, linkage studies and genome-wide association studies have identified significant associations between polymorphisms in the *ITPKC* gene, a T-cell regulator, with increased susceptibility to KD and to more-severe disease. Polymorphisms in a high-affinity receptor for immunoglobulin G (*FCGR2A)* have also been identified as significant variants in KD patients.

EPIDEMIOLOGY

For the majority of patients, KD is a disease of early childhood and nearly all epidemiologic studies show a higher susceptibility to KD in boys. Utilizing the Kids Inpatient Database to study trends in KD hospitalizations in 2006, Holman et al reported that more than 75% of all KD-associated hospitalizations in patients <18 yr were recorded in children <5 yr, with a mean age of 3 yr. Children of Asian and Pacific Islander descent had the highest hospitalization rate of 30.3/100,000 children, compared with 17.5/100,000 black, non-Hispanic children, 15.7/100,000 Hispanic children, and 12/100,000 white, non-Hispanic children. The hospitalization rate for KD in 2006 was 20.8/100,000 in children <5 yr of age, which was consistent with the prior 10 yr of hospitalization rates in the United States. In other countries, such as the United Kingdom, Korea, and Japan, the rate of KD seems to be increasing.

In Japan, nationwide surveys have been administered every 2 yr to monitor trends in KD incidence. In 2010, the highest recorded rate thus far of 239.6 per 100,000 children ages 0-4 yr was described, with the highest rate in very young children ages 6-11 mo. Infants <6 mo and children >5 yr were at the highest risk for CAA in the latest Japanese survey.

Several risk stratification models have been constructed to determine which patients with KD are at highest risk for CAA. Predictors of poor outcome across several studies include young age, male gender,

persistent fever, poor response to IVIG, and laboratory abnormalities including neutrophilia, thrombocytopenia, transaminitis, hyponatremia, hypoalbuminemia, elevated levels of N-terminal-probrain natriuretic protein and elevated C-reactive protein levels. Asian and Pacific Islander race and Hispanic ethnicity are also risk factors for CAA. Three specific risk scores have been constructed by Japanese researchers; of these, the Kobayashi score is the most widely used and has high sensitivity and specificity. Unfortunately, application of these risk scores in non-Japanese populations does not appear to accurately identify all children at risk for IVIG resistance and CAA.

PATHOLOGY

KD is a vasculitis that predominantly affects the medium-size arteries. The coronary arteries are the most commonly involved, although other arteries, such as the popliteal and brachial arteries, can also develop dilation. A 3-phase process to the arteriopathy of KD has been described. The 1st phase is a neutrophilic necrotizing arteritis occurring in the 1st 2 wk of illness that begins in the endothelium and moves through the coronary wall. Saccular aneurysms may form from this arteritis. The second phase is a subacute/chronic vasculitis driven by lymphocytes, plasma cells, and eosinophils, which may last weeks to years and results in fusiform aneurysms. The vessels affected by the subacute/chronic vasculitis then develop smooth muscle cell myofibroblasts, which cause progressive stenosis. Thrombi may form in the lumen and obstruct blood flow.

CLINICAL MANIFESTATIONS

Fever is characteristically high (≥38.3°C [101°F]), unremitting, and unresponsive to antibiotics. The duration of fever without treatment is generally 1-2 wk, but may persist for 3-4 wk. In addition to fever, the **5 principal clinical criteria** of KD are: bilateral **nonexudative** conjunctival injection with limbal sparing; erythema of the oral and pharyngeal mucosa with strawberry tongue and red, cracked lips; edema and erythema of the hands and feet; rash of various forms (maculopapular, erythema multiforme, or scarlatiniform); and nonsuppurative cervical lymphadenopathy, usually unilateral, with node size >1.5 cm (Table 166-1; Figs. 166-1 to 166-4). Perineal desquamation is common in the acute phase. Periungual desquamation of the fingers and toes begins 2-3 wk after the onset of illness and may progress to involve the entire hand and foot (Fig. 166-5).

Symptoms other than the clinical criteria are common in the 10 days prior to diagnosis of KD, which may be explained in part by the finding that up to a third of patients with KD have confirmed, concurrent infections. Gastrointestinal symptoms (vomiting, diarrhea, or abdominal pain) occur in more than 60% of patients, and at least 1 respiratory symptom (rhinorrhea or cough) occurs in 35%. Other clinical findings include significant irritability that is especially prominent in infants and likely a consequence of aseptic meningitis, mild hepatitis, hydrops of the gallbladder, urethritis and meatitis with sterile pyuria, and arthritis. Arthritis may occur early in the illness or may develop in the 2nd or 3rd wk. Small or large joints may be affected, and the arthralgias

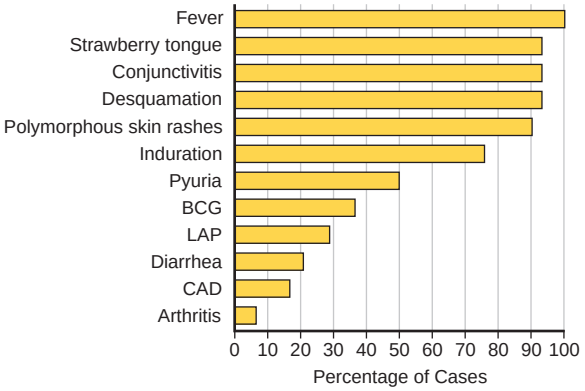

Figure 166-1 Clinical symptoms and signs of Kawasaki disease. A summary of the clinical features from 110 cases of Kawasaki disease seen in Kaohsiung, Taiwan. LAP, lymphadenopathy in head and neck area; BCG, reactivation of bacille Calmette-Guérin inoculation site; CAD, coronary artery dilation, defined by an internal diameter >3 mm. *(From Wang CL, Wu YT, Liu CA, et al: Kawasaki disease: infection, immunity and genetics,* Pediatr Infect Dis J *24:998–1004, 2005.)*

Table 166-1 Clinical and Laboratory Features of Kawasaki Disease

EPIDEMIOLOGIC CASE DEFINITION (CLASSIC CLINICAL CRITERIA)*
Fever persisting at least 5 days†
Presence of at least 4 principal features:
Changes in extremities:
Acute: Erythema of palms, soles; edema of hands, feet
Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
Polymorphous exanthem
Bilateral bulbar conjunctival injection without exudate
Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
Exclusion of other diseases with similar findings‡
OTHER CLINICAL AND LABORATORY FINDINGS
Cardiovascular findings:
Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
Coronary artery abnormalities
Aneurysms of medium-size noncoronary arteries
Raynaud phenomenon
Peripheral gangrene
Musculoskeletal system:
Arthritis, arthralgias
Gastrointestinal tract:
Diarrhea, vomiting, abdominal pain
Hepatic dysfunction
Hydrops of gallbladder
Central nervous system:
Extreme irritability
Aseptic meningitis
Sensorineural hearing loss
Genitourinary system:
Urethritis/meatitis
Other findings:
Erythema, induration at bacille Calmette-Guérin inoculation site
Anterior uveitis (mild)
Desquamating rash in groin
LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE
Leukocytosis with neutrophilia and immature forms
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Anemia
Abnormal plasma lipids
Hypoalbuminemia
Hyponatremia
Thrombocytosis after week 1§
Sterile pyuria
Elevated serum transaminases
Elevated serum gamma glutamyl transpeptidase
Pleocytosis of cerebrospinal fluid
Leukocytosis in synovial fluid

*Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by 2-dimensional echocardiography or angiography.

†In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness. Experienced clinicians who have treated many patients with Kawasaki disease may establish diagnosis before day 4.

‡See differential diagnosis (Table 166-2).

§Some infants present with thrombocytopenia and disseminated intravascular coagulation.

From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease, Pediatrics *114:1708–1733, 2004.*

Figure 166-2 Strawberry tongue in mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

Figure 166-3 Congestion of bulbar conjunctiva in a patient with mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

Figure 166-4 Indurative edema of the hands in mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

Figure 166-5 Desquamation of the fingers in a patient with mucocutaneous lymph node syndrome (Kawasaki disease). *(Courtesy of Tomisaku Kawasaki, MD. From Hurwitz S:* Clinical pediatric dermatology, *ed 2, Philadelphia, 1993, Saunders.)*

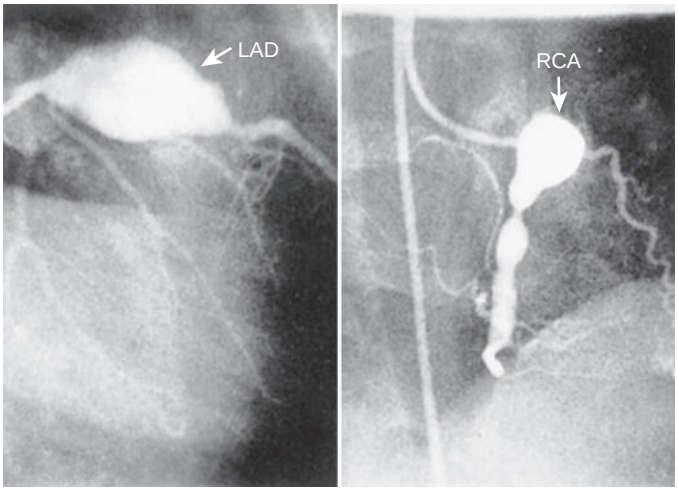

Figure 166-6 Coronary angiogram demonstrating giant aneurysm of the left anterior descending coronary artery (LAD) with obstruction and giant aneurysm of the right coronary artery (RCA) with an area of severe narrowing in 6 yr old boy. *(From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease,* Pediatrics *114:1708–1733, 2004.)*

may persist for several weeks. Clinical features that are less consistent with KD include exudative conjunctivitis, exudative pharyngitis, generalized lymphadenopathy, discrete oral lesions, and bullous, pustular, or vesicular rashes.

Cardiac involvement is the most important manifestation of KD. Myocarditis occurs in most patients with acute KD and manifests as tachycardia disproportionate to fever, along with diminished left ventricular systolic function. Occasionally, patients with KD present in cardiogenic shock (KD shock syndrome), with markedly diminished left ventricular function. Pericarditis with a small pericardial effusion can also occur during the acute illness. Mitral regurgitation of at least mild severity is evident on echocardiography in 10-25% of patients at presentation but diminishes over time, except among rare patients with coronary aneurysms and ischemic heart disease. CAA develop in up to 25% of untreated patients in the 2nd to 3rd wk of illness. Giant coronary artery aneurysms (classic definition of >8 mm internal diameter) pose the greatest risk for rupture, thrombosis or stenosis, and myocardial infarction (Fig. 166-6). Axillary, popliteal, iliac, or other arteries may also become dilated, which manifest as a localized pulsating mass.

Occasionally KD initially presents with only fever and lymphadenopathy (node-first KD). This presentation may be confused with

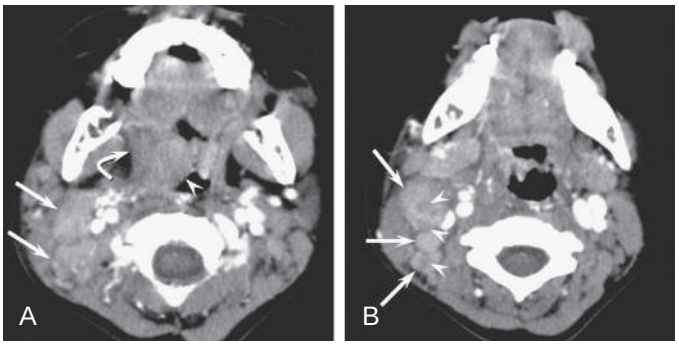

Figure 166-7 Kawasaki disease in a 3 yr old boy. **A,** Contrast-enhanced CT shows right-sided cervical lymphadenopathy *(arrows)*, peritonsillar hypodense area *(curved arrow)*, and swelling of right palatine tonsil *(arrowhead)*. **B,** Contrast-enhanced CT shows right-sided cervical lymphadenopathy with perinodal infiltration *(arrows)* and intranodal focal low attenuation *(arrowheads)*. *(From Kato H, Kanematsu M, Kato Z, et al: Computed tomographic findings of Kawasaki disease with cervical lymphadenopathy.* J Comput Assist Tomogr *36(1):138–142, 2012, Fig. 1, p. 139.)*

Table 166-2 Differential Diagnosis of Kawasaki Disease

VIRAL INFECTIONS
• Adenovirus
• Enterovirus
• Measles
• Epstein-Barr virus
• Cytomegalovirus
BACTERIAL INFECTIONS
• Scarlet fever
• Rocky Mountain spotted fever
• Leptospirosis
• Bacterial cervical lymphadenitis
• Meningococcemia
RHEUMATOLOGIC DISEASE
• Systemic-onset juvenile idiopathic arthritis
• Behçet disease
OTHER
• Toxic shock syndromes
• Staphylococcal scalded skin syndrome
• Drug hypersensitivity reactions
• Stevens-Johnson syndrome

bacterial or viral cervical lymphadenopathy/lymphadenitis and may delay the diagnosis of KD. Persistence of high fever, unresponsive to antibiotics and the eventual development of other signs of KD result in the diagnosis. Children with node-first KD tend to be older (4 vs. 2 yr) and have more days of fever and higher C-reactive protein levels. In addition to cervical adenopathy, many had retropharyngeal and peritonsillar inflammation on CT scans (Fig. 166-7).

KD can be divided into 3 clinical phases. The **acute febrile phase** is characterized by fever and the other acute signs of illness and usually lasts 1-2 wk. The **subacute phase** is associated with desquamation, thrombocytosis, the development of CAA, the highest risk of sudden death in patients in whom aneurysms have developed, and generally lasts about 3 wk. The **convalescent phase** begins when all clinical signs of illness have disappeared and continues until the erythrocyte sedimentation rate (ESR) returns to normal, typically about 6-8 wk after the onset of illness.

LABORATORY AND RADIOLOGY FINDINGS

There is no diagnostic test for KD, but patients usually have characteristic laboratory findings. The leukocyte count is often elevated, with a predominance of neutrophils and immature forms. Normocytic, normochromic anemia is common. The platelet count is generally normal in the 1st wk of illness and rapidly increases by the 2nd to 3rd wk of illness, sometimes exceeding 1,000,000/mm^3. An elevated ESR and/or C-reactive protein value is universally present in the acute phase of illness. The ESR may remain elevated for weeks, in part from the effect of IVIG. Sterile pyuria, mild elevations of the hepatic transaminases, hyperbilirubinemia, and cerebrospinal fluid pleocytosis may also be present.

Two-dimensional echocardiography is the most useful test to monitor for development of CAA and should be performed by a pediatric cardiologist. Although frank aneurysms are rarely detected early in the illness, lack of normal tapering of the vessels is typical. Moreover, coronary artery dimensions, adjusted for body surface area, may be increased in the 1st 5 wk after presentation. Body surface area–adjusted coronary artery dimensions on baseline echocardiography in the 1st 10 days of illness appear to be good predictors of involvement during early follow-up. However, children with non-KD febrile illnesses also have mildly increased z scores as compared to nonfebrile controls, but not to the same degree as patients with KD. Aneurysms have been defined with use of absolute dimensions by the Japanese Ministry of Health and are classified as small (<5 mm internal diameter), medium (5-8 mm internal diameter), or giant (>8 mm internal diameter). Some experts believe that a z-score–based system for classification of aneurysm size may be more discriminating given the range in sizes of patients with KD. Under such a system, a z score ≥10 is considered giant and hence defines the threshold at which anticoagulation should be initiated.

Echocardiography should be performed at diagnosis and again after 2-3 wk of illness. If the results are normal, a repeat study should be performed 6-8 wk after onset of illness. If results of either of the initial studies are abnormal or the patient has recurrent fever or symptoms, more frequent echocardiography or other studies may be necessary. In patients without coronary abnormalities at any time during the illness, performance of echocardiography and a lipid profile is recommended 1 year later. After this time, periodic evaluation for preventive cardiology counseling is warranted, and some experts recommend cardiologic follow-up every 5 yr. For patients with coronary abnormalities, the type of testing and the frequency of cardiology follow-up visits are tailored to the patients' coronary status.

DIAGNOSIS

The diagnosis of KD is based on the presence of characteristic clinical signs. For **classic KD,** the diagnostic criteria require the presence of fever for at least 4 days and at least 4 of 5 of the other principal characteristics of the illness (see Table 166-1). In **atypical or incomplete KD,** patients have persistent fever but fewer than 4 of the 5 characteristics. In these patients, laboratory and echocardiographic data can assist in the diagnosis (Fig. 166-8). Incomplete cases are most frequent in infants, who, unfortunately, also have the highest likelihood of development of CAA. Ambiguous cases should be referred to a center with experience in the diagnosis of KD. Establishing the diagnosis with prompt institution of treatment is essential to prevent potentially devastating coronary artery disease.

DIFFERENTIAL DIAGNOSIS

Adenovirus, measles, and scarlet fever lead the list of common childhood infections that mimic KD (Table 166-2). Children with adenovirus typically have exudative pharyngitis and exudative conjunctivitis, allowing differentiation from KD. A common clinical problem is the differentiation of scarlet fever from KD in a child who is a group A streptococcal carrier. Patients with scarlet fever typically have a rapid clinical response to appropriate antibiotic therapy. Such treatment for 24-48 hr with clinical reassessment generally clarifies the diagnosis. Furthermore, ocular findings are quite rare in group A streptococcal pharyngitis and may assist in the diagnosis of KD.

Features of measles that distinguish it from KD include exudative conjunctivitis, Koplik spots, rash that begins on the face and hairline and behind the ears, as well as leukopenia. Cervical lymphadenitis can

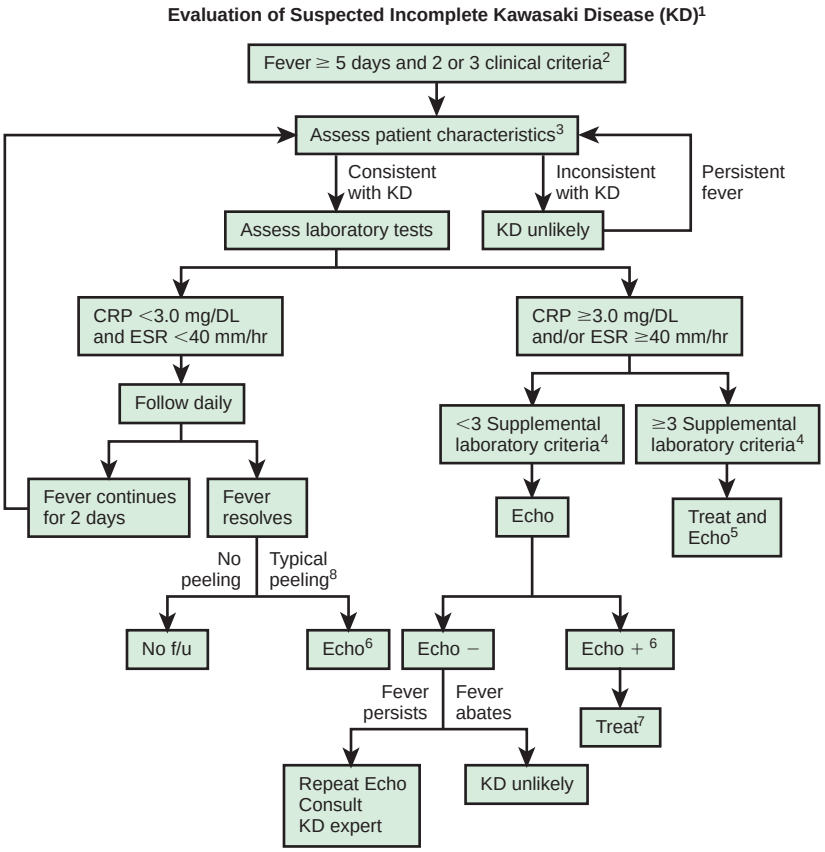

Figure 166-8 Algorithm for evaluation of suspected incomplete Kawasaki disease (KD). (1) In the absence of a gold standard for diagnosis, this algorithm cannot be evidence based, but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed. (2) Infants ≤6 mo old on day ≥7 of fever or later without other explanation should undergo laboratory testing and, if evidence of systemic inflammation is found, given an echocardiogram (Echo), even if they have no clinical criteria. (3) Patient characteristics suggesting KD are listed in Table 166-1. Characteristics suggesting disease other than KD include exudative conjunctivitis, exudative pharyngitis, discrete intraoral lesions, bullous or vesicular rash, and generalized adenopathy. Consider alternative diagnoses (see Table 166-2). (4) Supplemental laboratory criteria include albumin ≤3.0 g/dL, anemia for age, elevation of alanine aminotransferase, platelet count after 7 days ≥450,000/mm^3, white blood cell count ≥15,000/mm^3, and urine white blood cell count ≥10/high-power field. (5) Can treat before performing echocardiogram. (6) Echocardiogram findings are considered positive (Echo+) for purposes of this algorithm if any of 3 conditions are met: *z* score of left anterior descending coronary artery (LAD) or right coronary artery (RCA) ≥2.5; coronary arteries meet Japanese Ministry of Health criteria for aneurysms; ≥3 other suggestive features exist, including perivascular brightness, lack of tapering, decreased left ventricle (LV) function, mitral regurgitation, pericardial effusion, or *z* scores in LAD or RCA of 2-2.5. (7) If echocardiogram findings are positive, treatment should be given to children within 10 days of fever onset and to those beyond day 10 with clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (8) Typical peeling begins under nail beds of fingers and then toes. Echo−, negative echocardiogram findings; f/u, follow-up. *(From Newburger JW, Takahashi M, Gerber MA, et al: Diagnosis, treatment, and long-term management of Kawasaki disease,* Pediatrics *114:1708–1733, 2004.)*

be the initial diagnosis in children who are ultimately recognized to have KD. Less common infections such as Rocky Mountain spotted fever and leptospirosis are occasionally confused with KD. Rocky Mountain spotted fever is a potentially lethal bacterial infection and appropriate antibiotics should not be withheld if the diagnosis is under consideration. Its distinguishing features include pronounced myalgias and headache at onset, centripedal rash, and petechiae on the palms and soles. Leptospirosis can also be an illness of considerable severity. Risk factors include exposure to water contaminated with urine from infected animals. The classic description of leptospirosis is of a biphasic illness with a few asymptomatic days between an initial period of fever and headache and a late phase with renal and hepatic failure. In contrast, patients with KD have consecutive days of fever at diagnosis and rarely have renal or hepatic failure.

Children with KD and pronounced myocarditis may demonstrate hypotension with a clinical picture similar to that of toxic shock syndrome. Features of toxic shock syndrome that are not commonly seen in KD include renal insufficiency, coagulopathy, pancytopenia, and myositis. Drug hypersensitivity reactions, including Stevens-Johnson syndrome, share some characteristics with KD. Drug reaction features such as the presence of periorbital edema, oral ulcerations, and a normal or minimally elevated ESR are not seen in KD. Systemic-onset juvenile idiopathic arthritis is also characterized by fever and rash, but physical findings include diffuse lymphadenopathy and hepatosplenomegaly. Arthritis is required to develop at some point in the disease course to make the diagnosis, but may not be present in the 1st few wk of illness. Laboratory findings may include coagulopathy, elevated fibrin degradation product values, and hyperferritinemia. Interestingly, there are reports of children with systemic-onset juvenile idiopathic arthritis who have echocardiographic evidence of abnormal coronary arteries. Coronary aneurysms have also been reported in Behçet disease, primary cytomegalovirus infection, and meningococcemia.

TREATMENT

Patients with acute KD should be treated with 2 g/kg of IVIG and high-dose aspirin (80-100 mg/kg/day divided q6h) within 10 days of disease onset and ideally as soon as possible after diagnosis (Table 166-3). The

Table 166-3 Treatment of Kawasaki Disease

ACUTE STAGE • Intravenous immunoglobulin 2 g/kg over 10-12 hr *and* • Aspirin 80-100 mg/kg/day divided every 6 hr orally until patient is afebrile for at least 48 hr
CONVALESCENT STAGE • Aspirin 3-5 mg/kg once daily orally until 6-8 wk after illness onset if normal coronary findings throughout course
LONG-TERM THERAPY FOR PATIENTS WITH CORONARY ABNORMALITIES • Aspirin 3-5 mg/kg once daily orally • Clopidogrel 1 mg/kg/day (maximum: 75 mg/day) • Most experts add warfarin or low-molecular-weight heparin for those patients at particularly high risk of thrombosis
ACUTE CORONARY THROMBOSIS • Prompt fibrinolytic therapy with tissue plasminogen activator or other thrombolytic agent under supervision of a pediatric cardiologist

mechanism of action of IVIG in KD is unknown, but treatment results in defervescence and resolution of clinical signs of illness in approximately 85% of patients. The prevalence of coronary disease, 20-25% in children treated with aspirin alone, is <5% in those treated with IVIG and aspirin within the 1st 10 days of illness. Strong consideration should be given to treating patients with persistent fever and/or signs of systemic inflammation who are diagnosed after the 10th day of fever. The dose of aspirin is usually decreased from antiinflammatory to antithrombotic doses (3-5 mg/kg/day as a single dose) after the patient has been afebrile for 48 hr, although some experts prescribe high-dose aspirin until the 14th day of illness. Aspirin is continued for its antithrombotic effect until 6-8 wk after illness onset and is then discontinued in patients who have had normal echocardiography findings throughout the course of their illness. Patients with CAA continue with aspirin therapy and may require anticoagulation, depending on the degree of coronary dilation (see later).

Corticosteroids have been trialed as primary therapy with the first dose of IVIG in hopes of improving coronary outcomes. A North American trial using a single pulse dose of intravenous methylprednisolone (30 mg/kg) with IVIG as primary therapy did not improve coronary outcomes. However, a trial in Japan utilizing the Kobayashi score to identify high-risk children demonstrated improved coronary outcomes with a regimen of prednisolone (2 mg/kg) plus IVIG as primary therapy. Despite these promising results, administration of corticosteroids, as primary therapy to all children with KD awaits the development of a risk score that identifies high-risk children in a multiracial population.

IVIG-resistant KD occurs in approximately 15% of patients and is defined by persistent or recrudescent fever 36 hr after completion of the initial IVIG infusion. Patients with IVIG resistance are at increased risk for CAA. Typically, another dose of IVIG at 2 g/kg is administered to patients with IVIG resistance. Corticosteroids in varying doses and via different routes have also been used as secondary or "rescue" therapy when fever persists after the first IVIG. However, the lack of clear data regarding the most effective way to administer corticosteroids as rescue therapy has led to significant practice variation across centers. Tumor necrosis factor inhibitors, including infliximab and etanercept, have also been given for the treatment of IVIG-resistant disease. To date, there is no evidence of improved coronary outcomes with the use of these medications.

COMPLICATIONS

The patient with KD who has had a small solitary aneurysm should continue aspirin indefinitely. Patients with larger or numerous aneurysms may require the addition of other antiplatelet agents or anticoagulation; such decisions should be made in consultation with a pediatric cardiologist. Acute thrombosis may occasionally occur in an aneurysmal or stenotic coronary artery; thrombolytic therapy may be lifesaving in this circumstance.

Long-term follow-up of patients with coronary artery aneurysms should include periodic echocardiography with stress testing and possibly angiography if large aneurysms are present. Catheter intervention with percutaneous transluminal coronary rotational ablation, directional coronary atherectomy, and stent implantation have been used for the management of coronary stenosis due to KD, with some patients requiring coronary artery bypass grafting.

Patients undergoing long-term aspirin therapy should receive annual influenza vaccination to reduce the risk of Reye syndrome. A different antiplatelet agent can be substituted for aspirin during the 6 wk after varicella vaccination. As IVIG may interfere with the immune response to live virus vaccines as a result of specific antiviral antibody, the measles-mumps-rubella and varicella vaccinations should generally be deferred until 11 mo after IVIG administration. Non-live vaccinations do not need to be delayed.

PROGNOSIS

The vast majority of patients with KD return to normal health, as timely treatment reduces the risk of coronary aneurysms to less than 5%. Acute KD recurs in 1-3% of cases. The prognosis for patients with coronary abnormalities depends on the severity of coronary disease; therefore, recommendations for follow-up and management are stratified according to coronary artery status. Published fatality rates are very low, generally <1.0%. Overall, 50% of coronary artery aneurysms regress to normal lumen diameter by 1-2 yr after the illness, with smaller aneurysms being more likely to regress. Intravascular ultrasonography has demonstrated that regressed aneurysms are associated with marked myointimal thickening and abnormal functional behavior of the vessel wall. Giant aneurysms are less likely to regress to normal lumen diameter and are most likely to lead to thrombosis or stenosis. Coronary artery bypass grafting may be required if myocardial perfusion is significantly impaired; it is best accomplished with the use of arterial grafts, which grow with the child and are more likely than venous grafts to remain patent over the long-term. Heart transplantation has been required in rare cases in which revascularization is not feasible because of distal coronary stenoses, distal aneurysms, or severe ischemic cardiomyopathy. A study from Japan reported outcomes in adult patients with a history of KD and giant aneurysms. These patients required multiple cardiac and surgical procedures, but the 30-year survival rate approached 90%.

Whether children who have had KD and normal echocardiography findings throughout their course are at higher risk for the development of atherosclerotic heart disease in adulthood remains unclear, as studies of endothelial dysfunction in children with a history of KD and normal coronary dimensions have produced conflicting results. Reassuring data suggest that the standardized mortality ratio among adults in Japan who had KD in childhood without aneurysms is indistinguishable from that of the general population. All children with a history of KD should be counseled regarding a heart-healthy diet, adequate amounts of exercise, tobacco avoidance, and intermittent lipid monitoring. Among children with coronary aneurysms, the American Heart Association recommends treatment thresholds for risk factors for atherosclerotic heart disease that are lower than those for the normal population.

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Chapter 167

Vasculitis Syndromes

Stacy P. Ardoin and Edward Fels

Childhood vasculitis encompasses a broad spectrum of diseases that share in common inflammation of the blood vessels as the central pathophysiology. The pathogenesis of the vasculitides is generally idiopathic; some forms of vasculitis are associated with infectious agents and medications; others may occur in the setting of preexisting autoimmune disease. The pattern of vessel injury provides insight into the form of vasculitis and serves as a framework to delineate the different vasculitic syndromes. The distribution of vascular injury includes small vessels (capillaries, arterioles, and postcapillary venules), medium vessels (renal arteries, mesenteric vasculature, and coronary arteries), and large vessels (the aorta and its proximal branches). Additionally, some forms of small vessel vasculitis are characterized by the presence of antineutrophil cytoplasmic antibodies (ANCAs) (Table 167-1), whereas others are associated with immune complex deposition in affected tissues. A combination of clinical features, histologic appearance of involved vessels, and laboratory data is utilized to classify vasculitis (Tables 167-2 to 167-4).

Childhood vasculitis varies from a relatively benign and self-limited disease such as Henoch-Schönlein purpura to catastrophic disease with end-organ damage as can be seen in granulomatosis with polyangiitis (formerly Wegener granulomatosis). Vasculitis generally manifests as a heterogeneous multisystem disease. Although some features, such as purpura, are easily identifiable, others, such as hypertension secondary to renal artery occlusion or glomerulonephritis, can be more subtle. Ultimately, the key to recognizing vasculitis relies heavily on pattern recognition. Demonstration of vessel injury and inflammation on biopsy or vascular imaging is required to confirm a diagnosis of vasculitis.

Bibliography is available at Expert Consult.

Table 167-2 Classification of Childhood Vasculitis

I. Predominantly Large Vessel Vasculitis
- Takayasu arteritis

II. Predominantly Medium Vessel Vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis nodosa
- Kawasaki disease

III. Predominantly Small Vessel Vasculitis
A. Granulomatous:
- Granulomatosis with polyangiitis (Wegener granulomatosis)*
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)*

B. Nongranulomatous:
- Microscopic polyangiitis*
- Henoch-Schönlein purpura
- Isolated cutaneous leukocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

IV. Other Vasculitides
- Behçet disease
- Vasculitis secondary to infection (including hepatitis B–associated polyarteritis nodosa), malignancies, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue disease
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

*Associated with antineutrophil cytoplasmic antibody.

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798-806; 2010.*

Table 167-1 Common Disease Associations with Antibodies to Neutrophil Cytoplasmic Antigens

ANTIGEN	ANCA PATTERN	DISEASE ASSOCIATION	FREQUENCY (%)
PR3	cANCA	Wegener granulomatosis Churg-Strauss	30 to 90 25 to 50
MPO	pANCA	Microscopic polyarteritis Ulcerative colitis Sclerosing cholangitis Crohn disease	25 to 75 40 to 80 65 to 85 10 to 40
BPI	ANCA	Cystic fibrosis	80 to 90
Actin	pANCA	Autoimmune hepatitis type 1	70 to 75

ANCA, Antibodies directed at neutrophil cytoplasmic antigen; BPI, Bactericidal permeability increasing protein. cANCA, cytoplasmic ANCA; pANCA, perinuclear ANCA.

From Cabral D, Benseler S: Granulomatous vasculitis, microscopic polyangiitis and primary angiitis of the central nervous system. In Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors, Textbook of pediatric rheumatology, *ed 6, Philadelphia, 2011, Elsevier/Saunders, Table 34-3, p. 526.*

Table 167-3 Features That Suggest a Vasculitic Syndrome

CLINICAL FEATURES
- Fever, weight loss, fatigue of unknown origin
- Skin lesions (palpable purpura, vasculitic urticaria, livedo reticularis, nodules, ulcers)
- Neurologic lesions (headache, mononeuritis multiplex, focal central nervous system lesions)
- Arthralgia or arthritis, myalgia, or myositis
- Serositis
- Hypertension
- Pulmonary infiltrates or hemorrhage

LABORATORY FEATURES
- Increased erythrocytes sedimentation rate or C-reactive protein level
- Leukocytosis, anemia
- Eosinophilia
- Antineutrophil cytoplasmic antibodies
- Elevated factor VIII–related antigen (von Willebrand factor)
- Cryoglobulins
- Circulating immune complexes
- Hematuria, proteinuria, elevated serum creatinine

From Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

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Table 167-4 Clinical and Pathologic Characteristics of Some Vasculitides in Childhood

SYNDROME	FREQUENCY	VESSELS AFFECTED	CHARACTERISTIC PATHOLOGY
POLYARTERITIS			
Polyarteritis nodosa	Rare	Medium-size and small muscular arteries and sometimes arterioles	Focal segmental (often near bifurcations); fibrinoid necrosis; gastrointestinal, renal microaneurysms; lesions at various stages of evolution
Kawasaki disease	Common	Coronary and other muscular arteries	Thrombosis, fibrosis, aneurysms, especially of coronary vessels
LEUKOCYTOCLASTIC VASCULITIS			
Henoch-Schönlein purpura	Common	Arterioles and venules, often small arteries and veins	Leukocytoclasis; mixed cells, eosinophils, immunoglobulin A deposits in affected vessels
Hypersensitivity angitis	Rare	Arterioles and venules	Leukocytoclastic or lymphocytic, varying eosinophils, occasionally granulomatous; widespread lesions at same stage of evolution
GRANULOMATOUS VASCULITIS			
Granulomatosis with polyangiitis	Rare	Small arteries and veins, occasionally larger vessels	Upper and lower respiratory tract, necrotizing granulomata glomerulonephritis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Rare	Small arteries and veins, often arterioles and venules	Necrotizing extravascular granulomata; lung involvement; eosinophilia
GIANT CELL ARTERITIS			
Takayasu arteries	Uncommon	Large arteries	Granulomatous inflammation, giant cells; aneurysms, dissection
Temporal arteritis	Rare	Medium-size and large arteries	Granulomatous inflammation, giant cell arteries

Adapted from Cassidy JT, Petty RE: Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.*

167.1 Henoch-Schönlein Purpura

Stacy P. Ardoin and Edward Fels

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood and is characterized by leukocytoclastic vasculitis and immunoglobulin (Ig) A deposition in the small vessels in the skin, joints, gastrointestinal tract, and kidney.

EPIDEMIOLOGY

HSP occurs worldwide and affects all ethnic groups but is more common in white and Asian populations. The incidence of HSP is estimated at 14-20/100,000 children per year and affects males more than females, with a 1.2-1.8:1 male:female ratio. Approximately 90% of HSP cases occur in children, usually between the ages of 3 and 10 yr. HSP is distinctly less common in adults, in whom severe and chronic complications are often encountered. HSP is more common in the winter and spring, and is unusual in summer months. Many cases of HSP follow a documented upper respiratory infection.

PATHOLOGY

Skin biopsies demonstrate vasculitis of the dermal capillaries and postcapillary venules. The inflammatory infiltrate includes neutrophils and monocytes. Renal histopathology typically shows endocapillary proliferative glomerulonephritis, ranging from a focal segmental process to extensive crescentic involvement. In all tissues, immunofluorescence identifies IgA deposition in walls of small vessels (Fig. 167-1), accompanied to a lesser extent by deposition of C3, fibrin, and IgM.

PATHOGENESIS

The exact pathogenesis of HSP remains unknown. Given the seasonality of HSP and the frequency of preceding upper respiratory infections, infectious triggers such as group A β-hemolytic streptococcus, *Staphylococcus aureus,* mycoplasma, and adenovirus have been suspected. The common finding of deposition of IgA, specifically IgA_1, suggests that HSP is a disease mediated by IgA and IgA immune complexes. HSP occasionally clusters in families, suggesting a genetic component. HLA-B34 and HLA-DRB1*01 alleles have been linked to HSP nephritis. Patients with familial Mediterranean fever, hereditary periodic fever syndromes, and complement deficiencies are at increased risk for developing HSP, suggesting that genetically determined immune dysregulation may contribute.

CLINICAL MANIFESTATIONS

The hallmark of HSP is its rash: palpable purpura starting as pink macules or wheals and developing into petechiae, raised purpura, or larger ecchymoses. Occasionally, bullae and ulcerations develop. The skin lesions are usually symmetric and occur in gravity-dependent areas (lower extremities) or on pressure points (buttocks) (see Figs. 167-1 and 167-2). The skin lesions often evolve in groups, typically lasting 3-10 days, and may recur up to 4 mo after initial presentation. Subcutaneous edema localized to the dorsa of hands and feet, periorbital area, lips, scrotum, or scalp is also common.

Musculoskeletal involvement, including arthritis and arthralgias, is common, occurring in up to 75% of children with HSP. The arthritis tends to be self-limited and oligoarticular, with a predilection for the lower extremities, and does not lead to deformities. The arthritis usually resolves within 2 wk but can recur.

Gastrointestinal manifestations of HSP occur in up to 80% of children with HSP and include abdominal pain, vomiting, diarrhea, paralytic ileus and melena; intussusception, mesenteric ischemia, intestinal perforation are uncommon. Endoscopic evaluation is usually not needed but may identify purpura of the intestinal tract.

Renal involvement occurs in up to 50% of children with HSP, manifesting as microscopic hematuria, proteinuria, hypertension, frank nephritis, nephrotic syndrome, and acute or chronic renal failure. Progression to end-stage renal disease is uncommon in children (1-2%) (see Chapter 515).

Neurologic manifestations of HSP, caused by hypertension or central nervous system (CNS) vasculitis, may also occur. They include intracerebral hemorrhage, seizures, headaches, and behavior changes. Other less-common potential manifestations of HSP are orchitis, carditis, inflammatory eye disease, testicular torsion, and pulmonary hemorrhage.

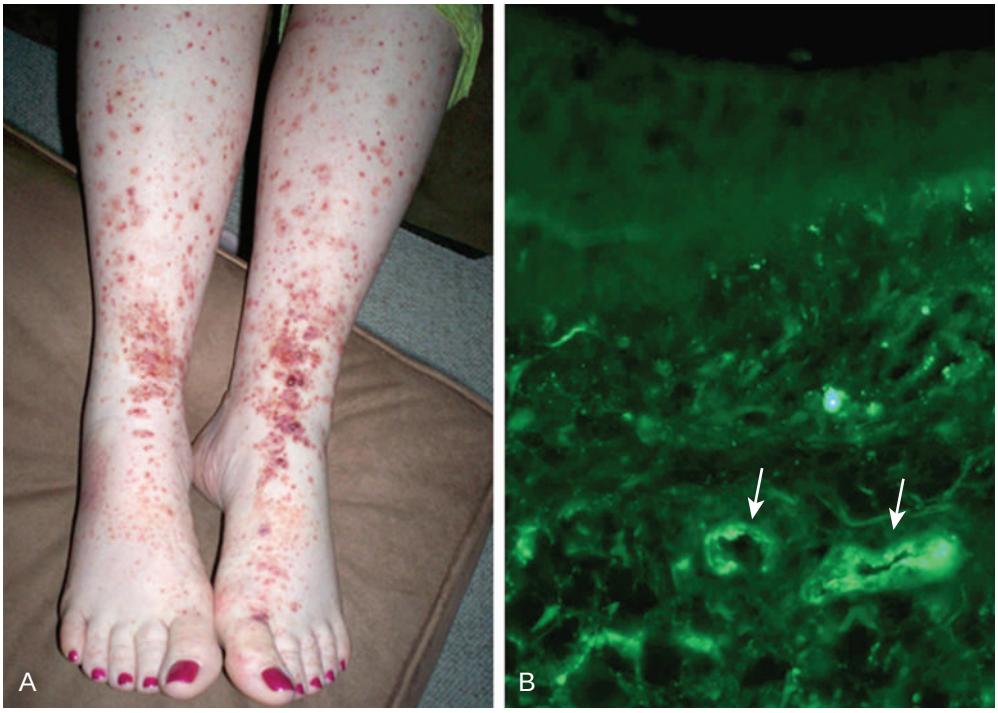

Figure 167-1 **A,** Typical palpable purpura in the lower extremities of a girl with Henoch-Schönlein purpura. **B,** Skin biopsy of lesion from the same patient, showing direct immunofluorescence of immunoglobulin A within the walls of dermal capillaries.

Figure 167-2 Henoch-Schönlein purpura. *(From Korting GW:* Hautkrankheiten bei Kindern und Jungendlichen, *ed 3, Stuttgart, 1982, FK Schattaur Verlag.)*

DIAGNOSIS

The diagnosis of HSP is a clinical one and is often straightforward when the typical rash is present. However, in at least 25% of cases, the rash appears after other manifestations, making early diagnosis challenging. Table 167-5 summarizes the classification criteria for HSP. The differential diagnosis for HSP depends on specific organ involvement but usually includes other small vessel vasculitides, infections, acute post streptococcal glomerulonephritis, hemolytic-uremic syndrome, coagulopathies, and other acute intraabdominal processes.

Acute hemorrhagic edema (AHE), an isolated cutaneous leukocytoclastic vasculitis that affects infants <2 yr of age, resembles HSP clinically. AHE manifests as fever; tender edema of the face, scrotum, hands, and feet; and ecchymosis (usually larger than the purpura of HSP) on the face and extremities (Fig. 167-3). The trunk is spared, but petechiae may be seen in mucous membranes. The patient usually appears well except for the rash. The platelet count is normal or elevated, and the urinalysis results are normal. The younger age, the nature of the lesions, absence of other organ involvement, and a biopsy may help distinguish AHE from HSP.

Papular-purpuric gloves-and-socks syndrome is most commonly caused by parvovirus B19 and initially manifests with symmetric edema and erythema over the hands and feet. These well-demarcated lesions end at the ankle and wrist and evolve into purpuric papules. Fever, oral lesions, and leukopenia are inconsistent findings. Complications include mononeuritis multiplex. Adolescents are more often affected than young children. In contrast to erythremia infectiosum, patients with papular-purpuric gloves-and-socks syndrome are usually infectious at the time of appearance of the rash.

LABORATORY FINDINGS

No laboratory finding is diagnostic of HSP. Common but nonspecific findings include leukocytosis, thrombocytosis, mild anemia, and elevations of erythrocyte sedimentation rate (ESR) and C-reactive protein

Figure 167-3 Typical lesions of acute hemorrhagic edema on the arm of an infant. *(From Eichenfield LF, Frieden IJ, Esterly NB:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders.)*

Table 167-5	Classification Criteria for Henoch-Schönlein Purpura*
AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION CRITERIA†	
Two of the following criteria must be present:	
• Palpable purpura	
• Age at onset ≤20 yr	
• Bowel angina (postprandial abdominal pain, bloody diarrhea)	
• Biopsy demonstrating intramural granulocytes in small arterioles and/or venules	
EUROPEAN LEAGUE AGAINST RHEUMATISM/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY CRITERIA‡	
Palpable purpura (in absence of coagulopathy or thrombocytopenia) and 1 or more of the following criteria must be present:	
• Abdominal pain (acute, diffuse, colicky pain)	
• Arthritis or arthralgia	
• Biopsy of affected tissue demonstrating predominant immunoglobulin A deposition	
• Renal involvement (proteinuria >3 grams/24 hr), hematuria or red cell casts	

*Classification criteria are developed for use in research and not validated for clinical diagnosis.

†Developed for use in adult and pediatric populations. Adapted from Mills JA, Michel BA, Bloch DA, et al: The American College of Rheumatology 1990 criteria for classification of Henoch-Schönlein purpura, *Arthritis Rheum* 33:1114–1121, 1990.

‡Developed for use in pediatric populations only.

Adapted from Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798–806; 2010.*

(CRP). The platelet count is normal in HSP. Occult blood is frequently found in stool specimens. Serum albumin levels may be low due to renal or intestinal protein loss. Autoantibody testing is not useful diagnostically except to exclude other diseases. Serum IgA values are often elevated but are not routinely measured. Assessment of renal involvement with blood pressure, urinalysis, and serum creatinine is necessary.

Ultrasound is often used in the setting of gastrointestinal complaints to look for bowel wall edema or the rare occurrence of an associated intussusception. Barium enema can also be used to both diagnose and treat intussusception. Although often unnecessary in typical HSP, biopsies of skin and kidney can provide important diagnostic information, particularly in atypical or severe cases, and characteristically show IgA deposition in affected tissues.

TREATMENT

Treatment for mild and self-limited HSP is supportive, with an emphasis on assuring adequate hydration, nutrition, and analgesia. Steroids are most often used to treat significant gastrointestinal involvement or other life-threatening manifestations. Prednisone (1 mg/kg/day for 1-2 wk, followed by taper) reduces abdominal and joint pain but does not alter overall prognosis nor prevent renal disease. Rapid tapering of corticosteroids may lead to a flare of HSP symptoms. Although few data are available to demonstrate efficacy, intravenous immune globulin and plasma exchange are sometimes used in the setting of severe disease. In some cases, chronic HSP renal disease is managed with a variety of immunosuppressants, including azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil. End-stage renal disease develops in up to 8% of children with HSP nephritis.

COMPLICATIONS

Acutely, serious gastrointestinal involvement such as intestinal perforation imparts significant morbidity and mortality. Renal disease is the major long-term complication, occurring in 1-2% of children with HSP. Renal disease can develop up to 6 mo after diagnosis but rarely does so if the initial urinalyses findings are normal. It is recommended that children with HSP undergo serial monitoring of blood pressure and urinalyses for several months after diagnosis to monitor for the development of nephritis.

PROGNOSIS

Overall, the prognosis for childhood HSP is excellent, and most children experience an acute, self-limited course lasting on average 4 wk. From 15-60% of children with HSP experience 1 or more recurrences, typically within 4-6 mo of diagnosis. With each relapse, symptoms are usually milder than at presentation. Children with a more-severe initial course are at higher risk for relapse. The long-term prognosis usually depends upon the severity and duration of gastrointestinal or renal involvement. Chronic renal disease develops in 1-2% of children with HSP, and approximately 8% of those with HSP nephritis go on to have end-stage renal disease. The risk of HSP recurrence and graft loss following renal transplantation is estimated at 7.5% after 10 yr.

Bibliography is available at Expert Consult.

167.2 Takayasu Arteritis

Stacy P. Ardoin and Edward Fels

Takayasu arteritis (TA), also known as "**pulseless disease**," is a chronic large vessel vasculitis of unknown etiology that predominantly involves the aorta and its major branches.

EPIDEMIOLOGY

Although TA occurs worldwide and can affect all ethnic groups, the disease is most common in Asians. Age of onset is typically between 10 and 40 yr. Most children are diagnosed as adolescents, on average at 13 yr of age. Up to 20% of individuals with TA are diagnosed prior to age 19 yr. Younger children may be affected but diagnosis in infancy is rare. TA preferentially affects females with a reported 2-4:1 female:male ratio in children and adolescents and a 9:1 ratio among

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adults. Occlusive complications are more common in the United States, Western Europe, and Japan, whereas aneurysms predominate in Southeast Asia and Africa.

PATHOLOGY

TA is characterized by inflammation of the vessel wall, starting in the vas vasorum. Involved vessels are infiltrated by T cells, natural killer cells, plasma cells, and macrophages. Giant cells and granulomatous inflammation develop in the media. Persistent inflammation damages the elastic lamina and muscular media, leading to blood vessel dilation and the formation of aneurysms. Progressive scarring and intimal proliferation can result in stenotic or occluded vessels. The subclavian, renal, and carotid arteries are the most commonly involved aortic branches; pulmonary, coronary, and vertebral arteries may also be affected.

PATHOGENESIS

The etiology of TA remains unknown. The presence of abundant T cells with a restricted repertoire of T-cell receptors in TA vascular lesions points to the importance of cellular immunity and suggests the existence of a specific but unknown aortic tissue antigen. Expression of interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) is reported to be higher in patients with active TA than in patients with inactive TA and in healthy controls. In some patient populations, IL-1 genetic polymorphisms are linked to TA. Some individuals with TA have elevated serum values of antiendothelial antibodies. The increased prevalence of TA in certain ethnic populations and its occasional occurrence in monozygotic twins and families suggest a genetic predisposition to the disease.

CLINICAL MANIFESTATIONS

The diagnosis of TA is challenging, because early disease manifestations are often nonspecific. As a result, diagnosis can be delayed for several months, and the time to diagnosis is usually longer in children than in adults. Fever, malaise, weight loss, headache, hypertension, myalgias, arthralgias, dizziness, and abdominal pain are common early complaints in the "pre-pulseless" phase of the disease. Among children, hypertension and headache are particularly common presenting manifestations and should prompt consideration of TA when present without alternative explanation. Some individuals with TA report no systemic symptoms and instead present with vascular complications. It is only after substantial vascular injury that evidence of hypoperfusion becomes clinically evident. Later manifestations of disease include diminished pulses, asymmetric blood pressures, claudication, Raynaud phenomenon, renal failure, and symptoms of pulmonary or cardiac ischemia. Inflammation can extend to the aortic valve, resulting in valvular insufficiency. Other findings may include pericardial effusion, pericarditis, pleuritis, splenomegaly, and arthritis.

Supradiaphragmatic (aortic arch) disease often manifests with CNS (stroke, transient ischemic attack), and cardiac (heart failure, palpitations) symptoms, while infradiaphragmatic (mid-aortic syndrome) disease may produce hypertension, abdominal bruits, and pain. Most patients have involvement in both areas.

DIAGNOSIS

Specific pediatric criteria for TA have been proposed (Table 167-6). Radiographic demonstration of large vessel vasculitis is necessary. A thorough physical examination is required to detect an aortic murmur, diminished or asymmetric pulses, and vascular bruits. Four extremity blood pressures should be measured >10 mm Hg; asymmetry in systolic pressure is indicative of disease.

DIFFERENTIAL DIAGNOSIS

In the early phase of TA, when nonspecific symptoms predominate, the differential diagnosis includes a wide array of systemic infections, autoimmune conditions, and malignancies. Although giant cell arteritis, also known as "temporal arteritis," is a common large vessel vasculitis in older adults, this entity is exceedingly rare in childhood. Noninflammatory conditions that can cause large vessel compromise include fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome.

Table 167-6 Proposed Classification Criteria for Pediatric-Onset Takayasu Arteritis

Angiographic abnormalities (conventional, CT, or magnetic resonance angiography) of the aorta or its main branches and at least one of the following criteria:

- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference between arms or legs of >10 mm Hg
- Bruits over the aorta and/or its major branches
- Hypertension (defined by childhood normative data)
- Elevated acute phase reactant (erythrocyte sedimentation rate or C-reactive protein)

Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. *Ann Rheum Dis* 69:798–806; 2010.

LABORATORY FINDINGS

The laboratory findings in TA are nonspecific, and there is no specific diagnostic laboratory test. ESR and CRP value are typically elevated, and other nonspecific markers of chronic inflammation may include leukocytosis, thrombocytosis, anemia of chronic inflammation, and hypergammaglobulinemia. Autoantibodies are not useful in diagnosing TA except to help exclude other autoimmune diseases.

Radiographic assessment is essential to establish large vessel arterial involvement. Conventional arteriography of the aorta and major branches, including carotid, subclavian, pulmonary, renal, and mesenteric branches can identify luminal defects, including dilation, aneurysms, and stenoses, even in smaller vessels such as the mesenteric arteries. Figure 167-4 shows a conventional arteriogram in a child with TA. Although not yet thoroughly validated in TA, magnetic resonance angiography and CT angiography also provide important information about vessel wall thickness and enhancement, although they may not image smaller vessels as well as conventional angiography. Positron emission tomography may detect vessel wall inflammation but has not been studied extensively. Ultrasound with duplex color-flow Doppler imaging also identifies vessel wall thickening and assesses arterial flow. Echocardiography is recommended to assess for aortic valvular involvement. Serial vascular imaging is usually necessary to assess response to treatment and to detect progressive vascular damage.

TREATMENT

Glucocorticoids are the mainstay of therapy, typically starting with high doses (1-2 mg/kg/day of prednisone) followed by gradual dosage tapering. When TA progresses or recurs, steroid-sparing therapy is often required, usually involving methotrexate or azathioprine. Cyclophosphamide is reserved for severe or refractory disease. Results of small case series also suggest that mycophenolate mofetil, tocilizumab or anti–TNF-α therapy may be beneficial in select patients. Antihypertensive medications are often necessary to control blood pressure caused by renovascular disease.

COMPLICATIONS

Progressive vascular damage can result in arterial stenoses, aneurysms, and occlusions, which produce ischemic symptoms and can be organ- or life-threatening. Potential ischemic complications include stroke, renal impairment or failure, myocardial infarction, mesenteric ischemia, and limb-threatening arterial disease. When these complications occur or are imminent, intervention with surgical vascular grafting or catheter-based angioplasty and stent placement may be necessary to restore adequate blood flow. A high rate of recurrent stenosis has been reported following angioplasty and stent placement. Aortic valve replacement may be required if significant aortic insufficiency develops.

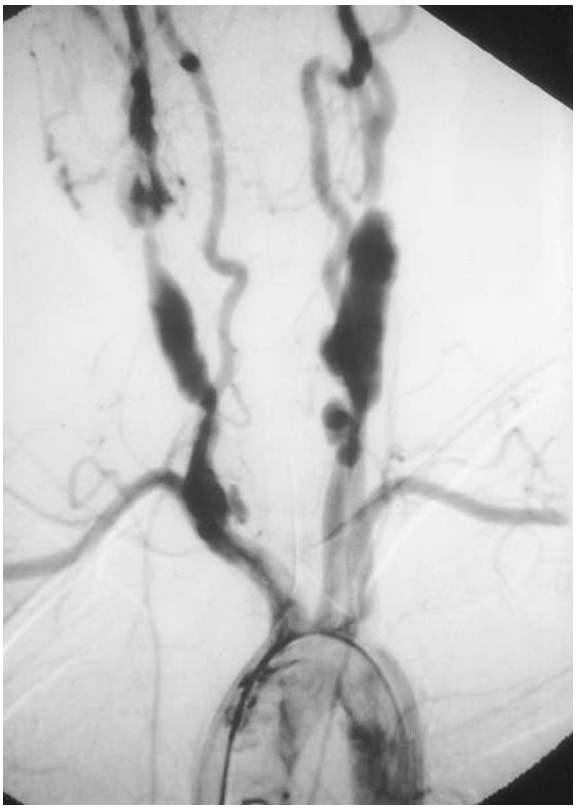

Figure 167-4 Conventional angiogram in a child with Takayasu arteritis showing massive bilateral carotid dilation, stenosis, and poststenotic dilation.

PROGNOSIS

Although up to 20% of individuals with TA have a monophasic course and achieve sustained remission, most suffer relapses. Survival for individuals with TA has improved considerably over the decades, although higher mortality rates are reported in children and adolescents. The overall estimated survival for individuals with TA is 93% at 5 yr and 87% at 10 yr. However, morbidity from vascular complications remains high, particularly when there is evidence of ongoing active inflammation as detected by elevated CRP or ESR. Given the chronic endothelial insult and inflammation, children and adolescents with TA are probably at high risk for accelerated atherosclerosis. Early detection and treatment are critical to optimizing outcome in TA.

Bibliography is available at Expert Consult.

167.3 Polyarteritis Nodosa and Cutaneous Polyarteritis Nodosa

Stacy P. Ardoin and Edward Fels

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis affecting small and medium-size arteries. Aneurysms and stenoses form at irregular intervals throughout affected arteries. Cutaneous PAN is limited to the skin.

EPIDEMIOLOGY

PAN is rare in childhood. Boys and girls are equally affected, and the mean age at presentation is 9 yr. The cause is unknown, but the development of PAN following infections, including group A streptococcus and chronic hepatitis B, suggests that PAN may represent a postinfectious autoimmune response. Infections with other organisms, including Epstein-Barr virus, *Mycobacterium tuberculosis*, cytomegalovirus, parvovirus B19, and hepatitis C virus, have also been associated with PAN. As in Henoch-Schönlein purpura, there is a possible association between PAN and familial Mediterranean fever.

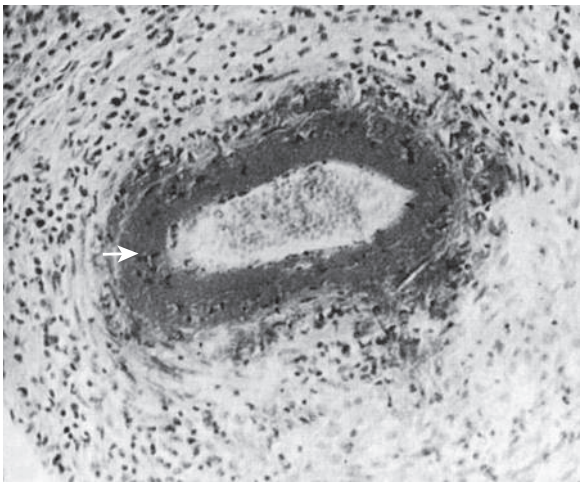

Figure 167-5 Biopsy specimen from a medium-size muscular artery that exhibits marked fibrinoid necrosis of the vessel wall *(arrow)*. *(From Cassidy JT, Petty RE: Polyarteritis and related vasculitides. In* Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.)*

PATHOLOGY

Biopsies show necrotizing vasculitis with granulocytes and monocytes infiltrating the walls of small and medium-size arteries (Fig. 167-5). Involvement is usually segmental and tends to occur at vessel bifurcations. Granulomatous inflammation is not present, and deposition of complement and immune complexes is rarely observed. Different stages of inflammation are found, ranging from mild inflammatory changes to panmural fibrinoid necrosis associated with aneurysm formation, thrombosis, and vascular occlusion.

PATHOGENESIS

Immune complexes are believed to be pathogenic, but the mechanism is poorly understood. There is no clear genetic association with PAN, and it is not known why PAN has a predilection for small- and medium-size blood vessels. The inflamed vessel wall becomes thickened and narrowed, impeding blood flow and contributing to end-organ damage characteristic of this disease. Familial disease in Georgian Jewish patients has been reported to be due to mutations in the *CECR1* gene, which encodes adenosine deaminase 2.

CLINICAL MANIFESTATIONS

The clinical presentation of PAN is variable but generally reflects the distribution of inflamed vessels. Constitutional symptoms are present in most children at disease onset. Weight loss and severe abdominal pain suggest mesenteric arterial inflammation and ischemia. Renovascular arteritis can cause hypertension, hematuria, or proteinuria, although glomerulonephritis is not typical. Cutaneous manifestations include purpura, livedo reticularis, ulcerations, digital ischemia and painful nodules. Arteritis affecting the nervous system can result in cerebrovascular accidents, transient ischemic attacks, psychosis, and ischemic motor or sensory peripheral neuropathy (mononeuritis multiplex). Myocarditis or coronary arteritis can lead to heart failure and myocardial ischemia; pericarditis and arrhythmias have also been reported. Arthralgias, arthritis, or myalgias are frequently present. Less common symptoms include testicular pain that mimics testicular torsion, bone pain, and vision loss as a result of retinal arteritis. The pulmonary vasculature is usually spared in PAN.

DIAGNOSIS

The diagnosis of PAN requires demonstration of vessel involvement on biopsy or angiography (Table 167-7). Biopsy of cutaneous lesions

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Table 167-7	Proposed Classification Criteria for Pediatric-Onset Polyarteritis Nodosa*
Histopathology	Necrotizing vasculitis in medium or small arteries
Angiographic abnormalities	Angiography showing aneurysm, stenosis, or occlusion of a medium or small size artery not from a noninflammatory cause
Cutaneous findings	Livedo reticularis, tender subcutaneous nodules, superficial skin ulcers, deep skin ulcers, digital necrosis, nail bed infarctions or splinter hemorrhages
Muscle involvement	Myalgia or muscle tenderness
Hypertension	Systolic or diastolic blood pressure >95th percentile for height
Peripheral neuropathy	Sensory peripheral neuropathy, motor mononeuritis multiplex
Renal involvement	Proteinuria (>300 mg/24 hr equivalent), hematuria or red blood cell casts, impaired renal function (glomerular filtration rate <50% normal)

*The presence of all 5 criteria provides 89.6% sensitivity and 99.6% specificity for the diagnosis of childhood onset polyarteritis nodosa.

Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. *Ann Rheum Dis* 69:798–806; 2010.

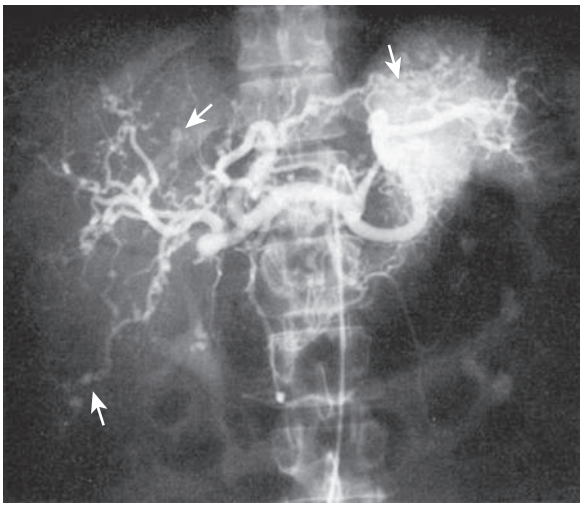

Figure 167-6 Celiac angiography in an 18 yr old boy showing aneurysms in multiple vessels. *(From Cassidy JT, Petty RE: Polyarteritis and related vasculitides. In* Textbook of pediatric rheumatology, *ed 5, Philadelphia, 2005, Elsevier/Saunders.)*

shows small or medium vessel vasculitis (see Fig. 167-5). Kidney biopsy in patients with renal manifestations may show necrotizing arteritis. Electromyography in children with peripheral neuropathy identifies affected nerves, and sural nerve biopsy may reveal vasculitis. Conventional arteriography is the gold standard diagnostic imaging study for PAN and reveals areas of aneurysmal dilation and segmental stenosis, the classic "beads on a string" appearance (Fig. 167-6). Magnetic resonance angiography and CT angiography, less-invasive imaging alternatives, are gaining acceptance, but may not be as effective in identifying small vessel disease or in younger children.

DIFFERENTIAL DIAGNOSIS

Early skin lesions may resemble those of HSP, although the finding of nodular lesions and presence of systemic features help distinguish PAN. Because pulmonary vascular involvement is very rare in PAN, pulmonary lesions suggest ANCA-associated vasculitis or Goodpasture disease. Other rheumatic diseases, including systemic lupus erythematosus, have characteristic target organ involvement and associated autoantibodies distinguishing them from PAN. Prolonged fever and weight loss should also prompt consideration of inflammatory bowel disease or malignancy.

LABORATORY FINDINGS

Nonspecific laboratory findings include elevations of ESR and CRP, anemia, leukocytosis, and hypergammaglobulinemia. Abnormal urine sediment, proteinuria, and hematuria indicate renal disease. Laboratory findings may be normal in cutaneous PAN or similar to those of systemic PAN. Elevated hepatic enzyme values may suggest hepatitis B or C infection. Serologic tests for hepatitis (hepatitis B surface antigen and hepatitis C antibody) should be performed in all patients.

TREATMENT

Oral (1-2 mg/kg/day) and intravenous pulse (30 mg/kg/day) prednisone is the mainstay of therapy. Oral or intravenous cyclophosphamide are often used as adjunctive therapy, and plasma exchange may be warranted for life-threatening disease. If hepatitis B is identified, appropriate antiviral therapy should be initiated (see Chapter 358). Most cases of cutaneous PAN can be treated with less-intense therapy such as corticosteroids alone, nonsteroidal antiinflammatory agents, and methotrexate. Azathioprine, mycophenolate mofetil, intravenous immunoglobulin, thalidomide, cyclosporine, and anti-TNF have all been reported as successful in treatment of refractory cutaneous or systemic PAN, although clinical trials are lacking. If an infectious trigger for PAN is identified, antibiotic prophylaxis can be considered.

COMPLICATIONS

Cutaneous nodules may ulcerate and become infected. Hypertension and chronic renal disease may develop from renovascular involvement in PAN. Cardiac involvement may lead to decreased cardiac function or coronary artery disease. Mesenteric vasculitis can predispose to bowel infarction, rupture, and malabsorption. Stroke and rupture of hepatic arterial aneurysm are uncommon complications of this disorder.

PROGNOSIS

The course of PAN varies from mild disease with few complications to a severe, multiorgan disease with high morbidity and mortality. Poor prognostic factors in PAN include elevated serum creatinine, proteinuria, severe gastrointestinal involvement, cardiomyopathy, and CNS involvement. Early and aggressive immunosuppressive therapy increases the likelihood of clinical remission. Compared with disease in adults, childhood PAN is associated with less mortality. Cutaneous PAN is unlikely to transition to systemic disease. Early recognition and treatment of the disease are important to minimizing potential long-term vascular complications.

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167.4 Antineutrophilic Cytoplasmic Antibody–Associated Vasculitis

Stacy P. Ardoin and Edward Fels

The ANCA-associated vasculitides are characterized by small vessel involvement, circulating ANCAs, and pauci-immune complex deposition in affected tissues. ANCA-associated vasculitis is categorized into 3 distinct forms: **granulomatosis with polyangiitis (GPA; formerly**

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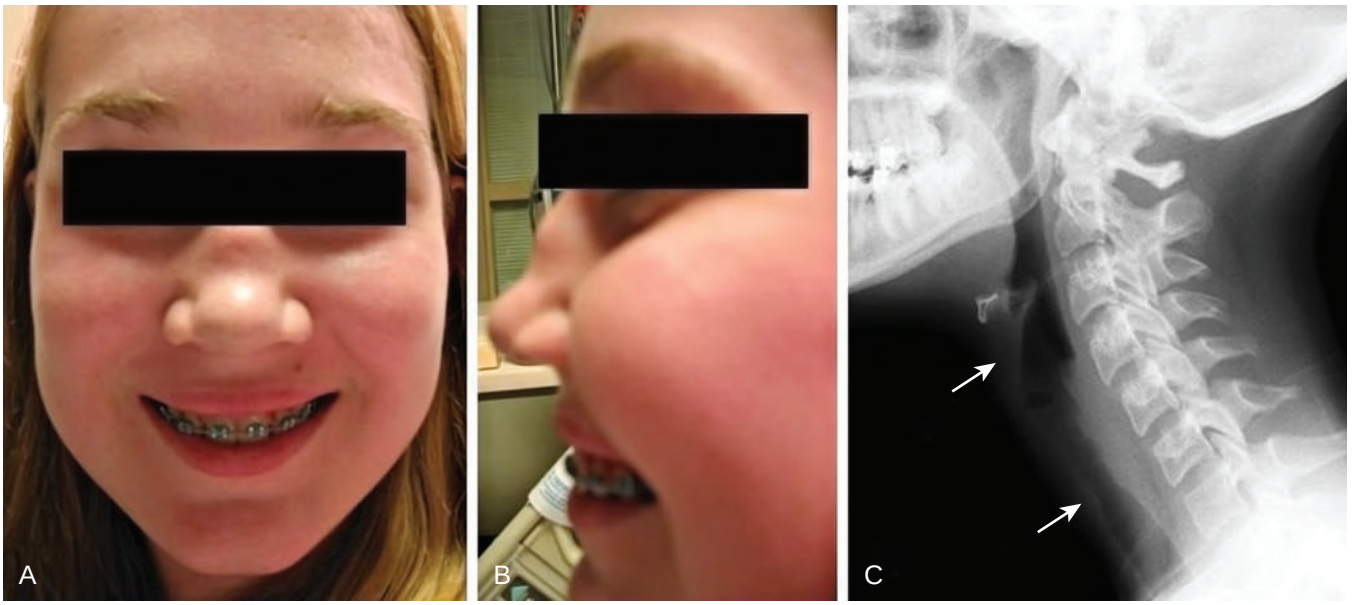

Figure 167-7 **A** and **B,** Anterior and lateral views of saddle nose deformity in an adolescent girl with Wegener granulomatosis. **C,** Segment of subglottic posterior tracheal irregularity (between *arrows*) on lateral neck radiograph in the same patient.

Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis, formerly called **Churg-Strauss syndrome (CSS)** (see Table 167-1).

EPIDEMIOLOGY

GPA is a necrotizing granulomatous small and medium vessel vasculitis that occurs at all ages and targets the upper and lower respiratory tracts and the kidneys. Although most cases of GPA occur in adults, the disease also occurs in children with a mean age at diagnosis of 14 yr. There is a female predominance of 3-4:1, and pediatric GPA is most prevalent in whites.

MPA is a small vessel necrotizing vasculitis with clinical features similar to those of GPA. **CSS** is a small vessel necrotizing granulomatous (allergic granulomatosis) vasculitis associated with a history of refractory asthma and peripheral eosinophilia. MPA and CSS are rare in children, and there does not appear to be a gender predilection in either disease.

PATHOLOGY

Necrotizing vasculitis is the cardinal histologic feature in both GPA and MPA. Kidney biopsies typically demonstrate crescentic glomerulonephritis with little or no immune complex deposition ("pauci-immune"), in contrast to biopsies from patients with systemic lupus erythematosus. Although granulomatous inflammation is common in GPA and CSS, it is typically not present in MPA. Biopsies showing perivascular eosinophilic infiltrates distinguish CSS syndrome from both MPA and GPA (see Table 167-7).

PATHOGENESIS

The etiology of ANCA-associated vasculitis remains unknown, although neutrophils, monocytes, and endothelial cells are involved in disease pathogenesis. Neutrophils and monocytes are activated by ANCAs, specifically by the ANCA-associated antigens proteinase-3 (PR3) and myeloperoxidase (MPO), and release proinflammatory cytokines such as TNF-α and IL-8. Localization of these inflammatory cells to the endothelium results in vascular damage characteristic of the ANCA vasculitides. Why the respiratory tract and kidneys are preferential targets in GPA and MPA is unknown.

CLINICAL MANIFESTATIONS

Early disease course is characterized by nonspecific constitutional symptoms, including fever, malaise, weight loss, myalgias, and arthralgias. In **GPA**, upper airway involvement can manifest as sinusitis, nasal ulceration, epistaxis, otitis media, and hearing loss. Lower respiratory tract symptoms in GPA include cough, wheezing, dyspnea, and hemoptysis. Pulmonary hemorrhage can cause rapid respiratory failure. Compared with adults, childhood GPA is more frequently complicated by subglottic stenosis (see Fig. 167-5). Inflammation-induced damage to the nasal cartilage can produce a saddle nose deformity (Fig. 167-7). Ophthalmic involvement includes conjunctivitis, scleritis, uveitis, optic neuritis, and invasive orbital pseudotumor (causing proptosis). Perineural vasculitis or direct compression on nerves by granulomatous lesions can cause cranial and peripheral neuropathies. Hematuria, proteinuria, and hypertension in GPA signal renal disease. Cutaneous lesions include palpable purpura and ulcers. Venous thromboembolism is a rare but potentially fatal complication of GPA. The frequencies of organ system involvement throughout the disease course in GPA are: respiratory tract, 84%; kidneys, 88%; joints, 44%; eyes, 60%; skin, 48%; sinuses, 56%; and nervous system, 12%. Table 167-8 outlines the classification criteria for pediatric-onset GPA.

The clinical presentation of **MPA** closely resembles that of GPA, although sinus disease is less common; systemic features of fever, malaise, weight loss, myalgias, arthralgias may be dominant. MPA predominantly affects the kidney and lungs; other organ systems include skin, CNS, muscle, heart, and eyes. **CSS** frequently causes inflammation of the upper and lower respiratory tracts, but cartilage destruction is rare. CSS may initially demonstrate chronic or recurrent rhinitis/sinusitis, nasal polyposis, and difficult to treat asthma. Eosinophilia with pulmonary infiltrates may precede a vasculitic phase. Other organ involvement includes skin, cardiac, peripheral nerves, gastrointestinal tract, and muscle. Renal involvement in CSS is uncommon.

DIAGNOSIS

GPA should be considered in children who have recalcitrant sinusitis, pulmonary infiltrates, and evidence of nephritis. Chest radiography often fails to detect pulmonary lesions, and chest CT may show nodules, ground-glass opacities, mediastinal lymphadenopathy, and cavitary lesions (Fig. 167-8). The diagnosis is confirmed by the presence of anti-PR3–specific ANCAs (PR3-ANCAs) and the finding of necrotizing granulomatous vasculitis on pulmonary, sinus, or renal biopsy. The ANCA test result is positive in approximately 90% of children with GPA, and the presence of anti-PR3 increases the specificity of the test.

In **MPA**, ANCAs are also frequently present but have reactivity to MPO (MPO-ANCAs). MPA can be distinguished from PAN by the

presence of ANCAs and the tendency for small vessel involvement. The ANCA test result is positive in approximately 70% of cases of **CSS**, and MPO-ANCAs are more common than PR3-ANCAs. The presence of chronic asthma and peripheral eosinophilia suggests the diagnosis of CSS.

Table 167-8 EULAR/PReS Classification Criteria for Pediatric-Onset Granulomatosis with Polyangiitis*

Histopathology showing granulomatous inflammation
Upper airway involvement
Laryngeal, tracheal or bronchial involvement
ANCA positivity
Renal involvement
Proteinuria, hematuria, red blood cell casts, necrotizing pauci-immune glomerulonephritis

*Diagnosis requires 3 of 6 criteria.
Adapted from: Ozen S, Pistorio A, Iusan SM, et al: EULAR/PRINTO/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: final classification criteria. Ann Rheum Dis *69:798–806; 2010.*

DIFFERENTIAL DIAGNOSIS

ANCAs are absent in other granulomatous diseases, such as sarcoidosis and tuberculosis. Goodpasture disease is characterized by antibodies to glomerular basement membrane. Medications such as propylthiouracil, hydralazine, and minocycline are associated with drug-induced ANCA (usually perinuclear ANCA) vasculitis. Systemic lupus erythematous and HSP can manifest as pulmonary hemorrhage and nephritis.

LABORATORY FINDINGS

Elevated ESR and CRP values, leukocytosis, and thrombocytosis are present in most patients with an ANCA-associated vasculitis but are nonspecific. Anemia may be caused by chronic inflammation or pulmonary hemorrhage. ANCA antibodies show 2 distinct immunofluorescence patterns: perinuclear and cytoplasmic. In addition, ANCAs can also be defined by their specificity for PR3 or MPO antigen. GPA is strongly associated with cytoplasmic ANCAs/anti-PR3 antibodies (see Tables 167-1 and 167-9).

TREATMENT

When the lower respiratory tract or kidneys are significantly involved, initial induction therapy usually consists of corticosteroids (2 mg/kg/day oral or 30 mg/kg/day × 3 days given intravenously) in conjunction with daily oral cyclophosphamide (2 mg/kg/day). Rituximab is an option for induction therapy in ANCA positive vasculitides although

Table 167-9 Differential Diagnostic Features of Small Vessel Vasculitis

FEATURE	HENOCH-SCHÖNLEIN PURPURA	GRANULOMATOSIS WITH POLYANGIITIS	CHURG-STRAUSS SYNDROME	MICROSCOPIC POLYANGIITIS
Signs and symptoms of small vessel vasculitis*	+	+	+	+
Immunoglobulin A–dominant immune deposits	+	–	–	–
Circulating antineutrophil cytoplasmic antibodies	–	+ (PR3)	+ (MPO > PR3)	+ (MPO)
Necrotizing vasculitis	–	+	+	+
Granulomatous inflammation	–	+	+	–
Asthma and eosinophilia	–	–	+	–

MPO, myeloperoxidase-reactive antibodies; PR3, proteinase 3–reactive antibodies; +, presence; –, absent.
*Signs and symptoms of small vessel vasculitis include purpura, other rash, arthralgias, arthritis, and constitutional symptoms.
Adapted from Jeannett JC, Falk RJ: Small-vessel vasculitis, N Engl J Med *337:1512–1523, 1997.*

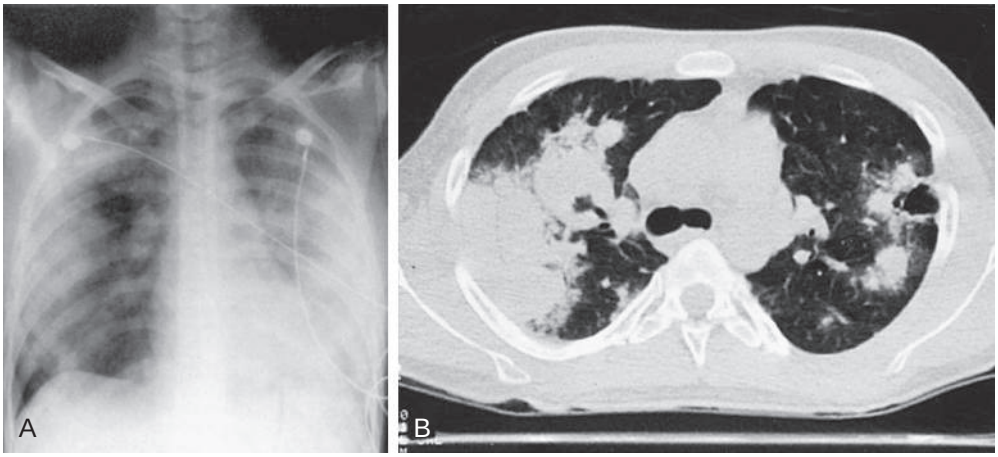

Figure 167-8 Radiographs of lower respiratory tract disease in granulomatosis with polyangiitis. **A,** A chest radiograph of a 14 yr old girl with Wegener granulomatosis and pulmonary hemorrhage. Extensive bilateral, fluffy infiltrates are visualized. **B,** CT scan of the chest in a 17 yr old boy with Wegener granulomatosis. Air space consolidation, septal thickening, and a single cavitary lesion are present. (***A,*** *From Cassidy JT, Petty RE: Granulomatous vasculitis, giant cell arteritis and sarcoidosis. In* Textbook of pediatric rheumatology, *ed 3, Philadelphia, 1995, WB Saunders;* ***B,*** *From Kuhn JP, Slovis TL, Haller JO:* Caffey's pediatric diagnostic imaging, *ed 10, vol 1, Philadelphia, 2004, Mosby.)*

has been studied primarily in adults. Patients are transitioned to a less toxic maintenance medication (usually methotrexate, azathioprine, or mycophenolate mofetil) within 3-6 mo once remission is achieved. Trimethoprim-sulfamethoxazole (one 180 mg/800 mg tablet 3 days/wk) is often prescribed both for prophylaxis against *Pneumocystis jiroveci* infection and to reduce upper respiratory bacterial colonization with *S. aureus,* which may trigger disease activity. If disease is limited to the upper respiratory tract, corticosteroids (1-2 mg/kg/day) and methotrexate (0.5-1.0 mg/kg/wk) may be first-line treatment.

COMPLICATIONS

Upper respiratory tract lesions can invade the orbit and threaten the optic nerve, and lesions in the ear can cause permanent hearing loss. Respiratory complications include potentially life-threatening pulmonary hemorrhage and upper airway obstruction due to subglottic stenosis. Chronic lung disease secondary to granulomatous inflammation, cavitary lesions, and scarring can predispose to infectious complications. Chronic glomerulonephritis may progress to end-stage renal disease in a subset of patients with advanced or undertreated disease.

PROGNOSIS

The course is variable but disease relapse occurs in up to 60% of patients. Mortality has been reduced with the introduction of cyclophosphamide and other immunosuppressive agents. Compared with adults, children are more likely to develop multiple organ involvement, renal involvement, and subglottic stenosis.

Bibliography is available at Expert Consult.

167.5 Other Vasculitis Syndromes

Stacy P. Ardoin and Edward Fels

In addition to the more common vasculitides discussed earlier in this chapter, other vasculitic conditions can occur in childhood, the most common of which is Kawasaki disease (see Chapter 166). **Hypersensitivity vasculitis** is a cutaneous vasculitis triggered by medication or toxin exposure. The rash consists of palpable purpura or other nonspecific rash. Skin biopsies reveal characteristic changes of **leukocytoclastic vasculitis** (small vessels with neutrophilic perivascular or extravascular neutrophilic infiltration). **Hypocomplementemic urticarial vasculitis** involves small vessels and manifests as recurrent urticaria that resolves over several days but leaves residual hyperpigmentation. This condition is associated with low levels of complement component C1q and systemic findings that include fever, gastrointestinal symptoms, arthritis, and glomerulonephritis. **Cryoglobulinemic vasculitis** can complicate mixed essential cryoglobulinemia and is a small vessel vasculitis affecting skin, joints, kidneys, and lungs.

Primary angiitis of the CNS represents vasculitis confined to the CNS and requires exclusion of other systemic vasculitides. Large vessel disease (angiography positive) may manifest with focal deficits similar to an occlusive stroke with hemiparesis, focal gross or fine motor deficits, language disorders, or cranial nerve deficits. Diffuse cognitive, memory, and concentration deficits plus behavioral disorders are seen in 30-40%. Small vessel (angiography negative, biopsy positive) involvement more often demonstrates language problems and diffuse deficits such as cognitive, memory, behavior, and concentration problems as well as focal seizures.

Benign angiitis of the CNS, also known as transient CNS angiopathy, represents a self-limited variant. **Cogan syndrome** is rare in children; its potential clinical manifestations include constitutional symptoms, inflammatory eye disease, vestibuloauditory dysfunction, arthritis, and aortitis.

Identification of these vasculitis syndromes requires a comprehensive history and physical exam. Table 167-10 outlines other diagnostic considerations. Although treatment is tailored to disease severity, treatment generally includes prednisone (up to 2 mg/kg/day) plus steroid-sparing immunosuppressive medications if necessary. For hypersensitivity vasculitis, withdrawal of the triggering medication or toxin is indicated if possible.

Table 167-10 Diagnostic Considerations for Other Vasculitis Syndromes

VASCULITIS SYNDROME	APPROACH TO DIAGNOSIS
Hypersensitivity vasculitis	Skin biopsy demonstrating leukocytoclastic vasculitis
Hypocomplementemic urticarial vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Low levels of circulating C1q
Cryoglobulinemic vasculitis	Biopsy of affected tissue demonstrating small vessel vasculitis Measurement of serum cryoglobulins Exclusion of hepatitides B and C infections
Primary angiitis of the CNS	Conventional, CT, or MR angiographic evidence of CNS vasculitis Consideration of dura or brain biopsy
Benign angiitis of the CNS	Conventional, CT, or MR angiographic evidence of CNS vasculitis
Cogan syndrome	Ophthalmology and audiology evaluations Conventional, CT, or MR angiographic evidence of CNS or aortic vasculitis

CNS, central nervous system; CT, computed tomography; MR, magnetic resonance.

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Chapter 168

Musculoskeletal Pain Syndromes

Kelly K. Anthony and Laura E. Schanberg

Musculoskeletal pain is a frequent complaint of children presenting to general pediatricians and is the most common presenting problem of children referred to pediatric rheumatology clinics. Prevalence estimates of persistent musculoskeletal pain in community samples range from roughly 10-30%. Although diseases such as juvenile idiopathic arthritis and systemic lupus erythematosus may manifest as persistent musculoskeletal pain, the majority of musculoskeletal pain complaints in children turn out to be benign in nature and attributable to trauma, overuse, and normal skeletal growth variations. There is a subset of children in whom chronic pain complaints develop in the absence of physical and laboratory abnormalities. Children with idiopathic musculoskeletal pain syndromes, also typically develop marked subjective distress and functional impairment. Therefore, the treatment of children with musculoskeletal pain syndromes optimally includes both pharmacologic and nonpharmacologic interventions.

CLINICAL MANIFESTATIONS

Chronic musculoskeletal pain syndromes involve pain complaints of at least 3 mo in duration in the absence of objective abnormalities on physical examination and laboratory screening. Additionally, children and adolescents with musculoskeletal pain syndromes often complain

of persistent pain despite previous treatment with nonsteroidal antiinflammatory drugs and analgesic agents. The location varies, with pain complaints either localized to a single extremity or more diffuse and involving multiple extremities. It is not uncommon for the pain to start in a single area of the body before intensifying and radiating to other areas over time. The prevalence of musculoskeletal pain syndromes increases with age and is higher in females, thus rendering adolescent girls at highest risk.

The somatic complaints of children and adolescents with musculoskeletal pain syndromes are commonly accompanied by psychological distress, sleep difficulties, and functional impairment across home, school, and peer domains. Psychological distress may include symptoms of anxiety and depression, such as frequent crying spells, fatigue, sleep disturbance, feelings of worthlessness, poor concentration, and frequent worry. Indeed, a substantial number of children with musculoskeletal pain syndromes display the full range of psychological symptoms warranting an additional diagnosis of a comorbid mood or anxiety disorder (e.g., major depressive episode, generalized anxiety disorder). **Sleep disturbance** in children with musculoskeletal pain syndromes may include difficulty falling asleep, multiple night awakenings, disrupted sleep-wake cycles with increased daytime sleeping, nonrestorative sleep, and fatigue.

For children and adolescents with musculoskeletal pain syndromes, the constellation of pain, psychological distress, and sleep disturbance often leads to a high degree of functional impairment. Poor school attendance is common, and children may struggle to complete other daily activities relating to self-care and participation in household chores. Decreased physical fitness can also occur, as well as changes in gait and posture, as children avoid contact with or use of the body area affected by pain. Peer relationships may also be disrupted due to decreased opportunities for social interaction due to pain. As such, children and adolescents with musculoskeletal pain syndromes often report loneliness and social isolation characterized by having few friends and lack of participation in extracurricular activities.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of a musculoskeletal pain syndrome is typically one of exclusion when careful, repeated physical examinations and laboratory testing do not reveal an etiology. At initial presentation, children with pain complaints require a thorough clinical history and a complete physical examination to look for an obvious etiology (e.g., sprains, strains, or fractures), characteristics of the pain (localized or diffuse), and evidence of systemic involvement. A comprehensive history can be particularly useful in providing clues to the possibility of underlying illness or systemic disease. The presence of current or recent fever can be indicative of an inflammatory or neoplastic process if the pain is also accompanied by worsening symptoms over time or weight loss.

Subsequent, repeated physical examinations of children with musculoskeletal pain complaints may reveal eventual development and manifestations of rheumatic or other diseases. The need for additional testing should be individualized, depending on the specific symptoms and physical findings. Laboratory screening and/or radiographs should be pursued if there is suspicion of certain underlying disease processes. Possible indicators of a serious, as opposed to a benign, cause of musculoskeletal pain include pain present at rest and relieved by activity, objective joint swelling on physical examination, stiffness or limited range of motion in joints, bony tenderness, muscle weakness, poor growth and/or weight loss, and constitutional symptoms (e.g., fever, malaise) (Table 168-1). In the case of laboratory screenings, a complete blood count and erythrocyte sedimentation rate are likely to be abnormal in children whose pain is secondary to a bone or joint infection, systemic lupus erythematosus, or a malignancy. Bone tumors, fractures, and other focal pathology resulting from infection, malignancy, or trauma can often be indentified through imaging studies, including plain film x-rays, MRI, and technetium-99m bone scans.

The presence of persistent pain, accompanied by psychological distress, sleep disturbance, and/or functional impairment, in the absence of objective laboratory or physical examination abnormalities, suggest the diagnosis of a musculoskeletal pain syndrome. All pediatric musculoskeletal pain syndromes share this general constellation of symptoms at presentation. Several more specific pain syndromes routinely seen by pediatric practitioners can be differentiated by anatomic region and associated symptoms. Pediatric musculoskeletal pain syndromes are listed in Table 168-2 and includes growing pains (see Chapter 168.1), fibromyalgia (see Chapter 168.3), complex regional pain syndrome (see Chapter 168.4), localized pain syndromes, low back pain, and chronic sports-related pain syndromes (e.g., Osgood-Schlatter disease).

TREATMENT

The primary goal of treatment for pediatric musculoskeletal pain syndromes is to improve function rather than relieve pain, and these two desirable outcomes may not occur simultaneously. Indeed, it is common for children with musculoskeletal pain syndromes to continue complaining of pain even as they resume normal function (e.g., increased school attendance and participation in extracurricular activities). For all children and adolescents with pediatric musculoskeletal pain syndromes, regular school attendance is crucial, as this is a hallmark of normal functioning in this age group. The dual nature of treatment, targeting both function and pain, needs to be clearly

Table 168-1 Potential Indicators of Benign Versus Serious Causes of Musculoskeletal Pain

CLINICAL FINDING	BENIGN CAUSE OF MUSCULOSKELETAL PAIN	SERIOUS CAUSE OF MUSCULOSKELETAL PAIN
Effects of rest versus activity on pain	Relieved by rest and worsened by activity	Relieved by activity and present at rest
Time of day pain occurs	End of the day and nights	Morning*
Objective joint swelling	No	Yes
Joint characteristics	Hypermobile/normal	Stiffness, limited range of motion
Bony tenderness	No	Yes
Muscle strength	Normal	Muscle weakness
Growth	Normal growth pattern or weight gain	Poor growth and/or weight loss
Constitutional symptoms (e.g., fever, malaise)	Fatigue without other constitutional symptoms	Yes
Lab findings	Normal CBC, ESR, CRP	Abnormal CBC, raised ESR and CRP
Radiographic findings	Normal	Effusion, osteopenia, radiolucent metaphyseal lines, joint space loss, bony destruction

CBC, complete blood count; CRP, C-reactive protein level; ESR, erythrocyte sedimentation rate.
*Cancer pain is often severe and worst at night.
Adapted from Malleson PN, Beauchamp RD: Diagnosing musculoskeletal pain in children. CMAJ *165:183–188, 2001.*

Table 168-2 Common Musculoskeletal Pain Syndromes in Children by Anatomic Region

ANATOMICAL REGION	PAIN SYNDROMES	
Shoulder	Impingement syndrome	
Elbow	Little League elbow Avulsion fractures Osteochondritis dissecans	Tennis elbow Panner disease
Arm	Localized hypermobility syndrome Complex regional pain syndrome	
Pelvis and hip	Avulsion injuries Legg-Calvé-Perthes syndrome	Slipped capital femoral epiphysis Congenital hip dysplasia
Knee	Osteochondritis dissecans Osgood-Schlatter disease Sinding-Larsen syndrome	Patellofemoral syndrome Malalignment syndromes
Leg	Growing pains Complex regional pain syndrome Localized hypermobility syndrome	Shin splints Stress fractures Compartment syndromes
Foot	Plantar fasciitis Tarsal coalition Stress fractures	Achilles tendonitis Juvenile bunion
Spine	Musculoskeletal strain Spondylolisthesis Spondylolysis	Scoliosis Scheuermann disease (kyphosis) Low back pain
Generalized	Hypermobility syndrome Juvenile fibromyalgia Generalized pain syndrome	

Adapted from Anthony KK, Schanberg LE. Box 1 in assessment and management of pain syndromes and arthritis pain in children and adolescents. Rheum Dis Clin North Am *33:625–660, 2007.*

explained to children and their families to better outline the goals by which treatment success will be measured. Indeed, children and families need to be supported in disengaging from the sole pursuit of pain relief and embracing broader treatment goals of improved functioning.

Recommended treatment modalities typically include physical and/or occupational therapy, pharmacologic interventions, and cognitive-behavioral and/or other psychotherapeutic interventions. The overarching goal of physical therapy is to improve children's physical function and should emphasize participation in aggressive, but graduated aerobic exercise. Pharmacologic interventions should be used judiciously. Low-dose tricyclic antidepressants (amitriptyline 10-50 mg orally 30 min before bedtime) are indicated for treatment of sleep disturbance; selective serotonin reuptake inhibitors (sertraline 10-20 mg daily) may prove useful in treating symptoms of depression and anxiety if present. Referral for psychological evaluation is warranted if these symptoms do not resolve with initial treatment efforts or if suicidal ideation is present. Cognitive-behavioral and/or other psychotherapeutic interventions are typically designed to teach children and adolescents coping skills for controlling the behavioral, cognitive, and physiologic responses to pain. Specific components often include cognitive restructuring, relaxation, distraction, and problem-solving skills; additional targets of therapy include sleep hygiene and activity scheduling, all with the goal of restoring normal sleep patterns and activities of daily living. Parent education and involvement in the psychological intervention is important to ensure maintenance of progress. More intensive family-based approaches are warranted if barriers to treatment success are identified at the family level. These could include parenting strategies or family dynamics that serve to maintain children's pain complaints, such as overly solicitous responses to child pain, and maladaptive models for pain coping in the family.

COMPLICATIONS AND PROGNOSIS

Musculoskeletal pain syndromes can negatively affect child development and future role functioning. Worsening pain and the associated symptoms of depression and anxiety can lead to substantial school absences, peer isolation, and developmental delays later in adolescence and early adulthood. Specifically, adolescents with musculoskeletal pain syndromes may fail to achieve the level of autonomy and independence necessary for age-appropriate activities such as attending college, living away from home, and maintaining a job. Fortunately, not all children and adolescents with musculoskeletal pain syndromes experience this degree of impairment and the likelihood of positive health outcomes is increased with multidisciplinary treatment.

168.1 Growing Pains

Kelly K. Anthony and Laura E. Schanberg

More appropriately termed **benign nocturnal pains of childhood** growing pains affect 10-20% of children, with a peak age incidence between 4 and 12 yr. Pain does not occur during periods of rapid growth or at growth sites. The most common cause of recurrent musculoskeletal pain in children, growing pains are intermittent and bilateral, predominantly affecting the anterior thigh, shin, and calf but not joints. Occasionally there may be bilateral upper extremity pain associated with leg pain; isolated upper extremity pain does not occur. Children most commonly describe cramping or aching that occurs in the late afternoon or evening. Pain may wake the child from sleep and may last a few minutes to hours, but resolves quickly with massage or analgesics; pain is never present the following morning (Table 168-3). Pain often follows a day with exercise or other physical activities. Physical findings are normal, and gait is not impaired. Growing pains are generally considered a benign, time-limited condition; there is evidence suggesting that growing pains represent a pain amplification syndrome. Indeed, growing pains persist in a significant percentage of children, with some children developing other pain syndromes such as abdominal pain and headaches. Growing pains are more likely to persist in children with a parent who has a history of a pain syndrome and in children who have lower pain thresholds. Treatment should also focus on reassurance, education, and healthy sleep hygiene. Massage

Table 168-3 Definition of "Growing Pains"

	INCLUSIONS	EXCLUSIONS
Nature of pain	Intermittent; some pain-free days and nights, deep aching, cramping	Persistent; increasing intensity, pain during the day
Unilateral or bilateral	Bilateral	Unilateral
Location of pain	Anterior thigh, calf, posterior knee—in muscles	Articular, back, or groin pain
Onset of pain	Late afternoon or evening	Pain still present next morning
Physical findings	Normal	Swelling, erythema, tenderness; local trauma or infection; reduced joint range of motion; limping, fever, weight loss, mass
Laboratory findings	Normal	Objective evidence of abnormalities; increased erythrocyte sedimentation rate, C-reactive protein, abnormal complete blood count, radiography, bone scan or MRI

From Evans AM, Scutter SD: Prevalence of "growing pains" in young children, J Pediatr 145:255–258, 2004.

during the episode is very effective, and nonsteroidal antiinflammatory drugs agents may be useful for frequent episodes.

Restless leg syndrome, seen more commonly among adults, is a sensorimotor disturbance that may be confused with growing pains (see Chapter 19). Restless leg syndrome is a difficult to control urge to move the leg that is exacerbated during rest and at night and is relieved by movement.

168.2 Small Fiber Polyneuropathy

Kelly K. Anthony and Laura E. Schanberg

Many patients with juvenile onset widespread pain syndromes, as well as patients with pediatric fibromyalgia (see Chapter 168.3), complex regional pain syndrome type I (see Chapter 168.4), and erythromelalgia have evidence of a small fiber polyneuropathy causing dysfunctional or degeneration of small diameter unmyelinated C-fibers and thinly myelinated A-delta fibers that mediate nociception and the autonomic nervous system. Fibromyalgia (see Chapter 168.3) includes chronic widespread pain defined as ≥3 mo duration of axial pain that is often bilateral and also affects the upper and lower extremities. In addition, many patients have associated chronic cardiovascular (dizziness, postural orthostasis syndrome) symptoms, as well as chronic abdominal pain and ileus, headaches, fatigue and erythromelalgia, suggestive of dysautonomia.

There are no typical findings on physical exam or standard laboratory tests. The diagnosis of small fiber polyneuropathy requires distal leg skin immunolabeled biopsy to identify epidermal nociceptive fibers and autonomic function testing to examine cardiovagal, adrenergic, and sudomotor small fiber function.

Treatment of patients with small fiber polyneuropathy and isolated juvenile-onset widespread pain syndrome, or those subsets of patients with small fiber polyneuropathy and fibromyalgia, complex regional pain syndrome, or erythromelalgia is evolving and has included prednisone or intravenous immunoglobulin.

Bibliography is available at Expert Consult.

168.3 Fibromyalgia

Kelly K. Anthony and Laura E. Schanberg

Juvenile primary fibromyalgia syndrome (JPFS) is a common pediatric musculoskeletal pain syndrome. Approximately 25-40% of children with chronic pain syndromes can be diagnosed with JPFS. Although specific diagnostic criteria for JPFS have not been determined, children and adolescents with JPFS have diffuse, multifocal, waxing and waning, and at times migratory musculoskeletal pain in at least 3 areas of the body that persists for at least 3 mo in the absence of an underlying condition. Results of laboratory tests are normal, and physical examination reveals at least 5 well-defined tender points (Fig. 168-1). Children and adolescents with JPFS also present with many associated symptoms, including nonrestorative sleep, fatigue, paresthesias, chronic anxiety or tension, chronic headaches, subjective soft-tissue swelling, and pain modulated by physical activity, weather, and anxiety or stress. There is considerable overlap among symptoms associated with JPFS and complaints associated with other **functional disorders** (e.g., irritable bowel disease, migraines, temporomandibular joint disorder, premenstrual syndrome, mood and anxiety disorders, and chronic fatigue syndrome), raising speculation that these disorders may be part of a larger spectrum of related syndromes.

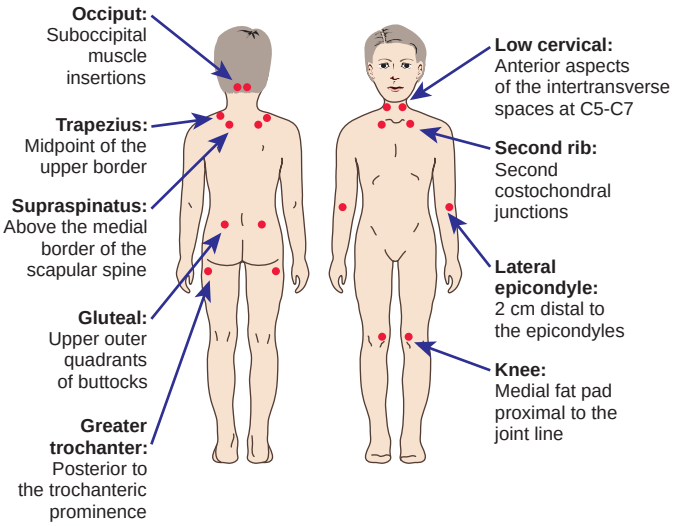

Figure 168-1 Fibromyalgia tender points.

Although the precise cause of JPFS is unknown, there is an emerging understanding that the development and maintenance of JPFS are related both to biologic and psychological factors. JPFS is an abnormality of central pain processing characterized by disordered sleep physiology, enhanced pain perception with abnormal levels of substance P in cerebrospinal fluid, disordered mood, and dysregulation of hypothalamic–pituitary–adrenal and other neuroendocrine axes resulting in lower tender-point pain thresholds and increased pain sensitivity. Children and adolescents with fibromyalgia often find themselves in a vicious cycle of pain, whereby symptoms build upon one another and contribute to the onset and maintenance of new symptoms (Fig. 168-2).

JPFS has a chronic course that can detrimentally affect child health and development. Adolescents with JPFS who do not receive

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Figure 168-2 Vicious cycle promoting juvenile primary fibromyalgia syndrome symptom maintenance. *(Adapted from Anthony KK, Schanberg LE. Juvenile primary fibromyalgia syndrome.* Curr Rheumatol Rep *3:167–171, 2001, Fig. 1.)*

treatment or are inadequately treated may withdraw from school and the social milieu, complicating their transition to adulthood. Treatment of JPFS generally follows consensus statements of the American Pain Society. The major goals are to restore function and alleviate pain, as well as improve comorbid mood and sleep disorders. Treatment strategies include parent/child education, pharmacologic interventions, exercise-based interventions, and psychological interventions. Graduated aerobic exercise is the recommended exercise-based intervention, whereas psychological interventions should include training in pain coping skills, stress management skills, emotional support, and sleep hygiene. Cognitive-behavioral interventions are particularly effective in reducing symptoms of depression in children and adolescents with JPFS and also help to reduce functional disability. Drug therapies, although largely unsuccessful in isolation, may include tricyclic antidepressants (amitriptyline 10-50 mg orally 30 min before bedtime), selective serotonin reuptake inhibitors (sertraline 10-20 mg daily), and anticonvulsants. Pregabalin and duloxetine hydrochloride are approved by the FDA for treatment of fibromyalgia in adults (18 yr of age and older), but neither has been studied in children. Muscle relaxants are generally not used in children because they affect school performance.

Evolving evidence suggests that up to 50% of patients with fibromyalgia may have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.

168.4 Complex Regional Pain Syndrome

Kelly K. Anthony and Laura E. Schanberg

Complex regional pain syndrome (CRPS) is characterized by ongoing burning limb pain that is subsequent to an injury, immobilization, or another noxious event affecting the extremity. CRPS1, formerly called reflex sympathetic dystrophy, has no evidence of nerve injury, whereas CRPS2, formerly called causalgia, follows a prior nerve injury. Key associated features are pain disproportionate to the inciting event, persisting **allodynia** (a heightened pain response to normally non-noxious stimuli), **hyperalgesia** (exaggerated pain reactivity to noxious stimuli), swelling of distal extremities, and indicators of **autonomic dysfunction** (i.e., cyanosis, mottling, and hyperhidrosis) (Table 168-4).

The diagnosis requires the following: an initiating noxious event or immobilization; continued pain, allodynia, and hyperalgesia out of proportion to the inciting event; evidence of edema, skin blood flow abnormalities, or sudomotor activity; and exclusion of other disorders. Associated features include atrophy of hair or nails; altered hair growth; loss of joint mobility; weakness, tremor, dystonia; and sympathetically maintained pain.

Table 168-4 Diagnostic Criteria for Complex Regional Pain Syndrome*

NEUROPATHIC DESCRIPTORS	AUTONOMIC DYSFUNCTION
Burning	Cyanosis
Dysesthesia	Mottling
Paresthesia	Hyperhidrosis
Allodynia	Coolness (≥3°)
Cold hyperalgesia	Edema

*A diagnosis of CRPS requires regional pain, sensory symptoms, plus 2 neuropathic pain descriptors and 2 physical signs of autonomic dysfunction.

Data from Wilder RT, Berde CB, Wolohan, M, et al. Reflex sympathetic dystrophy in children: clinical characteristics and follow-up of seventy patients. J Bone Joint Surg Am *74: 910–919, 1992.*

Although the majority of pediatric patients with CRPS present with a history of minor trauma or repeated stress injury (e.g., caused by competitive sports), a sizeable proportion are unable to identify a precipitating event. Usual age of onset is between 8 and 16 yr, and girls outnumber boys with the disease by as much as 6:1. Childhood CRPS differs from the adult form in that lower extremities, rather than upper extremities, are most commonly affected. The incidence of CRPS in children is unknown, largely because it is often undiagnosed or diagnosed late, with the diagnosis frequently delayed by nearly a year. Left untreated, CRPS can have severe consequences for children including bone demineralization, muscle wasting, and joint contractures.

An evidence-based approach to the treatment of CRPS continues to suggest a multistage treatment approach. Aggressive physical therapy should be initiated as soon as the diagnosis is made and cognitive-behavioral interventions (CBT) added as needed. Physical therapy (PT) is recommended 3-4 times per week, and children may need analgesic premedication at the onset, particularly prior to PT sessions. PT is initially limited to desensitization and then moves to weight-bearing, range-of-motion, and other functional activities. CBT used as an adjunctive therapy targets psychosocial obstacles to fully participating in PT and provides pain coping skills training. Sympathetic and epidural nerve blocks should be attempted only under the auspices of a pediatric pain specialist. The intent of both pharmacologic and adjunctive treatments for CRPS is to provide sufficient pain relief to allow the child to participate in aggressive physical rehabilitation. If CRPS is identified and treated early, the majority of children and adolescents with the disease can be treated successfully with low-dose amitriptyline (10-50 mg orally 30 min prior to bedtime), aggressive PT, and CBT interventions. Opioids and anticonvulsants such as gabapentin can also be helpful. Notably, multiple studies have shown noninvasive treatments, particularly PT and CBT, are at least as efficacious as nerve blocks in helping children with CRPS achieve resolution of their symptoms.

There is growing evidence that some patients with CRPS I have a small fiber polyneuropathy (see Chapter 168.2).

Bibliography is available at Expert Consult.

168.5 Erythromelalgia

Laura E. Schanberg

Children with **erythromelalgia** experience episodes of intense pain, erythema, and heat in their hands and feet (Fig. 168-3). Less commonly involved are the face, ears, or knees. Symptoms may be triggered by exercise and exposure to heat, lasting for hours and occasionally for days. It is more common in girls and in the teenage years and diagnosis is often delayed for years. Although most cases are sporadic, an

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Figure 168-3 Typical redness and edema of the foot in erythromelalgia. *(From Pfund Z, Stankovics J, Decsi T, Illes Z. Childhood steroid-responsive acute erythromelalgia with axonal neuropathy of large myelinated fibers: A dysimmune neuropathy?* Neuromuscul Disord *19:49-52, 2009, Fig. 1A, p. 50.)*

autosomal dominant hereditary form results from mutations of the SCN9A gene on chromosome 2q31-32, causing a painful channelopathy. Secondary erythromelalgia is associated with an array of disorders, including myeloproliferative diseases, peripheral neuropathy, frostbite, hypertension, and rheumatic disease. Treatment includes avoidance of heat exposure as well as other precipitating situations and the utilization of cooling techniques that do not cause tissue damage during attacks. Nonsteroidal antiinflammatories, narcotics, anesthetic agents (lidocaine patch), anticonvulsants (oxcarbazepine, carbamazepine, gabapentin), and antidepressants, as well as biofeedback and hypnosis may be useful in helping manage pain. Drugs acting on the vascular system (aspirin, sodium nitroprusside, magnesium, misoprostol) may also be somewhat effective. However, a reliably efficacious treatment is not available, resulting in substantial negative impact on physical and mental health.

There is growing evidence that some patients with erythromelalgia have a small fiber polyneuropathy (see Chapter 168.2).

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Chapter 169

Miscellaneous Conditions Associated with Arthritis

Reut Gurion, Angela Byun Robinson, and C. Egla Rabinovich

RELAPSING POLYCHONDRITIS

Relapsing polychondritis (RP) is a rare condition characterized by episodic chondritis causing cartilage destruction and deformation of the ears (sparing the earlobes), nose, larynx and tracheobronchial tree. Antibodies to matrillin-1 and collagen (types II, IX and XI) are present in approximately 60% of patients with RP, suggesting an autoimmune pathogenesis. Patients may experience arthritis, uveitis, and hearing loss due to inflammation near the auditory and vestibular nerves. Children may initially relate episodes of intense erythema over the outer ears. Other dermatologic manifestations such as erythema nodosum, maculopapular rash and purpura may be seen. Cardiac involvement, including conduction defects and coronary vasculitis, has been reported. Severe, progressive, and potentially fatal disease resulting from destruction of the tracheobronchial tree and airway obstruction is unusual in childhood. Diagnostic criteria established for adults are useful guidelines for evaluating children with suggestive symptoms (Table 169-1). The clinical course of RP is variable; flares of disease are often associated with elevations of acute-phase reactants and may remit spontaneously. Although seen more commonly in the adult population, RP may coexist with other inflammatory diseases, such as systemic lupus erythematosus, Sjögren syndrome, and Henoch-Schönlein purpura. The differential diagnosis includes antineutrophilic cytoplasmic antibody–associated vasculitis (granulomatosis with polyangiitis) (see Chapter 167.4) and Cogan syndrome, which is characterized by auditory nerve inflammation and keratitis but not chondritis. Many children respond to nonsteroidal antiinflammatory drugs, but some require corticosteroids or other immunosuppressive agents (azathioprine, methotrexate, hydroxychloroquine, colchicine, cyclophosphamide, cyclosporine, and anti–tumor necrosis factor agents), as reported in small series and case reports.

Table 169-1 Empiric Diagnostic Criteria for Relapsing Polychondritis*

MAJOR CRITERIA
Proven inflammatory episodes involving auricular cartilage
Proven inflammatory episodes involving nasal cartilage
Proven inflammatory episodes involving laryngotracheal cartilage
MINOR CRITERIA
Ocular inflammation (conjunctivitis, keratitis, episcleritis, uveitis)
Hearing loss
Vestibular dysfunction
Seronegative inflammatory arthritis

*The diagnosis is established by the presence of 2 major criteria or of 1 major and 2 minor criteria. Histologic examination of affected cartilage is not required.

From Michet CJ Jr, McKenna CH, Luthra HS, et al: Relapsing polychondritis: survival and predictive role of early disease manifestations, Ann Intern Med *104:74–78, 1986.*

MUCHA-HABERMANN DISEASE/PITYRIASIS LICHENOIDES ET VARIOLIFORMIS ACUTA

Pityriasis lichenoides et varioliformis acuta (PLEVA) is a benign, self-limited cutaneous vasculitis characterized by episodes of macules, papules, and papulovesicular lesions that can develop central ulceration, necrosis, and crusting. Different stages of development are usually seen at once. **PLEVA fulminans** or **febrile ulceronecrotic Mucha-Habermann disease** is the severe, life-threatening form of PLEVA. Large coalescing ulceronecrotic lesions are seen, and are accompanied by high fever and an elevated erythrocyte sedimentation rate. Systemic manifestations can include interstitial pneumonitis, abdominal pain, malabsorption, arthritis, and neurologic manifestations. There is a male predominance and it occurs more frequently in childhood. The diagnosis is confirmed by biopsy of skin lesions that reveal perivascular and intramural lymphocytic inflammation affecting capillaries and venules in the upper dermis that may lead to keratinocyte necrosis. When disease is severe, corticosteroids have been used with questionable effect, and methotrexate has been reported to induce rapid remission in resistant cases. Cyclosporine and anti–tumor necrosis factor agents have been efficacious in case reports.

SWEET SYNDROME

Sweet syndrome, or **acute febrile neutrophilic dermatosis,** is a rare entity in children. It is characterized by fever, elevated neutrophil count, and raised, tender erythematous plaques and nodules over the

Table 169-2 Diagnostic Criteria for Classic Sweet Syndrome*

MAJOR CRITERIA
Abrupt onset of painful erythematous plaques or nodules
Histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
MINOR CRITERIA
Pyrexia >38°C (100.4°F)
Association with underlying hematologic or visceral malignancy, inflammatory disease or pregnancy, *or* preceded by an upper respiratory or gastrointestinal infection or vaccination
Excellent response to systemic corticosteroids or potassium iodide
Abnormal laboratory values at presentation (3 of 4): erythrocyte sedimentation rate >20 mm/hr, positive C-reactive protein test result, >8,000 leukocytes/mm^3, >70% neutrophils/mm^3

*The diagnosis is established by the presence of 2 major criteria plus 2 of the 4 minor criteria.

From Cohen PR: Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis, Orphanet J Rare Dis *2:34, 2007.*

face, extremities, and trunk. Skin biopsy reveals neutrophilic perivascular infiltration in the upper dermis. Female predominance is seen in the adult population, whereas in children, gender distribution is equal. Established criteria are useful for diagnosis (Table 169-2). Children can also have arthritis, sterile osteomyelitis, myositis, and other extracutaneous manifestations. The syndrome may be idiopathic or secondary to malignancy (particularly acute myelogenous leukemia), drugs (granulocyte colony-stimulating factor), or rheumatic diseases (Behçet disease, antiphospholipid antibody syndrome, systemic lupus erythematosus). The condition usually responds to treatment with corticosteroids.

HYPERTROPHIC OSTEOARTHROPATHY

Children with chronic disease, especially pulmonary or cardiac disease, can demonstrate clubbing of the terminal phalanges, and have associated periosteal reaction and arthritis. These findings characterize the classic presentation of **hypertrophic osteoarthropathy (HOA)**. HOA can be primary (idiopathic), or secondary. Although rare, secondary HOA is more common in children, and is seen in children with chronic pulmonary disease (cystic fibrosis), congenital heart disease, gastrointestinal disease (malabsorption syndromes, biliary atresia, inflammatory bowel disease), and malignancies (nasopharyngeal sarcoma, osteosarcoma, Hodgkin disease). HOA may precede diagnosis of cardiopulmonary disease or malignancy. The pathogenesis of HOA is unknown; symptoms often improve if the underlying condition is treated successfully. HOA-related pain can be disabling, and in adults management with bisphosphonates has been reported. Evaluation of children presenting with HOA should include a chest radiograph to evaluate for pulmonary disease or intrathoracic mass.

PLANT THORN SYNOVITIS

A diagnosis of plant thorn synovitis should be considered in children with monoarticular arthritis nonresponsive to antiinflammatory therapy. Acute or chronic arthritis can occur after a plant thorn or other foreign object penetrates a joint. Unlike septic arthritis, children with plant thorn synovitis are commonly afebrile. The most common organism seen with plant thorn synovitis is *Pantoea agglomerans*, although cultures are often negative. The initial injury may be unknown or forgotten, making diagnosis difficult. Ultrasound or magnetic resonance imaging can be useful in identifying the foreign body. Removal of the foreign body via arthroscopy followed by an antibiotic course is the accepted therapy.

PIGMENTED VILLONODULAR SYNOVITIS

Proliferation of synovial tissue is seen in **pigmented villonodular synovitis** (PVNS). This proliferation is either localized or diffuse, and can affect the joint, tendon sheath or bursa. Macrophages and multinucleated giant cells with brownish hemosiderin are present histologically. It is unclear if the etiology of PVNS is inflammatory or neoplastic in nature. Although findings are not pathognomonic, MRI with contrast is a useful diagnostic tool where PVNS can be seen as a mass or bone erosion. Brown or bloody synovial fluid is seen with arthrocentesis, but the diagnosis is made by tissue biopsy. Surgical removal of the affected tissue is the therapeutic modality, and with diffuse disease, a total synovectomy is recommended.

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Infectious Diseases

PART XVII

Section 1

General Considerations

Chapter 170

Diagnostic Microbiology

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Laboratory evidence to support the diagnosis of an infectious disease may be based on 1 or more of the following: direct examination of specimens using microscopic or antigen detection techniques, isolation of microorganisms in culture, serologic testing, host gene expression patterns, and molecular detection of an organism, resistance determinant, or virulence factor. Additional important roles of the diagnostic microbiology lab are antimicrobial susceptibility testing to guide in the selection of the most appropriate antimicrobial therapy and supporting hospital infection prevention in the detection and characterization of pathogens associated with nosocomial infections.

SPECIMEN COLLECTION

The success of microbiology cultures, that is, isolation of a pathogen if present, is directly linked to specimen collection techniques. In general, this means collecting the correct specimen type for the disease or condition in question and promptly transporting the specimen to the laboratory for analysis. Although for some conditions swab specimens may be necessary, in general, a swab is a suboptimal specimen. A swab is only able to hold a very small amount of specimen (approximately 100 µL), and using a traditional swab, only a small fraction of organisms that are absorbed onto a swab will be released back into the culture. Flocked swabs, coupled with transport medium, improve organism recovery. However, when possible, fluid or tissue should be submitted to the laboratory for analysis. If anaerobic infection is suspected, the sample should be transported in appropriate medium to preserve viability of anaerobic bacteria. For the recovery of some organism types, such as viruses and *Neisseria gonorrhoeae*, specific transport media may be required. Considerations specific to the collection of blood cultures will be addressed in the blood culture section.

LABORATORY DIAGNOSIS OF BACTERIAL AND FUNGAL INFECTIONS

Although the scope and availability of molecular methods for detection of bacterial and fungal pathogens is increasing at a rapid pace, the state-of-the art for the diagnosis of many of these infections is dependent upon microscopic detection of organisms or cultivation of organisms on culture media.

Microscopy

The Gram stain is an extremely valuable diagnostic technique to provide rapid and inexpensive information regarding the absence or presence of inflammatory cells and organisms in clinical specimens. For some specimen types, the presence of inflammatory and epithelial cells is used to judge the suitability of a specimen for culture. For example, the presence of more than 10 epithelial cells per low-power field in a sputum specimen is highly suggestive of a specimen contaminated with oral secretions. In addition, a preliminary assessment of the etiologic agent can be made based upon the morphology (e.g., cocci vs rods) and stain reaction (e.g., Gram-positive isolates are purple; Gram-negative are red) of the microorganisms. However, a negative Gram stain does not rule out infection as 10^4 to 10^5 microorganisms per mL in the specimen are required for detection by this method.

In addition to the Gram stain, many other stains are used in microbiology, both to detect organisms and to help infer their identity. Table 170-1 provides an overview of the most commonly used stains.

Isolation and Identification

The approach to isolation of microorganisms in a clinical specimen will vary depending on the body site and pathogen suspected. For body sites that are usually sterile, such as cerebrospinal fluid, nutrient-rich media such as sheep blood agar and chocolate agar are used to aid in the recovery of fastidious pathogens. In contrast, stool specimens contain abundant amounts of commensal bacteria and thus to isolate pathogens, selective and differential media must be used. Selective media will inhibit the growth of some organisms to aid in isolation of suspect pathogens; differential media rely on growth characteristics or carbohydrate assimilation characteristics to impart a growth pattern that differentiates organisms. MacConkey agar supports growth of Gram-negative rods while suppressing Gram-positive organisms, and a color change in the media from clear to pink distinguishes lactose-fermenting organisms from other Gram-negative rods. Special media, such as Sabouraud dextrose agar and inhibitory mold agar, are used to recover fungi in clinical specimens. Many pathogens, including *Bartonella*, *Bordetella pertussis*, *Legionella*, *Mycoplasma*, and certain fungal pathogens such as *Malassezia furfur*, require specialized growth media or incubation conditions. Consultation with the laboratory is advised when these pathogens are suspected.

Once an organism is recovered in culture, additional testing will be performed to identify the isolate. Confirmation of microbial identity has classically been performed using phenotypic tests that rely on the phenotypic properties of an isolate. Some examples include carbohydrate assimilation patterns, indole production, and motility. However, these methods are not able to resolve all organisms to species level and require incubation time. In some instances, sequence based identification, for bacteria usually based on sequence analysis of the **bacterial 16S rRNA gene**, is used for organism identification (particularly organisms that are difficult to culture).

Matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) is a rapid and accurate technique that is based on generating a protein fingerprint of an organism and comparing that fingerprint to a library of known organisms to produce an identification. This method can identify bacteria or yeast growing in culture in a matter of minutes, and the consumable costs for these analyses are minimal.

Blood Culture

The performance of blood cultures is one of the most important functions of the clinical microbiology laboratory. Most blood cultures are performed by collecting blood into bottles of nutrient-rich broth to facilitate the growth of bacteria and yeast. Some blood culture media contain resins or other agents to help neutralize antibiotics that may be present in the patients' blood. Blood culture bottles are then incubated on an automated blood culture incubator that will monitor the blood culture bottle at regular intervals for evidence of growth. Once the instrument detects evidence of microbial growth, it will alarm to

Table 170-1 Stains Used for Microscopic Examination

TYPE OF STAIN	CLINICAL USE
Gram stain	Stains bacteria (with differentiation of Gram-positive and Gram-negative organisms), fungi, leukocytes, and epithelial cells
Potassium hydroxide (KOH)	A 10% solution dissolves cellular and organic debris and facilitates detection of fungal elements in clinical specimens
Calcofluor white stain	Nonspecific fluorochrome that binds to cellulose and chitin in fungal cell walls, can be combined with 10% KOH to dissolve cellular material
Ziehl-Neelsen and Kinyoun stains	Acid-fast stains, using basic carbolfuchsin, followed by acid–alcohol decolorization and methylene blue counterstaining Acid-fast organisms (e.g., *Mycobacterium*) resist decolorization and stain pink A weaker decolorizing agent is used for partially acid-fast organisms (e.g., *Nocardia, Cryptosporidium, Cyclospora, Isospora*)
Auramine-rhodamine stain	Acid-fast stain using fluorochromes that bind to mycolic acid in mycobacterial cell walls and resist acid–alcohol decolorization; usually performed directly on clinical specimens Acid-fast organisms stain orange-yellow against a black background
Acridine orange stain	Fluorescent dye that intercalates into DNA, used to aid in differentiation of organisms from debris during direct specimen examination, and also for detection of organisms that are not visible with Gram stain Bacteria and fungi stain orange, and background cellular material stains green
Lugol iodine stain	Added to wet preparations of fecal specimens for ova and parasites to enhance contrast of the internal structures (nuclei, glycogen vacuoles)
Wright and Giemsa stains	Primarily for detecting blood parasites (*Plasmodium, Babesia,* and *Leishmania*), detection of amoeba in preparations of cerebral spinal fluid, and fungi in tissues (yeasts, *Histoplasma*)
Trichrome stain	Stains stool specimens for identification of protozoa
Direct fluorescent-antibody stain	Used for direct detection of a variety of organisms in clinical specimens by using specific fluorescein-labeled antibodies (e.g., *Pneumocystis jiroveci,* many viruses)

alert the laboratory. Approximately 80% of blood cultures that will ultimately be positive are identified within the 1st 24 hr of incubation. A portion of broth from a blood culture bottle that has signaled positive is then Gram-stained and cultured onto appropriate growth media so that the organism can be isolated and identified. There are numerous pre-analytical variables that can influence the accuracy of blood culture results. In order to facilitate accurate interpretation of a positive blood culture, a minimum of 2 blood cultures drawn from different sites should be collected whenever possible. Growth of an organism that is part of the normal skin flora from a single blood culture raises concern that the isolate resulted from contamination of the culture.

To maximize detection of bloodstream infection, up to 4 blood cultures should be collected during a 24 hr period. Proper skin antisepsis is essential prior to blood collection. Chlorhexidine is frequently used for this purpose, but alcohol is also used. If blood is collected through an indwelling line, proper antisepsis prior to collection is also very important. The practice of obtaining blood for culture from intravascular catheters without accompanying peripheral venous blood cultures should be discouraged because it is difficult to determine the significance of coagulase-negative staphylococci and other skin flora or environmental organisms isolated from blood obtained from line cultures. Differential time to positivity of 2 hr or more between paired blood cultures drawn simultaneously from a catheter and peripheral vein is a useful indicator of catheter-related bloodstream infection.

The volume of blood collected is also an important factor in the recovery of bloodstream pathogens, especially as the number of organisms per milliliter of blood in sepsis may be low. The optimal amount of blood to collect from a pediatric patient varies depending on the weight of the child. The Clinical and Laboratory Standards Institute and Cumitech documents provide guidance on the amount of blood that is safe to collect from children of different sizes. Paired collection of aerobic and anaerobic blood culture bottles will result in maximal recovery of pathogens if present.

There are a number of rapid diagnostic assays that can be used directly on positive blood culture broth to identify pathogens commonly associated with bacteremia and some antimicrobial resistance determinants. Most of these rapid diagnostic assays are based on nucleic acid detection techniques. An example of this is the **Verigene system**, which can identify a number of streptococcal and enterococcal species, as well as *mecA* and *vanA* genes, in positive blood culture broth, in approximately 2 hr. MALDI-TOF MS can also be performed on blood culture broth that is positive for growth of microorganisms. These assays can help shorten the interval between a positive blood culture and definitive organism identification, with the goal of early optimization of antimicrobial therapy.

Detection of mycobacteria and some filamentous fungi (such as *Histoplasma capsulatum* and *Fusarium*) from the bloodstream is maximized using lysis-centrifugation techniques, such as the Isolator system (Wampole, Cranbury, NJ).

Cerebrospinal Fluid Culture

Cerebrospinal fluid (CSF) should be transported quickly to the laboratory and then cytocentrifuged to concentrate organisms for microscopic examination. CSF is routinely cultured on blood agar and chocolate agar, which support the growth of common pathogens causing meningitis. If tuberculosis is suspected, cultures for mycobacteria should be specifically requested. Culture of larger volumes of CSF (>5 mL) significantly improves yield of mycobacteria.

Historically, rapid antigen detection tests for bacterial pathogens such as *Haemophilus influenzae* type b and *Streptococcus pneumoniae* were used to attempt to detect organisms in CSF without the need for culture. These techniques have now been proven to lack sensitivity and, in some cases, specificity. It has been demonstrated that a cytospin Gram stain is as sensitive as bacterial antigen tests for detection of microorganisms in CSF. In contrast, the cryptococcal antigen test can be useful when cryptococcal meningitis is suspected. Historically, India Ink preparations were used to detect *Cryptococcus* in CSF,

but this method is insensitive compared to the antigen detection assay.

In the postvaccine era, the epidemiology of infectious meningitis is rapidly changing, and acute bacterial meningitis is now a relatively infrequent event in North America. Many CSF infections are associated with shunts or other hardware, and *Propionibacterium* and coagulase-negative staphylococci are the organisms most frequently isolated from shunt infections. The laboratory should include media to facilitate the growth of *Propionibacterium* in CSF specimens received from neurosurgery patients.

Urine Culture

Urine for culture (including colony count) can be obtained by collecting clean-voided midstream specimens, by catheterization, or by suprapubic aspiration. Urine samples collected by placing bags on the perineum are unacceptable for culture because samples are often contaminated. Rapid transport of urine to the laboratory (<2 hr) is imperative, and delay in transport or plating of specimens renders colony counts unreliable. Refrigeration or urine transport devices with boric acid preservative may be used when delay is unavoidable.

The specific colony counts used to define growth in a urine culture as "significant" are somewhat controversial and vary somewhat by laboratory. Urine obtained by suprapubic aspirate is normally sterile, and thus any organism growth is typically considered significant. Urine collected by catheterization is likely to reflect infection if there are $\geq 10^3$ to 10^4 organisms/mL. Clean-voided urine is considered abnormal if $\geq 10^4$ to 10^5 organisms/mL are present.

Genital Culture

N. gonorrhoeae is a fragile organism, and collection and transport in special medium is essential for efficient recovery. Selective agar, such as modified Thayer-Martin medium, should be used to enhance recovery of *N. gonorrhoeae* in clinical specimens, such as genital, anorectal, and pharyngeal swabs. Antimicrobial resistance is increasing in *N. gonorrhoeae,* although few clinical laboratories have the ability to perform antimicrobial susceptibility testing for this organism. In pediatric patients, the identification of an organism as *N. gonorrhoeae* should be confirmed using 2 independent methods.

Specimens for *Chlamydia trachomatis* culture are obtained by cotton-tipped, aluminum-shafted urethral swabs. Endocervical specimens, using swabs with aluminum or plastic shafts, should be collected by rubbing the swab vigorously against the endocervical wall to obtain as much cellular material as possible. *C. trachomatis* is an obligate intracellular organism and is cultured by inoculation into cell culture systems, followed by immunofluorescent staining with monoclonal antibody against the organism. Nonculture methods such as enzyme immunoassay (EIA) tests, direct immunofluorescent staining by monoclonal antibodies, and DNA amplification methods are widely used and are more cost-effective than culture.

Although **nucleic acid amplification assays (NAAT assays)** for *N. gonorrhoeae* and *C. trachomatis* are not FDA cleared for use in children, these assays are frequently used in this population to detect these organisms in urine specimens, endocervical and vaginal swabs, and penile swabs. The NAAT assays exhibit superior sensitivity compared to culture-based techniques. Some laboratories take the approach of confirming all NAAT-positive specimens with an alternative NAAT test that detects an alternative genetic target.

Throat and Respiratory Culture

Streptococcal pharyngitis and tonsillitis is a common diagnosis in pediatric patients; vigorous swabbing of the tonsillar area and posterior pharynx can be done to obtain a specimen for detection of group A streptococcus *(Streptococcus pyogenes).* Rapid antigen detection assays are frequently used when group A streptococcus pharyngitis is suspected. Negative rapid antigen assays should be confirmed using culture based techniques. NAAT assays for detection of group A streptococcus are also being used with increasing frequency. Most laboratories screen throat cultures exclusively for the presence of group A streptococci. However, large colony variants of group C and group G streptococci also cause pharyngitis, but are not associated with the same postinfectious sequelae attributed to group A streptococcus; laboratory practices for detecting and reporting group C and group G streptococci are variable and an area of controversy.

In addition to the detection of pathogenic streptococci, the clinical laboratory may query for diphtheria, gonococcal pharyngitis, or infection with *Arcanobacterium haemolyticum* in throat specimens. The laboratory should be notified if any of these pathogens are suspected to ensure that appropriate methods are used to recover these organisms if present.

Cultures for *Bordetella pertussis* can be obtained by aspiration or swabbing of the nasopharynx using a Dacron or calcium alginate swab. The aspirate or swab is inoculated onto special charcoal-blood (Regan-Lowe) or Bordet-Gengou media, although molecular assays are now frequently used for detection of *B. pertussis* in these specimens.

The cause of lower-respiratory-tract disease in children is frequently difficult to confirm microbiologically because of the challenge of obtaining adequate sputum specimens. Gram-stained smears of specimens should be performed to assess the adequacy of sputum samples; specimens with large numbers of epithelial cells (>10 per high-powered field) or with few neutrophils are unsuitable for culture, as there is a lack of correlation between upper respiratory tract flora and organisms causing lower-respiratory tract disease. For patients with cystic fibrosis, special media should be used to detect pathogens important in cystic fibrosis, such as *Burkholderia cepacia.*

Endotracheal aspirates from intubated patients may be useful if the Gram stain shows abundant neutrophils and bacteria, although pathogens recovered from such specimens might still reflect only contamination from the endotracheal tube or upper airway. Quantitative cultures of bronchoalveolar lavage fluid may be valuable for distinguishing upper respiratory tract contamination from lower tract disease.

If infection with *Legionella* is suspected, the laboratory should be alerted so that the specimen can be inoculated to special media (such as buffered charcoal yeast extract agar) to facilitate the recovery of this pathogen. The *Legionella* urinary antigen test is a sensitive and specific, noninvasive method for rapid detection of *Legionella pneumophila* serogroup 1.

The diagnosis of pulmonary tuberculosis in young children is best made by culture of early-morning gastric aspirates, obtained on 3 consecutive days. Sputum induction for obtaining specimens for mycobacterial culture has also proved useful in young children but requires skilled personnel and containment facilities to prevent exposure of healthcare workers. Cultures for *Mycobacterium tuberculosis* should be processed only in laboratories equipped with appropriate biologic safety cabinets and containment facilities. NAAT tests for detection of *M. tuberculosis* in smear-positive respiratory specimens are becoming more widely available.

Detection of Enteric Pathogens

In pediatric patients with diarrheal illnesses, culture of stool for enteric pathogens may be requested. A fresh stool specimen is preferred, but is not always possible to obtain. If there is an unavoidable delay in specimen transport, the specimens should be placed into an appropriate transport medium, such as Cary-Blair. Rectal swabs for enteric culture are also acceptable specimens if the swab is visibly soiled. In general, enteric cultures should be performed on specimens from outpatients or patients who have been hospitalized for fewer than 3 days, as nosocomial acquisition of an enteric pathogen is very unusual.

Stool specimens are typically plated on a series of selective and differential media to decrease the overgrowth of normal flora and recover pathogenic organisms if present. The specific pathogens queried vary by laboratory. Most laboratories in North America will routinely culture for *Salmonella*, *Shigella*, *Campylobacter,* and Shiga toxin–producing strains of *Escherichia coli*. The CDC recommends that all laboratories use an agar-based medium for recovery of *E. coli* O157 in addition to an assay for detection of Shiga toxin production for all specimens submitted for enteric culture. Practices surrounding the routine culture for *Yersinia enterocolitica*, *Vibrio cholerae*, *Edwardsiella*, *Aeromonas,* and *Plesiomonas* will vary with local epidemiology, and the

laboratory should always be notified if one of these pathogens is specifically suspected.

Clostridium difficile is an important cause of antibiotic-associated diarrhea. *C. difficile* was long characterized as a nosocomial pathogen of older adults, but community-associated disease is emerging and the incidence and severity of *C. difficile* infection in children is increasing. Although for many years laboratories relied on EIAs for detection of *C. difficile* toxins, these assays lack adequate sensitivity. Laboratories use nucleic acid detection methods to aid in the diagnosis of *C. difficile*. Testing for *C. difficile* in children <1 yr of age should be discouraged as a result of the high incidence of colonization in this patient population.

Viruses are an important cause of gastroenteritis in pediatric patients. Methods for viral detection will vary but may include antigen detection (e.g., for rotavirus or adenovirus 40/41) or nucleic acid detection methods (such as for norovirus).

In North America, the burden of parasitic gastroenteritis is low. Complete microscopic exams for ova and parasite detection in stool samples is usually of low yield, and antigen detection assays for *Cryptosporidium* and *Giardia*, the most commonly encountered agents, are a sensitive and cost-effective method for detection of these pathogens.

Multiplex nucleic acid detection tests for simultaneous detection of a dozen or more enteric pathogens, including bacteria, viruses, and parasites are emerging. It is not completely clear how these assays will be deployed by clinical laboratories.

Culture of Other Fluids and Tissues

Abscesses, wounds, pleural fluid, peritoneal fluid, joint fluid, and other purulent fluids are cultured onto solid agar and, in some cases, broth media. Whenever possible, fluid rather than swabs from infected sites should be sent to the laboratory, because culture of a larger volume of fluid can detect organisms present in low concentration. Anaerobic organisms are involved in many abdominal and wound abscesses. These specimens should be collected and transported to the laboratory rapidly in anaerobic transport tubes.

Although *Staphylococcus aureus* is the most common cause of bone and joint infections, *Kingella kingae* is an important cause of septic arthritis in children, especially in children <4 yr of age. The detection of *K. kingae* is maximized by inoculation of synovial fluid into blood culture broth in addition to plating on solid medium, as well as by molecular detection of *K. kingae* in specimens from young patients with suspected septic arthritis.

Screening Cultures

Clinical laboratories may perform surveillance cultures for specific pathogens either to assist infection control in identifying patients requiring contact isolation or for outbreak investigation. Screening cultures for detection of methicillin-resistant *S. aureus* or vancomycin-resistant enterococci may be routinely performed in certain patient populations. In addition, hospitals with carbapenem-resistant *Enterobacteriaceae* may screen patients for rectal carriage of these organisms. Chromogenic media are frequently used for this purpose. These media contain proprietary compounds to select for the agent of interest and result in growth of colored colonies to identify pathogens of interest.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Antimicrobial susceptibility tests are generally performed on organisms of clinical significance for which standards and interpretive criteria for susceptibility testing exist. In North America, most laboratories use commercial, automated systems for susceptibility testing. The output from these systems is a minimum inhibitory concentration (MIC) value and interpretation of that value as susceptible, intermediate, or resistant. The next most common technique is Kirby-Bauer disk diffusion, in which a standardized inoculum of the organism is seeded onto an agar plate. Antibiotic-impregnated filter paper disks are then placed on the agar surface. After overnight incubation, the zone of inhibition of bacterial growth around each disk is measured and compared with nationally determined standards for susceptibility or resistance.

A less-commonly used technique is broth or microbroth dilution testing. A standard concentration of a microorganism is inoculated into serially diluted concentrations of antibiotic, and the MIC in μg/mL, the lowest concentration of antibiotic required to inhibit growth of the microorganism, is determined. The E-test is a hybrid of disk diffusion and broth dilution and can be used to determine the MIC of individual antibiotics on an agar plate. It uses a paper strip impregnated with a known continuous concentration gradient of antibiotic that diffuses across the agar surface, inhibiting microbial growth in an elliptic zone. The MIC is read off the printed strip at the point at which the zone intersects the strip. Major advantages of the E-test are reliable interpretation, reproducibility, and applicability to organisms that require special media or growth conditions.

In addition to providing data to guide the treatment of individual patients, laboratories use aggregate susceptibility testing data to generate institution specific antibiogram reports. These reports summarize susceptibility trends for common organisms and can be used to guide empirical therapy prior to the availability of specific susceptibility testing results.

Antimicrobial susceptibility patterns are rapidly changing as microbes evolve new resistance mechanisms. Recommendations for performance standards for antimicrobial susceptibility tests and their interpretation are regularly updated by the Clinical and Laboratory Standards Institute.

FUNGAL CULTURES

Special growth media is used to recover fungi, both yeasts and molds, in clinical specimens. As most fungi prefer reduced growth temperatures, and some species grow slowly, fungal cultures are incubated at 30°C (86°F) for 4 wk.

Most yeasts are identified using methods similar to those used for bacteria. In contrast, the identification of filamentous fungi has not changed in nearly a century. The laboratory takes into consideration the growth rate, color, and colony characteristics of an isolate and then prepares the specimen in lactophenol alanine blue for microscopic evaluation. These features in aggregate are used to identify the isolate. In some cases, DNA sequencing is used for fungal identification and MALDI-TOF MS is also emerging for identification of filamentous fungi. All manipulations of filamentous fungi should take place in the biologic safety cabinet to avoid infecting laboratory personnel and prevent laboratory contamination.

Antigen detection assays are also available for some fungal pathogens such as *Cryptococcus neoformans* and *H. capsulatum*. Assays to detect galactomannan, a molecule found in the cell wall of *Aspergillus*, are commercially available and increasingly used to assist in making the diagnosis of invasive aspergillosis in immunocompromised populations.

POINT-OF-CARE DIAGNOSTICS

Some assays to detect infections may be performed in the office setting, provided the site is certified as meeting appropriate quality-assurance standards specified by the Clinical Laboratory Improvement Amendments (CLIA) of 1988. These include procedures listed under the category of "provider-performed microscopy" such as wet mounts, potassium hydroxide preparations, pinworm examinations, and urinalysis.

Many pediatric offices perform rapid antigen testing for detection of group A streptococcal pharyngitis. The sensitivity of point of case testing is dependent upon specimen collection technique, the type of kit used and on the concentration of streptococci present in the sample. However, in light of the fact that up to 30% of group A streptococcal rapid antigen tests are falsely negative, it is recommended that all negative results should be confirmed by culture.

Office laboratories licensed to perform waived tests are limited to performing these tests and avoid having to undergo inspections and proficiency testing, although they are still subject to CLIA certification requirements specific to these tests. Gram staining, culture inoculation, and isolation of bacteria are considered moderately to highly complex tests under CLIA specifications. Any office laboratory performing

Gram stains or cultures must comply with the same requirements and inspections for quality assurance, proficiency testing, and personnel requirements as fully licensed microbiology laboratories.

LABORATORY DETECTION OF PARASITIC INFECTIONS

Most parasites are detected by microscopic examination of clinical specimens. *Plasmodium* and *Babesia* can be detected in stained blood smears, *Leishmania* can be detected in stained bone marrow smears, and helminth eggs, *Entamoeba histolytica,* and *Giardia lamblia* can be detected in stained fecal smears (see Table 170-1). Serologic tests are important in documenting exposure to certain parasites that are not typically found in stool or blood, and thus are difficult to demonstrate in clinical specimens, such as *Trichinella*.

Pinworm is a relatively common parasitic infection in pediatric patients. A diagnosis of pinworm can be made by evaluating a "pinworm prep." The best time to obtain this specimen is first thing in the morning, before the patient has bathed or had a bowel movement. A piece of clear scotch tape is pressed onto the perianal region of the patient and then the tape is applied to a clear microscope slide. The slide is then examined for recovery of pinworm eggs or worms.

Fecal specimens should not be contaminated with water or urine, because water can contain free-living organisms that can be confused with human parasites, and urine can destroy motile organisms. Mineral oil, barium, and bismuth interfere with the detection of parasites, and specimen collection should be delayed for 7-10 days after ingestion of these substances. Because *Giardia* and many worm eggs are shed intermittently into feces, a minimum of 3 specimens on nonconsecutive days are required to adequately exclude the diagnosis of an enteric parasite. Because many protozoan parasites are easily destroyed, collection kits with appropriate stool preservatives (commonly a 2-vial system with formalin and polyvinyl alcohol fixatives) should be used if delay between time of specimen collection and transport to the laboratory is anticipated.

Ova and parasite examination of fecal specimens includes a wet mount (to detect motile organisms if fresh stool is received), concentration (to improve yield), and permanent staining, such as trichrome, for microscopic examination. *Cryptosporidium*, *Cyclospora,* and *Isospora* are detected by modified acid-fast stain, and microsporidia by a modification of the trichrome stain. In addition, *Cyclospora* and *Isospora* autofluoresce under UV microscopy. The laboratory should be alerted if these parasites are suspected. Detection of certain intestinal parasites, especially *Giardia* and *Cryptosporidium*, can be simplified by using antigen detection tests.

Amebic encephalitis, caused by *Acanthamoeba*, *Balamuthia*, or *Naegleria*, is a rare but devastating and rapidly progressive disease. Special laboratory stains and procedures are required to detect these organisms. The laboratory should be notified if this infection is suspected.

Rapid antigen detection tests for *Plasmodium* species are available. The sensitivity and specificity of these tests vary depending on the burden of parasite in the sample, and the specific *Plasmodium* species. In general, these tests are most sensitive for detecting *Plasmodium falciparum* and least sensitive for detecting *Plasmodium malariae*. These tests are particularly useful for laboratories lacking personnel trained in evaluation of thick and thin smears for malaria, or to provide a rapid preliminary result while awaiting microscopy. All positive and negative rapid malaria assays should be confirmed with blood smear analysis.

Trichomonas vaginalis is a sexually transmitted protozoan parasite that can also be transmitted on household fomites. Infected individuals may be asymptomatic or may have mild inflammation or severe inflammation and discomfort. *Trichomonas* may be detected using a wet mount, but this method is insensitive. Rapid antigen assays are available. Culture-based detection or nucleic acid amplification techniques are the most sensitive way to make the diagnosis.

SEROLOGIC DIAGNOSIS

Serologic tests are primarily used in the diagnosis of infectious agents that are difficult to culture in vitro or detect by direct examination, such as *Bartonella, Francisella, Legionella, Borrelia* (Lyme disease), *Treponema pallidum, Mycoplasma, Rickettsia,* some viruses (HIV, Epstein-Barr virus [EBV], hepatitis A virus), and parasites *(Toxoplasma, Trichinella).*

Antibody tests may be specific for immunoglobulin (Ig) G or IgM or can measure antibody response regardless of immunoglobulin class. In very general terms, the IgM response occurs earlier in the illness, generally peaking at 7-10 days after infection, and usually disappears within a few weeks, but for some infections (e.g., hepatitis A, West Nile Virus) it can persist for months. The IgG response peaks at 4-6 wk and often persists for life. Because the IgM response is transient, the presence of IgM antibody in most cases correlates with recent infection. Methods for IgM antibody detection are difficult to standardize, however, and false-positive results commonly occur with some tests. The presence of IgG antibody can indicate new seroconversion or past exposure to the pathogen. To confirm a new infection using IgG testing, it is essential to demonstrate either seroconversion or a rising IgG titer. A 4-fold increase in a convalescent titer obtained 3-4 wk following the acute titer is considered diagnostic in most situations. In neonates, interpretation of serologic tests is very difficult because of passive transfer of maternal IgG that can persist for 6-18 mo after birth.

Context is extremely important in the interpretation of serologic findings. Important considerations are the ability of the host to mount an immune response, the background rate of seropositivity (especially for IgG detection assays), and, for some diseases, the antibody titer. In addition, interpretation of some serologic assays, such as those used to diagnose Lyme disease, are problematic because of lack of specificity of the immunoassays. A confirmatory immunoblot (Western blot) is required for all positive and equivocal EIA results for Lyme disease.

LABORATORY DIAGNOSIS OF VIRAL INFECTIONS

Viral diseases are extremely important in pediatrics, and diagnostic virology has long been important to pediatric practice, especially in the inpatient setting.

Specimens

Specimens for viral diagnosis are selected on the basis of knowledge of the site that is most likely to yield the suspected pathogen. When evaluating patients with acute viral infections, specimens should be collected early in the course of infection when viral shedding tends to be maximal. Swabs should be rubbed vigorously against mucosal or skin surfaces to obtain as much cellular material as possible and sent in viral transport media that contain antibiotics to inhibit bacterial growth. Rectal swabs should contain visible fecal material. "Flocked" swabs have been shown to provide more material for the laboratory with consequent improvement in the performance of diagnostic tests. Fluids and respiratory secretions should be collected in sterile containers and promptly delivered to the laboratory. All specimens should be transported on ice if delay is anticipated. Freezing specimens, especially at −20°C (−4°F), can result in a significant decrease in culture sensitivity. Consultation with the laboratory is recommended, because some commercial diagnostic test kits used by laboratories may require specific collection devices.

Laboratory diagnosis of viral infections may be by electron microscopy, antigen detection, virus isolation in culture, serologic testing, or molecular techniques to detect viral nucleic acids. In the past few years, molecular tests have emerged as the primary means for detecting viral infections, with some virology laboratories abandoning the use of viral culture altogether. Serologic testing still has a role, especially for arboviral infections such as West Nile, acute EBV infections, HIV, hepatitides A to C, and diseases of childhood such as measles, rubella, and mumps. Serology is also uniquely useful for defining immunity to specific viral infections.

Antigen Detection Tests

Immunofluorescent-antibody (IFA) techniques or other methods, such as EIA, that use antibodies to detect viral antigens directly in clinical specimens to permit rapid identification of viruses, were the mainstay

of the diagnosis of respiratory viral infections but are now being replaced by molecular tests. Smears of cellular material from respiratory secretions stained by immunologic reagents can identify the antigens of respiratory syncytial virus (RSV), adenovirus, influenza A and B viruses, parainfluenza virus types 1-3, and human metapneumovirus within 2-3 hr after the specimen is received. The sensitivity of IFA staining for RSV exceeds that of culture in many laboratories. For influenzas A and B, IFA sensitivity approaches that of culture, whereas for parainfluenza viruses and adenoviruses, sensitivity of IFA is lower. Novel influenza strains, such as the one responsible for H1N1 pandemic influenza, may be poorly detected by IFA and other antigen detection techniques and require molecular tests for optimal sensitivity.

Sensitive IFA staining techniques are also commercially available for identifying varicella-zoster virus and herpes simplex virus (HSV). These specific methods have supplanted the Tzanck smear for multinucleated giant cells characteristic of varicella-zoster virus or HSV infections. A method for detecting cytomegalovirus (CMV) pp65 antigen in blood of immunocompromised patients is also available but is being replaced by molecular testing. IFA is not useful for detecting viruses in specimens that do not contain an adequate number of infected cells.

Rapid antigen tests usually based on lateral flow immunochromatography have been approved by the FDA for detection of influenzas A and B and RSV. Some of these tests have "waived" status under CLIA, meaning that they can be performed by personnel who are not trained laboratory technologists, with relatively little formal quality control other than controls that are incorporated into the test devices. Some require as little as 10 min to perform. Consequently, these tests can be performed in a doctor's office or an emergency unit. Sensitivity in children is higher than in adults and is in the range of 50-80%. Rapid antigen tests can be useful in managing patients with acute respiratory infections, provided the caregiver keeps in mind that a negative test does not rule out the diagnosis of influenza or RSV. Positive tests that are properly read tend to be reliable, but it is also important to keep in mind that the presence of a virus such as influenza or RSV does not rule out the presence of concomitant bacterial infection.

In addition to their role in respiratory virus infections, antigen-detection EIA tests are commonly used for the diagnosis of viruses that are difficult to culture, such as rotavirus, enteric adenovirus, and hepatitis B virus. The detection of the p24 antigen of HIV along with HIV antibodies is included in "fourth-generation" EIA tests used for the diagnosis of HIV.

Viral Culture

Viruses require living cells for propagation; the cells used most often are human- or animal-derived tissue culture monolayers, such as human embryonic lung fibroblasts or monkey kidney cells. Historically, in vivo methods such as inoculation of suckling mice were also used, but are rarely used today. Viral growth in susceptible cell culture is usually accomplished by detecting characteristic cytopathic effect that is visible by light microscopy under low magnification in the cultured cells. For some viruses (e.g., influenza, parainfluenza, and mumps viruses), this method is supplemented by hemadsorption, based on the production of virally encoded hemagglutinins on infected cell membranes that cause adherence of erythrocytes to infected cells. The most reliable confirmatory method for viral detection in cell culture involves fluorescein- or enzyme-labeled monoclonal antibody staining of infected cell monolayers. An important technical improvement in respiratory viral cultures is the development of cell culture systems that include more than 1 type of cell (R-Mix, Diagnostic Hybrids/Quidel, San Diego, CA) and employ IFA staining for virus detection. This system provides results in 16-40 hr from the time the specimen is received in the laboratory, compared to 2-10 days for conventional cultures. Cell culture methods are now being steadily replaced by molecular tests, which are faster, may be more sensitive, and have the potential to detect viruses that do not grow readily in cell cultures.

Molecular Diagnostics

Most molecular tests to detect viruses use the polymerase chain reaction (PCR) and other nucleic acid amplification tests. The first application of PCR to become widely accepted was a test to detect HSV DNA in CSF in patients with possible HSV encephalitis. The first FDA-cleared test for this purpose was approved in 2014. Many laboratories still use laboratory-developed tests, whose performance characteristics must be validated as specified by CLIA. The consequence of this situation is that testing is not standardized and the performance characteristics of this testing (sensitivity and specificity) may vary from laboratory to laboratory. At its best, PCR has sensitivity and specificity greater than 95% for HSV encephalitis. PCR is also increasingly used to diagnose mucocutaneous HSV and varicella-zoster virus infections. This testing is more sensitive than virus culture and provides a more rapid turnaround time.

An FDA-cleared test for enterovirus in CSF (GeneXpert, Cepheid, Sunnyvale, CA) provides sensitive detection of enteroviruses with a performance time of approximately 3 hr. Because this testing is simple to perform, some hospital laboratories are able to offer testing at all times, thus maximizing the clinical utility of the test. The parechoviruses, which may cause illnesses similar to those caused by enteroviruses, especially in infants <6 mo of age, must be detected by separate molecular assays. No parechovirus assays are currently approved by the FDA.

FDA-cleared molecular tests for respiratory viruses are increasingly replacing antigen detection and culture. Several FDA-cleared multiplex molecular tests are available for detection of influenza A and B and RSV. As of 2014, 4 multiplex tests that detect larger numbers of respiratory viruses are also available (Table 170-2). Viruses detected by these tests include influenza A and B, RSV, parainfluenza 1-4, human metapneumovirus, adenovirus, rhinovirus/enterovirus, and coronaviruses OC43, 229E, NL63, and OC43. The performance of each test for each of the viral targets must be approved or cleared by the FDA, so the tests vary among one another in the specific virus targets for which they have achieved FDA approval/clearance (Table 170-2). In addition, 1 of the tests (FilmArray) is also cleared for the detection of the bacterial agents *B. pertussis, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae*. This test is also notable because the performance time is only

Table 170-2 Multiplex Assays for the Detection of Respiratory Viruses

TEST	MANUFACTURER	VIRUSES DETECTED*
xTag	Luminex, Austin, TX	Flu A, AH1, AH3, Flu B, RSV, PIV 1-3, Ad B/C/E, HMPV, rhinovirus/enterovirus†
FAST	Luminex, Austin, TX	Flu A, AH1, AH3, Flu B, RSV, Ad B/C/E, HMPV, rhinovirus/enterovirus†
FilmArray	Biofire, Salt Lake City, UT	Flu A, AH1, AH1(2009), AH3, Flu B, RSV, PIV 1-4, rhinovirus/enterovirus†, HMPV, adenovirus, coronaviruses OC43, 229E, NL63, HKU1
eSensor	GenMark	Flu A, AH1, AH1(2009), AH3, Flu B, RSV, PIV 1-3, HMPV, adenovirus B/C/E, rhinovirus

*Cleared by the FDA as of July, 2013. Other versions that detect additional viruses are available outside of the United States.
†Detects rhinoviruses and enteroviruses but does not distinguish between them.
Ad, adenovirus; AH1, influenza A, hemagglutinin type 1; AH3, influenza A, hemagglutinin type 3; flu A, influenza A; flu B, influenza B; HMPV, human metapneumovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

approximately 1 hr, permitting very rapid turnaround time. A multiplex assay for the detection of viruses (norovirus and rotavirus), as well as important bacterial and parasitic pathogens (xTAG Gastrointestinal Panel, Luminex, Austin, TX), has been cleared by the FDA and similar tests are being developed by numerous other companies.

Another important area of application of molecular testing is the detection of viruses in the blood. FDA-approved assays to detect HIV and hepatitis C RNAs are essential for the management of these infections, including the prevention of transmission from mother to infant. Hepatitis B molecular testing is also increasingly used. In addition, molecular testing is now widely used for viruses that cause systemic disease in immunocompromised patients, especially CMV, EBV, HSV, the BK polyomavirus, and adenovirus. For these viruses, as well as for HIV and the hepatitisviruses, quantitative testing is required. An FDA-approved PCR assay for the quantitative measurement of CMV DNA in plasma is now available. In addition, international standards for CMV have been developed. This is important because it makes possible better comparability among different quantitative CMV assays if they are each referenced to the international standard. Testing for the other viruses must be carried out using laboratory-developed tests, sometimes with the use of analyte-specific reagents, a class of reagents that are regulated by the FDA although not incorporated into complete diagnostic test kits.

Laboratory-developed PCR and other molecular assays are used by some laboratories for numerous other viruses, including parvovirus B19; human herpesvirus 6; mumps, measles, and rubella viruses; and the JC polyomavirus.

Host gene expression patterns in whole blood have been used to differentiate viral from bacterial infections. This microarray-based assay may rapidly identify a viral or bacterial profile of host gene expression reprise, thus greatly shortening the time to diagnosis and potentially avoiding inappropriate treatment while suggesting indicated therapies.

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Chapter 171

The Microbiome and Pediatric Health

Patrick C. Seed

From the time of birth, the human infant is exposed to a myriad of microbes found on the mother and in the surrounding environment. Microbes rapidly form assemblages across exposed areas of the body, including the skin and enteral tract. The microbial communities are called the **microbiota** and make a substantial impact on short- and long-term physiology, including immunologic and metabolic development and function. Together the number of body-associated bacterial cells is estimated to be 10 times greater than the number of human cells in the body. In aggregate, the totality of the microbes, including their microbial genes and environmental interactions, constitute the microbiome, and the microbial genes in the human microbiome are estimated to exceed the number of human genes by at least 100-fold, together making a macroorganism with an inseparable collective physiology. Current evidence indicates that the microbiome evolves over the life span to influence health and disease.

MEASURING THE MICROBIOME

Prior knowledge of microbes on and around the human body was based on specific methods to cultivate organisms. Molecular technologies have revolutionized the identification of poorly cultivatable microbes, rare microbes, and microbes in complex communities like those associated with the human body (Fig. 171-1). The development of the polymerase chain reaction and the availability of modern nucleic acid sequencing have improved the sensitivity of detection of many organisms and have also resulted in the discovery of new organisms. Modern sequencing technologies, so-called next-generation sequencing platforms, allow sequencing in high volume and depth, with millions of sequences obtained from a single biologic sample. Three major approaches have utilized next-generation sequencing to understand the composition, diversity, and activity of the microbiome: (1) sequencing species-specific regions of genomes such as ribosomal RNA-encoding tracks and intergenic regions, (2) total DNA sequencing and assembly of sequence fragments into large genome pieces termed *metagenomics*, and (3) RNA transcript sequencing to decipher the composition and, as a surrogate for functional activity, the transcriptional activity of a microbiome. New bioinformatics tools have allowed the analysis and comparison of the large datasets arising from these methods.

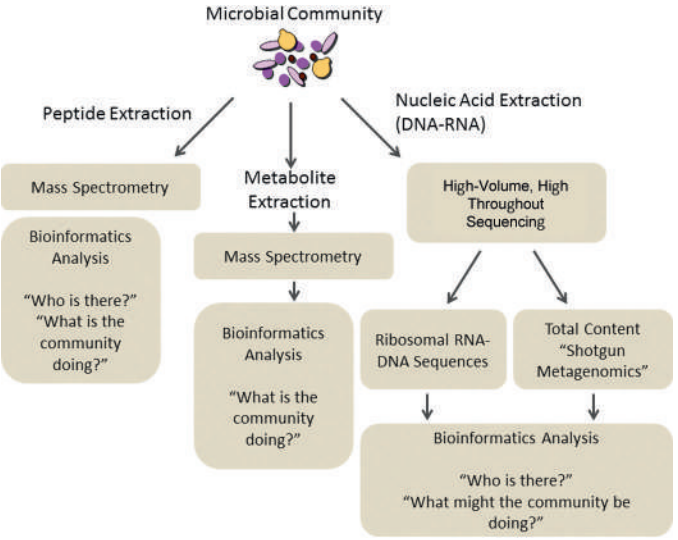

Figure 171-1 Common molecular methodologies for identifying the components and the functions of complex microbial communities.

Two additional approaches to measure the microbiome have been rapidly developing as well. First, large-scale measurements of the peptide composition of the microbiota, called **proteomics**, have been increasingly used to describe the activity of a microbiome sample, as peptides provide information about the composition and function of a microbiome. Second, in a complementary approach called **metabolomics**, microbiome-derived metabolites are measured using advanced mass spectrometry techniques. Together, proteomics and metabolomics better describe the activity of a microbiome than the nucleotide-sequencing approaches; however, at this point in time, they provide less depth of resolution and specificity of the composition of a microbiome.

Despite the power of these new methodologies to interrogate the microbiome, they do not yet replace cultivation of microbes in many clinical circumstances. Cultivation of organisms still represents the most practical means to differentiate potential pathogenic species from more benign species and to provide key information such as susceptibility to antimicrobials.

EARLY-CHILDHOOD DEVELOPMENT OF THE MICROBIOME

In healthy, uncomplicated term deliveries, infants are believed to be sterile until birth. The rupture of the fetal membranes and subsequent delivery is likely the first major exposure to colonizing microbes. Exceptions may be prematurity as a complication of infection of the

fetal membranes and either subclinical or clinical chorioamnionitis, where molecular analyses suggest that in utero exposure to microbes is common. Mode of delivery has a major influence on the early-life microbiome, with vaginally delivered infants becoming acutely colonized with intestinal organisms that reflect the mother's vaginal tract and infants delivered by cesarian section becoming colonized with intestinal organisms reflective of the maternal skin.

In the term infant delivered by vaginal delivery, the first intestinal microbes, so-called pioneering organisms, include aerobic organisms such as Enterobacteriaceae (e.g., *E. coli*), Streptococcaceae, and Staphylococcaceae. Some infants have anaerobes in their early colonizing microbiota, including Clostridiaceae and Bacteroidaceae. However, anaerobes are uncommon, likely because of the aerobic environment of the neonatal intestinal tract, the underdeveloped mucus layer, and relatively high intestinal motility. Exclusive breastfeeding has been reported to result in high levels of bifidobacteria and *Lactobacillus* in the week following the start of feeding. These probiotic organisms have unique capacities to exclude would-be pathogens from colonization by sequestering nutrients and producing antimicrobial factors while stimulating the intestinal epithelium to tighten cellular junctions and express antimicrobial peptides. However, these genera have been notably deficient from some breastfed infant cohorts, particularly within the United States.

The premature infant is more likely to be delivered by cesarian section and will often be colonized with skin-related organisms such as coagulase-negative staphylococci, similar to the term infant delivered through a similar mode of delivery. However, the premature infant may fail to progress through the same stages of expansion and diversification of the microbiome over the 1st wk to mo of life as the term infant. The factors related to the delayed maturation are not fully clear but are predictably related to delayed or limited enteral feeding, normal environmental exposure to the household environment, and exposure to medical interventions such as antimicrobials.

The most significant shift in the intestinal microbiota appears to occur after weaning and the introduction of solid foods. As the infant transitions from breast milk to a solid food diet containing complex plant-derived polysaccharides, the microbiota begins to reshape progressively into a more mature composition beginning to resemble the adult microbiota. A partial transition occurs from aerobic and facultative anaerobes such as streptococci and coliform enterics like *E. coli* to more strict anaerobes such as *Bacteroides* spp.; however, more studies are required in large numbers of children to fully understand the developmental stages of maturation and the likeness to the mature, healthy adult state.

Currently, development of the oral and skin microbiomes in childhood is not well understood. Past studies revealed remarkable diversity of the composition of the microbiota within the oral cavity in the presence of full adult dentition, with an estimated 1,000 bacterial species. Even with oral health, there is substantial diversity in the gingiva of different types of teeth, so-called geodiversity, and the diversity changes dramatically with the development of oral disease such as periodontitis. However, the oral microbiome predentition, during tooth eruption and during the transition from primary to secondary dentition is currently poorly understood. Furthermore, the placement and removal of oral hardware for orthodontics is common in childhood and may produce important alterations in the microbiome of the oral cavity.

The adult skin microbiome displays a high degree of geodiversity—differences in composition depending on site and local physiology with major differences in dry and wet skin sites. However, the linkage between skin development in childhood and maturation of the skin microbiome remains a key subject of future study.

Social structure and family interactions likely play a large role in the development of the early life microbiome. Breast milk feeding provides a microbiologic link between mothers and infants, including transmission of probiotic-like organisms such as lactobacilli and bifidobacteria, each of which may have some protective effects including protection against diarrheal diseases and atopy. Pediatricians have long been aware of the infectious disease risks and benefits of daycare attendance, with examples of shared pneumococcal strains producing otitis media and outbreaks of respiratory syncytial virus infection and associations with reduced atopy, allergy, and possibly asthma. Family contacts are risks for acquisition of methicillin-resistant *S. aureus* and subsequent disease. Recent studies demonstrate that at least parts of the human microbiome are transmitted between household individuals and domesticated pets such as dogs and cats. For instance, family members share the same strains of *E. coli* known to produce urinary tract infections in 1 of the household members. There may be differences in the oral microbiota among infants for whom the parents did and did not use the practice of pacifier sucking for cleaning. Thus, development of the microbiome during childhood is a complex process that is just beginning to be understood.

THE MICROBIOME AND PHYSIOLOGIC DEVELOPMENT

The microbiome has increasingly complex roles in the development of mammalian physiology (Fig. 171-2). These include the development of the enteral tract, the immunologic system, the hematologic system, the metabolic-endocrine system, and the neurologic system. The details of how the microbiome contributes to these developmental processes in humans are still under intense investigation; however, modeling in other mammalian systems predicts that the microbiome will have a critical role.

Microbiome and Metabolism

Soon after entry into the physical world, the mammalian enteral tract is colonized and the interaction of early pioneering microbes in the enteral tract stimulates the development of the intestinal mucosa. In neonatal and juvenile animal models, delayed or absent intestinal colonization results in incomplete development of the epithelium, flattening of the intestinal crypts, loss of vasculature, and severely reduced enzymatic function, including alkaline phosphatase and glucosidases.

The enteric microbiota has a large number of roles in the physiology of the intestinal tract. In addition to its function in mucosal and systemic immune development as well as development and regeneration of the epithelium, the microbiota plays a role in key aspects of metabolism: (1) the digestion of otherwise indigestible plant polysaccharides; (2) production of vitamins and cofactors; (3) metabolism of xenobiotics, including clinically relevant drugs; and (4) stimulation of local and systemic metabolism, including lipid storage. Germ-free animals lacking the enteric microbiota have limited nutrient extraction and have a failure to thrive phenotype.

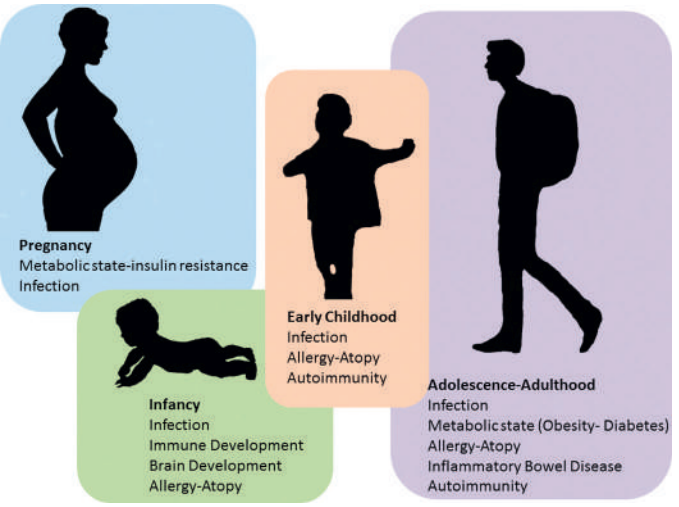

Figure 171-2 Physiologic and pathologic roles of the microbiome relevant to pediatrics. The human microbiome has an impact on health and development from pregnancy through to adulthood, including infection and non–infection-related processes.

Mice born into a sterile environment have been colonized with human fecal microbial communities. Feeding of "humanized" mice diets with and without polysaccharides, akin to the weaning to solid food transition, results in dramatic alterations in central metabolites. "Humanized mice" transitioned from a polysaccharide-rich, low-fat diet to a more "Westernized" diet high in fat and monosaccharides undergo a blossoming of the phyla Actinobacteria and Firmicutes in the enteric microbiota with a commensurate reduction in Bacteroidetes, similar to observations of increased Firmicutes and reduced Bacteroidetes in obesity.

Common patterns of mature enteric microbiota community composition and predicted function may exist among humans. Sequencing of the fecal microbes from adults across multiple nations revealed 3 common patterns of microbial community compositions, called enterotypes. Significant increases in the proportions of *Bacteroides, Prevotella,* and *Ruminococcus* were found as sentinels of the different enterotypes, and these enterotypes could be identified in individuals from multiple continents, including North America, Europe, and Asia. The different enterotypes among infants and children are not well defined, with the possibility that mature, stable enterotypes form in the early postweaning period or after infancy. Breast milk and formula feeding enterotypes have been described, with notable enrichment of enteric Gram-negative bacteria such as *E. coli* and anaerobic *Clostridia* spp. among the formula-fed infants.

Microbiome, Inflammation, and Immunity

The organisms that compose the microbiome are critical for early immune programming, the development of immune tolerance, and overall maintenance of immune set points. Cells produce a variety of receptors to recognize microbial ligands, in a process called *pattern recognition*. In turn, microbes produce intentional and unintentional stimulation of those cellular receptors to activate and repress inflammatory pathways. Classic examples of such regulatory interactions include peptidoglycan on bacteria binding to Toll-like receptor 2 (in complex with Toll-like receptor 3 and Toll-like receptor 6), lipopolysaccharide of Gram-negative bacteria binding to Toll-like receptor 4, and glucans of fungi binding to the dectin receptor. The results of these receptor interactions include the production of chemokines and cytokines, cell differentiation and development, alteration in metabolism, and stimulation of cell death and survival programs, all contingent on the type of cell, the state of the cell, and the magnitude of stimulation.

Microbial stimulation of these microbial recognition systems is so critical in development that animals raised in the absence of microbes have diminished innate immune responses such as antimicrobial peptides at mucosal surfaces, dysregulated proinflammatory and immunologic tolerance responses, and reduced T- and B-cell populations. Following restoration of normal colonization weeks after being sterile, animals have long-term aberrant cytokine responses with hyperactive proinflammatory responses to stimuli, demonstrating the long-lasting consequences of altering early microbial acquisition. Different early life colonization patterns also correlate with long-term immune development. In a Scandinavian study, children with persistent early life *E. coli* colonization had higher sustained memory B-cell (CD3+CD20+CD27+) levels by 1.5 yr of life compared to children with lower levels of *E. coli* colonization, even despite abundant colonization with prototypical probiotic bacteria *Lactobacillus* spp.

Microbiome-Neurobiologic Connections

Emerging studies are demonstrating a gut–brain axis that may be altered by the composition and activity of the enteric microbiome. Investigations in animal models have shown that the microbiome alters the hypothalamic-pituitary-adrenal system. Germ-free mice have exaggerated stress–anxiety behavior accompanied by elevated corticosterone and adrenocorticotropin levels compared with conventionally colonized, pathogen-free mice. Functional MRI has shown that the ingestion of 5 strains of probiotic-like bacteria alters brain activity in humans, resulting in decreased brain responses to emotional attention tasks in sensory and emotional input regions of the brain. Although the mechanism underlying these changes can only be inferred, the tractus solitarius and thus the vagus nerve appear to mediate the enteral tract-brain connection.

Another mechanism through which the enteric microbiome may alter brain activity is by the metabolites it produces. Administration of fermented milk with probiotic like organisms, most notably *Bifidobacterium animalis* subsp. *lactis*, to monozygotic human twins and to mice did not dramatically change the intestinal microbiome composition but did alter its transcriptional profiles, with a shift to increased carbohydrate fermentation to fatty acids, thought to attenuate sad emotional behavior in humans.

CONTRIBUTIONS OF MICROBIOME TO DISEASE

Studies demonstrate that some microbial communities may act in concert to exert negative health effects, whereas other communities may be restorative or resistant to disease. A number of examples of this concept of altered microbial communities, also termed **dysbiosis**, are provided in the sections to follow.

Microbiome of Premature Birth

While the etiology of premature birth is multifactorial, inflammatory conditions including subclinical and clinically overt infections of the mother and/or fetus have been proposed to be instigators of premature birth. Inflammatory biomarker profiling highlights this point, as women who proceed to preterm birth have increased angiotensin, interleukin 8, and tumor necrosis factor receptor 1, along with a number of race-specific alterations in additional cytokines and chemokines. Prior work reported that women experiencing preterm birth have increased vaginal colonization with *Gardnerella* spp. and *Lactobacillus crispatus.* There may be a lower diversity in microbiota of the posterior vaginal fornix of women experiencing preterm birth. A meta-analysis of early treatment of vaginosis with clindamycin prior to 22 wk of pregnancy demonstrated a reduction in spontaneous preterm birth at <37 wk, consistent with an association between dysbiosis of the pregnancy-associated microbiota and preterm birth.

Traditionally, the amniotic cavity and the fetus have been presumed to be sterile prior to the rupture of the fetal membranes and birth. However, several reports identify evidence for bacterial DNA in meconium with 2 predominant meconium types regardless of mode of delivery: (1) dominated by Enterobacteriaceae, and (2) dominated by Leuconostocaceae, Enterococcaceae, and Streptococcaceae. Furthermore, data indicate that the amniotic fluid in subclinical and clinically apparent chorioamnionitis has evidence of vaginal-derived microbes present, including poorly or noncultivatable organisms such as *Mycoplasma* spp., *Ureaplasma* spp., *Bacteroides* spp., *Fusobacterium, Sneathia sanguinegens,* and *Leptotrichia amnionii*. A correlation exists between the burden of intraamniotic organisms and the degree of prematurity. Microbial invasion of the amniotic space may lead to induction of inflammatory pathways through innate immune microbial pattern recognition receptors such as the Toll-like receptors. The result may be the induction of labor and physiologic stress on the fetus and mother. Exposure to microbial factors may have consequences on lung and intestinal development, setting the stage for postnatal pathology including necrotizing enterocolitis. Beyond the acute threat to the maternal-fetal dyad, chorioamnionitis may not produce the long-term neurodevelopmental consequences it once was thought to cause, with formerly premature infants born to women with chorioamnionitis having similar cognitive and neuropsychiatric outcomes even to age 18 yr as infants not exposed to chorioamnionitis.

Changes in the Microbiome with Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a devastating disease of the neonatal intestine that disproportionately affects severely premature infants who weigh less than 1,500 g at birth. The pathologic steps in NEC include intestinal inflammation with loss-of-barrier function, microbial invasion of the bowel, and eventual death of the affected bowel. Years of research implicated specific organisms as the cause of NEC in case

series; however, none of the proposed specific etiologies proved to be common to all cases of NEC and, instead, appeared to be the emergent organisms after serious intestinal pathology had ensued.

Contemporarily, a model of dysbiosis of the early life intestinal microbiome has been favored in the pathogenesis of NEC. Epidemiologic studies in very-low-birthweight infants have demonstrated an association of cephalosporins and duration of antibiotic exposure with the development of NEC, consistent with the idea that shifts in the microbiota predispose to or incite NEC. Studies demonstrate decreased diversity of the microbiota preceding and during NEC. The NEC microbiota at the time of clinical symptoms resembles the microbiota 72 hr prior to onset but not the microbiota 1 wk prior to onset of symptoms, suggesting that a shift in the intestinal microbiota begins well in advance of the appearance of NEC. Some differences in early colonization following birth may portend an increased risk for NEC.

Microbiome and Allergic Disorders

Given the role of the microbiome in the development and modulation of innate and adaptive immune responses, considerable interest has been given to its role in the development and exacerbation of allergic conditions such as atopic dermatitis.

The microbiome of the skin has been studied prior to, during, and following treatment of flares of atopic dermatitis. Flares result in the loss of diversity of bacteria on the affected area, and treatment introduces new diversity. *S. aureus* and *Staphylococcus epidermidis* increase prior to and during atopic flares, whereas *Streptococcus* spp. and *Corynebacterium* spp. increase immediately preceding and during clinical improvement. In mice, oral treatment of infant animals with nonabsorbable antibiotics increases serum immunoglobulin (Ig) E, increases clinical symptoms such as itching, and produces atopic-like features. These data suggest that atopic dermatitis is influenced by the local skin microbiome and more distant microbiomes such as in the intestinal tract, also suggesting why the administration of oral probiotics such as *Lactobacillus* spp. may decrease atopic dermatitis with an accompanying shift in the T-cell Th1/Th2 balance and increased interferon-γ, which are part of immune tolerance.

The respiratory tract is a common site of allergic disease, and infections have long been associated with allergic exacerbations of the respiratory tract. Traditional teaching is that the lower respiratory tree is sterile; however, studies of the airway microbiome in healthy and asthmatic children and adults indicate that this teaching is incorrect. Measured through careful bronchoscopic sampling and cytology brushings, the airways have a diverse microbiota during good health.

Measurement of the microbiota in the lower respiratory tract of healthy and asthmatic children indicates significant differences. Past culture-based studies indicate that early life colonization of the neonatal respiratory tree by *H. influenzae, Moraxella catarrhalis,* and *S. pneumoniae* is associated with an increased risk for childhood asthma. These same organisms also are closely associated with exacerbations of asthma. *M. pneumoniae* has been proposed as a major bacterial inducer of childhood asthma exacerbations when infection is identified. The employment of culture-independent measurements of lower airway microbiota composition (see Fig. 171-1) indicates that children with asthma are more likely to have higher levels of Proteobacteria, including *H. influenzae,* as well as Firmicutes such as *Staphylococcus* spp. and *Streptococcus* spp. Remarkably, healthy children are more likely than age-matched asthmatic children to have lower airway Bacteroidetes, particularly *Prevotella* spp., a group of anaerobic bacteria. The association of healthy airways with a lower respiratory tree anaerobic bacterial population is surprising because the high oxygen tension environment has been assumed to be toxic to anaerobes. This study indicates that the airway environment is significantly different than previously understood, and the potentially protective attributes of a native health-associated microbiota needs to be studied to determine if these associations are also causal.

Airway Microbiome of Cystic Fibrosis

Cystic fibrosis is characterized by progressive airway disease and inflammation with acute exacerbations accompanied by loss of pulmonary function. Cystic fibrosis has long been known to have an age-dependent change in lower airway colonization, which starts in early childhood with *S. aureus* and *H. influenzae* and progressively shifts toward more intrinsically multidrug-resistant organisms, including the notoriously persistent and treatment-refractory bacteria *Pseudomonas aeruginosa* and *B. cepacia* complex. Culture-independent molecular analysis of the lung-associated microbiota in cystic fibrosis has revealed far more complex microbial communities than previously expected and has demonstrated an association with patient age and disease severity. In addition to the presence of a variety of previously unexpected airway organisms such as anaerobes and mycobacteria, disease severity is inversely related to the lower airway microbial community diversity with less advanced disease associated with greater species richness and evenness. In contrast, the loss of diversity, including the shift from less complex microbial communities to those dominated by *P. aeruginosa,* is strongly correlated with disease severity, and levels of *H. influenzae,* the early childhood colonizer, have a negative correlation with disease severity. Although antibiotics decrease the rate of progressive lung function, they also decrease the community diversity, thus suggesting a balance between a diverse microbiota and reducing the dominance of certain organisms such as *P. aeruginosa*.

Microbiome During Antibiotic-Associated Diarrhea and *Clostridium difficile* Colitis

Treatment with oral and parenteral antibiotics results in a rapid and significant alteration of the intestinal microbiota. Studies of normal individuals taking ciprofloxacin demonstrated dramatic but individualized responses to the antibiotic, with significant reductions in bacteria outside the expected spectrum of the antibiotic, emphasizing the intradependence of microbial community members on one another for their stability in the community as a whole. Furthermore, the response to ciprofloxacin among subjects varied by individual, suggesting different degrees of stability of the microbiota and resilience under stress such as antibiotics. In general, with the exception of some rare members of the community, the community was largely restored within 4 wk after the completion of the antibiotic course.

Some antibiotics, such as amoxicillin-clavulanate, for which antibiotic-associated diarrhea is a well-known adverse event, produce a loss of *Clostridium* and *Bacteroides*, known to be important in the production of short-chain fatty acids (SCFA) and the metabolism of otherwise undigestible carbohydrates. Together, their loss may decrease the metabolic integrity of the intestinal epithelium that uses SCFA for energy while resulting in a high osmotic environment in which fluid is drawn into the intestinal lumen. Antibiotic-associated diarrhea may result from these combined effects.

One of the most serious complications from antibiotic exposure is the development of *C. difficile*–associated diarrhea (CDAD), which has high associated morbidity and even mortality. Microbiologic surveys suggest that *C. difficile* is a common constituent of the developing microbiota early in life with less prevalence over the life span. Over 30% of infants are colonized with *C. difficile* in the 1st mo of life, continuing until approximately 6 mo of age. By 1 yr of age, colonization ranges between approximately 15% and 70% and then declines through to adulthood, when carriage is estimated to be <3%. Although *C. difficile* has been found within the vaginal microbiota of pregnant women, vaginal delivery has not been associated with increased rates of neonatal *C. difficile* colonization, with vaginal and cesarian delivery having rates of colonization at 30% and 37%, respectively. CDAD has been reported to result in 35-45 hospitalizations per 10,000 pediatric admissions among children 1-9 yr of age.

Although the studies have not yet determined how the intestinal microbiome is altered preceding, during, and with resolution of CDAD in children, molecular studies of the intestinal microbiota in adults provide some details of the consequences of CDAD on the intestinal microbiota. Studies employing deep sequencing of stool from individuals with CDAD and *C. difficile* colonization without disease have revealed depletion of certain bacterial genera accompanying the presence of *C. difficile* colonization. These genera include *Blautia,*

Pseudobutyrivibrio, Roseburia, Faecalibacterium, Anaerostipes, Subdoligranulum, Ruminococcus, Streptococcus, Dorea, and *Coprococcus*. The relationship of cause and effect and the events triggering the transition from colonization to symptomatic disease remain unknown. Similar to the studies of antibiotic-associated diarrhea, these studies also demonstrate a reduction in butyrate-producing *Clostridium* spp., which are proposed to be important for producing butyrate as an energy sources for the intestinal epithelium and its robust integrity.

Although antibiotics such as metronidazole and vancomycin have been employed to treat CDAD, traditional treatment does not eliminate recurrent CDAD to the extent that might be expected. To address this problem, **fecal transplantation** or administration of feces from healthy donors to CDAD recipients is effective in treating CDAD and, more importantly, superior to these antibiotics in reducing the likelihood of recurrent disease. Accompanying clinical resolution is repletion of Bacteroidetes and *Clostridium* clusters IV and XIVa with a matched decrease in Proteobacteria. Most of the experience with fecal transplantation has been gained from adults with only a single published pediatrics report, although research studies are underway.

Microbiome and Association with Inflammatory Bowel Disease

Crohn disease and ulcerative colitis are chronic inflammatory diseases of the enteric tract and are believed to be the result of the intersection of host susceptibility and a dysbiosis, an alteration in the intestinal microbiota. Twin-twin studies indicate concordance rates in monozygotic twins of 10-15% in ulcerative colitis and 30-35% in Crohn disease, thus demonstrating a genetic component for each disease while highlighting environmental factors that likely induce and drive disease progression. More than 150 single-nucleotide polymorphisms are associated with the diseases, revealing potential defects in handling microbes, including those involved in barrier function, innate immunity, autophagy, adaptive immunity, and metabolism and cellular homeostasis.

In inflammatory bowel disease (IBD), the microbiota undergoes a shift in association with the disease throughout the intestinal tract. Although considerable heterogeneity has been described, IBD is often demonstrated to be accompanied by a decrease in bacteroides, clostridia, bifidobacteria, and Firmicutes. Reciprocally, outgrowths of *E. coli* and other Enterobacteriaceae are described. Increased sulfur-metabolizers have been described with IBD as well. Antibiotics along with biologic therapies such as antibodies directed at neutralizing tumor necrosis factor have been employed to manage the IBD dysbiosis and inflammatory reaction. Trials of fecal transplantation are underway to determine if a noninflammatory microbiota from a healthy donor may mitigate IBD symptoms and progression.

Microbiome of Obesity

Obesity and the metabolic syndrome are associated with notable changes in the intestinal microbiome in terms of composition and metabolic function, ultimately resulting in greater energy extraction from the diet. "Typical" changes in the microbiome include an increase in the ratio of the phyla Firmicutes : Bacteroidetes. Additional work has indicated that Prevotellaceae, a family within the Bacteroidetes phylum, may be specifically increased with obesity. However, there remains considerable debate about obesity-specific changes in the microbiome, as studies other than those mentioned previously have demonstrated decreased Firmicutes : Bacteroidetes ratios in the fecal microbiota from obese individuals compared to lean controls. Further studies show that proportions of phyla-level groups may be less important than changes in Firmicutes subgroups that produce butyrate, a known fatty acid substrate easily acquired and utilized by the intestinal epithelium, and thus ready calories for the host.

The intestinal microbiome benefits the host in important ways, including enhancing caloric extraction from indigestible substrates such as polysaccharides in the diet. The microbiome produces degradative enzymes to break down these substrates where enzymes with comparable functions, such as some glycosyl hydrolases, are not encoded in the human genome. Molecular studies indicate that the intestinal microbiome may also interact with the intestinal epithelium in such a way as to alter general energy homeostasis and fat storage. For instance, the intestinal microbiome may produce SCFA that, in turn, alter endocrine peptide expression such as glucagon-like peptide 1 and peptide YY, which alter glucose homeostasis and satiety, respectively. Furthermore through the production of SCFA and ketones, the microbiota may alter sympathetic tone. Certain microbiomes are known to suppress others to induce fastening-induced adipose factor (also called angiopoietin-like protein 4), a lipoprotein lipase inhibitor of intestinal, hepatic, and adipose origins. Colonization with a diverse microbiota suppresses fastening-induced adipose factor expression, and dietary supplementation of a Western diet with *Lactobacillus paracasei* further suppressed otherwise high fastening-induced adipose factor expression. Mice fed a Western diet developed adiposity, which was transferrable to recipient lean mice following transplantation with the obese mice microbiota. Reciprocally, obese mice treated with antibiotics experienced less insulin resistance, lower fasting glycemic indices, and improved glucose tolerance compared to untreated counterparts, further implicating the microbiome in these physiologic changes.

Microbiome During Malnutrition

Malnutrition is a leading cause of morbidity and mortality across the world. In its most severe form, malnutrition may result in kwashiorkor, which is characterized by generalized edema, anorexia, fatty enlarged liver, skin ulcerations, and irritability. Ready-to-use foods are employed to try to restore nutrition in areas with severe food restrictions. Monozygotic and dizygotic twins in Malawi were studied for the alterations in the microbiome in association with moderate to severe malnutrition, including kwashiorkor. Among the twins with discordant degrees of malnutrition on food supplements, the twins with mild preexisting malnutrition had intestinal microbiota that changed significantly over the course of supplementation. In contrast, the twins with preexisting kwashiorkor had microbiota with poor to no change in response to nutritional supplementation. These findings were recapitulated to some extent following transplantation of the twins' microbiota into previous sterile mice. Those mice receiving the microbiota of Malawian twins with kwashiorkor experienced more dramatic weight loss on a Malawian-type diet and more rapid loss of their weight gain once off ready to use food supplements than did mice transplanted with the feces of more healthy twins. The mice with the transplanted kwashiorkor microbiota had sustained problems with carbohydrate, lipid, and amino acid metabolism despite nutritional supplementation of the Malawian diet. Together these data indicate that severe malnutrition results from the combination of nutritional deficits and a microbiome with altered metabolic capabilities that are not readily restored with contemporary nutritional supplementation treatments.

THERAPEUTIC MANIPULATION OF THE MICROBIOME

Therapeutic manipulation of the microbiome falls into 5 general categories: (1) antimicrobials, (2) prebiotics, (3) probiotics, (4) postbiotics, and (5) fecal transplantation. Brief mention of fecal transplantation was discussed in the sections on *C. difficile* diarrhea and IBD. Postbiotics are nonviable microbial components or metabolites that may alter the microbiota or produce physiologic changes in the host. Insufficient data exist to warrant a discussion of postbiotic therapeutics here.

Prebiotics

"Prebiotic" is defined as "nondigestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon and thereby improving host health." While antimicrobials deplete portions of the microbiota, prebiotics aim to promote the growth of beneficial organisms such as bifidobacteria and lactobacteria. Typically, prebiotics are carbohydrates such as oligosaccharides that may be selectively metabolized by constituents of the microbiota. They may not only stimulate outgrowth of desirable organisms but also may be catabolized to beneficial end products such as SCFA, which may, in turn, be utilized as

energy substrates by the intestinal epithelium. Prebiotic oligosaccharides are naturally found in breast milk and have been used as supplements to human breast milk and formula.

Administration of prebiotics to term infants has demonstrated the expected outgrowth of bacteria; however, clinically significant benefits from prebiotic supplementation have not been clearly established. Treatment of term infants with fructooligosaccharides increases fecal bifidobacteria but without a change in infant growth, despite some infants having increased SCFA in the fecal mass. A systematic review of the topic provided a similar conclusion.

Preterm infants have low to absent levels of bifidobacteria and lactobacilli in their intestinal tracts, despite full breast milk nutrition. Prebiotic supplementation has been proposed as a means to increase these bacterial populations in the preterm infant intestinal tract. Among the proposed benefits may be a decrease in NEC. However, appropriately powered, randomized trials have not been performed to demonstrate the validity of this hypothesis.

Probiotics

Probiotics are viable organisms that have health benefits following administration. Nearly all probiotics are isolates from the human microbiota, although they may not necessarily reside in the individual taking them for therapeutic purposes. Alternatively, probiotics may be administrated to increase the levels of an organism already present within the microbiota. Generally, probiotics have been administered orally or as vaginal suppositories.

Multiple bacterial and fungal genera and species have been studied for probiotic effects. Common bacterial genera include bifidobacteria, lactobacilli, streptococci, enterococci, and *E. coli*. Fewer nonbacterial organisms, have been studied for probiotic effects. *Saccharomyces boulardii* is related to baker's yeast (*Saccharomyces cerevisiae*) but was isolated for specific beneficial effects.

These probiotic organisms should not be confused with more pathogenic strains within their genera and species. Most probiotics have been isolated on the basis of being associated with healthy states. For instance, bifidobacteria and lactobacilli are common to breast milk and stool among infants with low rates of diarrheal diseases and allergy. With the exception of individuals with significant immunodeficiencies, severely compromised mucosal barriers, and central line catheters, where many of these organisms may adhere to the catheter plastic with otherwise benign transient translocation from the intestinal tract, these bacterial probiotics have proven to be relatively safe even with the administration of billions of colony forming units. The most common adverse events associated with probiotics include abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance.

Although bacterial probiotics have been administered widely to humans, evidence for their efficacy is limited to a small number of conditions. Probiotics have consistently shown efficacy for specific conditions, including antibiotic-associated diarrhea, prevention and reduction of atopy in high risk children, and reductions in duration and recurrence of *C. difficile* infection. Trials indicate a reduction in NEC among preterm infants. Probiotics may reduce the risk for respiratory infections and recurrent UTI while reducing the symptoms and frequency of flares in IBD.

Antibiotic-associated diarrhea is reduced in frequency and duration. Metaanalysis indicated a relative risk of antibiotic-associated diarrhea with probiotic administration of 0.58 (95% confidence interval [CI], 0.05-0.68) among combined studies using *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus*. Administration of combinations of organisms has not generally resulted in greater efficacy.

Metaanalysis specifically for the efficacy of probiotics in decreasing the incidence of CDAD demonstrated moderate evidence for the practice. In an analysis of more than 1,800 trials, including many in the pediatric population, probiotics reduced CDAD by 64% with a relative risk of 0.36 (95% CI, 0.26-0.51). A pediatric subgroup was analyzed across relevant studies, revealing benefit in pediatric patients and a well child subgroup (relative risk 0.37; 95% CI 0.23-0.60). A number of probiotics were used, including different *Lactobacillus* strains and *S. boulardii*.

More than 15 trials have been performed to study the effect of probiotic administration during pregnancy and to infants to prevent atopic dermatitis. Metaanalysis suggests a modest benefit from probiotic administration to prevent the development of atopic dermatitis. Trials have primarily involved the administration of *Lactobacillus rhamnosus.* Studies included administration to the pregnant mother, or the infant, or both. The overall relative risk of 0.79 (95% CI, 0.71-0.88) was generally consistent regardless of the treatment of the mother or child, or both. The duration was generally >6 mo; however, duration did not appear to significantly alter the effect. The RR was similar for the prevention of IgE- and non-IgE–associated atopic dermatitis.

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Section 2

Preventive Measures

Chapter 172

Immunization Practices

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Immunization is one of the most beneficial and cost-effective disease-prevention measures available. As a result of effective and safe vaccines, smallpox has been eradicated, polio is close to worldwide eradication, and measles and rubella are no longer endemic in the United States, although cases of vaccine-preventable diseases, including measles, rubella, and pertussis, continue to occur in the United States. For most diseases of childhood preventable by vaccination, incidence of most vaccine-preventable diseases of childhood has been reduced by ≥99% from the annual morbidity prior to development of the corresponding vaccine (Table 172-1a), with newer vaccines not achieving quite the same percentage decrease (Table 172-1b). An analysis of effective prevention measures recommended for widespread use by the U.S. Preventive Services Task Force reported that childhood immunization received a perfect score, based on clinically preventable disease burden and cost-effectiveness.

Immunization is the process of inducing immunity against a specific disease. Immunity can be induced either **passively** through administration of antibody-containing preparations or **actively** by administering a vaccine or toxoid to stimulate the immune system to produce a prolonged humoral and/or cellular immune response. As of 2015, infants, children, and adolescents in the United States routinely are immunized against 16 diseases: diphtheria, tetanus, pertussis, poliomyelitis, *H. influenzae* type b (Hib) disease, hepatitis A, hepatitis B, measles, mumps, rubella, rotavirus, varicella, pneumococcal disease, meningococcal disease, influenza, and human papillomavirus (HPV) infection.

PASSIVE IMMUNITY

Passive immunity is achieved by administration of preformed antibodies to induce transient protection against an infectious agent. Products used include:

- Immunoglobulin (Ig) administered intramuscularly (IM)
- Specific or hyperimmune immunoglobulin preparations administered IM
- Intravenous immunoglobulin (IVIG)

Table 172-1a Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

DISEASE	20TH CENTURY ANNUAL MORBIDITY*	2013 REPORTED CASES†	PERCENT DECREASE
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	187	>99%
Mumps	162,344	584	>99%
Pertussis	200,752	28,639	86%
Polio (paralytic)	16,316	1	>99%
Rubella	47,745	9	>99%
Congenital Rubella Syndrome	152	1	99%
Tetanus	580	26	96%
Haemophilus influenzae	20,000	31‡	>99%

*Roush SW, Murphy TV, Vaccine-Preventable Disease Table Working Group: Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 298(18):2155–2163, 2007.

†Centers for Disease Control and Prevention (CDC). Notice to readers: Final 2013 reports of nationally notifiable infectious diseases. *MMWR Morb Mortal Wkly Rep*:63(32):702, 2014.

‡*Haemophilus influenzae* type b (Hib) <5 yr of age. An additional 10 cases of Hib are estimated to have occurred among the 185 reports of *H. influenzae* (<5 yr of age) with unknown serotype.

Table 172-1b Comparison of Pre–Vaccine Era Estimated Annual Morbidity with Current Estimate: Vaccine-Preventable Diseases

DISEASE	PRE–VACCINE ERA ANNUAL ESTIMATE*	2013 ESTIMATE (UNLESS OTHERWISE SPECIFIED)	PERCENT DECREASE
Hepatitis A	117,333*	2,890†	98%
Hepatitis B (acute)	66,232*	18,800†	72%
Pneumococcus (invasive)			
All ages	63,067*	33,500§	47%
<5 yr of age	16,069*	1,900‖	88%
Rotavirus (hospitalizations, <3 yr of age)	62,500‡	1,2500¶	80%
Varicella	4,085,120*	167,490**	96%

*Roush SW, Murphy TV and Vaccine-Preventable Disease Table Working Group: Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 298(18):2155–2163, 2007.

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‡Centers for Disease Control and Prevention (CDC): Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 58(RR-2): 1–25, 2009.

§Centers for Disease Control and Prevention (CDC): Active bacterial core surveillance provisional report; *S. pneumoniae* 2013.

‖Centers for Disease Control and Prevention (CDC). Active bacterial core surveillance [unpublished].

¶New Vaccine Surveillance Network 2013 data [unpublished]. U.S. rotavirus disease now has biennial pattern.

**Centers for Disease Control and Prevention (CDC). Varicella Program 2013 data [unpublished].

- Specific or hyperimmunoglobulin preparations administered IV
- Subcutaneous (SC) human immunoglobulin, which has been licensed to treat patients with primary immunodeficiencies
- Antibodies of animal origin
- Monoclonal antibodies

Passive immunity also can be induced naturally through transplacental transfer of maternal antibodies (IgG) during gestation. Maternally derived transplacental antibodies can provide protection during an infant's 1st mo of life and longer during breastfeeding. Protection for some diseases can persist for as long as 1 year after birth, depending on the quantity of antibody transferred and the time until levels fall below those considered protective.

The major indications for passive immunity are to provide protection to immunodeficient children with B-lymphocyte defects who have difficulties making antibodies, for people exposed to infectious diseases or who are at imminent risk of exposure where there is not adequate time for them to develop an active immune response to a vaccine, and for people with an infectious disease as part of specific therapy for that disease (Table 172-2).

Intramuscular Immunoglobulin

Immunoglobulin is a sterile antibody-containing solution, usually derived through cold ethanol fractionation of large pools of human plasma from adults. Antibody concentrations reflect the infectious disease exposure and immunization experience of plasma donors. Immunoglobulin contains 15-18% protein, is predominantly IgG, and is administered IM. IV use of human intramuscular immunoglobulin is contraindicated. Immunoglobulin is not known to transmit infectious agents, including viral hepatitis and HIV.

The major indications for immunoglobulin are:

- Replacement therapy for children with antibody deficiency disorders
- Measles prophylaxis
- Hepatitis A prophylaxis

For replacement therapy, the usual dose of intramuscular immunoglobulin is 100 mg/kg (equivalent to 0.66 mL/kg) monthly. The usual interval between doses is 2-4 wk depending on trough IgG serum concentrations and clinical response. In practice, **IVIG** has replaced intramuscular immunoglobulin for replacement therapy. Intramuscular immunoglobulin can be used to prevent or modify measles if administered to susceptible children within 6 days of exposure (usual dose: 0.5 mL/kg of body weight; maximum dose: 15 mL). The recommended dose of IVIG is 400 mL/kg. Data suggest that measles vaccine, if given within 72 hr of measles exposure, will provide protection in some cases. Measles vaccine and immunoglobulin should not be administered at the same time.

Two methods are available for postexposure prophylaxis against hepatitis A. In people 12 mo through 40 yr of age, hepatitis A immunization is preferred over immunoglobulin for postexposure prophylaxis and for protection of people traveling to areas where hepatitis A is endemic. Immunoglobulin may be administered to children <12 mo of age and people >40 yr of age for prophylaxis of hepatitis A and for postexposure prophylaxis for people traveling internationally to hepatitis A–endemic areas (0.06 mL/kg). In children <12 mo of age, adults >40 yr of age, and susceptible children and adults with underlying immunodeficiencies or chronic liver disease, immunoglobulin is preferred over hepatitis A immunization.

The most common adverse reaction to immunoglobulin is pain and discomfort at the injection site and, less commonly, flushing, headache, chills, and nausea. Serious adverse events are rare and include chest pain, dyspnea, anaphylaxis, and systemic collapse. Immunoglobulin should not be administered to people with selective IgA deficiency. Patients with selective IgA deficiency can produce antibodies against the trace amounts of IgA in immunoglobulin preparations and develop reactions after repeat doses. These reactions can include fever, chills,

Table 172-2 Immunoglobulin and Animal Antisera Preparations

PRODUCT	MAJOR INDICATIONS
Immunoglobulin for intramuscular injection	Replacement therapy in primary immunodeficiency disorders Hepatitis A prophylaxis Measles prophylaxis
Intravenous immunoglobulin (IVIG)	Replacement therapy in primary immune-deficiency disorders Kawasaki disease Pediatric HIV infection Hypogammaglobulinemia in chronic B-lymphocyte lymphocytic leukemia Immune-mediated thrombocytopenia Hematopoietic cell transplantation in adults to prevent graft-versus-host disease and infection May be useful in a variety of other conditions
Hepatitis B immunoglobulin (IM)	Postexposure prophylaxis Prevention of perinatal infection in infants born to hepatitis B surface antigen–positive mothers
Rabies immunoglobulin (IM)	Postexposure prophylaxis
Tetanus immunoglobulin (IM)	Wound prophylaxis Treatment of tetanus
Varicella-zoster immunoglobulin (IM) or IVIG	Postexposure prophylaxis of susceptible people at high risk for complications from varicella
Cytomegalovirus IVIG	Prophylaxis of disease in seronegative transplant recipients
Subcutaneous immunoglobulin	Treatment of patients with primary immunodeficiencies
Vaccinia immunoglobulin (IV)	Prevent or modify serious adverse events following smallpox vaccination caused by vaccinia replication
Botulism IVIG human	Treatment of infant botulism
Diphtheria antitoxin, equine	Treatment of diphtheria
Heptavalent botulinum antitoxin against all 7 (A-G) botulinum toxin types	Treatment of food and wound botulism
Palivizumab (monoclonal antibody) (IM)	Prophylaxis for infants against respiratory syncytial virus (see Chapter 260)

American Academy of Pediatrics, Passive immunization. In Pickering LK, Baker CJ, Kimberlin DW, Long SL, editors: Red book 2012: report of the Committee on Infectious Diseases, *Elk Grove Village, IL, 2012, American Academy of Pediatrics, pp. 56–63.*

and a shock-like syndrome. Because these reactions are rare, testing for selective IgA deficiencies is not recommended.

Intravenous Immunoglobulin

IVIG is a highly purified preparation of immunoglobulin antibodies prepared from adult plasma donors using alcohol fractionation and is modified to allow IV use. IVIG is more than 95% IgG, and is tested to ensure minimum antibody titers to *Corynebacterium diphtheriae*, hepatitis B virus, measles virus, and poliovirus. Antibody concentrations against other pathogens vary widely among products and even among lots from the same manufacturer. Liquid and lyophilized powder preparations are available. IVIG does not contain thimerosal.

Not all IVIG products are approved by the FDA for all indications. The major **recommended indications** for IVIG for which there is approval by the FDA are:

- Replacement therapy for primary immunodeficiency disorders
- Kawasaki disease to prevent coronary artery abnormalities and shorten the clinical course
- Replacement therapy for prevention of serious bacterial infections in children infected with HIV
- Prevention of serious bacterial infections in people with hypogammaglobulinemia in chronic B-lymphocyte leukemia
- Immune-mediated thrombocytopenia to increase platelet count
- Prophylaxis of infection following bone marrow transplantation

IVIG may be helpful for patients with severe toxic shock syndrome, Guillain-Barré syndrome, and anemia caused by parvovirus B19. IVIG is used for many other conditions based on clinical experience. IVIG may be used for varicella postexposure if varicella-zoster immune globulin is not available.

Reactions to IVIG range from 1-15%. Some of these reactions appear to be related to the rate of infusion and can be mitigated by decreasing the rate. Such reactions include fever, headache, myalgia, chills, nausea, and vomiting. More serious reactions rarely have been reported, including anaphylactoid events, thromboembolic disorders, aseptic meningitis, and renal insufficiency. Renal failure occurs mainly in patients with preexisting renal dysfunction.

Specific immunoglobulin preparations are derived from donors with high titers of antibodies to specific agents and designed to provide protection against those agents (see Table 172-2).

Subcutaneous Immunoglobulin

Subcutaneous administration of immunoglobulin is safe and effective in children and adults with primary immune deficiency disorders. Smaller doses administered less frequently (weekly) result in less fluctuation of serum IgG concentrations over time. Systemic reactions are less frequent than with IVIG and the most common adverse effects of subcutaneous immunoglobulin are injection-site reactions. There are no data on administration of intramuscular immunoglobulin by the subcutaneous route.

Hyperimmune Animal Antisera Preparations

Animal antisera preparations are derived from horses. The immunoglobulin fraction is concentrated using ammonium sulfate, and some products are further treated with enzymes to decrease reactions to foreign proteins. As of 2014, 2 equine antisera preparations are available for humans:

- Diphtheria antitoxin, which can be obtained from the CDC (http://www.cdc.gov/diphtheria/dat.html) and is used to treat diphtheria.
- Heptavalent botulinum antitoxin, which is available from the CDC (770-488-7100) for use in adults with botulism. This product contains antitoxin against all 7 (A-G) botulinum toxin types.

Great care must be exercised before administering animal-derived antisera because of the potential for severe allergic reactions. Due caution includes testing for sensitivity before administration; desensitization, if necessary; and treating potential reactions, including febrile events, serum sickness, and anaphylaxis. *For infant botulism, IVIG (BabyBIG), a human-derived antitoxin, is licensed and should be used.*

Monoclonal Antibodies

Monoclonal antibodies are antibody preparations produced against a single antigen. They are mass-produced from a hybridoma, created by fusing an antibody-producing B lymphocyte with a fast-growing immortal cell such as a cancer cell. **Palivizumab** is a monoclonal antibody that is used for prevention of severe disease from respiratory syncytial virus among children 24 mo of age and younger with chronic lung disease (also called bronchopulmonary dysplasia), with a history of premature birth or with congenital heart lesions or neuromuscular diseases. The American Academy of Pediatrics (AAP) has

developed specific recommendations for use of palivizumab (see Chapter 260). Respiratory syncytial virus–IVIG, a hyperimmunoglobulin formulated for intravenous administration, is no longer produced in the United States. Monoclonal antibodies also are used to prevent transplant rejection and to treat some types of cancer and autoimmune diseases. Monoclonal antibodies against interleukin 2 and tumor necrosis factor α are being used as part of the therapeutic approach to patients with a variety of malignant and autoimmune diseases.

Serious adverse events associated with palivizumab primarily are rare cases of anaphylaxis and hypersensitivity reactions. Adverse reactions to monoclonal antibodies directed at modifying the immune response, such as antibodies against interleukin 2 or tumor necrosis factor, can be more serious, and include cytokine release syndrome, fever, chills, tremors, chest pain, immunosuppression, and infection with various organisms, including mycobacteria.

ACTIVE IMMUNIZATION

Vaccines are defined as whole or parts of microorganisms administered to prevent an infectious disease. Vaccines can consist of whole inactivated microorganisms (e.g., polio and hepatitis A), parts of the organism (e.g., acellular pertussis, HPV, and hepatitis B), polysaccharide capsules (e.g., pneumococcal and meningococcal polysaccharide vaccines), polysaccharide capsules conjugated to protein carriers (e.g., Hib, pneumococcal, and meningococcal conjugate vaccines), live-attenuated microorganisms (measles, mumps, rubella, varicella, rotavirus, and live-attenuated influenza vaccines), and toxoids (tetanus and diphtheria) (Table 172-3). A **toxoid** is a modified bacterial toxin that is made nontoxic but is still able to induce an active immune response against the toxin.

Immunizing agents can contain a variety of other constituents besides the immunizing antigen. **Suspending fluids** may be sterile water or saline but could be a complex fluid containing small amounts of proteins or other constituents derived from the biologic system used to grow the immunobiologic. **Preservatives, stabilizers, and antimicrobial agents** are used to inhibit bacterial growth and to prevent degradation of the antigen. Such components can include gelatin, 2-phenoxyethanol, and specific antimicrobial agents. Preservatives are added to multidose vials of vaccines, primarily to prevent bacterial contamination on repeated entry of the vial. In the past, many vaccines for children contained thimerosal, a preservative containing ethyl mercury. Beginning in 1999, removal of thimerosal as a preservative from vaccines for children was begun as a precautionary measure in the absence of any data on harm from the preservative. This objective was accomplished by switching to single-dose packaging. Vaccines in the recommended schedule for young children that contain thimerosal as a preservative are some preparations of influenza vaccine. The thimerosal content in U.S.-licensed vaccines currently being manufactured can be found at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm096228.htm#pres. **Adjuvants** are used in some vaccines to enhance the immune response. In the United States, the only adjuvants currently licensed by the **FDA to be part of vaccines are aluminum salts and arsenate (AsO_4), an adjuvant that** contains aluminum hydroxide and monophosphoryl lipid A. Vaccines with adjuvants should be injected deeply into muscle masses to avoid local irritation, granuloma formation, and necrosis associated with SC or intracutaneous administration.

Vaccines can induce immunity by stimulating antibody formation, cellular immunity, or both. Protection induced by most vaccines is thought to be mediated primarily by B lymphocytes, which produce antibodies. Such antibodies can inactivate toxins, neutralize viruses and prevent their attachment to cellular receptors, facilitate phagocytosis and killing of bacteria, interact with complement to lyse bacteria, and prevent adhesion to mucosal surfaces by interacting with the bacterial cell surface.

Most B-lymphocyte responses require the assistance of CD4 helper T lymphocytes. These T-lymphocyte–dependent responses tend to induce high levels of functional antibody with high avidity, mature over time from primarily an IgM response to a long-term persistent IgG response, and induce immunologic memory that leads to enhanced responses upon boosting. **T-lymphocyte–dependent vaccines,** which include protein moieties, induce good immune responses even in young infants. In contrast, polysaccharide antigens induce B-lymphocyte responses in the absence of T-lymphocyte help. These **T-lymphocyte–independent vaccines** are associated with poor immune responses in children <2 yr of age, short-term immunity, and absence of an enhanced or booster response on repeat exposure to the antigen. With some polysaccharide vaccines, repeat doses actually are associated with reduced responses, as measured by antibody concentrations, compared to 1st doses (i.e., hyporesponsive). To overcome problems of plain polysaccharide vaccines, polysaccharides have been **conjugated,** or covalently linked, to protein carriers, converting the vaccine to a T-lymphocyte–dependent vaccine. In contrast to plain polysaccharide vaccines, conjugate vaccines induce higher-avidity antibody, immunologic memory leading to booster responses on repeat exposure to the antigen, long-term immunity, and herd protection by decreasing carriage of the organism (Table 172-4). As of 2014 in the United States, there were licensed conjugate vaccines to prevent Hib, pneumococcal, and meningococcal diseases.

Serum antibodies may be detected as soon as 7-10 days after injection of antigen. Early antibodies are usually of the IgM class that can fix complement. IgM antibodies tend to decline as IgG antibodies increase. The IgG antibodies tend to peak approximately 1 mo after vaccination and with most vaccines persist for some time after a primary vaccine course. Secondary or booster responses occur more rapidly and result from rapid proliferation of memory B and T lymphocytes.

Assessment of the immune response to most vaccines is performed by measuring serum antibodies. Although detection of serum antibody at levels considered protective after vaccination can indicate immunity, loss of detectable antibody over time does not necessarily mean susceptibility to disease. Some vaccines induce immunologic memory, leading to a booster or anamnestic response on exposure to the microorganism, with resultant protection from disease. In some instances, cellular immune response is used to evaluate immune status. For some vaccines (e.g., acellular pertussis), there is no accepted serologic correlate of protection.

Live-attenuated vaccines routinely recommended for children and adolescents include measles, mumps, and rubella (MMR); MMR and varicella (MMRV); rotavirus; and varicella. In addition, a cold-adapted, live-attenuated quadrivalent influenza vaccine (LAIV) is available for people 2 through 49 yr of age who do not have conditions that place them at high risk for complications from influenza. Live-attenuated vaccines tend to induce long-term immune responses. They replicate, often similarly to natural infections, until an immune response inhibits reproduction. Most live vaccines are administered in 1 or 2 dose schedules. The purpose of repeat doses, such as a 2nd dose of the MMR or MMRV vaccine, is to induce an initial immune response in people who failed to respond to the 1st dose. Influenza vaccines, including LAIV, are recommended to be administered yearly to provide protection against changes in circulating influenza strains.

The remaining vaccines in the recommended schedule for children and adolescents are inactivated vaccines. Inactivated vaccines tend to require multiple doses to induce an adequate immune response and are more likely to need booster doses to maintain that immunity than live-attenuated vaccines. However, some inactivated vaccines appear to induce long-term immunity, perhaps lifelong immunity, after a primary series, including hepatitis B vaccine and inactivated polio vaccine (IPV).

VACCINATION SYSTEM IN THE UNITED STATES

Vaccine Development

Basic scientific knowledge about an organism, its pathogenesis, and the immune responses thought to be associated with protection are financed primarily through government sponsorship of academic research and research conducted by private industry (Fig. 172-1). Private industry usually assumes the lead role for guiding potential

Table 172-3 Currently* Available Vaccines in the United States by Type

PRODUCT	TYPE
Anthrax vaccine adsorbed	Cell-free filtrate of components including protective antigen
Bacille Calmette-Guérin (BCG) vaccine	Live-attenuated mycobacterial strain used to prevent tuberculosis in very limited circumstances
Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine	Toxoids of diphtheria and tetanus and purified and detoxified components from *Bordetella pertussis*
DTaP–hepatitis B–inactivated polio vaccine (DTaP-HepB-IPV)	DTaP with hepatitis B surface antigen (HBsAg) produced through recombinant techniques in yeast with inactivated whole polioviruses
DTaP with IPV and Hib (DTaP-IPV/Hib)	DTaP with inactivated whole polioviruses and Hib polysaccharide conjugated to tetanus toxoid
DTaP and inactivated polio vaccine (DTaP-IPV)	DTaP with inactivated whole polioviruses
Hib conjugate vaccine (Hib)	Polysaccharide conjugated to either tetanus toxoid or meningococcal group B outer membrane protein
Hepatitis A vaccine (HAV)	Inactivated whole virus
Hepatitis A–hepatitis B vaccine (HAV-HBV)	Combined hepatitis A and B vaccine
Hepatitis B vaccine (HBV)	HBsAg produced through recombinant techniques in yeast
Hepatitis B–Hib vaccine (Hib-HBV)	Combined hepatitis B–Hib vaccine; the Hib component is polysaccharide conjugated to meningococcal group B outer membrane protein
Human papillomavirus vaccine (bivalent) (HPV2), (quadrivalent) (HPV4), and 9-valent (HPV9)	The L1 capsid proteins of HPV types 6, 11, 16, and 18 to prevent cervical cancer and genital warts (HPV4) and types 16 and 18 to prevent cervical cancer (HPV2); HPV9 also contains types 31, 33, 45, 52, and 58.
Influenzavirus vaccine inactivated (IIV)	Available either as trivalent (A/H_3N_2, A/H_1N_1, and B) split and purified inactivated vaccines containing the hemagglutinin (H) and neuraminidase (N) of each type or as quadrivalent preparations (which include representative strains from 2 B-lymphocyte clades in addition to the 2 influenza A strains in trivalent inactivated influenza vaccine)
Influenzavirus vaccine live, intranasal (LAIV)	Live-attenuated, temperature-sensitive, cold-adapted trivalent vaccine containing the H and N genes from the wild strains reassorted to have the 6 other genes from the cold-adapted parent, only available as quadrivalent preparation
Japanese encephalitis vaccine	Inactivated whole virus that is purified
Measles, mumps, rubella (MMR) vaccine	Live-attenuated viruses
Measles, mumps, rubella, varicella (MMRV) vaccine	Live-attenuated viruses
Meningococcal conjugate vaccine against serogroups A, C, W135, and Y (MCV4)	Polysaccharide from each serogroup conjugated to diphtheria toxoid or CRM 197
Meningococcal conjugate vaccine against serogroups C and Y and Hib conjugate vaccine	Polysaccharide from each serogroup conjugated to diphtheria toxoid and Hib polysaccharide conjugated to tetanus toxoid
Meningococcal polysaccharide vaccine against serogroups A, C, W135, and Y (MPSV4)	Polysaccharides from each of the serogroups
Pneumococcal conjugate vaccine (13 valent) (PCV13)	Pneumococcal polysaccharides conjugated to a nontoxic form of diphtheria toxin CRM197 Contains 13 serotypes that accounted for >80% of invasive disease in young children prior to vaccine licensure
Pneumococcal polysaccharide vaccine (23 valent) (PPSV23)	Pneumococcal polysaccharides of 23 serotypes responsible for 85-90% of bacteremic disease in the United States
Poliomyelitis (inactivated, enhanced potency) (IPV)	Inactivated whole virus
Rabies vaccines (human diploid and purified chick embryo cell)	Inactivated whole virus
Rotavirus vaccines (RV5 and RV1)	Bovine rotavirus pentavalent vaccine (RV5) live reassortment attenuated virus, and human live-attenuated virus (RV1)
Smallpox vaccine	Vaccinia virus, an attenuated poxvirus that provides cross-protection against smallpox
Tetanus and diphtheria toxoids, adsorbed (Td, adult use)	Tetanus toxoid plus a reduced quantity of diphtheria toxoid compared to diphtheria toxoid used for children <7 yr of age
Tetanus and diphtheria toxoids adsorbed plus acellular pertussis (Tdap) vaccine	Tetanus toxoid plus a reduced quantity of diphtheria toxoid plus acellular pertussis vaccine to be used in adolescents and adults and in children 7 through 9 yr of age who have not been appropriately immunized with DTaP
Typhoid vaccine (polysaccharide)	Vi capsular polysaccharide of *Salmonella typhi*
Typhoid vaccine (oral)	Live-attenuated Ty21a strain of *S. typhi*
Varicella vaccine	Live-attenuated Oka strain
Yellow fever vaccine	Live-attenuated 17D strain

*As of January 2015.

Data from Centers for Disease Control and Prevention: U.S. vaccine names. http://www.cdc.gov/vaccines/about/terms/USvaccines.html

vaccine candidates through preclinical testing in humans into human clinical trials. There are 3 phases of prelicensure clinical trials: **phase I,** generally involving <100 participants to gauge safety and dosing; **phase II,** involving several hundred or more participants to refine safety and dosing; and **phase III** or pivotal trials that can involve thousands or tens of thousands of participants. Data from phase III trials form the major basis for licensure. Following successful clinical development, the vaccine sponsor applies to the FDA for vaccine licensure. Estimates for the cost of development for each vaccine range to $800 million or more. Following licensure by the FDA, recommendations for use are made by the Advisory Committee on Immunization Practices (ACIP) and postlicensure monitoring is performed on hundreds of thousands to millions of people to monitor vaccine safety and effectiveness.

Vaccine Production

Vaccine production is primarily a responsibility of private industry. Many of the vaccines recommended routinely for children are produced by only 1 of the vaccine manufacturers. Only Hib, hepatitis B, HPV, rotavirus, MCV4 (meningococcal conjugate vaccine against serogroups A, C, W135, and Y), diphtheria and tetanus toxoids and acellular pertussis (DTaP), and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines for adolescents and adults have multiple manufacturers. IPV as an IPV-only vaccine has only 1 manufacturer, but IPV also is available in combination products DTaP–hepatitis B–IPV, DTaP-IPV/Hib, and DTaP-IPV from different manufacturers. Influenza vaccine for children 2 yr of age or younger is produced by fewer manufacturers (see http://www.cdc.gov/flu/protect/vaccine/vaccines.htm for available influenza vaccines). MMR, MMRV, varicella, pneumococcal conjugate vaccine (13 valent) (PCV13), and tetanus and diphtheria (Td) vaccines also are produced by single manufacturers.

Table 172-4 Characteristics of Polysaccharide and Conjugate Vaccines

CHARACTERISTIC	CONJUGATE	POLYSACCHARIDE
T-lymphocyte dependent immune response	Yes	No
Immune memory	Yes	No
Persistence of protection	Yes	No
Booster effect	Yes	No
Reduction of carriage	Yes	No
Herd protection	Yes	No
Lack of hyporesponsiveness	Yes	No

Vaccine Policy

There are 2 major committees that make vaccine policy recommendations for children: the Committee on Infectious Diseases (COID) of the AAP (the Red Book Committee) and the ACIP of the CDC. Annually, the AAP, the ACIP, and the American Academy of Family Physicians issue a **harmonized** childhood and adolescent immunization schedule (http://www.cdc.gov/vaccines/schedules/index.html). The COID consists primarily of academic pediatric infectious disease specialists with liaisons from practicing pediatricians, professional organizations, and government agencies including the FDA, CDC, National Institutes of Health, and National Vaccine Program Office. Recommendations of the COID must be approved by the AAP Board of Directors. The ACIP consists of 15 voting members who are academic infectious disease experts (for both children and adults), family physicians, state and local public health officials, nurses, and 1 consumer representative. The ACIP also has representatives from 29 liaison organizations, including major medical societies, professional organizations, managed care, and others, as well as 8 ex officio government entities that deal with vaccines. Only ACIP members vote on vaccine recommendations. Since October 2011, the ACIP has used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process to develop evidence-based vaccine recommendations. The ACIP recommendations, available at http://www.cdc.gov/vaccines/acip/recs/index.html, are official only after adoption by the CDC director, which leads to publication in the *Morbidity and Mortality Weekly Report (MMWR Morb Mortal Wkly Rep).* The AAP recommendations are published in the *Red Book* and in issues of *Pediatrics.*

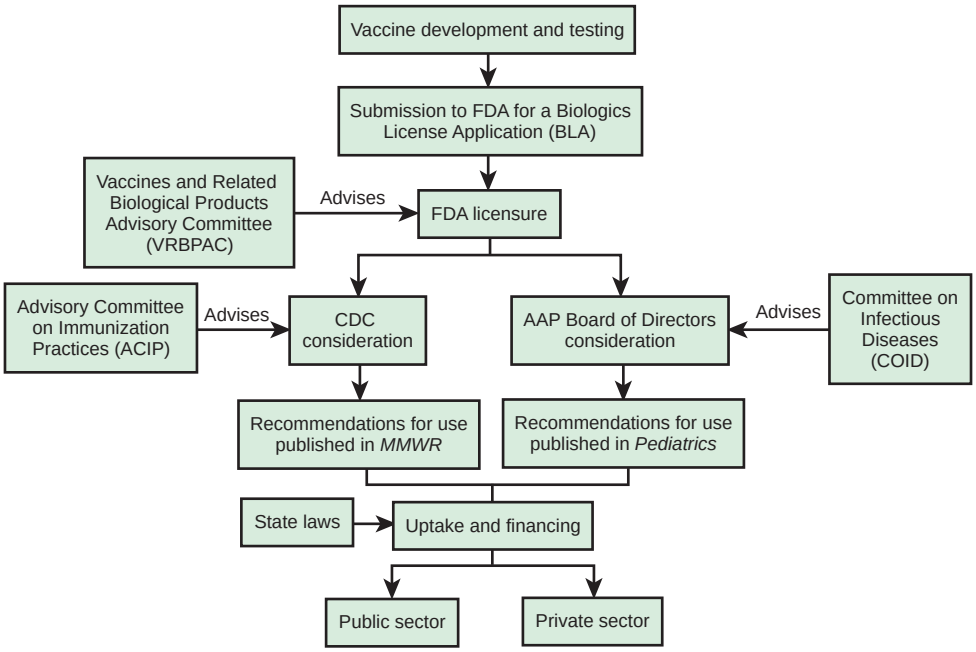


Figure 172-1 Vaccine development and testing. *(Modified from Pickering LK, Orenstein WE: Development of pediatric vaccine recommendations and policies,* Semin Pediatr Infect Dis *13[3]:148–154, 2002.)*

Vaccine Financing

Approximately 50% of vaccines routinely administered to children and adolescents <19 yr of age are purchased thorough a contract negotiated by the federal government with licensed vaccine manufacturers. There are 3 major sources of funds that can purchase vaccines through this contract.

The greatest portion comes from the Vaccines for Children (VFC) program (http://www.cdc.gov/vaccines/programs/vfc/index.html), a federal entitlement program established in 1993. The VFC program covers children on Medicaid, children without any insurance (uninsured), and Native Americans and Alaska Natives. In addition, children who have insurance but whose insurance does not cover immunization (underinsured) can be covered through VFC but only if they go to a federally qualified health center (http://www.cms.gov/center/fqhc.asp). In contrast to other public funding sources that require approval of discretionary funding by legislative bodies, VFC funds are immediately available for new recommendations provided the ACIP votes the vaccine and the recommendation for its use into the VFC program, the federal government negotiates a contract, and the Office of Management and Budget apportions funds. The VFC program can provide free vaccines to participating private providers for administration to children eligible for coverage under the program.

The second major federal funding source is the Section 317 Discretionary Federal Grant Program to states and selected localities. These funds must be appropriated annually by Congress, but in contrast to VFC, they have not had eligibility requirements for use. The third major public source of funds is state appropriations. The VFC program itself does not cover vaccine administration costs. Medicaid covers the administration fees for children enrolled in that program. Parents of other children eligible for VFC must pay administration fees out of pocket, although there is a stipulation in the law that no one eligible for the program can be denied vaccines because of inability to pay the administration fee. The Affordable Care Act states that all vaccines recommended by ACIP and included in the immunization schedules must be provided by qualified insurance programs with no copay and no deductible.

Vaccine Safety Monitoring

Monitoring vaccine safety is the responsibility of the FDA, CDC, and vaccine manufacturers. A critical part of that monitoring depends on reports provided to the Vaccine Adverse Event Reporting System. Adverse events following immunization can be reported by completing a Vaccine Adverse Event Reporting System form that can be obtained from http://www.vaers.hhs.gov, or by calling 1-800-822-7967. Individual Vaccine Adverse Event Reporting System case reports may be helpful in generating hypotheses about whether vaccines are causing certain clinical syndromes, but in general they are not helpful in evaluating the causal role of vaccines in the adverse event. This is because most clinical syndromes that follow vaccination are similar to syndromes that occur in the absence of vaccination, which constitute background rates. For causality assessment, epidemiologic studies are often necessary, comparing the incidence rate of the adverse event after vaccination with the rate in the unvaccinated. A statistically significant higher rate in the vaccinated would be consistent with causation.

The Vaccine Safety Datalink consists of inpatient and outpatient records of some of the largest managed-care organizations in the United States and facilitates causality evaluation. In addition, the clinical immunization safety assessment network has been established to advise primary care physicians on evaluation and management of adverse events (http://www.cdc.gov/vaccinesafety/Activities/CISA.html).

The Institute of Medicine (IOM) has reviewed independently a variety of vaccine safety concerns and published reports (available at http://www.iom.edu/Reports.aspx?Search=vaccine%20safety) summarizing its findings. From 2001 through 2004, the IOM released 8 reports concluding that the body of epidemiologic evidence did not show an association with vaccines and autism.

In 2011, the IOM released a report entitled "Adverse Effects of Vaccines: Evidence and Causality" (http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx), in which the IOM Committee reviewed a list of reported adverse effects associated with 8 vaccines to evaluate the scientific evidence, if any, of an event–vaccine relationship. For the purposes of the report, the committee developed 158 causality conclusions and assigned each relationship between a vaccine and an adverse health problem to 1 of 4 causation categories. The committee concluded that available evidence convincingly supported a causal relationship between MMR, varicella-zoster, influenza, hepatitis B, meningococcal, and tetanus-containing vaccines and anaphylaxis. Additionally, evidence favored rejection of 5 vaccine–adverse event relationships, including MMR vaccine and autism, inactivated influenza vaccines and asthma episodes, as well as Bell palsy, and MMR and DTaP and type 1 diabetes mellitus. For the majority of cases (135 vaccine–adverse event pairs), the evidence was inadequate to accept or reject a causal relationship because of rarity of the events. Overall, the committee concluded that few health problems are caused by or clearly associated with vaccines.

In 2013, the IOM released a report entitled "Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies" (http://www.iom.edu/Reports/2013/The-Childhood-Immunization-Schedule-and-Safety.aspx). The IOM committee uncovered no evidence of major safety concerns associated with adherence to the recommended childhood immunization schedule. For more information on IOM reports, see http://www.iom.edu/.

The National Vaccine Injury Compensation Program, established in 1988, is designed to compensate people injured by vaccines in the childhood and adolescent immunization schedule. The program is funded through an excise tax of $0.75 per disease prevented per dose. As of 2013, all of the routinely recommended vaccines that protect children against 16 diseases are covered by this program. The National Vaccine Injury Compensation Program was established to provide a no-fault system. There is a table of related injuries and time frames. All people alleging injury from covered vaccines must first file with the program. If the injury meets the requirements of the table, compensation is automatic. If not, the claimant has the responsibility to prove causality. If compensation is accepted, the claimant cannot sue the manufacturer or physician administering the vaccine. If the claimant rejects the judgment of the compensation system, the claimant can enter the tort system, which is uncommon. Information on the National Vaccine Injury Compensation Program is available at http://www.hrsa.gov/vaccinecompensation, or by calling 1-800-338-2382. All physicians administering a vaccine covered by the program are required by law to give the approved Vaccine Information Statement to the child's parent or guardian at each visit before administering vaccines. Information on the Vaccine Information Statement can be obtained from http://www.cdc.gov/vaccines/hcp/vis/index.html.

Vaccine Delivery

To ensure potency, vaccines should be stored at recommended temperatures before and after reconstitution. A comprehensive resource for providers on vaccine storage and handling recommendations and best practice strategies is available at http://www.cdc.gov/vaccines/recs/storage/default.htm. Expiration dates should be noted, and expired vaccines should be discarded. Lyophilized vaccines often have long shelf lives. However, the shelf life of reconstituted vaccines generally is short, ranging from 30 min for varicella vaccine to 8 hr for MMR vaccine.

All vaccines have a preferred route of administration, which is specified in package inserts and in AAP and ACIP recommendations. Most inactivated vaccines, including DTaP, hepatitis A, hepatitis B, Hib, inactivated influenza vaccine (IIV), HPV, PCV13, MCV4, and Tdap, are administered IM. In contrast, MPVS4 and the commonly used live-attenuated vaccines, MMR, MMRV, and varicella, should be dispensed by the SC route and rotavirus vaccine is administered orally. IPV and PPS23 (pneumococcal polysaccharide vaccine) can be given IM or SC. One influenza vaccine, LAIV, is administrated intranasally, and another influenza vaccine by the intradermal route. For IM injections, the anterolateral thigh muscle is the preferred site for infants and young children. The recommended needle length varies depending on

age and size: ⅝ inch for newborn infants, 1 inch for infants 2 through 12 mo of age, and 1-1.25 inches for older children. For adolescents and adults, the deltoid muscle of the arm is the preferred site for IM administration with needle lengths of 1-1.25 inches depending on the size of the patient. Most IM injections can be made with 23-25 gauge needles. For SC injections, needle lengths generally range from ⅝ to ¾ inches with 23-25 gauge needles.

Other areas dealing with various aspects of immunization are important for pediatricians and other healthcare providers. Table 172-5 lists websites providing information in these areas.

RECOMMENDED IMMUNIZATION SCHEDULE

All children in the United States should be vaccinated against 16 diseases (Figs. 172-2 and 172-3) (annually updated schedule available at http://www.cdc.gov/vaccines/schedules/index.html).

Hepatitis B vaccine is recommended in a 3 dose schedule starting at birth. The birth dose, as well as hepatitis B immunoglobulin, is critical for infants born to mothers who are hepatitis B surface antigen (HBsAg)–positive or whose hepatitis B immune status is unknown, but the recommendation is to administer hepatitis B vaccine to all newborns before hospital discharge.

The DTaP series consists of 5 doses administered at 2, 4, 6, and 15 through 18 mo of age, and 4 through 6 yr of age. The 4th dose of DTaP may be administered as early as 12 mo of age, provided 6 mo has elapsed since the 3rd dose. The 5th (booster) dose of DTaP vaccine is not necessary if the 4th dose was administered at 4 yr of age or older. One dose of an adult preparation of Tdap is recommended for all adolescents at 11 through 12 yr of age. Adolescents 13 through 18 yr of age who missed the 11 through 12 yr of age Tdap booster dose should receive a single dose of Tdap if they have completed the diphtheria, tetanus, and pertussis (DTP)/DTaP series. Tdap may be given at any interval following the last Td. Table 172-6 lists preparations in which DTaP is combined with other vaccines.

There are 3 licensed preparations of single-antigen Hib vaccines. The vaccine conjugated to tetanus toxoid (PRP-T) is given in a 4 dose series at 2, 4, 6, and 12 through 15 mo of age, and the Hib vaccine conjugated to meningococcal outer membrane protein (PRP-OMP) is recommended in a 3 dose series at 2, 4, and 12 through 15 mo of age. The 3rd Hib vaccine is licensed as a booster for children 15 mo through 4 yr of age. There are several vaccines in which Hib is a component, in addition to single-antigen Hib conjugate vaccines (Table 172-7).

Influenza vaccine is recommended for all children beginning at 6 mo of age, with a minimum age of 6 mo for IIVs and 24 mo of age for LAIVs. Various influenza vaccine preparations are FDA licensed for different age groups (see http://www.cdc.gov/flu/protect/vaccine/vaccines.htm and http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml#flu). Children 6 mo of age through 8 yr of age being vaccinated for the first time should receive 2 doses at least 4 wk apart. If such children only received a single dose of IIV the prior season, they need 2 doses the following season. For additional guidelines, follow dosing instructions in the influenza statement, which is updated annually by the CDC. Influenza vaccine usually is given in October or November, although there are benefits even when administered as late as February or March because influenza seasons most commonly peak in February. People 9 yr of age and older should receive 1 dose of influenza vaccine annually.

IPV should be administered at 2, 4, and 6 through 18 mo of age with a booster dose at 4 through 6 yr of age. The final dose in the series should be administered on or after 4 yr of age and at least 6 mo after the previous dose. The final dose in the IPV series should be administered at 4 yr of age or older regardless of the number of previous doses, and the minimal interval from dose 3 to dose 4 is 6 mo. For catch-up vaccine recommendations, see the recommended childhood immunization schedule at http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html.

MMR should be administered at 12 through 15 mo of age followed by a 2nd dose at 4 through 6 yr of age. Two doses of varicella vaccine should be given, the 1st at 12 through 18 mo of age and the 2nd at 4 through 6 yr of age. MMR and MMRV preparations are available. The quadrivalent MMRV vaccine is preferred in place of separate MMR and varicella vaccines at the 4 through 6 yr old visit. Because of a slight increase in febrile seizures associated with combined MMRV vaccine compared to the separate products, use of MMRV is not preferred over use of separate MMR and varicella vaccines for the initial dose at 12 through 15 mo of age.

Protection against pneumococcal and meningococcal disease can be provided by either conjugated or polysaccharide vaccines. Conjugated vaccines offer several benefits over polysaccharide vaccines (see Table 172-4). PCV13 is recommended as a 4 dose series at 2, 4, 6, and 12 through 15 mo of age. For children 14 through 59 mo of age who have received an age-appropriate series of PCV7, administer a single supplemental dose of PCV13. PPSV23 is recommended for select children with conditions that place them at risk for pneumococcal disease.

A 2 dose series of MCV4 includes a recommended dose for all adolescents at 11 through 12 yr of age and a booster dose at 16 yr of age. If the 1st dose is administered at 13 through 15 yr of age, a booster dose should be administered at 16 through 18 yr of age. No booster dose is needed if the 1st dose is administered at 16 yr of age. In addition, MCV4 should be administered to people 2 mo through 55 yr of age with underlying conditions that place them at high risk of meningococcal disease. People with high-risk conditions should receive 2 doses of MCV4 at 0 and 2 mo followed by booster doses.

Hepatitis A vaccine, licensed for administration to children 12 mo of age and older, is recommended for universal administration to all children at 12 through 23 mo of age and for certain high-risk groups. The 2 doses in the series should be separated by at least 6 mo. Children who have received 1 dose of hepatitis A vaccine before 24 mo of age should receive a 2nd dose 6-18 mo after the 1st dose. For anyone 2 yr of age or older who has not yet received the 2 dose hepatitis A vaccine series, 2 doses of vaccine separated by 6-18 mo may be administered if immunity against hepatitis A infection is desired.

Administer a 3 dose series of HPV vaccine to all adolescents 11 through 12 yr of age. Either HPV4 or HPV2 is recommended in a 3 dose series to females, and only HPV4 in the same schedule is recommended for males. The vaccine series can be started at 9 yr of age. Administer the 2nd dose at 1-2 mo after the 1st dose, and the 3rd dose 6 mo after the 1st dose (at least 24 wk after the 1st dose).

Two rotavirus vaccines are available, RotaTeq (RV5) and Rotarix (RV1). With both vaccines, the 1st dose can be administered as early as 6 wk of age and must be administered by 14 wk 6 days. The final dose in the series must be administered no later than 8 mo of age. The RV5 vaccine is administered in 3 doses at least 4 wk apart. The RV1 vaccine is administered in 2 doses at least 4 wk apart. Immunization should not be initiated for infants 15 wk of age and older as stated in the immunization schedule.

The present schedule, excluding influenza vaccine, can require as many as 34 doses, including 31 that must be administered by injection. Of the doses, 25 are recommended prior to 2 yr of age, including 22 injections. Influenza vaccination, starting at 6 mo of age, can add an additional 20 injections through 18 yr of age. To reduce the injection burdens, several combination vaccines are available (see Table 172-7).

The recommended childhood and adolescent immunization schedule establishes a routine adolescent visit at 11 through 12 yr of age. MCV4, a Tdap booster, and HPV vaccine should be administered during this visit. Influenza vaccine should be administered annually. In addition, the 11 through 12 yr old visit is an opportune time to review all of the immunizations the adolescent has received previously, to provide any doses that were missed, and to review other age-appropriate preventive services. The 11 through 12 year old visit establishes an important platform for incorporating other vaccines. Information on the current status of new vaccine licensure and recommendations for use can be obtained at http://aapredbook.aappublications.org/site/news/vaccstatus.xhtml and http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM093833.

For children who are at least 1 mo behind in their immunizations, catch-up immunization schedules are available for children 4 mo

Text continued on p. 1254

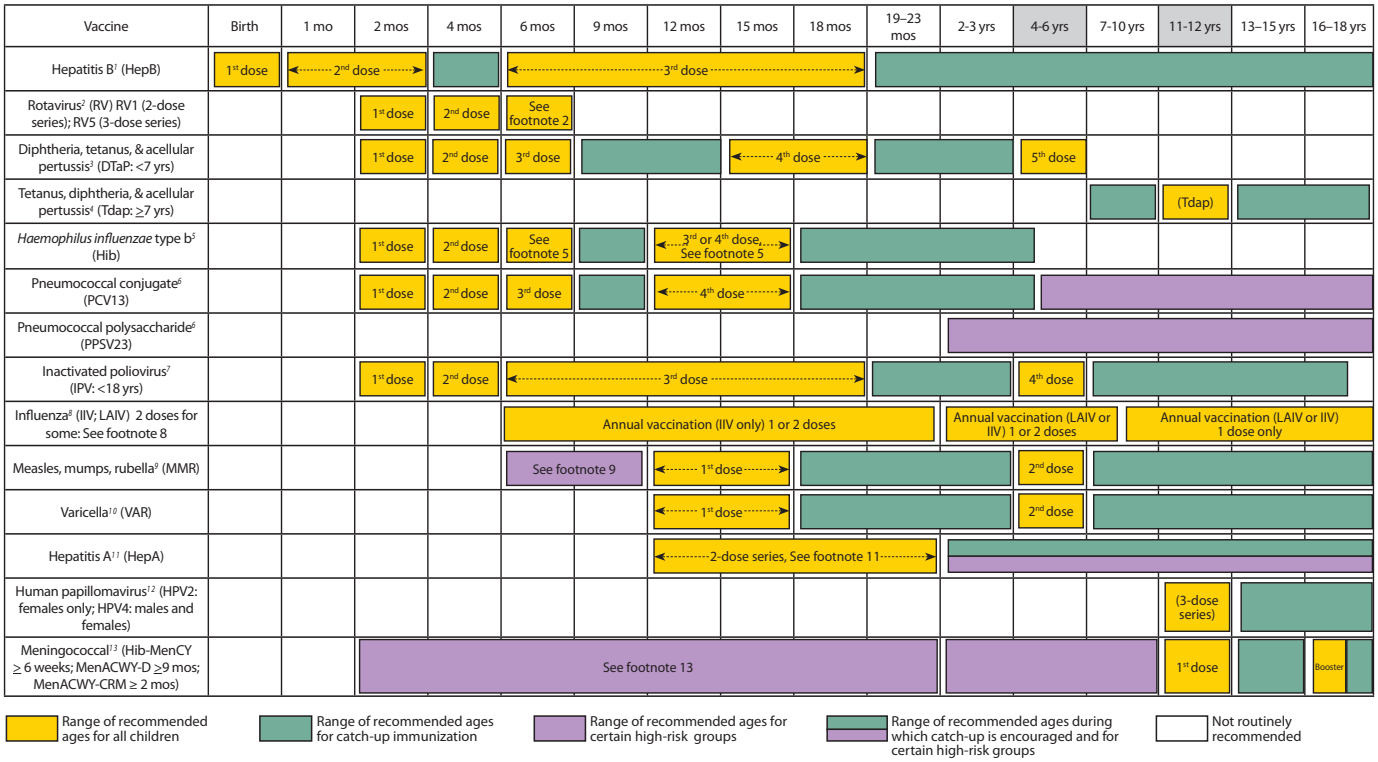
Table 172-5 Vaccine Websites and Resources

ORGANIZATION	WEBSITE
HEALTH PROFESSIONAL ASSOCIATIONS	
American Academy of Family Physicians (AAFP)	http://www.familydoctor.org/online/famdocen/home.html
American Academy of Pediatrics (AAP)	http://www.aap.org/
AAP Childhood Immunization Support Program	http://www.aap.org/immunization/
American Association of Occupational Health Nurses (AAOHN)	http://www.aaohn.org/
American College Health Association (ACHA)	http://www.acha.org/
American College of Obstetricians and Gynecologists (ACOG)–Immunization for Women	http://www.immunizationforwomen.org/
American Medical Association (AMA)	http://www.ama-assn.org/
American Nurses Association (ANA)	http://www.nursingworld.org/
American Pharmacists Association (APhA)	http://www.pharmacist.com/
American School Health Association (ASHA)	http://www.ashaweb.org/i4a/pages/index.cfm?pageid=1
American Travel Health Nurses Association (ATHNA)	http://www.ashaweb.org/i4a/pages/index.cfm?pageid=1
Association for Professionals in Infection Control and Epidemiology (APIC)	http://www.apic.org/
Association of State and Territorial Health Officials (ASTHO)	http://www.astho.org/
Association of Teachers of Preventive Medicine (ATPM)	http://www.atpm.org/
National Medical Association (NMA)	http://www.nmanet.org/
Society of Teachers of Family Medicine—Group on Immunization Education	http://www.immunizationed.org/
NONPROFIT GROUPS AND UNIVERSITIES	
Albert B. Sabin Vaccine Institute	http://www.sabin.org/
Allied Vaccine Group (AVG)	http://www.vaccine.org/
Brighton Collaboration	https://brightoncollaboration.org/public
Center for Vaccine Awareness and Research—Texas Children's Center	http://www.texaschildrens.org/Locate/Departments-and-Services/Vaccine/
Children's Vaccine Program	http://www.path.org/vaccineresources/
Every Child by Two (ECBT)	http://www.ecbt.org/
Families Fighting Flu	http://www.familiesfightingflu.org/
Global Alliance for Vaccines and Immunization (GAVI)	http://www.gavialliance.org/
Health on the Net Foundation (HON)	http://www.hon.ch/
Immunization Action Coalition (IAC)	http://www.immunize.org/
Infectious Diseases Society of America (IDSA)	http://www.idsociety.org/Index.aspx
Institute for Vaccine Safety (IVS), Johns Hopkins Bloomberg School of Public Health	http://www.vaccinesafety.edu/
Institute of Medicine (IOM)	http://www.iom.edu/Activities/PublicHealth/ImmunizationSafety.aspx
National Alliance for Hispanic Health	http://www.hispanichealth.org/
National Foundation for Infectious Diseases (NFID)	http://www.idsociety.org/Index.aspx
National Foundation for Infectious Diseases (NFID)—Childhood Influenza Immunization Coalition (CIIC)	http://www.preventchildhoodinfluenza.com/
National Healthy Mothers, Healthy Babies Coalition (HMHB)	http://www.hmhb.org/
National Network for Immunization Information (NNii)	http://www.immunizationinfo.org/
Parents of Kids with Infectious Diseases (PKIDS)	http://www.pkids.org/
PATH Vaccine Resource Library	http://www.cdc.gov/vaccines/acip/index.html
The Vaccine Education Center at the Children's Hospital of Philadelphia	http://www.chop.edu/service/vaccine-education-center/home.html
The Vaccine Place	http://www.vaccineplace.com/?fa=home
Vaccinate Your Baby	http://www.vaccinateyourbaby.org/
GOVERNMENT ORGANIZATIONS	
Centers for Disease Control and Prevention (CDC)	
Advisory Committee on Immunization Practices (ACIP)	http://www.cdc.gov/vaccines/acip/index.html
ACIP Vaccine Recommendations	http://www.cdc.gov/vaccines/hcp/acip-recs/index.html
Current Vaccine Delays and Shortages	http://www.cdc.gov/vaccines/vac-gen/shortages/
Public Health Image Library	http://www.phil.cdc.gov/phil/home.asp
Travelers' Health	http://www.cdc.gov/travel/
Vaccine Adverse Events Reporting System (VAERS)	http://www.cdc.gov/vaccinesafety/Activities/vaers.html
Vaccine Administration: Recommendations and Guidelines	http://www.cdc.gov/vaccines/recs/vac-admin/default.htm
Vaccines and Immunizations	http://www.cdc.gov/vaccines/
Vaccines for Children Program	http://www.cdc.gov/vaccines/programs/vfc/index.html
Vaccines for Children—Vaccine Price List	http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html
Vaccine Safety	http://www.cdc.gov/vaccinesafety/index.html
Vaccine Storage and Handling	http://www.cdc.gov/vaccines/recs/storage/default.htm
Department of Health and Human Services (HHS)	
National Vaccine Program Office (NVPO)	http://www.hhs.gov/nvpo/
Health Resources and Services Administration	
National Vaccine Injury Compensation Program	http://www.hrsa.gov/vaccinecompensation/
National Institute of Allergy and Infectious Diseases (NIAID)	
Vaccines	http://www.niaid.nih.gov/topics/vaccines/Pages/Default.aspx
World Health Organization (WHO)	
Immunization, Vaccines, and Biologicals	http://www.who.int/immunization/en/

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 years – United States, 2015.

(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 172-3]).

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 172-2. To determine minimum intervals between doses, see the catch-up schedule (Figure 172-3). School entry and adolescent vaccine age groups are shaded.



This schedule includes recommendations in effect as of January 1, 2015. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http//www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2015

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the Adult Immunization Schedule.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months.
- Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.
- For vaccination of persons with primary and secondary immunodeficiencies, see Table 13, *"Vaccination of persons with primary and secondary immunodeficiencies,"* in *General Recommendations on Immunization* (ACIP), available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and American Academy of Pediatrics. "Immunization in Special Clinical Circumstances," in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**

Routine vaccination:

At birth:

- Administer monovalent HepB vaccine to all newborns before hospital discharge.
- For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series at age 9 through 18 months (preferably at the next well-child visit).
- If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

Doses following the birth dose:

- The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
- Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Figure 2.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered **no earlier than age 24 weeks**.
- Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

Catch-up vaccination:

- Unvaccinated persons should complete a 3-dose series.
- A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
- For other catch-up guidance, see Figure 172-3.

2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])**

Routine vaccination:

Administer a series of RV vaccine to all infants as follows:

1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

Catch-up vaccination:

- The maximum age for the first dose in the series is 14 weeks, 6 days; vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
- The maximum age for the final dose in the series is 8 months, 0 days.
- For other catch-up guidance, see Figure 172-3.

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)**

Routine vaccination:

- Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP need not be repeated if it was administered at least 4 months after the third dose of DTaP.

Figure 172-2 Recommended immunization schedule for persons aged 0 through 18 yr—United States, 2015. *(From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html)*

Continued

3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine (cont'd)

Catch-up vaccination:
- The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
- For other catch-up guidance, see Figure 172-3.

4. Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for both Boostrix and Adacel)

Routine vaccination:
- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks' gestation) regardless of time since prior Td or Tdap vaccination.

Catch-up vaccination:
- Persons aged 7 years and older who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 dose (preferably the first) in the catch-up series; if additional doses are needed, use Td vaccine. For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
- Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoid (Td) booster doses every 10 years thereafter.
- Inadvertent doses of DTaP vaccine:
  - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
  - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
- For other catch-up guidance, see Figure 172-3.

5. *Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-MenCY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])

Routine vaccination:
- Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
- The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
- One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
- For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Catch-up vaccination:
- If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
- If both doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later.
- If first dose is administered before the first birthday and second dose administered at younger than 15 months, a third (and final) dose should be given 8 weeks later.
- For unvaccinated children aged 15 months or older, administer only 1 dose.
- For other catch-up guidance, see Figure 172-3. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* February 28, 2014 / 63(RR01);1-13, available at http://www.cdc.gov/mmwr/PDF/rr/rr6301.pdf.

Vaccination of persons with high-risk conditions:
- Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement deficiency, who have received either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
- For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
- Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
- A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
- Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

6. Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23)

Routine vaccination with PCV13:
- Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
- For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

Catch-up vaccination with PCV13:
- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:
- All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
- For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; solid organ transplantation; or congenital immunodeficiency:
  1. Administer 1 dose of PCV13 if any incomplete schedule of 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  2. Administer 2 doses of PCV13 at least 8 weeks apart if unvaccinated or any incomplete schedule of fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
  4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
  5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
  1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
  2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
  3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
- For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
- A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin's disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

7. Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)

Routine vaccination:
- Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

Catch-up vaccination:
- In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk of imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up guidance, see Figure 172-3.

8. Influenza vaccines. (Minimum age: 6 months for inactivated influenza vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])

Routine vaccination:
- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) persons who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine; 2) children 2 through 17 years receiving aspirin or aspirin-containing products; 3) persons who are allergic to eggs; 4) pregnant women; 5) immunosuppressed persons; 6) children 2 through 4 years of age with asthma or who had wheezing in the past 12 months; or 7) persons who have taken influenza antiviral medications in the previous 48 hours. For all other contraindications and precautions to use of LAIV, see *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.

Figure 172-2, cont'd

8. Influenza vaccines (cont'd)

For children aged 6 months through 8 years:

- For the 2014-15 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. Some children in this age group who have been vaccinated previously will also need 2 doses. For additional guidance, follow dosing guidelines in the 2014-15 ACIP influenza vaccine recommendations, *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.
- For the 2015–16 season, follow dosing guidelines in the 2015 ACIP influenza vaccine recommendations.

For persons aged 9 years and older:

- Administer 1 dose.

9. Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)

Routine vaccination:

- Administer a 2-dose series of MMR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the first at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:

- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. Varicella (VAR) vaccine. (Minimum age: 12 months)

Routine vaccination:

- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:

- Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007 / 56 [No. RR-4], available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. Hepatitis A (HepA) vaccine. (Minimum age: 12 months)

Routine vaccination:

- Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:

- The minimum interval between the two doses is 6 months.

Special populations:

- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. The first dose should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

12. Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardasil])

Routine vaccination:

- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks); administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).

Catch-up vaccination:

- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see Routine vaccination above) for vaccine series catch-up.

13. Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 months for MenACWY-CRM [Menveo])

Routine vaccination:

- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.
- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menveo with at least 8 weeks between doses.
- For children aged 2 months through 18 years with high-risk conditions, see below.

Catch-up vaccination:

- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Figure 172-3.

Vaccination of persons with high-risk conditions and other persons at increased risk of disease:

- Children with anatomic or functional asplenia (including sickle cell disease):
  1. Menveo
     - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.
- Children with persistent complement component deficiency:
  1. Menveo
     - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - *Children 9 through 23 months:* Administer 2 primary doses at least 12 weeks apart.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
- For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W meningococcal disease. Prior receipt of MenHibrix is not sufficient for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.
- For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
- For booster doses among persons with high-risk conditions, refer to *MMWR* 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.

For other catch-up recommendations for these persons, and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

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Figure 172-2, cont'd

FIGURE 172-3. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind —United States, 2015.
The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

Children age 4 months through 6 years					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B[1]	Birth	4 weeks	8 weeks *and* at least 16 weeks after first dose. Minimum age for the final dose is 24 weeks.		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, and acellular pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[5]	6 weeks	4 weeks if first dose was administered before the 1st birthday. 8 weeks (as final dose) if first dose was administered at age 12 through 14 months. No further doses needed if first dose was administered at age 15 months or older.	4 weeks[5] if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel) or unknown. 8 weeks *and* age 12 through 59 months (as final dose)[5] • if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR • if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR • if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday. No further doses needed if previous dose was administered at age 15 months or older.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal[6]	6 weeks	4 weeks if first dose administered before the 1st birthday. 8 weeks (as final dose for healthy children) if first dose was administered at the 1st birthday or after. No further doses needed for healthy children if first dose administered at age 24 months or older.	4 weeks if current age is younger than 12 months and previous dose given at <7months old. 8 weeks (as final dose for healthy children) if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months. No further doses needed for healthy children if previous dose administered at age 24 months or older.	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus[7]	6 weeks	4 weeks[7]	4 weeks[7]	6 months[7] (minimum age 4 years for final dose).	
Meningococcal[13]	6 weeks	8 weeks[13]	See footnote 13	See footnote 13	
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months			
Hepatitis A[11]	12 months	6 months			
Children and adolescents age 7 through 18 years					
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis[4]	7 years[4]	4 weeks	4 weeks if first dose of DTaP/DT was administered before the 1st birthday. 6 months (as final dose) if first dose of DTaP/DT was administered at or after the 1st birthday.	6 months if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus[12]	9 years	Routine dosing intervals are recommended.[12]			
Hepatitis A[11]	Not applicable (N/A)	6 months			
Hepatitis B[1]	N/A	4 weeks	8 weeks **and** at least 16 weeks after first dose.		
Inactivated poliovirus[7]	N/A	4 weeks	4 weeks[7]	6 months[7]	
Meningococcal[13]	N/A	8 weeks[13]			
Measles, mumps, rubella[9]	N/A	4 weeks			
Varicella[10]	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older.			

NOTE: The above recommendations must be read along with the footnotes of this schedule in Fig. 172-2.

Figure 172-3 Catch-up immunization schedule for persons aged 4 mo through 18 yr who start late or who are more than 1 mo old–United States, 2015. *(From Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/vaccines/schedules/downloads/child/catchup-schedule-pr.pdf)*

through 18 yr of age (http://www.cdc.gov/vaccines/schedules/hcp/imz/catchup.html). Also available are interactive immunization schedulers for children <6 yr of age at https://www.vacscheduler.org and for adolescents at http://www.cdc.gov/recs/scheduler/AdolscentScheduler.htm.

VACCINES RECOMMENDED IN SPECIAL CIRCUMSTANCES

There are 4 vaccines (PCV13, PPSV23, MCV4, and Hib) recommended for children and adolescents at increased risk for complications from vaccine-preventable diseases or children who have an increased risk for exposure to these diseases, who are outside the age groups for which these vaccines are normally recommended (PPSV23 is not routinely recommended for any age group of children and is only used for children with high-risk conditions; see Table 172-7). Specific recommendations for use of these vaccines in children with various underlying conditions can be found in the recommended immunization schedule.

PCV13 is recommended for all children <5 yr of age who have conditions that place them at high risk for pneumococcal disease. This recommendation includes children with sickle cell disease and other hemoglobinopathies, including hemoglobin SS, hemoglobin S-C, or hemoglobin S–β-thalassemia, or children who are functionally or anatomically asplenic; children with HIV infection; and children who have chronic disease (see Table 172-7). Children at high risk for pneumococcal disease also should receive PPSV23 to provide immunity to serotypes not contained in the 13-valent conjugate vaccine. PPSV23 should be administered on or after the 2nd birthday and should follow completion of the PCV13 series by at least 6-8 wk. Two doses of PPSV23 are recommended, with an interval of 5 yr between doses. Immunization of previously unvaccinated children with high-risk conditions who are >5 yr of age can be performed with either a dose of PCV13 or a dose of PPSV23.

MCV4 is recommended for people with HIV, children with functional or anatomic asplenia, persistent complement component or properdin deficiencies, and as part of outbreak-control programs. Hib

Table 172-6 Combination Vaccines Licensed and Available in the United States

VACCINE PRODUCT (MANUFACTURER)*	TRADE NAME (YEAR LICENSED)	COMPONENTS	Recommended Ages	
			PRIMARY SERIES	BOOSTER DOSE
Hib-HepB[†‡] (Merck & Co, Inc.)	Comvax (1996)	PRP-OMP + HepB vaccine	2, 4 mo of age	12 through 15 mo of age
MenCY/Hib (GlaxoSmithKline)	MenHibRix (2013)	MenCY + PRP-T	2, 4, 6 mo of age	12 through 15 mo of age
DTaP-IPV/Hib (Sanofi Pasteur)	Pentacel (2008)	DTaP-IPV + PRP-T	2, 4, 6 mo of age	15 through 18 mo of age
DTaP-HepB-IPV (GlaxoSmithKline)	Pediarix (2002)	DTaP + HepB + IPV	2, 4, 6 mo of age	
DTaP-IPV (GlaxoSmithKline)	Kinrix (2008)	DTaP + IPV		4 through 6 yr of age: • booster for 5th dose of DTaP • booster for 4th dose of IPV
HepA-HepB (GlaxoSmithKline)	Twinrix (2001)	HepA + HepB	>18 yr of age; 0, 1, and 6 mo schedule	
MMRV (Merck & Co, Inc.)	ProQuad (2005)	MMR + varicella	12 through 15 mo of age	4 through 6 yr of age

*Dash (-) indicates that products are supplied in their final form by the manufacturer and do not require mixing or reconstitution by user; slash (/) indicates that products are mixed or reconstituted by user.

[†]If a PRP-OMP vaccine is not administered as both doses in the primary series or if there is uncertainty about which products were administered previously, a 3rd dose of Hib conjugate vaccine is needed to complete the primary series.

[‡]Preferred for American Indian/Alaska Native children.

DTap, diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; IPV/Hib, trivalent inactivated polio vaccine and *Haemophilus influenzae* type b vaccine; MMRV, measles-mumps-rubella and varicella vaccine.

Modified from MMWR 62(2):1-28, 2013.

Table 172-7 Vaccines Recommended for Children and Adolescents with Underlying Conditions or at High Risk

VACCINES	CONDITIONS

PCV13 (and PPSV23 in certain conditions)	• Immunocompetent children with:
	  • Chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure)
	  • Chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy)
	  • Diabetes mellitus
	  • Cerebrospinal fluid leaks
	  • Cochlear implant
	• Anatomic or functional asplenia (including sickle cell disease and other hemoglobinopathies, congenital or acquired asplenia or splenic dysfunction)
	• Immunocompromising conditions: HIV infection; chronic renal failure and nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease or solid organ transplantation; congenital immunodeficiency

MCV4	• Anatomic or functional asplenia (including sickle cell disease) • Persistent complement component deficiency • Residents of or travelers to countries in African meningitis belt or pilgrims on the Haj • During outbreaks caused by a vaccine serogroup
Hib	• Anatomic or functional asplenia (including sickle cell disease) • Immunocompromising conditions: HIV disease; immunosuppressive therapy for malignant neoplasms; immunoglobulin deficiency including immunoglobulin G_2 subclass deficiency or early complement deficiency; recipients of a hematopoietic stem cell transplant (HSCT)

vaccine is recommended for children with certain high-risk conditions (see Table 172-7).

A variety of vaccines are available for children who will be **traveling** to areas of the world where certain infectious diseases are common in addition to vaccines in the recommended childhood and adolescent schedule (Table 172-8). Vaccines for travelers include typhoid fever, hepatitis A, hepatitis B, Japanese encephalitis, MCV4 or MPS4, rabies, and yellow fever, depending on the location and circumstances of travel. Measles is endemic in many parts of the world. Children 6 through 11 mo of age should receive a dose of MMR before international travel. However, doses of measles vaccine received before 12 mo of age should not be counted in determining compliance with the recommended 2 dose MMR schedule. Additional information on vaccines for international travel can be found at http://wwwnc.cdc.gov/travel/.

Vaccine recommendations for children with **immunocompromising conditions**, either primary (inherited) or secondary (acquired), vary according to the underlying condition, the degree of immune deficit, the risk for exposure to disease, and the vaccine (Table 172-9). Immunization of children with immunocompromise poses the following potential concerns: the incidence or severity of some vaccine-preventable diseases is higher, and therefore certain vaccines are recommended specifically for certain conditions; vaccines may be less effective during the period of altered immunocompetence and may need to be repeated when immune competence is restored; and because of altered immunocompetence, some children and adolescents may be

Table 172-8 Recommended Immunizations for Travelers to Developing Countries*

IMMUNIZATIONS	Length of Travel		
	BRIEF, <2 WK	INTERMEDIATE, 2 WK-3 MO	LONG-TERM RESIDENTIAL, >3 MO
Review and complete age-appropriate childhood and adolescent schedule (see text for details)	+	+	+
• DTaP, poliovirus, pneumococcal, and *Haemophilus influenzae* type b vaccines may be given at 4-wk intervals if necessary to complete the recommended schedule before departure • Measles: 2 additional doses given if <12 mo of age at 1st dose • Rotavirus • Varicella • HPV • Hepatitis B† • Tdap • MCV4			
Yellow fever‡	+	+	+
Hepatitis A§	+	+	+
Typhoid fever‖	±	+	+
Meningococcal disease¶	±	±	±
Rabies**	±	+	+
Japanese encephalitis††	±	±	+

*See disease-specific chapters in the Red Book for details. For further sources of information, see text.
†If there is insufficient time to complete 6 mo primary series, accelerated series can be given.
‡For regions with endemic infection, see Health Information for International Travel (http://www.cdc.gov/travel).
§Indicated for travelers to areas with intermediate or high endemic rates of hepatitis A virus infection.
‖Indicated for travelers who will consume food and liquids in areas of poor sanitation.
¶Recommended for regions of Africa with endemic infection and during local epidemics, and required for travel to Saudi Arabia for the Hajj.
**Indicated for people with high risk for animal exposure (especially to dogs) and for travelers to countries with endemic infection.
††For regions with endemic infection (see Health Information for International Travel). For high-risk activities in areas experiencing outbreaks, vaccine is recommended, even for brief travel.
+, Recommended; ±, consider; DTaP, diphtheria and tetanus toxoids and acellular pertussis.
Modified Pickering LK, Baker CJ, Kimberlin DW, Long SL, editors: Red Book 2012: report of the Committee on Infectious Diseases, *Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 104.*

at increased risk for an adverse event following receipt of a live viral vaccine. Live-attenuated vaccines generally are contraindicated in immunocompromised people. The exceptions include MMR, which may be given to a child with HIV infection provided the child is asymptomatic or symptomatic without evidence of severe immunosuppression, and varicella vaccine, which may be given to HIV-infected children if the $CD4^+$ lymphocyte count is at least 15%. MMRV is not recommended in these situations.

Altered immunocompetence is considered a precaution for rotavirus; however, the vaccine is contraindicated in children with severe combined immunodeficiency disease. Inactivated vaccines may be administered to immunocompromised children, although, depending on the immune deficit, their effectiveness might not be optimal. Children with complement deficiency disorders may receive all vaccines, including live-attenuated vaccines. In contrast, children with phagocytic disorders may receive both inactivated and live-attenuated viral vaccines but not live-attenuated bacterial vaccines.

Corticosteroids can suppress the immune system. Children receiving corticosteroids (≥2 mg/kg/day or ≥20 mg/day of prednisone or equivalent) for 14 or more days should not receive live vaccines until therapy has been discontinued for at least 1 mo. Children on the same dose levels but for <2 wk may receive live viral vaccines as soon as therapy is discontinued, although some experts would wait 2 wk after therapy has been discontinued. Children receiving lower doses of corticosteroids may be vaccinated while receiving therapy.

Children and adolescents with malignancy, and those who have undergone solid organ or hematopoietic stem cell transplantation and immunosuppressive or radiation therapy, should not receive live virus and live bacterial vaccines depending on their immune status. Children who have undergone chemotherapy for leukemia may need to be reimmunized with age-appropriate single doses of previously administered vaccines.

Preterm infants generally can be vaccinated at the same chronologic age as full-term infants according to the recommended childhood immunization schedule. An exception is the birth dose of hepatitis B vaccine. Infants weighing ≥2 kg and who are stable may receive a birth dose. However, hepatitis B vaccination should be deferred in infants weighing <2 kg at birth until 30 days of age, if born to an HBsAg-negative mother. All preterm, low birthweight infants born to HBsAg-positive mothers should receive hepatitis B immunoglobulin and hepatitis B vaccine within 12 hr of birth. However, such infants should receive an additional 3 doses of vaccine starting at 30 days of age (see Fig. 172-2).

Some children have situations that are not addressed directly in current immunization schedules. There are general rules that physicians can use to guide immunization decisions in some of these instances. In general, vaccines may be given simultaneously on the same day, whether inactivated or live. Different inactivated vaccines can be administered at any interval between doses. However, because of theoretical concerns about viral interference, different live-attenuated vaccines (MMR, varicella, LAIV) if not administered on the same day, should be given at least 1 mo apart. An inactivated and a live vaccine may be spaced at any interval from each other.

Immunoglobulin does not interfere with killed vaccines. However, immunoglobulin can interfere with the immune response to measles vaccine and by inference to varicella vaccine. In general, immunoglobulin, if needed, should be administered at least 2 wk after measles vaccine. Depending on the dose of immunoglobulin received, MMR

Table 172-9 Vaccination of Persons with Primary and Secondary Immune Deficiencies

PRIMARY

CATEGORY	SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
B lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV[†] Smallpox LAIV BCG Ty21a (live typhoid) YF	Pneumococcal Consider measles and varicella vaccination	The effectiveness of any vaccine will be uncertain if it depends only on the humoral response (e.g., PPSV, MPSV) IVIG interferes with the immune response to measles vaccine and possibly varicella vaccine
	Less-severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency)	OPV[†] BCG YF Other live vaccines appear to be safe	Pneumococcal	All vaccines probably effective Immune response may be attenuated
T lymphocyte (cell-mediated and humoral)	Complete defects (e.g., SCID, complete DiGeorge syndrome)	All live vaccines[‡§‖]	Pneumococcal	Vaccines may be ineffective
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines[‡§‖]	Pneumococcal Meningococcal Hib (if not administered in infancy)	Effectiveness of any vaccine depends on degree of immune suppression
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal	All routine vaccines probably effective
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency	Live bacterial vaccines[‡]	Pneumococcal[¶]	All inactivated vaccines safe and probably effective Live viral vaccines probably safe and effective

SECONDARY

SPECIFIC IMMUNODEFICIENCY	CONTRAINDICATED VACCINES*	RISK-SPECIFIC RECOMMENDED VACCINES*	EFFECTIVENESS AND COMMENTS
HIV/AIDS	OPV[†] Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons	Pneumococcal Consider Hib (if not administered in infancy) and meningococcal vaccination	MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, may be effective[#]
Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status[‡§]	Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression
Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines probably effective
Chronic renal disease	LAIV	Pneumococcal Hepatitis B**	All routine vaccines probably effective

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.

[†]OPV is no longer recommended for routine use in the United States.

[‡]Live bacterial vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.

[§]Live viral vaccines: MMR, MMRV, OPV, LAIV, YF, zoster, rotavirus, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

[‖]Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for SCID.

[¶]Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

[#]HIV-infected children should receive immunoglobulin after exposure to measles and may receive varicella, measles, and YF vaccine if CD4+ lymphocyte count is greater than 15%. (For YF vaccine, CD4+ T-lymphocyte count between 15% and 24% is a precaution.)

**Indicated based on the risk from dialysis-based bloodborne transmission.

BCG, bacille Calmette-Guérin vaccine; Hib, *Haemophilus influenzae* type b vaccine; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IVIG, intravenous immunoglobulin; LAIV, live-attenuated influenza vaccine; MMR, measles, mumps, rubella vaccine; MPSV, quadrivalent meningococcal polysaccharide vaccine; OPV, oral poliovirus vaccine (live); PPSV, pneumococcal polysaccharide vaccine; SCID, severe combined immunodeficiency disease; YF, yellow fever.

Adapted from American Academy of Pediatrics: Passive immunization. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors: Red book 2012 report of the Committee on Infectious Diseases, *Elk Grove Village, IL, 2012, American Academy of Pediatrics, pp. 75–77.*

should be deferred for as long as 3 through 11 mo. Immunoglobulin is not expected to interfere with the immune response to LAIV or rotavirus vaccines.

PRECAUTIONS AND CONTRAINDICATIONS

Observation of valid precautions and contraindications is critical to ensure that vaccines are used in the safest manner possible and to obtain optimal immunogenicity. When a child presents for immunization with a clinical condition considered a precaution, the physician must weigh benefits and risks to that individual child. If benefits are judged to outweigh risks, then the vaccine or vaccines in question may be administered. A contraindication means the vaccine should not be administered under any circumstances.

A general contraindication for all vaccines is anaphylactic reaction to a prior dose. Anaphylactic hypersensitivity to vaccine constituents is also a contraindication. However, if a vaccine is essential, there are desensitizing protocols for some vaccines. The major constituents of concern are egg proteins for vaccines grown in eggs; gelatin, a stabilizer in many vaccines; and antimicrobial agents. The measles and mumps components of MMR are grown in chick embryo fibroblast tissue culture. However, the amount of egg protein in MMR is so small as not to require any special procedures before administering vaccine to someone with a history of anaphylaxis following egg ingestion.

Vaccines usually should be deferred in children with moderate to severe acute illnesses, regardless of the presence of fever, until the child recovers. However, children with mild illnesses may be vaccinated. Studies of undervaccinated children have documented opportunities that were missed because mild illness was used as an invalid contraindication. Complete tables of contraindications and contraindication misperceptions can be found at http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm.

IMPROVING IMMUNIZATION COVERAGE

Standards for child and adolescent immunization practices have been developed to support achievement of high levels of immunization coverage while providing vaccines in a safe and effective manner and educating parents about risks and benefits of vaccines (Table 172-10).

Table 172-10 Standards for Child and Adolescent Immunization Practices

AVAILABILITY OF VACCINES
Vaccination services are readily available.
Vaccinations are coordinated with other healthcare services and provided in a medical home when possible.
Barriers to vaccination are identified and minimized.
Patient costs are minimized.
ASSESSMENT OF VACCINATION STATUS
Healthcare professionals review the vaccination and health status of patients at every encounter to determine which vaccines are indicated.
Healthcare professionals assess for and follow only medically accepted contraindications.
EFFECTIVE COMMUNICATION ABOUT VACCINE BENEFITS AND RISKS
Parents or guardians and patients are educated about the benefits and risks of vaccination in a culturally appropriate manner and in easy-to-understand language.
PROPER STORAGE AND ADMINISTRATION OF VACCINES AND DOCUMENTATION OF VACCINATIONS
Healthcare professionals follow appropriate procedures for vaccine storage and handling.
Up-to-date, written vaccination protocols are accessible at all locations where vaccines are administered.
Persons who administer vaccines and staff who manage or support vaccine administration are knowledgeable and receive ongoing education.
Healthcare professionals simultaneously administer as many indicated vaccine doses as possible.
Vaccination records for patients are accurate, complete, and easily accessible.
Healthcare professionals report adverse events following vaccination promptly and accurately to the Vaccine Adverse Event Reporting System (VAERS) and are aware of a separate program, the National Vaccine Injury Compensation Program (VICP).
All personnel who have contact with patients are appropriately vaccinated.
IMPLEMENTATION OF STRATEGIES TO IMPROVE VACCINATION COVERAGE
Systems are used to remind parents or guardians, patients, and healthcare professionals when vaccinations are due and to recall those who are overdue.
Office- or clinic-based patient record reviews and vaccination coverage assessments are performed annually.
Healthcare professionals practice community-based approaches.

From the National Vaccine Advisory Committee: Standards for child and adolescent immunization practices, Pediatrics *112:958–963, 2003.*

Despite benefits that vaccines have to offer, many children are underimmunized as a result of not receiving recommended vaccines or not receiving them at the recommended ages. Much of the underimmunization problem can be solved through physician actions. Most children have a regular source of healthcare. However, missed opportunities to provide immunizations at healthcare visits include failure to provide all recommended vaccines that could be administered at a single visit during that visit, failure to provide immunizations to children outside of well-child care when the conditions children may have are not contraindications to immunizations, and referral of children to public health clinics because of inability to pay for vaccines. Simultaneous administration of multiple vaccines generally is safe and effective. When the benefits of simultaneous vaccination are explained, many parents prefer such immunization rather than making an extra visit. Providing all needed vaccines simultaneously should be the standard of practice.

Only valid contraindications and precautions to vaccine administration should be observed. Ideally, immunizations should be provided during well-child visits, but using other visits to administer vaccines if there are no contraindications, particularly if a child is behind in the schedule, is important. There is no good evidence that providing immunizations outside of well-child care ultimately decreases well-child visits.

Financial barriers to immunization should be minimized. Participation in the Vaccines for Children program allows physicians to receive vaccines at no cost for their eligible patients, which helps such patients be immunized in their medical home.

Several interventions have been shown to help physicians increase immunization coverage in their practices. Reminder systems for children before an appointment or recall systems for children who fail to keep appointments have repeatedly been demonstrated to improve coverage. Assessment and feedback is also an important intervention. Many physicians overestimate the immunization coverage among patients they serve and thus are not motivated to make any changes in their practices to improve performance. Assessing the immunization coverage of patients served by an individual physician and feedback of results can be a major motivator for improvement. Often public health departments can be contacted to provide the assessments and feedback. Alternatively, physicians can perform some self-assessments. Review of approximately 60 consecutive charts of 2 yr old children may provide a reasonable estimate of practice coverage. Another approach is to have a staff member review the chart of every patient coming in for a visit and placing immunization needs reminders on the chart for the physician. Electronic medical records can be designed to accomplish this goal.

Some parents refuse, delay, or space out immunizations for their children. Pediatricians should try to open a dialog with such parents to understand reasons for refusal and try to work with them to overcome their concerns over time during the course of visits. Discussion should be based on the reason for refusal and the knowledge of the parent. Pediatricians should refer patients to reputable sources

for vaccine information (see Table 172-6) and discuss risks and benefits of vaccines. Provider resources for vaccine conversations with parents are available at http://www.cdc.gov/vaccines/hcp/patient-ed/conversations/index.html. Physician concerns about liability should be addressed by appropriate documentation of discussions in the chart. The Committee on Bioethics of the AAP has published guidelines for dealing with parents' refusal of immunization. Physicians also might wish to consider having parents sign a refusal waiver. A sample of a refusal to vaccinate waiver can be found at http://www2.aap.org/immunization/pediatricians/pdf/refusaltovaccinate.pdf.

Bibliography is available at Expert Consult.

172.1 International Immunization Practices

Jean-Marie Okwo-Bele and John David Clemens

Vaccines are used to prevent infectious diseases around the world. However, the types of vaccines in use, the indications and contraindications, and the immunization schedules vary substantially. Most developing countries follow the immunization schedules promulgated by the World Health Organization's Immunization Programme; the latest update is available at http://www.who.int/immunization/policy/Immunization_routine_table2.pdf.

According to this schedule, all children should be vaccinated at birth against tuberculosis with bacille Calmette-Guérin vaccine. Many children also receive a dose of the live-attenuated oral polio vaccine (OPV) at this time. Immunization visits are scheduled for 6, 10, and 14 wk of age when DTP vaccine and OPV are administered. Two doses of measles vaccines are recommended, with the first dose given between 9-12 mo and the second dose between 15-18 mo. Nearly all developing countries have implemented hepatitis B vaccination. Two schedule options may be used, depending on epidemiologic and programmatic considerations. Hepatitis B vaccine can be given at the same time as DTP vaccine doses at 6, 9, and 14 wk of age, often in combination vaccines. To prevent perinatal transmission, the 1st dose should be administered as soon as possible after birth (<24 hr) and at 6 and 14 wk of age. Yellow fever and Japanese encephalitis vaccines are recommended for infants 9 mo of age living in endemic areas. Substantial efforts have been made to incorporate Hib vaccines into all but 3 developing countries that are eligible for support by the GAVI Alliance, often within a DPT-based combination vaccine.

In the past few years, the support from the GAVI Alliance has facilitated the adoption of rotavirus and pneumococcal conjugate vaccines into developing country immunization programs. The increased coverage with these additional vaccines will considerably reduce the global childhood morbidity and mortality caused by pneumonia, meningitis, and diarrheal diseases.

In 1988, the World Health Assembly endorsed the goal of eradicating polio from the world by the end of 2000. Although that goal has not been reached, endemic polio transmission was contained to 3 countries worldwide (Afghanistan, Nigeria, and Pakistan) by the end of 2014. The principal strategy is use of OPV both for routine immunization and in mass campaigns, at least twice per year, during which all children <5 yr of age are targeted for immunization, regardless of prior immunization status. Once termination of wild polio virus transmission is achieved, the goal is to stop use of OPV, which rarely can cause vaccine-associated polio and which is capable of mutating and taking on the phenotypic characteristics of the wild viruses.

Latin American countries have maintained the elimination of indigenous circulation of measles since 2002. The strategy called for attainment of high routine immunization coverage of infants with a dose at 9 mo of age, a 1 time mass campaign targeting all persons 9 mo-14 yr of age regardless of prior immunization status, and follow-up campaigns of children born since the prior campaign, generally every 3-5 yr. While global measles deaths have decreased by 78% worldwide in recent years—from 562,000 deaths in 2000 to 122,000 in 2012—measles is still common in many developing countries, particularly in parts of Africa and Asia. Latin American countries have achieved the elimination of indigenous rubella with strategies consisting of both routine immunization and mass campaigns.

Immunization schedules in the industrialized world are substantially more variable than in the developing world. Immunization recommendations for Canada are developed by the Canadian National Advisory Committee on Immunization but are implemented somewhat differently by each province. The Canadian schedule is similar to the U.S. immunization schedule (http://www.phac-aspc.gc.ca/im/is-cv/index-eng.php), with a few exceptions. A birth dose of hepatitis B vaccine is not specifically recommended as it is in the United States. Conjugate meningococcal vaccine is recommended in a 3 dose series at 2, 4, and 6 mo of age. A single dose is recommended after 12 mo of age if the child has never been immunized or has received <3 doses in infancy. In contrast to the situation in the United States, hepatitis A vaccine is not recommended as a routine pediatric immunization.

There is tremendous variation in vaccines used and the immunization schedules recommended in Europe. European immunization schedules can be reviewed at http://apps.who.int/immunization_monitoring/globalsummary. As an example, the United Kingdom developed an immunization schedule during the late 1980s that includes visits at 2, 3, and 4 mo of age where a combination DTaP-Hib-IPV vaccine is administered. Following evidence that a 3 dose series of Hib vaccine at these ages was insufficient to ensure long-term, high-grade protection, a booster dose was added at 12-13 mo of age. MMR is recommended in a 2 dose schedule at 13 mo and 40 mo of age. During the 2nd MMR visit, a booster of DTaP and IPV is provided. A Td/IPV booster is recommended between 13 and 18 yr of age. PCV13 is recommended at 2, 4, and 12-13 mo of age. The United Kingdom was the first country to use conjugate meningococcal C vaccine (MCV-C) during a massive catch-up campaign for children, adolescents, and young adults. The effectiveness of the vaccine in the 1st yr was 88% or greater, and herd immunity was induced with an approximate two-thirds reduction in the incidence among unvaccinated children. MCV-C is administered at 3, 4, and 12-13 mo of age. In September 2008, HPV vaccine was recommended for girls 12-13 yr old. As of April, 2013, the UK schedule did not include hepatitis B vaccine, varicella vaccine, or influenza vaccine for universal childhood immunization (see http://www.nhs.uk/conditions/vaccinations/pages/vaccination-schedule-age-checklist.aspx).

The Japanese immunization schedule in 2013 is substantially different from that in the United States. The Japanese do not use MMR and rely on individual vaccines for measles and rubella or combined MR. Japanese children also are vaccinated routinely against polio with OPV; against diphtheria, tetanus, and pertussis with DTaP; against Japanese encephalitis; and against tuberculosis with bacille Calmette-Guérin. Adults 65 yr of age and older receive annual influenza vaccinations. A law passed in March 2013 made vaccination of children against Hib, pneumococci, and HPV mandatory.

Some children come to the United States having started or completed international immunization schedules with vaccines produced outside of the United States. In general, doses administered in other countries should be considered valid if administered at the same ages as recommended in the United States. For missing doses, age-inappropriate doses, lost immunization records, or other concerns, pediatricians have 2 options: administer or repeat missing or inappropriate doses or perform serologic tests, and if they are negative, administer vaccines.

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Chapter 173

Infection Prevention and Control

Michael J. Chusid and Mary M. Rotar

Infection prevention and control are playing an ever more important role in pediatric medicine. To be fully effective, such programs require a functional infrastructure that addresses collaboration with the public health system, widespread immunizations, and use of appropriate techniques to prevent transmission of infection within the general population and within healthcare institutions. The national focus upon preventing nosocomial infection is emphasized by the fact that 5 of the 15 elements of the Joint Commission's 2013 National Patient Safety Goals related to reduction and prevention of healthcare-associated infections (HAIs). Governmental agencies and insurance providers have reduced or eliminated payment to institutions for expenses associated with certain HAIs and a host of national organizations have been established to monitor and report rates of HAI at healthcare facilities. Ratings of healthcare facilities by periodicals such as *Parents Magazine* and *US News and World Report* incorporate institutional HAI rates in their reviews and rankings of facilities.

HAIs or nosocomial infections refer to infections acquired during hospitalization or acquired in other healthcare settings, such as nursing homes or ambulatory surgical care centers. An estimated 3-5% of children admitted to hospitals acquire an HAI. HAI rates are highest in patients undergoing invasive procedures. Infections can also be acquired in emergency departments, physicians' offices, daycare, and long-term care settings. Medical device-associated infections occur in both the home and hospital. Adequate education of home health providers as well as of families is essential to prevent or minimize device-associated infections as ever-greater numbers of children are sent home from the hospital with intravenous catheters and other medical devices in place.

Factors that increase susceptibility to HAIs include host factors, recent invasive procedures, presence of catheters or other devices, prolonged use of antibiotics, contaminated physical environment, and exposure to other patients, visitors, or healthcare providers with active contagious infections or colonized with invasive microorganisms. Host factors increasing the risk for HAIs include anatomic abnormalities (dermal sinuses, cleft palate, obstructive uropathy), abnormal skin, organ dysfunction, malnutrition, and underlying diseases or comorbidities. Invasive procedures can introduce potential pathogens by breaching normal anatomic host barriers. Intravenous and other catheters provide direct access to sterile anatomic sites for usually minimally pathogenic organisms, as well as adherent surfaces for microbial binding, and can disrupt patterns of normally protective flow of mucus (e.g., nasotracheal tubes and sinus ostia). Antibiotic use can alter the composition of bowel flora and encourage the multiplication and emergence of toxigenic or invasive organisms already present in small numbers in the gut, such as *C. difficile* and *Salmonella*.

Transmission of infectious agents occurs by various routes, but by far the most common and important route is via the hands. Medical equipment, toys, and hospital and office furnishings can become microbially contaminated and thus have a role in transmission of potential pathogens. Pagers, phones, computer keyboards, and even neckties become easily contaminated. These inanimate objects serve as fomites for bacteria. There is increasing recognition of the importance of the healthcare environment in the acquisition of organisms such as methicillin-resistant *S. aureus*, vancomycin-resistant enterococci, carbapenem-resistant Enterobacteriaceae, *C. difficile,* and respiratory syncytial virus. Thermometers and other equipment that come in contact with mucous membranes pose special risks. Some agents are easily disseminated via airborne transmission, such as varicella virus, measles virus, and *M. tuberculosis.* Food can be contaminated and has been involved in hospital outbreaks of nosocomial infection. The hospital physical environment can also serve as a risk factor for infection, particularly for immunocompromised patients. In particular, rainwater or plumbing leaks are associated with bacterial and fungal infections, new construction or renovation with airborne fungal infection, and contamination of an institution's potable water supply with bacterial, fungal, and atypical mycobacterial nosocomial infections.

Common causes of HAI in children are seasonal viruses such as rotavirus and respiratory viral agents, staphylococci, and Gram-negative bacilli. Fungi and multidrug-resistant organisms are common causes of infection in immunocompromised children, as well as those requiring intensive care and prolonged hospitalization. Common sites of infection are the respiratory tract, gastrointestinal tract, bloodstream, skin, and urinary tract.

Liberalization of visitation policies and spread of in-hospital animal visitation have increased the likelihood of HAI acquisition. The widespread use of contaminated pharmaceutical products like injectable depot corticosteroids has led to recent large outbreaks of fatal fungal HAIs.

HAIs cause considerable morbidity and occasional mortality of hospitalized children. Infections prolong hospital stays and increase healthcare costs. Surveillance, the initial step in identifying such infections and suggesting methods for prevention, is the responsibility of **infection preventionists.** Within hospitals, oversight of such surveillance is usually the responsibility of the **infection prevention and control committee**, a multidisciplinary group that collects and reviews surveillance data, establishes institutional policies, and investigates intrainstitutional infection outbreaks. The chair of the committee is often an infectious disease specialist. Surveillance in outpatient settings and during home care is often less-well defined. Local, state, and federal health departments play important roles in identifying and controlling outbreaks and in establishing public health policy.

HAND HYGIENE

The most important tool in any infection control program is good hand hygiene. Although much attention is directed at the type of cleansing agent employed, the most important aspect of hand washing is placing the hands under water and using friction with or without soap. Studies show that a 15 sec scrub removes the majority of transient flora but does not alter hand permanent flora. A variety of hand gels and rubs can be used in place of hand washing. **Waterless hand hygiene** products increase hand hygiene compliance and save time; these agents are the preferred agents for routine hand hygiene when hands are not visibly soiled. These products are effective in killing most microbes but do not remove dirt or debris. However, they are ineffective against *C. difficile* spores, requiring the use of other cleansing products during hospital *C. difficile* outbreaks. Hands should be cleaned before and after every patient encounter. In hospital hand washing compliance studies, physicians are usually the least-compliant group studied, and compliance programs must pay special attention to this group of caregivers.

STANDARD PRECAUTIONS

Standard precautions, formerly known as universal precautions, are intended to protect healthcare workers from pathogens and should be used whenever there is direct contact with patients. Infected patients are often contagious before symptoms of disease develop. Asymptomatic, infected patients are quite capable of transmitting infectious agents. Standard precautions involve the use of barriers—gloves, gowns, masks, goggles, and face shields—as needed, to prevent transmission of microbes associated with contact with blood and body fluids (Table 173-1).

ISOLATION

Isolation of patients infected with transmissible pathogens decreases the risk of nosocomial transmission of organisms to staff and other patients. The specific type of isolation depends upon the infecting agent and potential route of transmission. Transmission by contact is the most common mode of pathogen transmission and involves direct contact with the patient or contact with a contaminated intermediate object. **Contact isolation** requires the use of gown and gloves when in contact with the patient or immediate surroundings. Transmission by droplets involves the propulsion of infectious large particles over a short distance (<3 ft), with deposition on another's mucous membranes or skin. **Droplet isolation** requires the use of gloves and gowns, as well as masks and eye guards, when closer than 3-6 ft to the patient. Airborne transmission occurs by dissemination of evaporated droplet nuclei (≤5 μm) or dust particles carrying an infectious agent. **Airborne isolation** requires the use of masks and negative-pressure air-handling systems to prevent spread of the infectious agent. In the case of active pulmonary tuberculosis in older children and adults, severe acute respiratory syndrome, or avian influenza, the use of special high-density masks (N-95) or self-contained breathing systems (PAPR) is recommended. Positive-pressure HEPA-filtered air handling systems are used in some institutions for housing seriously immunocompromised patients.

Standard precautions are indicated for all patients and are appropriate for use in the clinic as well as the hospital. Additionally, for hospitalized patients, further transmission-based precautions are indicated for certain infections (Table 173-2). For contact and droplet isolation, single rooms are preferred but not required. Cohorting children infected with the same pathogen is acceptable, but the etiologic diagnosis should be confirmed by laboratory methods before exposing infected children to one another. Transmission-based isolation precautions should be continued for as long as a patient is considered contagious.

The use of isolation techniques in outpatient settings has not been well studied. Professional offices should establish procedures to ensure that proper cleaning, disinfection, and sterilization methods are employed. Many practices and clinics provide separate waiting areas

Table 173-1 Recommendations for Application of Standard Precautions for Care of All Patients in All Healthcare Settings

COMPONENT	RECOMMENDATIONS
Hand hygiene	Before and after each patient contact, regardless of whether gloves are used. After contact with blood, body fluids, secretions, excretions, or contaminated items; immediately after removing gloves; before and after entering patient rooms. Alcohol-containing antiseptic hand rubs preferred except when hands are visibly soiled with blood or other proteinaceous materials or if exposure to spores (e.g., *Clostridium difficile, Bacillus anthracis*) is likely to have occurred; in those cases, soap and water necessary.
PERSONAL PROTECTIVE EQUIPMENT	
Gloves	For touching blood, body fluids, secretions, excretions, or contaminated items; for touching mucous membranes and nonintact skin. Employ hand hygiene before and after glove use.
Gown	During procedures and patient-care activities when contact of clothing or exposed skin with blood/body fluids, secretions, or excretions is anticipated.
Mask, eye protection (goggles), face shield	During procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, or secretions, such as suctioning and endotracheal intubation, to protect healthcare personnel. For patient protection, use of a mask by the person inserting an epidural anesthesia needle or performing myelograms when prolonged exposure of the puncture site is likely to occur.
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment. Wear gloves if equipment is visibly contaminated. Perform hand hygiene.
ENVIRONMENT	
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient care areas.
Textiles (linens) and laundry	Handle in a manner that prevents transfer of microorganisms to others and the environment.
PATIENT CARE	
Injection practices (use of needles and other sharps)	Do not recap, bend, break, or handle used needles; if recapping is required, use a 1-handed scoop technique only. Use needle-free safety devices when available, placing used sharps in puncture-resistant container. Use a sterile, single-use, disposable needle and syringe for each injection. Single-dose medication vials preferred when medications may be administered to more than 1 patient.
Patient resuscitation	Use mouthpiece, resuscitation bag, or other ventilation devices to prevent contact with mouth and oral secretions.
Patient placement	Prioritize for single-patient room if patient is at increased risk for transmission, is likely to contaminate the environment, is unable to maintain appropriate hygiene, or is at increased risk for acquiring infection or developing adverse outcome following infection.
Respiratory hygiene/cough etiquette (source containment of infectious respiratory secretions in symptomatic patients) beginning at the initial point of encounter in such triage or reception areas in an emergency department or physician offices	Instruct symptomatic persons to cover nose/mouth when sneezing or coughing; use tissues with disposal in no-touch receptacles. Employ hand hygiene after soiling of hands with respiratory secretions. Wear surgical mask if tolerated or maintain spatial separation (>3 ft if possible).

From Pickering LK, editor: Red book 2012: report of the Committee on Infectious Diseases, *ed. 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 162.*

Table 173-2 Clinical Syndromes or Conditions Warranting Empiric Transmission-Based Precautions in Addition to Standard Precautions Pending Confirmation of Diagnosis*

CLINICAL SYNDROME OR CONDITION†	POTENTIAL PATHOGENS‡	EMPIRIC PRECAUTIONS (ALWAYS INCLUDES STANDARD PRECAUTIONS)
DIARRHEA		
Acute diarrhea with a likely infectious cause in an incontinent or diapered patient	Enteric pathogens§	Contact precautions (pediatrics and adult)
Meningitis	*Neisseria meningitidis*	Droplet precautions for 1st 24 hr of antimicrobial therapy; mask and face protection for intubation
	Enteroviruses	Contact precautions for infants and children
	Mycobacterium tuberculosis	Airborne precautions if pulmonary infiltrate Airborne precautions plus contact precautions if potentially infectious draining body fluid present
RASH OR EXANTHEMS, GENERALIZED, ETIOLOGY UNKNOWN		
Petechial/ecchymotic with fever (general)	*Neisseria meningitides*	Droplet precautions for 1st 24 hr of antimicrobial therapy
If positive history of travel to an area with an ongoing outbreak of VHF in the 10 days before onset of fever	Ebola, Lassa, Marburg viruses	Droplet precautions plus contact precautions, with face/eye protection, emphasizing safety sharps and barrier precautions when blood exposure likely. Use N-95 or higher respiratory protection when aerosol-generating procedure performed
Vesicular	Varicella-zoster, herpes simplex, variola (smallpox), vaccinia viruses	Airborne plus contact precautions
	Vaccinia virus	Contact precautions only if herpes simplex, localized zoster in an immunocompetent host or vaccinia viruses likely
Maculopapular with cough, coryza, and fever	Rubeola (measles) virus	Airborne precautions
RESPIRATORY INFECTIONS		
Cough/fever/upper lobe pulmonary infiltrate in an HIV-negative patient or a patient at low risk for human immunodeficiency virus (HIV) infection	*M. tuberculosis*, respiratory viruses, *Streptococcus pneumoniae*, *Staphylococcus aureus* (MSSA or MRSA)	Airborne precautions plus contact precautions
Cough/fever/pulmonary infiltrate in any lung location in an HIV-infected patient or a patient at high risk for HIV infection	*M. tuberculosis*, respiratory viruses, *S. pneumoniae, S. aureus* (MSSA or MRSA)	Airborne precautions plus contact precautions Use eye/face protection if aerosol-generating procedure performed or contact with respiratory secretions anticipated If tuberculosis is unlikely and there are no AIIRs and/or respirators available, use droplet precautions instead of airborne precautions Tuberculosis more likely in HIV-infected individual than in HIV-negative individual
Cough/fever/pulmonary infiltrate in any lung location in a patient with a history of recent travel (10-21 days) to countries with active outbreaks of SARS, avian influenza	*M. tuberculosis*, severe acute respiratory syndrome virus (SARS-CoV), avian influenza	Airborne plus contact precautions plus eye protection. If SARS and tuberculosis unlikely, use droplet precautions instead of airborne precautions
Respiratory infections, particularly bronchiolitis and pneumonia, in infants and young children	Respiratory syncytial virus, parainfluenza virus, adenovirus, influenzavirus, human metapneumovirus	Contact plus droplet precautions; droplet precautions may be discontinued when adenovirus and influenza have been ruled out
SKIN OR WOUND INFECTION		
Abscess or draining wound that cannot be covered	*S. aureus* (MSSA or MRSA), group A streptococcus	Contact precautions Add droplet precautions for the 1st 24 hr of appropriate antimicrobial therapy if invasive Group A streptococcal disease is suspected

*Infection control professionals should modify or adapt this table according to local conditions. To ensure that appropriate empiric precautions are implemented always, hospitals must have systems in place to evaluate patients routinely according to these criteria as part of their preadmission and admission care.

†Patients with the syndromes or conditions listed in the table may present with atypical signs or symptoms (e.g., neonates and adults with pertussis may not have paroxysmal or severe cough). The clinician's index of suspicion should be guided by the prevalence of specific conditions in the community, as well as clinical judgment.

‡The organisms listed under the column "Potential Pathogens" are not intended to represent the complete, or even most likely, diagnoses, but rather possible etiologic agents that require additional precautions beyond Standard Precautions until they can be ruled out.

§These pathogens include enterohemorrhagic *Escherichia coli* O157:H7, *Shigella* spp., hepatitis A virus, noroviruses, rotavirus, *Clostridium difficile*.

AIIR, airborne infection isolation rooms; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus;* SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome-associated coronavirus; VHF, viral hemorrhagic fever.

Adapted from Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Centers for Disease Control and Prevention. Table 2. Available at: http://www.cdc.gov/hicpac/2007ip/2007ip_table2.html

for sick and well children. Triage of patients is essential to ensure that contagious children or adults are not present in waiting areas. Outbreaks of measles and varicella in patients within the waiting area have been reported where the air exhaust from examination rooms is allowed to enter the waiting area. Cleaning the clinic environment is important, especially in "high touch" areas. Toys and items that are shared among patients should be cleaned between uses; if feasible, disposable toys should be used. Toys contaminated with blood or body fluids should be autoclaved or discarded.

ADDITIONAL MEASURES

Other preventive measures include aseptic technique, catheter care, prudent use of antibiotics, isolation of contagious patients, periodic cleaning of the environment, disinfection and sterilization of medical equipment, reporting of infections, safe handling of needles and other sharp instruments, and establishment of employee health services. Aseptic technique must be used for all invasive procedures, including catheter placement and manipulation. The use of barrier techniques at the time of intravenous catheter placement has reduced the rate of catheter-related bloodstream infections by half. Appropriate catheter use also includes limiting the duration and number of catheters employed, scrubbing catheter hubs periodically, and removing catheters as soon as they become unnecessary.

SURGICAL PROPHYLAXIS

Surgical antibiotic prophylaxis should be employed when there is a high risk of postoperative infection or when the consequences of such infection would be catastrophic. The choice of prophylactic antibiotic depends on the surgical site and type of surgery (Table 173-3). A useful classification of surgical procedures based upon infectious risk recognizes 4 preoperative wound categories: clean wounds, clean-contaminated wounds, contaminated wounds, and dirty and infected wounds. Clinical recommendations regarding antibiotic prophylaxis have been made by the American College of Surgeons, the Surgical Infection Society, and the American Academy of Pediatrics.

Clean wounds are uninfected operative wounds where no inflammation is noted at the operative site and respiratory, alimentary, and genitourinary tracts and the oropharynx are not entered. Such wounds are often the result of nonemergent procedures with primary closure or drained via a closed system. Operative incisional wounds after nonpenetrating trauma are included in this category. For clean wounds, prophylactic antimicrobial therapy is *not* recommended except in patients at high risk for infection and in circumstances in which the consequences of infection would be potentially life threatening, as with implantation of a foreign body such as a prosthetic heart valve or cerebrospinal fluid shunt, open heart surgery for repair of structural defects, and surgery in immunocompromised patients or small infants.

Clean-contaminated wounds are operative wounds in which the respiratory, alimentary, or genitourinary tract is entered under controlled conditions and that do not have unusual bacterial contamination preoperatively. These wounds occur in operations that involve the biliary tract, appendix, vagina, and oropharynx where no evidence of infection or major break in technique is encountered, as well as in urgent or emergency surgery in an otherwise clean procedure. In procedures involving clean-contaminated wounds, the risk for bacterial contamination and infection is variable. Recommendations for pediatric patients derived from data on adults suggest that antibiotic prophylaxis be provided for procedures in children with obstructive jaundice, certain alimentary tract procedures, and urinary tract surgery or instrumentation in the presence of bacteriuria or obstructive uropathy.

Contaminated wounds include open, fresh, and accidental wounds; major breaks in otherwise sterile operative technique; gross spillage from the gastrointestinal tract; penetrating trauma occurring <4 hr earlier; and incisions in which acute nonpurulent inflammation is encountered.

Dirty and infected wounds include penetrating traumatic wounds >4 hr prior to surgery, those with retained devitalized tissue, and those in which clinical infection is apparent or in which the viscera have been perforated. In contaminated and dirty or infected wound procedures, antimicrobial therapy is indicated and may need to be continued for several days. In these cases, antibiotic therapy is considered therapeutic rather than truly prophylactic.

Table 173-3 Common Surgical Procedures for Which Perioperative Prophylactic Antibiotics Are Recommended

SURGICAL PROCEDURE	LIKELY PATHOGENS	RECOMMENDED DRUGS	NON–β-LACTAM ALTERNATIVE
CLEAN WOUNDS			
Cardiac surgery (e.g., open heart surgery) Vascular surgery Neurosurgery Orthopedic surgery (e.g., joint replacement)	Skin flora, enteric Gram-negative bacilli	Cefazolin or cefuroxime	Clindamycin or vancomycin
CLEAN CONTAMINATED WOUNDS			
Head and neck surgery involving the oral cavity or pharynx	Skin flora, oral anaerobes, oral streptococci	Cefazolin + metronidazole, ampicillin-sulbactam	Clindamycin
Gastrointestinal and genitourinary surgery	Enteric Gram-negative bacilli, anaerobes, Gram-positive cocci	Cefazolin + metronidazole, cefotetan or piperacillin-tazobactam If colon is involved, consider bacterial reduction with PO neomycin and erythromycin	Clindamycin
CONTAMINATED WOUNDS			
Traumatic wounds (e.g., compound fracture)	Skin flora	Cefazolin	Clindamycin, vancomycin
DIRTY WOUNDS			
Appendectomy, penetrating abdominal wounds, colorectal surgery	Enteric Gram-negative bacilli, anaerobes, Gram-positive cocci	Cefazolin + metronidazole, cefoxitin, cefotetan or ampicillin-sulbactam	Clindamycin + aminoglycoside

Adapted from Bratzler DW, Dellinger PD, Olsen KM et al. Clinical practice guidelines from antimicrobial prophylaxis in surgery. Am J Health Syst Pharm *70:195–283, 2013.*

Prophylactic antibiotics should be administered, preferably intravenously, within an hour prior to skin incision, with the intent of having peak serum concentrations of the drug present in blood and tissues around the time of incision. Adequate plasma and tissue concentration of the antibiotic should be maintained until the incision is closed. Intraoperative antibiotic dosing may be necessary if surgery is prolonged and/or the antibiotic being employed has a short intravascular half-life. Continuation of prophylactic therapy after the procedure is not recommended. In cases of contaminated surgical sites, antibiotics are continued as therapy for infection at the site. For patients undergoing colonic procedures, additional oral antibiotics may be employed and should also be given on the day before surgery.

The selection of antibiotic regimen for prophylaxis is based on the procedure, the likely contaminating organisms, and antibiotic. Because of the variety of antibiotics available, many regimens are acceptable (see Table 173-2).

EMPLOYEE HEALTH

Employee health is important in hospital-based infection control because employees are at risk for acquiring infection from patients and infected employees pose a potential risk to patients. This risk is minimized by use of standard precautions and hand hygiene before and after all patient contacts. Within hospitals, employee health services or departments of occupational safety and health manage employee health issues. New employees should be screened for the presence of infectious diseases. Their immunization history should be noted, and necessary immunizations should be offered.

All healthcare workers (medical and nonmedical, paid or volunteer, full time or part time, student or nonstudent, with or without patient care responsibilities) who work within facilities providing healthcare, inpatient or outpatient, should be immune to measles, rubella, and varicella. All workers who are at risk of exposure to blood or body fluids should be immunized against hepatitis B. In pediatric institutions, employees with patient contact should be urged to receive the pertussis booster vaccine. Annual influenza immunization is strongly recommended for all healthcare workers, and institutions are being ranked publically regarding employee immunization rates as a measure of quality of care. Many healthcare facilities have now made annual influenza vaccination mandatory for employees unless there are legitimate medical reasons for nonimmunization. Such a program reduces staff illness and absenteeism and decreases HAI. Immunizations should be encouraged and should be provided free of charge whenever possible to enhance compliance.

All healthcare workers with duties involving face-to-face contact with patients with suspected or confirmed tuberculosis (including transport staff) should be included in a tuberculosis screening program at the time of hiring and may require periodic retesting if the workplace is determined to be a high-prevalence environment for tuberculosis. Each medical office and hospital must comply with the rules developed by the Occupational Safety and Health Administration. Each office and hospital should have written policies about exclusion of infected and ill staff from direct patient care. Staff should be encouraged to not report for work if they are ill. Regular educational sessions should be performed to ensure that staff are aware of prevention and control methods and that they adhere to such policies.

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Chapter 174

Childcare and Communicable Diseases

Linda A. Waggoner-Fountain

More than 25 million children <5 yr of age attend a childcare facility. These facilities can include some type of out-of-home care on a routine basis, such as nursery school, preschool, or a full-day program based either in a childcare center or in another person's home. Regardless of the age at entry, children entering daycare are more prone to infections. Exposure to larger groups of children increases a child's probability of getting sick. Childcare facilities can be classified on the basis of size of enrollment, ages of attendees, health status of the children enrolled, and type of setting. As defined in the United States, **childcare facilities** consist of childcare centers, small and large family childcare homes, and facilities for ill children or for children with special needs. Centers are licensed and regulated by state governments and care for a larger number of children than are cared for in family homes. In contrast, **family childcare homes** are designated as small (1-6 children) or large (7-12 children), may be full day or part day, and may be designed for either daily or sporadic attendance. Family childcare homes generally are not licensed or registered, depending on state requirements.

Although the majority of children who attend childcare facilities are cared for in childcare home settings, most studies of infectious diseases among children in out-of-home childcare have been conducted among infants (birth to 12 mo of age) and toddlers (13-36 mo of age) who are enrolled in a childcare center. Almost any organism has the potential to be spread and to cause disease in a childcare setting. Epidemiologic studies have established that children in childcare facilities are 2-18 times more likely to acquire a variety of infectious diseases than are children not enrolled in childcare (Table 174-1). Children in childcare facilities are more likely both to receive more courses of antimicrobial agents for longer periods and to acquire antibiotic-resistant organisms. Transmission of infectious agents in group care depends on the age and immune status of the children, season, hygiene practices, crowding, environmental characteristics of the facilities, and characteristics of the pathogen, including its infectivity, survivability in the environment, and virulence. Rates of infection, duration of illness, and risk for hospitalization tend to decrease among children in childcare facilities after the 1st 6 mo of attendance and decline to levels observed among home-bound children after 3 yr of age. Adult caregivers are also at increased risk for acquiring and transmitting infectious diseases, particularly in the 1st yr of contact with children in these settings.

EPIDEMIOLOGY

Infectious illnesses among children in childcare and their contacts occur in several different patterns. With many viral infections, children often are infectious 2-3 days before they exhibit symptoms of illness. Respiratory tract infections and diarrhea are the most common diseases associated with childcare. These infections occur in children, childcare staff, and household contacts, and can spread to the community. Respiratory tract pathogens and enteric pathogens can infect both children and adults in these settings but may have varying degrees of impact, depending on the person's underlying health, previous exposures, and age. Infections caused by hepatitis A virus might not be clinically apparent in young children who attend childcare, but can cause major clinical disease among older children and adult contacts, including childcare staff and household contacts. Other diseases, such as otitis media and varicella, usually affect children rather than adults. Some common infections, such as cytomegalovirus (CMV) and parvovirus B19 infections, can have serious consequences for the fetuses

Table 174-1 Infectious Diseases in the Childcare Setting

DISEASE	INCREASED INCIDENCE WITH CHILDCARE
RESPIRATORY TRACT INFECTIONS	
Otitis media	Yes
Sinusitis	Probably
Pharyngitis	Probably
Pneumonia	Yes
GASTROINTESTINAL TRACT INFECTIONS	
Diarrhea (rotavirus, calicivirus, astrovirus, enteric adenovirus, *Giardia lamblia*, *Cryptosporidium*, *Shigella*, *Escherichia coli* O157:H7, and *Clostridium difficile*)	Yes
Hepatitis A	Yes
SKIN DISEASES	
Impetigo	Probably
Scabies	Probably
Pediculosis	Probably
Tinea (ringworm)	Probably
INVASIVE BACTERIA INFECTIONS	
Haemophilus influenzae type b	No*
Neisseria meningitidis	Probably
Streptococcus pneumoniae	Yes
ASEPTIC MENINGITIS	
Enteroviruses	Probably
HERPESVIRUS INFECTIONS	
Cytomegalovirus	Yes
Varicella-zoster virus	Yes
Herpes simplex virus	Probably
BLOOD-BORNE INFECTIONS	
Hepatitis B	Few case reports
HIV	No cases reported
Hepatitis C	No cases reported
VACCINE-PREVENTABLE DISEASES	
Measles, mumps, rubella, diphtheria, pertussis, tetanus	Not established
Polio	No
H. influenzae type b	No*
Varicella	Yes
Rotavirus	Yes

*Not in the postvaccine era; yes in the prevaccine era.

of pregnant women or for immunocompromised persons. Hepatitis B virus (HBV) transmission has been reported rarely in a childcare setting. Transmission of hepatitis C virus (HCV), hepatitis D virus (HDV), and HIV has never been reported in a childcare setting. Both infections and infestations of the skin and hair may be acquired through contact with contaminated linens or through close personal contact.

RESPIRATORY TRACT INFECTIONS

Respiratory tract infections account for the majority of childcare-related illnesses. Children <2 yr of age who attend childcare centers have more upper and lower respiratory tract infections than do age-matched children not in childcare. The organisms responsible for these illnesses are similar to those that circulate in the community and include respiratory syncytial virus, parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, coronaviruses, parvovirus B19, and *S. pneumoniae*. The risk for developing otitis media is 2-3 times greater among children who attend childcare centers than among children cared for at home. Most prescriptions for antibiotics for children <3 yr of age in childcare are to treat otitis media. These children also are at increased risk for recurrent otitis media, which further increases use of antimicrobial agents in this population. Pharyngeal carriage of group A streptococcus occurs earlier among children in childcare, although outbreaks of clinical infections with this organism are uncommon. Airborne droplets from the respiratory tract can spread via direct contact with another person's mucous membranes or by touching surfaces contaminated with secretions. This intimate contact is a routine part of the play and care of young children, regardless of setting. The most common surfaces from which airborne droplets can be spread are the hands; consequently, the most efficient form of infection control in the childcare setting is good hand washing.

GASTROINTESTINAL TRACT INFECTIONS

Acute infectious diarrhea is 2-3 times more common among children in childcare than among children cared for in their homes. Outbreaks of diarrhea, which occur frequently in childcare centers, usually are caused by enteric viruses such as rotaviruses, caliciviruses including norovirus, enteric adenoviruses, and astroviruses, or by enteric parasites such as *G. lamblia* or *Cryptosporidium*. The most common enteropathogens, such as rotavirus and *G. lamblia*, are characterized by low infective doses and high rates of asymptomatic excretion among children in childcare. Bacterial enteropathogens such as *Shigella* and *E. coli* O157:H7 and, less commonly, *Campylobacter*, *C. difficile*, and *Bacillus cereus* also have caused outbreaks of diarrhea in childcare settings. *Salmonella* rarely is associated with outbreaks of diarrhea in childcare settings, because person-to-person spread of this organism is uncommon. Outbreaks of hepatitis A in children enrolled in childcare facilities have resulted in community-wide outbreaks. Hepatitis A usually is mild or asymptomatic in young children and often is identified only after symptomatic illness becomes apparent among either older children or adult contacts of children in childcare. Enteropathogens and hepatitis A virus are transmitted in childcare facilities by the fecal-oral route and only rarely by contaminated food or water. Children in diapers constitute a high risk for the spread of gastrointestinal infections through the fecal-oral route. Enteric illness and hepatitis A are more common in centers that care for children who are not toilet trained and where proper hygienic practices are not followed.

SKIN DISEASES

The most commonly recognized skin infections or infestations in children in childcare are impetigo caused by *S. aureus* or group A streptococcus, pediculosis, scabies, tinea capitis, and tinea corporis. Many of these diseases are spread by contact with infected linens, clothing, hairbrushes, and hats and through direct personal contact; they more often affect children >2 yr of age. The magnitude of these infections and infestations in children in childcare is not known. Parvovirus B19, which causes fifth disease (erythema infectiosum), is spread through the respiratory route, and outbreaks have occurred in childcare centers. The rash of fifth disease is a systemic manifestation of parvovirus B19 infection; the child is no longer contagious once the rash is present (see Chapter 251). The greatest health hazard is for pregnant women and immunocompromised hosts, owing to their respective risks for fetal loss and aplastic crisis.

INVASIVE ORGANISMS

Prior to universal immunization, primary *H. influenzae* type b invasive disease was more common among children in childcare, although evidence for increased risk for secondary cases from *H. influenzae* type b in a childcare setting remains less convincing. There is an indication that the risk for primary disease caused by *Neisseria meningitidis* is higher among children in childcare than among children cared for at home. Childcare attendance is associated with nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and invasive pneumococcal disease, especially among children with a history of recurrent otitis media and use of antibiotics. Secondary spread of *S. pneumoniae* and *N. meningitidis* has been reported, indicating the potential for outbreaks to occur in this setting. Routine use of pneumococcal conjugate vaccine has decreased the incidence of invasive disease and reduced carriage of serotypes of *S. pneumoniae* contained in the vaccine both

in the child and in younger siblings. The use of conjugate meningococcal vaccine in children <2 yr of age is anticipated in the near future and will alter the epidemiology of meningococcal disease in this age group. Outbreaks of aseptic meningitis from echovirus 30 have been reported among children in childcare centers, as well as among their parents and their teachers.

HERPESVIRUSES

Studies of CMV infection in childcare centers show that as many as 70% of diapered children continuously shed CMV in urine and saliva after they become infected. CMV-infected children often transmit the virus to other children with whom they have contact, as well as to their care providers and their mothers, at a rate of 8-20% per yr. Transmission occurs as a result of contact with either saliva or urine. The overwhelming majority of primary infection with and reactivation of CMV in otherwise healthy children results in asymptomatic shedding of CMV; nonetheless, this shedding can pose a health risk for previously uninfected pregnant childcare providers or immunocompromised persons (see Chapter 255). Varicella often is transmitted in childcare centers, but routine use of varicella vaccine has reduced this risk. Vaccinated children who become infected with varicella often have mild, atypical symptoms and signs of disease that can result in delayed recognition and spread of infection to susceptible contacts. The role of childcare facilities in the spread of herpes simplex virus, especially during episodes of gingivostomatitis, requires further clarification.

BLOOD-BORNE PATHOGENS

Because it is impossible to identify every child who might have a blood-borne infection such as hepatitis B, C, or D, or HIV, it is critical that standard universal precautions be observed routinely to reduce the risk for transmitting these viruses. Transmission of hepatitis B among children in childcare has been documented in a few rare instances, but the risk for transmission, which already was low, declined with implementation of universal immunization of infants with hepatitis B vaccine. Transmission of hepatitis C or D in childcare settings has not been reported.

Issues about HIV in childcare include the potential risk for HIV transmission within the childcare setting and concerns of opportunistic infections of HIV-infected children. No cases of HIV transmission in out-of-home childcare have been reported. Children with HIV infection enrolled in childcare facilities should be monitored for exposure to infectious diseases, and their health and immune status should be evaluated frequently.

Some infections are spread through contact of contaminated blood with either a mucous membrane or an open wound. Although it is theoretically possible, infection is unlikely to spread via toddler biting in a group setting. Most of these bites do not break the skin, and if a bite does break the skin, the mouth of the biter does not stay on the victim long enough for blood to transfer from the victim to the biter. If there are concerns about transmission of hepatitis B, hepatitis C, or HIV infection, it is recommended to check the status of the biter rather than the bite victim as part of the initial evaluation process.

ANTIBIOTIC USE AND BACTERIAL RESISTANCE

Antibiotic resistance has become a significant problem in childcare facilities, because the incidence of infection by organisms resistant to frequently used antimicrobial agents has increased dramatically. The estimated annual rate of antibiotic use among children in childcare is 2-4 times higher than among age-matched children cared for at home and the mean duration of antibiotic treatment is 4 times longer among children in childcare. This frequency of antibiotic use combined with the propensity for person-to-person transmission of pathogens in a crowded environment has resulted in an increased prevalence of antibiotic-resistant bacteria in the respiratory and intestinal tracts, including *S. pneumoniae, H. influenzae, M. catarrhalis, E. coli* O157:H7, and *Shigella* species. Preliminary data do not demonstrate a difference between methicillin-resistant *S. aureus* and methicillin-susceptible *S. aureus* strains in children in childcare.

PREVENTION

Written policies designed to prevent or to control the spread of infectious agents in a childcare center should be available and should be reviewed regularly. It is suggested that all programs use a health consultant to help with development and implementation of infection-control policies. Standards for environmental and personal hygiene should include maintenance of current immunization records for both children and staff; appropriate policies for exclusion of ill children and caretakers; targeting of potentially contaminated areas for frequent cleaning; adherence to appropriate procedures for changing diapers; appropriate handling of food; management of pets; and surveillance for and reporting of communicable diseases. Staff whose primary function is preparing food should not change diapers. Strategies for improving adherence to these standards should be implemented. Appropriate and thorough hand hygiene is the most important factor for reducing infectious diseases in the childcare setting. Children at risk for introducing an infectious disease should not attend childcare until they are no longer contagious (Tables 174-2 and 174-3).

In the United States, there are 15 diseases and organisms for which all children should be immunized unless there are contraindications: diphtheria, pertussis, tetanus, measles, mumps, rubella, polio, hepatitides A and B, varicella, *H. influenzae* type b, *S. pneumoniae,* rotavirus, *N. meningitidis,* and influenza. Rates of immunization among children in licensed childcare facilities are high, in part because of laws in almost all states that require age-appropriate immunizations of children who attend licensed childcare programs. Routine vaccination has had a significant beneficial effect on the health of children in childcare settings. Vaccines against influenza, *H. influenzae* type b, hepatitis B, rotavirus, varicella, *S. pneumoniae,* and hepatitis A are of particular benefit to children in childcare centers. Influenza vaccination of younger infants reduces influenza infection and secondary sequelae in both children and the adults who care for them in both their home and in childcare settings. Childcare providers should receive all immunizations that are recommended routinely for adults and have a preemployment health evaluation, including a tuberculin skin test. Local public

Table 174-2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
HAV infection	Serologic testing to confirm HAV infection in suspected cases Exclusion until 1 wk after onset of jaundice	If ≥1 case is confirmed in child or staff attendees or ≥2 cases in households of staff or attendees, HAV vaccine or Ig should be administered within 14 days of exposure to unimmunized staff and attendees In centers without diapered children, HAV vaccine or Ig should be given to unimmunized classroom contacts of index case Asymptomatic Ig recipients may return after receipt of Ig
Impetigo	Exclusion until 24 hr after treatment has been initiated Lesions on exposed skin covered with watertight dressing	No intervention needed unless additional lesions develop

Table 174-2 Disease- or Condition-Specific Recommendations for Exclusion of Children in Out-of-Home Childcare—cont'd

CONDITION	MANAGEMENT OF CASE	MANAGEMENT OF CONTACTS
Measles	Exclusion until 4 days after beginning of rash and when the child is able to participate	Immunize exposed children without evidence of immunity within 72 hr of exposure Children who do not receive vaccine within 72 hr or who remain unimmunized after exposure should be excluded until at least 2 wk after onset of rash in the last case of measles
Mumps	Exclusion until 5 days after onset of parotid gland swelling	In outbreak setting, people without documentation of immunity should be immunized or excluded Immediate readmission may occur following immunization Unimmunized people should be excluded for ≥26 days following onset of parotitis in last case
Pediculosis capitis (head lice)	Treatment at end of program day and readmission on completion of 1st treatment	Household and close contacts should be examined and treated if infested No exclusion is necessary
Pertussis	Exclusion until 5 days of appropriate antimicrobial therapy course have been completed	Immunization and chemoprophylaxis should be administered as recommended for household contacts Symptomatic children and staff should be excluded until completion of 5 days of antimicrobial therapy course Untreated adults should be excluded until 21 days after onset of cough
Rubella	Exclusion until 6 days after onset of rash for postnatal infection	Pregnant contacts should be evaluated
Salmonella serotype Typhi infection	Exclusion until diarrhea resolves 3 Negative stool culture results required before readmission	Stool cultures should be performed for attendees and staff; infected people should be excluded on the basis of age
Non–serotype Typhi *Salmonella* infection	Exclusion until diarrhea resolves. Negative stool culture results not required for non–serotype Typhi *Salmonella* species	Symptomatic contacts should be excluded until symptoms resolve Stool cultures are not required for asymptomatic contacts Antimicrobial therapy is not recommended for asymptomatic infection or uncomplicated diarrhea or for contacts
Scabies	Exclusion until after treatment given	Close contacts with prolonged skin-to-skin contact should have prophylactic therapy Bedding and clothing in contact with skin of infected people should be laundered
Shiga toxin–producing *Escherichia coli*, including *E. coli* O157:H7, or *Shigella* infection	Exclusion until diarrhea resolves and results of 2 stool cultures are negative for these organisms, depending on state regulations	Meticulous hand hygiene; stool cultures should be performed for contacts Center(s) with cases should be closed to new admissions during *E. coli* O157:H7 outbreak
Staphylococcus aureus skin infections	Exclusion only if skin lesions are draining and cannot be covered with a watertight dressing	Meticulous hand hygiene Cultures of contacts are not recommended
Streptococcal pharyngitis	Exclusion until 24 hr after treatment has been initiated and the child is able to participate in activities	Symptomatic contacts of documented cases of group A streptococcal infection should be tested and treated if test results are positive
Tuberculosis	For active disease, exclusion until determined to be noninfectious by physician or health department authority May return to activities after therapy is instituted, symptoms have diminished, and adherence to therapy is documented No exclusion for latent tuberculosis infection	Local health department personnel should be informed for contact investigation
Varicella	Exclusion until all lesions have dried and crusted, usually 6 days after onset of rash in immunocompetent people; may be longer in immunocompromised people	Varicella vaccine should be administered by 3-5 days after exposure, and varicella-zoster Ig should be administered up to 96 hr after exposure when indicated

HAV, hepatitis A virus; Ig, immunoglobulin.

From Pickering LK, Baker CJ, Kimberlin DW, et al, editors: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

Table 174-3 General Recommendations for Exclusion of Children in Out-of-Home Childcare

SYMPTOM(S)	MANAGEMENT
Illness preventing participation in activities, as determined by childcare staff	Exclusion until illness resolves and able to participate in activities
Illness that requires care greater than staff can provide without compromising health and safety of others	Exclusion or placement in care environment where appropriate care can be provided without compromising care of others
Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, progressive rash	Medical evaluation and exclusion until symptoms have resolved
Rash with fever or behavioral change	Medical evaluation and exclusion until illness is determined not to be communicable
Persistent abdominal pain (≥2 hr) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms	Medical evaluation and exclusion until symptoms have resolved
Vomiting ≥2 times in preceding 24 hr	Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities
Diarrhea or stools containing blood or mucus	Medical evaluation and exclusion until symptoms have resolved
Oral lesions	Exclusion until child or staff member is considered to be noninfectious (lesions crusted and dry)

From Pickering LK, Baker CJ, Kimberlin DW, et al, editors: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29, Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

health authorities should be notified of cases of reportable communicable disease that occur in children or providers in childcare settings.

STANDARDS

Every state has specific standards for licensing and reviewing childcare centers and family childcare homes. The American Academy of Pediatrics, the American Public Health Association, and the National Resource Center jointly publish comprehensive health and safety performance standards that can be used by pediatricians and other healthcare professionals to guide decisions about management of infectious diseases and other health-related matters in childcare facilities (available at http://cfoc.nrckids.org/). Specific standards set by all states also are available on this website.

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Chapter 175

Health Advice for Children Traveling Internationally

Stephen J. Swanson and Chandy C. John

Children are traveling internationally with increasing frequency and to more "exotic" destinations that pose unique injury and disease risks. Compared to adults, children are *less* likely to receive pretravel advice and *more* likely to be seen by a medical provider or be hospitalized upon return for a travel-related illness. Primary care providers are confronted with the challenge of trying to ensure safe, healthy travel for their patient, whether travel is occurring for purposes of tourism, study abroad, visiting friends and relatives, or volunteerism. Whenever possible, health professionals are encouraged to consult with Travel Medicine specialists, especially when uncertain about pretravel advice, unique travel medicine vaccines (e.g., yellow fever, Japanese encephalitis, typhoid, rabies), and recommendations for malaria medications.

Travel medicine is a unique specialty, and experienced travel medicine practitioners provide specialized guidance on the infectious and noninfectious risks based on age, itinerary, duration, season, purpose of travel, and underlying traveler characteristics (health and vaccination status). A pretravel consultation includes the essential elements of (1) safety and preventive counseling against injuries and diseases; (2) routine, recommended, and required vaccinations, based on individual risk assessment; (3) counseling and medications for self-treatment of traveler's diarrhea; and (4) when indicated by itinerary, malaria chemoprophylaxis.

In the United States, recommendations and vaccine requirements for travel to different countries are provided by the Centers for Disease Control and Prevention (CDC) and are available online at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/travel-vaccines-and-malaria-information-by-country. *Some travel vaccines and medications may not be recommended based on specifics of travel itinerary, trip duration, or patient characteristics. Alternatively, some vaccinations are not approved for younger children because of lack of data or limited immunologic response, but may still confer potential benefit to the young traveler with off-label vaccine administration. In both scenarios, consultation or referral to a knowledgeable travel medicine practitioner is encouraged, especially if uncertainty exists regarding pretravel recommendations.*

THE PEDIATRIC TRAVEL MEDICINE CONSULTATION

Parents of traveling children should seek medical consultation at least 4-6 wk before departure to review the travel itinerary, obtain safety and preventive counseling, ensure adequate vaccinations (routine, recommended, and required), receive necessary medications for chronic health conditions, and obtain important medications for self-treatment of traveler's diarrhea and, when indicated, malaria chemoprophylaxis with counseling. Preparing a child to travel internationally should begin with an emphasis on the positive aspects of the upcoming trip rather than solely focusing on travel risks and diseases. Subsequent advice, vaccinations, and medications should be emphasized as important measures with the provider goal of *keeping the child healthy during travel rather than to discourage traveling.*

Pediatric Travelers Visiting Friends and Relatives

Compared to most children traveling internationally, the pediatric visiting-friends-and-relatives (VFR) traveler is a vulnerable population uniquely at risk for travel-related illnesses. VFR travelers may include immigrants, refugees, migrants, students, or displaced persons who are traveling back to their country of origin for purposes of visiting friends and relatives. Pediatric VFR travelers are typically children accompanying their parents or family members back to their ancestral country, where relational, social, and cultural connections remain. Compared to tourist travelers, VFR travelers are more likely to travel for longer durations, visit more remote destinations, travel by higher-risk local transportation modes, experience closer contact with the local population, and utilize fewer insect, food, and water precautions. Adult and pediatric VFR travelers are also less likely to perceive a risk of travel-related illnesses, seek pretravel advice, receive travel immunizations, or use effective malaria prophylaxis upon arrival in the destination country. VFR travel comprises 50-84% of imported malaria in children in the United States (i.e., malaria acquired outside the United States), and pediatric VFR travelers are reported to be 4 times more likely to acquire malaria than tourist travelers. Among all travelers, pediatric VFR travelers remain at higher risk for contracting hepatitis A and having symptomatic illness. Several studies suggest that VFR travelers are at disproportionate risk of acquiring typhoid fever and possibly tuberculosis. Providers should inquire if their foreign-born patients will be traveling internationally and seek opportunities to encourage pretravel consultation for VFR travelers.

SAFETY AND PREVENTIVE COUNSELING TOPICS

Health and Evacuation Insurance, Underlying Health Conditions, and Medications

Parents should be made aware that their medical insurance policy might not provide coverage for hospitalizations or medical emergencies in foreign countries and is unlikely to cover the high cost of an emergency medical evacuation. Supplemental travel medical insurance and evacuation insurance may be purchased and are especially recommended for prolonged travel itineraries, for remote destinations, and for children with higher-risk preexistent health conditions going to countries where inpatient care at a level comparable to the traveler's home country may not be available. A list of medical and evacuation insurance providers can be found at the U.S. Department of State's International Travel advisory website (http://travel.state.gov/travel/cis_pa_tw/cis/cis_1470.html).

Parents of children with medical conditions should take with them a brief medical summary and a sufficient supply of prescription medications for their children, with bottles that are clearly identified by prescription labels. For children requiring care by specialists, an international directory for that specialty can be consulted. A directory of physicians worldwide who speak English and who have met certain qualifications is available from the International Association for Medical Assistance to Travelers (http://www.iamat.org/index.cfm). If medical care is needed urgently when abroad, sources of information include the American embassy or consulate, hotel managers, travel agents catering to foreign tourists, and missionary hospitals.

A travel health kit consisting of prescription medications and nonprescription items, such as acetaminophen, an antihistamine, oral rehydration solution packets, antibiotic ointment, bandages, insect repellent, and sunscreen, is highly recommended for all children. Children with persistent asthma should have bronchodilators and oral steroids prescribed for treatment of any acute asthma exacerbations encountered during overseas travel. Children with a history of angioedema, anaphylaxis, or severe allergies to food or insects should have an epinephrine autoinjector (EpiPen) and antihistamines available for use during travel.

Parents and family members should be aware of the prevalence of counterfeit medication and lack of quality control of medications in many areas of the world, particularly in low- and middle-income countries. Critical medications, including insulin and newly prescribed antimalarials, should be purchased prior to international travel and packed in original prescription containers.

Safety and Injury Prevention

Motor vehicle accidents are a leading cause of traumatic injuries to, hospitalizations of, and deaths of pediatric and adult travelers. Differences in traffic patterns should be emphasized to children, and the use of safety belts should be reinforced. When possible, child safety seats should be taken on the trip. Parents should also be aware of additional risks for small children that may exist overseas, such as open balconies, windows without screens or bars, exposed wires and electrical outlets, paint chips, pest and rodent poison, and stray animals. Water-related activities also are associated with significant injuries in pediatric travelers, and pools and oceanfronts are often unsupervised and without lifeguards at overseas destinations.

Animal Contact

Among travelers, attacks from domestic or stray animals are far more likely to occur than attacks from wild animals. Wounds from animal bites present a risk for bacterial infections, tetanus, and rabies. Dogs are responsible for more than 95% of all rabies transmission in Asia, Africa, and Latin America. Globally, the World Health Organization (WHO) estimates that there are approximately 55,000 human deaths from rabies each year, with the vast majority of cases occurring in South Asia, Southeast Asia, and Africa. Reports of rabies transmission have less commonly occurred following bites from cats and other carnivores, monkeys, and bats. Macaque monkeys, native to Asia and North Africa, can be found in urban centers and tourist sites and pose a risk for rabies and herpes B virus infections following bites and scratches.

Young children are more likely to be bitten and experience more severe facial wounds related to their short stature. As such, they are at higher risk for rabies exposure from dogs and other animals during travel and require greater supervision. Parents should always encourage their children to report bite injuries and to avoid petting, feeding, or handling dogs, monkeys, and stray animals. Before travel, tetanus vaccinations need to be current for all travelers. Children, long-term travelers, expatriates, and all individuals likely to come into contact with animals in a rabies-endemic region (primarily Africa and South and Southeast Asia) should consider preexposure vaccination for rabies before international travel (see "Rabies" below). Bite or scratch wounds should be washed thoroughly and for a prolonged time (15 min) with copious water and soap. Local wound care will substantially reduce the risk of canine and other mammalian rabies transmission. Rabies postexposure vaccination and rabies immunoglobulin should be considered. Antibiotics (amoxicillin–clavulanate) may need to be administered to a child to prevent secondary infections, especially for animal bites involving the hands and head/neck areas.

ROUTINE CHILDHOOD VACCINATIONS REQUIRED FOR PEDIATRIC TRAVEL

Parents should allow 4 or more weeks before departure for optimal administration of vaccines to their children. All children who travel should be immunized according to the routine childhood immunization schedule with all vaccines appropriate for their age. The immunization schedule can be accelerated to maximize protection for traveling children, especially for unvaccinated or incompletely vaccinated children (see Fig. 172-4 in Chapter 172). Routine and catch-up childhood vaccine schedules for healthcare professionals can be found at the CDC website (http://www.cdc.gov/vaccines/schedules/index.html).

Live-attenuated viral vaccines should be administered concurrently or 4 or more weeks apart to minimize immunologic interference. Intramuscular immunoglobulin interferes with the immune response to measles immunization and possibly to varicella immunization. If a child requires measles or varicella immunization, the vaccines should be given either 2 wk before or 3 mo after immunoglobulin administration (longer with higher doses of intravenous immunoglobulin).

Immunoglobulin does not interfere with the immune response to oral typhoid, poliovirus, or yellow fever vaccines.

Vaccine products produced in eggs (yellow fever, influenza) may be associated with hypersensitivity responses, including anaphylaxis in persons with known severe egg sensitivity. Screening by inquiring about adverse effects when eating eggs is a reasonable way to identify those at risk for anaphylaxis from receiving influenza or yellow fever vaccines. Although measles and mumps vaccines are produced in chick embryo cell cultures, children with egg allergy are at very low risk for anaphylaxis with these vaccines.

Diphtheria-Tetanus-Pertussis

Children traveling internationally should be fully vaccinated with diphtheria and tetanus toxoids and acellular pertussis (DTaP), having completed the 4th or 5th booster dose by 4-6 yr of age. A single dose of an adolescent/adult preparation of tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine is recommended at 11-12 yr of age for those who have completed the recommended primary DTaP (or DTP) series.

Adolescents and adults should receive a single Tdap booster if more than 5 yr have elapsed since the last dose, as a tetanus-containing booster (Td or Tdap) may not be readily available for tetanus-prone wounds during international travel or in remote settings (adventure travel, wilderness).

Haemophilus influenzae Type B

Haemophilus influenzae type b remains a leading cause of meningitis in children 6 mo to 3 yr of age in many low- and middle-income countries. Before they travel, all unimmunized children <5 yr of age should be vaccinated (see Chapter 172). A single dose of *H. influenzae* type b vaccine should also be administered to unvaccinated or partially vaccinated children who are 5 yr of age or older if they have anatomic or functional asplenia, sickle cell disease, HIV infection, leukemia, malignancy, or other immunocompromising condition. Unvaccinated children who are >5 yr of age do not need vaccination unless they have a high-risk condition.

Hepatitis A

Hepatitis A is a routine childhood vaccine in the United States but requires special considerations in the traveling pediatric patient, and protection from hepatitis A in specific children may also involve the provision of immunoglobulin. For this reason, hepatitis A vaccination is covered below in "Specialized Pediatric Travel Vaccinations."

Hepatitis B

Hepatitis B is a travel-associated infection. Hepatitis B is highly prevalent throughout much of the world, including areas of South America, sub-Saharan Africa, eastern and southeastern Asia, and most of the Pacific basin. In certain parts of the world, 8-15% of the population may be chronically infected. Disease can be transmitted via blood transfusions not screened for hepatitis B surface antigen, exposure to unsterilized needles, close contact with local children who have open skin lesions, and sexual exposure. Exposure to hepatitis B is more likely for travelers residing for prolonged periods in endemic areas. Partial protection may be provided by 1 or 2 doses, but ideally 3 doses should be given before travel. For unvaccinated adolescents, the 1st 2 doses are 4 wk apart and are followed by a 3rd dose 8 wk later (at least 16 wk after 1st dose).

All unvaccinated children and adolescents should receive the accelerated hepatitis B vaccine series prior to travel. Because 1 or 2 doses provide some protection, hepatitis B vaccination should be initiated even if the full series cannot be completed before travel.

Influenza and Avian Influenza

Influenza remains the most common vaccine-preventable disease occurring among pediatric and adult travelers. The risk for exposure to influenza during international travel varies depending on the time of yr, destination, and intermingling of persons from different parts of the world where influenza may be circulating. In tropical areas, influenza can occur throughout the year, whereas in the temperate regions of the Southern hemisphere, most activity occurs from April through September. In the Northern hemisphere, influenza generally occurs from November through March. Seasonal influenza vaccination is strongly recommended for all pediatric and adolescent travelers who do not have a contraindication or severe egg allergy.

Currently, there is no available vaccine effective against avian influenza, the H5N1 virus, which has become an increasing concern worldwide. However, there are precautions for those traveling to endemic areas, which include parts of Asia, Africa, Eastern Europe, and the Middle East (see the CDC's website for a detailed list of countries). Because H5N1 influenza is spread through contact with infected birds, these precautions include avoiding direct contact with birds or surfaces with bird droppings, avoiding poultry farms or bird markets, eating only well-cooked bird meat or products, and washing hands frequently. Human-to-human transmission has been reported but is very rare and has not involved spread past 1 person. Oseltamivir is the antiviral of choice to treat avian influenza, because the virus is resistant to amantadine and rimantadine. Oseltamivir is FDA-approved for children 1 yr of age and older but can be also be administered for treatment of influenza during infancy with weight-based dosing (http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm).

Measles-Mumps-Rubella

Measles is still endemic in many low- and middle-income countries and in some industrialized nations. It remains a leading cause of vaccine-preventable death in much of the world. Vaccine status for measles is important for all traveling children, particularly if they are traveling to low- and middle-income countries or areas with measles outbreaks. Measles vaccine, preferably in combination with mumps and rubella vaccines (MMR), should be given to all children at 12-15 mo of age and at 4-6 yr of age, unless there is a contraindication (see Chapter 172.2). In children traveling internationally, the 2nd vaccination can be given as soon as 4 wk after the 1st, to induce immunity among those children who did not respond to the 1st MMR vaccine.

Children between the ages of 6 and 12 mo who are traveling to the low- and middle-income world should be vaccinated with monovalent measles vaccine. If the monovalent vaccine is unavailable, MMR should be used. Early vaccination (i.e., between 6-12 mo of age) will provide some immunity to measles, but antibody response is not durable or lasting. Any MMR vaccine before 12 mo of age does not count toward the routine vaccination schedule; children vaccinated early for purposes of international travel must be revaccinated on or after their 1st birthday with 2 doses, separated by at least 4 wk. Infants <6 mo of age are generally protected by maternal antibodies and should not receive early MMR vaccination prior to travel.

Pneumococcal Vaccines

Streptococcus pneumoniae is the leading cause of childhood bacterial pneumonia and is among the leading causes of bacteremia and bacterial meningitis in children in low- and middle-income and industrialized nations. Preparing a child to travel internationally includes routine or catch-up vaccination with 13-valent pneumococcal conjugate vaccine (PCV13) and, for children with certain high-risk conditions, use of 23-valent pneumococcal polysaccharide vaccine (PPSV23). A single dose of PCV13 should be administered to previously unvaccinated children 6-18 yr old with underlying high-risk medical conditions: anatomic or functional asplenia (including sickle cell disease), HIV infection, a congenital immunodeficiency or immunocompromising condition, chronic heart or lung disease, chronic renal failure or nephrotic syndrome, diabetes mellitus, cerebrospinal fluid leak, or cochlear implant. The Advisory Committee on Immunization Practices also recommends that high-risk children age 2 yr and older receive the PPSV23 vaccine 8 or more weeks after their last PCV13 dose. Recommendations of the Advisory Committee on Immunization Practices on prevention of pneumococcal disease among infants and children using PCV13 and PPSV23 can be found at http://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html.

Polio Vaccine

Poliomyelitis was eradicated from the Western hemisphere in 1991. Polio remains endemic in 3 countries—Afghanistan, Nigeria, and Pakistan—with additional surrounding countries at risk for importation of polio. A number of countries continue to experience periodic outbreaks of importation polio, particularly countries extending from west Africa to the Horn of Africa. The poliovirus vaccination schedule in the United States is now a 4-dose, all-inactivated poliovirus (IPV) regimen (see Chapter 172). Traveling infants should begin IPV series as early as 6 wk of age. For an accelerated dosing schedule for children, see Figure 172-4 in Chapter 172. Length of immunity conferred by IPV immunization is not known; a single booster dose of IPV is therefore recommended for previously vaccinated adolescents and adults traveling to polio-endemic areas if approximately 10 yr has elapsed since they completed their primary series. Oral poliovirus vaccine is no longer available in the United States.

Varicella

All children 12 mo of age and older who have no history of varicella vaccination or chickenpox should be vaccinated unless there is a contraindication to vaccination (see Chapter 172). Infants <6 mo of age are generally protected by maternal antibodies. All children now require 2 doses, the 1st at 12 mo of age and the 2nd at 4-6 yr of age. The 2nd dose can be given as soon as 3 mo after the 1st dose. For unvaccinated children 13 yr of age and older, the 1st and 2nd doses can be separated by 4 wk.

SPECIALIZED PEDIATRIC TRAVEL VACCINATIONS

Table 175-1 summarizes the dosages and age restrictions of vaccines specifically given to children traveling internationally.

Cholera

Cholera is present in many low- and middle-income countries, but the risk for infection among travelers to these countries is extremely low. At present, there is no cholera vaccine available for travelers in the United States, although an effective vaccine is available in other countries. Travelers entering countries reporting cholera outbreaks are at minimal risk of acquiring cholera if they take adequate safe food and water precautions and utilize frequent handwashing. No country or territory currently requires cholera vaccination as a condition for entry.

Table 175-1 Travel Vaccinations for Children

VACCINE	PRIMARY SERIES	AGE AT VACCINATION	BOOSTER/COMMENTS
HEPATITIS A			
Havrix, Vaqta	0.5 mL IM × 2 doses ≥6 mo apart	>1 yr	No booster; see text about off-label administration (age 6-11 mo)
Immunoglobulin (Ig)	Travel <2 mo: 0.02 mL/kg IM once Travel >2 mo: 0.06 mL/kg IM once	Birth	See text about restrictions with live virus vaccinations (i.e., MMR) following Ig administration
INFLUENZA			
Inactivated	6-35 mo: 0.25 mL IM, 1 or 2 doses 3-8 yr: 0.5 mL IM, 1 or 2 doses >9 yr: 0.5 mL IM once	>6 mo	New vaccine yearly In children 6 mo-9 yr, 2 doses should be given ≥1 mo apart if no prior vaccination
Live-attenuated	0.25 mL in each nostril, 1 or 2 doses	>2 yr	New vaccine yearly
JAPANESE B ENCEPHALITIS			
Ixiaro (inactivated)	2 mo-2 yr: 0.25 mL IM on days 0 and 28	2 mo to <3 yr	Booster 1-2 yr after primary series
	>3 yr: 0.5 mL IM on days 0 and 28	>3 yr	Booster 1-2 yr after primary series
MEASLES			
MMR	Recommended schedule: 12-15 mo and 4-6 yr If >12 mo and traveling internationally, 2nd MMR dose can be administered 4 wk later	>6-11 mo: 1 dose recommended if traveling to measles-endemic area	See text. MMR at 6-11 mo does not count toward primary series; MMR should be administered simultaneously with other recommended/required live-virus travel vaccines (yellow fever)
MENINGOCOCCAL DISEASE			
Conjugate A/C/Y/W-135	0.5 mL IM 9-23 mo: 2 doses, 3 mo apart	9-23 mo	Booster 3 yr after primary series
	0.5 mL IM once	>2–6 yr	Booster after 3 yr (age 2-6 yr)
		>7 yr	Booster after 5 yr (age >7 yr) Children with functional/anatomic asplenia receive 2 dose primary series, 2 mo apart; conjugate vaccine recommended over polysaccharide A/C/Y/W-135
Polysaccharide A/C/Y/W-135	0.5 mL SC once	>2 yr	<4 yr of age: every 2 yr >4 yr of age: every 3-5 yr
RABIES			
	Preexposure: 1.0 mL IM × 3 doses, days 0, 7, and 21 or 28 days	Any age	See text for follow-up vaccination if bitten
TYPHOID			
Intramuscular Vi	0.5 mL IM once	≥2 yr	Every 2-3 yr
Oral Ty21	4 doses: 1 capsule PO every other day	≥6 yr	Every 5 yr; see text for administration
YELLOW FEVER			
	0.5 mL SC once	>9 mo	Every 10 yr (see text)

A/C/Y/W-135, serogroup A, C, Y, and W^{135} meningococcal vaccine.

Hepatitis A Vaccination and Preexposure Immunoglobulin

Hepatitis A virus is endemic in most of the world, and travelers are at risk, even if their travel is restricted to the usual tourist routes. Hepatitis A infection can occur as a result of eating shellfish harvested from sewage-contaminated waters, eating unwashed vegetables or fruits, or eating food prepared by an asymptomatic carrier of hepatitis A virus. Young children infected with hepatitis A are often asymptomatic but can transmit infection to older children and adults, who are more likely to develop clinical hepatitis. Few areas carry no risk of this infection, and therefore immunization is recommended for all travelers. Hepatitis A vaccine is recommended in the United States for universal immunization of all children 12 mo of age or older, administered as 2 doses 6 mo apart. A single dose of hepatitis A vaccine given to travelers will provide adequate protection in most instances. Protective immunity develops within 2 wk after the initial vaccine dose. A combined 3 dose hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline) is available in the United States but is licensed for use only in adolescents >18 yr of age. Pediatric combination hepatitis A–hepatitis B vaccine (Twinrix-Junior, GlaxoSmithKline) is licensed for use in children 1-18 yr in Canada and Europe.

Children <1 yr of age are at lower risk of clinical hepatitis A infection, especially if they are breastfed or residing in areas with safe water for formula reconstitution. Some experts recommend use of preexposure intramuscular immunoglobulin for children <12 mo who are traveling internationally to higher-risk destinations, particularly low-income destinations or regions where hygienic or sanitary conditions are limited. However, administration of immunoglobulin diminishes the immunogenicity of live-virus vaccines, in particular measles vaccine, that may be needed for infant travelers. Vaccination against measles should occur 2 or more weeks prior to any immunoglobulin administration, and a 3 mo interval is suggested between immunoglobulin administration and subsequent measles immunization.

Providers should be aware that infant travelers 6 mo of age or older who are being considered for preexposure immunoglobulin may also need measles (MMR) vaccination, as measles-endemic countries frequently overlap with higher-risk travel destinations for hepatitis A virus infection. For this reason, and on the basis of vaccine safety data, many travel medicine experts recommend immunization with hepatitis A vaccine rather than administration of intramuscular immunoglobulin to infants 6-11 mo of age who will be traveling to a hepatitis A virus–endemic area. Several studies demonstrate that infants as young as 6 mo old will develop antibodies following hepatitis A vaccine, especially if there are no interfering maternal antibodies from prior maternal vaccination or disease. There is potential for a more durable immune response to the hepatitis A vaccination especially in later infancy, when potential interfering maternal antibody concentrations are lower. If early hepatitis A vaccination is given rather than immunoglobulin to infant travelers (age 6-11 mo), it should not count toward the routine 2 dose vaccine series. Similar to MMR vaccination, an informed decision should be made, with the parents balancing the risk of travel-associated disease and vaccine adverse events with the potential protective benefit to the traveling infant.

Japanese Encephalitis

Japanese encephalitis is a disease transmitted by mosquitoes in many areas of Asia, especially in rural farming areas. Although it is a leading cause of vaccine-preventable encephalitis in children in many Asian countries and parts of western Pacific countries, the risk of disease to nonimmune travelers is low. A map showing where Japanese encephalitis transmission occurs can be found at http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/japanese-encephalitis#2473.

Most human infections with Japanese encephalitis virus are asymptomatic, and <1% of individuals develop clinical disease. With symptomatic disease, the fatality rate is 20-30% and the incidence of neurologic or psychiatric sequelae in survivors is 30-50%. The risk of Japanese encephalitis disease for pediatric travelers is unknown, but among all travelers, it is estimated to be less than 1 case per 1 million travelers to Asia. Risk of Japanese encephalitis neurologic disease following mosquito-bite transmission is thought to be higher in children than adults. The disease occurs primarily from June to September in temperate zones and throughout the entire year in tropical zones. Vaccination is recommended for travelers planning visits of longer than 1 mo to rural areas of Asia, where the disease is endemic, especially areas of rice or pig farming. Vaccination is recommended for shorter visits to such areas if the traveler will often be outdoors (e.g., camping or hiking). Risk for infection can be greatly reduced by following the standard precautions to avoid mosquito bites.

The inactivated Vero-cell culture-derived Japanese encephalitis vaccine (Ixiaro) has replaced the older inactivated mouse-brain-derived vaccine (JE-VAX), which is no longer manufactured. Japanese encephalitis (Ixiaro) vaccine efficacy is >95% in adults who receive 2 doses administered 28 days apart. The licensed range for Japanese encephalitis vaccine (Ixiaro) has been extended to include children as young as age 2 mo, with a dose administered on days 0 and 28.

Meningococcal Vaccines

There are currently 2 forms of meningococcal vaccine available in the United States: a quadrivalent polysaccharide A/C/Y/W-135 vaccine (Menomune) and 2 quadrivalent conjugate A/C/Y/W-135 vaccines (Menactra, Menveo). A single-dose conjugate quadrivalent A/C/Y/W-135 vaccine, Nimenrix (manufactured by GlaxoSmithKline), is licensed in Europe and Canada for individuals from 12 mo-55 yr of age.

Children traveling to those equatorial countries in sub-Saharan Africa where the incidence of meningococcal disease is highest should receive a *Neisseria meningitidis* vaccine, especially if travel is prolonged or occurs during the dry season of December to June. Risk is greatest in the "meningitis belt" of sub-Saharan Africa (see the map at http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/meningococcal-disease), with rates of meningococcal disease in endemic regions reaching up to 1,000 cases per 100,000 population per year. Children 9-23 mo of age who are traveling to these equatorial African countries where meningococcal disease is hyperendemic or epidemic should receive a 2 dose series of Menactra brand MCV4, 8-12 wk apart. Conjugate vaccine is preferred in children over the less-effective polysaccharide vaccine (Menomune). Booster doses of conjugate A/C/Y/W-135 should occur every 3-5 yr for travelers returning to endemic areas, depending on age of pediatric traveler. Providers may also wish to consider meningococcal vaccination for other pediatric travelers, especially if there is remote or rural travel to low-income countries with limited healthcare access, as meningococcal outbreaks can occur anywhere in the world. Proof of receipt of quadrivalent meningococcal vaccination is also necessary for individuals traveling to Mecca, Saudi Arabia, for the annual Hajj or Umrah pilgrimages.

Serogroups A and C are most commonly associated with epidemics of meningitis in sub-Saharan Africa, especially in the "meningitis belt" of equatorial Africa during the dry season mo (December to June). Serogroups Y and W-135 have also been found in meningococcal outbreaks. Serogroup B, currently not included in any licensed meningococcal vaccine in the United States, is associated with more sporadic cases of invasive meningococcal disease in industrialized countries, including the United States. Additional vaccine information on meningococcal vaccination regimens and booster intervals can be found at the CDC website (http://www.cdc.gov/vaccines/vpd-vac/mening/#recs).

Rabies

Rabies is endemic in many countries in Africa, Asia, and Central and South America. Children are at particular risk because they are less likely to report bites and because facial bites are more common in children. Rabies has the potential for an extended latency period (months) and is uniformly fatal once the clinical symptoms emerge. Preexposure prophylaxis is recommended for ambulatory children with extended travel to high-risk regions, especially expatriate children and younger children traveling to or living in rural areas where enzootic dog rabies is endemic. Rabies preexposure vaccination should also

be considered for adventure travelers (hikers, bikers), individuals likely to come into contact with rabies vectors (i.e., students working with animal or bat conservation), or travelers with itineraries to rabies-endemic regions where timely, effective postexposure prophylaxis might not be available following an animal bite. Most animal bites in a rabies-endemic area should be considered a medical emergency, especially bites from stray dogs, other carnivores, and bats. Immediate wound care washing should be followed by prompt administration of appropriate postexposure rabies prophylaxis at a medical facility. Postexposure prophylaxis is required even for persons who received preexposure vaccination. Algorithms for pre- and postexposure vaccination are the same regardless of patient age.

Numerous rabies vaccine formulations exist around the world. In the United States, 2 rabies vaccines are available: human diploid cell vaccine (HDCV; Imovax, Sanofi Pasteur, SA) and purified chick embryo cell (PCEC; RabAvert, Novartis) vaccine. Preexposure prophylaxis is given either intramuscularly (HDCV or PCEC) as 3 doses (1 mL) on days 0, 7, and 21 or 28. Postexposure prophylaxis is given as 4 doses (1 mL) of HDCV or PCEC vaccine intramuscularly on days 0, 3, 7, and 14 if previously unvaccinated and 2 doses (1 mL) intramuscularly on days 0 and 3 if previously vaccinated. Previously unvaccinated persons should also receive rabies immunoglobulin (RIG, 20 IU/kg), with as much of the dose as possible infiltrated around the wound site at the time of initial postexposure prophylaxis. Previously vaccinated persons should not receive RIG. Unpurified or purified equine RIG preparations are still used in some low- and middle-income countries and are associated with a higher risk for severe reactions, including serum sickness and anaphylaxis. Purified cell culture–derived vaccines are also not always available abroad; travelers should be aware that any rabies vaccines derived from neural tissue carry an increased risk for adverse reactions, often with neurologic sequelae. If rabies prophylaxis is initiated abroad, neutralizing titers should be checked on return and immunization completed with a cell culture–derived vaccine. If rabies prophylaxis cannot be provided abroad, children with high-risk bites (e.g., stray dog) should be emergently transported to a site where they can receive prophylaxis, as the vaccinations should be started as soon as possible after the bite and ideally within 24 hr. Infants and young children respond well to rabies vaccine, and both pre- and postexposure vaccinations can be given at any age, using the same dose and schedule as adults. Individual travelers simultaneously receiving mefloquine or chloroquine may have limited immune reactions to intradermal rabies vaccine and should be vaccinated intramuscularly.

Tuberculosis

The risk for tuberculosis in the typical traveler is low. Pre- and post-travel testing for tuberculosis is controversial, and should be done on an individualized basis depending on the itinerary, duration, and activities (i.e., working in a hospital setting). Immunization with bacillus Calmette-Guérin is even more controversial. It has variable efficacy in reducing severe tuberculosis disease in infants and young children, is not available in the United States, and is generally not recommended for pediatric travelers. Infection with *Mycobacterium bovis* can be prevented through avoiding consumption of unpasteurized dairy products.

Typhoid

Salmonella typhi infection, or typhoid fever, is common in many low- and middle-income countries in Asia, Africa, and Latin America (see Chapter 198). Typhoid vaccination is recommended for most children 2 yr of age or older who are traveling to the Indian subcontinent, as the incidence of typhoid is 10-100 times higher for travelers to the Indian subcontinent than all other travel destinations. Vaccination should be strongly considered for other travelers to low- and middle-income countries, particularly if they are visiting friends and relatives, lack access to reliable clean water and food, are traveling for a prolonged duration, or are adventurous eaters.

Two typhoid vaccines, the intramuscular Vi-polysaccharide vaccine and oral Ty21a strain live-attenuated vaccine, are recommended for use in children in the United States. Both produce a protective response in 50-80% of recipients. Neither vaccination offers meaningful protection against *Salmonella paratyphi*, another cause of enteric fever. Travelers who have had prior diagnoses of "typhoid fever" should still receive vaccination, as past infection does not confer long-term immunity.

The intramuscular Vi-polysaccharide vaccine is licensed for use in children 2 yr of age and older. It can be given any time before departure, but it should ideally be administered 2 wk before travel, with a booster needed 2-3 yr later. The oral Ty21a vaccine can only be used in children 6 yr of age or older and is given in 4 doses over a 1 wk period. Enteric-coated capsules are to be swallowed with a cool or room-temperature drink, at least 1 hr before a meal, every other day until the 4 doses are completed. Oral typhoid capsules must remain refrigerated (not frozen). Capsules should never be broken open, as vaccine efficacy is dependent on capsules being swallowed whole in order to get past the acidic stomach contents. The oral vaccine is associated with an immune response lasting 5-7 yr (depending on national labeling). Antibiotics inhibit the immune response to the oral Ty21a vaccine; the vaccine should not be given within 72 hr of antibiotic treatment, and antibiotics should be avoided until 7 days after completing the vaccine series. Studies demonstrate that mefloquine, chloroquine, and atovaquone-proguanil can be given concurrently with the oral Ty21a vaccine without affecting the immunogenicity of the vaccine. Oral Ty21a vaccine should not be given to immunocompromised children; these children should receive the intramuscular Vi-polysaccharide vaccine.

Yellow Fever

Yellow fever (see Chapter 270) is a mosquito-borne viral illness resembling other viral hemorrhagic fevers (see Chapter 271) but with more prominent hepatic involvement. Yellow fever is present in tropical areas of South America and Africa.

Yellow fever vaccination is indicated in children >9 mo of age traveling to an endemic area. Many countries require yellow fever vaccination by law for travelers arriving from endemic areas, and some African countries require evidence of vaccination from all entering travelers. Current recommendations can be obtained by contacting state or local health departments or the Division of Vector-Borne Infectious Diseases of the CDC (telephone: 404-332-4555; or website: http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/yellow-fever). Most countries accept a medical waiver for children who are too young to be vaccinated (<6 mo of age) and for persons with a contraindication to vaccination. Children with asymptomatic HIV infection may be vaccinated if exposure to yellow fever virus cannot be avoided.

Yellow fever vaccine (0.5 mL SC), a live-attenuated vaccine (17D strain) developed in chick embryos, is safe and highly effective in children >9 mo of age, but in young infants it is associated with a markedly increased risk for vaccine-associated encephalitis (0.5-4/1,000) and other severe reactions. Yellow fever vaccine should **never be given** to infants <6 mo of age; infants 6-8 mo of age should be vaccinated only in consultation with the CDC or a travel medicine expert to assess the current epidemiology, travel itinerary and duration, and whether the yellow fever virus exposure is greater than vaccine risks. In children >9 mo, adverse effects are rare, although vaccine-associated neurotropic and viscerotropic disease associated with the vaccine have been reported. The risk of these reactions is higher in those with thymus disease, altered immune status, age >60 yr, or multiple sclerosis and in infants <9 mo of age (neurotropic disease). Yellow fever vaccination is generally contraindicated in pregnancy and for nursing mothers, unless extended travel to a yellow fever–endemic area is unavoidable.

Children with immunodeficiency or an immunosuppressed state, a thymic disorder or dysfunction (i.e., DiGeorge syndrome), or a history of anaphylactic reactions to eggs should not receive yellow fever vaccine. Long-lived immunity develops with this vaccine, perhaps even lasting for a lifetime; however, international travel certificates require proof of immunization within 10 yr.

Traveler's Diarrhea

Ingestion of contaminated food or water makes travel-associated diarrhea the most common health complaint among international travelers. Traveler's diarrhea, characterized by a 2-fold or greater increase in the frequency of unformed bowel movements, occurs in as many as 40% of all travelers overseas (see Chapter 340.1). Children, especially those <3 yr of age, have a higher incidence of diarrhea, more-severe symptoms, and more-prolonged symptoms than adults, with a reported attack rate of 60% for those <3 yr of age in 1 study.

An important risk factor for traveler's diarrhea is the country of destination. High-risk areas (attack rates of 25-50%) include low- and middle-income countries of Latin America, Africa, the Middle East, and Asia. Intermediate risk occurs in the Mediterranean, China, and Israel. Low-risk areas include North America, Northern Europe, Australia, and New Zealand. Fecal-oral diarrheal pathogens that children acquire during travel are similar to those acquired by adults and include enterotoxigenic and enteroaggregative *Escherichia coli*, *Campylobacter, Salmonella* (nontyphoidal serotypes predominate), and *Shigella* species. Enteric protozoa are a much less common cause of traveler's diarrhea than bacterial pathogens—*G. lamblia* is the most likely protozoal cause of persistent diarrhea. Less-common travel-associated protozoa include *Cryptosporidium* species, *E. histolytica,* and *Cyclospora*. Viral infections, particularly rotavirus infections, may also cause travel-associated diarrhea in children. Clinicians should be aware that not all diarrheal illness in children is food borne or waterborne—febrile children with malaria may also present with vomiting and/or nonbloody diarrhea and may be misdiagnosed as having traveler's diarrhea.

Guidance on Prevention of Traveler's Diarrhea

Food and water hygiene remain important measures to reduce the incidence of traveler's diarrhea in children. However, creating long lists of foods to avoid or offering the popular, simple advice of "Boil it, peel it, cook it, or forget it!" is generally an ineffective method of reducing traveler's diarrhea. Most studies show that these kinds of dietary directives are difficult to keep and may have little impact on the incidence of traveler's diarrhea. In adult studies, the risk of developing traveler's diarrhea appears to be more associated with *where you eat rather than what you eat*. Eating in a relative's or friend's home is generally safer than eating in a restaurant, where restaurant kitchen hygiene and proper refrigeration may be lacking and employee handwashing may be sporadic.

In general, travel medicine providers can provide some common sense food and water advice to family travelers. Boiled or bottled water, hot beverages, and canned or bottled beverages are generally safe to consume. Ice should be avoided. In low- and middle-income countries, tap water is generally unsafe for drinking or brushing teeth. Boiling water for 1 min or longer (or 3 min at altitudes >2000 m) remains a reliable method of disinfecting water. Food that is thoroughly cooked and served hot is almost always safe to eat. Dry foods, such as pastry items, breads, and cookies, are generally safe to eat. Unpasteurized milk or other dairy products (cheese) should always be avoided. Breastfeeding should be encouraged for young children, especially infants <6 mo of age, to reduce exposure to contaminated water/formula. All children should be reminded to wash their hands before eating and after playing around soil or animals. Chemoprophylactic agents for traveler's diarrhea are not recommended for children.

Management of Traveler's Diarrhea

Dehydration is the greatest threat presented by a diarrheal illness in a small child. Parents should be made aware of the symptoms and signs of dehydration and should be given instructions on how to administer rehydration solutions. Prepackaged WHO oral rehydration solution packets, which are available at stores or pharmacies in almost all low- and middle-income countries, should be part of a child's travel kit. Oral rehydration solution should be mixed as directed with bottled or boiled water and given slowly, as tolerated, to the child while symptoms persist.

Antimotility agents such as diphenoxylate (Lomotil) and loperamide (Imodium) should be avoided in infants and young children, and the American Academy of Pediatrics does not recommend their routine use in acute gastroenteritis. Use of antimotility agents may be beneficial in older children and adolescents with afebrile, nonbloody traveler's diarrhea. In general, antimotility agents should not distract parents from giving frequent oral rehydration solution, as ongoing intestinal fluid losses likely continue despite a decrease in stooling. Bismuth subsalicylate for acute gastroenteritis should be avoided because of concern for toxicity and Reye syndrome.

Presumptive Antibiotic Treatment

Oral rehydration is the mainstay of treatment for pediatric traveler's diarrhea. However, antibiotics should be prescribed for the pediatric traveler, with parental instructions to start presumptive treatment early in the diarrheal illness. Systemic antibiotics can shorten the duration and severity of diarrheal illness, especially if presumptive antibiotics are initiated immediately after onset of traveler's diarrhea. For children, the drug of choice is azithromycin (10 mg/kg once daily for up to 3 days, with maximum daily dose of 500 mg). Ciprofloxacin (10 mg/kg per dose twice a day for up to 3 days, maximum dose of 500 mg twice a day) is an alternative for children >1 yr of age, but should not be prescribed for traveler's traveling to the Indian subcontinent or Southeast Asia, where fluoroquinolone resistance is common. Shiga-toxin producing *E. coli* such as *E. coli* O157:H7 is an extremely uncommon cause of pediatric traveler's diarrhea in nonindustrialized countries, and the benefit of presumptive antibiotic therapy in traveling children, even with bloody diarrhea, typically outweighs the low risk of developing hemolytic-uremic syndrome.

Azithromycin is highly effective against most bacterial pathogens that cause traveler's diarrhea, and is the preferred antibiotic among many travel experts. Azithromycin can be prescribed in powder form that can be reconstituted with safe water into a liquid suspension when needed. In addition, azithromycin 250 mg tablets can be cut to the nearest ¼ tablet size to achieve a dosage of approximately 10 mg/kg, and then crushed and mixed with food or water for younger children. Amoxicillin, trimethoprim-sulfamethoxazole (cotrimoxazole), and erythromycin should not be prescribed for self-treatment of traveler's diarrhea, because of widespread resistance among diarrheal pathogens. Traveler's diarrhea that results in bloody stools, persistently high fevers, systemic chills and rigors, severe or localizing abdominal pain, or continued fluid losses should prompt additional medical evaluation.

INSECT-BORNE INFECTIONS

Insect-borne infections for which traveling children are most at risk include malaria, dengue, chikungunya, yellow fever, and Japanese encephalitis, depending on the area of travel. Malaria is transmitted by night-biting *Anopheles* mosquitoes, whereas dengue occurs from mosquito species *(Culex*, *Aedes)* that are predominantly active during the day. Families should be encouraged to protect children against daytime and nighttime biting mosquitoes, as many regions of the world in which malaria is found also have diseases transmitted by daytime biting mosquitoes (dengue, chikungunya).

Exposure to insect bites can be reduced by wearing appropriate attire and using insect repellents containing *N,N*-diethyl-*m*-toluamide (DEET) or picaridin. The American Academy of Pediatrics recommends avoiding DEET-containing repellants in children <2 mo of age. Rare instances of neurologic events have been reported in very young children with exposure to inappropriate, frequent applications of DEET-containing repellants (>10 times a day) or who licked off DEET. Concentrations of 25-30% DEET need be applied every 4-6 hr as needed, whereas 5-7% DEET provides only 1-2 hr of protection time. DEET concentrations >40-50% do not confer a substantially longer protection time for children and generally should be avoided.

Picaridin is a newer insect repellant in the United States but has been used widely in Europe and Australia for yr. Picaridin is fragrance-free, effective, and generally well tolerated on exposed skin and faces. It has similar efficacy to DEET but with less inhalational or dermal irritation.

Picaridin at concentrations of 20% or higher provides adequate protection against *Anopheles* mosquitoes that have potential to transmit malaria. When applying sunscreen and insect repellant, sunscreen should be applied 1st followed by DEET or picaridin.

Spraying or treating clothing with permethrin, a synthetic pyrethroid, is a safe and effective method of further reducing insect bites in children. Permethrin can be applied to directly to clothing, bed nets, shoes, and hats, and should be allowed to fully dry before use. As an insecticide, permethrin should never be applied to skin. Permethrin-treated garments retain both repellency and insecticidal activity, even with repeated laundering. Clothing will eventually need to be retreated to maintain repellency, according to the product label. Bed nets, particularly permethrin-impregnated bed nets, also decrease the risk of insect bites, and their use is highly recommended in malarial areas.

Malaria Chemoprophylaxis

Malaria, a mosquito-borne infection, is the leading parasitic cause of death in children worldwide (see Chapter 288). Of the 4 *Plasmodium* species that infect humans, *Plasmodium falciparum* causes the greatest morbidity and mortality. Each yr, more than 8 million U.S. citizens visit parts of the world where malaria is endemic (sub-Saharan Africa, Central and South America, India, Southeast Asia, Oceania). Children accounted for 15-20% of imported malaria cases in a WHO study in Europe. Given the major resurgence of malaria and increased travel among families with young children, physicians in industrialized countries are increasingly required to give advice on prevention, diagnosis, and treatment of malaria. Risk factors for severe malaria and death include inadequate adherence to chemoprophylaxis, delay in seeking medical care, delay in diagnosis, and nonimmune status, but the case fatality rate of imported malaria remains <1% in children from nonendemic countries. The CDC maintains updated information at http://www.cdc.gov/malaria/travelers/index.html, as well as a malaria hotline for physicians (770-488-7788). It is important to check this updated information, because recommendations for prophylaxis and treatment are often modified owing to changes in the risk for developing malaria in different areas of the world, changing *Plasmodium* resistance patterns, and the availability of new antimalarial medications.

Avoidance of mosquitoes and barrier protection from mosquitoes are an important part of malaria prevention for travelers to endemic areas. The *Anopheles* mosquito feeds from dusk to dawn. Travelers should remain in well-screened areas, wear clothing that covers most of the body, sleep under a bed net (ideally one impregnated with permethrin), and use insect repellents with DEET during these hours. Parents should be discouraged from taking a young child on a trip that will entail evening or nighttime exposure in areas endemic for *P. falciparum.*

Chemoprophylaxis is the cornerstone of malaria prevention for nonimmune children and adults who travel to malaria-endemic areas but it is not a replacement for other protective measures. Travelers often do not take malaria prophylaxis as prescribed or at all. They are more likely to use prophylactic antimalarial drugs if their physicians provide appropriate recommendations and education before departure. However, in 1 survey, only 14% of persons who sought medical advice obtained correct information about malaria prevention and prophylaxis. Families with children visiting friends and relatives are particularly less likely to take malaria prophylaxis or seek pretravel medical advice.

Resistance of *P. falciparum* to the traditional chemoprophylactic agent, chloroquine, is widespread, and in most areas of the world other agents must be used (Table 175-2). Factors that must be considered in choosing appropriate chemoprophylaxis medications and dosing schedules include age of the child, travel itinerary (including whether the child will be traveling to areas of risk within a particular country and whether chloroquine-resistant *P. falciparum* is present in the country), vaccinations being given, allergies or other known adverse reactions to antimalarial agents, and the availability of medical care during travel.

Children traveling to areas with chloroquine-resistant *P. falciparum* can be given mefloquine, atovaquone-proguanil, or doxycycline (if >8 yr of age) as malaria prophylaxis. For trips shorter than 4 wk, atovaquone-proguanil is the preferred medication, because it is given for only a short period before and after travel. Atovaquone-proguanil or doxycycline is also indicated for travel of any duration to western Cambodia and the Thailand–Cambodia and Thailand–Myanmar borders because of mefloquine resistance in these areas. For periods of travel longer than 4 wk to all other areas with chloroquine-resistant *P. falciparum,* mefloquine is the preferred medication because it can be taken weekly.

Mefloquine is FDA-approved only for children weighing more than 15 kg, but the CDC recommends mefloquine prophylaxis for all children regardless of weight because the risk for acquiring severe malaria outweighs the risk for potential mefloquine toxicity. Adults taking mefloquine prophylaxis have a 10-25% incidence of sleep disturbance and dysphoria and, less frequently, more serious neuropsychiatric symptoms. These side effects appear to be less common in children. Other potential side effects of mefloquine therapy include nausea and vomiting. The lack of a liquid or suspension formulation can make chloroquine and mefloquine administration difficult. For children who cannot take tablets, parents should take a chloroquine or mefloquine prescription to a compounding pharmacy, which can pulverize the tablets and place exact dosages into gel capsules. Parents can then open the gel capsules and sprinkle the powder into food. "Disguising" these medications, which have a bitter taste, is important; chocolate syrup has been used successfully as a vehicle for the medication. Persons with depression, neuropsychiatric disorders, seizure disorders, and cardiac conduction defects should not take mefloquine.

Atovaquone-proguanil fixed combination (Malarone) is an effective and safe chemoprophylaxis for travelers to chloroquine-resistant malaria-endemic areas, but it is fairly expensive. Adverse effects are infrequent and mild (abdominal pain, vomiting, and headache) and infrequently result in discontinuation of the medication. Atovaquone-proguanil prophylaxis must be taken every day with food, so it is better suited for prophylaxis during short periods of exposure. Recent data allow dosing down to 5 kg of body weight, although the use of atovaquone-proguanil at a weight between 5 and 10 kg is considered off-label.

Daily doxycycline is an alternative chemoprophylaxis regimen for chloroquine-resistant *P. falciparum* malaria that is considerably less expensive than atovaquone-proguanil. Doxycycline has been used extensively and is highly effective, but it cannot be used in children <8 yr of age owing to the risk of permanent tooth staining, and adverse effects (nausea, vomiting, photosensitivity, vaginal candidiasis) are not uncommon. Persons given doxycycline prophylaxis should be warned to decrease exposure to direct sunlight to minimize the possibility of photosensitivity. Primaquine has also been used successfully as chemoprophylaxis, especially in areas of high prevalence of *Plasmodium vivax* and *Plasmodium ovale,* but there are limited data about its use in nonimmune children. Primaquine prophylaxis for children should only be given in consultation with the CDC or a travel medicine specialist. Chloroquine, chloroquine-proguanil, and azithromycin do not provide adequate protection for children traveling to a chloroquine-resistant malaria-endemic area.

In areas of the world where *P. falciparum* remains fully chloroquine-sensitive (Haiti, the Dominican Republic, Central America north of the Panama Canal, and some countries in the Middle East), weekly chloroquine is the drug of choice for malaria chemoprophylaxis. Updated information on chloroquine susceptibility and recommended malaria prophylaxis is available at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria.

On leaving an area endemic for *P. vivax* or *P. ovale* after a prolonged visit (usually >3 mo), travelers should consider terminal prophylaxis with primaquine (0.5 mg/kg base) daily, up to a maximum dose of 30 mg base or 52.6 mg salt, for 14 days, to eliminate extraerythrocytic forms of *P. vivax* and *P. ovale* and prevent relapses. Screening for

Table 175-2 Chemoprophylaxis of Malaria for Children

AREA	DRUG	DOSAGE (ORAL)	ADVANTAGES	DISADVANTAGES	BEST USE
Chloroquine-resistant area	Mefloquine*†	weight <10 kg: 4.6 mg base (5 mg salt)/kg/wk weight 10-19 kg: ¼ tab/wk weight 20-30 kg: ½ tab/wk weight 31-45 kg: ¾ tab/wk weight >45 kg: 1 tab/wk (228 mg base)	Once-weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria-endemic area for 4 wk or more Children unlikely to take daily medication
	Doxycycline‡	2 mg/kg daily (max: 100 mg)	Inexpensive	Cannot give to children <8 yr old Daily dosing Must take with food or causes stomach upset Photosensitivity	Children going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone/proguanil§ (Malarone)	Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil Adult tabs: 250 mg proguanil/100 mg proguanil weight 5-8 kg: ½ pediatric tab once daily (off-label) weight 9-10 kg: ¾ pediatric tab once daily (off-label) weight 11-20 kg: 1 pediatric tab once daily weight 21-30 kg: 2 pediatric tabs once daily weight 31-40 kg: 3 pediatric tabs once daily weight >40 kg: 1 adult tab once daily	Pediatric formulation Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria-endemic area for <4 wk
Chloroquine-susceptible area	Chloroquine phosphate	5 mg base/kg/wk (max: 300 mg base)	Once-weekly dosing Inexpensive Generally well tolerated	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *Plasmodium vivax* that is chloroquine susceptible
	Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas				

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.
†Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.
‡Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children <8 yr of age or in pregnant women.
§Atovaquone-proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children who weigh <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

glucose-6-phosphate dehydrogenase deficiency is mandatory before primaquine treatment, because primaquine is contraindicated in glucose-6-phosphate dehydrogenase–deficient persons because it can cause severe hemolysis in these persons.

Small amounts of antimalarial drugs are secreted into breast milk. The amounts of transferred drug are not considered to be either harmful or sufficient to provide adequate prophylaxis against malaria. Prolonged infant exposure to doxycycline via breast milk is not advisable.

Self-treatment of presumptive malaria during travel remains controversial. It should never be substituted for seeking appropriate medical care, but it can be considered in special circumstances such as travel to remote areas, intolerance of prophylaxis, or refusal of chemoprophylaxis by the traveler. Self-treatment medication should be different than the prescribed chemoprophylaxis. The CDC or a travel medicine specialist should be consulted if self-treatment medication is being considered for a traveler.

THE RETURNING TRAVELER

Posttravel evaluations are part of travel medicine and continuing care. Physicians unfamiliar with diseases that occur in low- and middle-income countries often misdiagnose the cause of illness in a child returning from travel abroad. Among returning patients identified from GeoSentinal sites who were ill, the common disorders included, in descending order of frequency, malaria, giardiasis, dengue fever, campylobacteriosis, cutaneous larva migrans, enteric fever, spotted

Table 175-3	Patterns of Illness Among Returning International Travelers
SYSTEMIC FEBRILE ILLNESS	
Malaria	
Dengue	
Enteric fever (typhoid/paratyphoid)	
Chikungunya virus	
Spotted fever rickettsia	
Hepatitis A	
Acute HIV	
Leptospirosis	
Measles	
Infectious mononucleosis	
Respiratory causes (pneumonia, influenza)	
Undetermined fever source	
ACUTE DIARRHEA	
Campylobacter	
Shigella spp.	
Salmonella spp.	
Diarrheagenic *Escherichia coli* (enterotoxigenic *E. coli*, enteroadherent *E. coli*–not tested for by routine stool culture methods)	
Giardiasis (acute, persistent, or recurrent)	
Entamoeba histolytica	
Cryptosporidium spp.	
Cyclospora cayetanensis	
Presumed viral enteritis	
DERMATOLOGIC MANIFESTATIONS	
Rash with fever (dengue)	
Arthropod-related dermatitis (insect bites)	
Cutaneous larva migrans *(Ancylostoma brasiliense)*	
Bacterial skin infections—pyoderma, impetigo, ecthyma, erysipelas	
Myiasis (tumbu and botfly)	
Scabies	
Tungiasis	
Superficial mycosis	
Animal bite	
Leishmaniasis	
Rickettsial diseases	
Marine envenomation/dermatitis	
Photoallergic and phytophotodermatitis	

fever (rickettsiosis), chikungunya fever, hepatitis A, and influenza. Returning pediatric travelers who are severely ill or with continued fevers should be seen in consultation with a pediatric travel medicine or infectious diseases physician.

There is very little literature that specifically addresses the causes of illness in children returning from travel. Among all persons returning from travel (children and adults), 3 major patterns of illness have been noted (Table 175-3). The etiology of each of these disease presentations in part depends on the country or geographic region visited.

Fever is a particularly worrisome symptom. Children with a febrile/systemic illness following recent travel to a malarial destination should be promptly evaluated for malaria, especially if having traveled to sub-Saharan Africa and Papua New Guinea. *P. falciparum* malaria will generally present within 1-2 mo after return from travel to a malaria-endemic area, but can occur within the 1st year after return. In contrast, symptoms of *P. vivax*/*P. ovale* malaria are typically later in onset following travel (i.e., several months), are milder in disease severity, and may occur in a relapsing pattern if undiagnosed or improperly untreated. Other symptoms of malaria can be nonspecific and include chills, malaise, headache, myalgias, vomiting, diarrhea, cough, and possible seizures. Children are more likely than adults to have higher fevers and also gastrointestinal symptoms, hepatomegaly, splenomegaly, and severe anemia. Thrombocytopenia (without increased bleeding) and fever in a child returning from an endemic area are highly suggestive of malaria.

Thick and thin blood smears need to be performed for diagnosis *if* malaria is clinically suspected. If results are negative initially, 2 or more additional smears should be done 12-24 hr after the initial smear. Rapid malaria antigen tests (Binax Now) are FDA-approved and sensitive for diagnosing falciparum malaria. Treatment should be initiated immediately once the diagnosis is confirmed or empirically if presentation is severe with suspected malaria. Treatment should be determined in consultation with a pediatric infectious disease specialist and the CDC, which has updated information on the drugs of choice, which are similar to those for adults (see Chapter 288 for more details on malaria infection). Great caution should be used with young children, nonimmune patients, and pregnant patients with falciparum malaria, and hospitalization of these patients should be strongly considered until reliable improvement is observed.

Enteric (typhoid) fever should be considered in children with persistent or recurrent fevers following return from the Indian subcontinent. Multiple blood cultures and a stool culture may both be necessary to diagnosis enteric fever. Dengue is another cause of fever and systemic illness in ill travelers, particularly when returning from Southeast Asia, the Caribbean, Central and South America, or the Indian subcontinent. Many bacterial and protozoal causes of acute traveler's diarrhea may also result in fever and systemic symptoms in children. Additional travel-associated febrile, diarrheal, and dermatologic illnesses exist, of which the most common etiologies can be found in Table 175-3.

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Chapter 176

Fever

Linda S. Nield and Deepak Kamat

DEFINITION

Fever is defined as a rectal temperature ≥38°C (100.4°F), and a value >40°C (104°F) is called hyperpyrexia. Body temperature fluctuates in a defined normal range (36.6-37.9°C [97.9-100.2°F] rectally), so that the highest point is reached in early evening and the lowest point is reached in the morning. Any abnormal rise in body temperature should be considered a symptom of an underlying condition.

PATHOGENESIS

Body temperature is regulated by thermosensitive neurons located in the preoptic or anterior hypothalamus that respond to changes in blood temperature as well as by cold and warm receptors located in skin and muscles. Thermoregulatory responses include redirecting blood to or from cutaneous vascular beds, increased or decreased sweating, regulation of extracellular fluid volume via arginine vasopressin, and behavioral responses, such as seeking a warmer or cooler environmental temperature.

Three different mechanisms can produce fever: pyrogens, heat production exceeding loss, and defective heat loss.

The first mechanism involves endogenous and exogenous pyrogens that raise the hypothalamic temperature set point. Endogenous pyrogens include the cytokines interleukins 1 and 6, tumor necrosis factor α, and interferons β and γ. Stimulated leukocytes and other cells produce lipids that also serve as endogenous pyrogens. The best-studied lipid mediator is prostaglandin E_2, which attaches to the prostaglandin receptors in the hypothalamus to produce the new temperature set point. Along with infectious diseases and drugs, malignancy and inflammatory diseases can cause fever through the production of endogenous pyrogens. Some substances produced within the

body are not pyrogens but are capable of stimulating endogenous pyrogens. Such substances include antigen–antibody complexes in the presence of complement, complement components, lymphocyte products, bile acids, and androgenic steroid metabolites.

Exogenous pyrogens or substances that come from outside the body include mainly infectious pathogens and drugs. Microbes, microbial toxins, or other products of microbes are the most common exogenous pyrogens and stimulate macrophages and other cells to produce endogenous pyrogens. Endotoxin is one of the few substances that can directly affect thermoregulation in the hypothalamus as well as stimulate endogenous pyrogen release.

Many drugs cause fever, and the mechanism for increasing body temperature varies with the class of drug. Drugs that are known to cause fever include vancomycin, amphotericin B, and allopurinol.

Heat production exceeding heat loss is the second mechanism that leads to fever, with examples including salicylate poisoning and malignant hyperthermia. Defective heat loss is the third mechanism of fever genesis; for example, in children with ectodermal dysplasia or victims of severe heat exposure.

ETIOLOGY

The causes of fever can be organized into 4 main categories: infectious, inflammatory, neoplastic, and miscellaneous. Self-limited viral infections (common cold, gastroenteritis) and uncomplicated bacterial infections (otitis media, pharyngitis, sinusitis) are the most common causes of acute fever. The body temperature rarely rises above potentially lethal levels (42°C [107.6°F]) in the neurologically intact child unless extreme hyperthermic environmental conditions are present or other extenuating circumstances exist, such as underlying malignant hyperthermia or thyrotoxicosis.

The pattern of the fever can provide clues to the underlying etiology. Viral infections typically are associated with a slow decline of fever over a wk, whereas bacterial infections are often associated with a prompt resolution of fever after effective antimicrobial treatment is employed. Although administration of antimicrobial agents can result in a very rapid elimination of bacteria, if tissue injury has been extensive, the inflammatory response and fever can continue for days after all microbes have been eradicated.

Intermittent fever is an exaggerated circadian rhythm that includes a period of normal temperatures on most days; extremely wide fluctuations may be termed septic or hectic fever. Sustained fever is persistent and does not vary by more than 0.5°C (0.9°F)/day. Remittent fever is persistent and varies by more than 0.5°C (0.9°F)/day. Relapsing fever is characterized by febrile periods that are separated by intervals of normal temperature; tertian fever occurs on the 1st and 3rd days (malaria caused by *Plasmodium vivax*), and quartan fever occurs on the 1st and 4th days (malaria caused by *Plasmodium malariae*). Diseases characterized by relapsing fevers (Table 176-1) should be distinguished from infectious diseases that have a tendency to relapse. Biphasic fever indicates a single illness with 2 distinct periods (camelback fever pattern); poliomyelitis is the classic example. A biphasic course is also characteristic of other enteroviral infections, leptospirosis, dengue fever, yellow fever, Colorado tick fever, spirillary rat bite fever *(Spirillum minus),* and the African hemorrhagic fevers (Marburg, Ebola, and Lassa fevers). The term *periodic fever* is used narrowly to describe fever syndromes with a regular periodicity (cyclic neutropenia and periodic fever, aphthous stomatitis, pharyngitis, and adenopathy) or more broadly to include disorders characterized by recurrent episodes of fever that do not follow a strictly periodic pattern (familial Mediterranean fever, tumor necrosis factor receptor–associated periodic syndrome [Hibernian fever], hyperimmunoglobulin D syndrome, the Muckle-Wells syndrome) (see Chapter 163). Factitious fever, or self-induced fever, may be caused by intentional manipulation of the thermometer or injection of pyrogenic material.

The double quotidian fever (or fever that peaks twice in 24 hr) is classically associated with inflammatory arthritis. In general, a single isolated fever spike is not associated with an infectious disease. Such a spike can be attributed to the infusion of blood products and some drugs, as well as to some procedures, or to manipulation of a catheter on a colonized or infected body surface. Similarly, temperatures in excess of 41°C (105.8°F) are most often associated with a noninfectious cause. Causes for very high temperatures (>41°C [105.8°F]) include central fever (resulting from central nervous system dysfunction involving the hypothalamus), malignant hyperthermia, malignant neuroleptic syndrome, drug fever, or heatstroke. Temperatures that are lower than normal (<36°C [96.8°F]) can be associated with overwhelming sepsis but are more commonly related to cold exposure, hypothyroidism, or overuse of antipyretics.

Table 176-1 Fevers Prone to Relapse

INFECTIOUS CAUSES
Relapsing fever *(Borrelia recurrentis)*
Trench fever *(Bartonella quintana)*
Q fever *(Coxiella burnetii)*
Typhoid fever *(Salmonella typhi)*
Syphilis *(Treponema pallidum)*
Tuberculosis
Histoplasmosis
Coccidioidomycosis
Blastomycosis
Melioidosis *(Pseudomonas pseudomallei)*
Lymphocytic choriomeningitis (LCM) infection
Dengue fever
Yellow fever
Chronic meningococcemia
Colorado tick fever
Leptospirosis
Brucellosis
Oroya fever *(Bartonella bacilliformis)*
Acute rheumatic fever
Rat bite fever *(Spirillum minus)*
Visceral leishmaniasis
Lyme disease *(Borrelia burgdorferi)*
Malaria
Babesiosis
Noninfluenza respiratory viral infection
Epstein-Barr virus infection
NONINFECTIOUS CAUSES
Behçet disease
Crohn disease
Weber-Christian disease (panniculitis)
Leukoclastic angiitis syndromes
Sweet syndrome
Systemic lupus erythematosus and other autoimmune disorders
PERIODIC FEVER SYNDROMES (see Chapter 163)
Familial Mediterranean fever
Cyclic neutropenia
Periodic fever, aphthous stomatitis, pharyngitis, adenopathy (PFAPA)
Hyperimmunoglobulin D syndrome
Hibernian fever (tumor necrosis factor superfamily immunoglobulin A–associated syndrome [TRAPS])
Muckle-Wells syndrome
Others

CLINICAL FEATURES

The clinical features of fever can range from no symptoms at all to extreme malaise. Children might complain of feeling hot or cold, display facial flushing, and experience shivering. Fatigue and irritability may be evident. Parents often report that the child looks ill or pale and has a decreased appetite. The underlying etiology also produces accompanying symptoms. Although the underlying etiologies can manifest in varied ways clinically, there are some predictable features. For instance, fever with petechiae in an ill-appearing patient indicates the high possibility of life-threatening conditions such as meningococcemia, Rocky Mountain spotted fever, or acute bacterial endocarditis.

Table 176-2 Evaluation of Acute Fever

Thorough history: onset, other symptoms, exposures (daycare, school, family, pets, playmates), travel, medications, other underlying disorders, immunizations
Physical examination: complete, with focus on localizing symptoms
Laboratory studies on a case-by-case basis:
- Rapid antigen testing
- Nasopharyngeal: respiratory viruses by polymerase chain reaction
- Throat: group A *Streptococcus*
- Stool: rotavirus
- Blood: complete blood count, blood culture, C-reactive protein, sedimentation rate, procalcitonin
- Urine: urinalysis, culture
- Stool: Hemoccult, culture
- Cerebrospinal fluid: cell count, glucose, protein, Gram stain, culture
- Chest radiograph or other imaging studies on a case-by-case basis

Changes in heart rate, most commonly tachycardia, accompany fever. Normally heart rate rises by 10 beats/min per 1°C (1.8°F) rise in temperature for children >2 mo of age. Relative tachycardia, when the pulse rate is elevated disproportionately to the temperature, is usually caused by noninfectious diseases or infectious diseases in which a toxin is responsible for the clinical manifestations. Relative bradycardia (temperature–pulse dissociation), when the pulse rate remains low in the presence of fever, can accompany typhoid fever, brucellosis, leptospirosis, or drug fever. Bradycardia in the presence of fever also may be a result of a conduction defect resulting from cardiac involvement with acute rheumatic fever, Lyme disease, viral myocarditis, or infective endocarditis.

EVALUATION

Most acute febrile episodes in a normal host can be diagnosed by a careful history and physical examination and require few, if any, laboratory tests. Because infection is the most likely etiology of the acute fever, the evaluation should initially be geared to discovering an underlying infectious cause (Table 176-2). The details of the history should include the onset and pattern of fever and any accompanying signs and symptoms. The patient often displays signs or symptoms that provide clues to the cause of the fever. Exposures to other ill persons at home, daycare, and school should be noted, along with any recent travel or medications. The past medical history should include information about underlying immune deficiencies or other major illnesses and receipt of childhood vaccines.

Physical examination should begin with a complete evaluation of vital signs, which should include pulse oximetry because hypoxia may indicate lower respiratory infection. In the acutely febrile child, the physical examination should focus on any localized complaints, but a complete head-to-toe screen is recommended, because clues to the underlying diagnosis may be found. For example, palm and sole lesions may be discovered during a thorough skin examination and provide a clue for infection with coxsackievirus.

If a fever has an obvious cause, then laboratory evaluation may not be required, and management is tailored to the underlying cause with as-needed reevaluation. If the cause of the fever is not apparent, then further diagnostic evaluation should be considered on a case-by-case basis. The history of presentation and abnormal physical examination findings guide the evaluation. The child with respiratory symptoms and hypoxia may require a chest radiograph or rapid antigen testing for respiratory syncytial virus or influenza. The child with pharyngitis can benefit from rapid antigen detection testing for group A *Streptococcus* and a throat culture. Dysuria, back pain, or a history of vesicoureteral reflux should prompt a urinalysis and urine culture, and bloody diarrhea should prompt a stool culture. A complete blood count and blood culture should be considered in the ill-appearing child, along with cerebrospinal fluid studies if the child has neck stiffness or if the possibility of meningitis is considered. Well-defined high-risk groups require a more-extensive evaluation on the basis of age, associated disease, or immunodeficiency status, and might warrant prompt antimicrobial therapy before a pathogen is identified. The evaluations of infants <3 mo of age and children with recurrent fevers are discussed in Chapter 177.

MANAGEMENT

Although fear of fever is a common parental worry, evidence is lacking to support the belief that high fever can result in brain damage or other bodily harm, except in rare instances of febrile status epilepticus and heatstroke. *Treating fever in self-limiting illnesses for the sole reason of bringing the body temperature back to normal is not necessary in the otherwise healthy child.* Most evidence suggests that fever is an adaptive response and should be treated only in selected circumstances. In humans, increased temperatures are associated with decreased microbial replication and an increased inflammatory response. Although fever can have beneficial effects, it also increases oxygen consumption, carbon dioxide production, and cardiac output, and can exacerbate cardiac insufficiency in patients with heart disease or chronic anemia (e.g., sickle cell disease), pulmonary insufficiency in patients with chronic lung disease, and metabolic instability in patients with diabetes mellitus or inborn errors of metabolism. Children between the ages of 6 mo and 5 yr are at increased risk for simple febrile seizures. *The focus of the evaluation and treatment of febrile seizures is aimed at determining the underlying cause of the fever.* Children with idiopathic epilepsy also often have an increased frequency of seizures associated with a fever. High fever during pregnancy may be teratogenic.

Fever with temperatures <39°C (102.2°F) in healthy children generally does not require treatment. However, as temperatures become higher, patients tend to become more uncomfortable, and treatment of fever is then reasonable. If a child is included in 1 of the high-risk groups or if the child's caregiver is concerned that the fever is adversely affecting the child's behavior and causing discomfort, treatment may be given to hasten the resolution of the fever. Other than providing symptomatic relief, antipyretic therapy does not change the course of infectious diseases. Encouraging good hydration is the first step to replace fluids that are lost related to the increased metabolic demands of fever. Antipyretic therapy is beneficial in high-risk patients who have chronic cardiopulmonary diseases, metabolic disorders, or neurologic diseases and in those who are at risk for febrile seizures. Hyperpyrexia (>41°C [105.8°F]) indicates high probability of hypothalamic disorders or central nervous system hemorrhage and should be treated with antipyretics. Some studies show that hyperpyrexia may be associated with a significantly increased risk of serious bacterial infection, but other studies have not substantiated this relationship. Acetaminophen at a dose of 10-15 mg/kg/dose every 4 hr and ibuprofen in children >6 mo at a dose of 5-10 mg/kg/dose every 8 hr are the most commonly employed antipyretics. Antipyretics reduce fever by reducing production of prostaglandins. If used appropriately, antipyretics are safe; potential adverse effects include liver damage (acetaminophen) and gastrointestinal or kidney disturbances (ibuprofen). To reduce fever most safely, the caregiver should choose 1 type of medication and clearly record the dose and time of administration, so overdosage does not occur, especially if multiple caregivers are involved in the management. Physical measures such as tepid baths and cooling blankets are not considered effective to reduce fever. Evidence is also scarce for the use of complementary and alternative medicine interventions.

Fever caused by specific underlying etiologies resolves when the condition is properly treated. Examples include administration of intravenous immunoglobulin to treat Kawasaki disease or the administration of antibiotics to treat bacterial infections.

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Chapter 177

Fever Without a Focus

Linda S. Nield and Deepak Kamat

Fever without a focus refers to a rectal temperature of 38°C (100.4°F) or higher as the sole presenting feature. The terms "fever without localizing signs" and "fever of unknown origin" (FUO) are subcategories of fever without a focus.

FEVER WITHOUT LOCALIZING SIGNS

Fever of acute onset, with duration of <1 wk and without localizing signs, is a common diagnostic dilemma in children <36 mo of age. The etiology and evaluation of fever without localizing signs depends on the age of the child. Traditionally, 3 age groups are considered: neonates or infants to 1 mo of age, infants >1 mo to 3 mo of age, and children >3 mo to 3 yr of age. In 1993, practice guidelines were published to aid the clinician in evaluating the otherwise healthy 0-36 mo old child with fever without a source. However, with the advent and extensive use of the conjugate *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* vaccines, the rates of infections with these 2 pathogens have decreased substantially. As a consequence, modifications to the 1993 guidelines have been advocated as described in the section "3-36 Months of Age." Children in high-risk groups (Table 177-1) require a more aggressive diagnostic approach and consideration of a broader differential diagnosis.

Table 177-1 Febrile Patients at Increased Risk for Serious Bacterial and Viral Infections

RISK GROUP	DIAGNOSTIC CONSIDERATIONS
IMMUNOCOMPETENT PATIENTS	
Neonates (<28 days)	Sepsis and meningitis caused by group B *Streptococcus*, *Escherichia coli*, *Listeria monocytogenes*; neonatal herpes simplex virus infection, enteroviruses, parechovirus
Infants 1-3 mo	Serious bacterial disease in 5-15%, including bacteremia in 5%; urinary tract infection most common serious bacterial infection; *E. coli* most common pathogen; enterovirus, parechovirus, influenza
Infants and children 3-36 mo	Occult bacteremia in <0.5% of children immunized with both *Haemophilus influenzae* type b and pneumococcal conjugate vaccines; urinary tract infections
Hyperpyrexia (>40°C [104°F])	Meningitis, bacteremia, pneumonia, heatstroke, hemorrhagic shock-encephalopathy syndrome
Fever with petechiae	Bacteremia and meningitis caused by *Neisseria meningitidis*, *H. influenzae* type b, and *Streptococcus pneumoniae* Rickettsial disease Viral exanthem
IMMUNOCOMPROMISED PATIENTS	
Sickle cell disease	Sepsis, pneumonia, and meningitis caused by *S. pneumoniae*, osteomyelitis caused by *Salmonella* and *Staphylococcus aureus*
Asplenia	Bacteremia and meningitis caused by *N. meningitidis*, *H. influenzae* type b, *S. pneumoniae*, and *Capnocytophaga* sp.
Complement or properdin deficiency	Sepsis caused by *N. meningitidis*
Agammaglobulinemia	Bacteremia, sinopulmonary infections
AIDS	*S. pneumoniae*, *H. influenzae* type b, and *Salmonella* infections
Congenital heart disease	Infective endocarditis; brain abscess with right-to-left shunting
Central venous line	*S. aureus*, coagulase-negative staphylococci, *Candida*
Malignancy	Bacteremia with gram-negative enteric bacteria, *S. aureus*, and coagulase-negative staphylococci; fungemia with *Candida* and *Aspergillus*

Neonates

Neonates who experience fever without focus are a challenge to evaluate because they display limited signs of infection, making it difficult to clinically distinguish between a serious bacterial or viral (herpes simplex virus [HSV]) infection and self-limited viral illness. Immature immune responses in the 1st few mo of life also increase the significance of fever in the young infant. In general, neonates who have a fever and do not appear ill have a 7% risk of having a serious bacterial infection. Serious bacterial infections include bacteremia, meningitis, pneumonia, osteomyelitis, septic arthritis, enteritis, and urinary tract infections. Although neonates with serious infection can acquire community pathogens, they are mainly at risk for late-onset neonatal bacterial diseases (group B streptococci, *E. coli*, and *Listeria monocytogenes*) and perinatally acquired herpes simplex virus (HSV) infection.

Practice guidelines recommend that if a neonate has had a fever recorded at home by a reliable parent, the patient should be treated as a febrile neonate. If excessive clothing and blankets encasing the infant are suspected of falsely elevating the body temperature, then the excessive coverings should be removed and the temperature retaken in 15-30 min. If body temperature is normal after the covers are removed, then the infant is considered afebrile.

Owing to the unreliability of physical findings and the presence of an immature immune system, all febrile neonates should be hospitalized; blood, urine, and cerebrospinal fluid (CSF) should be cultured, and the child should receive empirical intravenous antibiotics. CSF studies should include cell counts, glucose and protein levels, Gram stain, and culture; HSV and enterovirus polymerase chain reaction should be considered. Stool culture and chest radiograph may also be part of the evaluation. Combination antibiotics, such as ampicillin and cefotaxime or ampicillin and gentamicin, are recommended. Acyclovir should be included if HSV infection is suspected because of seizures, hypotension, transaminase elevation, CSF pleocytosis, or known maternal history of genital HSV, especially at the time of delivery.

1 to 3 Months of Age

The large majority of children with fever without localizing signs in the 1-3 mo age group likely have a viral syndrome. In contrast to bacterial infections, most viral diseases have a distinct seasonal pattern: respiratory syncytial virus and influenza A virus infections are more common during the winter, whereas enterovirus and parechovirus infections usually occur in the summer and fall. Although a viral infection is the most likely etiology, fever in this age group should always suggest the possibility of serious bacterial disease. Organisms to consider include *E. coli*, group B *Streptococcus*, *L. monocytogenes*, *Salmonella enteritidis*, *N. meningitidis*, *S. pneumoniae*, *H. influenzae* type b, and *S. aureus*. Pyelonephritis is the most common serious bacterial infection in this age group and is also more common in uncircumcised infant boys and infants with urinary tract anomalies. *E. coli* is the most common pathogen identified in bacteremic infants, the majority having pyelonephritis. Group B *Streptococcus* followed by *S. aureus* are the next most frequently identified pathogens causing bacteremia; pneumococcus tends to be seen in older infants. Most significant blood cultures turn positive within 24 hr (91%), with 99% positive by 48 hr. Other potential bacterial diseases in this age group include otitis media, pneumonia, omphalitis, mastitis, and other skin and soft tissue infections.

Ill-appearing (toxic) febrile infants 3 mo of age or younger require prompt hospitalization and immediate parenteral antimicrobial therapy after cultures of blood, urine, and CSF are obtained. Ampicillin (to cover *L. monocytogenes* and *Enterococcus*) plus either ceftriaxone

or cefotaxime is an effective initial antimicrobial regimen for ill-appearing infants without focal findings. This regimen is effective against the usual bacterial pathogens causing sepsis, urinary tract infection, and enteritis in young infants. However, if meningitis is suspected because of CSF abnormalities, vancomycin should be included to treat possible penicillin-resistant *S. pneumoniae* until the results of culture and susceptibility tests are known.

Many academic institutions have investigated the optimal management of low-risk patients in this age group with fever without a focus (Table 177-2). The use of viral diagnostic studies (enteroviruses, parechovirus, respiratory viruses, rotavirus, and herpesvirus) in combination with the Rochester Criteria or similar criteria can enhance the ability to determine which infants are at high risk for serious bacterial infections (Table 177-2). Febrile infants in whom a virus has been detected are at low or no risk of a serious bacterial infection. Well-appearing infants 1-3 mo of age can be managed safely using low-risk laboratory and clinical criteria as indicated in Table 177-2 if reliable parents are involved and close follow-up is assured.

Table 177-2 Low-Risk Criteria in a Child 1-3 Months Old with Fever

BOSTON CRITERIA Infants are at low risk if they appear well, have a normal physical examination, and have a caretaker reachable by telephone and if laboratory tests are as follows: • CBC: <20,000 WBC/μL • Urine: negative leukocyte esterase • CSF: leukocyte count less than 10×10^6/L
PHILADELPHIA PROTOCOL Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows: • CBC: <15,000 WBC/μL; band: total neutrophil ratio <0.2 • Urine: <10 WBC/HPF; no bacteria on Gram stain • CSF: <8 WBC/μL; no bacteria on Gram stain • Chest radiograph: no infiltrate • Stool: no RBC; few to no WBC
PITTSBURGH GUIDELINES Infants are at low risk if they appear well and have a normal physical examination and if laboratory tests are as follows: • CBC: 5,000-15,000 WBC/μL; peripheral absolute band count <1,500/μL • Urine (enhanced urinalysis): 9 WBC/μL and no bacteria on Gram stain • CSF: 5 WBC/μL and negative Gram stain; if bloody tap, then WBC:RBC ≤1 : 500 • Chest radiograph: no infiltrate • Stool: 5 WBC/HPF with diarrhea
ROCHESTER CRITERIA Infants are at low risk if they appear well and have a normal physical examination and if laboratory findings are as follows: • CBC: 5,000-15,000 WBC/μL; absolute band count ≤1,500/μL • Urine: <10 WBC/HPF at 40× • Stool: <5 WBC/HPF if diarrhea

CBC, complete blood count; CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

Infants 1-3 mo of age with fever who appear generally well; who have been previously healthy; who have no evidence of skin, soft tissue, bone, joint, or ear infection; and who have a peripheral white blood cell (WBC) count of 5,000-15,000 cells/μL, an absolute band count of <1,500 cells/μL, and normal urinalysis and negative culture (blood and urine) results are unlikely to have a serious bacterial infection. The negative predictive value with 95% confidence of these criteria for any serious bacterial infection is >98% and for bacteremia is >99%. Among serious bacterial infections, pyelonephritis is the most common and may be seen in well-appearing infants who have fever without a focus or in those who appear ill. Urinalysis may be negative in infants <2 mo of age with pyelonephritis. Bacteremia is present in <30% of infants with pyelonephritis. Procalcitonin, erythrocyte sedimentation rate (ESR), and C-reactive protein are biologic markers that may be considered in the evaluation of a child with fever. Host-based microarray gene expression profiles determined on the patient's leukocytes may be able to detect RNA transcriptional patterns (biosignatures) that distinguish viral from bacterial infection (Fig. 177-1).

The decision to obtain CSF studies in the well-appearing 1-3 mo old infant depends on the decision to administer empirical antibiotics. If close observation without antibiotics is planned, a lumbar puncture may be deferred. If the child deteriorates clinically, a full sepsis evaluation should be performed, and intravenous antibiotics should be administered. If empirical antibiotics are initiated, CSF studies should be obtained, preferably before administering antibiotics.

3 to 36 Months of Age

Approximately 30% of febrile children in the 3-36 mo age group have no localizing signs of infection. Viral infections are the cause of the vast majority of fevers in this population, but serious bacterial infections do occur and are caused by the same pathogens listed for patients 1-3 mo of age, except for the perinatally acquired infections. *S. pneumoniae*, *N. meningitidis,* and *Salmonella* account for most cases of occult bacteremia. *H. influenzae* type b was an important cause of occult bacteremia in young children before universal immunization with conjugate Hib vaccines and remains common in underdeveloped countries that have not implemented these vaccines in their immunization schedule.

Risk factors indicating increased probability of occult bacteremia include temperature ≥39°C (102.2°F), WBC count ≥15,000/μL, and

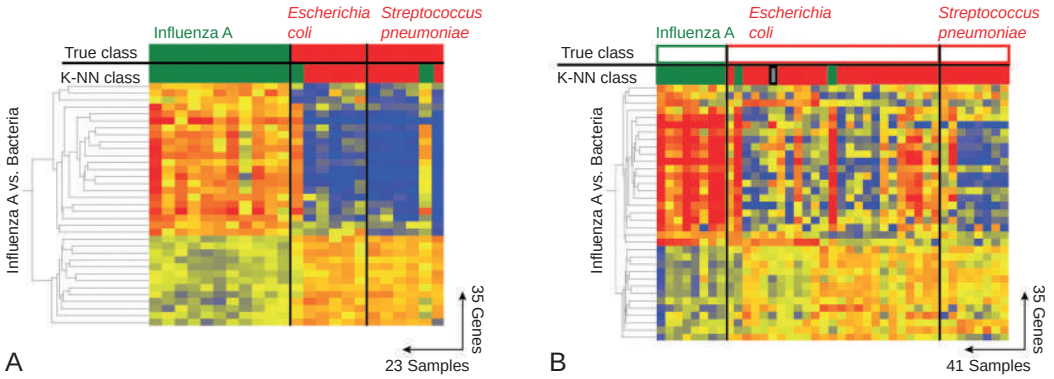

Figure 177-1 **Gene expression patterns may discriminate viral vs bacterial infections. A,** Set of 35 genes that discriminates patients with viral infections (influenza A; *green*) and bacterial infections (*Escherichia coli* and *Streptococcus pneumoniae; red*). The discriminative pattern is shown by the gene expression patterns in the heat map (*red* indicates overexpressed genes; *blue* indicates underexpressed genes). **B,** The diagnostic signature was tested in an independent set of patients that confirmed its accuracy. *K-NN* indicates nearest neighbor algorithm. *(Modified from Ramilo O, Allman W, Chung W, et al: Gene expression patterns in blood leukocytes discriminate patients with acute infections,* Blood *109:2066-2077, 2007. Fig 1.)*

elevated absolute neutrophil count, band count, erythrocyte sedimentation rate (ESR), or C-reactive protein. The probability of bacteremia and/or pneumonia or pyelonephritis among infants 3-36 mo of age increases as the temperature (especially >40°C [104°F]) and WBC count (especially >25,000/μL) increase. However, no combination of laboratory tests or clinical assessment is sensitive enough to predict the presence of occult bacteremia. Socioeconomic status, race, gender, and age (within the range of 3-36 mo) do not appear to affect the risk for occult bacteremia.

The pattern of sequelae of occult bacteremia may be related to host factors and the offending organism. In some children, the occult bacteremic illness can represent the early signs of serious localized infection rather than a transient disease state. Without therapy, occult bacteremia caused by pneumococcus can resolve spontaneously without sequelae, can persist, or can lead to localized infections such as meningitis, pneumonia, cellulitis, pericarditis, osteomyelitis, or suppurative arthritis. Among patients with pneumococcal bacteremia (occult or focal), spontaneous resolution occurs in 30-40%, with a higher rate of spontaneous resolution among well-appearing children.

Hib bacteremia is characteristically associated with a higher risk for localized serious infection than is bacteremia caused by *S. pneumoniae*. Hospitalized children with Hib bacteremia often develop focal infections, such as meningitis, epiglottitis, cellulitis, pericarditis, or osteoarticular infection, and spontaneous resolution of bacteremia is rare. Important bacterial infections among children 3-36 mo of age with localizing signs include otitis media, sinusitis, pneumonia (not always evident without a chest radiograph), enteritis, urinary tract infection, osteomyelitis, and meningitis.

Management of toxic-appearing febrile children 3-36 mo of age who do not have focal signs of infection includes hospitalization and prompt institution of antimicrobial therapy after specimens of blood, urine, and CSF are obtained for culture. Consensus practice guidelines published in 1993 recommended that children 3-36 mo of age who have a temperature of <39°C (102.2°F) and do not appear toxic be observed as outpatients without performing diagnostic tests or administering antimicrobial agents. For nontoxic-appearing infants with a rectal temperature of ≥39°C (102.2°F), options include obtaining a blood culture and administering empirical antibiotic therapy (ceftriaxone, a single dose of 50 mg/kg, not to exceed 1 g); if the WBC count is >15,000/μL, obtaining a blood culture and beginning empirical ceftriaxone; or obtaining a blood culture and observing as outpatients without empirical antibiotic therapy, with return for reevaluation within 24 hr. Guidelines for managing febrile children 3-36 mo of age who have received both Hib and *S. pneumoniae* conjugate vaccines have not been established, but careful observation without empirical administration of antibiotic therapy is generally prudent. Because fully vaccinated young children are at a much lower risk of occult bacteremia and meningitis as the cause of acute fever without localizing signs, some advocate that the only laboratory tests needed in this age group when temperature is >39°C (102.2°F) are a urinalysis and urine culture for circumcised boys <6 mo of age and uncircumcised boys and all girls <24 mo of age. Regardless of the management option (Table 177-3), the family should be instructed to return immediately if the child's condition deteriorates or new symptoms develop.

Empirical antibiotic therapy for well-appearing children <36 mo of age who have not received Hib and *S. pneumoniae* conjugate vaccines and who have a rectal temperature of >39°C (102.2°F) and a WBC count of >15,000/μL is strongly recommended. If blood cultures are obtained and *S. pneumoniae* is isolated from the blood, the child should return to the physician as soon as possible after the culture results are known. If the child appears well, is afebrile, and has a normal physical exam, a second blood culture should be obtained and the child should be treated with 7-10 days of oral antimicrobial therapy. If the child appears ill and continues to have fever with no identifiable focus of infection at the time of follow-up, or if *H. influenzae* or *N. meningitidis* is present in the initial blood culture, the child

Table 177-3 Management of Fever Without Localizing Signs

GROUP	MANAGEMENT
Any toxic-appearing child 0-36 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child <1 mo and temperature ≥38°C (100.4°F)	Hospitalize, broad cultures plus other tests,* parenteral antibiotics
Child 1-3 mo and temperature ≥38°C (100.4°F)	Two-step process 1. Determine risk based on history, physical examination, and laboratory studies. Low risk: • Uncomplicated medical history • Normal physical examination • Normal laboratory studies • Urine: negative leukocyte esterase, nitrite and <10 WBC/HPF • Peripheral blood: 5,000-15,000 WBC/mm^3; <1,500 bands or band: total neutrophil ratio <0.2 • Stool studies if diarrhea (no RBC and <5 WBC/HPF) • CSF cell count (<8 WBC/μL) and negative Gram stain • Chest radiograph without infiltrate 2. If child fulfills all low-risk criteria, administer no antibiotics, ensure follow-up in 24 hr and access to emergency care if child deteriorates. Daily follow-up should occur until blood, urine, and CSF cultures are final. If any cultures are positive, child returns for further evaluation and treatment. If child does not fulfill all low-risk criteria, hospitalize and administer parenteral antibiotics until all cultures are final and definitive diagnosis determined and treated
Child 3-36 mo and temperature 38-39°C (100.4-102.2°F)	Reassurance that diagnosis is likely self-limiting viral infection, but advise return with persistence of fever, temperatures >39°C (102.2°F), and new signs and symptoms
Child 3-36 mo and temperature >39°C (102.2°F)	Two-step process: 1. Determine immunization status 2. If received conjugate pneumococcal and *Haemophilus influenzae* type b vaccines, obtain urine studies (urine WBC, leukocyte esterase, nitrite, and culture) for all girls, all boys <6 mo old, all uncircumcised boys <2 yr, all children with recurrent urinary tract infections If did not receive conjugate pneumococcal and *H. influenzae* type b vaccines, manage according to the 1993 Guidelines (see Baraff et al. *Ann Emerg Med* 22:1198-1210, 1993.)

*Other tests may include chest radiograph, stool studies, herpes simplex polymerase chain reaction.
CSF, cerebrospinal fluid; HPF, high-powered field; RBC, red blood cell; WBC, white blood cell.

should have a repeat blood culture, be evaluated for meningitis (including lumbar puncture), and receive treatment in the hospital with appropriate intravenous antimicrobial agents. If the child develops a localized infection, therapy should be directed toward the likely pathogens.

FEVER OF UNKNOWN ORIGIN

The classification of fever of unknown origin (FUO) is best reserved for children with fever documented by a healthcare provider and for which the cause could not be identified after 3 wk of evaluation as an outpatient or after 1 wk of evaluation in the hospital (Table 177-4).

Etiology

The many causes of FUO in children are infections, rheumatologic (connective tissue or autoimmune) diseases, or autoinflammatory diseases (see Chapter 163) (Table 177-5). Neoplastic disorders should also be seriously considered, although most children with malignancies do not have fever alone. The possibility of drug fever should be considered if the patient is receiving any drug. Drug fever is usually sustained and not associated with other symptoms. Discontinuation of the drug is associated with resolution of the fever, generally within 72 hr, although certain drugs, such as iodides, are excreted for a prolonged period with fever that can persist for as long as 1 mo after drug withdrawal.

Most fevers of unknown or unrecognized origin result from atypical presentations of common diseases. In some cases, the presentation as an FUO is characteristic of the disease, such as juvenile idiopathic arthritis, but the definitive diagnosis can be established only after prolonged observation because initially there are no associated or specific findings on physical examination and all laboratory results are negative or normal.

In the United States, the systemic infectious diseases most commonly implicated in children with FUO are salmonellosis, tuberculosis, rickettsial diseases, syphilis, Lyme disease, cat-scratch disease, atypical prolonged presentations of common viral diseases, Epstein-Barr virus infection, cytomegalovirus (CMV) infection, viral hepatitis, coccidioidomycosis, histoplasmosis, malaria, and toxoplasmosis. Less-common infectious causes of FUO include tularemia, brucellosis, leptospirosis, and rat bite fever. AIDS alone is not usually responsible for FUO, although febrile illnesses often occur in patients with AIDS as a result of opportunistic infections (see Table 177-4).

Juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus are the connective tissue diseases associated most commonly with FUO. Inflammatory bowel disease and Kawasaki disease are also commonly reported as causes of FUO. If factitious fever (inoculation of pyogenic material or manipulation of the thermometer by the patient or parent) is suspected, the presence and pattern of fever should be documented in the hospital. Prolonged and continuous observation, which can include electronic or video surveillance, of patients is imperative. FUO lasting longer than 6 mo is uncommon in children and suggests granulomatous, autoinflammatory, or autoimmune disease.

Table 177-4 Summary of Definitions and Major Features of the 4 Subtypes of Fever of Unknown Origin

FEATURE	CLASSIC FUO	HEALTHCARE-ASSOCIATED FUO	IMMUNE-DEFICIENT FUO	HIV-RELATED FUO
Definition	>38°C (100.4°F), >3 wk, >2 visits or 1 wk in hospital	≥38°C (100.4°F), >1 wk, not present or incubating on admission	≥38°C (100.4°F), >1 wk, negative cultures after 48 hr	≥38°C (100.4°F), >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Healthcare-associated infections, postoperative complications, drug fever	Majority caused by infections, but cause documented in only 40-60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower-limb deep veins	Wounds, drains, devices, sinuses, urine	Skin folds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

CMV, cytomegalovirus; CXR, chest radiograph; FUO, fever of unknown origin.

Adapted from Mandell GL, Bennett, JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 780, Table 51-1.*

Table 177-5 Diagnostic Considerations of Fever of Unknown Origin in Children

ABSCESSES Abdominal Brain Dental Hepatic Pelvic Perinephric Rectal Subphrenic Psoas	**RHEUMATOLOGIC DISEASES** Behçet disease Juvenile dermatomyositis Juvenile idiopathic arthritis Rheumatic fever Systemic lupus erythematosus
BACTERIAL DISEASES Actinomycosis *Bartonella henselae* (cat-scratch disease) Brucellosis *Campylobacter* *Francisella tularensis* (tularemia) *Listeria monocytogenes* (listeriosis) Meningococcemia (chronic) *Mycoplasma pneumoniae* Rat bite fever (*Streptobacillus moniliformis;* streptobacillary form of rat bite fever) *Salmonella* Tuberculosis Whipple disease Yersiniosis	**HYPERSENSITIVITY DISEASES** Drug fever Hypersensitivity pneumonitis Serum sickness Weber-Christian disease
LOCALIZED INFECTIONS Cholangitis Infective endocarditis Mastoiditis Osteomyelitis Pneumonia Pyelonephritis Sinusitis	**NEOPLASMS** Atrial myxoma Cholesterol granuloma Hodgkin disease Inflammatory pseudotumor Leukemia Lymphoma Pheochromocytoma Neuroblastoma Wilms tumor
SPIROCHETES *Borrelia burgdorferi* (Lyme disease) Relapsing fever *(Borrelia recurrentis)* Leptospirosis Rat bite fever (*Spirillum minus;* spirillary form of rat bite fever) Syphilis	**GRANULOMATOUS DISEASES** Crohn disease Granulomatous hepatitis Sarcoidosis Angiitis
FUNGAL DISEASES Blastomycosis (extrapulmonary) Coccidioidomycosis (disseminated) Histoplasmosis (disseminated) *Chlamydia* Lymphogranuloma venereum Psittacosis	**FAMILIAL AND HEREDITARY DISEASES** Anhidrotic ectodermal dysplasia Autonomic neuropathies Fabry disease Familial dysautonomia Familial Hibernian fever Familial Mediterranean fever and the many other autoinflammatory diseases (see Chapter 163) Hypertriglyceridemia Ichthyosis Sickle cell crisis Spinal cord/brain injury
RICKETTSIA *Ehrlichia canis* Q fever Rocky Mountain spotted fever Tick-borne typhus	**MISCELLANEOUS** Addison disease Castleman disease Chronic active hepatitis Cyclic neutropenia Diabetes insipidus (nonnephrogenic and nephrogenic) Factitious fever Hemophagocytic syndromes Hypothalamic-central fever Infantile cortical hyperostosis Inflammatory bowel disease Kawasaki disease Kikuchi-Fujimoto disease Metal fume fever Pancreatitis Periodic fever syndromes Poisoning Pulmonary embolism Thrombophlebitis Thyrotoxicosis, thyroiditis
VIRUSES Cytomegalovirus Hepatitis viruses HIV Epstein-Barr virus	
PARASITIC DISEASES Amebiasis Babesiosis Giardiasis Malaria Toxoplasmosis Trichinosis Trypanosomiasis Visceral larva migrans *(Toxocara)*	

Repeat interval evaluation, including history, physical examination, laboratory evaluation, and imaging studies, is required.

Diagnosis

The evaluation of FUO requires a thorough history and physical examination supplemented by a few screening laboratory tests and additional laboratory and imaging evaluation as indicated by the history or abnormalities on examination or initial screening tests (see Table 177-5).

History

A detailed fever history including onset, frequency, duration of fever, response or nonresponse to therapy, recurrence, and associated symptoms should be obtained. Repetitive chills and temperature spikes are common in children with septicemia (regardless of cause), particularly when associated with kidney disease, liver or biliary disease, infective endocarditis, malaria, brucellosis, rat bite fever, or a loculated collection of pus.

The age of the patient is helpful in evaluating FUO. Children >6 yr of age often have a respiratory or genitourinary tract infection, localized infection (abscess, osteomyelitis), JIA, or, rarely, leukemia. Adolescent patients are more likely to have inflammatory bowel disease, autoimmune processes, lymphoma, or tuberculosis, in addition to the causes of FUO found in younger children.

A history of exposure to wild or domestic animals should be solicited. The incidence of zoonotic infections in the United States is increasing, and these infections are often acquired from pets that are not overtly ill. Immunization of dogs against specific disorders such as leptospirosis can prevent canine disease but does not always prevent the animal from carrying and shedding leptospires, which may be transmitted to household contacts. A history of ingestion of rabbit or squirrel meat might provide a clue to the diagnosis of oropharyngeal, glandular, or typhoidal tularemia. A history of tick bite or travel to tick- or parasite-infested areas should be obtained.

Any history of pica should be elicited. Ingestion of dirt is a particularly important clue to infection with *Toxocara canis* (visceral larva migrans) or *Toxoplasma gondii* (toxoplasmosis).

A history of unusual dietary habits or travel as early as the birth of the child should be sought. Malaria, histoplasmosis, and coccidioidomycosis can reemerge years after visiting or living in an endemic area. It is important to identify prophylactic immunizations and precautions taken by the patient against ingestion of contaminated water or food during foreign travel. Rocks, dirt, and artifacts from geographically distant regions that have been collected and brought into the home as souvenirs can serve as vectors of disease.

A medication history should be pursued rigorously. This history should elicit information about nonprescription preparations and topical agents, including eyedrops, that may be associated with atropine-induced fever.

The genetic background of a patient also is important. Descendants of the Ulster Scots may have FUO because they are afflicted with nephrogenic diabetes insipidus. Familial dysautonomia (Riley-Day syndrome), a disorder in which hyperthermia is recurrent, is more common among Jews than among other population groups. Ancestry from the Mediterranean region should suggest the possibility of familial Mediterranean fever. Both familial Mediterranean fever and hyperimmunoglobulin D syndrome are inherited as autosomal recessive disorders. Tumor necrosis factor receptor–associated periodic syndrome and Muckle-Wells syndrome are inherited as autosomal dominant traits.

Physical Examination

A complete physical examination is essential to search for any clues to the underlying diagnosis (Table 177-6). The child's general appearance, including sweating during fever, should be noted. The continuing absence of sweat in the presence of an elevated or changing body temperature suggests dehydration due to vomiting, diarrhea, or central or nephrogenic diabetes insipidus. It also should suggest anhidrotic ectodermal dysplasia, familial dysautonomia, or exposure to atropine. The general activity of the patient and the presence or absence of rashes should also be noted.

A careful ophthalmic examination is important. Red, weeping eyes may be a sign of connective tissue disease, particularly polyarteritis nodosa. Palpebral conjunctivitis in a febrile patient may be a clue to measles, coxsackievirus infection, tuberculosis, infectious mononucleosis, lymphogranuloma venereum, or cat-scratch disease. In contrast, bulbar conjunctivitis in a child with FUO suggests Kawasaki disease or leptospirosis. Petechial conjunctival hemorrhages suggest infective

Table 177-6 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Unknown Origin

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration	Disseminated histoplasmosis, SLE, IBD, Behcet syndrome, periodic fever syndromes
	Tender tooth	Periapical abscess
Fundi or conjunctivae	Choroid tubercle	Disseminated granulomatosis*
	Petechiae, Roth spot	Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa, cancer
	Epididymal nodule	Disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, granulomatosis with polyangiitis, and syphilis.

From Mandell GL, Bennett, JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7, Philadelphia, 2010, Churchill Livingstone/Elsevier, p. 785, Table 51-8.*

endocarditis. Uveitis suggests sarcoidosis, JIA, systemic lupus erythematosus, Kawasaki disease, Behçet disease, and vasculitis. Chorioretinitis suggests CMV, toxoplasmosis, and syphilis. Proptosis suggests an orbital tumor, thyrotoxicosis, metastasis (neuroblastoma), orbital infection, Wegener granulomatosis, or pseudotumor.

The ophthalmoscope should also be used to examine nailfold capillary abnormalities that are associated with connective tissue diseases such as juvenile dermatomyositis and systemic scleroderma. Immersion oil or lubricating jelly is placed on the skin adjacent to the nail bed, and the capillary pattern is observed with the ophthalmoscope set on +40.

FUO is sometimes caused by hypothalamic dysfunction. A clue to this disorder is failure of pupillary constriction because of absence of the sphincter constrictor muscle of the eye. This muscle develops embryologically when hypothalamic structure and function also are undergoing differentiation.

Fever resulting from familial dysautonomia may be suggested by lack of tears, an absent corneal reflex, or a smooth tongue with absence of fungiform papillae. Tenderness to tapping over the sinuses or the upper teeth suggests sinusitis. Recurrent oral candidiasis may be a clue to various disorders of the immune system especially involving the T lymphocytes. Hyperactive deep tendon reflexes can suggest thyrotoxicosis as the cause of FUO.

Fever blisters are common findings in patients with pneumococcal, streptococcal, malarial, and rickettsial infection as well as periodic fever syndromes. These lesions also are common in children with meningococcal meningitis (which usually does not manifest as FUO) but rarely are seen in children with meningococcemia. Fever blisters also are occasionally seen with *Salmonella* or staphylococcal infections.

Hyperemia of the pharynx, with or without exudate, suggests streptococcal infection, Epstein-Barr virus infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, Kawasaki disease, or leptospirosis.

The muscles and bones should be palpated carefully. Point tenderness over a bone can suggest occult osteomyelitis or bone marrow invasion from neoplastic disease. Tenderness over the trapezius muscle may be a clue to subdiaphragmatic abscess. Generalized muscle tenderness suggests dermatomyositis, trichinosis, polyarteritis, Kawasaki disease, or mycoplasmal or arboviral infection.

Rectal examination can reveal perirectal lymphadenopathy or tenderness, which suggests a deep pelvic abscess, iliac adenitis, or pelvic osteomyelitis. A guaiac test should be obtained; occult blood loss can suggest granulomatous colitis or ulcerative colitis as the cause of FUO.

Laboratory Evaluation

The laboratory evaluation of the child with FUO and whether the evaluation will occur in the inpatient or outpatient realm are determined on a case-by-case basis. Hospitalization may be required for laboratory or imaging studies that are unavailable or impractical in an ambulatory setting, for more-careful observation, or for temporary relief of parents' anxiety. The tempo of diagnostic evaluation should be adjusted to the tempo of the illness; haste may be imperative in a critically ill patient, but if the illness is more chronic, the evaluation can proceed in systematic fashion and can be carried out in an outpatient setting. If there are no clues in the patient's history or on physical examination that suggest a specific infection or area of suspicion, it is unlikely that diagnostic studies will be helpful. In that common scenario, continued surveillance and repeated reevaluations of the child should be employed to detect any new clinical findings.

Although ordering a large number of diagnostic tests in every child with FUO according to a predetermined list is discouraged, certain studies should be considered in the evaluation. A complete blood cell count with a differential WBC count and a urinalysis should be part of the initial laboratory evaluation. An absolute neutrophil count of <5,000/μL is evidence against indolent bacterial infection other than typhoid fever. Conversely, in patients with a polymorphonuclear leukocyte count of >10,000/μL or a nonsegmented polymorphonuclear leukocyte count of >500/μL a severe bacterial infection is highly likely. Direct examination of the blood smear with Giemsa or Wright stain can reveal organisms of malaria, trypanosomiasis, babesiosis, or relapsing fever.

An ESR of >30 mm/hr indicates inflammation and the need for further evaluation for infectious, autoimmune, autoinflammatory, or malignant diseases, tuberculosis, Kawasaki disease, or autoimmune disease. A low ESR does not eliminate the possibility of infection or JIA. C-reactive protein is another acute-phase reactant that becomes elevated and returns to normal more rapidly than the ESR. Experts recommend checking 1 of the 2 because there is no evidence that measuring both the ESR and C-reactive protein in the same patient with FUO is clinically useful.

Blood cultures should be obtained aerobically. Anaerobic blood cultures have an extremely low yield and should be obtained only if there are specific reasons to suspect anaerobic infection. Multiple or repeated blood cultures may be required to detect bacteremia associated with infective endocarditis, osteomyelitis, or deep-seated abscesses. Polymicrobial bacteremia suggests factitious self-induced infection or gastrointestinal (GI) pathology. The isolation of leptospires, *Francisella,* or *Yersinia* requires selective media or specific conditions not routinely used. Therefore, it is important to inform the laboratory what organisms you are suspecting in a particular case. Urine culture should be obtained in all cases.

Tuberculin skin testing should be performed with intradermal placement of 5 units of purified protein derivative that has been kept appropriately refrigerated.

Imaging studies of the chest, sinuses, mastoids, or GI tract may be indicated by specific historical or physical findings. Radiographic evaluation of the GI tract for inflammatory bowel disease may be helpful in evaluating selected children with FUO and no other localizing signs or symptoms.

Examination of the bone marrow can reveal leukemia; metastatic neoplasm; mycobacterial, fungal, or parasitic infections; histiocytosis; hemophagocytosis; or storage diseases. If a bone marrow aspirate is performed, cultures for bacteria, mycobacteria, and fungi should be obtained.

Serologic tests can aid in the diagnosis of Epstein-Barr virus infection, CMV infection, toxoplasmosis, salmonellosis, tularemia, brucellosis, leptospirosis, cat-scratch disease, Lyme disease, rickettsial disease, and, on some occasions, JIA. The clinician should be aware that the reliability and sensitivity and specificity of these tests vary; for instance, serologic tests for Lyme disease outside of reference laboratories have been generally unreliable.

Radionuclide scans may be helpful in detecting abdominal abscesses as well as osteomyelitis, especially if the focus cannot be localized to a specific limb or multifocal disease is suspected. Gallium citrate localizes inflammatory tissues (leukocytes) associated with tumors or abscesses. Technetium-99m phosphate is useful for detecting osteomyelitis before plain roentgenograms demonstrate bone lesions. Granulocytes tagged with indium or iodinated immunoglobulin G may be useful in detecting localized pyogenic processes. ^{18}F-fluorodeoxyglucose positron emission tomography is a helpful imaging modality in adults with an FUO and can contribute to an ultimate diagnosis in 30-60% of patients. Echocardiograms can demonstrate the presence of a vegetation on the leaflets of heart valves, suggesting infective endocarditis. Ultrasonography can identify intraabdominal abscesses of the liver, subphrenic space, pelvis, or spleen.

Total-body CT or MRI (both with contrast) is usually the first imaging study of choice; both permit detection of neoplasms and collections of purulent material without the use of surgical exploration or radioisotopes. CT and MRI are helpful in identifying lesions of the head, neck, chest, retroperitoneal spaces, liver, spleen, intraabdominal and intrathoracic lymph nodes, kidneys, pelvis, and mediastinum. CT or ultrasound-guided aspiration or biopsy of suspicious lesions has reduced the need for exploratory laparotomy or thoracotomy. MRI is particularly useful for detecting osteomyelitis or myositis if there is concern about a specific limb. Diagnostic imaging can be very helpful in confirming or evaluating a suspected diagnosis; in the case of CT scans, the child is exposed to large amounts of radiation.

Biopsy is occasionally helpful in establishing a diagnosis of FUO. Bronchoscopy, laparoscopy, mediastinoscopy, and GI endoscopy can provide direct visualization and biopsy material when organ-specific manifestations are present. When employing any of the more-invasive testing procedures, the risk:benefit ratio for the patient must always be taken into consideration before proceeding further.

Management

The ultimate treatment of FUO is tailored to the underlying diagnosis. Fever and infection in children are not synonymous; antimicrobial agents should not be used as antipyretics, and empirical trials of medication should generally be avoided. An exception may be the use of antituberculous treatment in critically ill children with suspected disseminated tuberculosis. Empirical trials of other antimicrobial agents may be dangerous and can obscure the diagnosis of infective endocarditis, meningitis, parameningeal infection, or osteomyelitis. After a complete evaluation, antipyretics may be indicated to control fever associated with adverse symptoms.

Prognosis

Children with FUO have a better prognosis than do adults. The outcome in a child depends on the primary disease process, which is usually an atypical presentation of a common childhood illness. In many cases, no diagnosis can be established and fever abates spontaneously. In as many as 25% of children in whom fever persists, the cause of the fever remains unclear, even after thorough evaluation.

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Chapter 178

Infections in Immunocompromised Persons

Marian G. Michaels and Michael Green

Table 178-1 Major Causes of Increased Risk for Infection in Immunocompromised Hosts

PRIMARY IMMUNODEFICIENCIES
Antibody deficiency (B-cell defects; see Chapter 124)
• X-linked agammaglobulinemia
• Common variable immunodeficiency
• Selective immunoglobulin IgA deficiency
• IgG subclass deficiencies
• Hyper-IgM syndrome
• Transient hypogammaglobulinemia of infancy
Cell-mediated deficiency (T-cell defects)
• Thymic dysplasia (DiGeorge syndrome)
• Defective T-cell receptor
• Defective cytokine production
• T-cell activation defects
• CD8 lymphocytopenia
• Chronic mucocutaneous candidiasis
Combined B- and T-cell defects (see Chapter 126)
• Severe combined immunodeficiency
• Combined immunodeficiency
• Omenn syndrome
• Thrombocytopenia and eczema (Wiskott-Aldrich syndrome)
• Ataxia-telangiectasia
• Hyper-IgE syndrome
Phagocyte defects (see Chapter 130)
• Leukocyte adhesion deficiency
• Chédiak-Higashi syndrome
• Myeloperoxidase deficiency
• Chronic granulomatous disease
Leukopenia (see Chapter 131)
• Congenital neutropenia (Kostmann syndrome)
• Shwachman-Diamond syndrome
Disorders of the complement system (see Chapter 133)
SECONDARY IMMUNODEFICIENCIES
HIV (see Chapter 276)
Malignancies (and cancer chemotherapy)
Transplantation (see Chapters 135, 339, 368, 443, 444, and 536)
• Bone marrow and hematopoietic stem cell
• Solid organ
Burns
Sickle cell disease
Cystic fibrosis (see Chapter 403)
Diabetes mellitus
Immunosuppressive drugs
Asplenia including heterotaxy syndrome
Implanted foreign body
Malnutrition

Infection and disease develop when the host immune system fails to adequately protect against potential pathogens. In individuals with an intact immune system, infection occurs in the setting of naiveté to the microbe and absence or inadequate preexisting microbe-specific immunity or when protective barriers of the body such as the skin have been breached. Healthy children are able to meet the challenge of most infectious agents with an immunologic armamentarium capable of preventing significant disease. Once an infection begins to develop, an array of immune responses is set into action to control the disease and prevent it from reappearing. In contrast, immunocompromised children might not have this same capability. Depending on the level and type of immune defect, the affected child might not be able to contain the pathogen or to develop an appropriate immune response to prevent recurrence (see Chapter 122).

General practitioners are likely to see children with abnormal immune systems in their practices because increasing numbers of children survive with primary immunodeficiencies or receive immunosuppressive therapy for treatment of malignancy, autoimmune disorders, or transplantation.

Primary immunodeficiencies are compromised states that result from genetic defects affecting 1 or more arms of the immune system (Table 178-1). **Acquired, or secondary, immunodeficiencies** may result from infection (e.g., infection with HIV), from malignancy, or as an adverse effect of immunomodulating or immunosuppressing medications. Such immunosuppressing medications include medications that affect T cells (steroids, calcineurin inhibitors, tumor necrosis factor inhibitors, and chemotherapy), neutrophils (myelosuppressive agents, idiosyncratic or immune-mediated neutropenia), specific immune regulatory cells (tumor necrosis factor blockers, interleukin-2 inhibitors), or all immune cells (chemotherapy). Perturbations of the mucosal and skin barriers or normal microbial flora can also be characterized as secondary immunodeficiencies, predisposing the host open to infections, if only for a temporary period.

The major pathogens causing infections among immunocompetent hosts are also the main pathogens responsible for infections among children with immunodeficiencies. In addition, less-virulent organisms, including normal skin flora, commensal bacteria of the oral pharynx or gastrointestinal tract, environmental fungi, and common community viruses of low-level pathogenicity, can cause severe, life-threatening illnesses in immunocompromised patients (Table 178-2). For this reason, close communication with the diagnostic laboratory is critical so that the laboratory does not disregard normal flora and organisms normally considered to be contaminants as being unimportant.

Table 178-2 Most Common Causes of Infections in Immunocompromised Children

BACTERIA, AEROBIC*
Acinetobacter
Bacillus
Burkholderia cepacia
Citrobacter
Corynebacterium
Enterobacter spp.
Enterococcus faecalis
Enterococcus faecium
Escherichia coli
Klebsiella spp.
Listeria monocytogenes
Mycobacterium spp.
Neisseria meningitidis
Nocardia
Pseudomonas aeruginosa
Staphylococcus aureus
Staphylococcus, coagulase-negative
Streptococcus pneumoniae
Streptococcus, viridans group
BACTERIA, ANAEROBIC*
Bacillus
Clostridium
Fusobacterium
Peptococcus
Peptostreptococcus
Propionibacterium
Veillonella
FUNGI*
Aspergillus
Candida albicans
Other *Candida* spp.
Cryptococcus neoformans
Fusarium spp.
Pneumocystis jiroveci
Zygomycoses *(Mucor, Rhizopus, Rhizomucor)*
VIRUSES*
Adenoviruses
Cytomegalovirus
Epstein-Barr virus
Herpes simplex virus
Human herpesvirus 6
Polyomavirus (BK)
Respiratory and enteric community-acquired viruses
Varicella-zoster virus
PROTOZOA*
Cryptosporidium parvum
Giardia lamblia
Toxoplasma gondii

*Listed alphabetically.

178.1 Infections Occurring with Primary Immunodeficiencies

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More than 120 genes have been identified, accounting for >150 different primary immunodeficiencies.

ABNORMALITIES OF THE PHAGOCYTIC SYSTEM

Children with abnormalities of the phagocytic and neutrophil system have problems with bacteria as well as environmental fungi. Disease manifests as recurrent infections of the skin, mucous membranes, lungs, liver, and bones. Dysfunction of this arm of the immune system can be a result of inadequate numbers, abnormal movement properties, or aberrant function of neutrophils (see Chapter 130).

Neutropenia is defined as an absolute neutrophil count of <1,000 cells/mm^3 and can be associated with significant risk for developing severe bacterial and fungal disease, particularly when the absolute count is <500 cells/mm^3 (see Chapter 127). Although acquired neutropenia secondary to bone marrow suppression from a virus or medication is common, genetic causes of neutropenia also exist. Primary congenital neutropenia most often manifests during the 1st yr of life with cellulitis, perirectal abscesses, or stomatitis from *Staphylococcus aureus* or *Pseudomonas aeruginosa.* Episodes of severe disease, including bacteremia or meningitis, are also possible. Bone marrow evaluation shows a failure of maturation of myeloid precursors. Most forms of congenital neutropenia are autosomal dominant, but some, such as Kostmann syndrome (see Chapter 127) and Shwachman-Diamond syndrome (see Chapter 469), are caused by autosomal recessive mutations. Cyclic neutropenia can be associated with autosomal dominant inheritance or de novo sporadic mutations and manifests as fixed cycles of severe neutropenia between periods of normal granulocyte numbers. Often the neutrophil count has normalized by the time the patient presents with symptoms, thus hampering the diagnosis. The cycles classically occur every 21 days (range: 14-36 days), with neutropenia lasting 3-6 days. Most often the disease is characterized by recurrent aphthous ulcers and stomatitis during the periods of neutropenia. However, life-threatening necrotizing myositis or cellulitis and systemic disease can occur, especially with *Clostridium septicum* or *Clostridium perfringens.* Many of the neutropenic syndromes respond to colony-stimulating factor.

Leukocyte adhesion defects are caused by defects in the β chain of integrin (CD18), which is required for the normal process of neutrophil aggregation and attachment to endothelial surfaces (see Chapter 130). In the most-severe form there is a total absence of CD18. Children with this defect can have a history of delayed cord separation and recurrent infections of the skin, oral mucosa, and genital tract beginning early in life. Ecthyma gangrenosum also occurs. Because the defect involves leukocyte migration and adherence, the neutrophil count in the peripheral blood is usually extremely elevated but pus is not found at the site of infection. Survival is usually <10 yr in the absence of hematopoietic stem cell transplantation (HSCT).

Chronic granulomatous disease is an inherited neutrophil dysfunction syndrome, which can be either X-linked or autosomal recessive (see Chapter 130). In addition, chronic granulomatous disease can develop in response to spontaneous mutations in the genes associated with heritable chronic granulomatous disease. Neutrophils and other myeloid cells have defects in their nicotinamide-adenine dinucleotide phosphate oxidase function, rendering them incapable of generating superoxide and thereby impairing intracellular killing. Accordingly, microbes that destroy their own hydrogen peroxide (*S. aureus, Serratia marcescens, B. cepacia, Nocardia* spp., *Aspergillus*) cause recurrent infections in these children. Infections have a predilection to involve the lungs, liver, and bone. In addition, these children can present with recurrent abscesses affecting the skin or perirectal region or lymph nodes. Prophylaxis with trimethoprim-sulfamethoxazole, recombinant human interferon-γ, and oral antifungal agents that have activity against *Aspergillus* spp., such as itraconazole or newer azoles, substantially reduce the incidence of severe infections. Patients with life-threatening infections are also reported to benefit from aggressive treatment with white cell transfusions in addition to antimicrobial agents directed against the specific pathogen. In addition, HSCT can be curative but because of associated risks is not routinely performed.

DEFECTIVE SPLENIC FUNCTION, OPSONIZATION, OR COMPLEMENT ACTIVITY

Children who have congenital asplenia or splenic dysfunction associated with polysplenia or hemoglobinopathies, such as sickle cell disease, as well as those who have undergone splenectomy, are at risk for serious infections from encapsulated bacteria and blood-borne protozoa such as *Plasmodium* and *Babesia.* Prophylaxis against bacterial

infection with penicillin should be considered for these patients, particularly children <5 yr of age. The most common causative organisms include *S. pneumoniae, H. influenzae* type b, and *Salmonella*, which can cause sepsis, pneumonia, meningitis, and osteomyelitis. Defects in the early complement components, particularly C2 and C3, can also be associated with severe infection from these bacteria. **Terminal complement defects** (C5, C6, C7, C8, and C9) are associated with recurrent infections with *Neisseria.* Patients with complement deficiency also have an increased incidence of autoimmune disorders. Vaccines for *S. pneumoniae, H. influenzae* type b, and *N. meningitidis* should be administered to all children with abnormalities in opsonization or complement pathways (see Chapter 134).

B-CELL DEFECTS (HUMORAL IMMUNODEFICIENCIES)

Antibody deficiencies account for the majority of primary immunodeficiencies among humans (see Chapter 124). Patients with defects in the B-cell arm of the immune system fail to develop appropriate antibody responses, with abnormalities that range from complete agammaglobulinemia to isolated failure to produce antibody against a specific antigen or organism. Antibody deficiencies found in children with diseases such as X-linked agammaglobulinemia or common variable immunodeficiency predispose to infections with encapsulated organisms such as *S. pneumoniae* and *H. influenzae* type b. Other bacteria can also be problematic in these children (see Table 178-2). Even though most other classes of microbes do not cause problems for these patients, some notable exceptions exist. Rotavirus can lead to chronic diarrhea, and enteroviruses can disseminate and cause a chronic meningoencephalitis syndrome in these patients. Paralytic polio has developed after immunization with live polio vaccine. Protozoan infections such as giardiasis can be severe and persistent. Children with B-cell defects can develop bronchiectasis over time following chronic or recurrent pulmonary infections.

Children with antibody deficiencies are usually asymptomatic until 5-6 mo of age, when maternally derived antibody levels begin to wane. These children begin to develop recurrent episodes of otitis media, bronchitis, pneumonia, bacteremia, and meningitis. Many of these infections respond quickly to antibiotics, which can delay the recognition of antibody deficiency. Children who require myringotomy tube placement before 2 yr of age because of recurrent episodes of otitis media (≥3 episodes within 6 mo, or ≥4 episodes within 12 mo) should be considered for screening measurement of immunoglobulin levels.

The significance and impact of specific **immunoglobulin (Ig) G subclass deficiencies** is less-well understood and remains controversial. Deficiencies of specific IgG subclasses were first noted in healthy adult blood donors in whom no increased susceptibility to infections was documented. However, others have identified specific IgG deficiencies to be associated with a predisposition to recurrent bacterial sinopulmonary infection, bacteremia, meningitis, osteomyelitis, and pyoderma. Deficiency of subclass IgG_2 is associated with poor antibody production after exposure to polysaccharide antigens, either after vaccination or after infection with a polysaccharide-encapsulated organism such as *S. pneumoniae* or *H. influenzae* type b.

Selective IgA deficiency leads to a lack of production of secretory antibody at the mucosal membranes (see Chapter 124). Even though most patients have no increased risk for infections, some have mild to moderate disease at sites of mucosal barriers. Accordingly, recurrent sinopulmonary infection and gastrointestinal disease are the major clinical manifestations. These patients also have an increased incidence of allergies and autoimmune disorders compared with the normal population.

Hyper-IgM syndrome is caused by a defect in the CD40 ligand on the T cell and is associated with a deficiency in the production of IgG and IgA antibody (see Chapter 124). In addition, recurrent neutropenia, hemolytic anemia, or aplastic anemia can be present. Similar to patients with agammaglobulinemia, these patients are at risk for bacterial sinopulmonary infections, *Pneumocystis jiroveci* pneumonia (PCP), and *Cryptosporidium* intestinal infection.

Replacement of antibody with **immunoglobulin, administered intravenously every 3-4 wk** or weekly, using a subcutaneous formulation, has been the mainstay of treatment for most of the primary IgG antibody deficiencies. Immunoglobulin replacement is not advocated for IgA deficiency, because it does not correct the defect. Prophylaxis with specific antibiotic regimens is controversial and should be individualized for patients who do not respond to immunoglobulin replacement.

T-CELL DEFECTS (CELL-MEDIATED IMMUNODEFICIENCIES)

Children with primary cell-mediated immunodeficiencies, either isolated or more commonly in combination with B-cell defects, present early in life and are susceptible to viral, fungal, and protozoan infections. Clinical manifestations include chronic diarrhea, mucocutaneous candidiasis, and recurrent pneumonia, rhinitis, and otitis media. In thymic hypoplasia (DiGeorge syndrome), hypoplasia or aplasia of the thymus and parathyroid glands occurs during fetal development in association with the presence of other congenital abnormalities. Hypocalcemia and cardiac anomalies are usually the presenting features of DiGeorge syndrome, which should prompt evaluation of the T-cell system. **Chronic mucocutaneous candidiasis** is a rare immunodeficiency associated primarily with T-cell dysfunction (see Chapter 125). These patients might not demonstrate delayed hypersensitivity to skin tests for *Candida* antigen despite having chronic superficial infection with yeast, but they do not appear to be at increased risk for systemic yeast infections. Endocrinopathies are commonly associated with chronic mucocutaneous candidiasis.

COMBINED B-CELL AND T-CELL DEFECTS

Patients with defects in both the T-cell and B-cell components of the immune system have variable manifestations depending on the extent of the defect (see Chapter 126). Complete or almost complete immunodeficiency is found with **severe combined immunodeficiency disorder**, whereas partial defects can be present in such states as ataxia-telangiectasia, Wiskott-Aldrich syndrome, hyper-IgE syndrome, and X-linked lymphoproliferative disorder. Rather than 1 disorder, it is now recognized that severe combined immunodeficiency disorder represents a heterogeneous group of genetic defects that leave the infant globally immune deficient and present in the 1st 6 mo of life with recurrent and typically severe infections caused by a variety of bacteria, fungi, and viruses. Failure to thrive, chronic diarrhea, mucocutaneous or systemic candidiasis, PCP, or cytomegalovirus (CMV) infections are common early in life. Passive maternal antibody is relatively protective against the bacterial pathogens during the 1st few mo of life, but thereafter patients are susceptible to both Gram-positive and Gram-negative organisms. Exposure to live virus vaccines can also lead to disseminated disease; accordingly, the use of live vaccines (including rotavirus vaccine) is contraindicated in patients with suspected or proven severe combined immunodeficiency disorder. Without stem cell transplantation or gene therapy, most affected children succumb to opportunistic infections within the 1st yr of life.

Children with **ataxia-telangiectasia** develop late onset of recurrent sinopulmonary infections from both bacteria and respiratory viruses. In addition, these children experience an increased incidence of malignancies. Wiskott-Aldrich syndrome is an X-linked recessive disease associated with eczema, thrombocytopenia, a reduced number of CD3 lymphocytes, moderately suppressed mitogen responses, and impaired antibody response to polysaccharide antigens. Accordingly, infections with *S. pneumoniae* or *H. influenzae* type b and PCP are common. Children with hyper-IgE syndrome have markedly elevated levels of IgE and present with recurrent episodes of *S. aureus* abscesses of the skin, lungs, and musculoskeletal system. Although the antibody abnormality is notable, these patients also have marked eosinophilia and poor cell-mediated responses to neoantigens and are also at increased risk for fungal infections.

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178.2 Infections Occurring with Acquired Immunodeficiencies

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Immunodeficiencies can be secondarily acquired as a result of infections or as a consequence of other underlying disorders such as malignancy, cystic fibrosis, diabetes mellitus, sickle cell disease, or malnutrition. Immunosuppressive medications used to prevent rejection after organ transplantation, to prevent graft-versus-host disease after stem cell transplantation (see Chapter 137), or to treat malignancies can also leave the host vulnerable to infections. Similarly, medications used to control rheumatologic or other autoimmune diseases may be associated with an increased risk for developing infection. Any process that disrupts the normal mucosal and skin barriers (e.g., burns, surgery, indwelling catheters) can lead to an increased risk for infection.

ACQUIRED IMMUNODEFICIENCY FROM INFECTIOUS AGENTS

Infection with HIV, the causative agent of AIDS, is the most important infectious cause of acquired immunodeficiency (see Chapter 276). Left untreated, HIV infection has profound effects on many parts of the immune system but in particular T-cell–mediated immunity that leads to susceptibility to the same types of infections as with primary T-cell immunodeficiencies.

Other organisms can also lead to temporary alterations of the immune system. Very rarely transient neutropenia associated with community-acquired viruses can lead to significant disease with bacterial infections. Secondary infections can occur because of impaired immunity or disruption of normal mucosal immunity, as exemplified by the increased risk for pneumonia from *S. pneumoniae* or *S. aureus* following influenza infection and group A streptococcus cellulitis and fasciitis following varicella.

MALIGNANCIES

The immune systems of children with malignancies are compromised by the therapies used to treat the cancer and, at times, by direct effects of the cancer itself. The type, duration, and intensity of anticancer therapy remain the major risk factors for infections in these children and often affect multiple arms of the immune system. The presence of mucous membrane abnormalities, indwelling catheters, malnutrition, prolonged exposure to antibiotics, and frequent hospitalizations adds to the risk for infection in these children.

Even though several arms of the immune system can be affected, the major abnormality predisposing to infection in children with cancer is **neutropenia**. The depth and duration of neutropenia are the primary predictors of the risk of infection in children being treated for cancer. Patients are at particular risk for bacterial and fungal infections if the absolute neutrophil count decreases to <500 cells/mm^3, and the risk is highest in those anticipated to have counts <100 cells/mm^3. Counts of >500 cells/mm^3 but <1,000 cells/mm^3 incur some increased risk for infection but not nearly as great. The lack of neutrophils can lead to a loss of inflammatory response, limiting the ability to localize sites of infection and potentially leaving fever as the only manifestation of infection. Accordingly, the absence of physical signs and symptoms does not reliably exclude the presence of infection, resulting in the need for empirical antibiotics (Fig. 178-1). Because patients with **fever** and **neutropenia** might only have subtle signs and symptoms of infection, the presence of fever warrants a thorough physical examination with careful attention to the oropharynx, lungs, perineum and anus, skin, nail beds, and intravascular catheter insertion sites (Table 178-3). A comprehensive laboratory evaluation, including a complete blood cell count, serum creatinine, blood urea nitrogen, and serum transaminases, should be obtained. Blood cultures should be taken from each port of any central venous catheter. Consideration should also be given to obtaining a peripheral venous sample for blood culture, especially in children with 1 or more positive cultures from a central venous catheter, facilitating localization of the source of the infection. Other microbiologic studies should be done if there are associated clinical symptoms, including nasal aspirate for viruses in patients with upper respiratory findings; stool for rotavirus in the winter months and for *C. difficile* toxin in patients with diarrhea; urinalysis and culture in young children or in older patients with symptoms of urgency, frequency, dysuria, or hematuria; and biopsy and culture of cutaneous lesions. Chest radiographs should be obtained in any patient with lower respiratory tract symptoms, although pulmonary infiltrates may be absent in children with severe neutropenia. Sinus films should be obtained for children >2 yr of age if rhinorrhea is prolonged. Abdominal CT scans should also be considered in children with profound neutropenia and abdominal pain to evaluate for the presence of typhlitis. Chest CT scan and galactomannan testing should be considered for children not responding to broad-spectrum antibiotics who have continued fever and neutropenia for longer than 96 hr. Biopsies for cytology, Gram stain, and culture should be considered if abnormalities are found during endoscopic procedures or if lung nodules are identified radiographically.

Before the routine institution of empirical antimicrobial therapy for fever and neutropenia, 75% of children with fever and neutropenia were ultimately found to have a documented site of infection, suggesting that most children with fever and neutropenia will have an underlying infection (see Table 178-3). Currently, Gram-positive cocci are the most common pathogens identified in these patients; however, Gram-negative organisms such as *P. aeruginosa, E. coli*, and *Klebsiella* can cause life-threatening infection and must be considered in the empirical treatment regimen. Other multidrug-resistant Enterobacteriaceae are increasingly recovered in these children. Although coagulase-negative staphylococci often cause infections in these

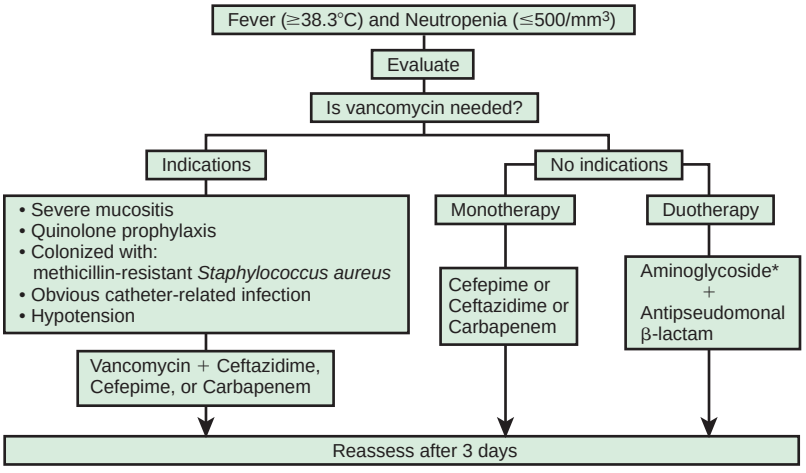

Figure 178-1 Guide to the initial management of the febrile neutropenic patient. Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanic acid. *Aminoglycoside antibiotics should be avoided if the patient is also receiving nephrotoxic, ototoxic, or neuromuscular blocking agents; has renal or severe electrolyte dysfunction; or is suspected of having meningitis (because of poor blood–brain perfusion). *(Adapted from Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America.* Clin Infect Dis *52:e56–e93, 2011.)*

Table 178-3 Possible Causes of Fever in Neutropenic Patients Not Responding to Broad-Spectrum Antibiotics

CAUSES	APPROXIMATE FREQUENCY IN HIGH-RISK PATIENTS (%)
Fungal infections susceptible to empirical therapy	40
Fungal infections resistant to empirical antifungal therapy	5
Bacterial infections (with cryptic foci, biofilms, and resistant organisms)	10
Toxoplasma gondii, mycobacteria, or fastidious pathogens *(Legionella, Mycoplasma, Chlamydophila pneumoniae, Bartonella)*	5
Viral infections (herpesviruses, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, herpes simplex virus, parainfluenza virus, respiratory syncytial virus, influenzaviruses)	5
Graft-versus-host disease after hematopoietic stem cell transplantation	10
Undefined (e.g., drug fever, toxic effects of chemotherapy, antitumor responses, undefined pathogens)	25

From Mandell GL, Bennett JE, Dolin R, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Churchill Livingstone.*

children in association with central venous catheters, these infections are typically indolent, and a short delay in treatment usually does not lead to a detrimental outcome. Other Gram-positive bacteria, such as *S. aureus* and *S. pneumoniae*, can cause more-fulminant disease and require prompt institution of therapy. Viridans streptococci are important potential pathogens in patients with the oral mucositis that is often associated with use of cytarabine and in patients who experience selective pressure from treatment with certain antibiotics such as quinolones. Infection caused by this organism can present as acute septic shock syndrome. Patients with prolonged neutropenia are at increased risk for opportunistic fungal infections, with *Candida* spp. and *Aspergillus* spp. being the most commonly identified fungi. Other fungi that can cause serious disease in these children include *Mucor* spp., *Fusarium* spp., and dematiaceous molds.

FEVER AND NEUTROPENIA

The use of empiric antimicrobial treatment as part of the management of fever and neutropenia decreases the risk of progression to sepsis, septic shock, acute respiratory distress syndrome, organ dysfunction, and death. In 2010, the Infectious Diseases Society of America updated a comprehensive guideline for the use of antimicrobial agents in neutropenic children and adults with cancer (see Fig. 178-1).

First-line antimicrobial therapy should take into consideration the types of microbes anticipated and the local resistance patterns encountered at each institution as well as the level of risk for severe infection associated with a given patient. In addition, antibiotic choices may be limited by specific circumstances, such as the presence of drug allergy and renal or hepatic dysfunction. The empirical use of oral antibiotics has been shown to be safe in some low-risk adults who have no evidence of bacterial focus or signs of significant illness (rigors, hypotension, mental status changes) and for whom a quick recovery of the bone marrow is anticipated. Guidelines for the management of fever and neutropenia in children with cancer and/or undergoing HSCT, which were published on 2012, conclude that the use of oral antimicrobial therapy as either initial or stepdown therapy can be considered in low-risk children who can tolerate oral antibiotics and in whom careful monitoring can be ensured. However, the authors of this guideline point out that oral medication use may present major challenges in children, including availability of liquid formulations of appropriate antibiotics, cooperation of young children, and presence of mucositis potentially interfering with absorption. Accordingly, decisions to implement this approach should be reserved for a very select subset of these children presenting with fever and neutropenia.

The decision to initially use intravenous monotherapy vs an expanded regimen of antibiotics depends on the severity of illness of the patient, history of previous colonization with resistant organisms, and obvious presence of catheter-related infection. Vancomycin should be added to the empiric initial regimen if the patient has hypotension or other evidence of septic shock, an obvious catheter-related infection, or a history of colonization with methicillin-resistant *S. aureus*, or if the patient is at high risk for viridans streptococci (severe mucositis, acute myelogenous leukemia, or prior use of quinolone prophylaxis). Monotherapy can be considered with cefepime, imipenem/cilastatin, meropenem, piperacillin-tazobactam, or ticarcillin-clavulanic acid. Ceftazidime should not be used as monotherapy if concern exists for Gram-positive organisms or resistant Gram-negative bacteria. The addition of a 2nd Gram-negative bacterial agent for empiric therapy can be considered in patients who are clinically unstable when resistant organisms are suspected.

Regardless of the regimen chosen initially, it is critical to carefully and continually evaluate the patient for response to therapy, development of secondary infections, and adverse effects. Management recommendations for these children are evolving. Based upon the 2012 published guidelines, patients who have negative blood cultures at 48 hr, who have been afebrile for at least 24 hr, and who have evidence of bone marrow recovery (absolute neutrophil counts of >100 cells/mm^3) can have antibiotics discontinued. However, if symptoms persist or evolve, intravenous antibiotics should be continued. Continuation of antibiotics in children whose fever has abated and who are clinically well but continue to have depression of neutrophils is more controversial. The 2012 pediatric guidelines advocate pediatric guidelines advocate discontinuing antibiotics in low-risk patients at 72 hr for patients who have negative blood cultures and who have been afebrile for at least 24 hr regardless of bone marrow recovery, as long as careful follow-up is ensured. In contrast, others continue to advocate for continuing antibiotics in this circumstance to prevent recurrence of fever.

Patients without an identified etiology but with **persistent fever** should be reassessed after 3-5 days. Those remaining clinically well may continue on the same regimen, although consideration should be given to discontinuing vancomycin or double Gram-negative bacterial coverage if they were included initially. Patients who remain febrile with clinical progression warrant the addition of vancomycin if it was not included initially and certain risk factors exist; clinicians should also consider changing the empirical antibacterial regimen to cover for the potential presence of antimicrobial resistance in these children. If fever persists for longer than 96 hr, the addition of an **antifungal agent** with antimold activity should be considered, particularly for those at high risk for invasive fungal infection (those with acute myelogenous leukemia or relapsed acute lymphocytic leukemia or who are receiving highly myelosuppressive chemotherapies for other cancers or with allogeneic HSCT). Medications, including liposomal amphotericin products or caspofungin, have been studied in children; voriconazole itraconazole, posaconazole, and micafungin have all been successfully used in adults. Studies comparing caspofungin to liposomal amphotericin for children with malignancies and fever and neutropenia showed caspofungin to be noninferior. The use of **antiviral agents** in fever and neutropenia is not warranted without specific evidence of viral disease. Active herpes simplex or varicella-zoster lesions merit treatment to decrease the time of healing; even if these lesions are not the source of fever, they are potential portals of entry

Table 178-4 Host Defense Defects and Common Pathogens by Time After Bone Marrow Transplantation/Hematopoietic Stem Cell Transplantation

TIME PERIOD	HOST DEFENSE DEFECTS	CAUSES	COMMON PATHOGENS
Pretransplant	Neutropenia Abnormal anatomic barriers	Underlying disease Prior chemotherapy	Aerobic Gram-negative bacilli
Preengraftment	Neutropenia Abnormal anatomic barriers	Chemotherapy Radiation Indwelling catheters	Aerobic Gram-positive cocci Aerobic Gram-negative bacilli *Candida* *Aspergillus* Herpes simplex virus (in previously infected patients) Community-acquired viral pathogens
Postengraftment	Abnormal cell-mediated immunity Abnormal anatomic barriers	Chemotherapy Immunosuppressive medications Radiation Indwelling catheters Unrelated cord blood donor	Gram-positive cocci Aerobic Gram-negative bacilli Cytomegalovirus Adenoviruses Community-acquired viral pathogens *Pneumocystis jiroveci*
Late posttransplant	Delayed recovery of immune function (cell-mediated, humoral, and abnormal anatomic barriers)	Time required to develop donor-related immune function Graft-versus-host disease	Varicella-zoster virus *Streptococcus pneumoniae*

for bacteria and fungi. CMV is a rare cause of fever in children with cancer and neutropenia. If CMV infection is suspected, assays to evaluate viral load in the blood and organ-specific infection should be obtained. Ganciclovir, foscarnet, or cidofovir may be considered while evaluation is pending, although ganciclovir can cause bone marrow suppression and foscarnet and cidofovir can be nephrotoxic (see Chapter 255). If influenza is identified, specific treatment with antiviral agents should be administered. Choice of treatment (oseltamivir, zanamivir) should be based on the anticipated susceptibility of the circulating influenza (see Chapter 258).

The use of **hematopoietic growth factors** shortens the duration of neutropenia but has not been proved to reduce morbidity or mortality. Accordingly, the 2010 recommendations from the Infectious Diseases Society of America do not endorse the routine use of hematopoietic growth factors in patients with established fever and neutropenia, although the recommendations do note that hematopoietic growth factors can be considered as prophylaxis in those with neutropenia who have a high risk for fever. Infections occur in children with cancer even without neutropenia. Most often these infections are viral in etiology. However, *P. jiroveci* can cause pneumonia regardless of the neutrophil count. Prophylaxis with trimethoprim-sulfamethoxazole against PCP is an effective preventive strategy and should be provided to all children undergoing active treatment for malignancy (see Chapter 244). Environmental fungi such as *Cryptococcus, Histoplasma*, and *Coccidioides* can also cause disease. *Toxoplasma gondii* is an uncommon but occasional pathogen in children with cancer. Infections encountered in healthy children (*S. pneumoniae,* group A *Streptococcus*) can cause disease in children with cancer regardless of the granulocyte count.

TRANSPLANTATION

Transplantation of hematopoietic stem cells and solid organs (including heart, liver, kidney, lungs, pancreas, and intestines) is increasingly used as therapy for a variety of disorders. Children undergoing transplantation are at risk for infections caused by many of the same microbial agents that cause disease in children with primary immunodeficiencies. Although the types of infections after transplantation are similar in general among all recipients of these procedures, some differences exist between patients depending on the type of transplantation performed, the type and amount of immunosuppression given, and the child's preexisting immunity to specific pathogens.

Stem Cell Transplantation

Infections following HSCT can be classified as occurring during the **pretransplantation period, preengraftment period** (0-30 days after transplantation), **postengraftment period** (30-100 days), or **late posttransplantation period** (>100 days). Specific defects in host defenses predisposing to infection vary within each of these periods (Table 178-4). Neutropenia and abnormalities in cell-mediated and humoral immune function occur predictably during specific periods of time following transplantation. In contrast, breaches of anatomic barriers caused by indwelling catheters and mucositis secondary to radiation or chemotherapy create defects in host defenses that may be present any time following transplantation.

Pretransplantation Period

Children come to HSCT with a heterogeneous history of underlying diseases, chemotherapy exposure, degree of immunosuppression, and previous infections. Approximately 12% of all infections among adult HSCT recipients occur during the pretransplantation period. These infections are often caused by aerobic Gram-negative bacilli and manifest as localized infections of the skin, soft tissue, and urinary tract. Importantly, the development of infection during this period does not delay or adversely affect the success of engraftment.

Preengraftment Period

Bacterial infections predominate in the preengraftment period (0-30 days). Bacteremia is the most common documented infection and occurs in as many as 50% of all HSCT recipients during the 1st 30 days following transplantation. Bacteremia is typically associated with the presence of either mucositis or an indwelling catheter, but may also be seen with pneumonia. Similarly, more than 40% of children undergoing HSCT experienced 1 or more infections in the preengraftment period. Gram-positive cocci, Gram-negative bacilli, yeast, and, less commonly, other fungi cause infection during this period. *Aspergillus* has been identified in 4-20% of HSCT recipients, most often after 3 wk of neutropenia. Infections caused by the emerging fungal pathogens *Fusarium* and *Pseudallescheria boydii* are associated with the prolonged neutropenia during the preengraftment period.

Viral infections also occur during the preengraftment period. Among adults, reactivation of herpes simplex virus is the most common viral disease observed, but this is less common among children, which is likely related to absence of the virus in the recipient before HSCT. A history of herpes simplex infection or seropositivity indicates the need for prophylaxis. Nosocomial exposure to community-acquired viral pathogens, including respiratory syncytial virus (RSV), influenza virus, adenovirus, and rotavirus, represents another important source of infection during this period. There is growing evidence that community-acquired viruses cause increased morbidity and mortality for HSCT

recipients during this period. Adenovirus is a particularly important viral pathogen that can occur early, although it typically presents after engraftment.

Postengraftment Period

The predominant defect in host defenses in the postengraftment period is altered cell-mediated immunity. Accordingly, organisms historically categorized as opportunistic pathogens predominate during this period. The risk is especially accentuated 50-100 days after transplantation when host immunity is lost and donor immunity is not yet established. *P. jiroveci* presents during this period if patients are not maintained on appropriate prophylaxis. Reactivation of *T. gondii,* a rare cause of disease among HSCT recipients, can also occur after engraftment. Hepatosplenic candidiasis often presents during the postengraftment period, although seeding likely occurred during the neutropenic phase.

CMV is an important cause of morbidity and mortality among HSCT recipients. Unlike patients undergoing solid-organ transplantation where primary infection from the donor causes the greatest harm, CMV reactivation in an HSCT recipient whose donor is naïve to the virus can cause severe disease. Disease risk from CMV after HSCT is also increased in recipients of matched unrelated T cell–depleted transplants and those who suffer from graft-versus-host disease. **Adenovirus** is another important viral pathogen; it has been recovered from up to 5% of adult and pediatric HSCT recipients and causes invasive disease in approximately 20% of cases. Children receiving matched unrelated donor organs or unrelated cord blood cell transplants have an incidence of adenovirus infection as high as 14% during this early postengraftment period. **Polyomaviruses** such as BK virus have been increasingly recognized as a cause of renal dysfunction and hemorrhagic cystitis after bone marrow transplantation. Infections with other herpesviruses (Epstein-Barr virus [EBV] and human herpesvirus 6), as well as community-acquired pathogens, are associated with excess morbidity and mortality during this period, similar to the preengraftment period.

Late Posttransplantation Period

Infection is unusual after 100 days in the absence of chronic graft-versus-host disease. However, the presence of chronic graft-versus-host disease significantly affects anatomic barriers and is associated with defects in humoral, splenic, and cell-mediated immune function (see Chapter 137). Viral infections, including primary infection with or reactivation of varicella-zoster virus, are responsible for more than 40% of infections during this period. Bacterial infections, particularly of the upper and lower respiratory tract, account for approximately 30% of infections. These may be associated with deficiencies in immunoglobulin production, especially IgG_2. Fungal infections account for <20% of confirmed infections during the late posttransplantation period.

Solid-Organ Transplantation

Factors predisposing to infection after organ transplantation include those that either existed before transplantation or are secondary to intraoperative events or posttransplantation therapies (Table 178-5). Some of these additional risks cannot be prevented, and some risks acquired during or after the operation depend on decisions or actions of members of the transplant team. Similar to other children who have undergone surgical procedures, surgical site infections are a frequent cause of infection early after transplantation. Beyond this, the need for immunosuppressive agents to prevent rejection is the major factor predisposing to infection following transplantation. Despite efforts to optimize immunosuppressive regimens to prevent or treat rejection with minimal impairment of immunity, all current regimens interfere with the ability of the immune system to prevent infection. The primary target of the majority of these immunosuppressive agents is the cell-mediated immune system, but regimens can and do impair many other aspects of the transplant recipient's immune system as well.

Timing

The timing of specific types of infections is generally predictable, regardless of which organ is transplanted (Table 178-6). Infectious complications typically develop in 1 of 3 time intervals: early (0-30 days after transplantation), intermediate (30-180 days), and late (>180 days); most infections present in the 1st 180 days after transplantation. Table 178-6 should be used as a general guideline to the types of infections encountered but may be modified with the introduction of newer immunosuppressive therapies and by the use of prophylaxis.

Table 178-5 Risk Factors for Infections Following Solid-Organ Transplantation in Children

PRETRANSPLANTATION FACTORS
Age of patient
Underlying disease, malnutrition
Specific organ transplanted
Previous exposures to infectious agents
Previous immunizations
Presence of infection in the donor
INTRAOPERATIVE FACTORS
Duration of transplant surgery
Exposure to blood products
Technical problems
Organisms transmitted with donor organ
POSTTRANSPLANTATION FACTORS
Immunosuppression
Induction immunosuppression
Maintenance immunosuppression
Augmented treatment for rejection
Indwelling catheters
Nosocomial exposures
Community exposures

Early infections are usually the result of a complication of the transplant surgery itself, the unexpected acquisition of a bacterial or fungal pathogen from the donor, or the presence of an indwelling catheter. In contrast, infections during the intermediate period typically result from a complication of the immunosuppression, which tends to be at its greatest intensity during the 1st 6 mo following transplantation. This is the period of greatest risk for infections caused by opportunistic pathogens such as CMV, EBV, and *P. jiroveci.* Anatomic abnormalities, such as bronchial stenosis and biliary stenosis, that develop as a consequence of the transplant surgery can also predispose to recurrent infection in this period.

Infections developing late after transplantation typically result as a consequence of uncorrected anatomic abnormalities, chronic rejection, or exposure to community-acquired pathogens. Acquisition of infection from community-acquired pathogens such as RSV can result in severe infection secondary to the immunocompromised state of the transplant recipient during the early and intermediate periods. Compared with the earlier periods, community-acquired infections in the late period are usually benign, because immunosuppression is typically maintained at significantly lower levels. However, certain pathogens such as varicella-zoster virus and EBV may be associated with severe disease even at this late period.

Bacterial and Fungal Infections

Although there are important graft-specific considerations for bacterial and fungal infections following transplantation, some principles are generally applicable to all transplant recipients. Bacterial and fungal infections following organ transplantation are usually a direct consequence of the surgery, a breach in an anatomic barrier, the presence of a foreign body, or an abnormal anatomic narrowing or obstruction. With the exception of infections related to the use of indwelling catheters, sites of bacterial infection tend to occur at or near the transplanted organ. Infections following abdominal transplantation (liver, intestine, or renal) usually occur in the abdomen or at the surgical wound. The pathogens are typically enteric Gram-negative bacteria, *Enterococcus,* and occasionally *Candida.* Infections following thoracic transplantation (heart, lung) usually occur in the lower respiratory tract or at the surgical wound. Pathogens associated with these infections include *S. aureus* and Gram-negative bacteria.

Table 178-6 Timing of Infectious Complications Following Solid-Organ Transplantation

EARLY PERIOD (0-30 DAYS)
Bacterial Infections
Gram-negative enteric bacilli
• Small bowel, liver, neonatal heart
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-positive organisms
• All transplant types
Fungal Infections
All transplant types
Viral Infections
Herpes simplex virus
• All transplant types
Nosocomial respiratory viruses
• All transplant types
MIDDLE PERIOD (1-6 MO)
Viral Infections
Cytomegalovirus
• All transplant types
• Seronegative recipient of seropositive donor
Epstein-Barr virus
• All transplant types (small bowel highest risk group)
• Seronegative recipient
Varicella-zoster virus
• All transplant types
• Opportunistic infections
Pneumocystis jiroveci
• All transplant types
Toxoplasma gondii
• Seronegative recipient of cardiac transplant from a seropositive donor
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
Gram-negative enteric bacilli
• Small bowel
LATE PERIOD (>6 MO)
Viral Infections
Epstein-Barr virus
• All transplant types, but less risk than middle period
Varicella-zoster virus
• All transplant types
Community-acquired viral infections
• All transplant types
Bacterial Infections
Pseudomonas, Burkholderia, Stenotrophomonas, Alcaligenes
• Cystic fibrosis lung
• Lung transplants with chronic rejection
Gram-negative bacillary bacteremia
• Small bowel
Fungal Infections
Aspergillus
• Lung transplants with chronic rejection

Adapted from Green M, Michaels MG: Infections in solid organ transplant recipients. In Long SS, Pickering L, Prober C, editors: Principles and practice of pediatric infectious disease, *ed 4. New York, 2012, WB Saunders.*

Patients undergoing lung transplantation for cystic fibrosis experience a particularly high rate of infectious complications, because they are often colonized with *P. aeruginosa* or *Aspergillus* before transplantation. Even though the infected lungs are removed, the sinuses and upper airways remain colonized with these pathogens, and subsequent reinfection of the transplanted lungs can occur. Children receiving organ transplants are often hospitalized for long periods and receive many antibiotics; thus, recovery of bacteria with multiple antibiotic resistance patterns is common after all types of organ transplantation. Infections caused by *Aspergillus* are less common but occur after all types of organ transplantation and are associated with high rates of morbidity and mortality.

Viral Infections

Viral pathogens, especially herpesviruses, are a major source of morbidity and mortality following solid organ transplantation. In addition, BK virus is a major cause of renal disease following kidney transplantation. The patterns of disease associated with individual viral pathogens are generally similar among all organ transplant recipients. However, the incidence, mode of presentation, and severity differ according to type of organ transplanted and, for many viral pathogens, pretransplant serologic status of the recipient.

Viral pathogens can be generally categorized as latent pathogens, which cause infection through reactivation in the host or via acquisition from the donor (e.g., CMV and EBV), or as community-acquired viruses (e.g., RSV). For CMV and EBV, primary infection occurring after transplantation is associated with the greatest degree of morbidity and mortality. The highest risk is seen in a naïve host who receives an organ from a donor who previously was infected with 1 of these viruses. This "mismatched" state is frequently associated with severe disease. However, even if the donor is negative for CMV and EBV, primary infection can be acquired from a close contact or via blood products. Secondary infections (reactivation of a latent strain within the host or superinfection with a new strain) tend to result in milder illness unless the patient is highly immunosuppressed, which can occur in the setting of treatment of significant rejection.

CMV is one of the most commonly recognized transplant viral pathogens. Disease from CMV has decreased significantly with the use of preventive strategies including antiviral prophylaxis as well as viral load monitoring to inform preemptive antiviral therapy. Clinical manifestations of CMV disease can range from a syndrome of fatigue and fever to disseminated disease that most often affects the liver, lungs, and gastrointestinal tract.

Infection caused by EBV is another important complication of solid-organ transplantation. Clinical symptoms range from a mild mononucleosis syndrome to disseminated **posttransplant lymphoproliferative disorder**. Posttransplant lymphoproliferative disorder is more common among children than adults because primary EBV infection in the immunosuppressed host is more likely to lead to uncontrolled proliferative disorders, including posttransplant lymphoma.

Other viruses, such as adenovirus, have the capacity to be donor associated, but appear to be less common. The unexpected development of donor-associated viral pathogens, including hepatitis B virus, hepatitis C virus, and HIV, is rare today owing to intensive donor screening.

Community-acquired viruses, including those associated with respiratory tract infection (RSV, influenza virus, adenovirus, and parainfluenza) and gastrointestinal infection (enteroviruses, rotavirus), can cause important disease in children following organ transplantation. In general, risk factors for more-severe infection include young age, acquisition of infection early after transplantation, and augmented immune suppression. Infection in the absence of these risk factors typically results in a clinical illness that is comparable with that seen in immunocompetent children. However, some community-acquired viruses, such as adenovirus, can be associated with graft dysfunction even when acquired late after transplantation.

Opportunistic Pathogens

Children undergoing solid-organ transplantation are also at risk for symptomatic infections from pathogens that do not usually cause clinical disease in immunocompetent hosts. Although these most commonly present in the intermediate period, these infections can also occur late in patients requiring prolonged and high levels of immunosuppression. *P. jiroveci* is a well-recognized cause of pneumonia following solid-organ transplantation, although routine prophylaxis has essentially eliminated this problem. *T. gondii* can complicate cardiac transplantations because of tropism of the organism for cardiac muscle and risk for donor transmission; less commonly it complicates other types of organ transplantation.

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178.3 Prevention of Infection in Immunocompromised Persons

Marian G. Michaels and Michael Green

Infections cannot be completely prevented in children who have defects in one or more arms of their immune system, although some measures can decrease the risks for infection. Replacement immunoglobulin is a benefit to children with primary B-cell deficiencies. Interferon-γ, trimethoprim-sulfamethoxazole, and oral antifungal agents reduce the number of infections occurring in children with chronic granulomatous disease. Children who have depressed cellular immunity resulting from primary diseases, advanced HIV infection, or immunosuppressive medications benefit from prophylaxis against *P. jiroveci*. Immunizations prevent many infections and are particularly important for children with compromised immune systems. When possible, immunizations should be administered before any treatment that would compromise the child's immune system.

Although immunodeficient children are a heterogeneous group, some principles of prevention are generally applicable. The use of inactivated vaccines does not lead to an increased risk for adverse effects, although their efficacy may be reduced due to an impaired immune response. In most cases, children with immunodeficiencies should receive all of the recommended inactivated vaccines. Live-attenuated virus vaccinations can cause disease in some children with immunologic defects, and therefore alternative immunizations should be used whenever possible, such as inactivated influenza vaccine rather than live virus attenuated influenza vaccine. In general, live virus vaccines should not be used in children with primary T-cell abnormalities; efforts should be made to ensure that close contacts are all immunized to decrease the risk of exposure. In some instances in which wild-type viral infection can be severe, immunizations, even with live virus vaccine, are warranted in the immunosuppressed child. For example, children with HIV infection and a CD4 percentage of >15% should receive vaccinations against measles and varicella. Some vaccines should be given to children with immunodeficiencies in addition to routine vaccinations. As an example, children with asplenia or splenic dysfunction should receive meningococcal vaccine and both the polysaccharide pneumococcal vaccine and the conjugate pneumococcal vaccine. Influenza vaccination is recommended for immunocompromised children as well as all household contacts to minimize risk for transmission to the immunocompromised child.

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Chapter 179

Infection Associated with Medical Devices

Joshua Wolf and Patricia M. Flynn

Use of implanted synthetic and prosthetic devices has revolutionized pediatric practice by providing long-term venous access, limb-salvage surgery, and successful treatment of hydrocephalus, urinary retention, and renal failure. However, infectious complications of these devices remain a major concern. These infections are related to the development of biofilms, organized communities of microorganisms protected from the immune system and antimicrobial therapy, on the device surface. A number of factors are important to the development of infection, including the host susceptibility, device composition, duration of implantation, and exposure to colonizing organisms.

INTRAVASCULAR ACCESS DEVICES

Intravascular access devices range from short, stainless steel needles or plastic cannulae inserted for brief periods to multilumen implantable synthetic plastic catheters that are expected to remain in use for years. Infectious complications include local skin and soft tissue infections such as exit site, tunnel, and device-pocket infections, and **catheter-related bloodstream infections (CRBSIs).** The use of central venous devices has improved the quality of life of high-risk patients but has also increased the risk of infection.

Catheter Types

Short-term peripheral cannulae are most commonly used in pediatric patients, and infectious complications occur infrequently. The rate of peripheral CRBSIs in children is <0.15%. Patient age <1 yr, duration of use for longer than 144 hr, and some infusates are associated with increased risk for catheter-related infection. Catheter-associated phlebitis is more common (1-6%) but is rarely infective and can be treated conservatively.

Central venous catheters (CVCs), which terminate in a central vein such as the superior vena cava or inferior vena cava, are widely used in both adults and pediatric patients and are responsible for the majority of catheter-related infections. These catheters are commonly used in critically ill patients, including neonates, who have many other risk factors for nosocomial infection. Patients in an intensive care unit with a CVC in place have a 5-fold greater risk for developing a nosocomial bloodstream infection than those without.

The use of **peripherally inserted central catheters,** which are inserted into a peripheral vein and terminate in a central vein, has increased in pediatric patients. Infection rates seem to be similar to long-term tunneled CVCs (~2/1,000 days), but other complications such as fracture, dislodgement, and occlusion are more common.

When prolonged intravenous access is required, a cuffed silicone rubber (Silastic) or polyurethane catheter may be inserted into the superior vena cava through the subclavian, cephalic, or jugular vein. The extravascular segment of the catheter passes through a subcutaneous tunnel before exiting the skin, usually on the superior aspect of the chest (Broviac or Hickman catheter). A cuff around the catheter near the exit site induces a fibrotic reaction to seal the tunnel. Totally implanted devices also include a subcutaneous reservoir or port with a self-sealing silicone septum immediately under the skin that permits repeated percutaneous needle access.

The incidence of local (exit site, tunnel, and pocket) infection with long-term catheters is 0.2-2.8/1,000 catheter-days. The incidence of Broviac or Hickman CRBSI is 0.5-11.0/1,000 catheter days, whereas that for implantable devices is 0.3-1.8/1,000 catheter-days. The risk for CRBSI is increased among premature infants, young children, and patients receiving total parenteral nutrition.

Catheter-Associated Skin and Soft Tissue Infection

A number of local infections can occur in the presence of a CVC. The **clinical manifestations** of local infection include erythema, tenderness, and purulent discharge at the exit site or along the subcutaneous tunnel tract of the catheter. **Exit-site infection** denotes infection localized to the exit site, without significant tracking along the tunnel, often with purulent discharge. **Tunnel-tract infection** indicates infection in the subcutaneous tissues tracking along a tunneled catheter, which may also include serous or serosanguineous discharge from a draining sinus along the path. **Pocket infection** indicates suppurative infection of a subcutaneous pocket containing a totally implanted device. Bloodstream infection may coexist with local infection.

The diagnosis of local infection is established clinically, but a gram-stained smear and culture of any exit-site drainage should be performed to identify the microbiologic cause. The source is usually contamination by skin or gastrointestinal flora, and the most common organisms are *S. aureus*, coagulase-negative staphylococci,

P. aeruginosa, Candida spp., and mycobacteria. Green discharge is strongly suggestive of mycobacterial infection and appropriate stains and culture should be performed.

Treatment of local infection related to a short-term peripheral cannula or CVC should include device removal. Exit-site infection may resolve with device removal alone, but systemic symptoms should be managed with antimicrobial therapy as recommended below for treatment of CRBSI. In the case of long-term CVCs, exit-site infections usually respond to local care with topical or systemic antibiotics alone. However, tunnel or pocket infections require removal of the catheter and systemic antibiotic therapy in most cases. When a CVC is removed as a result of tunnel infection, the cuff should also be removed and sent for culture if possible. In cases of mycobacterial infection, wide surgical debridement of the tissues is usually required for cure.

Catheter-Related Bloodstream Infection

CRBSI occurs when microorganisms attached to the CVC are shed into the bloodstream leading to bacteremia. On the device, the organisms are embedded in biofilms as organized communities. Colonization may be present even in the absence of symptoms or positive cultures.

Organisms may contaminate the external surface of the CVC during insertion, or the intraluminal surface through handling of the catheter hub or contaminated infusate. Most cases of CRBSI appear to be caused by intraluminal colonization, but external colonization may play a greater role in infections related to recently inserted (<30 days) catheters. Gram-positive cocci predominate, with around half of infections caused by coagulase-negative staphylococci. Gram-negative enteric bacteria are isolated in approximately 20-30% of episodes, and fungi account for 5-10% of episodes.

Fever without an identifiable focus is the most common clinical presentation of CRBSI; local soft tissue symptoms and signs are usually absent. Onset of fever or rigors during or soon after flushing of a catheter is highly suggestive of CRBSI. Symptoms and signs of complicated infection, such as septic thrombophlebitis, endocarditis, or ecthyma gangrenosum, may also be present.

Blood cultures collected prior to the beginning of antibiotic therapy are generally positive from both the CVC and peripheral blood. It is important not to collect cultures unless infection is suspected, as blood-culture contamination may occur and can lead to inappropriate therapy. Blood culture should be collected from at least 2 sites, preferably including all lumens of a CVC *and* the peripheral blood, before initiation of antibiotic therapy to help interpret positive cultures with common skin contaminants.

Tests to differentiate CRBSI from other sources of bacteremia in the presence of a CVC include culture of the catheter tip, quantitative blood cultures, or **differential time to positivity** of blood cultures drawn from different sites. Definitive diagnosis of CRBSI can be important to identify those patients who might benefit from catheter removal or adjunctive therapy. Although CVC tip culture can identify CRBSI, it precludes salvage of the catheter. The most readily available technique to confirm CRBSI without catheter removal is calculation of differential time to positivity between blood cultures drawn through a catheter and from a peripheral vein or separate lumen. During CRBSI, blood obtained through the responsible lumen will usually indicate growth at least 2-3 hr before peripheral blood or uncolonized lumens because of a higher intraluminal microorganism burden. Identical volumes of blood must be collected simultaneously from each site and a continuously monitored blood culture system is required. Specificity of this test is good (94-100%), and sensitivity is good when a peripheral blood culture is available (~90%) but poorer when comparing 2 lumens of a CVC (64%). Where available, quantitative blood culture showing at least a 3-fold higher number of organisms from central compared with peripheral blood is similarly diagnostic.

Treatment of CRBSI related to **long-term vascular access devices** (Hickman, Broviac, totally implantable devices) with systemic antibiotics is successful for many bacterial infections without removal of the device. Antibiotic therapy should be directed to the isolated pathogen and given for a total of 10-14 days from the date of blood culture clearance. Until identification and susceptibility testing are available, empiric therapy, based on local antimicrobial susceptibility data and usually including vancomycin plus an antipseudomonal aminoglycoside (e.g., gentamicin), penicillin (e.g., piperacillin-tazobactam), or cephalosporin (e.g., ceftazidime or cefepime) is indicated. An echinocandin should be initiated if fungemia is suspected. **Antibiotic lock or dwell therapy,** with administration of solutions of high concentrations of antibiotics or ethanol that remain in the catheter for up to 24 hr, might improve outcome when used as an adjuvant to systemic therapy and appear safe, but insufficient data are available to strongly recommend their use. If blood cultures remain positive after 72 hr of appropriate therapy, or if a patient deteriorates clinically, the device should be removed. Failure of CRBSI salvage therapy is very common in infections caused by *S. aureus* (~50%), *Candida* spp. (>70%), and *Mycobacterium* spp. (>70%), although some case reports of cure with antimicrobial lock therapy are promising. Other indications for removing a long-term catheter include severe sepsis, suppurative thrombophlebitis, and endocarditis. Prolonged therapy (4-6 wk) is indicated for persistent bacteremia or fungemia despite catheter removal. The decision to attempt catheter salvage should weigh the risk and clinical impact of persistent or relapsed infection against the risk of surgical intervention.

CRBSI may be complicated by other intravascular infections such as septic thrombophlebitis or endocarditis. Presence of these conditions may be suggested by preexisting risk factors (such as congenital heart disease), signs and symptoms, or persistent bacteremia or fungemia 72 hr after device removal and appropriate therapy. Screening for these complications in otherwise low-risk children, even those with *S. aureus* infection, is not recommended, as the overall frequency is low and the tests can be difficult to interpret and may lead to inappropriate therapy.

Prevention of Infection

Catheters should routinely be removed as soon as they are no longer needed. Although prevalence of infection increases with prolonged duration of catheter use, routine replacement of a required CVC, either at a new site or over a guidewire, results in significant morbidity and is not recommended. Optimal prevention of infections related to long-term vascular access devices includes "bundles" of interventions, including meticulous aseptic surgical insertion technique in an operating room–like environment, avoidance of bathing or swimming (except with totally implantable devices), and careful catheter care. Use of antibiotic or ethanol lock solutions, heparin with preservatives, and alcohol-impregnated caps and use of antimicrobial-impregnated or coated catheters may also be appropriate to reduce the risk for catheter-associated bloodstream infections in high-risk populations. Although the Centers for Disease Control and Prevention recommends that short-term peripheral catheters be replaced every 72-96 hr to prevent phlebitis, pediatric data do not support this practice.

CEREBROSPINAL FLUID SHUNTS

Cerebrospinal fluid (CSF) shunting is required for the treatment of many children with hydrocephalus. The usual procedure uses a silicone rubber device with a proximal portion inserted into the ventricle, a unidirectional valve, and a distant segment that diverts the CSF from the ventricles to either the peritoneal cavity (ventriculoperitoneal [VP] shunt) or right atrium (ventriculoatrial [VA] shunt). The incidence of shunt infection ranges from 1-20%, with an average of 10%. The highest rates are reported in young infants, prior shunt infections, and certain etiologies of hydrocephalus. Most infections are a result of intraoperative contamination of the surgical wound by skin flora. Accordingly, coagulase-negative staphylococci are isolated in more than half of the cases. *S. aureus* is isolated in approximately 20% and Gram-negative bacilli in 15% of cases.

Four distinct clinical syndromes have been described: colonization of the shunt, infection associated with wound infection, distal infection with peritonitis, and infection associated with meningitis.

The most common type of infection is colonization of the shunt with symptoms that reflect shunt malfunction as opposed to frank infection. Symptoms associated with colonized VP shunts include lethargy, headache, vomiting, a full fontanel, and abdominal pain. Fever is common but may be <39°C (102.2°F). Symptoms usually occur within months of the surgical procedure. Colonization of a VA shunt results

in more severe systemic symptoms and specific symptoms of shunt malfunction are often absent. Septic pulmonary emboli, pulmonary hypertension, and infective endocarditis are frequently reported complications of VA shunt colonization. Chronic VA shunt colonization may cause hypocomplementemic glomerulonephritis as a consequence of antigen–antibody complex deposition in the glomeruli, commonly called shunt nephritis; clinical findings include hypertension, microscopic hematuria, elevated blood urea nitrogen and serum creatinine levels, and anemia.

Diagnosis is by Gram stain, microscopy, biochemistry, and culture of CSF. CSF should be obtained by direct aspiration of the shunt, as CSF obtained from either lumbar or ventricular puncture is often sterile. It is unusual to observe signs of ventriculitis, and CSF findings can be only minimally abnormal. Blood culture results are usually positive in VA shunt colonization but negative in cases of VP colonization.

Wound infection presents with obvious erythema, swelling, discharge, or dehiscence along the shunt tract and most often occurs within days to weeks of the surgical procedure. *S. aureus* is the most common isolate. In addition to the physical findings, fever is common, and signs of shunt malfunction eventually ensue in most cases.

Distal infection of VP shunts with peritonitis presents with abdominal symptoms, usually without evidence of shunt malfunction. The pathogenesis is likely related to perforation of bowel at the time of VP shunt placement or translocation of bacteria across the bowel wall. Thus, Gram-negative isolates predominate and mixed infection is common. The infecting organisms are often isolated from only the distal portion of the shunt.

Common pathogens responsible for community-acquired meningitis, including *S. pneumoniae, N. meningitidis*, and *H. influenzae* type b, can also cause bacterial meningitis in patients with shunts. The clinical presentation is similar to that for acute bacterial meningitis in other children (see Chapter 602.1).

Treatment of shunt colonization includes removal of the shunt and systemic antibiotic therapy directed against the isolated organisms. After collection of appropriate samples for culture, empiric therapy is usually with vancomycin plus an antipseudomonal agent with relatively good CSF penetration such as ceftazidime or meropenem. Definitive therapy should be directed toward the isolate and account for poor penetration of most antibiotics into the CSF across noninflamed meninges. Accordingly, intraventricular antibiotics may be indicated but are usually reserved unless there is evidence of treatment failure. If the isolate is susceptible, a parenteral antistaphylococcal penicillin with or without intraventricular vancomycin is the treatment of choice. If the organism is resistant to penicillins, systemic vancomycin and possibly intraventricular vancomycin are recommended. In cases of Gram-negative infections, a combination of a third-generation cephalosporin with or without intraventricular aminoglycoside is optimal. When using intraventricular antibiotics, monitoring of CSF levels is necessary to avoid toxicity.

Removal of the colonized device is required for cure, and final replacement should be delayed until clearance of CSF cultures is documented. Many neurosurgeons immediately remove the shunt and place an external ventricular drain to relieve intracranial pressure, with a 2nd-stage shunt replacement once CSF sterilization has been confirmed. Others opt to initially exteriorize the distal end of the shunt, and replace the shunt in a single-stage procedure once CSF cultures remain sterile for 48-72 hr. Daily CSF cultures should be collected until clearance has been documented on 2-3 consecutive specimens, and antibiotics should be continued for at least 10 days after documented sterilization of the CSF. Gram-negative organisms may require a longer duration of therapy (up to 21 days). The CSF white cell count generally increases for the 1st 3-5 days of appropriate therapy and should not prompt concern for treatment failure. Distal shunt infection with peritonitis and wound infection are managed in a similar fashion.

Treatment of bacterial meningitis with typical community-acquired pathogens such as meningococcus or pneumococcus usually requires only systemic antibiotic therapy. Shunt replacement is not required in the absence of device malfunction, poor clinical response, persistent CSF culture positivity, or relapse of infection after antibiotic therapy.

Prevention of Infection

Prevention of shunt infection includes meticulous cutaneous preparation and surgical technique. Systemic and intraventricular antibiotics, antibiotic-impregnated shunts, and soaking the shunt tubing in antibiotics are used to reduce the incidence of infection, with varying success. Systemic prophylactic antibiotics given prior to shunt insertion reduce the risk for infection and should be used routinely. Antibiotic-impregnated catheters also appear to reduce the risk of infection, although limited evidence is available, and may be used in high-risk patients where the devices are available.

URETHRAL CATHETERS

Urinary catheters are a frequent cause of nosocomial infection, with about 14 infections per 1,000 admissions. Like other devices, microorganisms adhere to the catheter surface and establish a biofilm that allows proliferation. The physical presence of the catheter reduces the normal host defenses by preventing complete emptying of the bladder, thus providing a medium for growth, distending the urethra, and blocking periurethral glands. Almost all patients catheterized for longer than 30 days develop bacteriuria. The organism burden in catheter-associated urinary tract infection is typically ≥10,000 colony-forming units/mL. Lower thresholds may be used where there is a high index of suspicion, but these episodes may represent colonization rather than infection. Urine culture should only be performed in catheterized patients when infection is suspected, as asymptomatic colonization is ubiquitous and may lead to overtreatment and subsequent development of bacterial resistance. Gram-negative bacilli and *Enterococcus* spp. are the predominant organisms isolated in catheter-related urinary tract infection; coagulase-negative staphylococci are implicated in approximately 15% of cases. Symptomatic urinary tract infections should be treated with antibiotics and catheter removal. Catheter colonization with *Candida* spp. is common but rarely leads to invasive infection, and treatment does not have a long-term impact on colonization. Treatment for asymptomatic candiduria is therefore not recommended except in neonates, immunocompromised patients, and those with urinary tract obstruction.

Prevention of Infection

All urinary catheters introduce a risk for infection, and their casual use should be avoided. When they are in place, their duration of use should be minimized. Technologic advances have led to development of silver- or antibiotic-impregnated urinary catheters that are associated with lower rates of infection. Prophylactic antibiotics do not significantly reduce the infection rates for long-term catheters but clearly increase the risk for infection with antibiotic resistant organisms.

PERITONEAL DIALYSIS CATHETERS

During the 1st yr of peritoneal dialysis for end-stage renal disease, 65% of children will have 1 or more episodes of peritonitis. Bacterial entry comes from luminal or periluminal contamination of the catheter or by translocation across the intestinal wall. Hematogenous infection is rare. Infections can be localized at the exit site or associated with peritonitis, or both. Organisms responsible for peritonitis include coagulase-negative staphylococci (30-40%), *S. aureus* (10-20%), streptococci (10-15%), *E. coli* (5-10%), *Pseudomonas* spp. (5-10%), other Gram-negative bacteria (5-15%), *Enterococcus* spp. (3-6%), and fungi (2-10%). *S. aureus* is more common in localized exit-site or tunnel-tract infections (42%). Most infectious episodes are caused by a patient's own flora, and carriers of *S. aureus* have increased rates of infection as compared with noncarriers.

The **clinical manifestations** of peritonitis may be subtle and include low-grade fever with mild abdominal pain or tenderness. Cloudy peritoneal dialysis fluid may be the first and predominant sign. With peritonitis, the peritoneal fluid cell count is usually >100 white blood cells/μL. When peritonitis is suspected, the effluent dialysate should be submitted for a cell count, Gram stain, and culture. The Gram stain is positive in up to 40% of cases of peritonitis.

Patients with cloudy fluid and clinical symptoms should receive empiric therapy, preferably guided by results of a Gram stain. If no organisms are visualized, vancomycin and either an aminoglycoside or

third or fourth generation cephalosporin with antipseudomonal activity should be given via the intraperitoneal route. Blood levels should be measured for glycopeptides and aminoglycosides. Patients without cloudy fluid and with minimal symptoms may have therapy withheld pending culture results. Once the cause is identified by culture, changes in the therapeutic regimen may be needed. Oral rifampin may be added for *S. aureus* infections. Fungal peritonitis should be treated with a combination of oral flucytosine and intraperitoneal or oral fluconazole. The duration of therapy is a minimum of 14 days, with longer treatment of 21-28 days for episodes of *S. aureus*, *Pseudomonas* spp., and resistant Gram-negative bacteria and of 28-42 days for fungi. Repeat episodes of peritonitis within 4 wk of previous therapy represent "apparently relapsing" peritonitis. If the patient responds to reinstitution of antimicrobial therapy, a course of up to 6 wk should be continued. In all cases, if the infection fails to clear following appropriate therapy or if a patient's condition is deteriorating, the catheter should be removed. Exit-site and tunnel infections may occur independently of peritonitis or may precede it. Appropriate antibiotics should be administered on the basis of Gram stain and culture findings and are typically given systemically only unless peritonitis is also present. Some experts recommend that the peritoneal catheter be removed if *Pseudomonas* or fungal organisms are isolated.

Prevention of Infection

In addition to usual hygienic practices, regular application of mupirocin or gentamicin cream to the catheter exit site reduces exit-site infections and peritonitis. Some practitioners recommend against the use of gentamicin cream because of the risk of infection with gentamicin-resistant bacteria. Systemic antibiotic prophylaxis should be considered at the time of catheter insertion, if there is accidental contamination, and at the time of dental procedures. Antifungal prophylaxis can be considered during antibiotic therapy to prevent fungal infection.

ORTHOPEDIC PROSTHESES

Orthopedic prostheses are used infrequently in children. Infection most often follows introduction of microorganisms at surgery through airborne contamination or direct inoculation; via hematogenous spread; or via contiguous spread from an adjacent infection. Early postoperative infection occurs within 2-4 wk of surgery with typical manifestations that include fever, pain, and local symptoms of wound infection. Rapid assessment, including isolation of the infecting organism by joint aspiration or intraoperative culture, operative debridement, and antimicrobial treatment may allow salvage of the implant if the duration of symptoms is less than 1 mo, the prosthesis is stable, and the pathogen is susceptible to antibiotics. Chronic infection presents >1 mo after surgery and is often caused by organisms of low virulence that contaminated the implant at the time of surgery. Typical manifestations include pain and deterioration in function. Local symptoms such as erythema, swelling, or drainage may also occur. These infections respond poorly to antibiotic treatment and usually require removal of the implant using either a 1- or 2-stage procedure. Surgical debridement of the site with long-term suppressive antibiotic therapy may be considered, but eradication of infection is uncommon. Acute hematogenous infections are most often observed 2 yr or more after surgery. Retention of the prosthesis is sometimes attempted, but there are inadequate long-term data to determine the success rate. If salvage therapy is attempted, prompt debridement and appropriate antibiotic therapy are recommended. As with other long-term implanted devices, the most common organisms are about equally divided between coagulase-negative staphylococci and *S. aureus*. With prior antibiotic therapy, the prosthesis culture may be negative; in these situations, determining 16S ribosomal RNA typing may help identify the organism.

The use of systemic antibiotic prophylaxis, antibiotic-containing bone cement, and operating rooms fitted with laminar airflow all have been proposed as beneficial in reducing infection. To date, results from clinical studies are conflicting.

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Section 3

Antibiotic Therapy

Chapter 180

Principles of Antibacterial Therapy

Mark R. Schleiss

Antibacterial therapy in infants and children presents many challenges. A daunting problem is the paucity of pediatric data regarding pharmacokinetics and optimal dosages; as a consequence, pediatric recommendations are commonly extrapolated from studies in adults. A second challenge is the need for the clinician to consider important differences among various age groups with respect to the pathogenic species responsible for pediatric bacterial infections. Age-appropriate antibiotic dosing and toxicities must be considered, taking into account the developmental status and physiology of infants and children. Finally, the style of usage of antibiotics has some important differences compared with usage in adult patients. Specific antibiotic therapy is optimally driven by a **microbiologic diagnosis,** predicated on isolation of the pathogenic organism from a sterile body site, and supported by antimicrobial susceptibility testing. Given the inherent difficulties that can arise in collecting specimens from pediatric patients, and given the high risk of mortality and disability associated with serious bacterial infections in very young infants, much of pediatric infectious diseases practice is based on a **clinical diagnosis** with **empirical** use of antibacterial agents, administered before or even without eventual identification of the specific pathogen.

Several key considerations influence decisions about the appropriate empirical use of antibacterial agents in infants and children. It is important to know the age-appropriate differential diagnosis with respect to likely pathogens. This information affects the choice of antimicrobial agent and also the dose, dosing interval, and route of administration (oral vs parenteral). A complete history and physical examination, combined with appropriate laboratory and radiographic studies, are necessary to identify specific diagnoses, in turn affecting the choice, dosing, and degree of urgency of administration of antimicrobial agents. The vaccination history may reflect reduced risk for some invasive infections, but not necessarily elimination of risk. The risk of serious bacterial infection in pediatric practice is also affected by the child's immunologic status, which may be compromised by immaturity (neonates), underlying disease, and associated treatments (see Chapter 178). Infections in immunocompromised children may result from bacteria that are not considered pathogenic in immunocompetent children. The presence of foreign bodies also increases the risk of bacterial infections (see Chapter 179). The likelihood of central nervous system (CNS) involvement must be considered in all pediatric patients with serious bacterial infections, because many of the more common bacteremic infections in childhood, including disease caused by *Haemophilus influenzae* type b, pneumococcus, *Salmonella*, and meningococcus, carry a significant risk for hematogenous spread to the CNS.

The patterns of **antimicrobial resistance** in the community and for the potential causative pathogen being empirically treated must also be considered. Resistance to penicillin and cephalosporins is commonplace among strains of *Streptococcus pneumoniae,* often necessitating the use of other classes of antibiotics. Similarly, the striking emergence of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infections has complicated antibiotic choices for

this pathogen. Furthermore, carbapenem-resistant *Enterobacteriaceae* are an increasing problem among hospitalized patients.

Antimicrobial resistance occurs through many modifications of the bacterial genome (Tables 180-1 and 180-2). Mechanisms include enzyme inactivation of the antibiotic, decreased cell membrane permeability to intracellularly active antibiotics, efflux of antibiotics out of the bacteria, protection or alteration of the antibiotic target site, excessive production of the target site, and bypassing the antimicrobial site of action.

Antimicrobial resistance has reached **crisis proportions,** driven by the emergence of new resistance mechanisms (such as carbapenemases) and by overuse of antibiotics, both in healthcare and in other venues, such as agriculture. This increase in antibiotic resistance has rendered some bacterial infections encountered in clinical practice virtually untreatable. Accordingly, there is an urgent need to develop new antimicrobials. In addition, it is important for practitioners to use antibiotics only as necessary, with the narrowest feasible antimicrobial spectrum, to help thwart emergence of resistance. Advocacy for vaccines, particularly conjugate pneumococcal vaccine, can also decrease the selective pressure that excessive antimicrobial use exerts on resistance.

Effective antibiotic action requires achieving therapeutic levels of the drug at the site of infection. Although measuring the level of antibiotic at the site of infection is not always possible, one may measure the serum level and use this level as a surrogate marker for achievement of the desired effect at the tissue level. Various target serum levels are appropriate for different antibiotic agents and are assessed by the peak and trough serum levels, and the area under the therapeutic drug level curve (Fig. 180-1). These levels are, in turn, a reflection of the route of administration, drug absorption (IM, PO), volume of distribution, and drug elimination half-life, as well as of drug-drug interactions that might enhance or impede enzymatic inactivation of an antibiotic or result in antimicrobial synergism or antagonism (Fig. 180-2).

Table 180-1 Mechanisms of Resistance to β-Lactam Antibiotics

I. Alter target site (PBP)
  A. Decrease affinity of PBP for β-lactam antibiotic
    1. Modify existing PBP
      a. Create mosaic PBP
        Insert nucleotides obtained from neighboring bacteria (e.g., penicillin-resistant *Streptococcus pneumoniae*)
        Mutate structural gene of PBP(s) (e.g., ampicillin-resistant β-lactamase–negative *Haemophilus influenzae*)
    2. Import new PBP (e.g., mecA in methicillin-resistant *Staphylococcus aureus*)
II. Destroy β-lactam antibiotic
  A. Increase production of β-lactamases, carbapenemases
    1. Acquire more efficient promoter
      a. Mutate existing promoter
      b. Import new promoter
    2. Deregulate control of β-lactamase production
      a. Mutate regulator genes (e.g., ampD in "stably derepressed" *Enterobacter cloacae*)
  B. Modify structure of resident β-lactamase
    1. Mutate structural gene (e.g., extended-spectrum β-lactamases in *Klebsiella pneumoniae*)
  C. Import new β-lactamase(s) with different spectrum of activity
III. Decrease concentration of β-lactam antibiotic inside cell
  A. Restrict its entry (loss of porins)
  B. Pump it out (efflux mechanisms)

PBP, penicillin-binding protein.

Table 180-2 Aminoglycoside-Modifying Enzymes

ENZYMES	USUAL ANTIBIOTICS MODIFIED	COMMON GENERA
PHOSPHORYLATION		
APH(2″)	K, T, G	SA, SR
APH(3′)-I	K	E, PS, SA, SR
APH(3′)-III	K ± A	E, PS, SA, SR
ACETYLATION		
AAC(2′)	G	PR
AAC(3)-I	±T, G	E, PS
AAC(3)-III, -IV, OR-V	K, T, G	E, PS
AAC(6′)	K, T, A	E, PS, SA
ADENYLATION		
ANT(2″)	K, T, G	
ANT(4′)	K, T, A	SA

A, amikacin; AAC, aminoglycoside acetyltransferase; ANT, aminoglycoside nucleotidyltransferase; APH, aminoglycoside phosphotransferase; E, *Enterobacteriaceae*; G, gentamicin; K, kanamycin; PR, *Providencia-Proteus;* PS, pseudomonads; SA, staphylococci; SR, streptococci; T, tobramycin.

AGE- AND RISK-SPECIFIC USE OF ANTIBIOTICS IN CHILDREN

Neonates

The causative pathogens of neonatal infections are typically acquired around the time of delivery. Thus, empirical antibiotic selection must take into account the importance of these pathogens in neonates (see Chapter 109). Among the causes of neonatal sepsis in infants, group B streptococcus is the most common, although intrapartum antibiotic prophylaxis administered to women at increased risk for transmission of this pathogen to the infant has greatly decreased the incidence of this infection in neonates (see Chapter 184). Gram-negative enteric organisms acquired from the maternal birth canal, in particular *Escherichia coli,* are other common causes of neonatal sepsis. Although rare, *Listeria monocytogenes* is also an important pathogen, insofar as it is intrinsically resistant to cephalosporin antibiotics, which are often used as empirical therapy for serious bacterial infections in young children. *Salmonella* species are also being increasingly recognized as important pathogens in infancy. All of these organisms can be associated with meningitis in the neonate; therefore, lumbar puncture should always be considered in the setting of bacteremic infections in this age group, and, if meningitis cannot be excluded, antibiotic management should include agents capable of crossing the blood–brain barrier.

Older Children

Antibiotic choices in toddlers and young children were once driven by the high risk of this age group to invasive disease caused by *H. influenzae* type b (see Chapter 194). With the advent of conjugate vaccines against *H. influenzae* type b, invasive disease has declined dramatically. However, outbreaks of invasive disease still occur, particularly in the setting of parental refusal of vaccines. It is, therefore, still important to utilize antimicrobials that are active against this pathogen in many clinical settings, particularly if meningitis is a consideration. Other particularly important pathogens to be considered in this age group include *E. coli*, *S. pneumoniae, Neisseria meningitidis,* and *S. aureus*. Antimicrobial resistance is commonly exhibited by *S. pneumoniae* and *S. aureus*. Strains of *S. pneumoniae* that are resistant to penicillin and cephalosporin antibiotics are frequently encountered in clinical practice. Similarly, MRSA is highly prevalent in many regions. Resistance of *S. pneumoniae*, as well as MRSA, is a result of mutations that confer alterations in penicillin-binding proteins, the molecular targets of penicillin and cephalosporin activity (see Table 180-1).

Depending on the specific clinical diagnosis, other pathogens that are commonly encountered among older children include *Moraxella catarrhalis,* nontypable strains of *H. influenzae,* and *Mycoplasma pneumoniae,* which cause upper respiratory tract infections and pneumonia; group A streptococcus, which causes pharyngitis, skin and soft-tissue infections, osteomyelitis, septic arthritis, and, rarely, bacteremia with toxic shock syndrome; *Kingella kingae,* which causes bone and joint infections; viridans streptococci and *Enterococcus,* which cause endocarditis; and *Salmonella,* which causes enteritis, bacteremia, osteomyelitis, and septic arthritis. This complexity underscores the

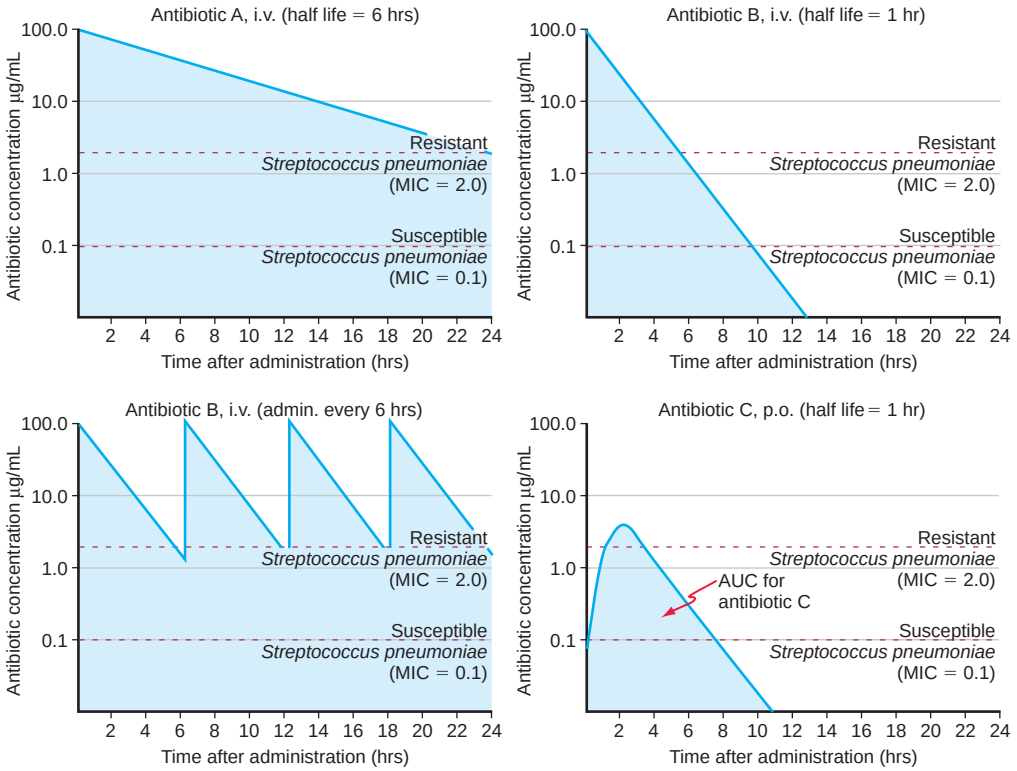

Figure 180-1 The area under the curve *(shaded area)* for different antibiotics. The area under the curve provides a measure of antibiotic exposure to bacterial pathogens. The greatest exposure comes with antibiotics that have a long serum half-life and are administered parenterally (*upper left panel,* antibiotic A). The lowest exposure occurs with oral administration (*lower right panel,* antibiotic C). Dosing of antibiotic B once a day *(upper right panel)* provides far less exposure than dosing the same antibiotic every 6 hr *(lower left panel).* MIC, minimal inhibitory concentration. *(From Pong AL, Bradley JS: Guidelines for the selection of antibacterial therapy in children,* Pediatr Clin North Am *52:869–894, 2005.)*

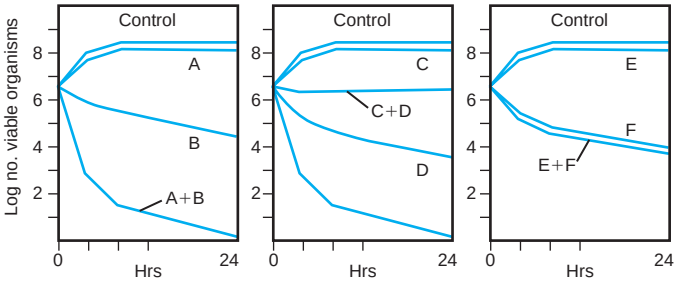

Figure 180-2 Antibacterial effects of antibiotic combinations. *Left:* Curve of A + B illustrates synergism (increased killing). *Center:* Curve of C + D illustrates antagonism (D is less effective when C is added). *Right:* Curve of E + F illustrates indifference, or additive effect (addition of E to F has no effect on F). *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2005, Elsevier, p. 247.)*

importance of formulation of a clear clinical diagnosis, including an assessment of the severity of the infection, in concert with knowledge of local susceptibility patterns in the community.

Immunocompromised and Hospitalized Patients

It is important to consider the risks associated with immunocompromising conditions (malignancy, solid-organ, or hematopoietic stem cell transplantation) and the risks conferred by conditions leading to prolonged hospitalization (intensive care, trauma, burns). Serious viral infections, particularly with influenza, can also predispose to invasive bacterial infections, especially with *S. aureus*. Immunocompromised children are predisposed to develop a wide range of bacterial, viral, fungal, or parasitic infections. Prolonged hospitalization can lead to nosocomial infections, often associated with indwelling lines and catheters and commonly caused by Gram-negative enteric organisms. In addition to the usual bacterial pathogens, *Pseudomonas aeruginosa* and enteric organisms, including *E. coli, Klebsiella pneumoniae, Enterobacter,* and *Serratia*, are important considerations as opportunistic pathogens in these settings. Selection of appropriate antimicrobials is challenging because of the diverse causes and scope of antimicrobial resistance exhibited by these organisms. Many strains of enteric organisms have resistance because of extended spectrum β-lactamases (see Table 180-1). Class B metallo-β-lactamases that hydrolyze all β–lactam antibiotics except aztreonam are increasingly being described. A worrisome development is the increasing reports of carbapenemases in *Enterobacteriaceae*. Carbapenemase-producing *Enterobacteriaceae* are different from other multidrug-resistant microorganisms in that they are susceptible to few (if any) antibacterial agents. *P. aeruginosa* encodes proteins that function as efflux pumps to eliminate multiple classes of antimicrobials from the cytoplasm or periplasmic space. In addition to these Gram-negative pathogens, infections caused by *Enterococcus faecalis* and *Enterococcus faecium* are inherently difficult to treat. These organisms may cause urinary tract infection or infective endocarditis in immunocompetent children and may be responsible for a variety of syndromes in immunocompromised patients, especially in the setting of prolonged intensive care. The emergence of infections caused by **vancomycin-resistant *Enterococcus* (VRE)** has further complicated antimicrobial selection in high-risk patients and has necessitated the development of newer antimicrobials that target these highly resistant Gram-positive bacteria. Although experience with many of these newer agents in the management of complex hospitalized pediatric patients is limited, they are important agents to be aware of (described below).

Infections Associated with Medical Devices

A special situation affecting antibiotic use is the presence of an indwelling medical device, such as a venous catheter, ventriculoperitoneal shunt, stent, or other catheter (see Chapter 179). In addition to *S. aureus,* coagulase-negative staphylococci are also a major

consideration. Coagulase-negative staphylococci seldom cause serious disease without a risk factor such as an indwelling catheter. Empirical antibiotic regimens must take this risk into consideration. In addition to appropriate antibiotic therapy, removal or replacement of the colonized prosthetic material is commonly required for cure.

ANTIBIOTICS COMMONLY USED IN PEDIATRIC PRACTICE

Table 180-3 lists commonly used antibiotics.

Penicillins

Although there has been ever-increasing emergence of resistance to penicillins, these agents remain valuable and are commonly used for management of many pediatric infectious diseases.

Penicillins remain the drugs of choice for pediatric infections caused by group A and group B *Streptococcus*, *Treponema pallidum* (syphilis), *L. monocytogenes*, and *N. meningitidis*. The **semisynthetic penicillins** (nafcillin, cloxacillin, dicloxacillin) are useful for management of susceptible staphylococcal infections, although the increasing incidence of MRSA has limited the usefulness of these drugs. The **aminopenicillins** (ampicillin, amoxicillin) were developed to provide broad-spectrum activity against Gram-negative organisms, including *E. coli* and *H. influenzae*, but the emergence of resistance has limited their utility in many clinical settings. The **carboxypenicillins** (carbenicillin, ticarcillin) and **ureidopenicillins** (piperacillin, mezlocillin, azlocillin) also have bactericidal activity against most strains of *P. aeruginosa*.

Text continued on p. 1311

Table 180-3 Antibacterial Medications (Antibiotics)*

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Amikacin sulfate Amikin Injection: 50 mg/mL, 250 mg/mL	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *Escherichia coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days: weight 1,200-2,000 g: 7.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 10 mg/kg q 12 hr IV or IM; postnatal age >7 days: weight 1,200-2,000 g IV or IM: 7.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 10 mg/kg q 8 hr IV or IM Children: 15-25 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 15 mg/kg/24 hr divided q 8-12 hr IV or IM	*Cautions:* Anaerobes, *Streptococcus* (including *S. pneumoniae*) are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 25-40 mg/L; trough <10 mg/L
Amoxicillin Amoxil, Polymox Capsule: 250, 500 mg Tablet: chewable: 125, 250 mg Suspension: 125 mg/5 mL, 250 mg/5 mL Drops: 50 mg/mL	**Penicillinase-susceptible β-lactam: Gram-positive pathogens except *Staphylococcus; Salmonella, Shigella, Neisseria, E. coli,* and *Proteus mirabilis*** Children: 20-50 mg/kg/24 hr divided q 8-12 hr PO. Higher dose of 80-90 mg/kg 24 hr PO for otitis media Adults: 250-500 mg q 8-12 hr PO Uncomplicated gonorrhea: 3 g with 1 g probenecid PO	*Cautions:* Rash, diarrhea, abdominal cramping. Drug eliminated renally *Drug interaction:* Probenecid
Amoxicillin-clavulanate Augmentin Tablet: 250, 500, 875 mg Tablet, chewable: 125, 200, 250, 400 mg Suspension: 125 mg/5 mL, 200 mg/5 mL, 250 mg/5 mL, 400 mg/5 mL	**β-Lactam (amoxicillin) combined with β-lactamase inhibitor (clavulanate) enhances amoxicillin activity against penicillinase-producing bacteria. *S. aureus* (not methicillin-resistant organism), *Streptococcus, Haemophilus influenzae, Moraxella catarrhalis, E. coli, Klebsiella, Bacteroides fragilis*** Neonates: 30 mg/kg/24 hr divided q 12 hr PO Children: 20-45 mg/kg 24 hr divided q 8-12 hr PO. Higher dose 80-90 mg/kg/24 hr PO for otitis media	*Cautions:* Drug dosed on amoxicillin component. May cause diarrhea, rash. Drug eliminated renally *Drug interaction:* Probenecid *Comment:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae*
Ampicillin Polycillin, Omnipen Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL Injection	**β-Lactam with same spectrum of antibacterial activity as amoxicillin** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 50 mg/kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr divided q 8 hr IV or IM). Postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV or IM q 12 hr (meningitis: 100 mg/kg/24 hr divided q 12 hr IV or IM); weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr divided q 8 hr IV or IM); weight >2,000 g: 100 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6 hr IV or IM) Children: 100-200 mg/kg/24 hr divided q 6 hr IV or IM (meningitis: 200-400 mg/kg/24 hr divided q 4-6 hr IV or IM) Adults: 250-500 mg q 4-8 hr IV or IM	*Cautions:* Less bioavailable than amoxicillin, causing greater diarrhea *Drug interaction:* Probenecid
Ampicillin-sulbactam Unasyn Injection	**β-Lactam (ampicillin) and β-lactamase inhibitor (sulbactam) enhances ampicillin activity against penicillinase-producing bacteria: *S. aureus, H. influenzae, M. catarrhalis, E. coli, Klebsiella, B. fragilis*** Children: 100-200 mg/kg/24 hr divided q 4-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max daily dose: 8 g)	*Cautions:* Drug dosed on ampicillin component. May cause diarrhea, rash. Drug eliminated renally *Note:* Higher dose may be active against penicillin-tolerant/resistant *S. pneumoniae* *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Azithromycin Zithromax Tablet: 250 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Azalide antibiotic with activity against *S. aureus*, *Streptococcus*, *H. influenzae*, *Mycoplasma*, *Legionella*, *Chlamydia trachomatis*** Children: 10 mg/kg PO on day 1 (max dose: 500 mg) followed by 5 mg/kg PO q 24 hr for 4 days Group A streptococcus pharyngitis: 12 mg/kg/24 hr PO (max dose: 500 mg) for 5 days. Adults: 500 mg PO day 1 followed by 250 mg for 4 days Uncomplicated *C. trachomatis* infection: single 1 g dose PO	*Note:* Very long half-life permitting once-daily dosing. No metabolic-based drug interactions (unlike erythromycin and clarithromycin), limited gastrointestinal distress. Shorter-course regimens (e.g., 1-3 days) under investigation. 3 day, therapy (10 mg/kg/24 hr × 3 days) and single-dose therapy (30 mg/kg): use with increasing frequency (not for streptococcus pharyngitis)
Aztreonam Azactam Injection	**β-Lactam (monobactam) antibiotic with activity against Gram-negative aerobic bacteria, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight <1,200 g: 60 mg/kg/24 hr divided q 12 hr IV or IM; weight 1,200-2,000 g: 90 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 120 mg/kg/24 hr divided q 6-8 hr IV or IM Children: 90-120 mg/kg/24 hr divided q 6-8 hr IV or IM. For cystic fibrosis up to 200 mg/kg/24 hr IV Adults: 1-2 g IV or IM q 8-12 hr (max dose: 8 g/24 hr)	*Cautions:* Rash, thrombophlebitis, eosinophilia. Renally eliminated *Drug interaction:* Probenecid
Carbenicillin Geopen Injection Geocillin oral tablet	**Extended-spectrum penicillin (remains susceptible to penicillinase destruction) active against *Enterobacter*, indole-positive *Proteus*, and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight ≤2,000 g: 225 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 300 mg/kg/24 hr divided q 6 hr IV or IM; >7 days: 300-400 mg/kg/24 hr divided q 6 hr IV or IM Children: 400-600 mg/kg/24 hr divided q 4-6 hr IV or IM	*Cautions:* Painful given intramuscularly; rash; each gram contains 5.3 mEq sodium. Interferes with platelet aggregation at high doses, increases in liver transaminase levels. Renally eliminated. Oral tablet for treatment of urinary tract infection only *Drug interaction:* Probenecid
Cefaclor Ceclor Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL, 375 mg/5 mL	**Second-generation cephalosporin active against *S. aureus*, *Streptococcus* including *S. pneumoniae*, *H. influenzae*, *E. coli*, *Klebsiella*, and *Proteus*** Children: 20-40 mg/kg/24 hr divided q 8-12 hr PO (max dose: 2 g) Adults: 250-500 mg q 6-8 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia) with high incidence of serum sickness reaction. Renally eliminated *Drug interaction:* Probenecid
Cefadroxil Duricef, Ultracef Capsule: 500 mg Tablet: 1,000 mg Suspension: 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL	**First-generation cephalosporin active against *S. aureus*, *Streptococcus*, *E. coli*, *Klebsiella*, and *Proteus*** Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 250-500 mg q 8-12 hr PO	*Cautions:* β-lactam safety profile (rash, eosinophilia). Renally eliminated. Long half-life permits q 12-24 hr dosing *Drug interaction:* Probenecid
Cefazolin Ancef, Kefzol Injection	**First-generation cephalosporin active against *S. aureus*, *Streptococcus*, *E. coli*, *Klebsiella*, and *Proteus*** Neonates: Postnatal age ≤7 days 40 mg/kg/24 hr divided q 12 hr IV or IM; >7 days 40-60 mg/kg/24 hr divided q 8 hr IV or IM Children: 50-100 mg/kg/24 hr divided q 8 hr IV or IM Adults: 0.5-2g q 8 hr IV or IM (max dose: 12 g/24 hr)	*Caution:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS *Drug interaction:* Probenecid
Cefdinir Omnicef Capsule: 300 mg Oral suspension: 125 mg/5 mL	**Extended-spectrum, semisynthetic cephalosporin** Children 6 mo-12 yr: 14 mg/kg/24 hr in 1 or 2 doses PO (max dose: 600 mg/24 hr) Adults: 600 mg q 24 hr PO	*Cautions:* Reduce dosage in renal insufficiency (creatinine clearance <60 mL/min). Avoid taking concurrently with iron-containing products and antacids because absorption is markedly decreased; take at least 2 hr apart *Drug interaction:* Probenecid
Cefepime Maxipime Injection	**Expanded-spectrum, fourth-generation cephalosporin active against many Gram-positive and Gram-negative pathogens, including *P. aeruginosa* many multidrug-resistant pathogens** Children: 100-150 mg/kg/24 hr q 8-12 hr IV or IM Adults: 2-4 g/24 hr q 12 hr IV or IM	*Adverse events:* Diarrhea, nausea, vaginal candidiasis Cautions: β-lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Cefixime Suprax Tablet: 200, 400 mg Suspension: 100 mg/5 mL	**Third-generation cephalosporin active against streptococci, *H. influenzae*, *M. catarrhalis*, *Neisseria gonorrhoeae*, *Serratia marcescens*, and *Proteus vulgaris*. No antistaphylococcal or antipseudomonal activity** Children: 8 mg/kg/24 hr divided q 12-24 hr PO Adults: 400 mg/24 hr divided q 12-24 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS *Drug interaction:* Probenecid
Cefoperazone sodium Cefobid Injection	**Third-generation cephalosporin active against many Gram-positive and Gram-negative pathogens** Neonates: 100 mg/kg/24 hr divided q 12 hr IV or IM Children: 100-150 mg/kg/24 hr divided q 8-12 hr IV or IM Adults: 2-4 g/24 hr divided q 8-12 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin with limited potency reflected by weak antipseudomonal activity. Variable Gram-positive activity. Primarily hepatically eliminated in bile *Drug interaction:* Disulfiram-like reaction with alcohol
Cefotaxime sodium Claforan Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Neonates: ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days: weight <1,200 g 100 mg/kg/24 hr divided q 12 hr IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM (meningitis: 200 mg/kg/24 hr divided q 6-8 hr IV) Adults: 1-2 g q 8-12 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Each gram of drug contains 2.2 mEq sodium. Active metabolite *Drug interaction:* Probenecid
Cefotetan disodium Cefotan Injection	**Second-generation cephalosporin active against *S. aureus*, *Streptococcus*, *H. influenzae*, *E. coli*, *Klebsiella*, *Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Children: 40-80 mg/kg/24 hr divided IV or IM q 12 hr Adults: 2-4 g/24 hr divided q 12 hr IV or IM (max dose: 6 g/24 hr)	*Cautions:* Highly protein-bound cephalosporin, poor CNS penetration; β-lactam safety profile (rash, eosinophilia), disulfiram-like reaction with alcohol. Renally eliminated (~20% in bile)
Cefoxitin sodium Mefoxin Injection	**Second-generation cephalosporin active against *S. aureus*, *Streptococcus*, *H. influenzae*, *E. coli*, *Klebsiella*, *Proteus*, and *Bacteroides*. Inactive against *Enterobacter*** Neonates: 70-100 mg/kg/24 hr divided q 8-12 hr IV or IM Children: 80-160 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* Poor CNS penetration; β-lactam safety profile (rash, eosinophilia). Renally eliminated. Painful given intramuscularly *Drug interaction:* Probenecid
Cefpodoxime proxetil Vantin Tablet: 100 mg, 200 mg Suspension: 50 mg/5 mL, 100 mg/5 mL	**Third-generation cephalosporin active against *S. aureus*, *Streptococcus*, *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, *E. coli*, *Klebsiella*, and *Proteus*. No antipseudomonal activity** Children: 10 mg/kg/24 hr divided q 12 hr PO Adults: 200-800 mg/24 hr divided q 12 hr PO (max dose: 800 mg/24 hr) Uncomplicated gonorrhea: 200 mg PO as single-dose therapy	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Does not adequately penetrate CNS. Increased bioavailability when taken with food *Drug interaction:* Probenecid; antacids and H-2 receptor antagonists may decrease absorption
Ceftaroline fosamil Teflaro Injection	**Fifth-generation cephalosporin active against *S. aureus* (including MRSA when used for skin and soft-tissue infection), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, *H. influenzae*, and *Klebsiella oxytoca*** *Children: 24 mg/kg/24 hr divided q 8 hr IV (<6 mo of age); 36 mg/kg/24 hr divided q 8 hr IV (weight ≤33 kg); 400 mg q 8 hr IV (weight >33 kg) Adults: 600 mg q 12 hr IV *Suggested dose; safety and effectiveness in pediatric patients have not yet been established	*Caution:* β-Lactam safety profile (rash, eosinophilia) *Drug interaction:* Probenecid
Cefprozil Cefzil Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Second-generation cephalosporin active against *S. aureus*, *Streptococcus*, *H. influenzae*, *E. coli*, *M. catarrhalis*, *Klebsiella*, and *Proteus*** Children: 30 mg/kg/24 hr divided q 8-12 hr PO Adults: 500-1,000 mg/24 hr divided q 12 hr PO (max dose: 1.5 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Good bioavailability; food does not affect bioavailability *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ceftazidime Fortaz, Ceptaz, Tazicef, Tazidime Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens, including *P. aeruginosa*** Neonates: Postnatal age ≤7 days: 100 mg/kg/24 hr divided q 12 hr IV or IM; >7 days weight ≤1,200 g: 100 mg/kg/24 hr divided q 12 hr IV or IM; weight >1,200 g: 150 mg/kg/24 hr divided q 8 hr IV or IM Children: 150 mg/kg/24 hr divided q 8 hr IV or IM (meningitis: 150 mg/kg/24 hr IV divided q 8 hr) Adults: 1-2 g q 8-12 hr IV or IM (max dose: 8-12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Increasing pathogen resistance developing with long-term, widespread use *Drug interaction:* Probenecid
Ceftizoxime Cefizox Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Children: 150 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 1-2 g q 6-8 hr IV or IM (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Ceftriaxone sodium Rocephin Injection	**Third-generation cephalosporin active against Gram-positive and Gram-negative pathogens. No antipseudomonal activity** Neonates: 50-75 mg/kg q 24 hr IV or IM Children: 50-75 mg/kg q 24 hr IV or IM (meningitis: 75 mg/kg dose 1 then 80-100 mg/kg/24 hr divided q 12-24 hr IV or IM) Adults: 1-2 g q 24 hr IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Eliminated via kidney (33-65%) and bile; can cause sludging. Long half-life and dose-dependent protein binding favors q 24 hr rather than q 12 hr dosing. Can add 1% lidocaine for IM injection *Drug interaction:* Probenecid. In neonates, coadministration with calcium-containing products can result in severe precipitation and attendant embolic complications
Cefuroxime (cefuroxime axetil for oral administration) Ceftin, Kefurox, Zinacef Injection Suspension: 125 mg/5 mL Tablet: 125, 250, 500 mg	**Second-generation cephalosporin active against *S. aureus, Streptococcus, H. influenzae, E. coli, M. catarrhalis, Klebsiella*, and *Proteus*** Neonates: 40-100 mg/kg/24 hr divided q 12 hr IV or IM Children: 200-240 mg/kg/24 hr divided q 8 hr IV or IM; PO administration: 20-30 mg/kg/24 hr divided q 8 hr PO Adults: 750-1,500 mg q 8 hr IV or IM (max dose: 6 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated. Food increases PO bioavailability *Drug interaction:* Probenecid
Cephalexin Keflex, Keftab Capsule: 250, 500 mg Tablet: 500 mg, 1 g Suspension: 125 mg/5 mL, 250 mg/5 mL, 100 mg/mL drops	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Children: 25-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Cephradine Velosef Capsule: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**First-generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Klebsiella*, and *Proteus*** Children: 50-100 mg/kg/24 hr divided q 6-12 hr PO Adults: 250-500 mg q 6-12 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Chloramphenicol Chloromycetin Injection Capsule: 250 mg Ophthalmic, otic solutions Ointment	**Broad-spectrum protein synthesis inhibitor active against many Gram-positive and Gram-negative bacteria, *Salmonella*, vancomycin-resistant *Enterococcus faecium, Bacteroides*, other anaerobes, *Mycoplasma, Chlamydia*, and *Rickettsia*; usually inactive against *Pseudomonas*** Neonates: Initial loading dose 20 mg/kg followed 12 hr later by: postnatal age ≤7 days: 25 mg/kg/24 hr q 24 hr IV; >7 days: weight ≤2,000 g: 25 mg/kg/24 hr q 24 hr IV; weight >2,000 g: 50 mg/kg/24 hr divided q 12 hr IV Children: 50-75 mg/kg/24 hr divided q 6-8 hr IV or PO (meningitis: 75-100 mg/kg/24 hr IV divided q 6 hr) Adults: 50 mg/kg/24 hr divided q 6 hr IV or PO (max dose: 4 g/24 hr)	*Cautions:* Gray-baby syndrome (from too-high dose in neonate), bone marrow suppression aplastic anemia (monitor hematocrit, free serum iron) *Drug interactions:* Phenytoin, phenobarbital, rifampin may decrease levels *Target serum concentrations:* Peak 20-30 mg/L; trough 5-10 mg/L

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Ciprofloxacin Cipro Tablet: 100, 250, 500, 750 mg Injection Ophthalmic solution and ointment Otic suspension Oral suspension: 250 and 500 mg/5 mL	**Quinolone antibiotic active against *P. aeruginosa*, *Serratia*, *Enterobacter*, *Shigella*, *Salmonella*, *Campylobacter*, *N. gonorrhoeae*, *H. influenzae*, *M. catarrhalis*, some *S. aureus*, and some *Streptococcus*** Neonates: 10 mg/kg q 12 hr PO or IV Children: 15-30 mg/kg/24 hr divided q 12 hr PO or IV; cystic fibrosis: 20-40 mg/kg/24 hr divided q 8-12 hr PO or IV Adults: 250-750 mg q 12 hr; 200-400 mg IV q 12 hr PO (max dose: 1.5 g/24 hr)	*Cautions:* Concerns of joint destruction in juvenile animals not seen in humans; tendonitis, superinfection, dizziness, confusion, crystalluria, some photosensitivity *Drug interactions:* Theophylline; magnesium-, aluminum-, or calcium-containing antacids; sucralfate; probenecid; warfarin; cyclosporine
Clarithromycin Biaxin Tablet: 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Macrolide antibiotic with activity against *S. aureus*, *Streptococcus*, *H. influenzae*, *Legionella*, *Mycoplasma*, and *C. trachomatis*** Children: 15 mg/kg/24 hr divided q 12 hr PO Adults: 250-500 mg q 12 hr PO (max dose: 1 g/24 hr)	*Cautions:* Adverse events less than erythromycin; gastrointestinal upset, dyspepsia, nausea, cramping *Drug interactions:* Same as erythromycin: astemizole carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus
Clindamycin Cleocin Capsule: 75, 150, 300 mg Suspension: 75 mg/5 mL Injection Topical solution, lotion, and gel Vaginal cream	**Protein synthesis inhibitor active against most Gram-positive aerobic and anaerobic cocci except *Enterococcus*** Neonates: Postnatal age ≤7 days weight <2,000 g; 10 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; >7 days weight <1,200 g: 10 mg/kg/24 hr IV or IM divided q 12 hr; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8 hr IV or IM; weight >2,000 g: 20 mg/kg/24 hr divided q 8 hr IV or IM Children: 10-40 mg/kg/24 hr divided q 6-8 hr IV, IM, or PO Adults: 150-600 mg q 6-8 hr IV, IM, or PO (max dose: 5 g/24 hr IV or IM or 2 g/24 hr PO)	*Cautions:* Diarrhea, nausea, *Clostridium difficile*–associated colitis, rash Administer slow IV over 30-60 min Topically active as an acne treatment
Cloxacillin sodium Tegopen Capsule: 250, 500 mg Suspension: 125 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 50-100 mg/kg/24 hr divided q 6 hr PO Adults: 250-500 mg q 6 hr PO (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily hepatically eliminated; requires dose reduction in renal disease. Food decreases bioavailability *Drug interaction:* Probenecid
Colistin (Colistimethate sodium; polymyxin E) Injection Inhalation	**Treatment of multidrug resistant Gram-negative organisms (*Enterobacteriaceae* including extended-spectrum betalactamase and carbapenemase-producing strains)** Children: 2.5-5 mg/kg/day divided in 2-4 divided doses IV Adults: 300 mg/day in 2-4 divided doses IV	*Cautions:* Nephrotoxicity (~3% in young children; higher rates in adolescents and adults); adjust dose for renal insufficiency; neurotoxicity (headaches, paresthesia, ataxia) *Drug interactions:* Should not be administered concomitantly with polymyxins or aminoglycosides
Co-trimoxazole (trimethoprim-sulfamethoxazole; TMP-SMZ) Bactrim, Cotrim, Septra, Sulfatrim Tablet: SMZ 400 mg and TMP 80 mg Tablet DS: SMZ 800 mg and TMP 160 mg Suspension: SMZ 200 mg and TMP 40 mg/5 mL Injection	**Antibiotic combination with sequential antagonism of bacterial folate synthesis with broad antibacterial activity: *Shigella*, *Legionella*, *Nocardia*, *Chlamydia*, *Pneumocystis jiroveci*. Dosage based on TMP component** Children: 6-20 mg TMP/kg/24 hr or IV divided q 12 hr PO *Pneumocystis carinii* pneumonia: 15-20 mg TMP/kg/24 hr divided q 12 hr PO or IV *P. carinii* prophylaxis: 5 mg TMP/kg/24 hr or 3 times/wk PO Adults: 160 mg TMP q 12 hr PO	*Cautions:* Drug dosed on TMP (trimethoprim) component. Sulfonamide skin reactions: rash, erythema multiforme, Stevens-Johnson syndrome, nausea, leukopenia. Renal and hepatic elimination; reduce dose in renal failure *Drug interactions:* Protein displacement with warfarin, possibly phenytoin, cyclosporine

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Daptomycin Cubicin	**Disrupts bacterial cell membrane function, causing depolarization leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death. Active against enterococci (including glycopeptide-resistant strains), staphylococci (including MRSA), streptococci, and corynebacteria. Approved for skin and soft-tissue infections. Acceptable for bacteremia and right-sided endocarditis with susceptible strains** Adults: In skin and soft-tissue infections, 4 mg/kg daptomycin is given intravenously once daily. For *S. aureus* bacteremia or right-sided endocarditis, the approved dose is 6 mg/kg given intravenously once daily Children: Unknown. Doses of 5-9 mg/kg/day in once-daily dosing have been reported in pediatric clinical trials	*Cautions:* Should not be used for pneumonia as drug inactivated by surfactants. Associated with rash, renal failure, anemia, headache. Is reported to cause myopathy, rhabdomyolysis, and eosinophilic pneumonia *Drug interactions:* Should not be administered with statins
Demeclocycline Declomycin Tablet: 150, 300 mg Capsule: 150 mg	**Tetracycline active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *Borrelia burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 8-12 mg/kg/24 hr divided q 6-12 hr PO Adults: 150 mg PO q 6-8 hr Syndrome of inappropriate antidiuretic hormone secretion: 900-1,200 mg/24 hr or 13-15 mg/kg/24 hr divided q 6-8 hr PO with dose reduction based on response to 600-900 mg/24 hr	*Cautions:* Teeth staining, possibly permanent (if administered <8 yr of age) with prolonged use; photosensitivity, diabetes insipidus, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc- and iron-containing food, milk, dairy products may decrease absorption
Dicloxacillin Dynapen, Pathocil Capsule: 125, 250, 500 mg Suspension: 62.5 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci except *Enterococcus* and coagulase-negative staphylococci** Children: 12.5-100 mg/kg/24 hr divided q 6 hr PO Adults: 125-500 mg q 6 hr PO	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Primarily renally (65%) and bile (30%) elimination. Food may decrease bioavailability *Drug interaction:* Probenecid
Doripenem Doribax Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes** Children: dose unknown. Adults: 500 mg q 8 hr IV	*Cautions:* β-Lactam safety profile; does not undergo hepatic metabolism. Renal elimination (70-75%); dose adjustment for renal failure *Drug interactions:* Valproic acid, probenecid
Doxycycline Vibramycin, Doxy Injection Capsule: 50, 100 mg Tablet: 50, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL	**Tetracycline antibiotic active against most Gram-positive cocci except *Enterococcus*, many Gram-negative bacilli, anaerobes, *B. burgdorferi* (Lyme disease), *Mycoplasma*, and *Chlamydia*** Children: 2-5 mg/kg/24 hr divided q 12-24 hr PO or IV (max dose: 200 mg/24 hr) Adults: 100-200 mg/24 hr divided q 12-24 hr PO or IV	*Cautions:* Teeth staining, possibly permanent (<8 yr of age) with prolonged use; photosensitivity, nausea, vomiting, diarrhea, superinfections *Drug interactions:* Aluminum-, calcium-, magnesium-, zinc-, iron-, kaolin-, and pectin-containing products, food, milk, dairy products may decrease absorption. Carbamazepine, rifampin, barbiturates may decrease half-life
Erythromycin E-Mycin, Ery-Tab, Eryc, Ilosone Estolate 125, 500 mg Tablet EES: 200 mg Tablet base: 250, 333, 500 mg Suspension: estolate 125 mg/5 mL, 250 mg/5 mL, EES 200 mg/5 mL, 400 mg/5 mL Estolate drops: 100 mg/mL. EES drops: 100 mg/2.5 mL. Available in combination with sulfisoxazole (Pediazole), dosed on erythromycin content	**Bacteriostatic macrolide antibiotic most active against Gram-positive organisms, *Corynebacterium diphtheriae*, and *Mycoplasma pneumoniae*** Neonates: Postnatal age ≤7 days: 20 mg/kg/24 hr divided q 12 hr PO; >7 days weight <1,200 g: 20 mg/kg/24 hr divided q 12 hr PO; weight >1,200 g: 30 mg/kg/24 hr divided q 8 hr PO (give as 5 mg/kg/dose q 6 hr to improve feeding intolerance) Children: Usual max dose 2 g/24 hr Base: 30-50 mg/kg/24 hr divided q 6-8 hr PO Estolate: 30-50 mg/kg/24 hr divided q 8-12 hr PO Stearate: 20-40 mg/kg/24 hr divided q 6 hr PO Lactobionate: 20-40 mg/kg/24 hr divided q 6-8 hr IV Gluceptate: 20-50 mg/kg/24 hr divided q 6 hr IV; usual max dose 4 g/24 hr IV Adults: Base: 333 mg PO q 8 hr; estolate/stearate/base: 250-500 mg q 6 hr PO	*Cautions:* Motilin agonist leading to marked abdominal cramping, nausea, vomiting, diarrhea. Associated with hypertrophic pyloric stenosis in young infants. Many different salts with questionable tempering of gastrointestinal adverse events. Rare cardiac toxicity with IV use. Dose of salts differ. Topical formulation for treatment of acne *Drug interactions:* Antagonizes hepatic CYP 3A4 activity: astemizole, carbamazepine, terfenadine, cyclosporine, theophylline, digoxin, tacrolimus, carbamazepine

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Gentamicin Garamycin Injection Ophthalmic solution, ointment, topical cream	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Proteus, Enterobacter, Serratia,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 2.5 mg/kg q 12-18 hr IV or IM; weight <2,000 g: 2.5 mg/kg q 12 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 8 hr IV or IM Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV once daily Intrathecal: Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr intrathecal; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM	Cautions: Anaerobes, *S. pneumoniae,* and other *Streptococcus* are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough >2 mg/L with intermittent daily dose regimens only
Imipenem-cilastatin Primaxin Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *Stenotrophomonas maltophilia*** Neonates: Postnatal age ≤7 days weight <1,200 g: 20 mg/kg q 18-24 hr IV or IM; weight >1,200 g: 40 mg/kg divided q 12 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 40 mg/kg q 12 hr IV or IM; weight >2,000 g: 60 mg/kg q 8 hr IV or IM Children: 60-100 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 2-4 g/24 hr divided q 6-8 hr IV or IM (max dose: 4 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), nausea, seizures. Cilastatin possesses no antibacterial activity; reduces renal imipenem metabolism. Primarily renally eliminated *Drug interaction:* Possibly ganciclovir
Linezolid Zyvox Tablet: 400, 600 mg Oral suspension: 100 mg/5 mL Injection: 100 mg/5 mL	**Oxazolidinone antibiotic active against Gram-positive cocci (especially drug-resistant organisms), including *Staphylococcus, Streptococcus, E. faecium,* and *Enterococcus faecalis*. Interferes with protein synthesis by binding to 50S ribosome subunit** Children: 10 mg/kg q 12 hr IV or PO Adults: Pneumonia: 600 mg q 12 hr IV or PO; skin infections: 400 mg q 12 hr IV or PO	*Adverse events:* Myelosuppression, pseudomembranous colitis, nausea, diarrhea, headache *Drug interaction:* Probenecid
Loracarbef Lorabid Capsule: 200 mg Suspension: 100 mg/5 mL, 200 mg/5 mL	**Carbacephem very closely related to cefaclor (second-generation cephalosporin) active against *S. aureus, Streptococcus, H. influenzae, M. catarrhalis, E. coli, Klebsiella,* and *Proteus*** Children: 30 mg/kg/24 hr divided q 12 hr PO (max dose: 2 g) Adults: 200-400 mg q 12 hr PO (max dose: 800 mg/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia). Renally eliminated *Drug interaction:* Probenecid
Meropenem Merrem Injection	**Carbapenem antibiotic with broad-spectrum activity against Gram-positive cocci and Gram-negative bacilli, including *P. aeruginosa* and anaerobes. No activity against *S. maltophilia*** Children: 60 mg/kg/24 hr divided q 8 hr IV meningitis: 120 mg/kg/24 hr (max dose: 6 g/24 hr) q 8 hr IV Adults: 1.5-3 g q 8 hr IV	*Cautions:* β-Lactam safety profile; appears to possess less CNS excitation than imipenem. 80% renal elimination *Drug interaction:* Probenecid
Metronidazole Flagyl, Metro I.V., Topical gel, vaginal gel Injection Tablet: 250, 500 mg	**Highly effective in the treatment of infections caused by anaerobes. Oral therapy of *C. difficile* colitis** Neonates: weight <1,200 g: 7.5 mg/kg 48 hr PO or IV; postnatal age ≤7 days weight 1,200-2,000 g: 7.5 mg/kg/24 hr q 24 hr PO or IV; weight 2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; postnatal age <7 days weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12 hr PO or IV; weight >2,000 g: 30 mg/kg/24 hr divided q 12 hr PO or IV Children: 30 mg/kg/24 hr divided q 6-8 hr PO or IV Adults: 30 mg/kg/24 hr divided q 6 hr PO or IV (max dose: 4 g/24 hr)	*Cautions:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol. Administer IV slow over 30-60 min. Adjust dose with hepatic impairment *Drug interactions:* Carbamazepine, rifampin, phenobarbital may enhance metabolism; may increase levels of warfarin, phenytoin, lithium

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Mezlocillin sodium Mezlin Infection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia*, and *Bacteroides;* limited antipseudomonal activity** Neonates: Postnatal age ≤7 days: 150 mg/kg/24 hr divided q 12 hr IV; >7 days: 225 mg/kg divided q 8 hr IV Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis 300-450 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.8 mEq sodium. Interferes with platelet aggregation with high doses; increases noted in liver function test results. Renally eliminated. Inactivated by β-lactamase enzyme *Drug interaction:* Probenecid
Mupirocin Bactroban Ointment	**Topical antibiotic active against *Staphylococcus* and *Streptococcus*** Topical application: Nasal (eliminate nasal carriage) and to the skin 2-4 times per day	*Caution:* Minimal systemic absorption as drug metabolized within the skin.
Nafcillin sodium Nafcil, Unipen Injection Capsule: 250 mg Tablet: 500 mg	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV or IM; weight >2,000 g: 75 mg/kg/24 hr divided q 8 hr IV or IM; postnatal age >7 days weight 1,200-2,000 g: 75 mg/kg/q 8 hr; weight >2,000 g: 100 mg/kg divided q 6-8 hr IV (meningitis: 200 mg/kg/24 hr divided q 6 hr IV) Children: 100-200 mg/kg/24 hr divided q 4-6 hr IV Adults: 4-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), phlebitis; painful given intramuscularly; oral absorption highly variable and erratic (not recommended) *Adverse effect:* Neutropenia
Nalidixic acid NegGram Tablet: 250, 500, 1,000 mg Suspension: 250 mg/5 mL	**First-generation quinolone effective for short-term treatment of lower urinary tract infections caused by *E. coli, Enterobacter, Klebsiella*, and *Proteus*** Children: 50-55 mg/kg/24 hr divided q 6 hr PO; suppressive therapy 25-33 mg/kg/24 hr divided q 6-8 hr PO Adults: 1 g q 6 hr PO; suppressive therapy: 500 mg q 6 hr PO	*Cautions:* Vertigo, dizziness, rash. Not for use in systemic infections *Drug interactions:* Liquid antacids
Neomycin sulfate Mycifradin Tablet: 500 mg Topical cream, ointment Solution: 125 mg/5 mL	**Aminoglycoside antibiotic used for topical application or orally before surgery to decrease gastrointestinal flora (nonabsorbable) and hyperammonemia** Infants: 50 mg/kg/24 hr divided q 6 hr PO Children: 50-100 mg/kg/24 hr divided q 6-8 hr PO Adults: 500-2,000 mg/dose q 6-8 hr PO	*Cautions:* In patients with renal dysfunction because small amount absorbed may accumulate *Adverse events:* Primarily related to topical application, abdominal cramps, diarrhea, rash Aminoglycoside ototoxicity and nephrotoxicity if absorbed
Nitrofurantoin Furadantin, Furan, Macrodantin Capsule: 50, 100 mg Extended-release capsule: 100 mg Macrocrystal: 50, 100 mg Suspension: 25 mg/5 mL	**Effective in the treatment of lower urinary tract infections caused by Gram-positive and Gram-negative pathogens** Children: 5-7 mg/kg/24 hr divided q 6 hr PO (max dose: 400 mg/24 hr); suppressive therapy 1-2.5 mg/kg/24 hr divided q 12-24 hr PO (max dose: 100 mg/24 hr) Adults: 50-100 mg/24 hr divided q 6 hr PO	*Cautions:* Vertigo, dizziness, rash, jaundice, interstitial pneumonitis. Do not use with moderate to severe renal dysfunction *Drug interactions:* Liquid antacids
Ofloxacin Ocuflox 0.3% ophthalmic solution: 1, 5, 10 mL Floxin 0.3% otic solution: 5, 10 mL	**Quinolone antibiotic for treatment of conjunctivitis or corneal ulcers (ophthalmic solution) and otitis externa or chronic suppurative otitis media (otic solution) caused by susceptible Gram-positive, Gram-negative, anaerobic bacteria, or *C. trachomatis*** *Child >1-12 yr:* Conjunctivitis: 1-2 drops in affected eye(s) q 2-4 hr for 2 days, then 1-2 drops qid for 5 days Corneal ulcers: 1-2 drops q 30 min while awake and at 4 hr intervals at night for 2 days, then 1-2 drops hourly for 5 days while awake, then 1-2 drops q 6 hr for 2 days Otitis externa (otic solution): 5 drops into affected ear bid for 10 days Chronic suppurative otitis media: treat for 14 days *Child >12 yr and adults:* Ophthalmic solution doses same as for younger children. Otitis externa (otic solution): Use 10 drops bid for 10 or 14 days as for younger children	*Adverse events:* Burning, stinging, eye redness (ophthalmic solution), dizziness with otic solution if not warmed

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Oxacillin sodium Prostaphlin Injection Capsule: 250, 500 mg Suspension: 250 mg/5 mL	**Penicillinase-resistant penicillin active against *S. aureus* and other Gram-positive cocci, except *Enterococcus* and coagulase-negative staphylococci** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50 mg/kg/24 hr divided q 12 hr IV; weight >2,000 g: 75 mg/kg/24 hr IV divided q 8 hr IV; postnatal age >7 days weight <1,200 g: 50 mg/kg/24 hr IV divided q 12 hr IV; weight 1,200-2,000 g: 75 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 100 mg/kg/24 hr IV divided q 6 hr IV Infants: 100-200 mg/kg/24 hr divided q 4-6 hr IV Children: PO 50-100 mg/kg/24 hr divided q 4-6 hr IV Adults: 2-12 g/24 hr divided q 4-6 hr IV (max dose: 12 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia) Moderate oral bioavailability (35-65%) Primarily renally eliminated *Drug interaction:* Probenecid *Adverse effect:* Neutropenia
Penicillin G Injection Tablets	**Penicillin active against most Gram-positive cocci; *S. pneumoniae* (resistance is increasing), group A *Streptococcus*, and some Gram-negative bacteria (e.g., *N. gonorrhoeae, N. meningitidis*)** Neonates: Postnatal age ≤7 days weight 1,200-2,000 g: 50,000 units/kg/24 hr divided q 12 hr IV or IM (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV or IM); weight >2,000 g: 75,000 units/kg/24 hr divided q 8 hr IV or IM (meningitis: 150,000 units/kg/24 hr divided q 8 hr IV or IM); postnatal age >7 days weight ≤1,200 g: 50,000 units/kg/24 hr divided q 12 hr IV (meningitis: 100,000 units/kg/24 hr divided q 12 hr IV); weight 1,200-2,000 g: 75,000 units/kg/24 hr q 8 hr IV (meningitis: 225,000 units/kg/24 hr divided q 8 hr IV); weight >2,000 g: 100,000 units/kg/24 hr divided q 6 hr IV (meningitis: 200,000 units/kg/24 hr divided q 6 hr IV) Children: 100,000-250,000 units/kg/24 hr divided q 4-6 hr IV or IM (max dose: 400,000 units/kg/24 hr) Adults: 2-24 million units/24 hr divided q 4-6 hr IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with marked renal disease. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, benzathine Bicillin Injection	**Long-acting repository form of penicillin effective in the treatment of infections responsive to persistent, low penicillin concentrations (1-4 wk), e.g., group A *Streptococcus* pharyngitis, rheumatic fever prophylaxis** Neonates weight >1,200 g: 50,000 units/kg IM once Children: 300,000-1.2 million units/kg q 3-4 wk IM (max dose: 1.2-2.4 million units/dose) Adults: 1.2 million units IM q 3-4 wk	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin G, procaine Crysticillin Injection	**Repository form of penicillin providing low penicillin concentrations for 12 hr** Neonates weight >1,200 g: 50,000 units/kg/24 hr IM Children: 25,000-50,000 units/kg/24 hr IM for 10 days (max dose: 4.8 million units/dose) Gonorrhea: 100,000 units/kg (max dose: 4.8 million units/24 hr) IM once with probenecid 25 mg/kg (max dose: 1 g) Adults: 0.6-4.8 million units q 12-24 hr IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia) allergy. Administer by IM injection only. Substantial pathogen resistance. Primarily renally eliminated *Drug interaction:* Probenecid
Penicillin V Pen VK, V-Cillin K Tablet: 125, 250, 500 mg Suspension: 125 mg/5 mL, 250 mg/5 mL	**Preferred oral dosing form of penicillin, active against most Gram-positive cocci; *S. pneumoniae* (resistance is increasing), other streptococci, and some Gram-negative bacteria (e.g., N. *gonorrhoeae, N. meningitidis*)** Children: 25-50 mg/kg/24 hr divided q 4-8 hr PO Adults: 125-500 mg q 6-8 hr PO (max dose: 3 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia), allergy, seizures with excessive doses particularly in patients with renal disease. Substantial pathogen resistance. Primarily renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid
Piperacillin Pipracil Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days 150 mg/kg/24 hr divided q 8-12 hr IV; >7 days; 200 mg/kg divided q 6-8 hr IV Children: 200-300 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 350-500 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr (max dose: 24 g/24 hr) IV	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium. Interferes with platelet aggregation/serum sickness-like reaction with high doses; increases in liver function tests. Renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Continued

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Piperacillin-tazobactam Zosyn Injection	**Extended-spectrum penicillin (piperacillin) combined with a β-lactamase inhibitor (tazobactam) active against *S. aureus, H. influenzae, E. coli, Enterobacter, Serratia, Acinetobacter, P. aeruginosa,* and *Bacteroides*** Children: 300-400 mg/kg/24 hr divided q 6-8 hr IV or IM Adults: 3.375 g q 6-8 hr IV or IM	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 1.9 mEq sodium Interferes with platelet aggregation, serum sickness–like reaction with high doses, increases in liver function test results. Renally eliminated *Drug interaction:* Probenecid
Quinupristin/dalfopristin Synercid IV injection: powder for reconstitution, 10 mL contains 150 mg quinupristin, 350 mg dalfopristin	**Streptogramin antibiotic (quinupristin) active against vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA). Not active against *E. faecalis*** Children and adults: VRE: 7.5 mg/kg q 8 hr IV for VRE; skin infections: 7.5 mg/kg q 12 hr IV	*Adverse events:* Pain, edema, or phlebitis at injection site, nausea, diarrhea *Drug interactions*: Synercid is a potent inhibitor of CYP 3A4
Sulfadiazine Tablet: 500 mg	**Sulfonamide antibiotic primarily indicated for the treatment of lower urinary tract infections caused by *E. coli, P. mirabilis,* and *Klebsiella*** Toxoplasmosis: Neonates: 100 mg/kg/24 hr divided q 12 hr PO with pyrimethamine 1 mg/kg/24 hr PO (with folinic acid) Children: 120-200 mg/kg/24 hr divided q 6 hr PO with pyrimethamine 2 mg/kg/24 hr divided q 12 hr PO ≥3 days then 1 mg/kg/24 hr (max dose: 25 mg/24 hr) with folinic acid Rheumatic fever prophylaxis: weight ≤30 kg: 500 mg/24 hr q 24 hr PO; weight >30 kg: 1 g/24 hr q 24 hr PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~10 hr *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfamethoxazole Gantanol Tablet: 500 mg Suspension: 500 mg/5 mL	**Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections due to susceptible bacteria** Children: 50-60 mg/kg/24 hr divided q 12 hr PO Adults: 1 g/dose q 12 hr PO (max dose: 3 g/24 hr)	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life 12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Sulfisoxazole Gantrisin Tablet: 500 mg Suspension: 500 mg/5 mL Ophthalmic solution, ointment	**Sulfonamide antibiotic used for the treatment of otitis media, chronic bronchitis, and lower urinary tract infections caused by susceptible bacteria** Children: 120-150 mg/kg/24 hr divided q 4-6 hr PO (max dose: 6 g/24 hr) Adults: 4-8 g/24 hr divided q 4-6 hr PO	*Cautions:* Rash, Stevens-Johnson syndrome, nausea, leukopenia, crystalluria. Renal and hepatic elimination; avoid use with renal disease. Half-life ~7-12 hr. Initial dose often a loading dose (doubled) *Drug interactions:* Protein displacement with warfarin, phenytoin, methotrexate
Ticarcillin Ticar Injection	**Extended-spectrum penicillin active against *E. coli, Enterobacter, Serratia, P. aeruginosa,* and *Bacteroides*** Neonates: Postnatal age ≤7 days weight <2,000 g: 150 mg/kg/24 hr divided q 8-12 hr IV; >7 days weight <2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; >7 days weight <1,200 g: 150 mg/kg/24 hr divided q 12 hr IV; weight 1,200-2,000 g: 225 mg/kg/24 hr divided q 8 hr IV; weight >2,000 g: 300 mg/kg/24 hr divided q 6-8 hr IV Children: 200-400 mg/kg/24 hr divided q 4-6 hr IV; cystic fibrosis: 400-600 mg/kg/24 hr IV Adults: 2-4 g/dose q 4-6 hr IV (max dose: 24 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated. Inactivated by penicillinase *Drug interaction:* Probenecid
Ticarcillin-clavulanate Timentin Injection	**Extended-spectrum penicillin (ticarcillin) combined with a β-lactamase inhibitor (clavulanate) active against *S. aureus, H. influenzae, Enterobacter, E. coli, Serratia, P. aeruginosa, Acinetobacter,* and *Bacteroides*** Children: 280-400 mg/kg/24 hr q 4-8 hr IV or IM Adults: 3.1 g q 4-8 hr IV or IM (max dose: 18-24 g/24 hr)	*Cautions:* β-Lactam safety profile (rash, eosinophilia); painful given intramuscularly; each gram contains 5-6 mEq sodium. Interferes with platelet aggregation; increases in liver function tests. Renally eliminated *Drug interaction:* Probenecid

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Table 180-3 Antibacterial Medications (Antibiotics)—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	INDICATIONS (MECHANISM OF ACTION) AND DOSING	COMMENTS
Tigecycline Tygacil Injection	**Tetracycline-class antibiotic (glycylcycline) active against Enterobacteriaceae, including extended spectrum β-lactamase producers; streptococci (including VRE); staphylococci (including MRSA); and anaerobes** Children: unknown Adults: 100 mg loading dose followed by 50 mg q 12 hr IV	*Cautions:* Pregnancy; children <8 yr of age; photosensitivity; hypersensitivity to tetracyclines; hepatic impairment (~60% hepatic clearance) *Drug interaction:* Warfarin; mycophenolate mofetil
Tobramycin Nebcin, Tobrex Injection Ophthalmic solution, ointment	**Aminoglycoside antibiotic active against Gram-negative bacilli, especially *E. coli, Klebsiella, Enterobacter, Serratia, Proteus,* and *Pseudomonas*** Neonates: Postnatal age ≤7 days, weight 1,200-2,000 g: 2.5 mg/kg q 12-18 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 12 hr IV or IM; postnatal age >7 days, weight 1,200-2,000 g: 2.5 mg/kg q 8-12 hr IV or IM; weight >2,000 g: 2.5 mg/kg q 8 hr IV or IM Children: 2.5 mg/kg/24 hr divided q 8-12 hr IV or IM. Alternatively may administer 5-7.5 mg/kg/24 hr IV. Preservative-free preparation for intraventricular or intrathecal use: neonate: 1 mg/24 hr; children: 1-2 mg/24 hr; adults: 4-8 mg/24 hr Adults: 3-6 mg/kg/24 hr divided q 8 hr IV or IM	*Cautions: S. pneumoniae*, other *Streptococcus,* and anaerobes are resistant. May cause ototoxicity and nephrotoxicity. Monitor renal function. Drug eliminated renally. Administered IV over 30-60 min *Drug interactions:* May potentiate other ototoxic and nephrotoxic drugs *Target serum concentrations:* Peak 6-12 mg/L; trough <2 mg/L
Trimethoprim Proloprim, Trimpex Tablet: 100, 200 mg	**Folic acid antagonist effective in the prophylaxis and treatment of *E. coli, Klebsiella, P. mirabilis,* and *Enterobacter* urinary tract infections; *P. carinii* pneumonia** Children: For urinary tract infection: 4-6 mg/kg/24 hr divided q 12 hr PO Children >12 yr and adults: 100-200 mg q 12 hr PO. *P. carinii* pneumonia (with dapsone): 15-20 mg/kg/24 hr divided q 6 hr for 21 days PO	*Cautions:* Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash *Drug interactions:* Possible interactions with phenytoin, cyclosporine, rifampin, warfarin
Vancomycin Vancocin, Lyphocin Injection Capsule: 125 mg, 250 mg Suspension	**Glycopeptide antibiotic active against most Gram-positive pathogens including staphylococci (including MRSA and coagulase-negative staphylococci), *S. pneumoniae* including penicillin-resistant strains, *Enterococcus* (resistance is increasing), and *C. difficile*–associated colitis** Neonates: Postnatal age ≤7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 12-18 hr IV; weight >2,000 g: 30 mg/kg/24 hr divided q 12 hr IV; postnatal age >7 days, weight <1,200 g: 15 mg/kg/24 hr divided q 24 hr IV; weight 1,200-2,000 g: 15 mg/kg/24 hr divided q 8-12 hr IV; weight >2,000 g: 45 mg/kg/24 hr divided q 8 hr IV Children: 45-60 mg/kg/24 hr divided q 8-12 hr IV; *C. difficile*–associated colitis; 40-50 mg/kg/24 hr divided q 6-8 hr PO.40-50 mg/kg/24 hr divided q 6-8 hr PO	*Cautions:* Ototoxicity and nephrotoxicity particularly when co-administered with other ototoxic and nephrotoxic drugs Infuse IV over 45-60 min. Flushing (red man syndrome) associated with rapid IV infusions, fever, chills, phlebitis (central line is preferred). Renally eliminated *Target serum concentrations:* Peak (1 hr after 1 hr infusion) 30-40 mg/L; trough 5-10 mg/L

*In the Drug column, the generic drug name is in **bold**. In the Indications column, **bold** indicates major organisms targeted and mechanisms of action.

Resistance to penicillin is mediated by a variety of mechanisms (see Table 180-1). The production of β-lactamase is a common mechanism exhibited by many organisms that may be overcome, with variable success, by including a β-lactamase inhibitor with the penicillin. Such combination products (ampicillin-sulbactam, amoxicillin-clavulanate, piperacillin-tazobactam) are potentially very useful for management of resistant isolates, but only if the resistance is β-lactamase mediated. Notably, *S. aureus* and *S. pneumoniae* mediate β-lactam resistance through mechanisms other than β-lactamase production, rendering these combination agents of little value for the management of β-lactam–resistant *S. aureus* and *S. pneumoniae* infections.

Table 180-4 lists adverse reactions to penicillins.

Cephalosporins

Cephalosporins differ structurally from penicillins insofar as the β-lactam ring exists as a 6-member ring, compared to the 5-member ring structure of the penicillins. These agents are widely used in pediatric practice, both in oral and parenteral formulations (Table 180-5). The **first-generation cephalosporins** (e.g., cefazolin, a parenteral formulation, and cephalexin, an oral equivalent) are commonly used for management of skin and soft-tissue infections caused by susceptible strains of *S. aureus* and group A *Streptococcus*. The **second-generation cephalosporins** (e.g., cefuroxime, cefoxitin) have better activity against Gram-negative bacterial infections than do first-generation cephalosporins and are used to treat respiratory tract infections, urinary tract infections, and skin and soft-tissue infections. A variety of orally administered second-generation agents (cefaclor, cefprozil, loracarbef, cefpodoxime) are commonly used in the outpatient management of sinopulmonary infections and otitis media. The **third-generation cephalosporins** (cefotaxime, ceftriaxone, and ceftazidime) are typically used for serious pediatric infections, including meningitis and sepsis. Ceftazidime is highly active against most strains of

Table 180-4 Adverse Reactions to Penicillins*

TYPE OF REACTION	FREQUENCY (%)	OCCURS MOST FREQUENTLY WITH*
ALLERGIC		
Immunoglobulin E antibody	0.004-0.4	Penicillin G
• Anaphylaxis		
• Early urticaria (<72 hr)		
Cytotoxic antibody	Rare	Penicillin G
• Hemolytic anemia		
Antigen–antibody complex disease	Rare	Penicillin G
• Serum sickness		
Delayed hypersensitivity	4-8	Ampicillin
• Contact dermatitis		
IDIOPATHIC	4-8	Ampicillin
Skin rash		
Fever		
Late-onset urticaria		
GASTROINTESTINAL	2-5	
Diarrhea	2-5	Ampicillin
Enterocolitis	<1	Ampicillin
HEMATOLOGIC		
Hemolytic anemia	Rare	Penicillin G
Neutropenia	1-4	Penicillin G, nafcillin, oxacillin, piperacillin
Platelet dysfunction	3	Ticarcillin
HEPATIC		
Elevated serum aspartate transaminase level	1-4	Flucloxacillin, nafcillin, oxacillin
ELECTROLYTE DISTURBANCE		
Sodium overload	Variable	Ticarcillin
Hypokalemia	Variable	Ticarcillin
Hyperkalemia—acute	Rare	Penicillin G
NEUROLOGIC		
Seizures	Rare	Penicillin G
Bizarre sensations		Procaine penicillin
RENAL		
Interstitial nephritis	<1%	Any penicillin

*All the reactions can occur with any of the penicillins.

Adapted from Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Table 21-7.*

P. aeruginosa, making this a useful agent for febrile, neutropenic oncology patients. Ceftriaxone should not be mixed or reconstituted with a calcium-containing product, such as Ringer or Hartmann solution or parenteral nutrition containing calcium, because particulate formation can result. Cases of fatal reactions with ceftriaxone–calcium precipitates in lungs and kidneys in neonates have been reported. **A fourth-generation cephalosporin,** called cefepime, has activity against *P. aeruginosa* and retains good activity against methicillin-susceptible staphylococcal infections. A **fifth-generation cephalosporin**, ceftaroline has been licensed. It is the active metabolite of the prodrug ceftaroline fosamil and is a broad-spectrum cephalosporin with bactericidal activity against resistant Gram-positive organisms, including MRSA, and common Gram-negative pathogens. It has been licensed in adult patients for use in skin and soft-tissue infection and community-acquired bacterial pneumonia. It is indicated for MRSA only in the treatment of skin and soft-tissue infection and not MRSA pneumonia. Its activity is attributed to its ability to bind to penicillin-binding protein 2a with higher affinity than other β-lactams. Its role in pediatric practice remains to be defined. Another fifth-generation cephalosporin, ceftobiprole, has been approved for use in Canada and the European Union. Another novel cephalosporin with activity against *P. aeruginosa*, ceftolozane, is approaching licensure and will be combined with the β-lactamase inhibitor, tazobactam, in its final licensed formulation.

Table 180-6 lists adverse reactions to cephalosporins.

Carbapenems

The carbapenems include imipenem formulated in combination with cilastatin, meropenem, ertapenem, and doripenem. The basic structure of these agents is similar to that of β-lactam antibiotics, and these drugs have a similar mechanism of action. The carbapenems provide the broadest spectrum of antibacterial activity of any licensed class of antibiotics and are active against Gram-positive, Gram-negative, and anaerobic organisms. Among the carbapenems, meropenem is the only agent licensed for treatment of pediatric meningitis. At this time, ertapenem and doripenem are not approved for pediatric use. Importantly, MRSA and *E. faecium* are not susceptible to carbapenems. Carbapenems also tend to be poorly active against *Stenotrophomonas maltophilia,* rendering their use for cystic fibrosis patients who are infected with this organism problematic. Ertapenem is poorly active against *P. aeruginosa* and *Acinetobacter* species and should be avoided when these pathogens are encountered. Although imipenem-cilastatin is the first carbapenem approved for clinical use and the carbapenem with which there is the greatest clinical experience, this antibiotic unfortunately has a propensity to cause seizures in children, particularly in the setting of intercurrent meningitis. Accordingly, meropenem is typically more suitable for pediatric use, where meningitis is commonly a consideration.

Other carbapenems in various stages of clinical trials include panipenem, biapenem, razupenem, tomopenem, and tebipenem/pivoxil (the first oral carbapenem). Panipenem and biapenem are licensed in Japan, but there is minimal experience with pediatric dosing.

Glycopeptides

Glycopeptide antibiotics include vancomycin and teicoplanin, the less commonly available analog. These agents are bactericidal and act via inhibition of cell wall biosynthesis. The antimicrobial activity of the glycopeptides is limited to Gram-positive organisms, including *S. aureus,* coagulase-negative staphylococci, pneumococcus, enterococci, *Bacillus,* and *Corynebacterium.* Vancomycin is frequently employed in pediatric practice and is of particular value for serious infections, including meningitis, caused by MRSA and penicillin- and cephalosporin-resistant *S. pneumoniae.* Vancomycin is also commonly used for infections in the setting of fever and neutropenia in oncology patients, in combination with other antibiotics (see Chapter 178), and for infections associated with indwelling medical devices (see Chapter 179). Oral formulations of vancomycin are occasionally used to treat pseudomembranous colitis caused by *Clostridium difficile* infections; intrathecal therapy may also be used for selected CNS infections. Vancomycin must be administered with care because of its propensity to produce red man syndrome, which is a reversible adverse effect that is rare in young children and can typically be readily managed by slowing the rate of infusion of the drug. Newer glycopeptides antibiotics include oritavancin, dalbavancin, and the glycolipodepsipeptide agent, ramoplanin. Telavancin has been approved by FDA for the treatment of skin and soft-tissue infections suspected or known to be caused by MRSA for situations where other alternatives are not suitable.

Aminoglycosides

Aminoglycoside antibiotics include streptomycin, kanamycin, gentamicin, tobramycin, netilmicin, and amikacin. The most commonly used aminoglycosides in pediatric practice are gentamicin and tobramycin. They exert their mechanism of action via inhibition of bacterial protein synthesis. Although they are most commonly used to treat Gram-negative infections, the aminoglycosides are broad-spectrum agents: they have activity against *S. aureus* and provide synergistic activity against group B streptococcus, *L. monocytogenes,* viridans

Table 180-5 Classification of Parenteral and Oral Cephalosporins

CEPHALOSPORINS	FIRST GENERATION	SECOND GENERATION	CEPHAMYCINS	THIRD GENERATION	FOURTH GENERATION	FIFTH GENERATION
Parenteral	Cefazolin (Ancef, Kefzol) Cephalothin (Keflin, Seffin) Cephapirin (Cefadyl) Cephradine (Velosef)	Cefamandole (Mandol) Cefonicid (Monocid) Cefuroxime (Kefurox, Zinacef)	Cefmetazole (Zefazone) Cefotetan (Cefotan) Cefoxitin (Mefoxin)	Cefoperazone (Cefobid) Cefotaxime (Claforan) Ceftazidime (Fortaz) Ceftizoxime (Cefizox) Ceftriaxone (Rocephin)	Cefepime (Maxipime) Cefpirome (Cefrom) Ceftolozane (combined with tazobactam; CXA-101)	Ceftaroline (Teflaro) Ceftobiprole (Zeftera)
Oral	Cefadroxil (Duricef, Ultracef) Cephalexin (Keflex, Biocef, Keftab) Cephradine (Velosef)	Cefaclor (Ceclor) Cefprozil (Cefzil) Cefuroxime-axetil (Ceftin) Loracarbef (Lorabid)		Cefdinir (Omnicef) Cefditoren (Spectracef) Cefixime (Suprax) Cefpodoxime (Vantin) Ceftibuten (Cedax)		

Adapted from Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Table 22-1.*

streptococci, corynebacteria JK, *Pseudomonas, Staphylococcus epidermidis,* and *Enterococcus* when coadministered with a β-lactam agent. Aminoglycoside use has decreased with the development of newer alternatives, but they still play a key role in pediatric practice in the management of neonatal sepsis, urinary tract infections, Gram-negative sepsis, and complicated intraabdominal infections; infections in cystic fibrosis patients (including both parenteral and aerosolized forms of therapy); and in oncology patients with fever and neutropenia. Aminoglycosides, in particular streptomycin, are also important in the management of *Francisella tularensis, Mycobacterium tuberculosis,* and atypical mycobacterial infections. Toxicities of aminoglycoside therapy include nephrotoxicity and ototoxicity (cochlear and/or vestibular), and serum levels as well as renal function and hearing should be monitored for patients on long-term therapy. Toxicities of aminoglycosides may be reduced by the use of once-daily dosing regimens with appropriate monitoring of serum levels. Hypokalemia, volume depletion, hypomagnesemia, and other nephrotoxic drugs may increase the renal toxicity of aminoglycosides. A rare complication of aminoglycosides is neuromuscular blockade, which may occur in the presence of other neuromuscular blocking agents and in the setting of infant botulism.

Tetracyclines

The tetracyclines (tetracycline hydrochloride, doxycycline, demeclocycline, and minocycline) are bacteriostatic antibiotics that exhibit their antimicrobial effect by binding to the bacterial 30S ribosomal subunit, inhibiting protein translation. These agents have a broad spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, rickettsia, and some parasites. The oral bioavailability of these agents facilitates oral dosing for many infections, including Rocky Mountain spotted fever, ehrlichiosis, Lyme disease, and malaria. Tetracyclines must be prescribed judiciously to children younger than 9 yr of age, because they can cause staining of teeth, hypoplasia of dental enamel, and abnormal bone growth in this age group. Tigecycline, a semisynthetic derivative of minocycline, is licensed in the United States. It is a parenteral agent of a new class of antibiotics (glycylcyclines). It has a broader spectrum of activity (bacteriostatic) than traditional tetracyclines, but retains the side–effect profile of tetracyclines. Tigecycline is active against tetracycline-resistant Gram-positive and Gram-negative pathogens, including MRSA, and possibly VRE, but not *Pseudomonas.*

Complications of tetracyclines include eosinophilia, leukopenia and thrombocytopenia (tetracycline), pseudotumor cerebri, anorexia, emesis and nausea, candidal superinfection, hepatitis, photosensitivity, and a hypersensitivity reaction (urticaria, asthma exacerbation, facial edema, dermatitis) as well as a systemic lupus erythematosus–like syndrome (minocycline). The FDA issued a black box warning regarding tigecycline in 2013 based on a meta-analysis of 10 studies that showed increased mortality among patients receiving this drug. A salutary side effect of demeclocycline has been identified: it is occasionally used as an off-label treatment of hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone.

Sulfonamides

Trimethoprim and the sulfonamides are bacteriostatic agents that inhibit the bacterial folate synthesis pathway, in the process impairing both nucleic acid and protein synthesis. Sulfonamides interfere with the synthesis of dihydropteroic acid from paraaminobenzoic acid, whereas trimethoprim acts at a site further downstream, interfering with synthesis of tetrahydrofolic acid from dihydrofolic acid. The sulfonamides are available in both parenteral and oral formulations. Although there have historically been a large number of sulfonamide antibiotics developed for clinical use, relatively few remain available for pediatric practice. The most important agent is the combination of trimethoprim-sulfamethoxazole (TMP-SMZ), which is commonly used for treatment of urinary tract infections. TMP-SMZ has also emerged as a commonly prescribed agent for staphylococcal skin and soft-tissue infections, since this antibiotic retains activity against MRSA. TMP-SMZ also plays a unique role in immunocompromised patients, as a prophylactic and therapeutic agent for *Pneumocystis jiroveci* infection. Other commonly used sulfonamides include sulfisoxazole, which is useful in the management of urinary tract infections, and sulfadiazine, which is a drug of choice in the treatment of toxoplasmosis.

Table 180-6 Potential Adverse Effects of Cephalosporins

TYPE	SPECIFIC	FREQUENCY
Hypersensitivity	Rash	1-3%
	Urticaria	<1%
	Serum sickness	<1%
	Anaphylaxis	0.01%
Gastrointestinal	Diarrhea	1-19%
	Nausea, vomiting	1-6%
	Transient transaminase elevation	1-7%
	Biliary sludge	20-46%*
Hematologic	Eosinophilia	1-10%
	Neutropenia	<1%
	Thrombocytopenia	<1-3%
	Hypoprothrombinemia	<1%
	Impaired platelet aggregation	<1%
	Hemolytic anemia	<1%
Renal	Interstitial nephritis	<1%
Central nervous system	Seizures	<1%
	Encephalopathy	<1%
False-positive laboratory	Coombs positive	3%
	Glucosuria	Rare
	Serum creatinine	Rare
Other	Drug fever	Rare
	Disulfiram-like reaction*	Rare
	Superinfection	Rare
	Phlebitis	Rare
	Calcium-antibiotic precipitation (ceftriaxone)	Unknown; is associated with embolic events

*Cephalosporins with thiomethyl tetrazole ring (MTT) side chain.

Adapted from: Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Table 22-6.*

Macrolides

The macrolide antibiotics most commonly used in pediatric practice include erythromycin and the newer agents, clarithromycin and azithromycin. This class of antimicrobials exerts its antibiotic effect through binding to the 50S subunit of the bacterial ribosome, producing a block in elongation of bacterial polypeptides. Clarithromycin is metabolized to 14-hydroxy clarithromycin, and interestingly this active metabolite also has potent antimicrobial activity. The spectrum of antibiotic activity includes many Gram-positive bacteria. Unfortunately, resistance to these agents among *S. aureus* and group A *Streptococcus* is fairly widespread, limiting the usefulness of macrolides for many skin and soft-tissue infections and for streptococcal pharyngitis. Azithromycin and clarithromycin have demonstrated efficacy for otitis media. All of the members of this class have an important role in the management of pediatric respiratory infections, including atypical pneumonia caused by *M. pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila,* as well as infections caused by *Bordetella pertussis.*

Telithromycin is a ketolide antibiotic derived from erythromycin. It was initially approved by the FDA for the treatment in adults of mild to moderate community-acquired pneumonia, acute exacerbations of chronic bronchitis, and acute sinusitis, having good activity against the agents causing these infections (*S. pneumoniae*, *M. pneumoniae, C. pneumoniae,* and *L. pneumophila* for community-acquired pneumonia; *M. catarrhalis* and *H. influenzae* for sinusitis). Reports of liver failure and myasthenia gravis from telithromycin in particular prompted the withdrawal of the indication for sinusitis and bronchitis by the FDA.

Drug interactions are common with erythromycin and telithromycin and to a lesser extent with clarithromycin. These agents can inhibit the CYP 3A4 enzyme system, resulting in increased levels of certain drugs such as astemizole, cisapride, statins, pimozide, and theophylline. Itraconazole may increase macrolide levels, while rifampin, carbamazepine, and phenytoin may decrease macrolide levels. There are few reported adverse drug interactions with azithromycin. *Cross-resistance may develop between a macrolide and the subsequent use of clindamycin.*

Lincosamides

The prototype of the lincosamide class of antibiotics is clindamycin, which acts at the ribosomal level to exert its antimicrobial effect. The 50S subunit of the bacterial ribosome is the molecular target of this agent. Its spectrum of activity includes Gram-positive aerobes and anaerobes. Clindamycin has no significant activity against Gram-negative organisms. An important role for clindamycin has emerged in the management of MRSA infections. Because of its outstanding penetration into body fluids (excluding the CNS) and tissues and bone, clindamycin can be utilized for therapy of serious infections caused by MRSA. Clindamycin is also useful in the management of invasive group A *Streptococcus* infections and in the management of many anaerobic infections, often in combination with a β-lactam. There is a form of **inducible clindamycin resistance** exhibited by some strains of MRSA; therefore, consultation with the clinical microbiology laboratory is necessary before treating a serious MRSA infection with clindamycin. Pseudomembranous colitis, a complication of clindamycin therapy commonly encountered in adults, is seldom observed in pediatric patients. Clindamycin also plays an important role in the treatment of malaria and babesiosis (when coadministered with quinine), *P. jiroveci* pneumonia (when coadministered with primaquine), and toxoplasmosis.

Quinolones

The fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin, besifloxacin) are antimicrobials that inhibit bacterial DNA replication by binding to the topoisomerases of the target pathogen, inhibiting the bacterial enzyme DNA gyrase. This class has very broad-spectrum activity against both Gram-positive and Gram-negative organisms. Some of the fluoroquinolones exhibit activity against penicillin-resistant *S. pneumoniae* as well as MRSA. These agents uniformly exhibit excellent activity against Gram-negative pathogens, including the *Enterobacteriaceae* and respiratory tract pathogens such as *M. catarrhalis* and *H. influenzae.* Quinolones are also very active against pathogens associated with atypical pneumonia, particularly *M. pneumoniae* and *L. pneumophila.*

Although these agents are not approved for use in children, there is a reasonable body of evidence that the fluoroquinolones are generally safe, well tolerated, and effective against a variety of bacterial infections commonly encountered in pediatric practice. Parenteral quinolones are appropriate for critically ill patients with Gram-negative infections. The use of oral quinolones in stable outpatients may also be reasonable for treatment of infections that would otherwise require parenteral antibiotics (*P. aeruginosa* soft-tissue infections such as osteochondritis) or selected genitourinary tract infections. However, they should be reserved for situations where no other oral antibiotic alternative is feasible. In 2013, the FDA announced that it was changing the warning labels for fluoroquinolones to more adequately describe the risk of permanent peripheral neuropathy associated with this class of antimicrobials. Additional risks include arrhythmias and retinal detachment. Moreover, in situations of overuse (such as typhoid fever and gonococcal infection), organisms have been demonstrated to rapidly develop resistance. Thus, the use of fluoroquinolones in pediatric practice should still be approached with continued caution, and consultation with an expert is recommended.

Streptogramins and Oxazolidinones

The emergence of highly resistant Gram-positive organisms, in particular VRE, has necessitated development of new classes of antibiotics.

One such class that is especially useful for resistant Gram-positive infections is the streptogramins. The currently licensed agent in this category is **dalfopristin-quinupristin,** which is available in a parenteral formulation. It is appropriate for treatment of MRSA, coagulase-negative staphylococci, penicillin-susceptible and penicillin-resistant *S. pneumoniae,* and vancomycin-resistant *E. faecium* but not *E. faecalis.*

Another licensed class of antibiotics for highly resistant Gram-positive infections is the oxazolidinone class. The prototype in this group is **linezolid,** which is available in both oral and parenteral formulations and is approved for use in pediatric patients. Its mechanism of action involves inhibition of ribosomal protein synthesis. It is indicated for MRSA, VRE, coagulase-negative staphylococci, and penicillin-resistant *S. pneumoniae*. There is little information on dalfopristin-quinupristin and linezolid in treatment of CNS infections, and neither agent is approved for pediatric meningitis. Linezolid can cause anemia and thrombocytopenia and is a monoamine oxidase inhibitor.

Daptomycin

Daptomycin is a novel member of the cyclic lipopeptide class of antibiotics. Its spectrum of activity includes virtually all Gram-positive organisms, including *E. faecalis* and *E. faecium* (including VRE) and *S. aureus* (including MRSA). The structure of daptomycin is a 13-member amino acid peptide linked to a 10-carbon lipophilic tail, which results in a novel mechanism of action of disruption of the bacterial membrane through the formation of transmembrane channels. These channels cause leakage of intracellular ions, leading to depolarization of the cellular membrane and inhibition of macromolecular synthesis. A theoretical advantage of daptomycin for serious infections is its bactericidal activity against MRSA and enterococci. It is administered IV. Experience in children is limited. Myopathy and elevations in creatine phosphokinase have been described. An FDA warning has been issued linking some cases of eosinophilic pneumonitis to the use of daptomycin. Daptomycin is inactivated by surfactant and should not be used to treat pneumonia.

Miscellaneous Agents

Although rarely used today because of safety concerns and limited availability, **chloramphenicol** occasionally plays a role in the management of pediatric infections, particularly those involving the CNS. This agent binds peptidyl transferase, a component of the 50S ribosome, inhibiting bacterial protein synthesis. **Metronidazole**, which functions by disruption of DNA synthesis, has a unique role as an antianaerobic agent and also possesses antiparasitic and anthelmintic activity. **Rifampin** is a rifamycin antibiotic that inhibits bacterial RNA polymerase and has a major role in the management of tuberculosis. It is also of value in the management of other bacterial infections in pediatric patients, usually used as a second (synergistic) agent in the treatment of *S. aureus* infections or to eliminate nasopharyngeal colonization of *H. influenzae* type b or *N. meningitidis.* **Rifaximin** is a nonabsorbed rifamycin that has been used as an adjunct agent to treat patients with multiple recurrences of *C. difficile* infection. The emerging crisis in antimicrobial resistance has also necessitated the "rediscovery" of antimicrobial agents seldom used in clinical practice in recent decades, such as **colistin (colistimethate sodium).** This agent is a member of the polymyxin family of antibiotics (polymyxin E). Polymyxins have a general structure consisting of a cyclic peptide with hydrophobic tails. After binding to lipopolysaccharide in the outer membrane of Gram-negative bacteria, polymyxins disrupt both the outer and inner membranes, leading to cell death. Colistin is broadly active against the *Enterobacteriaceae* family, including *P. aeruginosa.* It is also active against extended-spectrum β-lactamase– and carbapenemase-producing strains. Toxicities are chiefly renal and neurologic.

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Section 4

Gram-Positive Bacterial Infections

Chapter 181

Staphylococcus

James T. Gaensbauer and James K. Todd

Staphylococci are hardy, aerobic, Gram-positive bacteria that grow in pairs and clusters and are ubiquitous as normal flora of humans and present on fomites and in dust. They are resistant to heat and drying and may be recovered from nonbiologic environments weeks to months after contamination. Strains are classified as *Staphylococcus aureus* if they are coagulase positive or as 1 of the many species of **coagulase-negative staphylococci** (e.g., *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus haemolyticus,* etc.). Often, *S. aureus* produces a yellow or orange pigment and β-hemolysis on blood agar and *S. epidermidis* produces a white pigment with variable hemolysis results, although definitive species confirmation requires further testing. *S. aureus* has many virulence factors that mediate various serious diseases, whereas coagulase-negative staphylococci tend to be less pathogenic unless an indwelling foreign body (e.g., intravascular catheter) is present. Since 2000, *S. aureus* strains resistant to β-lactam antibiotics, commonly referred to as methicillin-resistant *S. aureus* (MRSA) have become a significant problem in both community and hospital settings. Vancomycin resistance is rare, but MRSA have been reported with an elevated vancomycin minimal inhibitory concentration (≥ 1.5 mg/L).

181.1 *Staphylococcus aureus*

James T. Gaensbauer and James K. Todd

S. aureus is the most common cause of pyogenic infection of the skin and soft tissues. Bacteremia (primary and secondary) is common and can be associated with or result in osteomyelitis, suppurative arthritis, pyomyositis, deep abscesses, pneumonia, empyema, endocarditis, pericarditis, and rarely meningitis. Toxin-mediated diseases, including food poisoning, staphylococcal scarlet fever, scalded skin syndrome, and toxic shock syndrome (TSS), are caused by certain *S. aureus* strains.

ETIOLOGY

Strains of *S. aureus* can be identified and characterized by the virulence factors they produce. These factors tend to play 1 or more of 4 pathogenic roles in human disease: *S. aureus* protecting the organism from host defenses, localizing infection, causing local tissue damage, and affecting noninfected sites through toxin elaboration.

Most strains of *S. aureus* possess factors that protect the organism from host defenses. Many staphylococci produce a loose polysaccharide capsule, or **slime layer,** which may interfere with opsonophagocytosis. Production of clumping factor and/or **coagulase** differentiates *S. aureus* from coagulase-negative staphylococci. Clumping factor interacts with fibrinogen to cause large clumps of organisms, interfering with effective phagocytosis. Coagulase causes plasma to clot by interacting with fibrinogen and this may have an important role in localization of infection (abscess formation). **Protein A** is present in most strains of *S. aureus* but not coagulase-negative staphylococci and reacts specifically with immunoglobulin G (IgG_1, IgG_2, and IgG_4). It is

located on the outermost coat of the cell wall and can absorb serum immunoglobulins, preventing antibacterial antibodies from acting as opsonins and thus inhibiting phagocytosis. Other enzymes elaborated by staphylococci include **catalase** (inactivates hydrogen peroxide, promoting intracellular survival), **penicillinase** or **β-lactamase** (inactivates penicillin at the molecular level), and lipase (associated with skin infection).

Many strains of *S. aureus* produce substances that cause local tissue destruction. A number of immunologically distinct hemolysins that act on cell membranes and cause tissue necrosis have been identified (α-toxin, β-hemolysin, δ-hemolysin). Much attention has been given to the **Panton-Valentine leukocidin,** a protein that *S. aureus* combines with phospholipid in the leukocytic cell membrane, producing increased permeability and eventual death of the cell. Strains of *S. aureus* that produce Panton-Valentine leukocidin are associated with more-severe and invasive skin disease, pneumonia, and osteomyelitis. Many strains of *S. aureus* release 1 or more exotoxins. **Exfoliatins A and B** are serologically distinct proteins that produce localized (bullous impetigo) or generalized (scalded skin syndrome, staphylococcal scarlet fever) dermatologic manifestations (see Chapter 659). Exfoliatins produce skin separation by splitting the desmosome and altering the intracellular matrix in the stratum granulosum.

S. aureus can produce more than 20 distinct enterotoxins (types A-V). Ingestion of preformed enterotoxin, particularly types A or B, can result in **food poisoning,** resulting in vomiting and diarrhea and, in some cases, profound hypotension. By 10 yr of age, almost all individuals have antibodies to at least 1 enterotoxin.

Toxic shock syndrome toxin-1 (TSST-1) is associated with TSS related to menstruation and focal staphylococcal infection. TSST-1 is a superantigen that induces production of interleukin-1 and tumor necrosis factor, resulting in hypotension, fever, and multisystem involvement. Enterotoxins A and B also may be associated with nonmenstrual TSS.

S. aureus also possesses intrinsic factors that can contribute to pathogenesis, including **teichoic acid** in the cell wall, which mediates adhesion to mucosal cells proteins that promote adhesion to fibrinogen, fibronectin, collagen, and other human proteins. Expression of proteins that mediate antibiotic resistance is also of critical importance. Though historically sensitive to penicillin, *S. aureus* isolates now almost universally produce penicillinase, an enzyme that disrupts the β-lactam structure of penicillin. Production of altered penicillin-binding proteins (PBPs) in the bacterial cell wall mediates resistance to penicillinase resistant antibiotics; an **altered PBP-2A** is responsible for the methicillin resistance of MRSA isolates. MRSA strains appear to be at least as virulent as their methicillin-sensitive counterparts.

EPIDEMIOLOGY

Approximately 20-40% of normal individuals carry at least 1 strain of *S. aureus* in the anterior nares at any given time, with intermittent carriage occurring in up to 70% of individuals. The organisms may be transmitted from the nose to the skin, where colonization is more transient. Persistent umbilical, vaginal, and perianal carriage may also occur. Many neonates are colonized within the 1st wk of life. Rates of colonization with MRSA in the general population are typically less than 2% but have increased since 2000. MRSA colonization rates greater than 20-30% have been reported in higher risk populations with significant healthcare exposure.

Exposure to *S. aureus* generally occurs by autoinoculation or direct contact with the hands of other colonized individuals. Heavily colonized nasal carriers (often aggravated by a viral upper respiratory tract infection) are particularly effective disseminators. Spread via fomites is rare, though an outbreak occurring in a high school football team was attributed to sharing towels. Infection control policies in healthcare facilities, particularly those emphasizing good hand hygiene, have been shown to decrease rates of nosocomial staphylococcal infection.

Outside of the hospital setting, outbreaks of staphylococcal disease, in particular disease due to methicillin-resistant strains, have been reported among athletes, military personnel, young children, veterinarians, injection drug users, and inmates in correctional facilities. Increased disease frequency is noted among household contacts of a MRSA colonized or infected individual. Skin infections caused by *S. aureus* are considerably more prevalent among persons living in low socioeconomic circumstances and particularly among those in tropical climates.

The burden of staphylococcal disease is significant. Most important is the role of *S. aureus,* including MRSA, in hospital acquired infections, including infections of the bloodstream, infection of surgical sites, and ventilator-associated pneumonia. *S. aureus* is a significant cause of morbidity and mortality in neonatal intensive care units. Two population-based studies suggested a decline in rates of MRSA-related hospital-acquired infection, possibly reflecting the benefits of aggressive infection control procedures.

Community-acquired staphylococcal infections are estimated to result in 14 million outpatient healthcare visits. In 2005 an estimated 478,000 hospitalizations were associated with *S. aureus* infection in the United States, over half of which were caused by MRSA.

PATHOGENESIS

Except in the case of food poisoning resulting from ingestion of preformed enterotoxins, disease associated with *S. aureus* typically begins with colonization as described above. Subsequent disease manifestations in susceptible individuals results either directly from tissue invasion or injury caused by various toxins and enzymes produced by the organism (Fig. 181-1).

The most significant risk factor for the development of infection is disruption of intact skin, including breaches from wounds, skin disease such as eczema, epidermolysis bullosa or burns, ventriculoperitoneal shunts, and indwelling intravascular or intrathecal catheters. Additional risk factors include corticosteroid treatment, malnutrition, and azotemia. Antibiotic therapy with a drug to which *S. aureus* is resistant favors colonization and the development of infection. Viral infections of the respiratory tract, especially influenza virus, may predispose to secondary bacterial infection with staphylococci in certain individuals.

Congenital defects in chemotaxis (Job syndrome, Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome) and defective phagocytosis and killing (neutropenia, chronic granulomatous disease) increase the risk for staphylococcal infections. Patients with HIV infection have neutrophils that are defective in their ability to kill *S. aureus* in vitro. Patients with recurrent staphylococcal infection should be evaluated for immune defects, especially those involving neutrophil dysfunction.

Infants may acquire type-specific humoral immunity to staphylococci transplacentally. Older children and adults develop antibodies to staphylococci as a result of colonization or minor infections. Antibody to the various *S. aureus* toxins appears to protect against those specific toxin-mediated diseases, but humoral immunity does not necessarily protect against focal or disseminated *S. aureus* infection with the same organisms.

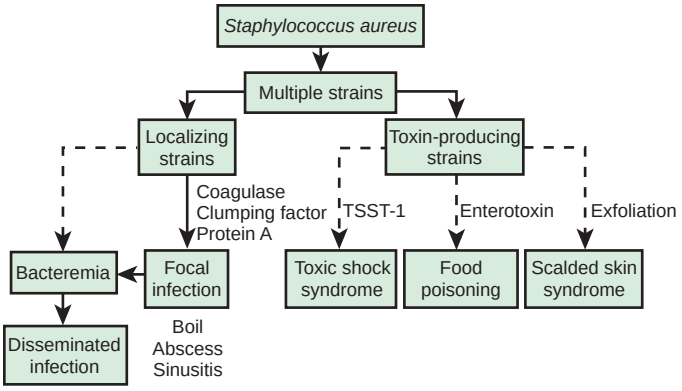

Figure 181-1 Relationship of virulence factors and diseases associated with *Staphylococcus aureus*. TSST-1, toxic shock syndrome toxin-1.

CLINICAL MANIFESTATIONS

Signs and symptoms vary with the location of the infection, which is most commonly the skin but may be any tissue. Disease states of various degrees of severity are generally a result of local suppuration, systemic dissemination with metastatic infection, or systemic effects of toxin production.

Newborn

S. aureus is an important cause of neonatal infections (see Chapter 109.5).

Skin

S. aureus is an important cause of pyogenic skin infections, including impetigo contagiosa, ecthyma, bullous impetigo, folliculitis, hydradenitis, furuncles (boils), carbuncles (multiple coalesced boils), paronychia, staphylococcal scalded skin syndrome, and staphylococcal scarlet fever. Infection may also cause superinfection of other noninfectious skin disease, for example, eczema, or bug bites. Recurrent furunculosis is associated with repeated episodes of pyoderma over months to years. Recurrent skin and soft-tissue infections are commonly noted with community-associated MRSA and often affect the lower extremities and buttocks. *S. aureus* is also an important cause of traumatic and surgical wound infections and can cause deep soft-tissue involvement, including cellulitis and rarely necrotizing fasciitis.

Respiratory Tract

Infections of the upper respiratory tract (otitis media, sinusitis) caused by *S. aureus* are rare, in particular considering the frequency with which the anterior nares are colonized. *S. aureus* sinusitis is relatively common in children with cystic fibrosis or defects in leukocyte function and may be the only focus of infection in some children with TSS. Suppurative parotitis is a rare infection, but *S. aureus* is a common cause of this infection. A membranous **tracheitis** that complicates viral croup may be a result of infection with *S. aureus,* but other organisms are also possible. Patients typically have high fever, leukocytosis, and evidence of severe upper airway obstruction. Direct laryngoscopy or bronchoscopy shows a normal epiglottis with subglottic narrowing and thick, purulent secretions within the trachea. Treatment requires careful airway management and appropriate antibiotic therapy.

Pneumonia (see Chapter 400) caused by *S. aureus* may be primary or secondary after a viral infection such as influenza. Hematogenous pneumonia may be secondary to septic emboli from right-sided endocarditis or septic thrombophlebitis, with or without the presence of intravascular devices. Inhalation pneumonia is caused by alteration of mucociliary clearance, leukocyte dysfunction, or bacterial adherence initiated by a viral infection. Common symptoms and signs include high fever, abdominal pain, tachypnea, dyspnea, and localized or diffuse bronchopneumonia or lobar disease. *S. aureus* often causes a **necrotizing pneumonitis** that may be associated with early development of empyema, pneumatoceles, pyopneumothorax, and bronchopleural fistulas.

Sepsis

S. aureus bacteremia and sepsis may be primary or associated with any localized infection. The onset may be acute and marked by nausea, vomiting, myalgia, fever, and chills. Organisms may localize subsequently at any site (usually a single deep focus) but are found especially in the heart valves, lungs, joints, bones, muscles, and deep tissue abscesses.

In some instances, especially in young adolescent males, disseminated *S. aureus* disease occurs, characterized by fever, persistent bacteremia despite antibiotics, and focal involvement of 2 or more separate tissue sites (skin, bone, joint, kidney, lung, liver, heart). In these cases, endocarditis and septic thrombophlebitis must be ruled out. All patients with primary *S. aureus* bacteremia, especially those with persistently positive blood cultures should be evaluated for endocarditis with transthoracic, and if that is negative, transesophageal, echocardiography.

Muscle

Localized staphylococcal abscesses in muscle sometimes without septicemia have been called **pyomyositis.** This disorder is reported most frequently from tropical areas and is termed tropical pyomyositis, but also occurs frequently in the United States in otherwise healthy children. Multiple abscesses occur in 30-40% of cases. History may include prior trauma at the site of the abscess. Surgical drainage and appropriate antibiotic therapy are essential.

Bones and Joints

S. aureus is the most common cause of osteomyelitis and suppurative arthritis in children (see Chapters 684 and 685).

Central Nervous System

Meningitis (see Chapter 603.1) caused by *S. aureus* is not common; it is associated with penetrating cranial trauma and neurosurgical procedures (craniotomy, cerebrospinal fluid [CSF] shunt placement), and less frequently with endocarditis, parameningeal foci (epidural or brain abscess), diabetes mellitus, or malignancy. The CSF profile of *S. aureus* meningitis is indistinguishable from that in other forms of bacterial meningitis.

Heart

S. aureus is a common cause of acute endocarditis (see Chapter 437) on native valves, and results in high rates of morbidity and mortality. Perforation of heart valves, myocardial abscesses, heart failure, conduction disturbances, acute hemopericardium, purulent pericarditis, and sudden death may ensue.

Kidney

S. aureus is a common cause of renal and perinephric abscess (see Chapter 538), usually of hematogenous origin. Pyelonephritis and cystitis caused by *S. aureus* are unusual.

Toxic Shock Syndrome

S. aureus is the principal cause of TSS (see Chapter 181.2), which should be suspected in anyone with fever, shock, and/or a scarlet fever-like rash.

Intestinal Tract

Staphylococcal enterocolitis rarely follows overgrowth of normal bowel flora by *S. aureus*, which can occur as a result of broad-spectrum oral antibiotic therapy. Diarrhea is associated with blood and mucus. Peritonitis associated with *S. aureus* in patients receiving long-term ambulatory peritoneal dialysis usually involves the catheter tunnel. Removal of the catheter is required to achieve a bacteriologic cure.

Food poisoning (see Chapter 340) may be caused by ingestion of **preformed** enterotoxins produced by staphylococci in contaminated foods. The source of contamination is often colonized or infected food workers. Approximately 2-7 hr after ingestion of the toxin, sudden, severe vomiting begins. Watery diarrhea may develop, but fever is absent or low. Symptoms rarely persist longer than 12-24 hr. Rarely, shock and death may occur.

DIAGNOSIS

The diagnosis of *S. aureus* infection depends on isolation of the organism from nonpermissive sites such as cellulitis aspirates, abscess cavities, blood, bone or joint aspirates, or other sites of infection. Swab cultures of surfaces are not as useful, as they may reflect surface contamination rather than the true cause of infection. Tissue samples or fluid aspirates in a syringe provide the best culture material. Cellulitic lesions are ideally cultured using a needle aspirate from the most inflamed area, inoculated directly into a blood culture bottle; use of injected saline and targeting the leading edge are less effective. Isolation from the nose or skin does not necessarily imply causation because these sites may be normally colonized sites. Because of the high prevalence of MRSA, the increasing severity of *S. aureus* infections, and the fact that bacteremia is not universally present even in severe *S. aureus* infections, it is important to obtain a nonpermissive culture of any

potential focus of infection as well as a blood culture prior to starting antibiotic treatment. The organism can be grown readily in liquid and on solid media. After isolation, identification is made on the basis of Gram stain and coagulase, clumping factor, and protein A reactivity. Patterns of susceptibility to antibiotics should be assessed in serious cases, as antimicrobial resistance is increasingly common. Identification of MRSA infection or colonization has become increasingly important, from both a therapeutic and infection control standpoint. Inoculation of samples onto selective (e.g., cefoxitin-containing) media or use of latex agglutination to identify altered PBP-2a in positive cultures are 2 commonly used methods. Molecular (polymerase chain reaction) techniques are being used increasingly for the rapid identification of colonized patients on admission to the hospital or intensive care unit. Polymerase chain reaction for ribosomal RNA is emerging as an technique for identifying bacterial pathogens and may eventually complement or replace traditional culture methods.

Diagnosis of *S. aureus* food poisoning is usually made on the basis of epidemiologic and clinical findings. Food suspected of contamination may be cultured and can be tested for enterotoxin.

Differential Diagnosis

Many of the clinical entities discussed above can also be caused by other bacterial pathogens, and consideration of the differential is particularly important when making empiric antibiotic choices prior to definitive identification of the offending pathogen. Skin lesions caused by *S. aureus* may be indistinguishable from those caused by group A streptococci, although the former usually expand slowly, while the latter are prone to spread more rapidly and can be very aggressive. Fluctuant skin and soft-tissue lesions also can be caused by other organisms, including *Mycobacterium tuberculosis,* atypical mycobacteria, *Bartonella henselae* (cat-scratch disease), *Francisella tularensis,* and various fungi, among others. Noncavitary *S. aureus* pneumonia can be difficult to differentiate from more common etiologies, although children with *S. aureus* are generally more ill. *S. aureus* pneumonia is often suspected after failure to improve on standard treatment which does not cover *Staphylococcus*, or on the basis of chest roentgenograms that reveal pneumatoceles, pyopneumothorax, or lung abscess (Fig. 181-2). Other etiologies of cavitary pneumonias include *Klebsiella pneumoniae* and *M. tuberculosis*. In bone and joint infections, culture is the only reliable way to differentiate *S. aureus* from other less-common etiologies including group A streptococci and in young children, *Kingella kingae*.

TREATMENT

Antibiotic therapy alone is rarely effective in individuals with undrained abscesses or with infected foreign bodies. Loculated collections of purulent material should be relieved by incision and drainage. Foreign bodies should be removed, if possible. Therapy always should be initiated with an antibiotic consistent with the local staphylococcal susceptibility patterns as well as the severity of infection. For most patients with serious *S. aureus* infection, intravenous treatment is recommended until the patient has become afebrile and other signs of infection have improved. Oral therapy is often continued for a period of time, especially in patients with chronic infection or underlying host defense problems. Serious *S. aureus* infections, with or without abscesses, tend to persist and recur, necessitating prolonged therapy.

The antibiotic used as well as the dose, route, and duration of treatment depend on the site and severity of infection, the response of the patient to treatment, and the susceptibility of the organisms recovered. Treatment of *S. aureus* osteomyelitis (see Chapter 684), meningitis (see Chapter 603.1), and endocarditis (see Chapter 437) is discussed in the respective chapters on these diagnoses.

Initial treatment for serious infections thought to be caused by methicillin-susceptible *S. aureus* (MSSA) should include semisynthetic penicillin (e.g., nafcillin) or a first-generation cephalosporin (e.g., cefazolin). Penicillin and ampicillin are not appropriate, because more than 90% of all staphylococci isolated, regardless of source, are resistant to these agents. Addition of a β-lactamase inhibitor (clavulanic acid, sulbactam, tazobactam) to a penicillin-based drug also confers antistaphylococcal activity but has no effect on MRSA. The spectrum of these agents (which includes Gram-negative bacteria) can be an advantage when broad empiric coverage is needed, but more narrow coverage should be selected once *S. aureus* is identified. Antistaphylococcal penicillins and cephalosporins do not provide activity against MRSA. For initial treatment for penicillin-allergic individuals and those with suspected serious infections caused by MRSA, vancomycin can be used. Serum levels of vancomycin should be monitored, with serum trough concentrations of 10-20 μg/mL, depending on the case. Many, but not all MSSA and community-acquired MRSA strains are susceptible to clindamycin, and initial treatment with IV clindamycin, followed by a transition to oral clindamycin has been effective in bone, joint, and soft-tissue infection. Inducible clindamycin resistance in isolates initially reported as susceptible must be ruled out by D-test or molecular methods. Clindamycin is bacteriostatic and should not be used to treat endocarditis, brain abscess, or meningitis caused by *S. aureus.* Given that the mechanism of action of clindamycin involves inhibition or protein synthesis, many experts use clindamycin to treat *S. aureus* toxin–mediated illnesses (TSS) to inhibit toxin production.

MRSA is also resistant to carbapenems and is unreliably susceptible to the quinolones. Rare vancomycin intermediate and vancomycin-resistant strains of *S. aureus* have also been reported, mostly in patients being treated with vancomycin. Linezolid, daptomycin, and

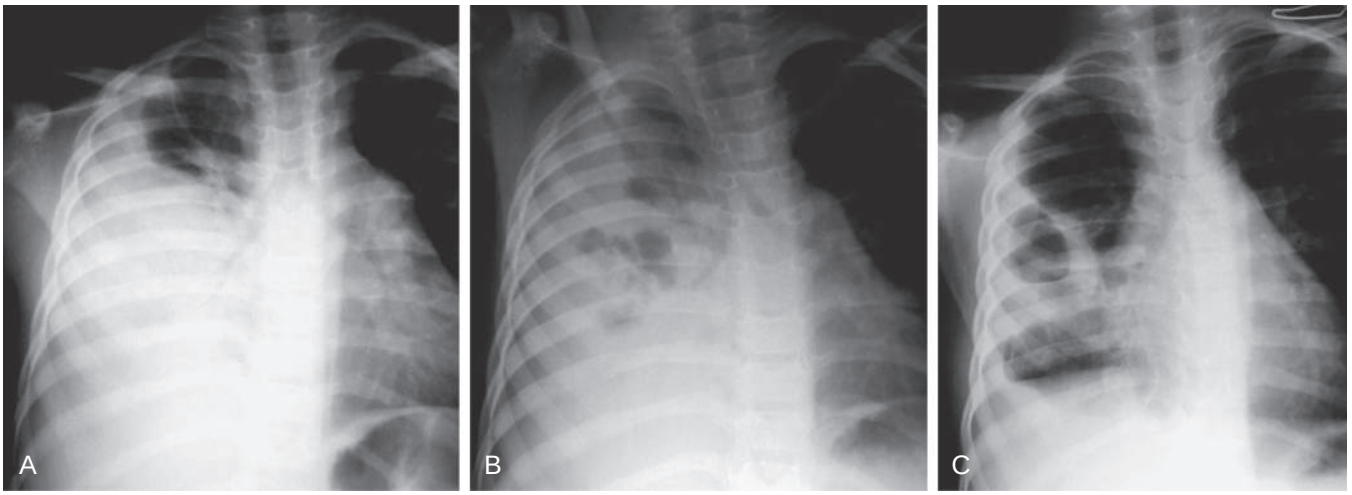

Figure 181-2 Pneumatocele formation. **A,** A 5 yr old child with *Staphylococcus aureus* pneumonia initially demonstrated consolidation of the right middle and lower zones. **B,** Seven days later, multiple lucent areas are noted as pneumatoceles develop. **C,** Two weeks later, significant resolution is evident, with a rather thick-walled pneumatocele persisting in the right midzone associated with significant residual pleural thickening. *(From Kuhn JP, Slovis TL, Haller JO:* Caffey's pediatric diagnostic imaging, *ed 10. Philadelphia, 2004, Mosby, pp. 1003–1004.)*

quinupristin-dalfopristin are useful for serious *S. aureus* infections highly resistant to other antibiotics (Table 181-1). Nonetheless, most *S. aureus* isolates with higher minimal inhibitory concentrations against vancomycin (≥1.5 mg/L) have been successfully treated with appropriate dosing of vancomycin. Ceftaroline (IV), a broad-spectrum antistaphylococcal cephalosporin, is approved for MRSA skin infections in adults, but pediatric experience is limited. Three new FDA approved antibiotics for adults with skin and soft tissue MRSA infections are oritavancin, dalbavancin, and tedizolid. Rifampin or gentamicin may be added to a β-lactam or vancomycin for synergy in serious infections such as endocarditis, particularly when prosthetic valve material is involved.

In many infections, oral antimicrobials may be substituted to complete the course of treatment after an initial period of parenteral therapy and determination of antimicrobial susceptibilities, or can be utilized as initial treatment in less-severe infections. Dicloxacillin (50-100 mg/kg/24 hr divided 4 times per day PO) and cephalexin (25-100 mg/kg/24 hr divided 3-4 times per day PO) are absorbed well orally and are effective against MSSA. Amoxicillin-clavulanate (40-80 mg amoxicillin/kg/24 hr divided 3 times per day PO) is also effective, as is clindamycin (30-40 mg/kg/24 hr divided 3-4 times per day PO). Trimethoprim-sulfamethoxazole may be an effective oral antibiotic for many strains of both MSSA and MRSA. Despite in vitro susceptibility of *S. aureus* to ciprofloxacin and other quinolone antibiotics, these agents should not be used in serious staphylococcal infections, because their use is associated with rapid development of resistance.

The duration of oral therapy depends on the response as determined by the clinical response and in some cases, roentgenographic and laboratory findings.

Table 181-1 Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections

SUSCEPTIBILITY	ANTIMICROBIAL AGENTS	COMMENTS
I. INITIAL EMPIRIC THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)		
Drugs of choice:	Vancomycin (15 mg/kg Q6-H + nafcillin or oxacillin)	For life-threatening infections (i.e., septicemia, endocarditis, CNS infection); linezolid could be substituted if the patient has received several recent courses of vancomycin
	Vancomycin (15 mg/kg Q8H)	For non–life-threatening infection without signs of severe sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial
	Clindamycin	For non–life-threatening infection without signs of severe sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is low
II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT *S. AUREUS*		
Drugs of choice:	Nafcillin or oxacillin[†]	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
Alternatives (depending on susceptibility results):	Cefazolin	
	Clindamycin	
	Vancomycin	Only for penicillin- and cephalosporin-allergic patients
	Ampicillin + sulbactam	
III. MRSA (OXACILLIN MIC, 4 μG/ML OR GREATER)		
A. Healthcare-Associated (Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin[†]	
Alternatives: susceptibility testing results available before alternative drugs are used	Trimethoprim-sulfamethoxazole	
	Linezolid[‡]	
	Quinupristin-dalfopristin[‡]	
	Fluoroquinolones	Not recommended for people younger than 18 yr of age or as monotherapy
B. Community (Not Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin[†]	For life-threatening infections
	Clindamycin (if strain susceptible)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole	For skin or soft tissue infections
Alternatives:	Vancomycin	
IV. VANCOMYCIN INTERMEDIATELY SUSCEPTIBLE OR *S. AUREUS*[†] (MIC, 4 TO 16 μG/ML)[‡]		
Drugs of choice:	Optimal therapy is not known	Dependent on in vitro susceptibility test results
	Linezolid[‡]	
	Daptomycin[§]	
	Quinupristin-dalfopristin[‡]	
	Tigecycline[‡]	
Alternatives:	Vancomycin + linezolid ± gentamicin	
	Vancomycin + trimethoprim-sulfamethoxazole[†]	

[†]One of the adjunctive agents, gentamicin or rifampin, should be added to the therapeutic regimen for life-threatening infections such as endocarditis or CNS infection or infections with a vancomycin-intermediate *S. aureus* strain. Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

[‡]Linezolid, quinupristin-dalfopristin, and tigecycline are agents with activity in vitro and efficacy in adults with multidrug-resistant, Gram-positive organisms, including *S. aureus*. Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use.

[§]Daptomycin is active in vitro against multidrug-resistant, Gram-positive organisms, including *S. aureus*, but has not been evaluated in children. Daptomycin is approved by the US FDA only for the treatment of complicated skin and skin structure infections and for *S. aureus* bloodstream infections. Daptomycin is ineffective for treatment of pneumonia and is not indicated for patients 18 yr of age and older.

CNS, central nervous system; MRSA, methicillin-resistant *S. aureus*; MIC, minimum inhibitory concentration.

From Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

PROGNOSIS

Untreated *S. aureus* septicemia is associated with a high fatality rate, which has been reduced significantly by appropriate antibiotic treatment. *S. aureus* pneumonia can be fatal at any age but is more likely to be associated with high morbidity and mortality in young infants or in patients whose therapy has been delayed. Prognosis also may be influenced by numerous host factors, including nutrition, immunologic competence, and the presence or absence of other debilitating diseases. In most cases with abscess formation, surgical drainage is necessary.

PREVENTION

S. aureus infection is transmitted primarily by direct contact. Strict attention to handwashing techniques is the most effective measure for preventing the spread of staphylococci from 1 individual to another (see Chapter 173). Use of a hand wash containing chlorhexidine or alcohol is recommended. In hospitals or other institutional settings, all persons with acute *S. aureus* infections should be isolated until they have been treated adequately. There should be constant surveillance for nosocomial *S. aureus* infections within hospitals. When MRSA is recovered, strict isolation of affected patients has been shown to be the most effective method for preventing nosocomial spread of infection. Thereafter, control measures should be directed toward identification of new isolates and strict isolation of newly colonized or infected patients. Clusters of cases may be defined by molecular typing. If associated with a singular molecular strain, it may also be necessary to identify colonized hospital personnel and attempt to eradicate carriage in affected individuals.

A number of protocols exist aimed at decolonization in patients with recurrent *S. aureus* skin infection, particularly in individuals colonized with MRSA. These often involve various combinations of decontaminating baths (hypochlorite, 1 teaspoon common bleach solution per gallon of water, or chlorhexidine 4% soap), an appropriate oral antibiotic, and nasal mupirocin. Although success is not universal, recurrent infections may be reduced, particularly when eradication is done in both patient and frequent or household contacts. Most cases of mild, recurrent disease will resolve in time without these measures.

Food poisoning (see Chapter 340) may be prevented by excluding individuals with *S. aureus* infections of the skin from the preparation and handling of food. Prepared foods should be eaten immediately or refrigerated appropriately to prevent multiplication of *S. aureus* with which the food may have been contaminated.

Bibliography is available at Expert Consult.

181.2 Toxic Shock Syndrome

James T. Gaensbauer and James K. Todd

Toxic shock syndrome (TSS) is an acute and potentially severe illness characterized by fever, hypotension, erythematous rash with subsequent desquamation on the hands and feet, and multisystem involvement, including vomiting, diarrhea, myalgias, nonfocal neurologic abnormalities, conjunctival hyperemia, and strawberry tongue.

ETIOLOGY

TSS is caused by TSST-1–producing and some enterotoxin-producing strains of *S. aureus,* which may colonize the vagina or cause focal sites of staphylococcal infection.

EPIDEMIOLOGY

TSS continues to occur in the United States in men, women, and children, with highest rates in menstruating women 15-25 yr of age. **Nonmenstrual TSS** is associated with *S. aureus* infected nasal packing and wounds, sinusitis, tracheitis, pneumonia, empyema, abscesses, burns, osteomyelitis, and primary bacteremia. Most strains of *S. aureus* associated with TSS are methicillin susceptible. While USA300, the predominant isolate of community-acquired MRSA in the United States, does not contain genes expressing the most common TSS superantigens, MRSA-associated TSS does occasionally occur.

PATHOGENESIS

The primary toxin associated with TSS is TSST-1, though a significant proportion of nonmenstrual TSS is caused by 1 or more staphylococcal enterotoxins. These toxins act as a superantigens, which trigger cytokine release causing massive loss of fluid from the intravascular space and end-organ cellular injury. Epidemiologic and in vitro studies suggest that these toxins are selectively produced in a clinical environment consisting of a neutral pH, a high P_{CO_2}, and an "aerobic" P_{O_2}, which are the conditions found in abscesses and the vagina with tampon use during menstruation. The risk factors for symptomatic disease include a nonimmune host colonized with a toxin-producing organism, which is exposed to focal growth conditions (menstruation plus tampon use or abscess) that induce toxin production. It appears that some hosts may have a varied cytokine response to exposure to TSST-1, helping to explain a spectrum of severity of TSS that may include staphylococcal scarlet fever. The overall mortality rate of treated patients is 3-5% with early treatment.

Approximately 90% of adults have antibody to TSST-1 without a history of clinical TSS, suggesting that most individuals are colonized at some point with a toxin-producing organism at a site (anterior nares) where low-grade or inactive toxin exposure results in an immune response without disease.

CLINICAL MANIFESTATIONS

The diagnosis of TSS is based on clinical manifestations (Table 181-2). The onset is abrupt, with high fever, vomiting, and diarrhea, and is accompanied by sore throat, headache, and myalgias. A diffuse erythematous macular rash (sunburn-like or scarlatiniform) appears within 24 hr and may be associated with hyperemia of pharyngeal, conjunctival, and vaginal mucous membranes. A strawberry tongue is common. Symptoms often include alterations in the level of consciousness, oliguria, and hypotension, which in severe cases may progress to shock and disseminated intravascular coagulation. Complications, including acute respiratory distress syndrome, myocardial dysfunction, and renal failure, are commensurate with the degree of shock. Recovery occurs within 7-10 days and is associated with

Table 181-2 Diagnostic Criteria of Staphylococcal Toxic Shock Syndrome

MAJOR CRITERIA (ALL REQUIRED)
Acute fever; temperature >38.8°C (101.8°F)
Hypotension (orthostatic, shock; blood pressure below age-appropriate norms)
Rash (erythroderma with convalescent desquamation)
MINOR CRITERIA (ANY 3 OR MORE)
Mucous membrane inflammation (vaginal, oropharyngeal or conjunctival hyperemia, strawberry tongue)
Vomiting, diarrhea
Liver abnormalities (bilirubin or transaminase greater than twice upper limit of normal)
Renal abnormalities (urea nitrogen or creatinine greater than twice upper limit of normal, or greater than 5 white blood cells per high-power field)
Muscle abnormalities (myalgia or creatinine phosphokinase greater than twice upper limit of normal)
Central nervous system abnormalities (alteration in consciousness without focal neurologic signs)
Thrombocytopenia (100,000/mm^3 or less)
EXCLUSIONARY CRITERIA
Absence of another explanation
Negative blood cultures (except occasionally for *Staphylococcus aureus*)

Data from Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

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desquamation, particularly of palms and soles; hair and nail loss have also been observed after 1-2 mo. Immunity to the toxins is slow to develop, so recurrences can occur, especially if there is inadequate antibiotic treatment and/or recurrent tampon use. Many cases of apparent scarlet fever without shock may be caused by TSST-1-producing *S. aureus* strains.

DIAGNOSIS

There is no specific laboratory test, and diagnosis is dependent on meeting certain clinical and laboratory criteria in the absence of an alternate diagnosis (see Fig. 181-2). Appropriate tests reveal involvement of multiple organ systems, including the hepatic, renal, muscular, gastrointestinal, cardiopulmonary, and central nervous systems. Bacterial cultures of the associated focus (vagina, abscess) before administration of antibiotics usually yield *S. aureus,* although this is not a required element of the definition.

Differential Diagnosis

Group A *Streptococcus* can cause a similar TSS-like illness, termed **streptococcal TSS** (see Chapter 183), which is often associated with severe streptococcal sepsis or a focal streptococcal infection such as cellulitis, necrotizing fasciitis, or pneumonia.

Kawasaki disease closely resembles TSS clinically but is usually not as severe or rapidly progressive. Both conditions are associated with fever unresponsive to antibiotics, hyperemia of mucous membranes, and an erythematous rash with subsequent desquamation. However, many of the clinical features of TSS are usually absent or rare in Kawasaki disease, including diffuse myalgia, vomiting, abdominal pain, diarrhea, azotemia, hypotension, acute respiratory distress syndrome, and shock (see Chapter 166). Kawasaki disease typically occurs in children younger than 5 yr. Scarlet fever, Rocky Mountain spotted fever, leptospirosis, toxic epidermal necrolysis, sepsis, and measles must also be considered in the differential diagnosis.

TREATMENT

Recommended antibiotic therapy for TSS should include the combination of a β-lactamase–resistant antistaphylococcal antibiotic (nafcillin, oxacillin, or a first-generation cephalosporin) plus clindamycin to reduce toxin production. Though TSS is most commonly caused by MSSA, clinicians should consider use of vancomycin in place of the β-lactam in areas where MRSA rates are very high, when hospital acquired MRSA is suspected, and when the clinical picture overlaps with staphylococcal sepsis. Drainage of the vagina by removal of any retained tampons in menstrual TSS and of focally infected sites in nonmenstrual TSS is important for successful treatment. Antistaphylococcal therapy and avoidance of tampon use may also reduce the risk for recurrence in menstrual TSS.

TSS often requires intensive supportive care, including aggressive fluid replacement to prevent or treat hypotension, renal failure, and cardiovascular collapse. Inotropic agents may be needed to treat shock; corticosteroids and intravenous immunoglobulin may be helpful in severe cases.

PREVENTION

The risk for acquiring menstrual TSS (1-2 cases/100,000 menstruating women) is low. Changing tampons at least every 8 hr is recommended. If a fever, rash, or dizziness develops during menstruation, any tampon should be removed immediately and medical attention should be sought.

Bibliography is available at Expert Consult.

181.3 Coagulase-Negative Staphylococci

James K. Todd

At present, there are approximately 30 species of coagulase negative staphylococci (CoNS) affecting or colonizing humans. *Staphylococcus epidermidis*, and less commonly *Staphylococcus hominis, S. haemolyticus,* and others, are widely distributed on the skin and are significant causes of nosocomial infection, particularly in the bloodstream of neonatal and immunocompromised hosts, in surgical patients and those with indwelling catheters and other medical devices. *S. saprophyticus* is a common cause of urinary tract infection. *Staphylococcus lugdunensis* has been increasingly recognized as cause of potentially severe infection.

EPIDEMIOLOGY

In the United States, CoNS are the most common cause of hospital acquired infection, particularly in neonatal units. In many instances, growth of CoNS from clinical specimens represents contamination from skin, rather than a cause of true disease, posing significant challenges for clinicians and infection control specialists. CoNS are normal inhabitants of the human skin, throat, mouth, vagina, and urethra. *S. epidermidis* is the most common and persistent species, representing 65-90% of staphylococci present on the skin and mucous membranes. Colonization, sometimes with strains acquired from hospital staff, precedes infection; alternatively, direct inoculation during surgery may initiate infection of CSF shunts, prosthetic valves, or indwelling vascular lines. For epidemiologic purposes, CoNS can be identified on the basis of molecular DNA methods.

PATHOGENESIS

CoNS produce an **exopolysaccharide** protective biofilm, or **slime layer,** that surrounds the organism and may enhance adhesion to foreign surfaces, resist phagocytosis, and impair penetration of antibiotics. However, the low virulence of CoNS usually requires the presence of another factor for development of clinical disease. Of these, the most significant is the presence of an indwelling catheter or other medical device, including hemodialysis shunts and grafts, CSF shunts (meningitis), peritoneal dialysis catheters (peritonitis), pacemaker wires and electrodes (local infection), prosthetic cardiac valves (endocarditis), and prosthetic joints (arthritis). Other risk factors for the development of infection include immature or compromised immunity and significant exposure to antibiotics.

CLINICAL MANIFESTATIONS

Bacteremia

CoNS, specifically *S. epidermidis,* are the most common cause of nosocomial bacteremia, usually in association with central vascular catheters. In neonates, CoNS bacteremia, with or without a central venous catheter, may be manifested as apnea, bradycardia, temperature instability, abdominal distention, hematochezia, meningitis in the absence of CSF pleocytosis, and cutaneous abscesses. Persistence of positive blood cultures despite adequate antimicrobial therapy is common, particularly when catheters are not removed. In older children, CoNS bacteremia is indolent and is not usually associated with overwhelming septic shock.

Endocarditis

Infection of native heart valves or the right atrial wall secondary to an infected thrombosis at the end of a central line may produce endocarditis. *S. epidermidis* and other CoNS may rarely produce native valve subacute endocarditis in previously normal patients without a central venous catheter. CoNS is a common cause of prosthetic valve endocarditis, presumably a result of inoculation at the time of surgery. Infection of the valve sewing ring, with abscess formation and dissection, produces valve dysfunction, dehiscence, arrhythmias, or valve obstruction (see Chapter 437). *S. lugdunensis* has been increasingly associated with severe endocardial infection in adults, but its role as a significant pediatric pathogen is unclear.

Central Venous Catheter Infection

Central venous catheters become infected through the exit site and subcutaneous tunnel, which provide a direct path to the bloodstream. *S. epidermidis* is the most frequent pathogen, owing in part to its high rate of cutaneous colonization. **Line sepsis** is usually manifested as

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fever and leukocytosis; tenderness and erythema may be present at the exit site or along the subcutaneous tunnel. Catheter thrombosis may complicate line sepsis. Disease severity with CoNS is often less severe than other etiologies of line infection.

Cerebrospinal Fluid Shunts

CoNS, introduced at the time of surgery, is the most common pathogen associated with CSF shunt meningitis. Most (70-80%) infections occur within 2 mo of the operation and are manifested by signs of meningeal irritation, fever, increased intracranial pressure (headache), or peritonitis from the intraabdominal position of the distal end of the shunt tubing.

Urinary Tract Infection

S. saprophyticus is a common cause of primary urinary tract infections in sexually active females. Manifestations are similar to those characteristics of urinary tract infection caused by *Escherichia coli* (see Chapter 538). CoNS also cause asymptomatic urinary tract infection in hospitalized patients with urinary catheters and after urinary tract surgery or transplantation.

DIAGNOSIS

Because *S. epidermidis* is a common skin inhabitant and may contaminate poorly collected blood cultures, differentiating bacteremia from contamination is often difficult. True bacteremia should be suspected if blood cultures grow rapidly (within 24 hr), ≥2 blood cultures are positive with the same CoNS strain, cultures from both line and peripheral sites are positive, and clinical and laboratory signs and symptoms compatible with CoNS sepsis are present and subsequently resolve with appropriate therapy. No blood culture that is positive for CoNS in a neonate or patient with intravascular catheter should be considered contaminated without careful assessment of the foregoing criteria and examination of the patient. Before initiating presumptive antimicrobial therapy in such patients, it is always prudent to draw 2 separate blood cultures to facilitate subsequent interpretation if CoNS is grown.

TREATMENT

Most CoNS strains are resistant to methicillin. *Vancomycin is the drug of choice for methicillin-resistant strains*. The addition of rifampin to vancomycin may increase antimicrobial efficacy. Other antibiotics with good in vitro activity against CoNS may be considered in certain circumstances. These include linezolid, quinupristin-dalfopristin, and daptomycin. Antibiotics with potential activity include teicoplanin, clindamycin, and trimethoprim-sulfamethoxazole. Removal of an infected catheter is ideal. However, this is not always possible owing to the therapeutic requirements of the underlying disease (nutrition for short bowel syndrome, chemotherapy for malignancy). A trial of intravenous vancomycin is indicated to attempt to preserve the use of the central line as long as systemic manifestations of infection are not severe. Antibiotic therapy given through an infected central venous catheter (alternating lumens if multiple), and the use of antibiotic locks in conjunction with systemic therapy may increase the likelihood of curing CoNS line sepsis without line removal. In many cases of CoNS infection associated with foreign bodies, the catheter, valve, or shunt must be removed to ensure a cure. Prosthetic heart valves and CSF shunts usually have to be removed to treat the infection adequately.

Peritonitis caused by *S. epidermidis* in patients on continuous ambulatory peritoneal dialysis is an infection that may be treated with intravenous or intraperitoneal antibiotics without removing the dialysis catheter. If the organism is resistant to methicillin, vancomycin adjusted for renal function is appropriate therapy. Unlike most CoNS, *S. saprophyticus* is usually methicillin susceptible, and urinary tract infection can typically be treated with a first-generation cephalosporin (cephalexin), amoxicillin-clavulanic acid, or trimethoprim-sulfamethoxazole.

PROGNOSIS

Most episodes of CoNS bacteremia respond successfully to antibiotics and removal of any foreign body that is present. Poor prognosis is associated with malignancy, neutropenia, and infected prosthetic or native heart valves. CoNS increases morbidity, the duration of hospitalization, and mortality rates among patients with underlying complicated illnesses.

PREVENTION

Iatrogenic morbidity and resource utilization caused by contaminated blood cultures, can be reduced by the use of gloves, good skin preparatory techniques, and through the use of trained, dedicated personnel to draw blood cultures. Prevention of CoNS infection of indwelling lines include basic techniques such as good hand hygiene, adequate decontamination of hubs and ports prior to access, minimizing frequency of access, and frequent replacement of external connections/infusion materials. Antibiotic impregnated catheters, antiseptic impregnated dressings, and the use of antibiotic or ethanol locks are being evaluated for reducing line-associated bloodstream infections.

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Chapter 182

Streptococcus pneumoniae (Pneumococcus)

James B. Wood and Timothy R. Peters

Streptococcus pneumoniae (pneumococcus) is a very important pathogen that kills more than 1 million children each year. Childhood pneumococcal disease is prevalent and commonly severe, causes numerous clinical syndromes, and is a major cause of life-threatening pneumonia, bacteremia, and meningitis. Antimicrobial resistance in pneumococcus is a major public health problem, with 15-30% of isolates worldwide classified as multidrug-resistant (MDR; resistant to ≥3 classes of antibiotics). Pneumococcal polysaccharide-protein conjugate vaccines (PCVs) developed for infants have been highly successful in the control of disease caused by virulent vaccine-specific serotypes. Epidemiologic surveillance reveals a dynamic pneumococcal ecology with emergence of highly virulent, MDR serotypes. Ongoing vaccine development and distribution efforts remain our best approach to control of this threat to childhood health.

ETIOLOGY

S. pneumoniae is a Gram-positive, lancet-shaped, polysaccharide encapsulated diplococcus, occurring occasionally as individual cocci or in chains. More than 90 serotypes have been identified by type-specific capsular polysaccharides. Antisera to some pneumococcal polysaccharides crossreact with other pneumococcal types, defining serogroups (e.g., 6A and 6B). Encapsulated strains cause most serious disease in humans. Capsular polysaccharides impede phagocytosis. Virulence is related in part to capsular size, but pneumococcal types with capsules of the same size can vary widely in virulence.

On solid media, *S. pneumoniae* forms unpigmented, umbilicated colonies surrounded by a zone of incomplete (α) hemolysis. *S. pneumoniae* is bile soluble (i.e., 10% deoxycholate) and Optochin-sensitive. *S. pneumoniae* is closely related to the viridans groups of *Streptococcus mitis*, which typically overlap phenotypically with pneumococci. The conventional laboratory definition of pneumococci continues to rely on bile and Optochin sensitivity, although considerable confusion occurs in distinguishing pneumococci and other α-hemolytic streptococci. Pneumococcal capsules can be microscopically visualized and typed by exposing organisms to type-specific antisera that combine with their unique capsular polysaccharide, rendering the capsule

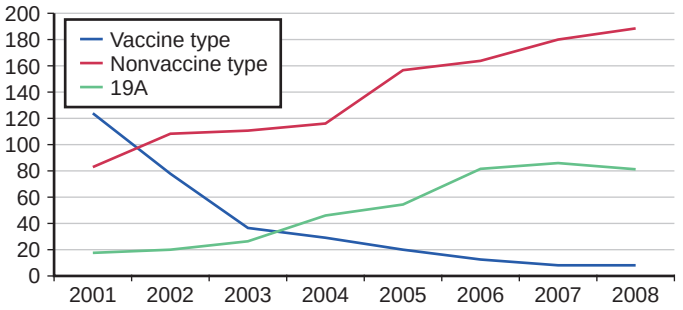

Figure 182-1 Number of invasive pneumococcal isolates (*y*-axis) that were vaccine serotype, nonvaccine serotype, or 19A in children from 8 children's hospitals according to study year from 2001-2008. The total annual admissions among the 8 children's hospitals were 91,950 in 2001, 94,055 in 2002, 95,809 in 2003, 96,472 in 2004, 99,008 in 2005, 101,116 in 2006, 103,524 in 2007, and 105,367 in 2008. *(From Kaplan SL, Barson WJ, Lin PL, et al: Serotype 19A is the most common serotype causing invasive pneumococcal infections in children,* Pediatrics *125:429–436, 2010.)*

refractile (Quellung reaction). Specific antibodies to capsular polysaccharides confer protection on the host, promoting opsonization and phagocytosis. Additionally, $CD4^+$ T cells have a direct role in antibody-independent immunity to pneumococcal nasopharyngeal colonization. Conjugated PCVs promote T-cell immunity and protect against pneumococcal colonization, in contrast to the pneumococcal polysaccharide vaccine (PPSV23) that is used in adults and certain high-risk pediatric populations and that does not affect nasopharyngeal colonization.

Table 182-1 Children at Increased Risk of Invasive Pneumococcal Infection

RISK GROUP	CONDITION
Immunocompetent children	Chronic heart disease* Chronic lung disease† Diabetes mellitus Cerebrospinal fluid leaks Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies Congenital or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection Chronic renal failure and nephrotic syndrome Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas and Hodgkin disease; or solid-organ transplantation Congenital immunodeficiency‡

*Particularly cyanotic congenital heart disease and cardiac failure.
†Including asthma if treated with high-dose oral corticosteroid therapy.
‡Includes B-(humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C1,C2,C3, and C4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).
Adapted from Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 1.*

EPIDEMIOLOGY

Most healthy individuals carry various *S. pneumoniae* serotypes in their upper respiratory tract; more than 90% of children between 6 mo and 5 yr of age harbor *S. pneumoniae* in the nasopharynx at some time. A single serotype usually is carried by a given individual for an extended period (45 days to 6 mo). Carriage does not consistently induce local or systemic immunity sufficient to prevent later reacquisition of the same serotype. Rates of pneumococcal carriage peak during the 1st and 2nd yr of life and decline gradually thereafter. Carriage rates are highest in institutional setting and during the winter, and rates are lowest in summer. Nasopharyngeal carriage of pneumococci is common among young children attending out-of-home care, with rates of 21-59% in point prevalence studies.

Prior to the introduction of heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F caused most invasive childhood pneumococcal infections in the United States. The introduction of PCVs resulted in a marked decrease in invasive pneumococcal infections (IPIs) in children. However, by 2005 IPIs began to increase slightly as a result of an increase in non-PCV7 serotypes, particularly serotype 19A (Fig. 182-1). The occurrence of "serotype replacement" can result from expansion of existing nonvaccine serotypes, as well as from vaccine type pneumococci acquiring the polysaccharide capsule of a nonvaccine serotype (serotype switching). Since the introduction of PCV13 in 2010 in the United States, there has been a decline in IPIs caused by new vaccine serotypes, including 19A. Indirect protection of unvaccinated persons has occurred since PCV introduction, and this herd protection is likely a result of decreases in nasopharyngeal carriage of virulent pneumococcal vaccine serotypes.

S. pneumoniae is the most frequent cause of bacteremia, bacterial pneumonia, otitis media, and bacterial meningitis in children. The decreased ability in children younger than 2 yr of age to produce antibody against the T-cell–independent polysaccharide antigens and the high prevalence of colonization may explain an increased susceptibility to pneumococcal infection and the decreased effectiveness of polysaccharide vaccines. Children at increased risk of pneumococcal infections include those with sickle cell disease, asplenia, deficiencies in humoral (B cell) and complement-mediated immunity, HIV infection, certain malignancies (e.g., leukemia, lymphoma), chronic heart, lung, or renal disease (particularly nephrotic syndrome), cerebrospinal fluid leak, and cochlear implants. Table 182-1 lists other high-risk groups. Some American Indian, Alaska Native, and African-American children may also be at increased risk. Children younger than 5 yr of age in out-of-home daycare are at increased risk (approximately 2-fold higher) of experiencing IPIs than other children. Males are more commonly affected than females.

Pneumococcal disease usually occurs sporadically but can be spread from person to person by respiratory droplet transmission. *S. pneumoniae* is an important cause of secondary bacterial pneumonia in patients with influenza. During influenza epidemics and pandemics, most deaths result from bacterial pneumonia, and *Pneumococcus* is the predominant bacterial pathogen isolated in this setting. Pneumococcal copathogenicity may be important in disease caused by other respiratory viruses as well.

PATHOGENESIS

Invasion of the host is affected by a number of factors. Nonspecific defense mechanisms, including the presence of other bacteria in the nasopharynx, may limit multiplication of pneumococci. Aspiration of secretions containing pneumococci is hindered by the epiglottic reflex and by respiratory epithelial cell cilia, which move infected mucus toward the pharynx. Similarly, normal ciliary flow of fluid from the middle ear through the eustachian tube and sinuses to the nasopharynx usually prevents infection with nasopharyngeal flora, including pneumococci. Interference with these normal clearance mechanisms by allergy, viral infection, or irritants (e.g., smoke) may allow colonization and subsequent infection with these organisms in otherwise normally sterile sites.

Virulent pneumococci are intrinsically resistant to phagocytosis by alveolar macrophages. Pneumococcal disease frequently is facilitated by viral respiratory tract infection, which may produce mucosal injury, diminish epithelial cell ciliary activity, and depress the function of alveolar macrophages and neutrophils. Phagocytosis may be impeded by respiratory secretions and alveolar exudate. In the lungs and other tissues, the spread of infection is facilitated by the antiphagocytic

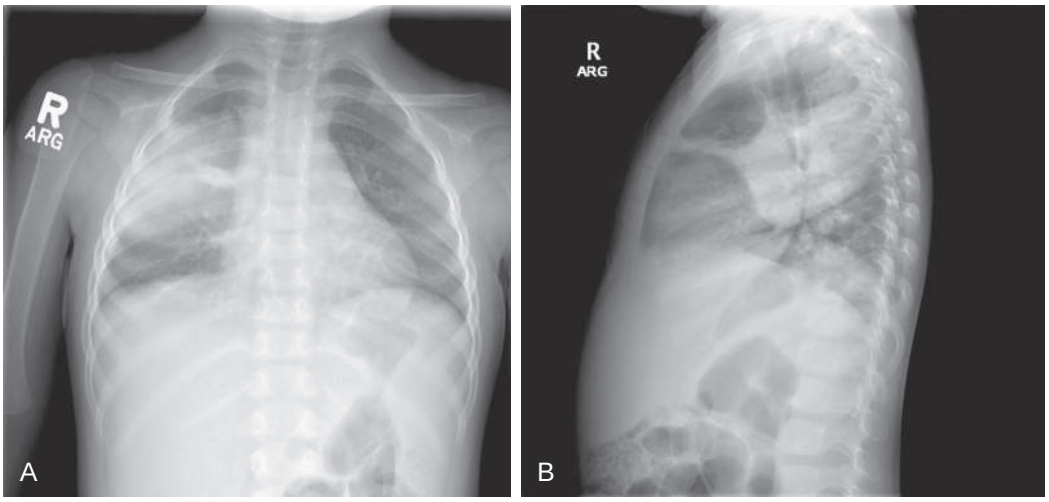

Figure 182-2 Bacterial pneumonia. "Round" pneumonia caused by *Streptococcus pneumoniae* in a 2 yr old girl with a 2-day history of cough, high fever, leukocytosis, and back pain.

properties of the pneumococcal capsule. Surface fluids of the respiratory tract contain only small amounts of immunoglobulin G and are deficient in complement. During inflammation, there is limited influx of immunoglobulin G, complement, and neutrophils. Phagocytosis of bacteria by neutrophils may occur, but normal human serum may not opsonize pneumococci and facilitate phagocytosis by alveolar macrophages. In tissues, pneumococci multiply and spread through the lymphatics or bloodstream or, less commonly, by direct extension from a local site of infection (e.g., sinuses). In bacteremia, the severity of disease is related to the number of organisms in the bloodstream and to the integrity of specific host defenses. A poor prognosis correlates with very large numbers of pneumococci and high concentrations of capsular polysaccharide in the blood and cerebrospinal fluid.

Invasive pneumococcal disease is 30- to 100-fold more prevalent in children with sickle cell disease and other hemoglobinopathies and in children with congenital or surgical asplenia than in the general population. This risk is greatest in infants younger than 2 yr of age, as at that age antibody production to most serotypes is poor. The increased frequency of pneumococcal disease in asplenic persons is related to both deficient opsonization of pneumococci as well as absence of clearance by the spleen of circulating bacteria. Children with sickle cell disease also have deficits in the antibody-independent properdin (alternative) pathway of complement activation, in addition to functional asplenia. Both complement pathways contribute to antibody-independent and antibody-dependent opsonophagocytosis of pneumococci. With advancing age (e.g., >5 yr), children with sickle cell disease produce anticapsular antibody, augmenting antibody-dependent opsonophagocytosis and greatly reducing, but not eliminating, the risk of severe pneumococcal disease. Deficiency of many of the complement components (e.g., C2 and C3) is associated with recurrent pyogenic infection, including *S. pneumoniae* infection. The efficacy of phagocytosis also is diminished in patients with B- and T-cell immunodeficiency syndromes (e.g., agammaglobulinemia, severe combined immune deficiency) or loss of immune globulin (e.g., nephrotic syndrome) and is largely caused by a deficiency of opsonic anticapsular antibody. These observations suggest that opsonization of pneumococci depends on the alternative complement pathway in antibody-deficient persons and that recovery from pneumococcal disease depends on the development of anticapsular antibodies that act as opsonins, enhancing phagocytosis and killing of pneumococci. Children with HIV infection also have high rates of IPI similar to or greater than rates in children with sickle cell disease, although rates of invasive pneumococcal disease decreased after the introduction of highly active antiretroviral therapy.

CLINICAL MANIFESTATIONS

The signs and symptoms of pneumococcal infection are related to the anatomic site of disease. Common clinical syndromes include otitis media (see Chapter 640), sinusitis (see Chapter 380), pneumonia (Fig. 182-2) (see Chapter 400), and sepsis (see Chapter 70). Before routine use of PCVs, pneumococci caused >80% of bacteremia episodes in infants 3-36 mo of age with fever without an identifiable source (i.e., occult bacteremia). Bacteremia may be followed by meningitis (see Chapter 603), osteomyelitis (see Chapter 684), suppurative arthritis (see Chapter 685), endocarditis (see Chapter 437), and, rarely, brain abscess (see Chapter 604). Primary peritonitis (see Chapter 371) may occur in children with peritoneal effusions due to nephrotic syndrome and other conditions. Local complications of infection may occur, causing empyema, pericarditis, mastoiditis, epidural abscess, periorbital cellulitis, or meningitis. Hemolytic-uremic syndrome (see Chapter 484.4) and disseminated intravascular coagulation also occur as rare complications of pneumococcal infections. Epidemic conjunctivitis caused by nonencapsulated or encapsulated pneumococci occurs as well.

DIAGNOSIS

The diagnosis of pneumococcal infection is established by recovery of *S. pneumoniae* from the site of infection or the blood/sterile body fluid. Although pneumococci may be found in the nose or throat of patients with otitis media, pneumonia, septicemia, or meningitis, cultures of these locations are generally not helpful for diagnosis, as they are not indicative of causation. Blood cultures should be obtained in children with pneumonia, meningitis, arthritis, osteomyelitis, peritonitis, pericarditis, or gangrenous skin lesions. Because of the implementation of universal vaccination with PCVs, there has been a substantial decrease in the incidence of occult bacteremia, but blood cultures should still be considered in febrile patients with clinical toxicity or significant leukocytosis. Leukocytosis often is pronounced, with total white blood cell counts frequently >15,000/μL. In severe cases of pneumococcal disease, white blood cell count may be low.

Pneumococci can be identified in body fluids as Gram-positive, lancet-shaped diplococci. Early in the course of pneumococcal meningitis, many bacteria may be seen in relatively acellular cerebrospinal fluid. With current methods of continuously monitored blood culture systems, the average time to isolation of pneumococcal organisms is 14-15 hr. Pneumococcal latex agglutination tests for urine or other body fluids suffer from poor sensitivity and add little to Gram-stained fluids and standard cultures.

TREATMENT

Antimicrobial resistance among *S. pneumoniae* continues to be a serious healthcare concern, especially for the widely used β-lactams, macrolides and fluoroquinolones. Serotypes 6A, 6B, 9V, 14, 19A, 19F, and 23F are the most common serotypes associated with resistance to penicillin. Consequently, the introduction of the 7- and 13-valent

pneumococcal conjugate vaccines (PCV7 and PCV13) has altered antimicrobial resistance patterns.

Resistance in pneumococcal organisms to penicillin and the extended-spectrum cephalosporins cefotaxime and ceftriaxone is defined by the minimum inhibitory concentration (MIC), as well as clinical syndrome. Pneumococci are considered susceptible, intermediate, or resistant to various antibacterial agents based on specific MIC breakpoints. For patients with pneumococcal meningitis, penicillin-susceptible strains have an MIC ≤0.06 μg/mL and penicillin-resistant strains have an MIC ≥0.12 μg/mL. For patients with nonmeningeal pneumococcal infections, breakpoints are higher; in particular, penicillin susceptible strains have an MIC ≤2 μg/mL, and penicillin resistant strains have an MIC ≥8 μg/mL. For patients with meningitis, cefotaxime and ceftriaxone susceptible strains have an MIC ≤0.5 μg/mL and resistant strains have an MIC ≥2.0 μg/mL. For patients with nonmeningeal pneumococcal disease, breakpoints are higher, and cefotaxime- and ceftriaxone-susceptible strains have an MIC ≤1 μg/mL and resistant strains have an MIC ≥4 μg/mL. In cases where the pneumococcus is resistant to erythromycin but sensitive to clindamycin, **a D-test should be performed** to determine whether clindamycin resistance can be induced; if the D-test is positive, clindamycin should not be used to complete treatment of the patient. More than 30% of pneumococcal isolates are resistant to trimethoprim-sulfamethoxazole; levofloxacin resistance is low, but has also been reported. All isolates from children with severe infections should be tested for antibiotic susceptibility given widespread pneumococcal MDR strains. Resistance to vancomycin has not been seen to as of the writing of this chapter, but vancomycin-tolerant pneumococci that are killed at a slower rate have been reported, and these tolerant pneumococci may be associated with a worse clinical outcome. Linezolid is an oxazolidinone antibacterial with activity against MDR Gram-positive organisms, including *Pneumococcus*, and has been used in the treatment of MDR pneumococcal pneumonia, meningitis, and severe otitis. Despite early favorable studies, use of this drug is limited by myelosuppression and high cost, and linezolid resistance in *Pneumococcus* is reported.

Children 1 mo of age or older with suspected pneumococcal meningitis should be treated with combination therapy using vancomycin (60 mg/kg/24 hr divided q 6 hr IV), and high-dose cefotaxime (300 mg/kg/24 hr divided q 8 hr IV) or ceftriaxone (100 mg/kg/24 hr divided q 12 hr IV). Proven pneumococcal meningitis can be treated with penicillin alone, or cefotaxime or ceftriaxone alone, if the isolate is penicillin-susceptible. If the organism is nonsusceptible (i.e., intermediate or full resistance) to penicillin but susceptible to cefotaxime and ceftriaxone, pneumococcal meningitis can be treated with cefotaxime or ceftriaxone alone. However, if the organism is nonsusceptible to penicillin and to cefotaxime or ceftriaxone, pneumococcal meningitis should be treated with combination vancomycin plus cefotaxime or ceftriaxone, not with vancomycin alone, and consideration should be given to the addition of rifampin. Some experts recommend use of corticosteroids in pneumococcal meningitis early in the course of disease, but data demonstrating clear benefit in children is lacking.

In 2011 the Infectious Diseases Society of America published guidelines for the management of community-acquired pneumonia in infants and children. Per these guidelines, amoxicillin may be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate uncomplicated community-acquired pneumonia. Ampicillin or penicillin G may be administered to the fully immunized infant or school-age child admitted to a hospital ward with uncomplicated community-acquired pneumonia, when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *S. pneumoniae*. Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents widespread penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia, given the degree of drug resistance currently seen in the United States.

For individuals who are allergic to penicillin, clindamycin, erythromycin (or related macrolides, e.g., azithromycin or clarithromycin), cephalosporins (standard dosing), and trimethoprim-sulfamethoxazole may provide effective alternative therapy for susceptible strains, depending on the site of infection (e.g., clindamycin may be effective for pneumococcal infections other than meningitis). Higher doses of amoxicillin (80-100 mg/kg/24 hr) have been successful in the treatment of otitis media caused by penicillin-nonsusceptible strains. Empirical treatment of pneumococcal disease should be based on knowledge of susceptibility patterns in specific communities.

PROGNOSIS

Prognosis depends on the integrity of host defenses, virulence and numbers of the infecting organism, the age of the host, the site and extent of the infection, and the adequacy of treatment. The mortality rate for pneumococcal meningitis is approximately 10% in most studies. Pneumococcal meningitis results in sensorineural hearing loss in 20-30% of patients and can cause other serious neurologic sequelae, including paralysis, epilepsy, blindness, and intellectual deficits.

PREVENTION

The highly successful PCVs have resulted in a marked decrease in IPIs in children. PCVs (Table 182-2) provoke protective antibody responses in 90% of infants given these vaccines at 2, 4, and 6 mo of age, and greatly enhanced responses (e.g., immunologic memory) are apparent after vaccine doses given at 12-15 mo of age. In a large clinical trial, PCV7 was shown to reduce invasive disease caused by vaccine serotypes by up to 97% and to reduce invasive disease caused by all serotypes, including serotypes not in the vaccine, by 89%. Children who received PCV7 had 7% fewer episodes of acute otitis media and underwent 20% fewer tympanostomy tube placements than did unvaccinated children. In preliminary studies following PCV 13, a 42% reduction in IPIs caused by vaccine serotypes has been seen. The greatest reduction in the number of cases occurred in children younger than 24 mo of age. Mastoiditis cases, which have been especially associated with serotype 19A isolates, had the greatest percentage decrease. In addition, pneumococcal conjugate vaccines significantly reduce nasopharyngeal carriage of vaccine serotypes. PCVs have significantly decreased rates of invasive pneumococcal disease in children with sickle cell disease, and studies suggest substantial protection for HIV-infected children and splenectomized adults. Adverse events after the administration of PCV have included local swelling and redness and slightly

Table 182-2 Comparison of Pneumococcal Vaccines Licensed in United States*

CARRIER PROTEIN	PNEUMOCOCCAL CAPSULAR POLYSACCHARIDES	MANUFACTURER
Diphtheria CRM_{197} protein	**4, 6B, 9V, 14, 18C, 19F, 23F**	Wyeth Lederle (PCV7, Prevnar)
Diphtheria CRM_{197} protein	1, 3, **4,** 5, 6A, **6B,** 7F, **9V, 14, 18C,** 19A, **19F, 23F**	Wyeth Lederle (PCV13, Prevnar 13)
None	1, 2, 3, **4,** 5, **6B,** 7F, 8, 9N, **9V,** 10A, 11A, 12F, **14,** 15B, 17F, **18C,** 19A, **19F,** 20, 22F, **23F,** 33F	Sanofi Pasteur MSD (PPSV23, Pneumovax II)

*PCV7 serotypes in bold.

increased rates of fever, when used in conjunction with other childhood vaccines.

Immunologic responsiveness and efficacy following administration of pneumococcal polysaccharide vaccines (PPSV23) is unpredictable in children younger than 2 yr of age. PPSV23 contains purified polysaccharide of 23 pneumococcal serotypes responsible for more than 95% of cases of invasive disease. The clinical efficacy of PPSV23 is controversial and studies have yielded conflicting results.

Immunization with PCV13 is recommended for all infants on a schedule for primary immunization, in previously unvaccinated infants, and for transition for those partially vaccinated with PCV7 (Tables 182-3 and 182-4). High-risk children 2 yr of age and older, such as those with asplenia, sickle cell disease, some types of immune deficiency (e.g., antibody deficiencies), HIV infection, cochlear implant, cerebrospinal fluid leak, diabetes mellitus, and chronic lung, heart, or kidney disease (including nephrotic syndrome), may benefit also from PPSV23 administered after 2 yr of age following priming with the scheduled doses of PCV13. Thus, it is recommended that children 2 yr of age and older with these underlying conditions receive supplemental vaccination with PPSV23. A 2nd dose of PPSV23 is recommended 5 yr after the 1st dose of PPSV23 for persons age 2 yr or older who are immunocompromised, have sickle cell disease, or functional or anatomic asplenia. Additional recommendations have been made for at-risk children between 6-18 yr (Table 182-5).

Immunization with pneumococcal vaccines also may prevent pneumococcal disease caused by nonvaccine serotypes that are serotypically related to a vaccine strain. However, because current vaccines do not eliminate all pneumococcal invasive infections, penicillin prophylaxis is recommended for children at high risk of invasive pneumococcal disease, including children with asplenia or sickle cell disease. Oral penicillin V potassium (125 mg bid for children <3 yr; 250 mg bid for children ≥3 yr) decreases the incidence of pneumococcal sepsis in children with sickle cell disease. Once-monthly intramuscular benzathine penicillin G (600,000 units q 3-4 wk for children weighing <60 lb; 1,200,000 units q 3-4 wk for children weighing ≥60 lb) may also provide prophylaxis. Erythromycin may be used in children with penicillin allergy, but its efficacy is unproved. Prophylaxis in sickle cell disease has been safely discontinued after the 5th birthday in children who have received all recommended pneumococcal vaccine doses and who had not experienced invasive pneumococcal disease. Prophylaxis is often administered for at least 2 yr after splenectomy or up to 5 yr of age. Efficacy in children older than 5 yr of age and adolescents is unproved. If oral antibiotic prophylaxis is used, strict compliance must

Table 182-3 Recommended Routine Vaccination Schedule for 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Among Infants and Children Who Have Not Received Previous Doses of 7-Valent Vaccine (PCV7) or PCV13, by Age at First Dose—Advisory Committee on Immunization Practices (ACIP), United States, 2010

AGE AT 1ST DOSE (MO)	PRIMARY PCV13 SERIES*	PCV13 BOOSTER DOSE†
2-6	3 doses	1 dose at age 12-15 mo
7-11	2 doses	1 dose at age 12-15 mo
12-23	2 doses	—
24-59 (healthy children)	1 dose	—
24-71 (children with certain chronic diseases or immunocompromising conditions)	2 doses	—

*Minimum interval between doses is 8 wk except for children vaccinated at age <12 mo for whom minimum interval between doses is 4 wk. Minimum age for administration of 1st dose is 6 wk.

†Given at least 8 wk after the previous dose.

From Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 2.*

Table 182-4 Recommended Transition Schedule from 7-Valent Pneumococcal Conjugate Vaccine (PCV7) to 13-Valent Vaccine (PCV13) Vaccination Among Infants and Children, According to Number of Previous PCV7 Doses Received—Advisory Committee on Immunization Practices (ACIP), United States, 2010

INFANT SERIES			BOOSTER DOSE	SUPPLEMENTAL PCV13 DOSE
2 mo	4 mo	6 mo	≥12 mo*	14-59 mo†
PCV7	PCV13	PCV13	PCV13	—
PCV7	PCV7	PCV13	PCV13	—
PCV7	PCV7	PCV7	PCV13	—
PCV7	PCV7	PCV7	PCV7	PCV13

*No additional PCV13 doses are indicated for children age 12-23 mo who have received 2 or 3 doses of PCV before age 12 mo and at least 1 dose of PCV13 at age ≥12 mo.

†For children with underlying medical conditions (see Table 182-1), a single supplemental PCV13 dose is recommended through age 71 mo.

From Centers for Disease Control and Prevention (CDC): Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children—Advisory Committee on Immunization Practices (ACIP), 2010, MMWR Morb Mortal Wkly Rep *59:258–261, 2010, Table 3.*

Table 182-5 Medical Conditions or Other Indications for Administration of PCV13,* and Indications for PPSV23† Administration, and Revaccination for Children Age 6–18 Years‡

RISK GROUP	UNDERLYING MEDICAL CONDITION	PCV13 RECOMMENDED	PPSV23 RECOMMENDED	REVACCINATION 5 YR AFTER 1ST DOSE
Immunocompetent persons	Chronic heart disease§		✓	
	Chronic lung disease‖		✓	
	Diabetes mellitus		✓	
	Cerebrospinal fluid leaks	✓	✓	
	Cochlear implants	✓	✓	
	Alcoholism		✓	
	Chronic liver disease		✓	
	Cigarette smoking		✓	
Persons with functional or anatomic asplenia	Sickle cell disease/other hemoglobinopathies	✓	✓	✓
	Congenital or acquired asplenia	✓	✓	✓

Table 182-5 Medical Conditions or Other Indications for Administration of PCV13,* and Indications for PPSV23† Administration, and Revaccination for Children Age 6–18 Years‡—cont'd

RISK GROUP	UNDERLYING MEDICAL CONDITION	PCV13 RECOMMENDED	PPSV23 RECOMMENDED	REVACCINATION 5 YR AFTER 1ST DOSE
Immunocompromised persons	Congenital or acquired immunodeficiencies¶	✓	✓	✓
	Human immunodeficiency virus infection	✓	✓	✓
	Chronic renal failure	✓	✓	✓
	Nephrotic syndrome	✓	✓	✓
	Leukemia	✓	✓	✓
	Lymphoma	✓	✓	✓
	Hodgkin disease	✓	✓	✓
	Generalized malignancy	✓	✓	✓
	Iatrogenic immunosuppression**	✓	✓	✓
	Solid organ transplant	✓	✓	✓
	Multiple myeloma	✓	✓	✓

*13-valent pneumococcal conjugate vaccine.

†23-valent pneumococcal polysaccharide vaccine.

‡Children age 2-5 yr with chronic conditions (e.g., heart disease or diabetes), immunocompromising conditions (e.g., HIV), functional or anatomic asplenia (including sickle cell disease), cerebrospinal fluid leaks, or cochlear implants, and who have not previously received PCV13, have been recommended to receive PCV13 since 2010.

§Including congestive heart failure and cardiomyopathies.

‖Including chronic obstructive pulmonary disease, emphysema, and asthma.

¶Includes B-(humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease).

**Diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy.

From Centers for Disease Control and Prevention CDC): Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Rep *62:521–524, 2013.*

be encouraged. Given the rapid emergence of penicillin-resistant pneumococci, especially in children receiving long-term, low-dose therapy, prophylaxis cannot be relied on to prevent disease. High-risk children with fever should be promptly evaluated and treated regardless of vaccination or penicillin prophylaxis history.

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Chapter 183

Group A Streptococcus

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Group A streptococcus (GAS), also known as *Streptococcus pyogenes,* is a very common cause of infections of the upper respiratory tract (pharyngitis) and the skin (impetigo, pyoderma) in children and less frequently causes perianal cellulitis, vaginitis, septicemia, pneumonia, endocarditis, pericarditis, osteomyelitis, suppurative arthritis, myositis, cellulitis, and omphalitis. This organism also causes distinct clinical entities (scarlet fever and erysipelas), as well as streptococcal toxic shock syndrome and necrotizing fasciitis. GAS is also the cause of 2 potentially serious nonsuppurative complications: rheumatic fever (see Chapters 183.1 and 438) and acute glomerulonephritis (see Chapter 511.1).

ETIOLOGY

Group A streptococci are Gram-positive coccoid-shaped bacteria that tend to grow in chains. They are broadly classified by their hemolytic activity on mammalian (typically sheep) red blood cells. The zone of complete hemolysis that surrounds colonies grown on blood agar distinguishes β-hemolytic (complete hemolysis) from α-hemolytic (green or partial hemolysis) and γ (nonhemolytic) species. The β-hemolytic streptococci can be divided into groups by a group-specific polysaccharide **(Lancefield C carbohydrate)** located in the bacterial cell wall. More than 20 serologic groups are identified, designated by the letters A through V. Serologic grouping by the Lancefield method is precise, but group A organisms can be identified more readily by any one of a number of latex agglutination, coagglutination, or enzyme immunoassay procedures. Group A strains can also be distinguished from other groups by differences in sensitivity to bacitracin. A disk containing 0.04 units of bacitracin inhibits the growth of most group A strains, whereas other groups are generally resistant to this antibiotic. This method is approximately 95% accurate. GAS can be subdivided into more than 220 serotypes on the basis of the **M protein** antigen, which is located on the cell surface and in fimbriae that project from the outer surface of the cell. Currently, a molecular approach to M typing GAS isolates using the polymerase chain reaction is based on sequencing the terminal portion of the *emm* gene of GAS that encodes the M protein. More than 220 distinct M types have been identified using *emm* typing, and there is excellent correlation between known serotypes and *emm* types. Immunity is largely based upon type-specific opsonic anti-M antibody.

M serotyping is valuable for epidemiologic studies; specific GAS diseases tend to be associated with certain M types. Types 1, 12, 28, 4, 3, and 2 (in that order) are the most common causes of uncomplicated streptococcal pharyngitis in the United States. M types commonly associated with pharyngitis rarely cause skin infections, and the M types commonly associated with skin infections rarely cause pharyngitis. A few **pharyngeal** strains (e.g., M type 12) are associated with glomerulonephritis, but many more **skin** strains (e.g., M types 49, 55, 57, and 60) are considered nephritogenic. Several pharyngeal serotypes (e.g., M types 1, 3, 5, 6, 18, 29), but no skin strains, are associated with acute rheumatic fever in North America. Rheumatogenic potential is not solely dependent on serotype but is likely a characteristic of specific strains within several serotypes.

EPIDEMIOLOGY

Humans are the natural reservoir for GAS. These bacteria are highly communicable and can cause disease in normal individuals of all ages who do not have type-specific immunity against the particular serotype involved. Disease in neonates is uncommon in developed countries, probably because of maternally acquired antibody. The incidence of pharyngeal infections is highest in children 5-15 yr of age, especially in young school-age children. These infections are most common in the northern regions of the United States, especially during winter and early spring. Children with untreated acute pharyngitis spread GAS by

airborne salivary droplets and nasal discharge. Transmission is favored by close proximity; therefore, schools, military barracks, and homes are important environments for spread. The incubation period for pharyngitis is usually 2-5 days. GAS has the potential to be an important upper respiratory tract pathogen and to produce outbreaks of disease in the daycare setting. Foods containing GAS occasionally cause explosive outbreaks of pharyngotonsillitis. Children are usually no longer infectious 24 hr after appropriate antibiotic therapy has been started. Chronic pharyngeal carriers of GAS rarely transmit this organism to others.

Streptococcal pyoderma (impetigo, pyoderma) occurs most frequently during the summer in temperate climates, or year round in warmer climates, when the skin is exposed and abrasions and insect bites are more likely to occur (see Chapter 665). Colonization of healthy skin by GAS usually precedes the development of impetigo. Because GAS cannot penetrate intact skin, impetigo usually occurs at the site of open lesions (insect bites, traumatic wounds, burns). Although impetigo serotypes may colonize the throat, spread is usually from skin to skin, not via the respiratory tract. Fingernails and the perianal region can harbor GAS and play a role in disseminating impetigo. Multiple cases of impetigo in the same family are common. Both impetigo and pharyngitis are more likely to occur among children living in crowded homes and in poor hygienic circumstances.

The incidence of **severe invasive** GAS infections, including bacteremia, streptococcal toxic shock syndrome, and necrotizing fasciitis, has increased in recent decades. The incidence appears to be highest in the very young and in the elderly. Prior to the routine use of varicella vaccine, varicella was the most commonly identified risk factor for invasive GAS infection in children. Other risk factors include diabetes mellitus, HIV infection, intravenous drug use, and chronic pulmonary or chronic cardiac disease. The portal of entry is unknown in almost 50% of cases of severe invasive GAS infection; in most cases, it is believed to be skin or mucous membrane. Severe invasive disease rarely follows clinically apparent GAS pharyngitis.

PATHOGENESIS

Virulence of GAS depends primarily on the M protein, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. M protein stimulates the production of protective opsonophagocytic antibodies that are type-specific, protecting against infection with a homologous M type but much less so against other M types. Therefore, multiple GAS infections attributable to various M types are common during childhood and adolescence. By adult life, individuals are probably immune to several or many of the common M types in the environment.

GAS produces a large variety of extracellular enzymes and toxins, including erythrogenic toxins (known as *streptococcal pyrogenic exotoxins*). Streptococcal **pyrogenic exotoxins** A, B, and C are responsible for the **rash of scarlet fever** and are elaborated by streptococci that contain a particular bacteriophage. These exotoxins stimulate the formation of specific antitoxin antibodies that provide immunity against the scarlatiniform rash but not against other streptococcal infections. GAS can produce up to 12 different pyrogenic exotoxins, and repeat attacks of scarlet fever are possible. Streptococcal pyrogenic exotoxins A, B, and C, as well as several newly discovered exotoxins, appear to be involved in the pathogenesis of invasive GAS disease, including the **streptococcal toxic shock syndrome.**

The importance of other streptococcal toxins and enzymes in human disease is not yet established. Many of these extracellular substances are antigenic and stimulate antibody production after an infection. However, these antibodies do not confer immunity. Their measurement is useful for establishing evidence of a recent streptococcal infection to aid in the diagnosis of postinfectious illnesses. Tests for antibodies against streptolysin O (antistreptolysin O) and DNAse B (anti–DNAse B) are the most commonly used antibody determinations. Because the immune response to extracellular antigens varies among individuals as well as with the site of infection, it is sometimes necessary to measure other streptococcal antibodies.

CLINICAL MANIFESTATIONS

The most common infections caused by GAS involve the respiratory tract and the skin and soft tissues.

Respiratory Tract Infections

GAS is an important cause of acute pharyngitis (see Chapter 381) and pneumonia (see Chapter 400).

Scarlet Fever

Scarlet fever is an upper respiratory tract infection associated with a characteristic rash, which is caused by an infection with **pyrogenic exotoxin (erythrogenic toxin)**–producing GAS in individuals who do not have antitoxin antibodies. It is now encountered less commonly and is less virulent than in the past, but the incidence is cyclic, depending on the prevalence of toxin-producing strains and the immune status of the population. The modes of transmission, age distribution, and other epidemiologic features are otherwise similar to those for GAS pharyngitis.

The rash appears within 24-48 hr after onset of symptoms, although it may appear with the first signs of illness (Fig. 183-1*A*). It often begins around the neck and spreads over the trunk and extremities. The rash is a diffuse, finely papular, erythematous eruption producing bright red discoloration of the skin, which blanches on pressure. It is often accentuated in the creases of the elbows, axillae, and groin. The skin has a goose-pimple appearance and feels rough. The cheeks are often erythematous with pallor around the mouth. After 3-4 days, the rash begins to fade and is followed by desquamation, initially on the face, progressing downward, and often resembling a mild sunburn. Occasionally, sheet-like desquamation may occur around the free margins of the fingernails, the palms, and the soles. Examination of the pharynx of a patient with scarlet fever reveals essentially the same findings as with GAS pharyngitis. In addition, the tongue is usually coated and the papillae are swollen (Fig. 183-1*B*). After desquamation, the reddened papillae are prominent, giving the tongue a strawberry appearance (Fig. 183-1*C*).

Typical scarlet fever is not difficult to diagnose; the milder form with equivocal pharyngeal findings can be confused with viral exanthems, Kawasaki disease, and drug eruptions. Staphylococcal infections are occasionally associated with a scarlatiniform rash. A history of recent exposure to a GAS infection is helpful. Identification of GAS in the pharynx confirms the diagnosis.

Impetigo

Impetigo (or pyoderma) has traditionally been classified into 2 clinical forms: bullous and nonbullous (see Chapter 665). Nonbullous impetigo is the more common form and is a superficial infection of the skin that appears first as a discrete papulovesicular lesion surrounded by a localized area of redness. The vesicles rapidly become purulent and covered with a thick, confluent, amber-colored crust that gives the appearance of having been stuck onto the skin. The lesions may occur anywhere but are most common on the face and extremities. If untreated, nonbullous impetigo is a mild but chronic illness, often spreading to other parts of the body, but occasionally self-limited. Regional **lymphadenitis** is common. Nonbullous impetigo is generally not accompanied by fever or other systemic signs or symptoms. Impetiginized excoriations around the nares are seen with active GAS infections of the nasopharynx particularly in young children. However, impetigo is not usually associated with an overt streptococcal infection of the upper respiratory tract.

Bullous impetigo is less common and occurs most often in neonates and young infants. It is characterized by flaccid, transparent bullae usually <3 cm in diameter on previously untraumatized skin. The usual distribution involves the face, buttocks, trunk, and perineum. Although *Staphylococcus aureus* has traditionally been accepted as the sole pathogen responsible for bullous impetigo, there has been confusion about the organisms responsible for nonbullous impetigo. In most episodes of nonbullous impetigo, either GAS or *S. aureus,* or both, is isolated. Earlier investigations suggested that GAS was the causative agent in most cases of nonbullous impetigo and that *S. aureus* was only

Figure 183-1 Scarlet fever. **A,** Punctate, erythematous rash (2nd day). **B,** White strawberry tongue (1st day). **C,** Red strawberry tongue (3rd day). *(Courtesy Dr. Franklin H. Top, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes. From Gershon AA, Hotez PJ, Katz SL:* Krugman's infectious diseases of children, *ed 11, Philadelphia, 2004, Mosby, plate 53.)*

a secondary invader. However, *S. aureus* has emerged recently as the causative agent in most cases of nonbullous impetigo. Culture of the lesions is the only way to distinguish nonbullous impetigo caused by *S. aureus* from that caused by GAS.

Erysipelas

Erysipelas is a now relatively rare acute GAS infection involving the deeper layers of the skin and the underlying connective tissue. The skin in the affected area is swollen, red, and very tender. Superficial blebs may be present. The most characteristic finding is a sharply defined, slightly elevated border. At times, reddish streaks of lymphangitis project out from the margins of the lesion. The onset is abrupt, and signs and symptoms of a systemic infection, such as high fever, are often present. Cultures obtained by needle aspirate of the advancing margin of the inflamed area often reveal the causative agent.

Perianal Dermatitis

Perianal dermatitis, also called perianal cellulitis or **perianal streptococcal disease,** is a distinct clinical entity characterized by well-demarcated, perianal erythema associated with anal pruritus, painful defecation, and occasionally blood-streaked stools. Physical examination reveals flat, pink to beefy-red perianal erythema with sharp margins extending as far as 2 cm from the anus. Erythema may involve the vulva and vagina. Lesions may be very tender and, particularly when chronic, may fissure and bleed. Systemic symptoms and fever are unusual. Culture or a rapid strep test of a perianal swab will yield group A streptococci or detect antigen.

Vaginitis

GAS is a common cause of vaginitis in prepubertal girls (see Chapter 549). Patients usually have a serous discharge with marked erythema and irritation of the vulvar area, accompanied by discomfort in walking and in urination.

Severe Invasive Disease

Invasive GAS infection is defined by isolation of GAS from a normally sterile body site and includes 3 overlapping clinical syndromes. The 1st is **GAS toxic shock syndrome**, which is differentiated from other types of invasive GAS infections by the presence of shock and multiorgan system failure early in the course of the infection (Table 183-1). The 2nd is **GAS necrotizing fasciitis** characterized by extensive local necrosis of subcutaneous soft tissues and skin. The 3rd is the group of focal and systemic infections that do not meet the criteria for toxic shock syndrome or necrotizing fasciitis and includes bacteremia with no identified focus, meningitis, pneumonia, peritonitis, puerperal sepsis, osteomyelitis, suppurative arthritis, myositis, and surgical wound infections. GAS toxic shock syndrome, necrotizing fasciitis, and focal and systemic infections can be present in any combination.

Table 183-1 Definition of Streptococcal Toxic Shock Syndrome

CLINICAL CRITERIA Hypotension plus 2 or more of the following: Renal impairment Coagulopathy Hepatic involvement Adult respiratory distress syndrome Generalized erythematous macular rash Soft-tissue necrosis
DEFINITE CASE Clinical criteria plus group A streptococcus from a normally sterile site
PROBABLE CASE Clinical criteria plus group A streptococcus from a nonsterile site

The pathogenic mechanisms responsible for severe, invasive GAS infections, including streptococcal toxic shock syndrome and necrotizing fasciitis, have yet to be defined completely, but an association with streptococcal pyrogenic exotoxins is strongly suspected. The 3 original streptococcal pyrogenic exotoxins (A, B, C), the newly discovered streptococcal pyrogenic exotoxins, and potentially other as yet unidentified toxins produced by GAS act as superantigens, which stimulate intense activation and proliferation of T lymphocytes and macrophages, resulting in the production of large quantities of proinflammatory cytokines. These cytokines are capable of inducing shock and tissue injury and appear to mediate many of the clinical manifestations of severe, invasive GAS infections.

DIAGNOSIS

When deciding whether to perform a diagnostic test on a patient presenting with acute pharyngitis, the clinical and epidemiologic findings should be considered. A history of close contact with a well-documented case of GAS pharyngitis is helpful, as is an awareness of a high prevalence of GAS infections in the community. The signs and symptoms of streptococcal and nonstreptococcal pharyngitis overlap too broadly to allow the requisite diagnostic precision on clinical grounds alone. The

clinical diagnosis of GAS pharyngitis cannot be made with reasonable accuracy even by the most experienced physicians, and bacteriologic confirmation is required. The only exception to this statement are those patients with overt viral signs and symptoms such as rhinorrhea, cough, mouth ulcers, and hoarseness, who generally do not need a diagnostic test performed.

Culture of a throat swab on a sheep blood agar plate is effective for documenting the presence of GAS in the upper respiratory tract and for confirming the clinical diagnosis of acute GAS pharyngitis. When performed correctly, a single throat swab cultured on a sheep blood-agar plate has a sensitivity of 90-95% for detecting the presence of GAS in the pharynx.

A significant disadvantage of culturing a throat swab on a blood-agar plate is the delay (overnight or longer) in obtaining the culture result. **Rapid antigen detection** tests are available for the identification of GAS directly from throat swabs. Although these rapid tests are more expensive than the blood-agar culture, the advantage they offer over the traditional procedure is the speed with which they can provide results, often less than 10-15 minutes. Rapid identification and treatment of patients with streptococcal pharyngitis can reduce the risk for spread of GAS, allowing the patient to return to school or work sooner, and can reduce the acute morbidity of this illness.

Almost all currently available rapid antigen detection tests have excellent specificity of >95% when compared with blood-agar plate cultures. False-positive test results are quite unusual, and, therefore, therapeutic decisions can be made with confidence on the basis of a positive test result. Unfortunately, the sensitivity of most of these tests is 80-90%, sometimes lower, when compared with blood-agar plate culture. Therefore, a negative rapid test does not completely exclude the presence of GAS, and a confirmatory throat culture should be performed in children and adolescents but not necessarily in adults, who are at exceptionally low risk for developing acute rheumatic fever. Definitive studies to determine whether some rapid antigen detection tests are significantly more sensitive than others, and, whether any of these tests are sensitive enough to be used routinely in children and adolescents without throat culture confirmation of negative test results, are not available. Some experts believe that physicians who use a rapid antigen detection test without culture backup should compare the results with that specific test to those of throat cultures to confirm adequate sensitivity in their practice.

Nucleic acid amplification tests including isothermal loop amplification are also available to detect GAS pharyngitis with a high degree of specificity and sensitivity as well as a rapid turn-around time.

GAS infection can also be diagnosed retrospectively on the basis of an elevated or increasing streptococcal antibody titer. The antistreptolysin O assay is the streptococcal antibody test most commonly used. Because streptolysin O also is produced by groups C and G streptococcus, the test is not specific for group A infection. The antistreptolysin O response can be feeble following streptococcal skin infection. In contrast, the anti–DNase B responses are generally present after either skin or throat infections. A significant antibody increase is usually defined as an increase in titer of 2 or more dilution increments (≥4-fold rise) between the acute phase and convalescent phase specimens, regardless of the actual height of the antibody titer. Physicians frequently misinterpret streptococcal antibody titers because of a failure to appreciate that the normal levels of these antibodies are substantially higher among school-age children compared to adults. Both the traditional antistreptolysin O and anti–DNase B tests are neutralization assays. Newer tests use latex agglutination or nephelometric assays. Unfortunately, these newer tests often have not been well-standardized against the traditional neutralization assays. Physicians should be aware of these potential problems when interpreting the results of streptococcal serologic testing.

A commercially available slide agglutination test for the detection of antibodies to several streptococcal antigens is the Streptozyme test (Wampole Laboratories, Stamford, CT). This test is much-less-well standardized and less reproducible than other antibody tests, and it should not be used as a test for evidence of a preceding GAS infection.

Differential Diagnosis

Viruses are the most common cause of acute pharyngitis in children. Respiratory viruses such as influenza virus, parainfluenza virus, rhinovirus, coronavirus, adenovirus, and respiratory syncytial virus are frequent causes of acute pharyngitis. Other viral causes of acute pharyngitis include enteroviruses and herpes simplex virus. Epstein-Barr virus is a frequent cause of acute pharyngitis that is often accompanied by other clinical findings of infectious mononucleosis (e.g., splenomegaly, generalized lymphadenopathy). Systemic infections with other viral agents including cytomegalovirus, rubella virus, measles virus, and HIV may be associated with acute pharyngitis.

GAS is by far the most common cause of bacterial pharyngitis, accounting for 15-30% of cases of acute pharyngitis in children and a lower proportion in adults. Groups C and G β-hemolytic streptococcus (see Chapter 185) also cause acute pharyngitis, typically in teens and young adults. *Arcanobacterium haemolyticum* and *Fusobacterium necrophorum* are additional less common causes. *Neisseria gonorrhoeae* can occasionally cause acute pharyngitis in sexually active adolescents. Other bacteria, such as *Francisella tularensis* and *Yersinia enterocolitica,* as well as mixed infections with anaerobic bacteria (Vincent angina), are rare causes of acute pharyngitis. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have been implicated as causes of acute pharyngitis, particularly in adults. *Corynebacterium diphtheriae* (see Chapter 187) is a serious cause of pharyngitis but is rare because of universal immunization. Although other bacteria, such as *S. aureus, Haemophilus influenzae,* and *Streptococcus pneumoniae,* are frequently cultured from the throats of children with acute pharyngitis, their etiologic role in pharyngitis has not been established.

GAS pharyngitis is the only common cause of acute pharyngitis for which antibiotic therapy is definitely indicated. Therefore, when confronted with a patient with acute pharyngitis, the clinical decision that usually needs to be made is whether or not the pharyngitis is attributable to GAS.

TREATMENT

Antibiotic therapy for patients with GAS pharyngitis can prevent acute rheumatic fever, shorten the clinical course of the illness, reduce transmission of the infection to others, and prevent suppurative complications. For the patient with classic scarlet fever, antibiotic therapy should be started immediately, but for the vast majority of patients who present with much less distinctive findings, treatment should be withheld until there is some form of bacteriologic confirmation, either by throat culture or rapid antigen detection test. Rapid antigen detection tests, because of their high degree of specificity, have made it possible to initiate antibiotic therapy immediately for one with a positive test result.

GAS is exquisitely sensitive to penicillin and cephalosporins, and resistant strains have never been encountered. Penicillin or amoxicillin is therefore the drug of choice (except in patients who are allergic to penicillins) for pharyngeal infections as well as for suppurative complications. Oral penicillin V (250 mg/dose bid-tid for children weighing ≤60 lb and 500 mg/dose bid-tid for children weighing >60 lb PO) is recommended but must be taken for a full 10 days even though there is symptomatic improvement within 3-4 days. Penicillin V (phenoxyethylpenicillin) is preferred over penicillin G because it may be given without regard to mealtime. The major concern with all forms of oral therapy is the risk that the drug will be discontinued before the 10-day course has been completed. Therefore, when oral treatment is prescribed, the necessity of completing a full course of therapy must be emphasized. If the parents seem unlikely to comply with oral therapy because of family disorganization, difficulties in comprehension, or other reasons, parenteral therapy with a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for children weighing >60 lb, IM) is the most efficacious and often the most practical method of treatment. Disadvantages include soreness around the site of injection, which may last for several days, and potential for injection into nerves or blood vessels if not administered correctly. The local reaction is diminished when benzathine penicillin G is combined in a single injection with procaine

penicillin G, although it is necessary to ensure that an adequate dose of benzathine penicillin G is administered.

In several comparative clinical trials, once-daily amoxicillin (50 mg/kg, maximum: 1,000 mg) for 10 days has been demonstrated to be effective in treating GAS pharyngitis. This somewhat broader-spectrum agent has the advantage of once-daily dosing, which may enhance adherence. In addition, amoxicillin is relatively inexpensive and is considerably more palatable than penicillin V suspension.

A 10-day course of a narrow spectrum oral cephalosporin is recommended for most penicillin-allergic individuals. It has been suggested that a 10-day course with an oral cephalosporin is superior to 10 days of oral penicillin in eradicating GAS from the pharynx. Analysis of these data suggests that the difference in eradication is mainly the result of a higher rate of eradication of carriers included unintentionally in these clinical trials. Some penicillin-allergic persons (up to 10%) are also allergic to cephalosporins, and these agents should be avoided in patients with immediate (anaphylactic-type) hypersensitivity to penicillin. Most oral broad-spectrum cephalosporins are considerably more expensive than penicillin or amoxicillin, and the former agents are more likely to select for antibiotic-resistant flora.

Oral clindamycin is an appropriate agent for treating penicillin-allergic patients, and resistance to clindamycin among GAS isolates in the United States is currently only approximately 1%. An oral macrolide (erythromycin or clarithromycin) or azalide (azithromycin) is also an appropriate agent for patients allergic to penicillins. Ten days of therapy is indicated except for azithromycin, which is given at 12 mg/kg once daily for 5 days. Erythromycin is associated with substantially higher rates of gastrointestinal side effects than the other agents. In recent years, macrolide resistance rates among pharyngeal isolates of GAS in most areas of the United States have been approximately 5-8%. Sulfonamides and the tetracyclines are not indicated for treatment of GAS infections.

Most oral antibiotics must be administered for the conventional 10 days to achieve maximal pharyngeal eradication rates of GAS and prevention of rheumatic fever, but certain newer agents are reported to achieve comparable bacteriologic and clinical cure rates when given for 5 days or less. However, definitive results from comprehensive studies are not available to allow full evaluation of these proposed shorter courses of oral antibiotic therapy. Therefore, they cannot be recommended at this time. In addition, these antibiotics have a much broader spectrum than penicillin and are generally more expensive, even when administered for short courses.

The majority of patients with GAS pharyngitis respond clinically to antimicrobial therapy, and GAS is eradicated from the pharynx. Post-treatment throat cultures are indicated only in the relatively few patients who remain symptomatic, whose symptoms recur, or who have had rheumatic fever or rheumatic heart disease and are, therefore, at unusually high risk for recurrence.

Antibiotic therapy for a patient with nonbullous impetigo can prevent local extension of the lesions, spread to distant infectious foci, and transmission of the infection to others. However, the ability of antibiotic therapy to prevent poststreptococcal glomerulonephritis has not been demonstrated. Patients with a few superficial, isolated lesions and no systemic signs can be treated with topical antibiotics. Mupirocin is a safe and effective agent that has become the topical treatment of choice. If there are widespread lesions or systemic signs, oral therapy with coverage for both GAS and *S. aureus* is needed. With the rapid emergence of methicillin-resistant *S. aureus* in many communities, consideration should be given to using clindamycin alone or a combination of trimethoprim-sulfamethoxazole and amoxicillin as first-line therapy. Oral cefuroxime is an effective treatment of perianal streptococcal disease.

Theoretical considerations and experimental data suggest that intravenous clindamycin is a more effective agent for the treatment of severe, invasive GAS infections than intravenous penicillin. However, because a small proportion (approximately 1%) of GAS isolates in the United States are resistant to clindamycin, clindamycin initially should be used in combination with penicillin for these infections until susceptibility to clindamycin has been established. If **necrotizing fasciitis** is suspected, immediate surgical exploration or biopsy is required to identify a deep soft-tissue infection that should be debrided immediately. Patients with **streptococcal toxic shock syndrome** require rapid and aggressive fluid replacement, management of respiratory or cardiac failure, if present, and anticipatory management of multiorgan system failure. Limited data suggest that intravenous immunoglobulin is effective as adjunctive therapy in the management of streptococcal toxic shock syndrome.

COMPLICATIONS

Suppurative complications from the spread of GAS to adjacent structures were extremely common in the preantibiotic era. Cervical lymphadenitis, peritonsillar abscess, retropharyngeal abscess, otitis media, mastoiditis, and sinusitis still occur in children in whom the primary illness has gone unnoticed or in whom treatment of the pharyngitis has been inadequate. GAS pneumonia can also occur.

Acute rheumatic fever (see Chapter 183.1) and acute poststreptococcal glomerulonephritis (see Chapter 511.1) are both nonsuppurative sequelae of infections with GAS that occur after an asymptomatic latent period. They are both characterized by disease remote from the site of the primary GAS infection. Acute rheumatic fever and acute glomerulonephritis differ in their clinical manifestations, epidemiology, and potential morbidity. In addition, acute glomerulonephritis follows a GAS infection of either the upper respiratory tract or the skin, but acute rheumatic fever only follows an infection of the upper respiratory tract.

Poststreptococcal Reactive Arthritis

Poststreptococcal reactive arthritis (PSRA) has been used to describe a syndrome characterized by the onset of acute arthritis following an episode of GAS pharyngitis in a patient whose illness does not fulfill the Jones criteria for the diagnosis of acute rheumatic fever. It is still unclear whether this entity represents a distinct syndrome or is a variant of acute rheumatic fever. Although PSRA usually involves the large joints like the arthritis of acute rheumatic fever, it may involve small peripheral joints, as well as the axial skeleton, and is typically nonmigratory, characteristics distinct from the arthritis of acute rheumatic fever. The latent period between the antecedent episode of GAS pharyngitis and PSRA may be considerably shorter (usually <10 days) than that typically seen with acute rheumatic fever (usually 14-21 days). In contrast to the arthritis of acute rheumatic fever, PSRA does not respond dramatically to therapy with aspirin or other nonsteroidal antiinflammatory agents. In addition, PSRA is usually not migratory, and fewer patients have a fever >38°C (100.4°F). Even though no more than half of patients with PSRA who have a throat culture performed have GAS isolated, all have serologic evidence of a recent GAS infection. Because a very small proportion of patients with PSRA have been reported to develop valvular heart disease subsequently, these patients should be carefully observed for several months for clinical evidence of carditis. Some recommend that these patients receive secondary prophylaxis for up to 1 yr. If clinical evidence of carditis is not observed, the prophylaxis can then be discontinued. If valvular disease is detected, the patient should be classified as having had acute rheumatic fever and should continue to receive secondary prophylaxis.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with *Streptococcus pyogenes*

Pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus pyogenes* (PANDAS) is a term proposed for a group of neuropsychiatric disorders (particularly obsessive-compulsive disorder, tic disorder, and Tourette syndrome) for which a possible relationship with GAS infections has been hypothesized (see Chapter 24). This relationship has not been proven. It has been proposed that this subset of patients with obsessive-compulsive and tic disorders may produce autoimmune antibodies in response to a GAS infection that crossreact with brain tissue similar to the autoimmune response believed to be responsible for the manifestations of Sydenham chorea. It has also been

suggested that secondary prophylaxis that prevents recurrences of rheumatic fever, including Sydenham chorea, might also be effective in preventing exacerbations of obsessive-compulsive and tic disorders in these patients, but clinical trials have not confirmed this. It has also been proposed that these patients may benefit from immunoregulatory therapy such as plasma exchange or intravenous immunoglobulin therapy, but these unproven modalities should only be utilized in a clinical research trial. That PANDAS may represent an extension of the spectrum of acute rheumatic fever is intriguing, but it should be considered only as a yet-unproven hypothesis. Until carefully designed and well-controlled studies have established a causal relationship between neurobehavioral abnormalities and GAS infections, routine diagnostic laboratory testing for GAS and antistreptococcal antibodies, long-term antistreptococcal prophylaxis, or immunoregulatory therapy (e.g., intravenous immunoglobulin, plasma exchange) to treat exacerbations of this disorder clearly are not recommended (see Chapter 24). It has also been suggested that a broad spectrum of infectious agents may have the ability to trigger exacerbations in children with these neurobehavioral disorders.

PROGNOSIS

The prognosis for appropriately treated GAS pharyngitis is excellent, and complete recovery is the rule. When therapy is instituted within 9 days of the onset of symptoms and continued for the full course, acute rheumatic fever is almost always prevented. There is no comparable evidence that acute poststreptococcal glomerulonephritis can be prevented once pharyngitis or pyoderma with a nephritogenic strain of GAS has occurred. In rare instances, particularly in neonates or in children whose response to infection is compromised, fulminant pneumonia, septicemia, and death may occur despite usually adequate therapy.

PREVENTION

The only specific indication for long-term use of an antibiotic to prevent GAS infections is for patients with a history of acute rheumatic fever and/or rheumatic heart disease. Mass prophylaxis is generally not feasible except to reduce the number of infections during epidemics of impetigo and to control epidemics of pharyngitis in military populations and in schools. Because the ability of antimicrobial agents to prevent GAS infections is limited, a group A streptococcal vaccine offers the possibility of a more effective approach.

Several candidate vaccines are in development, including a 30-valent M protein-based recombinant vaccine, another recombinant vaccine that includes several conserved non-M protein epitopes that induce protective antibody, and a M-protein vaccine that includes an epitope in a very conserved region of M protein to provide broad immunity. All of these vaccines are in relatively early stages of development.

Bibliography is available at Expert Consult.

183.1 Rheumatic Fever

Stanford T. Shulman

ETIOLOGY

Considerable evidence supports the link between antecedent GAS upper pharyngitis tract infections and acute rheumatic fever and rheumatic heart disease. As many as two-thirds of patients with an acute episode of rheumatic fever have history of an upper respiratory tract infection several weeks before, and the peak age and seasonal incidence of acute rheumatic fever closely parallel that of GAS pharyngitis. Patients with acute rheumatic fever almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually considerably higher than those seen in patients with uncomplicated GAS infections. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by outbreaks of acute rheumatic fever. Antimicrobial therapy that eliminates GAS from the pharynx also prevents initial episodes of acute rheumatic fever, and long-term, continuous antibiotic prophylaxis that prevents GAS pharyngitis also prevents recurrences of acute rheumatic fever.

Not all serotypes of GAS can cause rheumatic fever. When some GAS strains (e.g., M type 4) caused acute pharyngitis in a very susceptible rheumatic population, no recurrences of rheumatic fever occurred. In contrast, episodes of pharyngitis caused by other serotypes in the same population led to frequent recurrences of acute rheumatic fever, suggesting that the latter organisms were rheumatogenic. The concept of rheumatogenicity is further supported by the observation that although serotypes of GAS frequently associated with skin infection can often be isolated also from the upper respiratory tract, they rarely cause recurrences of rheumatic fever in individuals with a previous history of rheumatic fever or first episodes of rheumatic fever. In addition, certain serotypes of GAS (M types 1, 3, 5, 6, 18, 29) are more frequently isolated from patients with acute rheumatic fever than are other serotypes.

EPIDEMIOLOGY

The annual incidence of acute rheumatic fever in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand. Worldwide, rheumatic heart disease remains the most common form of acquired heart disease in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions in many developing countries. Striking differences in the incidence of acute rheumatic fever and rheumatic heart disease among different ethnic groups are often evident within the same country; these differences are partially related to differences in socioeconomic status, and there is a genetic basis for increased susceptibility.

In the United States at the beginning of the 20th century, acute rheumatic fever was a leading cause of death among children and adolescents, with annual incidence rates of 100-200 per 100,000 population. In addition, rheumatic heart disease was a leading cause of heart disease among adults younger than 40 yr of age. At that time, as many as 25% of hospital beds in the United States were occupied by patients with acute rheumatic fever or its complications. By the 1940s, the annual incidence of acute rheumatic fever had decreased to 50 per 100,000 population, and over the next 4 decades, the decline in incidence accelerated rapidly. By the early 1980s, the annual incidence in some areas of the United States was as low as 0.5 per 100,000 population. This sharp decline in the incidence of acute rheumatic fever has been observed in other industrialized countries as well.

The explanation for this dramatic decline in the incidence of acute rheumatic fever and rheumatic heart disease in the United States and other industrialized countries is not clear but is likely related in large part to decline in circulating rheumatogenic strains causing acute pharyngitis. Historically, acute rheumatic fever was associated with poverty and overcrowding, particularly in urban areas. Much of the decline in the incidence of acute rheumatic fever in industrialized countries during the preantibiotic era is probably the result of improved living conditions. Of the various manifestations of poverty, crowding, which facilitates spread of GAS infections, is most closely associated with the incidence of acute rheumatic fever. The decline in incidence of acute rheumatic fever in industrialized countries over the past 4 decades is also attributable to the greater availability of medical care and to the widespread use of antibiotics. Antibiotic therapy of GAS pharyngitis is important in preventing initial attacks and, particularly, recurrences of the disease. In addition, the decline in the United States is attributed to a shift in the prevalent strains of GAS from rheumatogenic to nonrheumatogenic strains.

A dramatic outbreak of acute rheumatic fever in the Salt Lake City area began in early 1985, and 198 cases were reported by the end of 1989. Other outbreaks were reported between 1984 and 1988 in Columbus and Akron, OH; Pittsburgh, PA; Nashville and Memphis, TN; New York, NY; Kansas City, MO; Dallas, TX; and among Navy

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recruits in California and Army recruits in Missouri. In virtually all areas of the United States rates now have declined very substantially.

Certain rheumatogenic serotypes (types 1, 3, 5, 6, and 18) that were isolated infrequently during the 1970s and early 1980s dramatically reappeared during rheumatic fever outbreaks, and their appearance in selected communities was probably a major factor. GAS that are associated with rheumatogenicity often form highly mucoid colonies on throat culture plates.

In addition to the specific characteristics of the infecting strain of GAS, the risk of developing acute rheumatic fever is also dependent on various host factors. The incidence of both initial attacks and recurrences of acute rheumatic fever peaks in children 5-15 yr of age, the age of greatest risk for GAS pharyngitis. Patients who have had an attack of acute rheumatic fever tend to have recurrences, and the clinical features of the recurrences tend to mimic those of the initial attack. In addition, there appears to be a genetic predisposition to acute rheumatic fever. Studies in twins show a higher concordance rate of acute rheumatic fever in monozygotic than in dizygotic twin pairs. Some investigators have also demonstrated an association between susceptibility to rheumatic fever and specific human leukocyte antigen markers.

PATHOGENESIS

The details of the pathogenic link between a GAS infection of the upper respiratory tract and an attack of acute rheumatic fever, characterized by organ and tissue involvement at sites far removed from the pharynx, is still not clear. A major obstacle to understanding the pathogenesis of acute rheumatic fever and rheumatic heart disease has been the inability to establish an animal model. Several theories of pathogenesis have been proposed, notably the cytotoxicity theory and immunologic theories.

The cytotoxicity theory suggests that a GAS toxin is involved in the pathogenesis of acute rheumatic fever and rheumatic heart disease. GAS produces a number of enzymes that are cytotoxic for mammalian cardiac cells, such as streptolysin O, which has a direct cytotoxic effect on mammalian cells in tissue culture. Most proponents of the cytotoxicity theory have focused on this enzyme. However, a major problem with the cytotoxicity hypothesis is its inability to explain the substantial latent period (approximately 2-4 wk) between GAS pharyngitis and the onset of acute rheumatic fever.

An immune-mediated pathogenesis for acute rheumatic fever and rheumatic heart disease has been suggested by its clinical similarity to other illnesses with an immunopathogenesis and by the latent period between the GAS infection and acute rheumatic fever. The antigenicity of several GAS cellular and extracellular epitopes and their immunologic crossreactivity with cardiac antigenic epitopes also lends support to the hypothesis of molecular mimicry. Common epitopes are shared between certain GAS components (e.g., M protein, cell membrane, group A cell wall carbohydrate, capsular hyaluronate) and specific mammalian tissues (e.g., heart valve, sarcomere, brain, joint). For example, certain rheumatogenic M proteins (M1, M5, M6, and M19) share epitopes with human myocardial proteins such as tropomyosin and myosin. Additionally, the involvement of GAS superantigens such as pyrogenic exotoxins in the pathogenesis of acute rheumatic fever has been proposed.

A more recently proposed pathogenetic hypothesis is that the binding of an M protein N-terminus domain to a region of collagen type IV leads to an antibody response to the collagen, resulting in ground substance inflammation especially in subendothelial areas like cardiac valves and myocardium.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Because no clinical or laboratory finding is pathognomonic for acute rheumatic fever, T. Duckett Jones, in 1944, proposed guidelines to aid in diagnosis and to limit overdiagnosis. The **Jones Criteria,** as revised in 2015 by the American Heart Association (AHA) (Table 183-2), is now intended for diagnosis of the initial attack of acute rheumatic fever and recurrent attacks. There are **5 major** and **4 minor criteria** and a requirement of evidence of recent GAS infection. The 2015 revision now includes separate criteria for Low-Risk populations (defined as those with incidence ≤2 per 100,000 school-age children per year or all-age rheumatic heart disease prevalence of ≤1 per thousand population) and Moderate/High-Risk populations (defined as those with higher incidence or prevalence rates). Virtually all of the United States, Canada, and Western Europe are Low Risk, whereas Moderate/High-Risk populations include Maoris in New Zealand, aborigines in Australia, Pacific Islanders, and most developing countries. Diagnosis of a first attack or recurrent attack of acute rheumatic fever can be established when a patient fulfills 2 major or 1 major and 2 minor criteria and has evidence of preceding GAS infection. Diagnosis of recurrent acute rheumatic fever can also be made only in the Moderate/High Risk population by presence of 3 minor criteria with evidence of preceding GAS infection. In the 2015 Jones Criteria revision, a major change from previous versions expands the definition of the major criterion–carditis–to include subclinical evidence (i.e., in the absence of a murmur, echocardiographic evidence of mitral regurgitation [MR] meeting specific criteria to distinguish physiologic from pathologic MR) (Table 183-3). Areas in which the Jones Criteria differ in Low-Risk populations from Moderate/High-Risk populations relate to the major criterion of arthritis and in the minor criteria of arthralgia, definition of fever, and of elevated inflammatory markers (see Table 183-2

Table 183-2 Guidelines for the Diagnosis of Initial or Recurrent Attack of Rheumatic Fever (Jones Criteria, Updated 2015)[1-5]

MAJOR MANIFESTATIONS	MINOR MANIFESTATIONS	SUPPORTING EVIDENCE OF ANTECEDENT GROUP A STREPTOCOCCAL INFECTION
Carditis Polyarthritis Erythema marginatum Subcutaneous nodules Chorea	**Clinical features:** Arthralgia Fever **Laboratory features:** Elevated acute phase reactants: Erythrocyte sedimentation rate C-reactive protein	Positive throat culture or rapid streptococcal antigen test Elevated or increasing streptococcal antibody titer
	Prolonged P-R interval	

From Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 2015 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association (in press).

1. *Initial attack:* 2 major manifestations, or 1 major and 2 minor manifestations, plus evidence of recent GAS infection. *Recurrent attack:* 2 major, or 1 major and 2 minor, or 3 minor manifestations (the latter only in the Moderate/High-Risk population), plus evidence of recent GAS infection (see text).
2. Low-Risk population is defined as ARF incidence <2 per 100,000 school-age children per year, or all-age RHD prevalence of <1 per 1000 population. Moderate/High-Risk population is defined as ARF incidence >2 per 100,000 school-age children per year, or all-age RHD prevalence of >1 per 1000 population.
3. Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis). See Table 183-3.
4. Arthritis (major) refers only to polyarthritis in Low-Risk populations, but also to monoarthritis or polyarthralgia in Moderate/High-Risk populations.
5. Minor criteria for Moderate/High-Risk populations only include monoarthralgia (polyarthralgia for Low-Risk populations), fever of >38° C (>38.5° C in Low-Risk populations), ESR >30 mm/hr (>60 mm/hr in Low-Risk populations).

Table 183-3 Echocardiographic Findings in Rheumatic Valvulitis

PATHOLOGIC MITRAL REGURGITATION (ALL 4 MET)	PATHOLOGIC AORTIC REGURGITATION (ALL 4 MET)
1. Seen in at least 2 views	1. Seen in at least 2 views
2. Jet length ≥2 cm in at least 1 view	2. Jet length ≥1 cm in at least 1 view
3. Peak velocity >3 meters/second	3. Peak velocity >3 meters/second
4. Pan-systolic jet in at least 1 envelope	4. Pan-diastolic jet in at least 1 envelope

and text below). These changes are designed to make it easier to fulfill the Jones Criteria in patients from Moderate/High-Risk populations. Even with strict application of the Jones criteria, overdiagnosis as well as underdiagnosis of acute rheumatic fever may occur. There are 3 circumstances in which the diagnosis of acute rheumatic fever can be made without strict adherence to the Jones criteria: (1) when chorea occurs as the only major manifestation of acute rheumatic fever, (2) when indolent carditis is the only manifestation in patients who first come to medical attention only months after the apparent onset of acute rheumatic fever, and (3) in a limited number of patients with recurrences of acute rheumatic fever in particularly high-risk populations.

The 5 Major Criteria

Migratory Polyarthritis

Arthritis occurs in approximately 75% of patients with acute rheumatic fever and typically involves larger joints, particularly the knees, ankles, wrists, and elbows. Involvement of the spine, small joints of the hands and feet, or hips is uncommon. Rheumatic joints are classically hot, red, swollen, and exquisitely tender, with even the friction of bedclothes being uncomfortable. The pain can precede and can appear to be disproportionate to the objective findings. The joint involvement is characteristically migratory in nature; that is, a severely inflamed joint can become normal within 1-3 days without treatment, even as 1 or more other large joints become involved. Severe arthritis can persist for several weeks in untreated patients. Monoarticular arthritis is unusual unless antiinflammatory therapy is initiated prematurely, aborting the progression of the migratory polyarthritis. If a child with fever and arthritis is suspected to have acute rheumatic fever, it is frequently useful to withhold salicylates and observe for migratory progression. A dramatic response to even low doses of salicylates is another characteristic feature of the arthritis, and the absence of such a response should suggest an alternative diagnosis. Rheumatic arthritis is almost never deforming. Synovial fluid in acute rheumatic fever usually has 10,000-100,000 white blood cells/μL with a predominance of neutrophils, a protein level of approximately 4 g/dL, a normal glucose level, and forms a good mucin clot. Frequently, arthritis is the earliest manifestation of acute rheumatic fever and may correlate temporally with peak antistreptococcal antibody titers. There is often an inverse relationship between the severity of arthritis and the severity of cardiac involvement. In Moderate/High-Risk populations only, monoarthritis in the absence of prior inflammatory therapies or even polyarthralgia without frank objective signs of arthritis can fulfill this major criterion. Before polyarthralgia should be considered a major criterion in the Moderate/High-Risk population, other potential causes should be excluded.

Carditis

A major change in the 2015 revision of the Jones Criteria is the acceptance of subclinical carditis (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or clinical carditis (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations. The echocardiographic features of subclinical carditis must meet those included in Table 183-3 in order to distinguish pathologic from physiologic degrees of valve regurgitation. Subclinical (echocardiographic) evidence of pathologic mitral regurgitation requires that a jet is seen in at least 2 views, the jet length is ≥2 cm in at least one view, peak jet velocity is >3 meters/second, and the peak systolic jet is in at least one envelope. Subclinical pathologic evidence of aortic regurgitation is similar except that the jet length is ≥1 cm in at least one view. Carditis and resultant chronic rheumatic heart disease are the most serious manifestations of acute rheumatic fever and account for essentially all of the associated morbidity and mortality. Rheumatic carditis is characterized by pancarditis, with active inflammation of myocardium, pericardium, and endocardium (see Chapter 438). Cardiac involvement during acute rheumatic fever varies in severity from fulminant, potentially fatal exudative pancarditis to mild, transient cardiac involvement. Endocarditis (valvulitis) is a universal finding in rheumatic carditis, whereas the presence of pericarditis or myocarditis is variable. Myocarditis and/or pericarditis without clinical evidence of endocarditis almost never is rheumatic carditis; alternate etiologies (especially viral) need to be sought. Most rheumatic heart disease is isolated mitral valvular disease or combined aortic and mitral valvular disease. Isolated aortic or right-sided valvular involvement is quite uncommon. Serious and long-term illness is related entirely to the severity of valvular heart disease as a consequence of a single attack or recurrent attacks of acute rheumatic fever. Valvular insufficiency is characteristic of both acute and convalescent stages of acute rheumatic fever, whereas mitral and/or aortic valvular stenosis usually appears years or even decades after the acute illness. However, in developing countries where acute rheumatic fever often occurs at a younger age, mitral stenosis and aortic stenosis may develop sooner after acute rheumatic fever than in developed countries and can occur in young children.

Acute rheumatic carditis usually presents as tachycardia and cardiac murmurs, with or without evidence of myocardial or pericardial involvement. Moderate to severe rheumatic carditis can result in cardiomegaly and heart failure with hepatomegaly and peripheral and pulmonary edema. Echocardiographic findings are not diagnostic but include pericardial effusion, decreased ventricular contractility, and aortic and/or mitral regurgitation. Mitral regurgitation is characterized typically by a high-pitched apical holosystolic murmur radiating to the axilla. In patients with significant mitral regurgitation, this may be associated with an apical mid-diastolic murmur of relative mitral stenosis. Aortic insufficiency is characterized by a high-pitched decrescendo diastolic murmur at the left sternal border.

Carditis occurs in approximately 50-60% of all cases of acute rheumatic fever. Recurrent attacks of acute rheumatic fever in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require valve replacement.

Chorea

Sydenham chorea occurs in approximately 10-15% of patients with acute rheumatic fever and usually presents as an isolated, frequently subtle, movement disorder. Emotional lability, incoordination, poor school performance, uncontrollable movements, and facial grimacing, all exacerbated by stress and disappearing with sleep, are characteristic. Chorea occasionally is unilateral (hemichorea). The latent period from acute GAS infection to chorea is usually substantially longer than for arthritis or carditis and can be months. Onset can be insidious, with symptoms being present for several months before recognition. Clinical maneuvers to elicit features of chorea include (1) demonstration of **milkmaid's grip** (irregular contractions and relaxations of the muscles of the fingers while squeezing the examiner's fingers), (2) spooning and pronation of the hands when the patient's arms are extended, (3) wormian darting movements of the tongue upon protrusion, and (4) examination of handwriting to evaluate fine motor movements. Diagnosis is based on clinical findings with supportive evidence of GAS antibodies. However, in the usual patient with a long latent period from the inciting streptococcal infection to onset of chorea, antibody levels have often declined to normal. Although the acute illness is distressing, chorea rarely, if ever, leads to permanent neurologic sequelae.

Figure 183-2 Polycyclic red borders of erythema marginatum in a febrile child with acute rheumatic fever. *(From Schachner LA, Hansen RC, editors:* Pediatric dermatology, *ed 3, Philadelphia, 2003, Mosby, p. 808.)*

Erythema Marginatum

Erythema marginatum is a rare (approximately 1% of patients with acute rheumatic fever) but characteristic rash of acute rheumatic fever. It consists of erythematous, serpiginous, macular lesions with pale centers that are not pruritic (Fig. 183-2). It occurs primarily on the trunk and extremities, but not on the face, and it can be accentuated by warming the skin.

Subcutaneous Nodules

Subcutaneous nodules are a rare (≤1% of patients with acute rheumatic fever) finding and consist of firm nodules approximately 1 cm in diameter along the extensor surfaces of tendons near bony prominences. There is a correlation between the presence of these nodules and significant rheumatic heart disease.

Minor Criteria

These are more nonspecific than major criteria, and the 2015 revised Jones Criteria have included some changes from previous criteria. The first of the 2 clinical minor criteria involve joint manifestations (only if arthritis is not used as a major criterion) and is defined as *polyarthralgia* in Low-Risk populations and *monoarthralgia* in Moderate/High-Risk populations. The second clinical minor manifestation is fever, defined as *at least 38.5° C* in Low-Risk populations and *at least 38.0° C* in Moderate/High-Risk populations. The 2 laboratory minor criteria are (1) elevated acute phase reactants (defined as ESR at least 60 mm/hr and/or CRP at least 3.0 mg/dl [30 mg/L] in Low-Risk populations, and ESR at least 30 mm/hr and/or CRP at least 3.0 mg/dl [30 mg/L] in Moderate/High-Risk populations) and (2) prolonged P-R interval on ECG (unless carditis is a major criterion). However, a prolonged P-R interval alone does not constitute evidence of carditis or predict long-term cardiac sequelae.

Recent Group A Streptococcus Infection

An absolute requirement for the diagnosis of acute rheumatic fever is supporting evidence of a recent GAS infection. Acute rheumatic fever typically develops 2-4 wk after an acute episode of GAS pharyngitis at a time when clinical findings of pharyngitis are no longer present and when only 10-20% of patients still harbor GAS in the throat. One-third of patients with acute rheumatic fever have no history of an antecedent pharyngitis. Therefore, evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers. A slide agglutination test (Streptozyme) purports to detect antibodies against 5 different GAS antigens. Although this test is rapid, relatively simple to perform, and widely available, it is less standardized and less reproducible than other tests and is not recommended as a diagnostic test for evidence of an antecedent GAS infection. If only a single antibody is measured (usually antistreptolysin O), only 80-85% of patients with acute rheumatic fever have an elevated titer; however, 95-100% have an elevation if 3 different antibodies (antistreptolysin O, anti–DNase B, antihyaluronidase) are measured. Therefore, when acute rheumatic fever is suspected clinically, multiple antibody tests should be performed. Except for chorea, the clinical findings of acute rheumatic fever generally coincide with peak antistreptococcal antibody responses. Most patients with chorea have elevation of antibodies to at least 1 GAS antigen. However, in patients with a long latent period from the inciting GAS infection, antibody levels may have declined to within the normal range. The diagnosis of acute rheumatic fever should *not* be made in those patients with elevated or increasing streptococcal antibody titers who do not fulfill the Jones criteria.

Table 183-4 Differential Diagnosis of Acute Rheumatic Fever

ARTHRITIS	CARDITIS	CHOREA
Juvenile idiopathic arthritis	Viral myocarditis	Huntington chorea
Reactive arthritis (e.g., *Shigella, Salmonella, Yersinia*)	Viral pericarditis	Wilson disease
Serum sickness	Infective endocarditis	Systemic lupus erythematosus
Sickle cell disease	Kawasaki disease	Cerebral palsy
Malignancy	Congenital heart disease	Tic disorder
Systemic lupus erythematosus	Mitral valve prolapse	Hyperactivity
Lyme disease *(Borrelia burgdorferi)*	Innocent murmurs	
Pyogenic arthritis		
Poststreptococcal reactive arthritis		

Differential Diagnosis

The differential diagnosis of rheumatic fever includes many infectious as well as noninfectious illnesses (Table 183-4). When children present with arthritis, a collagen vascular disease must be considered. Juvenile idiopathic arthritis in particular must be distinguished from acute rheumatic fever. Children with rheumatoid arthritis tend to be younger and usually have less joint pain relative to their other clinical findings than those with acute rheumatic fever. Spiking fevers, nonmigratory arthritis, lymphadenopathy, and splenomegaly are more suggestive of rheumatoid arthritis than acute rheumatic fever. The response to salicylate therapy is also much less dramatic with rheumatoid arthritis than with acute rheumatic fever. Systemic lupus erythematosus can usually be distinguished from acute rheumatic fever by antinuclear antibodies in systemic lupus erythematosus. Other causes of arthritis such as pyogenic arthritis, malignancies, serum sickness, Lyme disease, sickle cell disease, and reactive arthritis related to gastrointestinal infections (e.g., *Shigella, Salmonella, Yersinia*) should also be considered. Poststreptococcal reactive arthritis has been discussed earlier (see "Poststreptococcal Reactive Arthritis" above).

When carditis is the sole major manifestation of suspected acute rheumatic fever, viral myocarditis, viral pericarditis, Kawasaki disease, and infective endocarditis should also be considered. Patients with infective endocarditis may present with both joint and cardiac manifestations. These patients can usually be distinguished from patients with acute rheumatic fever by blood cultures and the presence of extracardiac findings (e.g., hematuria, splenomegaly, splinter hemorrhages). When chorea is the sole major manifestation of suspected acute rheumatic fever, Huntington chorea, Wilson disease, systemic lupus erythematosus, and various encephalitides should also be considered.

TREATMENT

All patients with acute rheumatic fever should be placed on bed rest and monitored closely for evidence of carditis. They can be allowed to ambulate when the signs of acute inflammation have subsided. However, patients with carditis require longer periods of bed rest.

Antibiotic Therapy

Once the diagnosis of acute rheumatic fever has been established and regardless of the throat culture results, the patient should receive 10 days of orally administered penicillin or amoxicillin or a single intramuscular injection of benzathine penicillin to ensure eradication of GAS from the upper respiratory tract. If penicillin-allergic, 10 days of erythromycin, azithromycin (5 days) or clindamycin is indicated. After this initial course of antibiotic therapy, long-term antibiotic prophylaxis should be instituted.

Antiinflammatory Therapy

Antiinflammatory agents (e.g., salicylates, corticosteroids) should be withheld if arthralgia or atypical arthritis is the only clinical manifestation of presumed acute rheumatic fever. Premature treatment with 1 of these agents may interfere with the development of the characteristic migratory polyarthritis and thus obscure the diagnosis of acute rheumatic fever. Acetaminophen can be used to control pain and fever while the patient is being observed for more definite signs of acute rheumatic fever or for evidence of another disease.

Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. The usual dose of aspirin is 50-70 mg/kg/day in 4 divided doses PO for 3-5 days, followed by 50 mg/kg/day in 4 divided doses PO for 3 wk and half that dose for another 2-4 wk. Determination of the serum salicylate level is not necessary unless the arthritis does not respond or signs of salicylate toxicity (tinnitus, hyperventilation) develop. There is no evidence that nonsteroidal antiinflammatory agents are any more effective than salicylates.

Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisone is 2 mg/kg/day in 4 divided doses for 2-3 wk followed by half the dose for 2-3 wk and then tapering of the dose by 5 mg/24 hr every 2-3 days. When prednisone is being tapered, aspirin should be started at 50 mg/kg/day in 4 divided doses for 6 wk to prevent rebound of inflammation. Supportive therapies for patients with moderate to severe carditis include digoxin, fluid and salt restriction, diuretics, and oxygen. The cardiac toxicity of digoxin is enhanced with myocarditis.

Termination of the antiinflammatory therapy may be followed by the reappearance of clinical manifestations or of elevated erythrocyte sedimentation rate and C-reactive protein (rebound). It may be prudent to increase salicylates or steroids until near-normalization is achieved.

Sydenham Chorea

Because chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease, antiinflammatory agents are usually not indicated. Sedatives may be helpful early in the course of chorea; phenobarbital (16-32 mg every 6-8 hr PO) is the drug of choice. If phenobarbital is ineffective, then haloperidol (0.01-0.03 mg/kg/24 hr divided bid PO) or chlorpromazine (0.5 mg/kg every 4-6 hr PO) should be initiated. Some patients may benefit from a few-week course of corticosteroids.

COMPLICATIONS

The arthritis and chorea of acute rheumatic fever resolve completely without sequelae. Therefore, the long-term sequelae of rheumatic fever are essentially limited to the heart (see Chapter 438).

The AHA has published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis (see Chapter 437). The AHA recommendations no longer suggest routine prophylaxis for patients with rheumatic heart disease. However, the maintenance of optimal oral healthcare remains an important component of an overall healthcare program. For the relatively few patients with rheumatic heart disease in whom infective endocarditis prophylaxis remains recommended, such as those with a prosthetic valve or prosthetic material used in valve repair, the current AHA recommendations should be followed (see Chapter 437). These recommendations advise using an agent other than a penicillin to prevent infective endocarditis in those receiving penicillin prophylaxis for rheumatic fever because oral α-hemolytic streptococci are likely to have developed resistance to penicillin.

PROGNOSIS

The prognosis for patients with acute rheumatic fever depends on the clinical manifestations present at the time of the initial episode, the severity of the initial episode, and the presence of recurrences. Approximately 50-70% of patients with carditis during the initial episode of acute rheumatic fever recover with no residual heart disease; the more severe the initial cardiac involvement, the greater the risk is for residual heart disease. Patients without carditis during the initial episode are less likely to have carditis with recurrent attacks, but there is a stepwise increase in cardiac involvement as the number of episodes increases. In contrast, patients with carditis during the initial episode are very likely to have carditis with recurrences, and the risk for permanent heart damage increases with each recurrence. Patients who have had acute rheumatic fever are susceptible to recurrent attacks following reinfection of the upper respiratory tract with GAS, with approximately 50% risk with each GAS pharyngitis. Therefore, these patients require long-term continuous chemoprophylaxis.

Before antibiotic prophylaxis was available, 75% of patients who had an initial episode of acute rheumatic fever had one or more recurrences during their lifetimes. These recurrences were a major source of morbidity and mortality. The risk of recurrence is highest in the 1st 5 yr after the initial episode and decreases with time.

Approximately 20% of patients who present with "pure" chorea who are not given secondary prophylaxis develop rheumatic heart disease within 20 yr. Therefore, patients with chorea, even in the absence of other manifestations of rheumatic fever, require long-term antibiotic prophylaxis (see Table 183-5).

PREVENTION

Prevention of both initial and recurrent episodes of acute rheumatic fever depends on controlling GAS infections of the upper respiratory tract. Prevention of initial attacks (primary prevention) depends on identification and eradication of GAS causing acute pharyngitis. Individuals who have already suffered an attack of acute rheumatic fever are particularly susceptible to recurrences of rheumatic fever with any subsequent GAS upper respiratory tract infection, whether or not they are symptomatic. Therefore, these patients should receive continuous antibiotic prophylaxis to prevent recurrences (secondary prevention).

Primary Prevention

Appropriate antibiotic therapy instituted before the 9th day of symptoms of acute GAS pharyngitis is highly effective in preventing first attacks of acute rheumatic fever. However, approximately 30% of patients with acute rheumatic fever do not recall a preceding episode of pharyngitis and did not seek therapy.

Secondary Prevention

Secondary prevention is directed at preventing acute GAS pharyngitis in patients at substantial risk of recurrent acute rheumatic fever. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of acute rheumatic fever has been made and immediately after a full course of antibiotic therapy has been completed. Because patients who have had carditis with their initial episode of acute rheumatic fever are at higher risk for having carditis with recurrences and for sustaining additional cardiac damage, they should receive long-term antibiotic prophylaxis well into adulthood and perhaps for life.

Patients who did not have carditis with their initial episode of acute rheumatic fever have a relatively low risk for carditis with recurrences.

Table 183-5	Chemoprophylaxis for Recurrences of Acute Rheumatic Fever (Secondary Prophylaxis)	
DRUG	**DOSE**	**ROUTE**
Penicillin G benzathine	600,000 IU for children weighing ≤60 lb 1.2 million IU for children weighing >60 lb, every 4 wk*	Intramuscular
or		
Penicillin V	250 mg, twice a day	Oral
or		
Sulfadiazine or sulfisoxazole	0.5 g, once a day for patients weighing ≤60 lb 1.0 g, once a day for patients weighing >60 lb	Oral
FOR PEOPLE WHO ARE ALLERGIC TO PENICILLIN AND SULFONAMIDE DRUGS		
Macrolide or azalide	Variable	Oral

*In high-risk situations, administration every 3 wk is recommended.

From Gerber MA, Baltimore RS, Eaton CB, et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Circulation *119:1541–1551, 2009.*

Table 183-6	Duration of Prophylaxis for People Who Have Had Acute Rheumatic Fever: Recommendations of the American Heart Association
CATEGORY	**DURATION**
Rheumatic fever without carditis	5 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease*)	10 yr or until 21 yr of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 yr or until 40 yr of age, whichever is longer; sometimes lifelong prophylaxis

*Clinical or echocardiographic evidence.

From Gerber MA, Baltimore RS, Eaton CB, et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Circulation *119:1541–1551, 2009.*

Antibiotic prophylaxis should continue in these patients until the patient reaches 21 yr of age or until 5 yr have elapsed since the last rheumatic fever attack, whichever is longer. The decision to discontinue prophylactic antibiotics should be made only after careful consideration of potential risks and benefits and of epidemiologic factors such as the risk for exposure to GAS infections.

The regimen of choice for secondary prevention is a single intramuscular injection of benzathine penicillin G (600,000 IU for children weighing ≤60 lb and 1.2 million IU for those weighing >60 lb) every 4 wk (Table 183-5). In certain high-risk patients, and in certain areas of the world where the incidence of rheumatic fever is particularly high, use of benzathine penicillin G every 3 wk may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after 3 wk. In the United States, the administration of benzathine penicillin G every 3 wk is recommended only for those who have recurrent acute rheumatic fever despite adherence to a 4 wk regimen. In compliant patients, continuous oral antimicrobial prophylaxis can be used. Penicillin V 250 mg twice daily and sulfadiazine or sulfasoxazole 500 mg for those weighing ≤60 pounds or 1,000 mg for those weighing >60 pounds given once daily are equally effective when used in such patients. For the exceptional patient who is allergic to both penicillin and sulfonamides, a macrolide (erythromycin or clarithromycin) or azalide (azithromycin) may be used. Table 183-6 notes the duration of secondary prophylaxis.

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Chapter 184

Group B Streptococcus

Catherine S. Lachenauer and Michael R. Wessels

Group B streptococcus (GBS), or *Streptococcus agalactiae,* is a major cause of neonatal bacterial sepsis in the United States. Although advances in prevention strategies have led to a decline in the incidence of neonatal disease, GBS remains a major pathogen for neonates, pregnant women, and nonpregnant adults.

ETIOLOGY

Group B streptococci are facultative anaerobic Gram-positive cocci that form chains or diplococci in broth and small gray-white colonies on solid medium. GBS is definitively identified by demonstration of the Lancefield group B carbohydrate antigen, such as with latex agglutination techniques widely used in clinical laboratories. Presumptive identification can be established on the basis of a narrow zone of β-hemolysis on blood agar, resistance to bacitracin and trimethoprim-sulfamethoxazole, lack of hydrolysis of bile esculin, and elaboration of CAMP factor (named for the discoverers, **C**hristie, **A**tkins, and **M**unch-**P**etersen), an extracellular protein that, in the presence of the β toxin of *Staphylococcus aureus,* produces a zone of enhanced hemolysis on sheep's blood agar. Individual GBS strains are serologically classified according to the presence of 1 of the structurally distinct capsular polysaccharides, which are important virulence factors and stimulators of antibody-associated immunity. Ten GBS capsular types have been identified: types Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX.

EPIDEMIOLOGY

GBS emerged as a prominent neonatal pathogen in the late 1960s. For the next 2 decades, the incidence of neonatal GBS disease remained fairly constant, affecting 1.0-5.4/1,000 liveborn infants in the United States. Two patterns of disease were seen: **early-onset disease,** which presents at <7 days of age, and **late-onset disease,** which presents at 7 days of age or later. Since the early 1990s, widespread implementation of maternal intrapartum chemoprophylaxis has led to a striking decrease in the incidence of early-onset neonatal GBS disease in the United States, decreasing from 1.7 per 1,000 live births to 0.25 per 1,000 live births in recent years. This strategy has not had a significant effect on the incidence of late-onset disease, which has remained stable at approximately 0.3-0.4 per 1,000 live births (Fig. 184-1). The incidence of neonatal GBS disease is higher in premature and low-birthweight infants, although most cases occur in full-term infants. Rates of both early- and late-onset disease are higher in black infants.

Colonization by GBS in healthy adults is common. Vaginal or rectal colonization occurs in up to approximately 30% of pregnant women and is the usual source for GBS transmission to newborn infants. In the absence of maternal chemoprophylaxis, approximately 50% of infants born to colonized women acquire GBS colonization, and 1-2% of infants born to colonized mothers develop early-onset disease.

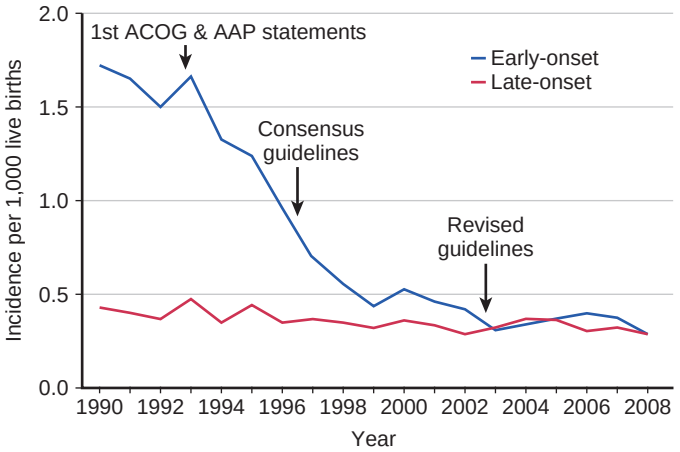


Figure 184-1 Incidence of early- and late-onset invasive group B streptococcal (GBS) disease–active bacterial core surveillance areas, 1990-2008, and activities for prevention of GBS disease. AAP, American Academy of Pediatrics; ACOG, American College of Obstetricians and Gynecologists. Incidence rates for 2008 are preliminary because the live birth denominator has not been finalized. *(Adapted from Jordan HT, Farley MM, Craig A, et al: Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease.* Pediatr Infect Dis J *27:1057–1064, 2008.)*

Heavy maternal colonization increases the risk for infant colonization and development of early-onset disease. Additional risk factors for early-onset disease include prolonged rupture of membranes, intrapartum fever, prematurity, maternal bacteriuria during pregnancy, or previous delivery of an infant who developed GBS disease. Risk factors for late-onset disease are less-well defined. Whereas late-onset disease may follow vertical transmission, horizontal acquisition from nursery or other community sources has also been described.

GBS is also an important cause of invasive disease in adults. GBS may cause urinary tract infections, bacteremia, endometritis, chorioamnionitis, and wound infection in pregnant and parturient women. In nonpregnant adults, especially those with underlying medical conditions such as diabetes mellitus, cirrhosis, or malignancy, GBS may cause serious infections such as bacteremia, skin and soft-tissue infections, bone and joint infections, endocarditis, pneumonia, and meningitis. In the era of maternal chemoprophylaxis, most invasive GBS infections occur in nonpregnant adults. Unlike neonatal disease, the incidence of invasive GBS disease in adults has increased substantially, doubling between 1990 and 2007.

The serotypes most commonly associated with neonatal GBS disease are types Ia, III, and V; Ib and IL are less frequent. Strains of serotype III are isolated in more than 50% of cases of late-onset disease and of meningitis associated with early- or late-onset disease. The serotype distribution of colonizing and invasive isolates from pregnant women is similar to that from infected newborns. In Japan, serotypes VI and VIII have been reported as common maternal colonizing serotypes, and case reports indicate that type VIII strains may cause neonatal disease indistinguishable from that caused by other serotypes.

PATHOGENESIS

A major risk factor for the development of early-onset neonatal GBS infection is maternal vaginal or rectal colonization by GBS. Infants acquire GBS via ascending infection or during passage through the birth canal. Fetal aspiration of infected amniotic fluid may occur. The incidence of early-onset GBS infection increases with the duration of rupture of membranes. Infection may also occur through seemingly intact membranes. In cases of late-onset infection, GBS may be vertically transmitted or acquired later from maternal or nonmaternal sources.

Several bacterial factors are implicated in the pathophysiology of invasive GBS disease. Foremost among these is the type-specific capsular polysaccharide. Strains that are associated with invasive disease in humans elaborate more capsular polysaccharide than do colonizing isolates. All GBS capsular polysaccharides are high-molecular-weight polymers and contain a short side chain terminating in *N*-acetylneuraminic acid (sialic acid). Studies in type III GBS show that the sialic acid component of the capsular polysaccharide prevents activation of the alternative complement pathway in the absence of type-specific antibody. Sialylated capsular polysaccharide on the GBS surface also interacts with sialic acid-binding lectins or siglecs on human leukocytes to dampen inflammatory gene activation. Thus, the capsular polysaccharide appears to exert a virulence effect by protecting the organism from opsonophagocytosis in the nonimmune host and by downregulating leukocyte activation. In addition, type-specific virulence attributes are suggested by the fact that type III strains are implicated in most cases of late-onset neonatal GBS disease and meningitis. Type III strains are taken up by brain endothelial cells more efficiently in vitro than are strains of other serotypes, although studies using acapsular mutant strains demonstrate that it is not the capsule itself that facilitates cellular invasion. A single clone of type III GBS is highly associated with late-onset disease and meningitis. This clonal group, ST-17, produces a surface-anchored protein called hypervirulent GBS adhesin (HvgA) that is not present in other GBS isolates. HvgA contributes to GBS adherence to intestinal and endothelial cells and mediates invasion into the central nervous system in an experimental infection model in mice. Other putative GBS virulence factors include GBS surface proteins, which may play a role in adhesion to host cells; C5a peptidase, which is postulated to inhibit the recruitment of polymorphonuclear cells into sites of infection; β-hemolysin, which has been associated with cell injury in vitro; and hyaluronidase, which has been postulated to act as a spreading factor in host tissues.

In a classic study among pregnant women colonized with type III GBS, those who gave birth to healthy infants had higher levels of capsular polysaccharide-specific antibody than those who gave birth to infants who developed invasive disease. In addition, there is a high correlation of antibody titer to GBS type III in mother–infant paired sera. These observations indicate that transplacental transfer of maternal antibody is critically involved in neonatal immunity to GBS. Optimal immunity to GBS also requires an intact complement system. The classical complement pathway is an important component of GBS immunity in the absence of specific antibody; in addition, antibody-mediated opsonophagocytosis may proceed via the alternative complement pathway. These and other results indicate that anticapsular antibody can overcome the prevention of C3 deposition on the bacterial surface by the sialic acid component of the type III capsule.

The precise steps between GBS colonization and invasive disease remain unclear. In vitro studies showing GBS entry into alveolar epithelial cells and pulmonary vasculature endothelial cells suggest that GBS may gain access to the bloodstream via invasion from the alveolar space, perhaps following intrapartum aspiration of infected fluid. β-Hemolysin/cytolysin may facilitate GBS entry into the bloodstream following inoculation into the lungs. However, highly encapsulated GBS strains enter eukaryotic cells poorly in vitro compared with capsule-deficient organisms are associated with virulence clinically and in experimental infection models.

GBS induces the release of proinflammatory cytokines. The group B antigen and the peptidoglycan component of the GBS cell wall are potent inducers of tumor necrosis factor-α release in vitro, whereas purified type III capsular polysaccharide is not. Even though the capsule plays a central role in virulence through avoidance of immune clearance, the capsule does not directly contribute to cytokine release and the resultant inflammatory response.

The complete genome sequences of types Ia, III, and V GBS strains have been reported, emphasizing a genomic approach to better understanding GBS. Analysis of these sequences shows that GBS is closely related to *Streptococcus pyogenes* and *Streptococcus pneumoniae*. Many known and putative GBS virulence genes are clustered in **pathogenicity islands** that also contain mobile genetic elements, suggesting that interspecies acquisition of genetic material plays an important role in genetic diversity.

Table 184-1 Characteristics of Early- and Late-Onset Group B Streptococcus Disease

	EARLY-ONSET DISEASE	LATE-ONSET DISEASE
Age at onset	0-6 days	7-90 days
Increased risk after obstetric complications	Yes	No
Common clinical manifestations	Sepsis, pneumonia, meningitis	Bacteremia, meningitis, other focal infections
Common serotypes	Ia, Ib, II, III, V	III predominates
Case fatality rate	4.7%	2.8%

Adapted from Schrag SJ, Zywicki S, Farley MM, et al: Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis, N Engl J Med *342:15–20, 2000.*

CLINICAL MANIFESTATIONS

Two syndromes of neonatal GBS disease are distinguishable on the basis of age at presentation, epidemiologic characteristics, and clinical features (Table 184-1). **Early-onset neonatal GBS disease** presents within the 1st 6 days of life and is often associated with maternal obstetric complications, including chorioamnionitis, prolonged rupture of membranes, and premature labor. Infants may appear ill at the time of delivery, and most infants become ill within the 1st 24 hr of birth. In utero infection may result in septic abortion. More than 80% of early-onset GBS disease presents as sepsis; pneumonia and meningitis are other common manifestations. Asymptomatic bacteremia is uncommon but can occur. In symptomatic patients, nonspecific signs such as hypothermia or fever, irritability, lethargy, apnea, and bradycardia may be present. Respiratory signs are prominent regardless of the presence of pneumonia and include cyanosis, apnea, tachypnea, grunting, flaring, and retractions. A fulminant course with hemodynamic abnormalities, including tachycardia, acidosis, and shock, may ensue. Persistent fetal circulation may develop. Clinically and radiographically, pneumonia associated with early-onset GBS disease is difficult to distinguish from respiratory distress syndrome. Patients with meningitis often present with nonspecific findings, as described for sepsis or pneumonia, with more specific signs of central nervous system involvement initially being absent.

Late-onset neonatal GBS disease occurs on or after 7 days of life and most commonly manifests as bacteremia (45-65%) and meningitis (25-35%). Focal infections involving bone and joints, skin and soft tissue, the urinary tract, or lungs may also be seen. Cellulitis and adenitis are often localized to the submandibular or parotid regions. In contrast to early-onset disease, maternal obstetric complications are not risk factors for the development of late-onset GBS disease. Infants with late-onset disease are often less-severely ill on presentation than infants with early-onset disease, and the disease is often less fulminant.

Invasive GBS disease in children beyond early infancy is uncommon. Bacteremia without a focus is the most common syndrome associated with childhood GBS disease beyond early infancy. Focal infections may include meningitis, pneumonia, endocarditis, and bone and joint infections.

DIAGNOSIS

A major challenge is distinguishing between respiratory distress syndrome and invasive neonatal GBS infection in preterm infants because the 2 illnesses share clinical and radiographic features. Severe apnea, early onset of shock, abnormalities in the peripheral leukocyte count, and greater lung compliance may be more likely in infants with GBS disease. Other neonatal pathogens, including *Escherichia coli* and *Listeria monocytogenes,* may cause illness that is clinically indistinguishable from that caused by GBS.

The diagnosis of invasive GBS disease is established by isolation and identification of the organism from a normally sterile site, such as blood, urine, or cerebrospinal fluid (CSF). Isolation of GBS from gastric or tracheal aspirates or from skin or mucous membranes indicates colonization and is not diagnostic of invasive disease. CSF should be examined in all neonates suspected of having sepsis, because specific central nervous system signs are often absent in the presence of meningitis, especially in early-onset disease. Antigen detection methods that use group B polysaccharide-specific antiserum, such as latex particle agglutination, are available for testing of urine, blood, and CSF, but these tests are less sensitive than culture. Moreover, antigen is often detected in urine samples collected by bag from otherwise healthy neonates who are colonized with GBS on the perineum or rectum.

Table 184-2 Recommended Duration of Therapy for Manifestations of Group B Streptococcus Disease

TREATMENT	DURATION
Bacteremia without a focus	10 days
Meningitis	2-3 wk
Ventriculitis	At least 4 wk
Septic arthritis or osteomyelitis	3-4 wk

Data from the American Academy of Pediatrics: Group B streptococcal infections. In Pickering LK, editor: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, pp. 680–685.*

LABORATORY FINDINGS

Frequently present are abnormalities in the peripheral white blood cell count, including an increased or decreased absolute neutrophil count, an elevated band count, an elevated ratio of bands to total neutrophils, or leukopenia. Elevation in the C-reactive protein level has been investigated as a potential early marker of GBS sepsis but is unreliable. Findings on chest radiograph are often indistinguishable from those of respiratory distress syndrome and may include reticulogranular patterns, patchy infiltrates, generalized opacification, pleural effusions, or increased interstitial markings.

TREATMENT

Penicillin G is the treatment of choice of confirmed GBS infection. Empirical therapy of neonatal sepsis that could be caused by GBS generally includes ampicillin and an aminoglycoside, both for the need for broad coverage pending organism identification and for synergistic bactericidal activity. Once GBS has been definitively identified and a good clinical response has occurred, therapy may be completed with penicillin alone. Especially in cases of meningitis, high doses of penicillin (450,000-500,000 units/kg/day) or ampicillin (300 mg/kg/day) are recommended because of the relatively high mean inhibitory concentration of penicillin for GBS as well as the potential for a high initial CSF inoculum. The duration of therapy varies according to the site of infection (Table 184-2) and should be guided by clinical circumstances. Extremely ill near-term patients with respiratory failure have been successfully treated with extracorporeal membrane oxygenation.

In cases of GBS meningitis, some experts recommend that additional CSF be sampled at 24-48 hr to determine whether sterility has been achieved. Persistent GBS growth may indicate an unsuspected intracranial focus or an insufficient antibiotic dose.

For **recurrent neonatal GBS** disease, standard intravenous antibiotic therapy followed by attempted eradication of GBS mucosal colonization has been suggested. This suggestion is based on the findings in several studies that invasive isolates from recurrent episodes are usually identical to each other and to colonizing isolates from the affected infant. Rifampin has most frequently been used for this purpose, but 1 report demonstrates that eradication of GBS colonization in infants is not reliably achieved by rifampin therapy. Optimal management of this uncommon situation remains unclear.

PROGNOSIS

Studies from the 1970s and 1980s showed that up to 30% of infants surviving GBS meningitis had major long-term neurologic sequelae, including developmental delay, spastic quadriplegia, microcephaly, seizure disorder, cortical blindness, or deafness; less severe neurologic complications may be present in other survivors. A study of infants who survived GBS meningitis diagnosed from 1998 through 2006 found that 19% had severe neurologic impairment and 25% had mild to moderate impairment at long-term follow-up. Periventricular leukomalacia and severe developmental delay may result from GBS disease and accompanying shock in premature infants, even in the absence of meningitis. The outcome of focal GBS infections outside of the central nervous system, such as bone or soft-tissue infections, is generally favorable.

In the 1990s, the case fatality rates associated with early- and late-onset neonatal GBS disease were 4.7% and 2.8%, respectively. Mortality is higher in premature infants; 1 study reported a case fatality rate of 30% in infants whose gestational age was <33 wk and 2% in infants whose gestational age was ≥37 wk. The case fatality rate in children aged 3 mo to 14 yr was 9%, and in nonpregnant adults was 11.5%.

PREVENTION

Persistent morbidity and mortality from perinatal GBS disease despite advances in neonatal care has spurred intense investigation into modes of prevention. Two basic approaches to GBS prevention have been investigated: (1) elimination of colonization from the mother or infant (chemoprophylaxis), and (2) induction of protective immunity (immunoprophylaxis).

Chemoprophylaxis

Administration of antibiotics to pregnant women **before** the onset of labor does not reliably eradicate maternal GBS colonization and is not an effective means of preventing neonatal GBS disease. Interruption of neonatal colonization is achievable through administration of antibiotics to the mother during labor (see Chapter 109). Infants born to GBS-colonized women with premature labor or prolonged rupture of membranes who were given intrapartum chemoprophylaxis had a substantially lower rate of GBS colonization (9% vs 51%) and early-onset disease (0% vs 6%) than did the infants born to women who were not treated. Maternal postpartum febrile illness was also decreased in the treatment group.

In the mid-1990s, guidelines for chemoprophylaxis were issued that specified administration of intrapartum antibiotics to women identified as high-risk by either culture-based or risk factor–based criteria. These guidelines were revised in 2002 after epidemiologic data indicated the superior protective effect of the culture-based approach in the prevention of neonatal GBS disease, and further revised guidelines were issued in 2010. According to current recommendations, vaginorectal GBS screening cultures should be performed for all pregnant women at 35-37 wk gestation, except for those with GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease. Any woman with a positive prenatal screening culture, GBS bacteriuria during pregnancy, or a previous infant with invasive GBS disease should receive intrapartum antibiotics. Women whose culture status is unknown (culture not done, incomplete, or results unknown) and who deliver prematurely (<37 wk gestation), experience prolonged rupture of membranes (≥18 hr), experience intrapartum fever (≥38°C [100.4°F]) or have a positive nucleic acid amplification test for GBS should also receive intrapartum chemoprophylaxis. Routine intrapartum prophylaxis is not recommended for women with GBS colonization undergoing planned cesarean delivery who have not begun labor or had rupture of membranes.

Penicillin remains the preferred agent for maternal chemoprophylaxis because of its narrow spectrum and the universal penicillin susceptibility of GBS isolates associated with human infection. Ampicillin is an acceptable alternative. If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent active against GBS should replace GBS prophylaxis. Occasional GBS isolates have demonstrated reduced in vitro susceptibility to penicillin and other β-lactam antibiotics in association with mutations in penicillin-binding proteins. However, such strains have not been reported in invasive infection. Because of recent reports indicating frequent resistance of GBS to clindamycin (up to 20%), cefazolin should be used in most cases of intrapartum chemoprophylaxis for penicillin-intolerant women. For penicillin-allergic women at high risk for anaphylaxis, clindamycin should be used, if isolates are demonstrated to be susceptible. Vancomycin should be used if isolates are resistant to, or demonstrate inducible resistance to, clindamycin or if clindamycin susceptibility is unknown.

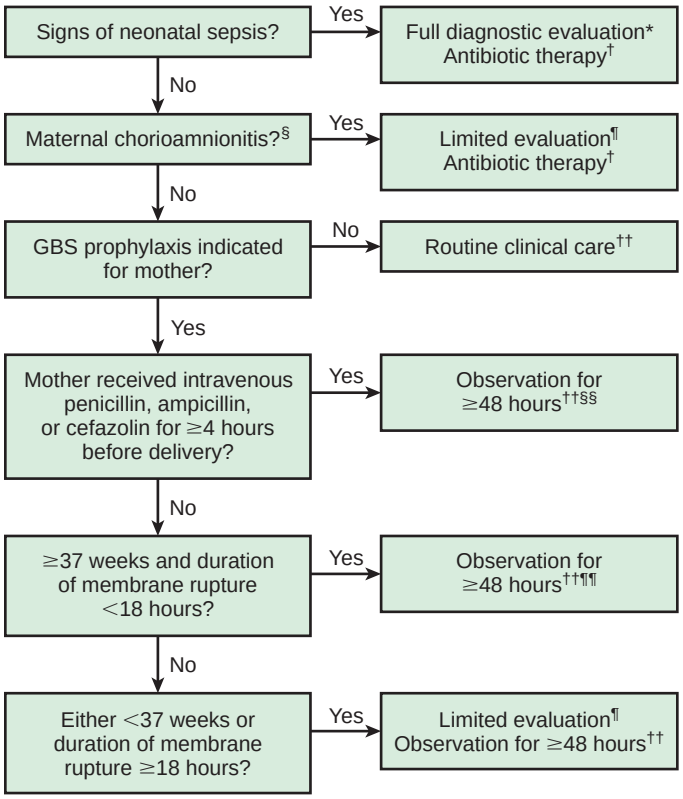
The Centers for Disease Control and Prevention (CDC) guidelines also provide recommendations for secondary prevention of early onset GBS disease among newborns (Fig. 184-2). Extent of newborn evaluation and decision to institute empiric antibiotics is guided by clinical evaluation of the infant as well as gestational age, maternal risk factors, and receipt of intrapartum prophylaxis. In the era of maternal chemoprophylaxis, most cases of early onset disease are seen in infants born to women with negative prenatal screening cultures. Data from a large epidemiologic study indicate that the administration of maternal intrapartum antibiotics does not change the clinical spectrum or delay the onset of clinical signs in infants who developed GBS disease despite maternal prophylaxis.

A significant concern with maternal intrapartum prophylaxis has been that large-scale antibiotic use among parturient women might lead to increased rates of antimicrobial resistance or infection in infants with organisms other than GBS. To date, an increase in the incidence of non-GBS early-onset neonatal infections has been seen only in premature, low-birthweight, and very-low-birthweight infants in whom risk factors other than maternal chemoprophylaxis may play a role. At present, the substantial decline in early-onset neonatal GBS disease favors continued broad-scale intrapartum chemoprophylaxis, but continued surveillance is required.

A limitation of the maternal chemoprophylaxis strategy is that intrapartum antibiotic use is unlikely to have an impact on late-onset neonatal disease, miscarriages or stillbirths attributed to GBS, or adult GBS disease. In addition, with wider implementation of maternal chemoprophylaxis, an increasing percentage of early-onset neonatal disease has been in patients born to women with negative cultures, that is, false-negative screens.

Maternal Immunization

Human studies demonstrate that transplacental transfer of naturally acquired maternal antibody to the GBS capsular polysaccharide protects newborns from invasive GBS infection and that efficient transplacental passage of vaccine-induced GBS antibodies occurs. Conjugate vaccines composed of the GBS capsular polysaccharides coupled to carrier proteins have been produced for human use. In early clinical trials, conjugate GBS vaccines were well tolerated and induced levels of functional antibodies well above the range believed to be protective in greater than 90% of recipients. A vaccine containing type III polysaccharide coupled to tetanus toxoid was safely administered to pregnant women and elicited functionally active type-specific antibody that was efficiently transported to the fetus. Administration of a multivalent polysaccharide-protein vaccine before or during pregnancy should lead to transplacental passage of vaccine-induced antibody that protects the fetus and newborn against infection by several GBS serotypes. Such a vaccine would eliminate the need for cumbersome cultures during pregnancy, would circumvent the various risks associated with large-scale antibiotic prophylaxis, and would likely have an impact on



* Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected).

† Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns.

§ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific.

¶ Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6–12 hours of life).

†† If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated.

§§ If ≥37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved.

¶¶ Some experts recommend a CBC with differential and platelets at age 6–12 hours.

Figure 184-2 Algorithm for secondary prevention of early-onset group B streptococcal disease among newborns. *(From Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention: Prevention of perinatal group B streptococcal disease—revised guidelines from CDC 2010.* MMWR Recomm Rep *59[RR-10]:22, 2010.)*

both early- and late-onset disease. Intrapartum chemoprophylaxis will likely remain an important aspect of prevention, particularly for women in whom opportunities for GBS immunization are missed and for infants born so early that levels of transplacentally acquired antibodies may not be high enough to be protective.

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Chapter 185

Non–Group A or B Streptococci

David B. Haslam

The genus *Streptococcus* is exceptionally diverse and includes the major human pathogens *Streptococcus pyogenes* (group A streptococcus), *Streptococcus agalactiae* (group B streptococcus) and *Streptococcus pneumoniae* (Table 185-1). Other important pathogens include large-colony species bearing groups C and G Lancefield antigens and numerous small-colony variants that may or may not express Lancefield carbohydrate antigen included among the viridians streptococci (Table 185-1). This chapter focuses on *Streptococcus dysgalactiae* subspecies *equisimilis,* commonly known as "group C and G streptococci," while Chapter 182 discusses *S. pneumoniae,* and Chapter 186 discusses enterococci, formerly classified among the streptococci but now comprising their own genus.

All members of the genus *Streptococcus* are Gram-positive, catalase-negative organisms. Lancefield carbohydrate antigen, hemolytic activity, and colony morphology have classically been used to further distinguish and classify streptococci. These features provide a useful framework for the clinician and are still the most commonly used classification schema. However, grouping based on these phenotypic features does not precisely correlate with genetic relatedness, and it is becoming clear that disease propensity is better correlated with sequence homology than Lancefield grouping or hemolytic activity. As a consequence, the streptococci are undergoing taxonomic reclassification as genome sequence information becomes available.

In this chapter, groups C and G streptococci refer exclusively to the large colony-forming organisms, often called *S. pyogenes–like,* as their microbiologic and clinical features tend to mimic those of group A streptococcus. Despite their different Lancefield antigens, the group C and G streptococci are nearly identical genetically and are placed within the *S. dysgalactiae*, *equisimilis* subspecies. Their genome sequences are approximately equidistant between *S. pyogenes* and animal pathogens that bear the group C antigen, which are classified as *S. dysgalactiae* subspecies *dysgalactiae.* It is likely that *S. dysgalactiae* will be split into distinct species in the future, when their sequence-based grouping will reflect their propensity to cause human (represented by subspecies *equisimilis*) and animal (represented by subspecies *dysgalactiae*) infections.

The groups C and G streptococci share a number of virulence factors with *S. pyogenes*, including the production of streptolysin O, M protein, streptococcal pyrogenic exotoxin B, and hyaluronidase. The M protein is similar to that of *S. pyogenes* and may account for postinfectious glomerulonephritis that is occasionally seen after infection with these organisms. A toxic-shock–like syndrome associated with groups C and G streptococcal infection has been related to production of a pyrogenic exotoxin by *S. dysgalactiae* subsp. *equisimilis.*

Groups C and G streptococci are common habitants of the pharynx, being detected in up to 5% of asymptomatic children. Other potential sites of colonization include the skin and gastrointestinal tract. Colonization of the vagina is reported and may be the source of occasional *S. dysgalactiae* subsp. *equisimilis* isolated from the umbilicus of healthy neonates.

Clinical manifestations of disease caused by groups C and G streptococci overlap those of *S. pyogenes*. In children, these organisms are implicated most commonly in pharyngitis. The true role of these organisms as a cause of pharyngitis is difficult to determine because asymptomatic colonization is common. Nevertheless, several epidemics of group C and group G streptococcal pharyngitis have been reported, including foodborne outbreaks. It is possible that primary infection with groups C and G streptococci has the same potential to

Table 185-1 Relationship of Streptococci Identified by Hemolysis and Lancefield Grouping to Sites of Colonization and Disease

	GROUP A STREPTOCOCCUS (*S. PYOGENES*)	GROUP B STREPTOCOCCUS (*S. AGALACTIAE*)	OTHER β-HEMOLYTIC STREPTOCOCCI	VIRIDANS STREPTOCOCCI
Hemolysis	β	β	β	α
Lancefield group	A	B	C-H, K-V Especially C and G	
Species or strains	M types (>180)	Serotypes (Ia, Ib, II, III, IV, V, VI, VII, and VIII)		*Streptococcus bovis* *Streptococcus mitis* *Streptococcus mutans* *Streptococcus sanguis* Many others
Normal flora	Pharynx, skin, anus	Gastrointestinal and genitourinary tract	Pharynx, skin, gastrointestinal and genitourinary tracts	Pharynx, nose, skin, genitourinary tract
Common human diseases	Pharyngitis, tonsillitis, erysipelas, impetigo, septicemia, wound infections, necrotizing fasciitis, cellulitis, meningitis, pneumonia, scarlet fever, toxic shock–like syndrome, rheumatic fever, acute glomerulonephritis	Puerperal sepsis chorioamnionitis, endocarditis, neonatal sepsis, meningitis, osteomyelitis, pneumonia	Wound infections, puerperal sepsis, cellulitis, sinusitis, endocarditis, brain abscess, sepsis, nosocomial infections, opportunistic infections	Endocarditis, human bite infections

α, Partial hemolysis; β, complete hemolysis; γ, no hemolysis (nonhemolytic).

result in disease as infection with *S. pyogenes,* whereas an immunologic response protects against subsequent disease, explaining why children in tropical environments are commonly colonized but less likely to have symptoms. Indeed, *S. dysgalactiae* subsp. *equisimilis* exposure may provide some cross-protection against *S. pyogenes* infection. When pharyngitis is a feature of group C or G infection, the clinical presentation is indistinguishable from *S. pyogenes*–associated pharyngitis. Isolated case reports have described group C streptococcal pneumonia in children, where abscess formation, empyema, and bacteremia are common. Additional respiratory infections include rare reports of groups C and G streptococcal epiglottitis and sinusitis.

Groups C and G streptococci are a significant cause of skin and soft-tissue infections. As with *S. pyogenes,* lymphangitis can complicate superficial infections caused by groups C and G organisms. Musculoskeletal infections, particularly pyogenic arthritis, occasionally are caused by groups C and G streptococci. Pediatric cases are uncommon but may be increasing in incidence.

These organisms can cause neonatal septicemia similar to early-onset group B streptococcal disease. Risk factors include prematurity and prolonged rupture of membranes. Respiratory distress, hypotension, apnea, bradycardia, and disseminated intravascular coagulation may be seen, and associated maternal infection is common. Neonatal toxic shock syndrome associated with *S. dysgalactiae* subsp. *equisimilis* has also been described.

Endocarditis, bacteremia, brain abscess, and toxic shock caused by groups C and G streptococcal infection have all been described but are uncommon in children. These infections generally occur in children with immune deficits or in adolescents after delayed recognition of sinusitis.

Reactive arthritis has been described after group C streptococcal infection; however, unlike *S. pyogenes*, there has been no convincing evidence of acute rheumatic fever after infection with group C streptococcus, and therefore antibiotic prophylaxis is not recommended following reactive arthritis with this this organism.

Treatment of groups C and G infections is similar to that of *S. pyogenes.* These organisms retain susceptibility to penicillin and other β-lactams. Other agents with reliable activity against groups C and G streptococci include linezolid, quinupristin-dalfopristin, and vancomycin, though occasional isolates demonstrate tolerance to vancomycin. Clindamycin and macrolides have poor bactericidal activity against these organisms, particularly against group G streptococci. Resistance to quinolones is reported, and up to 70% of group C streptococci are resistant to tetracycline.

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Chapter 186

Enterococcus

David B. Haslam

Enterococcus, long recognized as a pathogen in select populations, has become a common and particularly troublesome cause of hospital-acquired infection over the past 2 decades. Enterococci were formerly classified with *Streptococcus bovis* and *Streptococcus equinus* as Lancefield group D streptococci but are now placed in a separate genus and are notorious for their frequent resistance to antibiotics.

ETIOLOGY

Enterococci are Gram-positive, catalase-negative facultative anaerobes that grow in pairs or short chains. Most are nonhemolytic (also called γ-hemolytic) on sheep blood agar, although some isolates have α- or β-hemolytic activity. Enterococci are distinguished from most Lancefield groupable streptococci by their ability to grow in bile and hydrolyze esculin. Enterococci are able to grow in 6.5% NaCl and hydrolyze L-pyrrolidonyl-β-naphthylamide, features used by clinical laboratories to distinguish enterococci from group D streptococcus. Identification at the species level is enabled by differing patterns of carbohydrate fermentation.

EPIDEMIOLOGY

Enterococci are normal inhabitants of the gastrointestinal tract of humans, and organisms throughout the animal kingdom, suggesting

they are highly evolved to occupy this niche. Oral secretions and dental plaque, the upper respiratory tract, skin, and vagina may also be colonized by *Enterococcus*. *Enterococcus faecalis* is the predominant organism, with colonization commonly occurring in the 1st wk of life. By the time of adulthood, *E. faecalis* colonization is nearly ubiquitous. *Enterococcus faecium* colonization is less consistent, although approximately 25% of adults harbor this organism. Disruption of the normal intestinal microbiota by antibiotic exposure or hematopoietic stem cell transplantation markedly enriches for fecal enterococcal abundance and dramatically increases the risk of subsequent bloodstream infection.

E. faecalis accounts for approximately 80% of enterococcal infections, with almost all of the remaining infections caused by *E. faecium*. Only rarely are other species, such as *Enterococcus gallinarum* and *Enterococcus casseliflavus*, associated with invasive infection, but these organisms are notable for their intrinsic low-level vancomycin resistance. Whole-genome sequencing suggests that the patient's indigenous flora is the source of enterococcal infection in most cases. However, direct spread from person to person or from contaminated medical devices may occur, particularly within newborn nurseries and intensive care units where nosocomial spread has resulted in hospital outbreaks.

PATHOGENESIS

Enterococci are not aggressively invasive organisms, usually causing disease only in children with damaged mucosal surfaces or impaired immune response. Their dramatic emergence as a cause of nosocomial infection is predominantly a result of their resistance to antibiotics commonly used in the hospital setting. Hospital-associated enterococci generally lack CRISPR (clustered regularly interspaced short palindromic repeats) elements. Their diverse antimicrobial resistance repertoire is likely related to deficient CRISPR-mediated defense against phage-mediated horizontal gene transfer. Secreted and cell-surface molecules are implicated in pathogenesis. Adhesion-promoting factors such as the surface protein Eps likely account for the propensity of these organisms to cause endocarditis and urinary tract infections (UTIs). The ability to form biofilms likely facilitates the colonization of urinary and vascular catheters. Other proposed virulence factors include cytolysin, aggregation substance, gelatinase, and extracellular superoxide.

Antimicrobial Resistance

Enterococci are highly resistant to cephalosporins and semisynthetic penicillins such as nafcillin, oxacillin, and methicillin. They are moderately resistant to extended-spectrum penicillins such as ticarcillin and carbenicillin. Ampicillin, imipenem, and penicillin are the most active β-lactams against these organisms. Some strains of *E. faecalis* and *E. faecium* demonstrate decreased resistance to β-lactam antibiotics due to mutations in penicillin binding protein 5. In addition, occasional strains of *E. faecalis* produce a plasmid-encoded β-lactamase similar to that found in *Staphylococcus*. These isolates are completely resistant to penicillins, necessitating the combination of a penicillin plus a β-lactamase inhibitor or the use of imipenem or vancomycin. Any active drug may be insufficient if used alone for serious infections wherein high bactericidal activity is desired (Tables 186-1 and 186-2).

All enterococci have intrinsic low-level resistance to aminoglycosides because these antibiotics are poorly transported across the *Enterococcus* cell wall. Concomitant use of a cell wall active agent, such as a β-lactam or glycopeptide antibiotic, improves the permeability of the cell wall for the aminoglycosides, resulting in synergistic killing. However, some isolates demonstrate high-level resistance, defined as mean inhibitory concentration (MIC) >2,000 μg/mL a result of modification or inactivation of aminoglycoside agents. Strains demonstrating high-level resistance, and even some moderately resistant isolates, are not affected synergistically by aminoglycosides and cell wall–active antibiotics.

Resistance to almost all other antibiotic classes, including tetracyclines, macrolides, and chloramphenicol, has been described among the enterococci, necessitating individual susceptibility testing for these antibiotics when their use is considered. Despite apparent susceptibility in vitro, trimethoprim-sulfamethoxazole has poor activity in vivo and should not be used as the primary agent against *Enterococcus* infections.

Vancomycin has traditionally been effective against *Enterococcus* isolates, but resistance to vancomycin, defined as MIC >32 μg/mL, and other glycopeptides, including teicoplanin, is increasingly common. The emergence of vancomycin-resistant *Enterococcus* (VRE) has become a major challenge in the care of hospitalized patients. In particular, mortality in patients with VRE bloodstream infections is considerable, and treatment is complicated by frequent resistance of VRE to most other antibiotic classes. Both high- and moderate-level resistance are described in *E. faecalis* and *E. faecium*. High-level resistance (MIC ≥64 μg/mL) can be transferred by way of conjugation and usually results from plasmid-mediated transfer of the *vanA* gene. High-level resistance is most common among *E. faecium*, but is increasingly seen among *E. faecalis* isolates. Moderate-level resistance (MIC 8-256 μg/mL) results from a chromosomal homolog of *vanA*, known as *vanB*. Isolates that harbor the *vanB* gene are only moderately resistant to vancomycin and initially demonstrate susceptibility to teicoplanin, although resistance can emerge during therapy. Resistance to newer agents, including linezolid and daptomycin, is rare thus far. Linezolid resistance is a result of mutations in the 26S ribosomal subunit, whereas daptomycin resistance is associated with mutations in genes required for membrane synthesis and repair.

Table 186-1 Intrinsic Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin	Altered binding protein
Aminoglycoside (low level)	Decreased permeability, altered ribosomal binding
Clindamycin	Altered ribosomal binding
Erythromycin	Altered ribosomal binding
Tetracyclines	Efflux pump
Trimethoprim-sulfamethoxazole	Utilize exogenous folate

Table 186-2 Acquired Resistance Mechanisms Among Enterococci

ANTIMICROBIAL	MECHANISM
Ampicillin, penicillin (high level)	Mutation of PBP5
Aminoglycoside (high level)	Enzyme modification
Quinolones	DNA gyrase mutation
Chloramphenicol	Efflux pump
Glycopeptide	Altered cell wall binding
Quinupristin/dalfopristin	Ribosomal modification, efflux pump
Linezolid	Point mutation
Daptomycin	Unknown

CLINICAL MANIFESTATIONS

Enterococcus infections traditionally occurred predominantly in newborn infants; infection in older children is increasingly common. Most *Enterococcus* infections occur in patients with breakdown of normal physical barriers such as the gastrointestinal tract, skin, or urinary tract. Other risk factors for *Enterococcus* infection include

prolonged hospitalization, indwelling vascular catheters, prior use of antibiotics, and compromised immunity.

Neonatal Infections

Enterococcus accounts for up to 15% of all neonatal bacteremia and septicemia. Like group B streptococcus infections, *Enterococcus* infections are seen in 2 distinct settings in neonatal patients. Early-onset infection (<7 days of age) may mimic early-onset group B streptococcus septicemia, but tends to be milder. Early-onset *Enterococcus* sepsis most often occurs in full-term infants who are otherwise healthy. Late-onset infection (≥7 days of age) is associated with risk factors such as extreme prematurity, presence of an intravascular catheter, or necrotizing enterocolitis, or it follows an intraabdominal surgical procedure. Symptoms in late-onset disease are more severe than those in early-onset disease and include apnea, bradycardia, and deteriorating respiratory function. Focal infections such as scalp abscess and catheter infection are commonly associated. Mortality rates range from 6% in early-onset septicemia to 15% in late-onset infections associated with necrotizing enterocolitis.

Enterococci are an occasional cause of meningitis. In neonates in particular, meningitis usually occurs as a complication of septicemia. Alternatively, the organism may gain access to the central nervous system by way of contiguous spread, such as through a neural tube defect or in association with an intraventricular shunt. *Enterococcus* meningitis can be associated with minimal abnormality of cerebrospinal fluid.

Infections in Older Children

Enterococcus rarely causes UTIs in healthy children but accounts for approximately 15% of cases of nosocomially acquired UTIs in both children and adults. Presence of an indwelling urinary catheter is the major risk factor for nosocomial UTIs. *Enterococcus* is frequently isolated in intraabdominal infections following intestinal perforation or surgery. The significance of enterococci in polymicrobial infections has been questioned, although reported mortality rates are higher when intraabdominal infections include enterococci. *Enterococcus* is increasingly common as a cause of nosocomial bacteremia; these organisms accounted for approximately 10% of nosocomial bloodstream infection in children, ranking second only to coagulase-negative staphylococci. Predisposing factors for enterococcal bacteremia and endocarditis include an indwelling central venous catheter, gastrointestinal surgery, immunodeficiency, and cardiovascular abnormalities. Risk factors for vancomycin-resistant enterococcal bacteremia include prolonged mechanical ventilation, immunosuppression, and recent vancomycin exposure.

TREATMENT

Treatment of invasive *Enterococcus* infections must recognize that these organisms are resistant to antimicrobial agents frequently used as empirical therapy. In particular, cephalosporins should not be relied upon in situations where *Enterococcus* is known or suspected to be involved. In general, in the immunocompetent host, minor localized infections caused by susceptible *Enterococcus* can be treated with ampicillin alone. Antibiotics containing β-lactamase inhibitors (clavulanate or sulbactam) provide advantage only for the few organisms whose resistance is owing to production of β-lactamase. In uncomplicated UTIs, nitrofurantoin is efficacious when the organism is known to be sensitive to this antibiotic.

Invasive infections, such as sepsis, meningitis, and endocarditis, are usually treated with a combination of penicillin or ampicillin and an aminoglycoside when the isolate is susceptible. Vancomycin can be substituted for the penicillins in allergic patients, but should be used with an aminoglycoside, because vancomycin alone is not bactericidal. Endocarditis from strains possessing high-level aminoglycoside resistance may relapse even after prolonged therapy. High-dose or continuous infusion penicillin has been proposed for treatment of these infections in adults, yet ultimately valve replacement may be necessary. In patients with catheter-associated enterococcal bacteremia, the catheter should be removed promptly in most cases, although salvage of infected lines has occurred with the combined use of ampicillin or vancomycin with an aminoglycoside.

Treatment of Vancomycin-Resistant Enterococci

The treatment of serious infections caused by multiresistant, vancomycin-resistant strains is particularly challenging. Linezolid, an oxazolidinone antibiotic that inhibits protein synthesis, is bacteriostatic against most *E. faecium* and *E. faecalis,* including vancomycin-resistant isolates. Response rates are generally over 90%, including cases of bacteremia and sepsis, and this antibiotic has become the preferred agent in treatment of VRE infections in many institutions. Anecdotal reports reveal the success of linezolid in treating meningitis caused by vancomycin-resistant enterococci. Unfortunately, as seen with other antibiotics, linezolid resistance is documented and nosocomial spread of these organisms can occur. Linezolid frequently causes reversible bone marrow suppression after prolonged use and is associated with rare occurrences of lactic acidosis and irreversible peripheral neuropathy. Serotonin syndrome may be seen in patients taking concomitant selective serotonin uptake inhibitor antidepressants. Oxazolidinones in development include tedizolid, which has better in vitro activity against enterococci and appears to have favorable pharmacokinetic and toxicity profiles when compared to linezolid.

Quinupristin/dalfopristin is a combined streptogramin antibiotic that inhibits bacterial protein synthesis at 2 different stages. It has activity against most *E. faecium* strains, including those with high-level vancomycin resistance. Approximately 90% of *E. faecium* strains are susceptible to quinupristin/dalfopristin in vitro. Notably, it is inactive against *E. faecalis* and therefore should not be used as the sole agent against Gram-positive organisms until culture results exclude the presence of *E. faecalis*. Studies in children suggest that this antibiotic is effective and generally well tolerated, though episodes of arthralgia and myalgia during therapy are reported. Emergence of resistance to quinupristin/dalfopristin is rare but has been demonstrated.

Newer antibiotics with reliable activity against VRE include daptomycin and tigecycline. Daptomycin is a cyclic lipopeptide that is rapidly bactericidal against a broad range of Gram-positive organisms. The antibiotic inserts into the bacterial cell wall, causing membrane depolarization and cell death. It has been approved for the treatment of adults with serious skin and soft tissue infections, right-sided endocarditis, and bacteremia due to susceptible organisms. Most strains of VRE (both *E. faecium* and *E. faecalis*) are susceptible to daptomycin in vitro, and its efficacy in adult patients with VRE appears to be similar to that of linezolid. Experience with daptomycin in children is limited, particularly in the setting of *Enterococcus* infections. However, based on the experience with adult patients, daptomycin may be an alternative to linezolid when resistance or side-effects limit utility of that antibiotic. Daptomycin dosages may need to be higher in children when compared to adults because of more rapid renal clearance. The antibiotic has unreliable activity in the lung and therefore should not be used as a sole agent to treat pneumonia. Resistance of both *Staphylococcus aureus* and *Enterococcus* to daptomycin has rarely been described, sometimes arising during therapy. Ceftaroline, a fifth-generation cephalosporin with activity against methicillin-resistant *S. aureus*, has activity against many *E. faecalis* strains and may be highly synergistic with daptomycin against daptomycin-nonsusceptible strains.

Tigecycline is the first clinically available glycylcycline antibiotic, an expended-spectrum derivative of the tetracycline family. The agent inhibits protein synthesis by binding to the 30S ribosome and is bacteriostatic against susceptible organisms. Tigecycline has broad activity against Gram-positive, Gram-negative, and anaerobic organisms, including methicillin-resistant *S. aureus* and VRE, and is approved for the treatment of adults with skin and soft-tissue infections and intraabdominal infections caused by susceptible organisms. Its efficacy in VRE infections has not yet been demonstrated in clinical trials and there is little published experience with the use of tigecycline in children thus

far. Like other tetracycline antibiotics, tigecycline use may cause discoloration of the teeth, and its use in children younger than 8 yr of age should generally be avoided. Gastrointestinal side effects are common and may be intolerable.

Prevention

Strategies for preventing enterococcal infections include timely removal of urinary and intravenous catheters and debridement of necrotic tissue. Infection control strategies, including surveillance cultures, patient and staff cohorting, and strict gown and glove isolation are effective at decreasing colonization rates with vancomycin-resistant enterococci. Unfortunately, these organisms may persist on inanimate objects such as stethoscopes, complicating efforts to limit their nosocomial spread. In order to prevent the emergence and spread of vancomycin resistant organisms, the Centers for Disease Control and Prevention has developed a series of guidelines for prudent vancomycin use. Antibiotics with broad activity against anaerobic organisms are also thought to contribute to colonization with VRE, suggesting that prudent use of such antibiotics may also help limit spread of VRE. Decolonization strategies have been attempted but are generally ineffective in eradicating skin or gastrointestinal carriage of VRE. In particular, antimicrobial therapy is not indicated for this purpose. The role of probiotic agents in eliminating VRE colonization is currently unclear, but may be a useful adjunct to prudent antimicrobial usage and other infection control interventions in limiting nosocomial spread of VRE.

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Chapter 187

Diphtheria (*Corynebacterium diphtheriae*)

E. Stephen Buescher

Diphtheria is an acute toxic infection caused by *Corynebacterium* species, typically *Corynebacterium diphtheriae* and, rarely, toxigenic strains of *Corynebacterium ulcerans.* Although diphtheria was reduced from a major cause of childhood death to a medical rarity in the Western hemisphere in the early 20th century, recurring reminders of the fragility of this success emphasize the necessity to continue vigorous promotion of those same control principles across the global community.

ETIOLOGY

Corynebacteria are aerobic, nonencapsulated, non–spore-forming, mostly nonmotile, pleomorphic, Gram-positive bacilli. *C. diphtheriae* is by far the most commonly isolated agent of diphtheria. *C. ulcerans* is more commonly isolated from animal sources and can cause similar human disease. As Corynebacteria are not fastidious in growth requirements, their isolation is enhanced by use of a selective medium (e.g., cystine-tellurite blood agar or Tinsdale agar) that inhibits growth of competing organisms and, when reduced by *C. diphtheriae,* renders colonies gray-black. Differentiation of *C. diphtheriae* from *C. ulcerans* is based on urease activity, because *C. ulcerans* is urease-positive. Four *C. diphtheriae* biotypes (mitis, intermedius, belfanti, gravis) are capable of causing diphtheria and are differentiated by colonial morphology, hemolysis, and fermentation reactions. The ability to produce diphtheritic toxin results from acquisition of a lysogenic *Corynebacteriophage* by either *C. diphtheriae* or *C. ulcerans,* which encodes the diphtheritic toxin gene and confers diphtheria-producing potential on these strains. Thus, indigenous nontoxigenic *C. diphtheriae* can be rendered toxigenic and disease-producing after importation of a toxigenic *C. diphtheriae*. Demonstration of diphtheritic toxin production or potential for toxin production by an isolate is necessary to confirm disease. The former is done in vitro using the agar immunoprecipitin technique (Elek test) or in vivo with the toxin neutralization test in guinea pigs, and the latter by polymerase chain reaction testing for carriage of the toxin gene. Toxigenic and nontoxigenic strains are indistinguishable by colony type, microscopic features, or biochemical test results.

EPIDEMIOLOGY

Unlike other **diphtheroids (coryneform bacteria),** which are ubiquitous in nature, *C. diphtheriae* is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by airborne respiratory droplets, direct contact with respiratory secretions of symptomatic individuals, or exudate from infected skin lesions. Asymptomatic respiratory tract carriage is important in transmission. Where diphtheria is endemic, 3-5% of healthy individuals can carry toxigenic organisms, but carriage is exceedingly rare if diphtheria is rare. Skin infection and skin carriage are silent reservoirs of *C. diphtheriae,* and organisms can remain viable in dust or on fomites for up to 6 mo. Transmission through contaminated milk and through an infected food handler has been proven or suspected.

In the 1920s, more than 125,000 diphtheria cases, with 10,000 deaths, were reported annually in the United States, with the highest fatality rates among the very young and the elderly. The incidence then began to decrease and, with widespread use of diphtheria toxoid in the United States after World War II, declined steadily through the late 1970s. Since then, ≤5 cases have occurred annually in the United States, with no epidemics of respiratory tract diphtheria. Similar decreases occurred in Europe. Despite the worldwide decrease in disease incidence, diphtheria remains endemic in many developing countries with poor immunization rates against diphtheria.

When diphtheria was endemic, it primarily affected children younger than 15 yr of age. Since the introduction of toxoid immunization, the disease has shifted to adults who lack natural exposure to toxigenic *C. diphtheriae* in the vaccine era and have low rates of booster immunization. In the 27 sporadic cases of respiratory tract diphtheria reported in the United States in the 1980s, 70% occurred among persons older than 25 yr of age. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990-1996 in the newly independent countries of the former Soviet Union, involving more than 150,000 cases in 14 countries. Of these, more than 60% of cases occurred in individuals older than 14 yr of age. Case fatality rates ranged from 3-23% by country. Factors contributing to the epidemic included a large population of underimmunized adults, decreased childhood immunization rates, population migration, crowding, and failure to respond aggressively during early phases of the epidemic. Cases of diphtheria among travelers from these endemic areas were transported to many countries in Europe.

Most proven cases of respiratory tract diphtheria in the United States in the 1990s were associated with **importation** of toxigenic *C. diphtheriae,* although clonally related toxigenic *C. diphtheriae* has persisted in this country and Canada for at least 25 yr.

Cutaneous diphtheria, a curiosity when diphtheria was common, accounted for more than 50% of reported *C. diphtheriae* isolates in the United States by 1975. This indolent local infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, greater contamination of the environment, and increased transmission to the pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. It is no longer a tropical or subtropical disease; 1,100 *C. diphtheriae* infections were documented in a neighborhood in Seattle (site of the last major U.S.

outbreak), from 1971-1982; 86% were cutaneous, and 40% involved toxigenic strains. Cutaneous diphtheria is an important source for toxigenic *C. diphtheriae* in the United States, and its importation is frequently the source for subsequent sporadic cases of respiratory tract diphtheria.

PATHOGENESIS

Both toxigenic and nontoxigenic *C. diphtheriae* cause skin and mucosal infection and can rarely cause focal infection after bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing local inflammatory reaction. The major virulence of the organism lies in its ability to produce the potent 62-kDa polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis. Within the 1st few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown, leather-like adherent **pseudomembrane** (*Diphthera* is Greek for leather). Removal is difficult and reveals a bleeding edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheritic toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and/or demyelination of nerves. Because the latter 2 complications can occur 2-10 wk after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated.

CLINICAL MANIFESTATIONS

The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin.

Respiratory Tract Diphtheria

In a classic description of 1,400 cases of diphtheria in California (1954), the primary focus of infection was the tonsils or pharynx (94%), with the nose and larynx the next 2 most common sites. After an average incubation period of 2-4 days, local signs and symptoms of inflammation develop. Infection of the anterior nares is more common among infants and causes serosanguineous, purulent, erosive rhinitis with membrane formation. Shallow ulceration of the external nares and upper lip is characteristic. In tonsillar and pharyngeal diphtheria, sore throat is the universal early symptom. Only half of patients have fever, and fewer have dysphagia, hoarseness, malaise, or headache. Mild pharyngeal injection is followed by unilateral or bilateral tonsillar membrane formation, which can extend to involve the uvula (which may cause toxin-mediated paralysis), soft palate, posterior oropharynx, hypopharynx, or glottic areas (Fig. 187-1). Underlying soft-tissue edema and enlarged lymph nodes can cause a bull-neck appearance. The degree of local extension correlates directly with profound prostration, bull-neck appearance, and fatality due to airway compromise or toxin-mediated complications (Fig. 187-2).

The characteristic adherent membrane, extension beyond the faucial area, dysphagia, and relative lack of fever help differentiate diphtheria from exudative pharyngitis caused by *Streptococcus pyogenes* or Epstein-Barr virus. Vincent angina, infective phlebitis with thrombosis of the jugular veins (Lemierre disease), and mucositis in patients undergoing cancer chemotherapy are usually differentiated by the clinical setting. Infection of the larynx, trachea, and bronchi can be primary or a secondary extension from the pharyngeal infection. Hoarseness, stridor, dyspnea, and croupy cough are clues. Differentiation from bacterial epiglottitis, severe viral laryngotracheobronchitis, and staphylococcal or streptococcal tracheitis hinges partially on the relative paucity of other signs and symptoms in patients with diphtheria and primarily on visualization of the adherent pseudomembrane at the time of laryngoscopy and intubation.

Patients with laryngeal diphtheria are at significant risk for suffocation because of local soft-tissue edema and airway obstruction by the diphtheritic membrane, a dense cast of respiratory epithelium, and necrotic coagulum. Establishment of an artificial airway and resection of the pseudomembrane can be lifesaving, but further obstructive complications are common, and systemic toxic complications are inevitable.

Figure 187-1 Tonsillar diphtheria. *(Courtesy Franklin H. Top, MD, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes.)*

Figure 187-2 Diphtheria. Bull-neck appearance of diphtheritic cervical lymphadenopathy. *(Courtesy of the Centers for Disease Control and Prevention.)*

Cutaneous Diphtheria

Classic cutaneous diphtheria is an indolent, nonprogressive infection characterized by a superficial, ecthyma-like, nonhealing ulcer with a gray-brown membrane. Diphtheritic skin infections cannot always be differentiated from streptococcal or staphylococcal impetigo, and these conditions frequently coexist. In most cases, a primary process, such as dermatosis, laceration, burns, bite, or impetigo, becomes secondarily infected with *C. diphtheriae*. Extremities are more often affected than the trunk or head. Pain, tenderness, erythema, and exudate are typical. Local hyperesthesia or hypesthesia is unusual. Respiratory tract colonization or symptomatic infection with toxic complications occurs in the minority of patients with cutaneous diphtheria. Among infected adults in the Seattle outbreak, 3% with cutaneous infections and 21%

with symptomatic nasopharyngeal infection, with or without skin involvement, demonstrated toxic myocarditis, neuropathy, or obstructive respiratory tract complications. All had received at least 20,000 units of equine antitoxin at the time of hospitalization.

Infection at Other Sites

C. diphtheriae occasionally causes mucocutaneous infections at other sites, such as the ear (otitis externa), the eye (purulent and ulcerative conjunctivitis), and the genital tract (purulent and ulcerative vulvovaginitis). The clinical setting, ulceration, membrane formation, and submucosal bleeding help differentiate diphtheria from other bacterial and viral causes. Rare cases of septicemia are described and are universally fatal. Sporadic cases of endocarditis occur, and clusters among intravenous drug users have been reported in several countries; skin was the probable portal of entry, and almost all strains were nontoxigenic. Sporadic cases of pyogenic arthritis, mainly from nontoxigenic strains, have been reported in adults and children. Diphtheroids isolated from sterile body sites should not be routinely dismissed as contaminants without careful consideration of the clinical setting.

DIAGNOSIS

Specimens for culture should be obtained from the nose and throat and any other mucocutaneous lesion. A portion of membrane should be removed and submitted for culture along with underlying exudate. The laboratory must be notified to use selective medium. *C. diphtheriae* survives drying. If obtained in a remote area, a swab specimen can be placed in a silica gel pack and sent to the laboratory. Evaluation of a direct smear using Gram stain or specific fluorescent antibody is unreliable. Culture isolates of coryneform organisms should be identified to the species level, and toxigenicity and antimicrobial susceptibility tests should be performed for *C. diphtheriae* isolates.

COMPLICATIONS

Respiratory tract obstruction by pseudomembranes may require bronchoscopy or intubation and mechanical ventilation. Two other tissues usually remote from sites of *C. diphtheriae* infection can be significantly affected by **diphtheritic toxin:** the heart and the nervous system.

Toxic Cardiomyopathy

Toxic cardiomyopathy occurs in 10-25% of patients with respiratory diphtheria and is responsible for 50-60% of deaths. Subtle signs of myocarditis can be detected in most patients, especially the elderly, but the risk for significant complications correlates directly with the extent and severity of exudative local oropharyngeal disease as well as delay in administration of antitoxin. The first evidence of cardiac toxicity characteristically occurs during the 2nd and 3rd wk of illness as the pharyngeal disease improves but can appear acutely as early as the 1st wk of illness, a poor prognostic sign, or insidiously as late as the 6th wk. **Tachycardia** disproportionate to fever is common and may be evidence of cardiac toxicity or autonomic nervous system dysfunction. A prolonged P-R interval and changes in the ST-T wave on an electrocardiographic tracing are relatively frequent findings; dilated and hypertrophic cardiomyopathy detected by echocardiogram has been described. Single or progressive cardiac **dysrhythmias** can occur, including 1st-, 2nd-, and 3rd-degree heart block. Temporary transvenous pacing may improve outcomes. Atrioventricular dissociation and ventricular tachycardia are also described, the latter having a high associated mortality. Heart failure may appear insidiously or acutely. Elevation of the serum aspartate aminotransferase concentration closely parallels the severity of myonecrosis. Severe dysrhythmia portends death. Histologic postmortem findings are variable: little or diffuse myonecrosis with acute inflammatory response. Recovery from toxic myocardiopathy is usually complete, although survivors of more severe dysrhythmias can have permanent conduction defects.

Toxic Neuropathy

Neurologic complications parallel the severity of primary infection and are multiphasic in onset. Acutely or 2-3 wk after onset of oropharyngeal inflammation, it is common for hypesthesia and local **paralysis** of the soft palate to occur. Weakness of the posterior pharyngeal, laryngeal, and facial nerves may follow, causing a **nasal quality** in the voice, difficulty in swallowing, and risk for aspiration. **Cranial neuropathies** characteristically occur in the 5th wk, leading to oculomotor and ciliary paralysis, which can cause strabismus, blurred vision, or difficulty with accommodation. Symmetric **polyneuropathy** has its onset 10 days to 3 mo after oropharyngeal infection and causes principally motor deficits with diminished deep tendon reflexes. Distal muscle weakness in the extremities with proximal progression is more commonly described than proximal muscle weakness with distal progression. Clinical and cerebrospinal fluid findings in the former are indistinguishable from those of Guillain-Barré syndrome. Paralysis of the diaphragm may ensue. Complete neurologic recovery is likely, but rarely vasomotor center dysfunction 2-3 wk after onset of illness can cause hypotension or cardiac failure.

Recovery from the myocarditis and neuritis is often slow but usually complete. Corticosteroids do not diminish these complications and are not recommended.

TREATMENT

Specific antitoxin is the mainstay of therapy and should be administered on the basis of clinical diagnosis. Because it neutralizes only free toxin, antitoxin efficacy diminishes with elapsed time after the onset of mucocutaneous symptoms. Equine diphtheria antitoxin is available in the United States only from the Centers for Disease Control and Prevention (CDC). Physicians treating a case of suspected diphtheria should contact the CDC diphtheria duty officer (770-488-7100 at all times). Antitoxin is administered as a single empirical dose of 20,000-100,000 units based on the degree of toxicity, site and size of the membrane, and duration of illness. Antitoxin is probably of no value for local manifestations of cutaneous diphtheria, but its use is prudent because toxic sequelae can occur. Commercially available intravenous immunoglobulin preparations contain low titers of antibodies to diphtheria toxin; their use for therapy of diphtheria is not proven or approved. Antitoxin is not recommended for asymptomatic carriers.

The role of antimicrobial therapy is to halt toxin production, treat localized infection, and prevent transmission of the organism to contacts. *C. diphtheriae* is usually susceptible to various agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline. Resistance to erythromycin is common in populations if the drug has been used broadly. Only erythromycin or penicillin is recommended; erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is erythromycin (40-50 mg/kg/day divided every 6 hr by mouth [PO] or intravenously [IV]; maximum 2 g/day), aqueous crystalline penicillin G (100,000-150,000 units/kg/day divided every 6 hr IV or intramuscularly [IM]), or daily procaine penicillin (300,000 units/day IM for those <10 kg in weight; 600,000 units/day IM for those >10 kg in weight) for 14 days. Antibiotic therapy is not a substitute for antitoxin therapy. Some patients with cutaneous diphtheria have been treated for 7-10 days. Elimination of the organism should be documented by negative results of at least 2 successive cultures of specimens from the nose and throat (or skin) obtained 24 hr apart after completion of therapy. Treatment with erythromycin is repeated if either culture yields *C. diphtheriae.*

SUPPORTIVE CARE

Droplet precautions are instituted for patients with pharyngeal diphtheria; for patients with cutaneous diphtheria, contact precautions are observed until the results of cultures of specimens taken after cessation of therapy are negative. Cutaneous wounds are cleaned thoroughly with soap and water. Bed rest is essential during the acute phase of disease, usually for ≥2 wk until the risk for symptomatic cardiac damage has passed, with a return to physical activity guided by the degree of toxicity and cardiac involvement.

PROGNOSIS

The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies *gravis* has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration

of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case fatality rate of almost 10% for respiratory tract diphtheria has not changed in 50 yr; the rate was 8% in a Vietnamese series described in 2004. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheritic toxin after infection.

PREVENTION

Protection against serious disease caused by imported or indigenously acquired *C. diphtheriae* depends on immunization. In the absence of a precisely determined minimum protective level for diphtheria antitoxin, the presumed minimum is 0.01-0.10 IU/mL. In outbreaks, 90% of individuals with clinical disease have had antibody values <0.01 IU/mL, and 92% of asymptomatic carriers have had values >0.1 IU/mL. In serosurveys in the United States and Western Europe, where almost universal immunization during childhood has been achieved, 25% to >60% of adults lack protective antitoxin levels, with very low levels common in the elderly.

All suspected diphtheria cases should be reported to local and state health departments. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source and carriers to halt spread to unexposed individuals. Reported rates of carriage in household contacts of case patients are 0-25%. The risk for development of diphtheria after household exposure to a case is approximately 2%, and the risk is 0.3% after similar exposure to a carrier.

Asymptomatic Case Contacts

All household contacts and people who have had intimate respiratory or habitual physical contact with a patient are closely monitored for illness through the 7-day incubation period. Cultures of the nose, throat, and any cutaneous lesions are performed. Antimicrobial prophylaxis is presumed effective and is administered regardless of immunization status, using a single injection of benzathine penicillin G (600,000 units IM for patients younger than 6 yr of age, or 1,200,000 units IM for patients older than 6 yr of age) or erythromycin (40-50 mg/kg/day divided qid PO for 10 days; maximum: 2 g/day). Diphtheria toxoid vaccine, in age-appropriate form, is given to immunized individuals who have not received a booster dose within 5 yr. Children who have not received their 4th dose should be vaccinated. Those who have received fewer than 3 doses of diphtheria toxoid or who have uncertain immunization status are immunized with an age-appropriate preparation on a primary schedule.

Asymptomatic Carriers

When an asymptomatic carrier is identified, antimicrobial prophylaxis is given for 10-14 days and an age-appropriate preparation of diphtheria toxoid is administered immediately if a booster has not been given within 1 yr. Droplet precautions (respiratory tract colonization) or contact precautions (cutaneous colonization only) are observed until at least 2 subsequent cultures obtained 24 hr apart after cessation of therapy have negative results.

Repeat cultures are performed about 2 wk after completion of therapy for cases and carriers; if results are positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed. Susceptibility testing of isolates should be performed, as erythromycin resistance is reported. Neither antimicrobial agent eradicates carriage in 100% of individuals. In one report, a single course of therapy failed in 21% of carriers. Transmission of diphtheria in modern hospitals is rare. Only those who have an unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of the casual contacts of patients and carriers or persons in the community without known exposure has yielded extremely low carriage rates and is not routinely recommended.

Vaccine

Universal immunization with diphtheria toxoid throughout life, to provide constant protective antitoxin levels and to reduce severity of *C. diphtheriae* disease, is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic *C. diphtheriae,* it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 70-80% of a population is immunized.

Diphtheria toxoid is prepared by formaldehyde treatment of toxin, standardized for potency, and adsorbed to aluminum salts, enhancing immunogenicity. Two preparations of diphtheria toxoids are formulated according to the limit of flocculation (Lf) content, a measure of the quantity of toxoid. The pediatric (6 mo-6yr) preparations (i.e., DTaP [diphtheria and tetanus toxoids with acellular pertussis vaccine], DT [diphtheria and tetanus toxoids vaccine]) contain 6.7-25.0 Lf units of diphtheria toxoid per 0.5 mL dose; the adult preparation (dT; 10% of pediatric diphtheria toxoid dose, Tdap [diphtheria and tetanus toxoids with acellular pertussis vaccine]) contain no more than 2 Lf units of toxoid per 0.5 mL dose. The higher-potency (D) formulation of toxoid is used for primary series and booster doses for children through 6 yr of age because of superior immunogenicity and minimal reactogenicity. For individuals 7 yr of age or older, dT is recommended for the primary series and booster doses because the lower concentration of diphtheria toxoid is adequately immunogenic and increasing the content of diphtheria toxoid heightens reactogenicity with increasing age.

For children 6 wk to 6 yr of age, five 0.5 mL doses of diphtheria-containing (D) vaccine (DTaP preferred) are given in the primary series, including 3 doses at 2, 4, and 6 mo of age, and a 4th dose, an integral part of the primary series, 15-18 mo after the 3rd dose. A booster dose is given at 4-6 yr of age (unless the 4th primary dose was administered at age 4 yr or older). For persons 7 yr of age and older, three 0.5 mL doses of lower-level diphtheria-containing (d) vaccine are given in a primary series of 2 doses 4-8 wk apart and a 3rd dose 6-12 mo after the 2nd dose. The 1st dose should be Tdap, and subsequent doses should be Td. The only contraindication to tetanus and diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a prior dose. For children younger than 7 yr of age in whom pertussis immunization is contraindicated, DT is used. Those whose immunization is begun with DTaP or DT before 1 yr of age should have a total of five 0.5 mL doses of diphtheria-containing (D) vaccines by 6 yr of age. For those whose immunization is begun at around 1 yr of age, the primary series is three 0.5 mL doses of diphtheria-containing (D) vaccine, with a booster given at 4-6 yr, unless the 3rd dose was given after the 4th birthday.

A booster dose, consisting of the adult preparation of Tdap, is recommended at 11-12 yr of age. Adolescents 13-18 yr of age who missed the Td or Tdap booster dose at 11-12 yr or in whom it has been 5 or more years since the Td booster dose also should receive a single dose of Tdap if they have completed the DTP/DTaP series.

There is no association of DT or dT with convulsions. Local adverse effects alone do not preclude continued use. The patient who experiences an Arthus-type hypersensitivity reaction or a temperature >39.4°C (103°F) after a dose of dT, which is rare, usually has high serum tetanus antitoxin levels and should not be given dT more frequently than every 10 yr, even if the patient sustains a significant tetanus-prone injury. The DT or dT preparation can be given concurrently with other vaccines. *Haemophilus influenzae* conjugate vaccines containing diphtheria toxoid (PRP-D) or the variant of diphtheria toxin, CRM197 protein (HbOC), are not substitutes for diphtheria toxoid immunization and do not affect reactogenicity.

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Chapter 188

Listeria monocytogenes

Robert S. Baltimore and Thomas S. Murray

Listeriosis in humans is caused principally by *Listeria monocytogenes,* 1 of 6 species of the genus *Listeria* that are widely distributed in the environment and throughout the food chain. Human infections can usually be traced to an animal reservoir. Infection occurs most commonly at the extremes of age. In the pediatric population, perinatal infections predominate and usually occur secondary to maternal infection or colonization. Outside the newborn period, disease is most commonly encountered in immunosuppressed (T-cell deficiencies) children and adults and in the elderly. For most people the major risk for infection with *Listeria* is foodborne transmission. In the United States, foodborne outbreaks are caused by improperly processed dairy products and contaminated vegetables and principally affect the same individuals at risk for sporadic disease.

ETIOLOGY

Members of the genus *Listeria* are facultatively anaerobic, non–spore-forming, motile, Gram-positive bacilli that are catalase positive. In the laboratory *Listeria* can be distinguished from other Gram-positive bacilli by their characteristic tumbling motility and growth at cold temperature (4-10°C [39.2-50°F]). The 6 *Listeria* species are divided into 2 genomically distinct groups on the basis of DNA-DNA hybridization studies. One group contains the species *Listeria grayi,* considered nonpathogenic. The second group contains 5 species: the nonhemolytic species *Listeria innocua* and *Listeria welshimeri* and the hemolytic species *L. monocytogenes, Listeria seeligeri,* and *Listeria ivanovii. L. ivanovii* is pathogenic primarily in animals, and the vast majority of both human and animal disease is caused by *L. monocytogenes.*

Subtyping of *L. monocytogenes* isolates for epidemiologic purposes has been attempted with the use of heat-stable somatic O and heat-labile flagellar H antigens, phage typing, pulsed-field gel electrophoresis, ribotyping, and multilocus enzyme electrophoresis. Electrophoretic typing demonstrates the clonal structure of populations of *L. monocytogenes* as well as the sharing of populations between human and animal sources. Subtyping is an important component of determining whether cases are connected or sporadic but usually requires collaboration with a specialized laboratory.

Selected biochemical tests together with the demonstration of tumbling motility, umbrella-type formation below the surface in semisolid medium, hemolysis, and a typical cyclic adenosine monophosphate test are usually sufficient to establish a presumptive identification of *L. monocytogenes.*

EPIDEMIOLOGY

L. monocytogenes is widespread in nature, has been isolated throughout the environment, and is associated with epizootic disease and asymptomatic carriage in more than 42 species of wild and domestic animals and 22 avian species. Epizootic disease in large animals such as sheep and cattle is associated with abortion and "circling disease," a form of basilar meningitis. *L. monocytogenes* is isolated from sewage, silage, and soil, where it survives for longer than 295 days. Human-to-human transmission rarely occurs except in maternal-fetal transmission. The annual incidence of listeriosis decreased by 36% between 1996 and 2004 and has remained level since then. However, outbreaks continue to occur. In 2002, an outbreak that resulted in 54 illnesses, 8 deaths, and 3 fetal deaths in 9 states was traced to consumption of contaminated turkey meat. In 2011, an outbreak with 84 cases and 15 deaths in 19 states was traced to cantaloupes from a single source. The cases were connected by use of pulsed-field gel electrophoresis, which showed that 4 different strains traced to the same source. The rate of listeria infections varies among states. Epidemic human listeriosis has been associated with foodborne transmission in several large outbreaks, especially in association with aged soft cheeses; improperly pasteurized milk and milk products; contaminated raw and ready-to-eat beef, pork, and poultry, and packaged meats; and vegetables grown on farms where the ground is contaminated with the feces of colonized animals. The incidence of *Listeria* infections in the United States in 2008 was 0.29 cases per 100,000 population, being highest in children younger than 4 yr of age and next highest in adults older than 60 yr of age. The ability of *L. monocytogenes* to grow at temperatures as low as 4°C (39.2°F) increases the risk for transmission from aged soft cheeses and stored contaminated food. Small clusters of nosocomial person-to-person transmission have occurred in hospital nurseries and obstetric suites. Sporadic endemic listeriosis is less well characterized. Likely routes include foodborne infection and zoonotic spread. Zoonotic transmission with cutaneous infections occurs in veterinarians and farmers who handle sick animals.

Table 188-1 Types of *Listeria monocytogenes* Infections

Listeriosis in pregnancy
Neonatal listeriosis:
Early onset
Late onset
Foodborne outbreaks/febrile gastroenteritis
Listeriosis in normal children and adults (rare)
Focal listeria infections (e.g., meningitis, endocarditis, pneumonia, liver abscess, osteomyelitis, septic arthritis)
Listeriosis in immunocompromised persons:
Lymphohematogenous malignancies
Collagen vascular diseases
Diabetes mellitus
HIV infection
Transplantation
Renal failure with peritoneal dialysis
Listeriosis in the elderly

Reported cases of listeriosis are clustered at the extremes of age. Some studies show higher rates in males and a seasonal predominance in the late summer and fall in the Northern hemisphere. Outside the newborn period and during pregnancy, disease is usually reported in patients with underlying immunosuppression, with a 100-300 times increased risk in HIV-infected persons and in the elderly (Table 188-1). In a recent surveillance study from England, malignancies accounted for one-third of cases, with special risk associated with cancer in the elderly.

The incubation period, which is defined only for common-source foodborne disease, is 21-30 days but in some cases may be longer. Asymptomatic carriage and fecal excretion are reported in 1-5% of healthy persons and 5% of abattoir workers, but duration of excretion, when studied, is short (<1 mo).

PATHOLOGY

One of the major concepts of *Listeria* pathology and pathogenesis is its ability to survive as an intracellular pathogen. *Listeria* incites a mononuclear response and elaboration of cytokines, producing multisystem disease, particularly pyogenic meningitis. Granulomatous reactions and microabscess formation develop in many organs, including liver, lungs, adrenals, kidneys, central nervous system (CNS), and, notably, the placenta. Animal models demonstrate translocation, the transfer

of intraluminal organisms across intact intestinal mucosa. Histologic examination of tissues including the placenta shows granulomatous inflammation and microabscess formation. Intracellular organisms can often be demonstrated with special stains.

PATHOGENESIS

Listeria organisms usually enter the host through the gastrointestinal tract. Gastric acidity provides some protection, and drugs that raise gastric pH may promote infection. Studies of intracellular and intercellular spread of *L. monocytogenes* have revealed a complex pathogenesis. Four pathogenic steps are described: internalization by phagocytosis, escape from the phagocytic vacuole, nucleation of actin filaments, and cell-to-cell spread. Listeriolysin, a hemolysin and the best-characterized virulence factor, probably mediates lysis of vacuoles and is responsible for the zone of hemolysis around colonies on blood-containing solid media. In cell-to-cell spread, locomotion proceeds via cytochalasin-sensitive polymerization of actin filaments, which extrude the bacteria in pseudopods, which, in turn, are phagocytosed by adjacent cells, necessitating escape from a double-membrane vacuole. This mechanism protects intracellular bacteria from the humoral arm of immunity and is responsible for the well-known requirement of T-cell–mediated activation of monocytes by lymphokines for clearance of infection and establishment of immunity. It appears that secretion of cyclic-di-adenosine monophosphate by the bacteria induces the host to produce interferon, which activates the immune system to fight the organism. The significant risk for listeriosis in patients with depressed T-cell immunity speaks for the role of this arm of the immune system. The role of opsonizing antibody in protecting against infection is unclear. In addition, siderophores scavenge iron from the host, enhancing growth of the organism and likely explaining the relatively high risk of listeriosis in iron overload syndromes.

CLINICAL MANIFESTATIONS

The clinical presentation of listeriosis is highly dependent on the age of the patient and the circumstances of the infection.

Listeriosis in Pregnancy

Pregnant women have increased susceptibility to *Listeria* infectious (approximately 20 times higher than nonpregnant women), probably owing to a relative impairment in cell-mediated immunity. *L. monocytogenes* has been grown from placental and fetal cultures of pregnancies ending in spontaneous abortion. The usual presentation in the 2nd and 3rd trimesters is a flu-like illness that may result in seeding of the uterine contents by bacteremia. Rarely is maternal listeriosis severe, but meningitis in pregnancy has been reported. Recognition and treatment at this stage are associated with normal pregnancy outcomes, but the fetus may not be infected even if listeriosis in the mother is not treated. In other instances, placental listeriosis develops with infection of the fetus that may be associated with stillbirth or premature delivery. Delivery of an infected premature fetus is associated with very high infant mortality. Disseminated disease is apparent at birth, often with a diffuse pustular rash. Infection in the mother usually resolves without specific therapy after delivery, but postpartum fever and infected lochia may occur.

Neonatal Listeriosis

Two clinical presentations are recognized for neonatal listeriosis: early-onset neonatal disease (<5 days, usually within 1-2 days of birth), which is a predominantly septicemic form, and late-onset neonatal disease (>5 days, mean 14 days of life), which is a predominantly meningitic form (Table 188-2). The principal characteristics of the 2 presentations resemble the clinical syndromes described for group B streptococcus (see Chapter 184).

Early-onset disease occurs via milder transplacental or ascending infections from the female genital tract. There is a strong association with recovery of *L. monocytogenes* from the maternal genital tract, obstetric complications, prematurity, and neonatal sepsis with multiorgan involvement without CNS localization. The mortality rate is approximately 20-30%.

Table 188-2 Characteristic Features of Early- and Late-Onset Neonatal Listeriosis

EARLY ONSET (<5 DAYS)	LATE ONSET (≥5 DAYS)
Positive result of maternal *Listeria* culture	Negative results of maternal *Listeria* culture
Obstetric complications	Uncomplicated pregnancy
Premature delivery	Term delivery
Low birthweight	Normal birthweight
Neonatal sepsis	Neonatal meningitis
Mean age at onset 1.5 days	Mean age at onset 14.2 days
Mortality rate >30%	Mortality rate <10% Nosocomial outbreaks

The epidemiology of late-onset disease is poorly understood. Onset is usually after 5 days but before 30 days of age. Affected infants frequently are full-term, and the mothers are culture negative and asymptomatic. The presenting syndrome is usually purulent meningitis, which, if adequately treated, has a mortality rate of <20%.

Postneonatal Infections

Listeriosis beyond the newborn period may rarely occur in otherwise healthy children but is most often encountered in association with underlying malignancies or immunosuppression. When associated with foodborne outbreaks, disease may cause gastrointestinal symptoms or any of the *Listeria* syndromes. The clinical presentation is usually meningitis, less commonly sepsis, and rarely other CNS involvement, such as cerebritis, meningoencephalitis, brain abscess, spinal cord abscess, or a focus outside the CNS, such as suppurative arthritis, osteomyelitis, endocarditis, peritonitis (associated with peritoneal dialysis), or liver abscess. It is not known whether the frequent gastrointestinal signs and symptoms result from enteric infection, because the mode of acquisition is often unknown.

DIAGNOSIS

Listeriosis should be included in the differential diagnosis of infections in pregnancy, of neonatal sepsis and meningitis, and of sepsis or meningitis in older children who have underlying malignancies, are receiving immunosuppressive therapy, or have undergone transplantation. The diagnosis is established by culture of *L. monocytogenes* from blood or cerebrospinal fluid (CSF). Cultures from the maternal cervix, vagina, lochia, and placenta, if possible, should be obtained when intrauterine infections lead to premature delivery or early-onset neonatal sepsis. Cultures from closed-space infections may also be useful. It is helpful to alert the laboratory to suspected cases so that *Listeria* isolates are not discarded as contaminating diphtheroids.

Histologic examination of the placenta is also useful. Polymerase chain reaction assays detect *L. monocytogenes*, but commercial assays are available only as research use only, not for diagnostic purposes. Serodiagnostic tests have not proved useful.

Differential Diagnosis

Listeriosis is indistinguishable clinically from neonatal sepsis and meningitis due to other organisms. The presence of increased peripheral blood monocytes suggests the possibility of listeriosis. Monocytosis or lymphocytosis may be modest or striking. Beyond the neonatal period, *L. monocytogenes* CNS infection is associated with fever, headache, seizures, and signs of meningeal irritation. The brainstem may be characteristically affected. The white blood cell concentration may vary from normal to slightly elevated, and the CSF laboratory findings are variable and less striking than in the more common causes of bacterial meningitis. Polymorphonuclear leukocytes or mononuclear cells may predominate, with shifts from polymorphonuclear to mononuclear

cells in sequential lumbar puncture specimens. The CSF glucose concentration may be normal but a low level mirrors the severity of disease. The CSF protein concentration is moderately elevated. *L. monocytogenes* is isolated from the blood in 40-75% of cases of meningitis due to the organism. Deep focal infections caused by *L. monocytogenes,* such as endocarditis, osteomyelitis, and liver abscess, are also indistinguishable clinically from such infections caused by more common organisms. Cutaneous infections should be suspected in patients with a history of contact with animals, especially products of conception.

TREATMENT

The emergence of multiple-antibiotic resistance mandates routine susceptibility testing of all isolates. The recommended therapy is ampicillin (100-200 mg/kg/day divided every 6 hr IV; 200-400 mg/kg/day divided every 6 hr IV if meningitis is present) alone or in combination with an aminoglycoside (5.0-7.5 mg/kg/day divided every 8 hr IV). The aminoglycoside enhances the bactericidal activity and is generally recommended in cases of endocarditis and meningitis. The adult dose is ampicillin 4-6 g/day divided every 6 hr plus an aminoglycoside. The ampicillin dose is doubled if meningitis is present. Special attention to dosing is required for neonates, who require longer dosing intervals because of the longer half-lives of the antibiotics in their bodies. *L. monocytogenes* is not susceptible to the cephalosporins, including third-generation cephalosporins. If these agents are used for empirical therapy for neonatal sepsis or meningitis in a newborn, ampicillin must be added for the possibility of *L. monocytogenes* infection. Vancomycin, vancomycin plus an aminoglycoside, trimethoprim-sulfamethoxazole, and erythromycin are alternatives. The duration of therapy is usually 2-3 wk, with 3 wk recommended for immunocompromised persons and patients with meningitis. A longer course is needed for endocarditis, brain abscess, and osteomyelitis. Antibiotic treatment is unnecessary for gastroenteritis without invasive disease.

PROGNOSIS

Early gestational listeriosis may be associated with abortion or stillbirth, although maternal infection with sparing of the fetus has been reported. There is no convincing evidence that *L. monocytogenes* is associated with repeated spontaneous abortions in humans. The mortality rate is >50% for premature infants infected in utero, 30% for early-onset neonatal sepsis, 15% for late-onset neonatal meningitis, and <10% in older children with prompt institution of appropriate antimicrobial therapy. Mental retardation, hydrocephalus, and other CNS sequelae are reported in survivors of *Listeria* meningitis.

PREVENTION

Listeriosis can be prevented by pasteurization and thorough cooking of foods. Irradiation of meat products may also be beneficial. Consumption of unpasteurized or improperly processed dairy products, especially aged soft cheeses, uncooked and precooked meat products that have been stored at 4°C (39.2°F) for extended periods, and unwashed vegetables should be avoided (Table 188-3). This avoidance is particularly important during pregnancy and for immunocompromised persons. Infected domestic animals should be avoided when possible. Education regarding risk reduction is aimed particularly at pregnant women and people being treated for cancers.

Careful handwashing is essential to prevent nosocomial spread within obstetric and neonatal units. Immunocompromised patients given prophylaxis with trimethoprim-sulfamethoxazole are protected from *Listeria* infections. Cases and especially outbreaks should be reported immediately to public health authorities so that timely investigation can be initiated in order to interrupt transmission from the contaminated source.

Bibliography is available at Expert Consult.

Table 188-3 Prevention of Food-Borne Listeriosis

General recommendations to prevent an infection with *Listeria:*	FDA recommendations for washing and handling food.
	• Rinse raw produce, such as fruits and vegetables, thoroughly under running tap water before eating, cutting, or cooking. Even if the produce will be peeled, it should still be washed first.
	• Scrub firm produce, such as melons and cucumbers, with a clean produce brush.
	• Dry the produce with a clean cloth or paper towel.
	• Separate uncooked meats and poultry from vegetables, cooked foods, and ready-to-eat foods.
	Keep your kitchen and environment cleaner and safer.
	• Wash hands, knives, countertops, and cutting boards after handling and preparing uncooked foods.
	• Be aware that *Listeria monocytogenes* can grow in foods in the refrigerator. Use an appliance thermometer, such as a refrigerator thermometer, to check the temperature inside your refrigerator. The refrigerator should be 4.5°C (40°F) or lower and the freezer –17.8°C (0°F) or lower.
	• Clean up all spills in your refrigerator right away–especially juices from hot dog and lunch meat packages, raw meat, and raw poultry.
	• Clean the inside walls and shelves of your refrigerator with hot water and liquid soap, then rinse.
	Cook meat and poultry thoroughly.
	• Thoroughly cook raw food from animal sources, such as beef, pork, or poultry to a safe internal temperature. For a list of recommended temperatures for meat and poultry, visit the safe minimum cooking temperatures chart at http://www.FoodSafety.gov.
	Store foods safely.
	• Use precooked or ready-to-eat food as soon as you can. Do not store the product in the refrigerator beyond the use-by date; follow USDA refrigerator storage time guidelines:
	  • Hot dogs–store opened package no longer than 1 wk and unopened package no longer than 2 wk in the refrigerator.
	  • Luncheon and deli meat–store factory-sealed, unopened package no longer than 2 wk. Store-opened packages and meat sliced at a local deli no longer than 3-5 days in the refrigerator.
	• Divide leftovers into shallow containers to promote rapid, even cooling. Cover with airtight lids or enclose in plastic wrap or aluminum foil. Use leftovers within 3-4 days.
	Choose safer foods.
	• Do not drink raw (unpasteurized) milk, and do not eat foods that have unpasteurized milk in them.

Continued

Table 188-3	Prevention of Food-Borne Listeriosis—cont'd
Recommendations for persons at higher risk, such as pregnant women, persons with weakened immune systems, and older adults in addition to the recommendations listed above, include:	Meats • Do not eat hot dogs, luncheon meats, cold cuts, other deli meats (e.g., bologna), or fermented or dry sausages unless they are heated to an internal temperature of 73.9°C (165°F) or until steaming hot just before serving. • Avoid getting fluid from hot dog and lunch meat packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats. • Pay attention to labels. Do not eat refrigerated pâté or meat spreads from a deli or meat counter or from the refrigerated section of a store. Foods that do not need refrigeration, like canned or shelf-stable pâté and meat spreads, are safe to eat. Refrigerate after opening. Cheeses • Do not eat soft cheese such as feta, queso blanco, queso fresco, brie, Camembert, blue-veined, or panela (queso panela) unless it is labeled as made with pasteurized milk. Make sure the label says, "MADE WITH PASTEURIZED MILK." Seafood • Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole, or unless it is a canned or shelf-stable product. • Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna, and mackerel, is most often labeled as "nova-style," "lox," "kippered," "smoked," or "jerky." • These fish are typically found in the refrigerator section or sold at seafood and deli counters of grocery stores and delicatessens. • Canned and shelf stable tuna, salmon, and other fish products are safe to eat. Follow this general FDA advice for melon safety: • Consumers and food preparers should wash their hands with warm water and soap for at least 20 sec before and after handling any whole melon, such as cantaloupe, watermelon, or honeydew. • Scrub the surface of melons, such as cantaloupes, with a clean produce brush under running water and dry them with a clean cloth or paper towel before cutting. Be sure that your scrub brush is sanitized after each use, to avoid transferring bacteria between melons. • Promptly consume cut melon or refrigerate promptly. Keep your cut melon refrigerated at, or less than 4.5°C (40°F) (0-1.1°C [32-34°F] is best), for no more than 7 days. • Discard cut melons left at room temperature for more than 4 hr.

Adapted from the Centers for Disease Control and Prevention: Listeria *(Listeriosis): prevention. Available at: http://www.cdc.gov/listeria/prevention.html*

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Chapter 189

Actinomyces

Richard F. Jacobs and Gordon E. Schutze

Actinomyces organisms are anaerobic, nonsporulating, Gram-positive bacteria that are part of the endogenous oral flora in humans and have a filamentous and branching structure. Infection caused by these bacteria is termed **actinomycosis,** which is a chronic, granulomatous, suppurative disease characterized by direct extension to contiguous tissue across natural anatomic barriers with the formation of numerous draining fistulas and sinus tracts. These infections usually involve the cervicofacial, thoracic, abdominal, or pelvic regions.

ETIOLOGY

At least 21 species of *Actinomyces* causing human infection have been identified using 16S rRNA sequencing. *Actinomyces israelii* is the predominant species causing human actinomycosis. Other implicated species include: *Propionibacterium propionicum*, *Actinomyces odontolyticus, Actinomyces meyeri, Actinomyces naeslundii, Actinomyces gerencseriae,* and *Actinomyces viscosus.*

Actinomyces organisms are part of the endogenous flora of mucous membranes and are often found in clinical specimens such as sputum, bronchial washes, purulent exudates, and tissues obtained surgically or at necropsy. Staining of crushed tissue specimens rinsed with sterile saline or purulent exudate stained with Gram or acid-fast procedures may reveal organisms within the classic sulfur granules, which are characteristically associated with pulmonary disease caused by *A. israelii* or *A. meyeri.* Cultures on brain-heart infusion agar incubated at 37°C (98.6°F) anaerobically (95% nitrogen and 5% carbon dioxide) and a separate set incubated aerobically reveal organisms within the lines of streak at 24-48 hr. *A. israelii* colonies appear as loose masses of delicate, branching filaments with a characteristic spider-like growth. Colonies of *A. naeslundii, A. viscosus,* and *P. propionicum* may have similar growth characteristics. Biochemical testing is frequently used for speciation but is limited by the complexity within this group. Newer speciation methods are based on 16S recombinant RNA sequence analysis.

EPIDEMIOLOGY

Actinomycosis occurs worldwide among people of all ages, with higher incidence among males, possibly related to increased trauma or poorer dental hygiene. There is no relationship to race, season, or occupation. In a review of 85 cases of actinomycosis, 27% were in persons younger than 20 yr of age, with 7% among children younger than 10 yr of age. The youngest patient in this series was 28 days old. The source of human infection is almost always endogenous flora. The incidence has declined as a result of improved oral hygiene and early antibiotic treatment of oral infections. Risk factors in children include trauma, dental caries, debilitation, and poorly controlled diabetes mellitus. Although actinomycosis is not a common opportunistic infection, disease has been associated with corticosteroid use, leukemia, renal failure, congenital immunodeficiency diseases, and HIV infection. In one study, antecedent disease and surgery predisposed 81 of 181 subjects to infection.

PATHOGENESIS

The 3 significant sites of *Actinomyces* infection are, in order of frequency, cervicofacial, abdominal and pelvic, and pulmonary, although infection may involve any organ in the body. Infection typically follows introduction of the organism into tissues after trauma or surgery. The hallmark of actinomycosis is spread that fails to respect tissue or fascial

planes. The use of intrauterine devices may predispose to development of pelvic actinomycosis. Pulmonary actinomycosis occurs after inhalation or aspiration of organisms, introduction of a colonized foreign body, or spread from an existing cervicofacial or abdominal actinomycotic infection.

Infection spreads contiguously and, rarely, hematogenously. Actinomycosis is a chronic, suppurative, scarring inflammatory process. Sites of infection show dense cellular infiltrates and suppuration that form many interconnecting abscesses and sinus tracts. These abscesses and sinus tracts may be followed by cicatricial healing from which the organism spreads by burrowing along fascial planes, causing deep, communicating scarred sinus tracts. **Sulfur granules** are characteristic of actinomycosis. On hematoxylin-and-eosin staining, they appear as an adherent mass of polymorphonuclear neutrophils attached to the radially arranged eosinophilic clubs of the granule, which is the host immune response. They may be microscopic or macroscopic and are typically yellow, accounting for their name, but may be white, gray, or brown.

Actinomycosis, even in closed infections, is usually, if not always, polymicrobial in nature, involving mixed bacteria. In a large study of more than 650 cases, infection with *Actinomyces* was identified in pure culture in only 1 case and in others was usually identified with other oral flora, most notably members of the **HACEK group,** which includes *Haemophilus aphrophilus, Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae. A. actinomycetemcomitans* is a fastidious, Gram-negative bacillus that is part of the oral flora and has been implicated as a pathogen in periodontal disease. Other bacterial species frequently isolated concomitantly in human actinomycosis include *Fusobacterium, Bacteroides, Capnocytophaga, Staphylococcus*, aerobic and anaerobic streptococci, and Enterobacteriaceae.

CLINICAL MANIFESTATIONS

The 3 major forms of actinomycosis—cervicofacial, abdominal and pelvic, and pulmonary—arise by different routes but may progress to other forms of the disease. Actinomycosis in children suggests an underlying immunodeficiency, especially chronic granulomatous disease (see Chapter 130).

Cervicofacial Actinomycosis

In the patient with cervicofacial actinomycosis, there is often a history of oral trauma, oral surgery, dental procedures, or caries, facilitating entry of organisms into cervicofacial tissues. Cervicofacial actinomycosis usually manifests as a painless, slow-growing, hard mass and can produce cutaneous fistulas, a condition commonly known as **lumpy jaw** (Fig. 189-1). Less frequently, cervicofacial actinomycosis manifests clinically as an acute pyogenic infection with a tender, fluctuant mass with trismus, firm swelling, and fistulas with drainage containing the characteristic sulfur granules. Bone is not involved early in the disease, but periostitis, mandibular osteomyelitis, or perimandibular abscess may develop. Infection may spread by way of sinus tracts to the cranial bones, possibly giving rise to meningitis. The ability of *Actinomyces* to burrow through tissue planes and even bone is a key difference between actinomycosis and nocardiosis. The cervicofacial form of actinomycosis has the best prognosis and is usually cured with surgical debridement and excision combined with antibiotic therapy.

Figure 189-1 A 2 yr old boy with HIV infection who has cervicofacial actinomycosis and a chronic draining fistula.

Abdominal and Pelvic Actinomycosis

In abdominal and pelvic actinomycosis, characteristically there is some disruption of the mucosa of the gastrointestinal tract, usually as a result of an acute gastrointestinal perforation or abdominal trauma. Patients often present with a history of gastrointestinal surgery, diverticulitis, or appendicitis. Of all the forms of actinomycosis, delayed diagnosis is most typical for abdominal and pelvic infection. Gastrointestinal disease clinically develops as appendicitis in 25% of cases but can be manifested as various ulcerative diseases. Infection classically appears after appendectomy as a firm, irregular mass in the ileocecal area that softens and then drains externally through a fistula. Hepatic involvement occurs in approximately 15% of cases of abdominal actinomycosis, with solitary or multiple liver abscesses or in a miliary pattern. The clinical course is indolent, with chills, fever, night sweats, and weight loss, and the presentation is similar to that of tuberculous peritonitis. Infection usually spreads by direct extension or, rarely, hematogenously, possibly involving any tissue or organ, including muscle, spleen, kidneys, fallopian tubes, ovaries, uterus, testes, bladder, and rectum.

Women using intrauterine devices are at risk for development of pelvic actinomycosis, which classically manifests as vaginal discharge, pelvic pain, abdominal pain, menorrhagia, fever, pelvic mass, and a history of pelvic inflammatory disease. The risk is higher if the intrauterine device has been in place for longer than 2-3 yr.

Pulmonary Actinomycosis

Undetected aspiration in a predisposed host is the typical mechanism for thoracic actinomycosis. Neither the clinical nor the radiographic presentation of pulmonary actinomycosis is specific. Pulmonary actinomycosis may manifest as an endobronchial infection, a tumor-like lesion, diffuse pneumonia, or a pleural effusion. Principal symptoms include fever, productive cough, chest pain, and weight loss. Infection frequently dissects along tissue planes and may extend through the chest wall or diaphragm, characteristically producing numerous sinus tracts that contain small abscesses and purulent drainage. Other complications include bony destruction of adjacent ribs, sternum, and vertebral bodies. Multiple lobe involvement of the lungs is occasionally found. Predisposing conditions include dental caries, aspiration, thermal or chemical inhalation injury, introduction of a colonized foreign body, and preexisting cervicofacial or abdominal disease. The classic radiographic triad of thoracic actinomycosis is chronic lower lobe pulmonary consolidation, empyema, and wavy periostitis of the ribs. Accurate diagnosis is difficult because of the propensity of *Actinomyces* to infect preexisting pulmonary cavities. Diagnosis can be confirmed by examination of purulent sinus tract drainage for sulfur granules, and with appropriate cultures. The significance of the presence of *Actinomyces* in sputum or bronchoscopy specimens is limited because these organisms are normal oral flora.

Other Forms

Laryngeal actinomycosis rarely has been reported in older teenagers. Oropharyngeal colonization with *Actinomyces* may be involved in the development of obstructive tonsillar hypertrophy. *Actinomyces pyogenes* has only rarely been implicated as a cause of human infection, although there are reported cases of septicemia, endocarditis, meningitis, arthritis, empyema, pneumonia, otitis media, cystitis, mastoiditis, appendicitis, and cutaneous infection.

Severe forms of periodontitis, particularly localized juvenile periodontitis, are associated with *Actinomyces,* especially in children 10-19 yr of age. *Actinomyces* has a propensity for infecting heart valves, a process that results in an insidious presentation of endocarditis, with fever present in less than half of cases.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Microscopic examination with appropriate stains and culture of purulent drainage from fistulas, abscesses, draining sinus tracts, bronchoalveolar lavage, and sputum can reveal *Actinomyces.* Except for *A. meyeri,* which is nonbranching, *Actinomyces* organisms appear as branching, filamentous rods. Inoculation of anaerobic and aerobic cultures enhances the yield of cultures. Gram, Gomori methenamine silver, or Giemsa stains of purulent material or tissue reveal diagnostic filamentous, branching bacteria at the periphery of sulfur granules. *Nocardia* is indistinguishable from *Actinomyces* on Gram stain, but unlike *Actinomyces, Nocardia* stains with the modified acid-fast stain.

Cranial CT or MRI is important to evaluate the possibility of cerebral actinomycosis in patients with cervicofacial disease or neurologic findings. Infection that invades across tissue planes and ignores anatomic boundaries is highly suggestive of actinomycosis. Abdominal CT may be helpful in identifying the presence of a contrast-enhancing, multicystic lesion, which could be approached by CT-guided needle biopsy for culture.

The mass-like lesion of actinomycosis may manifest as a tumor, necessitating invasive approaches for diagnosis. Actinomycosis must be differentiated from other chronic inflammatory infections, including tuberculosis, nocardiosis, polymicrobial bacterial infections, and fungal infections. Actinomycosis may mimic appendicitis, pseudoappendicitis caused by *Yersinia enterocolitica,* amebiasis, hepatic abscess, lung abscess, and osteomyelitis.

TREATMENT

The mainstay of treatment for actinomycosis is an appropriate surgical approach to sinus tracts and abscesses, prolonged antibiotic therapy, and management of complications such as hemoptysis. Large abscesses usually require complete surgical excision. Bone disease may require multiple debridements. Prompt initiation of antibiotics results in a high cure rate. Actinomycosis is treated with penicillin G (250,000 units/kg/day IV divided every 4-6 hr; maximum: 18-24 million units/day). Other appropriate antibiotics may include tetracycline, clindamycin, and carbapenems. Although controversy still exists about the optimal dosage and duration of therapy, appropriate therapy usually includes parenteral antibiotics for 2-6 wk followed by oral antibiotics for 3-12 mo. The oral antibiotic of choice is penicillin V (100 mg/kg/day divided every 6 hr PO). Hepatic abscesses or other deep tissue infections should be treated for 6-12 mo. Although most *A. israelii* strains are sensitive to penicillin with minimum inhibitory concentrations of 0.03-0.5 μg/mL, some resistant strains have been identified. Antibiotic susceptibility testing should be performed on all isolates from patients who have significant disease or are immunocompromised.

A. actinomycetemcomitans is a **copathogen** in at least 30% of actinomycotic infections. It is important to consider also treating this organism empirically, especially in the critically ill patient. Failure to recognize this organism and treat it adequately has resulted in clinical relapse and deterioration in patients with actinomycosis. *A. actinomycetemcomitans* is susceptible to cephalosporins, amoxicillin-clavulanate, rifampin, trimethoprim-sulfamethoxazole, aminoglycosides, ciprofloxacin, tetracycline, and azithromycin. It is susceptible to penicillin and ampicillin in vitro, but test results do not correlate necessarily with clinical outcome. In some patients with periodontitis associated with *A. actinomycetemcomitans,* mechanical periodontal treatment combined with metronidazole plus amoxicillin is effective for subgingival suppression.

PROGNOSIS

The prognosis is excellent with early diagnosis, adequate surgical debridement, and antimicrobial therapy. Removal of chronically infected tonsils and treatment of periodontitis or caries may eliminate sources of possible reinfection.

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Chapter 190

Nocardia

Richard F. Jacobs and Gordon E. Schutze

Nocardia organisms cause localized and disseminated disease in children and adults. These organisms are primarily opportunistic pathogens infecting immunocompromised persons. Infection caused by these bacteria is termed **nocardiosis,** which consists of acute, subacute, or chronic suppurative infections with a tendency for remissions and exacerbations.

ETIOLOGY

There are more than 80 species to date in the *Nocardia* genus. *Nocardia* are Gram-positive filamentous bacteria. These organisms are environmental saprophytes that are ubiquitous in soil and decaying vegetable matter. They are obligate aerobes and grow on ordinary culture media. Growth is achieved best at 37° C (98.6° F) with 10% carbon dioxide, although many isolates of *Nocardia* are thermophilic and grow at temperatures up to 50° C (122° F). Colonies appear within 1-2 wk on brain–heart infusion agar, Lowenstein-Jensen media, and simple blood agar, usually as waxy, folded, or heaped colonies at the edges. With modified Kinyoun acid-fast staining of biopsy specimens or body fluids, *Nocardia* demonstrates fragmented bacilli with stain concentrated in a **beaded pattern** along portions of the branching filaments.

Ongoing identification of new species continues to challenge microbiology laboratories. Speciation and antimicrobial susceptibility testing is critical for optimal clinical outcomes, especially in severe disease in immunocompromised patients. The most common clinical isolates of *Nocardia asteroides* have now been classified into complex groups I-VI. Valid taxonomic clusters by gene sequencing and antimicrobial susceptibility testing have led to new information to guide clinicians. The term *N. asteroides* complex I-VI now refers to a cluster of similar strains. Non–*N. asteroides* complex organisms are usually *Nocardia brasiliensis* or *Nocardia otitidiscaviarum.*

N. asteroides complex includes the most common agents of systemic nocardiosis in the United States. *N. brasiliensis* is the principal cause of localized nocardial cellulitis and lymphadenitis in immunocompetent children and can also cause pulmonary and systemic disease, especially in immunocompromised persons. *N. brasiliensis* is found more commonly in the southern United States, Central America, South America, and Asia.

EPIDEMIOLOGY

Once thought to be a rare human disease, nocardiosis is being recognized more frequently and has been diagnosed in persons from 4 wk to 82 yr of age. Almost all patients have compromised cellular immunity from an underlying disease such as organ transplantation, malignancy, corticosteroids, diabetes, HIV infection, or primary immunodeficiency, especially chronic granulomatous disease (see Chapter 130). *Nocardia* infections among stem cell transplant recipients are associated with a high rate of concomitant invasive fungal infection and a notable lack of protection with trimethoprim-sulfamethoxazole prophylaxis. An evaluation of opportunistic infections in 547 organ transplant recipients receiving alemtuzumab (humanized monoclonal CD52 antibody) revealed that 62 opportunistic infections developed in 56 patients (10%), including *Nocardia* in 4 patients.

PATHOGENESIS

Soil is the natural habitat of *Nocardia,* which has been isolated worldwide. The organism is inhaled in aerosolized dust and causes pulmonary infection, with widespread dissemination in susceptible hosts. It can be transmitted by direct cutaneous inoculation, including after

arthropod and cat bites. Although human-to-human transmission is rare, a description of *Nocardia farcinica* sternal wound infections among patients undergoing open heart surgery raises concern about *Nocardia* as a nosocomial pathogen.

CLINICAL MANIFESTATIONS

Pulmonary nocardiosis accounts for 75% of cases of infection, almost all of which occur among immunocompromised patients or patients with underlying pulmonary disease. Demonstration of tissue invasion is important for identifying active pulmonary infection because the organism occasionally exists as a respiratory saprophyte. Clinical manifestations include pneumonia and necrotizing pneumonia with single or multiple abscesses.

Single or multiple metastatic lesions may occur anywhere in the body. The brain is the most common secondary site and is involved in 15-40% of cases of pulmonary nocardiosis. Brain abscess is the most common presentation, and meningitis is the second most common presentation, manifested by pleocytosis (with a lymphocytic or neutrophilic predominance), elevated cerebrospinal fluid protein, and hypoglycorrhachia. Persistent neutrophilic meningitis with sterile culture results is classic for central nervous system (CNS) infection. The onset may be gradual or sudden and includes manifestations varying from headache to coma.

The skin is the third most commonly involved organ, manifested by **sporotrichoid nocardiosis** or superficial ulcers (Fig. 190-1). **Mycetoma** is a chronic, progressive infection developing days to months after inoculation, usually on a distal location on the limbs. Renal nocardiosis, the fourth most common type of disease, typically manifests as dysuria, hematuria, or pyuria. Lesions may extend from the cortex into the medulla. Gastrointestinal involvement may also be associated with nausea, vomiting, diarrhea, abdominal distention, and melena. Infection may spread to skin, pericardium, myocardium, spleen, liver, or adrenal glands. Bone involvement is rare. Almost all of the involved organs have several abscesses. In contrast to actinomycosis, granules are rarely found in nocardiosis.

Figure 190-1 A 2 yr old girl with multiple pustules on the dorsum of the right foot caused by *Nocardia brasiliensis*. *(Courtesy of Jaime E. Fergie, MD.)*

DIAGNOSIS

Laboratory diagnosis of nocardiosis requires direct examination of clinical material for characteristic Gram-positive, acid-fast organisms and isolation by culture methods. Smears of clinical material are stained with Gram stain or the modified Kinyoun acid-fast stain. *N. asteroides* complex and *N. brasiliensis* appear as delicately branched, Gram-positive, coccoid to bacillary bacteria that tend to fragment. In properly stained and decolorized acid-fast smears, the organisms may appear as fragmented bacilli with the stain concentrated in a beaded pattern along the portions of the filaments. Gene sequence analysis (16S rRNA; multilocus sequence analysis) is required for definitive identification. Clinical laboratory susceptibility testing is now standardized with breakpoints.

Diagnosis of pulmonary nocardiosis is established in 30% of cases in adults by sputum analysis and culture. Bronchoalveolar lavage or lung biopsy may be required to establish the diagnosis in the remaining 60% of adults and in children.

Cranial CT or MRI is recommended for all immunocompromised patients with pulmonary nocardiosis, even if asymptomatic, because of the high frequency of CNS involvement, and should also be considered for immunocompetent patients.

TREATMENT

Surgical drainage of abscesses is important. The choice, dose, and duration of antimicrobial treatment depend on the site and extent of infection, host immune status, initial clinical response, and species and susceptibility testing of the *Nocardia* isolate. The initial selection of antimicrobial therapy must be empiric. Sulfonamides have been the cornerstone of therapy for the treatment of nocardiosis since the 1940s, but increasing reports of resistance have led to the use of other regimens. Trimethoprim-sulfamethoxazole (TMP-SMX) is the formulation that is recommended, although sulfadiazine and sulfisoxazole have been used. TMP-SMX resistance ranges from 20% for *N. brasiliensis* to 80% for *N. farcinica.* A susceptibility study of 78 clinical isolates of the *N. asteroides* complex from the United States found that 95% of strains exhibited 1 of 6 antibiotic resistance patterns. The most common pattern, occurring in 35% of isolates, showed resistance to ampicillin and erythromycin, but susceptibility to cefotaxime, ceftriaxone, and carbapenems. Approximately 20% of isolates, which were subsequently identified as *N. farcinica,* were resistant to cefotaxime and ceftriaxone. Based on analysis of all strains tested to date, resistance was lowest for amikacin (5%), imipenem (30%), and ceftriaxone (52%). *N. farcinica* is typically always resistant to ertapenem. Imipenem resistant *Nocardia cyriacigeorgica* infection in a child with chronic granulomatous disease has been reported. The most active oral agents were sulfonamides (100%) and minocycline (100%). Additional antimicrobial agents with oral bioavailability are desirable because of the increasing reports of sulfonamide resistance and the adverse effects reported among patients with HIV infection. In vitro studies show susceptibility of all strains to linezolid, which appears to be an effective alternative treatment, but potential toxicity with long-term oral therapy with this agent must be kept in mind.

Combination therapy involving a carbapenem or a third-generation cephalosporin with or without amikacin is usually recommended for severely ill patients and patients with CNS involvement. The mortality rate approaches 50% when a sulfonamide is used alone for treatment. On the basis of in vitro susceptibility testing for specific *N. asteroides* complex isolates, alternative drug combinations may include erythromycin and newer macrolides (azithromycin and clarithromycin), carbapenems, streptomycin, minocycline, quinolones, third-generation cephalosporins, and linezolid. The issues to be considered for use of linezolid include the limited data of use in children and the adverse effects of long-term use. Clinical trials show that ampicillin and amoxicillin-clavulanate are effective in *N. brasiliensis* infections.

Susceptibility testing of *Nocardia* should be performed by a reference laboratory for isolates from deep-seated or disseminated

infections of strains such as *N. farcinica* and *Nocardia otitidiscaviarum* that are commonly resistant to cephalosporins, if nonsulfonamide treatment regimens are being considered, for poor response to initial therapy, and for relapse.

Superficial cutaneous infection is treated for at least 6-12 wk. Mycetoma or pulmonary or systemic nocardiosis in immunocompetent persons is treated for 6-12 mo. CNS infection is treated for at least 12 mo, using at least 2-3 antibiotics with proven susceptibility for at least the 1st 4-12 wk, until some evidence of clinical and radiographic improvement. Relapses of systemic *Nocardia* infection that had been treated for <3 mo have occurred.

PROGNOSIS

Despite appropriate therapy, the overall mortality rate for nocardiosis is >50%. This high rate may be secondary to delay in diagnosis or to the debilitated state of patients with severely compromised host defenses.

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Section 5

Gram-Negative Bacterial Infections

Chapter 191

Neisseria meningitidis (Meningococcus)

Andrew J. Pollard and Manish Sadarangani

Neisseria meningitidis (the *meningococcus*) is a commensal of the human nasopharynx in approximately 10% of the population and rarely enters the bloodstream to cause devastating invasive disease such as meningitis and meningococcal septicemia (meningococcemia). Although a rare endemic disease in most countries, the epidemiology varies widely over time and in different geographic regions with both hyperendemic and epidemic disease patterns occurring. Onset of disease in susceptible individuals may be very rapid, within hours, and the case fatality rate is high, especially among those presenting with septic shock, despite access to modern critical care. Individual susceptibility is now known to involve a complex relationship between environmental, host, and bacterial factors, and prevention of disease through behavior modification (such as avoiding tobacco smoke) and vaccination offers the best prospect for control.

ETIOLOGY

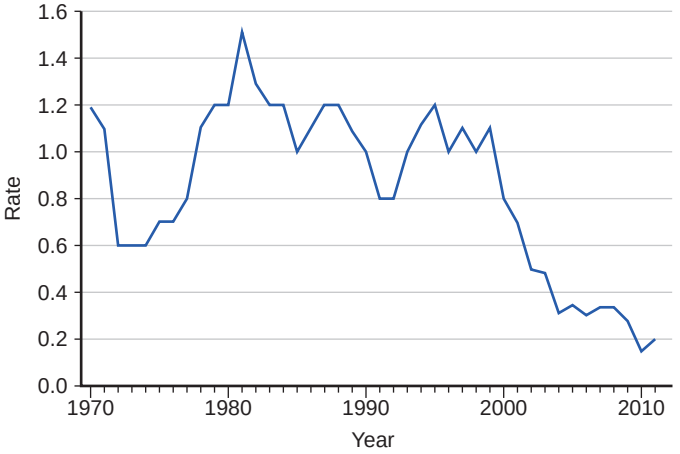
N. meningitidis was first described by Weichselbaum who observed the organism, which he called *Diplococcus intracellularis meningitidis,* in specimens from 6 patients who died of meningitis in 1887. *N. meningitidis* is a Gram-negative, fastidious, encapsulated, oxidase-positive, aerobic diplococcus. Differences in the chemistry of the polysaccharide capsule allow definition of 13 serologically distinct meningococcal capsular groups, of which 6, designated A, B, C, W (previously designated W135), X, and Y, are responsible for almost all cases of disease. Meningococcal strains may be subclassified on the basis of antigenic variation in 2 porin proteins found in the outer membrane, PorB (serotype) and PorA (serosubtype), and lipopolysaccharide (immunotype), using serology. Serologic typing is being replaced by molecular typing methods, which target genes under immune selection to provide antigen sequence typing (based on amino acid variation in various surface proteins, including PorA and FetA). Sequencing of antigen genes (such as *PorA, fHbp, NadA,* and *NHBA*) is set to be an important means of monitoring pressure on meningococcal populations by protein-based vaccines. Because meningococci readily exchange genetic material, typing based on a few antigens cannot provide an accurate picture of relatedness of strains, an important goal in monitoring epidemiology. Multilocus sequence typing, which types meningococci using variation in 7 housekeeping genes, is now widely used to map the distribution of genetic lineages of meningococci (http://pubmlst.org/neisseria/) and provides a clearer picture of the genetic and epidemiologic relatedness of strains. To provide still better definition of genetic variation, in some countries, including the United Kingdom, whole-genome sequencing is now being used to type meningococci and appears set to replace both antigen sequencing and multilocus sequence typing as costs continue to fall. The application of molecular approaches to epidemiology has established that (1) endemic meningococcal disease is caused by genetically heterogeneous strains, although only a small number of genetic lineages are associated with the majority of cases of invasive disease; and (2) outbreaks are usually clonal, caused by single strains.

EPIDEMIOLOGY

Meningococci are transmitted during close contact via aerosol droplets or exposure to respiratory secretions, such as through kissing. The organism does not survive for long periods in the environment. Enhanced rates of mucosal colonization and increased disease risk are associated with activities that increase the likelihood of exposure to a new strain or increase proximity to a carrier, thus facilitating transmission including kissing, bar patronage, binge drinking, attendance at nightclubs, and living in freshman college dormitories. Factors that damage the nasopharyngeal mucosa such as smoking and respiratory viral infection (notably influenza) are also associated with increased rates of carriage and disease, perhaps by driving upregulation of host adhesion molecules that are receptors for meningococci. Carriage is unusual in early childhood and peaks during adolescence and young adulthood.

Meningococcal disease is a global problem, but disease rates vary by a factor of 10-100–fold in different geographic locations at one point in time and in the same location at different times. Most cases of meningococcal disease are sporadic, but small outbreaks (usually in schools or colleges, representing <3% of U.S. cases), hyperendemic disease (increased rates of disease persisting for a decade or more as a result of a single clone), and epidemic disease are all recognized patterns. However, over the last decade, rates of meningococcal disease have declined in most industrialized countries partly through introduction of immunization programs, possibly aided by widespread legislation against smoking in public places. In the United States, the disease rate was 1.1 cases per 100,000 population in 1999 but had fallen to 0.2 cases per 100,000 population by 2011 (Fig. 191-1). By contrast, the rate of disease in Ireland in 1999 was >12 per 100,000 population and rates of 1,000 per 100,000 population have been described during epidemic disease in sub-Saharan Africa. Disease caused by dominant hyperendemic clones has been recognized in the last decade in Oregon, United States, across New Zealand, and in Normandy, France. Laboratory data underreport meningococcal disease incidence rates as up to 50% of cases are not culture confirmed. In the United Kingdom, polymerase chain reaction (PCR) methods are used routinely for diagnosis of suspected cases, doubling the number of confirmed cases.

The highest rate of meningococcal disease occurs in infants younger than 1 yr old, probably as a result of immunologic inexperience (antibody that recognizes meningococcal antigens is naturally acquired during later childhood), immaturity of the alternative and lectin complement pathways, and perhaps the poor responses made by infants to bacterial polysaccharides. In the absence of immunization, incidence



Source: CDC, Unpublished data, National Notifiable Diseases Surveillance System (NNDSS) for 1970–1996 and Active Bacterial Core surveillance (ABCs) system for 1997–2011.

* Per 100,000 population.

† ABCs cases from 1997–2011 estimated to the U.S. population. In 2010, estimated case counts from ABCs were lower than cases reported to NNDSS and might not be representative.

Figure 191-1 Rate of meningococcal disease, by year—United States, 1970-2011. *(From Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention (CDC): Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep *62(RR-2):1–28, 2013.)*

rates decline through childhood, apart from a peak of disease among adolescence and young adults, which may be related to increased opportunity for exposure from social activities.

In the United States, the majority of cases of disease in the 1st yr of life are caused by serogroup B strains. After age 1 yr, disease is roughly equally distributed among serogroups B, C, and Y strains. In most other industrialized countries, serogroup B strains predominate at all ages, in part because of introduction of routine serogroup C meningococcal conjugate vaccination among infants and/or toddlers. For reasons not understood, disease in children caused by group Y strains was uncommon in the United States before the 1990s and remains relatively uncommon outside the country.

Large outbreaks of serogroup A meningococcal disease occurred during and immediately after the 1st and 2nd World Wars in both Europe and the United States, but since the 1990s almost all cases caused by serogroup A strains have occurred in Eastern Europe, Russia, and developing countries. The highest incidence of serogroup A disease has occurred in a band across sub-Saharan Africa, the "meningitis belt," with annual endemic rates of 10-25 per 100,000 population. For more than a century, this region has experienced large serogroup A epidemics every 7-10 yr, with annual rates as high as 1,000 per 100,000 population. The onset of cases in the sub-Saharan region typically begins during the dry season, possibly related to drying and damage to the nasopharyngeal mucosa, and subsides with the rainy season, and may reemerge the following dry season. Rates of serogroup A meningococcal disease are currently falling across this region as a result of a mass vaccine implementation. However, both endemic and epidemic meningococcal disease in this region is also caused by serogroup W and X strains. These strains are infrequent causes of disease in other areas of the world, although both A and W strains have been associated with outbreaks among pilgrims returning from the Hajj.

PATHOGENESIS AND PATHOPHYSIOLOGY

Colonization of the nasopharynx by *N. meningitidis* is the first step in either carriage or invasive disease. Disease usually occurs 1-14 days after acquisition of the pathogen. Initial contact of meningococci with host epithelial cells is mediated by pili, which may interact with the host CD46 molecule or an integrin. Close adhesion is then mediated by Opa and Opc binding to carcinoembryonic antigen cell adhesion molecule receptors and integrins, respectively. Subsequent internalization of meningococci by epithelial cells is followed by transcytosis through to the basolateral tissues and dissemination into the bloodstream. Immunoglobulin A_1 protease secreted by invasive bacteria degrades secretory immunoglobulin A on the mucosal surface, circumventing this first-line host defense mechanism.

Once in the bloodstream, meningococci multiply rapidly to high levels to cause septicemia. Patients with a higher bacterial load have a more rapid clinical deterioration and longer period of hospitalization, as well as a higher risk of death and permanent sequelae. Resistance to complement-mediated lysis and phagocytosis is largely mediated by the polysaccharide capsule and lipopolysaccharide (LPS). Outer membrane vesicle blebs released from the surface of the organism contain LPS, outer membrane proteins, periplasmic proteins, and phospholipid, and play a major role in the inflammatory cascade that leads to severe disease.

Much of the tissue damage is caused by host immune mechanisms activated by meningococcal components, in particular LPS. During invasive disease LPS is bound to a circulating plasma protein, known as LPS binding protein. The host receptor complex for LPS consists of toll-like receptor 4, CD14, and myeloid differentiation protein 2. Binding of LPS to toll-like receptor 4, which is upregulated on circulating leukocytes during septicemia, results in activation of a number of different cell types. An intense inflammatory reaction ensues due to the secretion of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, and granulocyte macrophage colony-stimulating factor, levels of which are closely associated with plasma levels of LPS. The major antiinflammatory cytokines IL-1Ra, IL-2, IL-4, and IL-12. and transforming growth factor-β are present at very low levels. Both high and low levels have been observed for IL-10 and interferon-γ.

The pathophysiologic events that occur during meningococcal septicemia are largely related to microvascular injury. This leads to increased vascular permeability and the capillary leak syndrome, pathologic vasoconstriction and vasodilation, disseminated intravascular coagulation, and profound myocardial dysfunction. Increased vascular permeability can lead to dramatic fluid loss and severe hypovolemia. Capillary leak syndrome with or without aggressive fluid resuscitation (which is essential in severe cases) leads to pulmonary edema and respiratory failure. Initial vasoconstriction is a compensatory mechanism in response to hypovolemia and results in the clinical features of pallor and cold extremities. Following resuscitation, some patients experience "warm shock," that is, intense vasodilation with bounding pulses and warm extremities, despite persistent hypotension and metabolic acidosis. Virtually all antithrombotic mechanisms appear to be dysfunctional during meningococcal sepsis, leading to a procoagulant state and disseminated intravascular coagulation. All of these factors contribute to depressed myocardial function, but there is also a direct negative cytokine effect on myocardial contractility, thought to be largely mediated via IL-6. Hypoxia, acidosis, hypoglycemia, hypokalemia, hypocalcemia, and hypophosphatemia are all common in severe septicemia and further depress cardiac function. Some patients become unresponsive to the positive inotropic effects of catecholamines and require high levels of inotropic support during intensive care management. These processes result in impairment of microvascular blood flow throughout the body and ultimately lead to multiorgan failure, which is responsible for much of the mortality.

Following invasion of the circulation, meningococci may also penetrate the blood–brain barrier and enter the cerebrospinal fluid (CSF), facilitated by pili and possibly Opc. Once there, bacteria continue to proliferate and LPS and other outer membrane products can stimulate a proinflammatory cascade similar to that observed in the blood. This leads to upregulation of specific adhesion molecules and recruitment of leukocytes into the CSF. Central nervous system damage occurs directly by meningeal inflammation and indirectly by circulatory collapse and causes a high rate of neurologic sequelae in affected patients. Death can occur from cerebral edema, which leads to raised intracranial pressure and cerebral or cerebellar herniation.

Immunity

There is an inverse correlation between the incidence of disease and the prevalence of complement-dependent serum bactericidal antibody (SBA). The level of SBA is highest at birth and among adults and lowest in children between 6 mo and 2 yr of age when the highest incidence of disease occurs. Such antibodies are naturally elicited by asymptomatic carriage of pathogenic and nonpathogenic meningococci as well as by carriage of antigenically related species such as *Neisseria lactamica*. A similar relationship was described for serogroups A, B, and C. Vaccine trials support these earlier findings. For the meningococcal serogroup C conjugate vaccine, an SBA titer of ≥1 : 8 correlated strongly with postlicensure vaccine effectiveness. For serogroup B disease the data are less certain, but the proportions of serogroup B vaccine recipients with ≥4-fold rises in SBA following vaccination or SBA titers ≥1 : 4 have been correlated with clinical efficacy in trials of outer membrane vesicle vaccines. These cutoffs are, therefore, currently used for regulatory approval of new meningococcal vaccines.

There has been increasing evidence that mechanisms other than complement-dependent bactericidal antibodies are important in determining protection against meningococcal disease. The relationship between incidence of disease and prevalence of SBA was not observed in more recent studies in the United Kingdom and Canada, where a decline in disease incidence throughout childhood was not associated with a change in the seroprevalence of SBA. In the UK study, the second peak of disease in teenagers coincided with a paradoxical increase in the proportion with an SBA titer ≥1 : 4 and adults had a low risk of disease despite a much lower prevalence of SBA activity. In addition, disease in individuals with complement deficiency has a different age distribution has less-severe clinical features and often involves unusual serogroups. In particular, complement deficiency does not appear strongly related to an increased risk of serogroup B disease. Alternative surrogate markers of protection include the opsonophagocytic assay and antibody avidity, but there are no studies that have attempted to link these laboratory tests with vaccine efficacy or even population protection, as has been found with SBA.

Host Factors

Host susceptibility is strongly related to age as described above, indicating that immunologic responsiveness and/or naivety in infancy and early childhood are key determinants of risk. Complement is a key factor in protection against meningococcal disease. Individuals with inherited deficiencies of properdin, factor D, or terminal complement components have up to a 1,000-fold higher risk for development of meningococcal disease than complement-sufficient people. The risk of meningococcal disease is also increased in patients with acquired complement deficiencies associated with diseases such as nephrotic syndrome, systemic lupus erythematosus, and hepatic failure.

Among those with complement deficiencies, meningococcal disease is more prevalent during late childhood and adolescence, when carriage rates are higher than in children younger than age 10 yr; meningococcal infections may be recurrent. Although meningococcal disease can occasionally be overwhelming in patients with late complement component deficiency, cases are more typically described as being less severe than in complement-sufficient persons (properdin deficiency being the exception), perhaps reflecting the fact that these cases are often caused by unusual capsular serogroups. In 1 study, one-third of individuals with meningococcal disease caused by serogroups X, Y, and W had a complement deficiency. Although protective against early infection, extensive complement activation and bacteriolysis may contribute to the pathogenesis of severe disease once bacterial invasion has occurred.

The sibling risk ratio for meningococcal disease is similar to that for other diseases where susceptibility shows polygenic inheritance, and there are a number of host genetic factors that have now been identified to affect either susceptibility to meningococcal disease or severity of disease. The difficulties of these studies are the requirement for large numbers of cases and controls, and the need to confirm any potential associations in more than 1 population. The molecules implicated involved polymorphisms in genes expressed at epithelial surfaces, the complement cascade, pattern recognition receptors, clotting factors, or inflammatory mediators. Deficiencies in the complement pathways are consistently associated with an increased risk of meningococcal disease, with specific polymorphisms in mannose-binding lectin, and factor H found to be associated with disease susceptibility. A genome-wide association study of 7,522 individuals in Europe identified single-nucleotide polymorphisms within genes encoding complement factor H *(CFH)* and CFH-related protein 3 (*CFHR3*), which were associated with host susceptibility to meningococcal disease. Complement-mediated bacteriolysis is known to be extremely important in protection against meningococcal disease, giving these associations biologic plausibility. In particular, factor H attaches to various binding proteins expressed on the bacterial surface, downregulating complement activation and allowing the organism to evade host responses.

In terms of disease severity, a meta-analysis performed to collate data from smaller studies found that single-nucleotide polymorphisms in genes encoding plasminogen activator inhibitor 1 *(SERPINE1),* IL-1 receptor antagonist *(IL1RN)* and IL-1β *(IL1B)* are associated with increased mortality from meningococcal disease, which, again, is predictable from the known pathophysiologic changes that occur during invasive disease. Given that any single specific single-nucleotide polymorphism is likely to have only a small impact on disease susceptibility or severity, further large genome-wide association study in genetically different populations are required.

CLINICAL MANIFESTATIONS

The most common clinical manifestation of meningococcal infection is asymptomatic carriage of the organism in the nasopharynx. In the rare cases where invasive disease occurs, the clinical spectrum of meningococcal disease varies widely, but the highest proportion of cases present with meningococcal meningitis (30-50% of cases). Other recognized presentations include bacteremia without sepsis, meningococcal septicemia with or without meningitis, pneumonia, chronic bacteremia, and occult bacteremia. Focal infections in various sites (e.g., myocardium, joints, pericardium, bone, eye, peritoneum, sinuses, and middle ear) are well recognized, and all may progress to disseminated disease. Urethritis, cervicitis, vulvovaginitis, orchitis, and proctitis may also occur.

Acute meningococcal septicemia cannot be distinguished from other viral or bacterial infections early after onset of symptoms (Table 191-1). Typical nonspecific early symptoms include fever, irritability, lethargy, respiratory symptoms, refusal to drink, and vomiting. Less commonly, diarrhea, sore throat, and chills/shivering are reported. A fine maculopapular rash, which is indistinguishable from rashes seen after viral infections, is evident in approximately 7% of cases early in the course of infection. Limb pain, myalgia, or refusal to walk may occur as the primary complaint in 7% of otherwise clinically unsuspected cases. As disease progresses, cold hands or feet and abnormal skin color may be important signs, capillary refill time becomes prolonged, and a nonblanching or petechial rash will develop in more than 80% of cases. In fulminant meningococcal septicemia, the disease progresses rapidly over several hours from fever with nonspecific signs to septic shock characterized by prominent petechiae and purpura **(purpura fulminans)** with poor peripheral perfusion**,** tachycardia (to compensate for reduced blood volume resulting from capillary leak), increased respiratory rate (to compensate for pulmonary edema), hypotension (a late sign of shock in young children), confusion, and coma (resulting from decreased cerebral perfusion). Coagulopathy, electrolyte disturbance (especially hypokalemia), acidosis, adrenal hemorrhage, renal failure, and myocardial failure, may all develop (Fig. 191-2). Meningitis may be present.

Meningococcal meningitis is indistinguishable from meningitis caused by other bacteria. Nonspecific symptoms and signs (see Table 191-1), including fever and headache, predominate, especially in the young and early in the illness. Children younger than 5 yr of age rarely report headache. More specific symptoms of photophobia, nuchal rigidity, bulging of the fontanel, and clinical signs of meningeal irritation may develop but are unusual in infants. Seizures and focal neurologic signs occur less frequently than in patients with meningitis

Table 191-1 Prevalence of Symptoms and Signs in Children and Young People with Meningococcal Septicemia, Meningococcal Disease and Bacterial Meningitis

	Prevalence Range (Number of Studies)		
SYMPTOM OR SIGN	**BACTERIAL MENINGITIS**	**MENINGOCOCCAL DISEASE**	**MENINGOCOCCAL SEPTICEMIA**
Fever	66-97% (10)	58-97% (7)	98% (1)
Vomiting or nausea	18-70% (10)	44-76% (6)	64% (1)
Rash	9-62% (6)	59-100% (9)	70% (1)
Headache	3-59% (7)	16-49% (5)	40% (1)
Lethargy	13-87% (6)	36-65% (3)	59% (1)
Coughing	N/A (0)	15-27% (2)	33% (1)
Irritable or unsettled	21-79% (8)	36-67% (3)	32% (1)
Runny nose	N/A (0)	24% (1)	31% (1)
Muscle ache or joint pain	23% (1)	7-65% (3)	30% (1)
Refusing food or drink	26-76% (4)	13-60% (3)	27% (1)
Altered mental state*	26-93% (6)	45-81% (3)	N/A (0)
Stiff neck	13-74% (13)	5-71% (6)	N/A (0)
Impaired consciousness	60-87% (4)	10-72% (2)	N/A (0)
Unconsciousness	4-18% (4)	N/A (0)	N/A (0)
Chills or shivering	N/A (0)	39% (1)	N/A (0)
Photophobia	5-16% (2)	2-31% (5)	N/A (0)
Respiratory symptoms	25-49% (4)	16-23% (2)	N/A (0)
Breathing difficulty	13-34% (4)	11% (1)	N/A (0)
Cold hands or feet	N/A (0)	43% (1)	N/A (0)
Shock	8-16% (2)	27-29% (2)	N/A (0)
Seizures	14-38% (12)	7-17% (3)	N/A (0)
Diarrhea	21-29% (2)	7-9% (2)	N/A (0)
Abdominal pain or distention	17% (1)	4% (1)	N/A (0)
Leg pain	N/A (0)	11-37% (2)	N/A (0)
Thirst	N/A (0)	8% (1)	N/A (0)
Sore throat, coryza or throat infection	18% (1)	24% (1)	N/A (0)
Ill appearance	N/A (0)	79% (1)	N/A (0)
Capillary refill time >2 sec	N/A (0)	83% (1)	N/A (0)
Hypotension	N/A (0)	28% (1)	N/A (0)
Abnormal skin color	N/A (0)	19% (1)	N/A (0)
Bulging fontanelle†	13-45% (4)	N/A (0)	N/A (0)
Ear infection or ear, nose and throat infections‡	18-49% (5)	N/A (0)	N/A (0)
Chest infection	14% (1)	N/A (0)	N/A (0)
Brudzinski sign	11-66% (2)	N/A (0)	N/A (0)
Kernig sign	10-53% (3)	N/A (0)	N/A (0)
Abnormal pupils	10% (1)	N/A (0)	N/A (0)
Cranial nerve pair involvement	4% (1)	N/A (0)	N/A (0)
Toxic or moribund state	3-49% (2)	N/A (0)	N/A (0)
Back rigidity	46% (1)	N/A (0)	N/A (0)
Paresis	6% (1)	N/A (0)	N/A (0)
Focal neurological deficit	6-47% (3)	N/A (0)	N/A (0)

Classification of conditions presented in the table reflects the terminology used in the evidence.

*This includes confusion, delirium, and drowsiness.

†The age ranges in the 4 studies are 0-14 yr, 0-2 yr, 0-12 mo, and 0-13 wk.

‡One study reported the number of children and young people with ear, nose, and throat infections; the 4 other studies reported the number of ear infections only.

N/A, not applicable.

Modified from National Collaborating Center for Women's and Children's Health (UK): Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE clinical guidelines, No. 102. *London, 2010, RCOG Press.*

Figure 191-2 A, Purpuric rash in a 3 yr old with meningococcemia. **B,** Purpura fulminans in an 11 mo old with meningococcemia. *(From Thompson ED, Herzog KD: Fever and rash. In Zaoutis L, Chiang V, editors:* Comprehensive pediatric hospital medicine, *Philadelphia, 2007, Mosby, p. 332,* Figs. 62-6 *and* 62-7.*)*

caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* type b. A meningoencephalitis-like picture can occur that is associated with rapidly progressive cerebral edema and death from raised intracranial pressure, which may be more common with serogroup A infection.

Occult meningococcal bacteremia manifests as fever with or without associated symptoms that suggest a minor viral infection. Resolution of bacteremia may occur without antibiotics, but sustained bacteremia leads to meningitis in approximately 60% of cases and to distant infection of other tissues.

Chronic meningococcemia, which occurs rarely, is characterized by fever, nontoxic appearance, arthralgia, headache, splenomegaly, and a maculopapular or petechial rash. Symptoms are intermittent, with a mean duration of illness of 6-8 wk. Blood culture results are usually positive, but cultures may initially be sterile. Chronic meningococcemia may spontaneously resolve, but meningitis may develop in untreated cases. Some cases have been associated with complement deficiency and others with sulfonamide therapy. One report indicates that up to 47% of isolates from patients with chronic meningococcemia (compared with less than 10% in acute cases) have a mutation in the *lpxl* 1 gene, leading to a reduced inflammatory response and the milder course of infection.

DIAGNOSIS

The initial diagnosis of meningococcal disease should be made on clinical assessment to avoid delay in implementation of appropriate therapy. Laboratory findings are variable but may include leukocytopenia or leukocytosis, often with increased percentages of neutrophils and band forms, an anemia, thrombocytopenia, proteinuria, and hematuria. Elevations of erythrocyte sedimentation rate and C-reactive protein may occur, but in patients with rapid onset of disease, these values may be within normal limits at presentation. Conversely, a raised C-reactive protein in the presence of fever and petechiae makes the diagnosis likely. Hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hypophosphatemia, hypoglycemia, and metabolic acidosis, often with increased lactate levels, are common in patients with meningococcal septicemia. Patients with coagulopathy have decreased serum concentrations of prothrombin and fibrinogen and prolonged coagulation times.

A confirmed diagnosis of meningococcal disease is established by isolation of *N. meningitidis* from a normally sterile body fluid such as blood, CSF, or synovial fluid. Meningococci may be identified in a Gram stain preparation and/or culture of petechial or purpuric skin lesions, although this procedure is rarely undertaken, and occasionally are seen on Gram stain of the buffy coat layer of a centrifuged blood sample. Although blood culture may be positive in more than two-thirds of cases prior to antibiotic use, culture results often are negative if the patient has been treated with antibiotics prior to collection of the culture specimen; data suggest that less than 50% are culture-positive. Isolation of the organism from the nasopharynx is not diagnostic of invasive disease because the organism is a common commensal.

PCR using primers specific for meningococcal genes (e.g., *ctrA*), has high sensitivity and specificity for detection of meningococci using whole blood samples and has increased confirmation of suspected cases by more than 40% in the United Kingdom.

Lumbar puncture should be undertaken to establish a diagnosis of meningococcal meningitis in those patients without contraindications (including presence of septic shock, coagulopathy, thrombocytopenia, respiratory distress, seizures, raised intracranial pressure, or local infection). In patients with meningococcal meningitis, the cellular and chemical characteristics of the CSF are those of acute bacterial meningitis, showing Gram-negative diplococci on Gram stain in up to 75% of cases. CSF culture results may be positive in patients with meningococcemia in the absence of CSF pleocytosis or clinical evidence of meningitis; conversely, positive CSF specimens that are positive for Gram stain are sometimes culture negative. Over-decolorized pneumococci in Gram stain preparations can be mistaken for meningococci, and, therefore, empirical therapy should not be narrowed to *N. meningitidis* infection on the basis of Gram stain findings alone.

Detection of capsular polysaccharide antigens using rapid latex agglutination tests on CSF can support the diagnosis in cases clinically consistent with meningococcal disease, but the tests have not performed adequately in clinical practice (poor sensitivity and cross reactivity of the serogroup B test with *Escherichia coli* K1 antigen) and have been replaced by molecular diagnostic methods. Urine antigen testing is insensitive and should not be used. PCR-based assays for detection of meningococci in blood and CSF have been developed, and multiplex PCR assays that detect several bacterial species associated with meningitis, including the meningococcus, are used in some laboratories.

DIFFERENTIAL DIAGNOSIS

Meningococcal disease can appear similar to sepsis or meningitis caused by many other Gram-negative bacteria, *S. pneumoniae, Staphylococcus aureus,* or group A streptococcus; to Rocky Mountain spotted fever, ehrlichiosis, or epidemic typhus; and to bacterial endocarditis. Viral and other infectious etiologies of meningoencephalitis should be considered in some cases.

Petechial rashes are common in viral infections (enteroviruses, influenza and other respiratory viruses, measles, Epstein Barr virus, cytomegalovirus, parvovirus) and may be confused with meningococcal disease. Petechial or purpuric rashes are also associated with protein C or S deficiency, platelet disorders (including idiopathic thrombocytopenic purpura), Henoch-Schönlein purpura, connective tissue disorders, drug eruptions, and trauma, including nonaccidental injury. The nonpetechial, blanching maculopapular rash observed in some cases of meningococcal disease, especially early in the course, may initially be confused with a viral exanthem.

TREATMENT

Antibiotics

Empirical antimicrobial therapy should be initiated immediately after the diagnosis of invasive meningococcal infection is suspected and cultures are obtained, using a third-generation cephalosporin to cover the most likely bacterial pathogens until the diagnosis is confirmed. In regions with a high rate of β-lactam resistant *S. pneumoniae*, empiric addition of intravenous (IV) vancomycin is recommended (see Chapter 603.1) while awaiting the outcome of bacterial identification and sensitivity, but this is unnecessary in other settings where cephalosporin

Table 191-2 Treatment of *Neisseria meningitidis* Invasive Infections

DRUG	ROUTE OF ADMINISTRATION	DOSE	DOSING INTERVAL (hr)	MAXIMUM DAILY DOSE	NOTES
Penicillin G	IM or IV	300,000 units/kg/day	4-6	12-24 million units	Does not clear carriage and "prophylaxis" is required at the end of treatment
Ampicillin	IM or IV	200-400 mg/kg/day	6	6-12 g	Does not clear carriage and "prophylaxis" is required at the end of treatment
Cefotaxime	IM or IV	200-300 mg/kg/day	6-8	8-12 g	Recommended in the neonate
Ceftriaxone	IM or IV	100 mg/kg/day	12-24	2-4 g	Preferred treatment as only once or twice daily and may reduce skin complications
ALTERNATIVE THERAPY IN THE FACE OF LIFE-THREATENING β-LACTAM ALLERGY					
Chloramphenicol*	IV	50-100 mg/kg/day	6	2-4 g	
Ciprofloxacin†	IV	30-40 mg/kg/day	12	1-1.5 g	
Meropenem‡	IV	60-120 mg/kg/day	8	1.5-6 g	

*Monitor blood levels to avoid toxicity.
†Licensed for individuals older than age 18 yr.
‡Rate of crossreactivity in penicillin-allergic adults is 2-3%.
IM, intramuscular; IV, intravenous.

resistance of pneumococci is very rare (in these settings a risk assessment of each case should be made). Once the diagnosis of β-lactam sensitive meningococcal disease is confirmed in the laboratory, some authorities recommend a switch to penicillin; however, even though there is no evidence that survival outcomes are different, there is limited evidence from 1 study that, in meningococcal purpura, necrotic skin lesions are less common among children treated with ceftriaxone than with penicillin. Furthermore, there may be cost-saving by using a once-daily dose of ceftriaxone for therapy in younger children, and this is now recommended practice in the United Kingdom (Table 191-2). No adequate studies have investigated the optimal duration of therapy for children, but the course is generally continued for 5-7 days.

Early treatment of meningococcal infections may prevent serious sequelae, but timely early diagnosis is often difficult in the absence of petechial or purpuric skin findings. Among children presenting with petechial rashes, 1-10% may have underlying meningococcal disease and protocols have been established to ensure that these patients are identified without exposing the more than 90% of cases without meningococcal disease to unnecessary parenteral antibiotic therapy (Fig. 191-3).

Isolates of *N. meningitidis* with decreased susceptibility to penicillin (minimal inhibitory concentration of penicillin of 0.1-1.0 mg/mL) have been reported from Europe, Africa, Canada, and the United States (4% of isolates in 2006). Decreased susceptibility is caused, at least in part, by altered penicillin-binding protein 2 and does not appear to adversely affect the response to therapy, and is irrelevant if third-generation cephalosporins are being used for therapy.

Supportive Care

Most children with meningococcal disease can be managed with antibiotics and simple supportive care and will improve rapidly. However, with an overall 10% case-fatality rate, the priority in initiating management of children presenting with meningococcal disease is identification of the life-threatening features of the disease: shock and raised intracranial pressure. Delayed initiation of supportive therapy is associated with poor outcome, and protocols have therefore been established to aid clinicians in a step-by-step approach (http://www.meningitis.org). In all children presenting with meningococcal disease, assessment of the airway should be made, as the airway could be compromised as a result of a depressed level of consciousness (raised intracranial pressure in meningitis or poor cerebral perfusion in shock). In patients with meningococcal septicemia supplementary oxygen should be used to treat hypoxia, which is caused by pulmonary edema (from capillary leak), and some patients will require endotracheal intubation. Hypovolemia requires both volume replacement and inotropic support to maintain cardiac output. Because ongoing fluid resuscitation may lead to pulmonary edema, endotracheal intubation and ventilation should be initiated in a patient who remains in compensated shock after 40 mL/kg of fluid resuscitation to improve oxygenation and reduce work of breathing. Biochemical and hematologic abnormalities are common in meningococcal septicemia, and protocols recommend anticipation, assessment, and correction of glucose, potassium, calcium, magnesium, phosphate, clotting factors, and blood.

Children with meningococcal meningitis should be cautiously managed with maintenance fluids (fluid restriction is not recommended and may be harmful), and those with raised intracranial pressure should be managed with close attention to maneuvers to maintain normal cerebral perfusion. If there is shock in the presence of raised intracranial pressure, the shock should be carefully corrected to ensure that cerebral perfusion pressure is maintained.

Many adjunctive therapies have been attempted in patients with severe meningococcal septicemia, but few have been subjected to randomized controlled trials. There are insufficient data to recommend use of anticoagulant or fibrinolytic agents, extracorporeal membrane oxygenation, plasmapheresis, or hyperbaric oxygen. In well-designed clinical trials, an antibody directed against endotoxin (HA1A) did not confer any benefit in children with meningococcal disease, and, although initially promising in adult sepsis, activated protein C was not useful in pediatric sepsis and was associated with an increased risk of bleeding. Recombinant bactericidal permeability increasing protein was studied in an underpowered (survival end point) trial and showed some potentially beneficial effects against secondary end points (amputations, transfusions, functional outcome) and requires further investigation.

Although the benefits of steroids for adjunctive therapy in pediatric bacterial meningitis caused by *H. influenzae* type b (Hib) are accepted, there are no pediatric data specifically demonstrating benefit in meningococcal meningitis. However, some authorities extrapolate from animal data, from experience with Hib, and from compelling data from adult meningitis and recommend use of steroids as adjunctive therapy in meningococcal meningitis given with or soon after the 1st dose of antibiotics. Therapeutic doses of steroids should not be used routinely in meningococcal septicemia. Some intensivists recommend use of replacement doses of steroids in patients with severe septic shock, since severe sepsis caused by meningococcus is associated with adrenal insufficiency caused by adrenal necrosis/hemorrhage (Waterhouse-Friderichsen syndrome).

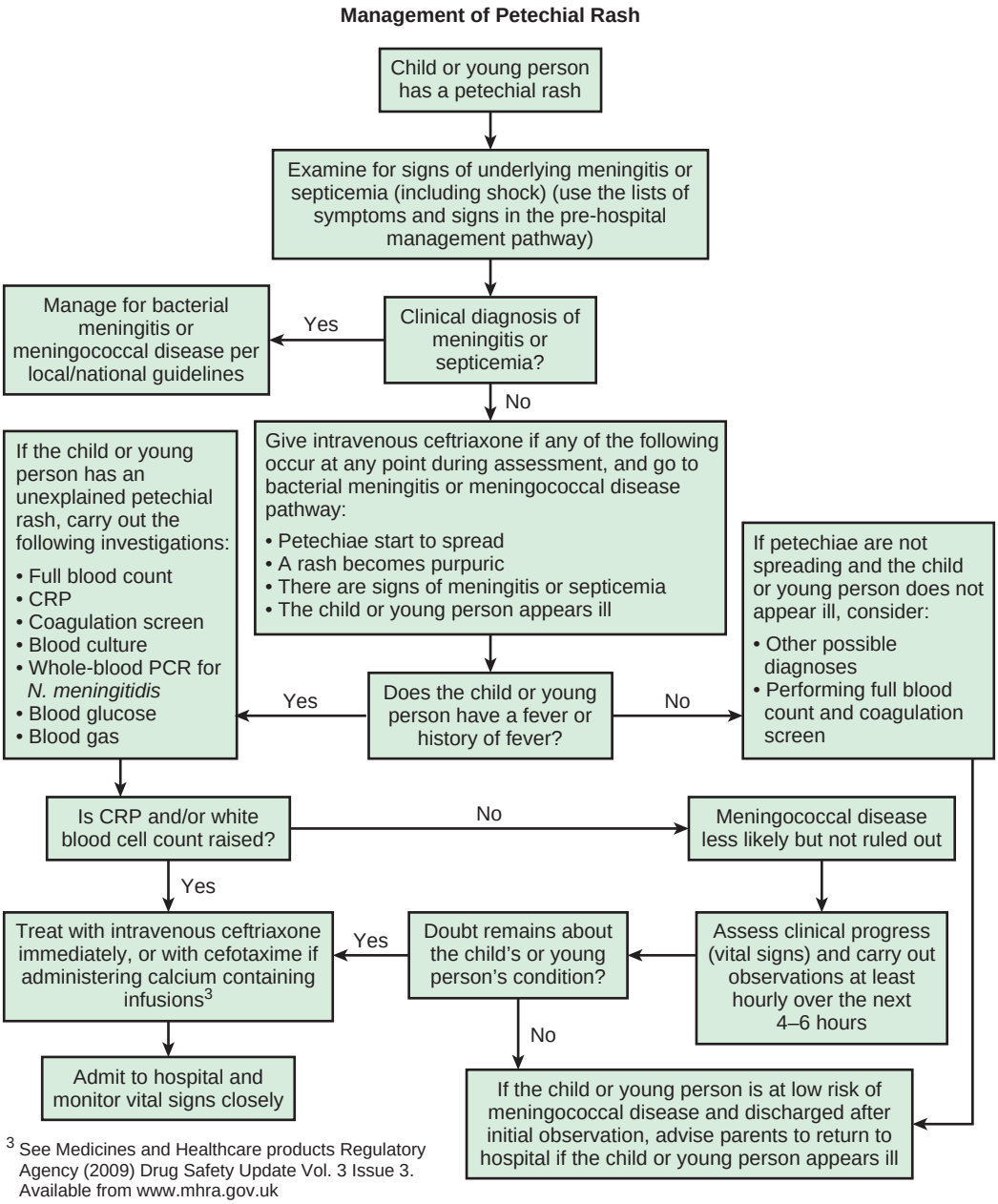


Figure 191-3 An approach to management of petechial rash. *(From National Collaborating Center for Women's and Children's Health (UK):* Bacterial meningitis and meningococcal septicaemia: management of bacterial meningitis and meningococcal septicaemia in children and young people younger than 16 years in primary and secondary care. NICE clinical guidelines, No. 102. *London, 2010, RCOG Press.)*

COMPLICATIONS

Adrenal hemorrhage, endophthalmitis, arthritis, endocarditis, pericarditis, myocarditis, pneumonia, lung abscess, peritonitis, and renal infarcts can occur during acute infection. Renal insufficiency requiring dialysis may result from prerenal failure. Reactivation of latent herpes simplex virus infections is common during meningococcal infection.

A self-limiting immune complex vasculitis may occur, usually in the 1st 10 days after onset of the disease, resulting in various manifestations, including fever, rash, arthritis, and, rarely, iritis, pericarditis, or carditis. The **arthritis** is monoarticular or oligoarticular, involves large joints, and is associated with sterile effusions that respond to nonsteroidal antiinflammatory agents. Because most patients with meningococcal meningitis become afebrile by the 7th hospital day, persistence or recrudescence of fever after 5 days of antibiotics warrants evaluation for immune complex–mediated complications.

The most common complication of acute severe meningococcal septicemia is focal skin infarction, which most commonly affects the lower limbs and can lead to substantial scarring and require skin grafting. Distal tissue necrosis in purpura fulminans may require amputation (which should be delayed to allow demarcation) in approximately 2% of survivors. Avascular necrosis of epiphyses and epiphyseal–metaphyseal defects can result from the generalized disseminated intravascular coagulation and may lead to growth disturbance and late skeletal deformities.

Deafness is the most frequent neurologic sequela of meningitis, occurring in 5-10% of children. Cerebral arterial or venous thrombosis with resultant cerebral infarction can occur in severe cases. Meningococcal meningitis is rarely complicated by subdural effusion or empyema or by brain abscess. Other rare neurologic sequelae include ataxia, seizures, blindness, cranial nerve palsies, hemiparesis or quadriparesis, and obstructive hydrocephalus (manifests 3-4 wk after onset

of illness). Finally, behavioral and psychosocial complications of the disease are frequently reported.

PROGNOSIS

The case-fatality rate for invasive meningococcal disease is 5-10%, with clear differences related to age of the patient and meningococcal genotype. Most deaths occur within 48 hr of hospitalization in children with meningococcemia. Poor prognostic factors on presentation include hypothermia or extreme hyperpyrexia, hypotension or shock, purpura fulminans, seizures, leukopenia, thrombocytopenia (including disseminated intravascular coagulation), acidosis, and high circulating levels of endotoxin and tumor necrosis factor-α. The presence of petechiae for <12 hr before admission, absence of meningitis, and low or normal erythrocyte sedimentation rate indicate rapid, fulminant progression and poorer prognosis.

Because complement deficiency is rare following capsular group B infection, s**creening** is unlikely to be useful in detecting cases caused by this group. However, with one-third or more of cases of disease caused by groups X, Y, and W apparently associated with complement deficiency, it is appropriate to screen after infection with non-B serogroups.

PREVENTION

Secondary Prevention

Close contacts of patients with meningococcal disease are at increased risk of infection because such individuals are likely to be colonized with the index's (hyperinvasive) strain. Antibiotic prophylaxis should be offered as soon as possible to individuals who have been exposed directly to a patient's oral secretions, for whom risk may be 1,000 times the background rate in the population. This includes household, kissing, and close family contacts of cases, as well as childcare and recent preschool contacts in the United States. Up to 30% of cases occur in the 1st wk, but risk persists for up to a year after presentation of the index case. Although prophylaxis is effective in preventing secondary cases, coprimary cases may occur in the days after presentation of the index case and contacts should be carefully evaluated if they develop symptoms. Advice on management of non–close contacts, such as those in daycare, nursery settings, or school and other institutions, varies in different countries because the risk of a secondary case in this situation is low and opinion on risk assessment varies. Ceftriaxone and ciprofloxacin are the most effective agents for prophylaxis, the latter being the drug of choice in some countries. Rifampin is most widely used but fails to eradicate colonization in 15% of cases (Table 191-3). Prophylaxis is not routinely recommended for medical personnel except those with exposure to aerosols of respiratory secretions, such as through mouth-to-mouth resuscitation, intubation, or suctioning before or in the 24 hr after antibiotic therapy is initiated in the index case.

Neither penicillin nor ampicillin treatment eradicates nasopharyngeal carriage and should not be routinely used for prophylaxis. Patients with meningococcal infection treated solely with penicillin or ampicillin are therefore at risk of relapse or transmission to a close contact and should receive antimicrobial prophylaxis with one of the agents listed in Table 191-3 prior to hospital discharge. As discussed above, our preference is to use ceftriaxone for treatment of the index case, in which case further prophylaxis is not required. Droplet precautions should be observed for hospitalized patients for 24 hr after initiation of effective therapy. All confirmed or probable cases of meningococcal infection must be reported to the local public health department according to national or regional regulations.

Close contacts of cases could also be immunized to further reduce the risk of secondary infection as is described below.

Table 191-3 Antibiotic Prophylaxis to Prevent *Neisseria meningitidis* Infection*

DRUG	DOSE	DURATION
RIFAMPIN†		
Infants <1 mo	5 mg/kg PO every 12 hr	2 days (4 doses)
Children ≥1 mo	10 mg/kg PO every 12 hr (maximum: 600 mg)	2 days (4 doses)
Adults	600 mg PO every 12 hr	2 days (4 doses)
CEFTRIAXONE		
Children <15 yr	125 mg IM	1 dose
Children ≥15 yr	250 mg IM	1 dose
CIPROFLOXACIN		
Children ≥1 mo†‡	20 mg/kg (maximum: 500 mg) PO	1 dose

*Recommended for household and kissing contacts. In the United States, chemoprophylaxis is recommended for:

- Household contact, especially children younger than 2 yr of age
- Childcare or preschool contact at any time during 7 days before onset of illness
- Direct exposure to index patient's secretions through kissing, sharing toothbrushes or eating utensils at any time during 7 days before onset of illness
- Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness
- Frequently slept in same dwelling as index patient during 7 days before onset of illness
- Passengers seated directly next to the index case during airline flights lasting more than 8 hr

†Not recommended for pregnant women.

‡Not recommended routinely for people younger than 18 yr of age; use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.

IM, intramuscular; PO, by mouth.

Vaccination

Meningococcal plain *polysaccharide* vaccines containing capsular polysaccharides from serogroups A + C or serogroups A, C, W, Y have been available since the 1960s and have been used in the control of outbreaks and epidemics and for high-risk groups. However, these vaccines are poorly immunogenic in infants, do not induce immunologic memory, and are associated with immunologic hyporesponsiveness (reduced response to future doses of polysaccharide). Plain polysaccharide vaccines have been superseded by meningococcal protein-polysaccharide conjugate vaccines, which are generally more immunogenic than plain polysaccharides, are immunogenic from early infancy, induce immunologic memory, and are not associated with hyporesponsiveness. The conjugate vaccines contain meningococcal polysaccharides that are chemically conjugated to a carrier protein. Three carrier proteins are used in various meningococcal conjugate vaccines: tetanus, diphtheria, and the mutant diphtheria toxin, CRM197. However, although plain polysaccharides vaccines should now be considered redundant in most industrialized countries where the new-generation conjugates are available, they may still have a role in some regions where conjugates are not yet available.

The first meningococcal conjugate vaccine to be used was a monovalent serogroup C meningococcal conjugate vaccine (MenC), which was introduced in the United Kingdom in 1999 and was administered to all children and young people under the age of 19 yr in a mass catch-up campaign before establishment in the routine infant immunization schedule. The MenC vaccine has proved highly (>95%) effective in controlling disease through both direct protection of the vaccinated population and induction of herd immunity, protecting the wider population. Herd immunity is induced through the impact of conjugate vaccines on colonization, reducing carriage and blocking transmission of meningococci among adolescents and young adults. Monovalent MenC vaccines are now used widely in the industrialized countries of Western Europe, Canada, and Australia, where disease caused by serogroup C meningococci has virtually disappeared. However, serologic surveys show that antibody levels wane, especially after infant immunization, and booster doses are now recommended during adolescence to sustain individual and population immunity.

Quadrivalent meningococcal A, C, Y, W conjugate vaccines (MenACWY) have been available since 2005 and are now routinely used for adolescents in the United States and as a single adolescent "booster" dose in some countries that had established MenC infant

programs more than a decade ago. MenACWY was initially introduced as a single dose at 11 yr of age in the United States, but concerns about waning immunity led to the adoption of a 2nd dose. The initial reports on effectiveness (>80%) of MenACWY in the U.S. program indicates that these vaccines are likely to provide control of disease caused by serogroups C, W, and Y (serogroup A being unimportant currently), although the program has taken some time to become fully established. As the population of immunized adolescents and young adults in the U.S. grows, it is likely that the effects of these vaccines on carriage of meningococci will reduce disease among other segments of the population through herd immunity, assuming that the transmission dynamics of Y and W meningococci are the same as for serogroup C. While MenACWY vaccines are not currently recommended in the United States for routine use in younger age groups in view of the low rate of disease caused by these serogroups in infancy, they may provide broader protection in countries that are already using MenC vaccines in infant programs. Other combination vaccines containing various conjugates, including Hib-MenC (used in the United Kingdom as a 12 mo booster) and Hib-MenCY, may have a role in broadening protection beyond MenC, in early life. Table 191-4 outlines the current U.S. programmatic recommendations.

Individuals at high risk of meningococcal disease, such as those with complement deficiency and travelers to regions where there is a risk of epidemic meningococcal disease caused by A or W, should receive MenACWY (Table 191-4 lists recommendations for use in the United States). The risk of disease among close contacts of cases of disease caused by vaccine serogroups may be further reduced if they are offered MenACWY in addition to antimicrobial prophylaxis. A possible association between MenACWY-diphtheria and Guillain-Barré syndrome, which caused concern early after the vaccine was first used in the United States, has not been substantiated.

A serogroup A meningococcal conjugate vaccine, MenA, has been developed for use in the sub-Saharan African meningitis belt, and implementation in 2010 through mass vaccination appears already to have interrupted disease caused by this serogroup. More than 100 million people had been vaccinated by the end of 2012.

As discussed above, the majority of disease in infants and in most industrialized countries is caused by serogroup B polysaccharide-bearing meningococci. This polysaccharide capsule has chemical identity with glycosylated protein antigens in the human fetus and, as a self-antigen, is therefore not immunogenic in humans and leads to the theoretical risk of induction of autoimmunity. Vaccine development has therefore focused on subcapsular protein antigens. Several countries (including Cuba, Norway, and New Zealand) successfully controlled serogroup B epidemics by immunizing with tailor-made outer membrane vesicle vaccines prepared from blebs of outer membrane harvested from the respective epidemic strains. The principal limitation of outer membrane vesicle vaccines is that the bactericidal antibody responses induced by immunization are limited to the vaccine strain, because the response is largely directed against the homologous PorA (serosubtype) protein, and they are therefore not considered for use in endemic settings, including the United States or most other industrialized countries.

Promising approaches for prevention of serogroup B disease have been developed over the past decade. One vaccine that was developed for adolescent immunization was licensed in the United States in 2014 and contains two variants of factor H-binding protein; it appears highly immunogenic in the target population. Recommendations for its use are awaited. Factor H-binding protein appears to be an important virulence determinant, aiding survival of meningococci in blood, and is expressed by virtually all strains.

Another 4-component meningococcal vaccine, 4CMenB, which has been licensed by the European Medicines Agency (2013) for use from infancy, is also available in various other regions and is expected to be licensed in the United States in 2015. This vaccine contains an outer membrane vesicle (derived from the New Zealand outbreak strain) and

Table 191-4 Recommendations for Meningococcal Vaccination

GENERAL POPULATION			
<2 YR	**2-10 YR**	**11-21 YR**	**22-55 YR**
Not recommended	Not recommended	A single dose of MenACWY-D or MenACWY-CRM at age 11-12 yr or at 13-18 yr if not previously vaccinated. Age 19-21 yr: not routinely recommended but may be given as catch-up for those who have not received a dose after their 16th birthday. A booster dose 5 yr later (see text)*	Not recommended

SPECIAL POPULATIONS AT INCREASED RISK OF MENINGOCOCCAL DISEASE‡			
RISK FACTOR	**2-18 MONTHS**	**9-23 MONTHS**	**2-55 YR†**
Persistent complement deficiencies, functional or anatomic asplenia	4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months	2 doses of MenACWY-D 12 wk apart§	2 doses of MenACWY 8-12 wk apart‖
At risk during a community outbreak with a vaccine serogroup	4 doses of Hib-MenCY-TT at 2, 4, 6, and 12-15 months	2 doses of MenACWY-D 12 wk apart	1 dose of MenACWY
Travel to or resident of countries where meningococcal disease is hyperendemic or epidemic¶	Should receive a quadrivalent meningococcal vaccination licensed for children aged ≥9 mo prior to travel	2 doses of MenACWY-D 12 wk apart**	1 dose of MenACWY
Have HIV, if another indication for vaccination exists	—	2 doses of MenACWY-D 12 wk apart	2 doses of MenACWY 8-12 wk apart‖
Other risk factors	—	—	1 dose MenACWY

*Otherwise healthy adolescents who received a 1st dose at age 11-12 yr should receive a booster dose of a meningococcal conjugate vaccine at 16 yr of age. For those given a 1st dose at age 13-15 yr, and who have not yet reached their 21st birthday, the booster dose should be given 5 yr after the 1st dose.

†Assuming not previously vaccinated.

‡Persons previously vaccinated at 7 yr of age or older who are at prolonged increased risk should be revaccinated 5 yr after their previous meningococcal vaccine and every 5 yr thereafter. Persons previously vaccinated at ages 2 mo-6 yr who are at prolonged increased risk should be revaccinated 3 yr after their previous meningococcal vaccination and every 5 yr thereafter.

§Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D before age 2 yr to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV).

‖If MenACWY-D is used, it should be administered at least 4 wk after completion of all PCV doses.

¶For example, visitors to the "meningitis belt" of sub-Saharan Africa. Vaccination also is required by the government of Saudi Arabia for all travelers to Mecca during the annual Hajj.

**If receiving the vaccine prior to travel, 2 doses may be administered as early as 8 wk apart.

Adapted from American Academy of Pediatrics Committee on Infectious Diseases: Updated recommendations on the use of meningococcal vaccines. Pediatrics *134:400–403, 2014.*

3 recombinant proteins: a single variant of factor H-binding protein, neisserial adhesin A, and neisserial heparin binding antigen. 4CMenB vaccine induced bactericidal antibodies against strains containing the vaccine antigens in infants, toddlers, and adolescents in clinical trials. The vaccine appears to have a generally favorable safety profile, although induction of fever in infants and pain at the injection site in other age groups are common. This vaccine has been used to control outbreaks of capsular group B meningococcal disease at two universities in the United States and hyperendemic disease in Canada. It was recommended for routine use in the infant immunization program in the United Kingdom in 2014 if a cost-effective price could be negotiated with the manufacturer.

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Chapter 192

Neisseria gonorrhoeae (Gonococcus)

Toni Darville

Neisseria gonorrhoeae produces several forms of **gonorrhea,** an infection of the genitourinary tract mucous membranes and rarely of the mucosa of the rectum, oropharynx, and conjunctiva. Gonorrhea transmitted by sexual contact or perinatally is second only to chlamydial infections in the number of cases reported to the Centers for Disease Control and Prevention (CDC) in the United States. This high prevalence and the development of antibiotic-resistant strains have produced significant morbidity in adolescents.

ETIOLOGY

N. gonorrhoeae is a nonmotile, aerobic, non–spore-forming, Gram-negative intracellular diplococcus with flattened adjacent surfaces. Optimal growth occurs at 35-37°C (95-98.6°F) and at pH 7.2-7.6 in an atmosphere of 3-5% carbon dioxide. The specimen should be inoculated immediately onto fresh, moist, modified Thayer-Martin or specialized transport media, because gonococci do not tolerate drying. Thayer-Martin medium contains antimicrobial agents that inhibit hardier normal flora present in clinical specimens that may otherwise overgrow gonococci. Presumptive identification may be based on colony appearance, Gram stain appearance, and production of cytochrome oxidase. Gonococci are differentiated from other *Neisseria* species by the fermentation of glucose but not maltose, sucrose, or lactose. Gram-negative diplococci are seen in infected material, often within polymorphonuclear leukocytes.

Like all Gram-negative bacteria, *N. gonorrhoeae* possesses a cell envelope composed of an inner cytoplasmic membrane, a middle layer of peptidoglycan, and an outer membrane. The outer membrane contains lipooligosaccharides (endotoxin), phospholipid, and a variety of proteins that contribute to cell adherence, tissue invasion, and resistance to host defenses. The 2 systems primarily used to characterize gonococcal strains are auxotyping and serotyping. Auxotyping is based on genetically stable requirements of strains for specific nutrients or cofactors as defined by an isolate's ability to grow on chemically defined media. The most widely used serotyping system is based on a porin called PorI, a trimeric outer membrane protein that makes up a substantial part of the gonococcal envelope structure. Antibodies generated to *PorI* have been used to serotype gonococci (e.g., PorIA-4 and PorIB-12), and changes in PorI proteins present in a community are believed to occur, at least in part, as a result of selective immune pressure.

EPIDEMIOLOGY

N. gonorrhoeae infection occurs only in humans. The organism is shed in the exudate and secretions of infected mucosal surfaces and is transmitted through intimate contact, such as sexual contact or parturition, and, rarely, by contact with fomites. Gonococcal infections in the newborn period are generally acquired during delivery. Gonorrhea is the most common sexually transmitted infection found in sexually abused children. Rarely, *N. gonorrhoeae* may be spread by sexual play among children, but the index patient is likely to be a victim of sexual abuse. Gonococcal infections in children are acquired rarely through household exposure to infected caretakers. In such cases, the possibility of sexual abuse should be seriously considered.

The number of reported cases of gonorrhea increased steadily in the United States from 1964 to 1977, fluctuated through the early 1980s, and increased until 1987, when reported rates were 323 per 100,000 population. After implementation of the national gonorrhea control program, rates decreased or were stable annually from 1987 to 2004. In 2005, the national rate (116 per 100,000 population) increased for the first time since 1999. In 2009, rates were 98.1 per 100,000 population, which is the lowest since recording of gonorrhea rates began. The rate increased slightly in 2010 to 100.2 per 100,000 population and increased again in 2011 to 104.2 per 100,000 population. The report of increasing minimum inhibitory concentrations for cephalosporin antibiotics in 2011 raises alarms for a threat of untreatable gonorrhea and need for intensive surveillance. The incidence of gonorrhea is highest in high-density urban areas among persons younger than 24 yr of age who have multiple sex partners and engage in unprotected sexual intercourse. Increases in gonorrhea prevalence have been noted among men who have sex with men. Risk factors include nonwhite race, homosexuality, increased number of sexual partners, prostitution, presence of other sexually transmitted infections, unmarried status, poverty, and failure to use condoms. Auxotyping and serotyping techniques and molecular typing methods are used to analyze the spread of individual strains of *N. gonorrhoeae* within a community.

Maintenance and subsequent spread of gonococcal infections in a community require a hyperendemic, high-risk core group such as prostitutes or adolescents with multiple sexual partners. This observation reflects the fact that most persons who have gonorrhea cease sexual activity and seek care, unless economic need or other factors (e.g., drug addiction) drive persistent sexual activity. Thus, many core transmitters belong to a subset of infected persons who lack or ignore symptoms and continue to be sexually active, underscoring the importance of seeking out and treating the sexual contacts of infected persons who present for treatment.

Gonococcal infection of **neonates** usually results from peripartum exposure to infected exudate from the cervix of the mother. An acute infection begins 2-5 days after birth. The incidence of neonatal infection depends on the prevalence of gonococcal infection among pregnant women, prenatal screening for gonorrhea, and neonatal ophthalmic prophylaxis.

PATHOGENESIS AND PATHOLOGY

N. gonorrhoeae infects primarily columnar epithelium, because stratified squamous epithelium is relatively resistant to invasion. Mucosal invasion by gonococci results in a local inflammatory response that produces a purulent exudate consisting of polymorphonuclear leukocytes, serum, and desquamated epithelium. The gonococcal lipooligosaccharide (endotoxin) exhibits direct cytotoxicity, causing ciliostasis and sloughing of ciliated epithelial cells. Once the gonococcus traverses the mucosal barrier, the lipooligosaccharide binds bactericidal immunoglobulin (Ig) M antibody and serum complement, causing an acute inflammatory response in the subepithelial space. Tumor necrosis factor and other cytokines are thought to mediate the cytotoxicity of gonococcal infections.

Gonococci may ascend the urogenital tract, causing urethritis or epididymitis in postpubertal males and acute endometritis, salpingitis, and peritonitis (collectively termed **acute pelvic inflammatory disease** or **PID)** in postpubertal females**.** Dissemination from the fallopian tubes through the peritoneum to the liver capsule results in

perihepatitis (Fitz-Hugh–Curtis syndrome). Gonococci that invade the lymphatics and blood vessels may cause inguinal lymphadenopathy; perineal, perianal, ischiorectal, and periprostatic abscesses; and disseminated gonococcal infection (DGI).

A number of gonococcal virulence and host immune factors are involved in the penetration of the mucosal barrier and subsequent manifestations of local and systemic infection. Selective pressure from different mucosal environments probably leads to changes in the outer membrane of the organism, including expression of variants of pili, opacity or Opa proteins (formerly protein II), and lipooligosaccharides. These changes may enhance gonococcal attachment, invasion, replication, and evasion of the host's immune response.

For infection to occur, the gonococcus must first attach to host cells. A gonococcal IgA protease inactivates IgA_1 by cleaving the molecule in the hinge region and may be an important factor in colonization or invasion of host mucosal surfaces. Gonococci adhere to the microvilli of nonciliated epithelial cells by hair-like protein structures (pili) that extend from the cell wall. Pili are thought to protect the gonococcus from phagocytosis and complement-mediated killing. Pili undergo high-frequency antigenic variation that may aid in the organism's escape from the host immune response and may provide specific ligands for different cell receptors. Opacity proteins, most of which confer an opaque appearance to colonies, are also thought to function as ligands to facilitate binding to human cells. Gonococci that express certain Opa proteins adhere to and are phagocytosed by human neutrophils in the absence of serum.

Other phenotypic changes that occur in response to environmental stresses allow gonococci to establish infection. Examples include iron-repressible proteins for binding transferrin or lactoferrin, anaerobically expressed proteins, and proteins that are synthesized in response to contact with epithelial cells. Gonococci may grow in vivo under anaerobic conditions or in an environment with a relative lack of iron.

Approximately 24 hr after attachment, the epithelial cell surface invaginates and surrounds the gonococcus in a phagocytic vacuole. This phenomenon is thought to be mediated by the insertion of gonococcal outer membrane protein I into the host cell, causing alterations in membrane permeability. Subsequently, phagocytic vacuoles begin releasing gonococci into the subepithelial space by means of exocytosis. Viable organisms may then cause local disease (i.e., salpingitis) or disseminate through the bloodstream or lymphatics.

Serum IgG and IgM directed against gonococcal proteins and lipooligosaccharides lead to complement-mediated bacterial lysis. Stable serum resistance to this bactericidal antibody probably results from a particular type of porin protein expressed in gonococci (most contain PorIA), predisposing to disseminated disease. *N. gonorrhoeae* differentially subverts the effectiveness of complement and alters the inflammatory responses elicited in human infection. Isolates from cases of DGI typically resist killing by normal serum (i.e., are serum resistant), inactivate more C3b, generate less C5a, and result in less inflammation at local sites. PID isolates are serum sensitive, inactivate less C3b, generate more C5a, and result in more inflammation at local sites. IgG antibody directed against gonococcal reduction-modifiable protein (Rmp) blocks complement-mediated killing of *N. gonorrhoeae.* Anti-Rmp blocking antibodies may harbor specificity for outer membrane protein sequences shared with other neisserial species or *Enterobacteriaceae*, may be directed against unique Rmp upstream of cysteine loop–specific sequences, or both. Preexisting antibodies directed against Rmp facilitate transmission of gonococcal infection to exposed women; Rmp is highly conserved in *N. gonorrhoeae,* and the blocking of mucosal defenses may be one of its functions. Gonococcal adaptation also appears to be important in the evasion of killing by neutrophils. Examples include sialylation of lipooligosaccharides, increases in catalase production, and changes in the expression of surface proteins.

Host factors may influence the incidence and manifestations of gonococcal infection. Prepubertal girls are susceptible to vulvovaginitis and, rarely, experience salpingitis. *N. gonorrhoeae* infects noncornified epithelium, and the thin noncornified vaginal epithelium and alkaline pH of the vaginal mucin predispose this age group to infection of the lower genital tract. Estrogen-induced cornification of the vaginal epithelium in neonates and mature females resists infection. Postpubertal females are more susceptible to salpingitis, especially during menses, when diminished bactericidal activity of the cervical mucus and reflux of blood from the uterine cavity into the fallopian tubes facilitate passage of gonococci into the upper reproductive tract.

Populations at risk for DGI include asymptomatic carriers; neonates; menstruating, pregnant, and postpartum women; homosexuals; and immunocompromised hosts. The asymptomatic carrier state implies failure of the host immune system to recognize the gonococcus as a pathogen, the capacity of the gonococcus to avoid being killed, or both. Pharyngeal colonization has been proposed as a risk factor for DGI. The high rate of asymptomatic infection in pharyngeal gonorrhea may account for this phenomenon. Women are at greater risk for development of DGI during menstruation, pregnancy, and the postpartum period, presumably because of the maximal endocervical shedding and decreased peroxidase bactericidal activity of the cervical mucus during these periods. A lack of neonatal bactericidal IgM antibody is thought to account for the increased susceptibility of neonates to DGI. Persons with terminal complement component deficiencies (C5-C9) are at considerable risk for development of recurrent episodes of DGI.

CLINICAL MANIFESTATIONS

Gonorrhea is manifested by a spectrum of clinical presentations from asymptomatic carriage, to the characteristic localized urogenital infections, to disseminated systemic infection (see Chapter 120).

Asymptomatic Gonorrhea

The incidence of asymptomatic gonorrhea in children has not been ascertained. Gonococci have been isolated from the oropharynx of young children who have been abused sexually by male contacts; oropharyngeal symptoms are usually absent. Most genital tract infections produce symptoms in children. However, as many as 80% of sexually mature females with urogenital gonorrhea infections are asymptomatic in settings in which most infections are detected through screening or other case-finding efforts. This situation is in contrast to that in men, who are asymptomatic only 10% of the time. Asymptomatic rectal carriage of *N. gonorrhoeae* has been documented in 40-60% of females with urogenital infection. Most persons with positive rectal culture results are asymptomatic. Most pharyngeal gonococcal infections are asymptomatic. The importance of documenting pharyngeal infection is debated. Most cases resolve spontaneously, transmission from the pharynx to other patients is uncommon, and the pharynx is rarely the only site of infection. Nevertheless, asymptomatic pharyngeal infection may lead to systemic infection and is occasionally the source of transmission to sexual partners.

Uncomplicated Gonorrhea

Genital gonorrhea has an incubation period of 2-5 days in men and 5-10 days in women. Primary infection develops in the urethra of males, the vulva and vagina of prepubertal females, and the cervix of postpubertal females. Neonatal ophthalmitis (ophthalmia neonatorum) occurs in both sexes.

Urethritis is usually characterized by a purulent discharge and by dysuria without urgency or frequency. Untreated urethritis in males resolves spontaneously in several weeks or may be complicated by epididymitis, penile edema, lymphangitis, prostatitis, or seminal vesiculitis. Gram-negative intracellular diplococci are found in the discharge.

In prepubertal females, **vulvovaginitis** is usually characterized by a purulent vaginal discharge with a swollen, erythematous, tender, and excoriated vulva. Dysuria may occur. In postpubertal females, symptomatic gonococcal cervicitis and urethritis are characterized by purulent discharge, suprapubic pain, dysuria, intermenstrual bleeding, and dyspareunia. The cervix may be inflamed and tender. In urogenital gonorrhea limited to the lower genital tract, pain is not enhanced by moving the cervix, and the adnexa are not tender to palpation. Purulent material may be expressed from the urethra or ducts of the Bartholin gland. Rectal gonorrhea is often asymptomatic but may cause

proctitis with symptoms of anal discharge, pruritus, bleeding, pain, tenesmus, and constipation. Asymptomatic rectal gonorrhea may not be from anal intercourse but may represent colonization from vaginal infection.

Gonococcal **ophthalmitis** may be unilateral or bilateral and may occur in any age group after inoculation of the eye with infected secretions. **Ophthalmia neonatorum** caused by *N. gonorrhoeae* usually appears from 1-4 days after birth (see Chapter 626). Ocular infection in older patients results from inoculation or autoinoculation from a genital site. The infection begins with mild inflammation and a serosanguineous discharge. Within 24 hr, the discharge becomes thick and purulent, and tense edema of the eyelids with marked chemosis occurs. If the disease is not treated promptly, corneal ulceration, rupture, and blindness may follow.

Disseminated Gonococcal Infection

Hematogenous dissemination occurs in 1-3% of all gonococcal infections, more frequently after asymptomatic primary infections than symptomatic infections. Women account for the majority of cases, with symptoms beginning 7-30 days after infection and within 7 days of menstruation. The most common manifestations are asymmetric arthralgia, petechial or pustular acral skin lesions, tenosynovitis, suppurative arthritis, and, rarely, carditis, meningitis, and osteomyelitis. The most common initial symptom is acute onset of polyarthralgia with fever. Only 25% of patients complain of skin lesions. Most deny genitourinary symptoms; however, primary mucosal infection is documented by genitourinary cultures. Results of approximately 80-90% of cervical cultures are positive in women with DGI. In males, urethral culture results are positive in 50-60%, pharyngeal culture results are positive in 10-20%, and rectal culture results are positive in 15% of cases.

DGI is classified into 2 clinical syndromes that have some overlapping features. The 1st and more common is the **tenosynovitis-dermatitis syndrome,** which is characterized by fever, chills, skin lesions, and polyarthralgia predominantly involving the wrists, hands, and fingers. Blood culture results are positive in approximately 30-40% of cases, and results of synovial fluid cultures are almost uniformly negative. The 2nd syndrome is the **suppurative arthritis syndrome,** in which systemic symptoms and signs are less prominent and monoarticular arthritis, often involving the knee, is more common. A polyarthralgia phase may precede the monoarticular infection. In cases of monoarticular involvement, synovial fluid culture results are positive in approximately 45-55%, and synovial fluid findings are consistent with septic arthritis. Blood culture results are usually negative. DGI in neonates usually occurs as a polyarticular suppurative arthritis.

Dermatologic lesions usually begin as painful, discrete, 1-20 mm pink or red macules that progress to maculopapular, vesicular, bullous, pustular, or petechial lesions. The typical necrotic pustule on an erythematous base is distributed unevenly over the extremities, including the palmar and plantar surfaces, usually sparing the face and scalp. The lesions number between 5 and 40, and 20-30% may contain gonococci. Although immune complexes may be present in DGI, complement levels are normal, and the role of the immune complexes in pathogenesis is uncertain.

Acute endocarditis is an uncommon (1-2%) but often fatal manifestation of DGI that usually leads to rapid destruction of the aortic valve. Acute pericarditis is a rarely described entity in patients with disseminated gonorrhea. Meningitis with *N. gonorrhoeae* has been documented, and signs and symptoms are similar to those of any acute bacterial meningitis.

DIAGNOSIS

It is not possible to distinguish gonococcal from nongonococcal urethritis on the basis of symptoms and signs alone. Gonococcal urethritis and vulvovaginitis must be distinguished from other infections that produce a purulent discharge, including β-hemolytic streptococci, *Chlamydia trachomatis, Mycoplasma hominis, Trichomonas vaginalis,* and *Candida albicans.* Rarely, infection with human herpes simplex virus type 2 may produce symptoms similar to those of gonorrhea.

In males with symptomatic urethritis, a presumptive diagnosis of gonorrhea can be made by identification of Gram-negative intracellular diplococci (within leukocytes) in the urethral discharge. A similar finding in females is not sufficient because *Mima polymorpha* and *Moraxella,* which are normal vaginal flora, have a similar appearance. The sensitivity of the Gram stain for diagnosing gonococcal cervicitis and asymptomatic infections is also low. The presence of commensal *Neisseria* species in the oropharynx prevents the use of the Gram stain for diagnosis of pharyngeal gonorrhea. Nonpathogenic *Neisseria* organisms are not found intracellularly.

Specific testing for *N. gonorrhoeae* is recommended because a specific diagnosis might enhance partner notification. Highly sensitive and specific testing methods are available. Culture, nucleic acid hybridization tests, and nucleic acid amplification tests (NAATs) are available for the detection of genitourinary infection. Disadvantages of culture include its lower sensitivity than DNA amplification techniques and a 48-hr delay in availability of results. Culture can be performed of any site, including nongenital sites. Nucleic acid hybridization tests require female endocervical or male urethral swab specimens and are inferior to NAAT testing in terms of sensitivity. The FDA has approved NAATs for use with endocervical swabs, vaginal swabs, male urethral swabs, and female and male urine. Although urine specimens are acceptable for women, the sensitivity appears to be lower when compared with vaginal swab samples. In contrast, the sensitivity and specificity of urine and urethral swab specimens from men are similar. Product inserts for each NAAT vendor must be carefully examined to assess current indications. Nonculture tests are not FDA cleared for use with specimens from the rectum, pharynx, or conjunctiva. However, some laboratories have established performance specifications for NAAT testing on non-genital samples, facilitating their use for clinical management. Nonculture gonococcal tests (e.g., Gram-stained smear, nucleic acid hybridization tests, and NAATs) should not be used without standard culture in children because of the legal implications of a diagnosis of *N. gonorrhoeae* infection in a child. Nonculture tests cannot provide antimicrobial susceptibility results, so in cases of persistent gonococcal infection after treatment, clinicians should perform both culture and antimicrobial susceptibility testing.

Material for cervical cultures is obtained as follows: After the exocervix is wiped, a swab is placed in the cervical os and rotated gently for several seconds. Male urethral specimens are obtained by placement of a small swab 2-3 cm into the urethra. Rectal swabs are best obtained by passing of a swab 2-4 cm into the anal canal; specimens that are heavily contaminated by feces should be discarded. For optimal culture results, specimens should be obtained with noncotton swabs (e.g., a urethrogenital calcium alginate–tipped swab [Calgiswab, Puritan Medical Products, Guilford, ME]), inoculated directly onto culture plates, and incubated immediately. The choice of anatomic sites to culture depends on the sites exposed and the clinical manifestations. Samples from the urethra should be cultured for heterosexual men, and samples from the endocervix and rectum should be cultured for all females, regardless of a history of anal intercourse. A pharyngeal culture specimen should be obtained from both men and women if symptoms of pharyngitis are present or in the case of oral exposure to a person known to have genital gonorrhea. In a suspected case of child sexual abuse, rectal, pharyngeal, and urethral (males) or vaginal (females) swabs should be cultured. Culture of the endocervix should not be attempted until after puberty.

Specimens from sites that are normally colonized by other organisms (e.g., cervix, rectum, pharynx) should be inoculated on a selective culture medium, such as modified Thayer-Martin medium (fortified with vancomycin, colistin, nystatin, and trimethoprim to inhibit growth of indigenous flora). Specimens from sites that are normally sterile or minimally contaminated (i.e., synovial fluid, blood, cerebrospinal fluid) should be inoculated on a nonselective chocolate agar medium. If DGI is suspected, blood, pharynx, rectum, urethra, cervix, and synovial fluid (if involved) should be cultured. Cultured specimens should be incubated promptly at 35-37°C (95-98.6°F) in 3-5% carbon dioxide. When specimens must be transported to a central laboratory for culture plating, a reduced, nonnutrient holding medium (i.e.,

Amies-modified Stuart medium) preserves specimens with minimal loss of viability for up to 6 hr. When transport may delay culture plating by more than 6 hr, it is preferable to inoculate the sample directly onto a culture medium and transport it at an ambient temperature in a candle jar. The Transgrow and JEMBEC (John E. Martin Biological Environmental Chamber) systems of modified Thayer-Martin medium are alternative transport systems.

Gonococcal arthritis must be distinguished from other forms of septic arthritis as well as from rheumatic fever, rheumatoid arthritis, inflammatory bowel disease, and arthritis secondary to rubella or rubella immunization. Gonococcal conjunctivitis in the newborn period must be differentiated from chemical conjunctivitis caused by silver nitrate drops as well as from conjunctivitis caused by *C. trachomatis, Staphylococcus aureus,* group A or B streptococcus, *Pseudomonas aeruginosa, Streptococcus pneumoniae,* or human herpes simplex virus type 2.

TREATMENT

All patients who are presumed or proven to have gonorrhea should be evaluated for concurrent syphilis, hepatitis B, HIV, and *C. trachomatis* infection. The incidence of *Chlamydia* coinfection is 15-25% among males and 35-50% among females. Patients beyond the neonatal period should be treated presumptively for *C. trachomatis* infection unless a negative chlamydial NAAT result is documented at the time treatment is initiated for gonorrhea. However, if chlamydial test results are not available or if a non-NAAT result is negative for *Chlamydia*, patients should be treated for both gonorrhea and *Chlamydia* infection (see Chapter 226.2). Sexual partners exposed in the preceding 60 days should be examined, culture specimens should be collected, and presumptive treatment should be started.

N. gonorrhoeae has progressively developed resistance to the antibiotics used to treat it over the years. Antimicrobial resistance in *N. gonorrhoeae* occurs as plasmid-mediated resistance to penicillin and tetracycline and chromosomally mediated resistance to penicillins, tetracyclines, spectinomycin, fluoroquinolones, and cephalosporins. In 2007, as a consequence of widespread fluoroquinolone-resistant gonorrhea in the United States, this class of antibiotics ceased being recommended for treatment. Surveillance data (2006-2011) from the CDC's Gonococcal Isolate Surveillance Project reveal increasing minimum inhibitory concentrations for the oral cephalosporin, cefixime, and the injectable third-generation cephalosporin, ceftriaxone, leading the CDC to revise its gonorrhea treatment guidelines in 2012 to dual therapy in an attempt to preserve the last commercially available effective treatment.

Adolescent and Adult Infections

Oral cefixime is no longer recommended as a treatment option. Combination therapy with ceftriaxone (250 mg IM) and either azithromycin (1 g PO as a single dose) or doxycycline (100 mg PO twice daily for 7 days) is recommended as the most reliably effective treatment for uncomplicated urogenital, anorectal, and pharyngeal gonorrhea. Other possible single-dose cephalosporin alternatives include ceftizoxime (500 mg IM); cefotaxime (500 mg IM); or cefoxitin (2 g IM), administered with probenecid (1 g PO). These agents do not provide any advantage over injectable ceftriaxone and should also be combined with azithromycin or doxycycline. A theoretical basis exists for using 2 antimicrobials with different molecular targets to improve treatment efficacy and potentially delay emergence and spread of resistance to cephalosporins. However, there are no data to support this hypothesis, and clinical trials are urgently needed to determine the most appropriate therapy for *N. gonorrhoeae* in the face of rising antimicrobial resistance. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the higher prevalence of gonococcal resistance to tetracycline compared to azithromycin among gonococcal surveillance isolates, particularly in strains with elevated minimum inhibitory concentrations to cefixime. If persistent infection is diagnosed in a patient after treatment with the above combination regimen, cultures should be obtained from all relevant clinical sites and *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility using disc diffusion, E-test, or agar dilution techniques.

If ceftriaxone is not available, cefixime (400 mg PO) plus either azithromycin (1 g PO) or doxycycline (100 mg PO twice daily for 7 days) can be used. The use of azithromycin (2 g PO in a single dose) as a single agent should be limited to patients with severe penicillin allergy who cannot undergo β-lactam desensitization. If a patient with gonorrhea is treated with an alternative oral regimen, the patient should return 1 wk after treatment for a test-of-cure of the infected anatomic site. The test-of-cure should be performed with culture or with a NAAT for *N. gonorrhoeae* if culture is not readily available. If the NAAT is positive, every effort should be made to perform a culture. All test-of-cure specimens that reveal positive growth should undergo phenotypic antimicrobial susceptibility testing. Patients who experience treatment failure after treatment with alternative regimens should be treated with ceftriaxone (250 mg IM) as a single dose and azithromycin (2 g PO as a single dose) and should receive infectious disease consultation. The case should be reported to CDC through the local or state health department.

Spectinomycin (2 g IM as a single dose) is a safe and effective parenteral alternative for urogenital gonorrhea but is not effective for pharyngeal infection. It is not currently available in the United States.

Pregnant women should not be treated with quinolones or tetracyclines. Those infected with *N. gonorrhoeae* should be treated with ceftriaxone (250 mg IM) and azithromycin (1 g PO as a single dose). If the patient is allergic to β-lactam antibiotics, desensitization procedures should be employed prior to administration.

The initial management of DGI includes hospitalization and parenteral administration of ceftriaxone (1 g/day). Alternative cephalosporins include cefotaxime (1 g IV q8h) and ceftizoxime (1g IV q8h). Patients should also receive azithromycin (1 g PO in a single dose), for dual therapy of gonococcal infections and to cover potential *C. trachomatis* coinfection. Doxycycline (100 mg PO twice daily for 7 days) is an alternative second agent. Patients should be examined for clinical evidence of endocarditis and meningitis. Ceftriaxone treatment should be continued for at least 7 days, and those with purulent arthritis require antibiotic therapy for 7-14 days, although the dose can be changed following clinical improvement to ceftriaxone (250 mg IM daily). Because of the decreasing susceptibility of *N. gonorrhoeae* to oral agents, "stepdown" therapy to oral agents to complete therapy, such as cefixime (400 mg PO bid) and cefpodoxime (400 mg PO bid), should only be considered if culture and susceptibility testing of the isolate are available and full susceptibility to the oral agent is documented. Fluoroquinolones may be an alternative treatment option if antimicrobial susceptibility to these agents can be documented by culture. Patients with purulent arthritis should also undergo joint drainage with needle aspiration, arthroscopically, or with an open surgical procedure. Open surgical drainage should be performed in patients who exhibit continued symptoms (leukocytosis, fever, severe joint pain, and effusion) despite aspiration and appropriate antibiotic therapy.

Gonococcal conjunctivitis should be treated with ceftriaxone (1g IM in a single dose) with lavage of the infected eye with saline. Meningitis is treated with ceftriaxone (1-2 g IV q12h) for 10-14 days. Endocarditis is treated for longer than 4 wk with ceftriaxone (1-2 g IV q12h). Concurrent therapy for treatment of genital *Chlamydia* infection is important.

Infant and Pediatric Infections

Uncomplicated gonococcal infections in children should be treated with ceftriaxone in a single dose (50 mg/kg IM, not to exceed 125 mg). Children who have bacteremia or arthritis should be treated with ceftriaxone (50 mg/kg/day; maximum: 1 g/day if weighs <45 kg) for a minimum of 7 days. Meningitis should be treated for 10-14 days, and endocarditis for a minimum of 28 days, with ceftriaxone (50 mg/kg/dose q12h with maximum of 1-2 g IV q12h). Neonatal gonococcal ophthalmia is treated effectively with a single dose of ceftriaxone (50 mg/kg IM, not to exceed 125 mg); a single dose of cefotaxime (100 mg/kg IM) is an acceptable alternative. The conjunctivae should be irrigated frequently with physiologic saline solution. Infants born

to mothers who have gonococcal infection should also receive a single dose of ceftriaxone (50 mg/kg IM, not to exceed 125 mg). Neonatal sepsis should be treated parenterally for a minimum of 7 days, and meningitis for a minimum of 10 days. Cefotaxime is recommended for infants with hyperbilirubinemia, because ceftriaxone competes for bilirubin binding sites on albumin. Neonates with gonococcal ophthalmitis must be hospitalized and evaluated for DGI.

Pelvic Inflammatory Disease

PID encompasses a spectrum of infectious diseases of the upper genital tract caused by *N. gonorrhoeae, C. trachomatis,* and endogenous flora (streptococci, anaerobes, Gram-negative bacilli). For women with more-severe symptoms, parenteral therapy should be initiated in the hospital. A commonly recommended therapeutic regimen is cefoxitin (2g IV q6h) or cefotetan (2g IV q12h) plus doxycycline (100 mg PO or IV q12h). Alternative regimens include clindamycin (900 mg IV q8h) plus a loading dose of gentamicin (2 mg/kg IV) followed by maintenance gentamicin (1.5 mg/kg q8h), and ampicillin/sulbactam (3 g IV q6h) plus doxycycline (100 mg PO or IV q12h). Clinical experience should guide transition to oral therapy, which usually can be initiated within 24 hr of improvement. Thereafter, oral doxycycline is given to complete 14 days of total therapy.

Parenteral therapy and oral therapy appear to be similar in clinical efficacy for women with PID of mild to moderate severity. Clinical response to outpatient treatment is similar among younger and older women. The decision to hospitalize adolescents with acute PID should be based on clinical criteria used for older women. Those who do not show response to oral therapy within 72 hr should be reevaluated to confirm the diagnosis and then should receive parenteral therapy. Recommended oral regimens are as follows: a single dose of ceftriaxone (250 mg IM) plus doxycycline (100 mg PO bid) with or without metronidazole (500 mg PO bid) for 14 days; and single doses of cefoxitin (2 g IM) and probenecid (1 g PO) plus doxycycline (100 mg PO bid) with or without metronidazole (500 mg PO bid) for 14 days. Sexual partners should be examined and treated for uncomplicated gonorrhea. Follow-up culture (test of cure) after cephalosporin-doxycycline therapy of gonococcal infection is not recommended owing to the low treatment failure rate. Patients receiving outpatient therapy should be carefully evaluated for clinical improvement within 72 hr. A follow-up examination and culture are recommended in 1-2 mo to evaluate the possibility of reinfection or, rarely, treatment failure.

COMPLICATIONS

Complications of gonorrhea result from the spread of gonococci from a local site of invasion. The interval between primary infection and development of a complication is usually days to weeks. In postpubertal females, endometritis may occur, especially during menses, and may progress to salpingitis and peritonitis (PID). Manifestations of PID include signs of lower genital tract infection (e.g., vaginal discharge, suprapubic pain, cervical tenderness) and upper genital tract infection (e.g., fever, leukocytosis, elevated erythrocyte sedimentation rate, and adnexal tenderness or mass). The differential diagnosis includes gynecologic diseases (ovarian cyst, ovarian tumor, ectopic pregnancy) and intraabdominal disorders (appendicitis, urinary tract infection, inflammatory bowel disease).

Once inside the peritoneum, gonococci may seed the liver capsule, causing a perihepatitis with right upper quadrant pain (Fitz-Hugh–Curtis syndrome), with or without signs of salpingitis. Perihepatitis may also be caused by *C. trachomatis.* Progression to PID occurs in approximately 20% of cases of gonococcal cervicitis, and *N. gonorrhoeae* is isolated in approximately 40% of cases of PID in the United States. Untreated cases may lead to hydrosalpinx, pyosalpinx, tuboovarian abscess, and eventual sterility. Even with adequate treatment of PID, the risk for sterility from bilateral tubal occlusion approaches 20% after 1 episode of salpingitis and exceeds 60% after 3 or more episodes. The risk for ectopic pregnancy is increased approximately 7-fold after 1 or more episodes of salpingitis. Additional sequelae of PID include chronic pain, dyspareunia, and increased risk for recurrent PID.

Urogenital gonococcal infection acquired during the 1st trimester of pregnancy carries a high risk for septic abortion. After 16 wk, infection leads to chorioamnionitis, a major cause of premature rupture of the membranes and premature delivery.

PROGNOSIS

Prompt diagnosis and correct therapy ensure complete recovery from uncomplicated gonococcal disease. Complications and permanent sequelae may be associated with delayed treatment, recurrent infection, metastatic sites of infection (meninges, aortic valve), and delayed or topical therapy of gonococcal ophthalmia.

PREVENTION

Efforts to develop a gonococcal pilus vaccine have been unsuccessful thus far. The high degree of interstrain and intrastrain antigenic variability of pili poses a formidable deterrent to the development of a single effective pilus vaccine. Other gonococcal surface structures, such as the porin protein, stress proteins, and lipooligosaccharides, may prove more promising as vaccine candidates. In the absence of a vaccine, prevention of gonorrhea can be achieved through education, use of barrier contraceptives (especially condoms and spermicides), intensive epidemiologic and bacteriologic surveillance (screening sexual contacts), and early identification and treatment of infected contacts. Gonococcal ophthalmia neonatorum can be prevented by instilling erythromycin (0.5%) ophthalmic ointment into the conjunctival sac (see Chapter 626).

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Chapter 193

Kingella kingae

Pablo Yagupsky

Kingella kingae is being increasingly recognized as the most common etiology of joint and bone infections in young children.

ETIOLOGY

K. kingae is a fastidious, facultative anaerobic, β-hemolytic member of the Neisseriaceae family that appears as pairs or short chains of Gram-negative coccobacilli with tapered ends (Fig. 193-1).

EPIDEMIOLOGY

K. kingae is asymptomatically carried in the posterior pharynx. Colonization usually starts after the age of 6 mo, reaches a prevalence of 10% between 12 and 24 mo of age, and decreases in older children. Pharyngeal colonization plays a crucial role in the transmission of the organism through intimate contact between siblings and playmates. Colonizing *K. kingae* strains differ in their invasive potential. Whereas certain clones are commonly found as respiratory colonizers but are seldom cultured from sites of disease, other clones are rarely detected in healthy children and, once acquired, readily penetrate into the bloodstream and disseminate to remote sites. Daycare attendance increases the risk for colonization and transmission, and clusters of invasive infection have been reported in childcare facilities.

Invasive *K. kingae* disease is most commonly diagnosed in otherwise healthy children between the ages of 6 mo and 3 yr, coinciding with the peak prevalence of pharyngeal carriage (Fig. 193-2). In contrast, older children and adults with *K. kingae* infections often suffer from underlying chronic diseases, immunosuppressing conditions, malignancy, or cardiac valve pathology. An annual incidence of 9.4 per 100,000 culture-proven invasive infections among Israeli children younger than 5 yr of age has been estimated.

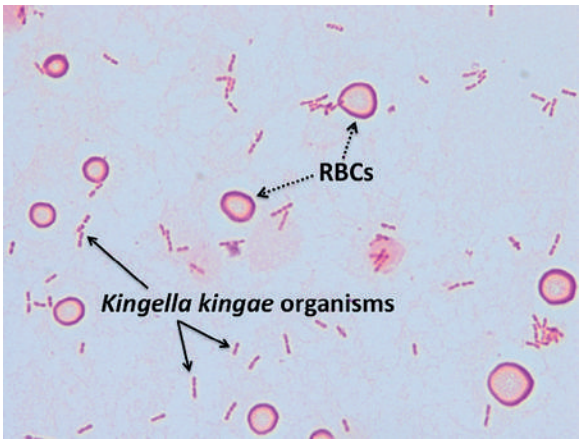

Figure 193-1 Typical Gram stain of a positive blood culture vial from a child with *K. kingae* bacteremia showing pairs and short chains of plump Gram-negative coccobacilli. *RBCs*, red blood cells.

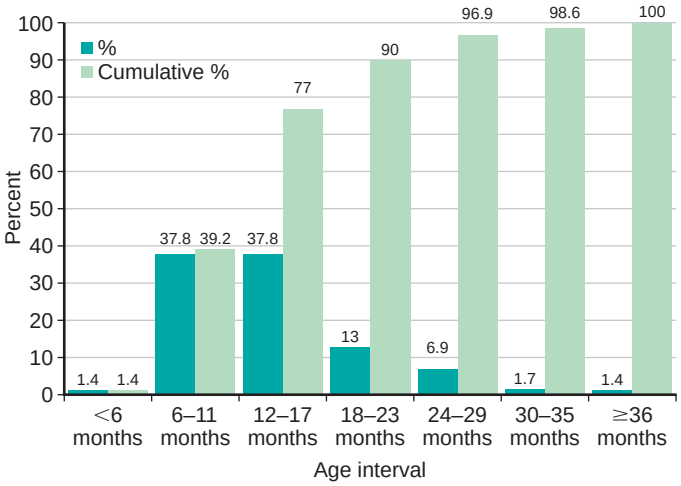

Figure 193-2 Age distribution of 291 previously healthy children with invasive *K. kingae* infections. *(Data from Dubnov-Raz G, Ephros M, Garty BZ, et al: Invasive pediatric* Kingella kingae *infections: a nationwide collaborative study. Pediatr Infect Dis J 2010; 29: 639-643.)*

PATHOGENESIS

The pathogenesis of *K. kingae* disease begins with adherence of the organism to the pharyngeal epithelium that is mediated by pili and nonpilus factors. *K. kingae* secretes a potent Repeat-in-Toxin (RTX) toxin that exhibits cytotoxic activity to respiratory epithelial cells, macrophages, and synoviocytes, suggesting that it may play a role in disrupting the respiratory epithelium, promoting survival of the bacterium in the bloodstream, and facilitating invasion of skeletal system tissues. Children with *K. kingae* disease frequently present with symptoms of an upper respiratory infection, herpetic stomatitis, or buccal aphthous ulcers, raising the possibility that viral-induced damage to the colonized mucosa facilitates invasion of the bloodstream.

CLINICAL DISEASE

Septic arthritis is the most common invasive *K. kingae* infection in children, followed by bacteremia, osteomyelitis, and endocarditis, whereas other clinical manifestations are infrequent (Table 193-1). The organism is the most frequent etiology of skeletal system infections in children 6 mo to 3 yr of age. With the exception of patients with endocarditis, the presentation of invasive *K. kingae* infections is frequently mild, and a body temperature <38°C (100.4°F), a normal C-reactive protein concentration, and a normal white blood cell count are common, requiring a high index of clinical suspicion.

Table 193-1 Clinical Spectrum and Relative Frequency of *Kingella kingae* Infections

CLINICAL DISEASE	FREQUENCY
Skeletal system	+++
Septic arthritis	+++
Osteomyelitis	++
Spondylodiscitis	+
Tenosynovitis	±
Dactylitis	±
Bursitis	±
Bacteremia with no focus	+++
Cardiac	+
Endocarditis	+
Pericarditis	±
Meningitis	±
Peritonitis	±
Cellulitis	±
Soft-tissue abscesses	±
Lower respiratory tract	±
Laryngotracheobronchitis	±
Pneumonia	±
Pleural empyema	±
Ocular	±
Keratitis	±
Corneal abscess	±
Endophthalmitis	±
Eyelid abscess	±

+++, Very common; ++, common; +, infrequent; ±, exceptional.

Septic Arthritis

Although *K. kingae*-driven arthritis especially affects the large weight-bearing joints, involvement of the small metacarpophalangeal, sternoclavicular, and tarsal joints is not unusual (see Chapter 685). The disease has an acute presentation, and children are brought to medical attention after a median of 3 days. The leukocyte count in the synovial fluid shows less than 50,000 white blood cells/μL in almost 25% of the patients, and the Gram stain of synovial fluid is positive in only a small percentage of cases.

Osteomyelitis

K. kingae osteomyelitis usually involves the long bones of the extremities (see Chapter 685). The calcaneus, talus, sternum, and clavicle are also frequently affected (and are rarely infected by other bacterial pathogens). Onset of *K. kingae* osteomyelitis is insidious, and the disease is diagnosed after 1 wk or more in 70% of patients. The MRI shows mild bone and soft tissue changes. Involvement of the epiphyseal cartilage appears to be specifically associated with the organism. Despite the frequent diagnostic delay, chronic osteomyelitis and functional orthopedic disabilities are unusual.

Spondylodiscitis

K. kingae is currently the second most common bacterium isolated in children younger than 4 yr of age with spondylodiscitis after *Staphylococcus aureus* (see Chapter 679.7). It is presumed that the organism penetrates into the rich network of blood vessels that traverse the cartilaginous vertebral endplates and enter the annulus in young children during a bacteremic episode. *K. kingae* spondylodiscitis usually involves the lumbar intervertebral spaces and, with decreasing frequency, the thoracolumbar, thoracic, lumbosacral, and cervical discs. Involvement of multiple discs is uncommon. Patients present with limping, lumbar pain, back stiffness, refusal to sit or walk, neurologic symptoms, or abdominal complaints. Radiography or MRI studies demonstrate narrowing of the intervertebral space. Patients respond

well to appropriate antibiotic treatment and recover without complications, although residual narrowing of the intervertebral space may occur.

Occult Bacteremia

Patients with *K. kingae* bacteremia and no focal infection (occult bacteremia) commonly present with mild to moderate fever, symptoms suggestive of a viral upper respiratory infection, a mean C-reactive protein level of 2.2 mg/dL, and a mean white blood cell count of 12,700/μL. Children with *K. kingae* bacteremia respond favorably to a short course of antibiotics.

Endocarditis

In contrast to other *K. kingae* infections, endocarditis is also diagnosed in school-age children, adolescents, and adult patients. The disease may affect native as well as prosthetic valves. Predisposing factors include congenital cardiac malformations or rheumatic valvular disease, but some patients have previously normal hearts. Typically, the left side of the heart is involved, usually the mitral valve. Fever and acute-phase reactants are more elevated in patients with endocarditis compared with those with uncomplicated bacteremia; no particular cutoff value accurately distinguishes between the 2 conditions. Despite the exquisite susceptibility of *K. kingae* to antibiotics, cardiac failure, septic shock, cerebrovascular accidents, and other life-threatening complications are common, and the mortality rate is high (~16%). Because of the potential severity of *K. kingae* endocarditis, routine echocardiographic evaluation of children with isolated bacteremia is indicated.

DIAGNOSIS

The diagnosis of *K. kingae* disease is established by isolation of the bacterium or by a positive nucleic acid amplification assay from a normally sterile site such as blood, synovial fluid, or bone tissue. Although *K. kingae* grows on routine bacteriologic media, its recovery from exudates is frequently unsuccessful. Detection is enhanced by inoculating synovial fluid specimens onto blood-culture vials, suggesting that diluting purulent samples in a large volume of nutrient broth reduces the concentration of detrimental factors, improving the isolation of this fastidious bacterium.

Testing bone and joint specimens by nucleic acid amplification assays that target specific *K. kingae* genes such as *cpn* or those encoding the bacterium RTX toxin, have further improved detection of the organism and reduced the fraction of "culture-negative septic arthritis" in young children.

TREATMENT

K. kingae is usually highly susceptible to penicillin and cephalosporins but exhibits decreased susceptibility to oxacillin. Although β-lactamase production is frequently detected in colonizing *K. kingae* strains, its prevalence among invasive organisms is low and shows wide geographic variation. Testing for β-lactamase production should be routinely performed in all isolates derived from normally sterile body sites.

Because of the lack of specific guidelines for treating *K. kingae* disease, patients have been administered a variety of antibiotic regimens according to protocols developed for infections caused by traditional pathogens. The first-line therapy for skeletal infections in young children usually consists of intravenous administration of a second- or third-generation cephalosporin, pending culture results. *K. kingae* is always resistant to glycopeptide antibiotics and 40% of isolates are also resistant to clindamycin, a serious concern in areas where skeletal infections caused by community-associated methicillin-resistant *S. aureus* are common, and vancomycin or clindamycin are initially administered to children with presumptive septic arthritis or osteomyelitis. The initial antibiotic regimen is frequently changed to ampicillin or cephalosporin (cefotaxime, ceftriaxone) once *K. kingae* is identified and β-lactamase production is excluded. A favorable clinical response and decreasing C-reactive protein levels to ≤20 μg/mL are used to guide switching to oral antibiotics and defining duration of therapy. Antibiotic treatment has ranged from 2-3 wk for *K. kingae* arthritis, from 3-6 wk for *K. kingae* osteomyelitis, and from 3-12 wk for *K. kingae* spondylodiscitis. Although some children with septic arthritis have been managed with repeat joint aspirations and lavage, most patients promptly respond to conservative treatment with appropriate antibiotics and do not require invasive surgical procedures.

Children with *K. kingae* bacteremia are initially treated with an intravenous β-lactam antibiotic and are subsequently switched to an oral drug once the clinical condition has improved. In most cases, the total duration of therapy ranges from 1-2 wk.

Patients with *K. kingae* endocarditis are usually treated with an intravenous β-lactam antibiotic alone or in combination with an aminoglycoside for 4-7 wk. Early surgical intervention is necessary for life-threatening complications unresponsive to medical therapy.

PREVENTION

Because the risk of asymptomatic pharyngeal carriers for developing an invasive *K. kingae* infection is low (<1% per year), in the absence of clinical disease, there is no indication to eradicate the organism from the colonized mucosal surfaces. Nonetheless, in the reported outbreaks of *K. kingae* infections in children daycare centers, 14 of 75 (18.7%) classmates developed a proven or presumptive infection, including fatal endocarditis, within a 1 mo period, indicating that the causative strains combined unusual transmissibility and virulence. Under these circumstances, administration of prophylactic antibiotics aimed to eradicate colonization in contacts and prevent further cases of disease has been attempted, employing either rifampin 10 mg/kg or 20 mg/kg twice daily for 2 days alone or in combination with amoxicillin (80 mg/kg per day) for 2 days or 4 days. The effectiveness of these regimens has ranged between 47% and 80%, indicating that eradication of *K. kingae* from colonized mucosae is difficult to achieve and precluding, at this stage, recommending routine use of prophylactic antibiotics in this setting.

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Chapter 194

Haemophilus influenzae

Robert S. Daum

An effective vaccine to prevent *Haemophilus influenzae* type b disease, introduced in the United States and most other countries, has resulted in a dramatic decrease in the incidence of infections caused by this organism. However, mortality and morbidity from *H. influenzae* type b infection remain a problem worldwide, primarily in developing countries. Occasional cases of invasive disease caused by non–type b organisms continue to occur but are infrequent. Nontypable members of the species are an important cause of otitis media, sinusitis, and chronic bronchitis.

ETIOLOGY

H. influenzae is a fastidious, Gram-negative, pleomorphic coccobacillus that requires factor X (hematin) and factor V (phosphopyridine nucleotide) for growth. Some *H. influenzae* isolates are surrounded by a polysaccharide capsule and can be serotyped into 6 antigenically and biochemically distinct types designated a, b, c, d, e, and f.

EPIDEMIOLOGY

Before the advent of an effective type b conjugate vaccine in 1988, *H. influenzae* type b was a major cause of serious disease among children. There was a striking age distribution of cases, with more than

90% in children younger than 5 yr of age and the majority in children younger than 2 yr of age. The annual attack rate of invasive disease was 64-129 cases per 100,000 children younger than 5 yr of age. Invasive disease caused by other capsular serotypes has been much less frequent but continues to occur. The incidence of invasive disease caused by type b and non–type b serotypes has been estimated at approximately 0.08 and 1.02 cases per 100,000 children younger than 5 yr of age per year, respectively, in the United States. Nonencapsulated (nontypable) *H. influenzae* strains also occasionally cause invasive disease, especially in neonates, immunocompromised children, and children in developing countries. The estimated rate of invasive disease caused by nontypable *H. influenzae* in the United States is 1.88 per 100,000 children younger than 5 yr of age per year. Nontypable isolates are common etiologic agents in otitis media, sinusitis, and chronic bronchitis.

Humans are the only natural hosts for *H. influenzae,* which is part of the normal respiratory flora in 60-90% of healthy children. Most isolates are nontypable. Before the advent of conjugate vaccine immunization, *H. influenzae* type b could be isolated from the pharynx of 2-5% of healthy preschool and school-age children, with lower rates among infants and adults. Asymptomatic colonization with *H. influenzae* type b occurs at a much lower rate in immunized populations.

The continued circulation of the type b organism despite current vaccine coverage levels suggests that elimination of type b disease may be a formidable task. The few cases of type b invasive disease in the United States now occur in both unvaccinated and fully vaccinated children. Approximately 50% of cases occur in young infants who are too young to have received a complete primary vaccine series. Among the cases in patients who are old enough to have received a complete vaccine series, the majority are underimmunized. To highlight this point, during a recent shortage of *H. influenzae* type b vaccine, invasive disease developed in 5 children in Minnesota, all of whom were incompletely immunized. Continued efforts are necessary to provide currently available conjugate vaccines to children in developing countries, where affordability remains an important issue.

In the prevaccine era, certain groups and individuals had an increased incidence of invasive type b disease, including Alaskan Eskimos, Apaches, Navajos, and African-Americans. Persons with certain chronic medical conditions were also known to be at increased risk for invasive disease, including those with sickle cell disease, asplenia, congenital and acquired immunodeficiencies, and malignancies. Unvaccinated infants with invasive *H. influenzae* type b infection are also at increased risk for recurrence, reflecting the fact that they typically do not develop a protective immune response to *H. influenzae.*

Socioeconomic risk factors for invasive *H. influenzae* type b disease include childcare outside the home, the presence of siblings of elementary school age or younger, short duration of breastfeeding, and parental smoking. A history of otitis media is associated with an increased risk for invasive disease. Much less is known about the epidemiology of invasive disease caused by non–type b strains, and it is not clear whether the epidemiologic features of type b disease apply to disease caused by non–type b isolates.

Among age-susceptible household contacts who have been exposed to a case of invasive *H. influenzae* type b disease, there is increased risk for secondary cases of invasive disease in the 1st 30 days, especially in susceptible children younger than 24 mo of age. Whether a similar increased risk occurs for contacts of individuals with non–type b disease is unknown.

The mode of transmission is most commonly direct contact or inhalation of respiratory tract droplets containing *H. influenzae.* The incubation period for invasive disease is variable, and the exact period of communicability is unknown. Most children with invasive *H. influenzae* type b disease are colonized in the nasopharynx before initiation of antimicrobial therapy; 25-40% may remain colonized during the 1st 24 hr of therapy.

With the decline of disease caused by type b organisms, disease caused by other serotypes (a, c-f) and nontypable organisms has been recognized more clearly. There is no evidence that these non–type b infections have increased in frequency. However, clusters of type a and, less often, type f and type e infections have occurred. Data from Israel suggest that nontypable *H. influenzae* is now the most common case of invasive *H. influenzae* disease in that country.

PATHOGENESIS

The pathogenesis of disease begins with adherence to respiratory epithelium and colonization of the nasopharynx, which is mediated by pilus and nonpilus adherence factors. The mechanism of entry into the intravascular compartment is unclear but appears to be influenced by cytotoxic factors. Once in the bloodstream, *H. influenzae* type b, and perhaps other encapsulated strains, resist intravascular clearance mechanisms at least in part via the presence of a polysaccharide capsule. In the case of *H. influenzae* type b, the magnitude and duration of bacteremia influence the likelihood of dissemination of bacteria to sites such as the meninges and joints.

Noninvasive *H. influenzae* infections such as otitis media, sinusitis, and bronchitis are usually caused by nontypable strains. These organisms gain access to sites such as the middle ear and sinus cavities by direct extension from the nasopharynx. Factors facilitating spread from the pharynx include eustachian tube dysfunction and antecedent viral infections of the upper respiratory tract.

Antibiotic Resistance

Most *H. influenzae* isolates are susceptible to ampicillin or amoxicillin, but about a third produce a β-lactamase and are therefore resistant to these antibiotics. β-Lactamase–negative ampicillin-resistant isolates have been identified and manifest resistance by production of a β-lactam–insensitive cell wall synthesis enzyme called PBP3.

Amoxicillin-clavulanate is uniformly active against *H. influenzae* clinical isolates except for the rare β-lactamase–negative ampicillin-resistant isolates. Among macrolides, azithromycin has in vitro activity against a high percentage of *H. influenzae* isolates; in contrast, the activity of erythromycin and clarithromycin against *H. influenzae* clinical isolates is poor. *H. influenzae* resistance to third-generation cephalosporins has not been documented. Resistance to trimethoprim-sulfamethoxazole is infrequent (≈10%), and resistance to quinolones is believed to be rare.

Immunity

In the prevaccine era, the most important known element of host defense was antibody directed against the type b capsular polysaccharide polyribosylribitol phosphate (PRP). Anti-PRP antibody is acquired in an age-related fashion and facilitates clearance of *H. influenzae* type b from blood, in part related to opsonic activity. Antibodies directed against antigens such as outer membrane proteins or lipopolysaccharide may also have a role in opsonization. Both the classic and alternative complement pathways are important in defense against *H. influenzae* type b.

Before the introduction of vaccination, protection from *H. influenzae* type b infection was presumed to correlate with the concentration of circulating anti-PRP antibody at the time of exposure. A serum antibody concentration of 0.15-1.0 μg/mL was considered protective against invasive infection. Unimmunized infants older than 6 mo of age and young children usually lacked an anti-PRP antibody concentration of this magnitude and were susceptible to disease after encountering *H. influenzae* type b. This lack of antibody in infants and young children may have reflected a maturational delay in the immunologic response to thymus-independent type 2 antigens such as unconjugated PRP, presumably explaining the high incidence of type b infections in infants and young children in the pre-vaccine era.

The conjugate vaccines (Table 194-1) act as thymus-dependent antigens and elicit serum antibody responses in infants and young children. These vaccines are believed to prime memory antibody responses on subsequent encounters with PRP. The concentration of circulating anti-PRP antibody in a child primed by a conjugate vaccine may not correlate precisely with protection, presumably because a memory response may occur rapidly on exposure to PRP and provide protection.

Much less is known about immunity to other *H. influenzae* serotypes or to nontypable isolates. For nontypable isolates, evidence suggests that antibodies directed against 1 or more outer membrane proteins

Table 194-1 *Haemophilus influenzae* Type B Conjugate Vaccines Available in the United States

VACCINE	TRADE NAME	COMPONENTS	MANUFACTURER
PRP-T*	Hiberix*	PRP conjugated to tetanus toxoid	GlaxoSmithKline Biologicals
PRP-OMP	PedvaxHIB	PRP conjugated to OMP	Merck & Co, Inc.
PRP-OMP-HepB	Comvax	PRP-OMP + hepatitis B vaccine	Merck & Co, Inc.
PRP-T/DTaP-IPV	Pentacel	PRP-T + DTaP-IPV vaccines	Sanofi Pasteur
PRP-T	MenHibRix	PRP-T + MenCY	GlaxoSmithKline Biolgicals

*PRP-T (Hiberix) is licensed only for the final (booster) dose of the Hib vaccine series and should not be used for primary immunization in infants at 2, 4, or 6 mo of age.

DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; HepB, hepatitis B vaccine; Hib, *H. influenzae* type b; IPV, trivalent inactivated polio vaccine; OMP, outer membrane protein complex from Neisseria meningitidis; PRP, polyribosylribitol phosphate.

are bactericidal and protect against experimental challenge. A variety of antigens have been evaluated in an attempt to identify vaccine candidates for nontypable *H. influenzae,* including outer membrane proteins (P1, P2, P4, P5, P6, D15, and Tbp A/B), lipopolysaccharide, various adhesins, and lipoprotein D.

DIAGNOSIS

Presumptive identification of *H. influenzae* is established by direct examination of the collected specimen after staining with Gram reagents. Because of its small size, pleomorphism, and occasional poor uptake of stain, as well as the tendency for proteinaceous fluids to have a red background, *H. influenzae* is sometimes difficult to visualize. Furthermore, given that identification of microorganisms on smear by either technique requires at least 10^5 bacteria/mL, failure to visualize them does not preclude their presence.

Culture of *H. influenzae* requires prompt transport and processing of specimens because the organism is fastidious. Specimens should not be exposed to drying or temperature extremes. Primary isolation of *H. influenzae* can be accomplished on chocolate agar or on blood agar plates using the staphylococcus streak technique.

Serotyping of *H. influenzae* is accomplished by slide agglutination with type-specific antisera. Accurate serotyping is essential to monitor progress toward elimination of type b invasive disease. Timely reporting of cases to public health authorities should be ensured.

CLINICAL MANIFESTATIONS AND TREATMENT

The initial antibiotic therapy of invasive infections possibly caused by *H. influenzae* should be a parenterally administered antimicrobial agent effective in sterilizing all foci of infection and effective against ampicillin-resistant strains, usually an extended-spectrum cephalosporin such as cefotaxime or ceftriaxone. These antibiotics have achieved popularity because of their relative lack of serious adverse effects and ease of administration. After the antimicrobial susceptibility of the isolate has been determined, an appropriate agent can be selected to complete the therapy. Ampicillin remains the drug of choice for the therapy of infections caused by susceptible isolates. If the isolate is resistant to ampicillin, ceftriaxone can be administered once daily in selected circumstances for outpatient therapy.

Oral antimicrobial agents are sometimes used to complete a course of therapy initiated by the parenteral route and are typically initial therapy for noninvasive infections such as otitis media and sinusitis. If the organism is susceptible, amoxicillin is the drug of choice. An oral second- or third-generation cephalosporin or amoxicillin-clavulanate may be used when the isolate is resistant to ampicillin.

Meningitis

In the prevaccine era, meningitis accounted for more than half of all cases of invasive *H. influenzae* disease. Clinically, meningitis caused by *H. influenzae* type b cannot be differentiated from meningitis caused by *Neisseria meningitidis* or *Streptococcus pneumoniae* (see Chapter 603.1). It may be complicated by other foci of infection such as the lungs, joints, bones, and pericardium.

Antimicrobial therapy should be administered intravenously for 7-14 days for uncomplicated cases. Cefotaxime, ceftriaxone, and ampicillin cross the blood–brain barrier during acute inflammation in concentrations adequate to treat *H. influenzae* meningitis. Intramuscular therapy with ceftriaxone is an alternative in patients with normal organ perfusion.

The prognosis of *H. influenzae* type b meningitis depends on the age at presentation, duration of illness before appropriate antimicrobial therapy, cerebrospinal fluid capsular polysaccharide concentration, and rapidity with which organisms are cleared from cerebrospinal fluid, blood, and urine. Clinically manifested inappropriate secretion of antidiuretic hormone and evidence of focal neurologic deficits at presentation are poor prognostic features. Approximately 6% of patients with *H. influenzae* type b meningitis are left with some hearing impairment, probably because of inflammation of the cochlea and the labyrinth. Dexamethasone (0.6 mg/kg/day divided every 6 hr for 2 days), particularly when given shortly before or concurrent with the initiation of antimicrobial therapy, decreases the incidence of hearing loss. Major neurologic sequelae of *H. influenzae* type b meningitis include behavior problems, language disorders, impaired vision, mental retardation, motor abnormalities, ataxia, seizures, and hydrocephalus.

Cellulitis

Children with *H. influenzae* type b cellulitis often have an antecedent upper respiratory tract infection. They usually have no prior history of trauma, and the infection is thought to represent seeding of the organism to the involved soft tissues during bacteremia. The head and neck, particularly the cheek and preseptal region of the eye, are the most common sites of involvement. The involved region generally has indistinct margins and is tender and indurated. Buccal cellulitis is classically erythematous with a violaceous hue, although this sign may be absent. *H. influenzae* may often be recovered directly from an aspirate of the leading edge, although this procedure is seldom performed. The blood culture may also reveal the causative organism. Other foci of infection may be present concomitantly, particularly in children younger than 18 mo of age. A diagnostic lumbar puncture should be considered at the time of diagnosis in these children.

Parenteral antimicrobial therapy is indicated until patients become afebrile, after which an appropriate orally administered antimicrobial agent may be substituted. A 7-10 day course is customary.

Preseptal Cellulitis

Infection involving the superficial tissue layers anterior to the orbital septum is termed preseptal cellulitis, which may be caused by *H. influenzae.* Uncomplicated preseptal cellulitis does not imply a risk for visual impairment or direct central nervous system extension. However, concurrent bacteremia may be associated with the development of meningitis. *H. influenzae* preseptal cellulitis is characterized by fever, edema, tenderness, warmth of the lid, and, occasionally, purple discoloration. Evidence of interruption of the integument is usually absent. Conjunctival drainage may be associated. *S. pneumoniae, Staphylococcus aureus,* and group A streptococcus cause

clinically indistinguishable preseptal cellulitis. The latter 2 pathogens are more likely when fever is absent and the integument is interrupted (e.g., an insect bite or trauma).

Children with preseptal cellulitis in whom *H. influenzae* and *S. pneumoniae* are etiologic considerations (young age, high fever, intact integument) should undergo blood culture, and a diagnostic lumbar puncture should be considered.

Parenteral antibiotics are indicated for preseptal cellulitis. Because methicillin-susceptible and methicillin-resistant *S. aureus, S. pneumoniae,* and group A β-hemolytic streptococci are other causes, empirical therapy should include agents active against these pathogens. Patients with preseptal cellulitis without concurrent meningitis should receive parenteral therapy for about 5 days, until fever and erythema have abated. In uncomplicated cases, antimicrobial therapy should be given for 10 days.

Orbital Cellulitis

Infections of the orbit are infrequent and usually develop as complications of acute ethmoid or sphenoid sinusitis. Orbital cellulitis may manifest as lid edema but is distinguished by the presence of proptosis, chemosis, impaired vision, limitation of the extraocular movements, decreased mobility of the globe, or pain on movement of the globe. The distinction between preseptal and orbital cellulitis may be difficult and is best delineated by CT.

Orbital infections are treated with parenteral therapy for at least 14 days. Underlying sinusitis or orbital abscess may require surgical drainage and more prolonged antimicrobial therapy.

Supraglottitis or Acute Epiglottitis

Supraglottitis is a cellulitis of the tissues comprising the laryngeal inlet (see Chapter 385). It has become exceedingly rare since the introduction of conjugate type b vaccines. Direct bacterial invasion of the involved tissues is probably the initiating pathophysiologic event. This dramatic, potentially lethal condition can occur at any age. Because of the risk of sudden, unpredictable airway obstruction, supraglottitis is a medical emergency. Other foci of infection, such as meningitis, are rare. Antimicrobial therapy directed against *H. influenzae* and other etiologic agents should be administered parenterally but only after the airway is secured, and therapy should be continued until patients are able to take fluids by mouth. The duration of antimicrobial therapy is typically 7 days.

Pneumonia

The true incidence of *H. influenzae* pneumonia in children is unknown because invasive procedures required to obtain culture specimens are seldom performed (see Chapter 400). In the prevaccine era, type b bacteria were believed to be the usual cause. The signs and symptoms of pneumonia caused by *H. influenzae* cannot be differentiated from those of pneumonia caused by many other microorganisms. Other foci of infection may be present concomitantly.

Children younger than 12 mo of age in whom *H. influenzae* pneumonia is suspected should receive parenteral antimicrobial therapy initially because of their increased risk for bacteremia and its complications. Older children who do not appear severely ill may be managed with an orally administered antimicrobial. Therapy is continued for 7-10 days. Uncomplicated pleural effusion associated with *H. influenzae* pneumonia requires no special intervention. However, if empyema develops, surgical drainage is indicated.

Suppurative Arthritis

Large joints, such as the knee, hip, ankle, and elbow, are affected most commonly (see Chapter 685). Other foci of infection may be present concomitantly. Although single joint involvement is the rule, multiple joint involvement occurs in approximately 6% of cases. The signs and symptoms of septic arthritis caused by *H. influenzae* are indistinguishable from those of arthritis caused by other bacteria.

Uncomplicated septic arthritis should be treated with an appropriate antimicrobial administered parenterally for at least 5-7 days. If the clinical response is satisfactory, the remainder of the course of antimicrobial treatment may be given orally. Therapy is typically given for 3 wk for uncomplicated septic arthritis, but it may be continued beyond 3 wk, until the C-reactive protein concentration is normal.

Pericarditis

H. influenzae is a rare cause of pericarditis (see Chapter 440). Affected children often have had an antecedent upper respiratory tract infection. Fever, respiratory distress, and tachycardia are consistent findings. Other foci of infection may be present concomitantly.

The diagnosis may be established by recovery of the organism from blood or pericardial fluid. Gram stain or detection of PRP in pericardial fluid, blood, or urine (when type b organisms are the cause) may aid the diagnosis. Antimicrobials should be provided parenterally in a regimen similar to that used for meningitis (see Chapter 603.1). Pericardiectomy is useful for draining the purulent material effectively and preventing tamponade and constrictive pericarditis.

Bacteremia Without an Associated Focus

Bacteremia caused by *H. influenzae* may be associated with fever without any apparent focus of infection (see Chapter 177). In this situation, risk factors for "occult" bacteremia include the magnitude of fever (≥39°C [102.2°F]) and the presence of leukocytosis (≥15,000 cells/μL). In the prevaccine era, meningitis developed in approximately 25% of children with occult *H. influenzae* type b bacteremia if left untreated. In the vaccine era, this *H. influenzae* infection has become exceedingly rare. When it does occur, the child should be reevaluated for a focus of infection and a second blood culture performed. The child should be hospitalized and given parenteral antimicrobial therapy after a diagnostic lumbar puncture and chest radiograph are obtained.

Miscellaneous Infections

Urinary tract infection, epididymoorchitis, cervical adenitis, acute glossitis, infected thyroglossal duct cysts, uvulitis, endocarditis, endophthalmitis, primary peritonitis, osteomyelitis, and periappendiceal abscess are rarely caused by *H. influenzae.*

Invasive Disease in Neonates

Neonates rarely have invasive *H. influenzae* infection. In the infant with illness within the 1st 24 hr of life, especially in association with maternal chorioamnionitis or prolonged rupture of membranes, transmission of the organism to the infant is likely to have occurred through the maternal genital tract, which may be (<1%) colonized with nontypable *H. influenzae.* Manifestations of neonatal invasive infection include bacteremia with sepsis, pneumonia, respiratory distress syndrome with shock, conjunctivitis, scalp abscess or cellulitis, and meningitis. Less commonly, mastoiditis, septic arthritis, and congenital vesicular eruption may occur.

Otitis Media

Acute otitis media is one of the most common infectious diseases of childhood (see Chapter 640). It results from the spread of bacteria from the nasopharynx through the eustachian tube into the middle ear cavity. Usually because of a preceding viral upper respiratory tract infection, the mucosa in the area becomes hyperemic and swollen, resulting in obstruction and an opportunity for bacterial multiplication in the middle ear.

The most common bacterial pathogens are *H. influenzae, S. pneumoniae,* and *Moraxella catarrhalis.* Most *H. influenzae* isolates causing otitis media are nontypable. Ipsilateral conjunctivitis may also be present. Amoxicillin (80-90 mg/kg/day) is a suitable first-line oral antimicrobial agent, because the probability that the causative isolate is resistant to amoxicillin and the risk for invasive potential are sufficiently low to justify this approach. Alternatively, in certain cases, a single dose of ceftriaxone constitutes adequate therapy.

In the case of treatment failure or if a β-lactamase–producing isolate is obtained by tympanocentesis or from drainage fluid, amoxicillin-clavulanate (Augmentin) is a suitable alternative.

Conjunctivitis

Acute infection of the conjunctivae is common in childhood (see Chapter 626). In neonates, *H. influenzae* is an infrequent cause. However, it is an important pathogen in older children. Most *H. influenzae* isolates associated with conjunctivitis are nontypable, although type b isolates and other serotypes are occasionally found. Empirical treatment of conjunctivitis beyond the neonatal period usually consists of topical antimicrobial therapy with sulfacetamide. Topical fluoroquinolone therapy is to be avoided because of its broad spectrum, high cost, and high rate of emerging resistance among many bacterial species. Ipsilateral **otitis media** caused by the same organism may be present and requires oral antibiotic therapy.

Sinusitis

H. influenzae is an important cause of acute sinusitis in children, second in frequency only to *S. pneumoniae* (see Chapter 380). Chronic sinusitis lasting longer than 1 yr or severe sinusitis requiring hospitalization is often caused by *S. aureus* or anaerobes such as *Peptococcus, Peptostreptococcus,* and *Bacteroides*. Nontypable *H. influenzae* and viridans group streptococci are also frequently recovered.

For uncomplicated sinusitis, amoxicillin is acceptable initial therapy. However, if clinical improvement does not occur, a broader-spectrum agent, such as amoxicillin-clavulanate, may be appropriate. A 10-day course is sufficient for uncomplicated sinusitis. Hospitalization for parenteral therapy is rarely required; the usual reason is suspicion of progression to orbital cellulitis.

PREVENTION

Immunization with *H. influenzae* type b conjugate vaccine is recommended for all infants. Prophylaxis is indicated if close contacts of an index patient with type b disease are unvaccinated. The contagiousness of non–type b *H. influenzae* infections is not known, and prophylaxis is not recommended.

Vaccine

Several *H. influenzae* type b conjugate vaccines are currently marketed in the United States, containing either PRP–outer membrane protein (PRP-OMP) or PRP–tetanus toxoid (PRP-T), which differ in the carrier protein used and the method of conjugating the polysaccharide to the protein (see Table 194-1 and Chapter 172). One of the combination vaccines consists of PRP-OMP combined with hepatitis B vaccine (Comvax, Merck & Co., Inc., Whitehouse Station, NJ) and can be used for doses recommended at 2, 4, and 12-15 mo of age. Another consists of PRP-T combined with DTaP vaccine (diphtheria and tetanus toxoids and acellular pertussis) and IPV vaccine (trivalent, inactivated polio vaccine) (Pentacel, Sanofi Pasteur Inc., Swiftwater, PA) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age. A third consists of PRP-T combined with *N. meningitidis* serogroups C and Y (GlaxoSmithKline Biologicals) and can be used for doses recommended at 2, 4, 6, and 12-15 mo of age for children at increased risk for *N. meningitidis* disease. PRP-T by itself is licensed for doses scheduled for children 15 mo of age or older.

The *H. influenzae* type b conjugate vaccines stimulate circulating anticapsular antibody and provide long-term immunity via B-cell memory.

Prophylaxis

Unvaccinated children younger than 48 mo of age who are in close contact with an index case of invasive *H. influenzae* type b infection are at increased risk for invasive infection. The risk for secondary disease for children older than 3 mo of age is inversely related to age. About half of the secondary cases among susceptible household contacts occur in the 1st wk after hospitalization of the index case. Because many children are now protected against *H. influenzae* type b by prior immunization, the need for prophylaxis has greatly decreased. When prophylaxis is used, rifampin is indicated for all members of the household or close contact group, including the index patient, if the group includes 1 or more children younger than 48 mo of age who are not fully immunized.

Parents of children hospitalized for invasive *H. influenzae* type b disease should be informed of the increased risk for secondary infection in other young children in the same household if they are not fully immunized. Parents of children exposed to a single case of invasive *H. influenzae* type b disease in a childcare center or nursery school should be similarly informed, although there is disagreement about the need for rifampin prophylaxis for these children.

For prophylaxis, children should be given rifampin orally (0-1 mo of age, 10 mg/kg/dose; >1 mo of age, 20 mg/kg/dose, not to exceed 600 mg/dose) once a day for 4 consecutive days. The adult dose is 600 mg once daily. Rifampin prophylaxis is not recommended for pregnant women.

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Chapter 195

Chancroid *(Haemophilus ducreyi)*

H. Dele Davies

Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inguinal lymphadenopathy.

ETIOLOGY AND EPIDEMIOLOGY

Chancroid is caused by *Haemophilus ducreyi,* a fastidious Gram-negative bacillus. It is prevalent in many developing countries but occurs sporadically in the developed world. Most Western cases occur in returning travelers (90% are male) from endemic areas or occasionally in localized urban outbreaks associated with commercial sex workers. It is a risk factor for transmission of HIV. Diagnosis of chancroid in infants and children is strong evidence of sexual abuse. Male circumcision lowers the risk for chancroid. The incidence of chancroid has declined significantly and remains low in the United States since 1981.

CLINICAL MANIFESTATIONS.

The incubation period is 4-7 days with a small inflammatory papule on the preputial orifice or frenulum in men and on the labia, fourchette, or perineal region in women. The lesion becomes pustular, eroded, and ulcerative within 2-3 days. The ulcer edge is classically ragged and undermined. Without treatment, the ulcers may persist for wk to mo. Painful, tender inguinal lymphadenitis occurs in more than 50% of cases, more often among men. The lymphadenopathy can become fluctuant to form **buboes,** which can spontaneously rupture.

DIAGNOSIS

Diagnosis is usually established by the clinical presentation and the exclusion of both syphilis *(Treponema pallidum)* and herpes simplex virus infections. Gram stain of ulcer secretions may show Gram-negative coccobacilli in parallel clusters (school of fish). Culture requires expensive, special media and has a sensitivity of only 80%. Polymerase chain reaction or indirect immunofluorescence using monoclonal antibodies remain either as research tools or are performed by some clinical laboratories using their own in-house CLIA (Clinical Laboratory Improvement Amendments) verified kits. There are currently no FDA-approved polymerase chain reaction tests for *H. ducreyi*. The ulcer of chancroid is accompanied by concurrent **lymphadenopathy** that is usually unilateral, unlike lymphogranuloma venereum (see Chapter 226.4). Genital herpes is characterized by vesicular lesions with a history of recurrence (see Chapter 252).

TREATMENT

Most *H. ducreyi* organisms are resistant to penicillin and ampicillin because of plasmid-mediated β-lactamase production. Spread of plasmid-mediated resistance among *H. ducreyi* has resulted in lack of efficacy of previously useful drugs such as sulfonamides and tetracyclines. Chancroid is easy to treat if recognized early. The current treatment recommendation is for azithromycin (1g as a single dose PO) or ceftriaxone (250 mg as a single dose IM). Alternative regimens include erythromycin (500 mg tid PO for 7 days), which is most often used in developing countries, and ciprofloxacin (500 mg bid PO for 3 days, for persons ≥18 yr of age). Fluctuant nodes may require drainage. Symptoms usually resolve within 3-7 days. Relapses can usually be treated successfully with the original treatment regimen. Patients with HIV infection may require longer duration of treatment. Persistence of the ulcer and the organism following therapy should raise suspicion of resistance to the prescribed antibiotic.

Patients with chancroid should be evaluated for other sexually transmitted infections, including syphilis, hepatitis B virus, HIV, chlamydia, and gonorrhea; an estimated 10% have concomitant syphilis or genital herpes. If initial HIV or syphilis testing is negative, they should be tested for again in 3 mo because of the high rates of coinfections. In developing countries, patients with a compatible genital ulcer are treated for both chancroid and syphilis. All sexual contacts of patients with chancroid should be evaluated and treated.

COMPLICATIONS

Complications include phimosis in men and secondary bacterial infection. Bubo formation may occur in untreated cases. Genital ulceration as a syndrome increases the risk for transmission of HIV.

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Chapter 196

Moraxella catarrhalis

Timothy F. Murphy

Moraxella catarrhalis is an unencapsulated Gram-negative diplococcus and is a human-specific pathogen that colonizes the respiratory tract beginning in infancy. Colonization and infection with *M. catarrhalis* are increasing in countries in which pneumococcal conjugate vaccines are used widely. The most important clinical manifestation of *M. catarrhalis* infection in children is otitis media.

ETIOLOGY

M. catarrhalis has long been considered to be an upper respiratory tract commensal. Substantial genetic heterogeneity exists among strains of *M. catarrhalis*. Several outer membrane proteins demonstrate sequence differences among strains, particularly in regions of the proteins that are exposed on the bacterial surface. *M. catarrhalis* endotoxin lacks repeating polysaccharide side chains and is thus a lipooligosaccharide. In contrast to other Gram-negative respiratory pathogens, such as *Haemophilus influenzae* and *Neisseria meningitidis,* the lipooligosaccharide of *M. catarrhalis* is relatively conserved among strains; only 3 serotypes (A, B, and C) that are based on oligosaccharide structure have been identified. Genetic and antigenic differences among strains account for the observation that resolving an infection by 1 strain does not induce protective immunity to other strains. *M. catarrhalis* causes recurrent infections, which generally represent reinfection by new strains.

EPIDEMIOLOGY

The ecologic niche of *M. catarrhalis* is the human respiratory tract. The bacterium has not been recovered from animals or environmental sources. Age is the most important determinant of the prevalence of upper respiratory tract colonization. Common throughout infancy, nasopharyngeal colonization is a dynamic process with active turnover as a result of acquisition and clearance of strains of *M. catarrhalis*. Some geographic variation in rates of colonization is observed. On the basis of monthly or bimonthly cultures, colonization during the 1st yr of life may range from 33-100%. Several factors likely account for this variability among studies, including living conditions, daycare attendance, hygiene, environmental factors (e.g., household smoking), and genetics of the population. The prevalence of colonization steadily decreases with age. Understanding nasopharyngeal colonization patterns is important, because the pathogenesis of otitis media involves migration of the bacterium from the nasopharynx to the middle ear via the eustachian tube.

The widespread use of pneumococcal polysaccharide vaccines in some countries has resulted in alteration of patterns of nasopharyngeal colonization in the population. A relative increase in colonization by nonvaccine pneumococcal serotypes, nontypable *H. influenzae,* and *M. catarrhalis* has occurred. These changes in colonization patterns may account for the increased rates of otitis media caused by nontypable *H. influenzae* and *M. catarrhalis*. Similar shifts in etiology are being observed in children with sinusitis as well.

PATHOGENESIS OF INFECTION

Strains of *M. catarrhalis* differ in their virulence properties. The species is composed of complement-resistant and complement-sensitive genetic lineages, the complement-resistant strains being more strongly associated with virulence. Strains that cause infection in children differ in several phenotypic characteristics from strains that cause infection in adults, in whom the most common clinical manifestation is lower respiratory tract infection in the setting of chronic obstructive pulmonary disease.

The presence of several adhesin molecules with differing specificities for various host cell receptors reflects the importance of adherence to the human respiratory epithelial surface in the pathogenesis of infection. *M. catarrhalis* has long been viewed as an exclusively extracellular pathogen. However, the bacterium is now known to invade multiple cell types, including bronchial epithelial cells, small airway cells, and type 2 alveolar cells. In addition, *M. catarrhalis* resides intracellularly in lymphoid tissue, providing a potential reservoir for persistence in the human respiratory tract. Like many Gram-negative bacteria *M. catarrhalis* sheds vesicles from its surface during growth. These vesicles are internalized by respiratory epithelial cells and mediate several virulence mechanisms including B-cell activation, induction of inflammation, and delivery of β-lactamases. Analysis of genomes reveals modest genetic heterogeneity among strains.

M. catarrhalis forms biofilms in vitro and in the middle ears of children with chronic and recurrent otitis media. Biofilms are communities of bacteria encased in a matrix attached to a surface. Bacteria in biofilms are more resistant to antibiotics and to host immune responses than bacteria growing individually in planktonic form.

CLINICAL MANIFESTATIONS

M. catarrhalis causes predominantly mucosal infections in children. The mechanism of infection is migration of the infecting strains from the nasopharynx to the middle ear in the case of otitis media or to the sinuses in the case of sinusitis. The inciting event for both otitis media and sinusitis is often a preceding viral infection.

Acute Otitis Media

Approximately 80% of children have 1 or more episodes of otitis media by age 3 yr. Otitis media is the most common reason for which children receive antibiotics. On the basis of culture of middle ear fluid obtained by tympanocentesis, the predominant causes of acute otitis media are *Streptococcus pneumoniae, H. influenzae,* and *M. catarrhalis* (Fig. 196-1). Overall, *M. catarrhalis* causes 15-20% of cases of otitis media. The distribution of the causative agents of otitis media is changing as a result of widespread administration of pneumococcal conjugate vaccines, with a relative increase in *H. influenzae* and *M. catarrhalis*.

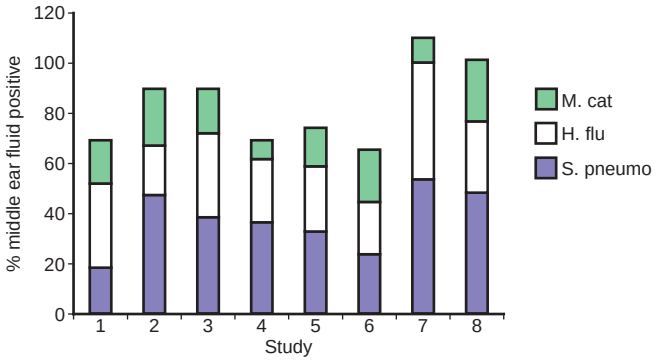

Figure 196-1 Bacterial causes of otitis media based on results of culture of middle ear fluid obtained by tympanocentesis from 8 studies published from 1992-2006. Bars represent percent-positive results of cultures of middle ear fluids. Some cultures had more than 1 species, accounting for totals greater than 100%. H. flu, nontypeable *Haemophilus influenzae;* M. cat, *Moraxella catarrhalis;* S. pneumo, *Streptococcus pneumoniae. (From Murphy TF, Paramswaran GI:* Moraxella catarrhalis, *a human respiratory tract pathogen,* Clin Infect Dis *49:124–131, 2009.)*

Acute otitis media caused by *M. catarrhalis* is clinically milder than otitis media caused by *H. influenzae* or *S. pneumoniae,* with less fever and lower prevalence of a red, bulging tympanic membrane. However, substantial overlap in symptoms is seen, making it impossible to predict etiology in an individual child on the basis of clinical features. Tympanocentesis is required to make an etiologic diagnosis but is not performed routinely, and thus, treatment of otitis media is generally empirical.

Recurrent Otitis Media and Otitis Media with Effusion

Otitis media with effusion refers to the presence of fluid in the middle ear in the absence of signs and symptoms of acute infection. Children who experience 4 or more episodes of acute otitis media in a year or who have at least 8 mo of middle ear effusion in a year are defined as *otitis prone*. These children suffer conductive hearing loss, which may lead to delays in speech and language development. Analysis of middle ear fluid from children with otitis media with effusion using sensitive molecular techniques such as polymerase chain reaction indicates that bacterial DNA is present in up to 80% of samples from such children. Indeed, *M. catarrhalis* DNA is present in a larger proportion of cases of otitis media with effusion than of acute otitis media. Biofilms may account for these observations, although definitive evidence for this conclusion is lacking.

Sinusitis

A small proportion of viral upper respiratory tract infections are complicated by bacterial sinusitis. According to findings of studies that use sinus puncture, *M. catarrhalis* accounts for approximately 20% of cases of acute bacterial sinusitis in children and a smaller proportion in adults. Sinusitis caused by *M. catarrhalis* is clinically indistinguishable from that caused by *S. pneumoniae* or *H. influenzae*.

Bacteremia

M. catarrhalis rarely causes bacteremia or invasive infections in children. When bacteremia occurs, the usual source is the respiratory tract. Some children have underlying immunocompromising conditions, but no particular immunodeficiency is associated with invasive *M. catarrhalis* infections.

DIAGNOSIS

The clinical diagnosis of otitis media is made by demonstration of fluid in the middle ear by pneumatic otoscopy. A tympanocentesis is required to establish an etiologic diagnosis, but this procedure is not performed routinely. Thus, the choice of antibiotic for otitis media is empirical and generally based on guidelines. Management of bacterial sinusitis is also empirical, because determining the etiology of sinusitis requires a sinus puncture, also a procedure that is not performed routinely.

The key to making a microbiologic diagnosis is distinguishing *M. catarrhalis* from commensal *Neisseria* that are part of the normal upper respiratory tract flora. Indeed, the difficulty in distinguishing colonies of *M. catarrhalis* from *Neisseria* species explains in part why *M. catarrhalis* has been overlooked in the past as a respiratory tract pathogen. *M. catarrhalis* produces round, opaque colonies that can be slid across the agar surface without disruption, the "hockey puck sign." In addition, after 48 hr, *M. catarrhalis* colonies tend to be larger than *Neisseria* and take on a pink color. A variety of biochemical tests distinguish *M. catarrhalis* from *Neisseria* species, and commercially available kits based on these tests are available.

Sensitive tests that employ polymerase chain reaction to detect respiratory tract bacterial pathogens in human respiratory tract secretions are in development. The application of such assays when they become available is likely to contribute new information about the epidemiology and disease patterns of *M. catarrhalis*.

TREATMENT

A proportion of cases of *M. catarrhalis* otitis media resolve spontaneously. Treatment of otitis media is empirical, and clinicians are advised to follow guidelines of the American Academy of Pediatrics (see Chapter 640).

Strains of *M. catarrhalis* rapidly acquired β-lactamase worldwide in the 1970s and 1980s, rendering essentially all strains resistant to amoxicillin. Antimicrobial susceptibility patterns have remained relatively stable since then. Most strains of *M. catarrhalis* are susceptible to amoxicillin/clavulanic acid, extended-spectrum cephalosporins, macrolides (azithromycin, clarithromycin), trimethoprim/sulfamethoxazole, and fluoroquinolones.

PREVENTION

Vaccines to prevent otitis media and other infections caused by *M. catarrhalis* are under development, but none is available yet.

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Chapter 197

Pertussis (*Bordetella pertussis* and *Bordetella parapertussis*)

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Pertussis is an acute respiratory tract infection that was well described initially in the 1500s. Sydenham first used the term *pertussis,* meaning intense cough, in 1670; it is preferable to *whooping cough* because most infected individuals do not "whoop."

ETIOLOGY

Bordetella pertussis is the cause of epidemic pertussis and the usual cause of sporadic pertussis. *Bordetella parapertussis* is an occasional cause of sporadic pertussis that contributes significantly to total cases of pertussis in Eastern and Western Europe but accounts for <5% of *Bordetella* isolates in the United States. *B. pertussis* and *B. parapertussis*

are exclusive pathogens of humans and some primates. *Bordetella holmesii*, first identified as a cause of bacteremia in immunocompromised hosts, is also reported to cause pertussis-like cough illness in healthy persons in Japan, France, and the United States. *Bordetella bronchiseptica* is a common animal pathogen. Occasional reports in humans describe a variety of body sites involved, and cases typically occur in immunocompromised persons or young children with intense exposure to animals. Protracted coughing (which in some cases is paroxysmal) can be caused by *Mycoplasma,* parainfluenza viruses, influenza viruses, enteroviruses, respiratory syncytial viruses, or adenoviruses.

EPIDEMIOLOGY

Estimates from the World Health Organization suggest that in 2008, approximately 16 million cases of pertussis and 195,000 childhood deaths occurred worldwide, 95% of which were in developing countries. The World Health Organization also estimated that in 2008, 82% of infants worldwide received 3 doses of pertussis vaccine, and that global vaccination against pertussis averted 687,000 deaths. Before vaccination was available, pertussis was the leading cause of death from communicable disease among children younger than 14 yr of age in the United States, with 10,000 deaths annually. Widespread use of whole-cell pertussis vaccine (DTP) led to a >99% decline in cases. After the low number of 1,010 cases in the United States reported in 1976, there was an increase in annual pertussis incidence to 1.2 cases per 100,000 population from 1980 through 1989, with epidemic pertussis in many states in 1989-1990, 1993, and 1996. Since then, pertussis has become increasingly endemic, with shifting burden of disease to young infants, adolescents, and adults. By 2004, the incidence of reported pertussis in the United States was 8.9 cases per 100,000 in the general population and approximately 150 per 100,000 in infants younger than 2 mo of age, resulting in a total of 25,827 cases, the highest number since 1959. Prospective and serologic studies suggested that pertussis is underrecognized, especially among adolescents and adults, in whom the actual number of cases is estimated to be 600,000 annually. A number of studies documented pertussis in 13-32% of adolescents and adults with cough illness for longer than 7 days. A total of 40 pertussis-related deaths were reported in 2005, and 16 were reported in 2006; more than 90% of these cases occurred among young infants.

Universal recommendation of tetanus toxoid, reduced content diphtheria toxoid, and acellular pertussis antigens (Tdap) in 2006 for 11-12 year olds was aimed to enhance control. With >70% uptake of Tdap in adolescents, the burden of disease in young adolescents has fallen commensurately, but without evidence of herd protection of young infants or older adolescents or adults. In fact, a new epidemiology of pertussis has emerged in this decade, with substantial evidence of rapidly waning protection following acellular pertussis vaccines (both DTaP and Tdap) and especially in those who never received, that is, were not "primed" with, DTP (whole cell), which was replaced with DTaP down to dose 1 in 1997 in the United States. The more than 42,000 cases of pertussis reported in 2012 was the highest number in more than 50 yr; increased numbers of cases were reported in all except 1 state; 10 yr old children had the highest age-related incidence after young infants.

Neither natural disease nor vaccination provides complete or lifelong immunity against pertussis reinfection or disease. Subclinical reinfection undoubtedly contributed significantly to immunity against disease ascribed previously to both vaccine and prior infection. The resurgence of pertussis has been attributed to a variety of factors, including partial control of pertussis leading to less continuous exposure, increased awareness, improved diagnostics, suboptimal vaccines, waning vaccine-induced immunity, and pathogen adaptation. Pertussis is the only vaccine-preventable disease for which universal immunization in the United States is recommended that continues to be endemic.

PATHOGENESIS

Bordetella organisms are small, fastidious, Gram-negative coccobacilli that colonize only ciliated epithelium. The exact mechanism of disease symptomatology remains unknown. *Bordetella* species share a high degree of DNA homology among virulence genes. Only *B. pertussis* expresses **pertussis toxin** (PT), the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction). Injection of PT in experimental animals causes lymphocytosis immediately by rerouting lymphocytes to remain in the circulating blood pool but does not cause cough. PT appears to have a central, but not a singular, role in pathogenesis. *B. pertussis* produces an array of other biologically active substances, many of which are postulated to have a role in disease and immunity. After aerosol acquisition, **filamentous hemagglutinin**, some **agglutinogens** (especially fimbriae [Fim] types 2 and 3), and a 69-kDa nonfimbrial surface protein called **pertactin** (Prn) are important for attachment to ciliated respiratory epithelial cells. **Tracheal cytotoxin,** adenylate cyclase, and PT appear to inhibit clearance of organisms. Tracheal cytotoxin, dermonecrotic factor, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT. Both antibody and cellular immune responses follow infection and immunization. Antibody to PT neutralizes toxin, and antibody to Prn enhances opsonophagocytosis.

Pertussis is extremely contagious, with attack rates as high as 100% in susceptible individuals exposed to aerosol droplets at close range. High airborne transmission rates were shown in a baboon model of pertussis despite vaccinated with the acellular vaccine. *B. pertussis* does not survive for prolonged periods in the environment. Chronic carriage by humans is not documented. After intense exposure as in households, the rate of subclinical infection is as high as 80% in fully immunized or previously infected individuals. When carefully sought, a symptomatic source case can be found for most patients.

CLINICAL MANIFESTATIONS

Classically, pertussis is a prolonged disease, divided into catarrhal, paroxysmal, and convalescent stages. The **catarrhal stage** (1-2 wk) begins insidiously after an incubation period ranging from 3-12 days with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion. As initial symptoms wane, coughing marks the onset of the **paroxysmal stage** (2-6 wk). The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted cough on a single exhalation, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. *Posttussive emesis* is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have more than 1 episode hourly. As the paroxysmal stage fades into the **convalescent stage** (≥2 wk), the number, severity, and duration of episodes diminish.

Infants younger than 3 mo of age do not display the classic stages. The catarrhal phase lasts only a few days or is unnoticed, and then, after the most insignificant startle from a draft, light, sound, sucking, or stretching, a well-appearing young infant begins to choke, gasp, gag, and flail the extremities, with face reddened. Cough may not be prominent, especially in the early phase. Whoop infrequently occurs in infants younger than 3 mo of age who at the end of a paroxysm lack stature or muscular strength to create sudden negative intrathoracic pressure. Apnea and cyanosis can follow a coughing paroxysm, or apnea can occur without a cough. Apnea may be the only symptom. Apnea and cyanosis both are more common with pertussis than with neonatal infections from viruses, including respiratory syncytial virus. The paroxysmal and convalescent stages in young infants are lengthy. Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. Convalescence includes intermittent paroxysmal coughing throughout the 1st yr of life, including "exacerbations" with subsequent respiratory illnesses; these are not a result of recurrent infection or reactivation of *B. pertussis.*

Adolescents and previously immunized children have foreshortening of all stages of pertussis. Adults have no distinct stages. Classically, adolescents and adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, bursting headache, diminished awareness, and then a gasping breath, usually without a whoop. Posttussive emesis and intermittency of paroxysms separated by hours of well-being are specific clues to the diagnosis in adolescents and adults. At least 30% of older individuals with pertussis have nonspecific cough illness, distinguished only by duration, which usually is longer than 21 days.

Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

DIAGNOSIS

Pertussis should be suspected in any individual who has a pure or predominant complaint of cough, especially if the following features are absent: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales. For sporadic cases, a clinical case definition of cough of 14 days or longer duration with at least 1 associated symptom of paroxysms, whoop, or posttussive vomiting has a sensitivity of 81% and a specificity of 58% for confirmation of pertussis. Pertussis should be suspected in older children whose cough illness is escalating at 7-10 days and whose coughing episodes are not continuous. Pertussis should be suspected in infants younger than 3 mo of age with gagging, gasping, apnea, cyanosis, or an apparent life-threatening event. Sudden infant death occasionally is caused by *B. pertussis*.

Adenoviral infections usually are distinguishable by associated features, such as fever, sore throat, and conjunctivitis. *Mycoplasma* causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and frequent finding of rales on auscultation of the chest. Epidemics of *Mycoplasma* and *B. pertussis* in young adults can be difficult to distinguish on clinical grounds. Although pertussis often is included in the laboratory evaluation of young infants with afebrile pneumonia, *B. pertussis* is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales or wheezes that typify infection by *Chlamydia trachomatis,* or predominant lower respiratory tract signs that typify infection by respiratory syncytial virus. Unless an infant with pertussis has secondary pneumonia (and then appears ill), the findings on examination between paroxysms including respiratory rate are entirely normal.

Leukocytosis (15,000-100,000 cells/μL) caused by absolute lymphocytosis is characteristic in the catarrhal stage. Lymphocytes are of T- and B-lymphocyte origin and are normal small cells, rather than the large atypical lymphocytes seen with viral infections. Adults, partially immune children, and, occasionally, young infants may have less-impressive lymphocytosis. Absolute increase in neutrophils suggests a different diagnosis or secondary bacterial infection. Eosinophilia is not a manifestation of pertussis. A severe course and death are correlated with rapid-rise and extreme leukocytosis (median peak white blood cell count in fatal vs nonfatal cases, 94,000 vs 18,000/μL, respectively) and thrombocytosis (median peak platelet count in fatal vs nonfatal cases, 782,000 vs 556,000/μL, respectively). Chest radiographic findings are only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Parenchymal consolidation suggests secondary bacterial infection. Pneumothorax, pneumomediastinum, and subcutaneous emphysema can be seen occasionally.

Current methods for confirmation of infection by *B. pertussis* (i.e., culture, polymerase chain reaction [PCR], and serology) have limitations in sensitivity, specificity, or practicality, and relative value depends on the setting, phase of disease, and purpose of use (e.g., as clinical diagnostic vs epidemiologic tool). For culture, careful attention must be directed to specimen collection, transport, and isolation technique. The specimen is obtained with deep nasopharyngeal aspiration or with the use of a flexible swab, preferably a Dacron or calcium alginate–tipped swab, held in the posterior nasopharynx for 15-30 sec (or until cough occurs). A 1% casamino acid liquid is acceptable for holding a specimen up to 2 hr; Stainer-Scholte broth or Regan-Lowe semisolid transport medium is used for longer transport periods, up to 4 days. The preferred isolation media are Regan-Lowe charcoal agar with 10% horse blood and 5-40 μg/mL cephalexin, and Stainer-Scholte media with cyclodextrin resins. Cultures are incubated at 35-37°C in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Direct fluorescent antibody testing of potential isolates using specific antibody for *B. pertussis* and *B. parapertussis* maximizes recovery rates. PCR testing on nasopharyngeal wash specimens has a sensitivity similar to that of culture and averts difficulties of isolation, but only standardized validated primers should be used. Results of culture and PCR are expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stages of disease. However, fewer than 20% of culture or PCR tests have positive results in partially or remotely immunized individuals tested in the paroxysmal stage. Serologic tests for detection of change in antibodies to *B. pertussis* antigens in acute and convalescent samples are the most sensitive tests in immunized individuals and are useful epidemiologically. A single serum sample showing immunoglobulin (Ig) G antibody to PT elevated >2 SD above the mean of the immunized population (>90 IU/mL) indicates recent symptomatic infection and usually is positive in the mid paroxysmal phase. Tests for IgA and IgM pertussis antibody, or antibody to antigens other than PT, are not reliable methods for serologic diagnosis of pertussis.

TREATMENT

Infants younger than 3 mo of age with suspected pertussis usually are admitted to hospital, as are many between 3 and 6 mo of age unless witnessed paroxysms are not severe, as well as are patients of any age if significant complications occur. Prematurely born young infants have a high risk for severe, potentially fatal disease, and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have increased risk of poor outcome beyond infancy. Table 197-1 lists caveats in assessment and care of infants with pertussis. The specific, limited goals of hospitalization are to: (1) assess progression of disease and likelihood of life-threatening events at peak of disease; (2) maximize nutrition; (3) prevent or treat complications; and (4) educate parents in the natural history of the disease and in care that will be given at home. Heart rate, respiratory rate, and pulse oximetry are monitored continuously with alarm settings so that paroxysms can be witnessed and recorded by healthcare personnel. Detailed cough records and documentation of feeding, vomiting, and weight change provide data to assess severity. Typical paroxysms that are not life-threatening have the following features: duration <45 sec; red but not blue color change; tachycardia, bradycardia (not <60 beats/min in

Table 197-1 Caveats in Assessment and Care of Infants with Pertussis

- Infants with potentially fatal pertussis may appear well between episodes.
- A paroxysm must be witnessed before a decision is made between hospital and home care.
- Only analysis of carefully compiled cough record permits assessment of severity and progression of illness.
- Suctioning of nose, oropharynx, or trachea should not be performed on a "preventive" schedule.
- Feeding in the period following a paroxysm may be more successful than after napping.
- Family support begins at the time of hospitalization with empathy for the child's and family's experience to date, transfer of the burden of responsibility for the child's safety to the healthcare team, and delineation of assessments and treatments to be performed.
- Family education, recruitment as part of the team, and continued support after discharge are essential.

infants), or oxygen desaturation that spontaneously resolves at the end of the paroxysm; whooping or strength for brisk self-rescue at the end of the paroxysm; self-expectorated mucus plug; and posttussive exhaustion but not unresponsiveness. Assessing the need to provide oxygen, stimulation, or suctioning requires skilled personnel who can watchfully observe an infant's ability for self-rescue but who will intervene rapidly and expertly when necessary. The benefit of a quiet, dimly lighted, undisturbed, comforting environment cannot be overestimated or forfeited in a desire to monitor and intervene. Feeding children with pertussis is challenging. The risk of precipitating cough by nipple feeding does not warrant nasogastric, nasojejunal, or parenteral alimentation in most infants. The composition or thickness of formula does not affect the quality of secretions, cough, or retention. Large-volume feedings are avoided.

Within 48-72 hr, the direction and severity of disease are obvious from analysis of recorded information. Many infants have marked improvement upon hospitalization and antibiotic therapy, especially if they are hospitalized early in the course of disease or have been removed from aggravating environmental smoke, excessive stimulation, or a dry or polluting heat source. Hospital discharge is appropriate if over a 48-hr period disease severity is unchanged or diminished, intervention is not required during paroxysms, nutrition is adequate, no complication has occurred, and parents are adequately prepared for care at home. Apnea and seizures occur in the incremental phase of illness and in patients with complicated disease. Portable oxygen, monitoring, or suction apparatus should not be needed at home.

Infants who have apnea, paroxysms that repeatedly lead to life-threatening events despite passive delivery of oxygen, or respiratory failure require intubation, pharmaceutically induced paralysis, and ventilation.

Antibiotics

An antimicrobial agent always is given when pertussis is suspected or confirmed, primarily to limit the spread of infection and secondarily for possible clinical benefit. Macrolides are preferred agents and are similar to one another in terms of in vitro activity (Table 197-2). Resistance has been reported rarely. A 7-10–fold relative risk for infantile hypertrophic pyloric stenosis has been reported in neonates treated with orally administered erythromycin. Azithromycin is the preferred agent in all age groups; rare cases of infantile hypertrophic pyloric stenosis have followed its use in neonates. All young infants treated with any macrolide should be monitored for symptoms of pyloric stenosis. Benefits of postexposure prophylaxis for infants far outweigh risk of infantile hypertrophic pyloric stenosis. The FDA also warns of risk of fatal heart rhythms with use of azithromycin in patients already at risk for cardiovascular events, especially those with prolongation of the QT interval.

Adjunct Therapies

No rigorous clinical trial has demonstrated a beneficial effect of β_2-adrenergic stimulants such as salbutamol and albuterol. Fussing associated with aerosol treatment triggers paroxysms. No randomized, blinded clinical trial of sufficient size has been performed to evaluate the usefulness of corticosteroids in the management of pertussis; their clinical use is not warranted. A randomized, double blind, placebo-controlled trial of pertussis intravenous immunoglobulin was halted prematurely because of expiration/lack of additional supply of study product; there was no indication of clinical benefit. Standard intravenous immunoglobulin has not been studied and should not be used for treatment or prophylaxis.

Isolation

Patients with suspected pertussis are placed in isolation with droplet precautions to reduce close respiratory or mucous membrane contact with respiratory secretions. All healthcare personnel should wear a mask upon entering the room. Screening for cough should be performed upon entrance of patients to emergency departments, offices, and clinics to begin isolation immediately and until 5 days after initiation of macrolide therapy. Children and staff with pertussis in childcare facilities or schools should be excluded until macrolide has been taken for 5 days.

Care of Household and Other Close Contacts

A macrolide agent should be given promptly to all household contacts and other close contacts, such as those in daycare, regardless of age, history of immunization, and symptoms (see Table 197-2). The same drugs and age-related doses used for treatment are used for prophylaxis. Visitation and movement of coughing family members in the

Table 197-2 Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, By Age Group

	Primary Agents		Alternate Agent*	
AGE GROUP	**AZITHROMYCIN**	**ERYTHROMYCIN**	**CLARITHROMYCIN**	**TMP-SMZ**
<1 mo	Recommended agent 10 mg/kg/day in a single dose for 5 days (only limited safety data available)	Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants <2 mo of age (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	Contraindicated at age <2 mo For infants age ≥2 mo: TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses for 14 days
Infants age ≥6 mo and children	10 mg/kg in a single dose on day 1 (maximum: 500 mg), then 5 mg/kg/day (maximum: 250 mg) on days 2-5	40-50 mg/kg/day (maximum: 2 g/day) in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses (maximum: 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in 2 divided doses (maximum TMP: 320 mg/day) for 14 days
Adults	500 mg in a single dose on day 1 then 250 mg/day on days 2-5	2 g/day in 4 divided doses for 14 days	1 g/day in 2 divided doses for 7 days	TMP 320 mg/day, SMZ 1,600 mg/day in 2 divided doses for 14 days

*Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients age ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

From Centers for Disease Control and Prevention (CDC): Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines, MMWR Morb Mortal Wkly Rep *54:1–16, 2005.*

hospital must be assiduously controlled until a macrolide has been taken for 5 days. In close contacts younger than 7 yr of age who have received fewer than 4 doses of pertussis-containing vaccines, DTaP should be initiated or continued to complete the recommended series. Children younger than 7 yr of age who received a 3rd dose more than 6 mo before exposure or a 4th dose 3 yr or more before exposure should receive a DTaP booster dose. Individuals 9 yr of age or older should be given Tdap if they have not received Tdap previously. Unmasked healthcare personnel exposed to untreated cases should be evaluated for postexposure prophylaxis and follow-up. Coughing healthcare personnel with or without known exposure to pertussis should be promptly evaluated for pertussis.

COMPLICATIONS

Infants younger than 6 mo of age have excessive mortality and morbidity; infants younger than 2 mo of age have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), and death (1%). Infants younger than 4 mo of age account for 90% of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis. Neonates with pertussis have substantially longer hospitalizations, greater need for oxygen, and greater need for mechanical ventilation than neonates with viral respiratory tract infection.

The principal complications of pertussis are apnea, secondary infections (such as otitis media and pneumonia), and physical sequelae of forceful coughing. Fever, tachypnea or respiratory distress between paroxysms, and absolute neutrophilia are clues to pneumonia. Expected pathogens include *Staphylococcus aureus, Streptococcus pneumoniae,* and bacteria of oropharyngeal flora. Increased intrathoracic and intraabdominal pressure during coughing can result in conjunctival and scleral hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system and retina, pneumothorax and subcutaneous emphysema, and umbilical and inguinal hernias. Laceration of the lingual frenulum occurs occasionally.

The need for intensive care and mechanical ventilation usually is limited to infants younger than 3 mo of age and infants with underlying conditions. Respiratory failure from apnea may precipitate need for intubation and ventilation through the days when disease peaks; prognosis is good. Progressive pulmonary hypertension in very young infants and secondary bacterial pneumonia are severe complications of pertussis and are the usual causes of death. Pulmonary hypertension and cardiogenic shock with fatal outcome are associated with extreme elevations of lymphocyte and platelet counts. Autopsies in fatal cases show luminal aggregates of leukocytes in the pulmonary vasculature. Extracorporeal membrane oxygenation of infants with pertussis in whom mechanical ventilation failed has been associated with >80% fatality (questioning the advisability of this procedure). Exchange transfusion or leukapheresis, however, is associated with drops in lymphocyte and platelet counts, with recovery in several reported cases. Echocardiography should be performed in critically ill infants with pertussis to detect presence of pulmonary hypertension and to intervene expeditiously.

Central nervous system abnormalities occur at a relatively high frequency in pertussis and are almost always a result of hypoxemia or hemorrhage associated with coughing or apnea in young infants. Apnea or bradycardia or both may result from apparent laryngospasm or vagal stimulation just before a coughing episode, from obstruction during an episode, or from hypoxemia following an episode. Seizures usually are a result of hypoxemia, but hyponatremia from excessive secretion of antidiuretic hormone during pneumonia can occur. The only neuropathology documented in pertussis is parenchymal hemorrhage and ischemic necrosis.

Bronchiectasis has been reported rarely after pertussis. Children who have pertussis before the age of 2 yr may have abnormal pulmonary function into adulthood.

PREVENTION

Universal immunization of children with pertussis vaccine, beginning in infancy with reinforcing dose(s) through adolescence and adulthood, is central to the *control* of pertussis. *Prevention* of pertussis in young infants depends on universal maternal immunization during every pregnancy and focused full immunization of contacts, both children and adults of all ages (see Chapter 172).

DTaP Vaccines

Several diphtheria and tetanus toxoids combined with acellular pertussis vaccines (DTaP) or combination products currently are licensed in the United States for children younger than 7 yr of age. DTaP vaccines have fewer adverse effects than the vaccines containing whole-cell pertussis (DTP), which are not available in the United States but are given to infants and children in many other countries. Acellular pertussis vaccines all contain inactivated PT and 2 or more other bacterial components (filamentous hemagglutinin, Prn, and Fim 2 and 3). Clinical efficacy against severe pertussis, defined as paroxysmal cough for longer than 21 days, is approximately 85%. Mild local and systemic adverse events as well as more serious events (including high fever, persistent crying for 3 hr or longer, hypotonic hyporesponsive episodes, and seizures) occur significantly less frequently among infants who receive DTaP than in those who receive DTP vaccine. DTaP-containing vaccines can be administered simultaneously with any other vaccines used in standard schedules for children.

Four doses of DTaP should be administered during the 1st 2 yr of life, generally at ages 2, 4, 6, and 15-18 mo of age. The 4th dose may be administered as early as 12 mo of age, provided that 6 mo have elapsed since the 3rd dose. The 5th dose of DTaP is recommended for children at 4-6 yr of age; a 5th dose is not necessary if the 4th dose in the series is administered on or after the 4th birthday. DTaP should not be given to a neonate because of interference with subsequent infant immunizations, but commencement of vaccination at 6 wk of age, with monthly doses through the 3rd dose, can be considered in high-risk settings.

When feasible, the same DTaP product is recommended for all doses of the primary vaccination series. Local reactions increase in rate and severity with successive doses of DTaP, although never reaching the magnitude of reactions following similar doses of DTP. Swelling of the entire thigh or upper arm, sometimes accompanied by pain, erythema, and fever, has been reported in 2-3% of vaccinees after the 4th or 5th dose of a variety of DTaP products. Limitation of activity is less than might be expected. Swelling subsides spontaneously without sequelae. The pathogenesis is unknown. Extensive limb swelling after the 4th dose of DTaP usually is not associated with a similar reaction to the 5th dose and is not a contraindication to subsequent dose(s) of pertussis vaccines.

Exempting children from pertussis immunization should be considered only within the narrow limits as recommended. Exemptors have significantly increased risk for pertussis and play a role in outbreaks of pertussis among immunized populations. Although well-documented pertussis confers short-term protection, the duration of protection is unknown; immunization should be completed on schedule in children diagnosed with pertussis. Improper vaccine storage reduces immunity.

Tdap Vaccines

Two tetanus toxoid, reduced-diphtheria toxoid, and acellular pertussis antigen vaccine (Tdap) products were licensed in 2005 and were recommended universally in 2006 for use in individuals 11-18 yr of age and in older individuals as a single-dose booster vaccine to provide protection against tetanus, diphtheria, and pertussis. The preferred age for Tdap vaccination is 11-12 yr. Recommendations for Tdap have expanded through 2012. All adolescents and adults of any age (including 65 yr of age and older) who have not received Tdap should receive a single dose of Tdap regardless of interval since Td. Pregnant women should be given Tdap during every pregnancy to provide passive antibody protection to the infant until administration of DTaP. Optimal timing of maternal Tdap is 26 through 37 wk of gestation but Tdap can be given at any time during pregnancy. Special effort should be made to ensure that contacts of infants have received DTaP or Tdap as is universally recommended. There is no recommendation for Tdap

revaccination of persons other than pregnant women. Relatively lower burden of pertussis in older adolescents and adults, modest Tdap effectiveness, and rapidly waning protection do not support cost-effectiveness of routine revaccination. There is no contraindication to concurrent administration of any other indicated vaccine. A single dose of Tdap is recommended for children 7-10 yr old who had incomplete pertussis vaccination prior to age 7 yr.

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Chapter 198

Salmonella

Zulfiqar Ahmed Bhutta

Salmonellosis is a common and widely distributed foodborne disease that is a global major public health problem affecting millions of individuals and resulting in significant mortality.

Salmonellae live in the intestinal tracts of warm- and cold-blooded animals. Some species are ubiquitous, whereas others are specifically adapted to a particular host.

The sequencing of the *Salmonella enterica* serovar Typhi (previously called *Salmonella typhi*) and *Salmonella typhimurium* genomes indicates an almost 95% genetic homology between the organisms. However, the clinical diseases caused by the 2 organisms differ considerably. Orally ingested salmonellae survive at the low pH of the stomach and evade the multiple defenses of the small intestine so as to gain access to the epithelium. Salmonellae preferentially enter M cells, which transport them to the lymphoid cells (T and B) in the underlying Peyer patches. Once across the epithelium, *Salmonella* serotypes that are associated with systemic illness enter intestinal macrophages and disseminate throughout the reticuloendothelial system. By contrast, nontyphoidal *Salmonella* (NTS) serovars induce an early local inflammatory response, which results in the infiltration of polymorphonuclear leukocytes into the intestinal lumen and diarrhea. The NTS serovars cause a gastroenteritis of rapid onset and brief duration, in contrast to typhoid fever, which has a considerably longer incubation period and duration of illness and in which systemic illness predominates and only a small proportion of children get diarrhea. These differences in the manifestations of infection by the 2 groups of pathogens, 1 predominantly causing intestinal inflammation and the other leading to systemic disease, may be related to specific genetic pathogenicity islands in the organisms. NTS serovars are unable to overcome defense mechanisms that limit bacterial dissemination from the intestine to systemic circulation in immunocompetent individuals and produce a self-limiting gastroenteritis. In contrast, *S. typhi* may possess unique virulence traits that allow it to overcome mucosal barrier functions in immunocompetent hosts, resulting in a severe systemic illness. Interestingly, the frequencies of typhoid fever in immunocompetent and immunocompromised individuals do not differ. Nonetheless, invasive nontyphoidal salmonellae strains have been noted in Africa among HIV-positive adults and among children with either HIV, malaria, or malnutrition. The presentation may be more like typhoid fever than gastroenteritis.

The nomenclature of *Salmonella* reflects the species name *Salmonella enterica* with a number of serovars. *Salmonella* nomenclature has undergone considerable alterations. The original taxonomy was based on clinical syndromes *(S. typhi, Salmonella choleraesuis, Salmonella paratyphi).* With adoption of serologic analysis, a *Salmonella* species was defined subsequently as "a group of related fermentation phagetype," with the result that each *Salmonella* serovar was regarded as a species in itself. Although this classification is simplistic, its use until 2004 resulted in identification of 2,501 serovars of *Salmonella,* which led to the need for further categorization to aid communication among scientists, public health officials, and the public.

All *Salmonella* serovars form a single DNA hybridization group, a single species called *S. enterica* composed of several subspecies (Table 198-1). Each subspecies contains various serotypes defined by the O and H antigens. To further simplify the nomenclature for physicians and epidemiologists, the names for the common serovars are kept for subspecies I strains, which represent >99.5% of the *Salmonella* strains isolated from humans and other warm-blooded animals.

198.1 Nontyphoidal Salmonellosis

Zulfiqar Ahmed Bhutta

ETIOLOGY

Salmonellae are motile, nonsporulating, nonencapsulated, Gram-negative rods that grow aerobically and are capable of facultative anaerobic growth. They are resistant to many physical agents but can be killed by heating to 54.4°C (130°F) for 1 hr or 60°C (140°F) for 15 min. They remain viable at ambient or reduced temperatures for days and may survive for weeks in sewage, dried foodstuffs, pharmaceutical agents, and fecal material. Like other members of the family Enterobacteriaceae, *Salmonella* possesses somatic O antigens and flagellar H antigens.

With the exception of a few serotypes that affect only 1 or a few animal species, such as *Salmonella dublin* in cattle and *S. choleraesuis* in pigs, most serotypes have a broad host spectrum. Typically, such strains cause gastroenteritis that is often uncomplicated and does not need treatment but can be severe in the young, the elderly, and patients with weakened immunity. The causes are typically *Salmonella* Enteritidis (*Salmonella enterica* serotype Enteritidis) and *Salmonella* Typhimurium (*S. enterica* serotype Typhimurium), the 2 most important serotypes for salmonellosis transmitted from animals to humans.

Table 198-1 *Salmonella* Species, Subspecies, and Serotypes and Their Usual Habitats

SALMONELLA SPECIES AND SUBSPECIES	NO. OF SEROTYPES WITHIN SUBSPECIES	USUAL HABITAT
S. enterica subsp. *enterica* (I)	1504	Warm-blooded animals
S. enterica subsp. *salmae* (II)	502	Cold-blooded animals and the environment*
S. enterica subsp. *arizonae* (IIIa)	95	Cold-blooded animals and the environment*
S. enterica subsp. *diarizonae* (IIIb)	333	Cold-blooded animals and the environment*
S. enterica subsp. *houtenae* (IV)	72	Cold-blooded animals and the environment*
S. enterica subsp. *indica* (VI)	13	Cold-blooded animals and the environment*
S. bongori (V)	22	Cold-blooded animals and the environment*
Total	2541	

*Isolates of all species and subspecies have occurred in humans.

Data from Popoff MY, Bockemühl J, Gheesling LL. Supplement 2002 (No. 46) to the Kauffmann-White scheme. Res Microbiol 155:568-570, 2004.

Nontyphoidal salmonellae have emerged as a major cause of bacteremia in Africa, especially among populations with a high incidence of HIV infection.

EPIDEMIOLOGY

Salmonellosis constitutes a major public health burden and represents a significant cost to society in many countries. Typhoid fever caused by this organism is a global problem, with more than 27 million cases worldwide each year, culminating in an estimated 217,000 deaths. Although there is little information on the epidemiology and the burden of *Salmonella* gastroenteritis in developing countries, *Salmonella* infections are recognized as major causes of childhood diarrheal illness. With the growing burden of HIV infections and malnutrition in Africa, NTS bacteremic infections have emerged as a major cause of morbidity and mortality among children and adults.

NTS infections have a worldwide distribution, with an incidence proportional to the standards of hygiene, sanitation, availability of safe water, and food preparation practices. In the developed world, the incidence of *Salmonella* infections and outbreaks has increased severalfold over the past few decades, which may be related to modern practices of mass food production that increase the potential for epidemics. The incidence of infections with NTS serovars, such as *S. enterica* serovar Typhimurium and *S.* Enteritidis cause a significant disease burden, with an estimated 93.8 million cases worldwide and 155,000 deaths each year. *Salmonella* gastroenteritis accounts for more than half of all episodes of bacterial diarrhea in the United States, with incidence peaks at the extremes of ages, among young infants and the elderly. Most human infections have been caused by *S.* Enteritidis; the prevalence of this organism has decreased over the past decade, with *S.* Typhimurium overtaking it in some countries.

The rise in *Salmonella* infections in many parts of the world over the past 3 decades may also be related to intensive animal husbandry practices, which selectively promote the rise of certain strains, especially drug-resistant varieties that emerge in response to the use of antimicrobials in food animals. Poultry products were traditionally regarded as a common source of salmonellosis, but consumption of a range of foods is now associated with outbreaks, including fruits and vegetables. Although this change in epidemiology may be related to selective pressure from the use of antimicrobials, there may be other factors, such as the rise of strains with a selective propensity to develop resistance and virulence. It appears that multidrug-resistant strains of *Salmonella* are more virulent than susceptible strains and that poorer outcome does not simply relate to the delay in treatment response because of empirical choice of an ineffective antibiotic. Strains of multidrug-resistant *Salmonella,* such as *S.* Typhimurium phage type DT104, harbor a genomic island that contains many of the drug-resistance genes. It is possible that these integrons also contain genes that encode virulence factors. The global spread of multidrug-resistant *S.* Typhimurium phage type DT104 in animals and humans may be related to the growing use of antimicrobials and may be facilitated by international and national trade of infected animals.

Several risk factors are associated with outbreaks of *Salmonella* infections. Animals constitute the principal source of human NTS disease, and cases have occurred in which individuals have had contact with infected animals, including domestic animals such as cats, dogs, reptiles, pet rodents, and amphibians. Specific serotypes may be associated with particular animal hosts; children with *S. enterica* serovar Marina typically have exposure to pet lizards. NTS serovars usually cause self-limiting diarrhea with secondary bacteremia occurring in less than 10% of patients. The NTS serovars have a broad host range, including poultry and cattle, and NTS infection is commonly from food poisoning in developed countries.

Domestic animals probably acquire the infection in the same way that humans do, through consumption of contaminated raw meat, poultry, or poultry-derived products. Animal feeds containing fishmeal or bone meal contaminated with *Salmonella* are an important source of infection for animals. Moreover, subtherapeutic concentrations of antibiotics are often added to animal feed to promote growth. Such practices promote the emergence of antibiotic-resistant bacteria, including *Salmonella,* in the gut flora of the animals, with subsequent contamination of their meat. There is strong evidence to link resistance of *S.* Typhimurium to fluoroquinolones with the use of this group of antimicrobials in animal feeds. Animal-to-animal transmission can occur, but most infected animals are asymptomatic.

An increasing number of produce-associated foodborne outbreaks in the United States that are associated with bacterial contamination are primarily from *Salmonella.* Although almost 80% of *Salmonella* infections are discrete, outbreaks can pose an inordinate burden on public health systems. During 1998-2008, a total of 1,491 outbreaks of *Salmonella* infections were reported to the Foodborne Disease Outbreak Surveillance System, and 80% of these were caused by a single serotype. Of the single-serotype outbreaks, 50% had an implicated food and 34% could be assigned to a single food commodity. Of the 47 serotypes reported, the 4 most common, causing more than two-thirds of the outbreaks, included Enteritidis, Typhimurium, Newport, and Heidelberg. Overall, eggs were the most commonly implicated food, followed by chicken, pork, beef, fruit, and turkey. *Salmonella* infections in chickens increase the risk for contamination of eggs, and both poultry and eggs are regarded as a dominant cause of common-source outbreaks. However, a growing proportion of *Salmonella* outbreaks are also associated with other food sources. The food sources include many fruits and vegetables, such as tomatoes, sprouts, watermelon, cantaloupe, lettuce, and mangoes.

In addition to the effect of antibiotic use in animal feeds, the relationship of *Salmonella* infections to prior antibiotic use among children in the previous month is well recognized. This increased risk for infection in people who have received antibiotics for an unrelated reason may be related to alterations in gut microbial ecology, which predispose them to colonization and infection with antibiotic-resistant *Salmonella* isolates. These resistant strains of *Salmonella* are also more virulent. The Centers for Disease Control and Prevention (CDC) reports resistance to ceftriaxone in approximately 3% of NTS tested and some level of resistance to ciprofloxacin in approximately 3% of isolates. Approximately 5% of NTS tested by the CDC are resistant to 5 or more types of drugs. Consequently, costs are also expected to be higher for resistant than for susceptible infections because of the severity of the former. Those patients are more likely to be hospitalized, and treatment is rendered less effective. The CDC is seeing some level of resistance to ciprofloxacin in two-thirds of *Salmonella* Typhi tested. The CDC has not yet detected resistance to ceftriaxone or azithromycin in the United States, but resistance to these antibiotics has been seen in other parts of the world.

Given the ubiquitous nature of the organism, nosocomial infections with NTS strains can also occur through contaminated equipment and diagnostic or pharmacologic preparations, particularly those of animal origin (pancreatic extracts, pituitary extracts, bile salts). Hospitalized children are at increased risk for severe and complicated *Salmonella* infections, especially with drug-resistant organisms.

PATHOGENESIS

The estimated number of bacteria that must be ingested to cause symptomatic disease in healthy adults is 10^6-10^8 *Salmonella* organisms. The gastric acidity inhibits multiplication of salmonellae, and most organisms are rapidly killed at gastric pH ≤2.0. Achlorhydria, buffering medications, rapid gastric emptying after gastrectomy or gastroenterostomy, and a large inoculum enable viable organisms to reach the small intestine. Neonates and young infants have hypochlorhydria and rapid gastric emptying, which contribute to their increased vulnerability to symptomatic salmonellosis. In infants who typically take fluids, the inoculum size required to produce disease is also comparatively smaller because of faster transit through the stomach.

Once they reach the small and large intestines, the ability of *Salmonella* organisms to multiply and cause infection depends on both the infecting dose and competition with normal flora. Prior antibiotic therapy may alter this relationship, as might factors such as coadministration of antimotility agents. The typical intestinal mucosal response to NTS infection is an enterocolitis with diffuse mucosal inflammation and edema, sometimes with erosions and microabscesses. *Salmonella*

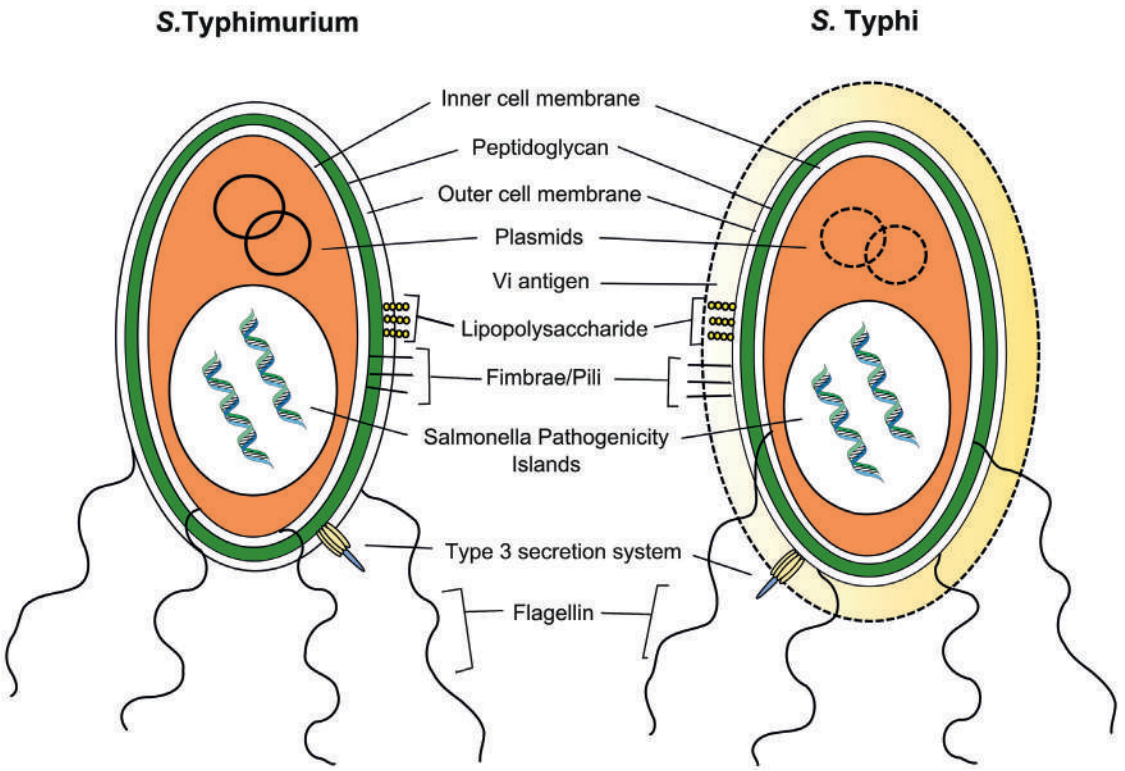

Figure 198-1 Overlapping and distinct virulence systems in *Salmonella typhi* and nontyphoidal *Salmonella*. *(From de Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host-pathogen interaction in invasive Salmonellosis.* PLoS Pathog *2012;8(10):e1002933.)*

organisms are capable of penetrating the intestinal mucosa, although destruction of epithelial cells and ulcers are usually not found. Intestinal inflammation with polymorphonuclear leukocytes and macrophages usually involves the lamina propria. Underlying intestinal lymphoid tissue and mesenteric lymph nodes enlarge and may demonstrate small areas of necrosis. Such lymphoid hypertrophy may cause interference with the blood supply to the gut mucosa. Hyperplasia of the reticuloendothelial system is also found within the liver and spleen. If bacteremia develops, it may lead to localized infection and suppuration in almost any organ.

Both *S.* Typhi and NTS possess overlapping and distinct virulence systems (Fig. 198-1). Although *S.* Typhimurium can cause systemic disease in humans, intestinal infection usually results in a localized enteritis that is associated with a secretory response in the intestinal epithelium. Intestinal infection also induces secretion of interleukin (IL)-8 from the basolateral surface and other chemoattractants from the apical surface, directing recruitment and transmigration of neutrophils into the gut lumen and thus preventing the systemic spread of the bacteria (Fig. 198-2).

Central to *S.* Typhimurium pathogenesis are 2 type III secretion systems encoded within the pathogenicity islands SPI-1 and SPI-2 that are responsible for the secretion and translocation of a set of bacterial proteins termed effectors into host cells with the intention of altering host cell physiology for bacterial entry and survival. Thus, once delivered by the type III secretion systems, the secreted effectors play critical roles in manipulating the host cell to allow for bacterial invasion, induction of inflammatory responses, and the assembly of an intracellular protective niche created for bacterial survival and replication. The type III secretion system encoded on SPI-1 mediates invasion of the intestinal epithelium, whereas the type III secretion system encoded on SPI-2 is required for survival within macrophages. In addition, the expression of strong agonists of innate pattern recognition receptors (lipopolysaccharide and flagellin) is important for triggering a Toll-like receptor (TLR)–mediated inflammatory response. These observations suggest that *S.* Typhimurium must have acquired additional factors that further modulate the host response during infection.

Salmonella species invade epithelial cells in vitro by a process of bacteria-mediated endocytosis involving cytoskeletal rearrangement, disruption of the epithelial cell brush-border, and the subsequent formation of membrane ruffles (Fig. 198-3). An adherent and invasive phenotype of *S.* Enterica is activated under conditions similar to those found in the human small intestine (high osmolarity, low oxygen). The invasive phenotype is mediated in part by SPI-1, a 40-kb region that encodes regulator proteins such as HilA, the type III secretion systems involved in invasion of epithelial cells, and a variety of other products. In humans the Toll-like receptor–dependent IL-12/interferon (IFN)-λ is a major immunoregulatory system that bridges innate and adaptive immunity and is responsible for restricting the systemic spread of nontyphoidal *Salmonella*.

Shortly following invasion of the gut epithelium, invasive *Salmonella* organisms encounter macrophages within the gut-associated lymphoid tissue. The interaction between *Salmonella* and macrophages results in alteration in the expression of a number of host genes, including those encoding proinflammatory mediators (inducible nitric oxide synthase, chemokines, IL-1β), receptors or adhesion molecules (tumor necrosis factor [TNF]-α receptor, CD40, intercellular adhesion molecule 1), and antiinflammatory mediators (transforming growth factor-β1 and transforming growth factor-β2). Other upregulated genes include those involved in cell death or apoptosis (intestinal epithelial cell protease, TNF-R1, Fas) and transcription factors (early growth response 1, IFN regulatory factor 1). *S.* Typhimurium can induce rapid macrophage death in vitro, which depends on the host cell protein caspase-1 and is mediated by the effector protein SipB (*Salmonella* invasion protein B). Intracellular *S.* Typhimurium is found within specialized vacuoles that have diverged from the normal endocytic pathway. This ability to survive within monocytes/macrophages is essential for *S.* Typhimurium to establish a systemic infection in the mouse. The mucosal proinflammatory response to *S.* Typhimurium infection and the subsequent recruitment of phagocytic cells to the site may also facilitate systemic spread of the bacteria.

Some virulence traits are shared by all salmonellae, but others are serotype restricted. These virulence traits have been defined in tissue

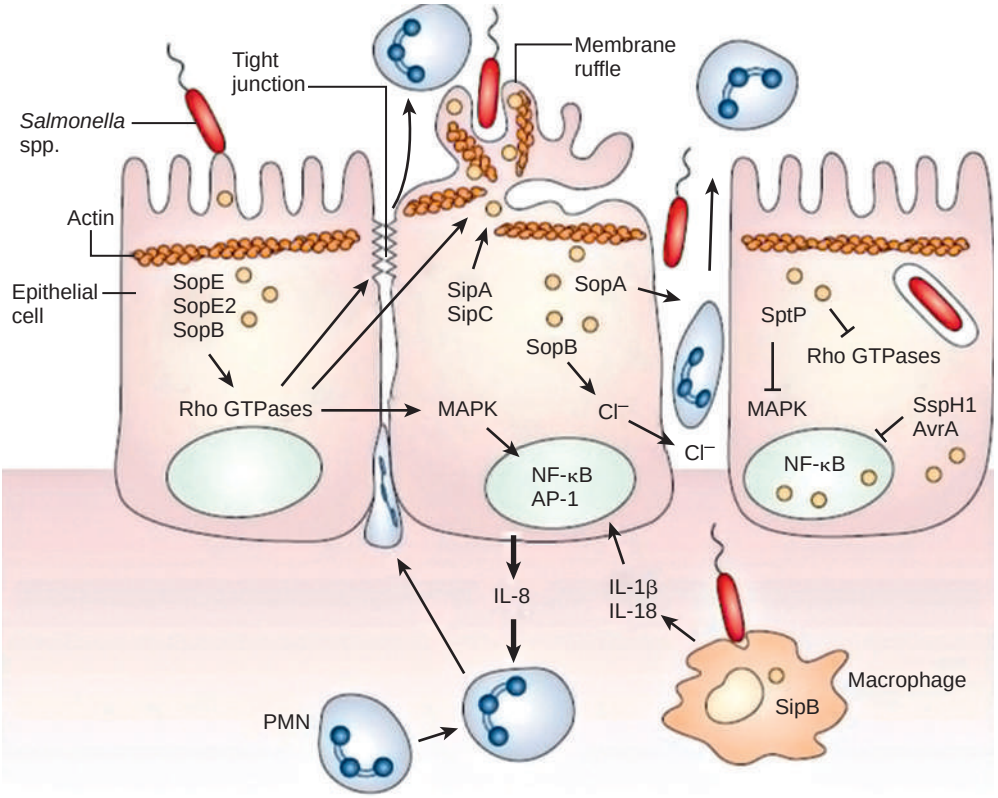

Figure 198-2 On contact with the epithelial cell, salmonellae assemble the *Salmonella* pathogenicity island 1-encoded type III secretion system (TTSS-1) and translocate effectors (*yellow spheres*) into the eukaryotic cytoplasm. Effectors such as SopE, SopE2, and SopB then activate host Rho guanosine triphosphatase (GTPase), resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase (MAPK) pathways, and destabilization of tight junctions. Changes in the actin cytoskeleton, which are further modulated by the actin-binding proteins SipA and SipC, lead to bacterial uptake. MAPK signaling activates the transcription factors activator protein-1 (AP-1) and nuclear factor-κB (NF-κB), which turn on production of the proinflammatory polymorphonuclear leukocyte (PMN) chemokine interleukin (IL)-8. SipB induces caspase-1 activation in macrophages, with the release of IL-1β and IL-18, augmenting the inflammatory response. In addition, SopB stimulates Cl^- secretion by its inositol phosphatase activity. The destabilization of tight junctions allows the transmigration of polymorphonuclear leukocytes (PMNs) from the basolateral to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. However, the transmigration of PMNs also occurs in the absence of tight-junction disruption and is further promoted by SopA. The actin cytoskeleton is restored, and MAPK signaling is turned off by the enzymatic activities of SptP. This also results in the down-modulation of inflammatory responses, to which SspH1 and AvrA also contribute by inhibiting activation of NF-κB. *(From Haraga A, Ohlson MB, Miller SI: Salmonellae interplay with host cells,* Nat Rev Microbiol *6:53–66, 2008.)*

culture and murine models, and it is likely that clinical features of human *Salmonella* infection will eventually be related to specific DNA sequences. With most diarrhea-associated nontyphoidal salmonelloses, the infection does not extend beyond the lamina propria and the local lymphatics. Specific virulence genes are related to the ability to cause bacteremia. These genes are found significantly more often in strains of *S.* Typhimurium isolated from the blood than in strains recovered from stool. Although both *S. dublin* and *S. choleraesuis* have a greater propensity to rapidly invade the bloodstream with little or no intestinal involvement, the development of disease after infection with *Salmonella* depends on the number of infecting organisms, their virulence traits, and several host defense factors. Various host factors may also affect the development of specific complications or clinical syndromes (Table 198-2) and of these, HIV infections are assuming greater importance in Africa in all age groups.

Bacteremia is possible with any *Salmonella* serotype, especially in individuals with reduced host defenses and especially in those with altered reticuloendothelial or cellular immune function. Thus, children with HIV infection, chronic granulomatous disease, and leukemia are more likely to develop bacteremia after *Salmonella* infection, although the majority of children with *Salmonella* bacteremia in Africa are HIV-negative. Children with *Schistosoma mansoni* infection and hepatosplenic involvement, as well as chronic malarial anemia, are also at a

Table 198-2 Host Factors and Conditions Predisposing to the Development of Systemic Disease with Nontyphoidal *Salmonella* Strains

Neonates and young infants (≤3 mo of age)
HIV/AIDS
Other immunodeficiencies and chronic granulomatous disease
Immunosuppressive and corticosteroid therapies
Malignancies, especially leukemia and lymphoma
Hemolytic anemia, including sickle cell disease, malaria, and bartonellosis
Collagen vascular disease
Inflammatory bowel disease
Achlorhydria or use of antacid medications
Impaired intestinal motility
Schistosomiasis, malaria
Malnutrition

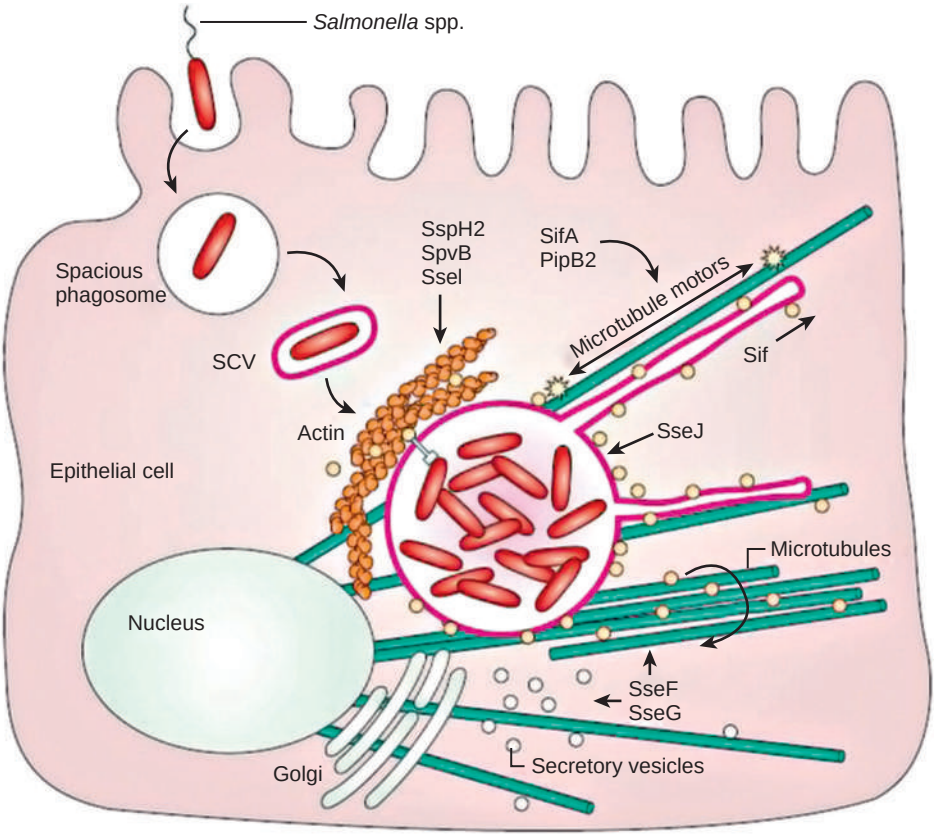

Figure 198-3 Formation of the *Salmonella*-containing vacuole (SCV) and induction of the *Salmonella* pathogenicity island 2 (SPI-2) type III secretion system (TTSS) within the host cell. Shortly after internalization by macropinocytosis, salmonellae are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, and is called the SCV. It contains the endocytic marker lysosomal-associated membrane protein 1 (LAMP-1; *purple*). The *Salmonella* SPI-2 is induced within the SCV and translocates effector proteins *(yellow spheres)* across the phagosomal membrane several hours after phagocytosis. The SPI-2 effectors SifA and PipB2 contribute to formation of *Salmonella*-induced filament along microtubules *(green)* and regulate microtubule motor *(yellow star shape)* accumulation on the Sif and the SCV. SseJ is a deacylase that is active on the phagosome membrane. SseF and SseG cause microtubule bundling adjacent to the SCV and direct Golgi-derived vesicle traffic toward the SCV. Actin accumulates around the SCV in a SPI-2 dependent manner, in which SspH2, SpvB, and SseI are thought to have a role. *(From Haraga A, Ohlson MB, Miller SI: Salmonellae interplay with host cells,* Nat Rev Microbiol *6:53–66, 2008.)*

greater risk for development of chronic salmonellosis. Children with sickle cell disease are at increased risk for *Salmonella* septicemia and osteomyelitis. This risk may be related to the presence of numerous infarcted areas in the gastrointestinal tract, bones, and reticuloendothelial system, as well as reduced phagocytic and opsonizing capacity of patients, which allow the organism to flourish.

Some inherited defects, such as IL-12 deficiency (IL-12β1 chain deficiency, IL-12p40 subunit deletion) are associated with increased risk for *Salmonella* infections, suggesting a key role for IL-12 in the clearance of *Salmonella*. IL-12 is produced by activated macrophages and is a potent inducer of IFN-γ by natural killer cells and T lymphocytes. Given the putative protective role of IL-12 against malarial infection, *Salmonella* infection of phagocytes may secondarily affect IL-12 production and thus produce a vicious circle of chronic malaria and *Salmonella* coinfection.

CLINICAL MANIFESTATIONS

Acute Enteritis

The most common clinical presentation of salmonellosis is acute enteritis. After an incubation period of 6-72 hr (mean: 24 hr), there is an abrupt onset of nausea, vomiting, and crampy abdominal pain, located primarily in the periumbilical area and right lower quadrant, followed by mild to severe watery diarrhea and sometimes by diarrhea containing blood and mucus. A large proportion of children with acute enteritis are febrile, although younger infants may exhibit a normal or subnormal temperature. Symptoms usually subside within 2-7 days in healthy children, and fatalities are rare. However, some children experience severe disease with a septicemia-like picture (high fever, headache, drowsiness, confusion, meningismus, seizures, abdominal distention). The stool typically contains a moderate number of polymorphonuclear leukocytes and occult blood. Mild leukocytosis may be detected.

Bacteremia

Although the precise incidence of bacteremia following *Salmonella* gastroenteritis is unclear, transient bacteremia can occur in 1-5% of children with *Salmonella* diarrhea. Bacteremia can occur with minimal associated symptoms in newborns and very young infants, but in older infants it typically follows gastroenteritis and can be associated with fever, chills, and septic shock. In patients with AIDS, recurrent septicemia appears despite antibiotic therapy, often with a negative stool culture result for *Salmonella* and sometimes with no identifiable focus of infection. NTS gastrointestinal infections commonly cause bacteremia in developing countries. High rates of invasive disease with *S.* Typhimurium and *S.* Enteritidis reported from Africa (38-70% of isolates) suggest an association with HIV infections and malaria.

Extraintestinal Focal Infections

Following bacteremia, salmonellae have the propensity to seed and cause focal suppurative infection of many organs. The most common focal infections involve the skeletal system, meninges, intravascular sites, and sites of preexisting abnormalities. The peak incidence of *Salmonella* meningitis is in infancy, and the infection may be

associated with a florid clinical course, high mortality, and neurologic sequelae in survivors.

COMPLICATIONS

Salmonella gastroenteritis can be associated with acute dehydration and complications that result from delayed presentation and inadequate treatment. Bacteremia in younger infants and immunocompromised individuals can have serious consequences and potentially fatal outcomes. *Salmonella* organisms can seed many organ systems, leading to osteomyelitis in children with sickle cell disease, among other infections. Reactive arthritis may follow *Salmonella* gastroenteritis, usually in adolescents with the HLA-B27 antigen.

In certain high-risk groups, especially those with impaired immunity, the course of *Salmonella* gastroenteritis may be more complicated. Neonates, infants younger than 6 mo, and children with primary or secondary immunodeficiency may have symptoms that persist for several weeks. The course of illness and complications may also be affected by coexisting pathologies. In children with AIDS, *Salmonella* infection frequently becomes widespread and overwhelming, causing multisystem involvement, septic shock, and death. In patients with inflammatory bowel disease, especially active ulcerative colitis, *Salmonella* gastroenteritis may lead to rapid development of toxic megacolon, bacterial translocation, and sepsis. In children with schistosomiasis, the *Salmonella* may persist and multiply within schistosomes, leading to chronic infection unless the schistosomiasis is effectively treated. Prolonged or intermittent bacteremia is associated with low-grade fever, anorexia, weight loss, diaphoresis, and myalgias and may occur in children with underlying problems and a reticuloendothelial system dysfunction such as hemolytic anemia or malaria.

DIAGNOSIS

Clinical features that are specific to *Salmonella* gastroenteritis and thus would allow differentiation from other bacterial causes of diarrhea are few. Definitive diagnosis of *Salmonella* infection is based on clinical correlation of the presentation and culture of and subsequent identification of *Salmonella* organisms from feces or other body fluids. In children with gastroenteritis, cultures of stools have higher yields than rectal swabs. In children with NTS gastroenteritis, prolonged fever lasting 5 or more days and young age should be recognized as risk factors closely associated with development of bacteremia. In patients with sites of local suppuration, aspirated specimens should be Gram-stained and cultured. *Salmonella* organisms grow well on nonselective or enriched media, such as blood agar, chocolate agar, and nutrient broth, but stool specimens containing mixed bacterial flora require a selective medium, such as MacConkey, xylose-lysine-deoxycholate, bismuth sulfite, or *Salmonella-Shigella* (SS) agar for isolation.

Although other rapid diagnostic methods, such as latex agglutination and immunofluorescence, have been developed for rapid diagnosis of *Salmonella* in cultures, there are few comparable tests for rapid serologic detection. Polymerase chain reaction techniques may offer a rapid alternative to classic cultures but are as yet not in widespread use in clinical settings.

TREATMENT

Appropriate therapy relates to the specific clinical presentation of *Salmonella* infection. In children with gastroenteritis, rapid clinical assessment, correction of dehydration and electrolyte disturbances, and supportive care are key (see Chapter 340). Antibiotics are not generally recommended for the treatment of isolated uncomplicated *Salmonella* gastroenteritis because they may suppress normal intestinal flora and prolong both the excretion of *Salmonella* and the remote risk for creating the chronic carrier state (usually in adults). However, given the risk for bacteremia in infants (<3 mo of age) and the risk of disseminated infection in high-risk groups with immune compromise (HIV, malignancies, immunosuppressive therapy, sickle cell anemia, immunodeficiency states), these children must receive an appropriate empirically chosen antibiotic until culture results are available (Table 198-3). The *S.* Typhimurium phage type DT104 strain is usually resistant to the following 5 drugs: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An increasing proportion of *S.* Typhimurium phage type DT104 isolates also have reduced susceptibility to fluoroquinolones. Given the higher mortality associated with multidrug-resistant *Salmonella* infections, it is necessary to perform susceptibility tests on all human isolates. Infections with suspected drug-resistant *Salmonella* should be closely monitored and treated with appropriate antimicrobial therapy.

Table 198-3 Treatment of *Salmonella* Gastroenteritis

ORGANISM AND INDICATION	DOSE AND DURATION OF TREATMENT
Salmonella infections in infants <3 mo of age or immunocompromised persons (in addition to appropriate treatment for underlying disorder)	Cefotaxime 100-200 mg/kg/day every 6-8 hr for 5-14 days *or* Ceftriaxone 75 mg/kg/day once daily for 7 days *or* Ampicillin 100 mg/kg/day every 6-8 hr for 7 days *or* Cefixime 15 mg/kg/day for 7-10 days

PROGNOSIS

Most healthy children with *Salmonella* gastroenteritis recover fully. However, malnourished children and children who do not receive optimal supportive treatment (see Chapters 58 and 340) are at risk for development of prolonged diarrhea and complications. Young infants and immunocompromised patients often have systemic involvement, a prolonged course, and extraintestinal foci. In particular, children with HIV infection and *Salmonella* infections can have a florid course.

After infection, NTS are excreted in feces for a median of 5 wk. A prolonged carrier state after nontyphoidal salmonellosis is rare (<1%) but may be seen in children with biliary tract disease and cholelithiasis after chronic hemolysis. Prolonged carriage of *Salmonella* organisms is rare in healthy children but has been reported in those with underlying immune deficiency. During the period of *Salmonella* excretion, the individual may infect others, directly by the fecal–oral route or indirectly by contaminating foods.

PREVENTION

Control of the transmission of *Salmonella* infections to humans requires control of the infection in the animal reservoir, judicious use of antibiotics in dairy and livestock farming, prevention of contamination of foodstuffs prepared from animals, and use of appropriate standards in food processing in commercial and private kitchens (Table 198-4). Because large outbreaks are often related to mass food production, it should be recognized that contamination of just 1 piece of machinery used in food processing may cause an outbreak; meticulous cleaning of equipment is essential. Clean water supply and education in handwashing and food preparation and storage are critical to reducing person-to-person transmission. *Salmonella* may remain viable when cooking practices prevent food from reaching a temperature greater than 65.5°C (150°F) for longer than 12 min. Parents should be advised of the risk of reptiles as pets in households with young infants.

In contrast to developed countries, relatively little is known about the transmission of NTS infections in developing countries, and it is likely that person-to-person transmission may be relatively more important in some settings. Although some vaccines have been used in animals, no human vaccine against NTS infections is currently available. Infections should be reported to public health authorities so that outbreaks can be recognized and investigated. Given the rapid rise of antimicrobial resistance among *Salmonella* isolates, it is imperative that there is rigorous regulation of the use of antimicrobials in animal feeds.

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Table 198-4	Recommendations for Preventing Transmission of *Salmonella* from Reptiles and Amphibians to Humans
Pet store owners, healthcare providers, and veterinarians should provide information to owners and potential purchasers of reptiles and amphibians about the risks for and prevention of salmonellosis from these pets.	
Persons at increased risk for infection or serious complications from salmonellosis (e.g., children <5 yr of age and immunocompromised persons) should avoid contact with reptiles and amphibians and any items that have been in contact with reptiles and amphibians.	
Reptiles and amphibians should be kept out of households that include children <5 yr of age or immunocompromised persons. A family expecting a child should remove any pet reptile or amphibian from the home before the infant arrives.	
Reptiles and amphibians should not be allowed in childcare centers.	
Persons should always wash their hands thoroughly with soap and water after handling reptiles and amphibians or their cages.	
Reptiles and amphibians should not be allowed to roam freely throughout a home or living area.	
Pet reptiles and amphibians should be kept out of kitchens and other food preparation areas. Kitchen sinks should not be used to bathe reptiles and amphibians or to wash their dishes, cages, or aquariums. If bathtubs are used for these purposes, they should be cleaned thoroughly and disinfected with bleach.	
Reptiles and amphibians in public settings (e.g., zoos and exhibits) should be kept from direct or indirect contact with patrons except in designated animal contact areas equipped with adequate handwashing facilities. Food and drink should not be allowed in animal contact areas.	

From the Centers for Disease Control and Prevention (CDC): Reptile-associated salmonellosis—selected states, 1998-2002, MMWR Morb Mortal Wkly Rep *52:1206–1210, 2003.*

198.2 Enteric Fever (Typhoid Fever)

Zulfiqar Ahmed Bhutta

Enteric fever (more commonly termed *typhoid fever*) remains endemic in many developing countries. Given the ease of modern travel, cases are regularly reported from most developed countries, usually from returning travelers.

ETIOLOGY

Typhoid fever is caused by *S. enterica* serovar Typhi (*S.* Typhi), a Gram-negative bacterium. A very similar but often less-severe disease is caused by *Salmonella* Paratyphi A and rarely by *S.* Paratyphi B (Schotmulleri) and *S.* Paratyphi C (Hirschfeldii). The ratio of disease caused by *S.* Typhi to that caused by *S.* Paratyphi is approximately 10:1, although the proportion of *S.* Paratyphi A infections is increasing in some parts of the world for reasons that are unclear. Although *S.* Typhi shares many genes with *Escherichia coli* and at least 95% of genes with *S.* Typhimurium, several unique gene clusters known as *pathogenicity islands* and other genes have been acquired during evolution. The inactivation of single genes, as well as the acquisition or loss of single genes or large islands of DNA, may have contributed to host adaptation and restriction of *S.* Typhi.

One of the most specific gene products is the polysaccharide capsule Vi (virulence), which is present in approximately 90% of all freshly isolated *S.* Typhi and has a protective effect against the bactericidal action of the serum of infected patients.

EPIDEMIOLOGY

It is estimated that more than 26.9 million typhoid fever cases occur annually, of which 1% result in death. The vast majority of this disease burden is witnessed in Asia. Additionally, an estimated 5.4 million cases caused by paratyphoid occur each year. In 2010, 13.5 million cases of typhoid fever were recorded, and both typhoid and paratyphoid fevers together accounted for more than 12 million disability-adjusted life years. The mortality caused by typhoid fever in the same year was found to be 7.2 per 100,000 population for the sub-Saharan region of Africa. Given the paucity of microbiologic facilities in developing countries, these figures may be more representative of the clinical syndrome rather than of culture-proven disease. In most developed countries, the incidence of typhoid fever is <15 cases per 100,000 population, with most cases occurring in travelers. In contrast, the incidence may vary considerably in the developing world, with estimated rates ranging from 100-1,000 cases per 100,000 population. There are significant differences in the age distribution and population at risk. Population-based studies from South Asia also indicate that the age-specific incidence of typhoid fever may be highest in children younger than 5 yr of age, in association with comparatively higher rates of complications and hospitalization.

Typhoid fever is notable for the emergence of drug resistance. Following sporadic outbreaks of chloramphenicol-resistant *S.* Typhi infections, many strains of *S.* Typhi have developed plasmid-mediated multidrug resistance to all 3 of the primary antimicrobials: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. There is also a considerable increase in nalidixic acid–resistant isolates of *S.* Typhi, as well as the emergence of fluoroquinolone-resistant isolates. Nalidixic acid–resistant isolates first emerged in Southeast Asia and India, and now account for the majority of travel-associated cases of typhoid fever in the United States.

S. Typhi is highly adapted to infection of humans to the point that it has lost the ability to cause transmissible disease in other animals. The discovery of the large number of pseudogenes in *S.* Typhi suggests that the genome of this pathogen has undergone degeneration to facilitate a specialized association with the human host. Thus, direct or indirect contact with an infected person (sick or chronic carrier) is a prerequisite for infection. Ingestion of foods or water contaminated with *S.* Typhi from human feces is the most common mode of transmission, although waterborne outbreaks as a consequence of poor sanitation or contamination have been described in developing countries. In other parts of the world, oysters and other shellfish cultivated in water contaminated by sewage and the use of night soil as fertilizer may also cause infection.

PATHOGENESIS

Enteric fever occurs through the ingestion of the organism, and a variety of sources of fecal contamination have been reported, including street foods and contamination of water reservoirs.

Human volunteer experiments established an infecting dose of about 10^5-10^9 organisms, with an incubation period ranging from 4-14 days, depending on the inoculating dose of viable bacteria. After ingestion, *S.* Typhi organisms are thought to invade the body through the gut mucosa in the terminal ileum, possibly through specialized antigen-sampling cells known as *M cells* that overlie gut-associated lymphoid tissues, through enterocytes, or via a paracellular route. *S.* Typhi crosses the intestinal mucosal barrier after attachment to the microvilli by an intricate mechanism involving membrane ruffling, actin rearrangement, and internalization in an intracellular vacuole. In contrast to NTS, *S.* Typhi expresses virulence factors that allow it to downregulate the pathogen recognition receptor–mediated host inflammatory response. Within the Peyer patches in the terminal ileum, *S.* Typhi can traverse the intestinal barrier through several mechanisms, including the M cells in the follicle-associated epithelium, epithelial cells, and dendritic cells. At the villi, *Salmonella* can enter through the M cells or by passage through or between compromised epithelial cells.

On contact with the epithelial cell, S. typhi assembles type III secretion system encoded on SPI-1 and translocates effectors into the cytoplasm. These effectors activate host Rho guanosine triphosphatases, resulting in the rearrangement of the actin cytoskeleton into membrane ruffles, induction of mitogen-activated protein kinase pathways,

and destabilization of tight junctions. Changes in the actin cytoskeleton are further modulated by the actin-binding proteins SipA and SipC and lead to bacterial uptake. Mitogen-activated protein kinase signaling activates the transcription factors activator protein-1 and nuclear factor-κB, which turn on production of IL-8. The destabilization of tight junctions allows the transmigration of polymorphonuclear leukocytes from the basolateral surface to the apical surface, paracellular fluid leakage, and access of bacteria to the basolateral surface. Shortly after internalization of *S.* Typhi by macropinocytosis, salmonellae are enclosed in a spacious phagosome that is formed by membrane ruffles. Later, the phagosome fuses with lysosomes, acidifies, and shrinks to become adherent around the bacterium, forming the *Salmonella*-containing vacuole. type III secretion system encoded on SPI-2 is induced within the *Salmonella*-containing vacuole and translocates effector proteins SifA and PipB2, which contribute to *Salmonella*-induced filament formation along microtubules. The *S.* Typhi toxin has been isolated and characterized composed of 2 A subunits, PltA and CdtB, which are homologs of the A subunits of the pertussis and cytolethal distending toxins, respectively. Its single B subunit, PltB, is a homolog of 1 of the components of the heteropentameric B subunit of pertussis toxin. Although the cellular targets of the adenosine diphosphate–ribosyl transferase activity of PltA have not yet been identified, CdtB is a DNase that inflicts DNA damage and induces cell-cycle arrest. *S.* Typhi produces typhoid toxin only within mammalian cells, and the toxin is then ferried to the extracellular environment by a unique transport mechanism that involves vesicle carrier intermediates (Fig. 198-4). These findings open the door to future opportunities for developing diagnostic and preventive strategies.

After passing through the intestinal mucosa, *S.* Typhi organisms enter the mesenteric lymphoid system and then pass into the bloodstream via the lymphatics. This primary bacteremia is usually asymptomatic, and blood culture results are frequently negative at this stage of the disease. The bloodborne bacteria are disseminated throughout the body and are thought to colonize the organs of the reticuloendothelial system, where they may replicate within macrophages. After a period of bacterial replication, *S.* Typhi organisms are shed back into the blood, causing a secondary bacteremia that coincides with the onset of clinical symptoms and marks the end of the incubation period.

In vitro studies with human cell lines have shown qualitative and quantitative differences in the epithelial cell response to *S.* Typhi and *S.* Typhimurium with regard to cytokine and chemokine secretion. Thus, by avoiding the triggering of an early inflammatory response in the gut, *S.* Typhi could instead colonize deeper tissues and organ systems. Infection with *S.* Typhi produces an inflammatory response in the deeper mucosal layers and underlying lymphoid tissue, with hyperplasia of Peyer patches and subsequent necrosis and sloughing of overlying epithelium. The resulting ulcers can bleed but usually heal without scarring or stricture formation. The inflammatory lesion may occasionally penetrate the muscularis and serosa of the intestine and produce perforation. The mesenteric lymph nodes, liver, and spleen are hyperemic and generally have areas of focal necrosis as well. A mononuclear response may be seen in the bone marrow in association with areas of focal necrosis. The morphologic changes of *S.* Typhi infection are less prominent in infants than in older children and adults.

It is thought that several virulence factors, including type III secretion system encoded on SPI-2, may be necessary for the virulence properties and ability to cause systemic infection. The surface Vi polysaccharide capsular antigen found in *S.* Typhi interferes with phagocytosis by preventing the binding of C3 to the surface of the bacterium. The ability of organisms to survive within macrophages after phagocytosis is an important virulence trait encoded by the PhoP regulon and may be related to metabolic effects on host cells. The occasional occurrence of diarrhea may be explained by the presence of a toxin related to cholera toxin and *E. coli* heat-labile enterotoxin. The clinical syndrome of fever and systemic symptoms is produced by a release of proinflammatory cytokines (IL-6, IL-1β, and TNF-α) from the infected cells.

In addition to the virulence of the infecting organisms, host factors and immunity may also play an important role in predisposition to infection. There is an association between susceptibility to typhoid fever and human genes within the major histocompatibility complex class II and class III loci. Patients who are infected with HIV are at significantly higher risk for clinical infection with *S.* Typhi and *S.* Paratyphi. Similarly, patients with *Helicobacter pylori* infection have an increased risk of acquiring typhoid fever.

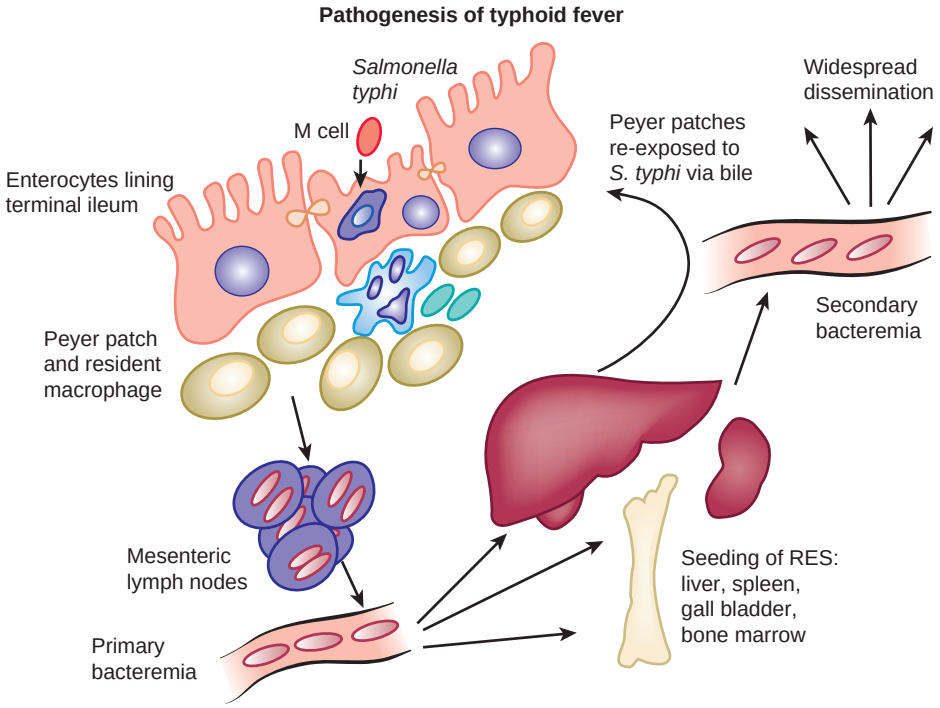

Figure 198-4 Pathogenesis of typhoid fever. *RES,* reticuloendothelial system. *(Adapted from Richens J: Typhoid fever. In Cohen J, Powderly WG, Opal SM, editors:* Infectious diseases, *ed 2, London, 2004, Mosby, pp. 1561–1566.)*

Table 198-5 Common Clinical Features of Typhoid Fever in Children*

FEATURE	RATE (%)
High-grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

*Data collected in Karachi, Pakistan, from 2,000 children.

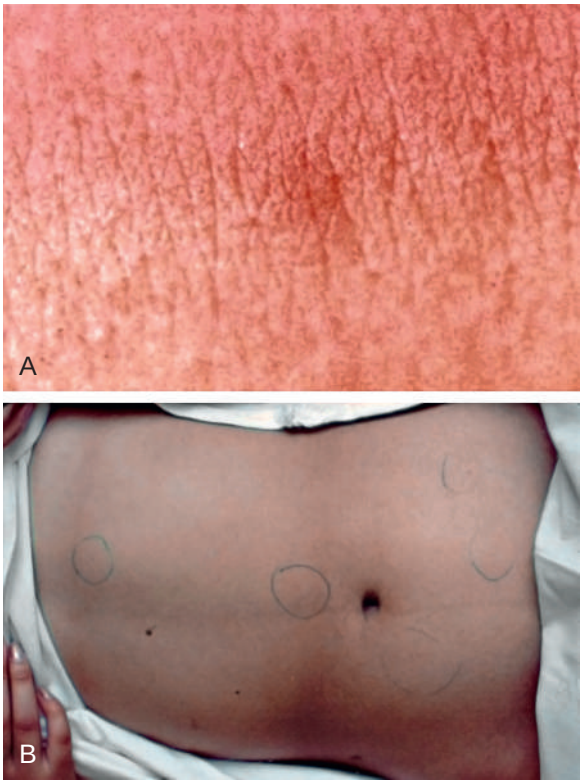

Figure 198-5 A, A rose spot in a volunteer with experimental typhoid fever. **B,** A small cluster of rose spots is usually located on the abdomen. These lesions may be difficult to identify, especially in dark-skinned people. *(From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of* Salmonella enterica *serotype Typhi infection,* Lancet Infect Dis *5:341–348, 2005.)*

CLINICAL FEATURES

The incubation period of typhoid fever is usually 7-14 days but depends on the infecting dose and ranges between 3 and 30 days. The clinical presentation varies from a mild illness with low-grade fever, malaise, and slight, dry cough to a severe clinical picture with abdominal discomfort and multiple complications.

Many factors influence the severity and overall clinical outcome of the infection. They include the duration of illness before the initiation of appropriate therapy, choice of antimicrobial treatment, age, previous exposure or vaccination history, virulence of the bacterial strain, quantity of inoculum ingested, and several host factors affecting immune status.

The presentation of typhoid fever may also differ according to age. Although data from South America and parts of Africa suggest that typhoid may manifest as a mild illness in young children, presentation may vary in different parts of the world. There is emerging evidence from south Asia that the presentation of typhoid may be more dramatic in children younger than 5 yr of age, with comparatively higher rates of complications and hospitalization. Diarrhea, toxicity, and complications such as disseminated intravascular coagulopathy are also more common in infancy, resulting in higher case fatality rates. However, some of the other features and complications of typhoid fever seen in adults, such as relative bradycardia, neurologic manifestations, and gastrointestinal bleeding, are rare in children.

Typhoid fever usually manifests as high-grade fever with a wide variety of associated features, such as generalized myalgia, abdominal pain, hepatosplenomegaly, abdominal pain, and anorexia (Table 198-5). In children, diarrhea may occur in the earlier stages of the illness and may be followed by constipation. In the absence of localizing signs, the early stage of the disease may be difficult to differentiate from other endemic diseases such as malaria and dengue fever. The fever may rise gradually, but the classic stepladder rise of fever is relatively rare. In approximately 25% of cases, a macular or maculopapular rash (rose spots) may be visible around the 7th-10th day of the illness, and lesions may appear in crops of 10-15 on the lower chest and abdomen and last 2-3 days (Fig. 198-5). These lesions may be difficult to see in dark-skinned children. Patients managed as outpatients present with fever (99%) but have less emesis, diarrhea, hepatomegaly, splenomegaly, and myalgias than patients who require admission to the hospital.

The presentation of typhoid fever may be tempered by coexisting morbidities and early diagnosis and administration of antibiotics. In malaria-endemic areas and in parts of the world where schistosomiasis is common, the presentation of typhoid may also be atypical. It is also recognized that multidrug-resistant *S.* Typhi infection is a more severe clinical illness with higher rates of toxicity, complications, and case fatality rates, which may be related to the greater virulence as well as higher numbers of circulating bacteria. The emergence of typhoid infections resistant to nalidixic acid and fluoroquinolones is associated with higher rates of morbidity and treatment failure. These findings may have implications for treatment algorithms, especially in endemic areas with high rates of multidrug-resistant and nalidixic acid– or fluoroquinolone-resistant typhoid.

If no complications occur, the symptoms and physical findings gradually resolve within 2-4 wk; however, the illness may be associated with malnutrition in a number of affected children. Although enteric fever caused by *S.* Paratyphi organisms has been classically regarded as a milder illness, there have been several outbreaks of infection with drug-resistant *S.* Paratyphi A, suggesting that paratyphoid fever may also be severe, with significant morbidity and complications.

COMPLICATIONS

Although altered liver function is found in many patients with enteric fever, clinically significant hepatitis, jaundice, and cholecystitis are relatively rare and may be associated with higher rates of adverse outcome. Intestinal hemorrhage (<1%) and perforation (0.5-1%) are infrequent among children. Intestinal perforation may be preceded by a marked increase in abdominal pain (usually in the right lower quadrant), tenderness, vomiting, and features of peritonitis. Intestinal

Table 198-6 Extraintestinal Infectious Complications of Typhoid Fever Caused By *Salmonella enterica* Serotype Typhi

ORGAN SYSTEM INVOLVED	PREVALENCE (%)	RISK FACTORS	COMPLICATIONS
Central nervous system	3-35	Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, and osteomyelitis of the skull	Encephalopathy, cerebral edema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis
Cardiovascular system	1-5	Cardiac abnormalities—e.g., existing valvular abnormalities, rheumatic heart disease, or congenital heart defects	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	1-6	Residence in endemic region, past pulmonary infection, sickle cell anemia, alcohol abuse, diabetes, HIV infection	Pneumonia, empyema, bronchopleural fistula
Bone and joint	<1	Sickle cell anemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, extremes of age, and steroid use	Osteomyelitis, septic arthritis
Hepatobiliary system	1-26	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, hemoglobinopathy	Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	<1	Urinary tract, pelvic pathology, and systemic abnormalities	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft-tissue infections	At least 17 cases reported in the English language literature	Diabetes	Psoas abscess, gluteal abscess, cutaneous vasculitis
Hematologic	At least 5 cases reported in the English language literature		Hemophagocytosis syndrome

From Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of Salmonella enterica *serotype Typhi infection,* Lancet Infect Dis *5:341–348, 2005.*

perforation and peritonitis may be accompanied by a sudden rise in pulse rate, hypotension, marked abdominal tenderness and guarding, and subsequent abdominal rigidity. A rising white blood cell count with a left shift and free air on abdominal radiographs may be seen in such cases.

Rare complications include toxic myocarditis, which may manifest as arrhythmias, sinoatrial block, or cardiogenic shock (Table 198-6). Neurologic complications are also relatively uncommon among children; they include delirium, psychosis, increased intracranial pressure, acute cerebellar ataxia, chorea, deafness, and Guillain-Barré syndrome. Although case fatality rates may be higher with neurologic manifestations, recovery usually occurs with no sequelae. Other reported complications include fatal bone marrow necrosis, disseminated intravascular coagulopathy, hemolytic–uremic syndrome, pyelonephritis, nephrotic syndrome, meningitis, endocarditis, parotitis, orchitis, and suppurative lymphadenitis.

The propensity to become a carrier follows the epidemiology of gallbladder disease, increasing with patient age and the antibiotic resistance of the prevalent strains. Although limited data are available, rates of chronic carriage are generally lower in children than adults.

DIAGNOSIS

The mainstay of the diagnosis of typhoid fever is a positive result of culture from the blood or another anatomic site. Results of blood cultures are positive in 40-60% of the patients seen early in the course of the disease, and stool and urine culture results become positive after the 1st wk. The stool culture result is also occasionally positive during the incubation period. However, the sensitivity of blood cultures in diagnosing typhoid fever in many parts of the developing world is limited because widespread liberal antibiotic use may render bacteriologic confirmation difficult. Although bone marrow cultures may increase the likelihood of bacteriologic confirmation of typhoid, collection of the specimens is difficult and relatively invasive.

Results of other laboratory investigations are nonspecific. Although blood leukocyte counts are frequently low in relation to the fever and toxicity, there is a wide range in counts; in younger children leukocytosis is common and may reach 20,000-25,000 cells/μL. Thrombocytopenia may be a marker of severe illness and may accompany disseminated intravascular coagulopathy. Liver function test results may be deranged, but significant hepatic dysfunction is rare.

The classic Widal test measures antibodies against O and H antigens of *S.* Typhi but lacks sensitivity and specificity in endemic areas. Because many false-positive and false-negative results occur, diagnosis of typhoid fever by Widal test alone is prone to error. Other relatively newer diagnostic tests using monoclonal antibodies have been developed that directly detect *S.* Typhi–specific antigens in the serum or *S.* Typhi Vi antigen in the urine. However, few have proved sufficiently robust in large-scale evaluations. A nested polymerase chain reaction analysis using *H1-d* primers has been used to amplify specific genes of *S.* Typhi in the blood of patients; it is a promising means of making a rapid diagnosis, especially given the low level of bacteremia in enteric fever. Despite these innovations, the mainstay of diagnosis of typhoid remains clinical in much of the developing world, and several diagnostic algorithms have been evaluated in endemic areas.

DIFFERENTIAL DIAGNOSIS

In endemic areas, typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multisystem features and no localizing signs, the early stages of enteric fever may be confused with alternative conditions, such as acute gastroenteritis,

bronchitis, and bronchopneumonia. Subsequently, the differential diagnosis includes malaria; sepsis with other bacterial pathogens; infections caused by intracellular microorganisms, such as tuberculosis, brucellosis, tularemia, leptospirosis, and rickettsial diseases; and viral infections such as Dengue fever, acute hepatitis, and infectious mononucleosis.

TREATMENT

An early diagnosis of typhoid fever and institution of appropriate treatment are essential. The vast majority of children with typhoid fever can be managed at home with oral antibiotics and close medical follow-up for complications or failure of response to therapy. Patients with persistent vomiting, severe diarrhea, and abdominal distention may require hospitalization and parenteral antibiotic therapy.

There are general principles of typhoid fever management. Adequate rest, hydration, and attention are important to correct fluid and electrolyte imbalance. Antipyretic therapy (acetaminophen 10-15 mg/kg every 4-6 hr PO) should be provided as required. A soft, easily digestible diet should be continued unless the patient has abdominal distention or ileus. Antibiotic therapy is critical to minimize complications (Table 198-7). It has been suggested that traditional therapy with either chloramphenicol or amoxicillin is associated with relapse rates of 5-15% and 4-8%, respectively, whereas use of the quinolones and third-generation cephalosporins is associated with higher cure rates. The antibiotic treatment of typhoid fever in children is also influenced by the prevalence of antimicrobial resistance. Over the past 2 decades, emergence of multidrug-resistant strains of *S.* Typhi (i.e., isolates fully resistant to amoxicillin, trimethoprim-sulfamethoxazole, and chloramphenicol) has necessitated treatment with fluoroquinolones, which are the antimicrobial drug of choice for treatment of salmonellosis in adults, with cephalosporins as an alternative. The emergence of resistance to quinolones places tremendous pressure on public health systems because alternative therapeutic options are limited.

Although some investigators suggest that children with typhoid fever should be treated with fluoroquinolones like adults, others question this approach on the basis of the potential development of further resistance to fluoroquinolones and the fact that quinolones are still not approved for widespread use in children. A Cochrane systematic review of the treatment of typhoid fever also indicates that there is little evidence to support the carte blanche administration of fluoroquinolones in all cases of typhoid fever. Azithromycin may be an alternative antibiotic for children with uncomplicated typhoid fever.

In addition to antibiotics, the importance of supportive treatment and maintenance of appropriate fluid and electrolyte balance must be underscored. Although additional treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hr for 48 hr) is recommended for severely ill patients with shock, obtundation, stupor, or coma; corticosteroids should be administered only under strict controlled conditions and supervision, because their use may mask signs of abdominal complications.

PROGNOSIS

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and institution of appropriate antibiotic therapy. Other factors are the patient's, age, general state of health, and nutrition, the causative *Salmonella* serotype, and the appearance of complications. Infants and children with underlying malnutrition and patients infected with multidrug-resistant isolates are at higher risk for adverse outcomes.

Despite appropriate therapy, 2-4% of infected children may experience relapse after initial clinical response to treatment. Individuals who excrete *S.* Typhi for 3 mo or longer after infection are regarded as chronic carriers. The risk for becoming a carrier is low in children (<2% for all infected children) and increases with age. A chronic urinary carrier state can develop in children with schistosomiasis.

PREVENTION

Of the major risk factors for outbreaks of typhoid fever, contamination of water supplies with sewage is the most important. Other risk factors for development of typhoid fever are congestion, contact with another patient or a febrile individual, and lack of water and sanitation services. During outbreaks, central chlorination as well as domestic water purification is important. In endemic situations, consumption of street foods, especially ice cream and cut fruit, is recognized as an important risk factor. The human-to-human spread by chronic carriers is also important, and attempts should be made to target food handlers and

Table 198-7 Treatment of Typhoid Fever in Children

	Optimal Therapy			Alternative Effective Drugs		
SUSCEPTIBILITY	**ANTIBIOTIC**	**DAILY DOSE (mg/kg/day)**	**DAYS**	**ANTIBIOTIC**	**DAILY DOSE (mg/kg/day)**	**DAYS**
UNCOMPLICATED TYPHOID FEVER						
Fully sensitive	Chloramphenicol	50-75	14-21	Fluoroquinolone, e.g., ofloxacin or ciprofloxacin	15	5-7*
	Amoxicillin	75-100	14			
Multidrug-resistant	Fluoroquinolone	15	5-7	Azithromycin	8-10	7
	or					
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone-resistant†	Azithromycin	8-10	7	Cefixime	20	7-14
	or					
	Ceftriaxone	75	10-14			
SEVERE TYPHOID FEVER						
Fully sensitive	Fluoroquinolone, e.g., ofloxacin	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	
Multidrug-resistant	Fluoroquinolone	15	10-14	Ceftriaxone	60	10-14
				or		
				Cefotaxime	80	10-14
Quinolone-resistant	Ceftriaxone	60	10-14	Azithromycin	10-20	7
	Cefotaxime	80	10-14	Fluoroquinolone	20	7-14

*A 3-day course is also effective, particularly for epidemic containment.

†The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, third-generation cephalosporins, or high-dose fluoroquinolones for 10-14 days is effective.

Modified from World Health Organization: Treatment of typhoid fever. In: World Health Organization: Background document: the diagnosis, prevention and treatment of typhoid fever. Communicable disease surveillance and response: vaccines and biologicals, *Geneva, 2003, World Health Organization, pp. 19–23. Available at: http://whqlibdoc.who.int/hq/2003/WHO_V&B_03.07.pdf*

high-risk groups for *S.* Typhi carriage screening. Once identified, chronic carriers must be counseled as to the risk for disease transmission and the importance of handwashing.

The classic heat-inactivated whole-cell vaccine for typhoid is associated with an unacceptably high rate of side effects and has been largely withdrawn from public health use. Globally, 2 vaccines are currently available for potential use in children. An oral, live-attenuated preparation of the Ty21a strain of *S.* Typhi has good efficacy (67-82%) for up to 5 yr. Significant adverse effects are rare. The Vi capsular polysaccharide can be used in people 2 yr of age and older. It is given as a single intramuscular dose, with a booster every 2 yr, and has a protective efficacy of 70-80%. The vaccines are currently recommended for anyone traveling into endemic areas, but a few countries have introduced large-scale vaccination strategies. Previous studies in South America have demonstrated protection against typhoid fever among schoolchildren with the use of an oral attenuated Ty21 strain vaccine.

Several large-scale demonstration projects using the Vi polysaccharide vaccine in Asia have demonstrated protective efficacy against typhoid fever across all age groups, but the data on protection among young children (<5 yr) showed important differences between studies. The recent Vi-conjugate vaccine has a protective efficacy exceeding 90% in younger children and may offer protection in parts of the world where a large proportion of preschool children are at risk for the disease enteric or typhoid fever.

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Chapter 199

Shigella

Theresa J. Ochoa and Thomas G. Cleary

Shigella causes an acute invasive enteric infection clinically manifested by diarrhea that is often bloody. The term *dysentery* is used to describe the syndrome of bloody diarrhea with fever, abdominal cramps, rectal pain, and mucoid stools. Bacillary dysentery is a term often used to distinguish dysentery caused by *Shigella* from amoebic dysentery caused by *Entamoeba histolytica*.

ETIOLOGY

Four species of *Shigella* are responsible for bacillary dysentery: *Shigella dysenteriae* (serogroup A), *Shigella flexneri* (serogroup B), *Shigella boydii* (serogroup C), and *Shigella sonnei* (serogroup D). There are 15 serotypes in group A, 19 serotypes in group B, 19 serotypes in group C, and one serotype in group D. Species classification has important therapeutic implications because the species differ in both geographic distribution and antimicrobial susceptibility.

EPIDEMIOLOGY

It is estimated that there are approximately 80-165 million cases of shigellosis each year worldwide, resulting in more than 1 million deaths; most of these cases and deaths occur in developing countries. Studies estimate similar illness rates but fewer deaths because of a decrease in the case-fatality rates. In the United States, approximately 14,000 cases per year are documented, although it is thought that the actual frequency of infection is 450,000 cases annually. *Shigella* is the third most important pathogen identified in the Foodborne Disease Active Surveillance Network in the United States. Although infection can occur at any age, it is most common in the 2nd and 3rd yr of life. Approximately 70% of all episodes and 60% of all *Shigella*-related deaths involve children younger than 5 yr of age. Infection in the 1st 6 mo of life is rare for reasons that are not clear. Breast milk from women living in endemic areas contains antibodies to both virulence plasmid-coded antigens and lipopolysaccharides, and breastfeeding might partially explain the age-related incidence.

Asymptomatic infection of children and adults occurs commonly in endemic areas. Infection with *Shigella* occurs most often during the warm months in temperate climates and during the rainy season in tropical climates. Both sexes are affected equally. In industrialized societies, *S. sonnei* is the most common cause of bacillary dysentery, with *S. flexneri* second in frequency; in preindustrial societies, *S. flexneri* is most common, with *S. sonnei* second in frequency. *S. boydii* is found primarily in India. *S. dysenteriae* serotype 1 tends to occur in massive epidemics, although it is also endemic in Asia and Africa, where it is associated with high mortality rates (5-15%). However, *Shigella* has shown temporal procession in serogroup dominance. Recently, epidemiologic transition has favored the emergence of *S. sonnei* as the dominant serogroup in some countries, although the reason for this is not clear.

Contaminated food (often a salad or other item requiring extensive handling of the ingredients) and water are important vectors. Exposure to both fresh and saltwater is a risk factor for infection. Rapid spread within families, custodial institutions, and childcare centers demonstrates the ability of shigellae to be transmitted from 1 individual to the next and the requirement for ingestion of very few organisms to cause illness. As few as 10 *S. dysenteriae* serotype 1 organisms can cause dysentery. In contrast, ingestion of 10^8-10^{10} *Vibrio cholerae* is necessary to cause cholera.

PATHOGENESIS

Shigella has specialized mechanisms to survive the low gastric pH. *Shigella* survives the acid environment in the stomach and moves through the gut to the colon, its target organ. The basic virulence trait shared by all shigellae is the ability to invade colonic epithelial cells by turning on a series of temperature-regulated proteins. This invasion mechanism is encoded on a large (220 kb) plasmid that at body temperature synthesizes of a group of polypeptides involved in cell invasion and killing. Shigellae that lose the virulence plasmid are no longer pathogenic. Enteroinvasive *Escherichia coli* that harbor a closely related plasmid containing these invasion genes behave clinically like shigellae. The virulence plasmid encodes a type III secretion system required to trigger entry into epithelial cells and apoptosis in macrophages. This secretion system translocates effector molecules from the bacterial cytoplasm to the membrane and cytoplasm of target host cells. The type III secretion system is composed of approximately 50 proteins, including the Mxi and Spa proteins involved in assembly and regulation of the type III secretion system, chaperones (IpgA, IpgC, IpgE, and Spa15), transcription activators (VirF, VirB, and MxiE), translocators (IpaB, IpaC, and IpaD), and approximately 30 effector proteins. In addition to the major plasmid-encoded virulence traits, chromosomally encoded factors are also required for full virulence.

Shigella passes the epithelial cell barrier by transcytosis through M cells and encounters resident macrophages. The bacteria evade degradation in macrophages by inducing apoptosis, which is accompanied by proinflammatory signaling. Free bacteria invade the epithelial cells from the basolateral side, move into the cytoplasm by actin polymerization, and spread to adjacent cells. Proinflammatory signaling by macrophages and epithelial cells further activates the innate immune response involving natural killer cells and attracts polymorphonuclear leukocytes (PMNs). The influx of PMNs disintegrates the epithelial cell lining, which initially exacerbates the infection and tissue destruction by facilitating the invasion of more bacteria. Ultimately, PMNs phagocytose and kill *Shigella*, thus contributing to the resolution of the infection.

Some shigellae make toxins, including *Shiga* toxin and enterotoxins. *Shiga* toxin is a potent exotoxin that inhibits protein synthesis and is produced in significant amounts by *S. dysenteriae* serotype 1, by a subset of *E. coli*, which are known as enterohemorrhagic or *Shiga* toxin–producing *E. coli*, and occasionally by other organisms. *Shiga* toxin inhibits protein synthesis to injure vascular endothelial cells to trigger the severe complication of hemolytic-uremic syndrome.

Targeted deletion of the genes for other enterotoxins *(ShET1* and *ShET2)* has decreased the incidence of fever and dysentery in volunteers during vaccine-development studies. Lipopolysaccharides are virulence factors for all shigellae; other traits are important for only a few serotypes (e.g., *Shiga* toxin synthesis by *S. dysenteriae* serotype 1 and *ShET1* by *S. flexneri* 2a).

The pathologic changes of shigellosis take place primarily in the colon. The changes are most intense in the distal colon, although pancolitis can occur. Shigellae cross the colonic epithelium through M cells in the follicle-associated epithelium overlying the Peyer patches. Grossly, localized or diffuse mucosal edema, ulcerations, friable mucosa, bleeding, and exudate may be seen. Microscopically, ulcerations, pseudomembranes, epithelial cell death, infiltration extending from the mucosa to the muscularis mucosae by PMNs and mononuclear cells, and submucosal edema occur.

IMMUNITY

Innate immunity to *Shigella* infection is characterized by the induction of acute inflammation with massive recruitment of PMNs and subsequently massive tissue destruction. In humans, analysis of cytokine expression in rectal biopsies of infected patients at the acute phase of the disease has revealed upregulation of proinflammatory genes, such as those encoding interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α, and tumor necrosis factor-β, although antiinflammatory genes encoding IL-10 and transforming growth factor-β are also upregulated. Control of *Shigella* invasion in intestinal epithelial cells depends on interferon-γ. *Shigella*-specific immunity elicited upon natural infection is characterized by the induction of a humoral response. Local secretory immunoglobulin A and serum immunoglobulin G are produced against lipopolysaccharide and some protein effectors (Ipas). Protection is thought to be serotype specific. Natural protective immunity arises only after several episodes of infection, is of short duration, and seems to be effective in limiting reinfection, particularly in young children.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Bacillary dysentery is clinically similar regardless of infecting serotype. There are some clinical differences, particularly relating to the greater severity and risk of complications with *S. dysenteriae* serotype 1 infection. Ingestion of shigellae is followed by an incubation period of 12 hr to several days before symptoms ensue. Severe abdominal pain, high fever, emesis, anorexia, generalized toxicity, urgency, and painful defecation characteristically occur. The diarrhea may be watery and of large volume initially, evolving into frequent, small-volume, bloody mucoid stools. Most children never progress to the stage of bloody diarrhea, but some have bloody stools from the outset. Significant dehydration is related to the fluid and electrolyte losses in feces and emesis. Untreated diarrhea can last 7-10 days; only approximately 10% of patients have diarrhea persisting for longer than 10 days. Persistent diarrhea occurs in malnourished infants, children with AIDS, and occasionally previously normal children. Even nondysenteric disease can be complicated by persistent illness.

Physical examination initially shows abdominal distention and tenderness, hyperactive bowel sounds, and a tender rectum on digital examination. Rectal prolapse may be present, particularly in malnourished children. Neurologic findings are among the most common extraintestinal manifestations of bacillary dysentery, occurring in as many as 40% of hospitalized children. Enteroinvasive *E. coli* can cause similar neurologic toxicity. Convulsions, headache, lethargy, confusion, nuchal rigidity, or hallucinations may be present before or after the onset of diarrhea. The cause of these neurologic findings is not understood. In the past, these symptoms were attributed to the neurotoxicity of *Shiga* toxin, but it is now clear that this explanation is wrong because the organisms isolated from children with *Shigella*-related seizures are usually not *Shiga* toxin producers. Seizures sometimes occur when little fever is present, suggesting that simple febrile convulsions do not explain their appearance. Hypocalcemia or hyponatremia may be associated with seizures in a small number of patients. Although symptoms often suggest central nervous system infection and cerebrospinal fluid pleocytosis with minimally elevated protein levels can occur, meningitis caused by shigellae is rare. Based on animal studies, it has been suggested that proinflammatory mediators, including tumor necrosis factor-α and IL-1β, nitric oxide, and corticotropin-releasing hormone, all play a role in the enhanced susceptibility to seizures caused by *S. dysenteriae.*

The most common complication of shigellosis is dehydration. Inappropriate secretion of antidiuretic hormone with profound hyponatremia can complicate dysentery, particularly when *S. dysenteriae* is the etiologic agent. Hypoglycemia and protein-losing enteropathy are common and are decreased by early appropriate antibiotic therapy. Severe protein-losing enteropathy is associated with prolonged illness and linear growth shortfalls. Bacteremia is uncommon except in girls or women infected with HIV, malnourished children, young infants, and children with *S. dysenteriae* serotype 1 infection. When bacteremia occurs with dysentery (<5%), it is as likely to be caused by other enteric bacteria as well as by the *Shigella* itself. The presence of *E. coli, Klebsiella*, and other enteric bacteria in blood cultures of children with shigellosis may reflect loss of the barrier function during severe colitis. The mortality rate is high (~20%) when sepsis occurs and is far more common in those with HIV than in non–HIV-infected persons. Other major complications include disseminated intravascular coagulation, particularly in very young, malnourished children. Given that shigellae penetrate the intestinal mucosal barrier, these events are surprisingly uncommon.

Neonatal shigellosis is rare. Neonates may have only low-grade fever with mild, nonbloody diarrhea. However, complications occur more commonly than in older children and include septicemia, meningitis, dehydration, colonic perforation, and toxic megacolon.

S. dysenteriae serotype 1 infection is commonly complicated by hemolysis, anemia, and hemolytic-uremic syndrome. This syndrome is caused by *Shiga* toxin–mediated vascular endothelial injury. *E. coli* that produce *Shiga* toxins (e.g., *E. coli* O157:H7, *E. coli* O111:NM, *E. coli* O26:H11, and less commonly in many other serotypes) also cause hemolytic-uremic syndrome (see Chapter 518).

Rectal prolapse, toxic megacolon or pseudomembranous colitis (usually associated with *S. dysenteriae*), cholestatic hepatitis, conjunctivitis, iritis, corneal ulcers, pneumonia, arthritis (usually 2-5 wk after enteritis), reactive arthritis, cystitis, myocarditis, and vaginitis (typically with a blood-tinged discharge associated with *S. flexneri*) are uncommon events. Although rare, surgical complications of shigellosis can be severe; the most common are intestinal obstruction and appendicitis with and without perforation.

On average, severity of illness and risk of death are least with disease caused by *S. sonnei* and greatest with infection by *S. dysenteriae* type 1. Risk groups for severe illness and poor outcomes include infants; adults older than age 50 yr; children who are not breastfed; children with HIV or who are recovering from measles; malnourished children and adults; and patients who develop dehydration, unconsciousness, or hypo- or hyperthermia, hyponatremia, lesser stool frequency, or have a history of convulsion when first seen. Death is a rare outcome in well-nourished older children. Multiple factors contribute to death in malnourished children with shigellosis, including illness in the 1st yr of life, altered consciousness, dehydration, hypothermia, thrombocytopenia, anemia, hyponatremia, renal failure, hyperkalemia hypoglycemia, bronchopneumonia, and bacteremia.

The rare syndrome of severe toxicity, convulsions, extreme hyperpyrexia, and headache followed by brain edema and a rapidly fatal outcome without sepsis or significant dehydration (Ekiri syndrome or "lethal toxic encephalopathy") is not well understood.

DIFFERENTIAL DIAGNOSIS

Although clinical features suggest shigellosis, they are insufficiently specific to allow confident diagnosis. Infection by *Campylobacter jejuni*, *Salmonella* spp., enteroinvasive *E. coli*, *Shiga* toxin–producing *E. coli* (e.g., *E. coli* O157:H7), *Yersinia enterocolitica*, *Clostridium difficile*,

and *E. histolytica,* as well as inflammatory bowel disease, can cause confusion.

DIAGNOSIS

Presumptive data supporting a diagnosis of bacillary dysentery include the finding of fecal leukocytes (usually >50 or 100 PMNs per high-power field, confirming the presence of colitis), fecal blood, and demonstration in peripheral blood of leukocytosis with a dramatic left shift (often with more bands than segmented neutrophils). The total peripheral white blood cell count is usually 5,000-15,000 cells/μL, although leukopenia and leukemoid reactions occur.

Culture of both stool and rectal swab specimens optimizes the chance of diagnosing *Shigella* infection. Culture media should include MacConkey agar as well as selective media such as xylose-lysine-deoxycholate and *Salmonella-Shigella* agar. Transport media should be used if specimens cannot be cultured promptly. Appropriate media should be used to exclude *Campylobacter* spp. and other agents. Studies of outbreaks and illness in volunteers show that the laboratory is often not able to confirm the clinical suspicion of shigellosis even when the pathogen is present. Studies using molecular methods such as polymerase chain reaction suggest that culture significantly underestimates the true frequency of infection. Quantitative polymerase chain reaction improves ascertainment of *Shigella* burden in children with moderate-to-severe diarrhea in low-income countries. However, these methods are usually available only in research laboratories. Multiple fecal cultures improve the yield of *Shigella*. The diagnostic inadequacy of cultures makes it incumbent on the clinician to use judgment in the management of clinical syndromes consistent with shigellosis. In children who appear to be toxic, blood cultures should be obtained, especially in very young or malnourished infants because of their increased risk of bacteremia.

TREATMENT

As with gastroenteritis from other causes, the first concern in a child with suspected shigellosis should be for fluid and electrolyte correction and maintenance (see Chapter 340). Drugs that retard intestinal motility (e.g., diphenoxylate hydrochloride with atropine [Lomotil] or loperamide [Imodium]) should not be used because of the risk of prolonging the illness.

Nutrition is a key concern in areas where malnutrition is common. A high-protein and high-caloric diet during convalescence enhances growth in the following 6 mo. Controlled studies show that cooked green bananas, a food rich in amylase-resistant starches, significantly improves outcome in severe disease. A single large dose of vitamin A (200,000 IU) lessens severity of shigellosis in settings where vitamin A deficiency is common. Zinc supplementation (20 mg elemental zinc for 14 days) significantly decreases the duration of diarrhea, improves weight gain during recovery and immune response to the *Shigella*, and decreases diarrheal disease in the subsequent 6 mo in malnourished children.

The next concern is a decision about the use of antibiotics. Although some authorities recommend withholding antibacterial therapy because of the self-limited nature of the infection, the cost of drugs, and the risk of emergence of resistant organisms, there is a persuasive logic in favor of empirical treatment of all children in whom shigellosis is strongly suspected. Even if not fatal, the untreated illness can cause a child to be quite ill for weeks; chronic or recurrent diarrhea can ensue. Malnutrition can develop or worsen during prolonged illness, particularly in children in developing countries. The risk of continued excretion and subsequent infection of family contacts further argues against the strategy of withholding antibiotics.

Shigella species have variable antimicrobial susceptibility. In general, *S. flexneri* tends to be more resistant than *S. boydii*. There are major geographic variations in antibiotic susceptibility of shigellae. In the United States, strains are commonly resistant to ampicillin (74%) and trimethoprim-sulfamethoxazole (TMP-SMX) (36%), but infrequently resistant to nalidixic acid (2%) or ciprofloxacin (0.5%); however, antimicrobial resistance in the United States differs by race, ethnicity, age, travel history, and species. In general, the proportion of antibiotic resistant isolates is lower in North America and Europe than in Asia or Africa. For example, in China, *S. sonnei* is commonly resistant to TMP-SMX (94.5%), ampicillin (40.3%), piperacillin (36.5%), and ceftriaxone (12.8%). In general, *Shigella* are susceptible in vitro to azithromycin, ceftriaxone, cefotaxime, cefixime, nalidixic acid, and quinolones. However, resistance to these antibiotics is being reported in several regions. For example, nalidixic acid–resistant *Shigella* has rapidly developed in Asia and Africa; resistance to ciprofloxacin is increasingly common in India; resistance to azithromycin and ceftriaxone is reported in some countries.

Currently, in most developed and developing countries, *Shigella* strains are often resistant to ampicillin and TMP-SMX; therefore, these drugs should not be used for empirical treatment of suspected shigellosis; they may be used only if the strain is known to be susceptible (e.g., in an outbreak from a defined strain). Given the frequent occurrence of resistant organisms, optimal empirical therapy in children with dysentery should include azithromycin, a third-generation cephalosporin, nalidixic acid or ciprofloxacin. Ceftriaxone (50 mg/kg/24 hr as a single daily dose IV or IM) can be used for empirical therapy, especially for small infants. The oral third-generation cephalosporin cefixime (8 mg/kg/24 hr divided every 12-24 hr) can also be used; however, oral first- and second-generation cephalosporins are inadequate as alternative drugs despite in vitro susceptibility. Nalidixic acid (55 mg/kg/24 hr orally divided 4 times/day) is also an acceptable alternative drug when available. Azithromycin (12 mg/kg/24 hr orally for the 1st day, followed by 6 mg/kg/24 hr for the next 4 days) has proven to be an effective alternative drug for shigellosis. Ciprofloxacin (20-30 mg/kg/24 hr divided into 2 doses) used to be a back-up drug to treat shigellosis but is now the drug of choice recommended by the World Health Organization for all patients with bloody diarrhea, irrespective of their ages.

Although quinolones are reported to cause arthropathy in immature animals, the risk of joint damage in children appears to be minimal and is outweighed by the value of these drugs for treatment of this potentially life-threatening disease. However, some experts recommend that these agents be reserved for seriously ill children with bacillary dysentery caused by an organism that is suspected or known to be resistant to other agents, because overuse of quinolones promotes development of resistance to these drugs.

Treatment of patients in whom *Shigella* infection is suspected on clinical grounds of should be initiated when they are first evaluated. Stool culture is obtained to exclude other pathogens and to assist in antibiotic changes should a child fail to respond to empirical therapy. A child who has typical dysentery and who responds to initial empirical antibiotic treatment should be continued on that drug for a full 5-day course even if the stool culture is negative. The logic of this recommendation is based on the proven difficulty of culturing *Shigella* from stools of ill patients during adult volunteer infection studies. In a child who fails to respond to therapy of a dysenteric syndrome in the presence of initially negative stool culture results, additional cultures should be obtained and the child should be reevaluated for other possible diagnoses.

PREVENTION

Numerous measures have been recommended to decrease the risk of *Shigella* transmission to children. Mothers should be encouraged to prolong breastfeeding of infants. Families and daycare personnel should be educated in proper handwashing techniques and encouraged to wash hands after using the toilet, changing diapers, or engaging in preparation of foods. They should be taught how to manage potentially contaminated materials such as raw vegetables, soiled diapers, and diaper-changing areas. Children with diarrhea should be excluded from childcare facilities. Children should be supervised when handwashing after they use the toilet. Caretakers should be informed of the risk of transmission if they prepare food when they are ill with diarrhea. Families should be educated regarding the risk of swallowing contaminated water from ponds, lakes, or untreated pools. In

developing countries, a safe water supply and appropriate sanitation systems are important measures for reducing the risk for shigellosis. There is not yet a vaccine that is effective for preventing infection by *Shigella*. Measles immunization can substantially reduce the incidence and severity of diarrheal diseases, including shigellosis. Every infant should be immunized against measles at the recommended age.

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Chapter 200

Escherichia coli

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Escherichia coli are important causes of enteric infections as well as urinary tract infections (see Chapter 538), sepsis and meningitis in the newborn (see Chapter 109), and bacteremia and sepsis in immunocompromised patients (see Chapter 178) and in patients with intravascular devices (see Chapter 179). In patients with non–diarrhea-associated *E. coli* infections, a significant number of these pathogens have acquired transferrable plasmids resulting in extended-spectrum β-lactamase production. This results in resistance to penicillins, cephalosporins and aztreonam; carbapenems remain effective.

E. coli species are members of the Enterobacteriaceae family. They are facultative anaerobic, Gram-negative bacilli that usually ferment lactose. Most fecal *E. coli* do not cause diarrhea. Six major groups of diarrheagenic *E. coli* have been characterized on the basis of clinical, biochemical, and molecular-genetic criteria: enterotoxigenic *E. coli* (ETEC); enteroinvasive *E. coli* (EIEC); enteropathogenic *E. coli* (EPEC); *Shiga* toxin–producing *E. coli* (STEC), also known as enterohemorrhagic *E. coli* (EHEC) or verotoxin producing *E. coli* (VTEC); enteroaggregative *E. coli* (EAEC or EggEC); and diffusely adherent *E. coli* (DAEC).

E. coli strains can also be categorized by their serogroup where O refers to the lipopolysaccharide (LPS) O-antigen or serotype where H refers to the flagellar antigen, for example, *E. coli* O157:H7. However, as each pathotype contains many serotypes (117 ETEC serotypes have been identified) and some serotypes can belong to more than 1 pathotype (e.g., O26:H11 can be either EPEC or EHEC depending on which specific virulence genes are present), serotyping frequently does not provide definitive identification of pathotypes.

Because *E. coli* are normal fecal flora, pathogenicity is defined by demonstration of virulence characteristics and association of those traits with illness (Table 200-1). The mechanism by which *E. coli* produces diarrhea typically involves adherence of organisms to a glycoprotein or glycolipid receptor, followed by production of some noxious substance that injures or disturbs the function of intestinal cells. The genes for virulence properties and for antibiotic resistance are often carried on transferable plasmids, pathogenicity islands, or bacteriophages. In the developing world, the various diarrheagenic *E. coli* cause frequent infections in the 1st few yr of life; diarrheagenic *E. coli* as a group are responsible for 30-40% of all diarrhea cases in children worldwide. They occur with increased frequency during the warm months in temperate climates and during rainy season months in tropical climates. Most diarrheagenic *E. coli* strains (except STEC) require a large inoculum of organisms to induce disease. Infection is most likely when food-handling or sewage-disposal practices are suboptimal. The diarrheagenic *E. coli* are also important in North America and Europe, although their epidemiology is less-well defined in these areas than in the developing world. In North America, the various diarrheagenic *E. coli* may be the etiology of as much as 30% of infectious diarrhea in children younger than 5 yr of age.

Many studies have found diarrheagenic *E. coli* pathotypes in a significant proportion of asymptomatic healthy children living in developing countries. Fecal contamination (human and animal), which is common in the underprivileged environments in which many young children live, facilitates the transmission of pathogens. In addition, with current modern, highly sensitive microbiologic methods, small numbers of bacteria can be detected in stool samples. Therefore, it is important to assess the prevalence of various enteropathogens in children with and without diarrhea, to interpret results. Excretion of enteropathogens by subjects without diarrhea may be explained by characteristics of the pathogens (virulence heterogeneity), the host (host susceptibility, age, nutritional status, breastfeeding, immunity), and environmental factors (inoculum size).

ENTEROTOXIGENIC *ESCHERICHIA COLI*

ETEC account for a sizeable fraction of dehydrating infantile diarrhea in the developing world (10-30%) and of traveler's diarrhea (20-60% of cases); ETEC is the most common cause of traveler's diarrhea. In a recent large multicenter diarrhea study (GEMS [global enteric multicenter study]) heat-stable enterotoxin (ST)-ETEC (with or without coexpression of heat-labile enterotoxin [LT]), was among the most important causes of diarrhea in young children in developing countries and was associated with increased risk of death. The typical signs and symptoms include explosive watery, nonmucoid, nonbloody diarrhea, abdominal pain, nausea, vomiting, and little or no fever. The illness is usually self-limited and resolves in 3-5 days but occasionally lasts longer than 1 wk.

ETEC cause few or no structural alterations in the gut mucosa. Diarrhea is caused by colonization of the small intestine and subsequent elaboration of enterotoxins. ETEC strains secrete an LT and/or an ST. LT, a large molecule consisting of 5 receptor-binding subunits and 1 enzymatically active subunit, is structurally, functionally, and immunologically related to cholera toxin produced by *Vibrio cholerae*. LT stimulates adenylate cyclase, resulting in increased cyclic adenosine monophosphate. ST is a small molecule not related to cholera toxin. ST stimulates guanylate cyclase, resulting in increased cyclic guanosine monophosphate. The genes for these toxins are encoded on plasmids.

Colonization of the intestine requires fimbrial colonization factor antigens (CFAs), which promote adhesion to the intestinal epithelium. CFAs are antigenic fimbriae that are currently targets for vaccine development. There are at least 25 CFA types; these antigens are composed of coli surface (CS) antigens and can be expressed alone or in combination. Prevalent colonization factors include CFA/I, CS1-CS7, CS14, and CS17. However, CFAs have not been detected on all ETEC strains. Although 30-50% of ETEC isolates have no characterized CFA by phenotypic screening, novel CFAs continue to be identified. The multiple CFAs and their allelic variants have made definition of immunity and development of useful vaccines difficult. A large proportion of strains produce a type IV pilus called *longus*, which functions as a colonization factor and is found among several other Gram-negative bacterial pathogens. ETEC strains also have the common pilus, produced by commensal and pathogenic *E. coli* strains. Among the nonfimbrial adhesions, TibA is a potent bacterial adhesin that mediates bacterial attachment and invasion of cells. For many years, the O serogroup was used to distinguish pathogenic from commensal *E. coli*. Because the pathogenic *E. coli* are now defined and classified by using probes or primers for specific virulence genes, determining the O serogroup has become less important. Of the more than 180 *E. coli* serogroups, only a relatively small number typically are ETEC. The most common O groups are O6, O8, O128, and O153, and based on some large retrospective studies, these serogroups only account for half of the ETEC strains.

ENTEROINVASIVE *ESCHERICHIA COLI*

Clinically, EIEC infections present either with watery diarrhea or a dysentery syndrome with blood, mucus, and leukocytes in the stools, as well as fever, systemic toxicity, crampy abdominal pain, tenesmus, and urgency. The illness resembles bacillary dysentery, because EIEC share virulence genes with *Shigella* spp. Sequencing of multiple housekeeping genes indicates that EIEC is more related to *Shigella* than to

Table 200-1 Clinical Characteristics, Pathogenesis, and Diagnosis of Diarrheagenic *E. coli*

PATHOGEN	POPULATIONS AT RISK	Characteristics of Diarrhea			Main Virulence Factors		DIAGNOSIS
		WATERY	BLOODY	DURATION	ADHERENCE FACTORS	TOXINS	
ETEC	>1 yr old and travelers	+++	—	Acute	Colonization factor antigens (CFs or CFAs); ECP	Heat-labile enterotoxin (LT) Heat-stable enterotoxin (ST)	Detection of enterotoxins (LT and ST) by enzyme immunoassays or PCR (*lt*, *st*)
EIEC	>1 yr old	+	++	Acute	Invasion plasmid antigen (IpaABCD)		Detection of invasion plasmid antigen of *Shigella* (*ipaH*) by PCR
EPEC	<2 yr old	+ + +	+	Acute, prolonged or persistent	A/E lesion, intimin/Tir, EspABD, Bfp	EspF, Map, EAST1, SPATEs (*EspC*)	Detection of intimin gene (*eae*) ± bundle-forming pili (*bfp*A) by PCR, and absence of *Shiga* toxins; HEp-2 cells adherence assay (LA, LLA)
STEC (EHEC/ VTEC)	6 mo-10 yr and the elderly	+	+++	Acute	A/E lesion, intimin/Tir, EspABD	*Shiga* toxins (Stx1, Stx2, and variants of Stx2)	Detection of *Shiga* toxins by enzyme immunoassays or PCR (*Stx*1, *Stx*2); stool culture on MacConkey-sorbitol media to detect *E. coli* O157. Simultaneous culture for O157 and nonculture assays to detect *Shiga* toxins
EAEC	<2 yr old, HIV-infected patients, and travelers	+++	+	Acute, prolonged, or persistent	Aggregative adherence fimbriae (AAF)	SPATEs (Pic, Pet), ShET1, EAST1	Detection of *AggR*, AA plasmid, and other virulence genes: *aap*, *aatA*, *astA*, *set1A* by PCR; HEp-2 cells adherence assay (AA)
DAEC	>1 yr old and travelers	++	—	Acute	Afa/Dr, AIDA-I	SPATEs (Sat)	Detection of Dr adhesins (daaC or daaD) and Dr-associated genes by PCR; HEp-2 cells adherence assay (DA)

—, Not present; +, present; ++, common; +++, very common; A/E lesion, attaching and effacing lesion; AA, aggregative adherence; Bfp, bundle-forming pili; DA, diffuse adherence; DAEC, diffusely adherent *E. coli;* EAEC, enteroaggregative *E. coli;* EAST1, enteroaggregative heat stable toxin; ECP, *E. coli* common pilus; EHEC, enterohemorrhagic *E. coli;* EIEC, enteroinvasive *E. coli;* EPEC, enteropathogenic *E. coli;* EspABD, *E. coli* secreted proteins A, B, and D; ETEC, enterotoxigenic *E. coli;* LA, localized adherence; LLA, localized-like adherence; PCR, polymerase chain reaction; ShET1, *Shigella* enterotoxin 1; SPATEs, serine protease autotransporter of Enterobacteriaceae; STEC, *Shiga* toxin–producing *E. coli;* Tir, translocated intimin receptor; VTEC, verotoxin-producing *E. coli*.

noninvasive *E. coli*. EIEC are mostly described in outbreaks; however, endemic disease occurs in developing countries where these bacteria can be isolated. In some areas of the developing world as many as 5% of sporadic diarrhea episodes and 20% of bloody diarrhea cases are caused by EIEC strains.

EIEC cause colonic lesions with ulcerations, hemorrhage, mucosal and submucosal edema, and infiltration by polymorphonuclear leukocytes. EIEC strains behave like *Shigella* in their capacity to invade gut epithelium and produce a dysentery-like illness. The invasive process involves initial entry into cells, intracellular multiplication, intracellular and intercellular spread, and host-cell death. All bacterial genes necessary for entry into the host cell are clustered within a 30-kb region of a large virulence plasmid; these genes are closely related to those found on the invasion plasmid of *Shigella* spp. This region carries genes encoding the entry-mediating proteins, which code for proteins forming a type III secretion apparatus required for secreting the invasins (IpaA-D and IpgD). IpaB and IpaC have been identified as the primary effector proteins of epithelial cell invasion. The type III secretion apparatus is a system triggered by contact with host cells; bacteria use it to transport proteins into the host cell plasma membrane and inject toxins into the cytoplasm.

EIEC encompass a small number of serogroups (O28ac, O29, O112ac, O124, O136, O143, O144, O152, O159, O164, O167, and some untypable strains). These serogroups have LPS antigens related to *Shigella* LPS, and, like shigellae, are nonmotile (they lack H or flagellar antigens) and are usually not lactose fermenting.

ENTEROPATHOGENIC *ESCHERICHIA COLI*

EPEC are a major cause of acute, prolonged, and persistent diarrhea in children younger than 2 yr of age in developing countries (20% of infant diarrhea). In developed countries, EPEC are responsible for occasional outbreaks in daycare centers and pediatric wards. Profuse watery, nonbloody diarrhea with mucus, vomiting, and low-grade fever are common symptoms. Prolonged diarrhea (>7 days) and persistent diarrhea (>14 days) can lead to malnutrition, a potentially serious outcome of EPEC infection in infants in the developing world. Studies show that breastfeeding is protective against diarrhea caused by EPEC.

EPEC colonization causes blunting of villi, inflammatory changes, and sloughing of superficial mucosal cells; these lesions can be found from the duodenum through the colon. EPEC induce a characteristic attaching and effacing histopathologic lesion, which is defined by the intimate attachment of bacteria to the epithelial surface and effacement of host cell microvilli. Factors responsible for the attaching and effacing lesion formation are encoded by the locus of enterocyte effacement, which is a pathogenicity island that contains the genes for a type III secretion system, the translocated intimin receptor (Tir) and intimin, and multiple effector proteins such as the *E. coli*–secreted proteins

(EspA-B-D). Some strains adhere to the host's intestinal epithelium in a pattern known as *localized adherence*; this trait is mediated in part by the type IV bundle-forming pilus (Bfp) encoded on a plasmid (the EAF plasmid). After initial contact, proteins are translocated through filamentous appendages forming a physical bridge between the bacteria and the host cell; bacterial effectors (EspB, EspD, Tir) are translocated through these conduits. Tir moves to the surface of host cells, where it is bound by a bacterial outer membrane protein intimin (encoded by the *eae* gene). Intimin-Tir binding triggers polymerization of actin and other cytoskeletal components at the site of attachment. The result of these cytoskeletal changes is intimate bacterial attachment to the host cell, enterocyte effacement, and pedestal formation.

Other locus of enterocyte effacement–encoded effectors include Map, EspF, EspG, EspH, and SepZ. Various other effector proteins are encoded outside the locus of enterocyte effacement and secreted by the type III secretion system (the non–locus of enterocyte effacement–encoded proteins or Nle). The contribution of these putative effectors (NleA/EspI, NleB, NleC, NleD, etc.) to virulence is still under investigation. There is variability in presence and expression of virulence genes among EPEC strains.

The *eae* (intimin) and *bfp*A genes are useful for identifying EPEC and for subdividing this group of bacteria into typical and atypical strains. *E. coli* strains that are *eae*$^+$/*bfp*A$^+$ are classified as "typical" EPEC; most of these strains belong to classic O:H serotypes. *E. coli* strains that are *eae*$^+$/*bfp*A$^-$ are classified as "atypical" EPEC. Typical EPEC have been considered for many years to be a leading cause of infantile diarrhea in developing countries and were considered rare in industrialized countries. However, current data suggest that atypical EPEC are more prevalent than typical EPEC in both developed and developing countries, even in persistent diarrhea cases. Determining which of these heterogeneous strains are true pathogens remains a work in progress. In the GEMS, typical EPEC was the main pathogen associated with increased risk of mortality, particularly in infants in Africa.

The classic EPEC serogroups include strains of 12 O serogroups: O26, O55, O86, O111, O114, O119, O125, O126, O127, O128, O142, and O158. However, various *E. coli* strains defined as EPEC based on presence of the intimin gene, belong to nonclassic EPEC serogroups, especially the atypical strains.

SHIGA TOXIN–PRODUCING *ESCHERICHIA COLI*

STEC cause a wide spectrum of diseases. STEC infections may be asymptomatic. Patients who develop intestinal symptoms can have mild diarrhea or severe hemorrhagic colitis. The gastrointestinal illness is characterized by abdominal pain with diarrhea that is initially watery but within a few days can become blood-streaked or grossly bloody. Although this pattern resembles that of shigellosis or EIEC disease, it differs in that fever is an uncommon manifestation. Most persons infected with STEC recover from the infection without further complication. However, 5-10% of children with STEC hemorrhagic colitis go on within a few days to develop systemic complications such as hemolytic–uremic syndrome (HUS), characterized by acute kidney failure, thrombocytopenia, and microangiopathic hemolytic anemia (see Chapter 518). Severe illness occurs most often among children from 6 mo-10 yr of age. STEC-positive young children with bloody diarrhea and neutrophilic leukocytosis in the early course of their diarrhea are at risk for HUS progression. The elderly can also develop HUS or thrombotic thrombocytopenic purpura.

STEC are transmitted person to person (e.g., in families and daycare centers) as well as by food and water; ingestion of a small number of organisms is sufficient to cause disease with some strains. Poorly cooked hamburger is a common cause of foodborne outbreaks, although many other foods (apple cider, lettuce, spinach, mayonnaise, salami, dry fermented sausage, and unpasteurized dairy products) have also been incriminated.

STEC affect the colon most severely. These organisms adhere to intestinal cells, and most strains that affect humans produce attaching-effacing lesions like those seen with EPEC. The attachment mechanism has genes (*intimin, Tir, EspA-D,* etc.) very closely related to those of EPEC. However, in addition to enterocyte attachment, these bacteria produce toxins that kill cells. These toxins (*Shiga* toxins [Stx]) are the key virulence factors of STEC. In the past, these toxins were also called verotoxins or *Shiga*-like toxins. There are 2 major *Shiga* toxin families, Stx1 and Stx2, with multiple subtypes identified by letters (e.g., Stx2a, Stx2c, etc.). Some STEC produce only Stx1 and others produce only one of the variants of Stx2, but many STEC have genes for several toxins. Stx1 is essentially identical to *Shiga* toxin, the protein synthesis–inhibiting exotoxin of *Shigella dysenteriae* serotype 1. Stx2 and variants of Stx2 are more distantly related to *Shiga* toxin, although they share key sequences with it.

These toxins are composed of a single A subunit noncovalently associated with a pentamer composed of identical B subunits. The B subunits bind to globotriaosylceramide (Gb_3), a glycosphingolipid receptor on host cells. The A subunit is taken up by endocytosis. The toxin target is the 28S rRNA, which is depurated by the toxin at a specific adenine residue, causing protein synthesis to cease and affected cells to die. These toxins are carried on lambdoid bacteriophages that are normally inactive when inserted into the bacterial chromosome; when the phages are induced to replicate (e.g., by the stress induced by many antibiotics), they cause lysis of the bacteria and release of large amounts of toxin. It is generally thought that the toxins enter the systemic circulation after translocation across the intestinal epithelium and damage vascular endothelial cells, resulting in activation of the coagulation cascade, formation of microthrombi, intravascular hemolysis, and ischemia.

Clinical outcome of STEC infection depends on both epithelial attachment and the toxin(s) produced by the infecting strain. The Stx2 family of toxins is associated with a higher risk of causing HUS. Strains that make only Stx1 often cause only watery diarrhea and are uncommonly associated with HUS.

The most common STEC serotypes are *E. coli* O157:H7, *E. coli* O111:NM, and *E. coli* O26:H11, although several hundred other STEC serotypes have also been described. *E. coli* O157:H7 is the most virulent serotype and the most frequently associated with HUS; however, other non-O157 serotypes also cause this illness.

ENTEROAGGREGATIVE *ESCHERICHIA COLI*

EAEC are associated with (1) acute, prolonged and persistent pediatric diarrhea in developing countries, most prominently in children younger than 2 yr of age and in malnourished children; (2) acute and persistent diarrhea in HIV-infected adults and children; and (3) acute traveler's diarrhea; EAEC is the second most common cause of travelers' diarrhea after ETEC. Typical EAEC illness is manifested by watery, mucoid, secretory diarrhea with low-grade fever and little or no vomiting. The watery diarrhea can persist for 14 days or longer. In some studies, many patients have grossly bloody stools. EAEC are associated with growth retardation and malnutrition in infants in the developing world.

EAEC form a characteristic biofilm on the intestinal mucosa and induce shortening of the villi, hemorrhagic necrosis, and inflammatory responses. The proposed model of pathogenesis of EAEC involves 3 phases: adherence to the intestinal mucosa by way of the aggregative adherence fimbriae or related adhesins; enhanced production of mucus; and production of toxins and inflammation that results in damage of the mucosa and intestinal secretion. Diarrhea caused by EAEC is predominantly secretory. The intestinal inflammatory response (elevated fecal lactoferrin, interleukin [IL]-8 and IL-1β) may be related to growth impairment and malnutrition.

EAEC are recognized by adherence to HEp-2 cells in an aggregative, stacked-brick–like pattern, called *aggregative adherence* (AA). EAEC virulence factors include the AA fimbriae (AAFI, -II, and -III) that confers the AA phenotype. Some strains produce toxins, including the plasmid-encoded enterotoxin EAST1 (encoded by *ast*A), homolog of the ETEC ST; an autotransporter toxin called Pet; other STATE toxins; and the chromosomally encoded enterotoxin ShET1 (encoded by *setA* and *setB*). Other virulence factors include outer membrane and

secreted proteins such as dispersin (*aap*), and the dispersin transport complex (aatPABCD). EAEC is a heterogeneous group of *E. coli*. The original diagnostic criteria (HEp-2 cell adherence pattern) identified many strains that are probably not true pathogens; genetic criteria appear to more reliably identify true pathogens. A transcriptional activator called AggR controls expression of plasmid-borne and chromosomal virulence factors. Identification of AggR appears to reliably identify illness-associated pathogenic EAEC strains ("typical" EAEC). It has been documented that EAEC *agg*R-positive strains carrying 1, 2, or 3 of the genes *aap*, *ast*A, and *set1A* are significantly associated with diarrhea compared with EAEC isolates lacking these genes. Other than AAF and AggR, there is a great deal of genomic diversity among EAEC strains with corresponding heterogeneity in virulence.

Strains of *E. coli* categorized as EAEC belong to multiple serogroups, including O3, O7, O15, O44, O77, O86, O126, and O127.

DIFFUSELY ADHERENT *ESCHERICHIA COLI*

Although the status of DAEC as true pathogens has been in doubt, multiple studies in both developed and developing countries have associated these organisms with diarrhea, particularly in children after the 1st yr or 2 of life. DAEC strains isolated from children and adults seem to represent 2 different bacterial populations. Discrepancies among epidemiologic studies may be explained by age-dependent susceptibility to diarrhea or by the use of inappropriate detection methods. Data suggest that these organisms also cause traveler's diarrhea in adults. DAEC produces acute watery diarrhea that is usually not dysenteric but is often prolonged.

DAEC strains have been identified on the basis of their diffuse adherence pattern on cultured epithelial cells. Two putative adherence factors have been described for DAEC strains. One of the adherence factors is the surface fimbriae (designated F1845) that are responsible for the diffuse adherence phenotype in a prototype strain. These fimbriae are homologous with members of the Afa/Dr family of adhesins, which are identified by hybridization with a specific probe, *daaC*, common to operons encoding Afa/Dr adhesions. A second putative adhesin associated with the diffuse adherence pattern phenotype is an outer membrane protein, designated AIDA-I. The contribution of other putative effectors (*icuA, fimH, afa, agg-3A, pap*, *astA, shET1)* to virulence is still under investigation. The only documented secreted factor associated with DAEC infection is the SPATE Sat. Bacteria expressing Afa/Dr adhesins interact with membrane-bound receptors, including decay-accelerating factor. The structural and functional lesions induced by DAEC include loss of microvilli and decrease in the expression and enzyme activities of functional brush-border–associated proteins. Afa/Dr DAEC isolates produce a secreted autotransporter toxin that induces marked fluid accumulation in the intestine. DAEC strains typically induce IL-8 production in vitro. Serogroups of DAEC strains are less-well defined than are those of other diarrheagenic *E. coli*.

ENTEROAGGREGATIVE HEMORRHAGIC *ESCHERICHIA COLI*

In 2011, a massive outbreak of an unusual O104:H4 strain of diarrheagenic *E. coli* began in Germany. Eventually more than 4,000 individuals were sickened with hemorrhagic colitis; illness involved primarily adults (<100 ill children were identified). More than 800 individuals developed HUS and more than 50 died. DNA sequencing showed that this strain was an EAEC that had acquired a lambdoid bacteriophage with genes for producing Stx2a. It was thus a hybrid pathogen with colonization mechanisms like a typical EAEC strain and toxin production typical of an STEC strain. This outbreak strain carries Pic on the chromosome and a pAA-like plasmid encoding AAF, AggR, Pet, ShET1, and dispersin. A second virulence plasmid encodes multiple antibiotic resistances. The high morbidity and mortality associated with this strain may reflect the stronger adherence of EAEC compared with STEC, allowing more Stx to be transferred and more resultant pathology. Some have called this strain an enteroaggregative hemorrhagic *E. coli* or *Shiga* toxin producing EAEC. Whether *Shiga* toxin production in an EAEC background merits separate classification is unclear. Organisms with *Shiga* toxin genes in an atypical EPEC background were designated as a separate group (referred to as STEC, EHEC or verotoxin-producing *E. coli*) before the relative importance of the various genes was clear. As noted above, EPEC are a heterogeneous group themselves. The important issue is not the nomenclature but rather the concept that virulence genes can move between *E. coli* and new variants can arise.

DIAGNOSIS

The clinical features of illness are seldom distinctive enough to allow confident diagnosis, and routine laboratory studies are of very limited value. Diagnosis currently depends heavily on laboratory studies that are not readily available to practitioners. Practical, non–DNA-dependent, methods for routine diagnosis of diarrheagenic *E. coli* have been developed primarily for the STEC. Serotype O157:H7 is suggested by isolation of an *E. coli* that fails to ferment sorbitol on MacConkey sorbitol medium; latex agglutination confirms that the organism contains O157 LPS. Other STEC can be detected in routine hospital laboratories using commercially available enzyme immunoassay or latex agglutination to detect *Shiga* toxins, although variable sensitivity of commercial immunoassays has limited their value.

Although some STEC (O157:H7 strains) can be detected in routine microbiology laboratories using selective media and appropriate antisera, the diagnosis of other diarrheagenic *E. coli* infection is typically made based on tissue culture assays (e.g., HEp-2-cells assay for EPEC, EAEC, DAEC) or identification of specific virulence factors of the bacteria by phenotype (e.g., toxins) or genotype. DNA probes for genes encoding the various virulence traits are the best diagnostic tests but are currently available only as a research tool. Multiplex, real-time, or conventional polymerase chain reaction can be used for presumptive diagnosis of isolated *E. coli* colonies. The genes commonly used for diagnostic polymerase chain reaction are *lt* and *st* for ETEC, *IpaH* or *iaL* for EIEC, *eae* and *bfp*A for EPEC, *eae, Stx1,* and *Stx2* for STEC, *AggR* or the AA plasmid for EAEC, and *daaC* or *daaD* for DAEC. Suspected organisms can be forwarded to reference or research laboratories for definitive evaluation, although such effort is seldom necessary.

Serotyping does not provide definitive identification of pathotypes (except for selected cases such as O157:H7) because each pathotype contains many serotypes and some serotypes can belong to more than 1 pathotype. Consequently, serotyping should not be used routinely for diarrheagenic *E. coli* identification in clinical laboratories (e.g., to diagnose EPEC in infantile diarrhea), except during an outbreak investigation.

Other laboratory data are at best nonspecific indicators of etiology. Fecal leukocyte examination of the stool is often positive with EIEC or occasionally positive with other diarrheagenic *E. coli*. With EIEC and STEC there may be an elevated peripheral blood polymorphonuclear leukocyte count with a left shift. Determination of *Stx2* blood levels in the early postbloody diarrhea period may be useful to identify children at risk of HUS; however, this method requires further evaluation. Fecal lactoferrin, IL-8, and IL-1β can be used as inflammatory markers. Electrolyte changes are nonspecific, reflecting only fluid loss.

TREATMENT

The cornerstone of management is appropriate fluid and electrolyte therapy. In general, this therapy should include oral replacement and maintenance with rehydration solutions such as those specified by the World Health Organization. Pedialyte and other readily available oral rehydration solutions are acceptable alternatives. After refeeding, continued supplementation with oral rehydration fluids is appropriate to prevent recurrence of dehydration. Early refeeding (within 6-8 hr of initiating rehydration) with breast milk or infant formula or solid foods should be encouraged. Prolonged withholding of feeding can lead to chronic diarrhea and malnutrition. If the child is malnourished, oral zinc should be given to speed recovery and decrease the risk of future diarrheal episodes.

Specific antimicrobial therapy of diarrheagenic *E. coli* is problematic because of the difficulty of making an accurate rapid diagnosis of these

pathogens and the unpredictability of antibiotic susceptibilities. Treatment is complicated by the fact that these organisms are often multiply resistant to antibiotics as a consequence of their previous exposure to inappropriate antibiotic therapy. Multiple studies in developing countries have found diarrheagenic *E. coli* strains to be commonly resistant to antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX) and ampicillin (60-70%). Most data come from case series or clinical trials in adults with traveler's diarrhea. ETEC respond to antimicrobial agents such as TMP-SMX when the *E. coli* strains are susceptible. ETEC cases from traveler's diarrhea trials respond to ciprofloxacin, azithromycin, and rifaximin. However, other than for a child recently returning from travel in the developing world, empirical treatment of severe *watery diarrhea* with antibiotics is seldom appropriate.

EIEC infections may be treated before the availability of culture results because the clinician suspects shigellosis and has begun empirical therapy. If the organisms prove to be susceptible, TMP-SMX is an appropriate choice. Although treatment of EPEC infection with TMP-SMX intravenously or orally for 5 days may be effective in speeding resolution, the lack of a rapid diagnostic test makes treatment decisions difficult. Ciprofloxacin or rifaximin are useful for EAEC traveler's diarrhea, but pediatric data are sparse. Specific therapy for DAEC has not been defined.

The STEC represent a particularly difficult therapeutic dilemma; many antibiotics can induce toxin production and phage-mediated bacterial lysis with toxin release. Antibiotics should not be given for STEC infection because they can increase the risk of HUS (see Chapter 518).

PREVENTION OF ILLNESS

In the developing world, prevention of disease caused by diarrheagenic *E. coli* is probably best done by maintaining prolonged breastfeeding, paying careful attention to personal hygiene, and following proper food- and water-handling procedures. People traveling to these places can be best protected by handwashing, consuming only processed water, bottled beverages, breads, fruit juices, fruits that can be peeled, or foods that are served steaming hot.

Prophylactic antibiotic therapy is effective in adult travelers but has not been studied in children and is not recommended. Public health measures, including sewage disposal and food-handling practices, have made pathogens that require large inocula to produce illness relatively uncommon in industrialized countries. Foodborne outbreaks of STEC are a problem for which no adequate solution has been found. During the occasional hospital outbreak of EPEC disease, attention to enteric isolation precautions and cohorting may be critical.

The nature of protective immunity against diarrheagenic *E. coli* is not fully understood, and no vaccines are available for clinical use in children. There are multiple vaccine candidates based on bacterial toxins and colonization factors that have shown promise for prevention of ETEC in adult travelers, but long-term protection with these vaccines has not been optimal, particularly in children.

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Chapter 201

Cholera

Anna Lena Lopez

Cholera is a dehydrating diarrheal disease that can rapidly lead to death, if appropriate treatment is not immediately initiated. One of the most outbreak-prone diseases, cholera is substantially underreported, with 590,000 cases recorded in 2011 but an estimated 2 million cases and at least 94,000 deaths occurring annually. The past decade has seen an increase in the number of cholera cases, which have been reported in 58 countries affecting all regions of the world over this period. The ongoing outbreak in Haiti that began in 2010 emphasizes how infectious diseases, including cholera, can easily reemerge in areas that have long been considered free of the disease.

ETIOLOGY

The disease is caused by *Vibrio cholerae*, a Gram-negative, comma-shaped bacillus, subdivided into serogroups by its somatic O antigen. Of the more than 200 serogroups, only serogroups O1 and O139 have been associated with epidemics, although some non-O1, non-O139 *V. cholerae* strains (e.g., O75 and O141) are pathogenic and can cause small outbreaks. A flagellar H antigen is present but is not used for species identification. The O1 serogroup is further divided into classical and the El Tor biotypes based on its biochemical characteristics. Since the turn of the 21st century, only O1 El Tor has been reported; hybrids and variants of *V. cholerae* O1 El Tor possessing classical genes have been reported worldwide. These hybrid and variant strains have been associated with more-severe disease.

Each biotype may be further subdivided into Inaba, Ogawa, and Hikojima serotypes based on the antigenic determinants on the O antigen. Inaba strains have A and C antigenic determinants, whereas Ogawa strains have A and B antigenic determinants. Hikojima strains produce all 3 antigenic determinants but are unstable and rare.

EPIDEMIOLOGY

The 1st 6 cholera pandemics originated in the Indian subcontinent and were caused by classical O1 *V. cholerae*. The 7th pandemic is the most extensive of all and is caused by *V. cholerae* O1 El Tor. It began in 1961 in Sulawesi, Indonesia, and has spread to the Indian subcontinent, Southeast Asia, Africa, Oceania, Southern Europe, and the Americas. In 1991, *V. cholerae* O1 El Tor first appeared in Peru before rapidly spreading in the Americas. Cholera becomes endemic in areas following outbreaks when a large segment of the population develops immunity to the disease after recurrent exposure. The disease is now endemic in parts of Africa and Asia and will likely be endemic in Haiti.

In 1992, the first non-O1 *V. cholerae* that resulted in epidemics was identified in India and Bangladesh and was designated *V. cholerae* O139. From 1992-1994, this organism replaced O1 as the predominant cause of cholera in South Asia but has since been an uncommon etiologic agent.

The hybrid El Tor strains were first identified sporadically in Bangladesh. In 2004, during routine surveillance in Mozambique, isolates of *V. cholerae* O1 El Tor carrying classical genes were identified. Since then, hybrid and variant El Tor strains have been reported in other parts of Asia and Africa and have caused outbreaks in India and Vietnam. Although the classical biotype has virtually disappeared, its genes remain within the El Tor biotype. The current circulating strain in Haiti is closely related to the South Asian strain.

Humans are the only known hosts for *V. cholerae* but free-living and plankton-associated *V. cholerae* exist in the marine environment. The organism thrives best in moderately salty water but can survive in rivers and freshwater if nutrient levels are high, as occurs when there is organic pollution such as human feces. The formation of a biofilm on abiotic surfaces and the ability to enter a viable but nonculturable state have been hypothesized as factors that allow *V. cholerae* to persist in the environment. Surface sea temperature, pH, chlorophyll content, the presence of iron compounds and chitin, and climatic conditions such as amount of rainfall and sea level rise are all important environmental factors that influence the survival of *V. cholerae* in the environment and the expression of cholera toxin, an important virulence determinant.

Consumption of contaminated water and ingestion of undercooked shellfish are the main modes of transmission, with the latter more often seen in developed countries. In cholera-endemic areas, the incidence is highest among children <2 yr of age; however, in epidemics, all age groups are commonly affected. Persons with blood group O, decreased gastric acidity, malnutrition, immunocompromised state, and absence of local intestinal immunity (prior exposure by infection or vaccination) are at increased risk for developing severe disease. Household

contacts of cholera-infected patients are at high risk for the disease, because the stools of infected patients contain high concentrations of *V. cholerae*. Moreover, as *V. cholerae* organisms are shed, they enter into a hyperinfective state, requiring a 10-100 times lower infectious dose compared to organisms that were not shed by humans.

PATHOGENESIS

Following ingestion of *V. cholerae* from the environment, several changes occur in the vibrios as they traverse the human intestine: increased expression of genes required for nutrient acquisition, down-regulation of chemotactic response, and expression of motility factors. Together these changes allow the vibrios to reach a hyperinfectious state, leading to lower infectious doses required in secondarily infected persons. This hyperinfectivity may remain for 5-24 hr after excretion.

Large inocula of bacteria ($>10^8$) are required for severe cholera to occur; however, for persons whose gastric barrier is disrupted, a much lower dose (10^5) is required. If the vibrios survive gastric acidity, they then colonize the small intestine through various factors such as toxin coregulated pili and motility, leading to efficient delivery of cholera toxin. The cholera toxin consists of 5 binding B subunits and 1 active A subunit. The B subunits are responsible for binding to the GM_1 ganglioside receptors located in the small intestinal epithelial cells. After binding, the A subunit is then released into the cell, where it stimulates adenylate cyclase and initiates a cascade of events. An increase in cyclic adenosine monophosphate leads to an increase in chloride secretion by the crypt cells, which, in turn, leads to inhibition of absorption of sodium and chloride by the microvilli. These events eventually lead to massive purging of electrolyte rich isotonic fluid in the small intestine that exceeds the absorptive capacity of the colon, resulting in rapid dehydration and depletion of electrolytes, including sodium, chloride, bicarbonate, and potassium. Metabolic acidosis and hypokalemia then ensue.

CLINICAL MANIFESTATIONS

Most cases of cholera are mild or inapparent. Among symptomatic cases, approximately 20% develop severe dehydration that can rapidly lead to death. Following an incubation period of 1-3 days (range: several hours to 5 days), acute watery diarrhea and vomiting ensues. The onset may be sudden, with profuse watery diarrhea, but some patients have a prodrome of anorexia and abdominal discomfort and the stool may initially be brown. Diarrhea can progress to painless purging of profuse rice-water stools (suspended flecks of mucus) with a fishy smell, which is the hallmark of the disease (Fig. 201-1). Vomiting with clear watery fluid is usually present at the onset of the disease.

Cholera gravis, the most severe form of the disease, results when purging rates of 500-1,000 mL/hr occur. This purging leads to dehydration manifested by decreased urine output, a sunken fontanel (in infants), sunken eyes, absence of tears, dry oral mucosa, shriveled hands and feet (washerwoman's hands), poor skin turgor, thready pulse, tachycardia, hypotension, and vascular collapse (Fig. 201-2). Patients with metabolic acidosis can present with typical Kussmaul breathing. Although patients may be initially thirsty and awake, they rapidly progress to obtundation and coma. If fluid losses are not rapidly corrected, death can occur within hours.

LABORATORY FINDINGS

Findings associated with dehydration such as elevated urine specific gravity and hemoconcentration are evident. Hypoglycemia is a common finding that is caused by decreased food intake during the acute illness. Serum potassium may be initially normal or even high in the presence of metabolic acidosis; however, as the acidosis is corrected, hypokalemia can become evident. Metabolic acidosis due to bicarbonate loss is a prominent finding in severe cholera. Serum sodium and chloride levels may be normal or decreased, depending on the severity of the disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In children who have acute watery diarrhea with severe dehydration residing in a cholera endemic area or who have recently traveled to an area known to have cholera, the disease may be suspected pending laboratory confirmation. Cholera differs from other diarrheal disease in that it often occurs in large outbreaks affecting both adults and children.

Treatment of dehydration should begin as soon as possible. Diarrhea caused by other etiologic causes (e.g., enterotoxigenic *Escherichia coli* or rotavirus) may be difficult to distinguish from cholera clinically. Microbiologic isolation of *V. cholerae* remains the gold standard for diagnosis. Although definitive diagnosis is not required for treatment to be initiated, laboratory confirmation is necessary for epidemiologic surveillance. *V. cholerae* may be isolated from stools, vomitus, or rectal swabs. Specimens may be transported on Cary-Blair media, if they

Figure 201-1 Rice water stool in a patient with cholera. *(Modified from Harris JB, LaRocque RC, Qadri F: Cholera.* Lancet *379:2466–2474, 2012.)*

Figure 201-2 A child, lying on a cholera cot, showing typical signs of severe dehydration from cholera. The patient has sunken eyes, lethargic appearance, and poor skin turgor, but within 2 hr was sitting up, alert, and eating normally. *(From Sack DA, Sack RB, Nair GB, et al: Cholera.* Lancet *363:223–233, 2004.)*

cannot be processed immediately. Selective media such as thiosulfate–citrate–bile salts sucrose agar that inhibit normal flora should be used. Because most laboratories in industrialized countries do not routinely culture for *V. cholerae*, clinicians should request appropriate cultures for clinically suspected cases.

Stool examination reveals few fecal leukocytes and erythrocytes because cholera does not cause inflammation. Dark-field microscopy may be used for rapid identification of typical "darting motility" in wet mounts of rice water stools, which disappears once specific antibodies against *V. cholerae* O1 or O139 are added. Rapid diagnostic tests are currently available and in the future may be used in areas with limited laboratory capacity, allowing early identification of cases at the onset of an outbreak and facilitating a timely response. Molecular identification with the use of polymerase chain reaction and DNA probes is available but often not used in areas where cholera exists.

COMPLICATIONS

Delayed initiation of rehydration therapy or inadequate rehydration often leads to complications. Renal failure from prolonged hypotension can occur. Unless potassium supplementation is provided, hypokalemia can lead to nephropathy and focal myocardial necrosis. Hypoglycemia is common among children and can lead to seizures unless it is appropriately corrected.

TREATMENT

Rehydration is the mainstay of therapy (see Chapter 57). Effective and timely case management considerably decreases mortality. Children with mild or moderate dehydration may be treated with oral rehydration solution (ORS) unless the patient is in shock, is obtunded, or has intestinal ileus. Vomiting is not a contraindication to ORS. Severely dehydrated patients require intravenous fluid, ideally with lactated Ringer solution. When available, rice-based ORS should be used during rehydration, because this fluid has been shown to be superior to standard ORS in children and adults with cholera. Close monitoring is necessary, especially during the 1st 24 hr of illness, when large amounts of stool may be passed. After rehydration, patients have to be reassessed every 1-2 hr, or more frequently if profuse diarrhea is ongoing. Feeding should not be withheld during diarrhea. Frequent, small feedings are better tolerated than less-frequent, large feedings.

Antibiotics should only be given in cases with moderately severe to severe dehydration (Table 201-1). As soon as vomiting stops (usually within 4-6 hr after initiation of rehydration therapy), an antibiotic to which local *V. cholerae* strains are sensitive must be administered. Antibiotics shorten the duration of illness, decrease fecal excretion of vibrios, decrease the volume of diarrhea, and reduce the fluid requirement during rehydration. Single-dose antibiotics increase compliance; doxycycline, ciprofloxacin, and azithromycin are effective against cholera. There are increasing reports of resistance to tetracyclines, trimethoprim-sulfamethoxazole, and other drugs. Because of these multidrug resistant strains, antibiotic treatment must be tailored based on available susceptibility results from the area. Cephalosporins and aminoglycosides are not clinically effective against cholera and therefore should not be used, even if in vitro tests show strains to be sensitive.

Zinc should be given as soon as vomiting stops. Zinc deficiency is common among children in many developing countries. Zinc supplementation among children younger than 5 yr of age shortens the duration of diarrhea and reduces subsequent diarrhea episodes when given daily for 14 days at the time of the illness. Children younger than 6 mo of age should receive 10 mg of oral zinc for 2 wk, and for children older than 6 mo, 20 mg of oral zinc may be given daily.

PREVENTION

Improved personal hygiene, access to clean water, and sanitation are the mainstays of cholera control. Appropriate case management substantially decreases case fatalities to <1%. Travelers from developed countries often have no prior exposure to cholera and are therefore at risk of developing the disease. Children traveling to cholera-affected areas should avoid drinking potentially contaminated water and eating high-risk foods such as raw or undercooked fish and shellfish. No country or territory requires vaccination against cholera as a condition for entry. There is no cholera vaccine licensed in the United States.

Alarmed by the increasing prevalence of cholera, in 2011, the World Health Assembly recommended the use of oral cholera vaccines to complement existing water, sanitation, and hygiene initiatives for cholera control. Older-generation parenteral cholera vaccines have not been recommended by World Health Organization because of the limited protection they confer and their high reactogenicity. Oral cholera vaccines are safe, protective for approximately 2-5 yr duration, and confer moderate herd protection. Two oral cholera vaccines are currently available internationally and recognized by World Health Organization (Table 201-2). An internationally licensed killed whole-cell oral cholera vaccine with recombinant B subunit (Dukoral, Crucell) has been available in more than 60 countries, including the European Union, and provides protection against cholera in endemic areas as well as cross-protection against certain strains of enterotoxigenic *E.*

Table 201-1 Recommended Antimicrobials for Cholera*

RECOMMENDING BODY	ANTIBIOTIC OF CHOICE	ALTERNATIVE
WHO† (antibiotics recommended for cases with severe dehydration)	**Adults** Doxycycline 300 mg given as a single dose PO *or* Tetracycline 500 mg 4 times a day × 3 days PO **Children** Tetracycline 12.5 mg/kg/dose 4 times a day × 3 days (up to 500 mg per dose × 3 days) PO	**Adults** Erythromycin 250 mg 4 times a day × 3 days PO **Children** Erythromycin 12.5 mg/kg/dose 4 times a day × 3 days (up to 250 mg 4 times a day × 3 days) PO
PAHO‡ (antibiotics recommended for cases with moderate to severe dehydration)	**Adults** Doxycycline 300 mg PO given as a single dose **Children** Erythromycin 12.5 mg/kg/dose 4 times a day × 3 days (up to 500 mg per dose × 3 days) *or* Azithromycin, 20 mg/kg as a single dose (up to 1 g)	**Adults** Ciprofloxacin 1g PO single dose *or* Azithromycin 1g PO single dose **Children** Ciprofloxacin 20 mg/kg PO as a single dose *or* Doxycycline 2-4 mg/kg PO as a single dose

*Antibiotic selection must be based on sensitivity patterns of strains of *Vibrio cholerae* O1 or O139 in the area.

†Adapted from World Health Organization: *The treatment of diarrhea: a manual for physicians and other senior health workers*, 4th revision, Geneva, 2005, World Health Organization.

‡Adapted from Pan American Health Organization: *Recommendations for clinical management of cholera*. Washington, DC, 4 November 2010. Available at: http://new.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=10813&Itemid=

Table 201-2 Available Oral Cholera Vaccines*

VACCINE TRADE NAME	CONTENTS	DOSING SCHEDULE
Dukoral (Crucell)	1 mg of recombinant B subunit of cholera toxin plus 2.5 × 10^{10} of the following strains of *V. cholerae*: - Formalin-killed El Tor Inaba (Phil 6973) - Heat-killed classical Inaba (Cairo 48) - Heat-killed classical Ogawa (Cairo 50) - Formalin-killed classical Ogawa (Cairo 50)	Children 2-6 yr: 3 doses, 1-6 wk apart Adults and children >6 yr: 2 doses, 1-6 wk apart
Shanchol (Shantha Biotech)	*V. cholerae* O1 - 600 EU Formalin-killed El Tor Inaba (Phil 6973) - 300 EU Heat-killed classical Inaba (Cairo 48) - 300 EU Heat-killed classical Ogawa (Cairo 50) - 300 EU Formalin-killed classical Ogawa (Cairo 50) *V. cholerae* O139-600 EU of Formalin-killed strain 4260B	Adults and children ≥1 year of age: 2 doses, 2 wk apart

*WHO prequalified vaccines.

coli. The 2nd vaccine (Shanchol, Shantha Biotech) is a variant of the 1st vaccine and contains both *V. cholerae* O1 and O139 antigens but does not contain the B-subunit. Because it does not contain the B-subunit, the vaccine does not require buffer for administration, thereby reducing administration costs and resources, making it easier to deploy.

Oral cholera vaccines have been available for more than 2 decades and are mostly used by travelers from industrialized countries going to cholera-affected regions. With the World Health Organization declaration, countries are now using oral cholera vaccines in mass vaccination campaigns where cholera remains a substantial problem. A cholera vaccine stockpile, established by WHO, is now available and can be accessed by countries at risk for cholera, supplementing efforts to lessen the impact of this ongoing cholera scourge.

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Chapter 202

Campylobacter

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Campylobacter, most commonly *Campylobacter jejuni* and *Campylobacter coli*, are found globally and are among the most common causes of human intestinal infections. Clinical presentation varies by age and underlying conditions.

ETIOLOGY

Eighteen species and 6 subspecies of *Campylobacter* are recognized at this time. Most of these have been isolated from humans, and many are considered pathogenic. The most significant of these are *C. jejuni* and *C. coli,* which may cause the majority of human enteritis. More than 100 serotypes of *C. jejuni* have been identified. *C. jejuni* has been subspeciated into *C. jejuni* subspecies *jejuni* and *C. jejuni* subspecies *doylei.* Although *C. jejuni* subspecies *doylei* has been isolated from humans, it is much less common, less hearty, and more difficult to isolate. Other species, including *Campylobacter fetus, Campylobacter lari,* and *Campylobacter upsaliensis,* among others, have been isolated from patients with diarrhea, although much less frequently (Table 202-1). Additional *Campylobacter* species have been isolated from clinical specimens, but their roles as pathogens have not been established.

Campylobacter organisms are Gram-negative, curved, thin (0.2-0.4 μm wide), non–spore-forming rods (1.5-3.5 μm long) that usually have tapered ends. They are smaller than most other enteric bacterial pathogens and have variable morphology, including short comma-shaped or S-shaped organisms and long, multispiraled, filamentous, seagull-shaped organisms. Individual organisms are usually motile with a flagellum at 1 or both poles. Such morphology enables these bacteria to colonize the mucosal surfaces of both the gastrointestinal and respiratory tracts and move through them in a spiraling motion. Most *Campylobacter* organisms are microaerophilic, occasionally partially anaerobic, and oxidase positive. Most can transform into coccoid forms under adverse conditions, especially oxidation.

C. jejuni has a circular chromosome of 1.64 million base pairs that is predicted to encode 1,654 proteins and 54 stable RNA species. The genome is unusual in that there are almost no insertion sequences or phage-associated sequences and very few repeat sequences.

EPIDEMIOLOGY

Worldwide, *Campylobacter* enteritis is a leading cause of acute diarrhea. Efforts to reduce *Campylobacter* contamination and safe handling practices have caused decreased incidence. *Campylobacter* infections can be both foodborne and waterborne, and most commonly result from ingestion of contaminated poultry (chicken, turkey) or raw milk. Less commonly, they come from drinking water, household pets (cats, dogs, hamsters), and farm animals. Infections are more common in resource-limited settings, are prevalent year-round in tropical areas, and can exhibit seasonal peaks in temperate regions (late spring with a peak midsummer in most of the United States, with a smaller secondary peak in late fall). In industrialized countries, *Campylobacter* infections peak in early childhood and again in young adulthood (15-44 yr of age). The second peak is not seen with *Salmonella* and *Shigella* infections. In developing countries, repeated infections are common in childhood, leading to increased immunity and rare disease in adulthood. Each year in the United States, there are an estimated 2.5 million cases of *Campylobacter* infection. Of these, death is rare, with 50-150 reports annually. In the Netherlands, medical record review shows that on average each resident acquires asymptomatic *Campylobacter* infection every 2 yr, progressing to symptomatic infection in approximately 1% of colonized people.

Foodborne illness is most common and can be seen with the consumption of raw or undercooked meat, as well as by cross-contamination of other foods. Although chickens are the classic source of *Campylobacter,* many animal sources of human food can also harbor *Campylobacter,* including seafood. *C. coli* has been linked to swine. Poultry is more likely to be heavily contaminated while red meats often have fewer organisms. Unpasteurized milk products are also a documented source. Additionally, many pets can carry *Campylobacter,* and insects inhabiting contaminated environments can acquire the organism. Shedding from animals can contaminate water sources. Humans can acquire infection from water, although much less frequently than from contaminated food. Airborne transmission of *Campylobacter* has occurred in farm workers. Use of antimicrobials in animal foods may

Table 202-1 *Campylobacter* Species Associated with Human Disease

SPECIES	DISEASES IN HUMANS	COMMON SOURCES
C. jejuni	Gastroenteritis, bacteremia, Guillain-Barré syndrome	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water
C. coli	Gastroenteritis, bacteremia	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, oysters, water
C. fetus	Bacteremia, meningitis, endocarditis, mycotic aneurysm, diarrhea	Sheep, cattle, birds, dogs
C. hyointestinalis	Diarrhea, bacteremia, proctitis	Swine, cattle, deer, hamsters, raw milk, oysters
C. lari	Diarrhea, colitis, appendicitis, bacteremia, urinary tract infection	Seagulls, water, poultry, cattle, dogs, cats, monkeys, oysters, mussels
C. upsaliensis	Diarrhea, bacteremia, abscesses, enteritis, colitis, hemolytic uremic syndrome	Cats, dogs, other domestic pets
C. concisus	Diarrhea, gastritis, enteritis, periodontitis	Human oral cavity, dogs
C. sputorum	Diarrhea, bedsores, abscesses, periodontitis	Human oral cavity, cattle, swine, dogs
C. rectus	Periodontitis	
C. mucosalis	Enteritis	Swine, dogs
C. jejuni subspecies *doylei*	Diarrhea, colitis, appendicitis, bacteremia, urinary tract infection	Swine
C. curvus	Gingivitis, alveolar abscess	Poultry, raw milk, cats, dogs, cattle, swine, monkeys, water, human oral cavity
C. gracilis	Head and neck abscesses, abdominal abscesses, empyema	Dogs
C. cryaerophila	Diarrhea	Swine

increase the prevalence of antibiotic-resistant *Campylobacter* isolated from humans.

Human infection can result from exposure to as few as 500 bacteria, although a higher dose (>9,000 bacteria) is often needed to cause illness. At times, *C. jejuni* and *C. coli* spread person to person, perinatally, and at childcare centers where diapered toddlers are present. People infected with *C. jejuni* usually shed the organism for weeks but can shed for months. Hand washing is key to preventing spread in these environments.

PATHOGENESIS

Most *Campylobacter* isolates are acid sensitive, and should, in theory, be eradicated in the stomach. Therefore, models for the pathogenesis of *C. jejuni* enteritis include mechanisms to transit the stomach, adhere to intestinal mucosal cells, and initiate intestinal lumen fluid accumulation. Host conditions associated with reduced gastric acidity, such as proton pump inhibitor use, and foods capable of shielding organisms in transit through the stomach may help allow *Campylobacter* to reach the intestine. Once there, *Campylobacter* are able to adhere to and invade intestinal mucosal cells through motility, including use of flagellae, as well as by the use of surface proteins (e.g., PEB1 and CadF), large plasmids (e.g., pVir), surface adhesins (e.g., JIpA), and chemotactic factors. Lumen fluid accumulation is associated with direct damage to mucosal cells resulting from bacterial invasion and potentially from a cholera-like toxin and other cytotoxins. Additionally, *C. jejuni* has mechanisms that enable transit away from the mucosal surface. The factors that are used are dependent on the species involved.

Campylobacter differ from other enteric bacterial pathogens in that they have both *N*- and *O*-linked glycosylation capacities. *N*-linked glycosylation is associated with molecules expressed on the bacterial surface, and *O*-linked glycosylation appears limited to flagellae. Slipped-strand mispairing in glycosylation loci results in modified, antigenically distinct surface structures. It is hypothesized that antigenic variation provides a mechanism for immune evasion.

C. fetus possesses a high-molecular-weight S-layer protein that mediates high-level resistance to serum-mediated killing and phagocytosis and is therefore thought to be responsible for the propensity to produce **bacteremia.** *C. jejuni* and *C. coli* are generally sensitive to serum-mediated killing, but serum-resistant variants exist. It has been suggested that these serum-resistant variants may be more capable of systemic dissemination.

Campylobacter infections can be followed by Guillain-Barré syndrome, reactive arthritis, and erythema nodosum. Such complications are thought to be from molecular mimicry between nerve tissue and *Campylobacter* surface antigens. Most *Campylobacter* infections are not followed by immunoreactive complications, indicating that host conditions as well as other factors, in addition to molecular mimicry, are required for these complications. There is some evidence of an association between *Campylobacter* infection and irritable bowel syndrome. It is proposed that low-grade inflammation caused by *Campylobacter,* below the threshold that can be detected by endoscopy, results in crosstalk with gut nerves, leading to symptoms.

CLINICAL MANIFESTATIONS

There are a variety of clinical presentations of *Campylobacter* infections, depending on host factors such as age, immunocompetence, and underlying conditions. Infection presents most commonly as gastroenteritis, but also as bacteremia, neonatal infections, and, occasionally, extraintestinal infections.

Acute Gastroenteritis

Diarrhea is most commonly caused by *C. jejuni* (90-95%) or *C. coli,* and rarely by *C. lari, Campylobacter hyointestinalis,* or *C. upsaliensis.* The average incubation period is 3 days (range: 1-7 days). One-third of symptomatic patients can have a prodrome with fever, headache, dizziness, and myalgias; 1-3 days later, they develop cramping abdominal pain and loose, watery stools or, less commonly, bloody, mucus-containing stools. In severe cases (approximately 15%), blood appears in the stools 2-4 days after the onset of symptoms. In younger children, more than 50% may develop blood in their stools. Some patients do not develop diarrhea at all, most commonly children 6-15 yr old. Fever may be the only manifestation initially and is most pronounced in patients older than 1 yr of age. Febrile seizures can also occur in this age group. Sixty percent to 90% of older children also complain of

abdominal pain. The abdominal pain is most commonly periumbilical and sometimes persists after the stools return to normal. The abdominal pain can mimic appendicitis, colitis, or intussusception. Nausea is common, with up to 25% of adults developing vomiting. Vomiting tends to be more common the younger the patient and is most frequent in infants.

Diarrhea lasts around 7 days and will resolve spontaneously. More mild disease can last 1-2 days; 20-30% of patients will have symptoms for 2 wk and 5-10% are symptomatic for longer than 2 wk. Relapse can occur in 5-10% of patients. Persistent or recurrent *Campylobacter* gastroenteritis has been reported in immunocompetent patients, in patients with hypogammaglobulinemia (both congenital and acquired), and in patients with AIDS. Persistent infection can mimic chronic inflammatory bowel disease; therefore, *Campylobacter* infection should also be considered when evaluating for inflammatory bowel disease. There is some suggestion that infection may also be the trigger for the development of inflammatory bowel disease. Fecal shedding of the organisms in untreated patients usually lasts for 2-3 wk, with a range from a few days to several months. Shedding tends to occur longer in young children. Acute appendicitis, mesenteric lymphadenitis, and ileocolitis have been reported in patients who have had appendectomies during *C. jejuni* infection.

Bacteremia

Transient bacteremia has been shown in early acute infection in 0.1-1% of patients. With the exception of bacteremia caused by *C. fetus*, bacteremia with *Campylobacter* occurs most often among malnourished children, patients with chronic illnesses or immunodeficiency, such as HIV, and in the very old and very young. Bacteremia can also occur in patients without underlying disease. The majority of cases of bacteremia are asymptomatic. *C. fetus* causes bacteremia in adults with or without identifiable focal infection, usually in the setting of underlying conditions such as malignancy or diabetes mellitus. When symptomatic, *C. jejuni* bacteremia is associated with fever, headache, malaise, and abdominal pain. Relapsing or intermittent fever is associated with night sweats, chills, and weight loss when the illness is prolonged. Lethargy and confusion can occur, but focal neurologic signs are unusual without cerebrovascular disease or meningitis. A cough is present occasionally, without additional evidence of pulmonary involvement. Moderate leukocytosis may be found. Variable presentations, including transient asymptomatic bacteremia, rapidly fatal septicemia, and prolonged bacteremia of 8-13 wk, have been described.

Focal Extraintestinal Infections

Focal infections caused by *C. jejuni* are rare and occur mainly among neonates and immunocompromised patients. Multiple sites have been reported including meningitis, pneumonia, thrombophlebitis, pancreatitis, cholecystitis, ileocecitis, urinary tract infection, arthritis, peritonitis, myocarditis, pericarditis, and endocarditis. *C. fetus* shows a predilection for vascular endothelium, leading to endocarditis, pericarditis, thrombophlebitis, and mycotic aneurysms. *C. hyointestinalis* has been associated with proctitis; *C. upsaliensis* has been associated with breast abscesses; *Campylobacter rectus* has been associated with periodontitis.

Perinatal Infections

Perinatal infections are most often acquired at birth from a mother infected with or shedding *Campylobacter.* Maternal *C. fetus* and *C. jejuni* infections may be asymptomatic and can result in abortion, stillbirth, premature delivery, or neonatal infection with sepsis and meningitis. Severe perinatal infections are uncommon and are caused most often by *C. fetus* and rarely by *C. jejuni*. Neonatal infection with *C. jejuni* is associated with diarrhea that may be bloody. Nosocomial infections in nurseries have also been described.

DIAGNOSIS

The clinical presentation of *Campylobacter* enteritis can be similar to that of enteritis caused by other bacterial pathogens. The differential diagnosis includes *Shigella, Salmonella, Escherichia coli*, *Yersinia enterocolitica, Aeromonas, Vibrio parahaemolyticus,* and amebiasis. Fecal leukocytes are found in as many as 75% of cases, and fecal blood is present in 50% of cases. *Campylobacter* should be considered in patients with bloody stools, fever, and abdominal pain.

The diagnosis of *Campylobacter* enteritis is usually confirmed by identification of the organism in cultures of stool or rectal swabs. Isolation is most likely from selective media such as CAMPY-agar grown in microaerophilic conditions (5-10% oxygen), 1-10% carbon dioxide, with some hydrogen. Some *C. jejuni* grow best at 42°C (107.6°F). Growth on solid media results in small (0.5-1.0 mm), slightly raised, smooth colonies. Organisms can be identified from stool under the microscope in approximately 50% of known *Campylobacter* cases. Gram stain is even less sensitive. Stool culture is greater than 90% sensitive and is the standard method of diagnosis. Visible growth on stool culture is most often present in 1-2 days. Visible growth in blood cultures is often not apparent until 5-14 days after inoculation.

Routine culture may be adequate for isolation of *C. jejuni* because of the large numbers of bacteria that are often present. However, because campylobacters grow more slowly under routine conditions than do other enteric bacteria, routine culture can result in failure because of overgrowth of other enteric bacteria. Culture for campylobacters can be enhanced, when necessary, with selective media. However, selective culture media developed to enhance isolation of *C. jejuni* may inhibit the growth of other *Campylobacter* species. Filtration methods are available and can preferentially enrich for *Campylobacter* by selecting for their small size. These methods allow subsequent culture of the enriched sample on antibiotic free media, enhancing rates of isolation of *Campylobacter* organisms inhibited by the antibiotics included in standard selective media. Isolation of *Campylobacter* from normally sterile sites does not require enhancement procedures. Clinically, it is not necessary to speciate *Campylobacter,* as clinical disease is the same. Speciation can be done, when needed, and specialized labs can perform strain typing when required for epidemiologic purposes.

For rapid diagnosis of *Campylobacter* enteritis, direct carbol fuchsin stain of fecal smear, indirect fluorescence antibody test, dark-field microscopy, or latex agglutination can be used. Enzyme immunoassay and polymerase chain reaction have been tested and used in research studies but are not currently available in the clinical setting. These tests are quite sensitive. However, there continues to be concern regarding the specificity of these tests. In a recent study published in 2013, enzyme immunoassay had a positive predictive value of 91% in verification studies, which dropped to 42% in routine diagnostic studies. Polymerase chain reaction seems to be more specific and currently is being studied regarding differentiation of species. At this time, the recommendation remains to confirm all positive rapid tests with culture. Serologic diagnosis is also possible. This is especially important in patients with late-onset reactive arthritis or Guillain-Barré syndrome, as these patients may have negative stool cultures.

COMPLICATIONS

Severe, prolonged *C. jejuni* infection can occur in patients with immunodeficiencies, including hypogammaglobulinemia and malnutrition. In patients with AIDS, increased frequency and severity of *C. jejuni* infection have been reported; severity correlates inversely with CD4 count. Complications can include acute complications, as described earlier, and late onset complications that may present after the acute infection has resolved. The most common late-onset complications include reactive arthritis and Guillain-Barré syndrome.

Reactive Arthritis

Reactive arthritis can accompany *Campylobacter* enteritis in adolescents and adults, especially in patients who are positive for HLA-B27. Reactive arthritis occurs in up to 3% of patients, though up to 13% may have joint symptoms. This manifestation appears most commonly 1-2 wk after the onset of diarrhea, but has been seen 5-40 days later. It involves mainly large joints and resolves without sequelae. The arthritis is typically migratory and occurs without fever. Synovial fluid lacks bacteria. The arthritis responds well to nonsteroidal antiinflammatory

drugs and typically resolves after 1 wk to several months. Reactive arthritis with conjunctivitis, urethritis, and rash (including erythema nodosum) also occurs, but is less common.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is an acute demyelinating disease of the peripheral nervous system characterized clinically by acute flaccid paralysis and is the most common cause of neuromuscular paralysis worldwide. GBS carries a mortality rate of approximately 2%, and approximately 20% of patients with this disease develop major neurologic sequelae. *C. jejuni* has been identified as the trigger in up to 45% of patients with GBS and is most closely linked to the serotypes Penner O19 and O14. It has been reported 1-12 wk after *C. jejuni* gastroenteritis in 1 of every 1,000 *C. jejuni* infections. Stool cultures obtained from patients with GBS at the onset of neurologic symptoms have yielded *C. jejuni* in greater than 25% of the cases. Serologic studies suggest that 20-45% of patients with GBS have evidence of recent *C. jejuni* infection. Molecular mimicry between nerve tissue GM_1 ganglioside and *Campylobacter* surface antigens may be the triggering factor in *Campylobacter*-associated GBS. The Miller-Fisher variant, which more commonly affects cranial nerves, is characterized by ataxia, areflexia, and ophthalmoplegia, and is linked to cross-reacting antibodies to the GQ1b ganglioside found in cranial nerve myelin. The next common serotype is Penner O2. When associated with *Campylobacter,* GBS is more likely to be the axonal form and has a worse prognosis with slower recovery and more neurologic disability. The management of GBS includes supportive care, intravenous immunoglobulin, and plasma exchange.

Other Complications

Immunoglobulin A nephropathy and immune complex glomerulonephritis with *C. jejuni* antigens in the kidneys have been reported. *Campylobacter* infection has also been associated with hemolytic anemia.

TREATMENT

Fluid replacement, correction of electrolyte imbalance, and supportive care are the mainstays of treatment of children with *Campylobacter* gastroenteritis. Antimotility agents can cause prolonged or fatal disease and should not be used. The need for antibiotic therapy in patients with uncomplicated gastroenteritis is controversial. Data suggest a shortened duration of symptoms (by an average of 1.3 days) and intestinal shedding of organisms if antibiotics are initiated early in the disease.

Most *Campylobacter* isolates are susceptible to macrolides, fluoroquinolones, aminoglycosides, chloramphenicol, tetracyclines, and clindamycin, and are resistant to cephalosporins, rifampin, penicillins, trimethoprim, and vancomycin. Resistance to tetracyclines, macrolides, and fluoroquinolones has been described. Antibiotic resistance among *C. jejuni* has become a serious worldwide problem. Macrolide resistance is increased in areas such as Thailand and Ireland, whereas fluoroquinolone resistance has been reported in Spain, Hungary, and multiple developing countries in greater than 50% of cultured *Campylobacter*. Fluoroquinolone resistance continues to increase in the United States and is related to the use of quinolones in veterinary medicine and food products, as well as acquisition from travelers. Erythromycin-resistant *Campylobacter* isolates are uncommon; therefore, erythromycin or azithromycin is the drug of choice if therapy is required. Drug sensitivities should be determined for patients who do not respond to therapy. Antibiotics are recommended for patients with bloody stools, high fever, or a severe course, and for children who are immunosuppressed or have underlying diseases. Sepsis is treated with parenteral antibiotics such as an aminoglycoside, meropenem, or imipenem. Extraintestinal infections should also be treated with antibiotics. For extraintestinal infection caused by *C. fetus*, prolonged therapy is advised. *C. fetus* isolates resistant to erythromycin have been reported.

PROGNOSIS

Although *Campylobacter* gastroenteritis is usually self-limited, immunosuppressed children (including children with AIDS) can experience a protracted or severe course. Septicemia in newborns and immunocompromised hosts has a poor prognosis, with an estimated mortality rate of 30-40%. Additional prognosis is based upon the secondary sequelae that may develop.

PREVENTION

Most human *Campylobacter* infections are sporadic and are acquired from infected animals or contaminated foods. Interventions to minimize transmission include cooking meats thoroughly, preventing recontamination after cooking by not using the same surfaces, utensils, or containers for both uncooked and cooked food, and avoiding unpasteurized dairy products. Also, it is important to ensure that water sources are not contaminated and that water is kept in clean containers. Contact with infected animals should be avoided. No specific isolation is required; standard precautions are sufficient. However, children in diapers should be kept out of daycare until the diarrhea resolves. Breastfeeding appears to decrease symptomatic *Campylobacter* disease but does not reduce colonization.

Several approaches at immunization have been studied, including the use of live-attenuated organisms, subunit vaccines, and killed whole-cell vaccines. No vaccine is currently available.

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Chapter 203

Yersinia

Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

The genus *Yersinia* is a member of the family Enterobacteriaceae and comprises more than 14 named species, 3 of which are established as human pathogens. *Yersinia enterocolitica* is by far the most common *Yersinia* species causing human disease and it produces fever, abdominal pain that can mimic appendicitis, and diarrhea. *Yersinia pseudotuberculosis* is most often associated with mesenteric lymphadenitis. *Yersinia pestis* is the agent of plague and most commonly causes an acute febrile lymphadenitis (bubonic plague) and less commonly occurs as septicemic, pneumonic, pharyngeal, or meningeal plague. Other *Yersinia* organisms are uncommon causes of infections of humans, and their identification is often an indicator of immunodeficiency. *Yersinia* is enzootic and can colonize pets. Infections in humans are incidental and most often result from contact with infected animals or their tissues; ingestion of contaminated water, milk, or meat; or, for *Y. pestis,* the bite of infected fleas. Association with human disease is less clear for *Yersinia frederiksenii, Yersinia intermedia, Yersinia kristensenii*, *Yersinia aldovae, Yersinia bercovieri, Yersinia mollaretii, Yersinia rohdei,* and *Yersinia ruckeri*. Some *Yersinia* isolates replicate at low temperatures (1-4°C [33.8-39.2°F]) or survive at high temperatures (50-60°C [122-140°F]). Thus, common food preparation and storage and common pasteurization methods might not limit the number of bacteria. Most are sensitive to oxidizing agents.

203.1 *Yersinia enterocolitica*

Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

ETIOLOGY

Y. enterocolitica is a large, Gram-negative coccobacillus that exhibits little or no bipolarity when stained with methylene blue and carbol

fuchsin. It ferments glucose and sucrose but not lactose, is oxidase-negative, and reduces nitrate to nitrite. These facultative anaerobes grow well on common culture media and are motile at 22°C (71.6°F) but not at 37°C (98.6°F). Optimal growth temperature is 25-28°C (77-82.4°F); however, the organism can grow at refrigerator temperature. *Y. enterocolitica* includes pathogenic and nonpathogenic members. It has 6 different biotypes (1A, 1B, and 2-5). *Y. enterocolitica* relies on other bacteria for iron uptake, and conditions associated with iron overload increase risk of infection.

EPIDEMIOLOGY

This agent is transmitted to humans through food, water, animal contact, and contaminated blood products. Transmission can occur from mother to newborn. *Y. enterocolitica* appears to have a global distribution but is seldom a cause of tropical diarrhea. In 2010, incidence of culture-confirmed *Y. enterocolitica* infection in the United States was 0.3 per 100,000 population (52% decrease from incidence in 1996-1998). Infection may be more common in Northern Europe. Prevalence in fecal samples from asymptomatic humans of nonvirulent *Y. enterocolitica* biotype 1A was 1.1% in 1 study. Most infections occur among children younger than 5 yr of age (incidence: 1.6-1.9 per 100,000 population), with the majority among children younger than 1 yr of age. It is estimated that *Y. enterocolitica* accounts for 5% of illnesses secondary to major bacterial enteric pathogens in children younger than 5 yr old in the United States. Cases are more common in colder months and among males.

Natural reservoirs of *Y. enterocolitica* include pigs, rodents, rabbits, sheep, cattle, horses, dogs, and cats, with pigs being the major animal reservoir. A recent publication estimated direct or indirect contact with animals, including pets, other domesticated animals, as well as wild animals, to be responsible for <1% of cases of enteric illnesses caused by *Y. enterocolitica*. Culture and molecular techniques have found the organism in a variety of foods and beverages, including vegetable juice, pasteurized milk, carrots, and water. Consumption of contaminated water or food, specially undercooked pork, is the most common form of transmission to humans. A source of sporadic *Y. enterocolitica* infections is pig offal (chitterlings). In 1 study, 71% of human isolates were indistinguishable from the strains isolated from pigs. *Y. enterocolitica* is an occupational threat to butchers. There is evidence that under conventional farm conditions pigs can be raised free of *Y. enterocolitica*.

In part because of its capacity to multiply at refrigerator temperatures, *Y. enterocolitica* can be transmitted by intravenous injection of contaminated fluids, including blood products.

Patients with conditions leading to iron overload are at higher risk of developing *Yersinia* infections.

PATHOGENESIS

The organisms most often enter by the alimentary tract and cause mucosal ulcerations in the ileum. Necrotic lesions of Peyer patches and mesenteric lymphadenitis occur. If septicemia develops, suppurative lesions can be found in infected organs. Infection can trigger reactive arthritis and erythema nodosum.

Virulence traits of pathogenic biotypes (1B and 2-5) are encoded by chromosomal genes and a highly conserved 70 kb virulence plasmid (pYV/pCD). The chromosomal genes control the production of heat stable enterotoxins and the plasmid allows penetration through the intestinal wall. Adherence, invasion, and toxin production are the essential mechanisms of pathogenesis. The bacteria mainly invade the intestinal epithelium in the Peyer patches of the ileum. After invasion plasmid encoded type III secretion of 3 antiphagocytic proteins protects *Yersinia* against the immunologic response of local macrophages. From Peyer patches bacteria can disseminate to cause local or systemic disease. Motility appears to be required for *Y. enterocolitica* pathogenesis. Serogroups that predominate in human illness are O:3, O:8, O:9, and O:5,27. Yersinia does not produce siderophores and uses analogous siderophores from other bacteria or host-chelated iron stores to thrive, placing patients with iron overload as in hemochromatosis, thalassemia, and sickle cell disease at higher risk for infection.

CLINICAL MANIFESTATIONS

Disease occurs most often as enterocolitis with diarrhea, fever, and abdominal pain. Acute enteritis is more common among younger children, and mesenteric lymphadenitis that can mimic appendicitis may be found in older children and adolescents. Stools may be watery or contain leukocytes and, less commonly, frank blood and mucus. *Y. enterocolitica* is excreted in stool for 1-4 wk. Family contacts of a patient are often found to be asymptomatically colonized with *Y. enterocolitica*. *Y. enterocolitica* septicemia is less common and is most often found in very young children (<3 mo of age) and immunocompromised persons. Systemic infection can be associated with splenic and hepatic abscesses, osteomyelitis, septic arthritis, meningitis, endocarditis, and mycotic aneurysms. Exudative pharyngitis, pneumonia, empyema, lung abscess, and acute respiratory distress syndrome uncommonly occur.

Reactive complications include erythema nodosum, reactive arthritis, and rarely uveitis. These manifestations may be more common in selected populations (northern Europeans), in association with HLA-B27, and in girls.

DIAGNOSIS

Diagnosis is made usually through isolation of the organism usually from the stool. *Y. enterocolitica* is easily cultured from normally sterile sites but requires special procedures for isolation from stool, where other bacteria can outgrow it. Cold enrichment, where a sample is held in buffered saline, can result in preferential growth of *Yersinia,* but the procedure takes weeks. Polymerase chain reaction (PCR) and DNA microarray are more sensitive than culture, with DNA microarray more sensitive and accurate than multiplex PCR. Many laboratories do not routinely perform the procedures required to detect *Y. enterocolitica*. Procedures targeted to this organism must be specifically requested. A history indicating contact with environmental sources of *Yersinia* and detection of fecal leukocytes are helpful indicators of a need to test for *Y. enterocolitica*. The isolation of a *Yersinia* from stool should be followed by tests to confirm that the isolate is a pathogen. Serodiagnosis is possible but not readily available.

DIFFERENTIAL DIAGNOSIS

The clinical presentation is similar to other forms of bacterial enterocolitis. The most common considerations include *Shigella, Salmonella, Campylobacter, Clostridium difficile,* enteroinvasive *Escherichia coli, Y. pseudotuberculosis*, and, occasionally, *Vibrio*-related diarrheal disease. Amebiasis, appendicitis, Crohn disease, ulcerative colitis, diverticulitis, and pseudomembranous colitis should also be considered.

TREATMENT

Enterocolitis in an immunocompetent patient is a self-limiting disease, and no benefit from antibiotic therapy is established. Patients with systemic infection and very young children (in whom septicemia is common) should be treated. *Yersinia* organisms are typically susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), aminoglycosides, third-generation cephalosporins, and quinolones, although strains resistant to quinolones have been recently reported. *Y. enterocolitica* produces β-lactamases, which are responsible for resistance to penicillins and first-generation cephalosporins. TMP-SMX is the recommended empirical treatment in children for enterocolitis (generally a 5-day course), because it has activity against most strains and is well tolerated. In severe infections such as bacteremia, third-generation cephalosporins, with or without aminoglycosides, are effective, and usually a 3 wk course of therapy is administered with possible transition to oral therapy. Patients on deferoxamine should discontinue iron chelation therapy during treatment for *Y. enterocolitica,* especially if they have complicated gastrointestinal infection or extraintestinal infection.

COMPLICATIONS

Reactive arthritis, erythema nodosum, erythema multiforme, hemolytic anemia, thrombocytopenia, and systemic dissemination of bacteria have been reported in association with *Y. enterocolitica* infection.

Septicemia is more common in younger children, and reactive arthritis is more common in older patients. Arthritis appears to be mediated by immune complexes, which form as a result of antigenic mimicry, and viable organisms are not present in involved joints.

PREVENTION

Prevention centers on reducing contact with environmental sources of *Yersinia.* Breaking or sterilization of the chain from animal reservoirs to humans holds the greatest potential to reduce infections, and the techniques applied must be tailored to the reservoirs in each geographic area. There is no licensed vaccine.

Bibliography is available at Expert Consult.

203.2 *Yersinia pseudotuberculosis*

Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

Y. pseudotuberculosis has a worldwide distribution; *Y. pseudotuberculosis* disease is less common than *Y. enterocolitica* disease. The most common form of disease is a mesenteric lymphadenitis that produces an appendicitis-like syndrome. *Y. pseudotuberculosis* is associated with a Kawasaki disease–like illness in approximately 8% of cases.

ETIOLOGY

Y. pseudotuberculosis is a small Gram-negative aerobic and facultative anaerobic coccobacillus. Like *Y. enterocolitica,* it ferments glucose and does not ferment lactose, is oxidase negative, is catalase producing, is urea splitting, and shares a number of morphologic and culture characteristics. It is differentiated biochemically from *Y. enterocolitica* on the basis of ornithine decarboxylase activity, fermentation of sucrose, sorbitol, and cellobiose, and other tests, although some overlap between species occurs. Antisera to somatic O antigens and sensitivity to *Yersinia* phages can also be used to differentiate the 2 species. Subspecies-specific DNA sequences that allow direct probe- and primer-specific differentiation of *Y. pestis, Y. pseudotuberculosis,* and *Y. enterocolitica* have been described. *Y. pseudotuberculosis* is more closely related phylogenetically to *Y. pestis* than to *Y. enterocolitica.*

EPIDEMIOLOGY

Y. pseudotuberculosis is zoonotic, with reservoirs in wild rodents, rabbits, deer, farm animals, various birds, and domestic animals, including cats and canaries. Transmission to humans is by consumption of or contact with contaminated animals or contact with an environmental source contaminated by animals (often water). Direct evidence of transmission of *Y. pseudotuberculosis* to humans by consumption of lettuce and raw carrots has been reported. The organism has a worldwide distribution; however, infections are more commonly reported in Europe, in boys, and in the winter. During 1996-2007 FoodNet reported 18 cases of infections secondary to *Y. pseudotuberculosis* in the United States, with an annual average incidence of 0.04 per 1,000,000 persons. When compared to *Y. enterocolitica* infections, those caused by *Y. pseudotuberculosis* are more likely to be invasive and occur in adolescents and adults. Iron-overloading conditions, HIV infection, and other debilitating diseases (including liver cirrhosis) may predispose to invasive *Y. pseudotuberculosis* infection.

PATHOGENESIS

Ileal and colonic mucosal ulceration and mesenteric lymphadenitis are hallmarks of the infection. Necrotizing epithelioid granulomas may be seen in the mesenteric lymph nodes, but the appendix is often grossly and microscopically normal. The mesenteric nodes are often the only source of isolation of the organism. *Y. pseudotuberculosis* antigens bind directly to human leukocyte antigen class II molecules and can function as superantigens, which might account for the clinical illness resembling Kawasaki disease.

CLINICAL MANIFESTATIONS

Pseudoappendicitis and mesenteric lymphadenitis with abdominal pain, right lower quadrant tenderness, fever, and leukocytosis is the most common clinical presentation. Enterocolitis and extraintestinal spread are uncommon. Iron overload, diabetes mellitus, and chronic liver disease are often found concomitantly with extraintestinal *Y. pseudotuberculosis* infection. Renal involvement with tubulointerstitial nephritis, azotemia, pyuria, and glucosuria can occur. *Y. pseudotuberculosis* can present as a Kawasaki disease-like illness with fever of 1-2 days duration; strawberry tongue; pharyngeal erythema; a scarlatiniform rash; cracked, red, swollen lips; conjunctivitis; sterile pyuria; periungual desquamation; and thrombocytosis. Other uncommon manifestations include septic arthritis, massive lower gastrointestinal bleeding, postaneurysmal prosthetic vascular infection, and acute encephalopathy.

DIAGNOSIS

PCR of involved tissue can be used to identify the organism; isolation by culture can require an extended interval. Involved mesenteric lymph nodes removed at appendectomy can yield the organism by culture. Abdominal CT scan or ultrasound examination of children with unexplained fever and abdominal pain can reveal a characteristic picture of enlarged mesenteric lymph nodes and thickening of the terminal ileum with or without peritoneal findings including appendiceal inflammation and periappendiceal fluid. *Y. pseudotuberculosis* is rarely recovered from stool. Serologic procedures are available, but not in most routine laboratories.

DIFFERENTIAL DIAGNOSIS

Appendicitis (most commonly), inflammatory bowel disease, and other intraabdominal infections should be considered. Kawasaki disease, staphylococcal or streptococcal disease, leptospirosis, Stevens-Johnson syndrome, and collagen vascular diseases, including acute-onset juvenile rheumatoid arthritis, can mimic the syndrome with prolonged fever and rash. *C. difficile* colitis, meningitis, encephalitis, enteropathic arthropathies, acute pancreatitis, sarcoidosis, toxic shock syndrome, typhoid fever, and ulcerative colitis may also be considered.

TREATMENT

Uncomplicated mesenteric lymphadenitis caused by *Y. pseudotuberculosis* is a self-limited disease, and antimicrobial therapy is not required. Few data exist on optimal treatment and duration of therapy. Infections with *Y. pseudotuberculosis* can generally be managed same as those caused by *Y. enterocolitica*. Culture-confirmed bacteremia should be treated with an aminoglycoside, ampicillin, TMP-SMX, a third-generation cephalosporin, a fluoroquinolones, or chloramphenicol.

COMPLICATIONS

Erythema nodosum and reactive arthritis can follow infection. Coronary aneurysm formation has been described with disease presenting as Kawasaki-like illness. Rare local complications of gastrointestinal disease include perforation, obstruction, and intussusception.

PREVENTION

Avoiding exposure to potentially infected animals and good food-handling practices can prevent infection. The sporadic nature of the disease makes application of targeted prevention measures difficult.

Bibliography is available at Expert Consult.

203.3 Plague *(Yersinia pestis)*

Ramia Zakhour, Gloria P. Heresi, and James R. Murphy

ETIOLOGY

Y. pestis is a Gram-negative, facultative anaerobe that is a pleomorphic nonmotile, non-spore-forming coccobacillus and is a potential agent

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of bioterrorism. It evolved from *Y. pseudotuberculosis* through acquisition of chromosomal changes and plasmid-associated factors that are essential to its virulence and survival in mammalian hosts and fleas. *Y. pestis* shares bipolar staining appearance with *Y. pseudotuberculosis* and can be differentiated by biochemical reactions, serology, phage sensitivity, and molecular techniques. The *Y. pestis* genome has been determined and is approximately 4,600,000 base pairs in size. *Y. pestis* exists in 3 biovars: Antigua (Africa), Medievalis (central Asia), and Orientalis (widespread).

EPIDEMIOLOGY

Plague is endemic in at least 24 countries. Approximately 3,000 cases are reported worldwide per year, with 100-200 deaths. Plague is uncommon in the United States (0-40 reported cases/yr); most of these cases occur west of a line from east Texas to east Montana, with 80% of cases in New Mexico, Arizona, and Colorado. The epidemic form of disease killed approximately 25% of the population of Europe in the Middle Ages in one of a number of epidemics and pandemics. The epidemiology of epidemic plague involves extension of infection from the zoonotic reservoirs to urban rats, *Rattus rattus* and *Rattus norvegicus,* and from fleas of urban rats to humans. Epidemics are no longer seen. Selective pressure exerted by plague pandemics in medieval Europe is hypothesized for enrichment of a deletion mutation in the gene encoding CCR5 (CCR5-Δ32). The enhanced frequency of this mutation in European populations endows approximately 10% of European descendants with resistance to HIV-1.

The most common mode of transmission of *Y. pestis* to humans is through flea bites. Historically, most human infections are thought to have resulted from bites of fleas that acquired infection from feeding on infected urban rats. Less commonly, infection is caused by contact with infectious body fluids or tissues or inhalation of respiratory secretions of infected animals. Nowadays most cases of plague secondary to direct animal contact or inhalation of animal secretions are related to domestic cats. Direct transmission from human to human through droplet inhalation is possible but extremely rare. Laboratory transmission of *Y. pestis* has been described as well. Sylvatic plague can exist as a stable enzootic infection or as an epizootic disease with high host mortality. Ground squirrels, rock squirrels, prairie dogs, rats, mice, bobcats, cats, rabbits, and chipmunks may be infected. Transmission among animals is usually by flea bite or by ingestion of contaminated tissue. *Xenopsylla cheopis* is the flea most commonly associated with transmission to humans, but more than 30 species of fleas have been demonstrated as vector competent, and *Pulex irritans,* the human flea, can transmit plague and might have been an important vector in some historical epidemics. Both sexes are similarly affected by plague, and transmission is more common in colder regions and seasons, possibly because of temperature effects on *Y. pestis* infections in vector fleas.

PATHOGENESIS

In the most common form of plague, infected fleas regurgitate organisms into a patient's skin during feeding. The bacteria translocate via lymphatics to regional lymph nodes, where *Y. pestis* replicates, resulting in bubonic plague. In the absence of rapidly implemented specific therapy, bacteremia can occur, resulting in purulent, necrotic, and hemorrhagic lesions in many organs. Both plasmid and chromosomal genes are required for full virulence. Pneumonic plague can be secondary to bacteremia or primary when infected material is inhaled. The organism is highly transmissible from persons with pneumonic plague and from domestic cats with pneumonic infection. This high transmissibility and high morbidity and mortality have provided an impetus for attempts to use *Y. pestis* as a biologic weapon.

CLINICAL MANIFESTATIONS

Y. pestis infection can manifest as several clinical syndromes; infection can also be subclinical. The 3 principal clinical presentations of plague are bubonic, septicemic, and pneumonic. **Bubonic plague** is the most common form and accounts for 80-90% of cases in the United States. From 2-8 days after a flea bite, lymphadenitis develops in lymph nodes closest to the inoculation site, including the inguinal (most common), axillary, or cervical region. These buboes are remarkable for tenderness. Fever, chills, weakness, prostration, headache, and the development of septicemia are common. The skin might show insect bites or scratch marks. Purpura and gangrene of the extremities can develop as a result of disseminated intravascular coagulation. These lesions may be the origin of the name Black Death. Untreated plague results in death in more than 50% of symptomatic patients. Death can occur within 2-4 days after onset of symptoms.

Occasionally, *Y. pestis* establishes systemic infection and induces the systemic symptoms seen with bubonic plague without causing a bubo **(primary septicemic plague).** Because of the delay in diagnosis linked to the lack of the bubo, septicemic plague carries a higher case fatality rate than bubonic plague. In some regions, bubo-free septicemic plague accounts for 25% of cases.

Pneumonic plague is the least common but most dangerous and lethal form of the disease. Pneumonic plague can result from hematogenous dissemination, or, rarely, as primary pneumonic plague after inhalation of the organism from a human or animal with plague pneumonia or potentially from a biologic attack. Signs of pneumonic plague include severe pneumonia with high fever, dyspnea, and hemoptysis.

Plague meningitis, tonsillitis, or gastroenteritis can occur. Meningitis tends to be a late complication following inadequate treatment. Tonsillitis and gastroenteritis can occur with or without apparent bubo formation or lymphadenopathy.

DIAGNOSIS

Plague should be suspected in patients with fever and history of exposure to small animals in endemic areas. Thus, bubonic plague is suspected in a patient with a painful swollen lymph node, fever, and prostration who has been exposed to fleas or rodents in the western United States. A history of camping or the presence of flea bites increases the index of suspicion.

Y. pestis is readily transmitted to humans by some routine laboratory manipulations. Thus, *it is imperative to clearly notify a laboratory* when submitting a sample suspected of containing *Y. pestis.* Laboratory diagnosis is based on bacteriologic culture or direct visualization using Gram, Giemsa, or Wayson stains of lymph node aspirates, blood, sputum, or exudates. *Y. pestis* grows slowly under routine culture conditions and best at temperatures that differ from those used for routine cultures in many clinical laboratories. Enzyme-linked immunosorbent assay and PCR are available but are not in routine clinical use. A rapid antigen test detecting *Y. pestis* F1 antigen in sputum and serum samples exists as well. Suspected isolates of *Y. pestis* should be forwarded to a reference laboratory for confirmation. Special containment shipping precautions are required. Cases of plague should be reported to local and state health departments and the Centers for Disease Control and Prevention (CDC).

DIFFERENTIAL DIAGNOSIS

The Gram stain of *Y. pestis* may be confused with *Enterobacter agglomerans.* Mild and subacute forms of bubonic plague may be confused with other disorders causing localized lymphadenitis and lymphadenopathy. Septicemic plague may be indistinguishable from other forms of overwhelming bacterial sepsis like tularemia and cat-scratch disease.

Pulmonary manifestations of plague are similar to those of anthrax, Q fever, and tularemia, all agents with bioterrorism and biological warfare potential. Thus, the presentation of a suspected case, and especially any cluster of cases, requires immediate reporting. Additional information on this aspect of plague and procedures can be found at http://www.bt.cdc.gov/agent/plague/.

TREATMENT

Patients with suspected plague should be placed on droplet isolation until pneumonia is ruled out, sputum cultures are negative, and antibiotic treatment has been administered for 48 hr. The treatment of choice for bubonic plague historically has been streptomycin (30 mg/kg/day, maximum 2 g/day, divided every 12 hr IM for 10 days). Intramuscular streptomycin is inappropriate for septicemia because absorption may be erratic when perfusion is poor. The poor central nervous

system penetration of streptomycin makes this an inappropriate drug for meningitis. Furthermore, streptomycin might not be widely and immediately available. Gentamicin (children, 7.5 mg/kg IM or IV divided every 8 hr; adults, 5 mg/kg IM or IV once daily) has been shown to be as efficacious as streptomycin. Alternative treatments include doxycycline (in children who weigh <45 kg: 2-5 mg/kg/day every 12 hr IV, maximum 200 mg/day; not recommended for children <8 yr of age; in children who weigh ≥45 kg, 100 mg every 12 hr PO), ciprofloxacin (30 mg/kg/day divided every 12 hr, maximum 400 mg every 12 hr IV), and chloramphenicol (50-100 mg/kg/day IV divided every 6 hr). Meningitis is usually treated with chloramphenicol or a fluoroquinolone. Resistance to these agents and relapses are rare. *Y. pestis* is susceptible to fluoroquinolones in vitro, which are effective in treating experimental plague in animals. *Y. pestis* is susceptible to penicillin in vitro, but penicillin is ineffective in treatment of human disease. Mild disease may be treated with oral chloramphenicol or tetracycline in children older than 8 yr of age. Clinical improvement is noted within 48 hr of initiating treatment. Typical duration of therapy is 7-10 days or a few days following clinical improvement.

Postexposure prophylaxis should be given to close contacts of patients with pneumonic plague. Antimicrobial prophylaxis is recommended within 7 days of exposure for persons with direct, close contact with patient with pneumonic plague or those exposed to an accidental or terrorist-induced aerosol. Recommended regimens include a 7-day course of tetracycline, doxycycline, or TMP-SMX. Contacts of cases of uncomplicated bubonic plague do not require prophylaxis. *Y. pestis* is a potential agent of bioterrorism that can require mass casualty prophylaxis.

PREVENTION

Avoidance of exposure to infected animals and fleas is the best method of prevention of infection. In the United States, special care is required in environments inhabited by rodent reservoirs of *Y. pestis* and their ectoparasites. Patients with plague should be isolated if they have pulmonary symptoms, and infected materials should be handled with extreme care. There is currently no available licensed vaccine for *Y. pestis* in the United States. Several vaccine development trials are underway, and recombinant subunit vaccines based on rF1 and rV antigens seem to be the most promising. Using baits containing live vaccines for oral immunization of wild animals may be a helpful alternative for control of epidemics.

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Chapter 204

Aeromonas and *Plesiomonas*

Amanda N. Shaw and Gloria P. Heresi

Aeromonas and *Plesiomonas* are Gram-negative bacilli that include species capable of causing enteritis and less frequently cause skin and soft-tissue infections and septicemia. They are common in fresh and brackish water and colonize animals and plants in these environments.

204.1 *Aeromonas*

Amanda N. Shaw and Gloria P. Heresi

ETIOLOGY

Aeromonas is a member of the Aeromonadaceae family and are oxidase-positive, facultative anaerobic, Gram-negative bacilli that ferment glucose. At least 24 phenotypic species are known, though there is controversy regarding species differentiation. Eleven are recognized as clinically significant human pathogens. *Aeromonas hydrophila, Aeromonas veronii* biotype sobria, and *Aeromonas caviae* are the species most often associated with human infection. *Aeromonas trota* continues to be isolated with increasing frequency from human stool. *A. hydrophila* strain ATCC 7966 has been sequenced and contains 5,195 predicted protein-encoding genes identified.

Aeromonas infects many cold- and warm-blooded animals. There are 2 major groups of *Aeromonas* isolates: the nonmotile psychrophilic organisms that infect cold-blooded animals, most commonly fish (optimal growth 22-25°C [71.6-77°F]), and the motile mesophilic organisms that infect humans and other warm-blooded animals (optimal growth 35-37°C [95-98.6°F]).

EPIDEMIOLOGY

Aeromonas organisms are ubiquitous and are found in fresh and brackish aquatic sources, including rivers and streams, well water, both treated and bottled drinking water, and sewage. They are most often cultivated from aquatic sources during warm weather months, when they are able to attain large populations. The prevalence of human infection tends to exhibit seasonality, depending on local conditions. For example, *Aeromonas* are isolated with increased frequency from May to October in the northern hemisphere. Some species can resist chlorination of water and show tolerance to high salt. *Aeromonas* has been isolated from meats, milk, seafood, seaweed, and vegetables consumed by humans. Most human infections with *Aeromonas* are associated with exposure to contaminated water. A systematic review of cases of traveler's diarrhea worldwide implicated *Aeromonas* in 0.8-3.3% of infections, with highest frequencies in travelers to Southeast Asia and Africa. A study in India of 3,500 stool samples from patients hospitalized with diarrhea found 4.7% positive for *Aeromonas*. *Aeromonas* infections have also been acquired at various sites of natural disasters. Following the 2004 Thailand tsunami, 305 survivors with skin and soft-tissue infections were found to have *Aeromonas*, making it the most common bacterial pathogen causing skin infections following this disaster. Asymptomatic colonization occurs in humans and is more common in inhabitants of tropical regions.

PATHOGENESIS

Clinical and epidemiologic data seem to support that *Aeromonas* organisms are enteric pathogens, although this is not universally accepted. Reasons for uncertainty include a lack of outbreaks with colonially distinct isolates, infrequent person to person transmission, absence of a good animal model, and overlapping prevalence in symptomatic and asymptomatic patients. Adult volunteers can ingest 10^4-10^{10} colony-forming units without developing diarrhea or becoming colonized.

Aeromonas isolates possess a variety of potential virulence factors, including: constitutive polar and inducible lateral flagella, fimbriae, outer membrane proteins, an S-layer, endotoxin (lipopolysaccharide), capsules, collagenase, elastase, nuclease, gelatinase, lipase, chitinase, enterotoxins, hemolysins, and multiple secretion systems. Polar flagella provide motility in liquid media, and lateral flagella act as adhesins. There are various hemolysins and heat labile- and heat-stable enterotoxins. *Aeromonas* cytotoxic enterotoxin (aerolysin) is secreted by a type II secretion system and is able to lyse erythrocytes, inhibit phagocytosis, and induce cytotoxicity in eukaryotic cells. *Aeromonas* also has a type III secretion system with an effector protein that causes actin reorganization and eventual apoptosis in vitro. A type VI secretion system has been identified in a clinical isolate and is being studied further. *Aeromonas sobria* is the most enterotoxic among clinical isolates, and cytotoxic activity with cytopathic and intracellular effects is found in 89% of isolates. A few strains produce *Shiga* toxin. *Aeromonas* has serine proteases that can cause a cascade of inflammatory mediators leading to vascular leakage, and in vitro studies show induction of apoptosis in murine macrophages by human isolates of *Aeromonas*. *Aeromonas* also has enzyme systems and efflux pumps that enable it to develop resistance to antibiotics. There are limited data on identified quorum-sensing molecules, which coordinate gene expression according to local density and may be involved in biofilm production or population control.

Human serum generally promotes phagocytosis and intracellular killing of *Aeromonas*. Absence of this serum action has been associated with a poor prognosis.

CLINICAL MANIFESTATIONS

Colonization with *Aeromonas* may be asymptomatic or cause illness, including enteritis, focal invasive infection, and septicemia. Although apparently immunologically normal individuals may present with any manifestation, invasive disease is more common among immunocompromised persons.

Enteritis

The most common clinical manifestation of infection with *Aeromonas* is enteritis, which occurs primarily among children younger than 3 yr of age. *Aeromonas* is the 3rd or 4th most common cause of childhood bacterial diarrhea and has been isolated from 2-10% of patients with diarrhea and 1-5% of asymptomatic control subjects. One study showed isolation from hospitalized neonates with diarrhea at rates of 0-19% depending on season. Diarrhea is often watery and self-limited, although a dysentery-like syndrome with blood and mucus in the stool has also been described. Fever, abdominal pain, and vomiting are common in children. Enteritis caused by *A. hydrophila* and *A. sobria* tends to be acute and self-limited, whereas 30% of the patients with *A. caviae* enteritis have chronic or intermittent diarrhea that may last 4-6 wk. *A. sobria* and *A. caviae* are most frequently associated with traveler's diarrhea. Complications of *Aeromonas* enteritis include intussusception, failure to thrive, hemolytic-uremic syndrome, bacteremia, and strangulated intestinal hernia. *A. caviae* infection may mimic inflammatory bowel disease.

Skin and Soft-Tissue Infections

Skin and soft-tissue infections are the second most common presentation of *Aeromonas*. Predisposing factors include local trauma and exposure to contaminated fresh water. *Aeromonas* soft-tissue infections have been reported following animal bites, including alligator, tiger, bear, and snake bites, as well as tick bites. It has also been reported following sports injuries and following medicinal leech therapy. Antibiotic prophylaxis is currently used in conjunction with medicinal leech therapy because of the presence of symbiotic *A. hydrophila*. The spectrum of skin and soft-tissue infections is broad, ranging from a localized skin nodule to life-threatening necrotizing fasciitis, myonecrosis, and gas gangrene. Soft-tissue infections are most commonly found on the extremities and are 3 times more likely in men than in women. *Aeromonas* cellulitis, the most common skin manifestation, clinically presents like any other bacterial cellulitis but should be suspected in wounds following contact with a water source, especially during the summer.

Septicemia

Aeromonas septicemia is the third most frequent presentation of infection and is associated with a mortality rate of 27-73%. Patients often present with fever and gastrointestinal symptoms including abdominal pain, nausea, vomiting, and diarrhea. Multiple pediatric cases of septicemia from *A. hydrophila* have been reported; symptoms include diarrhea, pneumonia, and acute renal failure. *Aeromonas* septicemia usually occurs in patients with underlying conditions, such as hepatobiliary disease or malignancy, but may occur in apparently immunocompetent persons. *Aeromonas* may be the only organism isolated or may be part of a polymicrobial bacteremic illness. The source of the infection is frequently not identified, and in these cases is most likely from the gastrointestinal tract. *A. sobria* bacteremia has resulted in disseminated intravascular gas production and subsequent acute death in the absence of any underlying condition.

Other Infections

Aeromonas is a rare cause of gastrointestinal infections such as necrotizing gastroenteritis, peritonitis, cholecystitis, appendicitis, and liver and pancreas abscess formation, cardiovascular infections including endocarditis and septic embolism, and pulmonary infections including tracheobronchitis, pneumonia, empyema, and abscess formation. *Aeromonas* is also associated with musculoskeletal infections, including osteomyelitis, pyogenic arthritis, pyomyositis, and necrotizing fasciitis, as well as ear, nose and throat infections, including endophthalmitis, keratitis, orbital cellulitis, otitis media, and epiglottitis. Other infections include meningitis, urinary tract infection, pelvic inflammatory disease, lymphadenitis, hot tub folliculitis, and surgical wound infections. *Aeromonas* is associated with tracheobronchitis and aspiration pneumonia after near-drowning.

DIAGNOSIS

Diagnosis is established by culture isolation of *Aeromonas*. The organism is easily grown on standard media when the source material is normally sterile. Isolation of the organism from samples containing numerous bacteria is more difficult, possibly because competing bacteria outgrow *Aeromonas*. Often, *Aeromonas* is not identified by typical lab protocols for examining stool specimens. If *Aeromonas* is suspected, the yield will increase if the lab is notified prior to testing. Previously suggested use of ampicillin containing agars is no longer recommended, because a significant number of *A. caviae* and all *A. trota* are sensitive to ampicillin and will not grow. Most (~90%) strains produce β-hemolysis on blood agar. However, lack of hemolysis is not a reliable indicator of lack of hemolysin in the isolate. Lactose-fermenting strains of *Aeromonas* may not be identified if the clinical laboratory does not routinely perform oxidase tests on lactose fermenters isolated on MacConkey agar. Automated identification systems are more routinely being used and can identify most *Aeromonas* as a group. More specific identification is not done as often, and when it is done, is often incomplete or erroneous.

TREATMENT

Aeromonas enteritis is usually self-limited, and antimicrobial therapy may not be indicated. Nevertheless, data from uncontrolled trials suggest that antimicrobial therapy shortens the course of the illness. Antimicrobial therapy is reasonable to consider in patients with protracted diarrhea, dysentery-like illness, or underlying conditions such as hepatobiliary disease or an immunocompromised state. Antibiotic sensitivity varies between species. Therefore, it is important to identify the species and sensitivities when antibiotics are used. Most species produce an inducible β-lactamase which may not be detected by automated systems. There is near-uniform resistance to penicillins. Septicemia should be treated with a third-generation cephalosporin or an aminoglycoside. Other options include imipenem, meropenem, chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMZ), quinolones, and tetracyclines. Many species have developed multidrug resistance, especially to quinolones. Sensitivities vary by geographic region. For example, in Taiwan there is increasing resistance to TMP-SMZ, so travel history should be taken into consideration when planning treatment. There are no clinic trial data available to guide duration of treatment. As a consequence, treatment is typically guided by clinical response. In general, diarrhea is treated for 3 days, wound infections for 7-10 days, and bacteremia for 14 days.

PREVENTION

Reducing contact with contaminated environmental fresh and brackish water and contaminated foods should reduce the risk for *Aeromonas* infections. *Aeromonas* expresses LamB-like outer membrane proteins that facilitate bacterial adherence to extracellular matrix components. Outer membrane proteins are strongly immunogenic and have been target antigens for vaccine development.

Bibliography is available at Expert Consult.

204.2 *Plesiomonas shigelloides*

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ETIOLOGY

Plesiomonas shigelloides is most commonly associated with acute enteritis and rarely with extraintestinal infections. The organism is a facultative anaerobic, Gram-negative non–spore-forming bacillus with more

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than 100 serotypes. It is catalase- and oxidase-positive, able to ferment xylose, and motile, with 2-5 polar flagellae.

P. shigelloides is the only oxidase positive member of the Enterobacteriaceae family. A high level of diversity has been recognized within *P. shigelloides* strains, reflecting the frequency of homologous recombination and differing from other members of the Enterobacteriaceae.

EPIDEMIOLOGY

P. shigelloides is ubiquitous in fresh water and can be found in estuarine water. Historically, it has been found most often in warmer and tropical waters or during warmer months, although there are increasing reports of isolation from surface water in colder climates. *P. shigelloides* colonizes numerous cold- and warm-blooded animals, has been isolated from fish and seafood, and may cause disease in cats. Infection of humans is thought to be the result of consumption of contaminated water or raw seafood and possibly through contact with colonized animals. There have also been cases of immunocompromised patients who are injured in fresh water. A majority of symptomatic patients in North America have known exposure to potentially contaminated water or seafood or have traveled abroad. In general, enteric infections with *Plesiomonas* occur more commonly in areas where development and hygiene are inadequate and have been associated with large outbreaks.

PATHOGENESIS

Epidemiologic evidence indicates that *P. shigelloides* is an enteropathogen. However, the pathogenic capacity of *P. shigelloides* has not been confirmed when volunteers have been fed the organism. The mechanism of enteritis is not known, but it appears that the species can commonly cause secretory and less commonly invasive disease. In vitro studies show that isolates of *P. shigelloides* are capable of invading and inducing apoptosis in cells of enteric origin. Most strains of *P. shigelloides* secrete a β-hemolysin, which is thought to be a major virulence factor. They also produce a β-lactamase, which renders them resistant to the penicillins. Studies show evidence of modulation of host defenses through inhibition of cathepsins involved in antigen processing and presentation.

CLINICAL MANIFESTATIONS

Clinical disease in humans generally begins 24-48 hr after exposure to the organism, although there have been cases 4 days after exposure. Diarrhea is commonly secretory or watery and less-often presents as invasive dysentery. In 13% of cases, diarrhea can last more than 2 wk and has been noted to last as long as 3 mo. The frequency of secretory vs dysenteric presentation seems to cluster by individual outbreak, suggesting that either the human populations or bacterial populations involved associate with their particular presentation. Symptoms include diarrhea (84-100%), vomiting (70%), fever (8-50%), headache, abdominal cramping (more common in adults), nausea, and transient arthralgias. Frequently, diarrhea is mild and watery without significant dehydration. Blood, mucus, or both may be passed with stool, and white blood cells may be visualized in stained preparations of stool.

Extraintestinal infections are rare and usually occur in patients with underlying conditions, such as immunodeficiency (including HIV), malignancy, sickle cell disease, thalassemia, splenectomy, or hepatobiliary disease. Traumatic wounds sustained in aquatic environments less commonly contain *P. shigelloides*. Rarely, bacteremia accompanying enteritis has been documented in apparently otherwise normal children. Extraintestinal disease includes septicemia, pneumonia, meningitis, osteomyelitis, septic arthritis, reactive arthritis, cellulitis with abscess formation, endophthalmitis, cholecystitis, pseudoappendicitis, pseudomembranous colitis, proctitis, epididymo-orchitis, and pyosalpinx. Early onset neonatal sepsis and meningitis are rare but make up most of the reported cases of *P. shigelloides* meningitis and have a very high mortality rate (80%). Septicemia has a high mortality rate in adults.

DIAGNOSIS

A history of foreign travel, ingestion of raw seafood, or exposure to contaminated water or an animal with diarrhea suggests possible *P. shigelloides* infection. Mixed infection with *Salmonella, Aeromonas,* rotavirus, or other enteric pathogens may occur in 30-50% of patients. *P. shigelloides* is a nonlactose fermenter and grows well on traditional enteric media, although selective techniques may be required to isolate the organism from mixed cultures and to differentiate *P. shigelloides* from *Shigella* species. Many strains cross react with *Shigella* on serologic testing, but can be differentiated easily as oxidase positive organisms. It may be underrecognized by clinical laboratories that do not routinely perform an oxidase test. Rapid identification systems are fairly accurate when identifying *P. shigelloides*.

TREATMENT

Enteritis caused by *P. shigelloides* is usually mild and self-limited. In cases associated with dehydration, patients respond favorably to oral rehydration solution. Antimicrobial therapy is reserved for those patients with prolonged or bloody diarrhea, those who are immunocompromised, the very old, and the very young. Data from uncontrolled studies suggest that antimicrobial therapy decreases the duration of symptoms, although no difference was found in an exclusively pediatric study. Most strains of *P. shigelloides* are susceptible to TMP-SMZ, cephalosporins, carbapenems, and fluoroquinolones. *P. shigelloides* is commonly resistant to broad-spectrum penicillins, aminoglycosides, and tetracyclines. In some strains resistance has also been found to TMP-SMZ and fluoroquinolones. Resistance to gentamicin, chloramphenicol, and nalidixic acid has been demonstrated in strains of *P. shigelloides* isolated from tilapia.

Antibiotics are essential for therapy of extraintestinal disease. Empirical therapy with a third-generation cephalosporin is often first-line management, because most isolates are susceptible in vitro. Alternatives include imipenem, aztreonam, β-lactam/β-lactamase inhibitor combinations, and quinolones. Definitive therapy should be guided by the susceptibility of the individual isolate. Duration of therapy ranges from 1-2 wk, but may be extended depending on underlying chronic conditions and clinical response.

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Chapter 205

Pseudomonas, Burkholderia, and *Stenotrophomonas*

205.1 *Pseudomonas aeruginosa*

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ETIOLOGY

Pseudomonas aeruginosa is a Gram-negative rod and is a strict aerobe. It can multiply in a great variety of environments that contain minimal amounts of organic compounds. Strains from clinical specimens do not ferment lactose, are oxidase positive, and may produce β-hemolysis on blood agar. Many strains produce pigments, including pyocyanin, pyoverdin, and pyorubrin, that diffuse into and color the surrounding medium. Strains of *P. aeruginosa* are differentiated for epidemiologic purposes by a variety of genotyping methods, including restriction fragment length polymorphisms using pulsed-field gel electrophoresis and multilocus sequence typing.

EPIDEMIOLOGY

P. aeruginosa is a classic opportunist. It rarely causes disease in people who do not have a predisposing risk factor. Compromised host defense mechanisms owing to trauma, neutropenia, mucositis, immunosuppression, or impaired mucociliary transport explain the predominant role of this organism in producing opportunistic infections. One series of neonatal intensive care unit infections reported that 33/862 (3.8%) episodes of neonatal bacteremia from 1989-2003 were caused by *P. aeruginosa*. Another children's hospital reported 232 episodes of *P. aeruginosa* bacteremia over a 10 yr period, with half the infected children diagnosed with an underlying malignancy. *P. aeruginosa* and other pseudomonads frequently enter the hospital environment on the clothes, skin, or shoes of patients or hospital personnel, with plants or vegetables brought into the hospital, and in the gastrointestinal tracts of patients. Colonization of any moist or liquid substance may ensue; the organisms may be found growing in any water reservoir, including distilled water, and in hospital kitchen sinks and laundries, some antiseptic solutions, and equipment used for respiratory therapy and urinary procedures. Colonization of skin, throat, stool, and nasal mucosa of patients is low at admission to the hospital but increases to as high as 50-70% with prolonged hospitalization and with the use of broad-spectrum antibiotics, chemotherapy, mechanical ventilation, and urinary catheters. Patients' intestinal microbial flora may be altered by the use of broad-spectrum antibiotics, which reduces resistance to colonization and permits *P. aeruginosa* in the environment to populate the gastrointestinal tract. Intestinal mucosal breakdown associated with medications, especially cytotoxic agents, and nosocomial enteritis may provide a pathway by which *P. aeruginosa* spreads to the lymphatics or bloodstream.

PATHOLOGY

The pathologic manifestations of *P. aeruginosa* infections depend on the site and type of infection. Because of its elaboration of toxins and invasive factors, the organism can often be seen invading blood vessels and causing vascular necrosis. In some infections there is spread through tissues with necrosis and microabscess formation. In patients with cystic fibrosis, focal and diffuse bronchitis/bronchiolitis leading to bronchiolitis obliterans has been reported.

Pathogenesis

Invasiveness of *P. aeruginosa* is mediated by a host of virulence factors. Bacterial attachment is facilitated by pili that adhere to epithelium damaged by prior injury or infection. Extracellular proteins, proteases, elastases, and cytotoxin disrupt cell membranes, and in response, host-produced cytokines cause capillary vascular permeability and induce an inflammatory response. Dissemination and bloodstream invasion follow extension of local tissue damage and are facilitated by the antiphagocytic properties of endotoxin, the exopolysaccharide, and protease cleavage of immunoglobulin G. *P. aeruginosa* also produces numerous exotoxins, including **exotoxin A,** which causes local necrosis and facilitates systemic bacterial invasion. *P. aeruginosa* possesses a type III secretion system that is important for virulence in multiple animal models. This needle structure inserts into host cell membranes and allows secretion of exotoxins directly into host cells. *P. aeruginosa* strains with the gene encoding the type III secretion system–dependent phospholipase ExoU are associated with increased mortality compared with ExoU-negative strains in retrospective studies of patients with *P. aeruginosa* ventilator-associated pneumonia. The host responds to infection with a robust inflammatory response, recruiting neutrophils to the infection site and by producing antibodies to *P. aeruginosa* proteins such as exotoxin A and endotoxin. There is a lack of convincing data that these antibodies are protective against the establishment of infection.

In addition to acute infection, *P. aeruginosa* is also capable of chronic persistence thought to be partly a result of the formation of biofilms, organized communities of bacteria encased in an extracellular matrix that protects the organisms from the host immune response and the effects of antibiotics. Biofilm formation requires pilus-mediated attachment to a surface, proliferation of the organism, and production of exopolysaccharide as the main component of the extracellular matrix. A mature biofilm can persist despite an intense host immune response, is resistant to many antimicrobials, and is difficult to eradicate with current therapies.

CLINICAL MANIFESTATIONS

Most clinical patterns (Table 205-1) are related to opportunistic infections in immunocompromised hosts (see Chapter 178) or are

Table 205-1 *Pseudomonas aeruginosa* Infections

INFECTION	COMMON CLINICAL CHARACTERISTICS
Endocarditis	Native right-sided (tricuspid) valve disease with intravenous drug abuse
Pneumonia	Compromised local (lung) or systemic host defense mechanisms; nosocomial (respiratory), bacteremic (malignancy), or abnormal mucociliary clearance (cystic fibrosis) may be pathogenetic; cystic fibrosis is associated with mucoid *P. aeruginosa* organisms producing capsular slime
Central nervous system infection	Meningitis, brain abscess; contiguous spread (mastoiditis, dermal sinus tracts, sinusitis); bacteremia or direct inoculation (trauma, surgery)
External otitis	Swimmer's ear; humid warm climates, swimming pool contamination
Malignant otitis externa	Invasive, indolent, febrile toxic, destructive necrotizing lesion in young infants, immunosuppressed neutropenic patients, or diabetic patients; associated with 7th nerve palsy and mastoiditis
Chronic mastoiditis	Ear drainage, swelling, erythema; perforated tympanic membrane
Keratitis	Corneal ulceration; contact lens keratitis
Endophthalmitis	Penetrating trauma, surgery, penetrating corneal ulceration; fulminant progression
Osteomyelitis/septic arthritis	Puncture wounds of foot and osteochondritis; intravenous drug abuse; fibrocartilaginous joints, sternum, vertebrae, pelvis; open fracture osteomyelitis; indolent pyelonephritis and vertebral osteomyelitis
Urinary tract infection	Iatrogenic, nosocomial; recurrent urinary tract infections in children, instrumented patients, and those with obstruction or stones
Intestinal tract infection	Immunocompromised, neutropenia, typhlitis, rectal abscess, ulceration, rarely diarrhea; peritonitis in peritoneal dialysis
Ecthyma gangrenosum	Metastatic dissemination; hemorrhage, necrosis, erythema, eschar, discrete lesions with bacterial invasion of blood vessels; also subcutaneous nodules, cellulitis, pustules, deep abscesses
Primary and secondary skin infections	Local infection; burns, trauma, decubitus ulcers, toe web infection, green nail (paronychia); whirlpool dermatitis; diffuse, pruritic, folliculitis, vesiculopustular or maculopapular, erythematous lesions

Figure 205-1 Round, nontender skin lesion on 2 yr old female's buttock. Note the black ulcerated center of the lesion and its red margin. *(From Ghanaiem H, Engelhard D: A healthy 2-year-old child with a round black skin lesion.* J Pediatr *163:1225, 2013.)*

associated with shunts and indwelling catheters (see Chapter 179). *P. aeruginosa* may be introduced into a minor wound of a healthy person as a secondary invader, and cellulitis and a localized abscess that exudes green or blue pus may follow. The characteristic skin lesions of *P. aeruginosa,* **ecthyma gangrenosum,** whether caused by direct inoculation or a metastatic focus secondary to septicemia, begin as pink macules and progress to hemorrhagic nodules and eventually to ulcers with ecchymotic and gangrenous centers with eschar formation, surrounded by an intense red areola (Fig. 205-1).

Outbreaks of dermatitis and urinary tract infections caused by *P. aeruginosa* have been reported in healthy persons after use of pools or hot tubs. Skin lesions of folliculitis develop several hours to 2 days after contact with these water sources. Skin lesions may be erythematous, macular, papular, or pustular. Illness may vary from a few scattered lesions to extensive truncal involvement. In some children, malaise, fever, vomiting, sore throat, conjunctivitis, rhinitis, and swollen breasts may be associated with dermal lesions. Urinary tract infections caused by *P. aeruginosa* are most often nosocomial and are commonly associated with the presence of an indwelling urinary catheter, urinary tract malformations, and previous antibiotic use. Urinary tract infections may be minimized or prevented by prompt removal of the catheter and by early identification and corrective surgery of obstructive lesions when present.

Burns and Wound Infection

The surfaces of burns or wounds are frequently populated by *P. aeruginosa* and other Gram-negative organisms; this initial colonization with a low number of adherent organisms is a necessary prerequisite to invasive disease. *P. aeruginosa* colonization of a burn site may develop into burn wound sepsis, which has a high mortality rate when the density of organisms reaches a critical concentration. Administration of antibiotics may diminish the susceptible microbiologic flora, permitting strains of relatively resistant *P. aeruginosa* to flourish. Multiplication of organisms in devitalized tissues or associated with prolonged use of intravenous or urinary catheters increases the risk for septicemia with *P. aeruginosa,* a major problem in burned patients (see Chapter 75).

Cystic Fibrosis

P. aeruginosa is common in children with cystic fibrosis, with a prevalence that increases with increasing age and severity of pulmonary disease (see Chapter 403). Initial infection is caused by **nonmucoid environmental strains** of *P. aeruginosa,* but after a variable period of time, **mucoid strains** of *P. aeruginosa* that produce the antiphagocytic exopolysaccharide alginate, which are rarely encountered in other conditions, predominate. Repeated isolation of mucoid *P. aeruginosa* from the sputum is associated with increased morbidity and mortality. The infection begins insidiously or even asymptomatically, and the progression has a highly variable pace. In children with cystic fibrosis, antibody does not eradicate the organism and antibiotics are only partially effective; thus, after infection becomes chronic, it cannot be completely eradicated. Repeated courses of antibiotics select for *P. aeruginosa* strains that are resistant to multiple antibiotics.

Immunocompromised Persons

Children with leukemia or other malignancies, particularly those who are receiving immunosuppressive therapy and who are neutropenic, typically with intravascular catheters, are extremely susceptible to septicemia caused by invasion of the bloodstream by *P. aeruginosa* that is colonizing the respiratory or gastrointestinal tract. Signs of sepsis are often accompanied by a generalized vasculitis, and hemorrhagic necrotic lesions may be found in all organs, including the skin (ecthyma gangrenosum) (see Fig. 205-1). Hemorrhagic or gangrenous perirectal cellulitis or abscesses may occur, associated with ileus and profound hypotension.

Nosocomial Pneumonia

Although not a frequent cause of community-acquired pneumonia in children, *P. aeruginosa* is an increasingly important cause of community-acquired pneumonia in adults and of nosocomial pneumonia, especially ventilator-associated pneumonia, in patients of all ages. *P. aeruginosa* has historically been found to contaminate ventilators, tubing, and humidifiers. Such contamination is uncommon because of disinfection practices and routine changing of equipment. Nevertheless, colonization of the upper respiratory tract and the gastrointestinal tract may be followed by aspiration of *P. aeruginosa*–contaminated secretions, resulting in severe pneumonia. Prior use of broad-spectrum antibiotics is a risk factor for colonization with antibiotic-resistant strains of *P. aeruginosa.* One of the most challenging situations is distinguishing between colonization and pneumonia in intubated patients. This distinction can often only be resolved by using invasive culture techniques such as quantitative bronchoalveolar lavage.

Infants

P. aeruginosa is an occasional cause of nosocomial bacteremia in newborns and accounts for 2-5% of positive blood culture results in neonatal intensive care units. A frequent focus preceding bacteremia is **conjunctivitis.** Older infants may occasionally present with community-acquired sepsis due to *P. aeruginosa,* but this circumstance is uncommon. In the few reports describing community-acquired sepsis, preceding conditions included ecthyma-like skin lesions, virus-associated transient neutropenia, and prolonged contact with contaminated bath water or a hot tub.

DIAGNOSIS

P. aeruginosa infection is rarely clinically distinctive. Diagnosis depends on recovery of the organism from the blood, cerebrospinal fluid, urine, or needle aspirate of the lung, or from purulent material obtained by aspiration of subcutaneous abscesses or areas of cellulitis. In the appropriate clinical setting the recovery of *P. aeruginosa* from a coughed or suctioned sputum may represent infection; but it also may only represent colonization and clinical judgment is required. Rarely, skin lesions that resemble *P. aeruginosa* infection may follow septicemia caused by *Aeromonas hydrophila,* other Gram-negative bacilli, and *Aspergillus.* When *P. aeruginosa* is recovered from nonsterile sites such as skin, mucous membranes, voided urine, quantitative cultures may be useful to differentiate colonization from invasive infection. In general, ≥100,000 colony forming units/mL of fluid or gram of tissue is evidence suggestive of invasive infection. Quantitative cultures of tissue and skin are not routine and may require consultation with the clinical microbiology laboratory.

TREATMENT

Systemic infections with *P. aeruginosa* should be treated promptly with an antibiotic to which the organism is susceptible in vitro. Response to treatment may be limited, and prolonged treatment may be necessary for systemic infection in immunocompromised hosts.

Septicemia and other aggressive infections should be treated with either 1 or 2 bactericidal agents. Although the number of agents required is controversial, the evidence continues to suggest that the benefit of adding a second agent is questionable, even when studies have included immunosuppressed patients. Whether the use of 2 agents delays the development of resistance is also controversial, with evidence both for and against. Appropriate antibiotics for single-agent therapy include ceftazidime, cefepime, ticarcillin-clavulanate, and piperacillin-tazobactam. Gentamicin or another aminoglycoside may be used concomitantly for synergistic effect.

Ceftazidime has proved to be extremely effective in patients with cystic fibrosis (150-250 mg/kg/day divided every 6-8 hr IV to a maximum of 6 g/day). Piperacillin or piperacillin-tazobactam (300-450 mg/kg/day divided every 6-8 hr IV to a maximum of 12 g/day) also has proven to be effective therapy for susceptible strains of *P. aeruginosa* when combined with an aminoglycoside. Additional effective antibiotics include imipenem-cilastatin, meropenem, and aztreonam. Ciprofloxacin is an effective outpatient therapy and while commonly used in children with cystic fibrosis, it is not approved in the United States for persons younger than 18 yr of age except for oral treatment of urinary tract infections or when there are no other agents to which the organism is susceptible. Inhaled therapy with either tobramycin or aztreonam is also used for chronic pulmonary infection with inhaled colistin reserved for the treatment of resistant pseudomonads. It is important to base continued treatment on the results of susceptibility tests because antibiotic resistance of *P. aeruginosa* to 1 or more antibiotics is increasing. Macrolide therapy decreases pulmonary exacerbations in patients with chronic lung disease and *P. aeruginosa* infection Although the mechanism is not entirely clear, it likely relates to altering the virulence properties of *P. aeruginosa* rather than direct bacterial killing.

P. aeruginosa displays intrinsic and acquired resistance to antibiotics. It has many mechanisms for resistance to multiple classes of antibiotics, including but not limited to genetic mutation, production of β-lactamases, and drug efflux pumps. Critical care units throughout the United States have documented a rising rate of resistance of *P. aeruginosa* to all of the major classes of antibiotics.

Meningitis can occur from spread from a contiguous focus, as a secondary focus when there is bacteremia, or after invasive procedures. *P. aeruginosa* meningitis is best treated with ceftazidime in combination with an aminoglycoside such as gentamicin, both given intravenously. Concomitant intraventricular or intrathecal treatment with gentamicin may be required when intravenous therapy fails but is not recommended for routine use.

SUPPORTIVE CARE

P. aeruginosa infections vary in severity from superficial to intense septic presentations. With severe infections there is often multisystem involvement and a systemic inflammatory response. Supportive care is similar to care for severe sepsis caused by other Gram-negative bacilli and requires support of blood pressure, oxygenation, and appropriate fluid management.

PROGNOSIS

The prognosis is dependent primarily on the nature of the underlying factors that predisposed the patient to *P. aeruginosa* infection. In severely immunocompromised patients, the prognosis for patients with *P. aeruginosa* sepsis is poor unless susceptibility factors such as neutropenia or hypogammaglobulinemia can be reversed. The overall mortality rate was 12.3% in 1 series of 232 children with *P. aeruginosa* bacteremia, with 3% dying within 48 hr of admission. Resistance of the organism to first-line antibiotics also decreases the chance of survival. The outcome may be improved when there is a urinary tract portal of entry, absence of neutropenia or recovery from neutropenia, and drainage of local sites of infection.

P. aeruginosa is recovered from the lungs of most children who die of cystic fibrosis and adds to the slow deterioration of these patients. The prognosis for normal development is poor in the few infants who survive *P. aeruginosa* meningitis.

PREVENTION

Prevention of infections is dependent on limiting contamination of the healthcare environment and preventing transmission to patients. Effective hospital infection control programs are necessary to identify and eradicate sources of the organism as quickly as possible. In hospitals, infection can be transmitted to children by the hands of personnel, from washbasin surfaces, from catheters and other hospital equipment, and from solutions used to rinse suction catheters.

Strict attention to hand hygiene before and between contacts with patients may prevent or interdict epidemic disease. Meticulous care and sterile procedures in suctioning of endotracheal tubes, insertion and maintenance of indwelling catheters, and removal of catheters as soon as medically reasonable greatly reduce the hazard of extrinsic contamination by *P. aeruginosa* and other Gram-negative organisms. Prevention of follicular dermatitis caused by *P. aeruginosa* contamination of whirlpools or hot tubs is possible by maintaining pool water at a pH of 7.2-7.8.

Infections in burned patients may be minimized by protective isolation, debridement of devitalized tissue, and topical applications of bactericidal cream. Administration of intravenous immunoglobulin may be used. Approaches under investigation to prevent infection include development of a *P. aeruginosa* vaccine. No vaccine is currently licensed in the United States.

Bibliography is available at Expert Consult.

205.2 *Burkholderia cepacia* Complex

Thomas S. Murray and Robert S. Baltimore

Burkholderia cepacia is a filamentous Gram-negative rod now recognized to be a group of related species or genomovars. It is ubiquitous in the environment but may be difficult to isolate from respiratory specimens in the laboratory, requiring an enriched, selective media oxidation fermentation base supplemented with polymyxin B–bacitracin-lactose agar (OFPBL) and as long as 3 days of incubation.

B. cepacia is a classic opportunist that rarely infects normal tissue but can be a pathogen for individuals with preexisting damage to respiratory epithelium, especially persons with cystic fibrosis or with immune dysfunction such as chronic granulomatous disease. *B. cepacia* has multiple virulence factors, including lipopolysaccharide and a type III secretion system that promotes invasion of respiratory epithelial cells. Resistance to many antibiotics and disinfectants appears to be a factor in the emergence of *B. cepacia* as a nosocomial pathogen. In critical care units it may colonize the tubing used to ventilate patients with respiratory failure. In some patients this colonization may lead to invasive pneumonia and septic shock. Although *B. cepacia* is found throughout the environment, human-to-human spread among patients with cystic fibrosis occurs either directly by inhalation of aerosols or indirectly from contaminated equipment or surfaces, accounting for the practice of cohorting patients with cystic fibrosis in some clinics, hospital wards, and social gatherings on the basis of *B. cepacia* colonization. *B. cepacia* infections in persons with cystic fibrosis may represent chronic infection in some patients but others, especially those with *Burkholderia cenocepacia*, genomovar III, can develop an acute respiratory syndrome of fever, leukocytosis, and progressive respiratory failure, and more rapid decline in pulmonary function and lower survival rate.

Treatment in hospitals should include standard precautions and avoidance of placing colonized and uncolonized patients in the same room. Patients with cystic fibrosis who are colonized with *B. cepacia* are asked not to attend events where other persons with cystic fibrosis will be present. The use of antibiotics is guided by susceptibility studies of a patient's isolates, because the susceptibility pattern of this species is quite variable and multiply resistant strains are common. Trimethoprim-sulfamethoxazole and doxycycline or minocycline are potential oral therapies for *B. cepacia complex*. For intravenous therapy meropenem along with a second agent such as trimethoprim-sulfamethoxazole, doxycycline, minocycline, ceftazidime, or amikacin

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are potential options. Even though there is primary resistance to aminoglycosides, these agents may be useful in combination with other antibiotics. Treatment with 2 or more agents may be necessary to control the infection and avoid the development of resistance. No vaccine is currently available.

BURKHOLDERIA MALLEI (GLANDERS)

Glanders is a severe infectious disease of horses and other domestic and farm animals that is caused by *Burkholderia mallei,* a nonmotile Gram-negative bacillus that is occasionally transmitted to humans. It is acquired by inoculation into the skin, usually at the site of a previous abrasion, or by inhalation of aerosols. Laboratory workers may acquire it from clinical specimens. The disease is relatively common in Asia, Africa, and the Middle East. The clinical manifestations include septicemia, acute or chronic pneumonitis, and hemorrhagic necrotic lesions of the skin, nasal mucous membranes, and lymph nodes. The diagnosis is usually made by recovery of the organism in cultures of affected tissue. Glanders is treated with sulfadiazine, tetracyclines, or chloramphenicol and streptomycin over a period of many months. The disease has been eliminated from the United States, but interest in this organism has increased because of the possibility of its use as a bioterrorism agent (see Chapter 723). Although standard precautions are appropriate when caring for hospitalized infected patients, biosafety level 3 precautions are required for laboratory staff working with *B. mallei.* No vaccine is available.

BURKHOLDERIA PSEUDOMALLEI (MELIOIDOSIS)

Melioidosis is an important disease of Southeast Asia and northern Australia and occurs in the United States mainly in persons returning from endemic areas. The causative agent is *Burkholderia pseudomallei,* an inhabitant of soil and water in the tropics. It is ubiquitous in endemic areas, and infection follows inhalation of dust, ingestion, or direct contamination of abrasions or wounds. Human-to-human transmission has only rarely been reported. Serologic surveys demonstrate that asymptomatic infection occurs in endemic areas. The disease may remain latent and appear when host resistance is reduced, sometimes years after the initial exposure. Diabetes mellitus is a risk factor for severe melioidosis.

Melioidosis may present as a single **primary skin lesion** (vesicle, bulla, or urticaria). Pulmonary infection may be subacute and mimic tuberculosis or may present as an acute necrotizing pneumonia. Occasionally, septicemia occurs and numerous abscesses are noted in various organs of the body. Myocarditis, pericarditis, endocarditis, intestinal abscess, cholecystitis, acute gastroenteritis, urinary tract infections, septic arthritis, paraspinal abscess, osteomyelitis, mycotic aneurysm, and generalized lymphadenopathy all have been observed. Melioidosis may also present as an encephalitic illness with fever and seizures. It is also an agent of severe wound infections following contact with contaminated water following a tsunami.

Diagnosis is based on visualization of characteristic small Gram-negative rods in exudates or growth on laboratory media such as eosin–methylene blue or MacConkey agar. Serologic tests are available, and diagnosis can be established by a 4-fold or greater increase in antibody titer in an individual with an appropriate syndrome. It has been recognized as a possible agent of bioterrorism (see Chapter 723).

B. pseudomallei is susceptible to many antimicrobial agents, and the Centers for Disease Control and Prevention (CDC) recommends meropenem or ceftazidime as intravenous therapies and trimethoprim-sulfamethoxazole or doxycycline as oral therapy. Other choices include aminoglycosides, tetracycline, chloramphenicol, and amoxicillin-clavulanate. Therapy should be guided by antimicrobial susceptibility tests; 2 or 3 agents such as ceftazidime or meropenem plus either trimethoprim-sulfamethoxazole, sulfisoxazole, or an aminoglycoside are usually chosen for severe or septicemic disease. For severe disease, prolonged treatment for 2-6 mo is recommended to prevent relapses. Appropriate antibiotic therapy generally results in recovery.

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205.3 *Stenotrophomonas*

Thomas S. Murray and Robert S. Baltimore

Stenotrophomonas maltophilia (formerly *Xanthomonas maltophilia* or *P. maltophilia*) is a short to medium-sized straight Gram-negative bacillus. It is ubiquitous in nature and can be found in the hospital environment, especially in tap water or standing water, and may contaminate sinks and hospital equipment such as nebulizers. Strains isolated in the laboratory may be contaminants, may be a commensal from the colonized surface of a patient, or may represent an invasive pathogen. The species is an opportunist and is often recovered from immunosuppressed patients and patients with cystic fibrosis after multiple courses of antimicrobial therapy. Serious infections usually occur among those requiring intensive care, including neonatal intensive care, typically patients with ventilator-associated pneumonia or catheter-associated infections. Prolonged antibiotic exposure appears to be a frequent factor in nosocomial *S. maltophilia* infections, probably because of its endogenous antibiotic resistance pattern. Common types of infection include pneumonia following airway colonization and aspiration, bacteremia, soft-tissue infections, endocarditis, and osteomyelitis. *S. maltophilia* bacteremia is a nosocomial infection associated with the presence of a central venous catheter.

Strains vary as to antibiotic susceptibility, and the treatment of *S. maltophilia* can be difficult because of inherent antimicrobial resistance. Data are lacking on whether there is clinical benefit to treat *S. maltophilia* recovered from the respiratory tract of a patient with cystic fibrosis. For invasive infections, trimethoprim-sulfamethoxazole is the treatment of choice and is the only antimicrobial for which susceptibility is routinely reported. Mean inhibitory concentration testing is available for other antibiotics, such as ticarcillin-clavulanate, and reserved for trimethoprim-sulfamethoxazole resistant isolates. For resistant organisms or for patients who cannot tolerate sulfa drugs, other options based on clinical outcome include ciprofloxacin, and ceftazidime alone, or in combination with other agents such as aminoglycosides. Tigecycline is a newer agent reported to have efficacy for treating a highly resistant isolate.

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Chapter 206

Tularemia *(Francisella tularensis)*

Gordon E. Schutze and Richard F. Jacobs

Tularemia is a zoonotic infection caused by the Gram-negative bacterium *Francisella tularensis*. Tularemia is primarily a disease of wild animals; human disease is incidental and usually results from contact with blood-sucking insects or live or dead wild animals. The illness caused by *F. tularensis* is manifested by different clinical syndromes, the most common consisting of an ulcerative lesion at the site of inoculation with regional lymphadenopathy or lymphadenitis. *F. tularensis* is also a potential agent of bioterrorism (see Chapter 723).

ETIOLOGY

F. tularensis is a small, nonmotile, pleomorphic, Gram-negative coccobacillus that can be classified into 4 main subspecies, namely *F. tularensis tularensis* [type A], *F. tularensis holarctica* [type B],

F. tularensis mediasiatica, and *F. tularensis novicida*. Type A can be further subdivided into 4 distinct genotypes designated A1a, A1b, A2a, and A2b, with A1b appearing to produce more serious disease in humans. Type A is found exclusively in North America and is associated with wild rabbits, ticks, and tabanid flies (e.g., deer flies), whereas type B is found in North America, Europe, and Asia and is associated with semiaquatic rodents, hares, mosquitoes, ticks, tabanid flies, water (e.g., ponds, rivers), and marine animals. Human infections with type B are usually milder and have lower mortality rates compared to infections with type A.

EPIDEMIOLOGY

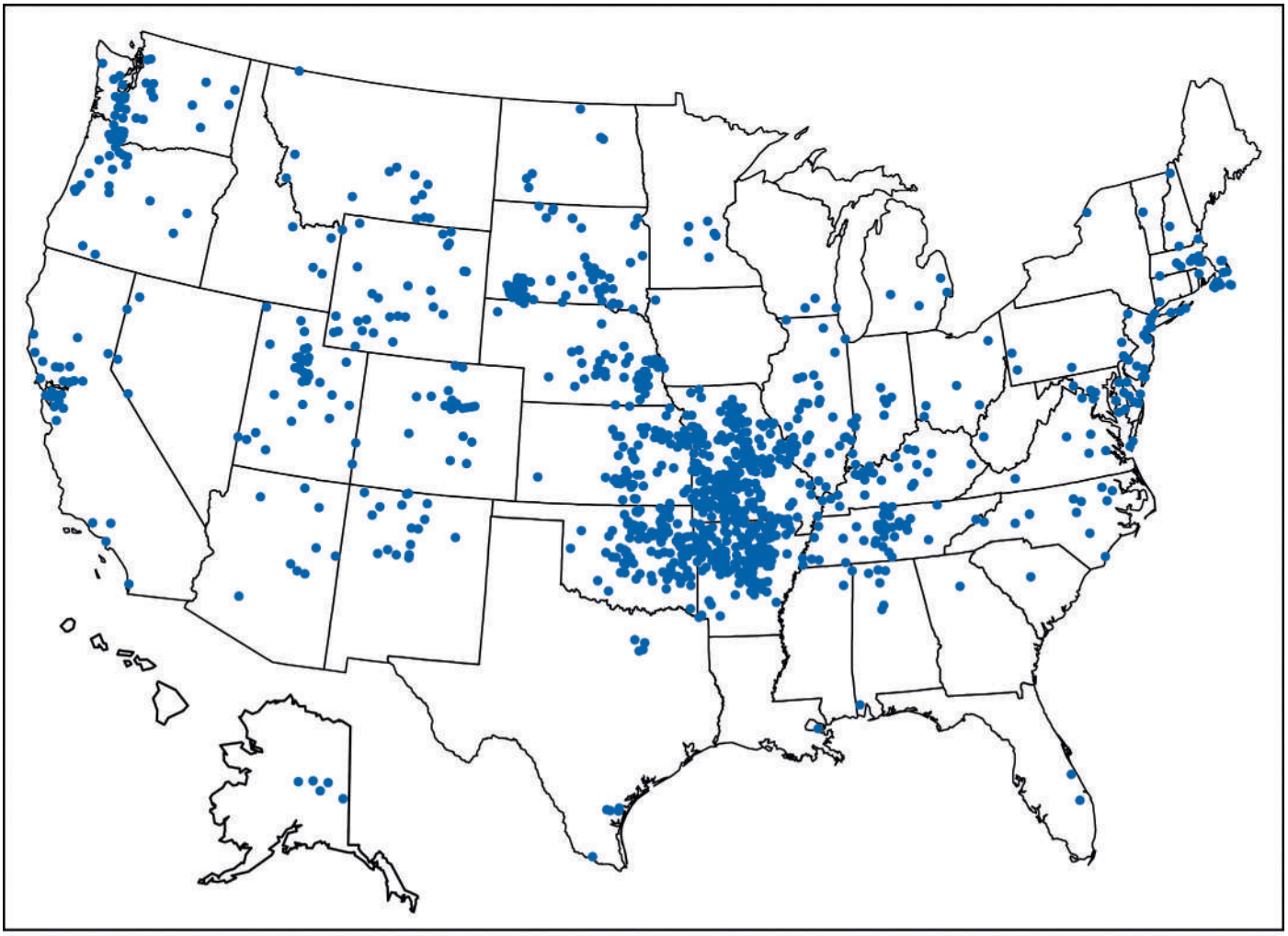
During 2001-2010, a total of 1,208 cases of tularemia were reported in the United States from 47 states, averaging 126.5 cases (range: 90-154) per year (Fig. 206-1). Six states accounted for 59% of all reported cases: Missouri, 231 cases (19%); Arkansas, 162 cases (13%); Oklahoma, 108 cases (9%); Massachusetts, 84 cases (7%); South Dakota, 65 cases (5%); and Kansas, 59 cases (5%).

Transmission

Of all the zoonotic diseases, tularemia is unusual because of the different modes of transmission of disease. A large number of animals serve as a reservoir for this organism, which can penetrate both intact skin and mucous membranes. Transmission can occur through the bite of infected ticks or other biting insects, by contact with infected animals or their carcasses, by consumption of contaminated foods or water, or through inhalation, as might occur in a laboratory setting. However, this organism is not transmitted from person to person. In the United States, rabbits and ticks are the principal reservoirs. Most disease caused by rabbit exposure occurs in the winter, and disease from tick exposure occurs in the warmer months (April-September). *Amblyomma americanum* (Lone Star tick), *Dermacentor variabilis* (dog tick), and *Dermacentor andersoni* (wood tick) are the most common tick vectors. These ticks usually feed on infected small rodents and later feed on humans. Taking that blood meal through a fecally contaminated field transmits the infection.

PATHOGENESIS

The most common portal of entry for human infection is through the skin or mucous membrane. Entry may occur through the bite of an infected insect or by way of unapparent abrasions. Inhalation or ingestion of *F. tularensis* can also result in infection. Usually $>10^8$ organisms are required to produce infection if they are ingested, but as few as 10 organisms may cause disease if they are inhaled or injected into the skin. Within 48-72 hr after injection into the skin, an erythematous, tender, or pruritic papule may appear at the portal of entry. This papule may enlarge and form an ulcer with a black base, followed by regional lymphadenopathy. Once *F. tularensis* reaches the lymph nodes, the



* One dot is placed randomly within county of residence for each reported case.

Figure 206-1 Reported cases of tularemia—United States, 2001–2010. *(From Centers for Disease Control and Prevention (CDC): Tularemia—United States, 2001-2010.* MMWR Morb Mortal Wkly Rep *62(47):963–966, 2013.)*

organism may multiply and form granulomas. Bacteremia may also be present and is most commonly associated with involvement of the reticuloendothelial system, although any organ of the body may be involved.

Conjunctival inoculation may result in infection of the eye with preauricular lymphadenopathy. Inhalation or hematogenous spread of the organisms can result in pneumonia. Chest roentgenograms of such patients may reveal patchy infiltrates rather than areas of consolidation. Pleural effusions may also be present and may contain blood. In pulmonary infections, mediastinal adenopathy may be present; in oropharyngeal disease, patients may develop cervical lymphadenopathy. Typhoidal tularemia is a term used to describe severe bacteremic disease, regardless of the mode of transmission or portal of entry.

Infection with *F. tularensis* stimulates the host to produce antibodies, which have only recently been recognized as important in the immune response to this organism. The body is most dependent on cell-mediated immunity to contain and eradicate *F. tularensis*. Tularemia is usually followed by specific protection; thus, chronic infection or reinfection is unlikely.

CLINICAL MANIFESTATIONS

Although it may vary, the average incubation period from infection until clinical symptoms is 3 days (range: 1-21 days). A sudden onset of fever with other associated symptoms is common (Table 206-1). Physical examination may include lymphadenopathy, hepatosplenomegaly, or skin lesions. Various skin lesions have been described, including erythema multiforme and erythema nodosum. Approximately 20% of patients may develop a generalized maculopapular rash that occasionally becomes pustular. These clinical manifestations of tularemia have been divided into various syndromes (Table 206-2).

Table 206-1 Common Clinical Manifestations of Tularemia in Children

SIGN OR SYMPTOM	FREQUENCY (%)
Lymphadenopathy	96
Fever (>38.3°C [100.9°F])	87
Ulcer/eschar/papule	45
Pharyngitis	43
Myalgias/arthralgias	39
Nausea/vomiting	35
Hepatosplenomegaly	35

Table 206-2 Clinical Syndromes of Tularemia in Children

CLINICAL SYNDROME	FREQUENCY (%)
Ulceroglandular	45
Glandular	25
Pneumonia	14
Oropharyngeal	4
Oculoglandular	2
Typhoidal	2
Other*	6

*Includes meningitis, pericarditis, hepatitis, peritonitis, endocarditis, and osteomyelitis.

Ulceroglandular and glandular disease are the 2 most common forms of tularemia diagnosed in children. The most common glands involved are the cervical or posterior auricular nodes owing to a tick bite on the head or neck. If an ulcer is present, it is erythematous and painful and may last from 1-3 wk. The ulcer is located at the portal of entry. After the ulcer develops, regional lymphadenopathy ensues. These nodes may vary in size from 0.5-10 cm and may appear singly or in clusters. These affected nodes may become fluctuant and drain spontaneously, but usually resolve with treatment. Late suppuration of the involved nodes has been described in 25-30% of patients despite effective therapy. Examination of this material from such lymph nodes usually reveals sterile necrotic material.

Pneumonia caused by *F. tularensis* usually presents as variable parenchymal infiltrates that are unresponsive to β-lactam antimicrobial agents. Inhalation-related infection has been described in laboratory workers who are working with the organism and results in a relatively high mortality rate. Aerosols from farming activities involving rodent contamination (haying, threshing) or animal carcass destruction with lawn mowers have been reported to cause pneumonia as well. Patchy parenchymal infiltrates can also be demonstrated in other forms of tularemia. Patchy segmental infiltrates, hilar adenopathy, and pleural effusions are the most common abnormalities demonstrated on chest roentgenograms. Patients may also complain of a nonproductive cough, dyspnea, or pleuritic chest pain.

Oropharyngeal tularemia results from consumption of poorly cooked meats or contaminated water. This syndrome is characterized by acute pharyngitis, with or without tonsillitis, and cervical lymphadenitis. Infected tonsils may become large and develop a yellowish-white membrane that may resemble the membranes associated with diphtheria. Gastrointestinal disease may also occur and usually presents with mild, unexplained diarrhea but may progress to rapidly fulminant and fatal disease.

Oculoglandular tularemia is uncommon, but when it does occur, the portal of entry is the conjunctiva. Contact with contaminated fingers or debris from crushed insects is the most common way of applying the organisms to the conjunctiva. The conjunctiva is painful and inflamed, with yellowish nodules and pinpoint ulcerations. Purulent conjunctivitis with ipsilateral preauricular or submandibular lymphadenopathy is referred to as **Parinaud oculoglandular syndrome.**

Typhoidal tularemia is usually associated with a large inoculum of organisms and usually presents with fever, headaches, and signs or symptoms of endotoxemia. Patients typically are critically ill, and symptoms mimic those with other forms of sepsis. Clinicians practicing in tularemia-endemic regions must always consider this diagnosis in critically ill children.

DIAGNOSIS

The history and physical examination of the patient may suggest the diagnosis of tularemia, especially if the patient lives in or has visited an endemic region. A history of animal or tick exposure may be especially helpful. Hematologic blood tests are nondiagnostic. Results of routine cultures and smears are positive in only approximately 10% of cases. *F. tularensis* can be cultured in the microbiology laboratory on cysteine–glucose–blood agar, but care should be taken to alert the personnel in the laboratory if this is attempted so that they can take the proper precautions to protect themselves from acquiring infection.

The diagnosis of tularemia is most commonly established through the use of a standard and highly reliable serum agglutination test. In the standard tube agglutination test, a single titer of ≥1:160 in a patient with a compatible history and physical findings can establish the diagnosis. A 4-fold increase in titer from paired serum samples collected 2-3 wk apart is also diagnostic. False-negative serologic responses can be obtained early in the infection, and as many as 30% of individuals require longer than 3 wk before testing positive. Once infected, patients may have a positive agglutination test result (1:20 to 1:80) that may persist for life.

Other testing techniques available include a microagglutination test, enzyme-linked immunosorbent assay, analysis of urine for tularemia

antigen, and polymerase chain reaction. These techniques may become more popular in the future but at this time have a limited role in establishing the diagnosis of tularemia.

Differential Diagnosis

The differential diagnosis of ulceroglandular or glandular tularemia includes cat scratch disease *(Bartonella henselae);* infectious mononucleosis; Kawasaki syndrome; lymphadenopathy caused by *Staphylococcus aureus,* group A streptococcus, *Mycobacterium tuberculosis, Toxoplasma gondii,* nontuberculous mycobacteria, or *Sporothrix schenckii;* plague; anthrax; melioidosis; and rat-bite fever. Oculoglandular disease may also occur with other infectious agents, such as *B. henselae, Treponema pallidum, Coccidioides immitis,* herpes simplex virus, adenoviruses, and the bacterial agents responsible for purulent conjunctivitis. Oropharyngeal tularemia must be differentiated from the same diseases that cause ulceroglandular/glandular disease and from cytomegalovirus, herpes simplex, adenovirus, and other viral or bacterial etiologies. Pneumonic tularemia must be differentiated from the other non–β-lactam-responsive organisms such as *Mycoplasma, Chlamydophila,* mycobacteria, fungi, and rickettsia. Typhoidal tularemia must be differentiated from other forms of sepsis as well as from enteric fever (typhoid and paratyphoid fever) and brucellosis.

TREATMENT

All strains of *F. tularensis* are susceptible to gentamicin and streptomycin. Gentamicin (5 mg/kg/day divided bid or tid IV or IM) is the drug of choice for the treatment of tularemia in children because of the limited availability of streptomycin (30-40 mg/kg/day divided bid IM) and the fewer adverse effects of gentamicin. Therapy is typically continued for 7-10 days, but in mild cases, 5-7 days may be sufficient. Chloramphenicol and tetracyclines have been used, but the high relapse rate has limited their use in children. Early data suggested that *F. tularensis* is susceptible to the third-generation cephalosporins (cefotaxime, ceftriaxone), but clinical case reports demonstrate a nearly universal failure rate with these agents. Fluoroquinolones have been used with success in cases of illness caused by the subspecies *holarctica*. Ciprofloxacin (15-20 mg/kg/day in 2 divided doses for 10-14 days) has been used in children, but the lack of treatment data for the subspecies *tularensis* and the issues related to the use of fluoroquinolones in patients younger than 18 yr of age limit the use of this group of medications in North American children at this time.

Patients typically have defervescence within 24-48 hr after starting therapy, and relapses are uncommon if gentamicin or streptomycin is used. Patients who have not started on appropriate therapy early may respond more slowly to antimicrobial therapy. Late suppuration of involved lymph nodes may occur despite adequate therapy.

PROGNOSIS

Poor outcomes are associated with a delay in recognition and treatment, but with rapid recognition and treatment, fatalities are exceedingly rare. The mortality rate for severe untreated disease (e.g., pneumonia, typhoidal disease) can be as high as 30% in these situations, but in general, the overall mortality rate is <1%.

PREVENTION

Prevention of tularemia is based on avoiding exposure. Children living in tick-endemic regions should be taught to avoid tick-infested areas, and families should have a tick control plan for their immediate environment and for their pets. Protective clothing should be worn when entering a tick-infested area. Insect repellents for use on the skin (e.g., DEET [*N,N*-diethyl-3-methylbenzamide] or picaridin) can be used safely in infants and children. If skin repellents are used, they should be used sparingly on the exposed skin, avoiding the hands and face on children younger than 1 yr of age. The repellent should be washed off completely after leaving the high-risk region. Clothing repellents that use permethrin have been demonstrated to be an effective addition to the use of protective clothing. Infants and young children should not be allowed to chew or suck on permethrin impregnated clothing. Children should undergo frequent tick checks during and after their time in tick-infested areas. If ticks are found on the child, forceps should be used to pull the tick straight out. The skin should be cleansed before and after this procedure.

Children should also be taught to avoid sick and dead animals. Dogs and cats are most likely to bring these animals to a child's attention. Children should be encouraged to wear gloves while cleaning wild game. Prophylactic antimicrobial agents are not effective in preventing tularemia and should not be used after exposure. No tularemia vaccine is currently available for the general public.

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Chapter 207

Brucella

Gordon E. Schutze and Richard F. Jacobs

Human brucellosis is caused by organisms of the genus *Brucella* and continues to be a major public health problem worldwide. Humans are accidental hosts and acquire this zoonotic disease from direct contact with an infected animal or consumption of products of an infected animal. Although brucellosis is widely recognized as an occupational risk among adults working with livestock, much of the brucellosis in children is foodborne and is associated with consumption of unpasteurized milk products. *Brucella* spp. are also potential agents of bioterrorism (see Chapter 723).

ETIOLOGY

Brucella abortus (cattle), *Brucella melitensis* (goat/sheep), *Brucella suis* (swine), and *Brucella canis* (dog) are the most common organisms responsible for human disease. These organisms are small, aerobic, non–spore-forming, nonmotile, Gram-negative coccobacillary bacteria that are fastidious in their growth but can be grown on various laboratory media, including blood and chocolate agars.

EPIDEMIOLOGY

Because of improved sanitation, brucellosis has become rare in industrialized countries. Brucellosis exists worldwide and is especially prevalent in the Mediterranean basin, Persian Gulf, Indian subcontinent, and parts of Mexico and Central and South America. In industrialized countries, recreational or occupational exposure to infected animals is a major risk factor for the development of disease. In the United States, more than 50% of cases occur in California, Florida, and Texas, and hunting feral swine in these states is a recently recognized risk factor. Among children, geographic locations that are endemic for *B. melitensis* remain areas of increased risk for the development of infection. In such locations, unpasteurized milk from goats or camels may be used to feed children, thus leading to the development of brucellosis. A history of travel to endemic regions or consumption of exotic food or unpasteurized dairy or dairy products may be an important clue to the diagnosis of human brucellosis.

PATHOGENESIS

Routes of infection for these organisms include inoculation through cuts or abrasions in the skin, inoculation of the conjunctival sac of the eye, inhalation of infectious aerosols, or ingestion of contaminated meat or dairy products. The risk for infection depends on the nutritional and immune status of the host, the route of inoculum, and the species of *Brucella.* For reasons that remain unclear, it has been suggested that *B. melitensis* and *B. suis* are more virulent than *B. abortus* or *B. canis.*

The major virulence factor for *Brucella* appears to be its cell wall lipopolysaccharide. Strains containing smooth lipopolysaccharide have been demonstrated to have greater virulence and are more resistant to killing by polymorphonuclear leukocytes. These organisms are facultative intracellular pathogens that can survive and replicate within the mononuclear phagocytic cells (monocytes, macrophages) of the reticuloendothelial system. Even though *Brucella* are chemotactic for entry of leukocytes into the body, the leukocytes are less efficient at killing these organisms than other bacteria despite the assistance of serum factors such as complement.

Organisms that are not phagocytosed by the leukocytes are ingested by the macrophages and become localized within the reticuloendothelial system. Specifically, they reside within the liver, spleen, lymph nodes, and bone marrow and result in **granuloma** formation. Antibodies are produced against the lipopolysaccharide and other cell wall antigens, providing a means of diagnosis and probably playing a role in long-term immunity. The major factor in recovery from infection appears to be development of a cell-mediated response resulting in macrophage activation and enhanced intracellular killing. Specifically, sensitized T lymphocytes release cytokines (e.g., interferon-γ and tumor necrosis factor-α), which activate the macrophages and enhance their intracellular killing capacity.

CLINICAL MANIFESTATIONS

Brucellosis is a systemic illness that can be very difficult to diagnose in children without a history of animal or food exposure. Symptoms can be acute or insidious in nature and are usually nonspecific, beginning 2-4 wk after inoculation. Although the clinical manifestations vary, the classic triad of fever, arthralgia/arthritis, and hepatosplenomegaly can be demonstrated in most patients. Some present as a fever of unknown origin. Other associated symptoms include abdominal pain, headache, diarrhea, rash, night sweats, weakness/fatigue, vomiting, cough, and pharyngitis. A common constellation of symptoms in children is refusal to eat, lassitude, refusal to bear weight, and failure to thrive. Besides hepatosplenomegaly, the physical findings on examination are usually few, with the exception of arthritis. The fever pattern can vary widely, and virtually any organ or tissue can be involved.

If abnormalities are demonstrated on physical examination, monoarticular arthritis of the knees and hips in children and of the sacroiliac joint in adolescents and adults can be found. Although headache, mental inattention, and depression may be demonstrated in patients with brucellosis, invasion of the nervous system occurs in only approximately 1% of cases. Neonatal and congenital infections with these organisms have also been described, resulting from transmission transplacentally, from breast milk, and through blood transfusions. The signs and symptoms associated with brucellosis are vague and not pathognomonic.

DIAGNOSIS

Routine laboratory examinations of the blood are not helpful; thrombocytopenia, neutropenia, anemia, or pancytopenia may occur. A history of exposure to animals or ingestion of unpasteurized dairy products may be more helpful. A definitive diagnosis is established by recovering the organisms in the blood, bone marrow, or other tissues. Although automated culture systems and the use of the lysis-centrifugation method have shortened the isolation time from weeks to days, it is prudent to alert the clinical microbiology laboratory that brucellosis is suspected. Isolation of the organism still may require as long as 4 wk from a blood culture sample unless the laboratory is using an automated culture system such as the lysis centrifugation method where the organism can be recovered in <5 days. Bone marrow cultures may be superior to blood cultures when evaluating patients with previous antimicrobial therapy. Caution is advised when using automated bacterial identification systems, because isolates have been misidentified as other Gram-negative organisms (*Haemophilus influenzae* type b).

In the absence of positive culture results, various serologic tests have been applied to the diagnosis of brucellosis. The serum agglutination test is the most widely used and detects antibodies against *B. abortus, B. melitensis,* and *B. suis.* This method does not detect antibodies against *B. canis* because this organism lacks the smooth lipopolysaccharide. No single titer is ever diagnostic, but most patients with acute infections have titers of ≥1 : 160. Low titers may be found early in the course of the illness, requiring the use of acute and convalescent sera testing to confirm the diagnosis. Because patients with active infection have both an immunoglobulin (Ig) M and an IgG response and the serum agglutination test measures the total quantity of agglutinating antibodies, the total quantity of IgG is measured by treatment of the serum with 2-mercaptoethanol. This fractionation is important in determining the significance of the antibody titer because low levels of IgM can remain in the serum for weeks to months after the infection has been treated. It is important to remember that all titers must be interpreted in light of a patient's history and physical examination. False-positive results resulting from crossreacting antibodies to other Gram-negative organisms, such as *Yersinia enterocolitica, Francisella tularensis,* and *Vibrio cholerae,* can occur. In addition, the prozone effect can give false-negative results in the presence of high titers of antibody. To avoid this issue, serum that is being tested should be diluted to ≥1 : 320.

Among newer tests, the enzyme immunoassay should only be used for suspected cases with negative serum agglutination tests or for the evaluation of patients in the following situations: (1) complicated cases; (2) suspected chronic brucellosis; (3) reinfection. Polymerase chain reaction assays have been developed but are not available in most clinical laboratories.

Differential Diagnosis

Brucellosis may be confused with other infections such as tularemia, cat scratch disease, typhoid fever, histoplasmosis, blastomycosis, and coccidioidomycosis. Infections caused by *Mycobacterium tuberculosis,* atypical mycobacteria, rickettsiae, and *Yersinia* can present in a similar fashion to brucellosis.

TREATMENT

Many antimicrobial agents are active in vitro against the *Brucella* species, but the clinical effectiveness does not always correlate with these results. Doxycycline is the most useful antimicrobial agent and, when combined with an aminoglycoside, is associated with the fewest relapses (Table 207-1). Treatment failures with β-lactam antimicrobial agents, including the third-generation cephalosporins, may be because of the intracellular nature of the organism. Agents that provide intracellular killing are required for eradication of this infection. Similarly, it is apparent that prolonged treatment is the key to preventing disease relapse. Relapse is confirmed by isolation of *Brucella* within weeks to months after therapy has ended and is usually not associated with antimicrobial resistance.

The onset of initial antimicrobial therapy may precipitate a Jarisch-Herxheimer–like reaction, presumably because of a large antigen load. It is rarely severe enough to require corticosteroid therapy.

PROGNOSIS

Before the use of antimicrobial agents, the course of brucellosis was often prolonged and may have led to death. Since the institution of specific therapy, most deaths are a result of specific organ system involvement (e.g., endocarditis) in complicated cases. The prognosis after specific therapy is excellent if patients are compliant with the prolonged therapy (see Table 207-1).

PREVENTION

Prevention of brucellosis is dependent on effective eradication of the organism from cattle, goats, and swineherds, as well as from other animals. Pasteurization of milk and dairy products for human consumption remains an important aspect of prevention. It should be noted that certification of raw milk does not eliminate the risk of brucellosis acquisition. No vaccine currently exists for use in children and, therefore, education of the public continues to have a prominent role in prevention of this disease.

Bibliography is available at Expert Consult.

Table 207-1 Recommended Therapy for the Treatment of Brucellosis

AGE AND CONDITION	ANTIMICROBIAL AGENT	DOSE	ROUTE	DURATION
≥8 yr	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	6 wk
	+			
	Rifampin	15-20 mg/kg/day; maximum: 600-900 mg/day	PO	6 wk
	Alternative:			
	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	6 wk
	+			
	Streptomycin	15-30 mg/kg/day; maximum: 1 g/day	IM	2-3 wk
	or			
	Gentamicin	3-5 mg/kg/day	IM/IV	1-2 wk
<8 yr	Trimethoprim-sulfamethoxazole (TMP-SMZ)	TMP (10 mg/kg/day; maximum: 480 mg/day) and SMZ (50 mg/kg/day; maximum: 2.4 g/day)	PO	4-8 wk
	+			
	Rifampin	15-20 mg/kg/day	PO	6 wk
Meningitis, osteomyelitis, endocarditis	Doxycycline	2-4 mg/kg/day; maximum: 200 mg/day	PO	4-6 mo
	+			
	Gentamicin	3-5 mg/kg/day	IV	1-2 wk
	±			
	Rifampin	15-20 mg/kg/day; maximum: 600-900 mg/day	PO	4-6 mo

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Chapter 208

Legionella

Lucy S. Tompkins and Elizabeth V. Robilotti

Legionellosis comprises **Legionnaires disease** (*Legionella* pneumonia), other invasive extrapulmonary *Legionella* infections, and an acute flu-like illness known as **Pontiac fever.** In contrast to the syndromes associated with invasive disease, Pontiac fever is a self-limited illness that develops after aerosol exposure and may represent a toxic or hypersensitivity response to *Legionella.*

ETIOLOGY

Legionellaceae are aerobic, non–spore-forming, unencapsulated Gram-negative bacilli that stain poorly with Gram stain when performed on smears from clinical specimens. Microorganisms in tissue can be better visualized with the Gimenez or silver stains (Dieterle or Warthin-Starry). Stained smears of *Legionella pneumophila* taken from colonial growth resemble *Pseudomonas.* Unlike other *Legionella* species, *Legionella micdadei* stains acid fast. Although more than 30 species of the genus have now been identified, the majority (90%) of clinical infections are caused by *L. pneumophila,* and most of the remainder are caused by *L. micdadei, Legionella bozemanii, Legionella dumoffii,* and *Legionella longbeachae.*

The organisms are fastidious and require L-cysteine, ferric ion, and α-keto acids for growth. Colonies develop within 3-5 days on buffered charcoal yeast extract agar, which may contain selected antibiotics to inhibit overgrowth by other microorganisms; *Legionella* rarely grows on routine laboratory media.

EPIDEMIOLOGY

The environmental reservoir of *Legionella* in nature is fresh water (lakes, streams, thermally polluted waters, potable water), and invasive pneumonia (Legionnaires disease) is related to exposure to potable water or to aerosols containing the bacteria. Growth of *Legionella* occurs more readily in warm water, and exposure to warm water sources is an important risk factor for disease. *Legionella* organisms are facultative intracellular parasites and grow inside protozoans present in biofilms consisting of organic and inorganic material found in plumbing and water storage tanks and various other bacterial species. Epidemic and sporadic cases of community-acquired Legionnaires disease can be attributed to potable water in the local environment of the patient. Risk factors for acquisition of sporadic community-acquired pneumonia include exposure to cooling towers, nonmunicipal water supply, residential plumbing repairs, and lower water heater temperatures, which facilitate growth of bacteria or lead to release of a bolus of biofilm containing *Legionella* into potable water. The mode of transmission may be by way of inhalation of aerosols or by microaspiration. Outbreaks of Legionnaires disease have been associated with protozoans in the implicated water source; replication within these eukaryotic cells presumably amplifies and maintains *Legionella* within the potable water distribution system or in cooling towers. Outbreaks of community-acquired pneumonia and some nosocomial outbreaks have been linked to common sources, including potable hot water heaters, evaporative condensers, cooling towers, whirlpool baths, humidifiers, and nebulizers. Travel-associated Legionnaires disease and Pontiac fever are increasingly recognized in major outbreaks.

Hospital-acquired infections are most often linked to potable water. Exposure may occur through 3 general mechanisms: (1) inhalation of contaminated water vapor through artificial ventilation; (2) aspiration of ingested microorganisms, including those in gastric feedings that are mixed with contaminated tap water; and (3) inhalation of aerosols from showers, sinks and fountains. Extrapulmonary legionellosis may occur through topical application of contaminated tap water into surgical or traumatic wounds. In contrast to Legionnaires disease, Pontiac fever outbreaks have occurred through exposure to aerosols from whirlpool baths and ventilation systems.

The incidence of legionellosis in the United States increased from 1,100 cases in 2000 to 3,522 cases in 2009 for a national incidence rate of 1.15 per 100,000 persons based on passive reporting to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Disease Surveillance System. Legionellosis demonstrates geographic differences, and the vast majority of cases are classified as Legionnaires disease (99.5%) vs a small fraction as Pontiac fever (0.5%). *Legionella* infections are reported most frequently in fall and summer, and recent studies show an association with total monthly rainfall and humidity. Approximately 0.5-5.0% of those exposed to a common source develop pneumonia, whereas the attack rate in Pontiac fever outbreaks is very high (85-100%). Although *Legionella* is associated with 2-9% of pneumonia cases in adults, it is a rare cause of disease in pediatric populations, accounting for fewer than 1% of cases. Taken together, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *L. pneumophila* have been identified in 3-23% of children studied with atypical pneumonia. These pathogens show a specific age distribution, with *M. pneumoniae* more commonly isolated in older children and *C. pneumoniae* more frequently recovered from infants. *Legionella* remains a rare cause of community-acquired pneumonia in those younger than 19 yr of age. Acquisition of antibodies to *L. pneumophila*

in healthy children occurs progressively over time, although these antibodies presumably reflect subclinical infection or mild respiratory disease or antibodies that crossreact with other bacterial species. Community-acquired Legionnaires disease in children is increasingly reported (1.7% of reported cases), and most cases occur in children ages 15-19 yr, followed by infants age younger than 1 yr. The incidence in infants is reported to be 0.11 per 100,000. It is likely that legionellosis is significantly underreported, both in children and adults.

As estimated by seroconversion to *L. pneumophila* among children hospitalized with pneumonia, the Legionnaires disease rate is quite low. Most nosocomial infections have been reported as case reports; consequently, the true incidence of disease in children is unknown. Nosocomial infection rates in adults are difficult to determine, because many hospital laboratories do not attempt to isolate *Legionella* by culture. Hospital-acquired legionellosis in children is associated with clinical risk factors and with environmental exposure.

PATHOGENESIS

Although *Legionella* can be grown on artificial media, the intracellular environment of eukaryotic cells provides the definitive site of growth. *Legionella* organisms are facultative intracellular parasites of eukaryotic cells. In nature, *Legionella* replicate within protozoans found in fresh water. In humans, the main target cell for *Legionella* is the alveolar macrophage, although other cell types may also be invaded. After entry, virulent strains of *L. pneumophila* stimulate the formation of a special phagosome that permits bacterial replication to proceed. The phagosome consists of components of the endoplasmic reticulum and escapes the degradative lysosomal pathway. Growth in macrophages occurs to the point of cell death, followed by reinfection of new cells, until these cells are activated and can subsequently kill intracellular microorganisms. Acute, severe infection of the lung provokes an acute inflammatory response and necrosis; early on, more bacteria are found in extracellular spaces as a result of intracellular replication, lysis, and release of bacteria. Subsequently, macrophage activation and other immune responses produce intense infiltration of tissue by macrophages that contain intracellular bacteria, ultimately leading to control of bacterial replication and killing. Corticosteroid therapy poses a high risk for infection by interfering with T-cell and macrophage function. Although community-acquired Legionnaires disease may occur in healthy, immunocompetent patients without other comorbid conditions, those who have defects in cellular-mediated immunity are at high risk for infection. As in other diseases caused by facultative intracellular microorganisms, the outcome is critically dependent on the specific and nonspecific immune responses of the host, particularly macrophage and T-cell responses.

CLINICAL MANIFESTATIONS

Legionnaires disease was originally believed to cause atypical pneumonia associated with extrapulmonary signs and symptoms, including diarrhea, confusion, hyponatremia, hypophosphatemia, abnormal results of liver function tests, and renal dysfunction. Although a subset of patients may exhibit these classic manifestations, *Legionella* infection typically causes pneumonia that is indistinguishable from disease produced by other infectious agents. Fever, cough, and chest pain are common presenting symptoms; the cough may be productive of purulent sputum or may be nonproductive. Although the classic chest radiographic appearance demonstrates rapidly progressive alveolar filling infiltrates, in usual cases of pneumonia the chest radiographic appearance is widely variable, appearing as tumor-like shadows, evidence of nodular infiltrates, unilateral or bilateral infiltrates, or cavitation, although cavitation is rarely seen in immunocompetent patients. This picture overlaps substantially with disease caused by *Streptococcus pneumoniae.* Although pleural effusion is less commonly associated with Legionnaires disease, its frequency varies so widely that neither the presence nor absence of effusion is helpful in differential diagnosis. If present, pleural fluid should be obtained for culture.

A few clinical features may help to differentiate *Legionella* pneumonia from other causes. *Legionella* pneumonia produces an acute-onset febrile illness and radiographic evidence of alveolar filling infiltrates, and usually there is no clinical response to broad-spectrum β-lactam (penicillins and cephalosporins) or aminoglycoside antibiotics.

Concomitant infection with other pathogens, including *M. pneumoniae* and *C. pneumoniae*, occurs in 5-10% of cases of Legionnaires disease; therefore, detection of another potential pulmonary pathogen does not preclude the diagnosis of legionellosis.

Most reports of nosocomial *Legionella* pneumonia in children demonstrate the following clinical features: rapid onset, temperature greater than 38.5°C (101.3°F), cough, pleuritic chest pain, tachypnea, and dyspnea. Abdominal pain, headache, and diarrhea are also common. Chest radiographs reveal lobar consolidations or diffuse bilateral infiltrates, and pleural effusions may be noted.

Risk factors for Legionnaires disease in adults include chronic diseases of the lung (smoking, bronchitis), older age, diabetes and renal failure, immunosuppression associated with organ transplantation, corticosteroid therapy, and episodes of aspiration. In surveys of community-acquired infection, a significant number of adults have no identified risk factors. The number of reported cases of community-acquired Legionnaires disease in children is small. Among these, immunocompromised status, especially corticosteroid treatment, coupled with exposure to contaminated potable water is the major risk factor. Infection in a few children with chronic pulmonary disease without immune deficiency has also been reported, but infection in children lacking any risk factors is very uncommon. The modes of transmission of community-acquired disease in children include exposure to mists, fresh water, water coolers, and other aerosol-generating apparatuses. Nosocomial *Legionella* infection occurs more frequently than community-acquired disease in children and occurs most commonly in those who are immunocompromised, although Legionnaires disease has been seen in immunocompetent children who are postoperative receiving artificial ventilation or exposed to other aerosols. The modes of acquisition include microaspiration, frequently associated with nasogastric tubes, and aerosol inhalation. Bronchopulmonary *Legionella* infections are reported in patients with cystic fibrosis and have been associated with aerosol therapy or mist tents. Legionnaires disease is also reported in pediatric patients with asthma and tracheal stenosis. Chronic corticosteroid therapy for asthma is a reported risk factor for *Legionella* infections in children. Molecular fingerprinting of strains has demonstrated that potable water serves as the major reservoir and source of nosocomial infection.

Pontiac fever in adults and children is characterized by high fever, myalgia, headache, and extreme debilitation, lasting for a few days. Cough, breathlessness, diarrhea, confusion, and chest pain may occur, but there is no evidence for invasive infection. The disease is self-limited without sequelae. Virtually all exposed individuals seroconvert to *Legionella* antigens. A very large outbreak in Scotland that affected 35 children was attributed to *L. micdadei,* which was isolated from a whirlpool spa. The onset of illness was 1-7 days (median: 3 days), and all exposed children developed significant titers of specific antibodies to *L. micdadei*. The pathogenesis of Pontiac fever is not known. In the absence of evidence of true infection, the most likely hypothesis is that this syndrome is caused by a toxic or hypersensitivity reaction to microbial, or protozoan, antigens.

DIAGNOSIS

Culture of *Legionella* from sputum, other respiratory tract specimens, blood, or tissue is the gold standard against which indirect methods of detection should be compared. Specimens obtained from the respiratory tract that are contaminated with oral flora must be treated and processed to reduce contaminants and plated onto selective media. Because these are costly and time-consuming methods, many laboratories do not process specimens for culture. The urinary antigen assay that detects *L. pneumophila* serogroup I has revolutionized the diagnosis of *Legionella* infection and has 80% sensitivity and 99% specificity. The assay is a useful method in the prompt diagnosis of Legionnaires disease caused by this serogroup, which accounts for the majority of symptomatic infections. In the United States, this test is frequently used because it is widely available in reference laboratories. Where available, polymerase chain reaction is used to identify *L. pneumophila* from bronchoscopic lavage and other clinical specimens to the exclusion of other respiratory pathogens. Other methods, including direct immunofluorescence, have low sensitivity and are generally not employed. Retrospective diagnosis can be made serologically using the enzyme-linked

immunosorbent assay or enzyme immunoassay to detect specific antibody production. Seroconversion may not occur for several weeks after onset of infection, and the available serologic assays do not detect all strains of *L. pneumophila* or all species. In view of the low sensitivity of direct detection and the slow growth of the microorganism in culture, the diagnosis of legionellosis should be pursued actively when there is suggestive clinical evidence, including the lack of response to usual antibiotics, even when results of other laboratory studies are negative.

TREATMENT

In community-acquired pneumonia in adults who are hospitalized, guidelines recommend empirical treatment with a broad-spectrum cephalosporin plus a macrolide or quinolone so as to treat atypical microorganisms *(Legionella, Chlamydophila pneumoniae, M. pneumoniae).* Evidence-based guidelines for management of community-acquired pneumonia in children do not yet include *Legionella* in the differential diagnosis or empiric treatment recommendations. Effective treatment of Legionnaires disease is based in part on the intracellular concentration of antibiotics. Erythromycin (40 mg/kg/day PO or IV) with or without rifampin (15 mg/kg/day) was considered effective therapy many years ago. Azithromycin (10 mg/kg on day 1, not to exceed 500 mg/day, and then 5 mg/kg daily for 4 days PO) and clarithromycin (15 mg/kg/day PO) and the quinolones (ciprofloxacin and levofloxacin) have generally replaced erythromycin as therapy for patients with diagnosed *Legionella* infection. Quinolones are not approved for children younger than 18 yr of age and should be avoided in those who have not achieved growth maturity. In serious infections or in high-risk patients, parenteral therapy is recommended initially; a switch to oral therapy can be made when a patient has had a clinical response. The duration of oral azithromycin therapy for Legionnaires disease in adults is 4 days, although therapy is usually continued for 10-14 days in more seriously ill or immunocompromised patients. Acute reversible hearing loss is associated with high-dose parenteral macrolide therapy. Treatment of extrapulmonary infections, including prosthetic valve endocarditis and sternal wound infections, may require prolonged therapy. Trimethoprim-sulfamethoxazole (TMP-SMZ; 15 mg TMP/kg/day and 75 mg SMZ/kg/day) is used as an alternative.

PROGNOSIS

The mortality rate for community-acquired Legionnaires disease in adults who are hospitalized is approximately 15% but may exceed 50% in immunocompromised patients. The prognosis depends on underlying host factors and possibly on the duration of illness before initiation of appropriate therapy. Despite appropriate antibiotic therapy, patients may succumb to respiratory complications, such as acute respiratory distress syndrome, associated with artificial ventilation and intubation. A high mortality rate is noted in case reports of premature infants and children, virtually all of whom have been immunocompromised. Delay in diagnosis is also associated with increased mortality. Consequently, *Legionella* should be considered in the differential diagnosis of both community-acquired and nosocomial pneumonia in children, especially in those refractory to empiric therapy or with epidemiologic risk factors for legionellosis.

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Chapter 209

Bartonella

Barbara W. Stechenberg

The spectrum of disease resulting from human infection with *Bartonella* species includes the association of bacillary angiomatosis and cat-scratch disease (CSD) with *Bartonella henselae.* There are more than 30 validated species of *Bartonella*; however, 6 major species are pathogenic for humans: *B. henselae, Bartonella quintana, Bartonella bacilliformis, Bartonella elizabethae, Bartonella vinsonii,* and *Bartonella clarridgeiae* (Table 209-1). Several other *Bartonella* species have been found in animals, particularly rodents and moles.

Members of the genus *Bartonella* are Gram-negative, oxidase-negative, fastidious aerobic rods that ferment no carbohydrates. *B. bacilliformis* is the only species that is motile, achieving motility by means of polar flagella. Optimal growth is obtained on fresh media containing 5% or more sheep or horse blood in the presence of 5% carbon dioxide. The use of lysis centrifugation for specimens from blood on chocolate agar for extended periods (2-6 wk) enhances recovery.

Bibliography is available at Expert Consult.

209.1 Cat-Scratch Disease (*Bartonella henselae*)

Barbara W. Stechenberg

The most common presentation of *Bartonella* infection is CSD, which is a subacute, regional lymphadenitis caused by *B. henselae.* It is the most common cause of chronic lymphadenitis that persists for longer than 3 wk.

ETIOLOGY

B. henselae can be cultured from the blood of healthy cats. *B. henselae* organisms are the small pleomorphic Gram-negative bacilli visualized with Warthin-Starry stain in affected lymph nodes from patients with CSD. Development of serologic tests that showed prevalence of antibodies in 84-100% of cases of CSD, culturing of *B. henselae* from CSD nodes, and detection of *B. henselae* by polymerase chain reaction in the majority of lymph node samples and pus from patients with CSD, confirmed the organism as the cause of CSD. Occasional cases of CSD may be caused by other organisms; 1 report described a veterinarian with CSD caused by *B. clarridgeiae.*

EPIDEMIOLOGY

CSD is common, with more than 24,000 estimated cases per year in the United States. It is transmitted by cutaneous inoculation. Most (87-99%) patients have had contact with cats, many of which are kittens younger than 6 mo of age, and more than 50% of patients have a definite history of a cat scratch or bite. Cats have high-level *Bartonella* bacteremia for months without any clinical symptoms; kittens are more frequently bacteremic than adult cats. Transmission between cats occurs via the cat flea, *Ctenocephalides felis.* In temperate zones, the majority of cases occur between September and March, perhaps in relation to the seasonal breeding of domestic cats or to the close proximity of family pets in the fall and winter. In tropical zones, there is no seasonal prevalence. Distribution is worldwide, and infection occurs in all races.

Cat scratches appear to be more common among children, and boys are affected more often than girls. CSD is a sporadic illness; usually only 1 family member is affected, even though many siblings play with the same kitten. However, clusters do occur, with family cases within weeks of one another. Anecdotal reports have implicated other sources, such as dog scratches, wood splinters, fishhooks, cactus spines, and porcupine quills.

PATHOGENESIS

The pathologic findings in the primary inoculation **papule** and affected lymph nodes are similar. Both show a central avascular necrotic area with surrounding lymphocytes, giant cells, and histiocytes. Three stages of involvement occur in affected nodes, sometimes simultaneously in the same node. The 1st stage consists of generalized enlargement with thickening of the cortex and hypertrophy of the germinal center and with a predominance of lymphocytes. Epithelioid granulomas with Langhans giant cells are scattered throughout the node. The middle stage is characterized by granulomas that increase in density, fuse, and become infiltrated with polymorphonuclear leukocytes, with

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beginning central necrosis. In the final stage, necrosis progresses with formation of large pus-filled sinuses. This purulent material may rupture into surrounding tissue. Similar granulomas have been found in the liver, spleen, and osteolytic lesions of bone when those organs are involved.

CLINICAL MANIFESTATIONS

After an incubation period of 7-12 days (range: 3-30 days), 1 or more 3-5 mm red papules develop at the site of cutaneous inoculation, often reflecting a linear cat scratch. These lesions are often overlooked because of their small size but are found in at least 65% of patients when careful examination is performed (Fig. 209-1). Lymphadenopathy is generally evident within a period of 1-4 wk (Fig. 209-2). Chronic regional lymphadenitis is the hallmark, affecting the 1st or 2nd set of nodes draining the entry site. Affected lymph nodes in order of frequency include the axillary, cervical, submandibular, preauricular, epitrochlear, femoral, and inguinal nodes. Involvement of more than 1 group of nodes occurs in 10-20% of patients, although at a given site, half the cases involve several nodes.

Nodes involved are usually tender and have overlying erythema but without cellulitis. They usually range between 1 and 5 cm in size, although they can become much larger. Between 10% and 40% eventually suppurate. The duration of enlargement is usually 1-2 mo, with persistence up to 1 yr in rare cases. Fever occurs in approximately 30% of patients, usually 38-39°C (100.4-102.2°F). Other nonspecific symptoms, including malaise, anorexia, fatigue, and headache, affect less than one-third of patients. Transient rashes, which may occur in approximately 5% of patients, are mainly truncal maculopapular rashes. Erythema nodosum, erythema multiforme, and erythema annulare are also reported.

CSD is usually a self-limited infection that spontaneous resolves within a few weeks to months. The most common atypical presentation is **Parinaud oculoglandular syndrome,** which is unilateral conjunctivitis followed by preauricular lymphadenopathy and occurs in 2-17% of patients with CSD (Fig. 209-3). Direct eye inoculation as a result of rubbing with the hands after cat contact is the presumed mode of spread. A conjunctival granuloma may be found at the inoculation site. The involved eye is usually not painful and has little or no discharge but may be quite red and swollen. Submandibular or cervical lymphadenopathy may also occur.

More severe, disseminated illness occurs in a small percentage of patients and is characterized by presentation with high fever, often persisting for several weeks. Other prominent symptoms include significant abdominal pain and weight loss. **Hepatosplenomegaly** may occur, although hepatic dysfunction is rare (Fig. 209-4). Granulomatous changes may be seen in the liver and spleen. Another common site of dissemination is bone, with the development of **granulomatous osteolytic lesions,** associated with localized pain but without erythema, tenderness, or swelling. Other uncommon manifestations are neuroretinitis with papilledema and stellate macular exudates, encephalitis, fever of unknown origin, and atypical pneumonia.

DIAGNOSIS

In most cases, the diagnosis can be strongly suspected on clinical grounds in a patient with history of exposure to a cat. The U.S. Centers for Disease Control and Prevention (CDC) has developed

Table 209-1 *Bartonella* Species Causing Human Disease

DISEASE	ORGANISM	VECTOR	PRIMARY RISK FACTOR
Bartonellosis	*B. bacilliformis*	Sandfly *(Lutzomyia verrucarum)*	Living in endemic areas (Andes Mountains)
Cat-scratch disease	*B. henselae* *B. clarridgeiae* (1 case)	Cat	Cat scratch or bite
Trench fever	*B. quintana*	Human body louse	Body louse infestation during outbreak
Bacteremia, endocarditis	*B. henselae* *B. quintana* *B. elizabethae* *B. vinsonii*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression
Bacillary angiomatosis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression
Peliosis hepatis	*B. henselae* *B. quintana*	Cat for *B. henselae* Human body louse for *B. quintana*	Severe immunosuppression

Figure 209-1 A child with typical cat-scratch disease demonstrating the original scratch injuries and the primary papule that soon thereafter developed proximal to the middle finger. *(Courtesy of Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*

Figure 209-2 Right axillary lymphadenopathy followed the scratches and development of a primary papule in this child with typical cat-scratch disease. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2006, Elsevier, p. 2737.)*

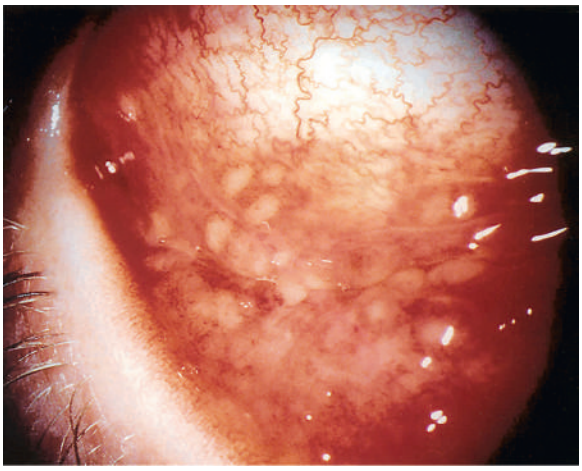

Figure 209-3 The granulomatous conjunctivitis of Parinaud oculoglandular syndrome is associated with ipsilateral local lymphadenopathy, usually preauricular and less commonly submandibular. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2006, Elsevier, p. 2739.)*

Figure 209-4 In this CT scan of a patient with hepatic involvement of cat-scratch disease, the absence of enhancement of the multiple lesions after contrast infusion is consistent with the granulomatous inflammation of this entity. Treated empirically with various antibiotics without improvement before establishment of this diagnosis, the patient subsequently recovered fully with no further antimicrobial therapy. *(Courtesy of Dr. V.H. San Joaquin, University of Oklahoma Health Sciences Center, Oklahoma City.)*

an indirect immunofluorescent assay that shows good correlation with disease. Other immunofluorescent assay and enzyme-linked immunoassay tests are commercially available, although little comparative data are available. Most patients have elevated antibody titers at presentation; however, the timing of immunoglobulin G and immunoglobulin M response to *B. henselae* can be quite variable. There is crossreactivity among *Bartonella* species, particularly *B. henselae* and *B. quintana*.

If tissue specimens are obtained, bacilli may be visualized with Warthin-Starry and Brown-Hopps tissue stains. *Bartonella* DNA can be identified through polymerase chain reaction analysis of tissue specimens. Culturing of the organism is not generally practical for clinical diagnosis.

Differential Diagnosis

The differential diagnosis of CSD includes virtually all causes of lymphadenopathy (see Chapter 490). The more-common entities include pyogenic (suppurative) lymphadenitis, primarily from staphylococcal or streptococcal infections, atypical mycobacterial infections, and malignancy. Less-common entities are tularemia, brucellosis, and sporotrichosis. Epstein-Barr virus, cytomegalovirus, and *Toxoplasma gondii* infections usually cause more generalized lymphadenopathy.

LABORATORY FINDINGS

Routine laboratory tests are not helpful. The erythrocyte sedimentation rate is often elevated. The white blood cell count may be normal or mildly elevated. Hepatic transaminases are often normal, but may be elevated in systemic disease. Ultrasonography or CT may reveal many granulomatous nodules in the liver and spleen; the nodules appear as hypodense round irregular lesions.

TREATMENT

Antibiotic treatment of CSD is not always needed and is not clearly beneficial. For most patients, treatment consists of conservative symptomatic care and observation. Studies show a significant discordance between in vitro activity of antibiotics and clinical effectiveness. For many patients, diagnosis is considered in the context of failure to respond to β-lactam antibiotic treatment of presumed staphylococcal lymphadenitis.

A small prospective study of oral azithromycin (500 mg on day 1, and then 250 mg on days 2-5; for smaller children, 10 mg/kg/24 hr on day 1 and 5 mg/kg/24 hr on days 2-5) showed a decrease in initial lymph node volume in 50% of patients during the 1st 30 days, but after 30 days there was no difference in lymph node volume. No other clinical benefit was found. For the majority of patients, CSD is self-limited, and resolution occurs over weeks to months without antibiotic treatment. Azithromycin, clarithromycin, trimethoprim-sulfamethoxazole, rifampin, ciprofloxacin, and gentamicin appear to be the best agents if treatment is considered.

Suppurative lymph nodes that become tense and extremely painful should be drained by needle aspiration, which may need to be repeated. Incision and drainage of nonsuppurative nodes should be avoided because chronic draining sinuses may result. Surgical excision of the node is rarely necessary.

Children with hepatosplenic CSD appear to respond well to rifampin at a dose of 20 mg/kg for 14 days, either alone or in combination with trimethoprim-sulfamethoxazole.

COMPLICATIONS

Encephalopathy, which can occur in as many as 5% of patients with CSD, typically manifests 1-3 wk after the onset of lymphadenitis as the sudden onset of neurologic symptoms, which often include seizures, combative or bizarre behavior, and altered level of consciousness. Imaging studies are generally normal. The cerebrospinal fluid is normal or shows minimal pleocytosis and protein elevation. Recovery occurs without sequelae in nearly all patients but may take place slowly over many months.

Other neurologic manifestations include peripheral facial nerve paralysis, myelitis, radiculitis, compression neuropathy, and cerebellar ataxia. One patient has been reported to have encephalopathy with persistent cognitive impairment and memory loss.

Stellate macular retinopathy is associated with several infections, including CSD. Children and young adults present with unilateral or rarely bilateral loss of vision with central scotoma, optic disc swelling, and macular star formation from exudates radiating out from the macula. The findings usually resolve completely, with recovery of vision, generally within 2-3 mo. The optimal treatment for the neuroretinitis is unknown, although treatment of adults with doxycycline and rifampin for 4-6 wk has had good results.

Hematologic manifestations include hemolytic anemia, thrombocytopenic purpura, nonthrombocytopenic purpura, and eosinophilia. **Leukocytoclastic vasculitis,** similar to Henoch-Schönlein purpura, has been reported in association with CSD in 1 child. A systemic presentation of CSD with pleurisy, arthralgia or arthritis, mediastinal masses, enlarged nodes at the head of the pancreas, and atypical pneumonia also has been reported.

PROGNOSIS
The prognosis for CSD in a normal host is generally excellent, with resolution of clinical findings over weeks to months. Recovery is occasionally slower and may take as long as a year.

PREVENTION
Person-to-person spread of *Bartonella* infections is not known. Isolation of the affected patient is not necessary. Prevention would require elimination of cats from households, which is not practical or necessarily desirable. Awareness of the risk of cat (and particularly kitten) scratches should be emphasized to parents. Cat scratches or bites should be washed immediately. Cat flea control is helpful.

Bibliography is available at Expert Consult.

209.2 Bartonellosis *(Bartonella bacilliformis)*

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The first human *Bartonella* infection described was bartonellosis, a geographically distinct disease caused by *B. bacilliformis.* There are 2 predominant forms of illness caused by *B. bacilliformis*: **Oroya fever,** a severe, febrile hemolytic anemia, and **verruca peruana** (verruga peruana), an eruption of hemangioma-like lesions. *B. bacilliformis* also causes asymptomatic infection. Bartonellosis is also called **Carrión disease**.

ETIOLOGY
B. bacilliformis is a small, motile, Gram-negative organism with a brush of 10 or more unipolar flagella, which appear to be important components for invasiveness. An obligate aerobe, it grows best at 28°C (82.4°F) in semisolid nutrient agar containing rabbit serum and hemoglobin.

EPIDEMIOLOGY
Bartonellosis is a zoonosis found only in mountain valleys of the Andes Mountains in Peru, Ecuador, Colombia, Chile, and Bolivia at altitudes and environmental conditions favorable for the vector, which is the sandfly, *Lutzomyia verrucarum.*

PATHOGENESIS
After the sandfly bite, *Bartonella* organisms enter the endothelial cells of blood vessels, where they proliferate. Found throughout the reticuloendothelial system, they then re-enter the bloodstream and parasitize erythrocytes. They bind on the cells, deform the membranes, and then enter intracellular vacuoles. The resultant **hemolytic anemia** may involve as many as 90% of circulating erythrocytes. Patients who survive this acute phase may or may not experience the cutaneous manifestations, which are nodular hemangiomatous lesions or verrucae ranging in size from a few millimeters to several centimeters.

CLINICAL MANIFESTATIONS
The incubation period is 2-14 wk. Patients may be totally asymptomatic or may have nonspecific symptoms such as headache and malaise without anemia.

Oroya fever is characterized by fever with rapid development of anemia. Clouding of the sensorium and delirium are common symptoms and may progress to overt psychosis. Physical examination demonstrates signs of severe hemolytic anemia, including icterus and pallor, sometimes in association with generalized lymphadenopathy.

In the preeruptive stage of **verruca peruana** (Fig. 209-5), patients may complain of arthralgias, myalgias, and paresthesias. Inflammatory reactions such as phlebitis, pleuritis, erythema nodosum, and encephalitis may develop. The appearance of verrucae is pathognomonic of the eruptive phase. Lesions vary greatly in size and number.

DIAGNOSIS
The diagnosis is established on clinical grounds in conjunction with a blood smear demonstrating organisms or with blood culture. The anemia is macrocytic and hypochromic, with reticulocyte counts as high as 50%. *B. bacilliformis* may be seen on Giemsa stain preparation as red-violet rods in the erythrocytes. In the recovery phase, organisms change to a more coccoid form and disappear from the blood. In the absence of anemia, the diagnosis depends on blood cultures. In the eruptive phase, the typical verruca confirms the diagnosis. Antibody testing has been used to document infection.

Figure 209-5 A single, large lesion of verruca peruana on the leg of an inhabitant of the Peruvian Andes. Such lesions are prone to superficial ulceration, and their vascular nature may lead to copious bleeding. Ecchymosis of the skin surrounding the lesion is also evident. *(Courtesy of Dr. J.M. Crutcher, Oklahoma State Department of Health, Oklahoma City.)*

TREATMENT
B. bacilliformis is sensitive to many antibiotics, including rifampin, tetracycline, and chloramphenicol. Treatment is very effective in rapidly diminishing fever and eradicating the organism from the blood. Chloramphenicol (50-75 mg/kg/day) is considered the drug of choice, because it is also useful in the treatment of concomitant infections such as *Salmonella.* Fluoroquinolones are used successfully as well. Blood transfusions and supportive care are critical in patients with severe anemia. Antimicrobial treatment for verruca peruana is considered when there are more than 10 cutaneous lesions, if the lesions are erythematous or violaceous, or if the onset of the lesions was <1 mo before presentation. Oral rifampin is effective in the healing of lesions. Surgical excision may be needed for lesions that are large and disfiguring or that interfere with function.

PREVENTION
Prevention depends on avoidance of the vector, particularly at night, by the use of protective clothing and insect repellents (see Chapter 175).

Bibliography is available at Expert Consult.

209.3 Trench Fever *(Bartonella quintana)*

Barbara W. Stechenberg

ETIOLOGY
The causative agent of trench fever was first designated *Rickettsia quintana,* was then assigned to the genus *Rochalimaea,* and now has been reassigned as *B. quintana.*

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EPIDEMIOLOGY

Trench fever was first recognized as a distinct clinical entity during World War I, when more than a million troops in the trenches were infected. The disease became quiescent until World War II, when it again was epidemic. It is extremely rare in the United States.

Humans are the only known reservoir. No other animal is naturally infected, and usual laboratory animals are not susceptible. The human **body louse,** *Pediculus humanus* var. *corporis,* is the vector and is capable of transmission to a new host 5-6 days after feeding on an infected person. Lice excrete the organism for life; transovarian passage does not occur. Humans may have prolonged asymptomatic bacteremia for years.

CLINICAL MANIFESTATIONS

The incubation period for trench fever averages about 22 days (range: 4-35 days). The clinical presentation is highly variable. Symptoms can be very mild and brief. About half of infected persons have a single febrile illness with abrupt onset lasting 3-6 days. In other patients, prolonged, sustained fever may occur. More commonly, patients have periodic febrile illness with 3-8 episodes lasting 4-5 days each, sometimes occurring over a period of a year or more. This form is reminiscent of malaria or relapsing fever *(Borrelia recurrentis).* Afebrile bacteremia can occur.

Clinical findings usually consist of fever (typically with a temperature of 38.5-40°C [101.3-104°F]), malaise, chills, sweats, anorexia, and severe headache. Common findings include marked conjunctival injection, tachycardia, myalgias, arthralgias, and severe pain in the neck, back, and legs. **Crops of erythematous macules** or **papules** may occur on the trunk on as many as 80% of patients. Splenomegaly and mild liver enlargement may be noted.

DIAGNOSIS

In nonepidemic situations, it is impossible to establish a diagnosis of trench fever on clinical grounds, because the findings are not distinctive. A history of body louse infection or having been in an area of epidemic disease should heighten suspicions. *B. quintana* can be cultured from the blood with modification to include culture on epithelial cells. Serologic tests for *B. quintana* are available, but there is cross reaction with *B. henselae.*

TREATMENT

There are no controlled trials of treatment, but patients with trench fever typically show dramatic response to tetracycline or chloramphenicol, with rapid defervescence.

209.4 Bacillary Angiomatosis and Bacillary Peliosis Hepatis (*Bartonella henselae* and *Bartonella quintana*)

Barbara W. Stechenberg

Both *B. henselae* and *B. quintana* cause vascular proliferative disease called **bacillary angiomatosis** and **bacillary peliosis** in severely immunocompromised persons, primarily adult patients with AIDS or cancer and organ transplant recipients. Subcutaneous and lytic bone lesions are strongly associated with *B. quintana,* whereas peliosis hepatis is associated exclusively with *B. henselae.*

BACILLARY ANGIOMATOSIS

Lesions of cutaneous bacillary angiomatosis, also known as *epithelioid angiomatosis*, are the most easily identified and recognized form of *Bartonella* infection in immunocompromised hosts. They are found primarily in patients with AIDS who have very low CD4 counts. The clinical appearance can be quite diverse. The vasoproliferative lesions of bacillary angiomatosis may be cutaneous or subcutaneous and may resemble the vascular lesions (verruca peruana) of *B. bacilliformis* in immunocompetent persons, characterized by erythematous papules on an erythematous base with a collarette of scale. They may enlarge to form large pedunculated lesions and may ulcerate. Trauma may result in profuse bleeding.

Bacillary angiomatosis may be clinically indistinguishable from Kaposi sarcoma. Other considerations in the differential diagnosis are pyogenic granuloma and verruca peruana *(B. bacilliformis).* Deep soft-tissue masses caused by bacillary angiomatosis may mimic a malignancy.

Osseous bacillary angiomatosis lesions commonly involve the long bones. These lytic lesions are very painful and highly vascular and are occasionally associated with an overlying erythematous plaque. The high degree of vascularity produces a very positive result on a technetium-Tc 99m methylene diphosphonate bone scan, resembling that of a malignant lesion.

Lesions can be found in virtually any organ, producing similar vascular proliferative lesions. They may appear raised, nodular, or ulcerative when seen on endoscopy or bronchoscopy. They may be associated with enlarged lymph nodes with or without an obvious local cutaneous lesion. Brain parenchymal lesions have been described.

BACILLARY PELIOSIS

Bacillary peliosis affects the reticuloendothelial system, primarily the liver **(peliosis hepatis)** and less frequently the spleen and lymph nodes. It is a vasoproliferative disorder characterized by random proliferation of venous lakes surrounded by fibromyxoid stroma harboring numerous bacillary organisms. Clinical findings include fever and abdominal pain in association with abnormal results of liver function tests, particularly a markedly increased alkaline phosphatase level. Cutaneous bacillary angiomatosis with splenomegaly may be associated with thrombocytopenia or pancytopenia. The vascular proliferative lesions in the liver and spleen appear on CT scan as hypodense lesions scattered throughout the parenchyma. The differential diagnosis includes hepatic Kaposi sarcoma, lymphoma, and disseminated infection with *Pneumocystis carinii* or *Mycobacterium avium* complex.

BACTEREMIA AND ENDOCARDITIS

B. henselae, B. quintana, B. vinsonii, and *B. elizabethae* all are reported to cause bacteremia or endocarditis. They are associated with symptoms such as prolonged fevers, night sweats, and profound weight loss. A cluster of cases in Seattle in 1993 occurred in a homeless population with chronic alcoholism. These patients with high fever or hypothermia were thought to represent "urban trench fever," but no body louse infestation was associated. Some cases of culture-negative endocarditis may represent *Bartonella* endocarditis. One report described central nervous system involvement with *B. quintana* infection in 2 children.

DIAGNOSIS

Diagnosis of bacillary angiomatosis is made initially by biopsy. The characteristic small vessel proliferation with mixed inflammatory response and the staining of bacilli by Warthin-Starry silver staining distinguish bacillary angiomatosis from pyogenic granuloma or Kaposi sarcoma (see Chapter 257). Travel history can usually preclude verruca peruana.

Culture is impractical for CSD but is the diagnostic procedure for suspected bacteremia or endocarditis. Use of the lysis centrifugation technique or fresh chocolate or heart infusion agar with 5% rabbit blood with prolonged incubation may increase the yield of culture. Polymerase chain reaction can also be a useful tool.

TREATMENT

Bartonella infections in immunocompromised hosts caused by both *B. henselae* and *B. quintana* have been treated successfully with antimicrobial agents. Bacillary angiomatosis responds rapidly to erythromycin, azithromycin, and clarithromycin, which are the drugs of choice. Alternative choices are doxycycline or tetracycline. Severely ill patients with peliosis hepatis, endocarditis, or osteomyelitis may be treated initially with intravenous erythromycin or doxycycline and the addition of rifampin or gentamicin. The use of an aminoglycoside for a minimum of 2 wk is associated with improved prognosis in

endocarditis. A Jarisch-Herxheimer reaction may occur. Relapses may follow, and prolonged treatment for several months may be necessary.

PREVENTION

Immunocompromised persons should consider the potential risks of cat ownership because of the risks for *Bartonella* infections as well as toxoplasmosis and enteric infections. Those who elect to obtain a cat should adopt or purchase a cat >1 yr of age and in good health. Prompt washing of any wounds from cat bites or scratches is essential.

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Section 6

Anaerobic Bacterial Infections

Chapter 210

Botulism *(Clostridium botulinum)*

Stephen S. Arnon

Three naturally occurring forms of human botulism are known: infant (intestinal toxemia) botulism (the most common in the United States), foodborne (classic) botulism, and wound botulism. Two other forms, both human-made, also occur: inhalational botulism from inhaling accidentally aerosolized toxin and iatrogenic botulism from overdosage of therapeutic or cosmetic use of botulinum toxin.

ETIOLOGY

Botulism is the acute, flaccid paralysis caused by the neurotoxin produced by *Clostridium botulinum* or, infrequently, an equivalent neurotoxin produced by rare strains of *Clostridium butyricum* and *Clostridium baratii*. *C. botulinum* is a Gram-positive, spore-forming, obligate anaerobe whose natural habitat worldwide is soil, dust, and marine sediments. The organism is found in a wide variety of fresh and cooked agricultural products. Spores of some *C. botulinum* strains endure boiling for several hours, enabling the organism to survive efforts at food preservation. In contrast, botulinum toxin is heat labile and easily destroyed by heating at ≥85°C (185°F) for 5 min. Neurotoxigenic *C. butyricum* has been isolated from a soybean food and from soils near Lake Weishan in China, the site of foodborne botulism outbreaks associated with this organism. Little is known about the ecology of neurotoxigenic *C. baratii*.

Botulinum toxin is a simple dichain protein consisting of a 100 kDa heavy chain that contains the neuronal attachment sites and a 50 kDa light chain that is taken into the cell after binding. Botulinum toxin is the most poisonous substance known, the parenteral human lethal dose being estimated at 10^{-6} mg/kg. The toxin blocks neuromuscular transmission and causes death through airway and respiratory muscle paralysis. Eight antigenic toxin types, designated by letters A-H, are distinguished by the inability of neutralizing antibody against 1 toxin type to protect against a different toxin type. Toxin types are further differentiated into subtypes by differences in the nucleotide sequences of their toxin genes. Like the gene for tetanus toxin, the gene for botulinum toxin for some toxin types and subtypes resides on a plasmid.

The 8 toxin types serve as convenient clinical and epidemiologic markers. Toxin types A, B, E, and F are well-established causes of human botulism, whereas types C and D cause illness in other animals. Neurotoxigenic *C. butyricum* strains produce a type E toxin, whereas neurotoxigenic *C. baratii* strains produce a type F toxin. Type G toxin has not been established as a cause of either human or animal disease. Type H toxin is a novel toxin that was discovered in 2013 and sickened an infant patient. The phenomenal potency of the botulinum toxins occurs because their 8 light chains are zinc endopeptidases whose substrates are 1 or 2 proteins of the docking complex by which synaptic vesicles fuse with the terminal neuronal cell membrane and release acetylcholine into the synaptic cleft.

EPIDEMIOLOGY

Infant botulism has been reported from all inhabited continents except Africa. Notably, the infant is the only family member who is ill. The most striking epidemiologic feature of infant botulism is its age distribution, with 95% of cases involving infants between 3 wk and 6 mo of age, with a broad peak from 2-4 mo of age. Cases have been recognized in infants as young as 1.5 days or as old as 382 days at onset. The male : female ratio of hospitalized cases is approximately 1 : 1, and cases have occurred in most racial and ethnic groups.

Although infant botulism is an uncommon and often unrecognized illness, it is the most common form of human botulism in the United States, with 80-120 hospitalized cases diagnosed annually. The full clinical spectrum of infant botulism includes mild outpatient cases and fulminant sudden death cases. Approximately 40% of U.S. hospitalized cases have been reported from California. Consistent with the known asymmetric soil distribution of *C. botulinum* toxin types, most cases west of the Mississippi River have been caused by type A strains, whereas most cases east of the Mississippi River have been caused by type B strains. One case each in New Mexico, Washington, Ohio, California, Iowa, and Colorado has been caused by *C. baratii* and type F toxin. Four cases in Italy have resulted from *C. butyricum* and type E toxin. Identified risk factors for the illness include breastfeeding, the ingestion of honey, a slow intestinal transit time (<1 stool/day), and ingestion of untreated well-water. Breastfeeding may provide protection against fulminant sudden death from infant botulism. Under rare circumstances of altered intestinal anatomy, physiology, and microflora, older children and adults may contract infant-type botulism.

Foodborne botulism results from the ingestion of a food in which *C. botulinum* has multiplied and produced its toxin. Outbreaks in North America have been associated with baked potatoes, sautéed onions, and chopped garlic served in restaurants, revising the traditional view of foodborne botulism as resulting mainly from home-canned foods. Other outbreaks in the United States have occurred from commercial foods sealed in plastic pouches that relied solely on refrigeration to prevent outgrowth of *C. botulinum* spores. Uncanned foods responsible for foodborne botulism cases include peyote tea, the hazelnut flavoring added to yogurt, sweet cream cheese, sautéed onions in "patty melt" sandwiches, potato salad, and fresh and dried fish. A trend toward a single case per outbreak or of cases manifesting separately in different cities or hospitals portends that physicians cannot rely on the temporal and geographic clustering of cases to suggest the diagnosis.

Most types of preserved foods have been implicated in foodborne botulism, but the usual offenders in the United States are the "low-acid" (pH ≥ 6.0) home-canned foods such as jalapeño peppers, asparagus, olives, and beans. The potential for foodborne botulism exists throughout the world, but outbreaks occur most commonly in the temperate zones rather than the tropics, where preservation of fruits, vegetables, and other foods is less common.

Approximately 5-10 outbreaks and 15-25 cases of foodborne botulism occur annually in the United States. Most of the continental U.S. outbreaks resulted from proteolytic type A or type B strains, which produce a strongly putrefactive odor in the food that some people find necessary to verify by tasting. In contrast, in Alaska and Canada, most foodborne outbreaks have resulted from nonproteolytic type E strains

in Native American foods, such as fermented salmon eggs and seal flippers, which do not exhibit signs of spoilage. A further hazard of type E strains is their ability to grow at the temperatures maintained by household refrigerators (5°C [41°F]).

Wound botulism is an exceptionally rare disease, with fewer than 400 cases reported worldwide, but it is important to pediatrics because adolescents and children may be affected. Although many cases have occurred in young, physically active males who are at greatest risk for traumatic injury, wound botulism also occurs with crush injuries in which no break in the skin is evident. In the past 15 yr, wound botulism from injection has become increasingly common in adult heroin abusers in the western United States and in Europe, not always with evident abscess formation or cellulitis.

A single outbreak of **inhalational botulism** was reported in 1962 in which 3 laboratory workers in Germany were exposed unintentionally to aerosolized botulinum toxin. Some patients in the United States have been hospitalized by accidental overdose of therapeutic or cosmetic botulinum toxin.

PATHOGENESIS

All forms of botulism produce disease through a final common pathway. Botulinum toxin is carried by the bloodstream to peripheral cholinergic synapses, where it binds irreversibly, blocking acetylcholine release and causing impaired neuromuscular and autonomic transmission. **Infant botulism** is an infectious disease that results from ingesting the spores of any of the 3 botulinum toxin-producing clostridial strains, with subsequent spore germination, multiplication, and production of botulinum toxin in the large intestine. **Foodborne botulism** is an intoxication that results when preformed botulinum toxin contained in an improperly preserved or inadequately cooked food is swallowed. **Wound botulism** results from spore germination and colonization of traumatized tissue by *C. botulinum;* it is the analog of tetanus. **Inhalational botulism** occurs when aerosolized botulinum toxin is inhaled. A bioterrorist attack could result in large or small outbreaks of inhalational or foodborne botulism (see Chapter 723).

Botulinum toxin is not a cytotoxin and does not cause overt macroscopic or microscopic pathology. Secondary pathologic changes (pneumonia, petechiae on intrathoracic organs) may be found at autopsy. No diagnostic technique is available to identify botulinum toxin bound at the neuromuscular junction. The healing process in botulism consists of sprouting of new terminal unmyelinated motor neurons. Movement resumes when these new twigs locate noncontracting muscle fibers and reinnervate them by inducing formation of a new motor end plate. In experimental animals, this process takes about 4 wk.

CLINICAL MANIFESTATIONS

Botulinum toxin is distributed hematogenously. Because relative blood flow and density of innervation are greatest in the bulbar musculature, all forms of botulism manifest neurologically as a symmetric, descending, flaccid paralysis beginning with the cranial nerve musculature. It is not possible to have botulism without having multiple bulbar palsies, yet in infants, such symptoms as poor feeding, weak suck, feeble cry, drooling, and even obstructive apnea are often not recognized as bulbar in origin (Fig. 210-1). Patients with evolving illness may already have generalized weakness and hypotonia in addition to bulbar palsies when first examined. In contrast to botulism caused by *C. botulinum,* a majority of the rare cases caused by intestinal colonization with *C. butyricum* are associated with a Meckel diverticulum accompanying abdominal distention, often leading to misdiagnosis as an acute abdomen. The also rare *C. baratii* type F infant botulism cases have been characterized by very young age at onset, rapidity of onset, and greater severity but shorter duration of paralysis.

In older children with **foodborne** or **wound botulism,** the onset of neurologic symptoms follows a characteristic pattern of diplopia, blurred vision, ptosis, dry mouth, dysphagia, dysphonia, and dysarthria, with decreased gag and corneal reflexes. Importantly, because the toxin acts only on motor nerves, paresthesias are not seen in botulism, except when a patient hyperventilates from anxiety. The sensorium remains clear, but this fact may be difficult to ascertain because of the slurred speech.

Figure 210-1 A 3 mo old infant with mild infant botulism showing signs of ptosis, an expressionless face, and hypotonia of the neck, trunk, and limbs. The additional bulbar palsies—ophthalmoplegia, weak cry, weak sucking, and dysphagia (drooling)—are not apparent in the photograph. *(From Arnon SS, Schechter R, Maslanka SE, et al: Human botulism immune globulin for the treatment of infant botulism,* N Engl J Med *354: 462–471, 2006.)*

Foodborne botulism begins with gastrointestinal symptoms of nausea, vomiting, or diarrhea in approximately 30% of cases. These symptoms are thought to result from metabolic by-products of growth of *C. botulinum* or from the presence of other toxic contaminants in the food, because gastrointestinal distress is rarely observed in wound botulism. Constipation may occur in foodborne botulism once flaccid paralysis becomes evident. Illness usually begins 12-36 hr after ingestion of the contaminated food but can range from as little as 2 hr to as long as 8 days. The incubation period in **wound botulism** is 4-14 days. Fever may be present in wound botulism but is absent in foodborne botulism unless a secondary infection (often pneumonia) is present. All forms of botulism display a wide spectrum of clinical severity, from the very mild, with minimal ptosis, flattened facial expression, minor dysphagia, and dysphonia, to the fulminant, with rapid onset of extensive paralysis, frank apnea, and fixed, dilated pupils. Fatigability with repetitive muscle activity is the clinical hallmark of botulism.

Infant botulism differs in apparent initial symptoms of illness only because the infant cannot verbalize them. Usually, the first indication of illness is a decreased frequency or even absence of defecation, although this sign is frequently overlooked. Parents typically notice inability to feed, lethargy, weak cry, and diminished spontaneous movement. Dysphagia may be evident as secretions drooling from the mouth. Gag, suck, and corneal reflexes diminish as the paralysis advances. Oculomotor palsies may be evident only with sustained observation. Paradoxically, the pupillary light reflex may be unaffected until the child is severely paralyzed, or it may be initially sluggish. Loss of head control is typically a prominent sign. Respiratory arrest may occur suddenly from airway occlusion by unswallowed secretions or

from obstructive flaccid pharyngeal musculature. Occasionally, the diagnosis of infant botulism is suggested by a respiratory arrest that occurs after the infant is curled into position for lumbar puncture.

In mild cases or in the early stages of illness, the physical signs of infant botulism may be subtle and easily missed. Eliciting cranial nerve palsies and fatigability of muscular function requires careful examination. Ptosis may not be seen unless the head of the child is kept erect.

DIAGNOSIS

Clinical diagnosis of botulism is confirmed by specialized laboratory testing that requires hours to days to complete. Therefore, clinical diagnosis is the foundation for early recognition of and response to all forms of botulism. Routine laboratory studies, including those of the cerebrospinal fluid, are normal in botulism unless dehydration, undernourishment (metabolic acidosis and ketosis), or secondary infection is present.

The **classic triad of botulism** is the acute onset of a symmetric flaccid descending paralysis with clear sensorium, no fever, and no paresthesias. Suspected botulism represents a medical and public health emergency that is immediately reportable by telephone in most U.S. health jurisdictions. State health departments (first call) and the U.S. Centers for Disease Control and Prevention (CDC; telephone 770-488-7100 at any time) can arrange for diagnostic testing, epidemiologic investigation, and provision of equine antitoxin.

The diagnosis of botulism is unequivocally established by demonstration of the presence of botulinum toxin in serum or of *C. botulinum* toxin or organisms in wound material, enema fluid, or feces. *C. botulinum* is not part of the normal resident intestinal flora of humans, and its presence in the setting of acute flaccid paralysis is diagnostic. An epidemiologic diagnosis of food-borne botulism can be established when *C. botulinum* organisms and toxin are found in food eaten by patients.

Electromyography can sometimes distinguish between causes of acute flaccid paralysis, although results may be variable, including normal, in patients with botulism. The distinctive electromyography finding in botulism is facilitation (potentiation) of the evoked muscle action potential at high-frequency (50 Hz) stimulation. In infant botulism, a characteristic pattern, known by the acronym **BSAP** (brief, small, abundant motor unit action potentials), is present only in clinically weak muscles. Nerve conduction velocity and sensory nerve function are normal in botulism.

Infant botulism requires a high index of suspicion for early diagnosis (Table 210-1). "Rule out sepsis" remains the most common admission diagnosis. If a previously healthy infant (commonly 2-4 mo of age) demonstrates weakness with difficulty in sucking, swallowing, crying, or breathing, infant botulism should be considered a likely diagnosis. A careful cranial nerve examination is then very helpful. Rare instances of coinfection with *Clostridium difficile*, respiratory syncytial virus, or influenza virus have occurred.

Differential Diagnosis

Botulism is frequently misdiagnosed, most often as a polyradiculoneuropathy (Guillain-Barré or Miller Fisher syndrome), myasthenia gravis, or a disease of the central nervous system (see Tables 210-1 and 210-2). In the United States, botulism is more likely than Guillain-Barré syndrome, intoxication, or poliomyelitis to cause a cluster of cases of acute flaccid paralysis. Botulism differs from other flaccid paralyses in its prominent cranial nerve palsies disproportionate to milder weakness and hypotonia below the neck, in its symmetry, and in its absence of sensory nerve damage. Spinal muscular atrophy may closely mimic infant botulism at presentation.

Additional diagnostic procedures may be useful in rapidly excluding botulism as the cause of paralysis. The cerebrospinal fluid is unchanged in botulism but is abnormal in many central nervous system diseases. Although the cerebrospinal fluid protein concentration is eventually elevated in Guillain-Barré syndrome, it may be normal early in illness. Imaging of the brain, spine, and chest may reveal hemorrhage, inflammation, or neoplasm. A test dose of edrophonium chloride briefly reverses paralytic symptoms in many patients with myasthenia gravis and, reportedly, in some with botulism. A close inspection of the skin, especially the scalp, may reveal an attached tick that is causing paralysis. Possible organophosphate intoxication should be pursued aggressively because specific antidotes (oximes) are available and because the patient may be part of a commonly exposed group, some of whom have yet to demonstrate illness. Other tests that require days for results include stool culture for *Campylobacter jejuni* as a precipitant of Guillain-Barré syndrome, spinal muscular atrophy and other genetic (including mitochondrial) disorders, and assays for the autoantibodies that cause myasthenia gravis, Lambert-Eaton syndrome, and Guillain-Barré syndrome.

TREATMENT

Human botulism immune globulin, given intravenously (BIG-IV), is licensed for the treatment of infant botulism caused by type A or B botulinum toxin. Treatment with BIG-IV consists of a single intravenous infusion of 50-100 mg/kg (see package insert) that should be given as soon as possible after infant botulism is suspected so as to

Table 210-1 Diagnoses Considered in Subsequently Laboratory-Confirmed Cases of Infant Botulism

ADMISSION DIAGNOSIS	SUBSEQUENTLY CONSIDERED DIAGNOSES
Suspected sepsis, meningitis	Guillain-Barré syndrome
Pneumonia	Myasthenia gravis
Dehydration	Disorders of amino acid metabolism
Viral syndrome	Hypothyroidism
Hypotonia of unknown etiology	Drug ingestion Organophosphate poisoning
Constipation	Brainstem encephalitis
Failure to thrive	Heavy metal poisoning (Pb, Mg, As)
Spinal muscular atrophy type 1 (Werdnig-Hoffmann disease)	Poliomyelitis Viral polyneuritis Hirschsprung disease Metabolic encephalopathy Medium chain acetyl–coenzyme A dehydrogenase deficiency

Table 210-2 Diagnoses Considered in Foodborne and Wound Botulism

Acute gastroenteritis
Myasthenia gravis
Guillain-Barré syndrome
Organophosphate poisoning
Meningitis
Encephalitis
Psychiatric illness
Cerebrovascular accident
Poliomyelitis
Hypothyroidism
Aminoglycoside-associated paralysis
Tick paralysis
Hypocalcemia
Hypermagnesemia
Carbon monoxide poisoning
Hyperemesis gravidarum
Laryngeal trauma
Diabetic complications
Inflammatory myopathy
Overexertion

immediately end the toxemia that is the cause of the illness. Treatment should not be delayed for laboratory confirmation. In the United States, BIG-IV may be obtained from the California Department of Public Health (24-hr telephone 510-231-7600; http://www.infantbotulism.org). The use of BIG-IV shortens mean hospital stay from approximately 6 wks to 2 wks. Most of the decrease in length of hospital stay results from the reduced time that the patient requires ventilation and intensive care. Hospital costs are reduced by more than $100,000 per case (in 2012 dollars).

Older patients with suspected food, wound, or inhalational botulism may be treated with 1 vial of licensed equine heptavalent (A-G) botulinum antitoxin, available in the United States through the Centers for Disease Control and Prevention (CDC) by way of state and local health departments.

Antibiotic therapy is not part of the treatment of uncomplicated infant or foodborne botulism, because the toxin is primarily an intracellular molecule that is released into the intestinal lumen with vegetative bacterial cell death and lysis. Antibiotics are reserved for the treatment of secondary infections, and in the absence of antitoxin therapy, a nonclostridiocidal antibiotic such as trimethoprim-sulfamethoxazole is preferred. Aminoglycoside antibiotics should be avoided because they may potentiate the blocking action of botulinum toxin at the neuromuscular junction. Wound botulism requires aggressive treatment with antibiotics and antitoxin in a manner analogous to that for tetanus (see Chapter 211).

SUPPORTIVE CARE

Management of botulism rests on the following 3 principles: (1) fatigability with repetitive muscle activity is the clinical hallmark of the disease; (2) complications are best avoided by anticipating them; and (3) meticulous supportive care is a necessity. The first principle applies mainly to feeding and breathing. Correct positioning is imperative to protect the airway and improve respiratory mechanics. The patient is placed face up on a rigid-bottomed crib (or bed), the head of which is tilted at 30 degrees. A small cloth roll is placed under the cervical vertebrae to tilt the head back so that secretions drain to the posterior pharynx and away from the airway. In this tilted position, the abdominal viscera pull the diaphragm down, thereby improving respiratory mechanics. The patient's head and torso should not be elevated by bending the middle of the bed; in such a position, the hypotonic thorax would slump into the abdomen and breathing would be compromised.

About half of patients with infant botulism require endotracheal intubation, which is best done prophylactically. The indications include diminished gag and cough reflexes and progressive airway obstruction by secretions. With meticulous management techniques (especially proper tube diameter), monitoring, and positioning, patients have tolerated months of intubation without subglottic stenosis or need for tracheostomy.

Feeding should be done by a nasogastric or nasojejunal tube until sufficient oropharyngeal strength and coordination enable feeding by breast or bottle. Expressed breast milk is the most desirable food for infants, in part because of its immunologic components (e.g., secretory immunoglobulin A, lactoferrin, leukocytes). Tube feeding also assists in the restoration of peristalsis, a nonspecific but probably essential part of eliminating *C. botulinum* from the intestinal flora. Intravenous feeding (hyperalimentation) is discouraged because of the potential for infection and the advantages of tube feeding.

Because sensation remains intact, providing auditory, tactile, and visual stimuli is beneficial. Maintaining strong central respiratory drive is essential, so sedatives and central nervous system depressants are best avoided. Full hydration and stool softeners such as lactulose may mitigate the protracted constipation. Cathartics are not recommended. Patients with foodborne and infant botulism excrete *C. botulinum* toxin and organisms in their feces, often for many weeks, and care should be taken in handling their excreta. When bladder palsy occurs in severe cases, gentle suprapubic pressure with the patient in the sitting position with the head supported may help attain complete voiding and reduce the risk for urinary tract infection. Families of affected patients may require emotional and financial support, especially when the paralysis of botulism is prolonged.

Table 210-3 Complications of Infant Botulism

Acute respiratory distress syndrome
Aspiration
Clostridium difficile enterocolitis
Hypotension
Inappropriate antidiuretic hormone secretion
Long bone fractures
Misplaced or plugged endotracheal tube
Nosocomial anemia
Otitis media
Pneumonia
Pneumothorax
Recurrent atelectasis
Seizures secondary to hyponatremia
Sepsis
Subglottic stenosis
Tracheal granuloma
Tracheitis
Transfusion reaction
Urinary tract infection

COMPLICATIONS

Almost all of the complications of botulism are nosocomial, and a few are iatrogenic (Table 210-3). Some critically ill, toxin-paralyzed patients who must spend weeks or months on ventilators in intensive care units inevitably experience some of these complications. Suspected "relapses" of infant botulism usually reflect premature hospital discharge or an inapparent underlying complication such as pneumonia, urinary tract infection, or otitis media.

PROGNOSIS

When the regenerating nerve endings have induced formation of a new motor end plate, neuromuscular transmission is restored. In the absence of complications, particularly those related to hypoxia, the prognosis in infant botulism is for full and complete recovery. Hospital stay in untreated infant botulism averages 5.7 wk but differs significantly by toxin type, with patients with untreated type B disease being hospitalized a mean of 4.2 wk and those with untreated type A disease being hospitalized a mean of 6.7 wk.

In the United States, the case fatality ratio for hospitalized cases of infant botulism is <1%. After recovery, patients with untreated infant botulism appear to have an increased incidence of strabismus that requires timely screening and treatment.

The case fatality ratio in foodborne and wound botulism varies by age, with younger patients having the best prognosis. Some adults with botulism have reported chronic weakness and fatigue for more than 1 yr as sequelae.

PREVENTION

Foodborne botulism is best prevented by adherence to safe methods of home canning (pressure cooker and acidification), by avoiding suspicious foods, and by heating all home canned foods to 85°C (185°F) for ≥5 min. Wound botulism is best prevented by not using illicit drugs and by treatment of contaminated wounds with thorough cleansing, surgical debridement, and provision of appropriate antibiotics.

Most patients with infant botulism probably inhaled and then swallowed airborne clostridial spores; these cases cannot be prevented. The 1 identified, avoidable source of botulinum spores for infants is honey. *Honey is an unsafe food for any child younger than 1 yr.* Corn syrups were once thought to be a possible source of botulinum spores, but evidence indicates otherwise. Breastfeeding appears to slow the onset of infant botulism and to diminish the risk for sudden death in infants in whom the disease develops.

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Chapter 211

Tetanus *(Clostridium tetani)*

Stephen S. Arnon

ETIOLOGY

Tetanus is an acute, spastic paralytic illness historically called **lockjaw** that is caused by the neurotoxin produced by *Clostridium tetani,* a motile, Gram-positive, spore-forming obligate anaerobe whose natural habitat worldwide is soil, dust, and the alimentary tracts of various animals. *C. tetani* forms spores terminally, producing a drumstick or tennis racket appearance microscopically. Tetanus spores can survive boiling but not autoclaving, whereas the vegetative cells are killed by antibiotics, heat, and standard disinfectants. Unlike many clostridia, *C. tetani* is not a tissue-invasive organism and instead causes illness through the effects of a single toxin, **tetanospasmin,** more commonly referred to as **tetanus toxin**. Tetanospasmin is the second most poisonous substance known, surpassed in potency only by botulinum toxin. The human lethal dose of tetanus toxin is estimated to be 10^{-5} mg/kg.

EPIDEMIOLOGY

Tetanus occurs worldwide and is endemic in approximately 90 developing countries, although its incidence varies considerably. The most common form, **neonatal (or umbilical) tetanus,** kills approximately 300,000 infants each year, with approximately 80% of deaths in just 12 tropical Asian and African countries. It occurs in infants whose mothers are not immunized. In addition, an estimated 15,000-30,000 unimmunized women worldwide die each year of **maternal tetanus,** which results from postpartum, postabortal, or postsurgical wound infection with *C. tetani.* Approximately 50 cases of tetanus are reported each year in the United States, mostly in persons older than 60 yr of age, although cases also occur in toddlers and neonates. Approximately 20% of children in the United States 10-16 yr of age lack a protective antibody level. The majority of childhood cases of tetanus in the United States have occurred in unimmunized children whose parents objected to vaccination.

Most nonneonatal cases of tetanus are associated with a traumatic injury, often a penetrating wound inflicted by a dirty object such as a nail, splinter, fragment of glass, or unsterile injection. Tetanus occurring after illicit drug injection is becoming more common. The disease also occurs after the use of contaminated suture material and after intramuscular injection of medicines, most notably quinine for chloroquine-resistant falciparum malaria. The disease may also occur in association with animal bites, abscesses (including dental abscesses), ear and other body piercing, chronic skin ulceration, burns, compound fractures, frostbite, gangrene, intestinal surgery, ritual scarification, infected insect bites, and female circumcision. Rare cases have no history of trauma.

PATHOGENESIS

Tetanus occurs after introduced spores germinate, multiply, and produce tetanus toxin in the low oxidation-reduction potential of an infected injury site. A plasmid carries the toxin gene. Toxin is released after vegetative bacterial cell death and lysis. Tetanus toxin (and the botulinum toxins) is a 150 kDa simple protein consisting of a heavy chain (100 kDa) and a light (50 kDa) chain joined by a single disulfide bond. Tetanus toxin binds at the neuromuscular junction and enters the motor nerve by endocytosis, after which it undergoes retrograde axonal transport to the cytoplasm of the α-motoneuron. In the sciatic nerve, the transport rate was found to be 3.4 mm/hr. The toxin exits the motoneuron in the spinal cord and next enters adjacent spinal inhibitory interneurons, where it prevents release of the neurotransmitters glycine and γ-aminobutyric acid. Tetanus toxin thus blocks the normal inhibition of antagonistic muscles on which voluntary coordinated movement depends; as a consequence, affected muscles sustain maximal contraction and cannot relax. The autonomic nervous system is also rendered unstable in tetanus.

The phenomenal potency of tetanus toxin is enzymatic. The light chain of tetanus toxin (and of several botulinum toxins) is a zinc-containing endoprotease whose substrate is synaptobrevin, a constituent protein of the docking complex that enables the synaptic vesicle to fuse with the terminal neuronal cell membrane. The heavy chain of the toxin contains its binding and internalization domains.

Because *C. tetani* is not an invasive organism, its toxin-producing vegetative cells remain where introduced into the wound, which may display local inflammatory changes and a mixed bacterial flora.

CLINICAL MANIFESTATIONS

Tetanus is most often generalized but may also be localized. The incubation period typically is 2-14 days but may be as long as months after the injury. In **generalized tetanus,** the presenting symptom in about half of cases is **trismus** (masseter muscle spasm, or lockjaw). Headache, restlessness, and irritability are early symptoms, often followed by stiffness, difficulty chewing, dysphagia, and neck muscle spasm. The so-called **sardonic smile of tetanus (risus sardonicus)** results from intractable spasms of facial and buccal muscles. When the paralysis extends to abdominal, lumbar, hip, and thigh muscles, the patient may assume an arched posture of extreme hyperextension of the body, or **opisthotonos,** with the head and the heels bent backward and the body bowed forward with only the back of the head and the heels touching the supporting surface. Opisthotonos is an equilibrium position that results from unrelenting total contraction of opposing muscles, all of which display the typical board-like rigidity of tetanus. Laryngeal and respiratory muscle spasm can lead to airway obstruction and asphyxiation. Because tetanus toxin does not affect sensory nerves or cortical function, the patient unfortunately remains conscious, in extreme pain, and in fearful anticipation of the next tetanic seizure. The seizures are characterized by sudden, severe tonic contractions of the muscles, with fist clenching, flexion, and adduction of the arms and hyperextension of the legs. Without treatment, the seizures range from a few seconds to a few minutes in length with intervening respite periods, but as the illness progresses, the spasms become sustained and exhausting. The smallest disturbance by sight, sound, or touch may trigger a tetanic spasm. Dysuria and urinary retention result from bladder sphincter spasm; forced defecation may occur. Fever, occasionally as high as 40°C (104°F), is common because of the substantial metabolic energy consumed by spastic muscles. Notable autonomic effects include tachycardia, dysrhythmias, labile hypertension, diaphoresis, and cutaneous vasoconstriction. The tetanic paralysis usually becomes more severe in the 1st wk after onset, stabilizes in the 2nd wk, and ameliorates gradually over the ensuing 1-4 wk.

Neonatal tetanus, the infantile form of generalized tetanus, typically manifests within 3-12 days of birth as progressive difficulty in feeding (sucking and swallowing), associated hunger, and crying. Paralysis or diminished movement, stiffness and rigidity to the touch, and spasms, with or without opisthotonos, are characteristic. The umbilical stump may hold remnants of dirt, dung, clotted blood, or serum, or it may appear relatively benign.

Localized tetanus results in painful spasms of the muscles adjacent to the wound site and may precede generalized tetanus. **Cephalic tetanus** is a rare form of localized tetanus involving the bulbar musculature that occurs with wounds or foreign bodies in the head, nostrils, or face. It also occurs in association with chronic otitis media. Cephalic tetanus is characterized by retracted eyelids, deviated gaze, trismus, risus sardonicus, and spastic paralysis of the tongue and pharyngeal musculature.

DIAGNOSIS

The picture of tetanus is one of the most dramatic in medicine, and the diagnosis may be established clinically. The typical setting is an

unimmunized patient (and/or mother) who was injured or born within the preceding 2 wk, who presents with trismus, other rigid muscles, and a clear sensorium.

Results of routine laboratory studies are usually normal. A peripheral leukocytosis may result from a secondary bacterial infection of the wound or may be stress induced from the sustained tetanic spasms. The cerebrospinal fluid is normal, although the intense muscle contractions may raise intracranial pressure. Neither the electroencephalogram nor the electromyogram shows a characteristic pattern. *C. tetani* is not always visible on Gram stain of wound material and is isolated in only approximately 30% of cases.

DIFFERENTIAL DIAGNOSIS

Fully developed, generalized tetanus cannot be mistaken for any other disease. However, trismus may result from parapharyngeal, retropharyngeal, or dental abscesses or, rarely, from acute encephalitis involving the brainstem. Either rabies or tetanus may follow an animal bite, and rabies may manifest as trismus with seizures. Rabies may be distinguished from tetanus by hydrophobia, marked dysphagia, predominantly clonic seizures, and pleocytosis (see Chapter 274). Although strychnine poisoning may result in tonic muscle spasms and generalized seizure activity, it seldom produces trismus, and unlike in tetanus, general relaxation usually occurs between spasms. Hypocalcemia may produce tetany that is characterized by laryngeal and carpopedal spasms, but trismus is absent. Occasionally, epileptic seizures, narcotic withdrawal, or other drug reactions may suggest tetanus.

TREATMENT

Management of tetanus requires eradication of *C. tetani* and the wound environment conducive to its anaerobic multiplication, neutralization of all accessible tetanus toxin, control of seizures and respiration, palliation, provision of meticulous supportive care, and, finally, prevention of recurrences.

Surgical wound excision and debridement are often needed to remove the foreign body or devitalized tissue that created anaerobic growth conditions. Surgery should be performed promptly after administration of **human tetanus immunoglobulin (TIG)** and antibiotics. Excision of the umbilical stump in the neonate with tetanus is no longer recommended.

Tetanus toxin cannot be neutralized by TIG after it has begun its axonal ascent to the spinal cord. TIG should be given as soon as possible so as to neutralize toxin that diffuses from the wound into the circulation before the toxin can bind at distant muscle groups. The optimal dose of TIG has not been determined. A single intramuscular injection of 500 units of TIG is sufficient to neutralize systemic tetanus toxin, but total doses as high as 3,000-6,000 units are also recommended. Infiltration of TIG into the wound is now considered unnecessary. If TIG is unavailable, use of human intravenous immunoglobulin may be necessary. Intravenous immunoglobulin contains 4-90 units/mL of TIG; the optimal dosage of intravenous immunoglobulin for treating tetanus is not known, and its use is not approved for this indication. Another alternative is equine- or bovine-derived tetanus antitoxin (TAT). The usual dose of TAT is 50,000-100,000 units, with half given intramuscularly and half intravenously, but as little as 10,000 units may be sufficient. TAT is not available in the United States. Approximately 15% of patients given the usual dose of TAT experience serum sickness. When TAT is used, it is essential to check for possible sensitivity to horse serum; desensitization may be needed. The human-derived immunoglobulins are much preferred because of their longer half-lives (30 days) and the virtual absence of allergic and serum sickness adverse effects. Intrathecal TIG, given to neutralize tetanus toxin in the spinal cord, is not effective.

Penicillin G (100,000 units/kg/day divided every 4-6 hr IV for 10-14 days) remains the antibiotic of choice because of its effective clostridiocidal action and its diffusibility, which is an important consideration because blood flow to injured tissue may be compromised. Metronidazole (500 mg every 8 hr IV for adults) appears to be equally effective. Erythromycin and tetracycline (for persons >8 yr of age) are alternatives for penicillin-allergic patients.

All patients with generalized tetanus need muscle relaxants. Diazepam provides both relaxation and seizure control. The initial dose of 0.1-0.2 mg/kg every 3-6 hr given intravenously is subsequently titrated to control the tetanic spasms, after which the effective dose is sustained for 2-6 wk before a tapered withdrawal. Magnesium sulfate, other benzodiazepines (midazolam), chlorpromazine, dantrolene, and baclofen are also used. Intrathecal baclofen produces such complete muscle relaxation that apnea often ensues; like most other agents listed, baclofen should be used only in an intensive care unit setting. The highest survival rates in generalized tetanus are achieved with neuromuscular blocking agents such as vecuronium and pancuronium, which produce a general flaccid paralysis that is then managed by mechanical ventilation. Autonomic instability is regulated with standard α- or β- (or both) blocking agents; morphine has also proved useful.

SUPPORTIVE CARE

Meticulous supportive care in a quiet, dark, secluded setting is most desirable. Because tetanic spasms may be triggered by minor stimuli, the patient should be sedated and protected from all unnecessary sounds, sights, and touch, and all therapeutic and other manipulations must be carefully scheduled and coordinated. Endotracheal intubation may not be required, but it should be done to prevent aspiration of secretions before laryngospasm develops. A tracheostomy kit should be immediately at hand for unintubated patients. Endotracheal intubation and suctioning easily provoke reflex tetanic seizures and spasms, so early tracheostomy should be considered in severe cases not managed by pharmacologically induced flaccid paralysis. Therapeutic botulinum toxin has been used for this purpose, that is, to overcome trismus.

Cardiorespiratory monitoring, frequent suctioning, and maintenance of the patient's substantial fluid, electrolyte, and caloric needs are fundamental. Careful nursing attention to mouth, skin, bladder, and bowel function is needed to avoid ulceration, infection, and obstipation. Prophylactic subcutaneous heparin may be of value but must be balanced with the risk for hemorrhage.

COMPLICATIONS

The seizures and the severe, sustained rigid paralysis of tetanus predispose the patient to many complications. Aspiration of secretions and pneumonia may have begun before the first medical attention was received. Maintaining airway patency often mandates endotracheal intubation and mechanical ventilation with their attendant hazards, including pneumothorax and mediastinal emphysema. The seizures may result in lacerations of the mouth or tongue, in intramuscular hematomas or rhabdomyolysis with myoglobinuria and renal failure, or in long bone or spinal fractures. Venous thrombosis, pulmonary embolism, gastric ulceration with or without hemorrhage, paralytic ileus, and decubitus ulceration are constant hazards. Excessive use of muscle relaxants, which are an integral part of care, may produce iatrogenic apnea. Cardiac arrhythmias, including asystole, unstable blood pressure, and labile temperature regulation reflect disordered autonomic nervous system control that may be aggravated by inattention to maintenance of intravascular volume needs.

PROGNOSIS

Recovery in tetanus occurs through regeneration of synapses within the spinal cord and thereby the restoration of muscle relaxation. However, because an episode of tetanus does not result in the production of toxin-neutralizing antibodies, active immunization with tetanus toxoid at discharge with provision for completion of the primary series is mandatory.

The most important factor that influences outcome is the quality of supportive care. Mortality is highest in the very young and the very old. A favorable prognosis is associated with a long incubation period, absence of fever, and localized disease. An unfavorable prognosis is associated with onset of trismus <7 days after injury and with onset of generalized tetanic spasms <3 days after onset of trismus. Sequelae of hypoxic brain injury, especially in infants, include cerebral palsy,

diminished mental abilities, and behavioral difficulties. Most fatalities occur within the 1st wk of illness. Reported case fatality rates for generalized tetanus are 5-35%, and for neonatal tetanus they extend from <10% with intensive care treatment to >75% without it. Cephalic tetanus has an especially poor prognosis because of breathing and feeding difficulties.

PREVENTION

Tetanus is an entirely preventable disease. A serum antibody titer of ≥0.01 units/mL is considered protective. Active immunization should begin in early infancy with combined diphtheria toxoid–tetanus toxoid–acellular pertussis (DTaP) vaccine at 2, 4, 6 and 15-18 mo of age, with boosters at 4-6 yr (DTaP) and 11-12 yr (Tdap) of age and at 10 yr intervals thereafter throughout adult life with tetanus and reduced diphtheria toxoid (Td). Immunization of women with tetanus toxoid prevents neonatal tetanus, and pregnant women should receive 1 dose of reduced diphtheria and pertussis toxoids (Tdap) during each pregnancy, preferably at 27-36 wk gestation. Recommended immunization schedules are regularly updated; the most current versions may be found at http://www.cdc.gov/vaccines/schedules.

Arthus reactions (type III hypersensitivity reactions), a localized vasculitis associated with deposition of immune complexes and activation of complement, are reported rarely after tetanus vaccination. Mass immunization campaigns in developing countries have occasionally provoked a widespread hysterical reaction.

Wound Management

Tetanus prevention measures after trauma consist of inducing active immunity to tetanus toxin and of passively providing antitoxic antibody (Table 211-1). Tetanus prophylaxis is an essential part of all wound management, but specific measures depend on the nature of the injury and the immunization status of the patient. Regrettably, prevention of tetanus must now be included in planning for the consequences of bombings and other possible civilian mass-casualty events.

Tetanus toxoid should always be given after a dog or other animal bite, even though *C. tetani* is infrequently found in canine mouth flora.

Table 211-1 Tetanus Prophylaxis in Routine Wound Management

	Clean, Minor Wounds		All Other Wounds*	
HISTORY OF ABSORBED TETANUS TOXOID	TDAP OR TD†	TIG‡	TDAP OR TD†	TIG‡
Uncertain or <3 doses	Yes	No	Yes	Yes
3 or more doses	No§	No	No‖	No

*Such as, but not limited to, wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, and frostbite.

†For children younger than 7 yr of age, DTaP is preferred to tetanus toxoid alone if <3 doses of DTaP have been previously given. If pertussis vaccine is contraindicated, DT is given. For persons 7 yr of age or older, Td (or Tdap for adolescents 11-18 yr of age) is preferred to tetanus toxoid alone. Tdap is preferred to Td for adolescents 11-18 yr of age who have never received Tdap. Td is preferred to tetanus toxoid for adolescents who received Tdap previously or when Tdap is not available.

‡TIG should be administered for tetanus-prone wounds in HIV-infected patients regardless of the history of tetanus immunizations.

§Yes, if 10 yr or longer since the last tetanus toxoid–containing vaccine dose.

‖Yes, if 5 yr or longer since the last tetanus toxoid–containing vaccine dose. (More frequent boosters are not needed and can accentuate adverse events.)

DT, diphtheria and tetanus toxoid vaccine; DTaP, combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; Td, tetanus toxoid and reduced diphtheria toxoid vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; TIG, tetanus immune globulin.

Adapted from the Centers for Disease Control and Prevention (CDC): Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR Morbid Mortal Wkly Rep *55:1–43, 2006.*

All nonminor wounds require human TIG except those in a fully immunized patient. In any other circumstance (e.g., patients with an unknown or incomplete immunization history; crush, puncture, or projectile wounds; wounds contaminated with saliva, soil, or feces; avulsion injuries; compound fractures; or frostbite), TIG 250 units should be given intramuscularly, with 500 units for highly tetanus-prone wounds (i.e., unable to be debrided, with substantial bacterial contamination, or longer than 24 hr since injury). If TIG is unavailable, use of human intravenous immunoglobulin may be considered. If neither of these products is available, then 3,000-5,000 units of equine- or bovine-derived TAT may be given intramuscularly after testing for hypersensitivity. Even at this dose, serum sickness may occur.

The wound should undergo immediate, thorough surgical cleansing and debridement to remove foreign bodies and any necrotic tissue in which anaerobic conditions might develop. Tetanus toxoid should be given to stimulate active immunity and may be administered concurrently with TIG (or TAT) if given in separate syringes at widely separated sites. A tetanus toxoid booster (preferably Td or Tdap) is administered to all persons with any wound if the tetanus immunization status is unknown or incomplete. A booster is administered to injured persons who have completed the primary immunization series if (1) the wound is clean and minor but 10 or more years have passed since the last booster or (2) the wound is more serious and 5 or more years have passed since the last booster. Persons who experienced an Arthus reaction after a dose of tetanus toxoid–containing vaccine should not receive Td more frequently than every 10 yr, even for tetanus prophylaxis as part of wound management. In a situation of delayed wound care, active immunization should be started at once. Although fluid tetanus toxoid produces a more rapid immune response than the absorbed or precipitated toxoids, the absorbed toxoid results in a more durable titer.

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Chapter 212

Clostridium difficile Infection

Ethan A. Mezoff and Mitchell B. Cohen

***Clostridium difficile* infection** (CDI), also known as *pseudomembranous colitis* or *C. difficile*–associated diarrhea, refers to gastrointestinal colonization with *C. difficile* resulting in a diarrheal illness. An increase in inpatient and outpatient acquisition of CDI has been observed and new risk factors identified, fueling the development of new therapeutic options.

ETIOLOGY

C. difficile is a Gram-positive, anaerobic bacillus capable of forming a spore that is resistant to killing by alcohol. Organisms causing symptomatic disease produce 1 or both of the following: **toxin A** and **toxin B**. These toxins affect intracellular signaling pathways, resulting in inflammation and cell death. The cytotoxic **binary toxin**, an AB toxin, is not present in the majority of strains but has been detected in epidemic strains.

EPIDEMIOLOGY

Once thought to be an infrequent infection of chronically ill and hospitalized patients, the incidence of CDI is increasing and the setting of acquisition is changing. The incidence in pediatric patients increased 48%, from 2.5 to 3.7 cases per 1,000 admissions between 2001 and 2006. A population-based cohort study over a similar time period found that 75% of cases were community-acquired and 16% had no

preceding hospitalization or antibiotic exposure. In addition to an overall increase in all strains, a hypervirulent strain, denoted NAP1/BI/027 (also called BI), has emerged and is estimated to cause approximately 10-20% of pediatric infections. This strain produces binary toxin and exhibits 16- and 23-fold increases in the production of toxins A and B, respectively. The specific role of this hypervirulent strain in the changing epidemiology of CDI is not completely understood.

Asymptomatic carriage occurs with potentially pathogenic strains; this is common in neonates and infants 1 year of age and younger. A carrier frequency rate of 50% may occur in children younger than age 1 yr, but the rate declines by age 3 yr. Carriers can infect other susceptible individuals.

Risk factors for CDI include the use of broad-spectrum antibiotics, hospitalization (particularly if the prior room occupant was infected), gastrointestinal surgery, inflammatory bowel disease, chemotherapy, enteral tube feeding, proton pump–inhibitor use, and chronic illness.

PATHOGENESIS

Disease is caused by gastrointestinal infection with a toxin-producing strain. Any process that disrupts normal flora, impairs the acid barrier defense, alters the normal gastrointestinal immune response (e.g., inflammatory bowel disease), or inhibits intestinal motility may lead to infection. Normal bowel flora appears to be protective, conferring "colonization resistance."

By affecting intracellular signaling pathways and cytoskeletal organization, toxins induce an inflammatory response and cell death, leading to diarrhea and pseudomembrane formation. Antibodies against toxin A have been shown to confer protection against symptomatic disease, and failure of antibody production has been shown to occur in patients with recurrent disease.

CLINICAL MANIFESTATIONS

Infection with toxin-producing strains of *C. difficile* leads to a spectrum of disease ranging from mild, self-limited diarrhea to explosive, watery diarrhea with occult blood or mucous, to pseudomembranous colitis, and even death. **Pseudomembranous colitis** describes a bloody diarrhea with accompanying fever, abdominal pain/cramps, nausea, and vomiting. Rarely, small gut involvement, bacteremia, abscess formation, toxic megacolon, and even death can occur.

Symptoms of CDI generally begin less than a week after colonization and may develop during or weeks after antibiotic exposure. They are generally more severe in certain populations, including patients receiving chemotherapy, patients with chronic gastrointestinal disease (e.g., inflammatory bowel disease), and some patients with cystic fibrosis.

DIAGNOSIS

CDI is diagnosed by the detection of a *C. difficile* **toxin** in the stool of a symptomatic patient. Most patients present with a history of recent antibiotic use, but the absence of antibiotic exposure should not dissuade the astute clinician from considering this diagnosis and ordering the appropriate test. Conversely, high carriage rates among infants should prompt careful consideration when testing and treating children younger than the age of 3 yr.

The cell culture cytotoxicity assay was replaced as the standard test for toxin detection by the enzyme immunoassay, a same-day test for 1 or both toxins with sufficient specificity (94-100%) but less-than-ideal sensitivity (88-93%). Nucleic acid amplification tests are used by some laboratories to supplement or supplant the immunoassay with the goal of improving sensitivity.

Culture for organism isolation is a sensitive test but is labor intensive, taking several days. Culture alone is not specific, as it does not differentiate between toxin-producing and non–toxin-producing strains. Pseudomembranous nodules and characteristic plaques may be seen on colonoscopy or sigmoidoscopy.

TREATMENT

Initial treatment of CDI involves discontinuation of any nonvital antibiotic therapy and administration of fluid/electrolyte replacement. For mild cases, this treatment may be curative. Persistent symptoms or moderate to severe disease warrants antimicrobial therapy directed against *C. difficile*.

Oral metronidazole (20-40 mg/kg/day PO divided every 6-8 hr for 7-10 days) works well in mild to moderate infection. Orally administered vancomycin (40 mg/kg/day PO divided every 6 hr for 7-10 days) is approved by the U.S. Food and Drug Administration for use against infection with *C. difficile*. Vancomycin exhibits ideal pharmacologic properties for treatment of this enteric pathogen, as it is not absorbed in the gut. This agent is suggested as a first-line agent for severe disease as manifested by hypotension, peripheral leukocytosis, or severe pseudomembranous colitis. Concern for the emergence of vancomycin-resistant enterococci and cost limit its use as first-line therapy in mild to moderate disease. Fidaxomicin, a second-line agent not yet approved for pediatric use, is a narrow spectrum macrolide antibiotic with noninferior efficacy to vancomycin but superior recurrence prevention. The cost of a course of fidaxomicin can be twice that of vancomycin and 125-fold higher than that of metronidazole. Reports have demonstrated a high success treatment efficacy for donor (unaffected) fecal therapy (transplant) (see below for recurrences).

PROGNOSIS

The response rate to initial treatment of CDI is greater than 95%; however, both the treatment failure rate and the recurrence rate have increased since the late 1990s. Additionally, the risk of subsequent reappearance increases with each recurrence.

Initial recurrence rates are between 5% and 20%, are diagnosed clinically and generally occur within 4 wk of treatment. Some recurrences are a result of incomplete eradication of the original strain and others are because of reinfection with a different strain. Treatment for the initial reoccurrence involves retreatment with the original antibiotic course.

Recurrences of CDI may be a consequence of a suboptimal immune response, failure to kill organisms that have sporulated, or failure of delivery of antibiotic to the site of infection in the case of ileus or toxic megacolon. In the case of the 1st 2 causes, treatment with pulsed or tapered vancomycin decreases recurrence rates. In addition to this approach, other antibiotics (rifaximin or nitazoxanide), toxin-binding polymers (Tolevamer), and probiotics (*Saccharomyces boulardii* or *Lactobacillus* GG) have been used as adjunctive therapy. Although not well studied in children, *S. boulardii* significantly decreases recurrence rates when used as an adjunct to vancomycin therapy in adults. Because failure to manifest an adequate antitoxin immune response is associated with a higher frequency of recurrent CDI, intravenous immune globulin has been used to treat recurrent disease. In the case of ileus or toxic megacolon, an enema of vancomycin may be used to directly place the antibiotic at the site of infection, although most often intravenous therapy is first attempted in this circumstance.

Fecal microbial transplantation has been used to address the disruption in normal gut flora felt to allow colonization with *C. difficile*. Transplantation involves the instillation of fecal material from a healthy donor into the patient's gastrointestinal tract by nasoenteric tube, enema, capsules, or colonoscopy. Initial reports indicate an overall success rate of approximately 90% in patients with recurrent CDI.

It is important to recognize that postinfectious diarrhea may be from other causes. Examples are postinfectious irritable bowel syndrome, microscopic colitis, and inflammatory bowel disease. A test of cure is not recommended in the asymptomatic patient, and a positive test for recurrence is not useful until at least 4 wk after the initial test.

PREVENTION

Strategies for prevention of CDI include recognition of common sites of acquisition (hospitals, childcare settings, extended care facilities); effective environmental cleaning (i.e., use of chlorinated cleaning solutions); appropriate antibiotic and proton-pump inhibitor prescription practices; cohorting of infected patients; and proper handwashing with soap and water. There is moderate evidence that probiotics may reduce the incidence of *C. difficile*–associated diarrhea.

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Chapter 213

Other Anaerobic Infections

Michael J. Chusid

Anaerobic bacteria are among the most numerous organisms colonizing humans. Anaerobes are present in soil and are normal inhabitants of all living animals, but infections caused by anaerobes are relatively uncommon. Anaerobes are relatively or entirely intolerant of exposure to oxygen. Most are **facultative anaerobes,** being able to survive in the presence of oxygen but growing better in reduced oxygen tensions. **Obligate anaerobes** cannot survive any exposure to oxygen.

Infections with anaerobes frequently occur adjacent to mucosal surfaces, often as **mixed infections** with aerobes. Conditions of reduced oxygen tension provide the optimal conditions for proliferation of anaerobes. Traumatized areas, devascularized areas, and areas of crush injury are all ideal sites for anaerobic infection. Often both aerobic and anaerobic organisms are inoculated in devitalized areas, with local extension and bacteremia most often caused by the more virulent aerobes. Abscess formation evolves over days to weeks and generally involves both aerobes and anaerobes. Examples of such infections include appendicitis and periappendiceal, pelvic, perirectal, peritonsillar, retropharyngeal, parapharyngeal, pulmonary, and dental abscesses. Septic thrombophlebitis, as a consequence of appendicitis, chronic sinusitis, pharyngitis, and otitis media, provides a route for hematogenous spread of anaerobic infection to parenchymal organs such as the liver, brain, and lungs.

Anaerobic infection is usually caused by endogenous flora. Combinations of impaired physical barriers to infection, compromised tissue viability, alterations in normal flora, impaired host immunity, and anaerobic bacterial virulence factors contribute to infection with normal anaerobic inhabitants of mucous membranes. Virulence factors include capsules, toxins, enzymes, and fatty acids.

CLINICAL MANIFESTATIONS

Anaerobic infections occur in a variety of sites throughout the body (Table 213-1). Anaerobes often coexist synergistically with aerobes. Infections with anaerobes are usually polymicrobial and also include aerobes.

Bacteremia

Anaerobes account for approximately 1% of bloodstream bacterial isolates in adults, but the rate is lower in children. Isolation of anaerobes from the blood is often an indication of a serious primary anaerobic infection. The most common blood isolates of anaerobic bacteria in children are *Bacteroides fragilis*, *Peptostreptococcus* spp., *Clostridium* spp., and *Fusobacterium* spp. As with aerobes, the cell walls of Gram-negative anaerobes may contain endotoxin and can be associated with the development of hypotension and shock when present in the circulatory system. Clostridia produce hemolysins, and the presence of these organisms in the blood can result in massive hemolysis and cardiovascular collapse.

Central Nervous System

Anaerobic meningitis is rare but can occur in neonates and as a complication of infections of the ear and neck or because of anatomic defects of meninges (sinus tracts). Brain abscess and subdural empyema are usually polymicrobial, with anaerobes commonly involved (see Chapter 604). Brain abscess usually occurs as a result of spread from infected sinuses, middle ear, or lung.

Upper Respiratory Tract

The respiratory tract is colonized by both aerobes and anaerobes. Anaerobic bacteria are involved in chronic sinusitis, chronic otitis media, peritonsillar infections, parapharyngeal and retropharyngeal abscesses, and periodontal infections. Anaerobic periodontal disease is most common in patients with poor dental hygiene or who are receiving drugs that provide hypertrophy of the gums. **Vincent angina,** also known as **acute necrotizing ulcerative gingivitis** or **trench mouth,** is an acute, fulminating, mixed anaerobic bacterial-spirochetal infection of the gingival margin and floor of the mouth. It is characterized by gingival pain, foul breath, and pseudomembrane formation. **Ludwig angina** is an acute, life-threatening cellulitis of dental origin of the sublingual and submandibular spaces. Infection spreads rapidly in the neck and may cause sudden airway obstruction.

Lemierre syndrome, or **postanginal sepsis,** is a suppurative infection of the lateral pharyngeal space, of increasing prevalence, that often begins as pharyngitis (see Chapter 381). It may complicate Epstein-Barr virus or other viral and bacterial infections of the pharynx. It usually manifests as a unilateral septic thrombophlebitis of the jugular venous system with septic pulmonary embolization. Clinical signs include unilateral painful neck swelling, trismus, and dysphagia, culminating with signs of sepsis and respiratory distress. *Fusobacterium necrophorum* is the most commonly isolated organism, although polymicrobial infection may occur. Metastatic infections involving muscles, bones, and solid organs can occur as a complication of Lemierre syndrome.

Lower Respiratory Tract

Anaerobic lung abscess, empyema, and anaerobic pneumonia are most common in children who have disordered swallowing or seizures or in whom an inhaled foreign body is occluding a bronchus. Children and adults can aspirate oral contents during sleep, seizure, or periods of unconsciousness. In most cases, lung cilia and phagocytes clear particulate matter and microbes. If the aspiration is of increased volume or frequency or a foreign body blocks normal ciliary clearance, normal pulmonary clearance mechanisms are overcome and infection ensues. In unusual cases, particularly in patients with poor dental hygiene, aspirated mouth contents may contain the anaerobe *Actinomyces israelii*, resulting in pulmonary actinomycosis (see Chapter 189). This anaerobic pneumonitis is remarkable for traversing tissues planes, and affected patients often have fistulas extruding distinctive particulate matter, called sulfur granules, from the chest wall overlying areas of intrathoracic infection.

Intraabdominal Infection

The entire digestive tract is heavily colonized by anaerobes. The density of organisms is highest in the colon, where anaerobes outnumber aerobes 1,000 : 1. Perforation of the gut leads to leakage of gut flora into the peritoneum, resulting in peritonitis involving both aerobes and anaerobes. Secondary sepsis caused by aerobes often occurs early. As the peritoneal infection is walled off, an abscess containing both aerobes and anaerobes often evolves. Secondary hepatic abscesses may then develop as complications of appendicitis, intestinal perforation, inflammatory bowel disease, or biliary tract disease. In children with malignancies who are receiving chemotherapy, the intestinal mucosa is often damaged, leading to translocation of bacteria and focal invasion of bowel flora. **Typhlitis** is a mixed infection of the gut wall usually beginning in the ileocecum and characterized by abdominal pain, diarrhea, fever, and abdominal distention in neutropenic patients. Empiric antimicrobial therapy of fever and neutropenia may not be optimal against the anaerobes involved in typhlitis (see Chapter 178). Similarly, a mixed aerobic–anaerobic infection of the intestinal wall and peritoneum may develop in a small infant as a complication of **necrotizing enterocolitis**, believed to be a result of the relative vascular insufficiency of the gut and hypoxia (see Chapter 102.2).

Genital Tract

Pelvic inflammatory disease and tuboovarian abscesses are frequently caused by mixed aerobic anaerobic infection. Vaginitis can be caused

Table 213-1 Infections Associated with Anaerobic Bacteria

SITE AND INFECTION	MAJOR RISK FACTORS	ANAEROBIC BACTERIA*
CENTRAL NERVOUS SYSTEM		
Cerebral abscess	Cyanotic heart disease Cystic fibrosis Penetrating trauma	Polymicrobial
Epidural and subdural empyemas, meningitis	Direct extension from contiguous sinusitis, otitis media, mastoiditis, or anatomic defect involving the dura	*Bacteroides fragilis*† *Fusobacterium* *Peptostreptococcus* *Veillonella*
UPPER RESPIRATORY TRACT		
Dental abscess	Poor periodontal hygiene	*Peptostreptococcus*
Ludwig angina (cellulitis of sublingual-submandibular space)	Drugs producing gingival hypertrophy	*Fusobacterium*
Necrotizing gingivitis (Vincent stomatitis)		*Prevotella melaninogenica*
Chronic otitis-mastoiditis-sinusitis	Tympanic perforation Tympanostomy tubes	
Peritonsillar abscess	Streptococcal pharyngitis	
Retropharyngeal abscess	Penetrating injury	
Lemierre syndrome	Preexisting viral or bacterial pharyngitis	*Fusobacterium*
LOWER RESPIRATORY TRACT		
Aspiration pneumonia	Periodontal disease	Polymicrobial
Necrotizing pneumonitis	Bronchial obstruction	*P. melaninogenica*
Lung abscess	Altered gag or consciousness Aspirated foreign body Sequestered lobe Vascular anomaly	*Bacteroides intermedius* *Fusobacterium* *Peptostreptococcus, Eubacterium* *B. fragilis, Veillonella*
Septic pulmonary emboli		*Fusobacterium*
INTRAABDOMINAL		
Abscess	Appendicitis	Polymicrobial
Secondary peritonitis	Penetrating trauma (especially of the colon)	*Bacteroides* spp. *Clostridium* *Peptostreptococcus* *Eubacterium* *Fusobacterium*
FEMALE GENITAL TRACT		
Bartholin abscess	Vaginosis	*B. fragilis*
Tuboovarian abscess	Intrauterine device	*Bacteroides bivius*
Endometritis		*Peptostreptococcus*
Pelvic thrombophlebitis		*Clostridium*
Salpingitis		*Mobiluncus*
Chorioamnionitis		*Actinomyces*
Septic abortion		*Clostridium*
SKIN AND SOFT TISSUE		
Cellulitis	Decubitus ulcers	Varies with site and contamination with oral or enteric flora
Perirectal cellulitis	Abdominal wounds	*Clostridium perfringens* (myonecrosis)
Myonecrosis (gas gangrene)	Pilonidal sinus	*Bacteroides* *Clostridia*
Necrotizing fasciitis and synergistic gangrene	Trauma Human and animal bites Immunosuppressed or neutropenic patients Varicella	*Fusobacterium* *Clostridium tertium* *Clostridium septicum* Anaerobic streptococci
BLOOD		
Bacteremia	Intraabdominal infection, abscesses, myonecrosis, necrotizing fasciitis	*B. fragilis* *Clostridium* *Peptostreptococcus* *Fusobacterium*

*Infections may also be from or may involve aerobic bacteria as the sole agent or as part of a mixed infection; brain abscess may contain microaerophilic streptococci; intraabdominal infections may contain Gram-negative enteric organisms and enterococci; and salpingitis may contain *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

†*Bacteroides fragilis* is usually isolated from infections below the diaphragm except for brain abscesses.

by overgrowth of anaerobic flora. Anaerobes frequently contribute to chorioamnionitis and premature labor and may result in anaerobic bacteremia of the newborn. Although these bacteremias are often transient, anaerobes occasionally cause invasive disease in the newborn, including central nervous system infection.

Skin and Soft Tissue

Anaerobic skin infections occur in the setting of bites, foreign bodies, and skin and tissue ulceration because of pressure necrosis or lack of adequate blood supply. Animal bites and human bites inoculate oral and skin flora into damaged and hypoxic cutaneous tissue. The extent

of the infection depends on the depth of the bite and the associated crush injury to the tissues. In immunocompromised patients, unusual oral anaerobes such as *Capnocytophaga canimorsus* can cause life-threatening infection.

Clostridial myonecrosis, or **gas gangrene,** is a rapidly progressive infection of deep soft tissues, primarily muscles, associated with *Clostridium perfringens*. **Necrotizing fasciitis** is a more superficial, polymicrobial infection of the subcutaneous space with acute onset and rapid progression that has significant morbidity and mortality (see Chapter 665.2). Group A streptococcus, known in the popular press as "the flesh-eating bacteria," and *Staphylococcus aureus* are occasionally the causative pathogens. Commonly, necrotizing fasciitis is produced by combined infection of *S. aureus* or Gram-negative bacilli and anaerobic streptococci, termed **synergistic gangrene**. This infection is often seen as a complication of varicella following secondary infection of cutaneous vesicles. Diabetic patients may have a particularly aggressive and destructive synergistic gangrene of the inguinal area and adjacent scrotum or vulva known as **Fournier gangrene**. Early recognition with aggressive surgical debridement and antimicrobial therapy is necessary to limit disfiguring morbidity and mortality.

Other Sites

Occasionally, the bone adjacent to an anaerobic infection becomes infected by direct extension from a contiguous infection or by direct inoculation associated with trauma. Anaerobic infections of the kidneys (renal and perirenal abscesses) and heart (pericarditis) are rare. **Enteritis necroticans (pigbel)** is a rare but often fatal gastrointestinal infection that most commonly follows ingestion of a large meal in a previously starved child or adult. Anaerobic osteomyelitis, particularly of fingers and toes, can complicate any process capable of producing hypoxic necrosis, including diabetes, neuropathies, vasculopathies, and coagulopathies.

DIAGNOSIS

The diagnosis of anaerobic infection requires a high index of suspicion and the collection of appropriate and adequate specimens for anaerobic culture (Table 213-2). Culture specimens should be obtained in a manner that protects them from contamination with mucosal bacteria and from exposure to ambient oxygen. Swab samples from mucosal surfaces, nasal secretions, respiratory specimens, and stool should not be sent for anaerobic culture, because these sites normally harbor many anaerobes. Aspirates of infected sites, abscess material, and biopsy specimens are appropriate for anaerobic culturing. Specimens must be protected from oxygen and transported to the laboratory immediately. Anaerobic **transport medium** is used to increase the likelihood of recovery of obligate anaerobes. Gram staining of abscess fluid from suspected anaerobic infections is useful because even if the organisms do not grow in culture, they can be seen on the smear. The use of DNA probe technology in the near future is likely to increase the sensitivity of microbiologic confirmation of an anaerobic infection. Methods for susceptibility testing exist but may not be routinely available. A rapid and simple screening test for antibiotic susceptibility can be used to detect β-lactamase production and presumptive penicillin resistance.

TREATMENT

Treatment of anaerobic infections usually requires adequate drainage and appropriate antimicrobial therapy. Antibiotic therapy varies depending on the suspected or proven anaerobe involved. Many oral anaerobic bacterial species are susceptible to penicillins, although some strains may produce a β-lactamase. Drugs that are active against such strains include metronidazole, penicillins combined with β-lactamase inhibitors (ampicillin-sulbactam, ticarcillin-clavulanate, and piperacillin-tazobactam), carbapenems (imipenem and meropenem), clindamycin, and cefoxitin. Penicillin and vancomycin are active against the Gram-positive anaerobes.

Aerobes are usually present with the anaerobes, necessitating broad-spectrum antibiotic combinations for empirical therapy. Specific therapy is based on culture results and clinical course.

Table 213-2 Clues to Presumptive Diagnosis of Anaerobic Infections*

- Infection contiguous to or near a mucosal surface colonized with anaerobic bacteria (oropharynx, intestinal–genitourinary tract)
- Putrid odor
- Severe tissue necrosis, abscesses, gangrene, or fasciitis
- Gas formation in tissues (crepitus on exam or visible on plain radiograph)
- Failure to recover organisms using conventional aerobic microbiologic methods, despite the presence of mixed pleomorphic organisms on smears
- Failure of organisms to grow after pretreatment with antibiotics effective against anaerobes
- Failure of clinical response to antibiotic therapy poorly effective against anaerobic bacteria (e.g., aminoglycosides)
- Toxin-mediated syndromes: botulism, tetanus, gas gangrene, food poisoning, pseudomembranous colitis
- Infections associated with anaerobic bacteria (see Table 213-1)
- Septic thrombophlebitis
- Septicemic syndrome with jaundice or intravascular hemolysis
- Typical appearance on Gram stain:
  - Bacteroides species—small, delicate, pleomorphic, pale, Gram-negative bacilli
  - *Fusobacterium nucleatum*—thin Gram-negative bacilli with fusiform shape, pointed ends
  - *Fusobacterium necrophorum*—pleomorphic Gram-negative bacilli with rounded ends
  - *Peptostreptococcus*—Gram-positive chained cocci similar to aerobic cocci
  - *Clostridium perfringens*—large, short, fat (boxcar-shaped), Gram-positive bacilli

*Suspicion of anaerobic infection is critical before specimens are sampled for culture, so as to ensure optimal microbiologic techniques and prompt, appropriate therapy.

For soft-tissue infections, providing adequate perfusion to the area is critical. At times, a muscle flap or skin flap procedure is needed to ensure that nutrients and antimicrobial agents are brought to the affected area and adequate oxygen tension is maintained. Drainage of infected areas is often necessary for cure. Bacteria may survive in abscesses because of high bacterial inoculum, lack of bactericidal activity, and local conditions that facilitate bacterial proliferation. Aspiration is sometimes effective for small collections, whereas incision and drainage may be required for larger abscesses. Extensive debridement and resection of all devitalized tissue are needed to control fasciitis and myonecrosis. The therapeutic benefit of hyperbaric oxygen therapy remains uncertain.

COMMON ANAEROBIC PATHOGENS

Clostridium

Strains of *Clostridium* cause disease by proliferation and often by production of toxins. Of the more than 60 species that have been identified, only a few cause infections in humans. The most frequently implicated species are *Clostridium difficile* (see Chapter 212), *C. perfringens*, *Clostridium botulinum* (see Chapter 210), *Clostridium tetani* (see Chapter 211), *Clostridium butyricum, Clostridium septicum, Clostridium sordellii, Clostridium tertium,* and *Clostridium histolyticum.*

C. perfringens produces a variety of toxins and virulence factors. Strains of *C. perfringens* are designated A through E. **Alpha toxin** is a phospholipase that hydrolyzes sphingomyelin and lecithin and is produced by all strains. This toxin causes hemolysis, platelet lysis, increased capillary permeability, and hepatotoxicity. **Beta toxin,** produced by strains B and C, causes hemorrhagic necrosis of the small bowel. **Epsilon toxin** is produced by B and D strains and injures vascular endothelial cells, leading to increased vascular permeability, edema, and organ dysfunction. **Iota toxin,** produced by E strains, causes dermal edema. An enterotoxin is produced by type A and some type

C and D strains. Hemolysins and a variety of enzymes are produced by many *C. perfringens* strains.

Clostridium species commonly invade the bloodstream shortly before, during, or just after death, leading to contamination of tissues that may be donated for transplantation. A large outbreak of *Clostridium* infections in tissue graft recipients was reported in 14 patients who received musculoskeletal grafts processed at a single tissue bank. As a result of this outbreak, recommendations for tissue processing now include a processing method that kills bacterial spores.

Myonecrosis (Gas Gangrene)

C. perfringens is the major etiologic cause of myonecrosis, a rapidly progressive anaerobic soft-tissue infection. In immunocompromised persons, especially patients receiving cancer chemotherapy, *C. septicum* is a classic cause of rapidly fatal gas gangrene. A clue to the diagnosis is pain out of proportion to the clinical appearance of the wound. Infection progresses rapidly with edema, swelling, myonecrosis, and sometimes crepitation of soft tissues. Hypotension, mental confusion, shock, and renal failure are common. A characteristic sweet odor is present in the serosanguineous discharge. Gram staining of the exudate reveals Gram-positive bacilli but few leukocytes. Early and complete debridement with excision of necrotic tissue is key to controlling the infection. Repeated, frequent assessment of tissue viability in the operating room is required. High-dose penicillin (250,000 units/kg/day divided every 4-6 hr IV) or clindamycin (25-40 mg/kg/day divided every 6-8 hr IV) should be started immediately. Amputation of affected limbs is often required. The role of hyperbaric oxygen remains unclear but has been reported to be beneficial in several studies. Unfortunately, the prognosis for patients with myonecrosis is poor, even with early, aggressive therapy.

Food Poisoning

C. perfringens type A produces an enterotoxin that causes food poisoning (see Chapter 340). This intoxication results in the acute onset of watery diarrhea and crampy abdominal pain. The usual foods containing toxin are improperly prepared or stored meats and gravies. A specific etiologic diagnosis is rarely made in children with food poisoning. Therapy consists of rehydration and electrolyte replacement if necessary. The illness resolves spontaneously within 24 hr of onset. Prevention requires the maintenance of hot food at a temperature ≥74°C (165.2°F).

Bacteroides and *Prevotella*

B. fragilis is one of the more virulent anaerobic pathogens and is most frequently recovered from blood cultures and cultures of tissue or pus. The most common *B. fragilis* infection in children occurs as a complication of appendicitis. The organism is part of normal colonic flora but is not common in the mouth or respiratory tract. *B. fragilis* is usually found as part of polymicrobial appendiceal and other intraabdominal abscesses and is often involved in genital tract infections such as pelvic inflammatory disease and tuboovarian abscess. *Prevotella* organisms are normal oral flora, and infection with them typically involves gums, teeth, tonsils, and parapharyngeal spaces. Both *B. fragilis* and *Prevotella* may be involved in aspiration pneumonitis and lung abscess.

Strains of *B. fragilis* and *Prevotella melaninogenica* produce β-lactamase and are resistant to penicillins. Recommended treatment is with ticarcillin-clavulanate, piperacillin-tazobactam, cefoxitin, metronidazole, clindamycin, imipenem, or meropenem. Because infections involving these organisms are usually polymicrobial, therapy should include antimicrobial agents active against likely concomitant aerobic pathogens. Drainage of any abscesses and debridement of necrotic tissue are often required for control of these infections.

Fusobacterium

Fusobacterium organisms inhabit the intestine, respiratory tract, and female genital tracts. These organisms, which are more virulent than most of the normal anaerobic flora, cause bacteremia and a variety of rapidly progressive infections. **Lemierre syndrome,** bone and joint infections, and abdominal and genital tract infections are most common. Some strains produce a β-lactamase and are resistant to penicillins, requiring therapy with drugs like ampicillin-sulbactam and clindamycin.

Veillonella

Veillonella organisms are normal flora of the mouth, upper respiratory tract, intestine, and vagina. These anaerobes rarely cause infection. Strains are recovered as part of the polymicrobial flora causing abscess, chronic sinusitis, empyema, peritonitis, and wound infection. *Veillonella* organisms are susceptible to penicillins, cephalosporins, clindamycin, metronidazole, and carbapenems.

Anaerobic Cocci

Peptostreptococcus species are normal flora of the skin, respiratory tract, and gut. These organisms are often present in brain abscesses, chronic sinusitis, chronic otitis, and lung abscesses. Such infections are often polymicrobial, and therapy is aimed at the accompanying aerobes as well as the anaerobes. Most of the Gram-positive cocci are susceptible to penicillin, cephalosporins, carbapenems, and vancomycin.

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Section 7

Mycobacterial Infections

Chapter 214

Principles of Antimycobacterial Therapy

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The treatment of mycobacterial infection and disease can be challenging. Patients require therapy with multiple agents, the offending pathogens commonly exhibit complex drug resistance patterns, and patients often have underlying conditions that affect drug choice and monitoring. Several of the drugs have not been well studied in children, and current recommendations are extrapolated from the experience in adults.

Single-drug therapy of *Mycobacterium tuberculosis* and nontuberculous mycobacteria is not recommended because of the high likelihood of developing antimicrobial resistance. Susceptibility testing of mycobacterial isolates often can aid in therapeutic decision making.

AGENTS USED AGAINST *MYCOBACTERIUM TUBERCULOSIS*

Commonly Used Agents

Isoniazid

Isoniazid (INH) is a hydrazide form of isonicotinic acid and is bactericidal for rapidly growing *M. tuberculosis.* The primary target of INH involves the INH A gene, which encodes the enoyl ACP (acyl carrier

Table 214-1 Recommended Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

INFECTION OR DISEASE CATEGORY	REGIMEN	REMARKS
LATENT TUBERCULOSIS INFECTION*		
Isoniazid susceptible	9 mo of isoniazid, once a day	If daily therapy is not possible, DOT twice a week can be used for 9 mo
Isoniazid resistant	6 mo of rifampin, once a day	If daily therapy is not possible, DOT twice a week can be used for 6 mo
Isoniazid-rifampin resistant‡	Consult a tuberculosis specialist	
PULMONARY AND EXTRAPULMONARY INFECTION		
Except meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily, followed by 4 mo of isoniazid and rifampin† by DOT§ for drug-susceptible *Mycobacterium tuberculosis* 9-12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	If possible drug resistance is a concern (see text), another drug (ethambutol or an aminoglycoside) is added to the initial 3 drug therapy until drug susceptibilities are determined; DOT is highly desirable If hilar adenopathy only, a 6-mo course of isoniazid and rifampin is sufficient Drugs can be given 2 or 3×/wk under DOT in the initial phase if nonadherence is likely
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside or ethambutol or ethionamide, once a day, followed by 7-10 mo of isoniazid and rifampin, once a day or twice a week (9-12 mo total) for drug-susceptible *M. tuberculosis* ≥12 mo of therapy without pyrazinamide for drug-susceptible *M. bovis*	A 4th drug, such as an aminoglycoside, is given with initial therapy until drug susceptibility is known For patients who might have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin

*Positive TST or IGRA result, no disease.
†Duration of therapy is longer for human immunodeficiency virus (HIV)-infected people, and additional drugs may be indicated.
‡Medications should be administered daily for the 1st 2 wk to 2 mo of treatment and then can be administered 2-3×/wk by DOT.
§If initial chest radiograph shows cavitary lesions and sputum after 2 mo of therapy remains positive, duration of therapy is extended to 9 mo.
DOT, directly observed therapy; IGRA, interferon-γ release assay; TST, tuberculin skin test.
From American Academy of Pediatrics: Tuberculosis. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, editors: Red book 2012: report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

protein) reductase needed for the last step of the mycolic acid biosynthesis pathway of cell wall production. Resistance to INH occurs following mutations in the INH A gene or in other genes encoding enzymes that activate INH, such as kat G.

INH is indicated for the treatment of *M. tuberculosis, Mycobacterium kansasii,* and *Mycobacterium bovis.* The pediatric dosage is 10-15 mg/kg/day PO in a single dose not to exceed 300 mg/day. The adult dosage is 5 mg/kg/day PO in a single dose not to exceed 300 mg/day. Alternative pediatric dosing is 20-30 mg/kg PO in a single dose not to exceed 900 mg/dose given twice weekly under **directly observed therapy,** in which patients are observed to ingest each dose of antituberculosis medication to maximize the likelihood of completing therapy. The duration of treatment depends on the disease being treated (Table 214-1). INH needs to be taken 1 hr before or 2 hr after meals because food decreases absorption. It is available in liquid, tablet, IV (not approved by the FDA), and IM preparations.

Major **adverse events** include hepatotoxicity in 1% of children and approximately 3% of adults (increasing with age) and dose-related peripheral neuropathy. Pyridoxine can prevent the peripheral neuropathy and is indicated for breastfeeding infants and their mothers, children and youth on milk- or meat-deficient diets, pregnant adolescents, and symptomatic HIV-infected children. Minor adverse events include rash, worsening of acne, epigastric pain with occasional nausea and vomiting, decreased vitamin D levels, and dizziness. The liquid formulation of INH contains sorbitol, which often causes diarrhea and stomach upset.

INH is accompanied by significant drug–drug interactions (Table 214-2). The metabolism of INH is by acetylation. Acetylation rates have little effect on efficacy, but **slow acetylators** have an increased risk for hepatotoxicity, especially when used in combination with rifampin. Routine baseline liver function testing or monthly monitoring is only indicated for persons with underlying hepatic disease or on concomitant hepatotoxic drugs, including other antimycobacterial agents, acetaminophen, and alcohol. Monthly clinic visits while on INH alone are encouraged to monitor adherence, adverse effects, and worsening of infection.

Table 214-2 Isoniazid Drug–Drug Interactions

DRUG USED WITH ISONIAZID	EFFECTS
Acetaminophen, alcohol, rifampin	Increased hepatotoxicity of isoniazid or listed drugs
Aluminum salts (antacids)	Decreased absorption of isoniazid
Carbamazepine, phenytoin, theophylline, diazepam, warfarin	Increased level, effect, or toxicity of listed drugs due to decreased metabolism
Itraconazole, ketoconazole, oral hypoglycemic agents	Decreased level or effect of listed drugs due to increased metabolism
Cycloserine, ethionamide	Increased central nervous system adverse effects of cycloserine and ethionamide
Prednisolone	Increased isoniazid metabolism

Rifamycins

The rifamycins (rifampin, rifabutin, rifapentine) are a class of macrolide antibiotics developed from *Streptomyces mediterranei.* Rifampin is a synthetic derivative of rifamycin B, and rifabutin is a derivative of rifamycin S. Rifapentine is a cyclopentyl derivative. The rifamycins inhibit the DNA-dependent RNA polymerase of mycobacteria, resulting in decreased RNA synthesis. They are generally bactericidal at treatment doses, but they may be bacteriostatic at lower doses.

Resistance is from a mutation in the DNA-dependent RNA polymerase gene (RpoB) that is often induced by previous incomplete therapy. Cross-resistance between rifampin and rifabutin has been demonstrated.

Rifampin is active against *M. tuberculosis, Mycobacterium leprae, M. kansasii,* and *Mycobacterium avium* complex. Rifampin is an integral drug in standard combination treatment of active *M. tuberculosis* disease and can be used as an alternative to INH in the treatment of latent tuberculosis infection in children who cannot tolerate INH. Rifabutin has a similar spectrum, with increased activity against *M. avium* complex. Rifapentine is undergoing pediatric clinical trials and appears to have activity similar to the activity of rifampin. The pediatric dosage of rifampin is 10-15 mg/kg/day PO in a single dose, not to exceed 600 mg/day. The adult dosage of rifampin is 5-10 mg/kg/day PO in a single dose, not to exceed 600 mg/day. Commonly used rifampin preparations include 150 and 300 mg capsules and a suspension that is usually formulated at a concentration of 10 mg/mL. The shelf life of rifampin suspension is short (approximately 4 wk), so it should not be compounded with other antimycobacterial agents. An intravenous form of rifampin is also available for initial treatment of patients who cannot take oral preparations. Dosage adjustment is needed for patients with liver failure. Other rifamycins (rifabutin and rifapentine) have been poorly studied in children and are not recommended for use in children.

Rifampin can be associated with **adverse events** such as transient elevations of liver enzymes; gastrointestinal (GI) upset with cramps, nausea, vomiting, and anorexia; headache; dizziness; and immunologically mediated fever and flu-like symptoms. Thrombocytopenia and hemolytic anemias can also occur. Rifabutin has a similar spectrum of toxicities, except for an increased incidence of rash (4%) and neutropenia (2%). Rifapentine has fewer adverse effects but is associated with hyperuricemia and cytopenias, especially lymphopenia and neutropenia. All rifamycins can turn urine and other secretions (tears, saliva, stool, sputum) orange, which can stain contact lenses. Patients and families should be warned about this common but otherwise innocuous adverse effect.

Rifamycins induce the hepatic cytochrome P450 isoenzyme system and are associated with the increased metabolism and decreased level of several drugs when administered concomitantly. These drugs include digoxin, corticosteroids such as prednisone and dexamethasone, dapsone, fluconazole, phenytoin, oral contraceptives, warfarin, and many antiretroviral agents, especially protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Rifabutin has less of an effect on lowering protease inhibitor levels.

The use of pyrazinamide in combination with rifampin for short-course latent tuberculosis therapy has been associated with serious liver dysfunction and death. This combination has never been well studied or recommended for pediatric patients and should not be used.

No routine laboratory monitoring for rifamycins is indicated unless the patient is symptomatic. In patients with signs of toxicity, complete blood count (CBC) and kidney and liver function tests are indicated.

Pyrazinamide

Pyrazinamide (PZA) is a synthetic pyrazide analog of nicotinamide that is bactericidal against intracellular *M. tuberculosis* organisms in acidic environments, such as within macrophages or inflammatory lesions. A bacteria-specific enzyme (pyrazinamidase) converts PZA to pyrazinoic acid, which leads to low pH levels not tolerated by *M. tuberculosis.* Resistance is poorly understood but can arise from bacterial pyrazinamidase alterations.

PZA is indicated for the initial treatment phase of active tuberculosis in combination with other antimycobacterial agents. The pediatric dosage is 15-30 mg/kg/day PO in a single dose, not to exceed 2,000 mg/day. Twice weekly dosing with directly observed therapy only is with 50 mg/kg/day PO in a single dose, not to exceed 4,000 mg/day. It is available in a 500 mg tablet and can be made into a suspension of 100 mg/mL.

Adverse events include GI upset (e.g., nausea, vomiting, poor appetite) in approximately 4% of children, dosage-dependent hepatotoxicity, and elevated serum uric acid levels that can precipitate gout in susceptible adults. Approximately 10% of pediatric patients have elevated uric acid levels but with no associated clinical sequelae. Minor reactions include arthralgias, fatigue, and, rarely, fever.

Use of PZA in combination with rifampin for short-course treatment of latent tuberculosis is associated with serious liver dysfunction and death, and this combination should be avoided.

No routine laboratory monitoring for PZA is required, but monthly visits to reinforce the importance of therapy are desirable.

Ethambutol

Ethambutol is a synthetic form of ethylenedi-imino-di-1-butanol dihydrochloride that inhibits RNA synthesis needed for cell wall formation. At standard dosages it is bacteriostatic, but at dosages of >25 mg/kg ethambutol has bactericidal activity. The mechanism of resistance to ethambutol is unknown, but resistance develops rapidly when ethambutol is used as a single agent against *M. tuberculosis.*

Ethambutol is indicated for the treatment of infections caused by *M. tuberculosis, M. kansasii, M. bovis,* and *M. avium* complex. Ethambutol should only be used as part of a combination treatment regimen for *M. tuberculosis.* Daily dosing is 15-20 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Twice-weekly dosing is with 50 mg/kg PO in a single dose, not to exceed 2,500 mg/day. Dosage adjustment is needed in renal insufficiency. Ethambutol is available in 100 and 400 mg tablets.

The **major adverse** effect with ethambutol is optic neuritis, and thus ethambutol should generally be reserved for children old enough to have visual acuity and color discrimination reliably monitored. Visual changes are usually dosage dependent and reversible. Other adverse events include headache, dizziness, confusion, hyperuricemia, GI upset, peripheral neuropathy, hepatotoxicity, and cytopenias, especially neutropenia and thrombocytopenia.

Routine laboratory monitoring includes baseline and periodic visual acuity and color discrimination testing, CBC, serum uric acid levels, and kidney and liver function tests.

Less Commonly Used Agents

Aminoglycosides

The aminoglycosides used for mycobacterial infections include streptomycin, amikacin, kanamycin, and capreomycin. Streptomycin is isolated from *Streptomyces griseus* and was the first drug used to treat *M. tuberculosis.* Capreomycin, a cyclic polypeptide from *Streptomyces capreolus,* and amikacin, a semisynthetic derivative of kanamycin, are newer agents that are recommended when streptomycin is unavailable. Aminoglycosides act by binding irreversibly to the 30S subunit of ribosomes and inhibiting subsequent protein synthesis. Streptomycin exhibits concentration-dependent bactericidal activity, and capreomycin is bacteriostatic. Resistance results from mutation in the binding site of the 30S ribosome, by decreased transport into cells, or by inactivation by bacterial enzymes. Cross-resistance between aminoglycosides has been demonstrated.

The aminoglycosides are indicated for the treatment of *M. tuberculosis* and *M. avium* complex. All are considered second-line drugs in the treatment of *M. tuberculosis* and should be used only when resistance patterns are known. Aminoglycosides are poorly absorbed orally and are administered by IM injection. Pediatric dosing ranges for streptomycin are 20 mg/kg/day if given daily and 20-40 mg/kg/day if given twice weekly; dosing is IM in a single daily dose. Capreomycin, amikacin, and kanamycin dosages are 15-30 mg/kg/day IM in a single dose, not to exceed 1 g/day. Dosage adjustment is necessary in renal insufficiency.

Aminoglycosides have **adverse effects** on proximal renal tubules, the cochlea, and the vestibular apparatus of the ear. Nephrotoxicity and ototoxicity account for most of the significant adverse events. Rarely, patients exhibit fever or rash with the administration of aminoglycosides. Concomitant use of other nephrotoxic or ototoxic agents should be avoided, because adverse effects may be additive. An infrequent but

serious, synergistic, dosage-dependent, aminoglycoside effect with nondepolarizing neuromuscular blockade agents can result in respiratory depression or paralysis.

Hearing and kidney function should be monitored at baseline and periodically. Early signs of ototoxicity include tinnitus, vertigo, and hearing loss. Ototoxicity appears to be irreversible, but early kidney damage may be reversible. As with other aminoglycosides, peak and trough drug levels are helpful in dosing and managing early toxicities.

Cycloserine

Cycloserine, derived from *Streptomyces orchidaceus* or *Streptomyces garyphalus,* is a synthetic analog of the amino acid D-alanine that interferes with bacterial cell wall synthesis via competitive inhibition of D-alanine components to be incorporated into the cell wall. It is bacteriostatic, and the mechanism of resistance is unknown.

Cycloserine is used to treat *M. tuberculosis* and *M. bovis*. The dosage is 10-20 mg/kg/day PO divided into 2 doses, not to exceed 1g/day. It is available in a 250 mg capsule.

The major **adverse event** is neurotoxicity with significant psychologic disturbance, including seizures, acute psychosis, headache, confusion, depression, and personality changes. The neurotoxic effects are additive with ethionamide and INH. It has also been associated with megaloblastic anemia. Cycloserine must be dosage adjusted with kidney impairment. It should be used with caution in patients with underlying psychiatric illness.

Routine laboratory monitoring includes kidney and hepatic function, CBC, and cycloserine levels. Psychiatric symptoms are less common at blood levels of <30 µg/mL.

Ethionamide

Ethionamide is structurally related to INH and is an ethyl derivative of thioisonicotinamide that inhibits peptide synthesis by an unclear mechanism thought to involve nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate dehydrogenase disruptions. Ethionamide is bacteriostatic at most therapeutic levels. Resistance develops quickly if ethionamide used as a single-agent therapy, although the mechanism is unknown.

Ethionamide is used as an alternative to streptomycin or ethambutol in the treatment of *M. tuberculosis* and has some activity against *M. kansasii* and *M. avium* complex. A metabolite, ethionamide sulfoxide, is bactericidal against *M. leprae.* Ethionamide has been shown to have good central nervous system (CNS) penetration and has been used as a 4th drug in combination with rifampin, INH, and PZA. The pediatric dosing is 15-20 mg/kg/day PO in 2 divided doses, not to exceed 1 g/day. It is available as a 250 mg tablet.

GI upset is common, and other **adverse effects** include neurologic disturbances (anxiety, dizziness, peripheral neuropathy, seizures, acute psychosis), hepatic enzyme elevations, hypothyroidism, hypoglycemia, and hypersensitivity reaction with rash and fever. It should be used with caution in patients with underlying psychiatric or thyroid disease. The psychiatric adverse effects can be potentiated with concomitant use of cycloserine.

In addition to close assessment of mood, routine monitoring includes thyroid and liver function tests. In diabetic patients, blood glucose levels should be monitored.

Fluoroquinolones

The fluoroquinolones are fluorinated derivatives of the quinolone class of antibiotics. Ciprofloxacin is a first-generation fluoroquinolone, and levofloxacin is the more active l-isomer of ofloxacin. Moxifloxacin and gatifloxacin are agents with emerging use in pediatric mycobacterial disease. Fluoroquinolones are not indicated for use in children younger than 18 yr of age, but studies of their use in pediatric patients continue to indicate that they may be used in special circumstances. Fluoroquinolones are bactericidal and exert their effect via inhibition of DNA gyrase. The alterations in DNA gyrase result in relaxation of supercoiled DNA and breaks in double-stranded DNA. The mechanism of resistance is not well defined but likely involves mutations in the DNA gyrase.

Levofloxacin is an important second-line drug in the treatment of multidrug-resistant *M. tuberculosis*. Ciprofloxacin has activity against *Mycobacterium fortuitum* complex and against *M. tuberculosis*. The pediatric dosage of ciprofloxacin is 20-30 mg/kg/day PO or IV, not to exceed 1.5 mg/day PO or 800 mg/day IV. The adult dosage of ciprofloxacin is 500-750 mg/dose PO divided into 2 doses or 200-400 mg/dose IV every 12 hr. Ciprofloxacin is available in 100, 250, 500, and 750 mg tablets and can be made in 5% (50 mg/mL) or 10% (100 mg/mL) suspensions. The dosage of levofloxacin for children is 5-10 mg/kg/day given once daily either PO or IV, not to exceed 1,000 mg/day, and for adults it is 500-1,000 mg/day PO or IV, not to exceed 1,000 mg/day. Levofloxacin is available in 250, 500, and 750 mg tablets, and a 50 mg/mL suspension can be extemporaneously compounded. The suspension has a shelf life of only 8 wk.

The most common **adverse effect** of fluoroquinolones is GI upset, with nausea, vomiting, abdominal pain, and diarrhea, including pseudomembranous colitis. Other less-common adverse effects include bone marrow depression, CNS effects (e.g., lowered seizure threshold, confusion, tremor, dizziness, headache), elevated liver transaminases, photosensitivity, and arthropathies. The potential for arthropathies (e.g., tendon ruptures, arthralgias, tendinitis) is the predominant reason that fluoroquinolones are not recommended for pediatric use. The mechanism of injury appears to involve the disruption of extracellular matrix of cartilage and depletion of collagen, a particular concern related to the bone and joint development of children.

Fluoroquinolones induce the cytochrome P450 isoenzymes that can increase the concentrations of dually administered theophylline and warfarin. Nonsteroidal antiinflammatories can potentiate the CNS effects of fluoroquinolones and should be avoided while taking a fluoroquinolone. Both ciprofloxacin and levofloxacin should be dosage adjusted in patients with significant renal dysfunction.

While taking fluoroquinolones, patients should be monitored for hepatic and renal dysfunction, arthropathies, and hematologic abnormalities.

Linezolid

Linezolid is a synthetic oxazolidinone derivative. This drug is not currently approved for use against mycobacterial infection in pediatric or adult patients but has activity against some mycobacterial species. Studies on efficacy of treatment of mycobacterial infections are under way. Linezolid inhibits translation by binding to the 23S ribosomal component of the 50S ribosome subunit, preventing coupling with the 70S subunit. Resistance is thought to be from a point mutation at the binding site but is poorly studied because only a few cases of resistance have been reported.

The approved indications for linezolid are for bacterial infections other than mycobacteria, but studies reveal in vitro activity against rapidly growing mycobacteria (*M. fortuitum* complex, *Mycobacterium chelonae, Mycobacterium abscessus*), *M. tuberculosis,* and *M. avium* complex. The dosage for 0-11 yr old children is 10 mg/kg/day PO or IV in divided doses every 8-12 hr. For persons older than 12 yr of age, the dosage is 600 mg PO or IV every 12 hr. Linezolid is available in 400 and 600 mg tablets and as a 20 mg/mL suspension.

Adverse effects of linezolid include GI upset (e.g., nausea, vomiting, diarrhea), CNS disturbances (e.g., dizziness, headache, insomnia, peripheral neuropathy), lactic acidosis, fever, myelosuppression, and pseudomembranous colitis. Linezolid is a weak inhibitor of monoamine oxidase A, and patients are advised to avoid foods with high tyramine content. Linezolid should be used cautiously in patients with preexisting myelosuppression.

In addition to monitoring for GI upset and CNS perturbations, routine laboratory monitoring includes CBC at least weekly.

Paraaminosalicylic Acid

Paraaminosalicylic acid (PAS) is a structural analog of paraaminobenzoic acid (PABA). It is bacteriostatic and acts by competitively inhibiting the synthesis of folic acid similar to the action of sulfonamides. Resistance mechanisms are poorly understood.

PAS acts against *M. tuberculosis.* The dosage is 150 mg/kg/day PO in 2 or 3 divided doses. PAS is dispensed in 4 g packets, and the granules should be mixed with liquid and swallowed whole.

Common **adverse events** include GI upset, and less-common events include hypokalemia, hematuria, albuminuria, crystalluria, and elevations of hepatic transaminases. PAS can decrease the absorption of rifampin, and coadministration with ethionamide potentiates the adverse effects of PAS.

In addition to monitoring for weight loss, routine laboratory monitoring includes liver and kidney function tests.

Bedaquiline Fumarate

This oral diarylquinoline has been recommended for the treatment of multidrug resistant tuberculosis. It should be used as part of combination therapy and administered by direct observation. Although approved for patients 18 yr of age and older, it may be considered for children on a case-by-case basis. Serious side effects include hepatotoxicity and a prolonged Qt interval.

AGENTS USED AGAINST *MYCOBACTERIUM LEPRAE*

Dapsone

Dapsone is a sulfone antibiotic with characteristics similar to sulfonamides. Similar to other sulfonamides, dapsone acts as a competitive antagonist of PABA, which is needed for the bacterial synthesis of folic acid. Dapsone is bacteriostatic against *M. leprae.* Resistance is not well understood but is thought to occur after alterations at the PABA-binding site.

Dapsone is used in the treatment of *M. leprae* in combination with other antileprosy agents (rifampin, clofazimine, ethionamide). The pediatric dosage is 1-2 mg/kg/day PO as a single dose, not to exceed 100 mg/day for a duration of 3-10 yr. The adult dosage is 100 mg/day PO as a single dose. Dapsone is available in 25 and 100 mg scored tablets and as an oral suspension of 2 mg/mL. The dosage should be adjusted in renal insufficiency.

Dapsone has many reported **adverse events,** including dosage-related hemolytic anemia, especially in patients with glucose-6-phosphate dehydrogenase deficiency, pancreatitis, renal complications (acute tubular necrosis, acute renal failure, albuminuria), increased liver enzymes, psychosis, tinnitus, peripheral neuropathy, photosensitivity, and a hypersensitivity syndrome with fever, rash, hepatic damage, and malaise. A **lepra reaction** may occur with treatment, which is a nontoxic, paradoxical worsening of lepromatous leprosy with the initiation of therapy. This hypersensitivity reaction is not an indication to discontinue therapy. Dapsone should be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency or taking other folic acid antagonists. Dapsone levels can decrease with concomitant rifampin and can increase with concomitant clotrimazole.

Routine laboratory monitoring includes CBC weekly during the 1st mo of therapy, weekly through 6 mo of therapy, and then every 6 mo thereafter. Other periodic assessments include kidney function with creatine levels and urinalysis and liver function tests.

Clofazimine

Clofazimine is a synthetic phendimetrazine tartrate derivative that acts by binding to the mycobacterial DNA at guanine sites. It has a slow bactericidal activity against *M. leprae.* Mechanisms of resistance are not well studied. No cross-resistance between clofazimine and dapsone or rifampin has been shown.

Clofazimine is indicated as part of a combination therapy for the treatment of *M. leprae.* It appears there may be some activity against other mycobacteria such as *M. avium* complex, although treatment failures are common. Safety and efficacy of clofazimine are poorly studied in children. The pediatric dosage is 1 mg/kg/day PO as a single dose, not to exceed 100 mg/day in combination with dapsone and rifampin for 2 yr and then additionally as a single agent for longer than 1 yr. The adult dosage is 100 mg/day PO. It should be taken with food to increase absorption.

The most common **adverse effect** is a dosage-related, reversible pink to tan-brown discoloration of the skin and conjunctiva. Other adverse effects include a dry, itchy skin rash, headache, dizziness, abdominal pain, diarrhea, vomiting, peripheral neuropathy, and elevated hepatic transaminases.

Routine laboratory monitoring includes periodic liver function tests.

AGENTS USED AGAINST NONTUBERCULOUS MYCOBACTERIA

Cefoxitin

Cefoxitin, a cephamycin derivative, is a second-generation cephalosporin that, like other cephalosporins, inhibits cell wall synthesis by linking with penicillin-binding proteins to create an unstable bacterial cell wall. Resistance develops by alterations in penicillin-binding proteins.

Cefoxitin is often used in combination therapy for mycobacterial disease (Table 214-3). Pediatric dosing is based on disease severity, with a range of 80-160 mg/kg/day divided every 4-8 hr, not to exceed 12 g/day. Adult dosages are 1-2 g/day, not to exceed 12 g/day. Cefoxitin is available in IV or IM formulations. Increased dosing intervals are needed with renal insufficiency.

Adverse effects are primarily hematologic (eosinophilia, granulocytopenia, thrombocytopenia, hemolytic anemia), GI (nausea, vomiting, diarrhea with possible pseudomembranous colitis), and CNS-related (dizziness, vertigo). Potential additive adverse effects can occur when cefoxitin is used with aminoglycosides.

Routine laboratory monitoring with long-term use includes CBC and liver and renal function tests.

Doxycycline

Doxycycline is in the tetracycline family of antibiotics and has limited use in pediatrics. Like other tetracyclines, doxycycline acts to decrease protein synthesis by binding to the 30S ribosome and to transfer RNA. It can also cause alterations to the cytoplasmic membrane of susceptible bacteria.

Doxycycline is used to treat *M. fortuitum* (see Table 214-3). Although it can be used to treat *Mycobacterium marinum,* adult treatment failures have occurred. Pediatric dosing is based on age and weight. For children older than 8 yr of age who weigh <45 kg, the dosage is 4.4 mg/kg/day divided twice daily. Dosing for larger children and adults is 100 mg twice daily. Doxycycline is available as 50 and 100 mg capsules or tablets and in 25 mg/5 mL and 50 mg/5 mL suspensions.

Doxycycline use in children is limited by a permanent tooth discoloration, which becomes worse with long-term use. Other **adverse effects** include photosensitivity, liver and kidney dysfunction, and esophagitis, which can be minimized by dosing with large volumes of liquid. Doxycycline can decrease the effectiveness of oral contraceptives. Rifampin, carbamazepine, and phenytoin can decrease the concentration of doxycycline.

Routine laboratory monitoring with long-term use includes kidney and liver function tests as well as CBC.

Macrolides

Clarithromycin and azithromycin belong to the macrolide family of antibiotics. Clarithromycin is a methoxy derivative of erythromycin. Macrolides act by binding the 50S subunit of ribosomes, subsequently inhibiting protein synthesis. Resistance mechanisms for mycobacteria are not well understood but might involve binding site alterations. Clarithromycin appears to have synergistic antimycobacterial activity when combined with rifamycins, ethambutol, or clofazimine.

Clarithromycin is widely used for the prophylaxis and treatment of *M. avium* complex disease and also has activity against *Mycobacterium abscessus, M. fortuitum,* and *M. marinum.* Azithromycin has significantly different pharmacokinetics compared with other macrolide agents and has not been studied and is not indicated for mycobacterial infections. The pediatric dosage of clarithromycin for primary

Table 214-3 Treatment of Nontuberculous Mycobacteria Infections in Children

ORGANISM	DISEASE	TREATMENT
SLOWLY GROWING SPECIES		
Mycobacterium avium complex (MAC); *Mycobacterium haemophilum; Mycobacterium lentiflavum*	Lymphadenitis	Complete excision of lymph nodes; if excision is incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol or rifampin (or rifabutin)
	Pulmonary infection	Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults support that 3×/wk therapy is as effective as daily therapy, with less toxicity. For patients with advanced disease, drugs should be given daily
	Disseminated	See text
Mycobacterium kansasii	Pulmonary infection	Rifampin plus ethambutol with isoniazid
	Osteomyelitis	Surgical debridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid
Mycobacterium marinum	Cutaneous infection	Trimethoprim-sulfamethoxazole, clarithromycin, or doxycycline for mild disease; ethambutol with clarithromycin or rifampicin for extensive disease; extensive lesions might require surgical debridement.
Mycobacterium ulcerans	Cutaneous and bone infections	Daily intramuscular streptomycin and oral rifampin × 8 wk; excision of tissue
RAPIDLY GROWING SPECIES		
Mycobacterium fortuitum group	Cutaneous infection	Initial therapy for serious disease is amikacin plus cefoxitin or imipenem IV, followed by clarithromycin, doxycycline,* or trimethoprim-sulfamethoxazole or ciprofloxacin, orally, on the basis of in vitro susceptibility testing; might require surgical excision
	Catheter infection	Catheter removal and amikacin plus cefoxitin or imipenem, IV; clarithromycin, trimethoprim-sulfamethoxazole, or ciprofloxacin, orally, on the basis of in vitro susceptibility testing
Mycobacterium abscessus	Otitis media	Clarithromycin plus initial course of amikacin plus cefoxitin or imipenem; might require surgical debridement. Base regimen on in vitro susceptibility testing (50% are amikacin resistant)
	Pulmonary infection (in cystic fibrosis)	Serious disease, clarithromycin, amikacin, and cefoxitin on the basis of susceptibility testing; might require surgical resection
Mycobacterium chelonae	Catheter infection	Catheter removal and tobramycin (initially) plus clarithromycin
	Disseminated cutaneous infection	Tobramycin and ciprofloxacin or linezolid (initially) plus clarithromycin

*Doxycycline should not be given to children younger than 8 yr of age unless the benefits of therapy are greater than the risks of dental staining. Only 50% of isolates of *Mycobacterium marinum* are susceptible to doxycycline.

From American Thoracic Society/Infectious Disease Society of America Statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367-416, 2007.

prophylaxis of *M. avium* complex infections is 7.5 mg/kg/dose PO given twice daily, not to exceed 500 mg/day. This dosage is used for recurrent *M. avium* complex disease in combination with ethambutol and rifampin. The adult dosage is 500 mg PO twice daily to be used as a single agent for primary prophylaxis or as part of combination therapy with ethambutol and rifampin. Dosage adjustment is needed for renal insufficiency but not liver failure. Clarithromycin is available in 250 and 500 mg tablets and suspensions of 125 mg/5 mL and 250 mg/5 mL.

The primary **adverse effect** of clarithromycin is GI upset, including vomiting (6%), diarrhea (6%), and abdominal pain (3%). Other adverse effects include taste disturbances, headache, and QT prolongation if used with inhaled anesthetics, clotrimazole, antiarrhythmic agents, or azoles. Clarithromycin should be used cautiously in patients with renal insufficiency or liver failure.

Routine laboratory monitoring with prolonged use of clarithromycin includes periodic liver enzyme tests. Diarrhea is an early sign of pseudomembranous colitis.

Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX) is formulated in a fixed ratio of 1 part TMP to 5 parts SMX. SMX is a sulfonamide that inhibits synthesis of dihydrofolic acid by competitively inhibiting PABA, similar to dapsone. TMP blocks production of tetrahydrofolic acid and downstream biosynthesis of nucleic acids and protein by reversibly binding to dihydrofolate reductase. The combination of the 2 agents is synergistic and often bactericidal.

TMP-SMX is often used in combination therapy for mycobacterial disease (see Table 214-3). Oral or IV dosing for pediatric patients is TMP 15-20 mg/kg/day divided every 6-8 hr for serious infections and TMP 6-12 mg/kg/day divided every 12 hr for mild infections. The adult dosage is 160 mg TMP and 800 mg SMX every 12 hr. Dosage reduction may be needed in renal insufficiency. TMP-SMX is available in single-strength tablets (80/400 mg TMP/SMX) and double-strength tablets (160/800 mg TMP/SMX) and in a suspension of 40 mg TMP and 200 mg SMX per 5 mL.

The most common **adverse effect** with TMP-SMX is myelosuppression. It must be used with caution in patients with glucose-6-phosphate dehydrogenase deficiency. Other adverse effects include renal abnormalities, rash, aseptic meningitis, GI disturbances (e.g., pancreatitis, diarrhea), and prolonged QT interval if coadministered with inhaled anesthetics, azoles, or macrolides.

Routine laboratory monitoring includes monthly CBC and periodic electrolytes and creatinine to monitor renal function.

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Chapter 215

Tuberculosis (*Mycobacterium tuberculosis*)

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Tuberculosis has caused human disease for more than 4,000 yr and is one of the most important infectious diseases worldwide. Tuberculosis was first recognized as a clinical entity in the early 19th century by Schönlein, who used the term *tuberculosis* in 1830, which was derived from the English term "tubercle," or lesion of consumption.

ETIOLOGY

There are 5 closely related mycobacteria in the *Mycobacterium tuberculosis* complex: *M. tuberculosis, Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti,* and *Mycobacterium canetti. M. tuberculosis* is the most important cause of tuberculosis disease in humans. The tubercle bacilli are non-spore-forming, nonmotile, pleomorphic, weakly Gram-positive curved rods 1-5 µm long, typically slender and slightly bent. They can appear beaded or clumped under microscopy. They are obligate aerobes that grow in synthetic media containing glycerol as the carbon source and ammonium salts as the nitrogen source (Löwenstein-Jensen culture media). These mycobacteria grow best at 37-41°C (98.6-105.8°F), produce niacin, and lack pigmentation. A lipid-rich cell wall accounts for resistance to the bactericidal actions of antibody and complement. A hallmark of all mycobacteria is **acid fastness**—the capacity to form stable mycolate complexes with arylmethane dyes (crystal violet, carbolfuchsin, auramine, and rhodamine). They resist decoloration with ethanol and hydrochloric or other acids.

Mycobacteria grow slowly, with a generation time of 12-24 hr. Isolation from clinical specimens on solid synthetic media usually takes 3-6 wk, and drug susceptibility testing requires an additional 2-4 wk. Growth can be detected in 1-3 wk in selective liquid medium using radiolabeled nutrients (e.g., the BACTEC radiometric system), and drug susceptibilities can be determined in an additional 3-5 days. Once mycobacterial growth is detected, the species of mycobacteria present can be determined within hours using high-pressure liquid chromatography analysis (identifying the mycolic acid fingerprint of each species) or DNA probes. Restriction fragment length polymorphism profiling of mycobacteria is a helpful tool to study the epidemiology of tuberculosis strain relatedness in both outbreaks and routine epidemiology of tuberculosis in a community.

TERMINOLOGY: EXPOSURE, INFECTION, DISEASE

There are 3 major clinical stages of tuberculosis: exposure, infection, and disease. Exposure means a child has had significant contact ("shared the air") with an adult or adolescent with infectious tuberculosis but lacks proof of infection. In this stage, the tuberculin skin test (TST) or interferon-γ release assay (IGRA) result is negative, the chest radiograph is normal, the physical examination is normal, and the child lacks signs or symptoms of disease. However, the child may be infected and develop tuberculosis disease rapidly, as there may not have been enough time for the TST or IGRA to turn positive. Infection occurs when the individual inhales droplet nuclei containing *M. tuberculosis,* which survive intracellularly within the lung and associated lymphoid tissue. The hallmark of tuberculosis infection is a positive TST or IGRA result. In this stage, the child has no signs or symptoms, a normal physical examination is normal, and the chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma. Disease occurs when signs or symptoms or radiographic manifestations caused by *M. tuberculosis* become apparent. Not all infected individuals have the same risk of developing disease. An immunocompetent adult with untreated tuberculosis infection has approximately a 5-10% **lifetime** risk of developing disease. In contrast, an infected child younger than 1 yr of age has a 40% chance of developing disease within 9 mo.

EPIDEMIOLOGY

The World Health Organization estimates that tuberculosis remains the second leading cause of death from an infectious disease worldwide (after HIV) and that almost one-third of the world's population (2.5 billion people) is infected with *M. tuberculosis.* Approximately 95% of tuberculosis cases occur in the developing world. The highest numbers of cases are in Asia, Africa, and the eastern Mediterranean region. An estimated 8.7 million incident cases, 12 million prevalent cases, and 1.4 million deaths from tuberculosis occurred worldwide in 2013 (Fig. 215-1). The World Health Organization estimates that in 2013, there were 550,000 childhood cases and 80,000 tuberculosis-associated deaths among non–HIV-infected children; no estimates were given for HIV-infected children who likely bear an even greater burden of tuberculosis. The global burden of tuberculosis is influenced by several factors including: the HIV pandemic; the development of multidrug-resistant (MDR) tuberculosis; and the disproportionate access of populations in low-resource settings worldwide to both diagnostic tests and effective medical therapy.

In the United States, tuberculosis case rates decreased steadily during the first half of the 20th century, long before the advent of antituberculosis drugs, as a result of improved living conditions and, likely, genetic selection favoring persons resistant to developing disease. A resurgence of tuberculosis in the late 1980s was associated primarily with the HIV epidemic; transmission of the organism in congregate settings including healthcare institutions; disease occurring in recent immigrants; and poor conduct of community tuberculosis control. Since 1992, the number of reported cases of tuberculosis has decreased each year, reaching a record low of 9,582 cases (a rate of 3.0 cases per 100,000 persons) in 2013 (Fig. 215-2). Of the cases in 2011, 786 (6.1%) occurred in children younger than 15 yr of age (rate 1.3 per 100,000 population). Despite the overall declining rates nationwide, racial and ethnic minorities and foreign-born persons are disproportionately affected by tuberculosis in the United States. In 2011, the Centers for Disease Control and Prevention (CDC) reported that 84% of all tuberculosis cases were among ethnic minority populations. The tuberculosis case rate among Asians, blacks, and Hispanics were 25.0, 7.3, and 6.6 times as high as among non-Hispanic whites, respectively. The tuberculosis rate among foreign-born persons in the United States was 11.5 times higher than among U.S.-born persons and accounted for 62% of all tuberculosis cases in 2011 (Fig. 215-3). In the non-Hispanic white population tuberculosis rates are highest among the elderly who acquired the infection decades ago. In contrast, among nonwhite populations, tuberculosis is most common in young adults and children younger than 5 yr of age. The age range of 5-14 yr is often called the "favored age"; in all human populations, this group has the lowest rate of tuberculosis disease. Among adults, two-thirds of cases occur in men, but in children there is no significant difference by gender.

Among children in the United States, being born in a country with a high rate of tuberculosis and being a household contact to a domestic case of tuberculosis are the most important risk factors for having tuberculosis infection. Most children are infected with *M. tuberculosis* in their home by someone close to them, but outbreaks of childhood tuberculosis also have occurred in elementary and high schools, nursery schools, daycare centers and homes, churches, school buses, and sports teams. HIV-infected adults with tuberculosis can transmit *M. tuberculosis* to children, and children with HIV infection are at increased risk for developing tuberculosis after infection. Specific groups are at high risk for acquiring tuberculosis infection and progressing from latent tuberculosis infection (LTBI) to tuberculosis (Table 215-1).

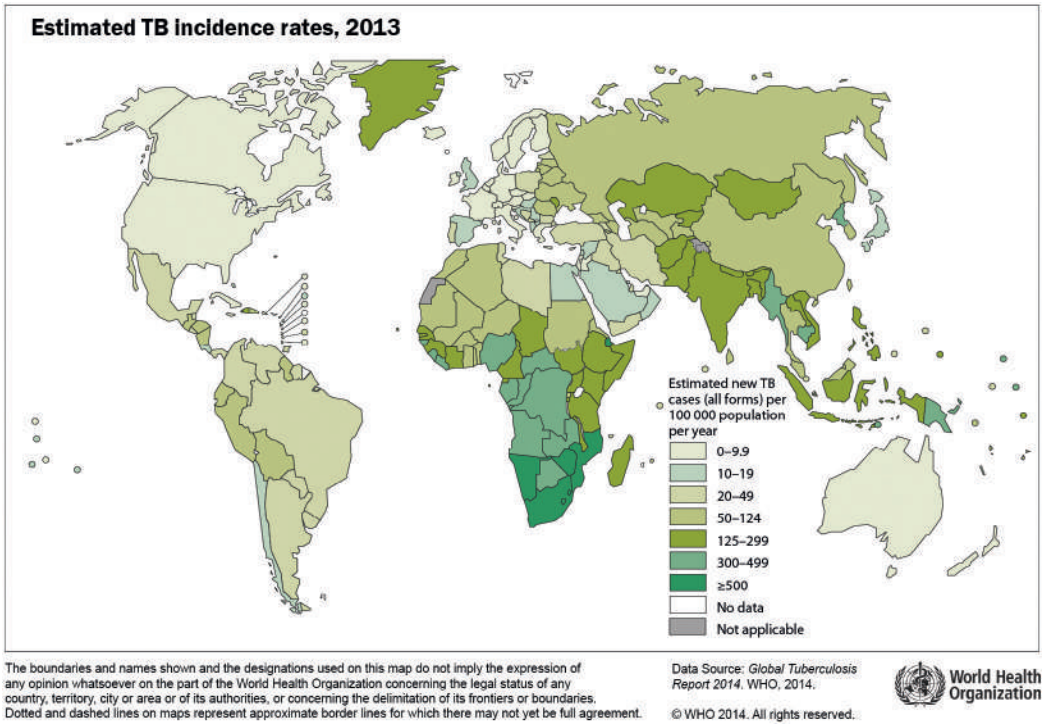

Figure 215-1 Estimated 2013 tuberculosis incidence rates. *(From The World Health Organization:* Global tuberculosis report 2014. *Geneva, 2014, World Health Organization.)*

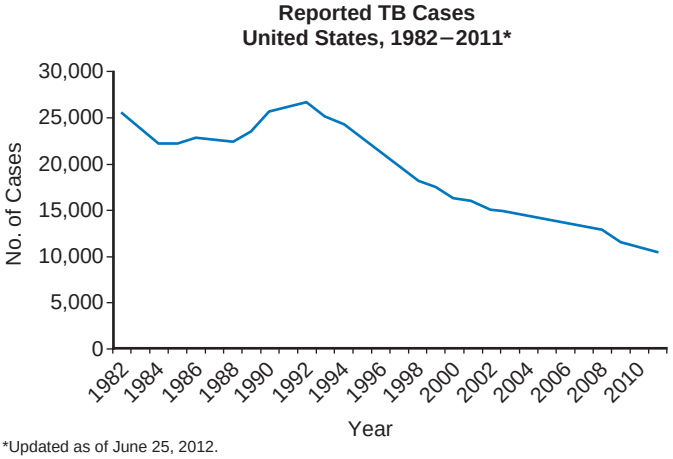

Figure 215-2 Reported tuberculosis cases in the United States for the years 1982-2011. *(From National Tuberculosis Surveillance System Highlights from 2011 an accompaniment to: Centers for Disease Control and Prevention:* Reported tuberculosis in the United States, 2011. *Atlanta, 2011, U.S. Department of Health and Human Services.)*

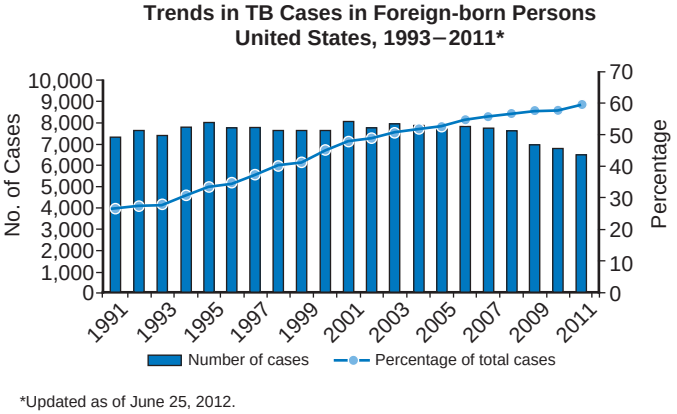

Figure 215-3 Tuberculosis cases, percentages, and case rates per 100,000 by Hispanic ethnicity and non-Hispanic race in the United States during the years 1991-2011. *(From the Centers for Disease Control and Prevention:* Reported tuberculosis in the United States, 2011. *Atlanta, 2011, U.S. Department of Health and Human Services.)*

The incidence of **drug-resistant** tuberculosis has increased dramatically throughout the world. The estimate for MDR tuberculosis is 4% globally, but rates as high as 26% have been reported in countries formerly part of the Soviet Union. A total of 127 cases of MDR tuberculosis were reported in the United States in 2011; of those, 85.8% were foreign-born (Fig. 215-4). MDR-TB is defined as resistance to at least isoniazid and rifampin; extensively drug-resistant tuberculosis includes MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable drugs (kanamycin, capreomycin, amikacin).

TRANSMISSION

Transmission of *M. tuberculosis* is usually by inhalation of airborne mucus droplet nuclei, particles 1-5 µm in diameter that contain *M. tuberculosis*. Transmission rarely occurs by direct contact with an infected discharge or a contaminated fomite. The chance of transmission increases when the patient has a positive acid-fast smear of sputum, an extensive upper lobe infiltrate or cavity, copious production of thin sputum, and severe and forceful cough. Environmental factors such as poor air circulation enhance transmission. Most adults no longer transmit the organism within several days to 2 wks after beginning adequate chemotherapy, but some patients remain infectious for many weeks. Young children with tuberculosis rarely infect other children or adults. Tubercle bacilli are sparse in the endobronchial secretions of children with pulmonary tuberculosis, and cough is often absent or lacks the tussive force required to suspend infectious particles of the correct size. Children and adolescents with adult-type cavitary or endobronchial pulmonary tuberculosis can transmit the organism.

Airborne transmission of *M. bovis* and *M. africanum* also occurs. *M. bovis* can penetrate the gastrointestinal mucosa or invade the lymphatic tissue of the oropharynx when large numbers of the organism are ingested. Human infection with *M. bovis* is rare in developed countries as a result of the pasteurization of milk and effective tuberculosis-control programs for cattle. Approximately 30% of culture-proven childhood tuberculosis cases in San Diego, California, since 1990, have been caused by *M. bovis*, likely acquired by children when visiting Mexico or another country with suboptimal veterinary tuberculosis control programs.

PATHOGENESIS

The primary complex (or Ghon complex) of tuberculosis includes local infection at the portal of entry and the regional lymph nodes that drain the area. The lung is the portal of entry in >98% of cases. The tubercle bacilli multiply initially within alveoli and alveolar ducts. Most of the bacilli are killed, but some survive within nonactivated macrophages, which carry them through lymphatic vessels to the regional lymph nodes. When the primary infection is in the lung, the hilar lymph nodes usually are involved, although an upper lobe focus can drain into paratracheal nodes. The tissue reaction in the lung parenchyma and lymph nodes intensifies over the next 2-12 wk as the organisms grow in number and tissue **hypersensitivity** develops. The parenchymal portion of the primary complex often heals completely by fibrosis or calcification after undergoing caseous necrosis and encapsulation (Fig. 215-5). Occasionally, this portion continues to enlarge, resulting in focal pneumonitis and pleuritis. If caseation is intense, the center of the lesion liquefies and empties into the associated bronchus, leaving a residual cavity.

The foci of infection in the regional lymph nodes develop some fibrosis and encapsulation, but healing is usually less complete than in the parenchymal lesion. Viable *M. tuberculosis* can persist for decades within these foci. In most cases of initial tuberculosis infection, the lymph nodes remain normal in size. However, hilar and paratracheal lymph nodes that enlarge significantly as part of the host inflammatory reaction can encroach on a regional bronchus (Figs. 215-6 and 215-7).

Table 215-1 Groups at High Risk for Acquiring Tuberculosis Infection and Developing Disease in Countries with Low Incidence

RISK FACTORS FOR TUBERCULOSIS INFECTION
Children exposed to high-risk adults
Foreign-born persons from high-prevalence countries
Homeless persons
Persons who inject drugs
Present and former residents or employees of correctional institutions, homeless shelters, and nursing homes
Healthcare workers caring for high-risk patients (if infection control is not adequate)
RISK FACTORS FOR PROGRESSION OF LATENT TUBERCULOSIS INFECTION TO TUBERCULOSIS DISEASE
Infants and children ≤4 yr of age, especially those <2 yr of age
Adolescents and young adults
Persons coinfected with HIV
Persons with skin test conversion in the past 1-2 yr
Persons who are immunocompromised, especially in cases of malignancy and solid organ transplantation, immunosuppressive medical treatments including anti–tumor necrosis factor therapies, diabetes mellitus, chronic renal failure, silicosis, and malnutrition
RISK FACTORS FOR DRUG-RESISTANT TUBERCULOSIS
Personal or contact history of treatment for tuberculosis
Contacts of patients with drug-resistant tuberculosis
Birth or residence in a country with a high rate of drug resistance
Poor response to standard therapy
Positive sputum smears (acid-fast bacilli) or culture ≥2 mo after initiating appropriate therapy

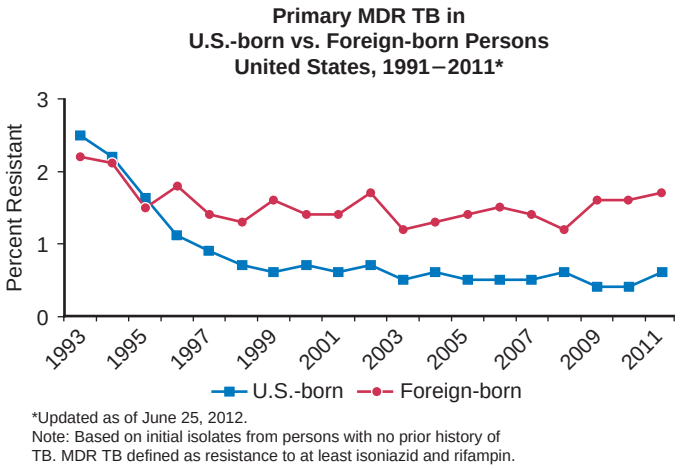

Figure 215-4 Primary isoniazid resistance in U.S.-born vs foreign-born persons in the United States during the years 1993-2011. *(From National Tuberculosis Surveillance System Highlights from 2011 an accompaniment to: Centers for Disease Control and Prevention:* Reported tuberculosis in the United States, 20011. *Atlanta, 2011, U.S. Department of Health and Human Services.)*

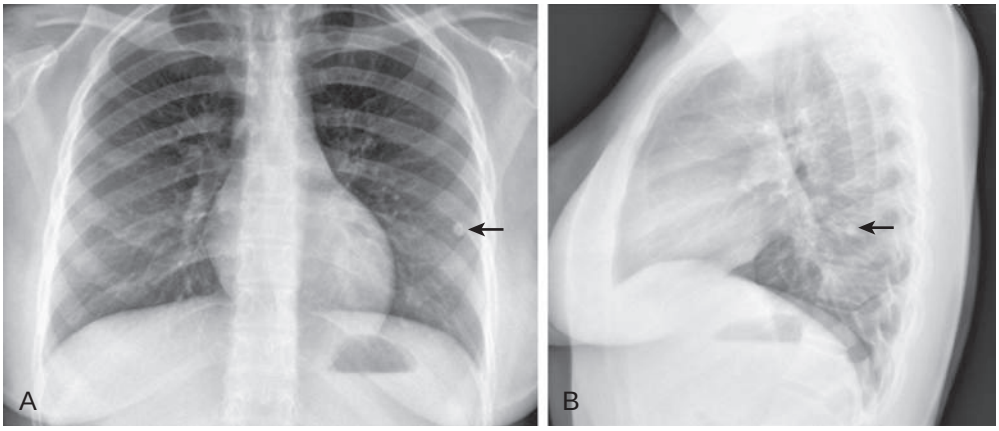

Figure 215-5 **A** and **B,** Posteroanterior and lateral chest radiograph images of an adolescent showing a 7 mm calcified granuloma in the left lower lobe *(arrows). (From Lighter J, Rigaud M: Diagnosing childhood tuberculosis: traditional and innovative modalities,* Curr Probl Pediatr Adolesc Health Care *39:55–88, 2009.)*

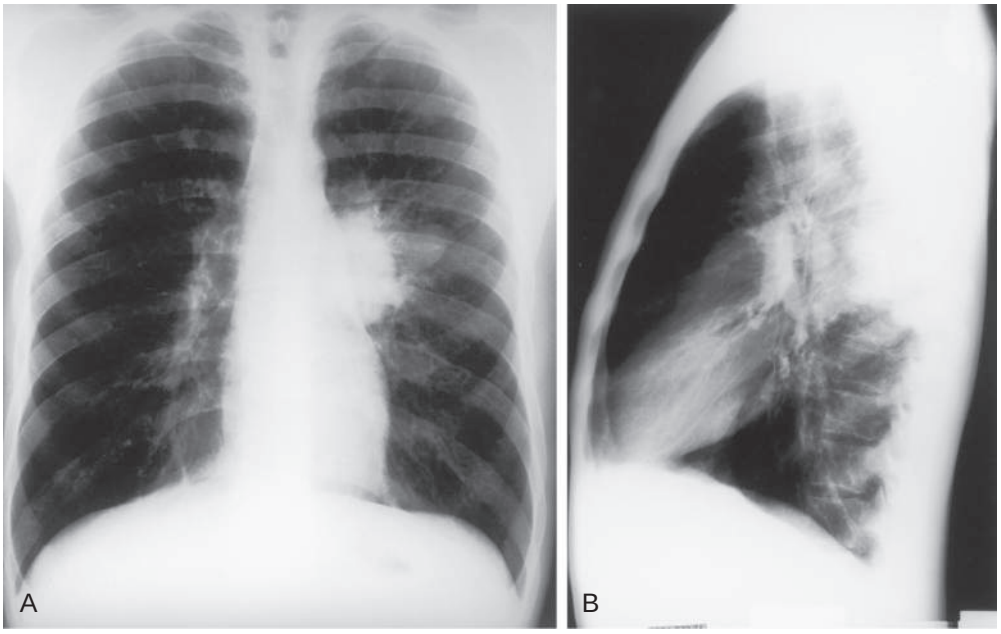

Figure 215-6 A 14 yr old child with proven primary tuberculosis. Frontal **(A)** and lateral **(B)** views of the chest show hyperinflation, prominent left hilar lymphadenopathy, and alveolar consolidation involving the posterior segment of the left upper lobe as well as the superior segment of the left lower lobe. *(From Hilton SVW, Edwards DK, editors:* Practical pediatric radiology, *ed 3, Philadelphia, 2003, Saunders, p. 334.)*

Figure 215-7 An 8 yr old child with a history of cough. A single frontal view of the chest shows marked right hilar and paratracheal lymphadenopathy with alveolar disease involving the right middle and lower lung fields. This was also a case of primary tuberculosis. *(From Hilton SVW, Edwards DK, editors:* Practical pediatric radiology, *ed 3, Philadelphia, 2003, Saunders, p. 335.)*

Figure 215-8 Right-sided hilar lymphadenopathy and collapse-consolidation lesions of primary tuberculosis in a 4 yr old child.

Partial obstruction of the bronchus caused by external compression can cause hyperinflation in the distal lung segment. Complete obstruction results in atelectasis. Inflamed caseous nodes can attach to the bronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus. The resulting lesion is a combination of pneumonitis and atelectasis and has been called a **collapse-consolidation** or **segmental lesion** (Fig. 215-8).

During the development of the **primary complex** tubercle bacilli are carried to most tissues of the body through the blood and lymphatic vessels. Although seeding of the organs of the reticuloendothelial system is common, bacterial replication is more likely to occur in organs with conditions that favor their growth, such as the lung apices, brain, kidneys, and bones. **Disseminated tuberculosis** occurs if the number of circulating bacilli is large and the host's cellular immune response is inadequate. More often the number of bacilli is small, leading to clinically inapparent metastatic foci in many organs. These remote foci usually become encapsulated, but they may be the origin of both extrapulmonary tuberculosis and reactivation pulmonary tuberculosis.

The time between initial infection and clinically apparent disease is variable. Disseminated and meningeal tuberculosis are early manifestations, often occurring within 2-6 mo of acquisition. Significant lymph node or endobronchial tuberculosis usually appears within 3-9 mo. Lesions of the bones and joints take several years to develop, whereas renal lesions become evident decades after infection. Extrapulmonary manifestations are more common in children than adults and develop in 25-35% of children with tuberculosis, compared to approximately 10% of immunocompetent adults.

Pulmonary tuberculosis that occurs more than 1 yr after the primary infection is usually caused by endogenous regrowth of bacilli persisting in partially encapsulated lesions. This reactivation tuberculosis is rare

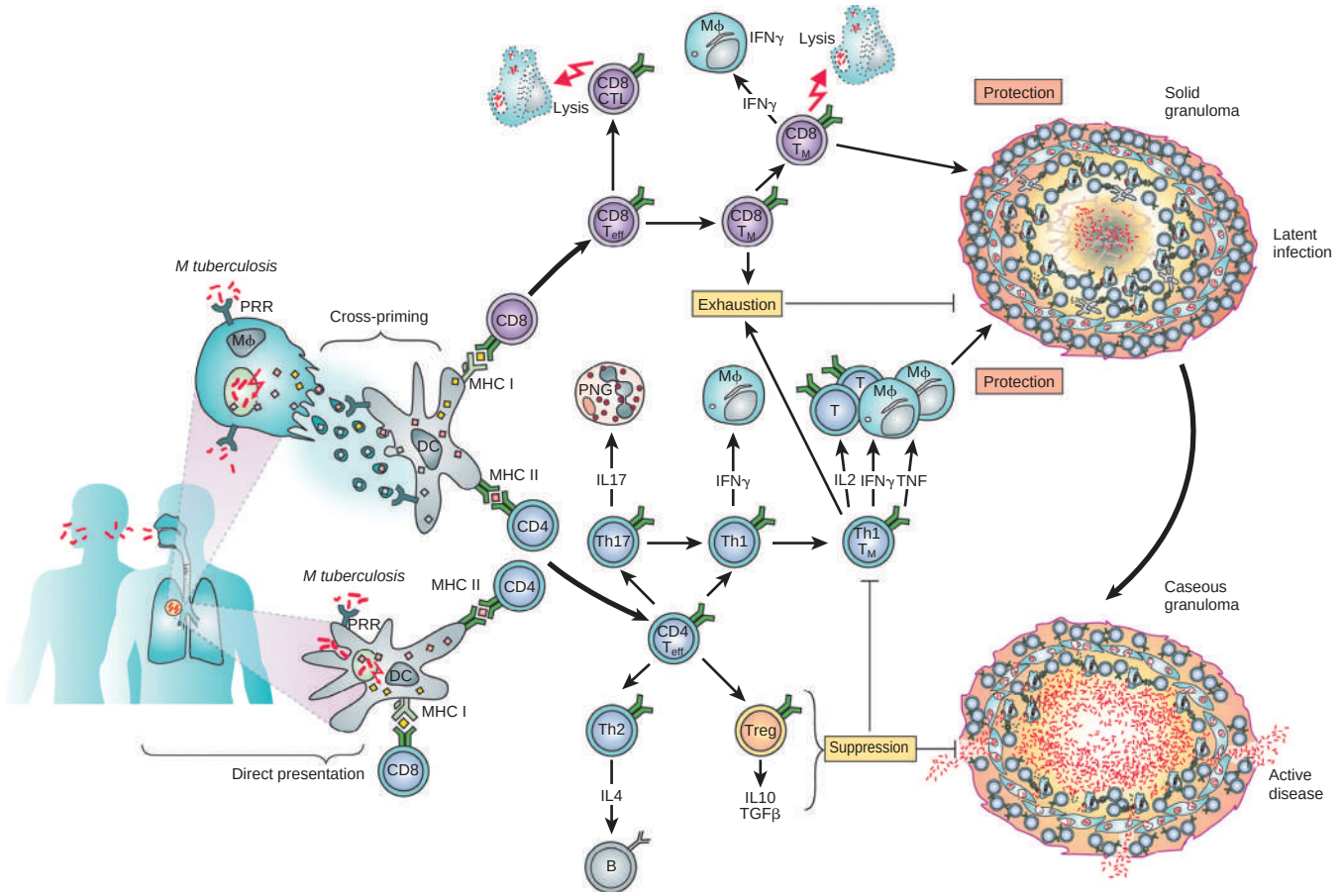

Figure 215-9 Overview of the immune response in tuberculosis. Control of *Mycobacterium tuberculosis* is mainly the result of productive teamwork between T-cell populations and macrophages (Mϕ). *M. tuberculosis* survives within macrophages and dendritic cells (DCs) inside the phagosomal compartment. Gene products of major histocompatibility complex (MHC) class II are loaded with mycobacterial peptides that are presented to CD4 T cells. CD8 T-cell stimulation requires loading of MHC I molecules by mycobacterial peptides in the cytosol, either by egression of mycobacterial antigens into the cytosol or cross-priming, by which macrophages release apoptotic bodies carrying mycobacterial peptides. These vesicles are taken up by DCs and peptides presented. The CD4 T-helper (Th) cells polarize into different subsets. DCs and macrophages express pattern recognition receptors (PRRs), which sense molecular patterns on pathogens. Th1 cells produce interleukin (IL)-2 for T-cell activation, interferon-γ (IFN-γ), or tumor necrosis factor (TNF) for macrophage activation. Th17 cells, which activate polymorphonuclear granulocytes (PNGs), contribute to the early formation of protective immunity in the lung after vaccination. Th2 cells and regulatory T cells (Treg) counterregulate Th1-mediated protection via IL4, transforming growth factor β (TGF-β), or IL-10. CD8 T cells produce IFN-γ and TNF, which activate macrophages. They also act as cytolytic T lymphocytes (CTL) by secreting perforin and granulysin, which lyse host cells and directly attack *M. tuberculosis*. These effector T cells (Teff) are succeeded by memory T cells T_M. T_M cells produce multiple cytokines, notably IL2, IFN-γ, and TNF. During active containment in solid granuloma, *M. tuberculosis* recesses into a dormant stage and is immune to attack. Exhaustion of T cells is mediated by interactions between T cells and DCs through members of the programmed death 1 system. Treg cells secrete IL-10 and TGF-β, which suppress Th1. This process allows resuscitation of *M. tuberculosis*, which leads to granuloma caseation and active disease. B, B cell. *(From Kaufman SHE, Hussey G, Lambert PH: New vaccines for tuberculosis.* Lancet *375:2110–2118, 2010.)*

in children but is common among adolescents and young adults. The most common form is an infiltrate or cavity in the apex of the upper lobes, where oxygen tension and blood flow are highest.

The risk for dissemination of *M. tuberculosis* is very high in HIV-infected persons. Reinfection also can occur in persons with advanced HIV or AIDS. In immunocompetent persons the response to the initial infection with *M. tuberculosis* usually provides protection against reinfection when a new exposure occurs. However, exogenous reinfection has been reported to occur in adults and children without immune compromise in highly endemic areas.

Immunity

Conditions that adversely affect cell-mediated immunity predispose to progression from tuberculosis infection to disease. Rare specific genetic defects associated with deficient cell-mediated immunity in response to mycobacteria include interleukin 12 receptor B1 deficiency and complete and partial interferon-γ (IFN-γ) receptor 1 chain deficiencies. Tuberculosis infection is associated with a humoral antibody response, which plays little known role in host defense. Shortly after infection, tubercle bacilli replicate in both free alveolar spaces and inactivated alveolar macrophages. Sulfatides in the mycobacterial cell wall inhibit fusion of the macrophage phagosome and lysosomes, allowing the organisms to escape destruction by intracellular enzymes. **Cell-mediated immunity** develops 2-12 wk after infection, along with tissue hypersensitivity (Fig. 215-9). After bacilli enter macrophages, lymphocytes that recognize mycobacterial antigens proliferate and secrete lymphokines and other mediators that attract other lymphocytes and macrophages to the area. Certain lymphokines activate macrophages, causing them to develop high concentrations of lytic enzymes that enhance their mycobactericidal capacity. A discrete subset of regulator helper and suppressor lymphocytes modulates the immune response. Development of specific cellular immunity prevents progression of the initial infection in most persons.

The pathologic events in the initial tuberculosis infection seem to depend on the balance among the mycobacterial antigen load; cell-mediated immunity, which enhances intracellular killing; and tissue

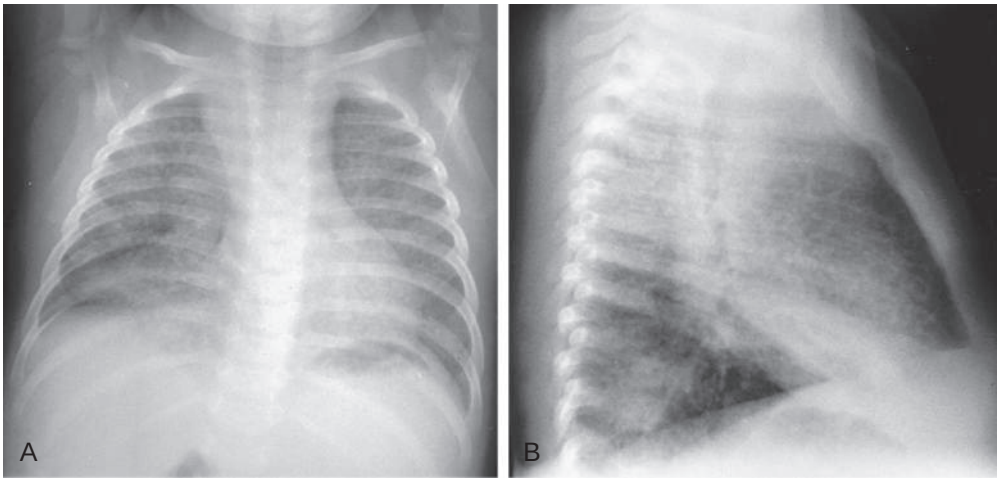

Figure 215-10 Posteroanterior **(A)** and lateral **(B)** chest radiographs of an infant with miliary tuberculosis. The child's mother had failed to complete treatment for pulmonary tuberculosis twice within 3 yr of this child's birth.

hypersensitivity, which promotes extracellular killing. When the antigen load is small and the degree of tissue sensitivity is high, granuloma formation results from the organization of lymphocytes, macrophages, and fibroblasts. When both antigen load and the degree of sensitivity are high, granuloma formation is less organized. Tissue necrosis is incomplete, resulting in formation of caseous material. When the degree of tissue sensitivity is low, as is often the case in infants or immunocompromised persons, the reaction is diffuse and the infection is not well contained, leading to dissemination and local tissue destruction. Tumor necrosis factor and other cytokines released by specific lymphocytes promote cellular destruction and tissue damage in susceptible persons.

CLINICAL MANIFESTATIONS

Primary Pulmonary Disease

The **primary complex** includes the parenchymal pulmonary focus and the regional lymph nodes. Approximately 70% of lung foci are subpleural, and localized pleurisy is common. The initial parenchymal inflammation usually is not visible on chest radiograph, but a localized, nonspecific infiltrate may be seen before the development of tissue hypersensitivity. All lobar segments of the lung are at equal risk for initial infection. Two or more primary foci are present in 25% of cases. The hallmark of primary tuberculosis in the lung is the relatively large size of the regional lymphadenitis compared with the relatively small size of the initial lung focus (see Figs. 215-6 to 215-8). As delayed-type hypersensitivity develops, the hilar lymph nodes continue to enlarge in some children, especially infants, compressing the regional bronchus and causing obstruction. The usual sequence is hilar lymphadenopathy, focal hyperinflation, and then atelectasis. The resulting radiographic shadows have been called collapse-consolidation or segmental tuberculosis (see Fig. 215-8). Rarely, inflamed caseous nodes attach to the endobronchial wall and erode through it, causing endobronchial tuberculosis or a fistula tract. The caseum causes complete obstruction of the bronchus, resulting in extensive infiltrate and collapse. Enlargement of the subcarinal lymph nodes can cause compression of the esophagus and, rarely, a bronchoesophageal fistula.

Most cases of tuberculous bronchial obstruction in children resolve fully with appropriate treatment. Occasionally, there is residual calcification of the primary focus or regional lymph nodes. The appearance of calcification implies that the lesion has been present for at least 6-12 mo. Healing of the segment can be complicated by scarring or contraction associated with cylindrical bronchiectasis, but this is rare.

Children can have lobar pneumonia without impressive hilar lymphadenopathy. If the primary infection is progressively destructive, liquefaction of the lung parenchyma can lead to formation of a thin-walled primary tuberculosis cavity. Rarely, bullous tuberculous lesions occur in the lungs and lead to pneumothorax if they rupture. Erosion of a parenchymal focus of tuberculosis into a blood or lymphatic vessel can result in dissemination of the bacilli and a **miliary pattern,** with small nodules evenly distributed on the chest radiograph (Fig. 215-10).

The symptoms and physical signs of primary pulmonary tuberculosis in children are surprisingly meager considering the degree of radiographic changes often present. When active case finding is performed, up to 50% of infants and children with radiographically moderate to severe pulmonary tuberculosis have no physical findings. Infants are more likely to experience signs and symptoms. Nonproductive cough and mild dyspnea are the most common symptoms. Systemic complaints such as fever, night sweats, anorexia, and decreased activity occur less often. Some infants have difficulty gaining weight or develop a true failure-to-thrive syndrome that often does not improve significantly until several months of effective treatment have been taken. Pulmonary signs are even less common. Some infants and young children with bronchial obstruction have localized wheezing or decreased breath sounds that may be accompanied by tachypnea or, rarely, respiratory distress. These pulmonary symptoms and signs are occasionally alleviated by antibiotics, suggesting bacterial superinfection.

Progressive Primary Pulmonary Disease

A rare but serious complication of tuberculosis in a child occurs when the primary focus enlarges steadily and develops a large caseous center. Liquefaction can cause formation of a primary cavity associated with large numbers of tubercle bacilli. The enlarging focus can slough necrotic debris into the adjacent bronchus, leading to further intrapulmonary dissemination. Significant signs or symptoms are common in locally progressive disease in children. High fever, severe cough with sputum production, weight loss, and night sweats are common. Physical signs include diminished breath sounds, rales, and dullness or egophony over the cavity. The prognosis for full recovery is excellent with appropriate therapy.

Reactivation Tuberculosis

Pulmonary tuberculosis in adults usually represents endogenous reactivation of a site of tuberculosis infection established previously in the body. This form of tuberculosis is rare in childhood but can occur in adolescence. Children with a healed tuberculosis infection acquired when they were younger than 2 yr of age rarely develop chronic reactivation pulmonary disease, which is more common in those who acquire the initial infection when they are older than 7 yr of age. The most common pulmonary sites are the original parenchymal focus, lymph nodes, or the apical seedings **(Simon foci)** established during the hematogenous phase of the early infection. This form of

tuberculosis disease usually remains localized in the lungs, as the established immune response prevents further extrapulmonary spread. The most common radiographic findings are extensive infiltrates or thick-walled cavities in the upper lobes.

Older children and adolescents with reactivation tuberculosis are more likely to experience fever, anorexia, malaise, weight loss, night sweats, productive cough, hemoptysis, and chest pain than children with primary pulmonary tuberculosis. However, physical examination findings usually are minor or absent, even when cavities or large infiltrates are present. Most signs and symptoms improve within several weeks of starting effective treatment, although the cough can last for several months. This form of tuberculosis may be highly contagious if there is significant sputum production and cough. The prognosis for full recovery is excellent with appropriate therapy.

Pleural Effusion

Tuberculous pleural effusions, which can be local or general, originate in the discharge of bacilli into the pleural space from a subpleural pulmonary focus or caseated lymph node. Asymptomatic local pleural effusion is so common in primary tuberculosis that it is considered as part of the primary complex. Larger and clinically significant effusions occur months to years after the primary infection. Tuberculous pleural effusion is uncommon in children younger than 6 yr of age and rare in children younger than 2 yr of age. Effusions are usually unilateral but can be bilateral. They are rarely associated with a segmental pulmonary lesion and are uncommon in disseminated tuberculosis. Often the radiographic abnormality is more extensive than would be suggested by physical findings or symptoms (Fig. 215-11).

Clinical onset of tuberculous pleurisy is often sudden, characterized by low to high fever, shortness of breath, chest pain on deep inspiration, and diminished breath sounds. The fever and other symptoms can last for several weeks after the start of antituberculosis chemotherapy. The TST is positive in only 70-80% of cases. The prognosis is excellent, but radiographic resolution often takes months. Scoliosis is a rare complication from a long-standing effusion.

Examination of pleural fluid and the pleural membrane is important to establish the diagnosis of tuberculous pleurisy. The pleural fluid is usually yellow and only occasionally tinged with blood. The specific gravity is usually 1.012-1.025, the protein level is usually 2-4 g/dL, and the glucose concentration may be low, although it is usually in the low-normal range (20-40 mg/dL). Typically there are several hundred to several thousand white blood cells per microliter, with an early predominance of polymorphonuclear cells followed by a high percentage of lymphocytes. Acid-fast smears of the pleural fluid are rarely positive. Cultures of the fluid are positive in <30% of cases. Biopsy of the pleural membrane is more likely to yield a positive acid-fast stain or culture, and granuloma formation can be demonstrated.

Figure 215-11 Pleural tuberculosis in a 16 yr old girl.

Pericardial Disease

The most common form of cardiac tuberculosis is pericarditis. It is rare, occurring in 0.5-4% of tuberculosis cases in children. Pericarditis usually arises from direct invasion or lymphatic drainage from subcarinal lymph nodes. The presenting symptoms are nonspecific, including low-grade fever, malaise, and weight loss. Chest pain is unusual in children. A pericardial friction rub or distant heart sounds with pulsus paradoxus may be present. The pericardial fluid is typically serofibrinous or hemorrhagic. Acid-fast smear of the fluid rarely reveals the organism, but cultures are positive in 30-70% of cases. The culture yield from pericardial biopsy may be higher, and the presence of granulomas often suggests the diagnosis. Partial or complete pericardiectomy may be required when constrictive pericarditis develops.

Lymphohematogenous (Disseminated) Disease

Tubercle bacilli are disseminated to distant sites, including liver, spleen, skin, and lung apices, in all cases of tuberculosis infection. Lymphohematogenous spread is usually asymptomatic. Rare patients experience protracted hematogenous tuberculosis caused by the intermittent release of tubercle bacilli as a caseous focus erodes through the wall of a blood vessel in the lung. The clinical picture subsequent to lymphohematogenous dissemination depends on the burden of organisms released from the primary focus to distant sites and the adequacy of the host's immune response. Although the clinical picture may be acute, more often it is indolent and prolonged, with spiking fever accompanying the release of organisms into the bloodstream. Multiple organ involvement is common, leading to hepatomegaly, splenomegaly, lymphadenitis in superficial or deep nodes, and papulonecrotic tuberculids appearing on the skin. Bones and joints or kidneys also can become involved. Meningitis occurs only late in the course of the disease. Early pulmonary involvement is surprisingly mild, but diffuse involvement becomes apparent with prolonged infection.

The most clinically significant form of disseminated tuberculosis is **miliary disease,** which occurs when massive numbers of tubercle bacilli are released into the bloodstream, causing disease in 2 or more organs. Miliary tuberculosis usually complicates the primary infection, occurring within 2-6 mo of the initial infection. Although this form of disease is most common in infants and young children, it is also found in adolescents and older adults, resulting from the breakdown of a previously healed primary pulmonary lesion. The clinical manifestations of miliary tuberculosis are protean, depending on the number of organisms that disseminate and where they lodge. Lesions are often larger and more numerous in the lungs, spleen, liver, and bone marrow than other tissues. Because this form of tuberculosis is most common in infants and malnourished or immunosuppressed patients, the host's immune incompetence likely plays a role in pathogenesis.

Rarely, the onset of miliary tuberculosis is explosive, and the patient can become gravely ill in several days. More often, the onset is insidious, with early systemic signs, including anorexia, weight loss, and low-grade fever. At this time, abnormal physical signs are usually absent. Generalized lymphadenopathy and hepatosplenomegaly develop within several weeks in approximately 50% of cases. The fever can then become higher and more sustained, although the chest radiograph usually is normal and respiratory symptoms are minor or absent. Within several more weeks, the lungs can become filled with tubercles, and dyspnea, cough, rales, or wheezing occur. The lesions of miliary tuberculosis are usually smaller than 2-3 mm in diameter when first visible on chest radiograph (see Fig. 215-10). The smaller lesions coalesce to form larger lesions and sometimes extensive infiltrates. As the pulmonary disease progresses, an alveolar-air block syndrome can result in frank respiratory distress, hypoxia, and pneumothorax, or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20-40% of patients with advanced disease. Chronic or

recurrent headache in a patient with miliary tuberculosis usually indicates the presence of meningitis, whereas the onset of abdominal pain or tenderness is a sign of tuberculous peritonitis. **Cutaneous lesions** include papulonecrotic tuberculids, nodules, or purpura. Choroid tubercles occur in 13-87% of patients and are highly specific for the diagnosis of miliary tuberculosis. Unfortunately, the TST is nonreactive in up to 40% of patients with disseminated tuberculosis.

Diagnosis of disseminated tuberculosis can be difficult, and a high index of suspicion by the clinician is required. Often the patient presents with fever of unknown origin. Early sputum or gastric aspirate cultures have a low sensitivity. Biopsy of the liver or bone marrow with appropriate bacteriologic and histologic examinations more often yields an early diagnosis. The most important clue is usually history of recent exposure to an adult with infectious tuberculosis.

The resolution of miliary tuberculosis is slow, even with proper therapy. Fever usually declines within 2-3 wk of starting chemotherapy, but the chest radiographic abnormalities might not resolve for many months. Occasionally, corticosteroids hasten symptomatic relief, especially when air block, peritonitis, or meningitis is present. The prognosis is excellent with early diagnosis and adequate chemotherapy.

Upper Respiratory Tract Disease

Tuberculosis of the upper respiratory tract is rare in developed countries but is still observed in developing countries. Children with laryngeal tuberculosis have a croup-like cough, sore throat, hoarseness, and dysphagia. Most children with laryngeal tuberculosis have extensive upper lobe pulmonary disease, but occasional patients have primary laryngeal disease with a normal chest radiograph. Tuberculosis of the middle ear results from aspiration of infected pulmonary secretions into the middle ear or from hematogenous dissemination in older children. The most common signs and symptoms are painless unilateral otorrhea, tinnitus, decreased hearing, facial paralysis, and a perforated tympanic membrane. Enlargement of lymph nodes in the preauricular or anterior cervical chains can accompany this infection. Diagnosis is difficult, because stains and cultures of ear fluid are often negative, and histology of the affected tissue often shows a nonspecific acute and chronic inflammation without granuloma formation.

Lymph Node Disease

Tuberculosis of the superficial lymph nodes, often referred to as **scrofula,** is the most common form of extrapulmonary tuberculosis in children (Fig. 215-12). Historically, scrofula was usually caused by drinking unpasteurized cow's milk laden with *M. bovis.* Most current cases occur within 6-9 mo of initial infection by *M. tuberculosis,* although some cases appear years later. The tonsillar, anterior cervical, submandibular, and supraclavicular nodes become involved secondary to extension of a primary lesion of the upper lung fields or abdomen. Infected nodes in the inguinal, epitrochlear, or axillary regions result from regional lymphadenitis associated with tuberculosis of the skin or skeletal system. The nodes usually enlarge gradually in the early stages of lymph node disease. They are discrete, nontender, and firm but not hard. The nodes often feel fixed to underlying or overlying tissue. Disease is most often **unilateral,** but bilateral involvement can occur because of the crossover drainage patterns of lymphatic vessels in the chest and lower neck. As infection progresses, multiple nodes are infected, resulting in a mass of matted nodes. Systemic signs and symptoms other than a low-grade fever are usually absent. The TST is usually reactive, but the chest radiograph is normal in 70% of cases. The onset of illness is occasionally more acute, with rapid enlargement, tenderness, and fluctuance of lymph nodes and with high fever. The initial presentation is rarely a fluctuant mass with overlying cellulitis or skin discoloration.

Lymph node tuberculosis can resolve if left untreated but more often progresses to caseation and necrosis. The capsule of the node breaks down, resulting in the spread of infection to adjacent nodes. Rupture of the node usually results in a draining sinus tract that can require surgical removal. Tuberculous lymphadenitis can usually be diagnosed by fine-needle aspiration of the node and responds well to antituberculosis therapy, although the lymph nodes do not return to normal size

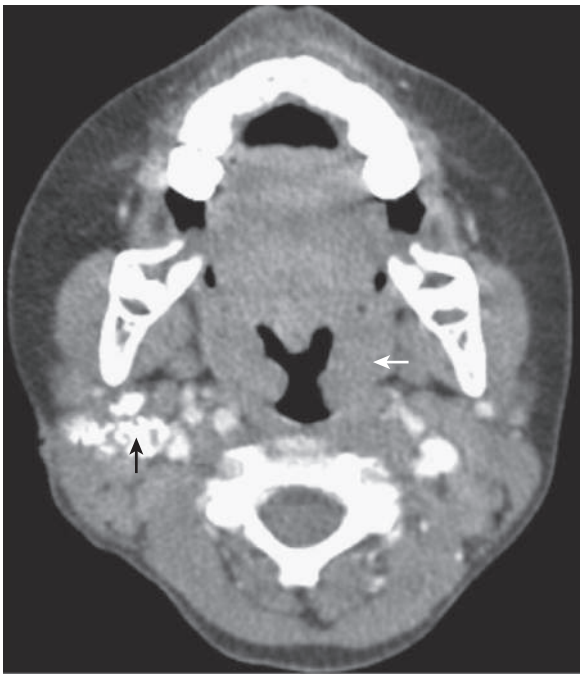

Figure 215-12 Axial CT image of the neck in an 8 yr old boy shows calcified right cervical lymphadenopathy *(black arrow)* with tonsillar swelling *(white arrow). (From Lighter J, Rigaud M: Diagnosing childhood tuberculosis: traditional and innovative modalities,* Curr Probl Pediatr Adolesc Health Care *39:55–88, 2009.)*

for months or even years. Surgical removal is not usually necessary and must be combined with antituberculosis medication, as the lymph node disease is only 1 part of a systemic infection.

A definitive diagnosis of tuberculous adenitis usually requires histologic or bacteriologic confirmation, which is best accomplished by fine-needle aspiration for culture, stain, and histology. If fine-needle aspiration is not successful in establishing a diagnosis, excisional biopsy of the involved node is indicated. Culture of lymph node tissue yields the organism in only approximately 50% of cases. Many other conditions can be confused with tuberculous adenitis, including infection caused by nontuberculous mycobacteria (NTM), cat-scratch disease *(Bartonella henselae),* tularemia, brucellosis, toxoplasmosis, pyogenic infection, or noninfectious causes, including tumor, branchial cleft cyst, and cystic hygroma. The most common problem is distinguishing infection caused by *M. tuberculosis* from lymphadenitis caused by NTM in geographic areas where NTM are common. Both conditions are usually associated with a normal chest radiograph and a reactive TST. An important clue to the diagnosis of tuberculous adenitis is an epidemiologic link to an adult with infectious tuberculosis. In areas where both diseases are common, culture of the involved tissue may be necessary to establish the exact cause of the disease.

Central Nervous System Disease

Tuberculosis of the central nervous system (CNS) is the most serious complication in children and is fatal without prompt and appropriate treatment. Tuberculous meningitis usually arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. This initial lesion increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate infiltrates the corticomeningeal blood vessels, producing inflammation, obstruction, and subsequent infarction of cerebral cortex. The brainstem is often the site of greatest involvement, which accounts for the commonly associated dysfunction of cranial nerves III, VI, and VII. The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular

system at the level of the basilar cisterns, leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in the severe damage that can occur gradually or rapidly. Profound abnormalities in electrolyte metabolism from salt wasting or the syndrome of inappropriate antidiuretic hormone secretion also contribute to the pathophysiology of tuberculous meningitis.

Tuberculous meningitis complicates approximately 0.3% of untreated tuberculosis infections in children. It is most common in children between 6 mo and 4 yr of age. Occasionally, tuberculous meningitis occurs many years after the infection, when rupture of 1 or more of the subependymal tubercles discharges tubercle bacilli into the subarachnoid space. The clinical progression of tuberculous meningitis may be rapid or gradual. Rapid progression tends to occur more often in infants and young children, who can experience symptoms for only several days before the onset of acute hydrocephalus, seizures, and cerebral edema. More commonly, the signs and symptoms progress slowly over weeks and are divided into 3 stages.

The **1st stage** typically lasts 1-2 wk and is characterized by nonspecific symptoms such as fever, headache, irritability, drowsiness, and malaise. Focal neurologic signs are absent, but infants can experience a stagnation or loss of developmental milestones. The **2nd stage** usually begins more abruptly. The most common features are lethargy, nuchal rigidity, seizures, positive Kernig and Brudzinski signs, hypertonia, vomiting, cranial nerve palsies, and other focal neurologic signs. The accelerating clinical illness usually correlates with the development of hydrocephalus, increased intracranial pressure, and vasculitis. Some children have no evidence of meningeal irritation but can have signs of encephalitis, such as disorientation, movement disorders, or speech impairment. The **3rd stage** is marked by coma, hemi- or paraplegia, hypertension, decerebrate posturing, deterioration of vital signs, and eventually death.

The prognosis of tuberculous meningitis correlates most closely with the clinical stage of illness at the time treatment is initiated. The majority of patients in the 1st stage have an excellent outcome, whereas most patients in the 3rd stage who survive have permanent disabilities, including blindness, deafness, paraplegia, diabetes insipidus, or mental retardation. The prognosis for young infants is generally worse than for older children. It is imperative that antituberculosis treatment be considered for any child who develops basilar meningitis and hydrocephalus, cranial nerve palsy, or stroke with no other apparent etiology. Often the key to the correct diagnosis is identifying an adult who has infectious tuberculosis and is in contact with the child. Because of the short incubation period of tuberculous meningitis, the illness has not yet been diagnosed in the adult in many cases.

The diagnosis of tuberculous meningitis can be difficult early in its course, requiring a high degree of suspicion on the part of the clinician. The TST is nonreactive in up to 50% of cases, and 20-50% of children have a normal chest radiograph. The most important laboratory test for the diagnosis of tuberculous meningitis is examination and culture of the lumbar CSF. The CSF leukocyte count usually ranges from 10-500 cells/μL. Polymorphonuclear leukocytes may be present initially, but lymphocytes predominate in the majority of cases. The CSF glucose is typically <40 mg/dL but rarely <20 mg/dL. The protein level is elevated and may be markedly high (400-5,000 mg/dL) secondary to hydrocephalus and spinal block. Although the lumbar CSF is grossly abnormal, ventricular CSF can have normal chemistries and cell counts because this fluid is obtained from a site proximal to the inflammation and obstruction. During early stage 1, the CSF can resemble that of viral aseptic meningitis only to progress to the more-severe CSF profile over several weeks. The success of the microscopic examination of acid-fast–stained CSF and mycobacterial culture is related directly to the volume of the CSF sample. Examinations or culture of small amounts of CSF are unlikely to demonstrate *M. tuberculosis.* When 5-10 mL of lumbar CSF can be obtained, the acid-fast stain of the CSF sediment is positive in up to 30% of cases and the culture is positive in 50-70% of cases. Polymerase chain reaction (PCR) testing of the CSF can improve diagnosis. Cultures of other body fluids can help confirm the diagnosis.

Figure 215-13 MRI of brain of a 3 yr old child showing multiple pontine tuberculomas.

Radiographic studies can aid in the diagnosis of tuberculous meningitis. CT or MRI of the brain of patients with tuberculous meningitis may be normal during early stages of the disease. As disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings. Some small children with tuberculous meningitis have one or several clinically silent tuberculomas, occurring most often in the cerebral cortex or thalamic regions.

Another manifestation of CNS tuberculosis is the **tuberculoma,** a tumor-like mass resulting from aggregation of caseous tubercles that usually manifests clinically as a brain tumor. Tuberculomas account for up to 30% of brain tumors in some areas of the world but are rare in North America. In adults tuberculomas are most often supratentorial, but in children they are often infratentorial, located at the base of the brain near the cerebellum (Fig. 215-13). Lesions are most often singular but may be multiple. The most common symptoms are headache, fever, focal neurologic findings, and convulsions. The TST is usually reactive, but the chest radiograph is usually normal. Surgical excision is sometimes necessary to distinguish tuberculoma from other causes of brain tumor. However, surgical removal is not necessary because most tuberculomas resolve with medical management. Corticosteroids are usually administered during the 1st few wk of treatment or in the immediate postoperative period to decrease cerebral edema. On CT or MRI of the brain, tuberculomas usually appear as discrete lesions with a significant amount of surrounding edema. Contrast medium enhancement is often impressive and can result in a ring-like lesion. Since the advent of CT, the paradoxical development of tuberculomas in patients with tuberculous meningitis who are receiving ultimately effective chemotherapy has been recognized. The cause and nature of these tuberculomas are poorly understood, but they do not represent failure of antimicrobial treatment. This phenomenon should be considered whenever a child with tuberculous meningitis deteriorates or develops focal neurologic findings while on treatment. Corticosteroids can alleviate the occasionally severe clinical signs and symptoms that occur. These lesions can persist for months or years.

Cutaneous Disease

Cutaneous tuberculosis is rare in the United States, but occurs worldwide and accounts for 1-2% of tuberculosis (see Chapter 665).

Bone and Joint Disease

Bone and joint infection complicating tuberculosis is most likely to involve the vertebrae. The classic manifestation of tuberculous spondylitis is progression to Pott disease, in which destruction of the vertebral bodies leads to gibbus deformity and kyphosis (see Chapter 679.4). Skeletal tuberculosis is a late complication of tuberculosis and has become a rare entity since the availability of antituberculosis therapy but is more likely to occur in children than in adults. Tuberculous bone lesions can resemble pyogenic and fungal infections or bone tumors. Multifocal bone involvement can occur. A bone biopsy is essential to confirm the diagnosis. Surgical intervention is generally not necessary for cure and prognosis is excellent with adequate medical treatment.

Abdominal and Gastrointestinal Disease

Tuberculosis of the oral cavity or pharynx is quite unusual. The most common lesion is a painless ulcer on the mucosa, palate, or tonsil with enlargement of the regional lymph nodes. Tuberculosis of the parotid gland has been reported rarely in endemic countries. Tuberculosis of the esophagus is rare in children but may be associated with a tracheoesophageal fistula in infants. These forms of tuberculosis are usually associated with extensive pulmonary disease and swallowing of infectious respiratory secretions. They can occur in the absence of pulmonary disease, by spread from mediastinal or peritoneal lymph nodes.

Tuberculous peritonitis occurs most often in young men and is uncommon in adolescents and rare in children. Generalized peritonitis can arise from subclinical or miliary hematogenous dissemination. Localized peritonitis is caused by direct extension from an abdominal lymph node, intestinal focus, or genitourinary tuberculosis. Rarely, the lymph nodes, omentum, and peritoneum become matted and can be palpated as a doughy irregular nontender mass. Abdominal pain or tenderness, ascites, anorexia, and low-grade fever are typical manifestations. The TST is usually reactive. The diagnosis can be confirmed by paracentesis with appropriate stains and cultures, but this procedure must be performed carefully to avoid entering a bowel that is adherent to the omentum.

Tuberculous enteritis is caused by hematogenous dissemination or by swallowing tubercle bacilli discharged from the patient's own lungs. The jejunum and ileum near Peyer patches and the appendix are the most common sites of involvement. The typical findings are shallow ulcers that cause pain, diarrhea or constipation, weight loss, and low-grade fever. Mesenteric adenitis usually complicates the infection. The enlarged nodes can cause intestinal obstruction or erode through the omentum to cause generalized peritonitis. The clinical presentation of tuberculous enteritis is nonspecific, mimicking other infections and conditions that cause diarrhea. The disease should be suspected in any child with chronic gastrointestinal complaints and a reactive TST or positive IGRA. Biopsy, acid-fast stain, and culture of the lesions are usually necessary to confirm the diagnosis.

Genitourinary Disease

Renal tuberculosis is rare in children, because the incubation period is several years or longer. Tubercle bacilli usually reach the kidney during lymphohematogenous dissemination. The organisms often can be recovered from the urine in cases of miliary tuberculosis and in some patients with pulmonary tuberculosis in the absence of renal parenchymal disease. In true renal tuberculosis, small caseous foci develop in the renal parenchyma and release *M. tuberculosis* into the tubules. A large mass develops near the renal cortex that discharges bacteria through a fistula into the renal pelvis. Infection then spreads locally to the ureters, prostate, or epididymis. Renal tuberculosis is often clinically silent in its early stages, marked only by sterile pyuria and microscopic hematuria. Dysuria, flank or abdominal pain, and gross hematuria develop as the disease progresses. Superinfection by other bacteria is common and can delay recognition of the underlying tuberculosis. Hydronephrosis or ureteral strictures can complicate the disease. Urine cultures for *M. tuberculosis* are positive in 80-90% of cases, and acid-fast stains of large volumes of urine sediment are positive in 50-70% of cases. The TST is nonreactive in up to 20% of patients. A pyelogram or CT scan often reveals mass lesions, dilation of the proximal ureters, multiple small filling defects, and hydronephrosis if ureteral stricture is present. Disease is most often unilateral.

Tuberculosis of the genital tract is uncommon in prepubescent boys and girls. This condition usually originates from lymphohematogenous spread, although it can be caused by direct spread from the intestinal tract or bone. Adolescent girls can develop genital tract tuberculosis during the primary infection. The fallopian tubes are most often involved (90-100% of cases), followed by the endometrium (50%), ovaries (25%), and cervix (5%). The most common symptoms are lower abdominal pain and dysmenorrhea or amenorrhea. Systemic manifestations are usually absent, and the chest radiograph is normal in the majority of cases. The TST is usually reactive. Genital tuberculosis in adolescent boys causes epididymitis or orchitis. The condition usually manifests as a unilateral nodular painless swelling of the scrotum. Involvement of the glans penis is extremely rare. Genital abnormalities and a positive TST in an adolescent boy or girl suggest genital tract tuberculosis.

Pregnancy and the Newborn

Pulmonary and particularly extrapulmonary tuberculosis other than lymphadenitis in a pregnant woman is associated with increased risk for prematurity, fetal growth retardation, low birthweight, and perinatal mortality. Congenital tuberculosis is rare because the most common result of female genital tract tuberculosis is infertility. Primary infection in the mother just before or during pregnancy is more likely to cause congenital infection than is reactivation of a previous infection. Congenital transmission usually occurs from a lesion in the placenta through the umbilical vein, when tubercle bacilli infect the fetal liver, where a primary focus with periportal lymph node involvement can occur. Organisms pass through the liver into the main fetal circulation and infect many organs. The bacilli in the lung usually remain dormant until after birth, when oxygenation and pulmonary circulation increase significantly. Congenital tuberculosis can also be caused by aspiration or ingestion of infected amniotic fluid. However, the most common route of infection for the neonate is postnatal airborne transmission from an adult with infectious pulmonary tuberculosis.

Perinatal Disease

Symptoms of congenital tuberculosis may be present at birth but more commonly begin by the 2nd or 3rd wk of life. The most common signs and symptoms are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions. The clinical manifestations vary in relation to the site and size of the caseous lesions. Many infants have an abnormal chest radiograph, most often with a miliary pattern. Some infants with no pulmonary findings early in the course of the disease later develop profound radiographic and clinical abnormalities. Hilar and mediastinal lymphadenopathy and lung infiltrates are common. Generalized lymphadenopathy and meningitis occur in 30-50% of patients.

The clinical presentation of tuberculosis in newborns is similar to that caused by bacterial sepsis and other congenital infections, such as syphilis, toxoplasmosis, and cytomegalovirus. The diagnosis should be suspected in an infant with signs and symptoms of bacterial or congenital infection whose response to antibiotic and supportive therapy is poor and in whom evaluation for other infections is unrevealing. The most important clue for rapid diagnosis of congenital tuberculosis is a maternal or family history of tuberculosis. Often, the mother's disease is discovered only after the neonate's diagnosis is suspected. The infant's TST is negative initially but can become positive in 1-3 mo. A positive acid-fast stain of an early morning gastric aspirate from a newborn usually indicates tuberculosis. Direct acid-fast stains on middle-ear discharge, bone marrow, tracheal aspirate, or biopsy tissue (especially liver) can be useful. The CSF should be examined, cultured and sent for PCR testing. The mortality rate of congenital tuberculosis remains very high because of delayed diagnosis; many children have a complete recovery if the diagnosis is made promptly and adequate chemotherapy is started.

Disease in HIV-Infected Children

Most cases of tuberculosis in HIV-infected children are seen in developing countries. However, the rate of tuberculosis disease in untreated HIV-infected children is 30 times higher than in non–HIV-infected children in the United States. Establishing the diagnosis of tuberculosis in an HIV-infected child may be difficult, because TST reactivity can be absent (also with a negative IGRA), culture confirmation is difficult, and the clinical features of tuberculosis are similar to many other HIV-related infections and conditions. Tuberculosis in HIV-infected children is often more severe, progressive, and likely to occur in extrapulmonary sites. Radiographic findings are similar to those in children with normal immune systems, but lobar disease and lung cavitation are more common. Nonspecific respiratory symptoms, fever, and weight loss are the most common complaints. Rates of drug-resistant tuberculosis tend to be higher in HIV-infected adults and probably are also higher in HIV-infected children. Recurrent disease and relapse occur more frequently in HIV-infected children. The prognosis generally is good if tuberculosis disease is not far advanced at diagnosis and appropriate antituberculosis drugs are available.

The mortality rate of HIV-infected children with tuberculosis is high, especially as the CD4 lymphocyte numbers decrease. In adults, the host immune response to tuberculosis infection appears to enhance HIV replication and accelerate the immune suppression caused by HIV. Increased mortality rates are attributed to progressive HIV infection rather than tuberculosis. Therefore, HIV-infected children with potential exposures and/or recent infection should be promptly evaluated and treated for tuberculosis. Conversely, all children with tuberculosis disease should be tested for HIV infection.

Children with HIV infection who are given highly active antiretroviral therapy (HAART) are at high risk of developing immune reconstitution inflammatory syndrome (IRIS). IRIS should be suspected in patients who experience a worsening of tuberculosis symptoms while on antituberculosis therapy (paradoxical IRIS) or who develop new-onset tuberculosis symptoms and radiographic findings after initiation of HAART (unmasking IRIS). Factors suggesting IRIS are temporal association (within 3 mo of starting HAART), unusual clinical manifestations, unexpected clinical course, exclusion of alternative explanations, evidence of preceding immune restoration (rise in CD4 lymphocyte count), and fall in HIV viral load.

The most common clinical manifestations of IRIS in children are fever, cough, new skin lesions, enlarging lymph nodes in the thorax or neck, and appearance or enlargement of tuberculomas in the brain, with or without accompanying meningitis. The treatment of IRIS in HIV-positive children with tuberculosis should be undertaken by a clinician with specific expertise in the treatment of tuberculosis.

DIAGNOSTIC TOOLS

Tuberculin Skin Testing

The development of delayed-type hypersensitivity in most persons infected with the tubercle bacillus makes the TST a useful diagnostic tool. The **Mantoux TST** is the intradermal injection of 0.1 mL purified protein derivative stabilized with Tween 80. T cells sensitized by prior infection are recruited to the skin, where they release lymphokines that induce induration through local vasodilation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area. The amount of induration in response to the test should be measured by a trained person 48-72 hr after administration. In some patients, the onset of induration is longer than 72 hr after placement; this is also a positive result. Immediate hypersensitivity reactions to tuberculin or other constituents of the preparation are short-lived (<24 hr) and not considered a positive result. Tuberculin sensitivity develops 3 wk to 3 mo (most often in 4-8 wk) after inhalation of organisms.

Host-related factors, including very young age, malnutrition, immunosuppression by disease or drugs, viral infections (measles, mumps, varicella, influenza), vaccination with live-virus vaccines, and overwhelming tuberculosis, can depress the skin test reaction in a child infected with *M. tuberculosis.* Corticosteroid therapy can decrease the reaction to tuberculin, but the effect is variable. TST done at the time of initiating corticosteroid therapy is usually reliable. Approximately 10% of immunocompetent children with tuberculosis disease (up to 50% of those with meningitis or disseminated disease) do not react initially to purified protein derivative; most become reactive after several months of antituberculosis therapy. False-positive reactions to tuberculin can be caused by cross-sensitization to antigens of NTM, which generally are more prevalent in the environment as one approaches the equator. These crossreactions are usually transient over months to years and produce <10-12 mm of induration. Previous vaccination with bacille Calmette-Guérin (BCG) also can cause a reaction to a TST, especially if a person has received 2 or more BCG vaccinations. Approximately 50% of the infants who receive a BCG vaccine never develop a reactive TST, and the reactivity usually wanes in 2-3 yr in those with initially positive skin test results. Older children and adults who receive a BCG vaccine are more likely to develop tuberculin reactivity, but most lose the reactivity by 5-10 yr after vaccination. When skin test reactivity is present, it usually causes <10 mm of induration, although larger reactions occur in some persons.

The appropriate size of induration indicating a positive Mantoux TST result varies with related epidemiologic and risk factors. In children with no risk factors for tuberculosis, skin test reactions are usually false-positive results. The American Academy of Pediatrics and the CDC discourage routine testing of all children and recommend targeted tuberculin testing of children at risk identified through periodic screening questionnaires (see Tables 215-1 and 215-2). Possible exposure to an adult with or at high risk for infectious pulmonary

Table 215-2 Tuberculin Skin Test Recommendations for Infants, Children, and Adolescents*

CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED†: • Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation) • Children with radiographic or clinical findings suggesting tuberculosis disease • Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries from the former Soviet Union), including international adoptees • Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries‡ • Children who should have annual TST or IGRA: • Children infected with HIV
CHILDREN AT INCREASED RISK FOR PROGRESSION OF LTBI TO TUBERCULOSIS DISEASE Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies deserve special consideration. Without recent exposure, these children are not at increased risk of acquiring tuberculosis infection. Underlying immunodeficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST should be considered. **An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged steroid administration, use of tumor necrosis factor-α antagonists, or immunosuppressive therapy in any child requiring these treatments.**

*Bacille Calmette-Guérin immunization is not a contraindication to a TST.

†Beginning as early as 3 mo of age.

‡If the child is well and has no history of exposure, the TST or IGRA should be delayed up to 10 wk after return.

HIV, human immunodeficiency virus; IGRA indicates interferon-γ release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 740.*

Table 215-3 Definitions of Positive Tuberculin Skin Test Results in Infants, Children, and Adolescents*

INDURATION ≥5 MM
Children in close contact with known or suspected contagious people with tuberculosis disease
Children suspected to have tuberculosis disease:
• Findings on chest radiograph consistent with active or previously tuberculosis disease
• Clinical evidence of tuberculosis disease†
Children receiving immunosuppressive therapy‡ or with immunosuppressive conditions, including HIV infection
INDURATION ≥10 MM
Children at increased risk of disseminated tuberculosis disease:
• Children younger than 4 yr of age
• Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 215-2)
Children with increased exposure to tuberculosis disease:
• Children born in high-prevalence regions of the world
• Children often exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers
• Children who travel to high-prevalence regions of the world
INDURATION ≥15 MM
Children ≥4 yr of age without any risk factors

*These definitions apply regardless of previous bacille Calmette-Guérin (BCG) immunization; erythema at TST site does not indicate a positive test result. Tests should be read at 48-72 hr after placement.

†Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).

‡Including immunosuppressive doses of corticosteroids or tumor necrosis factor-α antagonists.

HIV, human immunodeficiency virus; TST, tuberculin skin test.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 737.*

Table 215-4 Recommendations for Use of the Tuberculin Skin Test and an Interferon-γ Release Assay in Children

TST preferred, IGRA acceptable
• Children <5 yr of age*
IGRA preferred, TST acceptable
• Children >5 yr of age who have received the BCG vaccine
• Children >5 yr of age who are unlikely to return for TST reading
TST and IGRA should be considered when:
• The initial and repeat IGRA are indeterminate
• The initial test (TST or IGRA) is negative and:
• Clinical suspicion for tuberculosis disease is moderate to high†
• Risk of progression and poor outcome is high†
• The initial TST is positive and:
• >5 yr of age and history of BCG vaccination
• Additional evidence needed to increase compliance
• Nontuberculous mycobacterial disease is suspected

*Positive result of either test is considered significant in these groups.

†IGRAs should not be used in children younger than 2 yr of age unless tuberculosis disease is suspected. In children 2-4 yr of age, there are limited data about the usefulness of IGRAs in determining tuberculosis infection, but IGRA testing can be performed if tuberculosis disease is suspected.

IGRA indicates interferon-γ release assay; TST, tuberculin skin test.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 744.*

tuberculosis is the most crucial risk factor for children. Reaction size limits for determining a positive tuberculin test result vary with the person's risk for infection (Table 215-3). In those at highest risk of progression to tuberculosis disease, TST sensitivity is most important whereas specificity is more important for persons at low risk of progression.

Interferon-γ Release Assays

Two blood tests (T-SPOT.*TB* and QuantiFERON-TB) detect IFN-γ generation by the patient's T cells in response to specific *M. tuberculosis* antigens (ESAT-6, CFP-10, and TB7.7). The QuantiFERON-TB test measures whole blood concentrations of IFN-γ, and the T-SPOT.*TB* test measures the number of lymphocytes/monocytes producing IFN-γ. The test antigens are not present on *M. bovis*–BCG and *Mycobacterium avium* complex, the major group of environmental mycobacteria, so one would expect higher specificity compared with the TST and fewer false-positive results. Both IGRAs have internal positive and negative controls. Like the TST, IGRAs cannot differentiate between tuberculosis infection and disease. Two clear advantages of the IGRAs are the need for only 1 patient encounter (vs 2 with the TST) and the lack of crossreaction with BCG vaccination and most other mycobacteria.

IGRAs should be interpreted with caution when used for children younger than 5 yr of age and immunocompromised patients owing to the relative lack of data and the increased propensity for indeterminate results in these groups, making TSTs preferred in these populations. IGRAs are preferred and TSTs are considered acceptable in the BCG-immunized older child (≥5 yr) and in those ≥5 yr who are unlikely to return for TST reading. Both TST and IGRA testing should be obtained in children with an indeterminate initial and repeat IGRA testing; in those in whom initial TST or IGRA testing is negative and the suspicion for tuberculosis disease or risk of progression to disease is high; in those ≥5 yr who have a positive TST and have received the BCG vaccine; in those whose family is reluctant to treat infection based on a TST result alone; and in those in whom nontuberculous mycobacterial disease is suspected (Table 215-4). As most studies have not shown a consistent, significant difference between the IGRAs, the CDC recommends that the assays may be used interchangeably.

MYCOBACTERIAL SAMPLING, SUSCEPTIBILITY AND CULTURE

The most specific confirmation of pulmonary tuberculosis is isolation of *M. tuberculosis* from a clinical sample. Sputum specimens for culture should be collected from adolescents and older children who are able to expectorate. Induced sputum with a jet nebulizer, inhaled saline and chest percussion followed by nasopharyngeal suctioning is effective in children as young as 1 yr of age. Sputum induction provides samples for both culture and acid-fast bacilli staining. The traditional culture specimen in young children is the early morning gastric acid obtained before the child has arisen and peristalsis has emptied the stomach of the pooled respiratory secretions that have been swallowed overnight. However, even under optimal conditions, 3 consecutive morning gastric aspirates yield the organisms in <50% of cases. The culture yield from bronchoscopy is even lower, but this procedure can demonstrate the presence of endobronchial disease or a fistula. Negative cultures never exclude the diagnosis of tuberculosis in a child. The presence of a positive TST or IGRA, an abnormal chest radiograph consistent with tuberculosis, and history of exposure to an adult with infectious tuberculosis is adequate for the probable diagnosis of tuberculosis disease. If a likely adult source case has been identified, drug susceptibility test results of the isolate from the adult source can be used to determine the best therapeutic regimen for the child. Cultures should be obtained from the child whenever the source case is unknown, there are multiple possible source cases, or the source case has possible or confirmed drug-resistant tuberculosis.

Confirmation of extrapulmonary tuberculosis is best achieved with a positive culture. However, for many forms of tuberculosis, the culture yield is only 25-50%, and probable diagnosis is by a combination of clinical signs and symptoms, analysis of body fluids when possible, radiographic or histopathologic evidence of tuberculosis, and elimination of other possible diagnoses.

Nucleic Acid Amplification

The main form of nucleic acid amplification studied in children with tuberculosis is PCR, which uses specific DNA sequences as markers for microorganisms. Evaluation of PCR in childhood tuberculosis has been limited. Compared with a clinical diagnosis of pulmonary tuberculosis in children, the sensitivity of PCR has varied from 25-83%, and specificity has varied from 80-100%. A negative PCR result never eliminates the diagnosis of tuberculosis, and the diagnosis is not confirmed by a positive PCR result.

Gene Xpert MTB/RIF is a real-time PCR assay for *M. tuberculosis* that simultaneously detects rifampin resistance, which is often used as a proxy for MDR tuberculosis. This assay uses a self-contained cartridge system, which yields results from direct specimens in 2 hr and is less operator dependent than traditional PCR detection methods. Sensitivity and specificity were 72-77% and 99% in smear-negative adults and 98-99% and 99-100% in smear-positive adults, respectively. Pediatric studies reveal that compared to smear microscopy, this technology has superior diagnostic capability on direct sputum and gastric aspirates. Although cartridges for the Xpert system are expensive, it offers advantages in rapid detection of MDR tuberculosis and is especially useful in settings lacking laboratory infrastructure. Xpert should never replace mycobacterial cultures.

TREATMENT

The basic principles of management of tuberculosis disease in children and adolescents are the same as those in adults. Several drugs are used to affect a relatively rapid cure and prevent the emergence of secondary drug resistance during therapy (Tables 215-5 and 215-6). The choice of regimen depends on the extent of tuberculosis disease, the host, and the likelihood of drug resistance (see Chapter 214 and Table 214-1). The standard therapy of intrathoracic tuberculosis (pulmonary disease and/or hilar lymphadenopathy) in children, as recommended by the CDC and American Academy of Pediatrics, is a 6 mo regimen of isoniazid and rifampin supplemented in the 1st 2 mo of treatment by pyrazinamide and ethambutol. Several clinical trials have shown that this regimen yields a success rate approaching 100%, with an incidence of clinically significant adverse reactions of <2%. Nine-month regimens of only isoniazid and rifampin are also highly effective for drug-susceptible tuberculosis, but the necessary length of treatment, the need for good adherence by the patient, and the relative lack of protection against possible initial drug resistance have led to the favoring of treatment regimens with additional drugs for a short time period. Most experts recommend that all drug administration be directly observed, meaning that a healthcare worker is physically present when the medications are administered to the patients. When **directly observed therapy** is used, intermittent (twice or thrice weekly) administration of drugs after an initial period as short as 2 wk of daily therapy is as effective in children as daily therapy for the entire course.

Extrapulmonary tuberculosis is usually caused by small numbers of mycobacteria. In general, the treatment for most forms of extrapulmonary tuberculosis in children, including cervical lymphadenopathy, is the same as for pulmonary tuberculosis. Exceptions are bone and joint, disseminated, and CNS tuberculosis, for which there are inadequate data to recommend 6 mo of therapy. These conditions are treated for 9-12 mo. Surgical débridement in bone and joint disease and ventriculoperitoneal shunting in CNS disease may be necessary adjuncts to medical therapy.

The optimal treatment of tuberculosis in HIV-infected children has not been established. HIV-seropositive adults with tuberculosis can be treated successfully with standard regimens that include isoniazid, rifampin, pyrazinamide, and ethambutol. The total duration of therapy should be 6-9 mo, or 6 mo after culture of sputum becomes sterile, whichever is longer. Data for children are limited to relatively small series. Most experts believe that HIV-infected children with drug-susceptible tuberculosis should receive the standard 4-drug regimen for the 1st 2 mo followed by isoniazid and rifampin for a total duration of at least 9 mo. Children with HIV infection appear to have more frequent adverse reactions to antituberculosis drugs and must be monitored closely during therapy. Coadministration of rifampin and some antiretroviral agents results in subtherapeutic blood levels of protease inhibitors and nonnucleoside reverse transcriptase inhibitors and toxic levels of rifampin. Concomitant administration of these drugs is not recommended. Treatment of HIV-infected children is often empiric based on epidemiologic and radiographic information, because the radiographic appearance of other pulmonary complications of HIV in children, such as lymphoid interstitial pneumonitis and bacterial pneumonia, may be similar to that of tuberculosis. Therapy should be considered when tuberculosis cannot be excluded.

Table 215-5 Commonly Used Drugs for the Treatment of Tuberculosis in Infants, Children, and Adolescents

DRUG	DOSAGE FORMS	DAILY DOSAGE, mg/kg	TWICE A WEEK DOSAGE, mg/kg PER DOSE	MAXIMUM DOSE	ADVERSE REACTIONS
Ethambutol	Tablets: 100 mg 400 mg	20	50	2.5 g	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Isoniazid*	Scored tablets: 100 mg 300 mg Syrup: 10 mg/mL	10-15†	20-30	Daily, 300 mg Twice a week, 900 mg	Mild hepatic enzyme elevation, hepatitis,† peripheral neuritis, hypersensitivity
Pyrazinamide*	Scored tablets: 500 mg	30-40	50	2 g	Hepatotoxic effects, hyperuricemia, arthralgias, gastrointestinal tract upset
Rifampin*	Capsules: 150 mg 300 mg Syrup formulated from capsules	10-20	10-20	600 mg	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be ineffective

*Rifamate is a capsule containing 150 mg of isoniazid and 300 mg of rifampin. Two capsules provide the usual adult (i.e., person weighing >50 kg) daily doses of each drug. Rifater, in the United States, is a capsule containing 50 mg of isoniazid, 120 mg of rifampin, and 300 mg of pyrazinamide. Isoniazid and rifampin also are available for parenteral administration.

†When isoniazid in a dosage exceeding 10 mg/kg per day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 746.*

Table 215-6 Less-Commonly Used Drugs for Treating Drug-Resistant Tuberculosis in Infants, Children, and Adolescents*

DRUGS	DOSAGE, FORMS	DAILY DOSAGE, mg/kg	MAXIMUM DOSE	ADVERSE REACTIONS
Amikacin†	Vials: 500 mg, 1 g	15-30 (IV or IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Capreomycin†	Vials: 1 g	15-30 (IM administration)	1 g	Auditory and vestibular toxicity and nephrotoxic effects
Cycloserine	Capsules: 250 mg	10-20, given in 2 divided doses	1 g	Psychosis, personality changes, seizures, rash
Ethionamide	Tablets: 250 mg	15-20, given in 2-3 divided doses	1 g	Gastrointestinal tract disturbances, hepatotoxic effects, hypersensitivity reactions, hypothyroidism
Kanamycin	Vials: 75 mg/2 mL 500 mg/2 mL 1 g/3 mL	15-30 (IM or IV administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects
Levofloxacin‡	Tablets: 250 mg 500 mg 750 mg Vials: 25 mg/mL	Adults: 750-1000 mg (once daily) Children: 15 mg/kg daily	1 g	Theoretic effect on growing cartilage, gastrointestinal tract disturbances, rash, headache, restlessness, confusion
Ofloxacin	Tablets: 200 mg 300 mg 400 mg Vials: 20 mg/mL 40 mg/mL	Adults and adolescents: 800 mg Children 15-20 mg/kg daily	800 mg	Arthropathy, arthritis
Moxifloxacin	Tablets: 400 mg IV solution: 400 mg/250 mL in 0.8% saline	Adults and adolescents: 400 mg Children: 7.5-10 mg/kg daily	400 mg	Arthropathy, arthritis
Paraaminosalicylic acid (PAS)	Packets: 3 g	200-300 (2-4 times a day)	10 g	Gastrointestinal tract disturbances, hypersensitivity, hepatotoxic effects
Streptomycin†	Vials: 1 g 4 g	20-40 (IM administration)	1 g	Auditory and vestibular toxic effects, nephrotoxic effects, rash

*These drugs should be used in consultation with a specialist in tuberculosis.
†Dose adjustment in renal insufficiency.
‡Levofloxacin currently is not approved for use in children younger than 18 yr of age; its use in younger children necessitates assessment of the potential risks and benefits.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 748.*

Drug-Resistant Tuberculosis

The incidence of drug-resistant tuberculosis is increasing in many areas of the world, including North America. There are two major types of drug resistance. **Primary resistance** occurs when a person is infected with *M. tuberculosis* that is already resistant to a particular drug. **Secondary resistance** occurs when drug-resistant organisms emerge as the dominant population during treatment. The major causes of secondary drug resistance are poor adherence to the medication by the patient or inadequate treatment regimens prescribed by the physician. Nonadherence to 1 drug is more likely to lead to secondary resistance than is failure to take all drugs. Secondary resistance is rare in children because of the small size of their mycobacterial population. Consequently, most drug resistance in children is primary, and patterns of drug resistance among children tend to mirror those found among adults in the same population. The main predictors of drug-resistant tuberculosis among adults are history of previous antituberculosis treatment, coinfection with HIV, and exposure to another adult with infectious drug-resistant tuberculosis.

Treatment of drug-resistant tuberculosis is successful only when at least 2 bactericidal drugs are given to which the infecting strain of *M. tuberculosis* is susceptible. When a child has possible drug-resistant tuberculosis, usually 4 or 5 drugs should be administered initially until the susceptibility pattern is determined and a more-specific regimen can be designed. The specific treatment plan must be individualized for each patient according to the results of susceptibility testing on the isolates from the child or the adult source case. Treatment duration of 9 mo with rifampin, pyrazinamide, and ethambutol is usually adequate for isoniazid-resistant tuberculosis in children. When resistance to isoniazid and rifampin is present, the total duration of therapy often must be extended to 12-24 mo, and intermittent regimens should not be used. The prognosis of single- or multidrug-resistant tuberculosis in children is usually good if the drug resistance is identified early in the treatment, appropriate drugs are administered under directly observed therapy, adverse reactions from the drugs are minor, and the child and family are in a supportive environment. The treatment of drug-resistant tuberculosis in children always should be undertaken by a clinician with specific expertise in the treatment of tuberculosis.

Corticosteroids

Corticosteroids are useful in treating some children with tuberculosis disease. They are most beneficial when the host inflammatory reaction contributes significantly to tissue damage or impairment of organ function. There is convincing evidence that corticosteroids decrease

mortality rates and long-term neurologic sequelae in some patients with **tuberculous meningitis** by reducing vasculitis, inflammation, and, ultimately, intracranial pressure. Lowering the intracranial pressure limits tissue damage and favors circulation of antituberculosis drugs through the brain and meninges. Short courses of corticosteroids also may be effective for children with **endobronchial tuberculosis** that causes respiratory distress, localized emphysema, or segmental pulmonary lesions. Several randomized clinical trials have shown that corticosteroids can help relieve symptoms and constriction associated with acute tuberculous **pericardial effusion.** Corticosteroids can cause dramatic improvement in symptoms in some patients with tuberculous pleural effusion and shift of the mediastinum. However, the long-term course of disease is probably unaffected. Some children with severe **miliary tuberculosis** have dramatic improvement with corticosteroid therapy if the inflammatory reaction is so severe that alveolocapillary block is present. There is no convincing evidence to support a specific corticosteroid preparation. The most commonly used regimen is prednisone, 1-2 mg/kg/day in 1-2 divided doses orally for 4-6 wk, followed by a taper.

Supportive Care

Children receiving treatment should be followed carefully to promote adherence to therapy, to monitor for toxic reactions to medications, and to ensure that the tuberculosis is being adequately treated. Adequate nutrition is important. Patients should be seen at monthly intervals and should be given just enough medication to last until the next visit. Anticipatory guidance with regard to the administration of medications to children is crucial. The physician should foresee difficulties that the family might have in introducing several new medications in inconvenient dosage forms to a young child. The clinician must report all cases of suspected tuberculosis in a child to the local health department to be sure that the child and family receive appropriate care and evaluation.

Nonadherence to treatment is the major problem in tuberculosis therapy. The patient and family must know what is expected of them through verbal and written instructions in their primary language. Approximately 30-50% of patients taking long-term treatment are significantly nonadherent with self-administered medications, and clinicians are usually not able to determine in advance which patients will be nonadherent. Preferably, directly observed therapy should be instituted by the local health department.

Latent *Mycobacterium tuberculosis* Infection

The following aspects of the natural history and treatment of LTBI in children must be considered in the formulation of recommendations about therapy: (1) infants and children younger than 5 yr of age with LTBI have been infected recently; (2) the risk for progression to disease is high; (3) untreated infants with LTBI have up to a 40% chance of development of tuberculosis disease; (4) the risk for progression decreases gradually through childhood, until adolescence when the risk increases; (5) infants and young children are more likely to have life-threatening forms of tuberculosis, including meningitis and disseminated disease; and (6) children with LTBI have more years at risk for development of disease than adults. Because of these factors, and the excellent safety profile of isoniazid in children, there is a tendency to err on the side of overtreatment in infants, young children and adolescents.

Isoniazid therapy for LTBI appears to be more effective for children than adults, with several large clinical trials demonstrating risk reduction of 70-90%. The risk of isoniazid-related hepatitis is minimal in infants, children, and adolescents, who tolerate the drug better than adults.

The recommended regimen for treatment of LTBI in United States children is a 9 mo course of isoniazid as self-administered daily therapy or by twice-weekly directly observed therapy. Analysis of data from several studies demonstrates that the efficacy decreased significantly if isoniazid was taken for <9 mo. However, the international standard is 6 mo treatment with isoniazid. Isoniazid given twice weekly has been used extensively to treat LTBI in children, especially schoolchildren and close contacts of case patients. Directly observed therapy should be considered when it is unlikely that the child and family will adhere to daily self-administration, or if the child is at increased risk for rapid development of disease (newborns and infants, recent contacts, immunocompromised children). For healthy children taking isoniazid but no other potentially hepatotoxic drugs, routine biochemical monitoring and supplementation with pyridoxine are not necessary. A 3 mo regimen of rifampin and isoniazid has been used in Europe, with programmatic data suggesting that the regimen is effective, but this regimen is not recommended in the United States. Rifampin alone for 4-6 mo has been used for the treatment of LTBI in infants, children, and adolescents when isoniazid could not be tolerated or the child has had contact with a source case infected with an isoniazid-resistant but rifamycin-susceptible organism. However, no controlled clinical trials have been conducted. Rifapentine is a rifamycin with a very long half-life, allowing for weekly administration in conjunction with isoniazid. Studies have demonstrated that 12 doses of once weekly isoniazid and rifapentine are as effective for treating LTBI and as safe as 9 mo of daily isoniazid, and this regimen is recommended by the American Academy of Pediatrics and the CDC for treatment of LTBI in patients 12 yr of age and older. Given the risk of selecting for drug-resistant isolates by missing intermittent doses of rifamycins, this treatment regimen currently is recommended only under directly observed therapy under the supervision of local health departments.

For children with multidrug-resistant tuberculosis infection, the regimen will depend on the drug-susceptibility profile of the contract case's organism; an expert in tuberculosis should be consulted.

Few controlled studies have been published regarding the efficacy of any form of treatment for LTBI in HIV-infected children. A 9-mo course of daily isoniazid is recommended. Most experts recommend that routine monitoring of serum hepatic enzyme concentrations be performed and pyridoxine be given when HIV-infected children are treated with isoniazid. The optimal duration of rifampin therapy in children with LTBI is not known, but many experts recommend at least a 6 mo course.

Isoniazid should be given to children younger than 5 yr of age who have a negative TST or IGRA result but who have known recent exposure to an adult with potentially contagious tuberculosis disease. This practice is often referred to as **window prophylaxis**. By the time delayed hypersensitivity develops (2-3 mo), an untreated child already may have developed severe tuberculosis. For these children, tuberculin skin or IGRA testing is repeated 3 mo after contact with the source case for tuberculosis has been broken (*broken contact* is defined as physical separation or adequate initial treatment of the source case). If the second test result is positive, isoniazid therapy is continued for 9 mo, but if the result is negative, treatment can be stopped.

PREVENTION

The highest priority of any tuberculosis control program should be case finding and treatment, which interrupts transmission of infection between close contacts. All children and adults with symptoms suggestive of tuberculosis disease and those in close contact with an adult with suspected infectious pulmonary tuberculosis should be tested for tuberculosis infection (by TST or IGRA) and examined as soon as possible. On average, 30-50% of household contacts to infectious cases are infected, and 1% of contacts already have overt disease. This scheme relies on effective and adequate public health response and resources. Children, particularly young infants, should receive high priority during contact investigations, because their risk for infection is high and they are more likely to rapidly develop severe forms of tuberculosis.

Mass testing of large groups of children for tuberculosis infection is an inefficient process. When large groups of children at low risk for tuberculosis are tested, the vast majority of TST reactions are actually false-positive reactions because of biologic variability or cross sensitization with NTM. However, testing of high-risk groups of adults or children should be encouraged, because most of these persons with positive TST or IGRA results have tuberculosis infection. Testing

should take place only if effective mechanisms are in place to ensure adequate evaluation and treatment of the persons who test positive.

Bacille Calmette-Guérin Vaccination

The only available vaccine against tuberculosis is the BCG vaccine. The original vaccine organism was a strain of *M. bovis* attenuated by subculture every 3 wk for 13 yr. This strain was distributed to dozens of laboratories that continued to subculture the organism on different media under various conditions. The result has been production of many BCG vaccines that differ widely in morphology, growth characteristics, sensitizing potency, and animal virulence.

The administration route and dosing schedule for the BCG vaccines are important variables for efficacy. The preferred route of administration is intradermal injection with a syringe and needle, because it is the only method that permits accurate measurement of an individual dose.

The BCG vaccines are extremely safe in immunocompetent hosts. Local ulceration and regional suppurative adenitis occur in 0.1-1% of vaccine recipients. Local lesions do not suggest underlying host immune defects and do not affect the level of protection afforded by the vaccine. Most reactions are mild and usually resolve spontaneously, but chemotherapy is needed occasionally. Surgical excision of a suppurative draining node is rarely necessary and should be avoided if possible. Osteitis is a rare complication of BCG vaccination that appears to be related to certain strains of the vaccine that are no longer in wide use. Systemic complaints such as fever, convulsions, loss of appetite, and irritability are extraordinarily rare after BCG vaccination. Profoundly immunocompromised patients can develop disseminated BCG infection after vaccination. Children with HIV infection appear to have rates of local adverse reactions to BCG vaccines that are comparable with rates in immunocompetent children. However, the incidence in these children of disseminated infection months to years after vaccination is currently unknown.

Recommended vaccine schedules vary widely among countries. The official recommendation of the World Health Organization is a single dose administered during infancy, in populations where the risk for tuberculosis is high. However, infants with known HIV infection should not receive a BCG vaccination. In some countries repeat vaccination is universal, although no clinical trials support this practice. In others, it is based on either TST or the absence of a typical scar. The optimal age for administration and dosing schedule are unknown because adequate comparative trials have not been performed.

Although dozens of BCG trials have been reported in various human populations, the most useful data have come from several controlled trials. The results of these studies have been disparate. Some demonstrated a great deal of protection from BCG vaccines, but others showed no efficacy at all. A meta-analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary tuberculosis in adults and children. The protective effect for disseminated and meningeal tuberculosis appears to be slightly higher, with BCG preventing 50-80% of cases. A variety of explanations for the varied responses to BCG vaccines have been proposed, including methodologic and statistical variations within the trials, interaction with NTM that either enhances or decreases the protection afforded by BCG, different potencies among the various BCG vaccines, and genetic factors for BCG response within the study populations. BCG vaccination administered during infancy has little effect on the ultimate incidence of tuberculosis in adults, suggesting waning protection with time.

BCG vaccination has worked well in some situations but poorly in others. Clearly, BCG vaccination has had little effect on the ultimate control of tuberculosis throughout the world, because more than 5 billion doses have been administered but tuberculosis remains epidemic in most regions. BCG vaccination does not substantially influence the chain of transmission, because cases of contagious pulmonary tuberculosis in adults that can be prevented by BCG vaccination constitute a small fraction of the sources of infection in a population. The best use of BCG vaccination is to prevent life-threatening forms of tuberculosis in infants and young children.

BCG vaccination has never been adopted as part of the strategy for the control of tuberculosis in the United States. Widespread use of the vaccine would render subsequent TSTs less useful. However, BCG vaccination can contribute to tuberculosis control in selected population groups. BCG is recommended for TST-negative, HIV-negative infants and children who are at high risk for intimate and prolonged exposure to persistently untreated or ineffectively treated adults with infectious pulmonary tuberculosis and who cannot be removed from the source of infection or placed on long-term preventive therapy. It also is recommended for those who are continuously exposed to persons with tuberculosis who have bacilli that are resistant to isoniazid and rifampin. Any child receiving BCG vaccination should have a documented negative TST before receiving the vaccine. After receiving the vaccine, the child should be separated from the possible sources of infection until it can be demonstrated that the child has had a vaccine response, demonstrated by tuberculin reactivity, which usually develops within 1-3 mo.

Active research to develop new tuberculosis vaccines has led to the creation and preliminary testing of several vaccine candidates based on attenuated strains of mycobacteria, subunit proteins, or DNA. The genome of *M. tuberculosis* has been sequenced, allowing researchers to further study and better understand the pathogenesis and host immune responses to tuberculosis.

Prevention of Perinatal Tuberculosis

The most effective way of preventing tuberculosis infection and disease in the neonate or young infant is through appropriate testing and treatment of the mother and other family members. High-risk pregnant women should be tested with a TST or IGRA, and those with a positive test result should receive a chest radiograph with appropriate abdominal shielding. If the mother has a negative chest radiograph and is clinically well, no separation of the infant and mother is needed after delivery. The child needs no special evaluation or treatment if the child remains asymptomatic. **Other household members should undergo testing for tuberculosis infection and further evaluation as indicated.**

If the mother has suspected tuberculosis at the time of delivery, the newborn should be separated from the mother until the chest radiograph is obtained. If the mother's chest radiograph is abnormal, separation should be maintained until the mother has been evaluated thoroughly, including examination of the sputum. If the mother's chest radiograph is abnormal but the history, physical examination, sputum examination, and evaluation of the radiograph show no evidence of current active tuberculosis, it is reasonable to assume that the infant is at low risk for infection. The mother should receive appropriate treatment, and she and her infant should receive careful follow-up care.

If the mother's chest radiograph or acid-fast sputum smear shows evidence of current tuberculosis disease, additional steps are necessary to protect the infant. Isoniazid therapy for newborns has been so effective that separation of the mother and infant is no longer considered mandatory. Separation should occur only if the mother is ill enough to require hospitalization, has been or is expected to become nonadherent to treatment, or has suspected drug-resistant tuberculosis. Isoniazid treatment for the infant should be continued until the mother is sputum culture negative for ≥3 mo. At that time, a Mantoux TST should be placed on the child. If the test is positive, isoniazid is continued for a total duration of 9-12 mo; if the test is negative, isoniazid can be discontinued. Once the mother and child are taking adequate therapy, it is usually safe for the mother to breastfeed, as the medications, although found in milk, are present in low concentrations. If isoniazid resistance is suspected or the mother's adherence to medication is in question, continued separation of the infant from the mother should be considered. The duration of separation must be at least as long as is necessary to render the mother noninfectious. An expert in tuberculosis should be consulted if the young infant has potential exposure to the mother or another adult with tuberculosis disease caused by an isoniazid-resistant strain of *M. tuberculosis*.

Although isoniazid is not thought to be teratogenic, the treatment of pregnant women who have asymptomatic tuberculosis infection is

often deferred until after delivery. However, symptomatic pregnant women or those with radiographic evidence of tuberculosis disease should be appropriately evaluated. Because pulmonary tuberculosis is harmful to both the mother and the fetus and represents a great danger to the infant after delivery, tuberculosis in pregnant women always should be treated. The most common regimen for drug-susceptible tuberculosis is isoniazid, rifampin, and ethambutol. The aminoglycosides and ethionamide should be avoided because of their teratogenic effect. The safety of pyrazinamide in pregnancy has not been established.

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Chapter 216

Hansen Disease (*Mycobacterium leprae*)

Monica I. Ardura and Asuncion Mejias

Leprosy is a heterogeneous, chronic mycobacterial infection that primarily affects the upper airway, skin, and peripheral nerves. Disease manifestations are determined by the host's immunopathologic response to infection, resulting in a wide clinical spectrum. Hansen disease (HD) is currently the accepted designation of leprosy. Contrary to historical folklore, HD is not highly transmissible and is treatable. In addition, the associated morbidity and disability can be prevented with early diagnosis and appropriate treatment.

ETIOLOGY

Mycobacterium leprae, the etiologic agent of leprosy, is an obligate intracellular acid-fast Gram-positive bacillus of the family Mycobacteriaceae measuring 1-8 μm in length. It grows optimally at 27-33°C (80.6-91.4°F) yet cannot be cultured in vitro. Natural infection occurs in humans and possibly in armadillos, although mice and certain primates can be infected with *M. leprae* in the laboratory. Based on assays in footpads of immunodeficient mice, the doubling time of *M. leprae* is estimated to be 11-13 days. The incubation period between natural infection and overt clinical disease in humans ranges from 3 mo to 20 yr, with a mean of 4 yr for tuberculoid leprosy and 10 yr for lepromatous leprosy. The infectiousness of patients with HD becomes negligible within 24 hr of the first administration of effective multidrug therapy.

EPIDEMIOLOGY

The World Health Organization's goal to eliminate leprosy as a public health problem, defined as reduction in the prevalence of leprosy to less than 1 case per 10,000 population, was achieved at the global level in 2000. Yet, despite an overall decline in reported prevalence since the introduction of effective antimycobacterial therapy in the early 1980s, HD continues to afflict more than 2 million people worldwide. Approximately 245,000 new cases were reported globally in 2009, with more than 80% of cases occurring in Southeast Asia, Africa, and South America. In the United States, HD is a notifiable disease with 12,685 new HD cases since 1894. In 2009, there were 213 new U.S. cases, with 65% of them occurring in Texas, Louisiana, Hawaii, California, Florida, New York, Massachusetts, and Puerto Rico. Seventy-four percent of cases were among immigrants, with the largest proportion identifying themselves as Asian or South Pacific islanders. Less than 4% of U.S. cases in 2009 occurred in children younger than 16 yr of age. Although infection in infants is rare, the youngest patient reported in the literature is a 3 mo old.

The likelihood of developing HD is determined by several variables: age (with 2 incidence peaks: 10-14 yr and 30 yr), gender (male : female 2 : 1), and contact with a patient with multibacillary disease. Approximately 5% of people are genetically susceptible to infection with *M. leprae*. Whole-genome sequencing has allowed identification of genes and polymorphisms associated with increased susceptibility to leprosy. HD in immunocompromised hosts has been reported in solid-organ and bone marrow transplant recipients and patients receiving tumor necrosis factor (TNF)-blocking monoclonal antibodies. Patients with HIV infection do not appear to be at increased risk of acquiring leprosy, to have increased disease severity, or to have a poor response to treatment. However, clinicians should be aware that concomitant HIV infection and leprosy can result in worsening of symptoms of leprosy during HIV treatment as a result of an immune reconstitution inflammatory syndrome.

The exact mechanism of transmission is not fully understood but is thought to occur primarily via the respiratory route. Up to 10^7 viable bacilli per day can be shed in the respiratory secretions of patients with multibacillary leprosy. Type of disease (multibacillary) and proximity to contact cases are important determinants of human-to-human transmission; the relative risk for developing disease in household contacts is 8-10 for lepromatous disease and 2-4 for the tuberculoid form. Transmissions via breast milk and entry through broken skin have been reported. Autochthonous cases of leprosy have also been reported in the southern Gulf Coast area of the United States and represent a probable zoonosis from armadillos, though the transmission risk is low.

PATHOGENESIS

M. leprae is the only bacterium known to infect nerves. The mechanism of mycobacterial dissemination from the respiratory tract to the skin and nerves is thought to occur hematogenously but has not been completely elucidated. *M. leprae* has been shown to colonize the perineural space and gain entry into the endoneural space. The organism then binds to the laminin-2 glycoprotein present in the basal lamina of Schwann cells in peripheral nerves. It is then taken up inside the Schwann cell, where it replicates slowly intracellularly over several years. Specific T cells recognize the mycobacterial antigens within the nerve and initiate a chronic inflammatory response. In addition to the direct nerve invasion by *M. leprae*, the immune response to infection also contributes to nerve damage. Schwann cells express human leukocyte antigen class 2 molecules and play an important role in the immunologic reaction by presenting mycobacterial peptides to the human leukocyte antigen class 2–restricted CD4-positive T cells. This likely explains the nerve damage seen in paucibacillary disease and in reversal reactions. Swelling within the perineurium leads to ischemia, further nerve damage, and eventually to fibrosis and axonal death.

CLINICAL MANIFESTATIONS

Skin and serologic studies suggest that up to 90% of infected people develop immunity after exposure, without manifesting clinical disease. In susceptible individuals with sufficient exposure to become infected, the spectrum of clinical manifestations reflects *M. leprae*'s unique tropism for peripheral nerves, the host's immunologic response to infection, and disease subtype. Classic manifestations of leprosy include hypopigmented, erythematous, or infiltrative skin lesions with or without neurologic symptoms such as hypoesthesia or anesthesia, weakness, autonomic dysfunction, and peripheral nerve thickening.

Skin Involvement

Examination of the skin should ideally be performed in natural sunlight and be tested for hypoesthesia to light touch, pin prick, temperature, and anhidrosis. The most common skin lesions are macules or plaques. Diffuse infiltrative lesions and subcutaneous nodules are less common. Initial lesions are insidious hypopigmented macules, although they may appear erythematous on pale skin. Lesions may involve any area of the body, are more pronounced in cooler areas (for

example the earlobes and nose), and occur less frequently on the scalp, axillae, or perineum. Approximately 70% of skin lesions have reduced sensation; the degree of hypoesthesia depends on the location and size of the lesion and degree of Th1 immune response. Patients with tuberculous leprosy generally have 1-3 well-demarcated macules or plaques with elevated borders (Fig. 216-1) and reduced or absent sensation. In the lepromatous form, multiple lesions are present but are not all hypoesthetic or anesthetic.

Nerve Involvement

The skin lesions overlying a nerve trunk distribution predict the involvement of nerves in the vicinity. Peripheral nerves are most commonly affected early in the disease course and should be palpated for thickness (Fig. 216-2) and tenderness and evaluated for both motor and sensory function (particularly temperature and light touch). The posterior tibial nerve (medial malleolus) is the most common nerve affected, followed by the ulnar (elbow), median (wrist), lateral popliteal (fibular neck), and facial nerves. There is a pure neuritic form of leprosy, occurring most commonly in India and Nepal, in which patients present with asymmetrical neuropathy, but lack skin lesions. A nerve biopsy (usually of the sural nerve) is required to demonstrate granulomatous histopathology, thereby confirming the diagnosis.

Figure 216-1 A patient with tuberculous leprosy with a single skin lesion with a raised border and flattened center.

Figure 216-2 Thickened, superficial peroneal nerve of leprosy.

Other Involvement

Ocular involvement leading to vision loss results from both direct bacillary invasion of the eye and optic nerve damage. Lagophthalmos occurs when there is destruction of the facial nerve. Facial skin lesions are associated with a 10-fold higher risk of facial nerve damage. Damage to the trigeminal nerve causes anesthesia of the cornea and conjunctiva, leading to abrasions. Systemic involvement of other organs is seen mainly in patients with lepromatous leprosy where a high bacillary burden leads to infiltration of the nasal mucosa, bones, and testes. Renal involvement and amyloidosis are rare findings.

Patients may also present with leprosy reactions. Leprosy reactions are acute clinical exacerbations reflecting disturbances of the immunologic balance to *M. leprae* infection occurring in 30-50% of all leprosy patients. These sudden changes occur most commonly during the initial years after infection and in patients with borderline and multibacillary leprosy, but can occur before, during, or after completion of treatment. Three types of leprosy reactions have been described and require immediate treatment so as to prevent complications.

1. Type 1 reactions (also known as reversal reactions) occur in one-third of patients with borderline disease and are caused by a spontaneous increase in T-cell–mediated reactivity to mycobacterial antigens. This increase in the Th1 cellular immune response causes local production and increased infiltration of interferon-γ and TNF-α–secreting CD4+ lymphocytes into cutaneous and neural sites. Reversal reactions are characterized by acute edema and increased erythema, warmth, and painful inflammation of preexisting cutaneous plaques or nodules with acute swelling and tenderness of peripheral nerves that can quickly progress to cause nerve abscesses and necrosis. There may be a peripheral lymphocytosis and an increased cytokine response, but systemic symptoms are uncommon. Rapid and sustained reversal of the inflammatory process using corticosteroids is essential to prevent continued nerve damage.
2. Type 2 reactions (erythema nodosum leprosum [ENL]) occur in borderline lepromatous and lepromatous forms, as these patients have the highest levels of *M. leprae* antigens and antibodies, most commonly in the 1st 2 yr after starting therapy. ENL is distinguished from reversal reactions by the development of new painful, erythematous subcutaneous nodules with an accompanying systemic inflammatory response. ENL is accompanied by high circulating concentrations of TNF-α. Patients develop high fever and signs of systemic toxicity, and in severe cases, ENL can be life-threatening, presenting with features similar to septic shock. Patients present with either a single, acute episode, a relapsing form comprised of multiple acute episodes, or a chronic, continuous form. Deposition of extravascular immune complexes leads to neutrophil infiltration and activation of complement in the skin and other organs. Tender, erythematous dermal papules or nodules (resembling erythema nodosum) occur in clusters, typically on extensor surfaces of the lower extremities and face. Immune complex deposition also contributes to migrating polyarthralgias, painful swelling of lymph nodes and spleen, iridocyclitis, vasculitis, orchitis, and, rarely, nephritis.
3. Lucio's phenomenon (erythema necroticans) is an uncommon, but potentially fatal reaction distinct from type 1 or 2 reactions that occurs in patients with untreated lepromatous leprosy, most commonly from Mexico. It is a necrotizing vasculitis caused by *M. leprae* directly invading the endothelium. Clinically, patients develop violaceous or hemorrhagic plaques, followed by ulcerations in the absence of systemic complaints. Secondary bacterial infections are common.

DIAGNOSIS

The diagnosis of HD requires high clinical suspicion and should be considered in any patient with a hypoesthetic or anesthetic skin rash, especially if they have resided in an endemic region. Patients are considered to have HD if they have one or more of the 3 cardinal signs: loss of sensation in a localized skin lesion, thickened peripheral nerve with loss of sensation or weakness of muscles enervated by that nerve, or the presence of acid-fast bacilli on biopsy. The positive predictive value for the diagnosis of leprosy in patients meeting all 3 criteria is 98%. Histopathologic examination of full-thickness biopsies taken of active lesions is considered the gold standard for establishing the diagnosis and allows for precise disease classification. Two classification schemas are frequently applied:

A. The World Health Organization classification is a simple field classification based on the number of skin lesions.
   1. Paucibacillary, single lesion
   2. Paucibacillary (2-5 patches)
   3. Multibacillary (≥6 patches)
B. The Ridley-Jopling scale is commonly used in the United States and describes the 5 types of leprosy, according to clinical spectrum of disease, bacillary load, and findings on histopathology.
   1. Tuberculoid form: Patients usually have a vigorous and specific cellular immune response to *M. leprae* antigens and have a small number of skin lesions. The lesions are infiltrated by T-helper type 1 T cells producing abundant interferon-γ and TNF-α, forming well-demarcated granulomas, with few, if any bacilli found within the lesions.
   2. Borderline tuberculoid form
   3. Borderline
   4. Borderline lepromatous
   5. Lepromatous form: Patients have an absence of specific cellular immunity to *M. leprae* but intact immunity to *Mycobacterium tuberculosis*. Patients with lepromatous form have the most severe form of the disease, characterized by many skin lesions, clinically apparent infiltration of peripheral nerves and skin lesions, and a high load of bacilli in the absence of an effective cell mediated immune response. They also have involvement of the nasal mucosa causing nasal congestion and epistaxis. Skin biopsies reveal extensive infiltration of the skin and nerves, containing messenger RNA for T-helper type 2–like cytokines such as interleukin-4 and interleukin-10, poorly formed granulomas, and uncontrolled proliferation of bacilli within foamy macrophages. A large amount of circulating antibody to *M. leprae* is present but does not confer protective immunity. Over time, patients with the lepromatous form develop symmetrical peripheral nerve involvement and a diffuse infiltrative dermopathy that includes thickening of the facial skin with accentuation of the skin creases and hair loss of the eyelashes and eyebrows (madarosis), leading to the classic presentation of the "leonine facies."

Patients with the extremes of the disease (tuberculoid and lepromatous forms) are considered to have stable cell-mediated immunity, as their disease manifestations do not change much over time. In contrast, patients with borderline disease (borderline tuberculoid, borderline, borderline lepromatous) have unstable cell-mediated immunity and demonstrate changes in their clinical manifestations over time toward the polar forms or sudden reversal reactions. From borderline tuberculoid to borderline lepromatous forms, there is a progressive reduction in cellular immune responses, an increase in bacillary load, more frequent hypopigmented skin lesions (Fig. 216-3) and nerve involvement, and higher antibody titers.

Indeterminate leprosy is the earliest form of leprosy in which patients have a single hypopigmented macule with poorly defined borders, without erythema or induration. Anesthesia is minimal or absent, especially if the lesion is on the face. The diagnosis is usually one of exclusion in the setting of a contact investigation. Tissue biopsies show diagnostic evidence of leprosy but do not meet sufficient criteria for classification. Up to 50-75% of the lesions will heal spontaneously, while the rest will progress to another form of leprosy.

Figure 216-3 A patient with borderline leprosy with numerous, hypopigmented lesions with poorly defined borders.

To confirm the diagnosis, a full-thickness skin biopsy should be taken from the most active skin lesion, entirely within the lesion and including the active margin. *M. leprae* is best identified in tissue using the Fite stain. Lesions from patients with the lepromatous form reveal numerous acid fast bacilli in clumps (globi), whereas patients with the tuberculoid form of the disease rarely have mycobacteria identified but demonstrate well-formed noncaseating granulomas and nerve involvement. The presence of neural inflammation differentiates leprosy from other granulomatous disorders. Hematoxylin-and-eosin staining and immunohistochemistry may also contribute to the diagnosis. Mycobacterial culture of lesions is performed to exclude *M. tuberculosis* and nontuberculous cutaneous infections. Antibodies to *M. leprae* are present in 90% of patients with untreated lepromatous disease, 40-50% with paucibacillary disease, and 1-5% of healthy controls. Serologic testing is insensitive, however, and is not used for diagnosis.

In endemic countries with few medical resources, diagnosis is based primarily on clinical evidence. In areas with laboratory access, a slit-skin smear may be performed in lieu of a biopsy. The slit-skin procedure involves making a small incision in the dermis of a suspected lesion, scraping the dermal surface and edge of the lesion, smearing the scraping on a glass slide, heat fixing, and staining (Fite) the specimen to detect the mycobacteria. Although slit-skin smears have high specificity, they have low sensitivity, as only 30% of patients are smear positive, usually patients with the lepromatous form. The bacterial index can range from 0 (no bacilli in 100 oil-immersion fields), as is generally seen in paucibacillary disease, to 6+ (>1,000 bacilli/field), as can be seen in multibacillary disease.

Diagnostic and histopathologic consultation in the United States is available through the National Hansen's Disease Programs (NHDP; http://www.hrsa.gov/hansens or 800-642-2477). Specimens (formalin or paraffin embedded) can be sent to the NHDP for pathologic analysis free of charge. A polymerase chain reaction (PCR) test for *M. leprae* is

not readily available in clinical practice but may be performed at the NHDP. In nonendemic areas, PCR may be useful for diagnosis when acid-fast bacilli are discernable in tissue, but clinical and histopathologic features are not typical. *M. leprae* DNA is detectable by PCR in 95% of multibacillary disease (sensitivity >90%) and 55% of paucibacillary disease (sensitivity of 34-80%). PCR has also allowed detection of the organism in nasal secretions from asymptomatic people. Molecular testing for mutations causing drug resistance is also available through the NHDP.

TREATMENT

In the United States, clinical providers considering a diagnosis and treatment of a patient with HD should obtain consultation from the NHDP. The primary goal of treatment is early antimicrobial therapy to prevent permanent neuropathy. Effective treatment of leprosy requires multidrug therapy (MDT) with dapsone, clofazimine, and rifampin. Combination therapy is employed to prevent antimicrobial resistance. The recommended combination MDT can be obtained free of charge in the United States from the NHDP (Table 216-1) and in other countries, from the World Health Organization (Table 216-2).

Before starting combination MDT, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have a baseline complete blood cell count and liver function testing, and be evaluated for evidence of concomitant tuberculosis infection. The latter is imperative so as to avoid giving rifampin monotherapy to someone with active tuberculosis. Darkening of the skin is a common adverse reaction to clofazimine; this generally resolves 6-12 mo after completing therapy. Bone marrow suppression and hepatotoxicity have been reported and should be monitored every 3 mo during therapy. Yearly, a screening urinalysis should be performed. Other reactions such as methemoglobinemia and hypersensitivity reactions to dapsone are rare.

Response to therapy is seen clinically as flattening or disappearance of skin lesions and improvement in nerve function, usually within 1-2 mo after initiating MDT. Complete resolution or improvement may take 6-12 mo, depending on the severity of infection. Most skin lesions heal without scarring. A large number of dead bacilli may remain in the tissue for years before they are eliminated. After completion of MDT, annual follow up for ≥5 yr for paucibacillary and ≥10 yr for multibacillary disease is warranted. Relapse of the disease after completion of MDT is rare (0.01-4.0%) and must be distinguished from the more common leprosy immunologic reactions. Patients who have a bacillary index of ≥4 pre-MDT or ≥3 at the completion of MDT have the highest risk of relapse. When relapse occurs, it is usually within 5-10 yr of MDT completion and a result of reactivation of drug-susceptible mycobacteria, thus patients are treated with the same MDT regimen. Resistance to dapsone and rifampicin has been documented, although it rarely occurs with combination therapy. Minocycline, clarithromycin, rifapentine, diarylquinoline, and some fluoroquinolones (ofloxacin, moxifloxacin) have been shown to be bactericidal against *M. leprae*. Given limited data, these alternative antimicrobials are used in selected cases of intolerance to the routine combination MDT regimen or for documented resistance. It is important to note that some patients who have been adequately treated for HD may later show evidence of chronic reversal reactions and late neuropathies but are bacillus negative, thus they should not be considered relapses. In these patients, low-dose clofazimine (50-100 mg thrice weekly) is generally employed until all signs of the reaction have abated.

Treatment of leprosy reactions can be complicated and requires expert consultation. Generally, continuation of antimycobacterial drugs, effective and prolonged antiinflammatory therapy, and adequate analgesia and physical support is essential for patients with active neuritis to prevent nerve damage. For type 1 reactions, the addition of

Table 216-1 NHDP Recommended Multidrug Therapy Regimens for Hansen Disease in the United States

TYPE OF LEPROSY	ANTIMICROBIAL THERAPY	ADULT DOSING (GIVEN ORALLY)	PEDIATRIC DOSING* (GIVEN ORALLY)	DURATION OF THERAPY
MULTIBACILLARY LEPROSY (LL, BL, BB)				
	Dapsone *and*	100 mg/day	1 mg/kg/day	24 months
	Rifampin *and*	600 mg/day	10-20 mg/kg/day	24 months
	Clofazimine	50 mg/day	1 mg/kg/day†	24 months
PAUCIBACILLARY LEPROSY (TT, BT)				
	Dapsone *and*	100 mg/day	1-2 mg/kg/day	12 months
	Rifampin	600 mg/day	10-20 mg/kg/day	12 months

NHDP multidrug therapy therapy is daily and of longer duration than World Health Organization recommended regimen.
*Daily pediatric mg/kg dose should not exceed adult daily maximum.
†Clofazimine is only available through NHDP Investigational New Drug (IND) program; minimum formulation is 50 mg and capsules should not be cut. Alternative dosing includes: clofazimine 2 mg/kg every other day *or* clarithromycin 7.5 mg/kg/day.
BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; NHDP, National Hansen's Disease Program; TT, tuberculoid.

Table 216-2 World Health Organization Recommended Multidrug Therapy Regimens for Hansen Disease

TYPE OF LEPROSY		Antimicrobial Therapy: MONTHLY (SUPERVISED)	Antimicrobial Therapy: DAILY (SELF-ADMINISTERED)	DURATION OF THERAPY
Multibacillary (LL, BL, BB)	Adult	Rifampicin 600 mg *and* clofazimine 300 mg	Dapsone 100 mg *and* clofazimine 50 mg	12-24 months
	Pediatric*	Rifampicin 450 mg *and* clofazimine 150 mg	Dapsone 50 mg *and* clofazimine 50 mg *every other day*	
Paucibacillary (TT, BT)	Adult	Rifampicin 600 mg	Dapsone 100 mg	6-12 months
	Pediatric*	Rifampicin 450 mg	Dapsone 50 mg	6 months
Paucibacillary (single lesion)†		Rifampicin 600 mg *and* ofloxacin 400 mg *and* minocycline 100 mg		One time, single dose

*In children younger than 10 yr of age, dosages of multidrug therapy should be in mg/kg, not to exceed the adult daily maximum: rifampicin 10 mg/kg once monthly, dapsone 2 mg/kg/day, clofazimine 1 mg/kg on alternate days.
†Paucibacillary single-lesion, one-time single-dose therapy may be less effective than the 6 mo paucibacillary multidrug therapy regimen.
BB, borderline; BL, borderline lepromatous; BT, borderline tuberculoid; LL, lepromatous; TT, tuberculoid.

prednisone 1 mg/kg/day orally (40-60 mg) with a slow taper (decreasing by 5 mg every 2-4 wk after evidence of improvement over 3-6 mo) is recommended in addition to standard MDT. If there is evidence of peripheral nerve deterioration, higher doses and longer tapers may be needed. Nerve function improves after corticosteroid treatment in 60-70% of patients who did not have preexisting neuritis. For type 2 reactions in patients older than 12 yr of age with systemic symptoms, thalidomide (100 mg/day for 4 days) is the drug of choice. Given the teratogenicity of thalidomide, the drug is only available from the Celgene Corporation under the System for Thalidomide Education and Prescribing Safety (STEPS) program (http://www.celgene.com; 888-771-0141). In younger patients or pregnant females in whom thalidomide is contraindicated or in older patients with thalidomide-refractory ENL, corticosteroids may be used in daily doses of 1 mg/kg for 12 wk. Monitoring and management of the deleterious side effects of chronic corticosteroid therapy is challenging in chronic cases. Clofazimine (300 mg/day tapering to <100 mg/day for 12 mo) has been useful in managing patients with chronic ENL as well. Lucio's phenomenon is managed with corticosteroids and treatment of underlying infections.

In regards to care of the exposed contacts of index patients, standard isolation precautions are recommended in the hospital setting. Hand hygiene is recommended for all people in contact with a patient with lepromatous leprosy. Disinfection of nasal secretions and handkerchiefs should be performed until treatment is established. Household contacts of patients, particularly patients with multibacillary disease, should be examined at baseline and then yearly for 5 yr. Any suspected or newly diagnosed case of leprosy in the United States should be reported to local and state public health departments, the Centers for Disease Control and Prevention, and the NHDP.

In endemic countries, close monitoring of household contacts of HD patients, particularly those with multibacillary disease and either chemoprophylaxis or early treatment to contacts with evidence of early HD are effective control strategies. A single dose of bacilli Calmette-Guérin (BCG) vaccine gives variable protective efficacy against leprosy ranging from 28-80%; an additional dose demonstrated increased protection. A heat-killed leprosy vaccine, given as an immunotherapeutic adjuvant along with combination MDT, is approved for use in India. In nonendemic areas, disease presenting in the contacts of patients with HD is rare. Chemoprophylaxis after contact is not routinely recommended in the United States, but local public health departments should be contacted for consultation on individual cases. There are no leprosy vaccines available or recommended for use in the United States.

LONG-TERM COMPLICATIONS

Serious consequences of leprosy occur from the mycobacterium's direct effect on skin and nerve involvement as well as from immune reactions. Indeed, leprosy is a leading cause of permanent physical disability among communicable diseases worldwide. The major chronic complications and deformities of leprosy are caused by segmental demyelination and permanent nerve injury. The prognosis for arresting progression of tissue and nerve damage is good if therapy is started early, but recovery of lost sensory and motor function is variable and frequently incomplete. Nerve impairment may be purely sensory, motor, or autonomic, or may be a combination. Sensory deficits lead to undetected trauma, ulceration, and osteomyelitis. Motor deficits result in muscle paralysis, atrophy, and limb deformities, especially of small muscles of the hand and foot (claw hand or foot, foot drop). Autonomic deficits can lead to skin drying and cracking. The most chronic residual deformity is that of an insensitive foot and requires frequent, routine surveillance of the plantar aspect of both feet. Painful neuropathy is also observed. Nerve function impairment can occur before diagnosis, during MDT, or after MDT and can develop during a reaction or without overt signs of skin or nerve inflammation (silent neuropathy). Patients at highest risk of nerve impairment are those with multibacillary leprosy and preexisting nerve damage. These patients should undergo regular monthly surveillance during therapy and for at least 2 yr from the time of diagnosis. From 3-10% of children will develop deformities, with the risk being 6.1 times higher in children with nerve enlargement as compared with children who do not have nerve enlargement. Other factors contributing to risk of deformities include increasing age of children, delay in accessing medical care, multiple skin lesions, multibacillary disease, smear positivity, multiple nerve involvement, and leprosy reaction at the time of presentation. An ophthalmologist should routinely examine all patients with HD because ocular complications, such as lagophthalmos and blindness, can occur. Given the proclivity for testicular invasion in multibacillary leprosy with resultant testicular dysfunction and infertility, males should be screened for elevated follicle-stimulating hormone or luteinizing hormone concentrations and decreased testosterone levels.

PREVENTION

Patient education is key to the successful management of HD. Patients should be encouraged to be compliant with MDT, educated about the signs and symptoms of neuritis, and advised to practice self-examination and seek prompt medical care should they develop neuritis or other symptoms of clinical exacerbations or leprosy reactions. Surgery and rehabilitation therapies such as physical and occupational therapy as well as counseling for the social and psychologic effects of the disease may also be required for optimal outcomes. Patient reassurance of the ability to lead a normal and productive social life and education of the community, including refuting myths and social stigma, are important parts of management.

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Chapter 217

Nontuberculous Mycobacteria

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Nontuberculous mycobacteria (NTM), also referred to as **atypical mycobacteria** or **mycobacteria other than tuberculosis**, are all members of the genus *Mycobacterium* other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. The NTM constitute a highly diverse group of bacteria that differ from *M. tuberculosis* complex bacteria in their pathogenicity, interhuman transmissibility, nutritional requirements, ability to produce pigments, enzymatic activity, and drug susceptibility. In contrast to the *M. tuberculosis* complex, NTM are acquired from environmental sources and not by person-to-person spread, although the latter is now under debate, especially in patients with cystic fibrosis. Their omnipresence in our environment implies that the clinical relevance of NTM isolation from clinical specimens is often unclear; a positive culture might reflect occasional presence or contamination rather than true NTM disease. NTM are associated with pediatric lymphadenitis, otomastoiditis, serious lung infections, and, albeit rarely, disseminated disease. Treatment is long-term and cumbersome and often requires adjunctive surgical intervention. Guidelines on diagnosis and treatment are provided by the American and British Thoracic Societies.

ETIOLOGY

NTM are ubiquitous in the environment all over the world, existing as saprophytes in soil and (tap) water, environmental niches that are the supposed sources of human infections. Owing to the introduction of molecular identification tools such as 16S recombinant DNA gene sequencing, the number of identified NTM species has grown to more than 150; the clinical relevance (i.e., the percentage of isolates that are causative agents of true NTM disease, rather than occasional presence) differs significantly by species.

Mycobacterium avium complex (MAC; i.e., *M. avium*, *Mycobacterium intracellulare* and several closely related but more rare species) and *Mycobacterium kansasii* are most often isolated from clinical samples, yet the isolation frequency of these species differs significantly by geographic area. MAC bacteria have been commonly isolated from natural and synthetic environments, and cases of MAC disease have been successfully linked to home exposure to shower and tap water. Although the designation *M. avium* suggests that human *M. avium* infections are acquired from birds (*avium* being Latin for "of birds"), molecular typing has established that *M. avium* strains that cause pediatric lymphadenitis and adult pulmonary disease represent the *M. avium hominissuis* subgrouping that is mainly found in humans and pigs and not in birds.

Some NTM have well-defined ecologic niches that help explain infection patterns. The natural reservoir for *Mycobacterium marinum* is fish and other cold-blooded animals, and the "fish-tank granuloma," a localized skin infection caused by *M. marinum,* follows skin injury in an aquatic environment. *Mycobacterium fortuitum* complex bacteria and *Mycobacterium chelonae* are ubiquitous in water and have caused clusters of nosocomial surgical wound and venous catheter–related infections. *Mycobacterium ulcerans* is associated with severe, chronic skin infections (**Buruli ulcer disease**) and is endemic mainly in West Africa and Australia, although other foci exist. Its incidence is highest in children younger than 15 yr old. *M. ulcerans* had been commonly detected in environmental samples by polymerase chain reaction but was only recently recovered by culture from a Water Strider (*Gerris* sp.) from Benin.

EPIDEMIOLOGY

Humans are exposed to NTM on a daily basis. In rural counties in the United States, where *M. avium* is prevalent in swamps, the **prevalence** of asymptomatic infections with *M. avium* complex, as measured by skin test sensitization, approaches 70% by adulthood. Still, the incidence and prevalence of the various NTM disease types remain largely unknown, especially for pediatric NTM disease. In Australian children, the overall **incidence** of NTM infection is 0.84 per 100,000, with lymphadenitis accounting for two-thirds of cases. The incidence of pediatric NTM disease in the Netherlands is estimated at 0.77 infections per 100,000 children per year, with lymphadenitis making up 92% of all infections.

In comparison, estimations of the prevalence of NTM from respiratory samples in adults are 5-15 per 100,000 persons per year, with important differences between countries or regions. Because pulmonary NTM disease progresses slowly, over years rather than months, and usually takes several years to cure, the prevalence of pulmonary NTM disease is much higher than incidence rates would suggest.

The paradigm that NTM disease is a rare entity limited to developed countries is changing. In recent studies in African countries with a high prevalence of HIV infection, it has been found that NTM might play a much larger role as a cause of tuberculosis-like disease of children and adults than previously assumed and thus confuse the diagnosis of tuberculosis.

Although it is generally believed that NTM infections are contracted from environmental sources, recent whole genome sequence analysis of *Mycobacterium abscessus* strains of patients in a cystic fibrosis clinic in the United Kingdom has raised the possibility of nosocomial transmission among patients with cystic fibrosis.

PATHOGENESIS

The histologic appearances of lesions caused by *M. tuberculosis* and NTM are often indistinguishable. The classic pathologic lesion consists of **caseating granulomas.** Compared to *M. tuberculosis* infections, NTM infections are more likely to result in granulomas that are **non-caseating,** ill defined (nonpalisading), irregular or serpiginous or even absent, with only chronic inflammatory changes observed. The histology likely reflects the immune status of the patient.

In patients with AIDS and disseminated NTM infection, the inflammatory reaction is usually scant and tissues are filled with large numbers of histiocytes packed with acid-fast bacilli. These disseminated NTM infections typically occur only after the number of CD4 T-lymphocytes has fallen below 50/μL, suggesting that specific T-cell products or activities are required for immunity to mycobacteria.

The pivotal roles of interferon-γ, interleukin (IL)-12, and tumor necrosis factor-α in disease pathogenesis are demonstrated by the high incidence of mostly disseminated NTM disease in children with interferon-γ and IL-12 pathway deficiencies and in persons treated with agents that neutralize tumor necrosis factor-α.

Observed differences in pathogenicity, clinical relevance, and spectrum of clinical disease associated with the various NTM species emphasize the importance of bacterial factors in the pathogenesis of NTM disease, although exact virulence factors remain largely unknown.

CLINICAL MANIFESTATIONS

Lymphadenitis of the superior anterior cervical or submandibular lymph nodes is the most common manifestation of NTM infection in children (Table 217-1). Preauricular, posterior cervical, axillary, and inguinal nodes are involved occasionally. Lymphadenitis is most

Table 217-1 Diseases Caused by Nontuberculous Mycobacterial Species

CLINICAL DISEASE	COMMON SPECIES	LESS-COMMON SPECIES
Cutaneous infection	*Mycobacterium chelonae, Mycobacterium fortuitum, Mycobacterium abscessus, Mycobacterium marinum*	*Mycobacterium ulcerans**
Lymphadenitis	MAC	*Mycobacterium kansasii, Mycobacterium haemophilum, Mycobacterium malmoense*†
Otologic infection	*M. abscessus*, MAC	*M. fortuitum*
Pulmonary infection	MAC, *M. kansasii, M. abscessus*	*Mycobacterium xenopi, Mycobacterium malmoense,*† *Mycobacterium szulgai, M. fortuitum, Mycobacterium simiae*
Catheter-associated infection	*M. chelonae, M. fortuitum*	*M. abscessus*
Skeletal infection	MAC, *M. kansasii, M. fortuitum*	*M. chelonae, M. marinum, M. abscessus, M. ulcerans**
Disseminated	MAC	*M. kansasii, Mycobacterium genavense, M. haemophilum, M. chelonae*

*Endemic in West Africa and Australia, minor foci in East Asia and Latin America.
†Found primarily in Northern Europe.
MAC, *Mycobacterium avium* complex.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 761.*

Figure 217-1 An enlarging cervical lymph node infected with *Mycobacterium avium* complex infection. The node is firm, painless, freely movable, and not erythematous.

Figure 217-2 A suppurating cervical lymph node infected with *Mycobacterium avium* complex.

Figure 217-3 A ruptured cervical lymph node infected with *Mycobacterium avium* complex, which resembles the classic scrofula of tuberculosis.

common in children 1-5 yr of age and has been related to soil exposure (e.g., playing in sandpits) and teething, although exact predisposing conditions have not been found. Given the constant environmental exposure to NTM, the occurrence of these infections might also reflect an atypical immune response of a subset of the infected children during or after their first contact with NTM.

Affected children usually lack constitutional symptoms and present with a unilateral subacute and slowly enlarging lymph node or group of closely approximated nodes >1.5 cm in diameter that are firm, painless, freely movable, and not erythematous (Fig. 217-1). The involved nodes occasionally resolve without treatment, but most undergo rapid suppuration after several weeks (Fig. 217-2). The center of the node becomes fluctuant, and the overlying skin becomes erythematous and thin. Eventually, the nodes rupture and form cutaneous sinus tracts that drain for months or years, resembling the classic scrofula of tuberculosis (Fig. 217-3).

In the United States and Western Europe, *M. avium* complex accounts for approximately 80% of NTM lymphadenitis in children. Birds are an unlikely source of these *M. avium* complex infections, as molecular typing has shown that the lymphadenitis-associated *M. avium* bacteria are of the human or porcine subtype rather than the bird type. *M. kansasii* accounts for most other cases of lymphadenitis in the United States. *Mycobacterium malmoense* and *Mycobacterium haemophilum* have also been described as causative agents of lymphadenitis. The former is only common in Northwestern Europe; for the latter, underestimation of its importance is likely because the bacteria require specific culture conditions (hemin-enriched media, low incubation temperatures). On the basis of polymerase chain reaction analysis of lymph node samples from lymphadenitis cases in the Netherlands, *M. haemophilum* is the second most common cause of this infection after *M. avium* complex. One study suggests that children with *M. avium* complex lymphadenitis are significantly younger than those infected by *M. haemophilum*, possibly related to age-specific environmental exposures.

Cutaneous disease caused by NTM is rare in children (see Table 217-1). Infection usually follows percutaneous inoculation with fresh or salt water contaminated by *M. marinum.* Within 2-6 wk after exposure, an erythematous papule develops at the site of minor abrasions on the elbows, knees, or feet (**swimming pool granuloma**) and on the hands and fingers of fish tank owners, mostly inflicted during tank cleaning (**fish tank granuloma**). These lesions are usually nontender and enlarge over 3-5 wk to form violaceous plaques. Nodules or pustules can develop and occasionally will ulcerate, resulting in a serosanguineous discharge. The lesions sometimes resemble sporotrichosis, with satellite lesions near the site of entry, extending along the superficial lymphatics. Lymphadenopathy is usually absent. Although most infections remain localized to skin, penetrating *M. marinum* infections can result in tenosynovitis, bursitis, osteomyelitis, or arthritis.

M. ulcerans infection is the third most common mycobacterial infection in immunocompetent patients, after *M. tuberculosis* and *M. leprae* infection, and causes cutaneous disease in children living in tropical regions of Africa, South America, Asia, and parts of Australia. In some communities in West Africa, up to 16% of people have been affected. Infection follows percutaneous inoculation from minor trauma, such as pricks and cuts from plants or insect bites. After an incubation period of approximately 3 mo, lesions appear as an erythematous nodule, most commonly on legs or arms. The lesion undergoes central necrosis and ulceration. The lesion, often called a **Buruli ulcer** after the region in Uganda where a large number of cases was reported, has a characteristic undermined edge, expands over several weeks, and can result in extensive, deep soft-tissue destruction or bone involvement. Lesions are typically painless, and constitutional symptoms are unusual. Lesions might heal slowly over 6-9 mo or might continue to spread, leading to deformities and contractures.

Skin and soft-tissue infections caused by rapidly growing mycobacteria, such as *M. fortuitum, M. chelonae,* or *M. abscessus,* are rare in children and usually follow percutaneous inoculation from puncture or surgical wounds, minor abrasions, or following tattooing. Clinical disease usually arises after a 4-6 wk incubation period and manifests as localized cellulitis, painful nodules, or a draining abscess. *M. haemophilum* can cause painful subcutaneous nodules, which often ulcerate and suppurate in immunocompromised patients, particularly after kidney transplantation.

NTM are an uncommon cause of **catheter-associated infections** but are becoming increasingly recognized in this respect. Infections caused

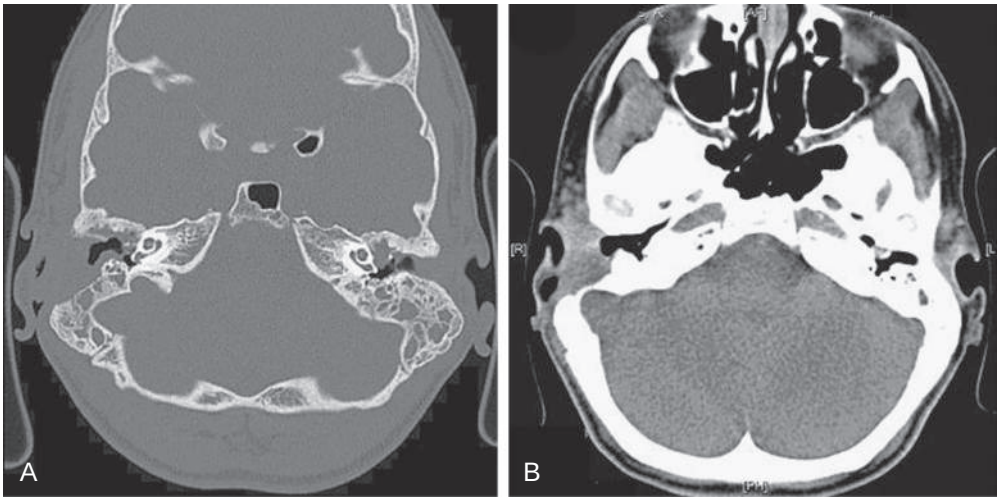

Figure 217-4 Computed tomography images of the middle ear of a 6 yr old child infected with *Mycobacterium abscessus* demonstrating extensive bone destruction in the right mastoid and associated right-sided mucosal swelling. **A,** Bone tissue window setting. **B,** Soft-tissue window setting.

by *M. fortuitum, M. chelonae,* or *M. abscessus* can manifest as bacteremia or localized catheter tunnel infections.

Otomastoiditis, or chronic otitis media, is a rare extrapulmonary NTM disease type that specifically affects children with tympanostomy tubes and a history of topical antibiotic or steroid use. *M. abscessus* is the most common causative agent, followed by *M. avium* complex (see Table 217-1). Patients present with painless, chronic otorrhea resistant to antibiotic therapy. CT imaging can reveal destruction of the mastoid bone with mucosal swelling (Fig. 217-4). Delayed or unsuccessful treatment can result in permanent hearing loss. In unusual circumstances, NTM causes other **bone** and **joint infections** that are indistinguishable from those produced by *M. tuberculosis* or other bacterial agents. Such infections usually result from operative incision or accidental puncture wounds. *M. fortuitum* infections from puncture wounds of the foot resemble infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Pulmonary infections are the most common form of NTM illness in adults but are rare in children. *M. avium* complex bacteria, the most commonly identified organisms (see Table 217-1), are capable of causing acute pneumonitis, chronic cough, or wheezing associated with paratracheal or peribronchial lymphadenitis and airway compression in normal children. Associated constitutional symptoms such as fever, anorexia, and weight loss occur in 60% of these children. Chest radiographic findings are very similar to those for primary tuberculosis, with unilateral infiltrates and hilar lymphadenopathy (Fig. 217-5). Pleural effusion is uncommon. Rare cases of progression to endobronchial granulation tissue have been reported.

Pulmonary infections usually occur in adults with underlying chronic lung disease. The onset is insidious and consists of cough and fatigue, progressing to weight loss, night sweats, low-grade fever, and generalized malaise in severe cases. Thin-walled cavities with minimal surrounding parenchymal infiltrates are characteristic, but radiographic findings can resemble those of tuberculosis. A separate disease manifestation occurs in postmenopausal women and is radiologically characterized by bronchiectasis and nodular lesions, often affecting the middle lobe and lingula.

Chronic pulmonary infections specifically affect children with **cystic fibrosis** and are generally caused by *M. abscessus* and *M. avium* complex. *M. abscessus* primarily affects children, and *M. avium* complex is most common among adults. The percentage of patients with cystic fibrosis with at least 1 sputum culture positive for NTM is 6-8.1% overall and increases with age; in cystic fibrosis patients younger than 12 yr of age, a prevalence of 3.9% has been reported. The strong representation of *M. abscessus* in these patients is remarkable, because this bacterium is an uncommon isolate in other categories of patients.

Figure 217-5 Chest radiograph of a 2 yr old child infected with *Mycobacterium avium* complex demonstrating a left upper lobe infiltrate and left hilar lymphadenopathy.

There are indications that NTM infections in patients with cystic fibrosis further accelerate the decline in lung function; antimycobacterial therapy can result in weight gain and improved lung function in affected patients.

Disseminated disease is usually associated with *M. avium* complex infection and occurs in immunocompromised children. The first category of patients with disseminated disease includes persons with mutations in genes coding for the interferon-γ receptor (IFNGR) or the IL-12 receptor, or for IL-12 production. Patients with complete **IFNGR deficiency** have severe disease that is difficult to treat. Those with partial IFNGR deficiency or IL-12 pathway mutations have milder disease that can respond to interferon-γ and antimycobacterial therapy. **Multifocal osteomyelitis** is particularly prevalent in persons with the IFNGR1 818del4 mutation. Recurrences, even years after a course of treatment, and multiple infections are well documented. The second

category of patients affected by **disseminated disease** is patients with **AIDS**. Disseminated NTM disease in patients with AIDS usually appears when CD4 cell counts are <50 cells/μL; in younger children (especially those <2 yr of age) these infections occur at higher CD4 cell counts. The most recent estimate of the incidence of disseminated NTM disease is 0.14-0.2 episodes per 100 person-years, a 10-fold decrease from its incidence before highly active antiretroviral therapy (HAART) was available.

Colonization of the respiratory or gastrointestinal tract probably precedes disseminated *M. avium* complex infections, but screening studies of respiratory secretions or stool samples are not useful to predict dissemination. Continuous high-grade bacteremia is common, and multiple organs are infected, most commonly including lymph nodes, liver, spleen, bone marrow, and gastrointestinal tract. Thyroid, pancreas, adrenal gland, kidney, muscle, and brain can also be involved. The most common signs and symptoms of disseminated *M. avium* complex infections in patients with AIDS are fever, night sweats, chills, anorexia, marked weight loss, wasting, weakness, generalized lymphadenopathy, and hepatosplenomegaly. Jaundice, elevated alkaline phosphatase or lactate dehydrogenase levels, anemia, and neutropenia can occur. Imaging studies usually demonstrate massive lymphadenopathy of hilar, mediastinal, mesenteric, or retroperitoneal nodes. The survival in children with AIDS has improved considerably with the availability of HAART therapy.

Disseminated disease in children without any apparent immunodeficiency is exceedingly rare.

DIAGNOSIS

For infections of lymph nodes, skin, bone, and soft tissues, isolation of the causative NTM bacteria by *Mycobacterium* **culture**, preferably with histologic confirmation of granulomatous inflammation, normally suffices for diagnosis. The differential diagnosis of NTM lymphadenitis includes acute bacterial lymphadenitis, tuberculosis, cat scratch disease (*Bartonella henselae*), mononucleosis, toxoplasmosis, brucellosis, tularemia, and malignancies, especially lymphomas. Differentiation between NTM and *M. tuberculosis* may be difficult, but children with NTM lymphadenitis usually have a Mantoux tuberculin skin test reaction of <15 mm induration, unilateral anterior cervical node involvement, a normal chest x-ray, and no history of exposure to adult tuberculosis. Definitive diagnosis requires excision of the involved nodes for culture and histology. Fine-needle aspiration for **polymerase chain reaction** and culture can enable earlier diagnosis, before excisional biopsy.

The diagnosis of **pulmonary NTM infection** in children is difficult because many species of NTM, including *M. avium* complex, are omnipresent in our environment and can contaminate, or occasionally be present in, clinical samples. As a result, isolation of these bacteria from nonsterile specimens (respiratory and digestive tract) does not necessarily reflect true disease. To determine the clinical relevance of isolation of NTM, the diagnostic criteria of the American and British Thoracic Societies are an important support. These criteria take into consideration clinical features and radiologic, pathologic, and microbiologic findings. The hallmark of these criteria is the need for **multiple positive cultures** yielding the same NTM species to make a definitive diagnosis of pulmonary NTM disease. In children, definitive diagnosis often requires invasive procedures such as bronchoscopy and pulmonary or endobronchial biopsy; in patients with cystic fibrosis, more-aggressive sample pretreatment is necessary to prevent overgrowth by other species, especially *Pseudomonas* spp. The chance that isolation of NTM is clinically relevant differs significantly by species; some species are more likely causative agents of true pulmonary disease (*M. avium*, *M. kansasii*, *M. abscessus*, *M. malmoense*), whereas others are most likely contaminants (*Mycobacterium gordonae*, *M. fortuitum*, *M. chelonae*).

Blood cultures are 90-95% sensitive in AIDS patients with disseminated infection. *M. avium* complex may be detected within 7-10 days of inoculation in nearly all patients by automated blood culture systems. In adults, liver biopsy cultures and stains have, in some studies, shown to be more sensitive than blood culture or bone marrow biopsy work-up. Commercially available DNA probes differentiate NTM from *M. tuberculosis.* If DNA probes cannot identify the causative mycobacteria, DNA sequencing of bacterial housekeeping genes will always yield a clue to the identity of these NTM. Identification of histiocytes containing numerous acid-fast bacilli from bone marrow and other biopsy tissues provides a rapid presumptive diagnosis of disseminated mycobacterial infection.

TREATMENT

Therapy for NTM infections is long-term and cumbersome; **expert consultation** is advised. Therapy involves medical, surgical, or combined treatment (see Chapter 214 and Table 214-3). Isolation of the infecting strain followed by **drug-susceptibility testing** is ideal, because it provides a baseline for drug susceptibility. Important discrepancies exist between in vitro drug susceptibility and in vivo response to treatment, explained in part by synergism, mainly among first-line antituberculosis drugs. In vitro, slow growers (*M. kansasii, M. marinum, Mycobacterium xenopi, M. ulcerans,* and *M. malmoense*) are usually susceptible to the first-line antituberculosis drugs rifampicin and ethambutol; *M. avium* complex bacteria are often resistant to these drugs alone but susceptible to the combination and have variable susceptibility to other antibiotics, most importantly the macrolides. Rapid growers (*M. fortuitum, M. chelonae, M. abscessus*) are highly resistant to antituberculosis drugs and often have inducible macrolide resistance mechanisms. Susceptibility to macrolides, aminoglycosides, carbapenems, tetracyclines, and glycylcyclines are most relevant for therapy guidance. In all NTM infections, multiple-drug therapy is essential to avoid development of resistance.

The preferred treatment of NTM lymphadenitis is complete **surgical excision;** clinical trials revealed that it is more effective than antibiotic treatment (see Table 214-3 in Chapter 214). Nodes should be removed while still firm and encapsulated. Excision is more difficult if extensive caseation with extension to surrounding tissue has occurred, and complications of facial nerve damage or recurrent infection are more likely in such cases. Incomplete surgical excision is not advised, because chronic drainage can develop. If there is concern for possible *M. tuberculosis* infection, therapy with isoniazid, rifampin, ethambutol, and pyrazinamide should be administered until cultures confirm the cause to be NTM (see Chapter 215). If for some reason surgery of NTM lymphadenitis cannot be performed, removal of infected tissue is incomplete, or recurrence or chronic drainage develops, a 3 mo trial of chemotherapy is warranted. Clarithromycin or azithromycin combined with rifabutin or ethambutol are the most commonly reported therapy regimens (see Table 214-3 in Chapter 214). In selected cases, a wait-and-see approach can be chosen, as the disease can resolve spontaneously.

Posttraumatic cutaneous NTM lesions in immunocompetent patients usually heal spontaneously after incision and drainage without other therapy (see Table 214-3 in Chapter 214). ***M. marinum*** is susceptible to rifampin, amikacin, ethambutol, sulfonamides, trimethoprim-sulfamethoxazole, and tetracycline. Therapy with a combination of these drugs, particularly clarithromycin and ethambutol, may be given for until 1 month after the lesion has disappeared. Corticosteroid injections should not be used. Superficial infections with *M. fortuitum* or *M. chelonae* usually resolve after surgical incision and open drainage, but deep-seated or catheter-related infections require removal of infected central lines and therapy with parenteral amikacin plus cefoxitin, ciprofloxacin, or clarithromycin.

Some localized forms of *M. ulcerans* skin disease (**Buruli ulcer**) can heal spontaneously; for most forms, excisional surgery with primary closure or skin grafting is recommended. Provisional guidelines by the World Health Organization recommend treatment with rifampin and streptomycin, with or without surgery. Currently, all-oral regimens of rifampicin and fluoroquinolones or macrolides are tested in clinical trials. In clinical experience, a drug treatment duration of 8 wk generally leads to low recurrence levels. Physiotherapy after surgery is essential to prevent contractures and functional disabilities.

Pulmonary infections should be treated initially with isoniazid, rifampin, ethambutol, and pyrazinamide pending culture identification

and drug-susceptibility testing. For slow-growing NTM, a combination of rifampin or rifabutin, ethambutol, and clarithromycin is recommended; exceptions are *M. kansasii*, for which a regimen of isoniazid, rifampicin, and ethambutol is advised, and *M. simiae*, for which no effective regimen is known and regimens are usually designed on the basis of in vitro drug susceptibilities. After culture conversion, treatment should be continued for at least 1 yr. For pulmonary disease caused by rapidly growing NTM, a combination of macrolides, fluoroquinolones, aminoglycosides, cefoxitin, and carbapenems is the optimal therapy; 3 or 4 drug regimens are selected on the basis of drug-susceptibility testing results. In patients with cystic fibrosis, there may be a role for inhaled antibiotics.

Patients with disseminated *M. avium* complex and IL-12 pathway defects or IFNGR deficiency should be treated for at least 12 mo with clarithromycin or azithromycin combined with rifampin or rifabutin and ethambutol. In vitro susceptibility testing for clarithromycin is important to guide therapy. Once the clinical illness has resolved, lifelong daily prophylaxis with azithromycin or clarithromycin is advisable to prevent recurrent disease. The use of interferon adjunctive therapy is determined by the specific genetic defect.

In children with **AIDS**, **prophylaxis** with azithromycin or clarithromycin is indicated to prevent infection with *M. avium* complex. Although few pediatric studies exist, the U.S. Public Health Service recommends either azithromycin (20 mg/kg once weekly PO; maximum: 1,200 mg/dose) or clarithromycin (7.5 mg/kg/dose twice daily PO; maximum:500 mg/dose) for HIV-infected children with significant immune deficiency as defined by the CD4 count (children ≥6 yr, CD4 count <50/μL; 2-6 yr, CD4 count <75/μL; 1-2 yr, CD4 count <500/μL; <1 yr, CD4 count <750/μL). Prophylaxis may be safely discontinued in children older than 2 yr of age receiving stable HAART for longer than 6 mo and experiencing sustained (>3 mo) CD4 cell recovery well above the age-specific target for initiation of prophylaxis: >100 cells/μL for children ≥6 yr of age and >200 cells/μL for children 2-5 yr of age. For children younger than 2 yr of age, no specific recommendations for discontinuing MAC prophylaxis exist.

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Section 8

Spirochetal Infections

Chapter 218

Syphilis (*Treponema pallidum*)

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Syphilis is a chronic systemic sexually transmitted infection that can be easily treated if detected early but manifests with protean clinical symptoms and significant morbidity if left unchecked.

ETIOLOGY

Syphilis is caused by *Treponema pallidum,* a delicate, tightly spiraled, motile spirochete with finely tapered ends belonging to the family Spirochaetaceae. The pathogenic members of this genus include *T. pallidum* subspecies *pallidum* (venereal syphilis), *T. pallidum* subspecies *pertenue* (yaws), *T. pallidum* subspecies *endemicum* (bejel or endemic syphilis), and *T. pallidum* subspecies *carateum* (pinta). Because these microorganisms stain poorly and are below the detection limits of conventional light microscopy, detection in clinical specimens requires dark-field or phase contrast microscopy or direct immunofluorescent staining. *T. pallidum* cannot be cultured in vitro.

EPIDEMIOLOGY

In addition to presentation at sexually transmitted disease clinics, patients with syphilis are increasingly seen by primary care providers in private practice settings. Two forms of syphilis occur in children and adolescents.

Acquired syphilis is transmitted almost exclusively by sexual contact, including vaginal, anal, and oral exposure. Less-common modes of transmission include transfusion of contaminated blood or direct contact with infected tissues. After an epidemic resurgence of primary and secondary syphilis in the United States that peaked in 1989, the annual rate declined 90% by 2000. The total number of cases of primary and secondary syphilis has subsequently increased since 2000, particularly among men who have sex with men. Despite a decrease among women for almost a decade, their rates increased every year from 2004-2008. Cases of congenital syphilis rose in the same time period, but have fallen from 2008 through 2011, reflecting the slight decrease among women (Fig. 218-1). Rates in the southern United States, in some urban areas, and among non-Hispanic blacks remain disproportionately high.

Congenital syphilis results from transplacental transmission of spirochetes or during birth by contact with infectious lesions. Women with primary and secondary syphilis and spirochetemia are more likely to transmit infection to the fetus than are women with latent infection. Transmission can occur at any stage of pregnancy, resulting in early fetal loss, preterm or low birthweight infants, stillbirths, neonatal deaths, or infants born with congenital disease. The incidence of congenital infection in offspring of untreated or inadequately treated infected women remains highest during the 1st 4 yr after acquisition of primary infection, secondary infection, and early latent disease. Maternal factors associated with congenital syphilis are limited access to healthcare, late or no prenatal care, drug use, multiple sex partners, unprotected sexual contact, work in the sex trade, and inadequate treatment of syphilis during pregnancy (Fig. 218-2). Confirmed cases of both acquired and congenital syphilis must be reported to the local health department.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Many persons infected with syphilis are asymptomatic for years or do not recognize the early signs of disease or seek treatment. The Centers for Disease Control and Prevention (CDC) recommends selective testing of adolescents, based on lesions or risk factors (those with other sexually transmitted diseases, men who have sex with men,

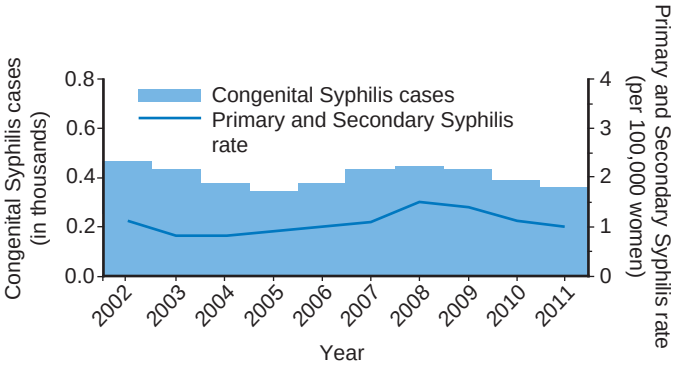


Figure 218-1 Congenital syphilis—reported cases among infants by year of birth and rates of primary and secondary syphilis among women, United States, 2002-2011. *(From Centers for Disease Control and Prevention [CDC]: 2011 Sexually transmitted disease surveillance. Available at: http://www.cdc.gov/std/stats11/figures/50.htm)*

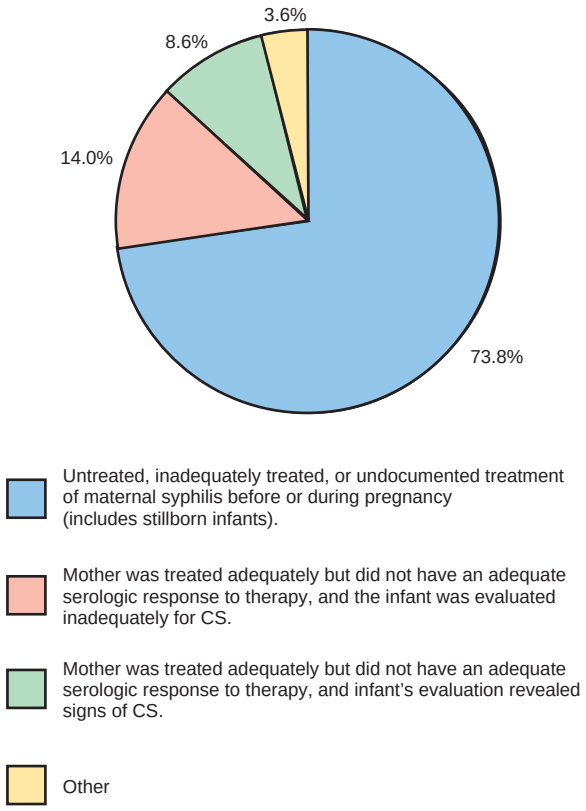


Figure 218-2 Diagnoses of congenital syphilis in the United States, 2002. *(From Centers for Disease Control and Prevention [CDC]: Primary and secondary syphilis—United States, 2002,* MMWR Morb Mortal Wkly Rep *52:1117–1120, 2003.)*

Figure 218-3 Secondary syphilis. Ham-colored palmar macules on an adolescent with secondary syphilis. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 3. St. Louis, 2002, Mosby.)*

incarcerated individuals, or persons who exchange sex for money or drugs). **Primary syphilis** is characterized by a chancre and regional lymphadenitis. A **painless papule** appears at the site of entry (usually the genitals) 2-6 wk after inoculation and develops into a clean, painless, but highly contagious ulcer with raised borders (**chancre**) containing abundant *T. pallidum*. Extragenital chancres can occur at other sites of primary entry and pose a diagnostic challenge. Oral lesions can be mistaken for aphthous ulcers or herpes. Lesions on the nipple can be confused with cellulitis or eczema. Adjacent lymph nodes are generally enlarged and nontender. The chancre heals spontaneously within 4-6 wk, leaving a thin scar.

Untreated patients develop manifestations of **secondary syphilis** related to spirochetemia 2-10 wk after the chancre heals. Manifestations of secondary syphilis include a generalized nonpruritic maculopapular rash, notably involving the palms and soles (Fig. 218-3). Pustular lesions can also develop. **Condylomata lata,** gray-white to erythematous wart-like plaques, can occur in moist areas around the anus and vagina, and white plaques (**mucous patches**) may be found in mucous membranes. Secondary syphilis should be considered in the differential diagnosis of virtually any rash of unknown etiology. A **flu-like illness** with low-grade fever, headache, malaise, anorexia, weight loss, sore throat, myalgias, arthralgias, and generalized lymphadenopathy is often present. Renal, hepatic, and ophthalmologic manifestations may be present. Meningitis occurs in 30% of patients with secondary syphilis and is characterized by cerebrospinal fluid (CSF) pleocytosis and elevated protein level. Patients with meningitis might not show neurologic symptoms. Even without treatment, secondary infection becomes **latent** within 1-2 mo after onset of rash. Relapses with secondary manifestations can occur during the 1st yr of latency (the **early latent period). Late syphilis** follows and may be either asymptomatic (**late latent**) or symptomatic (**tertiary**). Tertiary disease follows in about one-third of untreated cases and is marked by neurologic, cardiovascular, and **gummatous lesions** (nonsuppurative granulomas of the skin, bone, and liver, resulting from the host cytotoxic T-cell response). The clinical course of syphilis and its tissue manifestations reflect the immunopathobiology of the host humoral and delayed-type hypersensitivity responses.

Congenital Infection

Untreated syphilis during pregnancy has a vertical transmission rate approaching 100%, with profound effects on pregnancy outcome. Fetal or perinatal death occurs in 40% of affected infants. Premature delivery can also occur. Neonates can also be infected at delivery by contact with an active genital lesion. Most infected infants are asymptomatic at birth and are identified only by routine prenatal screening. In the absence of treatment, symptoms develop within weeks or months. Among infants symptomatic at birth or in the 1st few mo of life, manifestations have traditionally been divided into early and late stages. All stages of congenital syphilis are characterized by a vasculitis, with progression to necrosis and fibrosis. The **early signs** appear during the 1st 2 yr of life, and the **late signs** appear gradually during the 1st 2 decades. Early manifestations vary and involve multiple organ systems, resulting from transplacental spirochetemia and are analogous to the secondary stage of acquired syphilis (Table 218-1). Hepatosplenomegaly, jaundice, and elevated liver enzymes are common. Histologically, liver involvement includes bile stasis, fibrosis, and extramedullary hematopoiesis. Lymphadenopathy tends to be diffuse and resolve spontaneously, although shotty nodes can persist.

Coombs-negative hemolytic anemia is characteristic. Thrombocytopenia is often associated with platelet trapping in an enlarged spleen. Characteristic osteochondritis and periostitis (Fig. 218-4) and a mucocutaneous rash (Fig. 218-5*A* and *B*) manifesting with erythematous maculopapular or vesiculobullous lesions followed by desquamation involving hands and feet (Fig. 218-5*C*) are common. Mucous patches, persistent rhinitis (**snuffles**), and condylomatous lesions (Fig. 218-6) are highly characteristic features of mucous membrane involvement containing abundant spirochetes. Blood and moist open lesions from infants with congenital syphilis and children with acquired primary or secondary syphilis are infectious until 24 hr of appropriate treatment.

Bone involvement is common. Roentgenographic abnormalities include **Wimberger lines** (metaphyseal demineralization of the medial aspect of the proximal tibia), multiple sites of osteochondritis at the wrists, elbows, ankles, and knees, and periostitis of the long bones and rarely the skull. The osteochondritis is painful, often resulting in irritability and refusal to move the involved extremity (**pseudoparalysis of Parrot**).

Congenital neurosyphilis is often asymptomatic in the neonatal period although CSF abnormalities can occur even in such infants.

Table 218-1 Late Manifestations of Congenital Syphilis

SYMPTOM/SIGN	DESCRIPTION/COMMENTS
Olympian brow	Bony prominence of the forehead caused by persistent or recurrent periostitis
Clavicular or Higoumenakia sign	Unilateral or bilateral thickening of the sternoclavicular third of the clavicle
Saber shins	Anterior bowing of the midportion of the tibia
Scaphoid scapula	Convexity along the medial border of the scapula
Hutchinson teeth	Peg-shaped upper central incisors; they erupt during 6th yr of life with abnormal enamel, resulting in a notch along the biting surface
Mulberry molars	Abnormal 1st lower (6 yr) molars characterized by small biting surface and excessive number of cusps
Saddle nose*	Depression of the nasal root, a result of syphilitic rhinitis destroying adjacent bone and cartilage
Rhagades	Linear scars that extend in a spoke-like pattern from previous mucocutaneous fissures of the mouth, anus, and genitalia
Juvenile paresis	Latent meningovascular infection; it is rare and typically occurs during adolescence with behavioral changes, focal seizures, or loss of intellectual function
Juvenile tabes	Rare spinal cord involvement and cardiovascular involvement with aortitis
Hutchinson triad	Hutchinson teeth, interstitial keratitis, and 8th nerve deafness
Clutton joint	Unilateral or bilateral painless joint swelling (usually involving knees) from synovitis with sterile synovial fluid; spontaneous remission usually occurs after several weeks
Interstitial keratitis	Manifests with intense photophobia and lacrimation, followed within weeks or months by corneal opacification and complete blindness
8th nerve deafness	May be unilateral or bilateral, appears at any age, manifests initially as vertigo and high-tone hearing loss, and progresses to permanent deafness

*A perforated nasal septum may be an associated abnormality.

Figure 218-4 Osteochondritis and periostitis in a newborn with congenital syphilis.

Failure to thrive, chorioretinitis, nephritis, and nephrotic syndrome can also be seen. Manifestations of renal involvement include hypertension, hematuria, proteinuria, hypoproteinemia, hypercholesterolemia, and hypocomplementemia, probably related to glomerular deposition of circulating immune complexes. Less-common clinical manifestations of early congenital syphilis include gastroenteritis, peritonitis, pancreatitis, pneumonia, eye involvement (glaucoma and chorioretinitis), nonimmune hydrops, and testicular masses.

Late manifestations (children >2 yr of age) are rarely seen in developed countries. These result primarily from chronic granulomatous inflammation of bone, teeth, and central nervous system and are summarized in Table 218-1. Skeletal changes are caused by persistent or recurrent periostitis and associated thickening of the involved bone. Dental abnormalities, such as **Hutchinson teeth** (Fig. 218-7), are common. Defects in enamel formation lead to repeated caries and eventual tooth destruction. S**addle nose** (Fig. 218-8) is a depression of the nasal root and may be associated with a perforated nasal septum.

Other late manifestations of congenital syphilis can manifest as hypersensitivity phenomena. These include unilateral or bilateral interstitial keratitis and the **Clutton joint** (see Table 218-1). Other common ocular manifestations include choroiditis, retinitis, vascular occlusion, and optic atrophy. Soft-tissue gummas (identical to those of acquired disease) and paroxysmal cold hemoglobinuria are rare hypersensitivity phenomena.

DIAGNOSIS

Fundamental limitations of the currently available tests for syphilis are vexing, but results must always be interpreted in the context of patient history and physical examination. Physicians should treat presumptively when syphilis is suspected by clinical and epidemiologic data. Diagnosis of primary syphilis is confirmed when *T. pallidum* is demonstrated by darkfield microscopy or direct fluorescent antibody testing on specimens from skin lesions, placenta, or umbilical cord. Nucleic acid–based amplification assays, such as polymerase chain reaction, are not commercially available. Despite the absence of a true gold standard serologic assay, serologic testing for syphilis remains the principal means for diagnosis and traditionally involves screening

Figure 218-5 **A** and **B,** Papulosquamous plaques in 2 infants with syphilis. **C,** Desquamation on the palm of a newborn's hand. (***A*** *and* ***B*** *from Eichenfeld LF, Frieden IJ, Esterly NB, editors:* Textbook of neonatal dermatology, *Philadelphia, 2001, WB Saunders, p. 196.* ***C*** *courtesy of Dr. Patricia Treadwell.)*

Figure 218-6 Perianal condylomata lata. *(From Karthikeyan K, Thappa DM: Early congenital syphilis in the new millennium,* Pediatr Dermatol *19:275–276, 2002.)*

Figure 218-7 Hutchinson teeth as a late manifestation of congenital syphilis.

Figure 218-8 Saddle nose in a newborn with congenital syphilis.

with a nontreponemal test followed by a confirmatory treponemal test (Fig. 218-9*A*).

The **Venereal Disease Research Laboratory (VDRL)** and **rapid plasma reagin (RPR)** tests are sensitive **nontreponemal tests** that detect antibodies against phospholipid antigens on the treponeme surface that crossreact with cardiolipin-lecithin-cholesterol antigens of damaged host cells. The quantitative results of these tests are helpful both in screening and in monitoring therapy. Titers increase with active disease, including treatment failure or reinfection, and decline with adequate treatment (Fig. 218-10). Nontreponemal tests usually become nonreactive within 1 yr of adequate therapy for primary syphilis and within 2 yr of adequate treatment for secondary disease. Uncommonly some patients become **serofast** (nontreponemal titers persisting at low levels for long periods). In congenital infection, these tests become nonreactive within a few months after adequate treatment. Certain conditions such as infectious mononucleosis and other viral infections, autoimmune diseases, and pregnancy can give false-positive VDRL results. False-positive results are less common with the use of purified cardiolipin-lecithin-cholesterol antigen. All pregnant women should be screened early in pregnancy and at delivery. All positive maternal serologic tests for syphilis, regardless of titer, necessitate thorough investigation. Antibody excess can give a false-negative reading unless the serum is diluted **(prozone effect).** False-negative results can also occur in early primary syphilis, in latent syphilis of long duration, and in late congenital syphilis.

Treponemal tests traditionally are used to confirm diagnosis and measure specific *T. pallidum* antibodies (immunoglobulin [Ig] G, IgM and IgA), which appear earlier than nontreponemal antibodies. These treponemal tests include the *T. pallidum* particle agglutination test, the *T. pallidum* hemagglutination assay, and the fluorescent treponemal antibody absorption test. Treponemal antibody titers become positive soon after initial infection and usually remain positive for life, even with adequate therapy (see Fig. 218-10). These antibody titers do not correlate with disease activity. Traditionally they are useful for diagnosis of a first episode of syphilis and for distinguishing false-positive results of nontreponemal antibody tests but cannot accurately identify length of time of infection, response to therapy, or reinfection.

There is limited crossreactivity of treponemal antibody tests with other spirochetes, including the causative organisms of Lyme disease

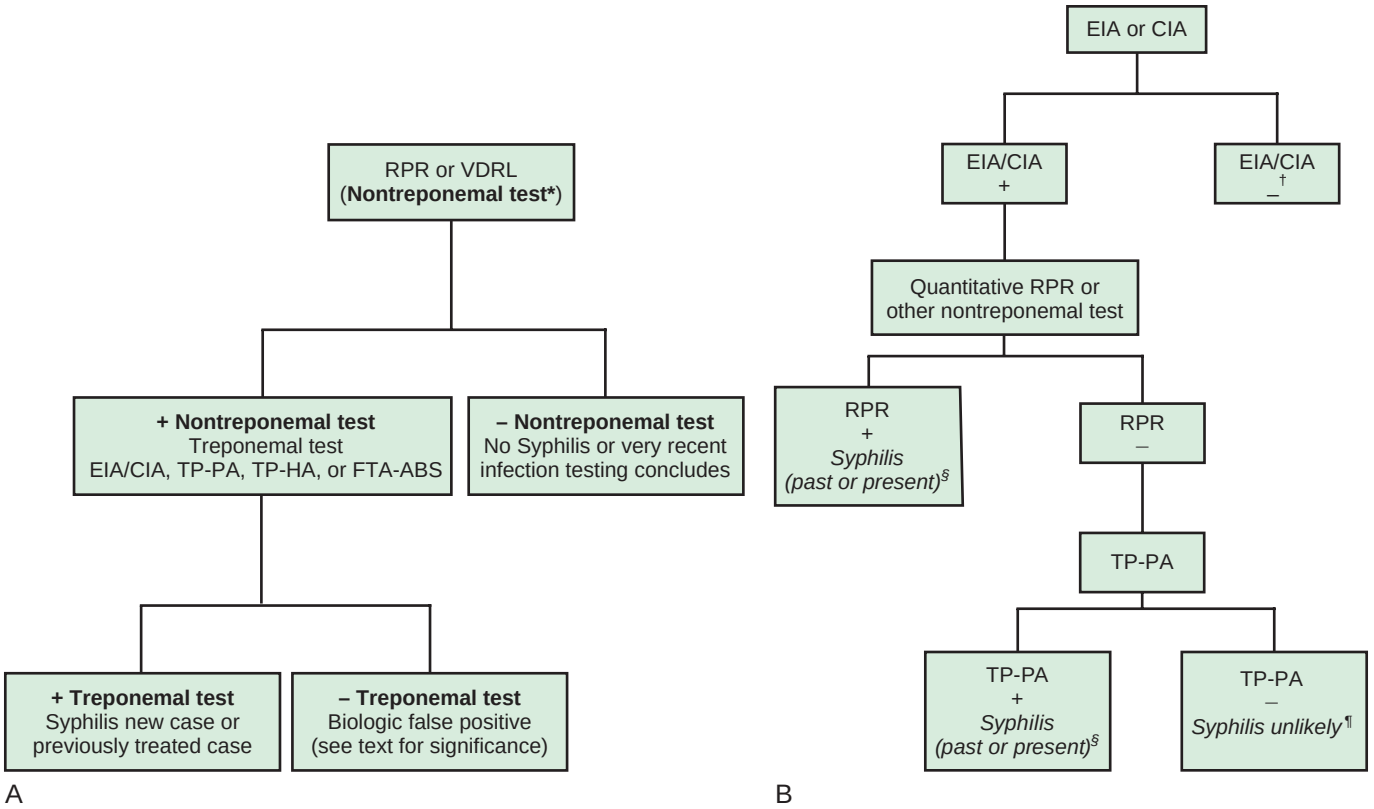
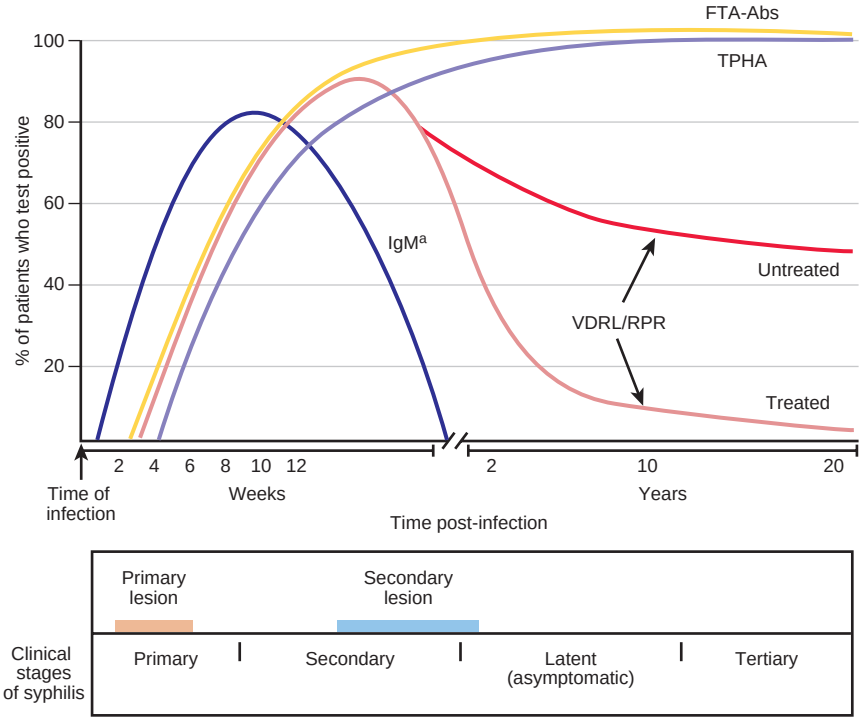


Figure 218-9 **A,** Traditional laboratory testing algorithm for syphilis. **B,** CDC-recommended algorithm for reverse sequence syphilis screening (treponemal test screening followed by nontreponemal test confirmation). Despite these recommendations for reverse sequence screening, the CDC continues to recommend the traditional algorithm with reactive nontreponemal tests confirmed by treponemal testing. *EIA/CIA*, enzyme immunoassay/chemiluminescence immunoassay; *FTA-ABS*, fluorescent treponemal antibody absorption; *RPR*, rapid plasma reagin; *TP-HA*, *Treponema pallidum* hemagglutination; *TP-PA*, Treponema pallidum particle agglutination; *VDRL*, Venereal Disease Research Laboratory. *If nontreponemal test is positive qualitatively, a titer is then quantitated. †If incubating or primary syphilis is suspected, treat with benzathine penicillin G 2.4 million units intramuscularly in a single dose. §Evaluate clinically, determine whether treated for syphilis in the past, assess risk for infection, and administer therapy according to CDC's 2010 STD Treatment Guidelines (available at http://www.cdc.gov/std/treatment/2010). ¶If at risk for syphilis, repeat RPR in several weeks. (***A*** *based on data from Workowski KA, Berman S; Centers for Diseases Control and Prevention [CDC]: Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep 59[RR-12]:1-110, 26-29, 2010;* ***B*** *from Centers for Disease Control and Prevention [CDC]: Discordant results from reverse sequence syphilis screening—five laboratories, United States, 2006-2010. MMWR Morb Mortal Wkly Rep 60(5):133-137, 2011.)*



[a]IgM by ELISA or FTA-ABS 195 or immunoblot

Figure 218-10 Common patterns of serologic reactivity in syphilis patients. *FTA-Abs*, fluorescent treponemal antibody absorption (test); *RPR*, rapid plasma reagin (test); *TPHA*, *Treponema pallidum* hemagglutination assay; *VDRL*, Venereal Disease Research Laboratory (test). *(From Peeling RW, Ye H: Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview,* Bull World Health Organ *82:439–446, 2004.)*

(Borrelia burgdorferi), yaws, endemic syphilis, and pinta. Only venereal syphilis and Lyme disease are found in the United States. Nontreponemal tests (VDRL, RPR) are uniformly nonreactive in Lyme disease.

Enzyme immunoassays and chemiluminescence immunoassays to detect treponemal IgG and IgM have been developed. These assays have increased sensitivity and are amenable to automation and high volume use. Such assays should allow developing countries quality screening programs at the point-of-service because the World Health Organization currently relies on syndromic management of sexually transmitted infections, where patients are treated for all likely causes of their constellation of signs and symptoms. In the United States, use of enzyme immunoassays has confounded screening because it switches the traditional algorithm: the treponemal-specific testing is done before the nontreponemal testing. Because the former remain positive for life, clinical and epidemiologic data are required to provide clear guidelines to distinguish cured disease, early syphilis, untreated late latent disease, and true false-positive tests. The benefits of reverse screening are increased detection of transmissible early syphilis and of late latent disease to afford monitoring for tertiary disease. Although the CDC continues to recommend the traditional screen (see Fig. 218-9*A*) they have provided guidelines for interpretation of the reverse screening algorithm (see Fig. 218-9*B*). Interpretation of nontreponemal and treponemal serologic tests in the newborn can be confounded by maternal IgG antibodies transferred to the fetus. Passively acquired antibody is suggested by a neonatal titer at least 4-fold (i.e., a 2 tube dilution) less than the maternal titer. This conclusion can be verified by gradual decline in antibody in the infant, usually becoming undetectable by 3-6 mo of age.

The diagnosis of neurosyphilis remains difficult but is often established by demonstrating pleocytosis and increased protein in the CSF and a positive CSF VDRL test along with neurologic symptoms. The CSF VDRL test is specific but relatively insensitive (22-69%) for neurosyphilis. CSF polymerase chain reaction (polymerase chain reaction) and IgM immunoblot tests are under development to assist in diagnosis of neurosyphilis.

Darkfield microscopy of scrapings from primary lesions or congenital or secondary lesions can reveal *T. pallidum,* often before serology becomes positive, but this technique is usually not available in clinical practice. Placental examination by gross and microscopic techniques can be useful in the diagnosis of congenital syphilis. The disproportionately large placentas are characterized histologically by focal proliferative villitis, endovascular and perivascular arteritis, and focal or diffuse immaturity of placental villi.

Congenital Syphilis

Diagnosis of congenital syphilis requires thorough review of maternal history of syphilis treatment preconception and testing, treatment, and the dynamics of response during the current pregnancy. Regardless of maternal treatment and the presence/absence of symptoms in the infant, proactive evaluation and treatment of exposed neonates is critical (Fig. 218-11 and Table 218-2). Symptomatic infants should be thoroughly evaluated and treated. Table 218-3 describes the guidelines for

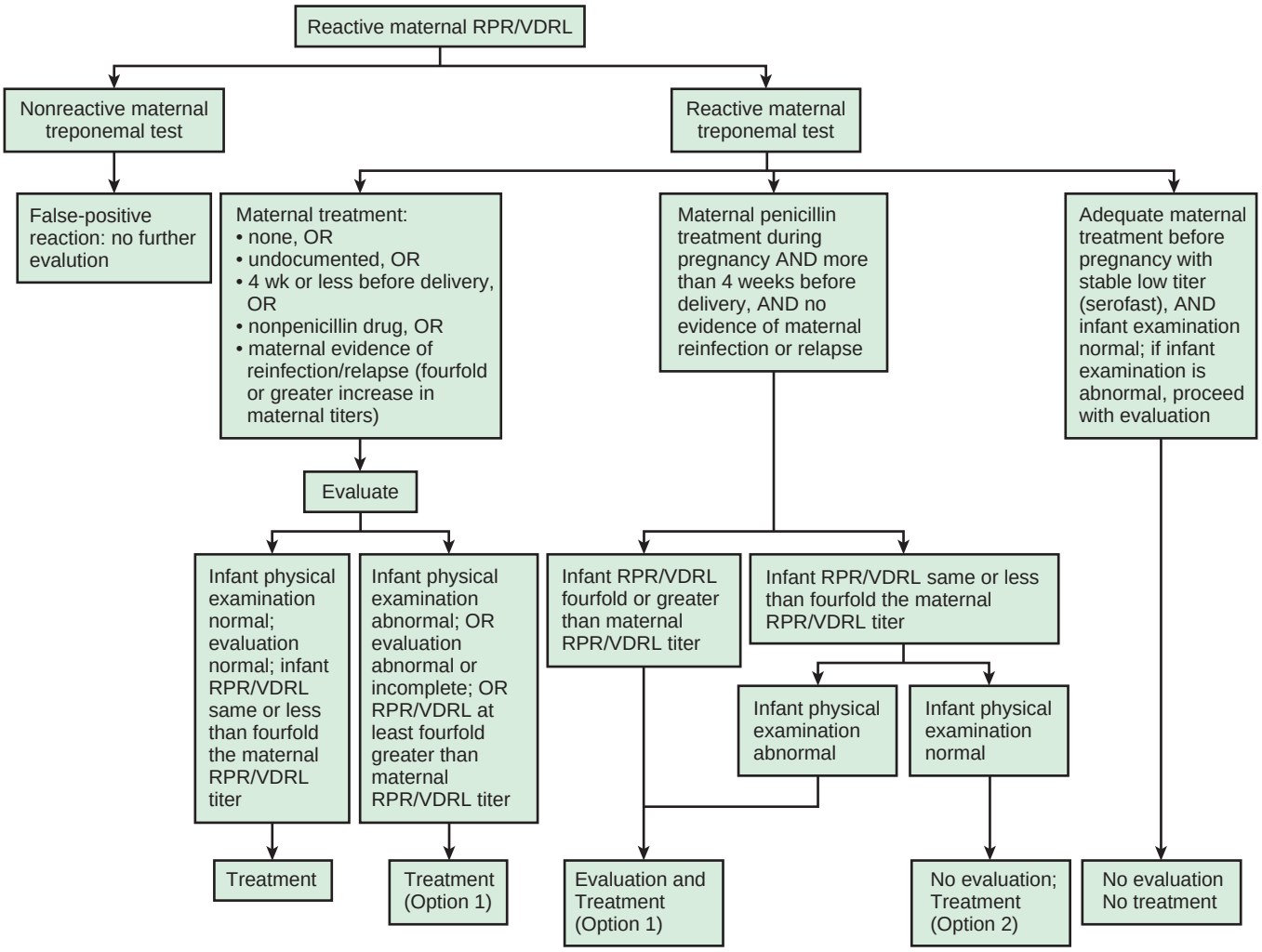


Figure 218-11 Algorithm for evaluating and treating infants born to mothers with reactive serologic tests for syphilis. *(From American Academy of Pediatrics:* Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics,* Fig. 3-7, *p. 695.)*

Table 218-2 Clues That Suggest a Diagnosis of Congenital Syphilis*

EPIDEMIOLOGIC BACKGROUND	CLINICAL FINDINGS
Untreated early syphilis in the mother Untreated latent syphilis in the mother An untreated mother who has contact with a known syphilitic during pregnancy Mother treated for syphilis during pregnancy with a drug other than penicillin Mother treated for syphilis during pregnancy without follow-up to demonstrate 4-fold change in titer Mother coinfected with HIV	Osteochondritis, periostitis Snuffles, hemorrhagic rhinitis Condylomata lata Bullous lesions, palmar or plantar rash Mucous patches Hepatomegaly, splenomegaly Jaundice Nonimmune hydrops fetalis Generalized lymphadenopathy Central nervous system signs; elevated cell count or protein in cerebrospinal fluid Hemolytic anemia, diffuse intravascular coagulation, thrombocytopenia Pneumonitis Nephrotic syndrome Placental villitis or vasculitis (unexplained enlarged placenta) Intrauterine growth restriction

*Arranged in decreasing order of confidence of diagnosis.

Modified from Remington JS, Klein JO, Wilson CB, et al, editors: Infectious diseases of the fetus and newborn infant, *ed 6. Philadelphia, 2006, WB Saunders, p. 556.*

Table 218-3 Recommended Management of Neonates (≤1 Month of Age) Born to Mothers with Serologic Tests for Syphilis

CLINICAL STATUS	EVALUATION (IN ADDITION TO PHYSICAL EXAMINATION AND QUANTITATIVE NONTREPONEMAL TESTING)	ANTIMICROBIAL THERAPY*
Proven or highly probable disease[†]	CSF analysis for VDRL, cell count, and protein CBC and platelet count Other tests as clinically indicated (e.g., long-bone radiography, liver function tests, ophthalmologic examination)	Aqueous crystalline penicillin G, 100,000-150,000 units/kg/day, administered as 50,000 units/kg/dose IV q12hr during the 1st 7 days of life and 18 hr thereafter for a total of 10 days *or* Penicillin G procaine, 50,000 units/kg/day IM in a single dose × 10 days
NORMAL PHYSICAL EXAMINATION AND SERUM QUANTITATIVE NONTREPONEMAL TITER ≤4 TIMES THE MATERNAL TITER:		
(a) (i) Mother was not treated or inadequately treated or has no documented treatment; (ii) mother was treated with erythromycin or other nonpenicillin regimen; (iii) mother received treatment ≤4 wk before delivery; (iv) maternal evidence of reinfection or relapse (<4-fold decrease in titers)	CSF analysis for VDRL, cell count, and protein[§] CBC and platelet count[§] Long-bone radiography[§]	Aqueous crystalline penicillin G IV × 10 days[§] *or* Penicillin G procaine[‡] 50,000 units/kg IM in a single dose × 10 days[§] *or* Penicillin G benzathine[‡] 50,000 units/kg IM in a single dose[§]
(b) (i) Adequate maternal therapy given >4 wk before delivery; (ii) mother has no evidence of reinfection or relapse	None	Clinical, serologic follow-up, and penicillin G benzathine 50,000 units/kg IM in a single dose[‖]
(c) Adequate therapy before pregnancy and mother's nontreponemal serologic titer remained low and stable during pregnancy and at delivery	None	None[¶]

*If more than 1 day of therapy is missed, the entire course should be restarted.

[†]Abnormal physical examination, serum quantitative nontreponemal titer that is 4-fold greater than the mother's titer, or positive result of darkfield or fluorescent antibody test of body fluid(s).

[‡]Penicillin G benzathine and penicillin G procaine are approved for IM administration only.

[§]A complete evaluation (CSF analysis, bone radiography, CBC) is not necessary if 10 days of parenteral therapy is administered, but it may be useful to support a diagnosis of congenital syphilis. If a single dose of penicillin G benzathine is used, then the infant must be evaluated fully, results of the full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is uninterpretable, the 10-day course of penicillin is required.

[‖]Some experts would not treat the infant but would provide close serologic follow-up.

[¶]Some experts would treat with penicillin G benzathine, 50,000 units/kg, as a single IM injection, if follow-up is uncertain.

CBC, complete blood cell count; CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.

From American Academy of Pediatrics: Red book: 2009 report of the Committee on Infectious Diseases, *28/e. Elk Grove Village, IL, 2009, American Academy of Pediatrics, p. 645.*

evaluating and managing asymptomatic infants who are considered at risk for congenital syphilis because the maternal nontreponemal and treponemal serology is positive. Internationally adopted children should also be screened.

Diagnosis of neurosyphilis in the newborn with syphilitic infection is confounded by poor sensitivity of the CSF VDRL test in this age group and lack of CSF abnormalities. A positive CSF VDRL test in a newborn warrants treatment for neurosyphilis, even though it might reflect passive transfer of antibodies from serum to CSF. It is now accepted that all infants with a presumptive diagnosis of congenital syphilis should be treated with regimens effective for neurosyphilis because central nervous system involvement cannot be reliably excluded. Diagnosis of syphilis beyond early infancy should lead to consideration of possible child abuse.

For infants with proven or highly probable disease or abnormal physical findings, complete evaluation including serologic tests (RPR or VDRL), complete blood count with differential and platelet count, liver function tests, long-bone radiographs, ophthalmology examination, auditory brainstem response, and other tests as indicated should be performed. For infants with a positive VDRL or RPR test result and normal physical examination whose mothers were inadequately treated, further evaluation is not necessary if 10 days of parenteral therapy is administered.

TREATMENT

T. pallidum remains extremely sensitive to penicillin, with no evidence of emerging penicillin resistance, and thus penicillin remains the treatment drug of choice (see Tables 218-3 and 218-4 and http://www.cdc.gov/std/treatment). Parenteral penicillin G is the only documented effective treatment for congenital syphilis, syphilis during pregnancy, and neurosyphilis. Aqueous crystalline penicillin G is preferred over procaine penicillin, because it better achieves and sustains the minimum concentration of 0.018 μg/mL (0.03 units/mL) needed for 7-10 days to achieve treponemicidal levels. Although nonpenicillin regimens are available to the penicillin-allergic patient, desensitization followed by standard penicillin therapy is the most reliable strategy. An acute systemic febrile reaction called the **Jarisch-Herxheimer reaction** (caused by massive release of endotoxin-like antigens during bacterial lysis) occurs in 15-20% of patients with acquired or congenital syphilis treated with penicillin. It is not an indication for discontinuing penicillin therapy.

Acquired Syphilis

Primary, secondary, and early latent disease is treated with a single dose of benzathine penicillin G (50,000 units/kg IM, maximum 2.4 million units). Persons with late latent or tertiary disease require 3 doses at 1 wk intervals. Nonpregnant penicillin-allergic patients without neurosyphilis may be treated with either doxycycline (100 mg PO twice daily for 2 wk) or tetracycline (500 mg PO 4 times daily for 2 wk). Emerging azalide and macrolide resistance has been documented in several U.S. cities, compromising the effective use of these antibiotics. Careful serologic follow-up is always necessary. Less than a 4-fold decline in titer reflects treatment failure.

The CDC recommends that all persons with syphilis be tested for HIV. Patients coinfected with HIV are at increased risk for neurologic complications and higher rates of treatment failure. CDC guidelines recommend the same treatment of primary and secondary syphilis as for patients who are not infected with HIV, but some experts recommend 3 weekly doses of benzathine penicillin G. HIV-infected patients with late latent syphilis or latent syphilis of unknown duration should have a CSF evaluation for neurosyphilis before treatment.

Sex partners of infected persons of any stage should be evaluated and treated. Persons exposed for 90 days or less preceding diagnosis in a sex partner should be treated presumptively even if seronegative. Persons exposed for more than 90 days before the diagnosis in a sex partner should be treated if seropositive or if serologic tests are not available. Follow-up serology should be performed on treated patients to establish adequacy of therapy, and all patients should be tested for other sexually transmitted diseases, including HIV.

Table 218-4 Recommended Treatment for Syphilis in Patients Older Than 1 Month of Age

STATUS	CHILDREN	ADULTS
Congenital syphilis	Aqueous crystalline penicillin G 200,000-300,000 units/kg/day IV administered as 50,000 units/kg q4-6hr × 10 days*	
Primary, secondary, and early latent syphilis†	Penicillin G benzathine,‡ 50,000 units/kg, IM, up to the adult dose of 2.4 million units in a single dose	Penicillin G benzathine,‡ 2.4 million units IM in a single dose *or* *If allergic to penicillin and not pregnant,* doxycycline 100 mg PO bid × 14 days *or* Tetracycline 500 mg PO qid × 14 days
Late latent syphilis§ or syphilis of unknown duration	Penicillin G benzathine,‡ 50,000 units/kg IM up to the adult dose of 2.4 million units, administered as 3 single doses at 1 wk intervals (total 150,000 units/kg, up to the adult dose of 7.2 million units)	Penicillin G benzathine‡ 7.2 million units total administered as 3 doses of 2.4 million units IM, each at 1 wk intervals *or* *If allergic to penicillin and not pregnant,* doxycycline 100 mg PO bid × 4 wk *or* Tetracycline 500 mg PO qid × 4 wk
Tertiary syphilis		Penicillin G benzathine‡ 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1 wk intervals *If allergic to penicillin and not pregnant, same as for late latent syphilis*
Neurosyphilis‖	Aqueous crystalline penicillin G 200,000-300,000 units/kg/day q4-6hr × 10-14 days in doses not to exceed the adult dose	Aqueous crystalline penicillin G 18-24 million units/day administered as 3-4 million units IV q4hr × 10-14 days¶ *or* Penicillin G procaine,‡ 2.4 million units IM once daily *plus* probenecid 500 mg PO qid, both × 10-14 days¶

*If the patient has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL result is negative, some experts would treat with up to 3 weekly doses of penicillin G benzathine 50,000 units/kg IM. Some experts also suggest giving these patients a single dose of penicillin G benzathine 50,000 units/kg IM after the 10-day course of IV aqueous penicillin.

†Early latent syphilis is defined as being acquired within the preceding year.

‡Penicillin G benzathine and penicillin G procaine are approved for IM administration only.

§Late latent syphilis is defined as syphilis beyond 1 year's duration.

‖Patients who are allergic to penicillin should be desensitized.

¶Some experts administer penicillin G benzathine 2.4 million units IM, once per week for up to 3 wk after completion of these neurosyphilis treatment regimens.

CSF, cerebrospinal fluid; VDRL, Venereal Disease Research Laboratory.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 698, Table 3.72.*

Syphilis in Pregnancy

When clinical or serologic findings suggest active infection or when diagnosis of active syphilis cannot be excluded with certainty, treatment is indicated. Patients should be treated with the penicillin regimen appropriate for the woman's stage of syphilis. Women who have been adequately treated in the past do not require additional therapy unless quantitative serology suggests evidence of reinfection (**4-fold elevation in titer**). Doxycycline and tetracycline should not be administered during pregnancy, and macrolides do not effectively prevent fetal infection. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin.

Congenital Syphilis

Adequate maternal therapy should eliminate the risk for congenital syphilis. All infants born to mothers with syphilis should be followed until nontreponemal serology is negative. The infant should be treated if there is any uncertainty about the adequacy of maternal treatment. Any infant at risk of congenital syphilis should be evaluated for HIV.

Congenital syphilis is treated with aqueous penicillin G (100,000-150,000 units/kg/24 hr divided every 12 hr IV for the 1st wk of life, and every 8 hr thereafter) or procaine penicillin G (50,000 units/kg IM once daily) given for 10 days. Both penicillin regimens are recognized as adequate therapy for congenital syphilis, but higher concentrations of penicillin are achieved in the CSF of infants treated with intravenous aqueous penicillin G than in those treated with intramuscular procaine penicillin. Treated infants should be followed every 2-3 mo to confirm at least a 4-fold decrease in nontreponemal titers. Treated infants with congenital neurosyphilis should undergo clinical and CSF evaluation at 6-mo intervals until CSF is normal. In a very-low-risk neonate who is asymptomatic and whose mother was treated appropriately, without evidence of relapse or reinfection, but with a low and stable VDRL titer (serofast), no evaluation is necessary. Some specialists would treat such an infant with a single dose of benzathine penicillin G 50,000 units/kg IM.

PREVENTION

Syphilis, including congenital syphilis, is a reportable disease in all 50 states and the District of Columbia. Testing is indicated at any time for persons with suspicious lesions, a history of recent sexual exposure to a person with syphilis, or diagnosis of another sexually transmitted infection, including HIV infection. Timely treatment lessens risk of community spread. Vaccine prevention remains elusive, confounded by the treponeme's ability to evade the immune system.

Congenital Syphilis

Congenital syphilis is a preventable disease, with primary prevention tied to prevention of syphilis in women of childbearing age and secondary prevention being early diagnosis and prompt treatment of women and their partners. Routine prenatal screening for syphilis remains the most important factor in identifying infants at risk for developing congenital syphilis. Screening all women at the beginning of prenatal care is an evidence-based standard of care and legally required in all states. In pregnant women without optimal prenatal care, serologic screening for syphilis should be performed at the time pregnancy is diagnosed. Any woman who is delivered of a stillborn infant at 20 wk or fewer of gestation should be tested for syphilis. In communities and populations with a high prevalence of syphilis and in patients at high risk, testing should be performed at least 2 additional times: at the beginning of the 3rd trimester (28 wk) and at delivery. Some states mandate repeat testing at delivery for all women, underscoring the importance of preventive screening. Women at high risk for syphilis should be screened even more frequently, either monthly or pragmatically in the case of inconsistent prenatal care, at every medical encounter because they can have repeat infections during pregnancy or reinfection late in pregnancy. Follow-up serologic testing of all treated women should be done after treatment to document titer decline, relapse, or reinfection.

No newborn should leave the hospital without the maternal serologic status having been determined at least once during pregnancy. In states conducting newborn screening for syphilis, both the mother's and infant's serologic results should be known before discharge. In addition, all previously uninvestigated infants of an infected mother should be screened.

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Chapter 219

Nonvenereal Treponemal Infections

Stephen K. Obaro and H. Dele Davies

Nonvenereal treponemal infections—yaws, bejel (endemic syphilis), and pinta—are caused by different subspecies of *Treponema pallidum* and occur in tropical and subtropical areas. The causative agents of nonvenereal treponematoses—*T. pallidum pertenue, T. pallidum* subspecies *endemicum,* and *Treponema carateum*—cannot be distinguished from *T. pallidum pallidum* by morphologic or serologic tests.

In general, nonvenereal treponematoses have prominent cutaneous manifestations and relapsing courses, as in venereal syphilis, but they are not found in urban centers, they are not sexually transmitted, and they are not congenitally acquired. Transmission is primarily through body contact, poor hygiene, crowded conditions, and poor access to healthcare. Children also serve as the primary reservoirs for these organisms, spreading infection via skin-to-skin and skin-to-mucous membrane contact, and possibly via fomites as well.

Penicillin remains the treatment of choice for syphilis and nonvenereal treponemal infections.

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219.1 Yaws (*Treponema pertenue*)

Stephen K. Obaro and H. Dele Davies

Yaws is the most prevalent nonvenereal treponematosis. The causative agent, *Treponema pertenue* bears very close genomic resemblance to *T. pallidum*. The *T. pallidum pertenue* genome was sequenced in 2010 and compared with *T. pallidum pallidum* strains; the overall sequence identity between the 2 genomes was 99.8%. It is a contagious, chronic, relapsing infection involving the skin and bony structures caused by the spirochete *T. pertenue,* which is identical to *T. pallidum* microscopically and serologically. It occurs in tropical regions with heavy rainfall and annual temperatures ≥27°C (80°F). Almost all cases occur in children in tropical and subtropical countries. It is also referred to as "framboesia," "pian," "parangi," and "bouba." A high percentage of the population is infected in endemic areas.

T. pertenue is transmitted by direct contact from an infected lesion through a skin abrasion or laceration. Transmission is facilitated by overcrowding and poor personal hygiene in the rain forest areas of the world. Yaws predominantly affects children, with approximately 75% of cases being reported in children younger than 15 yr of age. This population also constitutes the reservoir for disease transmission. The initial papular lesion, which constitutes **primary yaws**, also described as the **"mother yaw,"** occurs 2-8 wk after inoculation. This lesion typically involves the buttocks or lower extremities. The papule develops

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into a raised, raspberry-like papilloma and is often accompanied by regional lymphadenopathy. The skin pathology is very similar to that of venereal syphilis, consisting of epidermal hyperplasia and papillomatosis. Healing of the mother yaw leaves a hypopigmented scar. The **secondary stage** lesions can erupt anywhere on the body before or after the healing of the mother yaw and may be accompanied by lymphadenopathy, anorexia, and malaise. Multiple cutaneous lesions (daughter yaws, pianomas, or frambesias) appear, spread diffusely, ulcerate, and are covered by exudates containing treponemes. Secondary lesions heal without scarring. Recurrent lesions are common within 5 yr after the primary lesion.

The lesions are often associated with bone pain resulting from underlying periostitis or osteomyelitis, especially of the fingers, nose, and tibia. The initial period of clinical activity is followed by a 5-10 yr period of latency. The appearance of tertiary stage lesions develops in approximately 10% of infected patients, with onset typically at puberty with solitary and destructive lesions. These lesions occur as painful papillomas on the hands and feet, gummatous skin ulcerations, or osteitis. Bony destruction and deformity, juxtaarticular nodules, depigmentation, and painful hyperkeratosis **("dry crab yaws")** of the palms and soles are common. Approximately 10% of patients may progress and develop tertiary stage lesions after 5 yr or more of untreated infection, although this is now rare.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis. The nontreponemal agglutination tests such as the rapid plasma reagin and Venereal Diseases Research Laboratory tests are positive in untreated cases, and these tests can be used for test of cure, because they revert to negative following treatment. However, the treponemal tests (*T. pallidum* hemagglutination assay, *T. pallidum* particle agglutination assay, and fluorescent treponemal antibody absorption) are more specific and remain positive for life. New immunochromatographic test strips that can be applied for testing both whole blood and serum were developed. These are simple, cheap, and easy to use and do not require refrigeration.

Differential diagnosis includes other conditions with similar cutaneous manifestations such as eczema, psoriasis, excoriated chronic scabies, tungiasis, leishmaniasis, tropical ulcer cutaneous mycoses, and verrucae. Involvement of the bone may mimic dactylitis that is commonly associated with sickle cell disease

Treatment of yaws consists of a single dose of the long-acting benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr) for index patients and all contacts. Patients allergic to penicillin may be treated with erythromycin, doxycycline, or tetracycline at appropriate doses for venereal syphilis (see Chapter 218). One oral dose of azithromycin (30 mg/kg; maximum: 2 g) is as effective as benzathine penicillin. Treatment cures the lesions of active yaws, renders them noninfectious, and prevents relapse. Family members, contacts, and patients with latent infection should receive the same dose as those with active disease. Eradication of yaws from some endemic areas has been accomplished by treating the entire population with penicillin or azithromycin.

219.2 Bejel (Endemic Syphilis; *Treponema pallidum endemicum*)

Stephen K. Obaro and H. Dele Davies

Bejel, or endemic syphilis, affects children in remote rural communities living in poor hygienic conditions. Bejel, unlike yaws, can occur in temperate as well as dry, hot climates. Infection with *T. pallidum* subspecies *endemicum* follows penetration of the spirochete through traumatized skin or mucous membranes. In experimental infections, a primary papule forms at the inoculation site after an incubation period of 3 wk. A primary lesion is almost never visualized in human infections; however, primary ulcers have been described surrounding the nipples of nursing mothers with infected children.

The clinical manifestations of the **secondary stage** typically occurs 3-6 mo after inoculation and are confined to the skin and mucous membranes. They consist of highly infectious mucous patches on the oral mucosa and condyloma-like lesions on the moist areas of the body, especially the axilla and anus. These mucocutaneous lesions resolve spontaneously over a period of several months, but recurrences are common. The secondary stage is followed by a variable latency period before the onset of late or tertiary bejel. The tertiary stage can occur as early as 6 mo or as late as several years after resolution of initial symptoms. The lesions in the tertiary stage are identical to those of yaws and include gumma formation in skin, subcutaneous tissue, and bone, resulting in painful destructive ulcerations, swelling, and deformity.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Dark-field examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis.

Differentiation from venereal syphilis is extremely difficult in an endemic area. Bejel is distinguished by the absence of a primary chancre and lack of involvement of the central nervous system and cardiovascular system during the late stage.

Treatment of early infection consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr). Late infection is treated with 3 injections of the same dosage at intervals of 7 days. Patients allergic to penicillin may be treated with erythromycin or tetracycline.

219.3 Pinta (*Treponema carateum*)

Stephen K. Obaro and H. Dele Davies

Pinta is a chronic, nonvenereally transmitted infection caused by *T. pallidum* subsp. *carateum,* a spirochete morphologically and serologically indistinguishable from other human treponemes. This is perhaps the mildest of the nonvenereal treponematoses. The disease is endemic in Mexico, Central America, South America, and parts of the West Indies and largely affects children younger than 15 yr of age.

Infection follows direct inoculation of the treponeme through abraded skin. After a variable incubation period of days, the **primary** lesion appears at the inoculation site as a small asymptomatic erythematous papule resembling localized psoriasis or eczema. The regional lymph nodes are often enlarged. Spirochetes can be visualized on darkfield examination of skin scrapings or from biopsy of the involved lymph nodes. After a period of enlargement, the primary lesion disappears. Unlike primary yaws, the lesion does not ulcerate but can expand with central depigmented resolution. **Secondary** lesions follow within 6-8 mo and consist of small macules and papules on the face, scalp, and other sun-exposed portions of the body. These pigmented, highly infectious lesions are scaly and nonpruritic and can coalesce to form large plaque-like elevations resembling psoriasis. In the late or **tertiary** stage, atrophic and depigmented lesions develop on the hands, wrists, ankles, feet, face, and scalp. Hyperkeratosis of palms and soles is uncommon.

The diagnosis is based on the characteristic clinical manifestations of the disease in an endemic area. Darkfield examination of cutaneous lesions for treponemes and both treponemal and nontreponemal serologic tests for syphilis, which are positive because of crossreactivity, are used to confirm the diagnosis.

Treatment consists of a single dose of benzathine penicillin G (1.2 million units IM for adults and 0.6 million units for children <10 yr). Tetracycline and erythromycin are alternatives for patients allergic to penicillin. Treatment campaigns and improvement of standards of living are necessary for reduction and elimination of disease.

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Chapter 220

Leptospira

H. Dele Davies and Kari A. Simonsen

Leptospirosis is a common and widespread zoonosis caused by aerobic, motile spirochetes of the genus *Leptospira*.

ETIOLOGY

Pathogenic leptospires belong to 9 species, which include more than 300 antigenically distinct serovars. A single serovar can produce a variety of distinct syndromes, and a single clinical manifestation may be caused by multiple serotypes.

EPIDEMIOLOGY

Most human cases of leptospirosis occur in tropical and subtropical countries, but the distribution is worldwide. Leptospires survive for days to weeks in warm and damp environmental conditions, including water and moist soil. In the United States, Hawaii reports approximately 50% of all cases, with Pacific coastal states and Southern states having higher incidence than the remainder of the country. Leptospires infect many species of animals, including rats, mice, moles, livestock (such as cattle, goats, sheep, horses, and pigs), wild mammals like raccoons or opossums, and domestic dogs. Infected animals excrete spirochetes in their urine for prolonged periods. Worldwide, most human cases result from occupational exposure to water or soil contaminated with rat urine; however, the major animal reservoir in the United States is the dog. Groups at high risk for leptospirosis include persons exposed occupationally or recreationally to contaminated soil, water, or infected animals, including agricultural workers, veterinarians, abattoir workers, meat inspectors, rodent control workers, laboratory workers, and military personnel. Transmission via animal bites and directly from person to person has been rarely reported.

PATHOLOGY AND PATHOGENESIS

Leptospires enter humans through mucous membranes (primarily eyes, nose, and mouth) or abraded skin or by ingestion of contaminated water. After penetration, they circulate in the bloodstream to all body organs, causing endothelial lining damage of small blood vessels with secondary ischemic damage to end organs.

CLINICAL MANIFESTATIONS

The spectrum of human leptospirosis ranges from asymptomatic infection (most cases) to severe disease with multiorgan dysfunction and death. The onset is usually abrupt, and the illness tends to follow a biphasic course (Fig. 220-1). After an incubation period of 7-12 days, there is an **initial** or **septicemic phase** lasting 2-7 days, during which leptospires can be isolated from the blood, cerebrospinal fluid (CSF), and other tissues. This phase may be followed by a brief period of well-being before onset of a second symptomatic **immune** or **leptospiruric phase**. This phase is associated with the appearance of circulating immunoglobulin M antibody, disappearance of organisms from the blood and CSF, and appearance of signs and symptoms associated with localization of leptospires in the tissues. Despite the presence of circulating antibody, leptospires can persist in the kidney, urine, and aqueous humor. The immune phase can last for several weeks. Symptomatic infection may be anicteric or icteric.

Anicteric Leptospirosis

The **septicemic phase** of anicteric leptospirosis has an abrupt onset with flu-like symptoms of fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe debilitating myalgia most prominent in the lower extremities, lumbosacral spine, and abdomen. Bradycardia and hypotension can occur, but circulatory collapse is uncommon. Conjunctival suffusion with photophobia and orbital pain (in the absence of chemosis and purulent exudate), generalized lymphadenopathy, and hepatosplenomegaly may also be present. A transient (<24 hr) erythematous maculopapular, urticarial, petechial, purpuric, or desquamating rash occurs in 10% of cases. Rarer manifestations include pharyngitis, pneumonitis, arthritis, carditis, cholecystitis, and orchitis. The **second** or **immune phase** can follow a brief asymptomatic interlude and is characterized by recurrence of fever and aseptic meningitis. Although 80% of infected children have abnormal CSF profiles, only 50% have clinical meningeal manifestations. CSF abnormalities include a modest elevation in pressure, pleocytosis with early polymorphonuclear leukocytosis followed by mononuclear predominance rarely exceeding 500 cells/μL, normal or slightly elevated protein levels, and normal glucose values. Encephalitis, cranial and peripheral neuropathies, papilledema, and paralysis are uncommon. A self-limited unilateral or bilateral uveitis can occur during this phase, rarely resulting in permanent visual impairment. Central nervous system symptoms usually resolve spontaneously within 1 wk, with almost no mortality.

Icteric Leptospirosis (Weil Syndrome)

Weil syndrome is a rare (<10% of cases) severe form of leptospirosis seen more commonly in adults (>30 yr) than in children. The initial manifestations are similar to those described for anicteric leptospirosis. The immune phase, however, is characterized by jaundice, renal failure, thrombocytopenia, and, in fulminant cases, hemorrhage and cardiovascular collapse. Hepatic involvement leads to right upper quadrant pain, hepatomegaly, direct and indirect hyperbilirubinemia, and

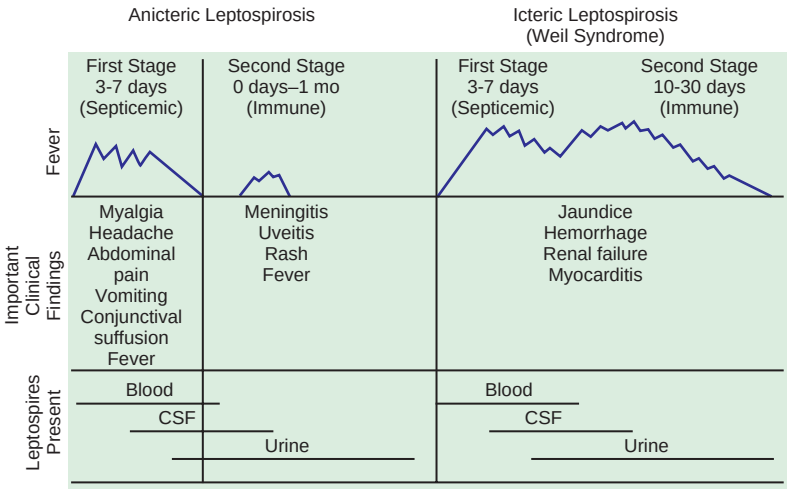

Figure 220-1 Stages of anicteric and icteric leptospirosis. Correlation between clinical findings and presence of leptospires in body fluids. CSF, cerebrospinal fluid. *(Reprinted with permission from Feigin RD, Anderson DC: Human leptospirosis,* CRC Crit Rev Clin Lab Sci *5:413–467, 1975. Copyright CRC Press, Inc, Boca Raton, FL.)*

modestly elevated serum levels of hepatic enzymes. Liver function usually returns to normal after recovery. All patients have abnormal findings on urinalysis (hematuria, proteinuria, and casts), and azotemia is common, often associated with oliguria or anuria. Acute kidney failure occurs in 16-40% of cases and is the principal cause of death. Abnormal electrocardiograms are present in 90% of cases, but congestive heart failure is uncommon. Transient thrombocytopenia occurs in >50% of cases. Rarely, hemorrhagic manifestations occur, including epistaxis, hemoptysis, and pulmonary, gastrointestinal, and adrenal hemorrhage. The mortality rate is 5-15%.

DIAGNOSIS

Leptospirosis should be considered in the differential diagnosis of acute flu-like febrile illnesses with a history of direct contact with animals or with soil or water contaminated with animal urine. This disease may be difficult to distinguish clinically from dengue or malaria.

The diagnosis is most often confirmed by serologic testing and less often by isolation of the infecting organism from clinical specimens. The "gold-standard" diagnostic method is the **microscopic agglutination test,** a serogroup-specific assay using live antigen suspension of leptospiral serovars and dark-field microscopy for agglutination. A 4-fold or greater increase in titer in paired sera confirms the diagnosis. Agglutinins usually appear by the 12th day of illness and reach a maximum titer by the 3rd wk. Low titers can persist for years. Approximately 10% of infected persons do not have detectable agglutinins, presumably because available antisera do not identify all *Leptospira* serotypes. Additionally, enzyme-linked immunosorbent assay methods, latex agglutination, and immunochromatography are commercially available, and DNA polymerase chain reaction diagnostics have been developed but are not in common clinical usage. Phase-contrast and darkfield microscopy are insensitive for spirochete detection, but organisms may be identified using Warthin-Starry silver stain or fluorescent antibody staining of tissue or body fluids. Unlike other pathogenic spirochetes, leptospires can be recovered from the blood or CSF during the 1st 10 days of illness and from urine after the 2nd wk by repeated culture of small inoculum (i.e., 1 drop of blood or CSF in 5 mL of medium) on commercially available selective media. However, the inoculum in clinical specimens is small, and growth can take up to 13 wk.

TREATMENT

Despite in vitro sensitivity of *Leptospira* to penicillin and tetracyclines, the effectiveness of these antibiotics in treating human leptospirosis is unclear because of the naturally high spontaneous recovery rates. Some studies suggest that initiation of treatment before the 7th day shortens the clinical course and decreases the severity of the infection; thus treatment with penicillin G, cefotaxime, or doxycycline (in children ≥8 yr of age) should be instituted early when the diagnosis is suspected. Parenteral penicillin G (6-8 million units/m^2/day divided every 4 hr IV for 7 days) is recommended, with doxycycline 2 mg/kg/day divided in 2 doses with maximum of 100 mg twice daily as an alternative for patients allergic to penicillin. Azithromycin was evaluated in a randomized, nonblinded clinical trial and shown to be as effective as doxycycline and can be used as an alternative in patients for whom doxycycline is contraindicated. In severe illness, supportive care with specific attention given to cardiopulmonary status, renal function, coagulopathy, and fluid and electrolyte balance is warranted.

PREVENTION

Prevention of human leptospirosis infection is facilitated by instituting rodent control measures and avoiding contaminated water and soil. Immunization of livestock and domestic dogs is recommended as a means of reducing animal reservoirs. Attempts at a human vaccine have been challenging, and the diversity of *Leptospira* serovars and their geographic distributions are important considerations in vaccine design. Protective clothing (i.e., boots, gloves, and goggles) should be worn by persons at risk for occupational exposure. In hospital settings, standard precautions are recommended, with contact precautions for exposure to, or handling of infected urine. Leptospirosis was successfully prevented in American soldiers stationed in the tropics by administering prophylactic doxycycline (200 mg PO once a week). This approach may be similarly effective for travelers to highly endemic areas for short periods; however, there are no specific pediatric data to support any prophylaxis regimen.

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Chapter 221

Relapsing Fever *(Borrelia)*

H. Dele Davies and Stephen K. Obaro

Relapsing fever is characterized by recurring fevers and "flu-like symptoms" such as headaches, myalgia, arthralgia, and rigors.

ETIOLOGY

It is an arthropod (lice or ticks)-transmitted infection caused by spirochetes of the genus *Borrelia*.

Louse-borne (epidemic) relapsing fever is caused by *Borrelia recurrentis* and is transmitted from person to person by *Pediculus humanus,* the human body louse. Human infection occurs as a result of crushing lice during scratching, facilitating entry of infected hemolymph through abraded or normal skin or mucous membranes.

Tick-borne (endemic) relapsing fever is caused by several species of *Borrelia* and is transmitted to humans by *Ornithodoros* ticks. *Borrelia hermsii* and *Borrelia turicatae* are the common species in the western United States, while *Borrelia dugesii* is the major cause of disease in Mexico and Central America. Human infection occurs when saliva, coxal fluid, or excrement is released by the tick during feeding, thereby permitting spirochetes to penetrate the skin and mucous membranes.

EPIDEMIOLOGY

Louse-borne relapsing fever tends to occur in epidemics associated with war, poverty, famine, and poor personal hygiene, often in association with typhus. This form of relapsing fever is no longer seen in the United States but is endemic in parts of East Africa. Up to 20.5% of all unexplained fever in the horn of Africa, including northwestern Morocco where the population traditionally lives in mud huts, is caused by tickborne relapsing fever using 16sRNA polymerase chain reaction assays for molecular detection, making this the most common cause of bacterial infections.

Ornithodoros ticks, which transmit endemic relapsing fever and are distributed worldwide, including in the western United States, prefer warm, humid environments and high altitudes, and are found in rodent burrows, caves, and other nesting sites (Fig. 221-1). Rodents (e.g., squirrels and chipmunks) are the principal reservoirs. Infected ticks gain access to human dwellings on the rodent host. Human contact is often unnoticed because these soft ticks have a painless bite, and detach immediately after a short blood meal.

PATHOLOGY AND PATHOGENESIS

Relapsing fever is cyclical because the *Borrelia* organisms undergo antigenic (phase) variation. Multiple variants evolve simultaneously during the first relapse, with 1 type becoming predominant. Spirochetes isolated during the primary febrile episode differ antigenically from those recovered during a subsequent relapse. During febrile episodes, spirochetes enter the bloodstream, induce the development of specific immunoglobulins M and G antibodies, and undergo

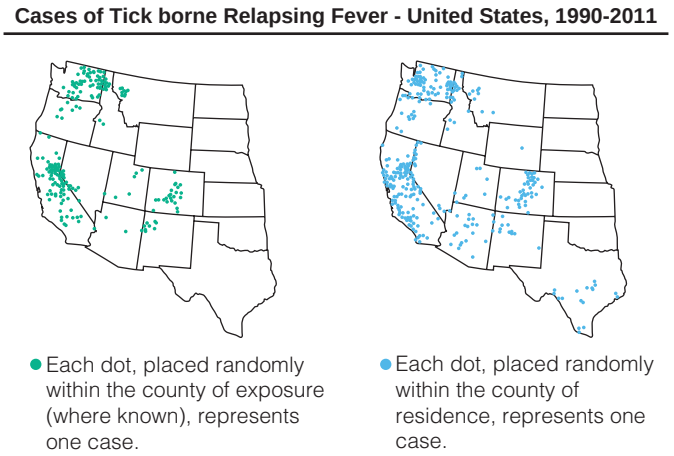

Figure 221-1 Cases of tickborne relapsing fever–United States, 1990-2011. During the years 1990-2011, 483 cases of tickborne relapsing fever were reported in the western United States, with infections being transmitted most frequently in California, Washington, and Colorado. *(From Centers for Disease Control and Prevention [CDC]: Tick-borne relapsing fever: distribution. Available at: http://www.cdc.gov/relapsing-fever/distribution)*

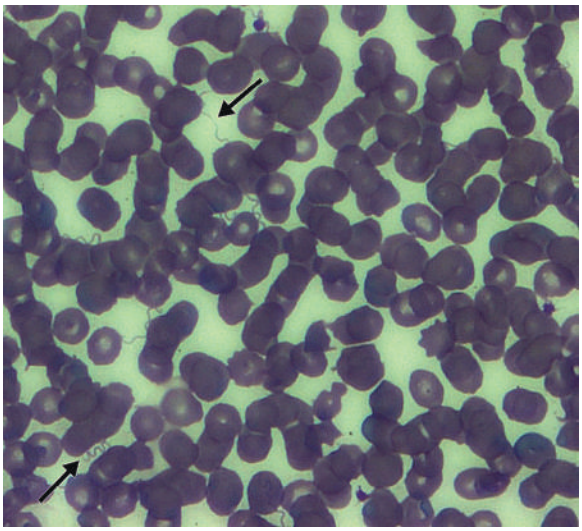

Figure 221-2 Stained thin smear of a newborn's peripheral blood, showing the presence of numerous spirochetes (indicated by *black arrows*) at ×63 magnification—Colorado, 2011. *(From Centers for Disease Control and Prevention [CDC]: Tickborne relapsing fever in a mother and newborn child–Colorado, 2011.* MMWR Morb Mortal Wkly Rep *61:174–176, 2012.)*

agglutination, immobilization, lysis, and phagocytosis. During remission, *Borrelia* spirochetes may remain in the bloodstream, but spirochetemia is insufficient to produce symptoms. The number of relapses in untreated patients depends on the number of antigenic variants of the infecting strain.

CLINICAL MANIFESTATIONS

Relapsing fever is characterized by febrile episodes lasting 2-9 days, separated by afebrile intervals of 2-7 days. Louse-borne disease has an incubation period of 2-14 days, longer periods of pyrexia, fewer relapses, and longer remission periods than tickborne disease. The incubation period of tickborne disease is usually 7 days (range: 2-9 days). Each form of relapsing fever is characterized by sudden onset of high fever, lethargy, headache, photophobia, nausea, vomiting, myalgia, and arthralgia. Additional symptoms may appear later and include abdominal pain, a productive cough, mild respiratory distress and bleeding manifestations, including epistaxis, hemoptysis, hematuria, and hematemesis. During the end of the primary febrile episode, a diffuse, erythematous, macular, or petechial rash lasting up to 2 days may develop over the trunk and shoulders. There may also be lymphadenopathy, pneumonia, and splenomegaly. Hepatic tenderness associated with hepatomegaly is a common sign, with jaundice in half of affected children. Central nervous system manifestations include lethargy, stupor, meningismus, convulsions, peripheral neuritis, focal neurologic deficits, and cranial nerve paralysis and may be the principal feature of late relapses in tickborne disease. Severe manifestations include myocarditis, hepatic failure, and disseminated intravascular coagulopathy.

The initial symptomatic period characteristically ends with a crisis in 2-9 days, marked by abrupt diaphoresis, hypothermia, hypotension, bradycardia, profound muscle weakness, and prostration. In untreated patients, the first relapse occurs within 1 wk, followed by usually 3 but up to 10 relapses, with symptoms during each relapse becoming milder and shorter as the afebrile remission period lengthens.

DIAGNOSIS

Diagnosis depends on demonstration of spirochetes by darkfield microscopy or in thin or thick blood smears stained with Giemsa or Wright stain and by blood culture (Fig. 221-2). During afebrile remissions, spirochetes are not found in the blood. Serologic tests have not been standardized, are generally not available, and produce crossreactions with other spirochetes, including *Borrelia burgdorferi,* the agent of Lyme disease. Molecular methods, including nested polymerase chain reaction or 16sRNA polymerase chain reaction assays, have been used for detection of tickborne and louse-borne recurrent fever and have been found to have improved sensitivity and specificity compared to blood smears. However, these assays are not yet routinely available for commercial use.

TREATMENT

Oral or parenteral tetracycline or doxycycline is the drug of choice for louse-borne and tickborne relapsing fever. For children older than 8 yr of age and young adults, tetracycline 500 mg PO every 6 hr or doxycycline 100 mg PO every 12 hr for 10 days is effective. Single-dose treatment with tetracycline (500 mg PO) or erythromycin is efficacious in adults, but experience in children is limited. In children younger than 8 yr of age, erythromycin (50 mg/kg/day divided every 6 hr PO) for a total of 10 days is recommended. Penicillin and chloramphenicol are also effective.

Resolution of each febrile episode either by natural crisis or as a result of antimicrobial treatment is often accompanied by the Jarisch-Herxheimer reaction, which is caused by massive antigen release. Corticosteroid or antipyretic pretreatment do not prevent the reaction.

PROGNOSIS

With adequate therapy, the mortality rate for relapsing fever is <5%. A majority of patients recover from their illness with or without treatment after the appearance of anti-*Borrelia* antibodies, which agglutinate, kill, or opsonize the spirochete. However, pregnant women and their neonates are at increased risk for tickborne recurrent fever-associated complications, including adult respiratory distress syndrome, Jarisch-Herxheimer reaction, and precipitous or premature delivery. Neonates have up to a 33% case-fatality rate.

PREVENTION

No vaccine is available. Disease control requires avoidance or elimination of the arthropod vectors. In epidemics of louse-borne disease, good personal hygiene and delousing of persons, dwellings, and clothing with commercially available insecticides can prevent dissemination. The risk for tickborne disease can be minimized in endemic areas by maintaining rodent-free dwellings. Giving prophylactic doxycycline for 4 days after a tick bite may prevent tickborne relapsing fever caused by *Borrelia persica.*

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Chapter 222

Lyme Disease *(Borrelia burgdorferi)*

Stephen C. Eppes

Lyme disease is the most common vector-borne disease in the United States and is an important public health problem.

ETIOLOGY

Lyme disease is caused by the spirochete *Borrelia burgdorferi* sensu lato (broad sense). In North America, *B. burgdorferi* sensu stricto (strict sense) causes virtually all cases, and in Europe, the species *Borrelia afzelii* and *Borrelia garinii* also cause disease. The 3 major outer-surface proteins, called OspA, OspB, and OspC (which are highly charged basic proteins of molecular weights of about 31, 34, and 23 kDa, respectively), and the 41 kDa flagellar protein are important targets for the immune response. Differences in the molecular structure of the different species are associated with differences in the clinical manifestations of Lyme borreliosis in Europe and the United States. These differences include the greater incidence of radiculoneuritis in Europe.

EPIDEMIOLOGY

Lyme disease has been reported from more than 50 countries. In the United States, more than 30,000 cases were reported in 2011; however, because of incomplete reporting of cases, it is estimated that the actual number of cases is much higher. In 2011, 93% of cases occurred in 13 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, and Wisconsin (Fig. 222-1). In endemic areas, the reported annual incidence ranges from 20-100 cases per 100,000 population, although this figure may be as high as 600 cases per 100,000 population in hyperendemic areas. In Europe, most cases occur in the Scandinavian countries and in central Europe, especially Germany, Austria, and Switzerland. The reported incidence is highest among children 5-9 yr of age, with a second peak of disease activity in middle-age adults. In the United States, Lyme disease is diagnosed in boys slightly more often than in girls, and 94% of patients are of European descent. Early Lyme disease (described later) usually occurs from spring to early fall, corresponding to deer tick activity. Late disease (chiefly arthritis) occurs year round. Among adults, outdoor occupation and leisure activities are risk factors; for children, location of residence in an endemic area is the most important risk for infection.

TRANSMISSION

Lyme disease is a zoonosis caused by the transmission of *B. burgdorferi* to humans through the bite of an infected tick of the *Ixodes* genus. In the eastern and midwestern United States, the vector is *Ixodes scapularis,* the black-legged tick that is commonly known as the deer tick, which is responsible for most cases of Lyme disease in the United States. The vector on the Pacific Coast is *Ixodes pacificus,* the western black-legged tick. *Ixodes* ticks have a 2 yr, 3 stage life cycle. The larvae hatch in the early summer and are usually uninfected with *B. burgdorferi*. The tick can become infected at any stage of its life cycle by feeding on a host, usually a small mammal such as the white-footed mouse (*Peromyscus leucopus*), which is a natural reservoir for *B. burgdorferi.* The larvae overwinter and emerge the following spring in the nymphal stage, which is the stage of the tick most likely to transmit the infection. The nymphs molt to adults in the fall, and then adults spend the second winter attached to white-tailed deer (*Odocoileus virginianus*). The females lay their eggs the following spring before they die, and the 2 yr life cycle begins again.

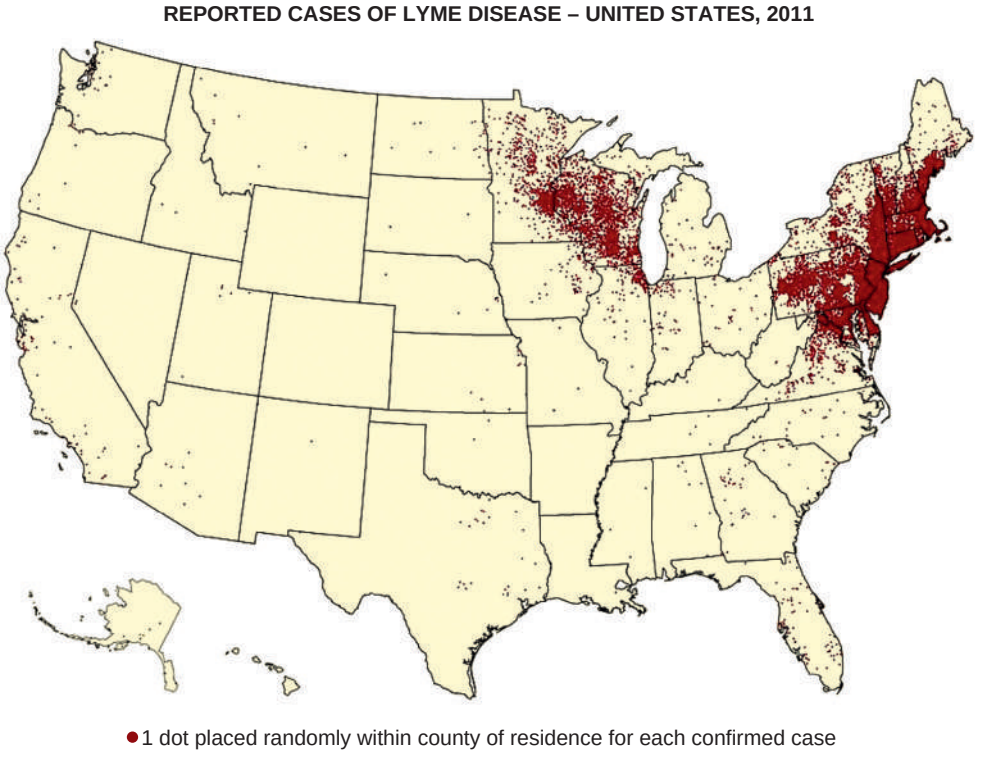

Figure 222-1 The approximate distribution of predicted risk for Lyme disease in the United States. The risk varies by the distribution of *Ixodes scapularis* and *Ixodes pacificus*, the proportion of ticks that are infected at each stage of the tick's life cycle, and the presence of grassy or wooded locations favored by white-tailed deer. *(From the Centers for Disease Control and Prevention [CDC]: Reported cases of Lyme disease—United States, 2011. Available at: http://www.cdc.gov/lyme/stats/maps/map2011.html)*

Several factors are associated with increased risk for transmission of *B. burgdorferi* from ticks to humans. The proportion of infected ticks varies by geographic area and by stage of the tick's life cycle. In endemic areas in the northeastern and midwestern United States, 15-25% of nymphal ticks and 35-50% of adult ticks are infected with *B. burgdorferi*. By contrast, *I. pacificus* often feeds on lizards, which are not a competent reservoir for *B. burgdorferi*, reducing the chance that these ticks will be infected. The risk for transmission of *B. burgdorferi* from infected *Ixodes* ticks is related to the duration of feeding. Experiments in animals show that infected nymphal ticks must feed for 36-48 hr, and infected adults must feed for 48-72 hr, before the risk for transmission of *B. burgdorferi* becomes substantial. If the tick is recognized and removed promptly, transmission of *B. burgdorferi* will not occur.

I. scapularis also transmits other microorganisms, namely *Anaplasma phagocytophilum* and *Babesia microti*. Simultaneous transmission can result in coinfections with these organisms and *B. burgdorferi*.

PATHOLOGY AND PATHOGENESIS

Similar to other spirochetal infections, untreated Lyme disease is characterized by asymptomatic infection, clinical disease that can occur in stages, and a propensity for cutaneous and neurologic manifestations.

The skin is the initial site of infection by *B. burgdorferi*. Inflammation induced by *B. burgdorferi* leads to the development of the characteristic rash, **erythema migrans**. Early disseminated Lyme disease results from the spread of spirochetes through the bloodstream to tissues throughout the body. The spirochete adheres to the surfaces of a wide variety of different types of cells, but the principal target organs are skin, central and peripheral nervous system, joints, heart, and eyes. Because the organism can persist in tissues for prolonged periods, symptoms can appear very late after initial infection.

The symptoms of early disseminated and late Lyme disease are a result of inflammation mediated by interleukin-1 and other lymphokines in response to the presence of the organism. It is likely that relatively few organisms actually invade the host, but cytokines serve to amplify the inflammatory response and lead to much of the tissue damage. Lyme disease is characterized by inflammatory lesions that contain both T and B lymphocytes, macrophages, plasma cells, and mast cells. The refractory symptoms of late Lyme disease can have an immunogenetic basis. Persons with certain HLA-DR allotypes may be genetically predisposed to develop chronic Lyme arthritis. An autoinflammatory response in the synovium can result in clinical symptoms long after the bacteria have been killed by antibiotics.

CLINICAL MANIFESTATIONS

The clinical manifestations of Lyme disease are divided into early and late stages (Table 222-1). Early Lyme disease is further classified as early localized or early disseminated disease. Untreated patients can progressively develop clinical symptoms of each stage of the disease, or they can present with early disseminated or with late disease without apparently having had any symptoms of the earlier stages of Lyme disease.

Early Localized Disease

The first clinical manifestation of Lyme disease in most patients is erythema migrans (Fig. 222-2). Although it usually occurs 7-14 days

Table 222-1 Clinical Stages of Lyme Disease

DISEASE STAGE	TIMING AFTER TICK BITE	TYPICAL CLINICAL MANIFESTATIONS
Early localized	3-30 days	Erythema migrans (single), variable constitutional symptoms (headache, fever, myalgia, arthralgia, fatigue)
Early disseminated	3-12 wk	Erythema migrans (single or multiple), worse constitutional symptoms, cranial neuritis, meningitis, carditis, ocular disease
Late	>2 mo	Arthritis

Figure 222-2 Skin manifestations of Lyme borreliosis. **A,** Erythema migrans on the upper leg, showing central clearing. **B,** Erythema migrans of the arm showing "bulls-eye" appearance. (***A*** *from Stanek G, Strle F: Lyme borreliosis.* Lancet *362:1639–1647, 2003).*

after the bite, the onset of the rash has been reported from 3-30 days later. The initial lesion occurs at the site of the bite. The rash is generally either uniformly erythematous or a target lesion with central clearing; rarely, there are vesicular or necrotic areas in the center of the rash. Occasionally the rash is itchy or painful, although usually it is asymptomatic. The lesion can occur anywhere on the body, although the most common locations are the axilla, periumbilical area, thigh, and groin. It is not unusual for the rash to occur on the neck or face, especially in young children. Without treatment, the rash gradually expands (hence the name *migrans*) to an average diameter of 15 cm and typically remains present for 1-2 wk. Erythema migrans may be associated with systemic features, including fever, myalgia, headache, or malaise. Coinfection with *B. microti* or *A. phagocytophilum* during early infection with *B. burgdorferi* is associated with more severe systemic symptoms. Powassan virus, *Borrelia miyamotoi*, and Wisconsin *Ehrlichia* species are also possible coinfections. Coinfections should be suspected with unusual features of Lyme disease, poor response to treatment, and prolonged fever, anemia, leukopenia, or thrombocytopenia.

Early Disseminated Disease

In the United States, approximately 20% of patients with acute *B. burgdorferi* infection develop secondary (multiple) erythema migrans lesions, a common manifestation of early disseminated Lyme disease, caused by hematogenous spread of the organisms to multiple skin sites (Fig. 222-3). The secondary lesions, which can develop several days or weeks after the first lesion, are usually smaller than the primary lesion, and are often accompanied by more-severe constitutional symptoms. The most common early neurologic manifestations are peripheral facial nerve palsy and meningitis. Lyme meningitis usually has an indolent onset with days to weeks of symptoms that can include headache, neck pain and stiffness, and fatigue. Fever is variably present.

The clinical findings of optic neuritis, cranial neuropathy (especially cranial nerve VII), and erythema migrans, which are present individually or together in 90% of cases, help differentiate Lyme from viral meningitis, in which these findings are rarely present. Lyme aseptic meningitis can be accompanied by significant elevations of intracranial pressure, which can sometimes last weeks or even months. All of the cranial nerves except the olfactory have been reported to be involved with Lyme disease, but the most common are VI and especially VII. In endemic areas, Lyme disease is the leading cause of peripheral facial nerve palsy. It is often the initial or the only manifestation of Lyme disease and is sometimes bilateral. Cerebrospinal fluid findings indicating meningitis are present in more than half of the cases of peripheral facial nerve palsy. The facial paralysis usually lasts 2-8 wk and resolves completely in most cases. Radiculoneuritis and other peripheral neuropathies can occur but are more common in Europe.

Figure 222-3 Multiple erythema migrans in a boy with early disseminated Lyme disease.

Cardiac involvement occurs in 5-15% of early disseminated Lyme disease and usually takes the form of heart block, which can be 1st, 2nd, or 3rd degree, and the rhythm can fluctuate rapidly. Rarely, myocardial dysfunction can occur. Patients presenting with suspected or proven early disseminated Lyme disease should have a careful cardiac examination, and electrocardiography should be strongly considered. Lyme carditis is a treatable condition and is the only manifestation of Lyme disease that has been fatal.

Of the ocular conditions reported in Lyme disease, papilledema and uveitis are most common.

Late Disease

Arthritis is the usual manifestation of late Lyme disease and begins weeks to months after the initial infection. Arthritis typically involves the large joints, especially the knee, which is affected in 90% of cases; involvement is usually monoarticular. The hallmark of Lyme arthritis is joint swelling, which is a result of synovial effusion and sometimes synovial hypertrophy. The swollen joint may be only mildly symptomatic or it may be painful and tender, although patients usually do not experience the severe pain and systemic toxicity that are common in pyogenic arthritis. If untreated, the arthritis can last several weeks, resolve, and then be followed by recurrent attacks in the same or other joints.

Late manifestations of Lyme disease involving the central nervous system, sometimes termed *late neuroborreliosis*, are rarely reported in children. In adults, chronic encephalitis and polyneuritis have been attributed to Lyme disease. The term *Lyme encephalopathy* has been used to describe chronic encephalitis (demonstrable by objective measures), but other literature has also used this term in reference to memory loss and other cognitive sequelae after Lyme disease has been treated. At times, the vague term *chronic Lyme disease* has been used to describe symptomatology in persons who might have never had well-documented infection with *B. burgdorferi* at all, have serologic evidence of prior infection but current symptoms not consistent with Lyme disease, or have persistent symptoms after having received appropriate antibiotic therapy. Post–Lyme disease syndrome is now the preferred term for this last group.

Congenital Lyme Disease

In endemic areas, infection can occur during pregnancy, although congenital infection appears to be a rare event. *B. burgdorferi* has been identified from several abortuses and from a few liveborn children with congenital anomalies; however, the tissues in which the spirochete has been identified usually have not shown histologic evidence of inflammation. Severe skin and cardiac manifestations have been described in a few cases, but no consistent pattern of fetal damage has been identified to suggest a clinical syndrome of congenital infection. Furthermore, studies conducted in endemic areas have indicated that there is no difference in the prevalence of congenital malformations among the offspring of women with serum antibodies against *B. burgdorferi* and the offspring of those without such antibodies.

LABORATORY FINDINGS

Standard laboratory tests rarely are helpful in diagnosing Lyme disease because any associated laboratory abnormalities usually are nonspecific. The peripheral white blood cell count may be either normal or elevated. The erythrocyte sedimentation rate may be mildly elevated. Liver transaminases are occasionally mildly elevated. In Lyme arthritis, the white blood cell count in joint fluid can range from 25,000 to 100,000/mL, often with a preponderance of polymorphonuclear cells. A lower erythrocyte sedimentation rate and a peripheral blood absolute neutrophil count of less than 10,000 may help to differentiate Lyme from septic arthritis. When meningitis is present, there usually is a low-grade pleocytosis with a lymphocytic and monocytic predominance. The cerebrospinal fluid (CSF) protein level may be elevated, but the glucose concentration usually is normal. Gram stain and routine bacterial cultures are negative. Imaging of the central nervous system

(e.g., MRI and single-photon emission computed tomography) occasionally reveals abnormalities, but there is no definitive pattern in Lyme disease. The main role of imaging is to exclude other diagnoses.

DIAGNOSIS

In the appropriate epidemiologic setting, typical erythema migrans is virtually pathognomonic. Occasionally, the diagnosis of erythema migrans may be difficult because the rash initially can be confused with nummular eczema, tinea corporis, granuloma annulare, an insect bite, southern tick-associated rash illness, or cellulitis. The relatively rapid expansion of erythema migrans helps distinguish it from these other skin lesions. The other clinical manifestations of Lyme disease are less specific and may be confused with other conditions; the monoarticular or pauciarticular arthritis sometimes is confused with a septic joint or other causes of arthritis in children, such as juvenile rheumatoid arthritis or rheumatic fever; the facial nerve palsy caused by Lyme disease is clinically indistinguishable from idiopathic Bell palsy, although bilateral involvement is much more common with Lyme disease; Lyme meningitis generally occurs in the warmer months, the same period that enteroviral meningitis is prevalent. Therefore, for all disease manifestations other than erythema migrans, it is recommended to have laboratory confirmation of infection with *B. burgdorferi*.

Although *B. burgdorferi* has been isolated from blood, skin, CSF, myocardium, and the synovium of patients with Lyme disease, the organism is difficult to isolate in culture (cultivation is largely relegated to research laboratories). Infection is usually identified by the detection of antibody in serum. Although some laboratories offer polymerase chain reaction as a diagnostic test for Lyme disease, its sensitivity may be poor because of the low concentrations of bacteria in many sites, especially CSF. Other antigen-based tests, including a test for *B. burgdorferi* antigens in urine, are unreliable. Clinicians should be aware that some laboratories use alternative diagnostic tests and/or alternative interpretive criteria that are not evidence based, leading to a false diagnosis of Lyme disease.

Serology

Following the transmission of *B. burgdorferi* from a tick bite, specific immunoglobulin (Ig) M antibodies appear first, usually within 2 wk, peak at 6-8 wk, and subsequently decline. Sometimes a prolonged elevation of IgM antibodies occurs despite effective antimicrobial treatment. (For that reason, the results of tests for specific IgM antibodies alone should not be used as a reliable indicator of either active or recent infection.) Specific IgG antibodies usually appear between 2 and 6 wk, peak after 4-6 mo, and can remain elevated for years, particularly in patients with arthritis. The antibody response to *B. burgdorferi* may be blunted in patients with early Lyme disease who are treated promptly with an effective antimicrobial agent. Serodiagnosis during the 1st 4 wk of infection is not sensitive and may need to be repeated.

By far the most common method used to detect IgG and IgM antibodies is the **enzyme-linked immunosorbent assay (ELISA)**. *This method is sensitive but not optimally specific*. The ELISA sometimes produces false-positive results because of antibodies that crossreact with other spirochetal infections (e.g., syphilis, leptospirosis, or relapsing fever), or certain viral infections (e.g., Epstein-Barr virus or parvovirus B19), or that occur in certain autoimmune diseases (e.g., systemic lupus erythematosus). The positive predictive value of the ELISA result depends primarily on the plausibility that the patient has Lyme disease based on the clinical and epidemiologic history and the physical examination (**the pretest probability**). For patients who have been in endemic areas with opportunities for *Ixodes* tick exposure and who have typical clinical manifestations of Lyme disease, the pretest probability is high and positive ELISA results are usually true positives. For patients who are from nonendemic areas and/or who have little risk for *Ixodes* tick exposures and/or have nonspecific symptoms (low pretest probability), rates of false-positive results are high.

Western immunoblotting is well standardized, and there are accepted criteria for interpretation. Five of 10 IgG bands and 2 of 3 IgM bands are considered reactive. The Western blot is not as sensitive as ELISA, especially in early infection, but it is highly specific. Any positive or equivocal ELISA should be confirmed with Western blotting. This 2-tier testing is the recommended laboratory evaluation of most cases of Lyme disease and is associated with a high degree of sensitivity and specificity when used appropriately.

Clinicians should be aware that Lyme disease might not be the cause of a patient's symptoms despite the presence of antibodies to *B. burgdorferi*. The test result may be falsely positive (as described for ELISA), or the patient might have been infected previously. Antibodies to *B. burgdorferi* that develop with infection can persist for many years despite adequate treatment and clinical cure of the disease. In addition, because some people who become infected with *B. burgdorferi* are asymptomatic, the background rate of seropositivity among patients who have never had clinically apparent Lyme disease may be substantial in endemic areas. Finally, because antibodies against *B. burgdorferi* persist after successful treatment, there is no reason to obtain follow-up serologic tests.

TREATMENT

Table 222-2 provides treatment recommendations. Most patients can be treated with an oral regimen of antibiotic therapy. Young children are generally treated with amoxicillin. Doxycycline has the advantages of good central nervous system penetration and activity against *A. phagocytophilum*, which may be transmitted at the same time as *B. burgdorferi* in certain geographic areas. In general, children younger than 8 yr of age should not be treated with doxycycline because of the risk of permanent staining of the teeth (although courses of ≤2 wk are usually safe in this regard). Patients who are treated with doxycycline should be alerted to the risk for developing photosensitivity in sun-exposed areas while taking the medication; long sleeves, long pants, and hat are recommended for activities in direct sunlight. The only oral cephalosporin proved to be effective for the treatment of Lyme disease is cefuroxime axetil, which is an alternative for persons who cannot take doxycycline or who are allergic to penicillin. Macrolide antibiotics, including azithromycin, appear to have limited activity.

Table 222-2 Recommended Treatment of Lyme Disease

DRUG	PEDIATRIC DOSING
Amoxicillin	50 mg/kg/day in 3 divided doses (max: 1,500 mg/day)
Doxycycline	4 mg/kg/day in 2 divided doses (max: 200 mg/day) (see text regarding doxycycline use in children)
Cefuroxime axetil	30 mg/kg/day in 2 divided doses (max: 1,000 mg/day)
Ceftriaxone (IV)*†	50-75 mg/kg/day once daily (max: 2,000 mg/day)
RECOMMENDED THERAPY BASED ON CLINICAL MANIFESTATION	
Erythema migrans	Oral regimen, 14-21 days
Meningitis	Ceftriaxone, 10-28 days
Cranial nerve palsy	Oral regimen, 14-21 days (see text regarding possible need for lumbar puncture)
Cardiac disease	Oral regimen or ceftriaxone, 14-21 days (see text for specifics)
Arthritis‡	Oral regimen, 28 days
Late neurologic disease	Ceftriaxone, 14-28 days

*Cefotaxime and penicillin G are alternative parenteral agents.
†Doses of 100 mg/kg/day should be used for meningitis.
‡Persistent arthritis can be treated with a second oral regimen or ceftriaxone.
From Wormser GP, Dattwyler RJ, Shapiro ED, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America, Clin Infect Dis *43:1089–1134, 2006.*

Parenteral therapy is recommended for patients with central nervous system infection and higher degrees of heart block. Patients with arthritis that fails to resolve after an initial course of oral therapy can be retreated with an oral regimen or can receive intravenous antibiotic therapy. Ceftriaxone is usually favored because of its excellent anti-*Borrelia* activity, tolerability, and once-daily dosing regimen, which can usually be done on an outpatient basis.

Peripheral facial nerve palsy can be treated using an oral antibiotic. However, many of these patients have concomitant meningitis; patients with meningitis should receive a parenteral antibiotic. Experts are divided on whether every patient with Lyme-associated facial palsy should have a CSF analysis, but clinicians should consider lumbar puncture for patients with significant headache, neck pain or stiffness, or papilledema.

Patients with symptomatic cardiac disease, 2nd- or 3rd-degree heart block, or significantly prolonged PR interval should be hospitalized and monitored closely. These patients should receive a parenteral antibiotic. Patients with mild 1st-degree heart block can be treated with an oral antibiotic.

Some patients develop a **Jarisch-Herxheimer reaction** soon after treatment is initiated; this results from lysis of the *Borrelia*. The manifestations of this reaction are low-grade fever and achiness. These symptoms resolve spontaneously within 24-48 hr, although administration of nonsteroidal antiinflammatory drugs often is beneficial. Nonsteroidal antiinflammatory drugs also may be useful in treating symptoms of early Lyme disease and of Lyme arthritis. Coinfections with other pathogens transmitted by *Ixodes* ticks should be treated according to standard recommendations.

Criteria for the post–Lyme disease syndrome have been proposed by the Infectious Disease Society of America. There is no clear evidence that this condition is related to persistence of the organism. Studies in adults show little benefit associated with prolonged or repeated treatment with oral or parenteral antibiotics.

PROGNOSIS

There is a widespread misconception that Lyme disease is difficult to cure and that chronic symptoms and clinical recurrences are common. The most likely reason for apparent treatment failure is an incorrect diagnosis of Lyme disease.

The prognosis for children treated for Lyme disease is excellent. Children treated for erythema migrans rarely progress to late Lyme disease. The long-term prognosis for patients who are treated beginning in the later stages of Lyme disease also is excellent. Although chronic and recurrent arthritis does occur rarely, especially among patients with certain human leukocyte antigen allotypes (an autoimmune process), most children who are treated for Lyme arthritis are cured and have no sequelae. Although there are rare reports of adults who have developed late neuroborreliosis, usually among persons with Lyme disease in whom treatment was delayed for months or years; similar cases in children are rare.

PREVENTION

The best way to avoid Lyme disease is to avoid tick-infested areas. Children should be examined for deer ticks after known or potential exposure (although many people are not able to identify the species or the stage of the tick). If a tick attachment is noted, the tick should be grasped at the mouthparts with a forceps or tweezers; if these are not available, the tick should be covered with a tissue. The recommended method of tick removal is to pull directly outward without twisting; infection is usually preventable if the tick is removed before 48 hr of attachment. The overall risk for acquiring Lyme disease after a tick bite is low (1-3%) in most endemic areas. Patients and families can be advised to watch the area for development of erythema migrans and to seek medical attention if the rash or constitutional symptoms occur. If infection develops, early treatment of the infection is highly effective. Although a study of prophylaxis after a tick bite found that a single dose of doxycycline in adults (200 mg PO) was 87% effective in preventing Lyme disease, data in children using this strategy are lacking. For these various reasons, **routine** administration of antimicrobial prophylaxis is **not recommended.** The routine testing of ticks that have been removed from humans for evidence of *B. burgdorferi* is not recommended, because the value of a positive test result for predicting infection in the human host is unknown.

Personal protective measures that may be effective in reducing the chance of tick bites include wearing protective clothing (long pants tucked into socks, long-sleeved shirts) when entering tick-infested areas, checking for and promptly removing ticks, and using tick repellents such as *N,N*-diethyl-3-methylbenzamide (DEET). This chemical can safely be used on pants, socks, and shoes; care must be used with heavy or repeated application on skin, particularly in infants, because of the risk of systemic absorption and toxicity.

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Section 9

Mycoplasmal Infections

Chapter 223

Mycoplasma pneumoniae

Asuncion Mejias and Octavio Ramilo

Among the 7 *Mycoplasma* species isolated from the human respiratory tract, *Mycoplasma pneumoniae* remains the most common species causing respiratory infections in school-age children and young adults.

THE ORGANISM

Mycoplasmas are the smallest self-replicating prokaryotes known to cause disease in humans. Their size of 150-250 nm is more on the order of viruses than bacteria. *M. pneumoniae* is a fastidious double-stranded DNA bacterium that is distinguished by a small genome (800,000 base pairs) and a long doubling time, which makes culturing of *Mycoplasma* a slow process (5-20 days) compared to other bacteria. Like other mycoplasmas, *M. pneumoniae* is distinguished by the complete absence of a cell wall that results (1) in their dependence to host cells for obtaining essential nutrients, (2) the intrinsic resistance to β-lactam agents, and (3) their pleomorphic shape and lack of visibility on Gram staining.

EPIDEMIOLOGY

M. pneumoniae infections occur worldwide and throughout the year. This organism is a frequent cause of community-acquired pneumonia (CAP) in school-age children and adults, accounting for 7-40% of all CAP in children 3-15 yr of age.

In contrast to the acute, short-lived epidemics of some respiratory viruses, *M. pneumoniae* infection is endemic in larger communities, with epidemic outbreaks occurring every 4-7 yr, usually beginning in the fall. Infection occurs through the respiratory route by large droplet spread during close contact with a symptomatic person. Community outbreaks have been described in closed settings (colleges, summer camps, military bases) and can spread largely through school contacts. High transmission rates have been documented within families with up to 40% of household contacts developing mycoplasma lower respiratory tract infection. In contrast to many other respiratory infections the incubation period is 2-3 wk; hence, the course of infection in a specific population (family) may last several weeks.

The occurrence of mycoplasmal illness is related, in part, to age and preexposure immunity. Overt illness is less common before 3 yr of age but can occur. Children younger than 5 yr of age appear to have mild

illness associated with upper respiratory tract involvement, vomiting, and diarrhea. Immunity after infection is not long lasting. Recurrent infections occur infrequently but are well documented in adults at intervals of 4-7 yr. Asymptomatic carriage after infection can last up to 4 mo despite antibiotic therapy and may contribute to prolonged outbreaks.

PATHOLOGY AND PATHOGENESIS

The pathogenicity of *M. pneumoniae* is dependent upon its extracellular attachment and the initiation of the host cell immune response. Cells of the ciliated respiratory epithelium are the target cells of *M. pneumoniae* infection. The organism is an elongated snake-like structure with a one-end organelle, which mediates the attachment to the ciliary membrane through different adherence-accessory proteins (P1, P30, P65, P116, and HMW1-3). *M. pneumoniae* rarely invades beyond the respiratory tract basement membrane. Virulent organisms attach to ciliated respiratory epithelial cell surfaces located in the bronchi, bronchioles, alveoli, and possibly upper respiratory tract and burrow down between cells, resulting in ciliostasis and eventual sloughing of the cells. In addition, *M. pneumoniae* causes cytolytic injury to the host cells in part by the production of hydrogen peroxide and possibly through an adenosine diphosphate–ribosylating and vacuolating toxin termed CARDS: community-acquired respiratory distress syndrome. This toxin is associated with more severe or even fatal disease.

Once *M. pneumoniae* reaches the lower respiratory tract, promotes the polyclonal activation of B-lymphocytes and CD4+ T-cells, and amplifies the immune response with the production of various proinflammatory and antiinflammatory cytokines and chemokines such as tumor necrosis factor-α, interferon-γ, and granulocyte-macrophage colony-stimulating factor.

Although it is well documented that specific cell-mediated immunity and antibody titers against *M. pneumoniae* increase with age (and therefore probably follow repeated infections), the immune mechanisms that protect against or clear the infection are not well defined. The high prevalence of infection in children, adolescents, and young adults, but the frequently mild disease in young children suggests the possible role of immune-mediated mechanisms associated with reinfections causing disease in older patients. Patients with congenital immunodeficiencies such as hypogammaglobulinemia as well as those with sickle cell disease or sickle-related hemoglobinopathies can have more severe forms of *Mycoplasma* pneumonia. *M. pneumoniae* is a common infectious cause of acute chest syndrome in sickle cell disease, and in patients with hypogammaglobulinemia it can persist for years in the respiratory tract despite multiple courses of antibiotics. On the other hand, *M. pneumoniae* does not seem to be a common opportunistic agent in patients with AIDS.

M. pneumoniae has been detected by polymerase chain reaction (PCR) in many nonrespiratory sites. The mechanisms of extrapulmonary disease associated with *M. pneumoniae* are unclear. The identification of *M. pneumoniae* by PCR from blood, pleural fluid, cerebrospinal fluid, or synovial fluid in some cases indicates that direct dissemination rather than an immune-mediated mechanism may occur.

CLINICAL MANIFESTATIONS

Respiratory Tract Disease

Tracheobronchitis and pneumonia are the most commonly recognized clinical syndromes associated with *M. pneumoniae* infection. This agent is responsible for up to 20% of all cases of pneumonia. Although the onset of illness may be abrupt, it is usually characterized by gradual onset of headache, malaise, fever, and sore throat, followed by progression of lower respiratory symptoms, including hoarseness and nonproductive cough. Coryza or gastrointestinal complaints are unusual with *M. pneumoniae* pneumonia and usually suggest a viral etiology. Although the clinical course in untreated patients is variable, cough, the clinical hallmark of *M. pneumoniae* infection, usually worsens during the 1st wk of illness, and symptoms generally resolve within 2 wk. Cough can last up to 4 wk and may be accompanied by wheezing. Patients generally recover without complications.

Chest exam is often unrevealing, even in patients with severe cough. There may be no auscultative or percussive findings or only minimum dry rales. Clinical findings are often less severe than suggested by the patient chest radiograph, explaining why the term "walking pneumonia" is often used to describe CAP caused by *M. pneumoniae*. Radiographic findings are variable and nonspecific, not allowing differentiation from viral or bacterial pathogens. Pneumonia is usually described as interstitial or bronchopneumonic, and involvement is most common in the lower lobes. Bilateral diffuse infiltrates, lobar pneumonia or hilar lymphadenopathy can occur in up to 30% of patients. Although unusual, large pleural effusions associated with lobar infiltrates and necrotizing pneumonia have been described in patients with sickle cell disease, immunodeficiencies, Down syndrome, and chronic cardiopulmonary disease. The white blood cell and differential counts are usually normal, whereas the erythrocyte sedimentation rate is often elevated.

Other respiratory illnesses caused occasionally by *M. pneumoniae* include undifferentiated upper respiratory tract infections, pharyngitis (usually without marked cervical lymphadenopathy), sinusitis, croup, and bronchiolitis. *M. pneumoniae* is a common trigger of wheezing in asthmatic children and can cause chronic colonization in the airways, resulting in lung dysfunction in adolescents and adult asthmatic patients. Otitis media and bullous myringitis, which also occur with other viral and bacterial infections, have been described but are rare, and their absence should not rule out the diagnosis of *M. pneumoniae*.

Extrapulmonary Disease

Despite the reportedly rare isolation of *M. pneumoniae* from nonrespiratory sites, the improved sensitivity of PCR for *M. pneumoniae* DNA detection has led to increasing identification of *M. pneumoniae* in nonrespiratory sites, particularly the central nervous system (CNS). Patients with or without respiratory symptoms can have involvement of the skin, CNS, blood, heart, gastrointestinal tract, and joints. Nonrespiratory manifestations of *M. pneumoniae* include:

1. ***CNS disease***, which may be the most common extrapulmonary site associated with *M. pneumoniae* infection and includes encephalitis, transverse myelitis, aseptic meningitis, Guillain-Barré syndrome, ataxia, Bell palsy, postinfectious demyelination, peripheral neuropathy, and acute disseminated encephalomyelitis. CNS disease manifestations occur 3-23 days (mean: 10 days) after onset of respiratory illness but may not be preceded by any signs of respiratory infection in up to 20% of cases. Encephalitis occurring within 5 days of the onset of prodromal symptoms may be caused by direct invasion of *M. pneumoniae* in the CNS, although cerebrospinal fluid (CSF) PCR is positive in <5% of cases. Encephalitis occurring more than 7 days after onset of prodromal symptoms is more likely to be caused by an autoimmune response to *M. pneumoniae* and accounts for up to 5-15% of all forms of childhood encephalitis. Involvement of the brainstem can result in severe dystonia and movement disorders. Concomitant infection with other pathogens such as enteroviruses or respiratory viruses is found in approximately 10% of children. The CSF may be normal or have mild mononuclear pleocytosis. Diagnosis is confirmed with positive CSF PCR, positive PCR from a throat swab, or the presence of definitive serum antibody titers. Findings on MRI include focal ischemic changes, ventriculomegaly, diffuse edema, or multifocal white matter inflammatory lesions consistent with postinfectious demyelinating encephalomyelitis. Long-term sequelae are not uncommon and have been reported in 23-64% of cases.
2. ***Dermatologic disease,*** which includes a variety of exanthemas, most notably maculopapular rash urticaria, and erythema multiforme or Stevens-Johnson syndrome (SJS). Gianotti-Crosti syndrome and erythema nodosum are also associated with *M. pneumoniae* infections. Approximately 10% of children with *M. pneumoniae* CAP will exhibit a maculopapular rash. *M. pneumoniae* is the most common infectious agent associated with SJS and has a male predominance. SJS usually develops

Figure 223-1 Lip changes found in Stevens-Johnson-like syndrome associated with *Mycoplasma pneumoniae* infection.

Figure 223-2 Classic erythema multiforme skin lesions found in Stevens-Johnson-like syndrome associated with *Mycoplasma pneumoniae* infection.

3-21 days after initial respiratory symptoms, lasts less than 14 days, and is rarely associated with severe complications (Figs. 223-1 and 223-2). *M. pneumoniae* is linked to atypical SJS with oral mucositis but absence of rash.

3. ***Hematologic abnormalities,*** which include mild degrees of hemolysis with a positive Coombs test and minor reticulocytosis 2-3 wk after the onset of illness. Severe hemolysis is associated with high titers of cold hemagglutinins (≥1:512) and occurs rarely. Thrombocytopenia, aplastic anemia, and coagulation defects occur occasionally.
4. ***Arthritis,*** which appears to be less common in children than adults, but monoarthritis, polyarthritis, and migratory arthritis have been described.
5. ***Other conditions,*** such as mild hepatitis, pancreatitis, acute glomerulonephritis, and cardiac complication (pericarditis, myocarditis, and rheumatic fever-like syndrome, most commonly seen in adults), are also described. Fatal *M. pneumoniae* infections are rare.

DIAGNOSIS

No specific clinical, epidemiologic, or laboratory parameters allow for a definite diagnosis of *M. pneumoniae* infection early in the clinical course. Nevertheless, pneumonia in school-age children and young adults with cough as a prominent finding suggests *M. pneumoniae* infection. The best method of diagnosis is a combination of PCR from respiratory samples and serology (acute and convalescent).

Cultures on special media (SP4 agar media) of the throat or sputum might demonstrate the classic *M. pneumoniae* "mulberry" colonies, but growth generally requires incubation for 1-3 wk, and few commercial laboratories maintain the capability of culturing *M. pneumoniae*. The fastidious nutritional requirements of *Mycoplasma* make cultures slow and impractical.

Serologic tests (immunofluorescence tests or enzyme-linked immune assays) to detect serum immunoglobulin (Ig) M and IgG antibodies against *M. pneumoniae* are commercially available. IgM antibodies have a high rate of false-positive and false-negative results. In most cases, IgM antibodies are not detected within the 1st wk after onset of symptoms or in children with recurrent infections and may be positive for up to 6-12 mo after infection. A 4-fold or greater increase in IgG antibody titers against *M. pneumoniae* between acute and convalescent sera obtained 10 days to 3 wk apart is diagnostic.

Cold hemagglutinins (cold-reacting antibodies against red blood cells) can be detected in approximately 50% of patients with *M. pneumoniae* atypical pneumonia. These antibodies are nonspecific, especially at titers <1:64, as modest increases in cold hemagglutinin can be observed in other viral infections. Cold agglutinin antibodies should not be used for the diagnosis of *M. pneumoniae* infections if other methods are available. Nonetheless the PCR may be positive in some asymptomatic patients.

PCR-based tests for *M. pneumoniae* have replaced other diagnostic tests. PCR of a nasopharyngeal or throat swab (doing both increases sensitivity) for *M. pneumoniae* DNA carries a sensitivity and a specificity of 80% to >97%. Different primers have been used to identify gene sequences of the P1 cytoadhesin protein or the ribosomal (r)RNA. PCR allows a more rapid diagnosis in acutely ill patients and can be positive earlier in the course of infection than serologic tests. Identification of *M. pneumoniae* by PCR (or culture) from a patient with compatible clinical manifestations suggests causation.

The diagnosis of extrapulmonary disease associated with *M. pneumoniae* is challenging. Although small case series identified *M. pneumoniae* by PCR in the CSF of children with encephalitis, there are currently no reliable tests for the diagnosis of CNS or other nonrespiratory sites associated with *M. pneumoniae.*

TREATMENT

M. pneumoniae illness is usually mild, and most cases of pneumonia can be managed without the need for hospitalization. Because mycoplasmas lack a cell wall, they inherently are resistant to β-lactam agents that act by inhibiting the cell wall synthesis.

Antimicrobial Therapy

M. pneumoniae is typically sensitive to macrolides (erythromycin, clarithromycin, azithromycin), the tetracyclines, and quinolones in vitro. Data from observational studies showed that macrolide treatment of children with *M. pneumoniae* CAP markedly shortened the course of illness. Treatment may be more effective when started within 3-4 days of illness onset. Although macrolides do not have bactericidal activity, they are preferred in children younger than 8 yr of age. Two multicenter studies of pediatric CAP demonstrated comparable clinical and bacteriologic success rates between erythromycin and clarithromycin or azithromycin. However, the newer macrolides were better tolerated. The recommended treatment is clarithromycin (15 mg/kg/day divided into 2 doses PO for 10 days) or azithromycin (10 mg/kg once PO on day 1 and 5 mg/kg once daily PO on days 2-5). In addition to the antibacterial effect, macrolides have immunomodulatory properties, but the relevance of the anti-inflammatory properties of macrolides for the treatment of *M. pneumoniae* CAP is not known. Tetracyclines (doxycycline 100 mg twice a day for 7-14 days) are also effective and may be used for children older than 8 yr of age. Fluoroquinolones such as levofloxacin (500 mg once a day for 7-14 days) are effective but are less active than macrolides and are not recommended as a first-line therapy in children.

Macrolide-resistant strains, mostly associated with mutations in the 23S rRNA, have been reported in Asia (>40% in Japan and 80-90% in China) and are also present in Europe and the United States (with rates ranging from 8-20%). Although not routinely done at commercial laboratories, identification of macrolide-resistant strains can be performed by sequencing and identification of specific mutations at the 23S rRNA gene. The tetracycline minocycline (for children > 8 yr) and the quinolone tosufloxacin (for children < 8 yr) are approved in Japan for pediatric use to treat macrolide-resistant *M. pneumoniae* infections. For patients with severe mycoplasma pneumonia not responding to macrolide therapy, the possibility of macrolide-resistant *M. pneumoniae* strains should be considered, and switching to a nonmacrolide antimicrobial agent might be prudent.

Adjunctive Therapy

There is no evidence that treatment of upper respiratory tract or nonrespiratory tract disease with antimicrobial agents alters the course of illness. However, patients with severe manifestations of extrapulmonary disease may benefit from antimicrobial treatment combined with immunotherapy. In this regard, corticosteroids with or without intravenous immunoglobulin are the most commonly used agents in the management of severe *M. pneumoniae* extrapulmonary manifestations, particularly with CNS involvement. Although definitive data are lacking, case studies suggest associated clinical benefit of steroids used in the management of severe lung disease, SJS, and hemolytic anemia.

PREVENTION

Trials with inactivated and live attenuated vaccines for *M. pneumoniae* have been conducted with disappointing results. In hospitalized patients standard and droplet precautions are recommended for the duration of symptoms. It is important to emphasize that *Mycoplasma* infection remains contagious as long as cough persists and despite successful antibiotic therapy. Prophylaxis with tetracyclines or azithromycin substantially reduces the secondary attack rates in institutional outbreaks and family close contacts. Antimicrobial prophylaxis is not recommended routinely; however, it can be considered in patients at high risk for severe disease, such as children with sickle cell disease.

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Chapter 224

Genital Mycoplasmas (*Mycoplasma Hominis, Mycoplasma Genitalium,* and *Ureaplasma Urealyticum*)

Rebecca Wallihan and Asuncion Mejias

ETIOLOGY

Mycoplasma species are small pleomorphic bacteria that typically lack a cell wall. These ubiquitous organisms are difficult to cultivate and belong to the family Mycoplasmataceae in the class Mollicutes and represent the smallest self-replicating organisms known to date. The family Mycoplasmataceae is composed of 2 genera responsible for human infection: *Mycoplasma* and *Ureaplasma.* Of those, *Mycoplasma hominis, Mycoplasma genitalium,* and *Ureaplasma* spp., which includes *Ureaplasma urealyticum (biovar 2)* and *Ureaplasma parvum (biovar 1),* are considered human urogenital pathogens and are reviewed in this chapter. Genital mycoplasmas are often associated with sexually transmitted infections such as cervicitis and nongonococcal urethritis (NGU) or with puerperal infections such as endometritis. *M. hominis* and *Ureaplasma* spp. commonly colonize the female genital tract and can cause chorioamnionitis, colonization of neonates, and perinatal infections. Two other genital *Mycoplasma* species, *Mycoplasma fermentans* and *Mycoplasma penetrans,* have been identified in respiratory or genitourinary secretions primarily in HIV-infected patients.

EPIDEMIOLOGY

M. hominis and *Ureaplasma* spp. are commensal organisms in the lower genital and urinary tracts of postpubertal women and men. Colonization rates are directly related to sexual activity and are highest among individuals with multiple sexual partners. Female colonization is maximal in the vagina and less in the endocervix, urethra, and endometrium, with rates varying from 40-80% for *Ureaplasma* spp. and 21-70% for *M. hominis* among sexually active asymptomatic women. Male colonization is less common and occurs primarily in the urethra. Among prepubertal children and sexually inactive adults, colonization rates are <10%. *M. genitalium* is implicated in approximately 25% of NGU cases in men and plays a role in cervicitis and pelvic inflammatory disease in women. Studies using polymerase chain reaction (PCR) show that colonization of the female lower urogenital tract with *M. genitalium* is less common than with *M. hominis* or *Ureaplasma* spp.

TRANSMISSION

Genital mycoplasmas are transmitted by sexual contact or by vertical transmission from mother to infant. As with other perinatal infections, vertical transmission can occur through ascending intrauterine infection, hematogenous spread from placental infection, or through a colonized birth canal at the time of delivery. Transmission rates among neonates born to women colonized with *Ureaplasma* spp. range from 18-88%. Neonatal colonization rates are higher among infants who weigh <1,000 g, are born in the presence of chorioamnionitis, or are born to mothers of lower socioeconomic status. Organisms may be recovered from the newborn's throat, vagina, rectum, and, occasionally, conjunctiva for as long as 3 mo after birth.

PATHOLOGY AND PATHOGENESIS

Genital mycoplasmas can cause chronic inflammation of the genitourinary tract and amniotic membranes. *Ureaplasma* spp. can infect the amniotic sac early in gestation without rupturing the amniotic membranes, resulting in a clinically silent, chronic chorioamnionitis characterized by an intense inflammatory response. Attachment to fetal human tracheal epithelium can cause ciliary disarray, clumping, and loss of epithelial cells. In vitro studies show that *Ureaplasma* spp. stimulates macrophage production of interleukin-6 and tumor necrosis factor-α. In addition, high concentrations of proinflammatory cytokines possibly associated with development of chronic lung disease (CLD) of prematurity, such as monocyte chemoattractant protein-1 and interleukin-8, have been found in tracheal secretions from very-low-birthweight infants colonized with *Ureaplasma* spp. Immunity appears to require serotype-specific antibody. Thus, lack of maternal antibodies might account for a higher disease risk in premature newborns.

CLINICAL MANIFESTATIONS

Intrauterine and Neonatal Infections

Genital mycoplasmas are associated with a variety of fetal and neonatal infections. *Ureaplasma* spp. can cause clinically inapparent chorioamnionitis resulting in spontaneous abortion, increased fetal death, or premature delivery. *Ureaplasma* spp. can also be recovered from tracheal, blood, cerebrospinal fluid (CSF), or lung biopsy specimens in up

to 50% of sick infants younger than 34 wk of gestational age. In a study of 351 preterm infants born between 23 and 32 wk of gestational age, isolation of *Ureaplasma* spp. or *M. hominis* from cord blood correlated with the development of systemic inflammatory response syndrome. The role of these organisms causing severe respiratory insufficiency, the need for mechanical ventilation, the development of CLD, or death remains controversial. Meta-analyses of published studies have identified respiratory colonization with *Ureaplasma* spp. as an independent risk factor for the development of CLD. However, trials of erythromycin therapy in high-risk preterm infants with tracheobronchial colonization of *U. urealyticum* have failed to show any difference in the development of CLD in treated vs nontreated infants.

M. hominis and *Ureaplasma* spp. have been isolated from the CSF of premature and, less commonly, full-term infants. However, the clinical significance of recovering these bacteria from the CSF is uncertain. Simultaneous isolation of other pathogens is unusual, and most infants have no overt signs of central nervous system (CNS) disease. Overall, CSF pleocytosis is not consistent, and spontaneous clearance of mycoplasmas has been documented without specific therapy. *Ureaplasma* spp. meningitis has been associated with intraventricular hemorrhage and hydrocephalus. Limited data suggest that meningitis caused by *M. hominis* can be associated with significant morbidity and mortality. In a review of 29 reported neonatal cases with *M. hominis* meningitis, 8 (28%) neonates died and 8 (28%) developed neurologic sequelae. The age of onset of meningitis ranges from 1 to 196 days of life, and organisms can persist in the CSF without therapy for days to weeks. Pachymeningitis may be evident on MRI scans. *M. hominis* and *Ureaplasma* spp. have also been associated with neonatal conjunctivitis, lymphadenitis, pharyngitis, pneumonitis, osteomyelitis, brain abscess, pericarditis, meningoencephalitis, and scalp abscess.

Genitourinary Infections

In sexually active adolescents and adults, genital mycoplasmas are associated with sexually transmitted diseases and are rarely associated with focal infections outside the genital tract. *Ureaplasma* spp. and *M. genitalium* are recognized etiologic agents of NGU. Approximately 30% of NGU in males may be caused by these organisms either alone or associated with *Chlamydia trachomatis* (see Chapter 226). *Ureaplasma* spp. are also associated with the development of urinary calculi. Disease is most common in young adults but is also prevalent in sexually active adolescents. The average incubation period is 2-3 wk, with symptoms typically consisting of scant mucoid-white urethral discharge, dysuria, and penile discomfort. The discharge is often evident only in the morning or after the urethra is stripped. Rare complications of NGU include epididymitis and proctitis. Approximately 20-60% of patients with *M. genitalium* NGU develop recurrent or chronic urethritis despite 1-2 wk of treatment with doxycycline.

Nongenital Infections

Extragenital *Ureaplasma* spp. infections are rarely described but include pneumonia, osteomyelitis, arthritis, meningitis, mediastinitis, infection of aortic grafts, and postcesarean wound infections. Patients with hypogammaglobulinemia appear to be at higher risk for chronic arthritis caused by various *Mycoplasma* spp. On the other hand, *M. hominis* is associated with septicemia, endocarditis, wound infections, osteomyelitis, lymphadenitis, pneumonia, meningitis, brain abscesses, arthritis, amnionitis, and postpartum fever. There are reports of life-threatening mediastinitis, sternal wound infections, pleuritis, peritonitis, and pericarditis with high mortality rates in patients following organ transplantation.

DIAGNOSIS

All Mollicutes lack a cell wall and are therefore not visible on Gram stain. *M. hominis* and *Ureaplasma* spp. can grow in cell-free media and require sterols for growth, producing characteristic colonies on agar. Colonies of *M. hominis* are 200-300 μm in diameter with a "fried-egg" appearance, while colonies of *Ureaplasma* spp. are smaller (16-60 μm in diameter). Although these organisms can grow in culture, PCR assays have a greater sensitivity. Assays for both *Ureaplasma* spp. and *M. hominis* are available at research and reference laboratories in the United States. *M. genitalium* is a fastidious organism and can be isolated with difficulty in cell culture systems; however, PCR provides a more practical method for detection.

Genital Tract Infection

Confirmation of genital tract infection is challenging because of the high colonization rates in the vagina and urethra. NGU is typically defined as new-onset urethral discharge or dysuria with Gram stain of urethral discharge showing ≥5 polymorphonuclear leukocytes per oil-immersion field in the absence of Gram-negative diplococci (i.e., *Neisseria gonorrhoeae*). A urethral swab or exudate can be cultured for *C. trachomatis* and *Ureaplasma* spp. Detection of *Ureaplasma* spp. or *M. hominis* by PCR is available for a variety of specimens, including urine, amniotic fluid, placental tissue, respiratory specimens, synovial fluid, and swabs of the cervix, urethra, and vagina. *M. genitalium* is often identified by PCR testing of first-void urine specimens in men and vaginal swabs in women.

Neonates

Ureaplasma spp. and *M. hominis* have been isolated from urine, blood, CSF, tracheal aspirates, pleural fluid, abscesses, and lung tissue. Premature neonates who are clinically ill with pneumonitis, focal abscesses, or CNS disease (particularly progressive hydrocephalus with or without pleocytosis) for whom bacterial cultures are negative or in whom there is no improvement with standard antibiotic therapy warrant cultures/PCR for genital mycoplasmas. Isolation requires special media, and clinical specimens must be cultured immediately or frozen at −70°C (−94°F) to prevent loss of organisms. When inoculated into broth containing arginine (for *M. hominis*) or urea (for *Ureaplasma* spp.), growth is indicated by an alkaline pH. Identification of *Ureaplasma* spp. on agar requires 1-2 days of growth and visualization with the dissecting microscope, whereas *M. hominis* is apparent to the eye but can require 1 wk to grow. Cultures from the upper respiratory tract may be less specific owing to high colonization rates. Cultures of the lower respiratory tract through endotracheal aspirate or biopsy are essential.

TREATMENT

These organisms lack a cell wall, and thus β-lactam agents are not effective. These bacteria are also resistant to sulfonamides and trimethoprim because they do not produce folic acid. Rifamycins do not have activity against Mollicutes. *M. hominis* is resistant to macrolides but generally susceptible to clindamycin and quinolones. Most *Ureaplasma* spp. are susceptible to macrolides and advanced generation quinolones, such as moxifloxacin, but often resistant to ciprofloxacin and clindamycin. Susceptibility to tetracyclines is variable for both organisms, with increasing resistance being reported. *M. genitalium* is typically susceptible to macrolides and moxifloxacin, with variable resistance to tetracyclines and clindamycin.

Adolescents and Adults

Recommended treatment for NGU in males is azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO twice daily for 7 days). Recurrent NGU after completion of treatment suggests the presence of azithromycin-resistant *M. genitalium*. Retreatment with moxifloxacin may be most effective. Sexual partners should also be treated to avoid recurrent disease in the index case. Nongenital mycoplasmal infections may require surgical drainage and prolonged antibiotic therapy.

Neonates

Therapy for neonates with genital mycoplasma infections is indicated if infections are associated with pure growth of the organism or if the organism is detected by PCR from a normally sterile site in conjunction with compatible disease manifestations to assure the treatment of an infectious process rather than merely colonization. The role of preventive therapy for the possible role of genital mycoplasmas in the genesis of CLD in very-low-birthweight infants awaits results of further studies. Treatment is based on predictable antimicrobial sensitivities,

because susceptibility testing is not readily available for individual isolates. For infants with symptomatic CNS infection, cures have been described with chloramphenicol, doxycycline, and moxifloxacin. The long-term consequences of asymptomatic CNS infection associated with genital mycoplasmas, especially in the absence of pleocytosis, are unknown. Because mycoplasmas can spontaneously clear from the CSF, therapy should involve minimal risks.

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Section 10

Chlamydial Infections

Chapter 225

Chlamydia (Chlamydophila) pneumoniae

Stephan A. Kohlhoff and Margaret R. Hammerschlag

Chlamydia pneumoniae is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults.

ETIOLOGY

Chlamydiae are obligate intracellular pathogens that have established a unique niche in host cells. Chlamydiae cause a variety of diseases in animal species at virtually all phylogenic levels. The most significant human pathogens are *C. pneumoniae* and *Chlamydia trachomatis* (see Chapter 226). *Chlamydia psittaci* is the cause of psittacosis, an important zoonosis (see Chapter 227).

Chlamydiae have a Gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. pneumoniae* and *C. trachomatis* encode proteins forming a nearly complete pathway for synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide antigen and use host adenosine triphosphate for the synthesis of chlamydial proteins. Although chlamydiae are auxotrophic for 3 of 4 nucleoside triphosphates, they encode functional glucose-catabolizing enzymes that can be used to generate adenosine triphosphate. As with peptidoglycan synthesis, for some reason these genes are turned off. All chlamydiae also encode an abundant surface exposed protein called the *major outer membrane protein.* The major outer membrane protein is the major determinant of the serologic classification of *C. trachomatis* and *C. psittaci* isolates.

EPIDEMIOLOGY

C. pneumoniae is primarily a human respiratory pathogen. The organism has also been isolated from nonhuman species, including horses, koalas, reptiles, and amphibians, where it also causes respiratory infection, although the role that these infections might play in transmission to humans is unknown. *C. pneumoniae* appears to affect individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2-19%, varying with geographic location, the age group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection in 0-18% of patients based on serology or culture for diagnosis. In 1 study, almost 20% of the children with *C. pneumoniae* infection were coinfected with *Mycoplasma pneumoniae. C. pneumoniae* may also be responsible for 10-20% of episodes of acute chest syndrome in children with sickle cell disease, up to 10% of asthma exacerbations, 10% of episodes of bronchitis, and 5-10% episodes of pharyngitis in children. Asymptomatic infection appears to be common based on epidemiologic studies.

Transmission probably occurs from person to person through respiratory droplets. Spread of the infection appears to be enhanced by close proximity, as is evident from localized outbreaks in enclosed populations, such as military recruits and in nursing homes.

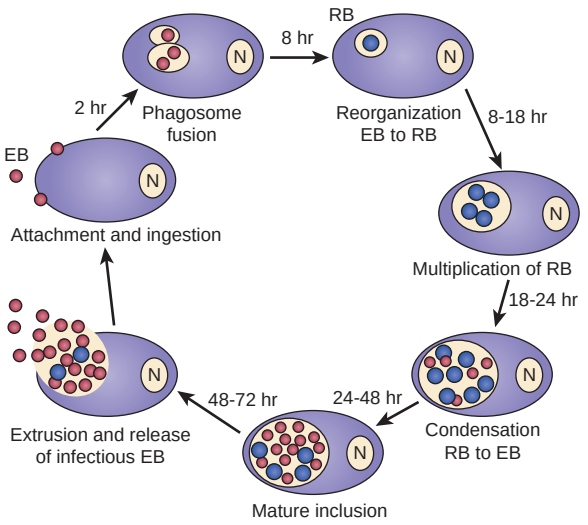

Figure 225-1 Life cycle of chlamydiae in epithelial cells. *EB,* elementary body; *RB,* reticulate body. *(From Hammerschlag MR: Infections due to* Chlamydia trachomatis *and* Chlamydia pneumoniae *in children and adolescents.* Pediatr Rev *25:43–50, 2004.)*

PATHOGENESIS

Chlamydiae are characterized by a unique developmental cycle (Fig. 225-1) with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). Following infection, the infectious EBs, which are 200-400 μm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests a functional interaction with the Golgi apparatus. The EBs then differentiate into RBs that undergo binary fission. After approximately 36 hr, the RBs differentiate into EBs. At approximately 48 hr, release can occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, leaving the host cell intact. Chlamydiae can also enter a persistent state after treatment with certain cytokines such as interferon-γ, treatment with antibiotics, or restriction of certain nutrients. While chlamydiae are in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical, infection is one of the major characteristics of chlamydiae.

CLINICAL MANIFESTATIONS

Infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae.* The pneumonia usually occurs as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms, including fever, malaise, headache, cough, and often pharyngitis. Severe pneumonia with pleural effusions and empyema has

been described. Milder respiratory infections have been described, which can manifest as a pertussis-like illness.

C. pneumoniae can serve as an infectious trigger for asthma, can cause pulmonary exacerbations in patients with cystic fibrosis, and produce acute chest syndrome in patients with sickle cell anemia. *C. pneumoniae* has been isolated from middle ear aspirates of children with acute otitis media, most of the time as co-infection with other bacteria. Asymptomatic respiratory infection has been documented in 2-5% of adults and children and can persist for 1 yr or longer.

DIAGNOSIS

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and can show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection is based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis*. The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. BioFire Technologies (formerly Idaho Technologies) has a nucleic acid amplification testing assay (Film Array) for the detection of 17 viruses and some of the atypical agents of pneumonia, including *C. pneumoniae*, *M. pneumoniae,* and *Bordetella pertussis*. This assay received FDA clearance in July 2012. The Film Array system combines nucleic acid extraction, nested polymerase chain reaction, detection, and data analysis.

Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation tests. The complement fixation test is genus specific and is also used for diagnosis of lymphogranuloma venereum (see Chapter 226.4) and psittacosis (see Chapter 227). Its sensitivity in hospitalized patients with *C. pneumoniae* infection and children is variable. The Centers for Disease Control and Prevention (CDC) has proposed modifications in the serologic criteria for diagnosis. Although the MIF test was considered to be the only currently acceptable serologic test, the criteria were made significantly more stringent. Acute infection, using the MIF test, was defined by a 4-fold increase in immunoglobulin (Ig) G titer or an IgM titer of ≥16; use of a single elevated IgG titer was discouraged. An IgG titer of ≥16 was thought to indicate past exposure, but neither elevated IgA titers nor any other serologic marker was thought to be a valid indicator of persistent or chronic infection. Because diagnosis would require paired sera, this would be a retrospective diagnosis. The CDC did not recommend the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because of concern about the inconsistent correlation of these results with culture results. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that more than 50% of children with culture-documented infection have no detectable MIF antibody.

TREATMENT

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. Most treatment studies have used only serology for diagnosis, and thus microbiologic efficacy cannot be assessed. Prolonged therapy for 2 wk or longer is required for some patients, because recrudescent symptoms and persistent positive cultures have been described following 2 wk of erythromycin and 30 days of tetracycline or doxycycline.

Tetracyclines, erythromycin, the macrolides (azithromycin and clarithromycin), and quinolones show in vitro activity. Like *C. psittaci, C. pneumoniae* is resistant to sulfonamides. The results of treatment studies have shown that erythromycin (40 mg/kg/day PO divided twice a day for 10 days), clarithromycin (15 mg/kg/day PO divided twice a day for 10 days), and azithromycin (10 mg/kg PO on day 1, and then 5 mg/kg/day PO on days 2-5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases.

PROGNOSIS

Clinical response to antibiotic therapy varies. Coughing often persists for several weeks even after therapy.

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Chapter 226

Chlamydia trachomatis

Margaret R. Hammerschlag

Chlamydia trachomatis is subdivided into 2 biovars: lymphogranuloma venereum (LGV) and trachoma, which is the agent of human oculogenital diseases other than LGV. Although the strains of both biovars have almost complete DNA homology, they differ in growth characteristics and virulence in tissue culture and animals. In developed countries, *C. trachomatis* is the most prevalent sexually transmitted disease, causing urethritis in men, cervicitis and salpingitis in women, and conjunctivitis and pneumonia in infants.

226.1 Trachoma

Margaret R. Hammerschlag

Trachoma is the most important preventable cause of **blindness** in the world. It is caused primarily by the A, B, Ba, and C serotypes of *C. trachomatis.* It is endemic in the Middle East and Southeast Asia and among Navajo Indians in the southwestern United States. In areas that are endemic for trachoma, such as Egypt, genital chlamydial infection is caused by the serotypes responsible for oculogenital disease: D, E, F, G, H, I, J, and K. The disease is spread from eye to eye. Flies are a common vector.

Trachoma begins as a **follicular conjunctivitis,** usually in early childhood. The follicles heal, leading to conjunctival scarring that can result in an entropion, with the eyelid turning inward so that the lashes abrade the cornea. It is the corneal ulceration secondary to the constant trauma that leads to scarring and blindness. Bacterial superinfection can also contribute to scarring. Blindness occurs years after the active disease.

Trachoma can be diagnosed clinically. The World Health Organization suggests that at least 2 of 4 criteria must be present for a diagnosis of trachoma: lymphoid follicles on the upper tarsal conjunctivae, typical conjunctival scarring, vascular pannus, and limbal follicles. The diagnosis is confirmed by culture or staining tests for *C. trachomatis* performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially. Endemic trachoma has been controlled in most instances by administering topical tetracyclines (or, rarely, erythromycin ointment) daily for periods of 6-10 wk or intermittently over a 6 mo period. Oral doxycycline is effective but is contraindicated in children younger than 8 yr of age. Oral erythromycin requires frequent dosing, which is impractical in the control of endemic trachoma.

Several studies have reported that 1-6 doses of oral azithromycin are equivalent to 30 days of treatment with topical oxytetracycline/polymyxin ointment. The World Health Organization recommends single-dose azithromycin (20 mg/kg; maximum: 1 g) for the treatment of trachoma in children. Mass treatment with a single dose of azithromycin to all the residents of a village dramatically reduced the prevalence and intensity of infection. This effect continued for 2 yr after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

Bibliography is available at Expert Consult.

226.2 Genital Tract Infections

Margaret R. Hammerschlag

EPIDEMIOLOGY

There are an estimated 3 million new cases of chlamydial sexually transmitted infections each year in the United States. *C. trachomatis* is a major cause of epididymitis and is the cause of 23-55% of all cases of nongonococcal urethritis, although the proportion of chlamydial nongonococcal urethritis has been gradually declining. As many as 50% of men with gonorrhea may be coinfected with *C. trachomatis*. The prevalence of chlamydial cervicitis among sexually active women is 2-35%. Rates of infection among girls 15-19 yr of age exceed 20% in many urban populations but can be as high as 15% in suburban populations as well.

Children who have been sexually abused can acquire anogenital *C. trachomatis* infection, which is usually asymptomatic. However, because perinatally acquired rectal and vaginal *C. trachomatis* infections can persist for 3 yr or longer, the detection of *C. trachomatis* in the vagina or rectum of a young child is not absolute evidence of sexual abuse.

CLINICAL MANIFESTATIONS

The trachoma biovar of *C. trachomatis* causes a spectrum of disease in sexually active adolescents and adults. Up to 75% of women with *C. trachomatis* have no symptoms of infection. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent. Asymptomatic urethral infection is common in sexually active men. Autoinoculation from the genital tract to the eyes can lead to concomitant inclusion conjunctivitis.

DIAGNOSIS

Definitive diagnosis of genital chlamydial infection is accomplished by isolation of the organism in tissue culture and confirmed by microscopic identification of the characteristic inclusions using fluorescent antibody staining in culture specimens obtained from the urethra in men and the endocervix in women. Care should be taken to obtain epithelial cells, not only discharge. *C. trachomatis* can be cultured in cycloheximide-treated HeLa, McCoy, and HEp-2 cells. Chlamydia culture has been further defined by the Centers for Disease Control and Prevention (CDC) as isolation of the organism in tissue culture and as confirmation of the characteristic intracytoplasmic inclusions by fluorescent antibody staining.

Alternatively, a nonculture method, specifically a nucleic acid amplification test (NAAT) can be used. These tests have high sensitivity, perhaps even detecting 10-20% greater than culture, while retaining high specificity. Currently, 4 FDA-approved NAATs are commercially available for detecting *C. trachomatis*: polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (ProbeTec, BD Diagnostic Systems, Sparks, MD), transcription-mediated amplification (Amp CT, Gen-Probe, San Diego, CA) and GeneXpert CT/NG assay (Cepheid, Sunnyvale, CA). PCR and strand displacement amplification are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that are present at approximately 10 copies in each infected cell. Transcription-mediated amplification is a ribosomal RNA amplification assay. GeneXpert is an on-demand qualitative real-time PCR. All these assays are also available as coamplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae*.

The currently available commercial NAATs are FDA approved for cervical swabs from adolescent girls and women, urethral swabs from adolescent boys and men, and urine from adolescents and adults. The latest version of transcription-mediated amplification was approved for use with vaginal swabs in adolescents and adults. Use of urine avoids the necessity for a clinical pelvic examination and can greatly facilitate screening in certain populations, especially adolescents, although several studies have now demonstrated that endocervical specimens and vaginal swabs are superior to urine for NAAT. Self-collected vaginal specimens appear to be as reliable as specimens obtained by a healthcare professional.

Data on use of NAATs for vaginal specimens or urine from children are very limited and insufficient to allow making a recommendation for their use. The CDC recommends that NAATs be used as an alternative to culture only if confirmation is available. Confirmation tests should consist of a second FDA-approved NAAT that targets a different gene sequence from the initial test.

The etiology of most cases of nonchlamydial nongonococcal urethritis is unknown, although *Ureaplasma urealyticum* and possibly *Mycoplasma genitalium* are implicated in up to one-third of cases (see Chapter 224). Proctocolitis may develop in individuals who have a rectal infection with an LGV strain (see Chapter 226.4).

TREATMENT

The first-line treatment regimens recommended by the CDC for uncomplicated *C. trachomatis* genital infection in men and nonpregnant women include azithromycin (1 g PO as a single dose) and doxycycline (100 mg PO twice a day for 7 days). Alternative regimens are erythromycin base (500 mg PO 4 times a day for 7 days), erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days), ofloxacin (300 mg PO twice a day for 7 days), and levofloxacin (500 mg PO once daily for 7 days). The high erythromycin dosages might not be well tolerated. Doxycycline and quinolones are contraindicated in pregnant women, and quinolones are contraindicated in persons younger than 18 yr. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days). Alternative regimens for pregnant women are erythromycin base (250 mg PO 4 times a day for 14 days), and erythromycin ethylsuccinate (800 mg PO 4 times a day for 7 days or 400 mg PO 4 times a day for 14 days).

Empirical treatment without microbiologic diagnosis is recommended only for patients at high risk for infection who are unlikely to return for follow-up evaluation, including adolescents with multiple sex partners. These patients should be treated empirically for both *C. trachomatis* and gonorrhea.

Sex partners of patients with nongonococcal urethritis should be treated if they have had sexual contact with the patient during the 60 days preceding the onset of symptoms. The most recent sexual partner should be treated even if the last sexual contact was more than 60 days from onset of symptoms.

COMPLICATIONS

Complications of genital chlamydial infections in women include perihepatitis (Fitz-Hugh-Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection

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(see Chapter 226.3). Women with *C. trachomatis* infection have a 3-5–fold increased risk for acquiring HIV infection.

PREVENTION

Timely treatment of sex partners is essential for decreasing risk for reinfection. Sex partners should be evaluated and treated if they had sexual contact during the 60 days preceding onset of symptoms in the patient. The most recent sex partner should be treated even if the last sexual contact was >60 days. Patients and their sex partners should abstain from sexual intercourse until 7 days after a single-dose regimen or after completion of a 7 day regimen.

Annual routine screening for *C. trachomatis* is recommended for all sexually active female adolescents, for all women 20-25 yr of age, and for older women with risk factors such as new or multiple partners or inconsistent use of barrier contraceptives. Sexual risk assessment might indicate more frequent screening of some women.

Bibliography is available at Expert Consult.

226.3 Conjunctivitis and Pneumonia in Newborns

Margaret R. Hammerschlag

EPIDEMIOLOGY

Chlamydial genital infection is reported in 5-30% of pregnant women, with a risk for vertical transmission at parturition to newborn infants of approximately 50%. The infant may become infected at 1 or more sites, including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare following cesarean section with intact membranes. The introduction of systematic prenatal screening for *C. trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the United States. However, in countries where prenatal screening is not done, such as the Netherlands, *C. trachomatis* remains an important cause of neonatal infection, accounting for >60% of neonatal conjunctivitis.

Inclusion Conjunctivitis

Approximately 30-50% of infants born to mothers with active, untreated chlamydial infection develop clinical conjunctivitis. Symptoms usually develop 5-14 days after delivery, or earlier in infants born after prolonged rupture of membranes. The presentation is extremely variable and ranges from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva may be very friable and might bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is sight threatening. At least 50% of infants with chlamydial conjunctivitis also have nasopharyngeal infection.

Pneumonia

Pneumonia caused by *C. trachomatis* can develop in 10-20% of infants born to women with active, untreated chlamydial infection. Only approximately 25% of infants with nasopharyngeal chlamydial infection develop pneumonia. *C. trachomatis* pneumonia of infancy has a very characteristic presentation. Onset usually occurs between 1 and 3 mo of age and is often insidious, with persistent cough, tachypnea, and absence of fever. Auscultation reveals rales; wheezing is uncommon. The absence of fever and wheezing helps to distinguish *C. trachomatis* pneumonia from respiratory syncytial virus pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/μL). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Infections at Other Sites

Infants born to mothers with *C. trachomatis* can develop infection in the rectum or vagina. Although infection in these sites appears to be totally asymptomatic, it can cause confusion if it is identified at a later date. Perinatally acquired rectal, vaginal, and nasopharyngeal infections can persist for 3 yr or longer. *Chlamydia pneumoniae* can also be confused with *C. trachomatis* infection in nasopharyngeal cultures if a genus-specific monoclonal antibody is used to confirm the culture.

DIAGNOSIS

Definitive diagnosis is achieved by isolation of *C. trachomatis* in cultures of specimens obtained from the conjunctiva or nasopharynx. Nonculture methods including direct fluorescent antibody and NAATs are available, but only the direct fluorescent antibody is currently approved for diagnosis of chlamydial conjunctivitis with sensitivities of ≥90% and specificities of ≥95% for conjunctival specimens compared with culture. Accuracy for nasopharyngeal specimens is not as good. Data on use of NAATs for diagnosis of *C. trachomatis* in children are limited. Limited data suggest that PCR may be equivalent to culture for detecting *C. trachomatis* in the conjunctiva of infants with conjunctivitis.

TREATMENT

The recommended treatment regimens for *C. trachomatis* conjunctivitis or pneumonia in infants are erythromycin (base or ethylsuccinate, 50 mg/kg/day divided 4 times a day PO for 14 days) and azithromycin suspension (20 mg/kg/day once daily PO for 3 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies demonstrate that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10-20%, and some infants require a second course of treatment. Mothers (and their sexual contacts) of infants with *C. trachomatis* infections should be empirically treated for genital infection. An association between treatment with oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 wk of age who were given the drug for prophylaxis after nursery exposure to pertussis.

PREVENTION

Neonatal gonococcal prophylaxis with topical erythromycin ointment does not prevent chlamydial ophthalmia or nasopharyngeal colonization with *C. trachomatis* or chlamydial pneumonia. *The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women.* For treatment of *C. trachomatis* infection in pregnant women, the CDC currently recommends either azithromycin (1 g PO as a single dose) or amoxicillin (500 mg PO 3 times a day for 7 days) as first-line regimens. Erythromycin base (250 mg PO 4 times a day for 14 days) and erythromycin ethylsuccinate (800 mg 4 times a day for 7 days, or 400 mg PO 4 times a day for 14 days) are listed as alternative regimens. Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from an untreated sexual partner.

Bibliography is available at Expert Consult.

226.4 Lymphogranuloma Venereum

Margaret R. Hammerschlag

LGV is a systemic sexually transmitted disease caused by the L_1, L_2, and L_3 serotypes of the LGV biovar of *C. trachomatis*. Unlike strains of the trachoma biovar, LGV strains have a predilection for lymphoid tissue. Less than 1,000 cases are reported in adults in the United States annually. There has been a resurgence of LGV infections among men who have sex with men in Europe and the United States. Many of the men were HIV infected and used illicit drugs, specifically methamphetamines. To our knowledge, cases in the pediatric population have not been reported since the emergence of the new clusters of HIV-associated cases in 2003. We reported a case of a 16 yr old boy who presented with LGV proctocolitis after having receptive unprotected anal intercourse with a 30 yr old man he met on the Internet. This history was obtained after the boy was found to be HIV-positive. The

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diagnosis of LGV, particularly when it presents with proctocolitis, relies on a high index of suspicion that would lead to emphasizing certain aspects of the history and ordering the pertinent diagnostic tests. Many pediatricians and pediatric gastroenterologists might not be very familiar with the entity and might not entertain it as a diagnostic consideration in the pediatric patients. The diagnosis can be further suggested by *C. trachomatis* testing: culturing the organism or, more commonly by NAATs. Currently available NAATs will not differentiate LGV from other *C. trachomatis* serovars. NAATs for *C. trachomatis* are also not FDA-cleared for testing rectal specimens. Trying to ascertain the *C. trachomatis* serovar for confirmation of LGV has therapeutic implications as a single-dose of azithromycin is unlikely to eradicate the infection and a 3 wk course of doxycycline is the preferred treatment.

CLINICAL MANIFESTATIONS

The 1st stage of LGV is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The 2nd stage is characterized by usually unilateral femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in men. In women, the vulvar lymph drains to the retroperitoneal nodes. Fever, myalgia, and headache are common. The 3rd stage is a genitoanorectal syndrome with rectovaginal fistulas, rectal strictures, and urethral destruction. Among men who have sex with men, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

DIAGNOSIS

LGV can be diagnosed by serologic testing or by culture of *C. trachomatis* or molecular testing for *C. trachomatis* from a specimen aspirated from a bubo. Most patients with LGV have complement-fixing antibody titers of >1 : 16. Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, co-infections can occur.

TREATMENT

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. The alternative regimen is erythromycin base (500 mg PO 4 times/day for 21 days). Azithromycin (1 g PO once weekly for 3 wk) may also be effective but clinical data are lacking. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

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Chapter 227

Psittacosis *(Chlamydia psittaci)*

Stephan A. Kohlhoff and Margaret R. Hammerschlag

Chlamydia psittaci, the agent of psittacosis (also known as **parrot fever** and **ornithosis**), is primarily an animal pathogen and causes human disease uncommonly. In birds, *C. psittaci* infection is known as *avian chlamydiosis*.

ETIOLOGY

C. psittaci affects both psittacine birds (e.g., parrots, parakeets, macaws) and nonpsittacine birds (ducks, turkeys); the known host range includes 130 avian species. The life cycle of *C. psittaci* is the same as for *Chlamydia pneumoniae* (see Chapter 217). Strains of *C. psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are 7 avian serovars. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the United States. Each is associated with important host preferences and disease characteristics.

EPIDEMIOLOGY

From 1988-2003 there were 935 reported cases of psittacosis in the United States. Of these, 85% of these cases were associated with exposure to birds, including 70% following exposure to caged pet birds, which were usually psittacine birds, including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most often in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include bird fanciers and owners of pet birds (43% of cases) and pet shop employees (10% of cases). Reported cases most likely underestimate the number of actual infections owing to a lack of awareness.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with *C. psittaci* is the primary route of infection. *Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings.* Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage. Several major outbreaks of psittacosis have occurred in turkey-processing plants; workers exposed to turkey viscera are at the highest risk for infection.

CLINICAL MANIFESTATIONS

Infection with *C. psittaci* in humans ranges from clinically inapparent to severe disease, including pneumonia and multiorgan involvement. The mean incubation period is 15 days after exposure, with a range of 5-21 days. Onset of disease is usually abrupt, with fever, cough, headache, myalgia, and malaise. The fever is high and is often associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastrointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal and are characterized by the presence of variable infiltrates, sometimes accompanied by pleural effusions. The white blood cell count is usually normal but is sometimes mildly elevated. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common.

DIAGNOSIS

Psittacosis can be difficult to diagnose because of the varying clinical presentations. A history of exposure to birds or association with an active case can be important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include routine bacterial and viral respiratory infections as well as *Coxiella burnetii* infection (Q fever), *Mycoplasma pneumoniae* infection, *C. pneumoniae* infection, tularemia, tuberculosis, fungal infections, and Legionnaires disease.

The Centers for Disease Control and Prevention and the Council of State and Territorial Epidemiologists have established national case definitions for epidemiologic surveillance of psittacosis. A patient is considered to have a confirmed case of psittacosis if clinical illness is compatible with psittacosis and the case is laboratory confirmed by either: isolation of *C. psittaci* from respiratory specimens (e.g., sputum, pleural fluid, or tissue) or blood, or 4-fold or greater increase in antibody (immunoglobulin G) against *C. psittaci* by complement fixation or microimmunofluorescence between paired acute- and convalescent-phase serum specimens obtained at least 2-4 wk apart. A patient is considered to have a probable case of psittacosis if the

clinical illness is compatible with psittacosis and 1 of the 2 following laboratory results is present: supportive serology (*e.g., C. psittaci* antibody titer [Immunoglobulin M] of greater ≥32 in at least 1 serum specimen obtained after onset of symptoms), or detection of *C. psittaci* DNA in a respiratory specimen (e.g., sputum, pleural fluid or tissue) via amplification of a specific target by polymerase chain reaction assay.

Although microimmunofluorescence has greater specificity to *C. psittaci* than complement fixation, crossreactions with other *Chlamydia* species can occur. Therefore acute- and convalescent-phase serum specimens should be analyzed at the same time in the same laboratory. False-negative microimmunofluorescence results can occur in acutely ill patients. Early treatment of psittacosis with tetracycline can abrogate the antibody response.

Although *C. psittaci* will grow in the same culture systems used for isolation of *Chlamydia trachomatis* and *C. pneumoniae,* very few laboratories culture for *C. psittaci,* mainly because of the potential biohazard. Real-time polymerase chain reaction assays have been developed for use in the detection of *C. psittaci* in respiratory specimens. These assays can distinguish *C. psittaci* from other chlamydial species and identify different *C. psittaci* genotypes. However, polymerase chain reaction–based tests have not been cleared by the FDA for use as diagnostic tests in humans samples.

TREATMENT

Recommended treatment regimens for psittacosis are doxycycline (100 mg PO twice daily) or tetracycline (500 mg PO 4 times a day) for at least 10-14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 hr IV; maximum: 100 mg/dose). Erythromycin (500 mg PO 4 times a day) and azithromycin (10 mg/kg PO day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2-5, not to exceed 250 mg) are alternative drugs if tetracyclines are contraindicated (e.g., children <8 yr of age and pregnant women) but may be less effective. Remission is usually evident within 48-72 hr. Initial infection does not appear to be followed by long-term immunity. Reinfection and clinical disease can develop within 2 mo of treatment.

PROGNOSIS

The mortality rate of psittacosis is 15-20% with no treatment but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

PREVENTION

Several control measures are recommended to prevent transmission of *C. psittaci* from birds. Bird fanciers should be cognizant of the potential risk. *C. psittaci* is susceptible to heat and to most disinfectants and detergents but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30-45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should not be sold or purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

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Section 11

Rickettsial Infections

Chapter 228

Spotted Fever Group Rickettsioses

J. Stephen Dumler and Megan E. Reller

Rickettsia species were classically divided into "spotted fever" and "typhus" groups based on serologic reactions and later on the presence or absence of the outer membrane protein A (*ompA*) gene. Sequencing of at least 45 complete genomes has refined distinctions. However, there is controversy regarding phylogeny and some data suggest that diversity and pathogenicity are the result of gene loss and lateral gene transfer from other prokaryotes or even eukaryotes, which further obscures accurate taxonomic classification. One proposal is to divide existing species into spotted fever and "transitional" groups based on genetic relatedness; both include pathogenic species and species not now known to cause human disease (Table 228-1). Although increasingly more is understood about the molecular basis by which these bacteria cause human illness, an alternative classification system based on pathogenetic mechanisms has not been defined. The list of pathogens and potential pathogens in the spotted fever group has expanded dramatically in recent years. Among them are the tickborne agents *Rickettsia rickettsii,* the cause of Rocky Mountain or Brazilian spotted fever (RMSF); *Rickettsia conorii,* the cause of Mediterranean spotted fever (MSF) or boutonneuse fever; *Rickettsia sibirica,* the cause of North Asian tick typhus; *Rickettsia japonica,* the cause of Oriental spotted fever; *Rickettsia honei,* the cause of Flinders Island spotted fever or Thai tick typhus; *Rickettsia africae,* the cause of African tick bite fever; *Rickettsia akari,* the cause of mite-transmitted rickettsialpox; *Rickettsia felis*, the cause of cat flea–transmitted typhus; and *Rickettsia australis,* the cause of tick-transmitted Queensland tick typhus. One proposal creates subspecies of *R. conorii*, including subsp. *conorii* (classical MSF), subsp. *indica* (Indian tick typhus), subsp. *caspia* (Astrakhan fever), and subsp. *israelensis* (Israeli spotted fever). The recognition that *Rickettsia parkeri* and "*Rickettsia philippi*" (*Rickettsia* 364D) both cause mild spotted fever in North America and the association of high seroprevalence for spotted fever group *Rickettsia* infections in humans where *Amblyomma* ticks frequently contain *Rickettsia amblyommii* suggest that the full range of agents that can cause spotted fever is still to be discerned.

Infections with other members of the spotted fever and transitional groups are clinically similar to MSF, with fever, maculopapular rash, and eschar at the site of the tick bite. Israeli spotted fever is generally associated with a more severe course, including death, in children. African tick bite fever is relatively mild, can include a vesicular rash, and often manifests with multiple eschars. New potentially pathogenic rickettsial species have been identified, including *Rickettsia slovaca,* the cause of tickborne lymphadenopathy or *Dermacentor*-borne necrosis and lymphadenopathy. *Rickettsia aeschlimannii, Rickettsia heilongjiangensis, Rickettsia helvetica, Rickettsia massiliae,* and *Rickettsia raoultii* are all reported to cause mild to moderate illnesses in humans, although few cases have been described. Fortunately, the vast majority of infections respond well to doxycycline treatment if instituted early in illness; however, this is a significant challenge.

Table 228-1 Summary of Rickettsial Diseases of Humans, Including *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Coxiella*

GROUP OR DISEASE AGENT		ARTHROPOD VECTOR, TRANSMISSION HOSTS		GEOGRAPHIC DISTRIBUTION	PRESENTING CLINICAL FEATURES*	COMMON LAB ABNORMALITIES	DIAGNOSTIC TESTS	TREATMENT†
SPOTTED FEVER GROUP								
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick bite: *Dermacentor* species (wood tick, dog tick) *Rhipicephalus sanguineus* (brown dog tick)	Dogs Rodents	Western hemisphere	Fever, headache, rash,* emesis, diarrhea, myalgias	AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol
Mediterranean spotted fever (Boutonneuse fever)	*Rickettsia conorii*	Tick bite: *R. sanguineus* (brown dog tick)	Dogs Rodents	Africa, Mediterranean, India, Middle East	Painless eschar (tache noir) with regional lymphadenopathy, fever, headache, rash,* myalgias	AST, ALT ↓Na (mild) ↓Platelets ±Leukopenia Left shift	Early: IH, DFA, PCR After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol Azithromycin Clarithromycin Fluoroquinolones
African tick-bite fever	*Rickettsia africae*	Tick bite	Cattle Goats?	Sub-Saharan Africa, Caribbean	Fever, single or multiple eschars, regional lymphadenopathy, rash* (can be vesicular)	AST, ALT ↓Platelets	Early: IH, DFA After 1st wk: IFA	**Doxycycline**
Tickborne lymphadenopathy (TIBOLA); Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)	*Rickettsia slovaca*	Tick bite: *Dermacentor*	?	Europe	Eschar (scalp), painful lymphadenopathy	?	PCR	**Doxycycline**
Rickettsia sp, 364D genotype	"*Rickettsia philippi*"	*Dermacentor occidentalis* (Pacific coast tick)		California	Eschar, fever, headache, lymphadenopathy malaise	Unremarkable	PCR	Doxycycline
TRANSITIONAL GROUP								
Rickettsialpox	*Rickettsia akari*	Mite bite	Mice	North America, Russia, Ukraine, Adriatic, Korea, South Africa	Painless eschar, ulcer or papule; tender regional lymphadenopathy, fever, headache, rash* (can be vesicular)	↓WBC	Early: IH, DFA After 1st wk: IFA	**Doxycycline** Chloramphenicol
Cat flea typhus	*Rickettsia felis*	Flea bite	Opossums Cats Dogs	Western hemisphere, Europe	Fever, rash,* headache	?	Early: PCR After 1st wk: IFA	**Doxycycline**
TYPHUS GROUP								
Murine typhus	*Rickettsia typhi*	Flea feces	Rats Opossums	Worldwide	Fever, headache, rash,* myalgias, emesis, lymphadenopathy, hepatosplenomegaly	AST, ALT ↓Na (mild) ↓WBC ↓ Platelets	Early: DFA After 1st wk: IFA	**Doxycycline** Chloramphenicol
Epidemic (louse-borne) typhus (recrudescent form: Brill-Zinsser disease)	*Rickettsia prowazekii*	Louse feces	Humans	South America, Central America, Mexico, Africa, Asia, Eastern Europe	Fever, headache, abdominal pain, rash,* CNS involvement	AST, ALT ↓Platelets	Early: none After 1st wk: IgG/IgM, IFA	**Doxycycline** Tetracycline Chloramphenicol
Flying squirrel (sylvatic) typhus	*Rickettsia prowazekii*	Louse feces? Flea feces or bite?	Flying squirrels	Eastern United States	Same as above (often milder)	AST, ALT ↓Platelets	Early: none After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol

SCRUB TYPHUS								
Scrub typhus	*Orientia tsutsugamushi*	Chigger bite: *Leptotrombidium*	Rodents?	South Asia, Japan, Indonesia, Korea, China, Russia, Australia	Fever, rash,* headache, painless eschar, hepatosplenomegaly, gastrointestinal symptoms	↓Platelets AST, ALT	Early: none After 1st wk: IFA	**Doxycycline** Tetracycline Chloramphenicol ***If doxycycline resistant:* rifampicin** Azithromycin
EHRLICHIOSIS AND ANAPLASMOSIS								
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	Tick bite: *Amblyomma americanum* (lone star tick)	Deer Dogs	United States Europe? Africa? Asia?	Fever, headache, malaise, myalgias, rash*‡, hepatosplenomegaly,‡ swollen hands/feet‡	AST, ALT ↓WBC ↓Platelets ↓Na (mild)	Early: PCR After 1st wk: IFA	**Doxycycline** Tetracycline
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	Tick bite: *Ixodes* species	Rodents Deer Ruminants	United States, Europe, Asia	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓ANC ↓Platelets ↓Na (mild)	Early: PCR, blood smear After 1st wk: IFA	**Doxycycline** Tetracycline Rifampin
Ewingii ehrlichiosis	*Ehrlichia ewingii*	Tick bite: *Amblyomma americanum* (lone star tick)	Dogs Deer	United States (south-central, southeast)	Fever, headache, malaise, myalgias	AST, ALT, ↓WBC ↓Platelets ↓Na (mild)	Early: PCR After 1st wk: IFA	**Doxycycline** Tetracycline
Ehrlichia muris–like agent (EMLA) infection	*Ehrlichia muris*–like agent	*Ixodes scapularis*	?	Minnesota, Wisconsin	Fever, headache, malaise, myalgias	AST, ALT ↓WBC, ↓Platelets	Early: PCR After 1st wk: IFA	**Doxycycline**
Sennetsu ehrlichiosis	*Neorickettsia sennetsu*	Ingestion of fish helminth?	?	Japan Malaysia	Fever, "mononucleosis" symptoms, postauricular and posterior cervical lymphadenopathy	Atypical lymphocytosis	Early: none After 1st wk: IFA	**Doxycycline** Tetracycline
Q FEVER								
Q Fever: acute (for chronic, see text)	*Coxiella burnetii*	Inhalation of infected aerosols: contact with parturient animals, abattoir, contaminated cheese and milk, ?ticks	Cattle Sheep Goats Cats Rabbits	Worldwide	Fever, headache, arthralgias, myalgias, gastrointestinal symptoms, cough, pneumonia, rash (children)	AST, ALT WBC ↓ Platelets Interstitial infiltrate	Early: PCR After 1st wk: IFA	**Doxycycline** Tetracycline Fluoroquinolones Trimethoprim-sulfamethoxazole

*Rash is infrequently present at initial presentation but appears during the 1st wk of illness.
†Preferred treatment is in **bold**.
‡Often present in children but not adults.
ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CNS, central nervous system; DFA, direct fluorescent antibody; IFA, indirect fluorescent antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; IH, immunohistochemistry; PCR, polymerase chain reaction; WBC, white blood cell count.

228.1 Rocky Mountain Spotted Fever (*Rickettsia rickettsii*)

Megan E. Reller and J. Stephen Dumler

RMSF is the most frequently identified and most severe rickettsial disease in the United States. It is also the most common vector-borne disease in the United States after Lyme disease. Although considered uncommon, RMSF is believed to be greatly underdiagnosed and underreported. RMSF should be considered in the differential diagnosis of fever, headache, and rash in the summer months, especially after tick exposure. Because fulminant disease and death are associated with delays in treatment, patients in whom the illness is clinically suspected should be treated promptly.

ETIOLOGY

RMSF results from systemic infection of endothelial cells by the obligate intracellular bacterium *Rickettsia rickettsii*.

EPIDEMIOLOGY

The term **Rocky Mountain spotted fever** is historical, because the agent was discovered in the Bitterroot Range of the Rocky Mountains of Montana. Few cases are now reported from this region. Cases have been reported throughout the continental United States (except Vermont and Maine), southwestern Canada, Mexico, Central America, and South America, but not from outside of the Western Hemisphere. In 2010, the Centers for Disease Control and Prevention (CDC) reporting criteria for "Rocky Mountain spotted fever" changed to **spotted fever group rickettsiosis** because serology often does not distinguish *R. rickettsii* from infection by other spotted fever group *Rickettsia*. Additionally, cases detected by enzyme immunoassay were classified as probable. Thus, in 2012, 2,802 confirmed and probable cases of spotted fever rickettsiosis were reported in Morbidity and Mortality Weekly Reports Summary of Notifiable Diseases. Unlike in prior years, most cases were reported from the west south-central states, especially from Arkansas, Oklahoma, and Missouri; high numbers of cases were also reported from North Carolina, Tennessee, Virginia, New Jersey, Georgia, Alabama, as well as Arizona. The incidence of RMSF cycles over 25-35 yr intervals but has generally increased over the past decades. The mean number of cases reported each year to the CDC has steadily increased (515 during 1993-1998, 946 during 1999-2004, and 2,068 cases in 2005-2010). Habitats favored by ticks, including wooded areas or coastal grassland and salt marshes, and, in the Southwestern United States and Mexico, shaded areas where dogs congregate are associated with disease. Foci of intense infection are found both in rural and urban areas. Clustering of cases within families likely reflects shared environmental exposures. In the United States, 90% of cases occur between April and September, months in which humans spend the most time outdoors. The highest age-specific incidence of RMSF among children is seen in those older than 5 yr of age, with boys outnumbering girls.

TRANSMISSION

Ticks are the natural hosts, reservoirs, and vectors of *R. rickettsii* and maintain the infection in nature by transovarial transmission (passage of the organism from infected ticks to their progeny). Ticks harboring rickettsiae are substantially less fecund than uninfected ticks; thus, horizontal transmission (acquisition of rickettsiae by taking a blood meal from transiently rickettsemic hosts such as small mammals or dogs) contributes to maintenance of rickettsial infections in ticks. Uninfected ticks that simultaneously feed (cofeed) with infected transmitting ticks easily become infected, even if feeding on an immune host and are also likely to be major contributors to natural transmission and maintenance. Ticks transmit the infectious agent to mammalian hosts (including humans) via infected saliva during feeding. The pathogen *R. rickettsii* in ticks becomes virulent after exposure to blood or increased temperature; thus, the longer the tick is attached, the greater the risk of transmission. The principal tick hosts of *R. rickettsii* are *Dermacentor variabilis* (the American dog tick) in the eastern United States and Canada, *Dermacentor andersoni* (the wood tick) in the western United States and Canada, *Rhipicephalus sanguineus* (the common brown dog tick) in the southwestern United States and in Mexico, and *Amblyomma cajennense* and *Amblyomma aureolatum* in Central and South America (Fig. 228-1).

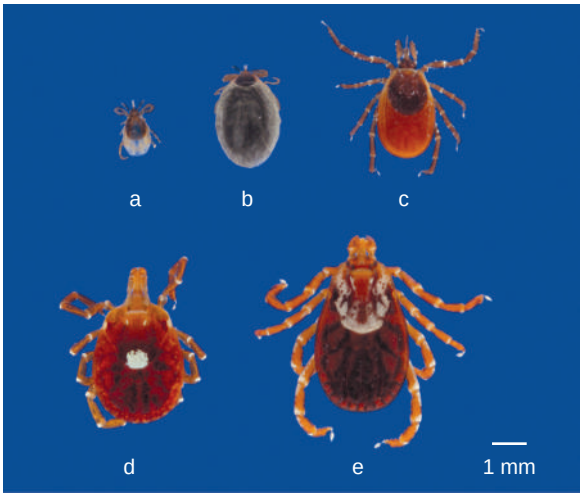

Figure 228-1 Tick vectors of agents of human rickettsial diseases. An unengaged nymph **(A),** engorged nymph **(B),** and adult female **(C)** of *Ixodes scapularis* (deer tick), the vector of *Anaplasma phagocytophilum* and *Ehrlichia muris*–like agent (EMLA), the causes of human granulocytic anaplasmosis and EMLA ehrlichiosis, respectively. An adult female **(D)** of *Amblyomma americanum* (lone star tick), the vector of *Ehrlichia chaffeensis* and *Ehrlichia ewingii*, the causes of human monocytic ehrlichiosis and ewingii ehrlichiosis, respectively. An adult female **(E)** of *Dermacentor variabilis* (American dog tick), the vector of *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever.

Dogs can serve as reservoir hosts for *R. rickettsii*, can develop RMSF themselves, and can bring infected ticks into contact with humans. Serologic studies suggest that many patients with RMSF likely acquired the illness from ticks carried by the family dog.

Humans can also become infected when trying to remove an attached tick, because *R. rickettsii*–containing tick fluids or feces can be rubbed into the open wound at the bite site or into the conjunctivae by contaminated fingers. Finally, inhalation of aerosolized rickettsiae has caused severe infections and deaths in laboratory workers.

PATHOLOGY AND PATHOGENESIS

Systemic infection is most obvious on the skin (rash), but nearly all organs and tissues are affected. Following inoculation of tick saliva into the dermis, rickettsial outer surface proteins bind to the vascular endothelial cell surface proteins, which signals focal cytoskeletal changes that lead to endocytosis. Thereafter, rickettsia phospholipase-mediated dissolution of the endosomal membranes allows escape into the cytosol. Members of the spotted fever group actively nucleate actin polymerization on one pole to achieve directional movement, allowing some rickettsiae to propel into neighboring cells despite minimal initial damage to its host cell. The rickettsiae proliferate and damage the host cells by oxidative membrane alterations, protease activation, or continued phospholipase activity. It is likely that some aspects of intracellular infection are mediated by rickettsial protein effectors delivered into the host cell by a type 4 secretion system.

The histologic correlate of the initial macular or maculopapular rash is perivascular infiltration of lymphoid and histiocytic cells with edema but without significant endothelial damage. Proliferation of rickettsiae within the cytoplasm of infected endothelial cells leads to endothelial injury and **lymphohistiocytic or leukocytoclastic vasculitis** of small venules and capillaries, which allows extravasation of intravascular erythrocytes into the dermis and manifests as a petechial rash. This process is systemic and ultimately results in widespread microvascular

leakage, tissue hypoperfusion, and possibly end-organ ischemic injury. Infrequently, inflammation leads to nonocclusive thrombi. Very rarely, small and large vessels become completely obliterated by thrombi, leading to tissue infarction or hemorrhagic necrosis. Interstitial pneumonitis and vascular leakage in the lungs can lead to noncardiogenic pulmonary edema, and meningoencephalitis can cause significant cerebral edema and herniation.

The presence of the infectious agent initiates an inflammatory cascade, including release of cytokines and chemokines such as tumor necrosis factor-α, interleukin-1β, and interferon-γ, and RANTES (regulated upon activation, normal T-cell expressed and secreted). Infection of endothelial cells by *R. rickettsii* induces surface E-selectin expression and procoagulant activity followed by chemokine recruitment of lymphocytes, macrophages, and, occasionally, neutrophils. Local inflammatory and immune responses are suspected to contribute to the vascular injury; however, the benefits of effective inflammation and immunity are greater. Blockade of tumor necrosis factor-α and interferon-γ action in animal models diminishes survival and increases morbidity; reactive oxygen intermediates, nitric oxide expression, and sequestration of tryptophan from rickettsiae are mechanisms by which rickettsiae are killed within cells. Direct contact of infected endothelial cells with perforin-producing CD8 T lymphocytes and interferon-γ–producing natural killer cells, accompanied by rickettsia antibody, helps control the infection. The timing and balance between rickettsia-mediated increases in vascular permeability and the benefits of induction of innate and adaptive immunity are likely the major determinants of severity and outcome.

CLINICAL MANIFESTATIONS

The incubation period of RMSF in children varies from 2-14 days (median: 7 days). In 49% of cases, patients or their parents report a history of removing an attached tick, although the site of the tick bite is usually inapparent. Epidemiologic clues include living in or visiting an endemic area, playing or hiking in the woods, typical season, similar illness in family members, and close contact with a dog. In patients presenting for care, the illness is initially nonspecific, and most patients are not diagnosed during their first visit with a healthcare practitioner. Manifestations often (>50%) include fever, rash, nausea and vomiting, and headache, and less often (<50%) myalgias, abdominal pain, diarrhea, conjunctival injection, altered mental status, lymphadenopathy, and peripheral edema. Pain and tenderness of calf muscles are particularly common in children.

The typical **clinical triad of fever, headache, and rash** is observed in 58% of pediatric patients overall, but is present in only 3% of all patients at presentation. Fever and headache persist if the illness is untreated. Fever can exceed 40°C (104°F) and may be persistently elevated or can fluctuate dramatically. Headache is severe, unremitting, and unresponsive to analgesics.

Rash usually appears after only 1-2 days of illness, and an estimated 3-5% of children never develop a rash that is recognized. Initially, discrete, pale, rose-red blanching macules or maculopapules appear; characteristically this initial rash is observed on the extremities, including the wrists, ankles, or lower legs (Fig. 228-2). In 65% of patients, the initial rash spreads rapidly to involve the entire body, including the soles and palms. The rash can become petechial or even hemorrhagic, sometimes with palpable purpura. In severe disease, the petechiae can enlarge into ecchymoses, which can become necrotic. Severe vascular obstruction secondary to the rickettsial vasculitis and thrombosis is uncommon but can result in gangrene of the digits, earlobes, scrotum, nose, or an entire limb.

Central nervous system infection usually manifests as changes in mental status (33%) or as photophobia (18%), seizure (17%), or meningismus (16%). Patients can also manifest ataxia, coma, or auditory deficits. Cerebrospinal fluid parameters are usually normal, but one-third have pleocytosis (<10-300 cells/μL), either mononuclear or less often neutrophil-dominated. Some (20%) have elevated protein (<200 mg/dL) in the cerebrospinal fluid; hypoglycorrhachia is rare. Neuroimaging studies generally reveal only subtle abnormalities that do not alter treatment. Cerebral edema, meningeal enhancement, and prominent perivascular spaces have been observed in patients with severe disease.

Figure 228-2 Rocky Mountain spotted fever. *(Courtesy of Debra Karp Skopocki, MD.)*

Other

Pulmonary disease occurs more often in adults than in children. However, 33% of children examined have a chest radiograph interpreted as an infiltrate or pneumonia. The clinical presentation in these cases can manifest as rales, infiltrates, and noncardiogenic pulmonary edema. Other findings can include conjunctival suffusion, periorbital edema, dorsal hand and foot edema, and hepatosplenomegaly. Severe disease can include myocarditis, acute renal failure, and vascular collapse.

Persons with glucose-6-phosphate dehydrogenase deficiency are at increased risk for fulminant RMSF, defined as death from *R. rickettsii* infection within 5 days. The clinical course of fulminant RMSF is characterized by profound coagulopathy and extensive thrombosis leading to kidney, liver, and respiratory failure. Features associated with increased risk of death include altered mental status, admission to an intensive care unit, need for inotropic support, coma, and need for rapidly administered intravenous fluid.

Occasionally, clinical signs and symptoms suggest a localized process such as appendicitis or cholecystitis. Thorough evaluation usually reveals evidence of a systemic process and unnecessary surgical interventions are avoided.

LABORATORY FINDINGS

Laboratory abnormalities are common but nonspecific. Thrombocytopenia occurs in 60%, and the total white blood cell count is most often normal, with leukocytosis in 24% and leukopenia in 9%. Other characteristic abnormalities include a left-shifted leukocyte differential, anemia (33%), hyponatremia (<135 mEq/mL in 52%), and elevated serum aminotransferase levels (50%).

DIAGNOSIS

Delays in diagnosis and treatment are associated with severe disease and death. Because no reliable diagnostic test is available to confirm RMSF during acute illness, the decision to treat must be based on compatible epidemiologic, clinical, and laboratory features. RMSF should be considered in patients presenting spring through fall with an acute febrile illness accompanied by headache and myalgia (particularly if they report exposure to ticks or contact with a dog or have been in forested or tick-infested rural areas). A history of tick exposure, a rash (especially if on the palms or soles), a normal or low leukocyte count with a marked left shift, a relatively low or decreasing platelet count, and a low serum sodium concentration are all clues that can support a diagnosis of RMSF. In patients without a rash or in dark-skinned patients in whom a rash can be difficult to appreciate, the diagnosis can be exceptionally elusive and delayed. One half of pediatric deaths occur within 9 days of onset of symptoms. Thus, treatment

should not be withheld pending definitive laboratory results for a patient with clinically suspected illness. Further, prompt response to early treatment is diagnostically helpful.

If a rash is present, a vasculotropic rickettsial infection can be diagnosed as early as day 1 or 2 of illness with biopsy of a petechial lesion and immunohistochemical or immunofluorescent demonstration of specific rickettsial antigen in the endothelium. Although very specific, the sensitivity of this method is probably 70% at most. Furthermore, it can be adversely influenced by prior antimicrobial therapy, suboptimal selection of skin lesions for biopsy, and examination of insufficient tissue because of the focal nature of the infection. Tissue or blood can also be evaluated for *R. rickettsii* nucleic acids by polymerase chain reaction (PCR) at the CDC and selected public health or reference laboratories; PCR on blood is less sensitive than PCR on tissue and of similar sensitivity to tissue immunohistology, probably because the level of rickettsemia is generally very low (<6 rickettsiae/mL).

Definitive diagnosis is most often accomplished by serology, which is retrospective, because a rise in titer is not seen until after the 1st wk of illness. The gold standard for the diagnosis of RMSF is a 4-fold increase in immunoglobulin G antibody titer by indirect fluorescent antibody assay between acute and convalescent (at 2-4 wk) sera or demonstration of seroconversion. A single titer is neither sensitive (patients can die before seroconversion) nor specific (an elevated titer can represent prior infection); despite the historic role of immunoglobulin M testing, its role in early diagnosis has recently become controversial and cannot be advocated. With current serologic methods, RMSF cannot be reliably distinguished from other spotted fever group rickettsiae infections. Cross-reactions with typhus group rickettsiae also occur, but titers may be lower for the typhus group. Cross-reactions are not seen with *Ehrlichia* or *Anaplasma* infections. Weil-Felix antibody testing should not be performed, because it lacks both sensitivity and specificity. RMSF and other spotted fever group rickettsioses are reportable diseases in the United States.

DIFFERENTIAL DIAGNOSIS

Other rickettsial infections are easily confused with RMSF, especially all forms of human ehrlichiosis and murine typhus and novel spotted fever group rickettsioses that result from *R. parkeri* or "*R. philippii*" infections. RMSF can also mimic a variety of other diseases, such as meningococcemia and enteroviral infections. Negative blood cultures can exclude meningococcemia. PCR can differentiate enterovirus from *R. rickettsii* in patients with aseptic meningitis and a lymphocytic cerebrospinal fluid pleocytosis. Other diseases in the differential diagnosis are typhoid fever, secondary syphilis, Lyme disease, leptospirosis, rat-bite fever, scarlet fever, toxic shock syndrome, rheumatic fever, rubella, parvovirus infection, Kawasaki disease, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Henoch-Schönlein purpura, hemolytic uremic syndrome, aseptic meningitis, acute gastrointestinal illness, acute abdomen, hepatitis, infectious mononucleosis, hemophagocytic syndromes, dengue fever, and drug reactions.

TREATMENT

The time-proven effective therapies for RMSF are tetracyclines and chloramphenicol. The treatment of choice for suspected RMSF in patients of all ages, including for young children, is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) is an alternative. Chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day) should be reserved for patients with doxycycline allergy and for pregnant women, because chloramphenicol is an independent risk factor for increased mortality vs tetracyclines. If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Chloramphenicol is preferred for pregnant women because of potential adverse effects of doxycycline on fetal teeth and bone and maternal liver function. Although tetracycline and doxycycline can be associated with tooth discoloration in children younger than 8 yr of age, RMSF is a life-threatening illness for which prompt therapy is imperative. Furthermore, tooth discoloration with tetracyclines is dose dependent and is unlikely to occur in children prescribed short-course therapy. Chloramphenicol is rarely associated with aplastic anemia and is no longer available as an oral preparation in the United States. An additional benefit of doxycycline over chloramphenicol is its effectiveness against potential concomitant ehrlichia infection. Sulfonamides should not be used, because they are associated with greater morbidity and mortality with all rickettsial infections. Other antibiotics, including penicillins, cephalosporins, and aminoglycosides, are not effective. The use of alternative antimicrobial agents, such as fluoroquinolones and the macrolides (azithromycin and clarithromycin), has not been evaluated.

Therapy should be continued for a minimum of 5-7 days and until the patient has been afebrile for at least 3 days to avoid relapse, especially in patients treated early. Treated patients usually defervesce within 48 hr, so the duration of therapy is usually <10 days.

SUPPORTIVE CARE

Most infections resolve rapidly with appropriate antimicrobial therapy and do not require hospitalization or other supportive care. Infection requires intensive care in 36% of cases. Particular attention to hemodynamic status is mandatory in severely ill children, because iatrogenic pulmonary or cerebral edema could be easily precipitated owing to diffuse microvascular injury of the lungs, meninges, and brain. Judicious use of corticosteroids for meningoencephalitis has been advocated by some, but no controlled trials have been conducted.

COMPLICATIONS

Complications of RMSF include noncardiogenic pulmonary edema from pulmonary microvascular leakage, cerebral edema from meningoencephalitis, and multiorgan damage (hepatitis, pancreatitis, cholecystitis, epidermal necrosis, and gangrene) mediated by rickettsial vasculitis and/or the accumulated effects of hypoperfusion and ischemia (acute renal failure). Long-term neurologic sequelae can occur in any child with RMSF but are more likely to occur in those hospitalized for ≥2 wk. Examples of neurologic sequelae include speech or swallowing disorders; global encephalopathy; cerebellar, vestibular, and motor dysfunction; hearing loss; and cortical blindness. Learning disabilities and behavioral problems are the most common neurologic sequelae among children who have survived severe disease.

PROGNOSIS

Delays in diagnosis and therapy are significant factors associated with death or severe illness. Before the advent of effective antimicrobial therapy for RMSF, the case fatality rate was 10% for children and 30% for adults. Although overall case fatality rate decreased to an historic low (0.3%) during 2003-2007, the case fatality rate of children 5-9 yr of age was 2.4%, and rates as high as 8.5% and 11.8% were documented in Texas (1986 through 1996) and in Arizona (1999-2007), respectively. Diagnosis based on serology alone underestimates the true mortality of RMSF, because death often occurs within 14 days (before developing a serologic response). Deaths occur despite the availability of effective therapeutic agents, indicating the need for clinical vigilance and a low threshold for early empiric therapy. Even with administration of appropriate antimicrobials, delayed therapy can lead to irreversible vascular or end-organ damage and long-term sequelae or death. Early therapy in uncomplicated cases usually leads to rapid defervescence within 1-3 days and recovery within 7-10 days. A slower response may be seen if therapy is delayed. In those who survive despite no treatment, fever subsides in 2-3 wks.

PREVENTION

No vaccines are available. Prevention of RMSF is best accomplished by preventing or treating tick infestation in dogs, avoiding areas where ticks reside, using insect repellents containing N,*N*-diethyl-3-methylbenzamide (DEET), wearing protective clothing, and carefully inspecting children after play in areas where they are potentially exposed to ticks. Recovery from infection yields lifelong immunity.

Prompt and complete removal of attached ticks helps reduce the risk for transmission because rickettsiae in the ticks need to be reactivated

to become virulent, and this requires at least several hours to days of exposure to body heat or blood. Contrary to popular belief, the application of petroleum jelly, 70% isopropyl alcohol, fingernail polish, or a hot match are not effective in removing ticks. A tick can be safely removed by grasping the mouth parts with a pair of forceps at the site of attachment to the skin and applying gentle and steady pressure to achieve retraction without twisting, thereby removing the entire tick and its mouth parts. The site of attachment should then be disinfected. Ticks should not be squeezed or crushed, because their fluids may be infectious. The removed tick should be soaked in alcohol or flushed down the toilet, and hands should be washed to avoid accidental inoculation into conjunctivae, mucous membranes, or breaks in skin. Typically, prophylactic antimicrobial therapy is not recommended because tetracyclines and chloramphenicol are only rickettsiostatic; however, the evidence to support this position is meager.

228.2 Mediterranean Spotted Fever or Boutonneuse Fever *(Rickettsia conorii)*

Megan E. Reller and J. Stephen Dumler

Boutonneuse fever is caused by *R. conorii* and its related subspecies; it is also called MSF, Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan fever. It is a moderately severe vasculotropic rickettsiosis in adults, and comparatively mild in children, that is often initially associated with an eschar at the site of the tick bite. Minor differences in clinical presentation could be associated with genetic diversity of the rickettsial subspecies.

ETIOLOGY

MSF is caused by systemic endothelial cell infection by the obligate intracellular bacterium *R. conorii.* Similar species are distributed globally, such as *R. sibirica* and *Rickettsia mongolotimonae* in Russia, China, Mongolia, and Pakistan; *R. australis* and *R. honei* in Australia; *R. japonica* in Japan; and *R. africae* in South Africa (see Table 220-1). Analysis of antigens and related DNA sequences show that all are closely related within a genetic clade that includes spotted fever group *Rickettsia* species such as *R. rickettsii*, the cause of RMSF.

EPIDEMIOLOGY

R. conorii is distributed over a large geographic region, including India, Pakistan, Russia, Ukraine, Georgia, Israel, Morocco, southern Europe, Ethiopia, Kenya, and South Africa. Reported cases of MSF in southern Europe have steadily increased since 1980, and the seroprevalence is 11-26% in some areas. The peak in reported cases occurs during July and August in the Mediterranean basin; in other regions it occurs during warm months when ticks are active.

TRANSMISSION

Transmission occurs after the bite of the brown dog tick, *R. sanguineus,* or other tick species such as *Dermacentor, Haemaphysalis, Amblyomma, Hyalomma,* and *Ixodes.* Clustering of human cases of boutonneuse fever, infected ticks, and infected dogs implicate the household dog as a potential vehicle for transmission.

PATHOLOGY AND PATHOGENESIS

The underlying pathology seen with MSF is nearly identical to that of RMSF, except that eschars are often present at the site of tick bite where inoculation of rickettsiae occurs. The histopathology of the resultant lesion includes necrosis of dermal and epidermal tissues with a superficial crust; a dermis densely infiltrated by lymphocytes, histiocytes, and scattered neutrophils; and damaged capillaries and venules in the dermis. Immunohistochemical stains and nucleic acid amplification tests confirm that the lesions contain rickettsia-infected endothelial cells, but the vascular structure might not be apparent owing to extensive inflammation and necrosis. The necrosis results from both direct rickettsia-mediated vasculitis and resultant extensive local inflammation. Rickettsiae thus have ready access to lymphatics and venous blood and disseminate to cause systemic disease.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Typical findings in children include fever (93-100%), a maculopapular rash that appears 3-5 days after onset of fever (94-100%), hepatosplenomegaly (20-66%), myalgias and arthralgias (10-42%), headache (29-63%), and nausea, vomiting, or diarrhea (5-28%). In 60-90% of patients, a painless eschar or **tache noire** appears at the site of the tick bite, often on the scalp, with accompanying regional lymphadenopathy (50-60%). Although previously considered self-limited, this infection can be severe, mimicking RMSF. Findings can include seizures, purpuric skin lesions, neurologic deficits, respiratory and/or acute renal failure, and severe thrombocytopenia. Even though the case fatality rate can be as high as 10% in adults and severe infections occur in approximately 9% of children, pediatric deaths are rare. As with RMSF, a particularly severe form occurs in patients with glucose-6-phosphate dehydrogenase deficiency and in patients with underlying conditions such as alcoholic liver disease or diabetes mellitus.

DIAGNOSIS

Laboratory diagnosis of MSF and related spotted fever group rickettsioses is the same as that for RMSF. Cases can be confirmed by immunohistologic or immunofluorescent or demonstration of or amplification of nucleic acids from rickettsiae in skin biopsies, in vitro cultivation via centrifugation-assisted shell vial tissue culture, or demonstration of seroconversion or accompanied by a 4-fold rise in serum antibody titer to spotted fever group rickettsiae between acute and convalescent sera. Antibodies to spotted fever group antigens crossreact, so RMSF or other spotted fever group rickettsiosis in the United States or MSF in Europe, Africa, and Asia cannot be distinguished by these methods.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes conditions also associated with single eschars, such as anthrax, bacterial ecthyma, brown recluse spider bite, rat-bite fever (caused by *Spirillum minus*), and other rickettsioses (such as rickettsialpox, African tick-bite fever, and scrub typhus). The spotted fever group rickettsia *R. africae* causes African tick-bite fever, a milder illness than MSF that is often associated with multiple eschars and occasionally a vesicular rash. African tick bite fever can be contracted in North Africa, where MSF also occurs and is a common infection of travelers to sub-Saharan Africa who encounter bush or high grasslands on safari.

TREATMENT AND SUPPORTIVE CARE

In adults, MSF is effectively treated with tetracycline, doxycycline, chloramphenicol, ciprofloxacin, ofloxacin, levofloxacin, azithromycin, or clarithromycin. For children, the treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Tetracycline and chloramphenicol are alternatives, as for RMSF. Azithromycin (10 mg/kg/day once daily PO for 3 days) and clarithromycin (15 mg/kg/day divided twice daily PO for 7 days) are also used. Specific fluoroquinolone regimens effective for children have not been established, although recent reports suggest the use of fluoroquinolones is associated with increased disease severity as compared with doxycycline. Intensive care may be required.

COMPLICATIONS

The complications of MSF are similar to those of RMSF. The case fatality rate is approximately 2%. Particularly severe infections have been noted in patients with underlying medical conditions, including glucose-6-phosphate dehydrogenase deficiency and diabetes mellitus.

PREVENTION

MSF is transmitted by tick bites, and prevention is the same as recommended for RMSF. No vaccine is currently available.

228.3 Rickettsialpox *(Rickettsia akari)*

Megan E. Reller and J. Stephen Dumler

Rickettsialpox is caused by *R. akari,* a transitional group *Rickettsia* species that is transmitted by the mouse mite, *Allodermanyssus sanguineus.* The mouse host for this mite is widely distributed in cities in the United States, Europe, and Asia. Seroepidemiologic studies suggest a high prevalence of this infection in urban settings. The disease is uncommon and is usually mild. Unlike the situation with most forms of rickettsiosis, the macrophage is an important target cell for *R. akari.*

Rickettsialpox is best known because of its association with a varicelliform rash. In fact, this rash is a modified form of an antecedent typical macular or maculopapular rash like those seen in other vasculotropic rickettsioses, and is occasionally seen with other rickettsioses such as African tick bite fever. Clinical descriptions in children are infrequent. At presentation, most patients have fever, headache, and chills. In up to 90% of cases, there is a painless papular or ulcerative lesion or eschar at the initial site of inoculation, which may be associated with regional lymphadenopathy that is often tender. In some patients, the maculopapular rash becomes vesicular, involving the trunk, head, and extremities. The infection generally resolves spontaneously and does not require therapy. However, a short course of doxycycline hastens resolution and is sometimes used in patients older than 8 yr of age and in young children with relatively severe illness. Complications and fatalities are rare; however, clear examples of severe disease in children like that observed with RMSF are described.

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Chapter 229

Scrub Typhus *(Orientia tsutsugamushi)*

Megan E. Reller and J. Stephen Dumler

Scrub typhus is an important cause of acute febrile illness in South and East Asia and the Pacific. The causative agent is distinct from, but related to, *Rickettsia* species. The infection is transmitted via chigger (larval mite) bites and involves many antigenically diverse strains of *Orientia tsutsugamushi*, hampering vaccine development.

ETIOLOGY

The causative agent of scrub typhus, or tsutsugamushi fever, is *O. tsutsugamushi,* which is distinct from other spotted fever and typhus group rickettsiae (see Table 228-1 in Chapter 228). *O. tsutsugamushi* lacks both lipopolysaccharide and peptidoglycan in its cell wall. Like other vasculotropic rickettsiae, *O. tsutsugamushi* infects endothelial cells and causes vasculitis, the predominant clinicopathologic feature of the disease. However, the organism also infects macrophages and cardiac myocytes. A new Candidatus species, *Orientia chuto*, was isolated from a patient in the Middle East, suggesting a wider range for scrub typhus and related infections.

EPIDEMIOLOGY

Approximately 1 million infections occur each year, and it is estimated that more than 1 billion people are at risk. Scrub typhus occurs mostly in Asia, including areas delimited by Korea, Pakistan, and northern Australia. Outside these tropical and subtropical regions, the disease occurs in Japan, the Primorye of far eastern Russia, Tajikistan, Nepal, and nontropical China, including Tibet. Cases imported to the United States and other parts of the world are reported. Most infections in children are acquired in rural areas. In Thailand and Sri Lanka, scrub typhus is the cause of 1-8% of acute fevers of unknown origin. Infections are most common during rainy months, usually June through November. Reported cases in boys are higher than in girls.

TRANSMISSION

O. tsutsugamushi is transmitted via the bite of the larval stage (chigger) of a trombiculid mite *(Leptotrombidium),* which serves as both vector and reservoir. Transovarial transmission (passage of the organism from infected mites to their progeny) is the major mechanism for maintenance in nature. Because only the larval stage takes blood meals, a role for horizontal transmission from infected rodent hosts to uninfected mites has not been proved, but transmission among cofeeding larval mites is a possibility. Multiple serotypes of *O. tsutsugamushi* are recognized, and some share antigenic cross reactivity; however, they do not stimulate protective cross-immunity.

PATHOLOGY AND PATHOGENESIS

The pathogenesis of scrub typhus is uncertain. Recent studies suggest that the process is stimulated by widespread infection of vascular endothelial cells, which corresponds to the distribution of disseminated vasculitic and perivascular inflammatory lesions observed in histopathologic examinations. In autopsy series, the major result of the vascular injury appears to be hemorrhage. However, data support the concept that vascular injury initiated by the infection is sustained by immune-mediated inflammation that together cause significant vascular leakage. The net result is significant vascular compromise and ensuing end-organ injury, most often manifested in the brain and lungs, as with other vasculotropic rickettsioses.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Scrub typhus can be mild or severe in children. Most patients present with fever for 9-11 days (range: 1-30 days) before seeking medical care. Regional or generalized lymphadenopathy is reported in 23-93% of patients, hepatomegaly in about two-thirds, and splenomegaly in about one-third of children with scrub typhus. Gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea, occur in up to 40% of children at presentation. A single painless eschar with an erythematous rim at the site of the chigger bite is seen in 7-68% of cases, and a maculopapular rash is present in <30%; both can be absent. Hemophagocytic lymphohistiocytosis has been described. Leukocyte and platelet counts are most commonly within normal ranges, although thrombocytopenia occurs in one-quarter to one-third of children, and leukocytosis is observed in approximately 40%.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Owing to the potential for severe complications, diagnosis and decision to initiate treatment should be based on clinical suspicion and confirmed by *O. tsutsugamushi* serologic tests such as indirect fluorescent antibody or immunoperoxidase assays. The indirect fluorescent antibody assay is approximately 90% sensitive with 11 days or more of fever. Although the rickettsiae can be cultivated using tissue culture methods, polymerase chain reaction tests are not highly sensitive, and these diagnostic methods are not widely available. The differential diagnosis includes fever of unknown origin, enteric fever, typhoid fever, dengue hemorrhagic fever, other rickettsioses, tularemia, anthrax, dengue, leptospirosis, malaria, and infectious mononucleosis.

TREATMENT AND SUPPORTIVE CARE

The recommended treatment regimen for scrub typhus is doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day PO divided every 6 hr; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/24 hr). If used, chloramphenicol should be monitored to maintain serum concentrations of 10-30 μg/mL. Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid

relapse. However, a single dose of oral doxycycline was reported effective for all 38 children treated with this regimen in a large series of children with scrub typhus from Thailand. Most children respond rapidly to doxycycline or chloramphenicol within 1-2 days (range: 1-5 days). Strains of *O. tsutsugamushi* with modestly higher doxycycline minimal inhibitory concentrations are reported in some regions of Thailand. Clinical trials showed that azithromycin could be as effective and that rifampicin is superior to doxycycline in such cases and may have a role as an alternative therapy, especially for pregnant women. The use of ciprofloxacin in pregnant women resulted in an adverse outcome in 5 of 5 pregnancies among Indian women. Intensive care may be required for hemodynamic management of severely affected patients.

COMPLICATIONS

Serious complications include pneumonitis in 20-35% and meningoencephalitis in approximately 10% of children. Acute renal failure, myocarditis, and a septic shock–like syndrome occur much less often. Cerebrospinal fluid examination shows a mild mononuclear pleocytosis with normal glucose levels. Chest radiographs reveal transient perihilar or peribronchial interstitial infiltrates in most children who are examined. The case fatality rate in untreated patients may be as high as 30%, although deaths in children are uncommon.

PREVENTION

Prevention is based on avoidance of the chiggers that transmit *O. tsutsugamushi.* Protective clothing is the next most useful mode of prevention. Infection provides immunity to reinfection by homologous but not heterologous strains; however, because natural strains are highly heterogeneous, infection does not always provide complete protection against reinfection. No vaccines are currently available.

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Chapter 230

Typhus Group Rickettsioses

Megan E. Reller and J. Stephen Dumler

Members of the typhus group of rickettsiae (see Table 228-1 in Chapter 228) include *Rickettsia typhi,* the cause of murine typhus, and *Rickettsia prowazekii,* the cause of louse-borne or epidemic typhus. *R. typhi* is transmitted to humans by fleas, and *R. prowazekii* is transmitted in the feces of body lice. Louse-borne or epidemic typhus is widely considered to be the most virulent of the rickettsial diseases, with a high case fatality rate even with treatment. Murine typhus is moderately severe and likely underreported worldwide. The genomes of both *R. typhi* and *R. prowazekii* are similar. *Rickettsia felis* is often considered within the typhus group because of flea transmission; however, phylogenetic studies place it more closely to the spotted fever group or within a "transitional" group in the *Rickettsia* genus.

230.1 Murine (Endemic or Flea-Borne) Typhus *(Rickettsia typhi)*

Megan E. Reller and J. Stephen Dumler

ETIOLOGY

Murine typhus is caused by *R. typhi,* a rickettsia transmitted from infected fleas to rats, other rodents, or opossums and back to fleas. Transovarial transmission (passage of the organism from infected fleas to their progeny) in fleas is inefficient. Transmission depends on infection from the flea to uninfected mammals that then sustain transient rickettsemia and serve as sources of the bacterium for uninfected fleas that bite during the period of rickettsemia.

R. felis is a species identified as a cause of a murine typhus-like illness worldwide. This rickettsia is genetically a member of a transitional *Rickettsia* group and is capable of highly efficient transovarial transmission in cat fleas. This organism is found in cat fleas obtained from areas endemic for murine typhus in the United States and increasingly worldwide.

EPIDEMIOLOGY

Murine typhus has a worldwide distribution and occurs especially in warm coastal ports, where it is maintained in a cycle involving rat fleas (*Xenopsylla cheopis*) and rats (*Rattus* species). Peak incidence occurs when rat populations are highest during spring, summer, and fall. Sentinel surveillance studies suggest that travel-acquired murine typhus occurs most often in those visiting Southeast Asia and Africa. In the United States, the disease is recognized most often in south Texas and southern California. However, seroprevalence studies among children indicate that murine typhus is acquired across the southeast and south-central United States, thus expanding the endemic areas in which pediatricians must be alert for this infection. In the coastal areas of south Texas and in Southern California, the disease is seen predominantly from March through June and is associated with a "sylvatic" cycle involving opossums and cat fleas (*Ctenocephalides felis*).

TRANSMISSION

R. typhi normally cycles between rodents or midsize animals such as opossums and their fleas. Human acquisition of murine typhus occurs when rickettsiae-infected flea feces contaminate flea bite wounds. Direct inoculation via flea bite is possible, but inefficient.

PATHOLOGY AND PATHOGENESIS

R. typhi is a vasculotropic rickettsia that causes disease in a manner similar to *Rickettsia rickettsii* (see Chapter 228.1). *R. typhi* organisms in flea feces deposited on the skin as part of the flea feeding reflex are inoculated into the pruritic flea bite wound. After an interval for local proliferation, the rickettsiae spread systemically via lymphatics to infect the endothelium in many tissues. As with spotted fever group rickettsiae, typhus group rickettsiae infect endothelial cells, but unlike the spotted fever group rickettsiae, they polymerize intracellular actin poorly, have limited intracellular mobility, and probably cause cellular injury by either enzymatic membrane or mechanical lysis after accumulating in large numbers within the endothelial cell cytoplasm. Intracellular infection leads to endothelial cell damage, recruitment of inflammatory cells, and vasculitis. The inflammatory cell infiltrates bring in a number of effector cells, including macrophages that produce proinflammatory cytokines, and CD4, CD8, and natural killer lymphocytes, which can produce immune cytokines such as interferon-γ or participate in cell-mediated cytotoxic responses. Intracellular rickettsial proliferation of typhus group rickettsiae is inhibited by cytokine-mediated mechanisms and nitric oxide–dependent and –independent mechanisms.

Pathologic findings include systemic vasculitis in response to rickettsiae within endothelial cells. This manifests as interstitial pneumonitis, meningoencephalitis, interstitial nephritis, myocarditis, and mild hepatitis with periportal lymphohistiocytic infiltrates. As vasculitis and inflammatory damage accumulate, multiorgan damage can ensue.

CLINICAL MANIFESTATIONS

Murine typhus is a moderately severe infection that is similar to other vasculotropic rickettsioses. The incubation period varies from 1-2 wk. The initial presentation is often nonspecific and mimics typhoid fever; fever of undetermined origin is the most common presentation. Pediatric patients with murine typhus exhibit symptoms classically attributed to other vasculotropic rickettsioses, such as rash (48-80%), myalgias (29-57%), vomiting (29-45%), cough (15-40%), headache (19-77%), and diarrhea or abdominal pain (10-40%). A petechial rash

is observed in <15% of children, and the usual appearance is that of macules or maculopapules distributed on the trunk and extremities. The rash can involve both the soles and palms. Lymphadenopathy and hepatosplenomegaly are reported often among children with murine typhus in Europe. Murine-typhus associated hemophagocytic syndrome was recently described. Although neurologic involvement is a common finding in adults with murine typhus, photophobia, confusion, stupor, coma, seizures, meningismus, and ataxia are seen in <20% of hospitalized children and <6% of infected children treated as outpatients.

LABORATORY FINDINGS

Although nonspecific, laboratory findings that could be helpful include mild leukopenia (36-40%) with a moderate left shift, mild to marked thrombocytopenia (43-60%), hyponatremia (20-66%), hypoalbuminemia (46-87%), and elevated aspartate aminotransferase (82%) and alanine aminotransferase (38%). Elevations in serum urea nitrogen are usually a result of prerenal mechanisms.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

As for other vasculotropic rickettsioses, delays in diagnosis and therapy are associated with increased morbidity and mortality; thus, diagnosis must be based on clinical suspicion. Occasionally, patients present with findings suggesting pharyngitis, bronchitis, hepatitis, gastroenteritis, or sepsis; thus, the differential diagnosis may be extensive.

Confirmation of the diagnosis is usually accomplished by comparing acute and convalescent-phase antibody titers obtained with the indirect fluorescent antibody assay to demonstrate a 4-fold rise in titer. Research tools now being evaluated include polymerase chain reaction amplification of rickettsial nucleic acids in acute-phase blood, rickettsial culture by the centrifugation-assisted shell vial assay, and immunohistology on skin biopsy.

TREATMENT

Therapy for murine typhus includes tetracyclines or chloramphenicol, similar to treatment for Rocky Mountain spotted fever. No controlled trials of other antimicrobial agents have been performed. Clinical studies show that ciprofloxacin is as effective as doxycycline and chloramphenicol to treat murine typhus; however, treatment failures have been reported. In vitro experiments suggest that minimal inhibitory concentrations of azithromycin and clarithromycin for *R. typhi* should be easily achieved.

The time-honored recommended treatment for murine typhus is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative regimens include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient has been afebrile for at least 3 days to avoid relapse, especially in patients treated early.

SUPPORTIVE CARE

Although disease is usually mild, 7% of children with murine typhus require intensive care to manage complications such as meningoencephalitis or a disseminated intravascular coagulation–like condition. As for other rickettsial infections with significant systemic vascular injury, careful hemodynamic management is mandatory to avoid pulmonary or cerebral edema.

COMPLICATIONS

Complications of murine typhus in pediatric patients are uncommon; however, relapse, stupor, facial edema, dehydration, splenic rupture, and meningoencephalitis are reported. Predominance of abdominal pain has led to surgical exploration to exclude a perforated viscus.

PREVENTION

Control of murine typhus was dependent on elimination of the flea reservoir and control of flea hosts, and this remains important. However, with the recognition of cat fleas as potentially significant reservoirs and vectors, the presence of these flea vectors and their mammalian hosts in suburban areas where close human exposures occur poses increasingly difficult control problems. It is not known with certainty if infection confers protective immunity; reinfection appears to be rare.

230.2 Epidemic (Louse-Borne) Typhus (*Rickettsia prowazekii*)

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ETIOLOGY

Humans are considered the principal reservoir of *R. prowazekii,* the causative agent of epidemic or louse-borne typhus and its recrudescent form, Brill-Zinsser disease. Another reservoir exists in flying squirrels, their ectoparasites, and potentially ticks, in a sylvatic cycle with small rodents. *R. prowazekii* is the most pathogenic member of the genus *Rickettsia* and multiplies to very large intracellular quantities before rupture of infected endothelial cells.

EPIDEMIOLOGY

The infection is characteristically seen in winter or spring and especially during times of poor hygienic practices associated with crowding, war, famine, extreme poverty, and civil strife. A cause of some sporadic cases of a mild, typhus-like illness in the United States is confirmed as *R. prowazekii;* such cases are associated with exposure to flying squirrels harboring infected lice or fleas. *R. prowazekii* organisms isolated from these squirrels appear to be genetically similar to isolates obtained during typical outbreaks.

Most cases of louse-borne typhus in the developed world are sporadic, but outbreaks have been identified in Africa (Ethiopia, Nigeria, and Burundi), Mexico, Central America, South America, Eastern Europe, Afghanistan, Russia, northern India, and China within the past 25 yr. Following the Burundi Civil War in 1993, 35,000-100,000 cases of epidemic typhus were diagnosed in displaced refugees, resulting in an estimated 6,000 deaths.

TRANSMISSION

Human body lice *(Pediculus humanus corporis)* become infected by feeding on persons who have rickettsiae circulating in their blood owing to endothelial infection. The ingested rickettsiae infect the midgut epithelial cells of the lice and are passed into the feces, which, in turn, are introduced into a susceptible human host through abrasions or perforations in the skin, through the conjunctivae, or rarely through inhalation as fomites in clothing, bedding, or furniture.

CLINICAL MANIFESTATIONS

Louse-borne typhus can be mild or severe in children. The incubation period is usually <14 days. The typical clinical manifestations include fever, severe headache, abdominal tenderness, and rash in most patients, as well as chills (82%), myalgias (70%), arthralgias (70%), anorexia (48%), nonproductive cough (38%), dizziness (35%), photophobia (33%), nausea (32%), abdominal pain (30%), tinnitus (23%), constipation (23%) meningismus (17%), visual disturbances (15%), vomiting (10%), and diarrhea (7%). However, investigation of recent African outbreaks has shown a lower incidence of rash (25%) and a high incidence of delirium (81%) and cough associated with pneumonitis (70%). The rash is initially pink or erythematous and blanches. In one-third of patients, red, nonblanching macules and petechiae appear predominantly on the trunk. Infections identified during the preantibiotic era typically produced a variety of central nervous system findings, including delirium (48%), coma (6%), and seizures (1%). Estimates of case fatality rates range between 3.8% and 20% in outbreaks.

Brill-Zinsser disease is a form of typhus that becomes recrudescent months to years after the primary infection, thus rarely affecting children. When bacteremic with rickettsiae, these infected patients can transmit the agent to lice, potentially providing the initial event that triggers an outbreak if hygienic conditions permit.

TREATMENT

Recommended treatment regimens for louse-borne or sylvatic typhus are identical to those used for murine typhus. The treatment of choice is doxycycline (4 mg/kg/day divided every 12 hr PO or IV; maximum: 200 mg/day). Alternative treatments include tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day) or chloramphenicol (50-100 mg/kg/day divided every 6 hr IV; maximum: 4 g/day). Therapy should be continued for a minimum of 5 days and until the patient is afebrile for at least 3 days to avoid relapse, especially in patients treated early. Good evidence exists that doxycycline as a single 200 mg oral dose (4.4 mg/kg if <45 kg) is also efficacious.

PREVENTION

Immediate destruction of vectors with an insecticide is important in the control of an epidemic. Lice live in clothing rather than on the skin; thus, searches for ectoparasites should include examination of clothes. For epidemic typhus, antibiotic therapy and delousing measures interrupt transmission, reduce the prevalence of infection in the human reservoir, and diminish the impact of an outbreak. Dust containing excreta from infected lice is stable and capable of transmitting typhus, and care must be taken to prevent its inhalation. Infection confers solid protective immunity. However, recrudescence can occur years later with Brill-Zinsser disease, implying that immunity is not complete.

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Chapter 231

Ehrlichiosis and Anaplasmosis

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ETIOLOGY

Ehrlichiosis in humans was first described in 1987, when clusters of bacteria confined within cytoplasmic vacuoles of circulating leukocytes (morulae), particularly mononuclear leukocytes, were detected in the peripheral blood of a patient with suspected Rocky Mountain spotted fever (RMSF). The etiologic agent, *Ehrlichia chaffeensis,* was cultivated from blood of an infected patient in 1990 and identified as the predominant cause of "human ehrlichiosis." Investigations showed that infection by *E. chaffeensis* is transmitted by *Amblyomma americanum* ticks and occurs more often than RMSF in some geographic areas. By 1994, other cases in which morulae were found only in neutrophils and lacked serologic evidence for *E. chaffeensis* infection led to the recognition of the species now classified as *Anaplasma phagocytophilum*, which encompasses several previously described veterinary pathogens on at least 2 different continents.

Since these first discoveries in humans, additional species in the *Anaplasmataceae* family have been identified as human pathogens, including: (1) *Ehrlichia ewingii* in 1996, a veterinary pathogen of canine neutrophils transmitted by *A. americanum* ticks; (2) the *Ixodes scapularis*–transmitted *Ehrlichia muris*–like agent in 2009, discovered in molecular screening tests for *E. chaffeensis*, *E. ewingii*, and *A. phagocytophilum* infections and only present so far in patients from Minnesota and Wisconsin in the United States; and (3) human infections by *Candidatus* Neoehrlichia mikurensis, presumably transmitted by *Ixodes* spp. or *Haemaphysalis concinna* ticks, first recognized in 2010 as a cause of sepsis-like infections of immune compromised patients in Europe, and also as a cause of mild febrile illness in healthy individuals in China. The latter 2 infections have not yet been identified in pediatric patients.

Although these infections are caused by bacteria assigned to various genera, the name ehrlichiosis has been applied to all and the etiologic agents are all classified within the Anaplasmataceae family. **Human monocytic ehrlichiosis (HME)** is used to describe disease characterized by infection of predominantly monocytes caused by *E. chaffeensis*, **human granulocytic anaplasmosis (HGA)** to describe disease of where circulating neutrophils are infected by *Anaplasma phagocytophilum*, and **ewingii ehrlichiosis** caused by *E. ewingii* (see Table 228-1 in Chapter 228).

All of these organisms are tick-transmitted, small, obligate intracellular bacteria with Gram-negative–type cell walls. *Neorickettsia sennetsu* is another related bacterium that rarely causes human disease and is not transmitted by ticks. *E. chaffeensis* alters host signaling and transcription once inside the cell. It survives in an endosome that enters a receptor recycling pathway to avoid phagosome-lysosome fusion and growth into a "**morula,**" an intravacuolar aggregate of bacteria. *A. phagocytophilum* survives in a unique vacuole that becomes decorated by microbial proteins which prevent endosomal maturation and lysosome fusion. Little is known about the vacuoles in which *E. ewingii* and *E. muris*–like agent grow. These bacteria are pathogens of phagocytic cells in mammals, and characteristically each species has a specific host cell affinity: *E. chaffeensis* infects mononuclear phagocytes, and *A. phagocytophilum* and *E. ewingii* infect neutrophils. Infection leads to direct modifications in function, in part the result of changes in intracellular signal transduction or epigenetic modulation of transcription of the host cell that diminish host defenses toward the bacterium; yet, host immune and inflammatory reactions are still activated and in part account for many of the clinical manifestations in ehrlichiosis.

EPIDEMIOLOGY

Infections with *E. chaffeensis* occur across the southeastern, south central, and mid-Atlantic states of the United States in a distribution that parallels that of RMSF; cases have also been reported in northern California. Suspected cases with appropriate serologic and occasionally molecular evidence have been reported in Europe, Africa, South America, and the Far East, including China and Korea. Human infections with *E. ewingii* have only been identified in the United States in areas where *E. chaffeensis* also exists, perhaps owing to the shared tick vector. Canine infections are documented in both sub-Saharan Africa and in South America.

Although the median age of patients with HME and HGA is generally older (>51 yr), many infected children have been identified, and for HME the case fatality rate is higher in those 5-9 yr of age. Little is known about the epidemiology of *E. ewingii* infections, although many patients have also been children. All infections are strongly associated with tick exposure and tick bites and are identified predominantly during May through September. Although both nymphal and adult ticks can transmit infection, nymphs are more likely to transmit disease, because they are most active during the summer.

TRANSMISSION

The predominant tick species that harbors *E. chaffeensis* and *E. ewingii* is *A. americanum,* the Lone Star tick (see Fig. 228-1D in Chapter 228). The tick vectors of *A. phagocytophilum* are *Ixodes* spp., including *I. scapularis* (black-legged or deer tick) in the eastern United States (see Fig. 228-1 in Chapter 228), *Ixodes pacificus* (western black-legged tick) in the western United States, *Ixodes ricinus* (sheep tick) in Europe, and *Ixodes persulcatus* in Eurasia. These ticks also transmit *Borrelia burgdorferi, Babesia microti,* and tickborne encephalitis-associated flaviviruses in Europe, Powassan viruses in North America. Coinfections with these agents and *A. phagocytophilum* have been documented in children and adults.

Ehrlichia and *Anaplasma* species are maintained in nature predominantly by horizontal transmission (tick to mammal to tick), because the organisms are not transmitted to the progeny of infected adult female ticks (transovarial transmission). The major reservoir for *E. chaffeensis* is the white-tailed deer (*Odocoileus virginianus*), which is found abundantly in many parts of the United States. A reservoir for

A. phagocytophilum in the eastern United States appears to be the white-footed mouse, *Peromyscus leucopus*. Deer or domestic ruminants may also have persistent asymptomatic infections, but the genetic variants in these reservoirs might not be infectious for humans. Efficient transmission requires persistent infections of mammals. Although *E. chaffeensis* and *A. phagocytophilum* can cause persistent infections in animals, documentation of chronic infections in humans is exceedingly rare. Transmission of *Ehrlichia* can occur within hours of tick attachment, in contrast to the 1-2 days of attachment required for transmission of *B. burgdorferi* to occur. Transmission of *A. phagocytophilum* is via the bite of the small nymphal stage of *Ixodes* spp., including *I. scapularis* (see Fig. 228-1A in Chapter 228), which is very active during late spring and early summer in the eastern United States.

PATHOLOGY AND PATHOGENESIS

Although HME and anaplasmosis often clinically mimic RMSF or typhus, vasculitis is rare. Pathologic findings include mild, diffuse perivascular lymphohistiocytic infiltrates; Kupffer cell hyperplasia and mild lobular hepatitis with infrequent apoptotic hepatocytes and less frequently centrilobular necrosis, cholestasis and steatosis; infiltrates of mononuclear phagocytes in the spleen, lymph nodes, and bone marrow with occasional erythrophagocytosis; granulomas of the liver and bone marrow in patients with *E. chaffeensis* infections; and hyperplasia of one or more bone marrow hematopoietic lineages.

The exact pathogenetic mechanisms are poorly understood, but histopathologic examinations suggest diffuse macrophage activation and poorly regulated host immune and inflammatory reactions. This activation results in moderate to profound leukopenia and thrombocytopenia despite a hypercellular bone marrow, and deaths often are related to severe hemorrhage or secondary opportunistic infections. Hepatic and other organ-specific injury occurs by a mechanism that appears to be triggered by the bacterium but more closely related to induction of innate and adaptive immune effectors. Meningoencephalitis with a mononuclear cell pleocytosis in the cerebrospinal fluid (CSF) occurs with HME, but is rare with HGA.

CLINICAL MANIFESTATIONS

The clinical manifestations of HME, HGA, and ewingii ehrlichiosis are similar. Many well-characterized infections of HME and HGA of variable severity have been reported in children, including deaths. Children with ehrlichiosis are often ill for 4-12 days, shorter than in adults. In series of children with HME, most required hospitalization and many (25%) required intensive care; these statistics might represent preferential reporting of severe cases. However, review of case reports and electronic surveillance of HGA to the Centers for Disease Control and Prevention identified that 42% of patients 5-9 yr of age required hospitalization. Population-based studies document that seroconversion often occurs in children who are well or who have only a mild illness. Fewer pediatric cases of *E. ewingii* infection are reported, so the clinical manifestations related to this infection are less-well characterized. However, in adults *E. ewingii* is clinically similar to HME, yet less severe. The incubation period (time from last tick bite or exposure) appears to range from 2 days to 3 wk. Nearly 25% of patients do not report a tick bite.

Clinically, ehrlichioses are undifferentiated febrile illnesses. In HME, fever (~100%), headache (77%), and myalgia (77%) are most common, but many patients also report abdominal pain, nausea, and vomiting. Altered mental status accompanied by other signs of central nervous system involvement is present in 36%. Rash is a common feature (~60%) in children. The rash is usually macular or maculopapular, but petechial lesions can occur. Photophobia, conjunctivitis, pharyngitis, arthralgias, and lymphadenopathy can occur but are less consistently present. Lymphadenopathy, hepatomegaly, and splenomegaly are detected in nearly 50% of children with ehrlichiosis. Edema of the face, hands, and feet occurs more commonly in children than in adults, but arthritis is uncommon in both groups.

Similar but less severe manifestations occur with HGA in children, including fever (93%), headache (73%), myalgia (73%), rigors (60%); nausea, vomiting, abdominal pain, and anorexia occur in 30% or less. Cough is present in 20%; rash is very infrequent and most often is erythema migrans that results from concurrent Lyme disease.

Meningoencephalitis with a lymphocyte-predominant CSF pleocytosis is an uncommon but potentially severe complication of HME that appears to be rare with HGA. CSF protein may be elevated and glucose may be mildly depressed in adults with HME meningoencephalitis, but CSF protein and glucose in affected children are typically normal. In 1 series, 19% of adult patients with central nervous system symptoms and abnormal CSF died despite normal CTs of the brain.

Chronic or persistent disease with low or absent fever is very unlikely to be any form of ehrlichiosis.

LABORATORY FINDINGS

Characteristically, most children with HME and HGA present with leukopenia (57-80%) and thrombocytopenia (38-93%); cytopenias reach a nadir several days into the illness. Lymphopenia is common in both HME and HGA, and neutropenia is reported in adults with HGA. Leukocytosis can also occur, but usually after the 1st wk of illness or with effective antimicrobial treatment. Adults with pancytopenia often have a cellular or reactive bone marrow examination, and in nearly 75% of bone marrow specimens from adults with HME, granulomas and granulomatous inflammation are present; this finding is not a feature of adults with HGA. Mild to severely elevated serum hepatic transaminase levels are frequent in both HME (85-92%) and HGA (40-50%). Hyponatremia (<135 mEq/L) is present in most cases. A clinical picture similar to disseminated intravascular coagulopathy has also been reported.

DIAGNOSIS

Any delays in diagnosis or treatment are major contributors to increased morbidity or mortality in adults, where those not started on doxycycline at hospital admission are much more likely to require intensive care and a significantly longer course of illness and hospitalization. Thus, treatment must begin as early as possible based on clinical suspicion. Because both HME and anaplasmosis can be fatal, therapy should not be withheld while waiting for the results of confirmatory testing. In fact, prompt response to therapy supports the diagnosis.

While several reports document pediatric patients with *E. chaffeensis* infection diagnosed based on typical *Ehrlichia* morulae in peripheral blood leukocytes (Fig. 231-1*A*), this finding is too infrequent to be considered a useful diagnostic approach. In contrast, HGA in adults presents with a small but significant percentage (1-40%) of circulating neutrophils (Fig. 231-1*B*) containing typical morulae in 20-60% of patients.

E. chaffeensis and *A. phagocytophilum* infections can be confirmed by demonstrating a 4-fold change in immunoglobulin G titer by indirect immunofluorescence assay between paired sera *or* detection of specific DNA by polymerase chain reaction *or* demonstration of specific antigen in a tissue sample by immunohistochemistry *or* isolation of the organism in cell culture. A single specific titer of ≥64 or identification of morulae in monocytes or macrophages for *E. chaffeensis* or in neutrophils or eosinophils for *A. phagocytophilum* by microscopy is suggestive. *E. ewingii* infection can only be confirmed by polymerase chain reaction, because it has not been cultured and serologic antigens are not available. *E. ewingii* antibodies cross react with *E. chaffeensis* in routine serologic tests. Up to 15% of patients with HGA have serologic cross-reactions with *E. chaffeensis;* thus, serodiagnosis depends on testing with both *E. chaffeensis* and *A. phagocytophilum* antigens and demonstrating a 4-fold or higher difference between titers. During the acute phase of illness when antibodies are often not detected, polymerase chain reaction amplification of *E. chaffeensis* or *A. phagocytophilum* DNA is sensitive in >86% of cases. Although *E. chaffeensis* and *A. phagocytophilum* can be cultivated in tissue culture, this method is not timely or widely available.

DIFFERENTIAL DIAGNOSIS

Because of the nonspecific presentation, ehrlichiosis mimics other arthropod-borne infections such as RMSF, tularemia, babesiosis, Lyme

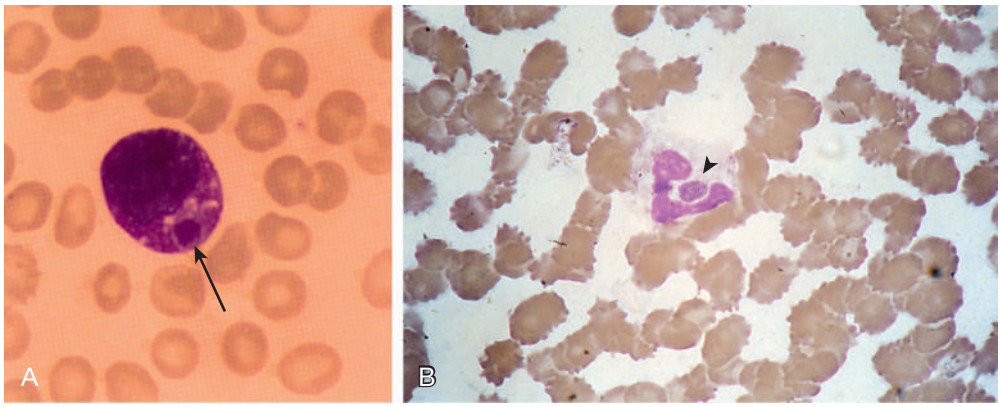

Figure 231-1 Morulae in peripheral blood leukocytes in patients with human monocytic ehrlichiosis and human granulocytic anaplasmosis. **A,** A morula *(arrow)* containing *Ehrlichia chaffeensis* in a monocyte. **B,** A morula *(arrowhead)* containing *Anaplasma phagocytophilum* in a neutrophil. Wright stains, original magnifications ×1,200. *E. chaffeensis* and *A. phagocytophilum* have similar morphologies but are serologically and genetically distinct.

disease, murine typhus, relapsing fever, and Colorado tick fever. Other potential diagnoses often considered include otitis media, streptococcal pharyngitis, infectious mononucleosis, Kawasaki disease, endocarditis, respiratory or gastrointestinal viral syndromes, hepatitis, leptospirosis, Q fever, collagen–vascular diseases, hemophagocytic syndromes, and leukemia. If rash and disseminated intravascular coagulopathy predominate, meningococcemia, bacterial sepsis, and toxic shock syndrome are also suspected. Meningoencephalitis might suggest aseptic meningitis caused by enterovirus or herpes simplex virus, bacterial meningitis, or RMSF. Severe respiratory disease may be confused with bacterial, viral, and fungal causes of pneumonia.

TREATMENT

Both HME and HGA are effectively treated with tetracyclines, especially doxycycline, and the majority of patients improve within 48 hr. In vitro tests document that both *E. chaffeensis* and *A. phagocytophilum* have minimal inhibitory concentrations to chloramphenicol above blood levels that can be safely achieved. Therefore, a short course of doxycycline is the recommended regimen. Doxycycline is used safely in children younger than 8 yr of age because tooth discoloration is dose dependent and the need for multiple courses is unlikely. Few data exist to recommend alternative therapies; however, both *E. chaffeensis* and *A. phagocytophilum* are susceptible in vitro to rifampin, which has been used successfully to treat HGA in pregnant women and children.

The recommended regimen for patients of all ages with severe or complicated HME and HGA is doxycycline (for those who weigh <45 kg, 4 mg/kg/day PO or IV divided every 12 hr; maximum: dose 100 mg/dose). An alternative regimen is tetracycline (25-50 mg/kg/day divided every 6 hr PO; maximum: 2 g/day). For children who weigh more than 45 kg, the adult dose, 100 mg twice daily by oral or intravenous route can be used. Therapy should be continued for ≥5 days and until the patient has been afebrile for ≥2-4 days.

Other broad-spectrum antibiotics, including penicillins, cephalosporins, aminoglycosides, and macrolides, are not effective. In vitro studies suggest that fluoroquinolones are active against *A. phagocytophilum*, although at least 1 patient relapsed when levofloxacin was discontinued. *E. chaffeensis* is naturally resistant to fluoroquinolones owing to a single nucleotide change in *gyrA,* which suggests that *A. phagocytophilum* could also become resistant to fluoroquinolones rapidly.

COMPLICATIONS AND PROGNOSIS

Fatal HME is reported in at least 1 pediatric patient, where the findings were initially dominated by pulmonary involvement with respiratory failure complicated by nosocomial bacterial pneumonia. The pattern of severe pulmonary involvement culminating in diffuse alveolar damage and acute respiratory distress syndrome and secondary nosocomial or opportunistic infections is now well-documented with HME and HGA in adults. One child with HGA died after 3 wk of fever, thrombocytopenia, and lymphadenopathy suspected to be a hematologic malignancy. Other severe complications include a toxic shock–like illness, meningoencephalitis with long-term neurologic sequelae, brachial plexopathy, demyelinating polyneuropathy, myocarditis, rhabdomyolysis, and renal failure. Hemophagocytic lymphohistiocytosis is increasingly reported in children with both HME and HGA. Patients who are immunocompromised (e.g., HIV infection, high-dose corticosteroid therapy, cancer chemotherapy, immunosuppression for organ transplantation) are at high risk for fulminant *E. chaffeensis* infection, and severe HGA has been reported after stem cell transplantation in pediatric oncology.

PREVENTION

HME, HGA, and ewingii ehrlichiosis are tickborne diseases, and any activity that increases exposure to ticks increases risk. Avoiding tick-infested areas, wearing appropriate light-colored clothing, spraying tick repellents on clothing, carefully inspecting for ticks after exposure, and promptly removing any attached ticks diminish the risk. The interval between tick attachment and transmission of the agents may be as short as 4 hr; thus, attached ticks should be removed promptly. A role of prophylactic therapy for ehrlichiosis and anaplasmosis after tick bites has not been investigated. It is not known if infection confers protective immunity; however, reinfection appears to be exceedingly rare.

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Chapter 232

Q Fever (*Coxiella burnetii*)

Megan E. Reller and J. Stephen Dumler

Q fever (for **query fever,** the name given following an outbreak of febrile illness in an abattoir in Queensland, Australia) is rarely reported in children but is probably underdiagnosed. Symptomatic patients can have acute or chronic disease.

ETIOLOGY

Although previously classified within the order Rickettsiales, *Coxiella burnetii* (the causative agent of Q fever) is genetically distinct from the

genera *Rickettsia, Orientia*, *Ehrlichia,* and *Anaplasma*. Hence, based on small genome analysis, it best aligns within the order Legionellales, family Coxiellaceae. *C. burnetii* is highly infectious for both humans and animals; even a single organism can cause infection. The agent has been nationally notifiable since 1999 and is listed as a Category B agent of bioterrorism by the Centers for Disease Control and Prevention (CDC). Unlike *Rickettsia,* the organism can enter a sporogenic differentiation cycle, which renders it highly resistant to chemical and physical treatments.

C. burnetii resides intracellularly within macrophages. In vitro, the organism undergoes lipopolysaccharide phase variation similar to that described for smooth and rough strains of Enterobacteriaceae. Unlike *Ehrlichia, Anaplasma,* and *Chlamydia, C. burnetii* survives and proliferates within acidified phagosomes to form aggregates of >100 bacteria.

EPIDEMIOLOGY

The disease is reported worldwide, except in New Zealand. Although seroepidemiologic studies suggest that infection occurs just as often in children as in adults, children less often present with clinical disease than do adults. During the large outbreak of Q fever in the Netherlands in 2007-2009, only 3.5% of those diagnosed with Q fever were age 19 yr or younger. Although infections are recognized more often in men than in women, reported cases in boys and girls are equal. Approximately 60% of infections are asymptomatic, and only 5% of symptomatic patients require hospitalization. Seroprevalence surveys show that 6-70% of children in endemic European and African communities have evidence of past infection. In France, the overall incidence of Q fever is estimated to be 50 cases per 100,000 persons. A similar estimate is not available for Africa, where cases are likely misdiagnosed as malaria. The seroprevalence of Q fever in the United States is estimated to be 3.1%. Reported cases of Q fever in the United States, which have been received from every state, increased by greater than 9-fold from 17 cases in 2000 to 167 cases in 2008, which might reflect an increase in incidence, increased reporting after September 11, 2001, improved diagnostic tools, or a combination of factors. Reported cases in Asia and Australia have also increased. Most infections in children are identified during the lamb birthing season in Europe (January through June), following farm visits, or after exposure to placentas of dogs, cats, and rabbits. The largest (~4,000 human cases) community outbreak ever described occurred in the Netherlands in 2007-2010 and was associated with intensive farming of dairy goats and dairy sheep. In 2011, the first multistate outbreak of Q fever in humans was linked to interstate sale of infected goats; an outbreak of unknown source was also reported. From 2000-2010, 60% of cases reported to CDC occurred in those without reported exposure to livestock. More than 20% of cases of clinically recognized acute or chronic Q fever occur in immunosuppressed hosts or in persons with prosthetic valves or damaged native valves or vessels. These findings highlight the need for considering Q fever in those with clinically compatible illness, especially but not exclusively in those with likely exposures and in vulnerable hosts.

TRANSMISSION

In contrast to other rickettsial infections, humans usually acquire *C. burnetii* by inhaling infectious aerosols (e.g., contaminated barnyard dust) or ingesting (and likely aspirating) contaminated foods. Ticks are rarely implicated. Cattle, sheep, and goats are the primary reservoirs, but infection in other livestock and domestic pets is also described. Organisms are excreted in milk, urine, and feces of infected animals, but especially in amniotic fluids and the placenta. An increase in incidence is associated with the seasonal mistral winds in France that coincide with lamb birthing season and with consumption of cheese among children in Greece. In Nova Scotia and Maine, exposure to newborn animals, especially kittens, has been associated with small outbreaks of Q fever in families. Exposure to domestic ruminants is the major risk in Europe and Australia, although many urban dwellers in France also acquire Q fever without such an exposure. Person-to-person transmission is possible but rare. Clinical Q fever during pregnancy can result from primary infection or reactivation of latent infection and is associated with miscarriage, intrauterine growth retardation, and premature births. Obstetricians and other related healthcare workers are at risk for acquiring infection because of the quantity of *C. burnetii* sequestered in the placenta. Sexual transmission and cases attributable to blood transfusion or bone marrow transplantation are also reported.

PATHOLOGY AND PATHOGENESIS

The pathology of Q fever depends on the mode of transmission, route of dissemination, specific tissues involved, and course of the infection. When acquired via inhalation, a mild interstitial lymphocytic pneumonitis and macrophage- and organism-rich intraalveolar exudates are often seen. When the liver is involved, a mild to moderate lymphocytic lobular hepatitis can be seen. Inflammatory pseudotumors can develop in the pulmonary parenchyma or other tissues. Classic fibrin-ring ("doughnut") granulomas, generally associated with acute, self-limited infections, are occasionally identified in liver, bone marrow, meninges, and other organs. Typically, infected tissues are also infiltrated by lymphocytes and histiocytes.

Recovery from symptomatic or asymptomatic acute infection can result in persistent subclinical infection and possibly maintained by dysregulated cytokine responses. The persistence of *C. burnetii* in tissue macrophages at sites of preexisting tissue damage elicits low-grade chronic inflammation and, depending on the site of involvement, can result in irreversible cardiac valve damage, persistent vascular injury, or osteomyelitis. Endocarditis of native or prosthetic valves is characterized by infiltrates of macrophages and lymphocytes in necrotic fibrinous valvular vegetations and an absence of granulomas.

CLINICAL MANIFESTATIONS AND COMPLICATIONS

Only approximately 40-50% of people infected with *C. burnetii* develop symptoms. Two forms of symptomatic disease occur. **Acute Q fever** is more common and usually manifests as self-limited undifferentiated fever or an influenza-like illness with interstitial pneumonitis. **Chronic Q fever** in adults usually involves native heart valves, prosthetic valves, or other endovascular prostheses. Q fever osteomyelitis is less common but proportionally more common in children.

Acute Q Fever

Acute Q fever develops approximately 3 wk (range: 14-39 days) after exposure to the causative agent. The severity of illness in children ranges from subclinical infection to a systemic illness of sudden onset characterized by high fever, severe frontal headache, nonproductive cough, chest pain, vomiting, diarrhea, abdominal pain, arthralgias, and myalgias. Approximately 40% of children with acute Q fever present with fever, 25% with pneumonia or an influenza-like illness, >10% with meningoencephalitis, and >10% with myocarditis. Other manifestations include pericarditis, hepatitis, hemophagocytosis, rhabdomyolysis, and a hemolytic uremic–like syndrome. Rash, ranging from maculopapular to purpuric lesions, is an unusual finding in adults with Q fever but is observed in approximately 50% of pediatric patients. Rigors and night sweats are common in adults with Q fever and occur less often in children. Prominent clinical findings that can create diagnostic confusion include fatigue, vomiting, abdominal pain, and meningismus. Hepatomegaly and splenomegaly may be detected in some patients.

Routine laboratory investigations in pediatric acute Q fever are usually normal but can reveal mild leukocytosis and thrombocytopenia. Up to 85% of children have modestly elevated serum hepatic transaminase levels that usually normalize within 10 days. Hyperbilirubinemia is uncommon in the absence of complications. C-reactive protein is uniformly elevated in pediatric Q fever. Chest radiographs are abnormal in 27% of all patients; in children, the most common findings include single or multiple bilateral infiltrates with reticular markings in the lower lobes.

Acute Q fever in children is usually a self-limited illness, with fever persisting for only 7-10 days compared with 2-3 wk in adults. However, severe manifestations of acute illness, such as myocarditis requiring cardiac transplantation, meningoencephalitis, pericarditis, and hemophagocytosis, as well as a relapsing febrile illness lasting for several months have been reported.

Chronic Q Fever

The risk for developing chronic Q fever is strongly correlated with advancing age and underlying conditions such as cardiac valve damage or immunosuppression; chronic Q fever is rarely diagnosed in children. A review identified only 5 cases of chronic Q fever endocarditis and 6 cases of osteomyelitis among children, none of whom had known predisposing immune deficiencies. Four of the 5 cases of endocarditis occurred in children with underlying congenital heart abnormalities and involved the aortic, pulmonary, and tricuspid valves. Four of the 6 children with Q fever osteomyelitis had a prior diagnosis or clinical course consistent with idiopathic chronic recurrent multifocal osteomyelitis. A long interval before diagnosis and lack of high fever are common in pediatric cases of chronic Q fever.

Although Q fever endocarditis often results in death (23-65% of cases) in adults, mortality has not been reported for children. Endocarditis associated with chronic Q fever can occur months to years after acute infection and can occur in the absence of recognized acute Q fever. Chronic hepatitis has also been reported.

LABORATORY FINDINGS

Laboratory features in children with chronic Q fever are poorly documented; adult patients often have an erythrocyte sedimentation rate of >20 mm/hr (80% of cases), hypergammaglobulinemia (54%), and hyperfibrinogenemia (67%). In children, the presence of rheumatoid factor in >50% of cases and circulating immune complexes in nearly 90% suggest an autoimmune process, as do antiplatelet antibodies, anti–smooth muscle antibodies, antimitochondrial antibodies, circulating anticoagulants, and positive direct Coombs tests.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Although uncommonly diagnosed, Q fever should be considered in children who have fever of unknown origin, atypical pneumonia, myocarditis, meningoencephalitis, culture-negative endocarditis, or recurrent osteomyelitis and who live in rural areas or who are in close contact with domestic livestock, cats, or animal products.

The diagnosis of Q fever is most easily and commonly confirmed by testing acute and convalescent sera (2-4 wk apart), which show a 4-fold increase in indirect fluorescent immunoglobulin G antibody titers to phase II *C. burnetii* antigens. The phase II antibody response to *C. burnetii* appears first and is higher than the phase I antibody response. Phase II immunoglobulin G antibodies can remain elevated for months to years regardless of initial symptoms or lack thereof. In contrast chronic Q fever is characterized by the rise of phase I immunoglobulin G antibodies and an antibody titer greater than 800 raises the suspicion of Q fever endocarditis in patients with valvular heart disease or other sites of chronic, active Q fever infection. Cross-reactions with antibodies to *Legionella* and *Bartonella* can occur.

Although culture has been considered the gold standard, sensitivity (compared with a composite standard including serology and polymerase chain reaction) is low. *C. burnetii* has been cultivated in tissue culture cells, which can become positive within 48 hr, but isolation and antimicrobial susceptibility testing of *C. burnetii* should be attempted only in specialized biohazard facilities. Testing by polymerase chain reaction can be performed on blood, serum, and tissue samples and is available only in some public health, reference, or research laboratories. Although polymerase chain reaction has been helpful in patients with equivocal titers, sensitivity has been improved by real-time methods and use of repeated sequences as targets. Immunohistochemical staining has also been used, but is not readily available.

The differential diagnosis depends on the clinical presentation. In patients with respiratory disease, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* legionellosis, psittacosis, and Epstein-Barr virus infection should be considered. In patients with granulomatous hepatitis, tuberculous and nontuberculous mycobacterial infections, salmonellosis, visceral leishmaniasis, toxoplasmosis, Hodgkin disease, monocytic ehrlichiosis, granulocytic anaplasmosis, brucellosis, cat scratch disease (*Bartonella henselae*), or autoimmune disorders such as sarcoidosis should be considered. Culture-negative endocarditis suggests infection with *Brucella, Bartonella,* or HACEK organisms *(Haemophilus, Aggregatibacter, Cardiobacterium hominis, Eikenella corrodens, Kingella)*, partially treated bacterial endocarditis, or nonbacterial endocarditis.

TREATMENT

Selection of an appropriate antimicrobial regimen for children is difficult owing to the lack of rigorous studies, the limited therapeutic window for drugs that are known to be efficacious, and the potential length of therapy required to preclude relapse.

Most pediatric patients with Q fever have a self-limited illness that is identified only on retrospective serologic evaluation. However, to prevent potential complications, treatment should be considered for patients who present with acute Q fever within 3 days of onset of symptoms, because therapy started more than 3 days after onset of illness has little effect on the course of acute Q fever. Because confirmatory testing in early acute infection is not possible and because tetracycline and doxycycline can be associated with tooth discoloration in children younger than 9 yr of age, empirical therapy is warranted in those with clinically suspected Q fever who are 8 yr of age or older or at high risk for severe illness. Doxycycline (4 mg/kg/day PO or IV divided every 12 hr; maximum: 200 mg/day) is the drug of choice; the usual course is 2 wk. Children at high risk include those hospitalized or with severe illness; those diagnosed after prolonged (>2 wk) unremitting symptoms; and those with preexisting valvular heart disease or who are immunocompromised. Because tooth discoloration is both dose and duration dependent and few children require multiple courses, younger children with mild Q fever could be treated with 5 days of doxycycline followed by 14 days of trimethoprim-sulfamethoxazole if symptoms persist. During pregnancy, Q fever is best treated with trimethoprim-sulfamethoxazole. The fluoroquinolones are also effective, and success with a combination of a fluoroquinolone and rifampin is also achieved with prolonged therapy (16-21 days). Macrolides, including erythromycin and clarithromycin, are less-effective alternatives.

For chronic Q fever, especially endocarditis and mostly in adults, therapy for 18-36 mo is mandatory. The current recommended regimen for chronic Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for 18 mo or longer. For patients with heart failure, valve replacement could be necessary. Interferon-γ therapy has been used as adjunct therapy for intractable Q fever.

PREVENTION

Recognition of the disease in livestock or other domestic animals should alert communities to the risk for human infection. Milk from infected herds must be pasteurized at temperatures sufficient to destroy *C. burnetii. C. burnetii* is resistant to significant environmental conditions but can be inactivated with a solution of 1% Lysol, 1% formaldehyde, or 5% hydrogen peroxide. Special isolation measures are not required because person-to-person transmission is rare, except when others are exposed to the placenta of an infected patient. A vaccine is available and provides protection against Q fever for at least 5 yr in abattoir workers. Because the vaccine is strongly reactogenic and no trials in children have been conducted, it should only be used when extreme risk is judged to exist. Clusters of cases resulting from intense natural exposures, such as in slaughterhouses or on farms, are well documented. Clusters of cases that occur in the absence of such an exposure should be investigated as potential sentinel events for bioterrorism.

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Section 12

Fungal Infections

Chapter 233

Principles of Antifungal Therapy

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As a result of advances in aggressive antineoplastic agents and organ transplantation, invasive fungal infections are a major cause of morbidity and mortality in children. Fortunately, the therapeutic armamentarium for invasive fungal infections has markedly increased since the 1990s (Table 233-1).

POLYENES

Amphotericin B

The prototype of the oldest antifungal class, the polyene macrolides, is amphotericin B deoxycholate. Amphotericin B was once the preferred treatment for invasive fungal infections as well as the standard of comparison for all newer antifungal agents. Amphotericin B is so named because it is amphoteric, forming soluble salts in both acidic and basic environments. However, because of its insolubility in water, amphotericin B for clinical use is actually amphotericin B mixed with the detergent deoxycholate. Amphotericin B binds to ergosterol, the major sterol found in fungal cytoplasmic membranes, and acts by creating transmembrane channels. The fungicidal activity is the result of a damaged barrier and subsequent cell death through leakage of essential nutrients from the fungal cell.

Amphotericin B is released from its carrier and distributes very efficiently with lipoproteins, taken up preferentially by organs of the reticuloendothelial system. Following an initial 24-48 hr distributional half-life there is very slow release and a subsequent terminal elimination half-life of up to 15 days. In addition to conventional amphotericin B deoxycholate, 3 fundamentally different lipid-associated formulations have been developed that offer the advantage of an increased daily dosage of the parent drug, better delivery to the primary reticuloendothelial organs (lungs, liver, spleen), and reduced toxicity. Amphotericin B lipid complex is a tightly packed ribbon-like structure of a bilayered membrane, amphotericin B colloidal dispersion is composed of disk-like structures of cholesteryl sulfate complexed with amphotericin B, and liposomal amphotericin B (L-amphotericin B) consists of small uniformly sized vesicles of a lipid bilayer of amphotericin B. Lipid formulations of amphotericin B generally have a slower onset of action, presumably owing to the required disassociation of free amphotericin B from the lipid vehicle. The ability to safely administer higher daily doses of the parent drugs improves their efficacy, comparing favorably with amphotericin B deoxycholate but with less toxicity. Lipid formulations have the added benefit of increased tissue concentrations compared to conventional amphotericin B, specifically in the liver, lungs, and spleen. However, it is not entirely clear if these higher concentrations in tissue are truly available to the microfoci of infection.

Tolerance to amphotericin B deoxycholate is limited by its acute and chronic toxicities. In addition to interacting with fungal ergosterol, the drug also interacts with cholesterol in human cell membranes, likely accounting for its toxicity. Up to 80% of patients receiving amphotericin B develop either infusion-related toxicity or nephrotoxicity, especially with concomitant therapy with nephrotoxic drugs such as aminoglycosides, vancomycin, cyclosporine, or tacrolimus. Renal function usually returns to normal after cessation of amphotericin B, although permanent renal impairment is common after larger doses. Amphotericin B nephrotoxicity is generally less severe in infants and children than in adults, likely because of the more rapid clearance of the drug in children. Lipid formulations appear to stabilize amphotericin B in a self-associated state so that it is not available to interact with the cholesterol of human cellular membranes.

Unlike older guidelines, there is no total dosage of amphotericin B recommended, and the key to success is to give high dosages in the initial phase of therapy and to reduce the dosage if toxicity develops. There are no data or consensus opinions among authorities indicating improved efficacy of any new amphotericin B lipid formulation over conventional amphotericin B deoxycholate. One exception is that

Table 233-1 Suggested Dosing of Antifungal Agents in Children and Neonates

DRUG	FORMULATIONS	SUGGESTED PEDIATRIC DOSAGE	COMMENTS
Amphotericin B deoxycholate	IV	1 mg/kg/day	Generally less toxicity in children than adults; do not start with smaller test doses
Lipid amphotericin B formulations	IV	5 mg/kg/day	Generally all lipid formulations are dosed the same; there is no clear indication of one formulation over another for clinical efficacy
Fluconazole	IV, PO	12 mg/kg/day	Loading dose (25 mg/kg) is suggested based on pharmacokinetic simulations, but insufficiently studied
Itraconazole	IV, PO	2.5 mg/kg/dose bid	Divide dosage twice daily in children; follow trough levels
Voriconazole	IV, PO	8 mg/kg/dose bid IV maintenance; 9 mg/kg/dose bid oral maintenance	Linear pharmacokinetics in children requires higher dosing than in adults; 9 mg/kg/dose bid IV loading, followed by maintenance dosing; follow trough levels
Posaconazole	PO	12-24 mg/kg/day divided tid	Dosage unclear in children at present In adults, max dosage is 800 mg/day, and optimally divide this into 2 or 3 doses; follow trough levels
Micafungin	IV	2-10 mg/kg/day	Highest dosages in neonates (10 mg/kg/day), and lower dosages in children; older than 8 yr of age, use adult dosage
Anidulafungin	IV	1.5 mg/kg/day	Loading dose of 3 mg/kg/day
Caspofungin	IV	50 mg/m^2/day	Load with 70 mg/m^2/day, then 50/mg/m^2/day as maintenance dosage

L-amphotericin B shows fewer infusion-related adverse events than the other lipid formulations or conventional amphotericin B.

PYRIMIDINE ANALOGS

5-Fluorocytosine

5-Fluorocytosine is a fluorinated analog of cytosine, and its antifungal activity results from the rapid conversion into 5-fluorouracil (5-FU) within susceptible fungal cells. Clinical and microbiologic antifungal resistance appears to develop quickly to 5-fluorocytosine (5-FC) monotherapy, so clinicians have reserved it for combination approaches to augment other, more potent antifungals. Fungistatic 5-FC is thought to enhance the antifungal activity of amphotericin B, especially in anatomic sites where amphotericin B penetration is often suboptimal, such as cerebrospinal fluid (CSF), heart valves, and the vitreal body. 5-FC penetrates well into most body sites because it is small, highly water soluble, and not bound by serum proteins to any great extent. One explanation for the synergism detected with the combination of amphotericin B plus 5-FC is that the membrane-permeabilizing effects of low concentrations of amphotericin B facilitate penetration of 5-FC to the cell interior. 5-FC is only available as an oral formulation in the United States, and the correct dosage is 150 mg/kg/day in 4 divided doses.

5-FC can exacerbate myelosuppression in patients with neutropenia, and toxic levels can develop when used in combination with amphotericin B owing to nephrotoxicity of the amphotericin B and decreased renal clearance of 5-FC. Routine serum 5-FC level monitoring is warranted in high-risk patients, because peak serum concentrations of ≥100 μg/mL (2 hr after dose) are associated with bone marrow aplasia. Toxicities can include azotemia, renal tubular acidosis, leukopenia, thrombocytopenia, and others and appear in approximately 50% of patients in the 1st 2 wk of therapy.

Nearly all clinical studies involving 5-FC are combination antifungal protocols for cryptococcal meningitis, owing to the inherently rather weak antifungal activity of 5-FC monotherapy. The use of 5-FC in premature neonates is discouraged. A study evaluating risk factors and mortality rates of neonatal candidiasis among extremely premature infants showed that infants with *Candida* meningitis who received amphotericin B in combination with 5-FC had a prolonged time to sterilization of the CSF compared to infants receiving amphotericin B monotherapy.

AZOLES

The azole antifungals inhibit the fungal cytochrome $P450_{14DM}$ (also known as lanosterol 14α-demethylase), which catalyzes a late step in fungal cell membrane ergosterol biosynthesis. Of the older first-generation triazoles, itraconazole has activity against *Aspergillus* but fluconazole is ineffective against *Aspergillus* and other molds. Second-generation triazoles (voriconazole and posaconazole) are modifications of prior triazoles with an expanded antifungal spectrum of activity, including activity against molds, and generally greater in vitro antifungal activity.

Fluconazole

Fluconazole is fungistatic, and this activity is not influenced by concentration once the maximal fungistatic concentration is surpassed (concentration independent), in contrast to the concentration-dependent fungicidal activity of amphotericin B. Fluconazole is available as either an oral or intravenous form, and oral administration has a bioavailability of approximately 90% relative to intravenous administration. Fluconazole passes into tissues and fluids very rapidly, probably because of its relatively low lipophilicity and limited degree of binding to plasma proteins. Concentrations of fluconazole are 10-20–fold higher in the urine than blood, making it an ideal agent for treating fungal urinary tract infections. Concentrations in the CSF and vitreous humor of the eye are approximately 80% of those found simultaneously in blood.

It is clear that simple conversion of the corresponding adult dosage of fluconazole on a weight basis is inappropriate for pediatric patients. Fluconazole clearance is generally more rapid in children than adults, with a mean plasma half-life of approximately 20 hr in children and approximately 30 hr in adult patients. Therefore, to achieve comparable exposure in pediatric patients, the daily fluconazole dosage needs to be essentially doubled. Correct pediatric fluconazole dosages should be proportionately higher than adult dosages, generally 12 mg/kg/day. In neonates the volume of distribution is significantly greater and more variable than in infants and children, and doubling the dosage for neonatal patients is necessary to achieve comparable plasma concentrations. The increased volume of distribution is thought to be from the larger amount of body water found in the total body volume of neonates. A pharmacokinetic study in premature infants suggests that maintenance fluconazole dosages of 12 mg/kg/day are necessary to achieve exposures similar to those in older children and adults. In addition, a loading dose of 25 mg/kg would achieve steady-state concentrations sooner than the traditional dosing scheme. Side effects of fluconazole are uncommon but generally include gastrointestinal upset (vomiting, diarrhea, nausea) and skin rash.

Fluconazole plays an important role in the treatment of invasive candidiasis. The latest guidelines suggest use of the fungistatic fluconazole in patients who have invasive candidiasis but who are not critically ill or neutropenic. Although most isolates of *Candida albicans* remain susceptible to fluconazole, for certain *Candida* species fluconazole is not an ideal agent: *Candida krusei* is generally resistant and *Candida glabrata* is often resistant. In treating infection caused by these *Candida* species, it is critical to treat with an echinocandin or amphotericin B rather than fluconazole. There is no confirmed role for combination antifungal therapy with fluconazole and another antifungal against invasive candidiasis.

Prophylaxis with fluconazole to prevent neonatal candidiasis in premature infants remains a controversial topic. In a prospective, randomized double-blind trial over a 30 mo period of 100 infants with birth weights <1,000 g, infants who received fluconazole for 6 wk had a decrease in fungal colonization (22% vs 60%) and a decrease in the development of invasive fungal infection (0% vs 20%) compared to placebo. Other studies have yielded similarly encouraging results and have demonstrated that use of fluconazole prophylaxis for 4-6 wk in high-risk infants does not increase the incidence of fungal colonization and infections caused by natively fluconazole-resistant *Candida* species. The universal implementation of such a strategy across nurseries is discouraged, because the rate of *Candida* infections varies greatly among centers and there are insufficient neurodevelopmental follow-up data in these infants to justify prophylaxis.

Itraconazole

Compared to fluconazole, itraconazole has the benefit of antifungal activity against *Aspergillus* species but comes with several practical constraints, such as erratic oral absorption in high- risk patients and significant drug interactions. These pharmacokinetic concerns have been addressed with both an intravenous formulation and a better-absorbed oral solution to replace the capsules used earlier. Itraconazole has a high volume of distribution and accumulates in tissues, and tissue-bound levels are probably more clinically relevant to infection treatment than serum levels. Dissolution and absorption of itraconazole are affected by gastric pH. Patients with achlorhydria or taking H_2-receptor antagonists might demonstrate impaired absorption, and coadministration of the capsule with acidic beverages such as colas or cranberry juice can enhance absorption. Administration with food significantly increases the absorption of the capsule formulation, but the oral suspension with a cyclodextrin base is better absorbed on an empty stomach.

Side effects are relatively few and include nausea and vomiting (10%), elevated transaminases (5%), and peripheral edema. There are reports in adults of development of cardiomyopathy. Itraconazole also is associated with important drug interactions, and prior or concurrent use of rifampin, phenytoin, carbamazepine, and phenobarbital should be avoided.

Itraconazole has a role in treating less-serious infections with endemic mycoses (histoplasmosis, coccidioidomycosis, and blastomycosis), as well as use in prophylaxis against invasive fungal infections

in high-risk patients. The plethora of drug interactions make itraconazole a concern in complex patients receiving other medications, and itraconazole serum levels (to achieve ≥0.5 μg/mL) are recommended to confirm appropriate dosing. Itraconazole is no longer recommended for primary therapy of invasive aspergillosis.

Voriconazole

Voriconazole is a second-generation triazole and a synthetic derivative of fluconazole. Voriconazole generally has the spectrum of activity of itraconazole but the better bioavailability than fluconazole. Importantly, it is fungicidal against *Aspergillus* and fungistatic against *Candida*. It is extensively metabolized by the liver and has approximately 90% oral bioavailability. The cytochrome P450 2C19 (CYP2C19) enzyme appears to play a major role in the metabolism of voriconazole, and polymorphisms in CYP2C19 are associated with slow voriconazole metabolism. As many as 20% of non-Indian Asians have low CYP2C19 activity and develop voriconazole levels as much as 4-fold higher than those in homozygous subjects, leading to potentially increased toxicity.

Voriconazole is available as an oral tablet, an oral suspension, and an intravenous solution. In adults, voriconazole exhibits nonlinear pharmacokinetics, has a variable half-life of approximately 6 hr with large interpatient variation in blood levels, and achieves good CSF penetration. In contrast to the situation in adults, elimination of voriconazole is linear in children. A multicenter safety, population pharmacokinetic study of intravenous voriconazole dosages in immunocompromised pediatric patients showed that body weight was more influential than age in accounting for the observed variability in voriconazole pharmacokinetics, and voriconazole needs to be dosed higher in pediatric patients than adult patients. Adult patients load with 6 mg/kg/dose and then transition to a maintenance dosage of 4 mg/kg/dose, but children should begin and continue with 9 mg/kg/dose intravenously (see Table 233-1) and continue maintenance dosing at 8 mg/kg/dose. This need for an increased dosage in treating children is crucial to understand and is mandated by the fundamentally different pharmacokinetics of this drug in pediatric patients. Obtaining voriconazole serum levels (to achieve ≥1-2 μg/mL) is critical for therapeutic success. Oral voriconazole is best absorbed on an empty stomach. Generally a trough level greater than the minimum inhibitory concentration of the infecting organism is preferred, and very high voriconazole levels have been associated with toxicity (generally >7 μg/mL). The main side effects of voriconazole include reversible dosage-dependent visual disturbances (increased brightness, blurred vision) in as many as one-third of treated patients, elevated hepatic transaminases with increasing dosages, and occasional skin reactions likely caused by photosensitization.

The largest prospective clinical trial of voriconazole as primary therapy for invasive aspergillosis compared initial randomized therapy with voriconazole vs amphotericin B and demonstrated improved response and survival with voriconazole over amphotericin B. Voriconazole is guideline-recommended as the preferred primary therapy against invasive aspergillosis. Voriconazole also has a role in treating candidiasis, but its fungistatic nature makes it often less than ideal for treating critically ill or neutropenic patients where the fungicidal echinocandin antifungals are preferred.

Posaconazole

Posaconazole is a second-generation triazole that is a derivative of itraconazole and is currently available as an intravenous formulation, an extended-release oral tablet, and an oral suspension. The antimicrobial spectrum of posaconazole is similar to that of voriconazole; however, the former is active against *Zygomycetes* such as mucormycosis, and voriconazole is not active against these particular mold infections. When administered with a nonfat or high-fat diet, posaconazole exposure and maximum concentration are 3-4 times higher than when administered in the fasting state, emphasizing the importance of diet to increase serum levels of posaconazole (the opposite of voriconazole). Posaconazole exposure is maximized with acidic beverages, administration in divided doses, and the absence of proton pump inhibitors. Posaconazole causes transient hepatic reactions, including mild to moderate elevations in liver transaminases, alkaline phosphatase, and total bilirubin.

The correct pediatric dosage of posaconazole is not known, because initial studies are still ongoing. In adult patients, dosages >800 mg/day do not result in increased serum levels, and division of daily dosing into 3 or 4 doses/day results in greater serum levels than a once- or twice-daily dosing scheme. Similar to itraconazole and voriconazole, posaconazole should be monitored with trough levels (to achieve ≥0.7 μg/mL).

In an international randomized, single-blinded study of posaconazole vs fluconazole or itraconazole in neutropenic patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, posaconazole was superior in preventing invasive fungal infections. Fewer patients in the posaconazole group had invasive aspergillosis, and survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole. Another multisite international randomized, double-blinded study in patients with allogeneic hematopoietic stem-cell transplantation and graft-versus-host disease showed that posaconazole was not inferior to fluconazole in the prevention of invasive fungal infections. Posaconazole is approved for prophylaxis against invasive fungal infections but has shown great efficacy in clinical experience with recalcitrant mold infections.

In patients with chronic granulomatous disease and proven invasive fungal infection refractory to standard therapy, posaconazole proved to be well tolerated and quite effective. This agent might prove to be very useful in this patient population where long-term therapy with an oral agent is required.

ECHINOCANDINS

The echinocandins are a class of antifungals and interfere with cell wall biosynthesis by noncompetitive inhibition of 1,3-β-D-glucan synthase, an enzyme present in fungi but absent in mammalian cells. 1,3-β-D-Glucan is an essential cell wall polysaccharide and provides structural integrity for the fungal cell wall. Echinocandins are generally fungicidal in vitro against *Candida* species, although not as rapidly as amphotericin B, and are fungistatic against *Aspergillus*. As a class these agents are not metabolized through the CYP enzyme system, lessening some of the drug interactions and side effects seen with the azole class. The echinocandins appear to have a prolonged and dosage-dependent fungicidal antifungal effect on *C. albicans*, compared to the fungistatic fluconazole. Three compounds in this class (caspofungin, micafungin, and anidulafungin) are FDA approved for use. Owing to the large size of the molecules, the current echinocandins are only available in an intravenous formulation. Because 1,3-β-D-glucan is a selective target present only in fungal cell walls and not in mammalian cells, this eliminates much of the drug mechanism–based toxicity for the echinocandins, and there appears to be no apparent myelotoxicity or nephrotoxicity with the agents.

Caspofungin

At present there is no known maximum tolerated dosage and no toxicity-determined maximum length of therapy for caspofungin. The usual course is to begin with a loading dose followed by a lesser daily maintenance dosage, which is 70 mg followed by 50 mg daily in adult patients. Much of the dosage accumulation is achieved in the 1st wk of dosing, and renal insufficiency has little effect on the pharmacokinetics of caspofungin. Caspofungin has been evaluated at double the recommended dosage (100 mg/day in adults) with no adverse effects, and it is unclear if higher dosage of this relatively safe agent results in greater clinical efficacy.

Pharmacokinetics are slightly different in children, with caspofungin levels lower in smaller children and with a reduced half-life. A study evaluated the pharmacokinetics of caspofungin in children with neutropenia and showed that in patients receiving 50 mg/m^2/day (maximum: 70 mg/day), the levels were similar to those in adults receiving 50 mg/day and were consistent across age ranges. In this study, weight-based dosing (1 mg/kg/day) was suboptimal when

compared to body surface area regimens, so caspofungin should be appropriately dosed in children as a loading dose of 70 mg/m^2/day, followed by daily maintenance dosing of 50 mg/m^2/day.

Caspofungin was approved for refractory aspergillosis or intolerance to other therapies and for candidemia and various other sites of invasive *Candida* infections. In the pivotal clinical study, patients with acute invasive aspergillosis underwent "salvage" therapy after failing primary therapy, and recipients had a 41% favorable response with caspofungin. In a multicenter trial of patients with invasive candidiasis, 73% of patients who received caspofungin had a favorable response at the end of therapy, compared to 62% in the amphotericin B group. Importantly, caspofungin treatment performed equally well to amphotericin B treatment for all the major *Candida* species, but other studies show that some infections with *Candida parapsilosis* do not clear as effectively with an echinocandin. Current guideline recommendations state that infection with *C. parapsilosis* should be treated initially with fluconazole or amphotericin B for this reason. Caspofungin was also evaluated against L-amphotericin B in the empirical treatment of patients with persistent fever and neutropenia and was not inferior to liposomal amphotericin B in more than 1,000 patients.

Caspofungin in children is reported to be safe. Caspofungin pharmacokinetics were evaluated in older infants and toddlers at 50 mg/m^2/day and found to be similar to adults receiving the standard 50 mg daily dose. Caspofungin in newborns has been used as single or adjuvant therapy for refractory cases of disseminated candidiasis. Neonates with invasive candidiasis are at high risk for central nervous system involvement; it is not known if the dosages of caspofungin studied provide sufficient exposure to penetrate the central nervous system at levels necessary to cure infection. Therefore, caspofungin is not recommended as monotherapy in neonatal candidiasis.

Micafungin

The pharmacokinetics of micafungin have been evaluated in children and young infants. An inverse relation between age and clearance was observed, where mean systemic clearance was significantly greater and mean half-life was significantly shorter in patients 2-8 yr of age compared to patients 9-17 yr of age. Therefore, dosing of micafungin in children is age-related and needs to be higher in children younger than 8 yr old. To achieve micafungin exposures equivalent to exposures in adults receiving 100, 150, and 200 mg daily, as evidenced by simulation profiles, children require dosages >3 mg/kg.

Several pharmacokinetic studies of micafungin in term and preterm infants show that micafungin in infants has a shorter half-life and a more rapid rate of clearance compared with published data in older children and adults. These results suggest that young infants should receive 10 mg/kg daily of micafungin if used to treat invasive candidiasis.

The safety profile of micafungin is optimal when compared to other antifungal agents. Clinical trials including those of micafungin used for treatment of localized and invasive candidiasis as well as prophylaxis studies in patients following stem cell transplantation have demonstrated fewer adverse events compared to liposomal amphotericin B and fluconazole. The most common adverse events experienced by these patients are related to the gastrointestinal tract (nausea, diarrhea). Hypersensitivity reactions associated with micafungin have been reported, and liver enzymes are elevated in 5% of patients receiving this agent. Hyperbilirubinemia, renal impairment, and hemolytic anemia related to micafungin use have also been identified in postmarketing surveillance of the drug.

An open-label, noncomparative, multinational study in adult and pediatric patients with a variety of diagnoses evaluated the use of micafungin monotherapy and combination therapy in 225 patients with invasive aspergillosis. Of those only treated with micafungin, favorable responses were seen in 50% of the primary and 41% of the salvage therapy group.

Micafungin at dosages of 100 and 150 mg daily was also noninferior to caspofungin in an international, randomized, double-blinded study of adults with candidemia or invasive candidiasis and was found to be superior to fluconazole in the prevention of invasive fungal infections in a randomized study of adults undergoing hematopoietic stem cell transplantation.

Of the 3 drugs within the echinocandin class, micafungin has been the one most extensively studied in children, including several pharmacokinetic studies in neonates. A pediatric substudy as part of a double-blind, randomized, multinational trial comparing micafungin (2 mg/kg/day) with liposomal amphotericin B (3 mg/kg/day) as first-line treatment for invasive candidiasis showed similar success for micafungin and liposomal amphotericin B. In general, micafungin was better tolerated than liposomal amphotericin B as evidenced by fewer adverse events leading to discontinuation of therapy. Micafungin doses up to 15 mg/kg/day have been evaluated in small cohorts of premature infants and found to be well tolerated; doses of 8-10 mg/kg/day achieve exposures comparable to adults in this population.

Anidulafungin

Anidulafungin has the longest half-life of all the echinocandins (approximately 18 hr). In a study of 25 neutropenic children receiving anidulafungin as empirical therapy, 4 patients in the group receiving 0.75 mg/kg/day experienced adverse events such as facial erythema and rash, elevation in serum blood urea nitrogen, and fever and hypotension. In a pharmacokinetic study in neonates and young infants, anidulafungin exposures comparable to adults were achieved with doses of 1.5 mg/kg/day (3 mg/kg loading dose). One infant in this cohort supported by extracorporeal membrane oxygenation achieved the lowest exposure, which suggests that dose adjustments are required in this population.

A randomized, double-blind study in adult patients without neutropenia with invasive candidiasis showed that anidulafungin was not inferior to fluconazole in the treatment of invasive candidiasis. In this study, the incidence and types of adverse events were similar in the 2 groups, and all-cause mortality was 31% in the fluconazole group and 23% in the anidulafungin group. No clinical studies of anidulafungin in pediatric patients are currently available.

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Chapter 234

Candida

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

Candidiasis encompasses many clinical syndromes that may be caused by several species of *Candida*. Invasive candidiasis (*Candida* infections of the blood and other sterile body fluids) is a leading cause of infection-related mortality in hospitalized immunocompromised patients.

Candida exists in 3 morphologic forms: oval to round **blastospores or yeast cells** (3-6 mm in diameter); double-walled **chlamydospores** (7-17 mm in diameter), which are usually at the terminal end of a pseudohypha; and **pseudomycelium,** which is a mass of pseudohyphae and represents the tissue phase of *Candida.* **Pseudohyphae** are filamentous processes that elongate from the yeast cell without the cytoplasmic connection of a true hypha. *Candida* grows aerobically on routine laboratory media but can require several days of incubation for visible growth.

Candida albicans accounts for most human infections, but *Candida parapsilosis, Candida tropicalis, Candida krusei, Candida lusitaniae, Candida glabrata,* and several other species are commonly isolated from hospitalized children. *C. albicans* forms a germ tube when suspended in rabbit or human serum and incubated for 1-2 hr; consequently, a rapid germ tube test should be performed before further

identification tests are conducted. The other clinically important *Candida* species can be identified within 48 hr on the basis of biochemical test results. Differentiation and susceptibility testing are important owing to increasing frequency of fluconazole resistance.

Treatment of invasive *Candida* infections is complicated by the emergence of non-*albicans* strains. Amphotericin B deoxycholate is inactive against approximately 20% of strains of *C. lusitaniae.* Fluconazole is useful for many *Candida* infections but is inactive against all strains of *C. krusei* and 5-25% of strains of *C. glabrata.* Susceptibility testing of these clinical isolates is recommended.

234.1 Neonatal Infections

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

Candida is a common cause of oral mucous membrane infections **(thrush)** and perineal skin infections **(*Candida* diaper dermatitis)** in young infants. Rare presentations include **congenital cutaneous candidiasis,** caused by an ascending infection into the uterus during gestation, and **invasive fungal dermatitis,** a postnatal skin infection resulting in positive blood cultures. Invasive candidiasis is a common infectious complication in the neonatal intensive care unit (NICU) because of improved survival of extremely preterm infants.

EPIDEMIOLOGY

Candida species are the third most common cause of bloodstream infection in premature infants. The cumulative incidence is <0.3% among infants >2,500 g birthweight admitted to the NICU. The cumulative incidence increases to 8% for infants <750 g birthweight. In addition, the incidence varies greatly by individual NICU. Among centers in the National Institutes of Health-sponsored Neonatal Research Network, the cumulative incidence of candidiasis among infants <1,000 g birthweight ranges from 2-28%. Colonization is associated with a significantly increased risk of future invasive *Candida* infection. Up to 10% of full-term infants are colonized as the result of vertical transmission from the mother at birth, with slightly higher rates of colonization in premature infants. Colonization rates increase to >50% among infants admitted to the NICU by 1 mo of age. Histamine-2 blockers and broad-spectrum antibiotics facilitate *Candida* colonization and overgrowth.

Significant risk factors for neonatal invasive candidiasis include prematurity, low birthweight, exposure to broad-spectrum antibiotics, abdominal surgery, and presence of a central venous catheter.

PATHOGENESIS

Immunologic immaturity along with an underdeveloped layer of skin, need for invasive measures (endotracheal tubes, central venous catheters), and exposure to broad-spectrum antibiotics places preterm infants at great risk for invasive candidiasis. Premature infants are also at high risk for spontaneous intestinal perforations and necrotizing enterocolitis. Both conditions require abdominal surgery, prolonged exposure to broad-spectrum antibiotics, and total parenteral nutrition administration requiring placement of central venous catheters. Each of these factors increases the risk of invasive candidiasis by decreasing the physiologic barriers that protect against invasive infection.

CLINICAL MANIFESTATIONS

The manifestations of neonatal candidiasis vary in severity from oral thrush and *Candida* diaper dermatitis (see Chapter 234.2) to invasive candidiasis that can manifest with overwhelming sepsis (see Chapter 234.3). Signs of invasive candidiasis among premature infants are often nonspecific and include temperature instability, lethargy, apnea, hypotension, respiratory distress, abdominal distention, and thrombocytopenia.

Central nervous system involvement is common and is most accurately described as meningoencephalitis. *Candida* infections involving the central nervous system often result in abscesses leading to unremarkable cerebrospinal fluid parameters (white blood cell count, glucose, protein) even though central nervous system infection is present. Endophthalmitis is an uncommon complication affecting <5% of infants with invasive candidiasis. In addition, candidemia is associated with an increased risk of severe retinopathy of prematurity. Renal involvement commonly complicates neonatal invasive candidiasis. Renal involvement may be limited to candiduria or can manifest with diffuse infiltration of *Candida* throughout the renal parenchyma or the presence of *Candida* and debris within the collecting system. Other affected organs include the heart, bones, joints, liver, and spleen.

DIAGNOSIS

Mucocutaneous infections are most often diagnosed by direct clinical exam. Scrapings of skin lesions may be examined with a microscope after Gram staining or suspension in KOH. Definitive diagnosis of invasive disease requires histologic demonstration of the fungus in tissue specimens or recovery of the fungus from normally sterile body fluids. Hematologic parameters are sensitive but not specific. Thrombocytopenia occurs in more than 80% of premature infants with invasive candidiasis, but also occurs in 75% of premature infants with Gram-negative bacterial sepsis and nearly 50% of infants with Gram-positive bacterial sepsis. Blood cultures have very low sensitivity for invasive candidiasis. In a study of autopsy-proven candidiasis in adult patients, the sensitivity of multiple blood cultures for detecting single-organ disease was 28%. Blood culture volumes in infants are often only 0.5-1 mL, making the sensitivity in this population almost certainly lower. Blood culture volume should be maximized as much as possible to increase sensitivity. Fungal-specific media can improve sensitivity when *Candida* is present as a coinfection with bacteria and can also decrease the time to positivity leading to more rapid diagnosis.

Further assessment of infants in the presence of documented candidemia should include ultrasound or computerized tomography of the head to evaluate for abscesses; ultrasound of the liver, kidney, and spleen; cardiac echocardiography; ophthalmologic exam; lumbar puncture; and urine culture. These tests are necessary to determine if more than 1 body system is infected, which is commonly the case.

PROPHYLAXIS

NICUs with a high incidence of invasive candidiasis should consider prophylaxis with fluconazole in infants <1,000 g birthweight. Twice-weekly fluconazole at 3 and 6 mg/kg/dose decreases rates of both colonization with *Candida* species and invasive fungal infections. Use of this dosing strategy has not been shown to increase the frequency of infections caused by fluconazole-resistant strains, but use of an alternative antifungal class for cases of breakthrough infection is suggested.

TREATMENT

In the absence of systemic manifestations, topical antifungal therapy is the treatment of choice for congenital cutaneous candidiasis in full-term infants. Congenital cutaneous candidiasis in preterm infants can progress to systemic disease, and therefore systemic therapy is warranted.

Every attempt should be made to remove or replace central venous catheters once the diagnosis of candidemia is confirmed. Delayed removal has been consistently associated with increased mortality and morbidity including poor neurodevelopmental outcomes.

Although no well-powered randomized, controlled trials exist to guide length and type of therapy, 21 days of systemic antifungal therapy from the last positive *Candida* culture is recommended in infants. Antifungal therapy should be targeted based on susceptibility testing. Amphotericin B deoxycholate has been the mainstay of therapy for systemic candidiasis and is active against both yeast and mycelial forms. Nephrotoxicity, hypokalemia, and hypomagnesemia are common, but amphotericin B deoxycholate is better tolerated in infants than in adult patients. *C. lusitaniae*, an uncommon pathogen in infants, is often resistant to amphotericin B deoxycholate. Liposomal amphotericin is associated with worse outcomes in infants and should be used only when urinary tract involvement can reliably be excluded. Fluconazole is often used instead of amphotericin B deoxycholate for treatment of invasive neonatal *Candida* infections because of its effectiveness and low incidence of side effects. It is particularly useful for urinary

Table 234-1 Dosing of Antifungal Agents in Infants* and Number of Infants Younger Than 1 Yr of Age Studied with Reported Pharmacokinetic Parameters

DRUG	INFANTS STUDIED	SUGGESTED DOSE
Amphotericin B deoxycholate	27	1 mg/kg/day
Amphotericin B lipid complex	28	5 mg/kg/day
Liposomal amphotericin B	17	5 mg/kg/day
Amphotericin B colloidal dispersion	0	5 mg/kg/day
Fluconazole†	65	12 mg/kg/day
Micafungin‡	120	10 mg/kg/day
Caspofungin§	22	50 mg/m^2/day
Anidulafungin‡	15	1.5 mg/kg/day

*Voriconazole dosing has not been investigated in the nursery.
†A loading dose of 25 mg/kg of fluconazole is necessary to achieve therapeutic serum concentrations in the early days of therapy.
‡Micafungin has been studied in infants <120 days of life at this dosage.
§Caspofungin and anidulafungin should generally be avoided because dosing sufficient to penetrate brain tissue has not been studied.

tract infections, obtaining high concentrations in the urine. A loading dose should be given to obtain therapeutic serum concentrations in a timely manner. Fluconazole is inactive against all strains of *C. krusei* and some isolates of *C. glabrata.* Additionally, in centers where fluconazole prophylaxis is used, another agent, such as amphotericin B deoxycholate, should be used for treatment. The echinocandins have excellent activity against most *Candida* species and have been used successfully in patients with resistant organisms or in whom other therapies have failed. Several studies have described the pharmacokinetics of antifungals in infants (Table 234-1).

PROGNOSIS

Mortality following invasive candidiasis in premature infants has been consistently reported to be around 20% in large studies. Candidiasis is also associated with poor neurodevelopmental outcomes, chronic lung disease, and severe retinopathy of prematurity.

Bibliography is available at Expert Consult.

234.2 Infections in Immunocompetent Children and Adolescents

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

ORAL CANDIDIASIS

Oral thrush is a superficial mucous membrane infection that affects approximately 2-5% of normal neonates. *C. albicans* is the most commonly isolated species. Oral thrush can develop as early as 7-10 days of age. The use of antibiotics, especially in the 1st yr of life, can lead to recurrent or persistent thrush. It is characterized by pearly white, curdish material visible on the tongue, palate, and buccal mucosa. Oral thrush may be asymptomatic or can cause pain, fussiness, and decreased feeding, leading to inadequate nutritional intake and dehydration. It is uncommon after 1 yr of age but can occur in older children treated with antibiotics. Persistent or recurrent thrush with no obvious predisposing reason, such as recent antibiotic treatment, warrants investigation of an underlying immunodeficiency, especially vertically transmitted HIV infection or a primary congenital genetic immune defect.

Treatment of mild cases might not be necessary. When treatment is warranted, the most commonly prescribed antifungal agent is nystatin. For recalcitrant or recurrent infections, a single dose of fluconazole may be useful. In breastfed infants, simultaneous treatment of infant and mother with topical nystatin or oral fluconazole may be indicated.

DIAPER DERMATITIS

Diaper dermatitis is the most common infection caused by *Candida* (see Chapter 666) and is characterized by a confluent erythematous rash with satellite pustules. *Candida* diaper dermatitis often complicates other noninfectious diaper dermatitides and often occurs following a course of oral antibiotics.

A common practice is to presumptively treat any diaper rash that has been present for longer than 3 days with topical antifungal therapy such as nystatin, clotrimazole, or miconazole. If significant inflammation is present, the addition of hydrocortisone 1% may be useful for the 1st 1-2 days, but topical corticosteroids should be used cautiously in infants because the relatively potent topical corticosteroid can lead to adverse effects. Frequent diaper changes and short periods without diapers are important adjunctive treatments.

UNGUAL AND PERIUNGUAL INFECTIONS

Paronychia and onychomycosis may be caused by *Candida,* although *Trichophyton* and *Epidermophyton* are more common causes (see Chapter 663). *Candida* onychomycosis differs from tinea infections by its propensity to involve the fingernails and not the toenails, and by the associated paronychia. *Candida* paronychia often responds to treatment consisting of keeping the hands dry and using a topical antifungal agent. Psoriasis and immune dysfunction, including HIV and primary immunodeficiencies, predispose to *Candida* ungual infections. Ungual infections often require systemic antifungal therapy. Once-weekly fluconazole for 4-12 mo is an effective treatment strategy with fairly low toxicity.

VULVOVAGINITIS

Vulvovaginitis is a common *Candida* infection of pubertal and postpubertal female patients (see Chapter 549). Predisposing factors include pregnancy, use of oral contraceptives, and use of oral antibiotics. Prepubertal girls with *Candida* vulvovaginitis usually have a predisposing factor such as diabetes mellitus or prolonged antibiotic treatment. Clinical manifestations can include pain or itching, dysuria, vulvar or vaginal erythema, and an opaque white or cheesy exudate. More than 80% of cases are caused by *C. albicans.*

Candida vulvovaginitis can be effectively treated with either vaginal creams or troches of nystatin, clotrimazole, or miconazole. Oral therapy with a single dose of fluconazole is also effective.

Bibliography is available at Expert Consult.

234.3 Infections in Immunocompromised Children and Adolescents

Jessica Ericson, P. Brian Smith, and Daniel K. Benjamin Jr.

ETIOLOGY

C. albicans is the most common cause of invasive candidiasis among immunocompromised pediatric patients and is associated with higher rates of mortality and end-organ involvement than are non-*albicans* species.

CLINICAL MANIFESTATIONS

HIV-Infected Children

Oral thrush and diaper dermatitis are the most common *Candida* infections in HIV-infected children. Besides oral thrush, 3 other types of oral *Candida* infections can occur in HIV-infected children: atrophic candidiasis, which manifests as a fiery erythema of the mucosa or loss of papillae of the tongue; chronic hyperplastic candidiasis, which presents with oral symmetric white plaques; and angular cheilitis, in which there is erythema and fissuring of the angles of the mouth. Topical antifungal therapy may be effective, but systemic treatment

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with fluconazole or itraconazole is usually necessary. Symptoms of dysphagia or poor oral intake can indicate progression to *Candida* esophagitis, requiring systemic antifungal therapy. In HIV patients, esophagitis can also be caused by cytomegalovirus, herpes simplex virus, reflux, or lymphoma; *Candida* is the most common cause, and *Candida* esophagitis can occur in the absence of thrush.

Candida dermatitis and onychomycosis are more common in HIV-infected children. These infections are generally more severe than they are in immunocompetent children and can require systemic antifungal therapy.

Cancer and Transplant Patients

Fungal infections, especially *Candida* and *Aspergillus* infections, are a significant problem in oncology patients with chemotherapy-associated neutropenia (see Chapter 178). Greater than 5 days of fever during a neutropenic episode is associated with presence of an invasive fungal infection. Accordingly, empirical antifungal therapy should be started if fever and neutropenia persist for 5 or more days. Fluconazole can be used if the patient is not critically ill and the drug is not already being used for prophylaxis. An echinocandin or liposomal amphotericin B should be used when these conditions are not met. High-risk oncology patients warrant prophylaxis against invasive *Candida* infection. Both fluconazole and echinocandins are used for this indication; lower doses are typically used for this purpose than those used for treatment.

Bone marrow transplant recipients have a much higher risk of fungal infections because of the dramatically prolonged duration of neutropenia. Voriconazole prophylaxis decreases the incidence of candidemia in bone marrow transplant recipients with the additional benefit over fluconazole of mold prophylaxis. The use of myelopoietic colony-stimulating factor reduces the duration of neutropenia after chemotherapy and is associated with decreased risk for candidemia. When *Candida* infection occurs in this population, the lung, spleen, kidney, and liver are involved in more than 50% of cases.

Solid-organ transplant recipients are also at increased risk for superficial and invasive *Candida* infections. Studies in liver transplant recipients demonstrate the utility of antifungal prophylaxis with amphotericin B deoxycholate, fluconazole, voriconazole, or caspofungin in high-risk patients (those with prolonged surgical time, comorbidities, recent antibiotic exposure, or bile leak).

Catheter-Associated Infections

Central venous catheter infections occur most often in oncology patients but can affect any patient with a central catheter (see Chapter 179). Neutropenia, use of broad-spectrum antibiotics, and parenteral alimentation are associated with increased risk for *Candida* central catheter infection. Treatment typically requires removing or replacing the catheter followed by a 2-3 wk course of systemic antifungal therapy. Removal of the central catheter in place at time of positive blood culture and use of a peripheral IV or enteral support for at least 48 hr prior to obtaining central access is advocated. Removal of the original catheter followed by immediate replacement with a new central catheter in a different anatomic location is acceptable if an interval without central access is not feasible.

DIAGNOSIS

The diagnosis is often presumptive in neutropenic patients with prolonged fever because positive blood cultures for *Candida* occur only in a minority of patients who are later found to have disseminated infection. If isolated, *Candida* grows readily on routine blood culture media, with ≥90% of positive cultures identified within 72 hr. CT may demonstrate findings consistent with invasive fungal infection but also is limited by nonspecific findings and false negatives. The role of screening by CT scan has not been well defined.

TREATMENT

Echinocandins are favored as empirical therapy for moderately or severely ill children; fluconazole is acceptable for those who are infected with a susceptible organism and are less critically ill; amphotericin B products are also acceptable. Definitive antifungal selection should be made based on susceptibility testing results. Fluconazole is not effective against *C. krusei* and some isolates of *C. glabrata. C. parapsilosis* has occasional resistance to the echinocandins, but the overall rate is still low. Amphotericin B deoxycholate is inactive against approximately 20% of the strains of *C. lusitaniae,* and therefore susceptibility testing should be performed for all strains (Table 234-2).

Table 234-2 Dosing of Antifungal Agents in Children Older Than 1 Year of Age for Treatment of Invasive Disease

DRUG	SUGGESTED DOSAGE
Amphotericin B deoxycholate	1 mg/kg/day
Amphotericin B lipid complex	5 mg/kg/day
Liposomal amphotericin B	5 mg/kg/day
Amphotericin B colloidal dispersion	5 mg/kg/day
Fluconazole†	12 mg/kg/day
Voriconazole	8 mg/kg every 12 hr
Micafungin*	2-4 mg/kg/day
Caspofungin	50 mg/m^2/day
Anidulafungin	1.5 mg/kg/day

*Use adult dosages in children older than 8 yr of age.
†Loading doses should be used for fluconazole (25 mg/kg), voriconazole (9 mg/kg q 12 × 24 hr), caspofungin (70 mg/m^2), and anidulafungin (3 mg/kg).

PRIMARY IMMUNE DEFECTS

Chronic mucocutaneous candidiasis involves *Candida* infections of the oral cavity, esophagus, and/or genital mucosa, as well as involvement of skin and nails, that is recurrent or persistent and difficult to treat. There is a broad spectrum of genetic immune defects associated with chronic mucocutaneous candidiasis mostly related to severe T-cell defects or disorders of interleukin-17 production (see Chapter 125). Genes or disorders associated with chronic mucocutaneous candidiasis include severe combined immunodeficiency syndrome, NEMO or IKBG deficiency, DOCK8 deficiency, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), autoimmune polyendocrinopathy type 1, CARD9 deficiency, *STAT1* gain of function mutations, and *IL17RA* mutations.

Primary immunodeficiencies associated with an increased risk of invasive *Candida* infections include severe congenital neutropenia, CARD 9 deficiency, chronic granulomatous disease, and leukocyte adhesion deficiency type 1.

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Chapter 235

Cryptococcus neoformans

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Cryptococcosis is an invasive fungal disease caused by a monomorphic, encapsulated yeast. *Cryptococcus neoformans* var. *neoformans* is the most common etiologic agent worldwide and is the predominant pathogenic fungal infection among persons infected with HIV.

EPIDEMIOLOGY

C. neoformans var. *neoformans* (serotypes A, D, and AD) is distributed in temperate climates predominantly in soil contaminated with droppings from certain avian species, including pigeons, canaries, and cockatoos. It may also be found on fruits and vegetables and may be carried by cockroaches. *C. neoformans* var. *gattii* (serotypes B and C) is found in the tropics and subtropics and is associated with several species of eucalyptus trees. This species causes endemic disease primarily in immunologically competent hosts living in the tropics and is associated with the formation of large granulomas known as **cryptococcomas**. The distribution and ecology of *C. gattii* seem to be changing, and this organism can now be found in association with a wide range of trees, including firs and oaks. *C. gattii* has caused disease in approximately 24 patients residing in Oregon and Washington, most occurring since 2006. Pulmonary disease with or without meningoencephalitis was the most common manifestation. *C. gattii* is believed to be more virulent clinically than *C. neoformans*. It is critical to distinguish between the 2 cryptococcal species because *C. gattii* is less susceptible to fluconazole. *Cryptococcus laurentii* is occasionally reported as a cause of invasive fungal disease, usually in immunocompromised patients and most recently in the premature neonatal population.

C. neoformans exposure is much more common than previously thought. Seroprevalence studies in temperate urban environments have shown that most children older than 2 yr of age and nearly all adults have been exposed to this organism. Despite this high prevalence, clinical disease is unusual in immunocompetent persons and is rare in children. Pigeon breeders and laboratory personnel who work with *Cryptococcus* are at greatest risk. Cryptococcosis is also rare (<1%) among HIV-infected children but occurs in 5-10% of HIV-infected adults, with higher rates of infection reported from developing countries. Pediatric cases of cryptococcosis are evenly divided among immunocompetent and immunocompromised persons. Cryptococcosis is the third most common invasive fungal infection after candidiasis and aspergillosis in solid organ transplant patients. Other risk factors for cryptococcal infection include diabetes mellitus, renal failure, cirrhosis, and use of corticosteroids, chemotherapy agents, and monoclonal antibodies such as etanercept, infliximab, and alemtuzumab. Children with primary immunodeficiency diseases are at increased risk for infection; these include those with autoantibodies to granulocyte-macrophage colony-stimulating factor or interferon-γ, CD40 ligand deficiency, and monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia). Interestingly organ transplant recipients who are receiving calcineurin-inhibitor–based immunosuppression are less likely to have cryptococcal central nervous system (CNS) infection and more likely to have disease limited to the lung, because these agents have antifungal activity in vivo.

PATHOGENESIS

In most cases *C. neoformans* is acquired by inhalation of fungal spores (<5-10 μm), which are engulfed by alveolar macrophages. Local inoculation leads to cutaneous or ophthalmic infection rarely. An additional portal of entry can be seen with organ transplantation of infected tissue. Direct entry through the gastrointestinal tract can also occur. After entry into the body, either latent infection or acute disease is produced. Cell-mediated immunity is the most important host defense for producing granulomatous inflammation and thus containing cryptococcal infection. Patients with compromised cell-mediated immunity have the highest risk for developing cryptococcal disease. In most immunocompetent persons, infection is limited to the lung. When the immune system fails to contain the infection, dissemination follows, with potential involvement of the brain, meninges, skin, eyes, prostate, and skeletal system.

In immunocompetent patients, *C. neoformans* can produce both a suppurative and granulomatous tissue reaction or a granulomatous reaction alone with varying degrees of necrosis. Healing is characterized by fibrosis usually without calcification. In immunocompromised patients tissue reactions may be minimal or absent, leading to the proliferation of yeast and the development of mucoid cystic lesions. Pulmonary cryptococcosis produces granulomas that are often subpleural in location and contain yeast forms. Cystic cryptococcomas occur in the CNS of 20% of non–HIV-infected patients with disseminated disease and may be found in the absence of overt meningitis. Granulomas and microabscesses containing yeast occur in patients with skin and bone infection.

CLINICAL MANIFESTATIONS

The manifestations of cryptococcal infection reflect the route of inoculation and the immunocompetence of the host. Sites of infection include lung, CNS, blood, skin, bone, and mucous membranes.

Pneumonia

Pneumonia is the most common form of cryptococcosis. Asymptomatic pulmonary infections occur often, especially among pigeon breeders, bird fanciers, and laboratory workers. Asymptomatic carriage can occur in persons with underlying chronic lung disease. Progressive pulmonary disease is symptomatic with fever, cough, pleuritic chest pain, and constitutional symptoms. In a 2006 review of 24 patients with pulmonary cryptococcosis, cough was the most common symptom. Pulmonary disease often precedes disseminated infection in immunocompromised persons. Chest radiographs can demonstrate a poorly localized bronchopneumonia, nodular changes, or lobar consolidations; cavities and pleural effusions are rare. Immunocompromised patients can have alveolar and interstitial infiltrates that can mimic *Pneumocystis* pneumonia. In adults with HIV infection, cryptococcal pneumonia is usually asymptomatic, although >90% of patients have concomitant CNS infection.

Disseminated Infection

Disseminated infection usually follows primary pulmonary disease, especially among immunocompromised persons. Advanced HIV infection is the most common predisposing factor for disseminated cryptococcosis. Other major predisposing conditions include lymphoproliferative disorders, corticosteroid therapy, primary immunodeficiencies affecting both T- and B-cell lineages, and immunosuppressive therapy for rheumatic disorders, celiac disease, and organ transplantation.

Meningitis

Subacute or chronic meningitis is the most common clinical manifestation of disseminated cryptococcal infection. The clinical presentation is variable and prognostic. Good outcomes are associated with headache as the initial symptom, normal mental status, absence of a predisposing condition, normal cerebrospinal fluid (CSF) opening pressure, normal CSF glucose, negative India ink stain, absence of extraneural infection by culture, and cryptococcal antigen titers in CSF and serum of <1 : 32. Overt symptoms of meningitis and HIV infection predict a poor outcome. HIV-infected patients typically present with unexplained fevers, headache, and malaise; cryptococcal antigen titers in these patients are often >1 : 1,024. Computed tomography of the brain identifies cryptococcomas in as many as 30% of patients with disseminated infection, even with no clinical signs of CNS involvement. The mortality rate for cryptococcal meningitis is 15-30%, and most deaths occur within several weeks of diagnosis. The fatality rates are higher among HIV-infected patients, who had relapse rates of >50% before the use of lifelong maintenance highly active antiretroviral therapy (HAART). In adults, relapse rates have decreased to <5% with daily fluconazole therapy. Relapse is unusual in adequately treated immunocompetent persons. Postinfectious sequelae are common and include hydrocephalus, decreased visual acuity, deafness, cranial nerve palsies, seizures, and ataxia.

Sepsis Syndrome

Sepsis syndrome is a rare manifestation of cryptococcosis and occurs almost exclusively among HIV-infected patients. Fever is followed by respiratory distress and multiorgan system disease that is often fatal.

Cutaneous Infection

Cutaneous disease most commonly follows disseminated cryptococcosis and rarely local inoculation. Early lesions are erythematous, may be single or multiple, and are variably indurated and tender. Lesions often become ulcerated with central necrosis and raised borders. Cutaneous cryptococcosis in immunocompromised patients can resemble molluscum contagiosum.

Skeletal Infection

Skeletal infection occurs in approximately 5% of patients with disseminated infection but rarely in HIV-infected patients. The onset of symptoms is insidious and chronic. Bone involvement is typified by soft tissue swelling and tenderness, and arthritis is characterized by effusion, erythema, and pain on motion. Skeletal disease is unifocal in approximately 75% of cases. The vertebrae are the most common sites of infection, followed by the tibia, ileum, rib, femur, and humerus. Concomitant bone and joint disease results from contiguous spread.

Ocular Infection

Chorioretinitis is rare, occurs primarily in adults, and is usually a manifestation of disseminated disease, although direct inoculation of the eye has been described. Eye infection is characterized by the acute loss of visual acuity, eye pain, visual floaters, and photophobia. Examination usually reveals choroiditis with or without retinitis. Retinal and vitreal masses and anterior uveitis are seen less commonly. Eye disease is often a manifestation of disseminated infection and is associated with a mortality rate of >20%. Only 15% of survivors recover full vision.

Lymph Nodes

Lymphonodular disease has been reported in 2 children, 1 of whom had an underlying immunodeficiency. Lymphonodular cryptococcosis is characterized by disseminated lymphadenopathy including thoracic and abdominal nodes, subcutaneous lesions, liver granulomas, and concomitant pulmonary disease.

DIAGNOSIS

Recovery of the fungus by culture or demonstration of the fungus in histologic sections of infected tissue is definitive. A latex agglutination test, which detects cryptococcal antigen in serum and CSF, is the most useful diagnostic test. Titers of >1 : 4 in bodily fluid strongly suggest infection, and titers of >1 : 1,024 reflect high burden of yeast, poor host immune response, and greater likelihood of therapeutic failure. India ink preparations of CSF are useful prognostically but are less sensitive than culture and antigen detection. Skin test antigens are poorly characterized, and the sensitivity and specificity of this test are unknown. Serum cryptococcal antibody tests have poor sensitivity and specificity and are generally not helpful in diagnosing cryptococcosis. Cryptococci can grow easily on standard fungal and bacterial culture media. Colonies can be seen within 48-72 hr when grown aerobically at standard temperatures. Polymerase chain reaction tests are in development.

TREATMENT

The choice of treatment depends on the sites of involvement and the host immune status. The immunocompetent patient with asymptomatic or mild disease limited to the lungs may be closely observed without therapy or, alternatively, treated with oral fluconazole (pediatric dose 6-12 mg/kg/day and adult dose 200-400 mg/day) or itraconazole (pediatric dose 5-10 mg/kg/day divided every 12 hr and adult dose 200-400 mg/day) for 3-12 mo, with the duration dependent on clinical response.

Patients with cryptococcemia or severe symptoms and non–HIV-immunocompromised hosts with lung disease with cryptococcal antigen titers of >1 : 8 or with CNS, urinary tract, or cutaneous disease should be treated in a staged approach, because these factors suggest disseminated disease. In general, these patients receive induction therapy with amphotericin B (0.7-1 mg/kg/day) plus flucytosine (100-150 mg/kg/day divided every 6 hr assuming normal kidney function) for a minimum of 2 wk, keeping serum flucytosine concentrations between 40 and 60 μg/mL. Depending on the clinical response, induction therapy may be continued as long as 6-10 wk.

Induction is followed by a consolidation phase with oral fluconazole or itraconazole for 6-12 mo. Itraconazole does not penetrate well into CSF, so consolidation therapy for CNS disease should be accomplished with fluconazole. Lifelong maintenance therapy may be required for children who remain immunocompromised. Lipid-complex amphotericin B (3-6 mg/kg/day) is recommended for patients intolerant of the deoxycholate amphotericin, although experience with this agent in children with cryptococcosis is limited. The current echinocandins do not have clinical activity against cryptococcal infections. Effectiveness of anticryptococcal therapy is monitored by serial cryptococcal antigen testing. Serum or CSF values of ≥1 : 8 predict relapse. Ventriculoperitoneal shunts may be required for patients with hydrocephalus, and aggressive medical management of increased intracranial pressure might also be required.

Because of the high rate of relapse, pulmonary, CNS, or disseminated cryptococcal infections in HIV-infected patients require induction, consolidation, and maintenance therapy. Patients with pulmonary disease most often require lifelong therapy with fluconazole or itraconazole. For those with CNS disease, the most commonly used regimen is amphotericin B (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) for a minimum of 2 wk and as long as 6-10 wk (induction), followed by fluconazole for a minimum of 8-10 wk (consolidation). Fluconazole should be continued for life (maintenance therapy) after the completion of consolidation therapy. Itraconazole should be used only in cases where the patient is intolerant or has failed fluconazole therapy due to the higher relapse rates with itraconazole. Cessation of maintenance therapy in children whose HIV infection is well controlled with HAART has not been well studied to date.

Cutaneous infections are usually treated medically, although surgical biopsy may be required for diagnosis. Skeletal infections generally require surgical debridement in addition to systemic antifungal therapy. Chorioretinitis also requires systemic antifungal therapy with amphotericin B and either fluconazole or flucytosine, both of which achieve high drug concentrations in the vitreous.

PREVENTION

Persons at high risk should avoid exposures such as bird droppings. Effective HAART for persons with HIV infection reduces the risk of cryptococcal disease. Fluconazole prophylaxis is effective for preventing cryptococcosis in patients with AIDS and $CD4^+$ lymphocyte counts <100/μL. A cryptococcal glucuronoxylomannan–tetanus toxoid conjugate vaccine has been developed that elicits protective antibodies in mice but awaits clinical trials in children. Passive immunization with protective monoclonal antibodies has yet to be studied in children.

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Chapter 236

Malassezia

Ashley M. Maranich and Martin E. Weisse

Members of the genus *Malassezia* include the causative agents of **tinea versicolor** (also pityriasis versicolor) (Fig. 236-1) and are associated with other dermatologic conditions and with fungemia in patients with indwelling catheters. *Malassezia* species are commensal lipophilic yeasts with a predilection for the sebum-rich areas of the skin. They are considered a part of the normal skin flora, with presence established by 3-6 mo of age.

The history of *Malassezia* nomenclature is complex and can be confusing. Because the yeast forms may be oval or round, these organisms were formally designated *Pityrosporum ovale* and *Pityrosporum*

Figure 236-1 A young adult with tinea versicolor. Notice the characteristic hypopigmented scaling macules. The asymmetric pattern seen in this patient is not characteristic of all patients with this infection. *(Photo courtesy of Navin S. Arora, DO.)*

orbiculare. Newer technologies have allowed an improved classification system, with 13 recognized species. Only *Malassezia pachydermatis*, a zoophilic yeast that causes dermatitis in dogs, is not lipophilic.

Transformation of the yeast form to a hyphal form facilitates invasive disease. The clusters of thick-walled blastospores together with the hyphae produce the characteristic **spaghetti-and-meatballs** appearance of *Malassezia* species.

Malassezia globosa, *Malassezia sympodialis*, *Malassezia restricta*, and *Malassezia furfur* are the major causes of tinea versicolor (see Chapter 666). *Malassezia* organisms are also increasingly associated with other dermatologic conditions. *M. sympodialis* and *M. globosa* are implicated in neonatal acne, and *M. globosa* and *M. restricta* are most closely associated with seborrheic dermatitis and dandruff. *Malassezia* are also causally associated with scalp psoriasis, *Pityrosporum* folliculitis, and head and neck atopic dermatitis. *Malassezia* may be isolated from sebum-rich areas of asymptomatic persons, emphasizing that demonstration of the fungus does not equate with infection.

The traditional primary **therapy for tinea versicolor** is topical selenium sulfide 2.5% applied daily for at least 10 min for a week, followed by weekly to monthly applications for several months to prevent relapse. Additional topical agents that have efficacy include terbinafine, clotrimazole, and topical azoles. *Malassezia*-associated skin diseases limited to the head and neck can be managed with either 1% ciclopirox, ketoconazole, or zinc pyrithione shampoos.

Oral therapy for tinea versicolor with fluconazole, itraconazole, or ketoconazole is easier to administer but is more expensive, has higher side effect risks, and may be less effective than topical therapy. Various dosing regimens have been used with success, including ketoconazole 200 mg daily for 10 days, fluconazole 300 mg weekly for 2-4 wk, and itraconazole 200 mg daily for 3-7 days or 100 mg daily for 2 wk. Single-dose therapy with 400 mg of ketoconazole has also been used but with lower success rates. Regardless of the regimen chosen, patients should be encouraged to exercise while taking these medications so as to increase the skin concentration of the drug through sweating.

Despite successful treatment, repigmentation might not occur for several months. Relapses are common and can require repeat or alternative therapies.

M. furfur is the species most commonly causing **fungemia**, and *M. pachydermatis* has been implicated in several outbreaks in neonatal intensive care units. The use of lipid emulsions containing medium-chain triglycerides inhibits the growth of *Malassezia* and can prevent infection. Infection is most common in premature infants, although immunocompromised patients, especially those with malignancies, can also be infected. Symptoms of catheter-associated fungemia are indistinguishable from other causes of catheter-associated infections (see Chapter 179) but should be suspected in patients, especially neonates, receiving intravenous lipid infusions. Compared with other causes of fungal sepsis, it is unusual for catheter-related *Malassezia* fungemia to be associated with secondary focal infection.

Malassezia species do not grow readily on standard fungal media, and successful culture requires overlaying the agar with olive oil. Recovery of *Malassezia* from blood culture is optimized by supplementing the medium with olive oil or palmitic acid.

Fungemia caused by *M. furfur* or other species can be successfully treated in most cases by immediately discontinuing the lipid infusion and removing the involved catheter. For persistent or invasive infections, amphotericin B (deoxycholate or lipid-complex formulations), fluconazole, and itraconazole are effective. Flucytosine has no activity against *Malassezia*.

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Chapter 237

Aspergillus

William J. Steinbach

The aspergilli are ubiquitous fungi whose normal ecologic niche is that of a soil saprophyte that recycles carbon and nitrogen. The genus *Aspergillus* contains approximately 185 species, but most human disease is caused by *Aspergillus fumigatus*, *A. flavus*, *A. niger*, *A. terreus,* and *A. nidulans*. Invasive disease is most commonly caused by *A. fumigatus*. *Aspergillus* reproduces asexually via production of spores (conidia). Most cases of *Aspergillus* disease **(aspergillosis)** are a result of inhalation of airborne conidia that subsequently germinate into fungal hyphae and invade host tissue. People are likely exposed to conidia on a daily basis. When inhaled by an immunocompetent person, conidia are rarely deleterious, presumably because they are efficiently cleared by phagocytic cells. Macrophage- and neutrophil-mediated host defenses are required for resistance to invasive disease.

Aspergillus is a relatively unusual pathogen in that it can create very different disease states depending on the host characteristics, including allergic (hypersensitivity), saprophytic (noninvasive), chronic, or invasive disease. Immunodeficient hosts are at risk for invasive disease, whereas immunocompetent hosts tend to develop allergic disease. Disease manifestations include primary allergic reactions; colonization of the lungs or sinuses; localized infection of the lung or skin; chronic infection; invasive pulmonary disease; or widely disseminated disease of the lungs, brain, skin, eye, bone, heart, and other organs. Clinically, these syndromes often manifest with mild, nonspecific, and late-onset symptoms, particularly in the immunosuppressed host, complicating accurate diagnosis and timely treatment. Immunocompromised patients, at risk for invasive disease, include those treated for malignancies with myelosuppressing chemotherapy but may also include those with primary immunodeficiency syndromes. Genetic disorders of immune regulation in the latter group of patients include those with chronic granulomatous disease, STAT3 deficiency (autosomal dominant hyperimmunoglobulin E syndrome), severe congenital neutropenia, monoMAC syndrome (monocytopenia, B and natural killer cell lymphopenia), and leukocyte adhesion deficiency type 1.

237.1 Allergic Disease (Hypersensitivity Syndromes)

William J. Steinbach

ASTHMA

Attacks of atopic asthma can be triggered by inhalation of *Aspergillus* conidia, producing allergic responses and subsequent bronchospasm.

Exposure to fungi, especially *Aspergillus*, needs to be considered as a trigger in a patient with an asthma flare, especially in those patients with severe asthma.

EXTRINSIC ALVEOLAR ALVEOLITIS

Extrinsic alveolar alveolitis is a hypersensitivity pneumonitis that occurs from repetitive inhalational exposure to inciting materials, including *Aspergillus* conidia. Symptoms typically occur shortly after exposure and include fever, cough, and dyspnea. Neither blood nor sputum eosinophilia is present. Chronic exposure to the triggering material can lead to pulmonary fibrosis.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease resulting from immunologic sensitization to *Aspergillus* antigens. It is primarily seen in patients with asthma or cystic fibrosis. Inhalation of conidia produces noninvasive colonization of the bronchial airways, resulting in persistent inflammation and development of hypersensitivity inflammatory responses. Disease manifestations are a result of abnormal immunologic responses to *A. fumigatus* antigens and include wheezing, pulmonary infiltrates, bronchiectasis, and even fibrosis.

There are 7 primary diagnostic criteria for ABPA: episodic bronchial obstruction, peripheral eosinophilia, immediate cutaneous reactivity to *Aspergillus* antigen, precipitating antibodies to *Aspergillus* antigen, elevated immunoglobulin (Ig) E, pulmonary infiltrates, and central bronchiectasis. Secondary diagnostic criteria include repeated detection of *Aspergillus* from sputum by identification of morphologically consistent fungal elements or direct culture, coughing brown plugs or specks, elevated *Aspergillus* antigen–specific IgE antibodies, and late skin reaction to *Aspergillus* antigen. Radiologically, bronchial wall thickening, pulmonary infiltrates, and central bronchiectasis can be seen.

Treatment depends on relieving inflammation via an extended course of systemic corticosteroids. Addition of oral antifungal agents, such as itraconazole or voriconazole, is used to decrease the fungal burden and diminish the inciting stimulus for inflammation. Because disease activity is correlated with serum IgE levels, these levels are used as 1 marker to define duration of therapy. An area of research interest is the utility of anti-IgE antibody therapy in the management of ABPA.

ALLERGIC *ASPERGILLUS* SINUSITIS

Allergic *Aspergillus* sinusitis is thought to be similar in etiology to ABPA. It has been primarily described in young adult patients with asthma and may or may not be seen in combination with ABPA. Patients often present with symptoms of chronic sinusitis or recurrent acute sinusitis, such as congestion, headaches, and rhinitis, and are found to have nasal polyps and opacification of multiple sinuses on imaging. Laboratory findings can include elevated IgE levels, precipitating antibodies to *Aspergillus* antigen, and immediate cutaneous reactivity to *Aspergillus* antigen. Sinus tissue specimens might contain eosinophils, Charcot-Leyden crystals, and fungal elements consistent with *Aspergillus* species. Surgical drainage is an important aspect of treatment, often accompanied by courses of either systemic or inhaled steroids. Use of an antifungal agent may also be considered.

Bibliography is available at Expert Consult.

237.2 Saprophytic (Noninvasive) Syndromes

William J. Steinbach

PULMONARY ASPERGILLOMA

Aspergillomas are masses of fungal hyphae, cellular debris, and inflammatory cells that proliferate without vascular invasion, generally in the setting of preexisting cavitary lesions or ectatic bronchi. These cavitary lesions can occur as a result of infections such as tuberculosis, histoplasmosis, or resolved abscesses, or secondary to congenital or acquired defects such as pulmonary cysts or bullous emphysema. Patients may be asymptomatic, with diagnosis made through imaging for other reasons, or they might present with hemoptysis, cough, or fever. On imaging, there may be thickening of the walls of a cavity initially, or later, a solid round mass separated from the cavity wall, as the fungal ball develops. Detection of *Aspergillus* antibody in the serum suggests this diagnosis. Treatment is indicated for control of complications, such as hemoptysis. Surgical resection is the definitive treatment but has been associated with significant risks. Systemic antifungal treatment with azole-class agents may be indicated in certain patients.

CHRONIC PULMONARY ASPERGILLOSIS

Chronic aspergillosis can occur in patients with normal immune systems or mild degrees of immunosuppression, including intermittent corticosteroids. Three categories have been proposed to describe different manifestations of chronic aspergillosis. The first is chronic cavitary pulmonary aspergillosis, which is similar to aspergilloma, except that multiple cavities form and expand with occupying fungal balls. The second is chronic fibrosing pulmonary aspergillosis, where the multiple individual lesions progress to significant pulmonary fibrosis. The third is chronic necrotizing pulmonary aspergillosis, also known as *subacute invasive* or *semiinvasive pulmonary aspergillosis*, a slowly progressive subset found in patients with mild to moderate immune impairment.

Management of chronic cavitary pulmonary aspergillosis can sometimes be via surgical resection, although long-term antifungal therapy is indicated. Management of chronic necrotizing pulmonary aspergillosis is similar to that of invasive pulmonary aspergillosis; however, the disease is more indolent, and thus there is a greater emphasis on oral therapy. Direct instillation of antifungals into the lesion cavity has been employed with some success.

SINUSITIS

Sinus aspergillosis typically manifests with chronic sinus symptoms that are refractory to antibacterial treatment. Imaging can demonstrate mucosal thickening in the case of *Aspergillus* sinusitis or a single mass within the maxillary or ethmoid sinus in the case of sinus aspergilloma. If untreated, sinusitis can progress and extend into the ethmoid sinuses and orbits. Therapy of sinusitis depends on surgical debridement and drainage, including surgical removal of the fungal mass in cases of sinus aspergilloma.

OTOMYCOSIS

Aspergillus can colonize the external auditory canal, with possible extension to the middle ear and mastoid air spaces if the tympanic membrane is disrupted by concurrent bacterial infection. Symptoms include pain, itching, decreased unilateral hearing, or otorrhea. Otomycosis is more often seen in patients with impaired mucosal immunity, such as patients with hypogammaglobulinemia, diabetes mellitus, chronic eczema, or HIV and those using chronic steroids. Treatments have not been well studied, but topical treatment with acetic or boric acid instillations or azole creams as well as oral azoles, such as voriconazole, itraconazole, and posaconazole, have been described.

Bibliography is available at Expert Consult.

237.3 Invasive Disease

William J. Steinbach

Invasive aspergillosis (IA) occurs after conidia enter the body, escape immunologic control mechanisms, and germinate into fungal hyphae that subsequently invade tissue parenchyma and vasculature. The invasion of the vasculature can result in thrombosis and localized necrosis and facilitates hematogenous dissemination. The incidence of IA increased over the last 2 decades, likely as a result of more use of

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severely immunosuppressive therapies for a widening array of underlying diseases and better management of other infections found in the at-risk populations. The most common site of primary infection is the lung, but primary infection is also seen in the sinuses and skin, and rarely elsewhere. Secondary infection can be seen after hematogenous spread, often to the skin, central nervous system (CNS), eye, bone, and heart.

IA is primarily a disease of immunocompromised hosts, and common risk factors include cancer or chemotherapy-induced neutropenia, particularly if severe and/or prolonged; hematopoietic stem cell transplantation, especially during the initial preengraftment phase or if complicated by graft-versus-host disease; neutrophil or macrophage dysfunction such as occurs in severe combined immunodeficiency or chronic granulomatous disease (CGD); prolonged high-dose steroid use; solid organ transplantation; and, rarely, HIV. Studies in the pediatric age group have identified similar risk factors for IA, but a well-defined incidence of IA among pediatric patients has not been determined to date.

INVASIVE PULMONARY ASPERGILLOSIS

Invasive pulmonary aspergillosis is the most common form of aspergillosis. It plays a significant role in morbidity and mortality in the patient populations mentioned at increased risk for IA. Presenting symptoms can include fever despite initiation of empirical broad-spectrum antibacterial therapy, cough, chest pain, hemoptysis, and pulmonary infiltrates. Patients on high-dose steroids are less likely to present with fever. Symptoms in these immunocompromised patients can be very vague, and thus maintaining a high index of suspicion when confronted with a high-risk patient is essential.

Diagnosis

Imaging can be helpful, although no finding is pathognomonic for invasive pulmonary aspergillosis. Characteristically, multiple, ill-defined nodules can be seen, though lobar or diffuse consolidation is not uncommon and normal chest radiographs do not rule out disease. Classic radiologic signs on CT during neutropenia include the **halo sign,** when angioinvasion produces a hemorrhagic nodule surrounded by ischemia. Early on there is a rim of ground-glass opacification surrounding a nodule. Over time, these lesions evolve into cavitary lesions or lesions with an **air crescent** when the lung necroses around the fungal mass, often seen during recovery from neutropenia. Unfortunately, these findings are not specific to invasive pulmonary aspergillosis and can also be seen in other pulmonary fungal infections, as well as pulmonary hemorrhage and organizing pneumonia. In addition, several reviews of imaging results of pediatric aspergillosis cases suggest that cavitation and air crescent formation are less common among these patients than among adult patients. Computed tomographic pulmonary angiography demonstrates interruption or invasion of arterial vessels and may enhance the diagnosis of invasive pulmonary aspergillosis (Fig. 237-1). On MRI, the typical finding for

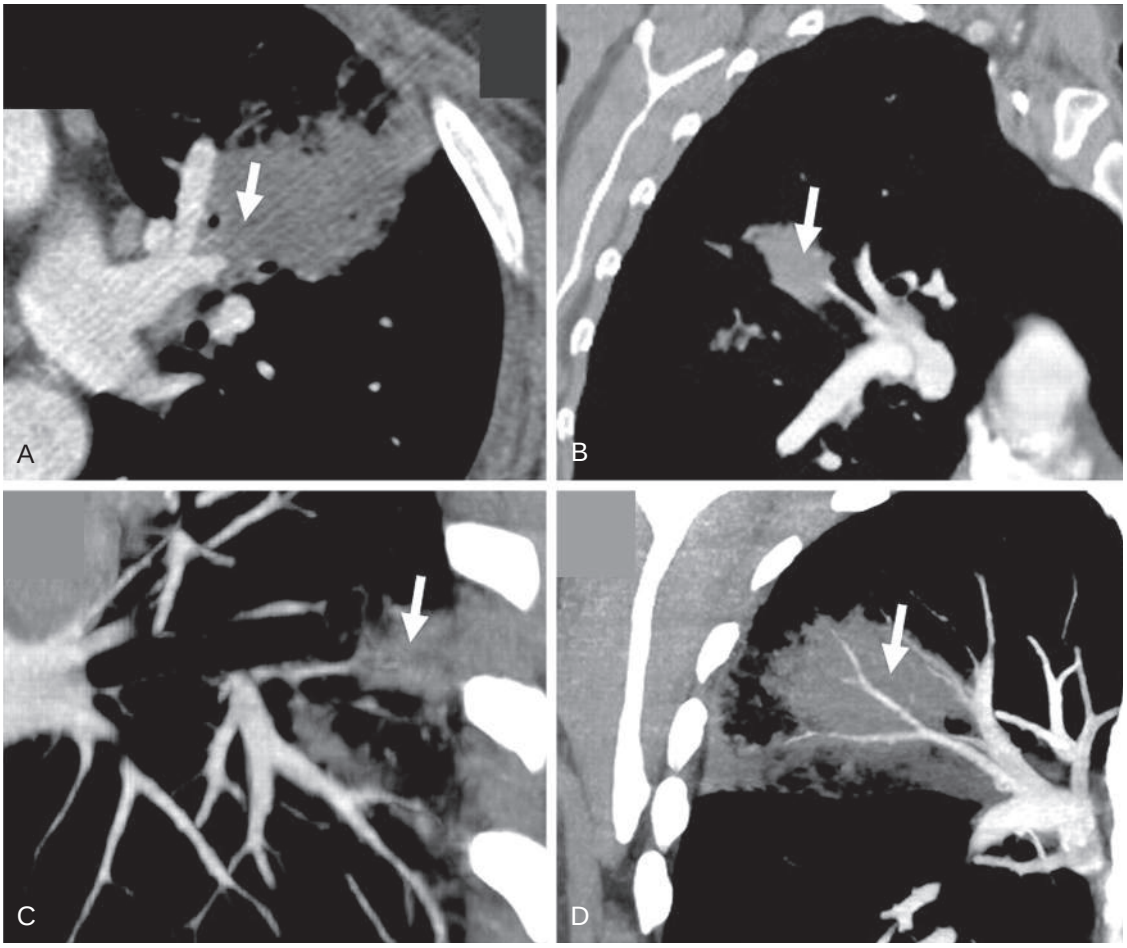

Figure 237-1 **A** and **B,** Representative high-resolution computed tomographic findings for patients with positive CT pulmonary angiographic (CTPA) findings and proven invasive mold disease. **C,** False-positive CTPA findings for a patient with *Staphylococcus aureus* pneumonia with septic emboli. **D,** Negative CTPA findings for a patient with bacterial pneumonia. *Arrows* indicate areas of vessel interruption **(A-C)** or lack of vessel interruption **(D).** *(From Stanzani M, Battista G, Sassi C, et al: Computed tomographic pulmonary angiography for diagnosis of invasive mold diseases in patients with hematological malignancies.* Clin Infect Dis *54:610–616, 2012, Fig.1.)*

pulmonary disease is the **target sign,** in which a nodule has a central signal that is lower than that of the rim-enhancing periphery.

Diagnosis of IA can be complicated for a number of reasons. Conclusive diagnosis requires culture of *Aspergillus* from a normally sterile site and histologic identification of tissue invasion by fungal hyphae consistent with *Aspergillus* morphology. However, obtaining tissue specimens is often impractical in critically ill, often thrombocytopenic, patients. In addition, depending on the specimen type, a positive result from culture can represent colonization rather than infection; however, this should be interpreted conservatively in high-risk patients. Isolation of *Aspergillus* from blood cultures is uncommon, likely because fungemia is low-level and intermittent.

Serology can be useful in the diagnosis of allergic *Aspergillus* syndromes as well as aspergilloma but is of low yield for invasive disease, likely because of deficient immune responses in the high-risk immunocompromised population. Bronchoalveolar lavage can be useful, but negative culture results cannot be used to rule out disease, owing to inadequate sensitivity. Addition of molecular biologic assays such as antigen detection and polymerase chain reaction can improve the diagnostic yield of bronchoalveolar lavage for aspergillosis. An enzyme-linked immunosorbent assay–based assay for galactomannan, one of the components of the *Aspergillus* cell wall, is useful for the diagnosis of IA in serum, bronchoalveolar lavage fluid, and cerebrospinal fluid. This molecular test is best used in serial monitoring for development of infection and is the most sensitive in detecting disease in cancer patients or hematopoietic stem cell transplant recipients, with less utility in solid organ transplant recipients. Earlier reports of increased false-positive reactions in children vs adults have been refuted, and the galactomannan assay is effective in diagnosing IA in children. This test does possess high rates of false negativity in patients with congenital immunodeficiency (e.g., CGD) and invasive *Aspergillus* infections. Another molecular assay, the β-glucan assay, is a fungal-nonspecific assay that detects the major component of the fungal cell wall and has been used to diagnose IA. Unlike the galactomannan assay, which is specific for *Aspergillus*, despite some cross reactivity with other fungi, the β-glucan assay will not discriminate which fungal infection is infecting the patient. Polymerase chain reaction–based assays are in development for the diagnosis of aspergillosis but are still being optimized and are not yet commercially available.

Treatment

Successful treatment of IA hinges on the ability to reconstitute normal immune function and use of effective antifungal agents until immune recovery can be achieved. Therefore, lowering overall immunosuppression, specifically via cessation of corticosteroid use, is vital to improve the ultimate outcome. In 2008, new treatment guidelines for *Aspergillus* infections were published by the Infectious Diseases Society of America, marking a major shift in management recommendations. In the past, first-line therapy was amphotericin B, notable for low response rates and significant infusion reactions and drug toxicity. Liposomal formulations of amphotericin B exist, which are associated with decreased toxicity and may still have a role as first-line therapy for invasive infection in certain patients.

Primary therapy is now the azole-class antifungal voriconazole, based on multiple studies showing both improved response rates and survival in patients receiving voriconazole when compared to amphotericin B. In addition, voriconazole is better tolerated than amphotericin B and can be given orally as well as intravenously. Azoles are metabolized through the cytochrome P450 system, and thus medication interactions can be a significant complication, specifically some contraindications with chemotherapeutic agents. Other triazole antifungals are also available, including posaconazole, which is approved for antifungal prophylaxis and may be an alternative agent for first-line treatment of IA. Although the dosing of itraconazole and voriconazole are established for pediatric patients, the pharmacokinetic studies for posaconazole are not yet complete. Importantly, the dose of voriconazole used in children is higher than that used in adults (see Chapter 233).

The echinocandin class of antifungals may also a play a role in treatment of IA, but to date, these agents are generally employed as second-line medications, particularly for salvage therapy. Combination antifungal therapy has revealed disparate results in anecdotal studies, and currently there are no firm recommendations for combination antifungal therapy. However, it is possible that combination therapy may be beneficial to certain specific patient groups. Unfortunately, even with newer antifungals, complete or partial response rates for treatment of IA are only approximately 50%. To augment antifungal therapies, patients have been treated with growth factors to increase neutrophil counts, granulocyte transfusions, interferon-γ, and surgery.

Special Populations

Patients with CGD represent a pediatric population at particular risk for pulmonary aspergillosis. Invasive pulmonary aspergillosis can be the first serious infection identified in these patients, and the lifetime risk of development is estimated to be 33%. Unlike classical IA in cancer patients, the onset of symptoms is often gradual, with slow development of fever, fatigue, pneumonia, and elevated sedimentation rate. The neutrophils of patients with CGD surround the collections of fungal elements but cannot kill them, thereby permitting local invasion with extension of disease to the pleura, ribs, and vertebrae, although angioinvasion is not seen. Imaging in these patients is much less likely to reveal the halo sign, infarcts, or cavitary lesions and instead generally shows areas of tissue destruction due to the ongoing inflammatory processes.

CUTANEOUS ASPERGILLOSIS

Cutaneous aspergillosis can occur as a primary disease or as a consequence of hematogenous dissemination or spread from underlying structures. Primary cutaneous disease classically occurs at sites of skin disruption, such as intravenous access device locations, adhesive dressings, or sites of injury or surgery. Premature infants are particularly at risk, given their immature skin and need for multiple access devices. Cutaneous disease in transplant recipients tends to reflect hematogenous distribution from a primary site of infection, often the lungs. Lesions are erythematous indurated papules that progress to painful, ulcerated, necrotic lesions. Treatment depends on the combination of surgical debridement and antifungal therapy, with systemic voriconazole recommended as primary therapy.

INVASIVE SINONASAL DISEASE

Invasive *Aspergillus* sinusitis represents a difficult diagnosis because the clinical presentation tends to be highly variable. Patients can present with congestion, rhinorrhea, epistaxis, headache, facial pain or swelling, orbital swelling, fever, or abnormal appearance of the nasal turbinates. Because noninvasive imaging can be normal, diagnosis rests on direct visualization via endoscopy and biopsy. Sinus mucosa may be pale, discolored, granulating, or necrotic depending on the stage and extent of disease. The infection can invade adjacent structures, including the eye and brain. This syndrome is difficult to distinguish clinically from other types of invasive fungal disease of the sinuses such as mucormycosis, rendering obtaining specimens for culture and histology extremely important. *If the diagnosis is confirmed, treatment should be with voriconazole, similar to invasive pulmonary disease. Because voriconazole is not active against mucormycosis, amphotericin B formulations should be considered in invasive fungal sinusitis pending definitive identification.*

CENTRAL NERVOUS SYSTEM

The primary site of *Aspergillus* infection tends to be the lungs, but as the hyphae invade the vasculature, fungal elements can dislodge and travel through the bloodstream, permitting establishment of secondary infection sites. One site commonly involved in disseminated disease is the CNS. Cerebral aspergillosis can also arise secondary to local extension of sinus disease. The presentation of cerebral aspergillosis is highly variable but can include changes in mental status, seizures, paralysis,

coma, and ophthalmoplegia. As the hyphae invade the CNS vasculature, hemorrhagic infarcts develop that convert to abscesses. Biopsy is required for definitive diagnosis, but patients are often too ill to tolerate surgery. Imaging can be helpful for diagnosis, and MRI is preferred. Lesions tend to be multiple, located in the basal ganglia, have intermediate intensity with no enhancement, and have no mass effect. CT shows hypodense, well-demarcated lesions, sometimes with ring enhancement and edema. Diagnosis often depends on characteristic imaging findings in a patient with known aspergillosis at other sites. Galactomannan assay testing of cerebrospinal fluid has been studied and may become a future methodology to confirm the diagnosis. In general, the prognosis for CNS aspergillosis is extremely poor, likely owing to the late onset at presentation. Reversal of immunosuppression is extremely important. Surgical resection of lesions may be useful. *Voriconazole, usually at high doses, is the best therapy, and itraconazole, posaconazole, and liposomal formulations of amphotericin B are alternative options.*

EYE

Fungal endophthalmitis and keratitis may be seen in patients with disseminated *Aspergillus* infection. Pain, photophobia, and decreased visual acuity may be present, though many patients are asymptomatic. Emergent ophthalmologic evaluation is important when these entities are suspected. Endophthalmitis is treated with intravitreal injection of either amphotericin B or voriconazole along with surgical intervention and systemic antifungal therapy with voriconazole. Keratitis requires topical and systemic antifungal therapy.

BONE

Aspergillus osteomyelitis can occur, most commonly in the vertebrae. Rib involvement occurs owing to extension of disease in patients with CGD and is most often caused by *A. nidulans*. Treatment depends on the combination of surgical débridement and systemic antifungals. Arthritis can develop owing to hematogenous dissemination or local extension, and treatment depends on joint drainage combined with antifungal therapy. Amphotericin B has been the most commonly employed agent in the past, although voriconazole is the preferred first-line therapy now.

HEART

Cardiac infection can occur as a result of surgical contamination, secondary to disseminated infection, or as a result of direct extension from a contiguous focus of infection and includes endocarditis, myocarditis, and pericarditis. Treatment requires surgical intervention in the case of endocarditis and pericarditis, along with systemic antifungals, sometimes lifelong because of the possibility of recurrent infection.

EMPIRICAL ANTIFUNGAL THERAPY

Because the diagnosis of invasive *Aspergillus* infections is often complicated and delayed, empirical initiation of antifungal therapy is often considered in high-risk patients. At present, antifungal coverage with amphotericin B (conventional or liposomal), voriconazole, itraconazole, or the echinocandin caspofungin or micafungin should be considered in patients at risk for prolonged neutropenia or with findings suggesting invasive fungal infections. At this time, our ability to diagnose and treat infections caused by *Aspergillus* remains suboptimal. Additional study of antigen detection assays based on galactomannan and other *Aspergillus* cell wall components, as well as standardization of polymerase chain reaction–based assays, will facilitate diagnosis. The optimal treatment remains another challenging question, because current therapeutic regimens tend to produce complete or partial response only approximately half of the time. Novel antifungals currently under development offer a future with hopefully improved survival, but immune reconstitution remains of paramount importance.

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Chapter 238

Histoplasmosis (*Histoplasma capsulatum*)

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Histoplasmosis is caused by *Histoplasma capsulatum,* a dimorphic fungus found in the environment as a saprophyte in the mycelial (mold) form and in tissues in the parasitic form as yeast.

EPIDEMIOLOGY

The saprophytic form is found in soil throughout the midwestern United States, primarily along the Ohio and Mississippi rivers. Sporadic cases of human and animal histoplasmosis have been reported from 31 of the 48 contiguous states. In parts of Kentucky and Tennessee, almost 90% of the population older than 20 yr of age have positive skin test results for histoplasmin. *Histoplasma* is endemic to parts of the Caribbean islands, Central and South America, certain areas of Southeast Asia, and the Mediterranean. *H. capsulatum* thrives in soil rich in nitrates such as areas that are heavily contaminated with bird or bat droppings or decayed wood. Fungal spores are often carried on the wings of birds. Focal outbreaks of histoplasmosis have been reported after aerosolization of microconidia resulting from construction in areas previously occupied by starling roosts or chicken coops or by chopping decayed wood or burning bamboo exposed to a blackbird roost. Unlike birds, bats are actively infected with *Histoplasma*. Focal outbreaks of histoplasmosis have also been reported after intense exposure to bat guano in caves and along bridges frequented by bats. Person-to-person transmission does not occur.

PATHOGENESIS

Inhalation of microconidia (fungal spores) is the initial stage of human infection. The conidia reach the alveoli, germinate, and proliferate as yeast. Alternatively, spores can remain as mold with the potential for activation. Most infections are asymptomatic or self-limited. When disseminated disease occurs, any organ system can be involved. The initial infection is a bronchopneumonia. As the initial pulmonary lesion ages, giant cells form, followed by formation of caseating or noncaseating granulomas and central necrosis. Granulomas contain viable yeast, and disease can relapse. At the time of spore germination, yeast cells are phagocytosed by alveolar macrophages, where they replicate and gain access to the reticuloendothelial system via the pulmonary lymphatic system and hilar lymph nodes. Dissemination with splenic involvement typically follows the primary pulmonary infection. In normal hosts, specific cell-mediated immunity follows in approximately 2 wk, enabling sensitized T cells to activate macrophages and kill the organism. The initial pulmonary lesion resolves within 2-4 mo but may undergo calcification resembling the Ghon complex of tuberculosis. Alternatively, "buckshot" calcifications involving the lung and spleen may be seen. Unlike tuberculosis, reinfection with *H. capsulatum* occurs and can lead to exaggerated host responses in some cases.

Children with certain primary congenital immune defects are at increased risk of histoplasmosis; these include interferon-γR1 deficiency, interleukin-12Rβ1 deficiency, *STAT1* gain-of-function mutations, idiopathic CD4 lymphopenia, DOCK8 deficiency, X-linked CD4OL deficiency, and monoMAC syndrome (monocytopenia, B-cell and natural killer cell lymphoma).

CLINICAL MANIFESTATIONS

There are 3 forms of human histoplasmosis: acute pulmonary infection, chronic pulmonary histoplasmosis, and progressive disseminated histoplasmosis.

Acute pulmonary histoplasmosis follows initial or recurrent respiratory exposure to microconidia. The majority of patients are asymptomatic. Symptomatic disease occurs more often in young children; in older patients, symptoms follow exposure to large inocula in closed spaces (e.g., chicken coops or caves) or prolonged exposure (e.g., camping on contaminated soil, chopping decayed wood). The median incubation time is 14 days. The prodrome is not specific and usually consists of flu-like symptoms including headache, fever, chest pain, cough, and myalgias. Hepatosplenomegaly occurs more often in infants and young children. Symptomatic infections may be associated with significant respiratory distress and hypoxia and can require intubation, ventilation, and steroid therapy. Acute pulmonary disease can also manifest with a prolonged illness (10 days to 3 wk) consisting of weight loss, dyspnea, high fever, asthenia, and fatigue. In 10% of patients, infection is a sarcoid-like disease with arthritis or arthralgia, erythema nodosum, keratoconjunctivitis, iridocyclitis, and pericarditis. Pericarditis, with effusions both pericardial and pleural, is a self-limited benign condition that develops as a result of an inflammatory reaction to adjacent mediastinal disease. The effusions are exudative, and the organism is rarely culturable from fluid. Most children with acute pulmonary disease have normal chest radiographs. Patients with symptomatic disease typically have a patchy bronchopneumonia; hilar lymphadenopathy is variably present (Fig. 238-1). In young children, the pneumonia can coalesce. Focal or buckshot calcifications are convalescent findings in patients with acute pulmonary infection.

Exaggerated host responses to fungal antigens within the lung parenchyma or hilar lymph nodes produce thoracic complications of acute pulmonary histoplasmosis. Histoplasmomas are of parenchymal origin and are usually asymptomatic. These fibroma-like lesions are often concentrically calcified and single. Rarely, these lesions produce broncholithiasis associated with "stone spitting," wheezing, and hemoptysis. In endemic regions, these lesions can mimic parenchymal tumors and are occasionally diagnosed at lung biopsy. Mediastinal granulomas form when reactive hilar lymph nodes coalesce and mat together. Although these lesions are usually asymptomatic, huge granulomas can compress the mediastinal structures, producing symptoms of esophageal, bronchial, or vena caval obstruction. Local extension and necrosis can produce pericarditis or pleural effusions. Mediastinal fibrosis is a rare complication of mediastinal granulomas and represents an uncontrolled fibrotic reaction arising from the hilar nodes. Structures within the mediastinum become encased within a fibrotic mass, producing obstructive symptomatology. Superior vena cava syndrome, pulmonary venous obstruction with a mitral stenosis–like syndrome, and pulmonary artery obstruction with congestive heart failure have been described. Dysphagia accompanies esophageal entrapment, and a syndrome of cough, wheeze, hemoptysis, and dyspnea accompanies bronchial obstruction.

Figure 238-1 Radiograph of an 8 yr old child with acute pulmonary histoplasmosis showing hilar enlargement with bilateral infiltrates. *(From Fischer GB, Mocelin H, Severo CB, et al: Histoplasmosis in children.* Paediatr Respir Rev *10:172–177, 2009, Fig. 1.)*

Chronic pulmonary histoplasmosis is an opportunistic infection in adult patients with centrilobular emphysema. This entity is rare in children.

Progressive disseminated histoplasmosis accounts for 10% of histoplasmosis cases and affects infants and immunocompromised patients. Disseminated disease of childhood occurs almost exclusively in children younger than 2 yr of age because of a relatively immature cellular immune system and follows primary pulmonary infection. The mortality of progressive disseminated histoplasmosis without therapy is 100%. Fever is the most common finding and can persist for weeks to months before the condition is diagnosed. The majority of patients have hepatosplenomegaly, lymphadenopathy, anemia, and thrombocytopenia. Pneumonia and pancytopenia are variably present. Some patients develop mucous membrane ulcerations and skin findings such as nodules, ulcers, or molluscum-like papules. Half of the infected infants have transient T-cell deficiencies, and many experience transient hyperglobulinemia. Elevated acute-phase reactants and hypercalcemia are typically seen but are not specific for disseminated histoplasmosis. Although chest radiographs are normal in more than half of these children, the yeast can often be identified on bone marrow examination.

Children who are immunosuppressed (cancer patients, organ transplant recipients, patients with HIV infection) are at increased risk for disseminated histoplasmosis. In children who are not infected with HIV, disseminated disease manifests with unexplained fevers, weight loss, lymphadenopathy, and interstitial pulmonary disease. Extrapulmonary infection is a characteristic of disseminated disease and can include destructive bony lesions, oropharyngeal ulcers, Addison disease, meningitis, multifocal chorioretinitis, cutaneous infection, and endocarditis. Elevated liver function test results and high serum concentrations of angiotensin-converting enzyme may be observed.

Disseminated histoplasmosis in an HIV-infected patient is an AIDS-defining illness. Disseminated disease is often preceded or followed by another opportunistic infection in this patient population. HIV-infected patients at greatest risk for acquiring disseminated histoplasmosis are those with a history of exposure to avian excreta or bat guano, no prior history of antiretroviral therapy, or no history of previous antifungal prophylaxis. Fever and weight loss occur in most patients. In the majority of patients, pulmonary disease develops; hepatosplenomegaly, lymphadenopathy, skin rashes, and meningoencephalitis are variably present. A sepsis-like syndrome has been identified in a small number of HIV-infected patients with disseminated histoplasmosis and is characterized by the rapid onset of shock, multiorgan failure, and coagulopathy. Reactive hemophagocytic syndrome has been described in immunocompromised patients with severe disseminated histoplasmosis. Transplacental transmission of *H. capsulatum* has been reported in immunocompromised mothers.

DIAGNOSIS

Histoplasma typically grows within 6 wk on Sabouraud agar at 25°C (77°F). Identification of tuberculate macroconidia allows for only a presumptive diagnosis, because *Sepedonium* species form similar structures. A confirmatory test using a chemiluminescent DNA probe for *H. capsulatum* is necessary to establish a definitive identification. Recovery of *H. capsulatum* by culture differs with the form of infection. In normal hosts with symptomatic or asymptomatic acute pulmonary histoplasmosis, sputum cultures are rarely obtained and are variably positive; cultures of bronchoalveolar lavage fluid appear to have a slightly higher yield than sputum cultures. Sputum cultures are positive in 60% of adults with chronic pulmonary histoplasmosis. The yeast can be recovered from blood or bone marrow in >90% of patients with progressive disseminated histoplasmosis. Blood cultures are sterile in patients with acute pulmonary histoplasmosis, and cultures from any source are typically sterile in patients with the sarcoid form of the

disease. Yeast forms may be demonstrated histologically in tissue from patients with complicated forms of acute pulmonary disease (histoplasmoma, mediastinal granuloma, and mediastinal fibrosis). Tissue should be stained with methenamine silver or periodic acid–Schiff stains, and yeast can be found within or outside of macrophages. Wright stain of peripheral blood can demonstrate fungal elements within leukocytes. Real-time polymerase chain reaction has been used on formalin-fixed, paraffin-embedded biopsy tissue and has an analytical sensitivity of at least 6 pg/μL from tissue-extracted DNA and a clinical sensitivity and specificity of 88.9% and 100%, respectively. Although not widely available, molecular methods may ultimately provide a more timely and accurate diagnosis.

Detection of fungal polysaccharide antigen by radioimmunoassay is the most widely available diagnostic study for patients with suspected progressive disseminated histoplasmosis. In HIV-infected patients as well as others at risk for disseminated disease, histoplasma-associated antigen can be demonstrated in the urine, blood, or bronchoalveolar lavage fluid in more than 90% of cases. Antigenuria has been shown to correlate with severity of disseminated histoplasmosis. The likelihood of hospitalization was 2.75 and need for intensive care was 3.11 if the antigen was ≥19 ng/mL. Additionally, antigenuria was present in 83% of patients with acute disease and 30% of patients with subacute pulmonary disease. False-positive results on urinary antigen testing can occur in patients with *Blastomyces dermatitidis, Coccidioides immitis* and *Coccidioides posadasii, Paracoccidioides brasiliensis,* and *Penicillium marneffei*. False-positive results on serum antigen testing can occur in the presence of rheumatoid factor and following treatment with rabbit antithymocyte globulin. Antigen detection by enzyme immunoassay has comparable sensitivity and improved specificity but limited availability; however, both the radioimmunoassay and the enzyme immunoassay are more sensitive when urine is tested rather than serum. Serum, urine, and bronchoalveolar lavage fluid from patients with acute or chronic pulmonary infections are variably antigen positive. Sequential measurement of antigen in patients with disseminated disease is useful for monitoring response to therapy.

Seroconversion continues to be useful for the diagnosis of acute pulmonary histoplasmosis, its complications, and chronic pulmonary disease. Serum antibody to yeast and mycelium-associated antigens is classically measured by complement fixation. Although titers of >1:8 are found in more than 80% of patients with histoplasmosis, titers of ≥1:32 are most significant for the diagnosis of recent infection. Complement-fixation antibody titers are often not significant early in the infection and do not become positive until 4-6 wk after exposure. A 4-fold increase in either yeast or mycelial-phase titers or a single titer of ≥1:32 is presumptive evidence of active infection. Complement-fixation titers may be falsely positive in patients with other systemic mycoses such as *B. dermatitidis* and *C. immitis* and may be falsely negative in immunocompromised patients. Antibody detection by immunodiffusion is less sensitive but more specific than complement fixation and is used to confirm questionably positive complement-fixation titers. The highest sensitivity for antibody testing can be achieved by combining complement fixation and immunodiffusion testing. Skin testing is useful only for epidemiologic studies because cutaneous reactivity is lifelong, and intradermal injection can elicit an immune response in otherwise seronegative persons.

TREATMENT

Antifungal therapy is not warranted for persons with asymptomatic or mildly symptomatic acute pulmonary histoplasmosis. Oral itraconazole or fluconazole should be considered in patients with acute pulmonary infections who fail to improve clinically within 1 mo. Itraconazole is superior to fluconazole in treatment of histoplasmosis in adults. Patients with primary or reexposure pulmonary histoplasmosis who become hypoxemic or require ventilatory support should receive amphotericin B (0.7-1.0 mg/kg/day) or amphotericin B lipid complex (3-5 mg/kg/day) until improved; continued therapy with oral itraconazole (5-10 mg/kg/day in 2 divided doses, not to exceed 400 mg daily) for a minimum of 12 wk is also recommended. The lipid preparations of amphotericin are not preferred. Patients with severe obstructive symptoms caused by granulomatous mediastinal disease may be treated sequentially with amphotericin B followed by itraconazole for 6-12 mo. Patients with milder mediastinal disease may be treated with oral itraconazole alone. Some experts recommend that surgery be reserved for patients who fail to improve after 1 mo of intensive amphotericin B therapy. Sarcoid-like disease with or without pericarditis may be treated with nonsteroidal antiinflammatory agents for 2-12 wk.

Amphotericin B continues to be the cornerstone of therapy for infants with progressive disseminated histoplasmosis. In one study, sequential therapy with amphotericin B and oral ketoconazole for 3 mo was curative in 88% of patients. Alternatively, amphotericin B (1 mg/kg/day) or its lipid complex may be given acutely for 4-6 wk or amphotericin B (1 mg/kg/day) may be given for 2-4 wk followed by oral itraconazole (5-10 mg/kg/day in 2 divided doses) as maintenance therapy for 3 mo, depending on *Histoplasma* antigen status. Longer therapy may be needed in patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. It is recommended to monitor blood levels of itraconazole during treatment, aiming for a concentration of ≥1 μg/mL but <10 μg/mL to avoid potential drug toxicity. It is also recommended to monitor urine antigen levels during therapy and for 12 mo after therapy has ended to ensure cure. In general, amphotericin B lipid complex may be substituted in severely ill children who are intolerant of the classic drug preparation. The newer azoles (voriconazole and posaconazole) have not been well studied in the treatment of histoplasmosis and are currently not recommended.

Relapses in HIV-infected patients with progressive disseminated histoplasmosis are common. Currently, induction therapy with amphotericin B or lipid complex amphotericin B is recommended. Lifelong suppressive therapy with daily itraconazole (5 mg/kg/day up to adult dose of 200 mg/day) is also required. For severely immunocompromised HIV-infected children living in endemic regions, itraconazole (2-5 mg/kg every 12-24 hr) may be used prophylactically. Care must be taken to avoid interactions between antifungal azoles and protease inhibitors.

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Chapter 239

Blastomycosis (*Blastomyces dermatitidis*)

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ETIOLOGY

Blastomyces dermatitidis belongs to a group of fungi that exhibit thermal dimorphism. In the soil (22-25°C [71.6-77°F]), these fungi grow as mold and produce spores, which are the infectious particles. Following soil disruption, aerosolized mycelial fragments and spores inhaled into the lungs (37°C [98.6°F]) convert into pathogenic yeast and cause infection.

EPIDEMIOLOGY

B. dermatitidis causes disease in immunocompetent and immunocompromised children. Only 2-13% of blastomycosis cases occur in the pediatric population (average age: 9.1-11.5 yr; range: 19 days to 18 yr). Blastomycosis of newborns and infants is rare. In North America, the geographic distribution of blastomycosis cases is restricted to the Midwest, South-Central, and Southeastern United States and parts of

Canada bordering the Great Lakes and Saint Lawrence River Valley. In these geographic regions, several areas are hyperendemic for blastomycosis (e.g., Marathon and Vilas Counties, Wisconsin; Washington Parish, Louisiana; central and south-central Mississippi; Kenora, Ontario). Outside of North America, autochthonous infections have been reported from Africa (~100 cases) and India (<12 cases). *B. dermatitidis* is not endemic to the Middle East, Central America, South America, Europe, Asia, or Australia. In North America, *B. dermatitidis* grows in an ecologic niche characterized by forested, sandy soils with an acidic pH that have decaying vegetation and are near water. Most *B. dermatitidis* infections are sporadic; however, 15 outbreaks have been reported and most have involved pediatric patients. Outbreaks are associated with outdoor activities (camping, hiking, fishing); nonetheless some outbreaks have no identifiable risk factors other than geography. The severity of infection is influenced by the size of the inhaled inoculum and the integrity of the patient's immune system. Those immunosuppressed by solid organ transplantation, AIDS, and tumor necrosis factor-α inhibitors are at risk for developing severe or disseminated infection.

PATHOGENESIS

The ability of mycelial fragments and spores to convert to yeast in the lung is a crucial event in the pathogenesis of infection with *B. dermatitidis* and other dimorphic fungi. This conversion, which is known as the phase transition, enables *B. dermatitidis* to evade the host immune system and establish infection. In the yeast form, *B. dermatitidis* produces BAD1 (B*lastomyces ad*hesin-1; formerly WI-1), an essential virulence factor that is secreted into the extracellular milieu and binds back to chitin on the fungal cell wall. BAD1 promotes binding of yeast to macrophages in lung alveoli, blocks the deposition of complement on the yeast surface, binds calcium, and suppresses the production of proinflammatory cytokines such as tumor necrosis factor-α in the host.

The phase transition from mold to yeast is a complex event that involves alteration in cell wall composition, metabolism, intracellular signaling, and gene expression. In *B. dermatitidis*, this transition is regulated, in part, by a histidine kinase known as *DRK1* (*d*imorphism *r*egulating *k*inase-1). This sensor kinase controls not only the conversion of mold to yeast but also spore production, cell wall composition, and *BAD-1* expression; the loss of *DRK1* expression through gene disruption renders *B. dermatitidis* avirulent in a murine model of blastomycosis.

The phase transition is reversible and following a drop in temperature from 37°C (98.6°F) to 22°C (71.6°F), *B. dermatitidis* yeast convert to sporulating mold. Growth as mold promotes survival in the soil, allows for sexual reproduction to enhance genetic diversity, and facilitates transmission to new hosts. The transition from yeast to mold is influenced by *SREB* (siderophore biosynthesis repressor in *Blastomyces*), which encodes a transcription factor. Deletion of *SREB* results in the failure of *B. dermatitidis* yeast to complete the conversion to mold.

Innate and adaptive immune systems are required to effectively control *B. dermatitidis* infection; humoral immunity is dispensable. Macrophages and neutrophils are capable of ingesting and killing *B. dermatitidis* conidia. In contrast, yeast are poorly killed by nonactivated macrophages, are resistant to reactive oxygen species, and suppress nitric oxide production. Adaptive immunity is mediated by T lymphocytes (Th1 and Th17), which activate macrophages and neutrophils to facilitate clearance of infection. Following infection, cell-mediated immunity against *B. dermatitidis* can last for at least 2 yr.

CLINICAL MANIFESTATIONS

The clinical manifestations of blastomycosis are diverse and include subclinical infection, symptomatic pneumonia, and disseminated disease. Clinical disease develops 3 wk to 3 mo following exposure to *B. dermatitidis*. Asymptomatic or subclinical infections are estimated to occur in 50% of patients.

The most common clinical manifestation of blastomycosis is pneumonia, which can range from acute to chronic. Acute symptoms resemble community-acquired pneumonia and include fever, dyspnea, cough, chest pain, and malaise. Respiratory failure, including acute respiratory distress syndrome, can occur in patients with an overwhelming burden of infection. Chest imaging typically demonstrates air space consolidation, which can involve the upper or lower lobes. Other radiographic features include nodular, reticulonodular, and miliary patterns. Hilar adenopathy and pleural effusions are uncommon. Because the clinical and radiographic features can mimic bacterial pneumonia, patients can be mistakenly treated with antibiotics, resulting in disease progression. Patients with subacute or chronic pneumonia also present with fevers, chills, night sweats, cough, weight loss, hemoptysis, dyspnea, and chest pain. Air space consolidation, mass lesions, or cavitary disease can be present on chest roentgenography. These features can mimic tuberculosis or malignancy.

Extrapulmonary blastomycosis most often affects the skin or bone but can involve almost any organ. The incidence of extrapulmonary disease in children ranges from 38-50%, which is similar to rates in adult patients (25-40%). The skin is the most common site for extrapulmonary blastomycosis, which is usually the result of hematogenous dissemination. Direct inoculation of *B. dermatitidis* into the skin from trauma or a laboratory accident can result in primary cutaneous blastomycosis. Skin manifestations include plaques, papules, ulcers, nodules, and verrucous lesions. Erythema nodosum is rare in blastomycosis. Dissemination of *B. dermatitidis* to the bone results in lytic destruction, pain, soft tissue swelling, sinus tract formation, and ulceration. The ribs, skull, spine, and long bones are most commonly affected. Patients with osteomyelitis often have pulmonary or cutaneous involvement. Vertebral osteomyelitis can be complicated by paraspinal abscess, psoas abscess, and vertebral body collapse. Extension of long bone osteomyelitis can result in pathologic fracture or septic arthritis. Genitourinary blastomycosis occurs in 10-30% of adults but is rare in children.

Blastomycosis of the central nervous system occurs in <10% of immunocompetent patients and can result in brain abscess or meningitis. Some patients with central nervous system blastomycosis have widely disseminated disease. Symptoms include headache, altered mental status, memory loss, seizure, cranial nerve deficits, and focal neurologic deficits. Complications include hydrocephalus, cerebral herniation, infarction, panhypopituitarism, residual weakness, and poor functioning in school. Lumbar puncture demonstrates leukocytosis with a neutrophil or lymphocyte predominance, elevated protein, and low glucose. Growth of *B. dermatitidis* in culture from cerebral spinal fluid occurs in less than 50% of affected patients.

Blastomycosis can complicate pregnancy, and clinical information is limited to case reports. Disseminated infection involving the lungs, skin, and bone is common. Spread of infection to the placenta has been documented by histopathology; however, the frequency of placental blastomycosis remains unknown. Transmission of *B. dermatitidis* to the fetus may involve transplacental transmission or aspiration of infected vaginal secretions. Although clinical data are limited, blastomycosis during pregnancy does not appear to increase the risk for congenital malformations.

DIAGNOSIS

The diagnosis of blastomycosis requires a high index of suspicion, because the clinical and radiographic manifestations can mimic other diseases including community-acquired pneumonia, tuberculosis, and malignancy. Blastomycosis should be included in the differential diagnosis for patients with pneumonia who live in or visit areas in which this pathogen is endemic, fail to respond to antibiotics, or have chronic skin lesions or osteomyelitis. A detailed medical history regarding exposure risks (e.g., canoeing, hiking, fishing, playing in outdoor forts, beaver dam exploration, home remodeling, nearby road or commercial construction, use of a woodpile for a wood burning stove) should be obtained. In addition, the health of family pets such as dogs should also be ascertained, as **canine disease** may be a harbinger of human infection. The incidence of blastomycosis in dogs is 10-fold higher than in humans, and canine infection suggests a common source of exposure.

Growth of *B. dermatitidis* in culture from sputum, skin, bone, or other clinical specimens provides a definitive diagnosis. Sputum specimens should be stained with 10% potassium hydroxide or calcofluor white. Histopathology shows neutrophilic infiltration with noncaseating granulomas (pyogranulomas). *B. dermatitidis* yeast in tissue samples can be visualized using Gomori methenamine silver or peri-

odic acid–Schiff stains. Yeasts are 8-20 μm in size, have a double refractile cell wall, and display broad-based budding.

Nonculture diagnostic techniques should be used in conjunction with fungal smears and cultures to facilitate the diagnosis of blastomycosis. The development of a *Blastomyces* antigen test has supplanted insensitive serologic methods such as complement fixation and immunodiffusion. Urine, serum, cerebrospinal fluid, and bronchoalveolar fluid specimens can be collected for the *Blastomyces* antigen test. Sensitivity of the urine antigen test ranges from 85.1-92.9% and is influenced by the burden of infection. The antigen test can crossreact with other dimorphic fungi including *Histoplasma capsulatum, Paracoccidioides brasiliensis,* and *Penicillium marneffei*, which decreases the specificity to 76.9-79%. An antibody test against the BAD1 protein has been developed with a sensitivity of 87.8% and a specificity of 94-99%. Combination antigen and BAD1 antibody testing can increase diagnostic sensitivity to 97.6%.

TREATMENT

Antifungal therapy is influenced by the severity of the infection, involvement of the central nervous system, the integrity of the host's immune system, and pregnancy. All persons diagnosed with blastomycosis should receive antifungal therapy. Newborns with blastomycosis should be treated with amphotericin B deoxycholate 1 mg/kg/day. Children with mild to moderately severe infection can be treated with itraconazole 10 mg/kg/day (maximum: 400 mg/day) for 6-12 mo. Children with severe disease or underlying immunodeficiency or immunosuppression should be treated with amphotericin B deoxycholate 0.7-1.0 mg/kg/day or lipid amphotericin B 3-5 mg/kg/day until there is clinical improvement, generally 7-14 days, and then itraconazole 10 mg/kg/day (maximum: 400 mg/day) for a total of 12 mo. Central nervous system blastomycosis requires therapy with lipid amphotericin B 5 mg/kg/day for 4-6 wk followed by itraconazole, fluconazole, or voriconazole for ≥12 mo.

All pediatric patients of childbearing age should undergo pregnancy testing prior to initiation of azole antifungals. Itraconazole can increase the risk for spontaneous abortion and fluconazole can cause craniofacial defects resembling Antley-Bixler syndrome. Voriconazole and posaconazole cause skeletal abnormalities in animal models. Treatment of blastomycosis in pregnant patients consists of lipid amphotericin B 3-5 mg/kg/day.

For patients receiving itraconazole, the oral antifungal of choice, serum drug levels need to be measured 14 days into therapy (goal ≥1 μg/mL) and liver function tests should be monitored periodically. The newest azole antifungal drugs, voriconazole and posaconazole, have activity against *B. dermatitidis*; however, clinical experience with these drugs remains limited. The echinocandins (caspofungin, micafungin, and anidulafungin) should not be used to treat blastomycosis. Serial measurement of urine antigen levels to assess response to therapy appears promising, but the clinical usefulness of this strategy remains to be determined.

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Chapter 240

Coccidioidomycosis (*Coccidioides* Species)

Martin B. Kleiman

ETIOLOGY

Coccidioidomycosis (valley fever, San Joaquin fever, desert rheumatism, coccidioidal granuloma) is caused by *Coccidioides* spp., a soil-dwelling dimorphic fungi. *Coccidioides* spp. grow in the environment as spore-bearing (arthroconidia-bearing) mycelial forms. In their parasitic form, they appear as unique, endosporulating spherules in infected tissue. The 2 recognized species, *C. immitis* and *C. posadasii,* cause similar illnesses.

EPIDEMIOLOGY

Coccidioides spp. inhabit soil in arid regions. *C. immitis* is primarily found in California's San Joaquin Valley. *C. posadasii* is endemic to southern regions of Arizona, Utah, Nevada, New Mexico, western Texas and regions of Mexico and Central and South America.

Population migrations into endemic areas and increasing numbers of immunosuppressed persons have caused coccidioidomycosis to become an important health problem. Infection rates increased from 2000-2007. Approximately 150,000 newly reported infections occur annually in the United States. Coccidioidin skin test positivity in 5-7 yr old students in a highly endemic area demonstrated a decline from 10% to 2% in a 58 yr period ending in 2000. During 2002, 153 children required hospitalization for coccidioidomycosis, and infection was fatal in 9% of cases.

Infection results from inhalation of aerosolized spores. Incidence increases during windy, dry periods that follow rainy seasons. Seismic events, archaeologic excavations, and other activities that disturb contaminated sites have caused outbreaks. Person-to-person transmission does not occur. Rarely, infections result from spores that contaminate fomites or grow beneath casts or wound dressings of infected patients. Infection has also resulted from transplantation of organs from infected donors and from mother to fetus or newborn. Visitors to endemic areas can acquire infections, and diagnosis may be delayed when they are evaluated in nonendemic areas. Spores are highly virulent, and *Coccidioides* spp. are potential agents of bioterrorism (see Chapter 723).

PATHOGENESIS

Inhaled spores reach terminal bronchioles, where they transform into septated spherules that resist phagocytosis and within which many endospores develop. Released endospores transform into new spherules, and the process results in an acute focus of infection. Endospores can also disseminate lymphohematogenously. Eventually, a granulomatous reaction predominates. Both recovery and protection upon reexposure depend on effective cellular immunity.

Children with congenital primary immunodeficiency disorders may be at increased risk for infection; these disorders include interleukin-12Rβ1 deficiency, interferon-γR1 deficiency, and *STAT1* gain-of-function mutations.

CLINICAL MANIFESTATIONS

The clinical spectrum (Fig. 240-1) encompasses pulmonary and extrapulmonary disease. Pulmonary infection occurs in 95% of cases and can be divided into primary, complicated, and residual infections. Approximately 60% of infections are asymptomatic. Symptoms in children are milder than those in adults. The incidence of extrapulmonary dissemination in children approaches that of adults.

Primary Coccidioidomycosis

The incubation period is 1-4 wk, with an average of 10-16 days. Early symptoms include malaise, chills, fever, and night sweats. Chest

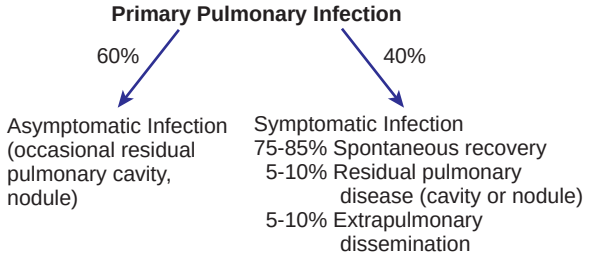

Figure 240-1 Natural history of coccidioidomycosis.

Figure 240-2 Chest radiograph of a 19 yr old man with acute primary coccidioidomycosis. There is prominent hilar lymphadenopathy and mediastinal widening.

discomfort occurs in 50-70% of patients and varies from mild tightness to severe pain. Headache and/or backache are sometimes reported. An evanescent, generalized, fine macular erythematous or urticarial eruption may be seen within the 1st few days of infection. Erythema nodosum can occur (more often in women) and is sometimes accompanied by an erythema multiforme rash, usually 3-21 days after the onset of symptoms. The clinical constellation of erythema nodosum, fever, chest pain, and arthralgias (especially knees and ankles) has been termed *desert rheumatism* and *valley fever.* The chest examination is often normal even if radiographic findings are present. Dullness to percussion, friction rub, or fine rales may be present. Pleural effusions can occur and can become large enough to compromise respiratory status. Hilar and mediastinal lymphadenopathy are common (Fig. 240-2).

Complicated Pulmonary Infection

Complicated infections include severe and persistent pneumonia, progressive primary coccidioidomycosis, progressive fibrocavitary disease, transient cavities that develop in areas of pulmonary consolidation, and empyema that follows rupture of a cavity into the pleural space. Some cavities persist, are thin walled and peripheral, and cause no symptoms; occasionally there is mild hemoptysis, and rarely there is serious hemorrhage. Rarely, acute respiratory insufficiency occurs following intense exposure; this is associated with high mortality rates.

Residual Pulmonary Coccidioidomycosis

Residual pulmonary coccidioidomycosis includes fibrosis as well as persisting pulmonary nodules. Nodules are present in 5-7% of infections and sometimes require differentiation from malignancy.

Disseminated (Extrapulmonary) Infection

Clinically apparent dissemination occurs in 0.5% of patients. Its incidence is increased in infants; men; persons of Filipino, African, and Latin American ancestry; and persons from other Asian backgrounds. Primary or acquired disorders of cellular immunity (Table 240-1) markedly increase the risk of dissemination.

Table 240-1 Risk Factors for Poor Outcome in Patients with Active Coccidioidomycosis

PRIMARY INFECTIONS
Severe, prolonged (≥6 wk), or progressive infection
RISK FACTORS FOR EXTRAPULMONARY DISSEMINATION
Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors)
Neonates, infants, the elderly
Male sex (adult)
Filipino, African, Native American, or Latin American ethnicity
Late-stage pregnancy and early postpartum period
Standardized complement fixation antibody titer >1:16 or increasing titer with persisting symptoms
Blood group B
Human leukocyte antigen (HLA) class II allele-DRBI*1301

Symptoms usually occur within 6 mo of primary infection. Prolonged fever, toxicity, skin lesions, subcutaneous and/or osseous cold abscesses, and laryngeal lesions can herald the onset. Organism-specific skin lesions have a predilection for the nasolabial area and appear initially as papules, which evolve to form pustules, plaques, abscesses, and verrucous plaques. Biopsy of these lesions demonstrates spherules. Basilar meningitis is the most common manifestation and may be accompanied by ventriculitis, ependymitis, cerebral vasculitis, abscess, and syringomyelia. Headache, vomiting, meningismus, and cranial nerve dysfunction are often present. Untreated meningitis is almost invariably fatal. Bone infections account for 20-50% of extrapulmonary manifestations, are often multifocal, and can affect adjacent structures. Miliary dissemination and peritonitis can mimic tuberculosis.

DIAGNOSIS

Nonspecific tests have limited usefulness. The complete blood count might show an elevated eosinophil count, and marked eosinophilia can accompany dissemination.

Culture, Histopathologic Findings, and Antigen Detection

Although diagnostic, culture is positive in only 8.3% of respiratory tract specimens and in only 3.2% of all other sites. *Coccidioides* is isolated from clinical specimens as the spore-bearing mold form, and thus the laboratory should be informed and use special precautions when the diagnosis is suspected. The observation of endosporulating spherules in histopathologic specimens is also diagnostic.

A quantitative enzyme immunoassay (EIA) (MiraVista Diagnostics) that detects coccidioidal galactomannan in urine has excellent specificity and is positive in 70% of patients with severe infections. Although the EIA can cross react with other endemic mycoses, interpretation is often straightforward because there is negligible geographic overlap with areas endemic for other mycoses.

Cerebrospinal fluid (CSF) analysis should be performed in patients with suspected dissemination. The findings in meningitis are similar to those seen with tuberculous meningitis (see Chapter 215). Eosinophilic pleocytosis may be present. Fungal stains and culture are usually negative. Volumes of 10 mL in adults have improved the yield of culture.

Serology

Serologic tests provide valuable diagnostic information but may be falsely negative early in self-limited infections and in immunocompromised patients. Three major methods are used, including EIA, complement fixation (CF), and immunodiffusion. EIA and CF tests are best done in experienced reference laboratories.

Immunoglobulin (Ig) M–specific antibody becomes measurable in 50% of infected patients 1 wk after onset and in 90% of infected patients by 3 wk. EIA is sensitive and can detect IgM and IgG antibody; it is less specific than other methods, and confirmation with immunodiffusion or CF may be needed. IgG antibodies measured by CF appear between the 2nd and 3rd wk but can take several months; follow-up testing is needed if tests are negative and clinical suspicion persists. In the presence of CF titers of 1:2 or 1:4, a positive immunodiffusion test can help corroborate significance. IgG-specific antibody can persist for months, with titers elevated in proportion to the severity of illness. CF titers >1:16 are suggestive of dissemination. Direct comparison of the results of CF (IgG) antibody tests measured by different methodologies should be interpreted with caution. IgG antibody titers used to monitor disease activity should be tested concurrently with serum samples taken earlier in the illness using the same methodology.

C. immitis antibody is present in CSF in 95% of patients with meningitis and is usually diagnostic. Rarely, "spillover" in patients without meningitis but with high IgG titers in serum can be present in CSF. Isolation of *Coccidioides* from CSF culture of patients with meningitis is uncommon, although culture of large volumes of CSF may improve sensitivity.

Imaging Procedures

During primary infection, chest radiography may be normal or demonstrate consolidation, single or multiple circumscribed lesions, or soft pulmonary densities. Hilar and subcarinal lymphadenopathy is often present (see Fig. 240-2). Cavities tend to be thin walled (Fig. 240-3). Pleural effusions vary in size. The presence of miliary or reticulonodular lesions is prognostically unfavorable. Isolated or multiple osseous lesions are usually lytic and often affect cancellous bone. Lesions can affect adjacent structures, and vertebral lesions can impact the spinal cord.

TREATMENT

Based on the few rigorous clinical trials performed in adults and the opinions of experts in the management of coccidioidomycosis, consensus treatment guidelines have been developed (Table 240-2). Consultation with experts in an area of endemicity should be considered when formulating a plan of management.

Patients should be followed closely because late relapse can occur, especially in patients who are immunosuppressed or have severe manifestations. Treatment is recommended for all HIV-infected patients

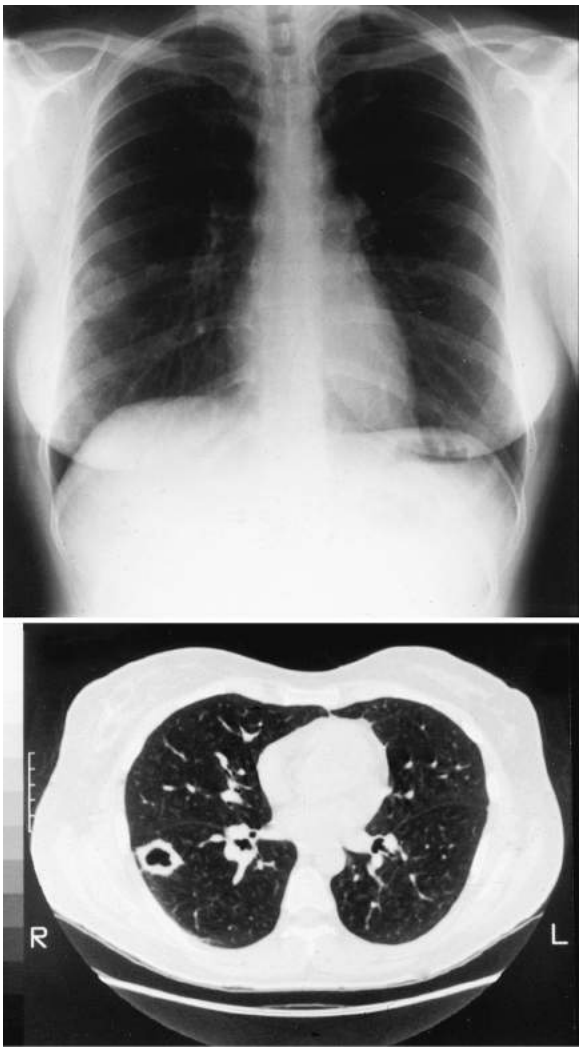

Figure 240-3 **Top,** Chest radiograph revealing a chronic cavitary lesion in the right lung of a woman with coccidioidomycosis. **Bottom,** CT showing the same cavity in the right lung.

Table 240-2 Indications for Treatment of Coccidioidomycosis in Adults

INDICATION	TREATMENT
Acute pneumonia, mild	Observe without antifungal treatment at 1-3 mo intervals for ≥1 yr; some experts recommend antifungal treatment
Weight loss >10%; sweats >3 wk; infiltrates at least half of 1 lung or parts of both lungs; prominent or persistent hilar lymphadenopathy; complement fixation titers >1:16; inability to work, symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1-3 mo intervals for ≥1 yr
Uncomplicated acute pneumonia, special circumstances: immunosuppression, late pregnancy, Filipino or African ancestry, age >55 yr, other chronic diseases (diabetes, cardiopulmonary disease), symptoms >2 mo	Treat with an azole daily for 3-6 mo, with follow-up at 1-3 mo intervals for ≥1 yr Treat with amphotericin B if in late pregnancy
Diffuse pneumonia: reticulonodular or miliary infiltrates suggest underlying immunodeficiency and possible fungemia, pain	Treat initially with amphotericin B if significant hypoxia or rapid deterioration, followed by an azole for ≥1 yr In mild cases, an azole for ≥1 yr
Chronic pneumonia	Treat with an azole for ≥1 yr
Disseminated disease, nonmeningeal	Treat with an azole for ≥1 yr except in severe or rapidly worsening cases, for which amphotericin B is recommended
Disseminated disease, meningeal	Treat with fluconazole (some add intrathecal amphotericin B) and treat indefinitely

with active coccidioidomycosis and CD4 counts <250/μL. Following successful treatment, antifungals may be stopped if the CD4 count exceeds 250/μL. Treatment should be continued if the CD4 count remains less than 250/μL and should be given indefinitely in all HIV-infected patients with coccidioidal meningitis.

First-line agents include oral and intravenous preparations of fluconazole (6-12 mg/kg/day IV or PO) and itraconazole (5-10 mg/kg/day). Serum levels of itraconazole should be monitored.

Amphotericin B is preferred for initial treatment of severe infections. Amphotericin B deoxycholate is less costly than lipid formulations and is often well tolerated in children. Once a daily dose of amphotericin B deoxycholate of 1-1.5 mg/kg/day is achieved, the frequency of administration can be reduced to 3 times weekly. The recommended total dosage ranges from 15 mg/kg to 45 mg/kg and is determined by the clinical response. Lipid formulations of amphotericin are recommended for patients with impaired renal function, patients receiving other nephrotoxic agents, or if amphotericin B deoxycholate is not tolerated. Some experts prefer liposomal amphotericin to treat central nervous system infections because it achieves higher levels in brain parenchyma. Amphotericin B preparations do not cross the blood–brain barrier to effectively treat *Coccidioides* spp., but they can mask the signs of meningitis. Infections during pregnancy should be treated with amphotericin B, because the azoles are potentially teratogenic. Voriconazole and posaconazole have been used successfully as salvage therapy in infections failing the standard agents.

Primary Pulmonary Infection

Primary pulmonary coccidioidomycosis resolves in 95% of patients without risk factors for dissemination; antifungal therapy does not lessen the frequency of dissemination or pulmonary residua. When it is elected to defer antifungal therapy, visits are recommended at 3-6 mo intervals for 2 yr and as needed.

Patients with significant or prolonged symptoms are more likely to incur benefit from antifungal agents, but there are no established criteria upon which to base the decision. Table 240-2 summarizes commonly used indicators in adults. A treatment trial in adults with primary respiratory infections examined outcomes of antifungal therapy prescribed on the basis of severity and compared them to an untreated group with less-severe symptoms; complications occurred only in patients in the treatment group and only in those in whom treatment was stopped. If treatment is elected, a 3-6 mo course of fluconazole (6-12 mg/kg/day) or itraconazole (5-10 mg/kg/day) is recommended.

Diffuse Pneumonia

Diffuse reticulonodular densities or miliary infiltrates, sometimes accompanied by severe illness, can occur in dissemination or follow exposure to a large fungal inoculum. In this setting, amphotericin B is recommended for initial treatment, followed thereafter by extended treatment with high-dose fluconazole (see Table 240-2).

Disseminated (Extrapulmonary) Infection

For **nonmeningeal infection** (see Table 240-2), oral fluconazole and itraconazole are effective for treating disseminated coccidioidomycosis that is not extensive, is not progressing rapidly, and has not affected the central nervous system. Some experts recommend higher doses for adults than were used in clinical trials. A subgroup analysis showed a tendency for improved response of skeletal infections that were treated with itraconazole. Amphotericin B deoxycholate is used as an alternative, especially if there is rapid worsening and lesions are in critical locations. Voriconazole has been used successfully as salvage therapy. The optimal duration of therapy with the azoles has not been clearly defined. Late relapses have occurred after lengthy treatment and favorable clinical response.

Meningitis

Therapy with oral fluconazole is currently preferred for coccidioidal meningitis. In adults, a dosage >400 mg/day is recommended by some experts. Itraconazole at a dosage of 400-600 mg/day in adults is reported to have a comparable effect. Some experts use intrathecal, intraventricular, or intracisternally administered amphotericin B in addition to an azole, believing that the clinical response may be faster. Patients who respond to the azole should continue treatment indefinitely. Hydrocephalus is a common occurrence and is not necessarily a marker of treatment failure. In the event of treatment failure with azoles, intrathecal therapy with amphotericin B deoxycholate is indicated, with or without the azole treatment. Cerebral vasculitis can occur and can predispose to cerebral ischemia, infarction, or hemorrhage. The efficacy of steroids in high dosage is unresolved. Salvage therapy with voriconazole has been found to be effective.

Surgical Management

If a cavity is located peripherally or there is recurrent bleeding or pleural extension, excision may be needed. Infrequently, bronchopleural fistula or recurrent cavitation occurs as a surgical complication; rarely, dissemination can result. Perioperative intravenous therapy with amphotericin B may be considered. Drainage of cold abscesses, synovectomy, and curettage or excision of osseous lesions is sometimes needed. Local and systemic administration of amphotericin B can be used to treat coccidioidal articular disease.

PREVENTION

Prevention relies on education about ways to reduce exposure. Physicians practicing in nonendemic regions should incorporate careful travel histories when evaluating patients with symptoms compatible with coccidioidomycosis.

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Chapter 241

Paracoccidioides brasiliensis

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Paracoccidioidomycosis (South American or Brazilian blastomycosis, Lutz-Splendore-Almeida disease) is an uncommon fungal infection endemic in South America, with cases reported in Central America and Mexico. Brazil accounts for more than 80% of all reported cases. The etiologic agent, *Paracoccidioides brasiliensis,* is a thermally dimorphic fungus found in the environment in the mycelial (mold) form and in tissues as yeast.

EPIDEMIOLOGY

P. brasiliensis, a soil-inhabiting microorganism, is ecologically unique to Central and South America. Endemic outbreaks occur mainly in the tropical rain forests of Brazil, with cases scattered in Argentina, Colombia, and Venezuela. There is an increased incidence in areas with moderately high altitude, with high humidity and rainfall, and where coffee and tobacco are grown. Armadillos appear to be a natural reservoir for *P. brasiliensis.* The most common route of infection is by inhalation of conidia. The disease is not usually thought to be contagious, and person-to-person transmission has not been confirmed. Paracoccidioidomycosis is more common among boys after puberty because of the role of estrogen in preventing the transition of conidia to the yeast form. Children account for <10% of the total number of cases.

PATHOGENESIS

The entry route into the body is via the respiratory tract, and the lungs are the site of primary infection, although not all patients have respiratory symptoms. Once the conidia reach the alveoli, yeast

transformation takes place. The infection then spreads to the mucous membranes of the nose, mouth, and gastrointestinal tract. Cell-mediated immunity, specifically a T-helper type 2–type response, is crucial to containing the infection. Tumor necrosis factor-α and interferon-γ activated macrophages are responsible for intracellular killing of *P. brasiliensis*. The yeast can disseminate by the lymphohematogenous route to skin, lymph nodes, and other organs and remain dormant in lymph nodes, producing a latent infection with reactivation occurring later on in life. There are cases of patients who developed disease 30 or more years after leaving an endemic region.

Histopathologically, the yeast-like cells are round, with the parent cell being quite large and surrounded by small buds, giving it the appearance of a ship's wheel. A mixed suppurative and granulomatous inflammatory reaction with areas of necrosis is seen in pulmonary infections. In chronic infections fibrosis and calcification may be seen. Mucocutaneous infections are typified by ulceration and pseudoepitheliomatous hyperplasia.

CLINICAL MANIFESTATIONS

There are 2 clinical forms of disease. The **acute** form is rare, occurs almost exclusively in children and persons with impaired immunity, and targets the reticuloendothelial system. Pulmonary symptoms may be absent, although chest radiographs often show patchy, confluent, or nodular densities. Patients typically present acutely with fever, malaise, wasting, lymphadenopathy, and abdominal enlargement from intraabdominal lymphadenopathy. Hepatomegaly and splenomegaly are nearly constant. Localized bony lesions have been reported in children and can progress to systemic disease. Multifocal osteomyelitis, arthritis, and pericardial effusions can also occur. Nonspecific laboratory findings include anemia, eosinophilia, and hypergammaglobulinemia. Acute paracoccidioidomycosis has a 25% mortality rate.

Adults develop a **chronic,** progressive illness that manifests initially with flu-like symptoms, fever, and weight loss. Pulmonary infection develops with dyspnea, cough, chest pain, and hemoptysis. Findings on physical examination are scant, although chest radiographs can show infiltrates that are disproportionate with mild clinical findings. Mucositis involving the mouth and its structures as well as the nose can manifest as localized pain, change in voice, or dysphagia. Lesions can extend beyond the oral cavity onto the skin. Generalized lymphadenopathy, hepatosplenomegaly, and adrenal involvement (seen in 15-50% of cases) can lead to Addison disease. Meningoencephalitis and central nervous system granulomas can occur as presenting or secondary symptoms. Adults with extensive exposure to soil, such as farmers, are most likely to develop the chronic form of the disease.

DIAGNOSIS

Demonstration of the fungus by direct wet mount (potassium hydroxide) preparation of sputum, exudate, or pus supports the diagnosis in many cases. Histopathologic examination of biopsy specimens using special fungal staining techniques is also diagnostic. Immunohistochemistry using monoclonal antibodies to specific glycoproteins can also be done on tissue sections. Culture of the fungus on Sabouraud-dextrose or yeast extract agar confirms the diagnosis. Antibodies to *P. brasiliensis* can be demonstrated in most patients. Serial antibody titers and lymphocyte proliferative responses to fungal antigens are useful for monitoring the response to therapy. The 43 kDa glycoprotein (gp43) is present in sera of more than 90% of patients with paracoccidioidomycosis by immunodiffusion (the most commonly used diagnostic test) and in 100% by immunoblotting. A latex particle agglutination test using pooled crude fungal exoantigens is being developed for the detection of anti–*P. brasiliensis* antibodies and has shown 92% agreement with the double immunodiffusion test. Newer diagnostic methods that might prove to be very useful in the future include polymerase chain reaction, detection of gp43, and capture enzyme-linked immunosorbent assay to detect specific immunoglobulin E in patient sera. Skin testing with paracoccidioidin is not reliable, because 30-50% of patients with active disease are nonreactive initially and a positive test indicates previous exposure but not necessarily active disease.

TREATMENT

Itraconazole (5-10 mg/kg/day with maximum dosage of 400 mg/day) orally for 6 mo is the treatment of choice for paracoccidioidomycosis. Fluconazole has also been used, but high doses (≥600 mg/day) and longer treatment periods are required. Terbinafine, an allylamine, has potent in vitro activity against *P. brasiliensis* and has been used for successful treatment of paracoccidioidomycosis unresponsive to treatment with trimethoprim-sulfamethoxazole (TMP-SMX) (8-10 mg/kg/day). Amphotericin B is recommended for disseminated disease and if other therapies fail. Therapy with sulfonamide compounds, including sulfadiazine, TMP-SMX, and dapsone, have been used historically and are generally less expensive than the newer azoles and allylamines. The primary disadvantage is that the treatment course is very long, lasting months to years, depending on the agent selected. Relapse can occur following any form of therapy, including with amphotericin B.

Two therapies currently under investigation include the use of curcumin, an antioxidant found in the Indian spice turmeric, and the calcineurin inhibitor cyclosporine. Curcumin was found to have more antifungal activity than fluconazole against *P. brasiliensis* when studied in vitro using human buccal epithelial cells. Cyclosporine blocks the thermodimorphism of *P. brasiliensis*. Animal models demonstrate that fungal whole cells, purified antigens, peptides, and DNA vaccines have great potential toward the development of a vaccine for use in humans.

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Chapter 242

Sporotrichosis *(Sporothrix schenckii)*

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ETIOLOGY

Sporotrichosis is a rare fungal infection that occurs worldwide both sporadically and in outbreaks. The etiologic agent, *Sporothrix schenckii,* exhibits temperature dimorphism, existing as a mold at environmental temperatures (25-30°C [77-86°F]) and as a yeast in vivo (37°C [98.6°F]).

EPIDEMIOLOGY

S. schenckii is found throughout the world, but most cases of sporotrichosis are reported from North and South America and Japan. In the United States, the majority of cases have occurred in the Midwest, particularly in areas along the Mississippi and Missouri rivers. The fungus is found in decaying vegetation and has been isolated most commonly from sphagnum moss, rosebushes, barberry, straw, and some types of hay. Sporotrichosis can occur as an occupational disease among farmers, gardeners, veterinarians, and laboratory workers. Transmission from bites and scratches of animals, most commonly cats and armadillos, has occurred. Reports of human-to-human transmission are rare. Sporotrichosis has rarely been reported in infants. The mechanism of transmission in children may be zoonotic but usually is unclear. In 1 endemic area of Peru, the incidence of infection in children is greater than adults; risk factors for infection in these children were playing in crop fields, living in houses with dirt floors, and owning a cat.

PATHOGENESIS

Disease in humans usually follows cutaneous inoculation of the fungus into a minor wound. Pulmonary infection can result from the

inhalation of large numbers of spores. Disseminated infection is unusual but can occur in immunocompromised patients following ingestion or inhalation of spores. The cellular immune response to *S. schenckii* infection is both neutrophilic and monocytic. Histologically, the coexistence of noncaseating granulomas and microabscess formation is characteristic. T-cell–mediated immunity appears to be important in limiting infection, and antibody does not protect against infection. As a result of the paucity of organisms, it is usually difficult to demonstrate the fungi in biopsy specimens.

CLINICAL MANIFESTATIONS

Cutaneous sporotrichosis is the most common form of disease in all age groups. Cutaneous disease may either be lymphocutaneous or fixed cutaneous, the former being much more common. Lymphocutaneous sporotrichosis accounts for more than 75% of reported cases in children and occurs after traumatic subcutaneous inoculation. After a variable and often prolonged incubation period (1-12 wk), an isolated, painless erythematous papule develops at the inoculation site. The initial lesion is usually on an extremity in adults but is often on the face in children. The original papule enlarges and ulcerates. Although the infection might remain limited to the inoculation site (fixed cutaneous form), satellite lesions follow lymphangitic spread and appear as multiple tender subcutaneous nodules tracking along the lymphatic channels that drain the lesion. These secondary nodules are subcutaneous granulomas that adhere to the overlying skin and subsequently ulcerate. Sporotrichosis does not heal spontaneously, and these ulcerative lesions can persist for years if they are untreated. Systemic signs and symptoms are uncommon.

Extracutaneous sporotrichosis is rare in children, and most cases are reported in adults with underlying medical conditions, including AIDS and other immunosuppressing diseases. The most common form of extracutaneous sporotrichosis involves infection of the bones and joints. Pulmonary sporotrichosis usually manifests as a chronic pneumonitis similar to the presentation of pulmonary tuberculosis.

DIAGNOSIS

Cutaneous and lymphocutaneous sporotrichosis must be differentiated from other causes of nodular lymphangitis, including atypical mycobacterial infection, nocardiosis, leishmaniasis, tularemia, melioidosis, cutaneous anthrax, and other systemic mycoses, including coccidioidomycosis. Definitive diagnosis requires isolation of the fungus from the site of infection by culture. Special histologic staining such as periodic acid–Schiff and methenamine silver is required to identify yeast forms in tissues. In spite of special staining techniques, diagnostic yield from biopsy specimens is low because of the small number of organisms present in the tissues. In cases of disseminated disease, demonstration of serum antibody against *S. schenckii*–related antigens can be diagnostically useful. Serologic testing is not commercially available, but it is offered by specialized laboratories including the Centers for Disease Control and Prevention in the United States.

TREATMENT

Although comparative trials and extensive experience in children are not available, itraconazole is the recommended treatment of choice for infections outside the central nervous system. The recommended dosage for children is 5-10 mg/kg/day orally, with a target of 200 mg daily. Dosing may be increased up to 400 mg daily if there is no initial response. Alternatively, younger children with cutaneous disease only may be treated with a saturated solution of potassium iodide given orally once daily beginning at 5-10 drops 3 times per day. The dose is gradually advanced to 25-40 drops 3 times per day for children or 40-50 drops 3 times per day for adolescents and adults. Adverse reactions, usually in the form of nausea and vomiting, should be managed with temporary cessation of therapy and reinstitution at a lower dosage. Therapy is continued until the cutaneous lesions have resolved, which usually takes 6-12 wk. Terbinafine, an allylamine, also has been used successfully to treat cutaneous sporotrichosis. Further clinical efficacy data are needed to routinely recommend its use. Amphotericin B is the treatment of choice for pulmonary infections, disseminated infections, central nervous system disease, and infections in immunocompromised persons.

Therapy with azoles or a saturated solution of potassium iodide should not be used in pregnant women. Amphotericin B can safely be used for cases of pulmonary or disseminated disease in pregnancy. Pregnant patients with cutaneous disease can be treated with local hyperthermia, or therapy can be delayed until the pregnancy is completed. Hyperthermia, in which the affected area is heated to 42-45°C (107.6-113°F) using water baths or heating pads, inhibits growth of the fungus. Dissemination to the fetus does not occur, and the disease is not worsened by pregnancy. Surgical debridement has a role in the treatment of some cases of sporotrichosis, particularly in osteoarticular disease.

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Chapter 243

Zygomycosis (Mucormycosis)

Jane M. Gould and Stephen C. Aronoff

ETIOLOGY

Zygomycosis refers to a group of opportunistic fungal infections caused by dimorphic fungi of the class Zygomycetes, which are primitive, fast-growing fungi that are largely saprophytic and ubiquitous. These organisms are found commonly in soil, in decaying plant and animal matter, and on moldy cheese, fruit, and bread.

This class is subdivided into 2 orders, Mucorales and Entomophthorales, each containing human pathogens. The term **mucormycosis** refers only to infections caused by Mucorales, which includes the genera *Absidia, Apophysomyces, Mucor, Rhizomucor,* and *Rhizopus* and represents the more-common cause of zygomycosis in humans. Infections caused by organisms of the genera *Cunninghamella, Saksenaea,* and *Cokeromyces* are seen less often. Mucorales disease in humans is characterized by a rapidly evolving course, tissue necrosis, and blood vessel invasion in addition to subcutaneous infection. These infections are most acute and fulminant in debilitated patients. Genera of the order Entomophthorales causing infection in humans include *Conidiobolus* and *Basidiobolus.* These agents typically cause indolent sinus or subcutaneous infections in immunocompetent persons.

EPIDEMIOLOGY

Zygomycosis is primarily a disease of persons with underlying conditions that impair host immunity. Predisposing factors include diabetes, hematologic malignancies, persistent acidosis, corticosteroid or deferoxamine therapy, organ transplantation, prematurity, and, less commonly, AIDS. Fungi that are pathogenic in humans grow on almost any carbohydrate substrate and are able to grow at temperatures >37°C (98.6°F). Acidosis diminishes the phagocytic and chemotactic ability of neutrophils while increasing the availability of unbound iron. Deferoxamine-bound iron can also be used by the fungus to enhance its growth.

PATHOGENESIS

Macrophages and neutrophils are the main host defense against Zygomycetes and other filamentous fungi and provide almost complete immunity against Zygomycetes by phagocytosis and oxidative killing

of spores, perhaps explaining the predilection for zygomycosis in patients with neutropenia or neutrophil dysfunction. Many of the Zygomycetes have virulence mechanisms that scavenge iron, an element essential for cell growth, from the host. The primary route of infection from Zygomycetes is inhalation of spores from the environment. In immunocompromised persons, if spores are not cleared by macrophages they germinate into hyphae, resulting in local invasion and tissue destruction. Cutaneous or percutaneous routes of infection can lead to cutaneous and subcutaneous zygomycosis. Ingestion of contaminated food or drinks has been linked to gastrointestinal disease. Typically these infections are characterized by extensive angioinvasion resulting in thrombosis, infarction, and tissue necrosis, which can limit the delivery of antifungal agents and leukocytes to the site of infection and contribute to dissemination of the organism to other organs.

CLINICAL MANIFESTATIONS

There are no unique signs or symptoms of zygomycosis. It can occur as any of several clinical syndromes, including sinus/rhinocerebral, pulmonary, gastrointestinal, disseminated, or cutaneous or subcutaneous disease.

Sinus and rhinocerebral infection are the most common forms of zygomycosis and occur primarily in persons with diabetes mellitus or who are immunocompromised. Infection typically originates in the paranasal sinuses. Initial symptoms are consistent with sinusitis and include headache, retroorbital pain, fever, and nasal discharge. Infection can evolve rapidly or be slowly progressive. Orbital involvement manifesting as periorbital edema, proptosis, ptosis, and ophthalmoplegia can occur early in the disease. The nasal discharge is often dark and bloody; examination of the nasal mucosa reveals the hallmark finding of black, necrotic areas; however, its absence does not exclude the diagnosis. Extension beyond the nasal cavity into the mouth is common. Involved tissues become red, then violaceous, and then black as vessel thrombosis and tissue necrosis occur. Direct bony involvement is common as a result of contiguous pressure effects or because of direct invasion and infarction. Destructive paranasal sinusitis with intracranial extension can be demonstrated by CT or MRI. Cases complicated by cavernous sinus thrombosis and thrombosis of the internal carotid artery have been reported. Brain abscesses can occur in patients with rhinocerebral infection that extends directly from the nasal cavity and sinuses, usually to the frontal or frontotemporal lobes. In patients with disseminated disease, abscesses can involve the occipital lobe or brainstem.

Pulmonary zygomycosis infection usually occurs in severely neutropenic patients and is characterized by fever, tachypnea, and productive cough with pleuritic chest pain and hemoptysis. A wide range of pulmonary radiologic findings, including solitary pulmonary nodule, segmental or lobar consolidation, and cavitary and bronchopneumonic changes, are recognized.

Gastrointestinal zygomycosis is uncommon. Often the diagnosis is delayed; only 25% of cases are diagnosed antemortem, and the subsequent mortality is as high as 85%. It can occur as a complication of disseminated disease or as an isolated intestinal infection in diabetics, immunosuppressed or malnourished children, or preterm infants. Any part of the gastrointestinal tract can be involved, with the stomach followed by colon and ileum being the most commonly affected. Abdominal pain and distention with hematemesis, hematochezia, or melena can occur. Stomach or bowel wall perforation is not uncommon.

Disseminated zygomycosis is associated with a very high mortality rate, especially among immunocompromised persons. Pulmonary involvement is most common, but infection can originate from any of the primary sites of infection. A metastatic skin lesion is an important clue to early diagnosis.

Cutaneous and soft tissue zygomycosis can complicate burns or surgical wounds. An outbreak occurred among preterm infants following the use of contaminated wooden tongue depressors to immobilize the extremities. Primary cutaneous disease may be invasive locally, progressing through all tissue layers, including muscle, fascia, and bone. Necrotizing fasciitis may occur. Infection manifests as an erythematous papule that ulcerates, leaving a black necrotic center. The skin lesions are painful, and affected patients may be febrile. Cutaneous lesions from hematogenous seeding tend to be nodular, with minimal destruction of the epidermis.

DIAGNOSIS

The diagnosis relies on direct morphologic identification of mycotic elements and recovery of Zygomycetes in culture or by biopsy identification in specimens obtained at the site of presumed involvement. To identify the fungus from scrapings, sputum, and exudates under direct microscopy, the use of calcofluor white or 10% potassium hydroxide and Parker ink is recommended. In lung and other tissue biopsy specimens, demonstration of fungal elements with fungal specific stains is recommended. Mucorales appear as broad (5-25 μm in diameter), infrequently septate, thin-walled hyphae, branching irregularly at right angles when stained with Gomori methenamine silver or hematoxylin and eosin. Secondary to their thin-walled structure and lack of regular septation, they often appear twisted, collapsed, or folded. Angiotropism is a hallmark of zygomycosis. The fungi can be cultured on standard laboratory media from sputum, bronchoalveolar lavage fluid, skin lesions, or biopsy material. Mucorales are common culture contaminants. Serologic tests for detecting zygomycosis are not clinically useful. Real-time quantitative polymerase chain reaction assay targeting the 28S rRNA gene has been tested in a rabbit model of experimental pulmonary zygomycosis and shows great promise as a rapid, sensitive, and specific diagnostic test. Additionally, direct sequencing of cultured organisms or formalin fixed tissue and fluorescent in situ hybridization are methods that show great promise to increase the sensitivity, specificity, and speed of laboratory-based diagnostics.

TREATMENT

All forms of the disease can be aggressive and difficult to treat, with high fatality rates. The optimal therapy for zygomycosis in children requires early diagnosis and prompt institution of medical therapy combined with extensive surgical debridement of all devitalized tissue. Correction of the underlying disease, if possible, is an essential component of management. Use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor to reverse immunosuppression is recommended in conjunction with antifungal agents.

Amphotericin B deoxycholate (1-1.5 mg/kg/day to a total dose of 70 mg/kg or 3-4 g over several weeks) or amphotericin B lipid complex (3-5 mg/kg/day) has been successful in treating infection. Anecdotal reports suggest that higher total doses of amphotericin B lipid complex (15-20 mg/kg/day) are associated with better outcomes in invasive infection. Pulmonary and cutaneous disease has been successfully treated with intermediate dosages of amphotericin B (30 mg/kg total dose).

Surveillance in the United States suggests an association between use of voriconazole prophylaxis and the emergence of zygomycosis in transplant patients, which might represent increased patient survival or selection of resistant organisms. Voriconazole is inactive against the Zygomycetes. Posaconazole appears to be active against most of the Zygomycetes both in vitro and in vivo and together with surgery has been associated with dramatic clinical responses and holds promise as a therapeutic agent for mucormycosis. Caspofungin has limited or no in vitro activity against Zygomycetes; however, when combined with amphotericin lipid complex, caspofungin has been found to be more active than lipid complex alone or caspofungin alone for the treatment of experimental zygomycosis in diabetic mice. Caspofungin has been shown to uncover β-glucan in the cell wall of *Rhizopus,* which results in an increase in neutrophil activity. Hyperbaric oxygen has been used anecdotally as an adjunctive therapy, and iron chelation with deferasirox has been tried as salvage therapy in refractory mucormycosis.

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Chapter 244

Pneumocystis jiroveci

Francis Gigliotti and Terry W. Wright

Pneumocystis jiroveci pneumonia (interstitial plasma cell pneumonitis) in an immunocompromised person is a life-threatening infection. Primary infection in the immunocompetent person is usually subclinical and goes unrecognized. The disease most likely results from new or repeat acquisition of the organism rather than reactivation of latent organisms. Even in the most severe cases, with rare exceptions, the organisms remain localized to the lungs.

ETIOLOGY

P. jiroveci is a common extracellular parasite found worldwide in the lungs of mammals. The taxonomic placement of this organism has not been unequivocally established, but nucleic acid homologies place it closest to fungi despite sharing morphologic features and drug susceptibility with protozoa. Detailed studies of the basic biology of the organism are not possible because of the inability to maintain *P. jiroveci* in culture. Phenotypic and genotypic analyses demonstrate that each mammalian species is infected by a unique strain (or possibly species) of *Pneumocystis*. A biologic correlate of these differences is evidenced by animal experiments that have shown organisms are not transmissible from one mammalian species to another. These observations have led to the suggestion that organisms be renamed, with those infecting humans renamed *P. jiroveci*. Alternative acceptable nomenclature retains the use of *Pneumocystis carinii* but uses the annotation *forma specialis* to designate the host of origin such that *P. carinii* infecting humans, rats, or mice would carry the *forma specialis* designation *hominis, ratti,* or *muris,* respectively. Both nomenclatures appear in the medical literature.

EPIDEMIOLOGY

Serologic surveys show that most humans are infected with *P. jiroveci* before 4 yr of age. In the immunocompetent child, these infections are usually asymptomatic. *P. jiroveci* DNA can occasionally be detected in nasopharyngeal aspirates of normal infants. Pneumonia caused by *P. jiroveci* occurs almost exclusively in severely immunocompromised hosts, including those with congenital or acquired immunodeficiency disorders, malignancies, or transplanted organs. Patients with primary immunodeficiency diseases at risk for infection include severe immunodeficiency disease, X-linked CD40 ligand deficiency, major histocompatibility complex class II deficiency, nuclear factor kappa B essential modulator deficiency, dedicator of cytokinesis 8 deficiency, Wiskott-Aldrich syndrome, and caspase recruitment domain 11 deficiency. Small numbers of *P. jiroveci* can be found in the lungs of infants who have died with the diagnosis of sudden infant death syndrome. This observation could indicate a cause-and-effect relationship or simply that there is overlap in the timing of the primary infection with *P. jiroveci* and sudden infant death syndrome.

Without chemoprophylaxis, approximately 40% of infants and children with AIDS, 70% of adults with AIDS, 12% of children with leukemia, and 10% of patients with organ transplants experience *P. jiroveci* pneumonia. Epidemics that occurred among debilitated infants in Europe during and after World War II are attributed to malnutrition. The use of new biologic immunosuppressive agents has expanded at-risk populations. The addition of tumor necrosis factor-α inhibitors to the management of patients with inflammatory bowel disease has resulted in a demonstrable increase in *P. jiroveci* pneumonia in this patient population as has the use of rituximab in patients with hematologic malignancies.

The natural habitat and mode of transmission to humans are unknown, but animal studies clearly demonstrate airborne transmission. Animal-to-human transmission is unlikely because of the host specificity of *P. jiroveci*. Thus, person-to-person transmission is likely but has not been conclusively demonstrated.

PATHOGENESIS

Two forms of *P. jiroveci* are found in the alveolar spaces: cysts, which are 5-8 μm in diameter and contain up to 8 pleomorphic intracystic sporozoites (or intracystic bodies), and extracystic trophozoites (or trophic forms), which are 2-5 μm cells derived from excysted sporozoites. The terminology of sporozoite and trophozoite is based on the morphologic similarities to protozoa, because there are no exact correlates for these forms of the organism among the fungi. *P. jiroveci* attaches to type I alveolar epithelial cells, possibly by adhesive proteins such as fibronectin and or mannose-dependent ligands.

Control of infection depends on intact cell-mediated immunity. Studies in patients with AIDS show an increased incidence of *P. jiroveci* pneumonia with markedly decreased $CD4^+$ T-lymphocyte counts. The $CD4^+$ cell count provides a useful indicator in both older children and adults of the need for prophylaxis for *P. jiroveci* pneumonia. Although normally functioning $CD4^+$ T cells are central to controlling infection by *P. jiroveci,* the final effector pathway for destruction of *P. jiroveci* is poorly understood but likely depends on alveolar macrophages. A role for $CD4^+$ T cells could be to provide help for the production of specific antibody that is then involved in the clearance of organisms through interaction with complement, phagocytes, or T cells or through direct activation of alveolar macrophages.

In the absence of an adaptive immune response, as can be modeled in severe combined immunodeficient mice, infection with *P. jiroveci* produces little alteration in lung histology or function until late in the course of the disease. If functional lymphocytes are given to severe combined immunodeficient mice infected with *P. jiroveci,* there is a rapid onset of an inflammatory response that results in an intense cellular infiltrate, markedly reduced lung compliance, and significant hypoxia, which are the characteristic changes of *P. jiroveci* pneumonia in humans. These inflammatory changes are also associated with marked disruption of surfactant function. T-cell subset analysis has shown that $CD4^+$ T cells produce an inflammatory response that clears the organisms but also results in lung injury. $CD8^+$ T cells are ineffective in the eradication of *P. jiroveci.* $CD8^+$ T cells do help modulate the inflammation produced by $CD4^+$ T cells, but in the absence of $CD4^+$ T cells the ineffectual inflammatory response of $CD8^+$ T cells contributes significantly to lung injury. These various T-cell effects are likely responsible for the variations in presentation and outcome of *P. jiroveci* pneumonia observed in different patient populations.

PATHOLOGY

The histopathologic features of *P. jiroveci* pneumonia are of 2 types. The first type is infantile interstitial plasma cell pneumonitis, which was seen in epidemic outbreaks in debilitated infants 3-6 mo of age. Extensive infiltration with thickening of the alveolar septum occurs, and plasma cells are prominent. The second type is a diffuse desquamative alveolar pneumonitis found in immunocompromised children and adults. The alveoli contain large numbers of *P. jiroveci* in a foamy exudate with alveolar macrophages active in the phagocytosis of organisms. The alveolar septum is not infiltrated to the extent it is in the infantile type, and plasma cells are usually absent.

CLINICAL MANIFESTATIONS

There are at least 3 distinct clinical presentations of *P. jiroveci* pneumonia. In patients with profound congenital immunodeficiency or in AIDS patients with very few $CD4^+$ T cells, the onset of hypoxia and symptoms is subtle, with tachypnea progressing to nasal flaring, often without fever; intercostal, suprasternal, and infrasternal retractions; and cyanosis in severe cases. In cases of *P. jiroveci* pneumonia occurring in children and adults with immunodeficiency resulting from immunosuppressive medications, the onset of hypoxia and symptoms is often more abrupt, with fever, tachypnea, dyspnea, and cough, progressing to severe respiratory compromise. This type accounts for the

majority of cases, although the severity of clinical expression can vary. Rales are usually not detected on physical examination. The third pattern of disease is seen in severely immunocompromised patients with *P. jiroveci* pneumonia who appear to be responding to therapy but then have an acute and seemingly paradoxical deterioration thought to be associated with return of immune function. This condition is referred to as *immune restitution inflammatory syndrome* and is most commonly seen in patients with newly diagnosed AIDS who present with *P. jiroveci* pneumonia and who have a rapid response to antiretroviral therapy that is instituted at the same time as anti-*Pneumocystis* therapy. It can also occur in stem cell transplant recipients who engraft while infected with *P. jiroveci.*

LABORATORY FINDINGS

The chest radiograph reveals bilateral diffuse alveolar disease with a granular pattern. The earliest densities are perihilar, and progression proceeds peripherally, sparing the apical areas until last. The arterial oxygen tension (Pao_2) is invariably decreased. The major role of the laboratory in establishing a diagnosis of *P. jiroveci* pneumonia is in identifying organisms in lung specimens by a variety of methods. Once obtained, the specimens are typically stained with 1 of 4 commonly used stains: Grocott-Gomori silver stain and toluidine blue stain for the cyst form, polychrome stains such as Giemsa stain for the trophozoites and sporozoites, and the fluorescein-labeled monoclonal antibody stains for both trophozoites and cysts. Polymerase chain reaction analysis of respiratory specimens offers promise as a rapid diagnostic method, but a standardized system for clinical use has not been established.

DIAGNOSIS

Definitive diagnosis requires demonstration of *P. jiroveci* in the lung in the presence of clinical signs and symptoms of the infection. Organisms can be detected in specimens collected by bronchoalveolar lavage (BAL), tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration, and open lung biopsy. Hypertonic saline–induced sputum samples are helpful if *P. jiroveci* is found, but the absence of the organisms in induced sputum does not exclude the infection and BAL should be performed. Open lung biopsy is the most reliable method, although BAL is more practical in most cases. Estimates of the diagnostic yield of the various specimens are 20-40% for induced sputum, 50-60% for tracheal aspirate, 75-95% for BAL, 75-85% for transbronchial biopsy, and 90-100% for open lung biopsy.

TREATMENT

The recommended therapy for *P. jiroveci* pneumonia is trimethoprim-sulfamethoxazole (TMP-SMX) (15-20 mg TMP and 75-100 mg SMX/kg/day in 4 divided doses) administered intravenously, or orally if there is mild disease and no malabsorption or diarrhea. The duration of treatment is 3 wk for patients with AIDS and 2 wk for other patients. Unfortunately, adverse reactions often occur with TMP-SMX, especially rash and neutropenia in patients with AIDS. For patients who cannot tolerate or who fail to respond to TMP-SMX after 5-7 days, pentamidine isethionate (4 mg/kg/day as a single dose IV) may be used. Adverse reactions are frequent and include renal and hepatic dysfunction, hyperglycemia or hypoglycemia, rash, and thrombocytopenia. Atovaquone (750 mg twice daily with food, for patients >13 yr of age) is an alternative treatment that has been used primarily in adults with mild to moderate disease. Limited experience is available for younger children. Pharmacokinetic studies of atovaquone show that a dose of 30 mg/kg/day PO in 2 divided doses for children 0-3 mo of age and older than 2 yr of age is adequate and safe; a dose of 45 mg/kg/day PO in 2 divided doses is needed for children between 4 mo and 2 yr of age. Other effective therapies include trimetrexate glucuronate or combinations of trimethoprim plus dapsone or clindamycin plus primaquine.

Some studies in adults suggest that administration of corticosteroids as adjunctive therapy to suppress the inflammatory response increases the chances for survival in moderate and severe cases of *P. jiroveci* pneumonia. The recommended regimen of corticosteroids for adolescents older than 13 yr of age and for adults is oral prednisone, 80 mg/day PO in 2 divided doses on days 1-5, 40 mg/day PO once daily on days 6-10, and 20 mg/day PO once daily on days 11-21. A reasonable regimen for children is oral prednisone, 2 mg/kg/day for the 1st 7-10 days, followed by a tapering regimen for the next 10-14 days.

SUPPORTIVE CARE

Basic supportive care is dictated by the condition of the patient, with careful attention to maintain appropriate hydration and oxygenation. Only 5-10% of AIDS patients require mechanical ventilation compared to 50-60% of patients without AIDS, consistent with the hypothesis that the patient's ability to mount an inflammatory response correlates with severity and outcome. There are anecdotal reports of giving surfactant to children with severe *P. jiroveci* pneumonia, although the use of surfactant to treat adult-type respiratory distress syndrome is controversial.

COMPLICATIONS

Most complications occur as adverse events associated with the drugs used or the mechanical ventilation used for treatment. The most severe pulmonary complication of *P. jiroveci* pneumonia is adult-type respiratory distress syndrome. Rarely, *P. jiroveci* infection affects extrapulmonary sites (e.g., retina, spleen, and bone marrow), but such infections are usually not symptomatic and also respond to treatment.

PROGNOSIS

Without treatment, *P. jiroveci* pneumonitis is fatal in almost all immunocompromised hosts within 3-4 wk of onset. The mortality rate varies with patient population and is related to inflammatory response rather than organism burden. AIDS patients have a mortality rate of 5-10%, and patients with other diseases such as malignancies have mortality rates as high as 20-25%. Patients who require mechanical ventilation have mortality rates of 60-90%. Patients remain at risk for *P. jiroveci* pneumonia as long as they are immunocompromised. Continuous prophylaxis should be initiated or reinstituted at the end of therapy for patients with AIDS (see Chapter 276).

PREVENTION

Patients at high risk for *P. jiroveci* pneumonia should be placed on chemoprophylaxis. Prophylaxis in infants born to HIV-infected mothers and for HIV-infected infants and children is based on age and CD4 cell counts (see Chapter 276). Patients with severe combined immunodeficiency syndrome, patients receiving intensive immunosuppressive therapy for cancer or other diseases, and organ transplant recipients are also candidates for prophylaxis. TMP-SMX (5 mg/kg TMP and 25 mg SMX/kg PO once daily or divided into 2 doses daily) is the drug of choice and may be given for 3 consecutive days each week, or, alternatively, each day. Alternatives for prophylaxis include dapsone (2 mg/kg/day PO, maximum: 100 mg/dose; or 4 mg/kg PO once weekly, maximum: 200 mg/dose), atovaquone (30 mg/kg/day PO for infants 1-3 mo and ≥24 mo of age; 45 mg/kg/day for infants and toddlers 4-23 mo of age), and aerosolized pentamidine (300 mg monthly by Respirgard II nebulizer), but all of these agents are inferior to TMP-SMX. Finally, limited clinical experience suggests that pentamidine can be given intravenously once monthly to prevent *P. jiroveci* pneumonia. Prophylaxis must be continued as long as the patient remains immunocompromised. Some AIDS patients who reconstitute adequate immune response during highly active antiretroviral therapy may have prophylaxis withdrawn.

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Section 13

Viral Infections

Chapter 245

Principles of Antiviral Therapy

Mark R. Schleiss

Antiviral chemotherapy typically requires a delicate balance between targeting critical steps in viral replication without interfering with host cellular function. Because viruses require cellular functions to complete replication, many antiviral agents exert significant host cellular toxicity, a limitation that has hindered antiviral drug development. In spite of this limitation, a number of agents are licensed for use against viruses, particularly herpesviruses, respiratory viruses, and hepatitis viruses (Table 245-1).

In making the decision to commence antiviral drugs, it is important for the clinician to obtain appropriate diagnostic specimens, which can help clarify the antiviral of choice. The choice of a specific antiviral is based on the recommended agent of choice for a particular clinical condition, pharmacokinetics, toxicities, cost, and the potential for development of resistance (Table 245-2). Intercurrent conditions in the patient, such as renal insufficiency, should also be considered. Clinicians must monitor antiviral therapy closely for adverse events or toxicities, both anticipated and unanticipated.

In vitro sensitivity testing of virus isolates to antiviral compounds usually involves a complex tissue culture system. The potency of an antiviral is determined by the **50% inhibitory dose (ID_{50}),** which is the antiviral concentration required to inhibit the growth in cell culture of a standardized viral inoculum by 50%. Because of the complexity of these assays, the results vary widely, and the actual relationship between antiviral sensitivity testing and antiviral therapy outcomes is sometimes unclear. Moreover, these assays are often not readily available and take considerable time to complete, limiting their utility and value in clinical practice. Fortunately, **genotypic analysis** of antiviral resistance mutations is increasingly available for clinical testing, based on identification by molecular techniques of known mutations associated with antiviral resistance.

Knowledge of the precise status of a patient's immune system, particularly cell-mediated immunity, is important in the decision making for using an antiviral agent. Treatment of cytomegalovirus (CMV) infection in an immunocompetent patient is seldom necessary, whereas antiviral therapy may be lifesaving when administered to an immunocompromised solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT) patient. Antivirals can be employed with a variety of clinical goals in mind. Antivirals can be used for **treatment** of active end-organ disease, as **prophylaxis** to prevent viral infection or disease, or as **preemptive therapy** of viral infection to prevent viral disease. In preemptive therapy, a patient will demonstrate evidence of an active infection, usually by molecular means such as polymerase chain reaction–based identification of viral nucleic acids in clinical samples (blood or body fluids), but may have no symptoms. However, SOT and HSCT patients are at high risk of developing disease in this setting (particularly CMV infection), a scenario that warrants preemptive

Table 245-1 Currently Licensed Antiviral Drugs*

ANTIVIRAL	TRADE NAME	MECHANISM OF ACTION
Acyclovir	Zovirax	Inhibits viral DNA polymerase
Adefovir	Hepsera	Nucleotide reverse transcriptase inhibitor
Amantadine	Symmetrel	Blocks M2 protein ion channel
Cidofovir	Vistide	Inhibits viral DNA polymerase
Famciclovir	Famvir	Inhibits viral DNA polymerase
Fomivirsen	Vitravene	Phosphorothioate oligonucleotide inhibits viral replication via antisense mechanism
Foscarnet	Foscavir	Inhibits viral DNA polymerase and reverse transcriptase at pyrophosphate-binding site
Ganciclovir	Cytovene	Inhibits viral DNA polymerase
Idoxuridine	Herplex	Inhibits viral DNA polymerase
Interferon-α	Intro-A (interferon-α2b) Roferon-A (interferon-α2a) Infergen (interferon alfacon-1)	Produces multiple effector proteins that exert antiviral effects; also directly interacts with immune system components
Interferon-α2b plus ribavirin	Rebetron	Not established
Lamivudine	Epivir	Inhibits viral DNA polymerase and reverse transcriptase
Oseltamivir	Tamiflu	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
Pegylated interferon	PEG-Intron (α2b), Pegasys (α2a)	Same as interferon
Penciclovir	Denavir	Inhibits viral DNA polymerase
Ribavirin	Virazole, Rebetol, Copegus	Interference with viral messenger RNA
Rimantadine	Flumadine	Blocks M2 protein ion channel
Trifluridine	Viroptic	Inhibits viral DNA polymerase
Valacyclovir	Valtrex	Same as acyclovir
Valganciclovir	Valcyte	Same as ganciclovir
Vidarabine	ara-A	Inhibits viral DNA polymerase (and to lesser extent, cellular DNA polymerase)
Zanamivir	Relenza	Neuraminidase inhibitor; interference with deaggregation and release of viral progeny
FDA-APPROVED COMBINATION THERAPIES		
Interferon-α2b + ribavirin	Rebetron (Intron-A plus Rebetol)	
Interferon-α2a + ribavirin	Roferon-A + ribavirin	
Pegylated interferon-α2b + ribavirin	PEG-Intron + Rebetol	
Pegylated interferon-α2a + ribavirin	Pegasys + Copegus	

*See Chapter 276 for antiretroviral drugs.

Table 245-2 Antiviral Therapies for Non-HIV Clinical Conditions

VIRUS	CLINICAL SYNDROME	ANTIVIRAL AGENT OF CHOICE	ALTERNATIVE ANTIVIRAL AGENTS
Influenza A	Treatment	Oseltamivir (>1 yr old)	Rimantadine Amantadine
	Prophylaxis	Oseltamivir (>1 yr old)	Amantadine Rimantadine Zanamivir (>7 yr old)
Influenza B	Treatment	Oseltamivir	Zanamivir (>7 yr old)
Respiratory syncytial virus	Bronchiolitis or pneumonia in high-risk host	Ribavirin aerosol	
Cytomegalovirus (CMV)	Congenital CMV infection	Ganciclovir (IV)	Valganciclovir (if oral therapy appropriate; long-term oral valganciclovir investigational but may improve developmental and hearing outcomes)
	Retinitis in AIDS patients	Valganciclovir	Ganciclovir Cidofovir Foscarnet Ganciclovir ocular insert
	Pneumonitis, colitis; esophagitis in immunocompromised patients	Ganciclovir (IV)	Foscarnet Cidofovir Valganciclovir
Herpes simplex virus (HSV)	Neonatal herpes	Acyclovir (IV)	
	Suppressive therapy following neonatal herpes with central nervous system involvement	Acyclovir (PO)	
	HSV encephalitis	Acyclovir (IV)	
	HSV gingivostomatitis	Acyclovir (PO)	Acyclovir (IV)
	First episode genital infection	Acyclovir (PO)	Valacyclovir Famciclovir Acyclovir (IV) (severe disease)
	Recurrent genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
	Suppression of genital herpes	Acyclovir (PO)	Valacyclovir Famciclovir
	Cutaneous HSV (whitlow, herpes gladiatorum)	Acyclovir (PO)	Penciclovir (topical)
	Eczema herpeticum	Acyclovir (PO)	Acyclovir (IV) (severe disease)
	Mucocutaneous infection in immunocompromised host (mild)	Acyclovir (IV)	Acyclovir (PO) (if outpatient therapy acceptable)
	Mucocutaneous infection in immunocompromised host (moderate to severe)	Acyclovir (IV)	
	Prophylaxis in bone marrow transplant recipients	Acyclovir (IV)	Valacyclovir Famciclovir
	Acyclovir-resistant HSV	Foscarnet	Cidofovir
	Keratitis or keratoconjunctivitis	Trifluridine	Vidarabine
Varicella-zoster virus	Chickenpox, healthy child	Supportive care	Acyclovir (PO)
	Chickenpox, immunocompromised child	Acyclovir (IV)	
	Zoster (not ophthalmic branch of trigeminal nerve), healthy child	Supportive care	Acyclovir (PO)
	Zoster (ophthalmic branch of trigeminal nerve), healthy child	Acyclovir (IV)	
	Zoster, immunocompromised child	Acyclovir (IV)	Valacyclovir

Modified from Kimberlin DW: Antiviral therapies in children: Has their time arrived? Pediatr Clin North Am *52:837–867, 2005.*

treatment with an antiviral agent. In contrast, prophylaxis is administered to seropositive patients who are at risk to reactivate latent viral infection but do not yet have evidence of active viral replication or shedding.

A fundamental concept important in the understanding of the mechanism of action of most antivirals is that viruses must use host cell components to replicate. Thus, mechanisms of action for antiviral compounds must be selective to virus-specific functions whenever possible, and antiviral agents may have significant toxicities to the host if these compounds impact cellular physiology. Many of the approved antiviral drugs active against the herpesviruses are analogs of deoxynucleosides and subsequently inhibit viral DNA polymerase. Some of the more commonly targeted sites of action for antiviral agents include viral entry, absorption, penetration, and uncoating (amantadine, rimantadine); transcription or replication of the viral genome (acyclovir, valacyclovir, cidofovir, famciclovir, penciclovir, foscarnet, ganciclovir, valganciclovir, ribavirin, trifluridine); viral protein synthesis (interferons); and viral assembly, release, or deaggregation (oseltamivir, zanamivir, interferons).

An understudied and underappreciated issue in antiviral therapy is emergence of resistance, particularly in the setting of high viral load, high intrinsic viral mutation rate, and prolonged or repeated courses of antiviral therapy. Resistant viruses are more likely to develop in or be selected for immunocompromised patients, because these patients are more likely to have multiple or long-term exposures to an antiviral agent.

ANTIVIRALS USED FOR HERPESVIRUSES

The herpesviruses are important pediatric pathogens, particularly in newborns and immunocompromised children. Most of the licensed antivirals are nucleoside analogs that inhibit viral DNA polymerase,

inducing premature chain termination during viral DNA synthesis in infected cells.

Acyclovir

Acyclovir is a safe and effective therapy for herpes simplex virus (HSV) infections. The favorable safety profile of acyclovir derives from its requirement for activation to its active form via phosphorylation by a viral enzyme, thymidine kinase (TK). Thus, acyclovir can only be activated in cells already infected with HSV that express the viral TK enzyme, a strategy that maximizes selectivity and reduces the potential for cellular toxicity in uninfected cells. Acyclovir is most active against HSV and also is active against varicella-zoster virus (VZV); therapy is indicated for infections with these viruses in a variety of clinical settings. Activity of acyclovir against CMV is less pronounced, and activity against Epstein-Barr virus is modest, both in vitro and clinically. Therefore, under most circumstances acyclovir should not be used to treat CMV or Epstein-Barr virus infections.

The biggest impact of acyclovir in clinical practice is in the treatment of primary and recurrent genital HSV infections. Oral nucleoside therapy plays an important role in the management of acute primary genital herpes, treatment of episodic symptomatic reactivations, and prophylaxis against reactivation. Acyclovir is also indicated in the management of suspected or proven HSV encephalitis in patients of all ages, and for treatment of neonatal HSV infection, with or without central nervous system (CNS) involvement. With respect to neonatal HSV infection, the routine use of acyclovir as empiric therapy against HSV infection in infants admitted with fever of unknown origin in the 1st 4-8 wk of life is controversial. Acyclovir should be routinely empirically used in infants born to women with risk factors for primary genital herpes or infants presenting with any combination of vesicular lesions, seizures, meningoencephalitis, hepatitis, pneumonia, or disseminated intravascular coagulation. Some advocate initiation of acyclovir in all febrile infants pending the collection and analysis of viral culture and polymerase chain reaction studies. Others have argued that a selective approach based on the history and physical exam is more appropriate when making decisions about the use of acyclovir in febrile infants. Given the safety of the drug, prudence would dictate the use of acyclovir in such patients if HSV infection cannot be excluded. In neonates with HSV infection including CNS involvement, the use of suppressive therapy with oral acyclovir for 6 mo has been demonstrated to improve neurodevelopmental outcome.

Acyclovir is indicated for the treatment of primary HSV gingivostomatitis and for primary genital HSV infection. Long-term suppressive therapy for genital HSV and for recurrent oropharyngeal infections (herpes labialis) is also effective. Acyclovir is also recommended for less-commonly encountered HSV infections, including herpetic whitlow, *eczema herpeticum*, and *herpes gladiatorum*. In addition, acyclovir is commonly used for prophylaxis against HSV reactivation in SOT and HSCT transplant patients. Severe end-organ HSV disease, including disseminated infection, is occasionally encountered in immunocompromised or pregnant patients, representing another clinical scenario where acyclovir therapy is warranted.

Acyclovir modifies the course of primary VZV infection, although the effect is modest. Acyclovir or another nucleoside analog should always be used in localized or disseminated VZV infections, such as pneumonia, particularly in immunocompromised patients. Primary VZV infection in pregnancy is another setting where acyclovir is indicated; this is a high-risk scenario and can be associated with a substantial risk of maternal mortality, particularly if pneumonia is present.

Acyclovir is available in topical, parenteral, and oral formulations, including an oral suspension formulation for pediatric use. Topical therapy has little role in pediatric practice and should be avoided in favor of alternative modes of delivery, particularly in infants with vesicular lesions compatible with herpetic infection; indeed, neonatal infection represents a setting in which topical therapy should never be used. The bioavailability of oral formulations is modest, with only 15-30% of the oral formulation being absorbed. There is widespread tissue distribution following systemic administration, and high concentrations of drug are achieved in the kidneys, lungs, liver, myocardium, and skin vesicles. Cerebrospinal fluid concentrations are approximately 50% of plasma concentrations. Acyclovir crosses the placenta, and breast milk concentrations are approximately 3 times plasma concentrations, although there are no data on efficacy of in utero therapy or impact of acyclovir therapy on nursing infants. Acyclovir therapy in a nursing mother is not a contraindication to breastfeeding. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Hemodialysis also eliminates acyclovir.

Acyclovir has an exceptional safety profile. Toxicity is observed typically only in exceptional circumstances: for example, if administered by rapid infusion to a dehydrated patient or a patient with underlying renal insufficiency, acyclovir can crystallize in renal tubules and produce a reversible obstructive uropathy. High doses of acyclovir are associated with neurotoxicity, and prolonged use can cause neutropenia. The favorable safety profile of acyclovir is underscored by recent studies of its safe use during pregnancy, and suppressive therapy in pregnant women with histories of recurrent genital HSV infection, typically with valacyclovir (see "Valacyclovir" below), has become standard of care among many obstetricians. One uncommon but important complication of long-term use of acyclovir is the selection for acyclovir-resistant HSV strains, which usually occurs from mutations in the HSV TK gene. Resistance is rarely observed in pediatric practice but should be considered in any patient who has been on long-term antiviral therapy and who has an HSV or VZV infection that fails to clinically respond to acyclovir therapy.

Valacyclovir

Valacyclovir is the L-valyl ester of acyclovir and is rapidly converted to acyclovir following oral administration. This agent has a safety and activity profile similar to that of acyclovir, but it has a bioavailability of >50%, 3-5–fold greater than that of acyclovir. Plasma concentrations approach those observed with intravenous acyclovir. Valacyclovir is only available for oral administration. A suspension formulation is not commercially available, but an oral suspension (25 mg/mL or 50 mg/mL) may be prepared extemporaneously from 500-mg caplets for use in pediatric patients for whom a solid dosage form is not appropriate. Suppressive therapy with valacyclovir is commonly prescribed in the 2nd and 3rd trimesters of pregnancy in women who have a clinical history of recurrent genital herpes. It is important to be aware that perinatal transmission of HSV can occur, leading to symptomatic disease in spite of maternal antenatal antiviral prophylaxis. In such settings, the possibility of emergence of acyclovir-resistant virus should be considered.

Penciclovir and Famciclovir

Penciclovir is an acyclic nucleoside analog that, like acyclovir, inhibits the viral DNA polymerase following phosphorylation to its active form. Compared with acyclovir, penciclovir has a substantially longer intracellular half-life, which in theory can confer superior antiviral activity at the intracellular level: however, there is no evidence that this effect confers clinical superiority. Penciclovir is licensed only as a topical formulation (1% penciclovir cream), and this formulation is indicated for therapy of cutaneous HSV infections. Topical therapy for primary or recurrent herpes labialis or cutaneous HSV infection is an appropriate use of penciclovir in children older than 2 yr of age.

Famciclovir is the prodrug formulation (diacetyl ester) of penciclovir. In contrast to penciclovir, famciclovir may be administered orally and has bioavailability of approximately 70%. Following oral administration, famciclovir is deacetylated to the parent drug, penciclovir. The efficacy of famciclovir for HSV and VZV infections appears equivalent to that of acyclovir, although the pharmacokinetic profile is more favorable. Famciclovir is indicated for oral therapy of HSV and VZV infections. There is currently no liquid or suspension formulation available. The toxicity profile is identical to that of acyclovir. In a clinical trial, valacyclovir was found to be superior to famciclovir in prevention of reactivation and reduction of viral shedding in the setting of recurrent genital HSV infection.

Ganciclovir

Ganciclovir is a nucleoside analog with structural similarity to acyclovir. Like acyclovir, ganciclovir must be phosphorylated for antiviral activity, which is targeted against the viral polymerase. The gene responsible for

ganciclovir phosphorylation is not *TK* but rather the virally encoded UL97 phosphotransferase gene. Antiviral resistance in CMV can be observed with prolonged use of nucleoside antivirals, and resistance should be considered in patients on long-term therapy who appear to fail to respond clinically and virologically. Ganciclovir is broadly active against many herpesviruses, including HSV and VZV, but its greatest value is derived from its activity against CMV. Ganciclovir was the first antiviral agent licensed specifically to treat and prevent CMV infection. It is indicated for prophylaxis against and therapy of CMV infections in high-risk patients, including HIV-infected patients and SOT or HSCT recipients. Of particular importance is the use of ganciclovir in the management of CMV retinitis, a sight-threatening complication of HIV infection. Ganciclovir is also of benefit for newborns with symptomatic congenital CMV infection and may be of value in partially ameliorating the sensorineural hearing loss and developmental disabilities that are common complications of congenital CMV infection.

Ganciclovir is supplied as parenteral and oral formulations. Ganciclovir ocular implants are also available for the management of CMV retinitis. The bioavailability of oral ganciclovir is poor, <10%. An oral prodrug, valganciclovir, is well absorbed from the gastrointestinal tract and quickly converted to ganciclovir by intestinal or hepatic metabolism. Bioavailability of ganciclovir (from valganciclovir) is approximately 60% from tablet and solution formulations. Significant concentrations are found in aqueous humor, subretinal fluid, cerebrospinal fluid, and brain tissue (enough to inhibit susceptible strains of CMV). Subretinal concentrations are comparable to plasma concentrations, but intravitreal concentrations are lower. Drug concentrations in the CNS range from 24-70% of plasma concentrations. The main route of elimination is renal, and dosage adjustments are necessary for renal insufficiency. Dose reduction is proportional to the creatinine clearance. Hemodialysis efficiently eliminates ganciclovir, so administration of additional doses after dialysis is necessary.

Ganciclovir has several important toxicities. Reversible myelosuppression is the most important toxicity associated with ganciclovir therapy and commonly requires either discontinuation of therapy or the intercurrent administration of granulocyte colony-stimulating factor. There are also the theoretical risks for carcinogenicity and gonadal toxicity; although these effects have been observed in some animal models, they have never been observed in patients. The decision to administer ganciclovir to a pediatric patient is complex and should be made in consultation with a pediatric infectious diseases specialist.

Foscarnet

Foscarnet has a unique profile, insofar as it is not a nucleoside analog but rather a pyrophosphate analog. The drug has broad activity against most herpesviruses. Like the nucleoside analogs, foscarnet inhibits viral DNA polymerase. On the other hand, foscarnet does not require phosphorylation to exert its antiviral activity, thus differing from the nucleoside analogs. It binds to a different site on the viral DNA polymerase to exert its antiviral effect and therefore retains activity against strains of HSV and CMV that are resistant to nucleoside analogs. Its clinical utility is as a second-line agent for management of CMV infections in high-risk patients who cannot tolerate ganciclovir and as an alternative for patients with persistent or refractory HSV, CMV, or VZV disease with suspected or documented antiviral drug resistance.

Foscarnet is only available as a parenteral formulation and is a toxic agent that must be administered cautiously. Nephrotoxicity is common, and reversible renal insufficiency is often observed, as evidenced by an increase in serum creatinine. Abnormalities in calcium and phosphorus homeostasis are common, and electrolytes and renal function must be monitored carefully during treatment.

Cidofovir

Cidofovir is an acyclic nucleotide analog that requires phosphorylation to its active form, cidofovir diphosphate, to exert its antiviral effect. Analogous to penciclovir, it has an extended intracellular half-life that contributes to its prolonged antiviral activity. Cidofovir is active against HSV, VZV, and CMV. In contrast to most of the other agents with activity against herpesviruses, cidofovir also exhibits broad-spectrum activity against other DNA viruses, most notably the poxviruses. Cidofovir has activity against the BK virus, a polyomavirus, and therapy may be warranted in some settings of BK reactivation post-HSCT and SOT. Cidofovir is also useful in the management of CMV disease caused by strains with documented ganciclovir resistance.

Cidofovir is administered intravenously and is cleared renally by tubular secretion. Extensive prehydration and coadministration of probenecid are recommended. Nephrotoxicity is commonly encountered, even with appropriate prehydration; cidofovir must be coadministered with other nephrotoxic medications with care. Other potential toxicities include reproductive toxicity and carcinogenesis.

Trifluridine

Trifluridine is a pyrimidine nucleoside analog with activity against HSV, CMV, and adenovirus. It is formulated as a 1% ophthalmic solution and approved for topical use in the treatment of HSV keratitis and keratoconjunctivitis. Trifluridine is the treatment of choice for HSV keratitis, a disease that should always be managed in consultation with an ophthalmologist.

Vidarabine

Vidarabine is a nucleoside analog that has activity against HSV. It was the first parenteral antiviral agent for HSV infection, although it is no longer available for intravenous administration. A topical preparation remains available to treat HSV keratitis and is considered a second-line agent for this indication.

Fomivirsen

Fomivirsen is a novel anti-CMV compound that is used as a second-line agent for CMV retinitis by direct injection into the vitreous space. It is an antisense 21-mer DNA oligonucleotide that binds directly to complementary messenger RNA. This agent was the first antisense antiviral agent approved by the FDA. The standard dosage is 330 μg via intravitreal injection every 2 wk for 2 doses followed by maintenance therapy of 330 μg every 4 wk. There is no systemic absorption following intravitreal injection.

New Agents

There is a major need for development of new, nontoxic antivirals for HSV infection. Two new agents are approaching licensure that will be very useful in the management of HSCT and SOT patients. The oral lipid conjugate prodrug of cidofovir, **CMX001**, has improved activity against herpesviruses compared to parenterally administered cidofovir and a markedly reduced risk of nephrotoxicity. Another novel agent, letermovir (AIC246), is highly orally bioavailable and has a novel mechanism of action, exerting its antiviral effect by interfering with the viral terminase complex. This agent demonstrates substantial promise as an alternative to more toxic antivirals in patients at high risk for CMV disease, particularly in the transplantation setting. It is also active against BK virus and poxviruses.

ANTIVIRALS USED FOR RESPIRATORY VIRAL INFECTIONS

Antiviral therapies are available for many respiratory pathogens, including respiratory syncytial virus (RSV), influenza A, and influenza B. Antiviral therapy for respiratory viral infections is of particular value for infants, children with chronic lung disease, and immunocompromised children.

Ribavirin

Ribavirin is a guanosine analog that has broad-spectrum activity against a variety of viruses, particularly RNA viruses. Its precise mechanism of action is incompletely understood but is probably related to interference with viral messenger RNA processing and translation. Ribavirin is available in oral, parenteral, and aerosolized formulations. Although intravenous ribavirin is highly effective in the management of Lassa fever and other hemorrhagic fevers, this formulation is not licensed for use in the United States. The only licensed formulations in the United States are an aqueous formulation for aerosol administration (indicated for RSV infection) and an oral formulation that is combined with interferon-α for the treatment of hepatitis C. (For more information about antivirals

for hepatitis, see Chapter 358.) Administration of ribavirin by aerosol should be considered for serious RSV lower respiratory tract disease in immunocompromised children, young infants with serious RSV-associated illness, and high-risk infants and children (children with chronic lung disease or cyanotic congenital heart disease). In vitro testing and uncontrolled clinical studies also suggest efficacy of aerosolized ribavirin for parainfluenza, influenza, and measles infections.

Ribavirin is generally nontoxic, particularly when administered by aerosol. Ribavirin and its metabolites concentrate in red blood cells and can persist for several weeks and, in rare instances, may be associated with anemia. Conjunctivitis and bronchospasm have been reported following exposure to aerosolized drug. Care must be taken when using aerosolized ribavirin in children undergoing mechanical ventilation to avoid precipitation of particles in ventilator tubing; the drug is not formally approved for use in the mechanically ventilated patient, although there is published experience with this approach and it can be considered for mechanically ventilated patients, particularly in a "high-dose, short-duration" regimen. Concerns regarding potential teratogenicity from animal studies have not been borne out in clinical practice, although care should be taken to prevent inadvertent exposure to aerosolized drug in pregnant healthcare providers.

Amantadine and Rimantadine

Amantadine and rimantadine are tricyclic amines that are highly similar to each other, both structurally and functionally. Both are indicated for the prophylaxis and therapy of influenza A, and neither has discernible activity against influenza B or any other respiratory viruses. For maximal therapeutic efficacy, therapy should begin as soon as possible and within 48 hr of the onset of symptoms. Influenza immunization is a greatly preferred method of disease control, but these agents can be useful for prophylaxis, particularly in unimmunized, high-risk persons during annual seasonal epidemics of influenza.

The mechanism of action of the tricyclic amines against influenza A virus is unclear, but they appear to exert their antiviral effect at the level of uncoating of the virus. Both agents are extremely well absorbed after oral administration and are eliminated via the kidneys (90% of the dose is unchanged), necessitating dosage adjustments for renal insufficiency. The toxicities of the tricyclic amines are modest and include CNS adverse effects such as anxiety, difficulty concentrating, and lightheadedness and gastrointestinal adverse effects such as nausea and loss of appetite. Adverse effects are less common with rimantadine than with amantadine.

Oseltamivir, Zanamivir, and Peramivir

Oseltamivir and zanamivir are active against both influenza A and B, although the importance of this broader spectrum of antiinfluenza activity in disease control is modest because influenza B infection is typically a much milder illness. Emerging strains of influenza, including H5N1 and the 2009-2010 pandemic strain, H1N1 (swine flu), are susceptible to oseltamivir and zanamivir but resistant to amantadine. Therefore, these agents are emerging as the antivirals of choice for influenza infection. Neither agent has appreciable activity against other respiratory viruses. The mechanism of antiviral activity of these agents is via inhibition of the influenza neuraminidase.

Zanamivir has poor oral bioavailability and is licensed only for inhalational administration. With inhaled administration, >75% of the dose is deposited in the oropharynx and much of it is swallowed. The actual amount distributed to the airways and lungs depends on factors such as the patient's inspiratory flow. Approximately 13% of the dose appears to be distributed to the airways and lungs, with approximately 10% of the inhaled dose distributed systemically. Local respiratory mucosal drug concentrations greatly exceed the drug concentration needed to inhibit influenza A and B viruses. Elimination is via the kidneys, and no dosage adjustment is necessary with renal insufficiency, because the amount that is systemically absorbed is low.

Oseltamivir is administered as an esterified prodrug that has high oral bioavailability. It is eliminated by tubular secretion, and dosage adjustment is required for patients with renal insufficiency. Gastrointestinal adverse effects, including nausea and vomiting, are occasionally observed. The drug is indicated for both treatment and prophylaxis. The usual adult dosage for treatment of influenza is 75 mg twice daily for 5 days. Treatment should be initiated within 2 days of the appearance of symptoms. Recommended treatment dosages for children vary by age and weight. The recommended dose for children younger than 1 yr of age is 3 mg/kg/dose twice a day. For children older than 1 yr of age, doses are 30 mg twice a day for children weighing ≤15 kg, 45 mg twice a day for children weighing 15-23 kg, 60 mg twice a day for those weighing 23-40 kg, and 75 mg twice a day for children weighing ≥40 kg. Dosages for chemoprophylaxis are the same for each weight group in children older than 1 yr of age, but the drug should be administered only once daily rather than twice daily. Oseltamivir is FDA-approved for therapy of influenza A and B treatment in children 2 wk of age and older, whereas zanamivir is recommended for treatment of children 7 yr of age and older. Current treatment and dosage recommendations for treatment of influenza in children and for chemoprophylaxis are available at: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Oseltamivir has been described to produce neuropsychiatric (narcolepsy) and psychologic (suicidal events) side effects in some patient populations; the drug should be discontinued if behavioral or psychiatric side effects are observed. In late 2014 the FDA approved another neuraminidase inhibitor, peramivir, for treatment of influenza. It is available as a single-dose, intravenous option. The standard adult dose is 600 mg IV in a single, one-time dose. The drug is currently approved for use only in adults.

ANTIVIRAL IMMUNE GLOBULINS

Immune globulins are useful adjuncts in the management of viral disease. However, they are most useful when administered as prophylaxis against infection and disease in high-risk patients; their value as therapeutic agents in the setting of established infection is less clear. **Varicella-zoster immune globulin (human)** is valuable for prophylaxis against VZV in high-risk children, particularly newborns and immunocompromised children (see Chapter 253). **Cytomegalovirus immune globulin** is warranted for children at high risk for CMV disease, particularly SOT and HSCT patients, and can play a role in preventing injury to the infected fetus when administered to the pregnant patient (see Chapter 255). **Palivizumab,** a monoclonal antibody with anti-RSV activity, is effective for preventing severe RSV lower respiratory tract disease in high-risk premature infants and has replaced **RSV immune globulin** (see Chapter 260). **Hepatitis B immune globulin** is indicated in infants born to hepatitis B surface antigen-positive mothers (see Chapter 358).

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Chapter 246

Measles

Wilbert H. Mason

Measles is highly contagious but owing to widespread vaccination, endemic transmission has been interrupted in the United States; indigenous or imported cases (in children or adults) have occasionally resulted in epidemics in the United States in unimmunized or partially immunized American or foreign-born children (adopted children, refugees, returning tourists). In some areas of the world, measles remains a serious threat to children.

ETIOLOGY

Measles virus is a single-stranded, lipid-enveloped RNA virus in the family Paramyxoviridae and genus *Morbillivirus.* Other members of the genus *Morbillivirus* affect a variety of mammals, such as rinderpest virus in cattle and distemper virus in dogs, but humans are

the only host of measles virus. Of the 6 major structural proteins of measles virus, the 2 most important in terms of induction of immunity are the hemagglutinin (H) protein and the fusion (F) protein. The neutralizing antibodies are directed against the H protein, and antibodies to the F protein limit proliferation of the virus during infection. Small variations in genetic composition have also been identified that result in no effect on protective immunity but provide molecular markers that can distinguish between viral types. Related genotypes have been grouped by clades, and the World Health Organization recognizes 8 clades, A-H, and 23 genotypes. These markers have been useful in the evaluation of endemic and epidemic spread of measles.

EPIDEMIOLOGY

The measles vaccine has changed the epidemiology of measles dramatically. Once worldwide in distribution, endemic transmission of measles has been interrupted in many countries where there is widespread vaccine coverage. Historically, measles caused universal infection in childhood in the United States, with 90% of children acquiring the infection before 15 yr of age. Morbidity and mortality associated with measles decreased prior to the introduction of the vaccine as a result of improvements in healthcare and nutrition. However, the incidence declined dramatically following the introduction of the measles vaccine in 1963. The attack rate fell from 313 cases per 100,000 population in 1956-1960 to 1.3 cases per 100,000 in 1982-1988.

A nationwide indigenous measles outbreak occurred in the United States in 1989-1991, resulting in more than 55,000 cases, 11,000 hospitalizations, and 123 deaths, demonstrating that the infection had not yet been conquered. This resurgence was attributed to vaccine failure in a small number of school-age children, low coverage of preschool-age children, and more rapid waning of maternal antibodies in infants born to mothers who had never experienced wild-type measles infection. Implementation of the 2 dose vaccine policy and more intensive immunization strategies resulted in interruption of endemic transmission in the United States in 1993. The current rate is <1 case per 1,000,000 population.

Measles continues to be imported into the United States from abroad; therefore, continued maintenance of >90% immunity through vaccination is necessary to prevent widespread outbreaks from occurring (Fig. 246-1).

In 2011, 222 cases of measles were reported to the U.S. Centers for Disease Control and Prevention (CDC), an incidence rate of 0.7 per 1,000,000 population. There were 17 outbreaks reported compared to a median of 4 outbreaks reported annually during 2001-2010. Of the 222 cases, 200 were associated with importations from other countries (returning tourists, adoptees, refugees) and 112 were associated with outbreaks. Measles rates remain high in the World Health Organization European Region, which reported more than 30,000 cases in 2011. Almost half of the measles importations to the United States were from this World Health Organization region.

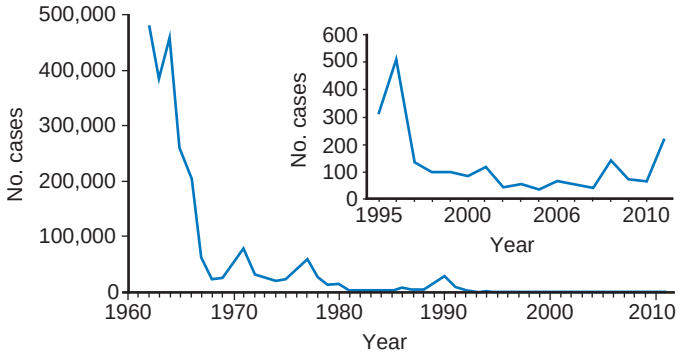

Figure 246-1 Number of measles cases—United States, 1962–2011. Measles data provided were reported voluntarily to Centers for Disease Control and Prevention (CDC) from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS; Centers for Disease Control and Prevention: Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP).* MMWR Recomm Rep *62(RR-04):1–34, 2013, Fig. 1.)*

High measles vaccination coverage rates early in life are essential to maintain the endemic spread of measles in the United States (>90% 1 dose coverage at 12-15 mo and >95% 2 dose coverage in school-age children.) While measles-mumps-rubella coverage was high (median: 94.8%) in the 2011-2012 school year, pockets of lower coverage rates exist because of reluctance of parents to vaccinate their children because of personal beliefs. This variability in vaccination has contributed to outbreaks among school-age children in recent years. In addition, measles may occur more often in children receiving the first dose at age 12-13 mo when compared to those immunized at age 15 mo and older.

TRANSMISSION

The portal of entry of measles virus is through the respiratory tract or conjunctivae following contact with large droplets or small-droplet aerosols in which the virus is suspended. Patients are infectious from 3 days before to up to 4-6 days after the onset of rash. Approximately 90% of exposed susceptible individuals experience measles. Face-to-face contact is not necessary, because viable virus may be suspended in air for as long as 1 hr after the patient with the source case leaves a room. Secondary cases from spread of aerosolized virus have been reported in airplanes, physicians' offices, and hospitals.

PATHOLOGY

Measles infection causes necrosis of the respiratory tract epithelium and an accompanying lymphocytic infiltrate. Measles produces a small-vessel vasculitis on the skin and on the oral mucous membranes. Histology of the rash and exanthem reveals intracellular edema and dyskeratosis associated with formation of epidermal syncytial giant cells with up to 26 nuclei. Viral particles have been identified within these giant cells. In lymphoreticular tissue, lymphoid hyperplasia is prominent. Fusion of infected cells results in multinucleated giant cells, the **Warthin-Finkeldey giant cells** that are pathognomonic for measles, with up to 100 nuclei and intracytoplasmic and intranuclear inclusions.

PATHOGENESIS

Measles consists of 4 phases: incubation period, prodromal illness, exanthematous phase, and recovery. During incubation, measles virus migrates to regional lymph nodes. A primary viremia ensues that disseminates the virus to the reticuloendothelial system. A secondary viremia spreads virus to body surfaces. The prodromal illness begins after the secondary viremia and is associated with epithelial necrosis and giant cell formation in body tissues. Cells are killed by cell-to-cell plasma membrane fusion associated with viral replication that occurs in many body tissues, including cells of the central nervous system. Virus shedding begins in the prodromal phase. With onset of the rash, antibody production begins, and viral replication and symptoms begin to subside. Measles virus also infects $CD4^+$ T cells, resulting in suppression of the Th1 immune response and a multitude of other immunosuppressive effects.

Recent research has clarified the pathogenesis of disease caused by measles virus. Unlike other Paramyxoviridae members that utilize sialic acid molecules on the virus surface to enter cells, measles virus attaches to specific cell receptors to infect host cells. Studies in primates show that the initial targets for measles virus are alveolar macrophages, dendritic cells, and lymphocytes. The cell receptor used appears to be the signaling lymphocyte activating molecule or more properly CD150. Subsequently, respiratory epithelial cells become infected but do not express CD150. The mechanism of infection of respiratory tissues is attachment to the PVRL4 receptor (Nectin4) that is expressed on cells in the trachea, oral mucosa, nasopharynx, and lungs. These 2 receptors, CD150 and PVRL4, account for the lymphotropic and epitheliotropic nature of natural measles virus infection, and along with the prolonged immunosuppressive effects of measles, suggest that it is more characteristic of human immunodeficiency virus infection than a respiratory illness.

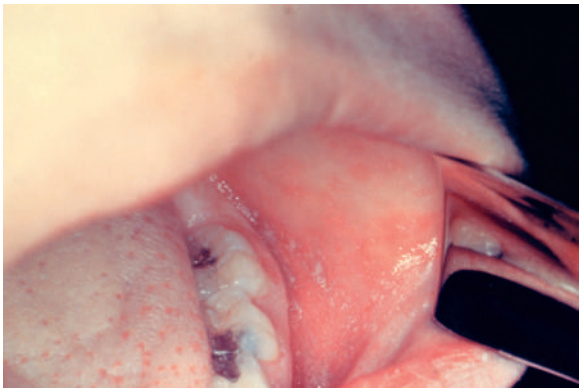

Figure 246-2 Koplik spots on the buccal mucosa during the 3rd day of rash. *(From Centers for Disease Control and Prevention (CDC): Public health image library, image #4500. Available at: http://phil.cdc.gov/phil/details.asp)*

CLINICAL MANIFESTATIONS

Measles is a serious infection characterized by high fever, an enanthem, cough, coryza, conjunctivitis, and a prominent exanthem. After an incubation period of 8-12 days, the prodromal phase begins with a mild fever followed by the onset of conjunctivitis with photophobia, coryza, a prominent cough, and increasing fever. **Koplik spots** represent the enanthem and are the pathognomonic sign of measles, appearing 1-4 days prior to the onset of the rash (Fig. 246-2). They first appear as discrete red lesions with bluish white spots in the center on the inner aspects of the cheeks at the level of the premolars. They may spread to involve the lips, hard palate, and gingiva. They also may occur in conjunctival folds and in the vaginal mucosa. Koplik spots have been reported in 50-70% of measles cases but probably occur in the great majority.

Symptoms increase in intensity for 2-4 days until the 1st day of the rash. The rash begins on the forehead (around the hairline), behind the ears, and on the upper neck as a red maculopapular eruption. It then spreads downward to the torso and extremities, reaching the palms and soles in up to 50% of cases. The exanthem frequently becomes confluent on the face and upper trunk (Fig. 246-3).

With the onset of the rash, symptoms begin to subside. The rash fades over about 7 days in the same progression as it evolved, often leaving a fine desquamation of skin in its wake. Of the major symptoms of measles, the cough lasts the longest, often up to 10 days. In more-severe cases, generalized lymphadenopathy may be present, with cervical and occipital lymph nodes especially prominent.

INAPPARENT MEASLES INFECTION

In individuals with passively acquired antibody, such as infants and recipients of blood products, a subclinical form of measles may occur. The rash may be indistinct, brief, or, rarely, entirely absent. Likewise, some individuals who have received vaccine, when exposed to measles, may have a rash but few other symptoms. Persons with inapparent or subclinical measles do not shed measles virus and do not transmit infection to household contacts.

LABORATORY FINDINGS

The diagnosis of measles is almost always based on clinical and epidemiologic findings. Laboratory findings in the acute phase include reduction in the total white blood cell count, with lymphocytes decreased more than neutrophils. Absolute neutropenia has been known to occur, however. In measles not complicated by bacterial infection, the erythrocyte sedimentation rate and C-reactive protein level are normal.

DIAGNOSIS

In the absence of a recognized measles outbreak, confirmation of the clinical diagnosis is often recommended. Serologic confirmation is most conveniently made by identification of immunoglobulin (Ig) M antibody in serum. IgM antibody appears 1-2 days after the onset of the rash and remains detectable for about 1 mo. If a serum specimen is collected <72 hr after onset of rash and is negative for measles antibody, a second specimen should be obtained. Serologic confirmation may also be made by demonstration of a 4-fold rise in IgG antibodies in acute and convalescent specimens collected 2-4 wk apart. Viral isolation from blood, urine, or respiratory secretions can be accomplished by culture at the CDC or local or state laboratories. Molecular detection by polymerase chain reaction is available through some state and local health departments and through the CDC.

Figure 246-3 A child with measles displaying the characteristic red blotchy pattern on his face and body. *(From Kremer JR, Muller CP: Measles in Europe—there is room for improvement,* Lancet *373:356–358, 2009.)*

DIFFERENTIAL DIAGNOSIS

Typical measles is unlikely to be confused with other illnesses, especially if Koplik spots are observed. Measles in the later stages or inapparent or subclinical infections may be confused with a number of other exanthematous immune-mediated illnesses and infections, including rubella, adenovirus infection, enterovirus infection, and Epstein-Barr virus infection. Exanthem subitum (in infants) and erythema infectiosum (in older children) may also be confused with measles. *Mycoplasma pneumoniae* and group A streptococcus may also produce rashes similar to that of measles. Kawasaki syndrome can cause many of the same findings as measles but lacks discrete intraoral lesions (Koplik spots) and a severe prodromal cough, and typically leads to elevations of neutrophils and acute-phase reactants. In addition, the characteristic thrombocytosis of Kawasaki syndrome is absent in measles (see Chapter 166). Drug eruptions may occasionally be mistaken for measles.

COMPLICATIONS

Complications of measles are largely attributable to the pathogenic effects of the virus on the respiratory tract and immune system (Table 246-1). Several factors make complications more likely. Morbidity and mortality from measles are greatest in patients younger than 5 yr of age (especially <1 yr of age) and older than 20 yr of age. In developing countries, higher case fatality rates have been associated with crowding, possibly attributable to larger inoculum doses after household exposure. Severe malnutrition in children results in a suboptimal

Table 246-1 Complications By Age for Reported Measles Cases, United States, 1987-2000

COMPLICATION	OVERALL (67,032 CASES WITH AGE INFORMATION)	No. (%) of Persons with Complication by Age Group				
		<5 YR (N = 28,730)	5-9 YR (N = 6,492)	10-19 YR (N = 18,580)	20-29 YR (N = 9,161)	<30 YR (N = 4,069)
Any	19,480 (29.1)	11,883 (41.4)	1,173 (18.1)	2,369 (12.8)	2,656 (29.0)	1,399 (34.4)
Death	177 (0.3)	97 (0.3)	9 (0.1)	18 (0.1)	26 (0.3)	27 (0.7)
Diarrhea	5,482 (8.2)	3,294 (11.5)	408 (6.3)	627 (3.4)	767 (8.4)	386 (9.5)
Encephalitis	97 (0.1)	43 (0.2)	9 (0.1)	13 (0.1)	21 (0.2)	11 (0.3)
Hospitalization	12,876 (19.2)	7,470 (26.0)	612 (9.4)	1,612 (8.7)	2,075 (22.7)	1,107 (27.2)
Otitis media	4,879 (7.3)	4,009 (14.0)	305 (4.7)	338 (1.8)	157 (1.7)	70 (1.7)
Pneumonia	3,959 (5.9)	2,480 (8.6)	183 (2.8)	363 (2.0)	554 (6.1)	379 (9.3)

From Perry RT, Halsey NA: The clinical significance of measles: a review, Clin Infect Dis *189(Suppl 1):S4–S16, 2004.*

immune response and higher morbidity and mortality with measles infection. Low serum retinol levels in children with measles are associated with higher measles morbidity and mortality in developing countries and in the United States. Measles infection lowers serum retinol concentrations, so subclinical cases of hyporetinolemia may be made symptomatic during measles. Measles infection in immunocompromised persons is associated with increased morbidity and mortality. Among patients with malignancy in whom measles develops, pneumonitis occurs in 58% and encephalitis occurs in 20%.

Pneumonia is the most common cause of death in measles. It may manifest as **giant cell pneumonia** caused directly by the viral infection or as superimposed bacterial infection. The most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus*. Following severe measles pneumonia, the final common pathway to a fatal outcome is often the development of bronchiolitis obliterans.

Croup, tracheitis, and bronchiolitis are common complications in infants and toddlers with measles. The clinical severity of these complications frequently requires intubation and ventilatory support until the infection resolves.

Acute otitis media is the most common complication of measles and was of particularly high incidence during the epidemic of the late 1980s and early 1990s because of the relatively young age of affected children. Sinusitis and mastoiditis also occur as complications. Viral and/or bacterial tracheitis is seen and can be life-threatening. Retropharyngeal abscess has also been reported.

Measles infection is known to suppress skin test responsiveness to purified tuberculin antigen. There may be a higher rate of activation of pulmonary tuberculoses in populations of individuals infected with *Mycobacterium tuberculosis* who are then exposed to measles.

Diarrhea and vomiting are common symptoms associated with acute measles, and diffuse giant cell formation is found in the epithelium in the gastrointestinal tract. Dehydration is a common consequence, especially in young infants and children. Appendicitis or abdominal pain may occur from obstruction of the appendiceal lumen by lymphoid hyperplasia.

Febrile seizures occur in <3% of children with measles. Encephalitis following measles is a long-associated complication, often with an unfavorable outcome. Rates of 1-3 per 1,000 cases of measles have been reported, with greater numbers occurring in adolescents and adults than in preschool- or school-age children. Encephalitis is a postinfectious, immunologically mediated process and is not the result of a direct effect by the virus. Clinical onset begins during the exanthem and manifests as seizures (56%), lethargy (46%), coma (28%), and irritability (26%). Findings in cerebrospinal fluid include lymphocytic pleocytosis in 85% of cases and elevated protein concentrations. Approximately 15% of patients with measles encephalitis die. Another 20-40% of patients suffer long-term sequelae, including mental retardation, motor disabilities, and deafness.

Measles encephalitis in immunocompromised patients results from direct damage to the brain by the virus. Subacute measles encephalitis manifests 1-10 mo after measles in immunocompromised patients, particularly those with AIDS, lymphoreticular malignancies, and immunosuppression. Signs and symptoms include seizures, myoclonus, stupor, and coma. In addition to intracellular inclusions, abundant viral nucleocapsids and viral antigen are seen in brain tissue. Progressive disease and death almost always occur.

A severe form of measles rarely seen now is **hemorrhagic measles** or **"black measles."** It manifested as a hemorrhagic skin eruption and was often fatal. Keratitis, appearing as multiple punctate epithelial foci, resolved with recovery from the infection. Thrombocytopenia sometimes occurred following measles.

Myocarditis is a rare complication of measles. Miscellaneous bacterial infections have been reported, including bacteremia, cellulitis, and toxic shock syndrome. Measles during pregnancy is associated with high rates of maternal morbidity, fetal wastage, and stillbirths with and congenital malformations in 3% of liveborn infants.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic complication of measles with a delayed onset and an outcome that is nearly always fatal. It appears to result from a persistent infection with an altered measles virus that is harbored intracellularly in the central nervous system for several years. After 7-10 yr the virus apparently regains virulence and attacks the cells in the central nervous system that offered the virus protection. This "slow virus infection" results in inflammation and cell death, leading to an inexorable neurodegenerative process.

SSPE is a rare disease and generally follows the prevalence of measles in a population. The incidence in the United States in 1960 was 0.61 cases per million persons younger than age 20 yr. By 1980 the rate had fallen to 0.06 cases per million. Between 1956 and 1982 a total of 634 cases of SSPE had been reported to the national SSPE registry. After 1982 approximately 5 cases/yr were reported annually in the United States, and only 2-3 cases/yr were reported in the early 1990s. However, between 1995 and 2000, reported cases in the United States increased and 13 cases were reported in 2000. Nine of the 13 cases occurred in foreign-born individuals. This "resurgence" may be the result of an increased incidence of measles between 1989 and 1991. Although the age of onset ranges from <1 yr to <30 yr, the illness is primarily one of children and adolescents. Measles at an early age favors the development of SSPE: 50% of patients with SSPE had primary measles before 2 yr of age, and 75% had measles before 4 yr of age. Males are affected twice as often as females, and there appear to be more cases reported from rural than urban populations. Recent observations from the registry indicate a higher prevalence among children of Hispanic origin.

The pathogenesis of SSPE remains enigmatic. Factors that seem to be involved include defective measles virus and interaction with a defective or immature immune system. The virus isolated from brain tissue of patients with SSPE is missing 1 of the 6 structural proteins, the matrix or M protein. This protein is responsible for assembly, orientation, and alignment of the virus in preparation for budding during

viral replication. Immature virus may be able to reside, and possibly propagate, within neuronal cells for long periods. The fact that most patients with SSPE were exposed at a young age suggests that immune immaturity is involved in pathogenesis. In addition, the intracellular location of the virus sequesters it from the immune system, especially from humoral immunity.

Clinical manifestations of SSPE begin insidiously 7-13 yr after primary measles infection. Subtle changes in behavior or school performance appear, including irritability, reduced attention span, and temper outbursts. This initial phase (stage I) may at times be missed because of brevity or mildness of the symptoms. Fever, headache, and other signs of encephalitis are absent. The hallmark of the 2nd stage is massive myoclonus, which coincides with extension of the inflammatory process site to deeper structures in the brain, including the basal ganglia. Involuntary movements and repetitive myoclonic jerks begin in single muscle groups but give way to massive spasms and jerks involving both axial and appendicular muscles. Consciousness is maintained. In the 3rd stage, involuntary movements disappear and are replaced by choreoathetosis, immobility, dystonia, and lead pipe rigidity that result from destruction of deeper centers in the basal ganglia. The sensorium deteriorates into dementia, stupor, and then coma. The 4th stage is characterized by loss of critical centers that support breathing, heart rate, and blood pressure. Death soon ensues. Progression through the clinical stages may follow courses characterized as acute, subacute, or chronic progressive.

The diagnosis of SSPE can be established through documentation of a compatible clinical course and at least 1 of the following supporting findings: (1) measles antibody detected in cerebrospinal fluid, (2) characteristic electroencephalographic findings, and (3) typical histologic findings in and/or isolation of virus or viral antigen from brain tissue obtained by biopsy or postmortem examination.

Cerebrospinal fluid analysis reveals normal cells but elevated IgG and IgM antibody titers in dilutions >1:8. Electroencephalographic patterns are normal in stage I, but in the myoclonic phase, suppression-burst episodes are seen that are characteristic of, but not pathognomonic for, SSPE. Brain biopsy is no longer routinely indicated for diagnosis of SSPE.

Management of SSPE is primarily supportive and similar to care provided to patients with other neurodegenerative diseases. Clinical trials using isoprinosine with or without interferon suggest significant benefit (30-34% remission rate) compared to patients without treatment (5-10% with spontaneous remissions).

It is recognized that carbamazepine is of significant benefit in the control of myoclonic jerks in the early stages of the illness.

Virtually all patients eventually succumb to SSPE. Most die within 1-3 yr of onset from infection or loss of autonomic control mechanisms. Prevention of SSPE depends on prevention of primary measles infection through vaccination. SSPE has been described in patients who have no history of measles infection and only exposure to the vaccine virus. However, wild-type virus, not vaccine virus, has been found in brain tissue of at least some of these patients, suggesting that they had had subclinical measles previously.

TREATMENT

Management of measles is supportive. Antiviral therapy is not effective in the treatment of measles in otherwise normal patients. Maintenance of hydration, oxygenation, and comfort are goals of therapy. Antipyretics for comfort and fever control are useful. For patients with respiratory tract involvement, airway humidification and supplemental oxygen may be of benefit. Respiratory failure from croup or pneumonia may require ventilatory support. Oral rehydration is effective in most cases, but severe dehydration may require intravenous therapy. Prophylactic antimicrobial therapy to prevent bacterial infection is not indicated.

Measles infection in immunocompromised patients is highly lethal. Ribavirin is active in vitro against measles virus. Anecdotal reports of ribavirin therapy with or without intravenous gamma globulin suggest some benefit in individual patients. However, no controlled trials have been performed, and ribavirin is not licensed in the United States for treatment of measles.

Vitamin A

Vitamin A deficiency in children in developing countries has long been known to be associated with increased mortality from a variety of infectious diseases, including measles. In the United States, studies in the early 1990s documented that 22-72% of children with measles had low retinol levels. In addition, 1 study demonstrated an inverse correlation between the level of retinol and severity of illness. Several randomized controlled trials of vitamin A therapy in the developing world and the United States have demonstrated reduced morbidity and mortality from measles. Vitamin A therapy is indicated for all patients with measles. Vitamin A should be administered once daily for 2 days at doses of 200,000 IU for children 12 mo of age or older; 100,000 IU for infants 6 mo through 11 mo of age; and 50,000 IU for infants younger than 6 mo of age.

In children with signs and symptoms of vitamin A deficiency, a 3rd age-appropriate dose is recommended 2 through 4 wk after the 2nd dose.

PROGNOSIS

In the early 20th century, deaths from measles in the United States varied between 2,000 and 10,000 per year, or about 10 deaths per 1,000 cases of measles. With improvements in healthcare and antimicrobial therapy, better nutrition, and decreased crowding, the death : case ratio fell to 1 per 1,000 cases. Between 1982 and 2002, the CDC estimated that there were 259 deaths caused by measles in the United States, with a death : case ratio of 2.5-2.8 per 1,000 cases of measles. Pneumonia and encephalitis were complications in most of the fatal cases, and immunodeficiency conditions were identified in 14-16% of deaths. In 2011, of the 222 cases reported in the United States, 70 (32%) were hospitalized, including 17 (24%) with diarrhea, 15 (21%) with dehydration, and 12 (17%) with pneumonia. No cases of encephalitis or deaths were reported.

PREVENTION

Patients shed measles virus from 7 days after exposure to 4-6 days after the onset of rash. Exposure of susceptible individuals to patients with measles should be avoided during this period. In hospitals, standard and airborne precautions should be observed for this period. Immunocompromised patients with measles will shed virus for the duration of the illness, so isolation should be maintained throughout the disease.

Vaccine

Measles vaccine in the United States is available as a monovalent preparation or combined with the measles-rubella or measles-mumps-rubella vaccine, the last of which is the recommended form in most circumstances (Table 246-2). Following the measles resurgence of 1989-1991, a 2nd dose of measles vaccine was added to the schedule. The current recommendations include a 1st dose at 12-15 mo of age, followed by a 2nd dose at 4-6 yr of age. Seroconversion is slightly lower in children who receive the 1st dose before or at 12 mo of age (87% at 9 mo, 95% at 12 mo, and 98% at 15 mo) because of persisting maternal antibody. For children who have not received 2 doses by 11-12 yr of age, a 2nd dose should be provided. Infants who receive a dose before 12 mo of age should be given 2 additional doses at 12-15 mo and 4-6 yr of age.

Adverse events from the measles-mumps-rubella vaccine include fever (usually 6-12 days following vaccination), rash in approximately 5% of vaccinated persons, and, rarely, transient thrombocytopenia. Children prone to febrile seizures may experience an event following vaccination, so the risks and benefits of vaccination should be discussed with parents. Encephalopathy and autism have not been shown to be causally associated with the measles-mumps-rubella vaccine or vaccine constituents.

A review of the effect of measles vaccination on the epidemiology of SSPE has demonstrated that measles vaccination protects against SSPE and does not accelerate the course of SSPE or trigger the disease in those already infected with wild measles virus.

Passively administered immune globulin may inhibit the immune response to live measles vaccine, and administration should be delayed for variable amounts of time based on the dose of immune globulin (Table 246-3).

Table 246-2 Recommendations for Measles Immunization

CATEGORY	RECOMMENDATIONS
Unimmunized, no history of measles (12-15 mo of age)	A 2 dose schedule (with MMR) is recommended The 1st dose is recommended at 12-15 mo of age; the 2nd is recommended at 4-6 yr of age
Children 6-11 mo of age in epidemic situations or prior to international travel	Immunize with MMR vaccine, but this dose is not considered valid, and 2 valid doses administered on or after the 1st birthday are required, The 1st valid dose should be administered at 12-15 mo of age. The 2nd valid dose is recommended at least 28 days later and is given at 4 through 6 yr of age
Students in kindergarten or elementary, middle, and high school who have received 1 dose of measles vaccine at 12 mo of age or older	Administer the 2nd dose
Students in college and other post–high school institutions who have received 1 dose of measles vaccine at ≥12 mo of age	Administer the 2nd dose
History of immunization before the 1st birthday	Do not consider valid and immunize (2 doses)
History of receipt of inactivated measles vaccine or unknown type of vaccine, 1963-1967	Do not consider valid and immunize (2 doses)
Further attenuated or unknown vaccine given with Ig	Do not consider valid and immunize (2 doses)
Allergy to eggs	Immunize; no reactions likely
Neomycin allergy, nonanaphylactic	Immunize; no reactions likely
Severe hypersensitivity (anaphylaxis) to neomycin or gelatin	Avoid immunization
Tuberculosis	Immunize; if patient has untreated tuberculosis disease, start antituberculosis therapy before immunizing
Measles exposure	Immunize and/or give Ig, depending on circumstances
HIV-infected	Immunize (2 doses) unless severely immunocompromised, and give Ig if exposed to measles
Personal or family history of seizures	Immunize; advise parents of slightly increased risk of seizures
Ig or blood recipient	Immunize at the appropriate interval (see Table 246-3)

Ig, immunoglobulin; MMR, measles-mumps-rubella vaccine.
From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, p. 494.*

Table 246-3 Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*

INDICATION FOR IMMUNOGLOBULIN	ROUTE	Dose: UNITS (U) OR MILLILITERS (mL)	Dose: mg IgG/kg	INTERVAL (mo)†
Tetanus (as tetanus Ig)	IM	250 U	10	3
Hepatitis A prophylaxis (as Ig):				
Contact prophylaxis	IM	0.02 mL/kg	3.3	3
International travel	IM	0.06 mL/kg	10	3
Hepatitis B prophylaxis (as hepatitis B Ig)	IM	0.06 mL/kg	10	3
Rabies prophylaxis (as rabies Ig)	IM	20 IU/kg	22	4
Varicella prophylaxis (as VariZIG)	IM	125 U/10 kg (maximum 625 U)	20-40	5
Measles prophylaxis (as Ig):				
Standard	IM	0.25 mL/kg	40	5
Immunocompromised host	IM	0.50 mL/kg	80	6
Respiratory syncytial virus prophylaxis (palivizumab monoclonal antibody)‡	IM	—	15 mg/kg (monoclonal)	None
Cytomegalovirus immune globulin	IV	3 mL/kg	150	6
Blood transfusion:				
Washed RBCs	IV	10 mL/kg	Negligible	0
RBCs, adenine-saline added	IV	10 mL/kg	10	3
Packed RBCs	IV	10 mL/kg	20-60	5
Whole blood	IV	10 mL/kg	80-100	6
Plasma or platelet products	IV	10 mL/kg	160	7

Continued

Table 246-3 Suggested Intervals Between Immunoglobulin Administration and Measles Immunization*—cont'd

INDICATION FOR IMMUNOGLOBULIN	Dose			
	ROUTE	UNITS (U) OR MILLILITERS (mL)	mg IgG/kg	INTERVAL (mo)†
Replacement (or therapy) of immune deficiencies (as IVIG)	IV	—	300-400	8
ITP (as IVIG)	IV	—	400	8
ITP	IV	—	1,000	10
ITP or Kawasaki disease	IV	—	1,600-2,000	11

*Immunization in the form of measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), or monovalent measles vaccine.

†These intervals should provide sufficient time for decreases in passive antibodies in all children to allow for an adequate response to measles vaccine. Physicians should not assume that children are fully protected against measles during these intervals. Additional doses of Ig or measles vaccine may be indicated after exposure to measles (see text).

‡Monoclonal antibodies, such as palivizumab, do not interfere with the immune response to vaccines.

Ig, immunoglobulin; IgG, immunoglobulin G; ITP, immune (formerly termed "idiopathic") thrombocytopenic purpura; IVIG, intravenous Ig; RBCs, red blood cells.

From American Academy of Pediatrics: Red book: 2012 report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics, Fig. 1-9.*

Live vaccines should not be administered to pregnant women or to immunodeficient or immunosuppressed patients. However, patients with HIV who are not severely immunocompromised should be immunized. Because measles virus may suppress the cutaneous response to tuberculosis antigen, skin testing for tuberculosis should be performed before or at the same time as administration of the vaccine. Individuals infected with *M. tuberculosis* should be receiving appropriate treatment at the time of administration of measles vaccine.

Postexposure Prophylaxis

Susceptible individuals exposed to measles may be protected from infection by either vaccine administration or immunization with immune globulin. The vaccine is effective in prevention or modification of measles if given within 72 hr of exposure. Immune globulin may be given up to 6 days after exposure to prevent or modify infection. Immunocompetent children should receive 0.25 mL/kg intramuscularly, and immunocompromised children should receive 0.5 mL/kg (maximum dose in both cases is 15 mL/kg). Immune globulin is indicated for susceptible household contacts of measles patients, especially infants younger than 6 mo of age, pregnant women, and immunocompromised persons.

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Chapter 247

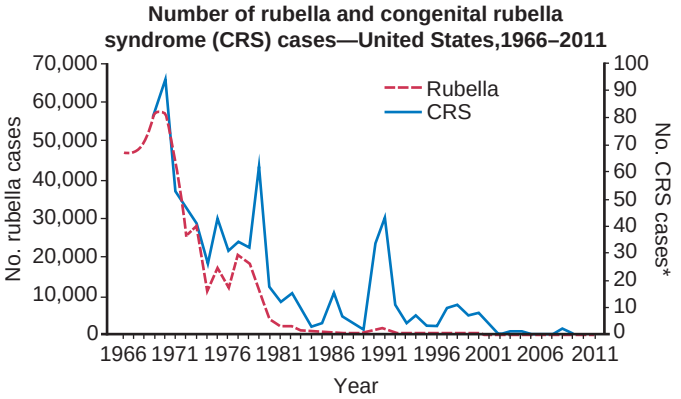
Rubella

Wilbert H. Mason

Rubella (**German measles** or **3 day measles**) is a mild, often exanthematous disease of infants and children that is typically more severe and associated with more complications in adults. Its major clinical significance is transplacental infection and fetal damage as part of the **congenital rubella syndrome (CRS).**

ETIOLOGY

Rubella virus is a member of the family Togaviridae and is the only species of the genus *Rubivirus.* It is a single-stranded RNA virus with a lipid envelope and 3 structural proteins, including a nucleocapsid protein that is associated with the nucleus and 2 glycoproteins, E1 and E2, that are associated with the envelope. The virus is sensitive to heat, ultraviolet light, and extremes of pH but is relatively stable at cold temperatures. Humans are the only known host.



*By year of birth.

Figure 247-1 Number of rubella and congenital rubella syndrome cases—United States, 1966-2011. Rubella and CRS data provided were reported voluntarily to Centers for Disease Control and Prevention (CDC) from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, Wallace GH: Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013,* MMWR Recomm Rep *62(RR-04): 1–34, 2013.)*

EPIDEMIOLOGY

In the prevaccine era, rubella appeared to occur in major epidemics every 6-9 yr, with smaller peaks interspersed every 3-4 yr, and was most common in preschool-age and school-age children. During the rubella epidemic of 1964-1965 there were an estimated 12.5 million cases of rubella associated with 2,000 cases of encephalitis, more than 13,000 abortions or perinatal deaths, and 20,000 cases of CRS. Following introduction of the rubella vaccine in 1969, the incidence of rubella fell 78% by 1976 and CRS cases fell 69% (Fig. 247-1). Further decline in rubella and CRS cases occurred when certain at-risk populations were added to those for whom rubella immunization is indicated, including adolescents and college students. After years of decline, a resurgence of rubella and CRS cases occurred during 1989-1991 in association with the epidemic of measles during that period (Fig. 247-1). Subsequently, a 2 dose recommendation for rubella vaccine was implemented and resulted in a decrease in incidence of rubella from 0.45 per 100,000 population in 1990 to 0.1 per 100,000 in 1999 and a corresponding decrease of CRS, with an average of 6 infants with CRS reported annually from 1992-2004. Mothers of these infants tended to be young, Hispanic, or foreign born. The number of reported cases of rubella continued to decline through the 1990s and first decade of this century.

The endemic spread of rubella has been eliminated in the United States; elimination of transmission of rubella in the Americas also may have been achieved. However, cases of rubella continue to be imported

into the United States from countries where it remains endemic. From 2004-2012 there were 79 cases of rubella and 6 cases of CRS, all of which were imported cases of unknown source. Three of the CRS cases were acquired in Africa. Between January 1 and May 1, 2013, 5,442 cases of rubella and 10 cases of CRS were reported, demonstrating that the elimination of rubella internationally has not been achieved and continued vigilance and maintenance of high levels of immunity in the United States are necessary.

PATHOLOGY

Little information is available on the pathologic findings in rubella occurring postnatally. The few reported studies of biopsy or autopsy material from cases of rubella revealed only nonspecific findings of lymphoreticular inflammation and mononuclear perivascular and meningeal infiltration. The pathologic findings for CRS are often severe and may involve nearly every organ system (Table 247-1).

PATHOGENESIS

The viral mechanisms for cell injury and death in postnatal or congenital rubella are not well understood. Following infection, the virus replicates in the respiratory epithelium and then spreads to regional lymph nodes (Fig. 247-2). Viremia ensues and is most intense from 10-17 days after infection. Viral shedding from the nasopharynx begins approximately 10 days after infection and may be detected up to 2 wk following onset of the rash. The period of highest communicability is from 5 days before to 6 days after the appearance of the rash.

The most important risk factor for severe congenital defects is the stage of gestation at the time of infection. Maternal infection during the 1st 8 wk of gestation results in the most severe and widespread defects. The risk for congenital defects has been estimated at 90% for maternal infection before 11 wk of gestation, 33% at 11-12 wk, 11% at 13-14 wk, and 24% at 15-16 wk. Defects occurring after 16 wk of gestation are uncommon, even if fetal infection occurs.

Causes of cellular and tissue damage in the infected fetus may include tissue necrosis due to vascular insufficiency, reduced cellular multiplication time, chromosomal breaks, and production of a protein inhibitor causing mitotic arrests in certain cell types. The most distinctive feature of congenital rubella is chronicity. Once the fetus is infected early in gestation, the virus persists in fetal tissue until well beyond delivery. Persistence suggests the possibility of ongoing tissue damage and reactivation, most notably in the brain.

CLINICAL MANIFESTATIONS

Postnatal infection with rubella is a mild disease not easily discernible from other viral infections, especially in children. Following an incubation period of 14-21 days, a prodrome consisting of low-grade fever, sore throat, red eyes with or without eye pain, headache, malaise, anorexia, and lymphadenopathy begins. Suboccipital, postauricular, and anterior cervical lymph nodes are most prominent. In children, the first manifestation of rubella is usually the rash, which is variable and not distinctive. It begins on the face and neck as small, irregular pink macules that coalesce, and it spreads centrifugally to involve the torso and extremities, where it tends to occur as discrete macules (Fig. 247-3). About the time of onset of the rash, examination of the oropharynx may reveal tiny, rose-colored lesions (**Forchheimer spots**)

Table 247-1 Pathologic Findings in Congenital Rubella Syndrome

SYSTEM	PATHOLOGIC FINDINGS
Cardiovascular	Patent ductus arteriosus Pulmonary artery stenosis Ventriculoseptal defect Myocarditis
Central nervous system	Chronic meningitis Parenchymal necrosis Vasculitis with calcification
Eye	Microphthalmia Cataract Iridocyclitis Ciliary body necrosis Glaucoma Retinopathy
Ear	Cochlear hemorrhage Endothelial necrosis
Lung	Chronic mononuclear interstitial pneumonitis
Liver	Hepatic giant cell transformation Fibrosis Lobular disarray Bile stasis
Kidney	Interstitial nephritis
Adrenal gland	Cortical cytomegaly
Bone	Malformed osteoid Poor mineralization of osteoid Thinning cartilage
Spleen, lymph node	Extramedullary hematopoiesis
Thymus	Histiocytic reaction Absence of germinal centers
Skin	Erythropoiesis in dermis

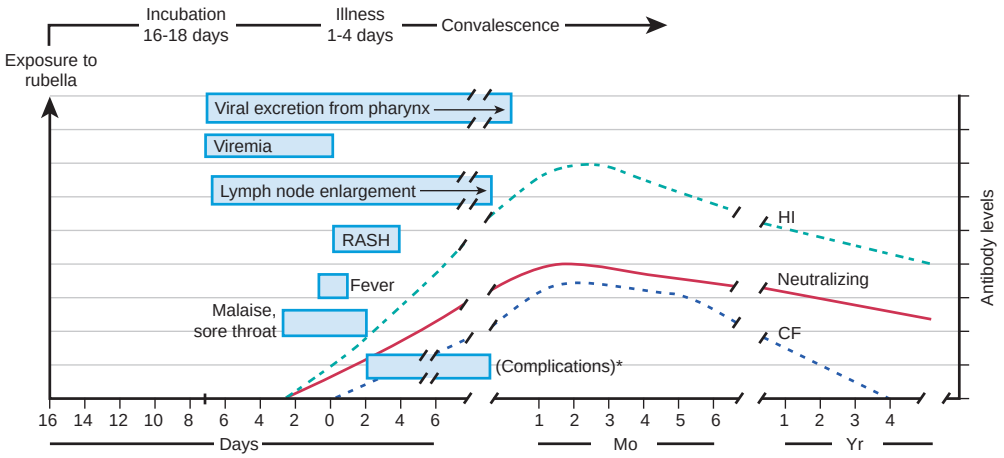


Figure 247-2 Pathophysiologic events in postnatally acquired rubella virus infection. *Possible complications include arthralgia and/or arthritis, thrombocytopenic purpura, and encephalitis. CF, complement fixation titer; HI, hemagglutination-inhibition titer. *(From Lamprecht CL: Rubella virus. In Beshe RB, editor:* Textbook of human virology, *ed 2, Littleton, MA, 1990, PSG Publishing, p. 685.)*

Figure 247-3 Rash of rubella.

Table 247-2 Clinical Manifestations of Congenital Rubella Syndrome in 376 Children Following Maternal Rubella*

MANIFESTATION	RATE (%)
Deafness	67
Ocular	71
Cataracts	29
Retinopathy	39
Heart disease†	48
Patent ductus arteriosus	78
Right pulmonary artery stenosis	70
Left pulmonary artery stenosis	56
Valvular pulmonic stenosis	40
Low birthweight	60
Psychomotor retardation	45
Neonatal purpura	23
Death	35

*Other findings: hepatitis, linear streaking of bone, hazy cornea, congenital glaucoma, delayed growth.

†Findings in 87 patients with congenital rubella syndrome and heart disease who underwent cardiac angiography.

From Cooper LZ, Ziring PR, Ockerse AB, et al: Rubella: clinical manifestations and management, Am J Dis Child *118:18–29, 1969.*

or petechial hemorrhages on the soft palate. The rash fades from the face as it extends to the rest of the body so that the whole body may not be involved at any one time. The duration of the rash is generally 3 days, and it usually resolves without desquamation. Subclinical infections are common, and 25-40% of children may not have a rash.

LABORATORY FINDINGS

Leukopenia, neutropenia, and mild thrombocytopenia have been described during postnatal rubella.

DIAGNOSES

A specific diagnosis of rubella is important for epidemiologic reasons, for diagnosis of infection in pregnant women, and for confirmation of the diagnosis of congenital rubella. The most common diagnostic test is rubella immunoglobulin (Ig) M enzyme immunosorbent assay. As with any serologic test, the positive predictive value of testing decreases in populations with low prevalence of disease. Tests should be performed in the context of a supportive history of exposure or consistent clinical findings. The relative sensitivity and specificity of commercial kits used in most laboratories range from 96-99% and 86-97%, respectively. A caveat for testing of congenitally infected infants early in infancy is that false-negative results may occur owing to competing IgG antibodies circulating in these patients. In such patients, an IgM capture assay, reverse transcriptase polymerase chain reaction test, or viral culture should be performed for confirmation.

DIFFERENTIAL DIAGNOSES

Rubella may manifest as distinctive features suggesting the diagnosis. It is frequently confused with other infections because it is uncommon, similar to other viral exanthematous diseases, and demonstrates variability in the presence of typical findings. In severe cases, it may resemble measles. The absence of Koplik spots and a severe prodrome as well as a shorter course allow for differentiation from measles. Other diseases frequently confused with rubella include infections caused by adenoviruses, parvovirus B19 (erythema infectiosum), Epstein-Barr virus, enteroviruses, and *Mycoplasma pneumoniae.*

COMPLICATIONS

Complications following postnatal infection with rubella are infrequent and generally not life-threatening.

Postinfectious **thrombocytopenia** occurs in approximately 1 in 3,000 cases of rubella and occurs more frequently among children and in girls. It manifests about 2 wk following the onset of the rash as petechiae, epistaxis, gastrointestinal bleeding, and hematuria. It is usually self-limited.

Arthritis following rubella occurs more commonly among adults, especially women. It begins within 1 wk of onset of the exanthem and classically involves the small joints of the hands. It also is self-limited and resolves within weeks without sequelae. There are anecdotal reports and some serologic evidence linking rubella with rheumatoid arthritis, but a true causal association remains speculative.

Encephalitis is the most serious complication of postnatal rubella. It occurs in 2 forms: a postinfectious syndrome following acute rubella and a rare progressive panencephalitis manifesting as a neurodegenerative disorder years following rubella.

Postinfectious encephalitis is uncommon, occurring in 1 in 5,000 cases of rubella. It appears within 7 days after onset of the rash, consisting of headache, seizures, confusion, coma, focal neurologic signs, and ataxia. Fever may recrudesce with the onset of neurologic symptoms. Cerebrospinal fluid may be normal or have a mild mononuclear pleocytosis and/or elevated protein concentration. Virus is rarely, if ever, isolated from cerebrospinal fluid or brain, suggesting a noninfectious pathogenesis. Most patients recover completely, but mortality rates of 20% and long-term neurologic sequelae have been reported.

Progressive rubella panencephalitis (PRP) is an extremely rare complication of either acquired rubella or CRS. It has an onset and course similar to those of the subacute sclerosing panencephalitis associated with measles (see Chapter 246). Unlike in the postinfectious form of rubella encephalitis, however, rubella virus may be isolated from brain tissue of the patient with PRP, suggesting an infectious pathogenesis, albeit a "slow" one. The clinical findings and course are undistinguishable from those of subacute sclerosing panencephalitis and transmissible spongiform encephalopathies (see Chapter 278). Death occurs 2-5 yr after onset.

Other neurologic syndromes rarely reported with rubella include Guillain-Barré syndrome and peripheral neuritis. Myocarditis is a rare complication.

Congenital Rubella Syndrome

In 1941, an ophthalmologist first described a syndrome of cataracts and congenital heart disease that he correctly associated with rubella infections in the mothers during early pregnancy (Table 247-2). Shortly after the first description, hearing loss was recognized as a common

Figure 247-4 Bilateral cataracts in infant with congenital rubella syndrome.

finding often associated with microcephaly. In 1964-1965 a pandemic of rubella occurred, with 20,000 cases reported in the United States, leading to more than 11,000 spontaneous or therapeutic abortions and 2,100 neonatal deaths. From this experience emerged the expanded definition of CRS that includes numerous other transient or permanent abnormalities.

Nerve deafness is the single most common finding among infants with CRS. Most infants have some degree of intrauterine growth restriction. Retinal findings described as **salt-and-pepper retinopathy** are the most common ocular abnormality but have little early effect on vision. Unilateral or bilateral cataracts are the most serious eye finding, occurring in about a third of infants (Fig. 247-4). Cardiac abnormalities occur in half of the children infected during the 1st 8 wk of gestation. Patent ductus arteriosus is the most frequently reported cardiac defect, followed by lesions of the pulmonary arteries and valvular disease. Interstitial pneumonitis leading to death in some cases has been reported. Neurologic abnormalities are common and may progress following birth. Meningoencephalitis is present in 10-20% of infants with CRS and may persist for up to 12 mo. Longitudinal follow-up through 9-12 yr of infants without initial retardation revealed progressive development of additional sensory, motor, and behavioral abnormalities, including hearing loss and autism. PRP has also been recognized rarely after CRS. Subsequent postnatal growth retardation and ultimate short stature have been reported in a minority of cases. Rare reports of immunologic deficiency syndromes have also been described.

A variety of late-onset manifestations of CRS have been recognized. In addition to PRP, they include diabetes mellitus (20%), thyroid dysfunction (5%), and glaucoma and visual abnormalities associated with the retinopathy, which had previously been considered benign.

TREATMENT

There is no specific treatment available for either acquired rubella or CRS.

SUPPORTIVE CARE

Postnatal rubella is generally a mild illness that requires no care beyond antipyretics and analgesics. Intravenous immunoglobulin or corticosteroids can be considered for severe, nonremitting thrombocytopenia.

Management of children with CRS is more complex and requires pediatric, cardiac, audiologic, ophthalmologic, and neurologic evaluation and follow-up because many manifestations may not be readily apparent initially or may worsen with time. Hearing screening is of special importance, because early intervention may improve outcomes in children with hearing problems caused by CRS.

PROGNOSIS

Postnatal infection with rubella has an excellent prognosis. Long-term outcomes of CRS are less favorable and somewhat variable. In an Australian cohort evaluated 50 yr after infection, many had chronic conditions but most were married and had made good social adjustments. A cohort from New York from the mid-1960s epidemic had less-favorable outcomes, with 30% leading normal lives, 30% in dependent situations but functional, and 30% requiring institutionalization and continuous care.

Reinfection with wild virus occurs postnatally in both individuals who were previously infected with wild-virus rubella and in vaccinated individuals. Reinfection is defined serologically as a significant increase in IgG antibody level and/or an IgM response in an individual who has a documented preexisting rubella-specific IgG above an accepted cutoff. Reinfection may result in an anamnestic IgG response, an IgM and IgG response, or clinical rubella. There are 29 reports of CRS following maternal reinfection in the literature. Reinfection with serious adverse outcomes to adults or children is rare and of unknown significance.

PREVENTION

Patients with postnatal infection should be isolated from susceptible individuals for 7 days after onset of the rash. Standard plus droplet precautions are recommended for hospitalized patients. Children with CRS may excrete the virus in respiratory secretions up to 1 yr of age, so contact precautions should be maintained for them until then, unless repeated cultures of urine and pharyngeal secretions have negative results. Similar precautions apply to patients with CRS with regard to attendance in school and out-of-home childcare.

Exposure of susceptible pregnant women poses a potential risk to the fetus. For pregnant women exposed to rubella, a blood specimen should be obtained as soon as possible for rubella IgG-specific antibody testing; a frozen aliquot also should be saved for later testing. If the rubella antibody test result is positive, the mother is likely immune. If the rubella antibody test is negative, a 2nd specimen should be obtained 2-3 wk later and tested concurrently with the saved specimen. If both of these test negative, a 3rd specimen should be obtained 6 wk after exposure and tested concurrently with the saved specimen. If both the 2nd and 3rd specimens test negative, infection has not occurred. A negative 1st specimen and a positive test result in either the 2nd and 3rd specimen indicate that seroconversion has occurred in the mother, suggesting recent infection. Counseling should be provided about the risks and benefits of termination of pregnancy. The routine use of immunoglobulin for susceptible pregnant women exposed to rubella is not recommended and is considered only if termination of pregnancy is not an option because of maternal preferences. In such circumstances, immunoglobulin 0.55 mL/kg IM may be given with the understanding that prophylaxis may reduce the risk for clinically apparent infection but does not guarantee prevention of fetal infection.

VACCINATION

Rubella vaccine in the United States consists of the attenuated Wistar RA 27/3 strain that is usually administered in combination with measles and mumps (MMR) or also with varicella (MMRV) in a 2 dose regimen at 12-15 mo and 4-6 yr of age. It theoretically may be effective as postexposure prophylaxis if administered within 3 days of exposure. Vaccine should not be administered to severely immunocompromised patients (e.g., transplant recipients). Patients with HIV infection who are not severely immunocompromised may benefit from vaccination. Fever is not a contraindication, but if a more serious illness is suspected, immunization should be delayed. Immunoglobulin preparations may inhibit the serologic response to the vaccine (see Chapter 172). Vaccine should not be administered during pregnancy. If pregnancy occurs within 28 days of immunization, the patient should be counseled on the theoretical risks to the fetus. Studies of more than 200 women who had been inadvertently immunized with rubella vaccine during pregnancy showed that none of their offspring developed CRS. Therefore, interruption of pregnancy is probably not warranted.

Following a single dose of rubella RA 27/3 vaccine, 95% of persons 12 mo of age and older develop serologic immunity, and after 2 doses 99% have detectable antibody. Rubella RA 27/3 vaccine is highly protective as 97% of those vaccinated are protected from clinical disease after

1 dose. Detectable antibodies remain for 15 yr in most individuals vaccinated following 1 dose, and 91% to 100% had antibodies after 12-15 yr after 2 doses. Although antibody levels may wane, especially after 1 dose of vaccine, increased susceptibility to rubella disease does not occur.

Adverse reactions to rubella vaccination are uncommon in children. MMR administration is associated with fever in 5-15% of vaccinees and with rash in approximately 5% of vaccinees. Arthralgia and arthritis are more common following rubella vaccination in adults. Approximately 25% of postpubertal women experience arthralgia, and 10% experience arthritis. Peripheral neuropathies and transient thrombocytopenia may also occur.

As part of the worldwide effort to eliminate endemic rubella virus transmission and occurrence of CRS, maintaining high population immunity through vaccination coverage and high-quality integrated measles-rubella surveillance have been emphasized as being vital to its success.

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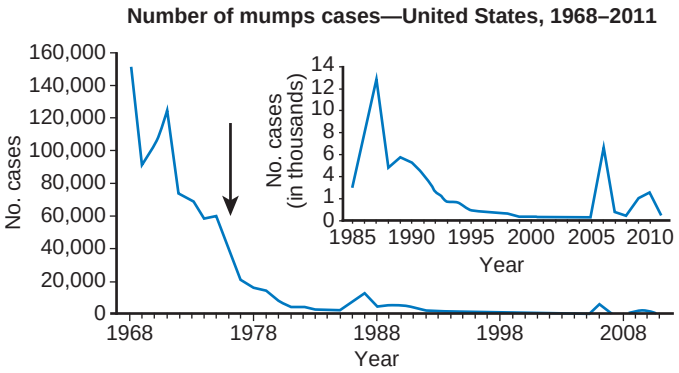

Figure 248-1 **Mumps cases in the United States from 1967, when the live mumps vaccine was introduced, to 2011.** There was a steady decline following introduction of the vaccine and recommendation for routine vaccination in 1977 *(arrow)*. Note national increases in activity in 1986-1987 and 2006. Mumps data provided were reported voluntarily to Centers for Disease Control and Prevention from state health departments. *(From McLean HQ, Fiebelkorn AP, Temte JL, Wallace GS: Prevention of measles, rubella, congenital rubella syndrome and mumps, 2013,* MMWR Recomm Rep *62(RR-04):1–34, 2013.)*

Chapter 248

Mumps

Wilbert H. Mason

Mumps is an acute self-limited infection that was once commonplace but is now unusual in developed countries because of widespread use of vaccination. It is characterized by fever, bilateral or unilateral parotid swelling and tenderness, and the frequent occurrence of meningoencephalitis and orchitis. Although no longer common in countries with extensive vaccination programs, mumps remains endemic in the rest of the world, warranting continued vaccine protection.

ETIOLOGY

Mumps virus is in the family Paramyxoviridae and the genus *Rubulavirus*. It is a single-stranded pleomorphic RNA virus encapsulated in a lipoprotein envelope and possessing 7 structural proteins. Surface glycoproteins called HN (hemagglutinin-neuraminidase) and F (fusion) mediate absorption of the virus to host cells and penetration of the virus into cells, respectively. Both of these proteins stimulate production of protective antibodies. Mumps virus exists as a single immunotype, and humans are the only natural host.

EPIDEMIOLOGY

In the prevaccine era, mumps occurred primarily in young children between the ages of 5 and 9 yr and in epidemics about every 4 yr. Mumps infection occurred more often in the winter and spring months. In 1968, just after the introduction of the mumps vaccine, 185,691 cases were reported in the United States. Following the recommendation for routine use of mumps vaccine in 1977, the incidence of mumps fell dramatically in young children (Fig. 248-1) and shifted instead to older children, adolescents, and young adults. Outbreaks continued to occur *even in highly vaccinated* populations as a result of vaccine failure and also because of undervaccination of susceptible persons. After implementation of the 2 dose recommendation for the measles-mumps-rubella (MMR) vaccine for measles control in 1989, the number of mumps cases declined further. During 2001-2003, fewer than 300 mumps cases were reported each year. In 2006, the largest mumps epidemic in the last 20 yr occurred in the United States. A total of 6,584 cases occurred, 85% of them in 8 midwestern states. Twenty-nine percent of the cases occurred in patients 18-24 yr old, most of whom were attending college. An analysis of 4,039 patients with mumps seen in the 1st 7 mo of the epidemic indicated that 63% had received more than 2 doses of the MMR vaccine. Subsequently, several outbreaks of mumps have been documented in highly vaccinated populations in the Northeast United States, in a large public university in the Western United States, and in Guam.

Mumps is spread from person to person by respiratory droplets. Virus appears in the saliva from up to 7 days before to as long as 7 days after onset of parotid swelling. The period of maximum infectiousness is 1-2 days before to 5 days after onset of parotid swelling. Viral shedding before onset of symptoms and in asymptomatic infected individuals impairs efforts to contain the infection in susceptible populations. The U.S. Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Health Infection Control Practices Advisory Committee recommend an isolation period of 5 days after onset of parotitis for patients with mumps in both community and healthcare settings.

PATHOLOGY AND PATHOGENESIS

Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and, to a lesser extent, thyroid, ovaries, heart, kidneys, liver, and joint synovia.

Following infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues. Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains a mononuclear pleocytosis, even in individuals without clinical signs of meningitis.

CLINICAL MANIFESTATIONS

The incubation period for mumps ranges from 12-25 days but is usually 16-18 days. Mumps virus infection may result in clinical presentation ranging from asymptomatic or nonspecific symptoms to the typical illness associated with parotitis with or without complications involving several body systems. The typical patient presents with a prodrome lasting 1-2 days and consisting of fever, headache, vomiting, and achiness. Parotitis then appears and may be unilateral initially but becomes bilateral in approximately 70% of cases (Fig. 248-2). The parotid gland is tender, and parotitis may be preceded or accompanied by ear pain on the ipsilateral side. Ingestion of sour or acidic foods or liquids may enhance pain in the parotid area. As swelling progresses, the angle of the jaw is obscured and the ear lobe may be lifted upward and outward (Figs. 248-2 and 248-3). The opening of the Stensen duct may be red and edematous. The parotid swelling peaks in approximately 3 days and then gradually subsides over 7 days. Fever and the

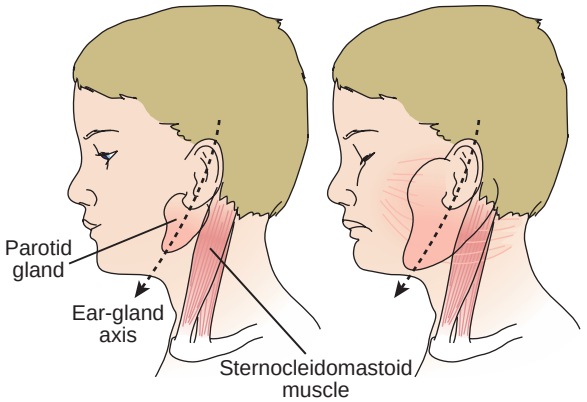

Figure 248-2 Schematic of a parotid gland infected with mumps *(right)* compared with a normal gland *(left)*. An imaginary line bisecting the long axis of the ear divides the parotid gland into 2 equal parts. These anatomic relationships are not altered in the enlarged gland. An enlarged cervical lymph node is usually posterior to the imaginary line. *(From Mumps [epidemic parotitis]. In Krugman S, Ward R, Katz SL, editors:* Infectious diseases in children, *ed 6, St. Louis, 1977, Mosby, p. 182.)*

Figure 248-3 A child with mumps showing parotid swelling. *(From the Centers for Disease Control and Prevention [CDC]: Public health image library [PHIL], image #4491. Available at: http://phil.cdc.gov/phil/home.asp)*

other systemic symptoms resolve in 3-5 days. A morbilliform rash is rarely seen. Submandibular salivary glands may also be involved or may be enlarged without parotid swelling. Edema over the sternum as a result of lymphatic obstruction may also occur.

DIAGNOSIS

When mumps was highly prevalent, the diagnosis could be made on the basis of a history of exposure to mumps infection, an appropriate incubation period, and development of typical clinical findings. Confirmation of the presence of parotitis could be made with demonstration of an elevated serum amylase value. Leukopenia with a relative lymphocytosis was a common finding. Today, in patients with parotitis lasting longer than 2 days and of unknown cause, a specific diagnosis of mumps should be confirmed or ruled out by virologic or serologic means. This step may be accomplished by isolation of the virus in cell culture, detection of viral antigen by direct immunofluorescence, or identification of nucleic acid by reverse transcriptase polymerase chain reaction. Virus can be isolated from upper respiratory tract secretions, CSF, or urine during the acute illness. Serologic testing is usually a more convenient and available mode of diagnosis. A significant increase in serum mumps immunoglobulin G antibody between acute and convalescent serum specimens as detected by complement fixation, neutralization hemagglutination, or enzyme immunoassay tests establishes the diagnosis. Mumps immunoglobulin G antibodies may cross react with antibodies to parainfluenza virus in serologic testing. More commonly, an enzyme immunoassay for mumps immunoglobulin M antibody is used to identify recent infection. Skin testing for mumps is neither sensitive nor specific and should not be used.

DIFFERENTIAL DIAGNOSIS

Parotid swelling may be caused by many other infectious and noninfectious conditions. Viruses that cause parotitis include parainfluenza 1 and parainfluenza 3 viruses, influenza A virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus, and HIV. Purulent parotitis, usually caused by *Staphylococcus aureus,* is unilateral, is extremely tender, is associated with an elevated white blood cell count, and may involve purulent drainage from the Stensen duct. Submandibular or anterior cervical adenitis from a variety of pathogens may also be confused with parotitis. Other noninfectious causes of parotid swelling include obstruction of the Stensen duct, collagen vascular diseases such as Sjögren syndrome, systemic lupus erythematosus, and tumor.

COMPLICATIONS

The most common complications of mumps are meningitis, with or without encephalitis, and gonadal involvement. Uncommon complications include conjunctivitis, optic neuritis, pneumonia, nephritis, pancreatitis, and thrombocytopenia.

Maternal infection with mumps during the 1st trimester of pregnancy results in increased fetal wastage. No fetal malformations have been associated with intrauterine mumps infection. However, perinatal mumps disease has been reported in infants born to mothers who acquired mumps late in gestation.

Meningitis and Meningoencephalitis

Mumps virus is neurotropic and is thought to enter the CNS via the choroid plexus and infect the choroidal epithelium and ependymal cells, both of which can be found in CSF along with mononuclear leukocytes. Symptomatic CNS involvement occurs in 10-30% of infected individuals, but CSF pleocytosis has been found in 40-60% of patients with mumps parotitis. The meningoencephalitis may occur before, along with, or following the parotitis. It most commonly manifests 5 days after the parotitis. Clinical findings vary with age. Infants and young children have fever, malaise, and lethargy, whereas older children, adolescents, and adults complain of headache and demonstrate meningeal signs. In 1 series of children with mumps and meningeal involvement, findings were fever in 94%, vomiting in 84%, headache in 47%, parotitis in 47%, neck stiffness in 71%, lethargy in 69%, and seizures in 18%. In typical cases, symptoms resolve in 7-10 days. CSF in mumps meningitis has a white blood cell pleocytosis of 200-600/μL with a predominance of lymphocytes. The CSF glucose content is normal in most patients, but a moderate hypoglycorrhachia (glucose content 20-40 mg/dL) may be seen in 10-20% of patients. The CSF protein content is normal or mildly elevated.

Less-common CNS complications of mumps include transverse myelitis, aqueductal stenosis, and facial palsy. Sensorineural hearing loss is rare and has been estimated to occur in 0.5-5.0 in 100,000 cases of mumps. There is some evidence that this sequela is more likely in patients with meningoencephalitis.

Orchitis and Oophoritis

In adolescent and adult males, orchitis is second only to parotitis as a common finding in mumps. Involvement in prepubescent boys is extremely rare, but after puberty, orchitis occurs in 30-40% of males. It begins within days following onset of parotitis in the majority of cases and is associated with moderate to high fever, chills, and exquisite pain and swelling of the testes. In 30% or less of cases, the orchitis is bilateral. Atrophy of the testes may occur, but sterility is rare even with bilateral involvement.

Oophoritis is uncommon in postpubertal females but may cause severe pain and may be confused with appendicitis when located on the right side.

Pancreatitis

Pancreatitis may occur in mumps with or without parotid involvement. Severe disease is rare, but fever, epigastric pain, and vomiting are suggestive. Epidemiologic studies have suggested that mumps may be associated with the subsequent development of diabetes mellitus, but a causal link has not been established.

Cardiac Involvement

Myocarditis has been reported in mumps, and molecular studies have identified mumps virus in heart tissue taken from patients with endocardial fibroelastosis.

Arthritis

Arthralgia, monoarthritis, and migratory polyarthritis have been reported in mumps. Arthritis is seen with or without parotitis and usually occurs within 3 wk of onset of parotid swelling. It is generally mild and self-limited.

Thyroiditis

Thyroiditis is rare following mumps. It has not been reported without parotitis and may occur weeks after the acute infection. Most cases resolve, but some become relapsing and result in hypothyroidism.

TREATMENT

No specific antiviral therapy is available for mumps. Management should be aimed at reducing the pain associated with meningitis or orchitis and maintaining adequate hydration. Antipyretics may be given for fever.

PROGNOSIS

The outcome of mumps is nearly always excellent, even when the disease is complicated by encephalitis, although fatal cases from CNS involvement or myocarditis have been reported.

PREVENTION

Immunization with the live mumps vaccine is the primary mode of prevention used in the United States. It is given as part of the MMR 2 dose vaccine schedule, at 12-15 mo of age for the 1st dose and 4-6 yr of age for the 2nd dose. If not given at 4-6 yr, the 2nd dose should be given before children enter puberty. Antibody develops in 94% (range: 89-97%) of vaccinees after 1 dose. Antibody levels achieved following vaccination are lower than following natural infection.

The median vaccine effectiveness of mumps vaccine after 1 dose of vaccine is 78% (range: 49-92%) and after 2 doses is 88% (range: 66-95%). Duration of effectiveness is ≥10 yr after 1 dose and ≥15 yr after 2 doses.

As a live-virus vaccine, MMR should not be administered to pregnant women or to severely immunodeficient or immunosuppressed individuals. HIV-infected patients who are not severely immunocompromised may receive the vaccine, because the risk for severe infection with mumps outweighs the risk for serious reaction to the vaccine. Individuals with anaphylactoid reactions to egg or neomycin may be at risk for immediate-type hypersensitivity reactions to the vaccine. Persons with other types of reactions to egg or reactions to other components of the vaccine are not restricted from receiving the vaccine.

In 2006, in response to the multistate outbreak in the United States, evidence of immunity to mumps through vaccination was redefined. Acceptable presumptive evidence of immunity to mumps now consists of 1 of the following: (1) documentation of adequate vaccination at age 12 mo or older, (2) laboratory evidence of immunity, (3) birth before 1957, and (4) documentation of physician-diagnosed mumps. Evidence of immunity through documentation of adequate vaccination is now defined as 1 dose of a live mumps virus vaccine for preschool-age children and adults not at high risk and 2 doses for school-age children (i.e., grades K-12) and for adults at high risk (e.g., healthcare workers, international travelers, and students at post–high school educational institutions).

All persons who work in healthcare facilities should be immune to mumps. Adequate mumps vaccination for healthcare workers born during or after 1957 consists of 2 doses of a live mumps virus vaccine. Healthcare workers with no history of mumps vaccination and no other evidence of immunity should receive 2 doses, with >28 days between doses. Healthcare workers who have received only 1 dose previously should receive a 2nd dose. Because birth before 1957 is only presumptive evidence of immunity, healthcare facilities should consider recommending 1 dose of a live mumps virus vaccine for unvaccinated workers born before 1957 who do not have a history of physician-diagnosed mumps or laboratory evidence of mumps immunity. During an outbreak, healthcare facilities should strongly consider recommending 2 doses of a live mumps virus vaccine to unvaccinated workers born before 1957 who do not have evidence of mumps immunity.

Adverse reactions to mumps virus vaccine are rare. Parotitis and orchitis have been reported rarely. Other reactions, such as febrile seizures, deafness, rash, purpura, encephalitis, and meningitis, may not be causally related to the strain of mumps vaccine virus used for immunization in the United States. Higher rates of aseptic meningitis following vaccination for mumps are associated with vaccine strains used elsewhere in the world, including the Leningrad 3 and Urabe Am 9 strains. Transient suppression of reactivity to tuberculin skin testing has been reported after mumps vaccination.

In 2005, the quadrivalent measles, mumps, rubella, and varicella vaccine (MMRV) was made available. However, in 2010 studies showed a greater risk of febrile seizures in children 12-23 mo of age 5-12 days following administration of the vaccine. No increased risk of seizures was seen in children receiving the 1st dose of the MMRV at older than 48 mo of age. As a result, the American Academy of Pediatrics currently recommends either the MMR vaccine and separate varicella vaccine or the MMRV vaccine in children 12 through 47 mo of age. After 48 mo of age, the MMRV is generally preferred.

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Chapter 249

Polioviruses

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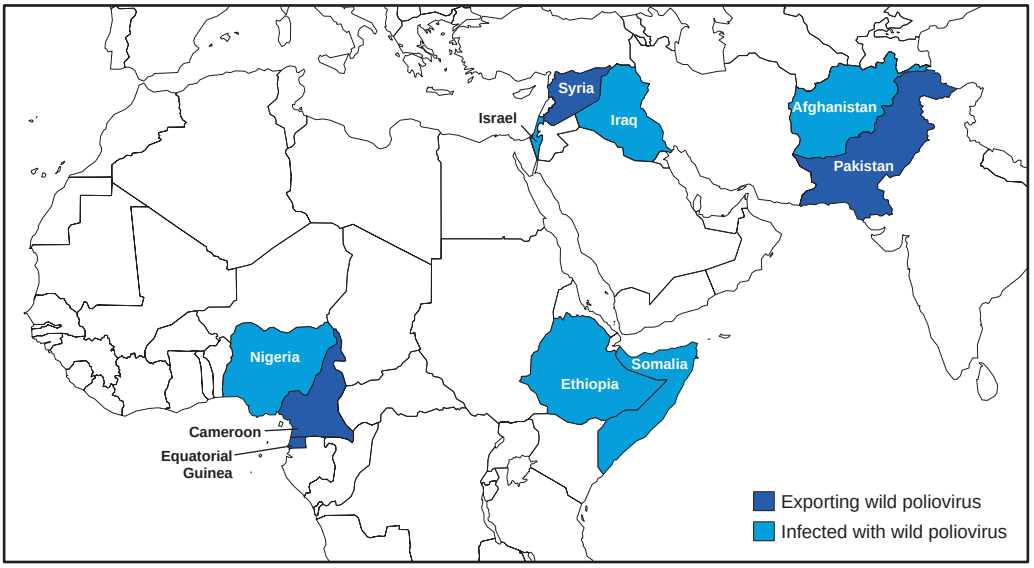
ETIOLOGY

The polioviruses are nonenveloped, positive-stranded RNA viruses belonging to the Picornaviridae family, in the genus *Enterovirus,* and consist of 3 antigenically distinct serotypes (types 1, 2, and 3). Polioviruses spread from the intestinal tract to the central nervous system (CNS), where they cause aseptic meningitis and poliomyelitis, or polio. The polioviruses are extremely hardy and can retain infectivity for several days at room temperature.

EPIDEMIOLOGY

The most devastating result of poliovirus infection is paralysis, although 90-95% of infections are inapparent but induce protective immunity. Clinically apparent but nonparalytic illness occurs in approximately 5% of all infections, with paralytic polio occurring in approximately 1 in 1,000 infections among infants to approximately 1 in 100 infections among adolescents. In developed countries prior to universal vaccination, epidemics of paralytic poliomyelitis occurred primarily in adolescents. Conversely, in developing countries with poor sanitation, infection early in life results in infantile paralysis. Improved sanitation explains the virtual eradication of polio from the United States in the early 1960s, when only approximately 65% of the population was immunized with the Salk vaccine, which contributed to the disappearance of circulating wild-type poliovirus in the United States and



As of June 30, 2014.

Figure 249-1 Countries identified by the World Health Organization as exporting wild poliovirus and those in which wild poliovirus infection is currently found, worldwide, 2014. *(From Wallace GS, Seward JF, Pallansch MA; Centers for Disease Control and Prevention: Interim CDC guidelines for polio vaccination for travel to and from countries affected by wild poliovirus.* MMWR Morb Mortal Wkly Rep *63:591–594, 2014.)*

Europe. Poor sanitation and crowding have permitted the continued transmission of poliovirus in certain poor countries in Africa and Asia, despite massive global efforts to eradicate polio, which in some areas involve an average of 12-13 doses of polio vaccine administered to children in the 1st 5 yr of life (Fig. 249-1).

TRANSMISSION

Humans are the only known reservoir for the polioviruses, which are spread by the fecal-oral route. Poliovirus has been isolated from feces for longer than 2 wk before paralysis to several weeks after the onset of symptoms.

PATHOGENESIS

Polioviruses infect cells by adsorbing to the genetically determined **poliovirus receptor.** The virus penetrates the cell, is uncoated, and releases viral RNA. The RNA is translated to produce proteins responsible for replication of the RNA, shutoff of host cell protein synthesis, and synthesis of structural elements that compose the capsid. Mature virus particles are produced in 6-8 hr and are released into the environment by disruption of the cell.

In the contact host, wild-type and vaccine strains of polioviruses gain host entry via the gastrointestinal tract. The primary site of replication is in the M cells lining the mucosa of the small intestine. Regional lymph nodes are infected, and primary viremia occurs after 2-3 days. The virus seeds multiple sites, including the reticuloendothelial system, brown fat deposits, and skeletal muscle. Wild-type poliovirus probably accesses the CNS along peripheral nerves. Vaccine strains of polioviruses do not replicate in the CNS, a feature that accounts for the safety of the live-attenuated vaccine. Occasional **revertants** (by nucleotide substitution) of these vaccine strains develop a neurovirulent phenotype and cause **vaccine-associated paralytic poliomyelitis (VAPP).** Reversion occurs in the small intestine and probably accesses the CNS via the peripheral nerves. Because poliovirus replicates in endothelial cells, the theory of viremic spread to the CNS was favored; however, poliovirus has almost never been cultured from the cerebrospinal fluid (CSF) of patients with paralytic disease, and patients with aseptic meningitis caused by poliovirus never have paralytic disease. With the first appearance of non-CNS symptoms, a secondary viremia probably occurs as a result of enormous viral replication in the reticuloendothelial system.

The exact mechanism of entry into the CNS is not known. However, once entry is gained the virus may traverse neural pathways, and multiple sites within the CNS are often affected. The effect on motor and vegetative neurons is most striking and correlates with the clinical manifestations. Perineuronal inflammation, a mixed inflammatory reaction with both polymorphonuclear leukocytes and lymphocytes, is associated with extensive neuronal destruction. Petechial hemorrhages and considerable inflammatory edema also occur in areas of poliovirus infection. The poliovirus primarily infects motor neuron cells in the spinal cord (**the anterior horn cells**) and the medulla oblongata (the cranial nerve nuclei). Because of the overlap in muscle innervation by 2-3 adjacent segments of the spinal cord, clinical signs of weakness in the limbs develop when more than 50% of motor neurons are destroyed. In the medulla, less-extensive lesions cause paralysis, and involvement of the reticular formation that contains the vital centers controlling respiration and circulation may have a catastrophic outcome. Involvement of the intermediate and dorsal areas of the horn and the dorsal root ganglia in the spinal cord results in hyperesthesia and myalgias that are typical of acute poliomyelitis. Other neurons affected are the nuclei in the roof and vermis of the cerebellum, the substantia nigra, and, occasionally, the red nucleus in the pons; there may be variable involvement of thalamic, hypothalamic, and pallidal nuclei and the motor cortex.

Apart from the histopathology of the CNS, inflammatory changes occur generally in the reticuloendothelial system. Inflammatory edema and sparse lymphocytic infiltration are prominently associated with hyperplastic lymphocytic follicles.

Infants acquire immunity transplacentally from their mothers. Transplacental immunity disappears at a variable rate during the 1st 4-6 mo of life. Active immunity after natural infection is probably lifelong but protects against the infecting serotype only; infections with other serotypes are possible. Poliovirus neutralizing antibodies develop within several days after exposure as a result of replication of the virus in the M cells in the intestinal tract and deep lymphatic tissues. This early production of circulating immunoglobulin (Ig) G antibodies protects against CNS invasion. Local (mucosal) immunity, conferred mainly by secretory IgA, is an important defense against subsequent reinfection of the gastrointestinal tract.

CLINICAL MANIFESTATIONS

The incubation period of poliovirus from contact to initial clinical symptoms is usually considered to be 8-12 days, with a range of 5-35 days. Poliovirus infections with wild-type virus may follow 1 of several courses: **inapparent infection,** which occurs in 90-95% of cases and causes no disease and no sequelae; abortive poliomyelitis; nonparalytic

poliomyelitis; or paralytic poliomyelitis. Paralysis, if it occurs, appears 3-8 days after the initial symptoms. The clinical manifestations of paralytic polio caused by wild or vaccine strains are comparable, although the incidence of abortive and nonparalytic paralysis with vaccine-associated poliomyelitis is unknown.

Abortive Poliomyelitis

In approximately 5% of patients, a nonspecific influenza-like syndrome occurs 1-2 wk after infection, which is termed *abortive poliomyelitis*. Fever, malaise, anorexia, and headache are prominent features, and there may be sore throat and abdominal or muscular pain. Vomiting occurs irregularly. The illness is short lived, lasting up to 2-3 days. The **physical examination** may be normal or may reveal nonspecific pharyngitis, abdominal or muscular tenderness, and weakness. Recovery is complete, and no neurologic signs or sequelae develop.

Nonparalytic Poliomyelitis

In approximately 1% of patients infected with wild-type poliovirus, signs of abortive poliomyelitis are present, as are more intense headache, nausea, and vomiting, as well as soreness and stiffness of the posterior muscles of the neck, trunk, and limbs. Fleeting paralysis of the bladder and constipation are frequent. Approximately two thirds of these children have a short symptom-free interlude between the 1st phase (**minor illness**) and the 2nd phase (CNS disease or **major illness**). Nuchal rigidity and spinal rigidity are the basis for the diagnosis of nonparalytic poliomyelitis during the second phase.

Physical examination reveals nuchal-spinal signs and changes in superficial and deep reflexes. Gentle forward flexion of the occiput and neck elicits nuchal rigidity. The examiner can demonstrate head drop by placing the hands under the patient's shoulders and raising the patient's trunk. Although normally the head follows the plane of the trunk, in poliomyelitis it often falls backward limply, but this response is not attributable to true paresis of the neck flexors. In struggling infants it may be difficult to distinguish voluntary resistance from clinically important true nuchal rigidity. The examiner may place the infant's shoulders flush with the edge of the table, support the weight of the occiput in the hand, and then flex the head anteriorly. True nuchal rigidity persists during this maneuver. When open, the anterior fontanel may be tense or bulging.

In the early stages the reflexes are normally active and remain so unless paralysis supervenes. Changes in reflexes, either increased or decreased, may precede weakness by 12-24 hr. The superficial reflexes, the cremasteric and abdominal reflexes, and the reflexes of the spinal and gluteal muscles are usually the first to diminish. The spinal and gluteal reflexes may disappear before the abdominal and cremasteric reflexes. Changes in the deep tendon reflexes generally occur 8-24 hr after the superficial reflexes are depressed and indicate impending paresis of the extremities. Tendon reflexes are absent with paralysis. Sensory defects do not occur in poliomyelitis.

Paralytic Poliomyelitis

Paralytic poliomyelitis develops in approximately 0.1% of persons infected with poliovirus, causing 3 clinically recognizable syndromes that represent a continuum of infection differentiated only by the portions of the CNS most severely affected. These are (1) spinal paralytic poliomyelitis, (2) bulbar poliomyelitis, and (3) polioencephalitis.

Spinal paralytic poliomyelitis may occur as the 2nd phase of a biphasic illness, the 1st phase of which corresponds to abortive poliomyelitis. The patient then appears to recover and feels better for 2-5 days, after which severe headache and fever occur with exacerbation of the previous systemic symptoms. Severe muscle pain is present, and sensory and motor phenomena (e.g., paresthesia, hyperesthesia, fasciculations, and spasms) may develop. On physical examination the distribution of paralysis is characteristically spotty. Single muscles, multiple muscles, or groups of muscles may be involved in any pattern. Within 1-2 days, asymmetric flaccid paralysis or paresis occurs. Involvement of one leg is most common, followed by involvement of one arm. The proximal areas of the extremities tend to be involved to a greater extent than the distal areas. To detect mild muscular weakness, it is often necessary to apply gentle resistance in opposition to the muscle group being tested. Examination at this point may reveal nuchal stiffness or rigidity, muscle tenderness, initially hyperactive deep tendon reflexes (for a short period) followed by absence or diminution of reflexes, and paresis or flaccid paralysis. In the spinal form, there is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm, thorax, or extremities. Sensation is intact; sensory disturbances, if present, suggest a disease other than poliomyelitis.

The paralytic phase of poliomyelitis is extremely variable; some patients progress during observation from paresis to paralysis, whereas others recover, either slowly or rapidly. The extent of paresis or paralysis is directly related to the extent of neuronal involvement; paralysis occurs if >50% of the neurons supplying the muscles are destroyed. The extent of involvement is usually obvious within 2-3 days; only rarely does progression occur beyond this interval. Bowel and bladder dysfunction ranging from transient incontinence to paralysis with constipation and urinary retention often accompany paralysis of the lower limbs.

The onset and course of paralysis are variable in developing countries. The biphasic course is rare; typically the disease manifests in a single phase in which prodromal symptoms and paralysis occur in a continuous fashion. In developing countries, where a history of intramuscular injections precedes paralytic poliomyelitis in approximately 50-60% of patients, patients may present initially with fever and paralysis (**provocation paralysis**). The degree and duration of muscle pain are also variable, ranging from a few days usually to a week. Occasionally spasm and increased muscle tone with a transient increase in deep tendon reflexes occur in some patients, whereas in most patients, flaccid paralysis occurs abruptly. Once the temperature returns to normal, progression of paralytic manifestations stops. Little recovery from paralysis is noted in the 1st days or weeks, but, if it is to occur, it is usually evident within 6 mo. The return of strength and reflexes is slow and may continue to improve for as long as 18 mo after the acute disease. Lack of improvement from paralysis within the 1st several weeks or months after onset is usually evidence of permanent paralysis. Atrophy of the limb, failure of growth, and deformity are common and are especially evident in the growing child.

Bulbar poliomyelitis may occur as a clinical entity without apparent involvement of the spinal cord. Infection is a continuum, and designation of the disease as bulbar implies only dominance of the clinical manifestations by dysfunctions of the cranial nerves and medullary centers. The clinical findings seen with bulbar poliomyelitis with respiratory difficulty (other than paralysis of extraocular, facial, and masticatory muscles) include (1) nasal twang to the voice or cry caused by palatal and pharyngeal weakness (hard-consonant words such as "cookie" and "candy" bring this feature out best); (2) inability to swallow smoothly, resulting in accumulation of saliva in the pharynx, indicating partial immobility (holding the larynx lightly and asking the patient to swallow will confirm such immobility); (3) accumulated pharyngeal secretions, which may cause irregular respirations that appear interrupted and abnormal even to the point of falsely simulating intercostal or diaphragmatic weakness; (4) absence of effective coughing, shown by constant fatiguing efforts to clear the throat; (5) nasal regurgitation of saliva and fluids as a result of palatal paralysis, with inability to separate the oropharynx from the nasopharynx during swallowing; (6) deviation of the palate, uvula, or tongue; (7) involvement of vital centers in the medulla, which manifest as irregularities in rate, depth, and rhythm of respiration; as cardiovascular alterations, including blood pressure changes (especially increased blood pressure), alternate flushing and mottling of the skin, and cardiac arrhythmias; and as rapid changes in body temperature; (8) paralysis of 1 or both vocal cords, causing hoarseness, aphonia, and, ultimately, asphyxia unless the problem is recognized on laryngoscopy and managed by immediate tracheostomy; and (9) the **rope sign,** an acute angulation between the chin and larynx caused by weakness of the hyoid muscles (the hyoid bone is pulled posteriorly, narrowing the hypopharyngeal inlet).

Uncommonly, bulbar disease may culminate in an ascending paralysis (Landry type), in which there is progression cephalad from initial involvement of the lower extremities. Hypertension and other

autonomic disturbances are common in bulbar involvement and may persist for a week or more or may be transient. Occasionally, hypertension is followed by hypotension and shock and is associated with irregular or failed respiratory effort, delirium, or coma. This kind of bulbar disease may be rapidly fatal.

The course of bulbar disease is variable; some patients die as a result of extensive, severe involvement of the various centers in the medulla; others recover partially but require ongoing respiratory support, and others recover completely. Cranial nerve involvement is seldom permanent. Atrophy of muscles may be evident, patients immobilized for long periods may experience pneumonia, and renal stones may form as a result of hypercalcemia and hypercalciuria secondary to bone resorption.

Polioencephalitis is a rare form of the disease in which higher centers of the brain are severely involved. Seizures, coma, and spastic paralysis with increased reflexes may be observed. Irritability, disorientation, drowsiness, and coarse tremors are often present with peripheral or cranial nerve paralysis that coexists or ensues. Hypoxia and hypercapnia caused by inadequate ventilation due to respiratory insufficiency may produce disorientation without true encephalitis. The manifestations are common to encephalitis of any cause and can be attributed to polioviruses only with specific viral diagnosis or if accompanied by flaccid paralysis.

Paralytic poliomyelitis with ventilatory insufficiency results from several components acting together to produce ventilatory insufficiency resulting in hypoxia and hypercapnia. It may have profound effects on many other systems. Because respiratory insufficiency may develop rapidly, close continued clinical evaluation is essential. Despite weakness of the respiratory muscles, the patient may respond with so much respiratory effort associated with anxiety and fear that overventilation may occur at the outset, resulting in respiratory alkalosis. Such effort is fatiguing and contributes to respiratory failure.

There are certain characteristic patterns of disease. Pure spinal poliomyelitis with respiratory insufficiency involves tightness, weakness, or paralysis of the respiratory muscles (chiefly the diaphragm and intercostals) without discernible clinical involvement of the cranial nerves or vital centers that control respiration, circulation, and body temperature. The cervical and thoracic spinal cord segments are chiefly affected. Pure bulbar poliomyelitis involves paralysis of the motor cranial nerve nuclei with or without involvement of the vital centers. Involvement of the 9th, 10th, and 12th cranial nerves results in paralysis of the pharynx, tongue, and larynx with consequent airway obstruction. Bulbospinal poliomyelitis with respiratory insufficiency affects the respiratory muscles and results in coexisting bulbar paralysis.

The clinical findings associated with involvement of the respiratory muscles include (1) anxious expression; (2) inability to speak without frequent pauses, resulting in short, jerky, "breathless" sentences; (3) increased respiratory rate; (4) movement of the ala nasi and of the accessory muscles of respiration; (5) inability to cough or sniff with full depth; (6) paradoxical abdominal movements caused by diaphragmatic immobility caused by spasm or weakness of 1 or both leaves; and (7) relative immobility of the intercostal spaces, which may be segmental, unilateral, or bilateral. When the arms are weak, and especially when deltoid paralysis occurs, there may be impending respiratory paralysis because the phrenic nerve nuclei are in adjacent areas of the spinal cord. Observation of the patient's capacity for thoracic breathing while the abdominal muscles are splinted manually indicates minor degrees of paresis. Light manual splinting of the thoracic cage helps assess the effectiveness of diaphragmatic movement.

DIAGNOSIS

Poliomyelitis should be considered in any unimmunized or incompletely immunized child with paralytic disease. While this guideline is most applicable in poliomyelitis endemic countries (Afghanistan, Pakistan, and Nigeria), the spread of polio in 2013 from endemic countries to many nonendemic countries (Niger, Chad, Cameroon, Ethiopia, Kenya, Somalia, and Syria) and the isolation of wild poliovirus type 1 in Israel suggest that the diagnosis of polio should still be entertained in all countries. VAPP should be considered in any child with paralytic disease occurring 7-14 days after receiving the orally administered polio vaccine (OPV). VAPP can occur at later times after administration and should be considered in any child with paralytic disease in countries or regions where wild-type poliovirus has been eradicated and the OPV has been administered to the child or a contact. The combination of fever, headache, neck and back pain, asymmetric flaccid paralysis without sensory loss, and pleocytosis does not regularly occur in any other illness.

The World Health Organization (WHO) recommends that the laboratory diagnosis of poliomyelitis be confirmed by isolation and identification of poliovirus in the stool, with specific identification of wild-type and vaccine-type strains. In suspected cases of acute flaccid paralysis, 2 stool specimens should be collected 24-48 hr apart as soon as possible after the diagnosis of poliomyelitis is suspected. Poliovirus concentrations are high in the stool in the 1st wk after the onset of paralysis, which is the optimal time for collection of stool specimens. Polioviruses may be isolated from 80-90% of specimens from acutely ill patients, whereas <20% of specimens from such patients may yield virus within 3-4 wk after onset of paralysis. Because most children with spinal or bulbospinal poliomyelitis have constipation, rectal straws may be used to obtain specimens; ideally a minimum of 8-10 g of stool should be collected. In laboratories that can isolate poliovirus, isolates should be sent to either the U.S. Centers for Disease Control and Prevention or to one of the WHO-certified poliomyelitis laboratories where DNA sequence analysis can be performed to distinguish between wild poliovirus and neurovirulent, revertant OPV strains. With the current WHO plan for global eradication of poliomyelitis, most regions of the world (the Americas, Europe, Australia) have been certified wild-poliovirus free; in these areas, poliomyelitis is most often caused by vaccine strains. Hence it is critical to differentiate between wild-type and revertant vaccine-type strains.

The CSF is often normal during the minor illness and typically contains a pleocytosis with 20-300 cells/μL with CNS involvement. The cells in the CSF may be polymorphonuclear early during the course of the disease but shift to mononuclear cells soon afterward. By the 2nd wk of major illness, the CSF cell count falls to near-normal values. In contrast, the CSF protein content is normal or only slightly elevated at the outset of CNS disease but usually rises to 50-100 mg/dL by the 2nd wk of illness. In polioencephalitis, the CSF may remain normal or show minor changes. Serologic testing demonstrates seroconversion or a 4-fold or greater increase in antibody titers from the acute phase of illness to 3-6 wk later.

DIFFERENTIAL DIAGNOSIS

Poliomyelitis should be considered in the differential diagnosis of any case of paralysis, and is only 1 of many causes of acute flaccid paralysis in children and adults. There are numerous other causes of acute flaccid paralysis (Table 249-1). In most conditions, the clinical features are sufficient to differentiate between these various causes, but in some cases nerve conduction studies and electromyograms, in addition to muscle biopsies, may be required.

The possibility of polio should be considered in any case of acute flaccid paralysis, even in countries where polio has been eradicated. The diagnoses most often confused with polio are VAPP, West Nile virus infection, infections caused by other enteroviruses, as well as Guillain-Barré syndrome, transverse myelitis, and traumatic paralysis. In Guillain-Barré syndrome, which is the most difficult to distinguish from poliomyelitis, the paralysis is characteristically symmetric, and sensory changes and pyramidal tract signs are common, contrasting with poliomyelitis. Fever, headache, and meningeal signs are less notable, and the CSF has few cells but an elevated protein content. Transverse myelitis progresses rapidly over hours to days, causing an acute symmetric paralysis of the lower limbs with concomitant anesthesia and diminished sensory perception. Autonomic signs of hypothermia in the affected limbs are common, and there is bladder dysfunction. The CSF is usually normal. Traumatic neuritis occurs from a few hours to a few days after the traumatic event, is asymmetric, is acute, and affects only 1 limb. Muscle tone and deep tendon reflexes are reduced or absent in the affected limb with pain in the gluteus. The CSF is normal.

Table 249-1 Differential Diagnosis of Acute Flaccid Paralysis

SITE, CONDITION, FACTOR, OR AGENT	CLINICAL FINDINGS	ONSET OF PARALYSIS	PROGRESSION OF PARALYSIS	SENSORY SIGNS AND SYMPTOMS	REDUCTION OR ABSENCE OF DEEP TENDON REFLEXES	RESIDUAL PARALYSIS	PLEOCYTOSIS
ANTERIOR HORN CELLS OF SPINAL CORD							
Poliomyelitis (wild and vaccine-associated paralytic poliomyelitis)	Paralysis	Incubation period 7-14 days (range: 4-35 days)	24-48 hr to onset of full paralysis; proximal → distal, asymmetric	No	Yes	Yes	Aseptic meningitis (moderate polymorphonuclear leukocytes at 2-3 days)
Nonpolio enteroviruses	Hand-foot-and-mouth disease, aseptic meningitis, acute hemorrhagic conjunctivitis, possibly idiopathic epidemic flaccid paralysis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	As in poliomyelitis
West Nile virus	Meningitis encephalitis	As in poliomyelitis	As in poliomyelitis	No	Yes	Yes	Yes
OTHER NEUROTROPIC VIRUSES							
Rabies virus		Month–year	Acute, symmetric, ascending	Yes	Yes	No	±
Varicella-zoster virus	Exanthematous vesicular eruptions	Incubation period 10-21 days	Acute, symmetric, ascending	Yes	±	±	Yes
Japanese encephalitis virus		Incubation period 5-15 days	Acute, proximal, asymmetric	±	±	±	Yes
GUILLAIN-BARRÉ SYNDROME							
Acute inflammatory polyradiculoneuropathy	Preceding infection, bilateral facial weakness	Hours to 10 days	Acute, symmetric, ascending (days to 4 wk)	Yes	Yes	±	No
Acute motor axonal neuropathy	Fulminant, widespread paralysis, bilateral facial weakness, tongue involvement	Hours to 10 days	1-6 days	No	Yes	±	No

ACUTE TRAUMATIC SCIATIC NEURITIS							
Intramuscular gluteal injection	Acute, asymmetric	Hours to 4 days	Complete, affected limb	Yes	Yes	±	No
Acute transverse myelitis	Preceding *Mycoplasma pneumoniae, Schistosoma,* other parasitic or viral infection	Acute, symmetric hypotonia of lower limbs	Hours to days	Yes	Yes, early	Yes	Yes
Epidural abscess	Headache, back pain, local spinal tenderness, meningismus	Complete		Yes	Yes	±	Yes
Spinal cord compression; trauma		Complete	Hours to days	Yes	Yes	±	±
NEUROPATHIES							
Exotoxin of *Corynebacterium diphtheriae*	In severe cases, palatal paralysis, blurred vision	Incubation period 1-8 wk (paralysis 8-12 wk after onset of illness)		Yes	Yes		±
Toxin of *Clostridium botulinum*	Abdominal pain, diplopia, loss of accommodation, mydriasis	Incubation period 18-36 hr	Rapid, descending, symmetric	±	No		No
Tick bite paralysis	Ocular symptoms	Latency period 5-10 days	Acute, symmetric, ascending	No	Yes		No
DISEASES OF THE NEUROMUSCULAR JUNCTION							
Myasthenia gravis	Weakness, fatigability, diplopia, ptosis, dysarthria		Multifocal	No	No	No	No
DISORDERS OF MUSCLE							
Polymyositis	Neoplasm, autoimmune disease	Subacute, proximal → distal	Weeks to months	No	Yes		No
Viral myositis		Pseudoparalysis	Hours to days	No	No		No
METABOLIC DISORDERS							
Hypokalemic periodic paralysis		Proximal limb, respiratory muscles	Sudden postprandial	No	Yes	±	No
INTENSIVE CARE UNIT WEAKNESS							
Critical illness polyneuropathy	Flaccid limbs and respiratory weakness	Acute, following systemic inflammatory response syndrome/sepsis	Hours to days	±	Yes	±	No

Modified from Marx A, Glass JD, Sutter RW: Differential diagnosis of acute flaccid paralysis and its role in poliomyelitis surveillance, Epidemiol Rev *22:298–316, 2000.*

Conditions causing pseudoparalysis do not present with nuchal-spinal rigidity or pleocytosis. These causes include unrecognized trauma, transient (toxic) synovitis, acute osteomyelitis, acute rheumatic fever, scurvy, and congenital syphilis (pseudoparalysis of Parrot).

TREATMENT

There is no specific antiviral treatment for poliomyelitis. The management is supportive and aimed at limiting progression of disease, preventing ensuing skeletal deformities, and preparing the child and family for the prolonged treatment required and for permanent disability if this seems likely. Patients with the nonparalytic and mildly paralytic forms of poliomyelitis may be treated at home. All intramuscular injections and surgical procedures are contraindicated during the acute phase of the illness, especially in the 1st wk of illness, because they might result in progression of disease.

Abortive Poliomyelitis

Supportive treatment with analgesics, sedatives, an attractive diet, and bed rest until the child's temperature is normal for several days is usually sufficient. Avoidance of exertion for the ensuing 2 wk is desirable, and careful neurologic and musculoskeletal examinations should be performed 2 mo later to detect any minor involvement.

Nonparalytic Poliomyelitis

Treatment for the nonparalytic form is similar to that for the abortive form; in particular, relief is indicated for the discomfort of muscle tightness and spasm of the neck, trunk, and extremities. Analgesics are more effective when they are combined with the application of hot packs for 15-30 min every 2-4 hr. Hot tub baths are sometimes useful. A firm bed is desirable and can be improvised at home by placing table leaves or a sheet of plywood beneath the mattress. A footboard or splint should be used to keep the feet at a right angle to the legs. Because muscular discomfort and spasm may continue for some weeks, even in the nonparalytic form, hot packs and gentle physical therapy may be necessary. Patients with nonparalytic poliomyelitis should also be carefully examined 2 mo after apparent recovery to detect minor residual effects that might cause postural problems in later years.

Paralytic Poliomyelitis

Most patients with the paralytic form of poliomyelitis require hospitalization with complete physical rest in a calm atmosphere for the 1st 2-3 wk. Suitable body alignment is necessary for comfort and to avoid excessive skeletal deformity. A neutral position with the feet at right angles to the legs, the knees slightly flexed, and the hips and spine straight is achieved by use of boards, sandbags, and, occasionally, light splint shells. The position should be changed every 3-6 hr. Active and passive movements are indicated as soon as the pain has disappeared. Moist hot packs may relieve muscle pain and spasm. Opiates and sedatives are permissible only if no impairment of ventilation is present or impending. Constipation is common, and fecal impaction should be prevented. When bladder paralysis occurs, a parasympathetic stimulant such as bethanechol may induce voiding in 15-30 min; some patients show no response to this agent, and others respond with nausea, vomiting, and palpitations. Bladder paresis rarely lasts more than a few days. If bethanechol fails, manual compression of the bladder and the psychologic effect of running water should be tried. If catheterization must be performed, care must be taken to prevent urinary tract infections. An appealing diet and a relatively high fluid intake should be started at once unless the patient is vomiting. Additional salt should be provided if the environmental temperature is high or if the application of hot packs induces sweating. Anorexia is common initially. Adequate dietary and fluid intake can be maintained by placement of a central venous catheter. An orthopedist and a physiatrist should see patients as early in the course of the illness as possible and should assume responsibility for their care before fixed deformities develop.

The management of pure bulbar poliomyelitis consists of maintaining the airway and avoiding all risk of inhalation of saliva, food, and vomitus. Gravity drainage of accumulated secretions is favored by using the head-low (foot of bed elevated 20-25 degrees) prone position with the face to one side. Patients with weakness of the muscles of respiration or swallowing should be nursed in a lateral or semiprone position. Aspirators with rigid or semirigid tips are preferred for direct oral and pharyngeal aspiration, and soft, flexible catheters may be used for nasopharyngeal aspiration. Fluid and electrolyte equilibrium is best maintained by intravenous infusion because tube or oral feeding in the 1st few days may incite vomiting. In addition to close observation for respiratory insufficiency, the blood pressure should be measured at least twice daily because hypertension is not uncommon and occasionally leads to hypertensive encephalopathy. Patients with pure bulbar poliomyelitis may require tracheostomy because of vocal cord paralysis or constriction of the hypopharynx; most patients who recover have little residual impairment, although some exhibit mild dysphagia and occasional vocal fatigue with slurring of speech.

Impaired ventilation must be recognized early; mounting anxiety, restlessness, and fatigue are early indications for preemptive intervention. Tracheostomy is indicated for some patients with pure bulbar poliomyelitis, spinal respiratory muscle paralysis, or bulbospinal paralysis because such patients are generally unable to cough, sometimes for many months. Mechanical respirators are often needed.

COMPLICATIONS

Paralytic poliomyelitis may be associated with numerous complications. Acute gastric dilation may occur abruptly during the acute or convalescent stage, causing further respiratory embarrassment; immediate gastric aspiration and external application of ice bags are indicated. Melena severe enough to require transfusion may result from single or multiple superficial intestinal erosions; perforation is rare. Mild hypertension for days or weeks is common in the acute stage and probably related to lesions of the vasoregulatory centers in the medulla and especially to underventilation. In the later stages, because of immobilization, hypertension may occur along with hypercalcemia, nephrocalcinosis, and vascular lesions. Dimness of vision, headache, and a lightheaded feeling associated with hypertension should be regarded as premonitory of a frank convulsion. Cardiac irregularities are uncommon, but electrocardiographic abnormalities suggesting myocarditis occur with some frequency. Acute pulmonary edema occurs occasionally, particularly in patients with arterial hypertension. Hypercalcemia occurs because of skeletal decalcification that begins soon after immobilization and results in hypercalciuria, which in turn predisposes the patient to urinary calculi, especially when urinary stasis and infection are present. High fluid intake is the only effective prophylactic measure.

PROGNOSIS

The outcome of inapparent, abortive poliomyelitis and aseptic meningitis syndromes is uniformly good, with death being exceedingly rare and with no long-term sequelae. The outcome of paralytic disease is determined primarily by degree and severity of CNS involvement. In severe bulbar poliomyelitis, the mortality rate may be as high as 60%, whereas in less-severe bulbar involvement and/or spinal poliomyelitis, the mortality rate varies from 5-10%, death generally occurring from causes other than the poliovirus infection.

Maximum paralysis usually occurs 2-3 days after the onset of the paralytic phase of the illness, with stabilization followed by gradual return of muscle function. The recovery phase lasts usually about 6 mo, beyond which persisting paralysis is permanent. Generally, paralysis is more likely to develop in male children and female adults. Mortality and the degree of disability are greater after the age of puberty. Pregnancy is associated with an increased risk for paralytic disease. Tonsillectomy and intramuscular injections may enhance the risk for acquisition of bulbar and localized disease, respectively. Increased physical activity, exercise, and fatigue during the early phase of illness have been cited as factors leading to a higher risk for paralytic disease. Finally, it has been clearly demonstrated that type 1 poliovirus has the greatest propensity for natural poliomyelitis, and type 3 poliovirus has a predilection for producing VAPP.

Postpolio Syndrome

After an interval of 30-40 yr, as many as 30-40% of persons who survived paralytic poliomyelitis in childhood may experience muscle pain

and exacerbation of existing weakness or development of new weakness or paralysis. This entity, referred to as postpolio syndrome, has been reported only in persons who were infected in the era of wild-type poliovirus circulation. Risk factors for postpolio syndrome include increasing length of time since acute poliovirus infection, presence of permanent residual impairment after recovery from acute illness, and female sex.

PREVENTION

Vaccination is the only effective method of preventing poliomyelitis. Hygienic measures help limit the spread of the infection among young children, but immunization is necessary to control transmission among all age groups. Both the inactivated polio vaccine (IPV), which is currently produced using better methods than those for the original vaccine and is sometimes referred to as enhanced IPV, and the live-attenuated OPV have established efficacy in preventing poliovirus infection and paralytic poliomyelitis. Both vaccines induce production of antibodies against the 3 strains of poliovirus. IPV elicits higher serum IgG antibody titers, but the OPV also induces significantly greater mucosal IgA immunity in the oropharynx and gastrointestinal tract, which limits replication of the wild poliovirus at these sites. Transmission of wild poliovirus by fecal spread is limited in OPV recipients. The immunogenicity of IPV is not affected by the presence of maternal antibodies, and IPV has no adverse effects. Live vaccine may undergo reversion to neurovirulence as it multiplies in the human intestinal tract and may cause VAPP in vaccinees or in their contacts. The overall risk for recipients varies from 1 case per 750,000 immunized infants in the United States to 1 in 143,000 immunized infants in India. The risk for paralysis in the B-cell–immunodeficient recipient may be as much as 6,800 times that in normal subjects. HIV infection has not been found to result in long-term excretion of virus. As of January 2000, the IPV-only schedule is recommended for routine polio vaccination in the United States. All children should receive 4 doses of IPV, at 2 mo, 4 mo, 6-18 mo, and 4-6 yr of age.

In 1988, the World Health Assembly resolved to eradicate poliomyelitis globally by 2000, and remarkable progress had been made toward reaching this target. To achieve this goal, the WHO used 4 basic strategies: routine immunization, National Immunization Days, acute flaccid paralysis surveillance, and "mop-up" immunization. This strategy has resulted in a >99% decline in poliomyelitis cases; in early 2002, there were only 10 countries in the world endemic for poliomyelitis. In 2012, there were the fewest cases of poliomyelitis ever, and the virus was endemic in only 3 countries (Afghanistan, Pakistan, and Nigeria). India has not had a child paralyzed with wild poliovirus type 2 since February 2011. The last case of wild poliovirus type 3 infection occurred in Nigeria in 2012, and the last case of wild poliovirus type 2 infection occurred in India in 1999. This progress prompted the WHO assembly, in May 2013, to recommend the development of a *Polio Eradication and Endgame Strategic Plan 2013-2018*. This plan includes the withdrawal of trivalent OPV with bivalent OPV (bOPV) in all countries by 2016 and the introduction of initially one dose of IPV followed by the replacement of bivalent OPV with IPV in all countries of the world by 2019. As long as the OPV is being used, there is the potential that vaccine-derived poliovirus will acquire the neurovirulent phenotype and transmission characteristics of the wild-type polioviruses. Vaccine-derived poliovirus emerges from the OPV because of continuous replication in immunodeficient persons or by circulation in populations with low vaccine coverage (cVDPVs). The risk appears to be highest with the type 2 strain. Currently, 90% of all cVDPV outbreaks are caused by type 2 strains (Fig. 249-2). Outbreaks of cVDPV2 occurred in Hispaniola, the Philippines, and Madagascar in 2001, and endemic cVDPV2 circulation occurred in Egypt from 1983-1993. As of 2012, 5 outbreaks of cVDPV2 were detected in the 3 polio endemic countries and in Chad, Democratic Republic of Congo, Kenya, Somalia, and China.

Several countries are global priorities because they face challenges in eradication of the disease (see Fig. 249-1). Polioviruses are endemic in Pakistan, Afghanistan, and Nigeria. Twenty previously polio-free countries were infected by importations of wild poliovirus type 1 originating from Nigeria, and 3 polio-free African countries experienced

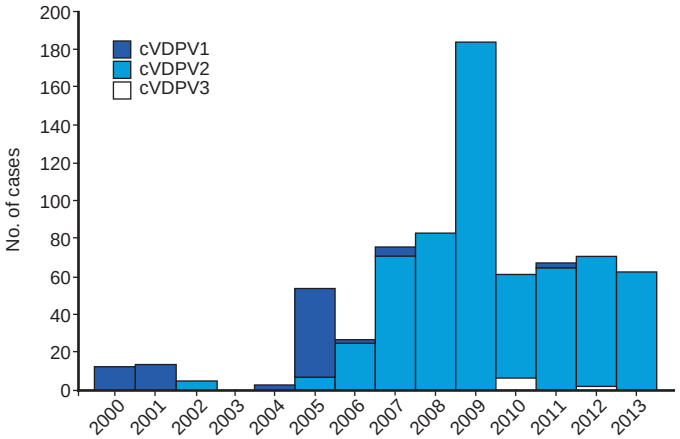


Figure 249-2 Circulating vaccine-derived poliovirus (cVDPV) cases detected worldwide, by serotype and year—2000–2013. *(From Diop OM, Burns CC, Wassilak SG, Kew OM; Centers for Disease Control and Prevention (CDC): Update on vaccine-derived polioviruses–worldwide, July 2012-December 2013.* MMWR Morb Mortal Wkly Rep *63:242–248, 2014.)*

infections with wild poliovirus type 1 imported from India. For the 3 countries with uninterrupted outbreaks, there are 2 main reasons for the failure to eradicate polio. The suboptimal campaign quality in Nigeria, parts of Pakistan and southern Afghanistan, and the countries with prolonged transmission of imported virus as well as security-compromised areas in parts of Afghanistan and Pakistan are still the main difficulties faced in 2014. Of the 416 wild poliovirus cases in 2012, 160 cases were in the 3 endemic countries and 256 were in nonendemic countries. There have been importations from Nigeria into the horn of Africa and the Middle East (Cameroon, Ethiopia, Kenya, Somalia, and Syrian Arab Republic). However, since December 2014 this ratio has changed, and the number of cases in endemic countries (especially Nigeria and Afghanistan) has increased to 306, mostly in Pakistan (276). Equally worrisome to the strategy of switching completely to IPV is the detection of a Pakistani strain of wild poliovirus type 1 in Israel and the West Bank, first in sewage, and now found in up to 4% of children and adults. Israel has used IPV exclusively for the past 10 yr and has introduced bOPV as a single continuous supplementary immunization activity (SIA). bOPV is included in routine immunization, following at least 1 dose of IPV. This follows the experience in the United States that reported no VAPP following a sequential use of IPV followed by OPV. Global synchronous cessation of OPV will need to be coordinated by the WHO, but the recent experiences in the horn of Africa and Israel/West Bank suggest that stopping transmission of wild poliovirus type 1 in the 3 endemic countries is of the utmost urgency, if we are ever going to be able to stop using OPV.

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Chapter 250

Nonpolio Enteroviruses

Mark J. Abzug

The genus *Enterovirus* contains a large number of agents that produce a broad range of illnesses. The genus name reflects the importance of the gastrointestinal tract as the primary site of invasion and replication and the source for transmission. Viremic spread to distant sites accounts for the majority of clinical manifestations.

Table 250-1 Classification of Human Enteroviruses

Family	Picornaviridae
Genus	*Enterovirus*
Subgroups*	Poliovirus serotypes 1-3 Coxsackie A virus serotypes 1-22, 24 (23 **reclassified** as echovirus 9) Coxsackie B virus serotypes 1-6 Echovirus serotypes 1-9, 11-27, 29-33 (echoviruses 10 and 28 **reclassified** as nonenteroviruses; echovirus 34 **reclassified** as a variant of coxsackie A virus 24; echoviruses 22 and 23 **reclassified** within the genus *Parechovirus*) Numbered enterovirus serotypes (enterovirus 72 **reclassified** as hepatitis A virus)

*The human enteroviruses have been alternatively classified on the basis of nucleotide and amino acid sequences into 5 species (polioviruses and human enteroviruses A-D).

ETIOLOGY

Enteroviruses are nonenveloped, single-stranded, positive-sense viruses in the Picornaviridae ("small RNA virus") family, which also includes the genera *Rhinovirus, Hepatovirus* (hepatitis A virus), and *Parechovirus* and genera containing related animal viruses. The original human enterovirus subgroups—polioviruses (see Chapter 249), coxsackieviruses (named after Coxsackie, New York, where they were discovered), and echoviruses (*e*nteric *c*ytopathic *h*uman *o*rphan *viruses*)—were differentiated by their replication patterns in tissue culture and animals (Table 250-1). The human enteroviruses have been reclassified on the basis of genetic similarity into 5 species, polioviruses and human enteroviruses A-D. Enterovirus types are distinguished by antigenic and genetic sequence differences; newer enteroviruses are classified by numbering. Although more than 100 types have been described, 10-15 account for the majority of disease. No disease is uniquely associated with any specific serotype, although certain manifestations are preferentially associated with specific serotypes. It has been observed that human parechoviruses can manifest clinical presentations similar to those of enteroviruses.

EPIDEMIOLOGY

Enterovirus infections are common and have a worldwide distribution. In temperate climates there is an annual epidemic peak in summer/fall, although some transmission occurs year-round. Enteroviruses are responsible for 33-65% of acute febrile illnesses and 55-65% of hospitalizations for suspected sepsis in infants during the summer and fall in the United States, and 25% year-round. In tropical and semitropical areas, enteroviruses circulate year-round. In general, only a few serotypes circulate simultaneously. Infections by different serotypes can occur within the same season. Factors associated with increased incidence and/or severity include young age, male sex, exposure to children, poor hygiene, overcrowding, and low socioeconomic status; >25% of symptomatic infections occur in children younger than 1 yr of age. Breastfeeding reduces the risk for infection, likely via enterovirus-specific antibodies.

Humans are the only known reservoir for human enteroviruses, although some nonhuman primates can be infected. Virus is primarily spread person to person, by the fecal-oral and respiratory routes, although types causing acute hemorrhagic conjunctivitis may be spread via airborne transmission. Virus can be transmitted vertically prenatally or in the peripartum period, or, possibly, via breastfeeding. Enteroviruses can survive on environmental surfaces, permitting transmission via fomites. Enteroviruses also can frequently be isolated from water sources and sewage and can survive for months in wet soil. Although environmental contamination (of drinking water, swimming pools and ponds, and hospital water reservoirs) may occasionally be responsible for transmission, it is often considered the result, rather than the cause, of human infection. Transmission occurs within families (≥50% risk of spread to nonimmune household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks. Transmission risk is increased by diaper changing and decreased by handwashing. Tickborne transmission has been suggested.

Large enterovirus outbreaks have included echovirus meningitis epidemics in numerous countries (echoviruses 4, 6, 9, 13, and 30 commonly); epidemics of hand-foot-and-mouth disease with severe central nervous system (CNS) and/or cardiopulmonary disease caused by enterovirus 71 in Asia and Australia; outbreaks of atypical hand-foot-and-mouth disease caused by coxsackievirus A6 in the United States and United Kingdom; outbreaks of human enterovirus 68 producing respiratory illness and possibly acute flaccid paralysis in the United States, Europe, and Asia; outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus 70, coxsackievirus A24, and coxsackievirus A24 variant in tropical and temperate regions; and community outbreaks of uveitis. Reverse transcription polymerase chain reaction (RT-PCR), restriction fragment length polymorphism analysis, single-strand conformation polymorphism analysis, heteroduplex mobility analysis, and genomic sequencing help identify outbreaks and allow phylogenetic analyses that demonstrate, depending on the outbreak, commonality of outbreak strains, differences among epidemic strains and older prototype strains, changes in circulating viral subgroups over time, cocirculation of multiple genetic lineages, coinfections with different enterovirus serotypes, and associations between specific genogroups and/or substitutions at specific genetic loci and epidemiologic and clinical characteristics. Genetic analyses have demonstrated recombination and genetic drift that lead to evolutionary changes in genomic sequence and antigenicity and extensive genetic diversity. Rapid genetic evolution and recombination events associated with emergence of new subgenotypes and genetic lineages of enterovirus 71 may contribute to sequential outbreaks and increases in viral circulation.

The incubation period is typically 3-6 days, except for a 1-3 day incubation period for acute hemorrhagic conjunctivitis. Infected children, both symptomatic and asymptomatic, frequently shed cultivable enteroviruses from the respiratory tract for <1-3 wk, whereas fecal shedding continues for as long as 7-11 wk. Enterovirus RNA can be shed from mucosal sites for comparable, and, possibly, longer periods.

PATHOGENESIS

Following oral or respiratory acquisition, initial replication occurs in the pharynx and intestine, possibly within mucosal M cells. The absence of an envelope favors survival in the gastrointestinal tract. Cell surface macromolecules, including poliovirus receptor, integrin very-late-activation antigen (VLA)-2, decay-accelerating factor/complement regulatory protein (DAF/CD55), intercellular adhesion molecule-1 (ICAM-1), and coxsackievirus-adenovirus receptor, serve as receptors, as do sialic acid for enterovirus 68, enterovirus 70, and coxsackievirus A24 variants and human scavenger receptor class B2 (SCARB2), human P-selectin glycoprotein ligand-1, and DC-SIGN for enterovirus 71. Two or more enteroviruses may invade and replicate in the gastrointestinal tract simultaneously, but replication of 1 type often hinders growth of the heterologous type (**interference**).

After the virus attaches to a cell surface receptor, a conformational change in surface capsid proteins facilitates penetration and uncoating with release of viral RNA in the cytoplasm. Translation of the positive-sense RNA produces a polyprotein that undergoes cleavage by proteinases encoded in the polyprotein. Several proteins produced guide synthesis of negative-sense RNA that serves as a template for

replication of new positive-sense RNA. The genome is approximately 7,500 nucleotides long and includes a highly conserved 5′ noncoding region important for replication efficiency and a highly conserved 3′ polyA region, which flank a continuous region encoding viral proteins. The 5′ end is covalently linked to a small viral protein (VPg) necessary for initiation of RNA synthesis. There is significant variation within genomic regions encoding the structural proteins (with corresponding variability in antigenicity). Replication is followed by further cleavage of proteins and assembly into 30 nm icosahedral virions. Of the 4 structural proteins (VP1-VP4) in the capsid (additional regulatory proteins such as an RNA-dependent RNA polymerase and proteases are also present in the virion), VP1 is the most important determinant of serotype specificity. Approximately 10^4-10^5 virions are released from an infected cell by lysis within 5-10 hr of infection.

Initial replication in the pharynx and intestine is followed within days by multiplication in lymphoid tissue such as tonsils, Peyer patches, and regional lymph nodes. A primary, transient viremia (**minor viremia**) results in spread to distant parts of the reticuloendothelial system, including the liver, spleen, bone marrow, and distant lymph nodes. Host immune responses may limit replication and progression beyond the reticuloendothelial system, resulting in subclinical infection. Clinical infection occurs if replication proceeds in the reticuloendothelial system and virus spreads via a secondary, sustained viremia (**major viremia**) to target organs such as the CNS, heart, and skin. Tropism to target organs is determined in part by the infecting serotype.

Enteroviruses can damage a wide variety of organs and systems, including the CNS, heart, liver, lungs, pancreas, kidneys, muscle, and skin. Damage is mediated by necrosis and the inflammatory response. CNS infections are often associated with mononuclear pleocytosis of the cerebrospinal fluid (CSF), composed of macrophages and activated T lymphocytes, and a mixed meningeal inflammatory response. Parenchymal involvement may affect the cerebral white and gray matter, cerebellum, basal ganglia, brainstem, and spinal cord with perivascular and parenchymal mixed or lymphocytic inflammation, gliosis, cellular degeneration, and neuronophagocytosis. Encephalitis during enterovirus 71 epidemics has been characterized by severe involvement of the brainstem, spinal cord gray matter, hypothalamus, and subthalamic and dentate nuclei, and frequently complicated by pulmonary edema, hemorrhage and/or interstitial pneumonitis and cardiopulmonary failure, presumed secondary to brainstem damage, sympathetic hyperactivity, autonomic dysfunction, and CNS and systemic inflammatory responses (including cytokine and chemokine overexpression), and, only occasionally, myocarditis. Immunologic cross-reactivity with brain tissue has been postulated as one mechanism responsible for neurologic damage and sequelae following enterovirus 71 infection.

Enterovirus myocarditis is characterized by perivascular and interstitial mixed inflammatory infiltrates and myocyte damage, possibly mediated by viral cytolytic (e.g., cleavage of dystrophin or serum response factor) and innate and adaptive immune-mediated mechanisms. Chronic inflammation may persist after viral clearance.

The potential for enteroviruses to cause persistent infection is controversial. Persistent infection has been implicated in dilated cardiomyopathy and in myocardial infarction, with enteroviral RNA sequences and/or antigens demonstrated in cardiac tissues in some, but not other, series. Infections with enteroviruses such as coxsackievirus B4, during gestation or subsequently, have been implicated as a trigger for development of β-cell autoantibodies and/or type 1 diabetes in genetically susceptible hosts. Persistent infection in the pancreas, intestine, or peripheral blood mononuclear cells, with downstream immunomodulatory effects, has also been suggested, but data are inconsistent. Similarly, persistent infection is implicated in amyotrophic lateral sclerosis, Sjögren syndrome, and gastrointestinal tract tumors, and evidence of chronic infection has been described in some studies of chronic fatigue syndrome but not in others.

Severe **neonatal infections** can manifest as hepatic necrosis, hemorrhage, inflammation, endotheliitis, and venoocclusive disease; myocardial mixed inflammatory infiltrates, edema, and necrosis; meningeal and brain inflammation, hemorrhage, gliosis, necrosis, and white matter damage; inflammation, hemorrhage, thrombosis, and necrosis in the lungs, pancreas, and adrenal glands; and disseminated intravascular coagulation. In utero infections are characterized by placentitis and infection of multiple fetal organs such as heart, lung, and brain.

Development of type-specific neutralizing antibodies appears to be the most important immune defense, mediating prevention against and recovery from infection. Immunoglobulin (Ig) M antibodies, followed by long-lasting IgA and IgG antibodies, and secretory IgA, mediating mucosal immunity, are produced. Although local reinfection of the gastrointestinal tract can occur, replication is usually limited and not associated with disease. In vitro and animal experiments suggest that heterotypic antibody may enhance disease caused by a different serotype. Evidence also suggests that subneutralizing concentrations of serotype-specific antibody may lead to antibody-dependent enhancement of enterovirus 71 infection. Innate and cellular defenses (macrophages and cytotoxic T lymphocytes) may play important roles in recovery from infection. Altered cellular responses to enterovirus 71, including T lymphocyte and natural killer cell depletion, were associated with severe meningoencephalitis ± pulmonary edema.

Hypogammaglobulinemia and agammaglobulinemia predispose to severe, often chronic enterovirus infections. Similarly, perinatally infected neonates lacking maternal type-specific antibody to the infecting virus are at risk for severe disease. Enterovirus 71 disease increases after 6 mo of age, when maternal serotype-specific antibody levels have declined. Other risk factors for significant illness include young age, immune suppression (posttransplantation and lymphoid malignancy), and, according to animal models and/or epidemiologic observations, exercise, cold exposure, malnutrition, and pregnancy. Specific human leukocyte antigen genes, immune response gene (e.g., interleukin-10 and interferon-γ) polymorphisms, and low vitamin A levels have been linked to enterovirus 71 susceptibility and severe disease.

CLINICAL MANIFESTATIONS

Manifestations are protean, ranging from asymptomatic infection or undifferentiated febrile or respiratory illnesses in the majority, to, less frequently, severe diseases such as meningoencephalitis, myocarditis, and neonatal sepsis. A majority of individuals are asymptomatic or have very mild illness, yet may serve as significant sources for spread of infection. Symptomatic disease is generally more common in young children.

Nonspecific Febrile Illness

Nonspecific febrile illnesses are the most common symptomatic manifestations, especially in infants and young children. These are difficult to clinically differentiate from serious infections such as bacteremia and bacterial meningitis, necessitating diagnostic testing, presumptive therapy, and hospitalizations for suspected bacterial infection in young infants.

Illness usually begins abruptly with fever of 38.5-40°C (101-104°F), malaise, and irritability. Other symptoms are lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms, and, in older children, headache and myalgia. Findings are generally nonspecific and may include mild conjunctivitis, pharyngeal injection, and cervical lymphadenopathy. Meningitis may be present, but, in infants, specific clinical features distinguishing those with meningitis are often lacking. Fever lasts a mean of 3 days and, occasionally, is biphasic. Duration of illness is usually 4-7 days but can range from 1 day to >1 wk. White blood cell (WBC) count and results of routine laboratory tests are generally normal, although transient neutropenia can be seen. Concomitant enterovirus and bacterial infection has been observed in a small number of infants.

Enterovirus illnesses may be associated with a wide variety of skin manifestations, including macular, maculopapular, urticarial, vesicular, and petechial eruptions. Rare cases of idiopathic thrombocytopenic purpura have been reported. Enteroviruses have also been implicated in pityriasis rosea. In general, the frequency of cutaneous manifestations is inversely related to age. Serotypes commonly associated with rashes are echoviruses 9, 11, 16, and 25; coxsackie A viruses 2, 4, 6, 9, and 16; coxsackie B viruses 3-5; and enterovirus 71. Virus can occasionally be recovered from vesicular skin lesions.

Figure 250-1 **A,** Oval blisters of the palms in a child with hand-foot-and-mouth disease (coxsackievirus A16 infection). **B,** Oval blisters on the feet of a child with hand-foot-and-mouth disease. **C,** Erosion of the tongue in a child with hand-foot-and-mouth disease. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 3, St. Louis, 2002, Mosby, p. 109.)*

Hand-Foot-and-Mouth Disease

Hand-foot-and-mouth disease, one of the more distinctive rash syndromes, is most frequently caused by coxsackievirus A16, sometimes in large outbreaks, and can also be caused by enterovirus 71; coxsackie A viruses 5, 6, 7, 9, and 10; coxsackie B viruses 2 and 5; and some echoviruses. It is usually a mild illness, with or without low-grade fever. The oropharynx is inflamed and contains scattered vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips (Fig. 250-1). These may ulcerate, leaving 4-8 mm shallow lesions with surrounding erythema. Maculopapular, vesicular, and/or pustular lesions may occur on the hands and fingers, feet, and buttocks and groin; the hands are more commonly involved than the feet (see Fig. 250-1). Lesions on the hands and feet are usually tender, 3-7 mm vesicles that occur more commonly on dorsal surfaces but frequently also on palms and soles. Vesicles resolve in about 1 wk. Buttock lesions do not usually progress to vesiculation. Disseminated vesicular rashes may complicate preexisting eczema. Hand-foot-and-mouth disease caused by enterovirus 71 is frequently more severe than coxsackievirus A16 disease, with high rates of neurologic and cardiopulmonary involvement, especially in young children (see "Neurologic Manifestations" below). Coxsackievirus A16 also can occasionally be associated with complications such as encephalitis, acute flaccid paralysis, myocarditis, pericarditis, and shock. Coxsackievirus A6 is also responsible for atypical hand-foot-and-mouth disease (and herpangina), notable for affecting adults and children and causing relatively severe disease, including fever, generalized rash (face, proximal extremities, and trunk, in addition to hands, feet, and buttocks), pain, dehydration, and desquamation of palms and soles. **Onychomadesis** (nail shedding) has been observed following coxsackievirus A6 and other coxsackievirus infections.

Herpangina

Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and lesions in the posterior pharynx. Temperatures range from normal to 41°C (106°F); fever tends to be greater in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25% of cases. Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1-2 mm vesicles and ulcers that enlarge over 2-3 days to 3-4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. Typically, approximately 5 lesions are present, with a range of 1 to >15. The remainder of the pharynx appears normal or minimally erythematous. Most cases are mild and have no complications; however, some are associated with meningitis or more severe illness. Fever generally lasts 1-4 days, and resolution of symptoms occurs in 3-7 days. A variety of enteroviruses cause herpangina, including enterovirus 71, although coxsackie A viruses are implicated most often.

Respiratory Manifestations

Symptoms such as sore throat and coryza frequently accompany and sometimes dominate enterovirus illnesses. Other respiratory findings may include wheezing, exacerbation of asthma, apnea, respiratory distress, pneumonia, otitis media, bronchiolitis, croup, parotitis, and pharyngotonsillitis, which may occasionally be exudative. Lower respiratory tract infection may be significant in immunocompromised patients. Clusters and outbreaks of cases of severe respiratory disease, including pneumonia and wheezing (both in children with a history of asthma and those unaffected by asthma), have been observed in association with multiple lineages of enterovirus 68.

Pleurodynia (**Bornholm disease**), caused most frequently by coxsackie B viruses 3, 5, 1, and 2 and echoviruses 1 and 6, is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, due to myositis involving chest and abdominal wall muscles and, possibly, pleural inflammation. In epidemics, children and adults are affected, but most cases occur in persons younger than age 30 yr. Malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain in the chest or upper abdomen aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe and respirations are usually rapid, shallow, and grunting, suggesting pneumonia or pleural inflammation. A pleural friction rub may be noted during pain episodes. Chest radiographs are generally normal but can demonstrate pulmonary infiltrates or pleural effusions. Pain localized to the abdomen may suggest colic, intestinal obstruction, appendicitis, or peritonitis. Illness usually lasts 3-6 days, and, occasionally, up to 2 wk. It is frequently biphasic and is rarely associated with recurrent episodes over a few weeks, with less prominent fever during recurrences. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis.

Life-threatening pulmonary edema, hemorrhage, and/or interstitial pneumonitis may occur in patients with enterovirus 71 encephalitis.

Ocular Manifestations

Epidemics of **acute hemorrhagic conjunctivitis,** primarily caused by enterovirus 70 and coxsackievirus A24/A24 variant, are explosive, spreading mainly via eye-hand-fomite-eye transmission. School-age children, teenagers, and adults 20-50 yr of age have the highest attack rates. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms including fever are rare, although manifestations suggestive of pharyngoconjunctival fever occasionally occur. Recovery is usually complete within 1-2 wk. Polyradiculoneuropathy or paralytic disease following enterovirus 70 disease occurs

occasionally. Other enteroviruses have occasionally been implicated as causes of keratoconjunctivitis.

Epidemic and sporadic uveitis in infants caused by subtypes of enteroviruses 11 and 19 can be associated with severe complications, including destruction of the iris, cataracts, and glaucoma. Enteroviruses have been implicated in cases of chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

Myocarditis and Pericarditis

Enteroviruses account for approximately 25-35% of cases of myocarditis and pericarditis with proven cause (see Chapters 440 and 441). Coxsackie B viruses are most commonly implicated, although coxsackie A viruses and echoviruses also may be causative. Adolescents and young adults, especially males, are disproportionately affected. Myopericarditis may be the dominant feature or it may be part of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Upper respiratory symptoms frequently precede fatigue, dyspnea, chest pain, congestive heart failure, and dysrhythmias. Presentations may mimic myocardial infarction; sudden death may also occur (including apparent sudden infant death syndrome). A pericardial friction rub indicates pericardial involvement. Chest radiography often demonstrates cardiac enlargement. Electrocardiography frequently reveals ST segment, T wave, and/or rhythm abnormalities, and echocardiography may confirm cardiac dilation, reduced contractility, and/or pericardial effusion. Myocardial enzyme serum concentrations may be elevated. The acute mortality of enterovirus myocarditis is 0-4%. Recovery is complete without residual disability in the majority. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result. The role of persistent infection in chronic dilated cardiomyopathy is controversial. Enteroviruses have also been implicated in late adverse cardiac events following heart transplantation and in acute coronary events, including myocardial infarction, endocarditis, and peripartum cardiomyopathy. Myocardial dysfunction observed in enterovirus 71 epidemics most commonly has occurred without evidence of myocarditis and may be of neurogenic origin; however, true myocarditis has also been described.

Gastrointestinal and Genitourinary Manifestations

Symptoms such as emesis (especially with meningitis), diarrhea (rarely severe), and abdominal pain are frequent but generally not dominant. Diarrhea, hematochezia, pneumatosis intestinalis, and necrotizing enterocolitis have occurred in premature infants during nursery outbreaks. Enterovirus infection has been implicated in acute and chronic gastritis, intussusception, chronic intestinal inflammation in hypogammaglobulinemic patients, sporadic hepatitis in normal children, severe hepatitis in neonates, and pancreatitis, which may result in transient exocrine pancreatic insufficiency.

Coxsackie B viruses are second only to mumps as causes of orchitis. The illness is frequently biphasic; fever and pleurodynia or meningitis are followed, in approximately 2 wk, by orchitis, often with epididymitis. Enteroviruses have also been implicated in cases of nephritis and IgA nephropathy.

Neurologic Manifestations

Enteroviruses are the most common cause of viral meningitis in mumps-immunized populations, accounting for up to 90% or more of cases in which a cause is identified. Meningitis is particularly common in infants, especially in those younger than 3 mo of age, often in community epidemics. Frequently implicated serotypes include coxsackie B viruses 2-5; echoviruses 4, 6, 7, 9, 11, 13, 16, and 30; and enteroviruses 70 and 71. Most cases in infants and young children are mild and lack specific signs and symptoms. Fever is present in 50-100%, accompanied by irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, hypotonia, rash, cough, rhinorrhea, pharyngitis, diarrhea, and/or myalgia. Nuchal rigidity is apparent in more than half of children older than 1-2 yr of age. Some cases are biphasic, with fever and nonspecific symptoms for a few days followed by return of fever with meningeal signs several days later. Fever usually resolves in 3-5 days, and other symptoms in infants and young children usually resolve within 1 wk. Symptoms tend to be more severe and longer lasting in adults. CSF findings include pleocytosis (generally <500 but occasionally as high as 1,000-8,000 WBCs/μL; often predominantly polymorphonuclear cells in the 1st 48 hr before becoming mostly mononuclear); normal or slightly low glucose content (10% <40 mg/dL); and normal or mildly increased protein content (generally <100 mg/dL). CSF can have normal parameters despite positive viral culture or polymerase chain reaction (PCR) results, particularly in the 1st few months of life and early after illness onset. Complications occur in approximately 10% of young children, including simple and complex seizures, obtundation, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The prognosis for most children is good.

Enteroviruses are also responsible for ≥10-20% of cases of encephalitis with an identified cause. Frequently implicated serotypes include echoviruses 3, 4, 6, 9, and 11; coxsackie B viruses 2, 4, and 5; coxsackie A virus 9; and enterovirus 71. After initial nonspecific symptoms, there is progression to confusion, weakness, lethargy, and/or irritability. Depression is usually generalized, although focal findings, including focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities, may occur. Manifestations range from altered mental status to coma to decerebrate status. Long-term sequelae, including epilepsy, weakness, cranial nerve palsy, spasticity, psychomotor retardation, and hearing loss, or death may follow severe disease. Persistent or recurrent cases have been observed rarely.

Neurologic disorders have been prominent in recent epidemics in Asia and Australia of enterovirus 71, and, to a lesser extent, coxsackievirus A16 disease. The majority of affected children had hand-foot-and-mouth disease, some had herpangina, and others had no mucocutaneous manifestations. Neurologic syndromes in a fraction of children included meningitis, meningoencephalomyelitis, poliomyelitis-like acute flaccid paralysis, Guillain-Barré syndrome, transverse myelitis, cerebellar ataxia, opsoclonus-myoclonus syndrome, benign intracranial hypertension, and brainstem encephalitis (**rhombencephalitis** involving the midbrain, pons, and medulla). The last is characterized by altered consciousness, myoclonus, vomiting, ataxia, nystagmus, tremor, cranial nerve abnormalities, autonomic dysfunction, and MRI demonstrating lesions in the brainstem, thalamus, and cerebellum. Although the disease was mild and reversible in some children, others had rapid progression to neurogenic pulmonary edema and hemorrhage, cardiopulmonary failure, shock, and coma. High mortality rates have been reported in children younger than 5 yr of age, especially in those younger than 1 yr of age. Deficits such as central hypoventilation, bulbar dysfunction, neurodevelopmental delay, cerebellar defects, attention deficit/hyperactivity–related symptoms, and limb weakness and atrophy have been observed among survivors, especially those who experienced cardiopulmonary failure during their acute illness. Although the most severe cases have been associated with enterovirus 71, similar clinical pictures have been produced by other enterovirus serotypes (e.g., coxsackieviruses A16 and B5, echovirus 7).

Patients with **antibody or combined immunodeficiencies** (including human immunodeficiency virus infection, acute lymphocytic leukemia, and transplantation) and patients receiving anti-CD20 antibody therapy are at risk for acute or, more commonly, **chronic meningoencephalitis.** The latter is characterized by persistent CSF abnormalities, viral detection by culture or PCR for years, and recurrent encephalitis and/or progressive neurologic deterioration, including insidious intellectual or personality deterioration, altered mental status, seizures, motor weakness, and increased intracranial pressure. Although disease may wax and wane, deficits generally become progressive and ultimately are frequently fatal or lead to long-term sequelae. A **dermatomyositis-like syndrome,** hepatitis, arthritis, myocarditis, or disseminated infection may also occur. Chronic enterovirus meningoencephalitis has become less common with high-dose intravenous immunoglobulin replacement.

A variety of nonpoliovirus enteroviruses, including enteroviruses 70 and 71, coxsackie A viruses 7 and 24, coxsackie B viruses, several

echoviruses, and possibly enterovirus 68, can cause poliomyelitis-like acute flaccid paralysis with motor weakness because of spinal cord anterior horn cell involvement. Disease tends to be milder than that caused by poliovirus, with less bulbar involvement and less persistent weakness. Other neurologic syndromes include cerebellar ataxia; transverse myelitis; Guillain-Barré syndrome, axonal polyneuropathy, and Miller-Fisher syndrome; acute disseminated encephalomyelitis; peripheral neuritis; optic neuritis; sudden hearing loss, tinnitus, and inner ear disorders such as vestibular neuritis; and other cranial neuropathies.

Myositis and Arthritis

Although myalgia is common, direct evidence of muscle involvement, including rhabdomyolysis, muscle swelling, focal myositis, and polymyositis, has uncommonly been reported. A dermatomyositis-like syndrome and arthritis can be seen in enterovirus-infected hypogammaglobulinemic patients. Enteroviruses are a rare cause of arthritis in normal hosts.

Neonatal Infections

Neonatal infections are relatively common, with a disease incidence comparable to or greater than that of neonatal herpes simplex virus, cytomegalovirus, and group B streptococcus disease. Infection frequently is caused by coxsackie B viruses 2-5 and echoviruses 6, 9, 11, and 19, although many serotypes have been implicated, including, in more recent years, coxsackie B virus 1 and echovirus 30. Enteroviruses may be acquired vertically before, during, or after delivery, including possible transmission via breast milk; horizontally from family members; or by sporadic or epidemic transmission in nurseries. In utero infection can lead to fetal demise, nonimmune hydrops fetalis, or neonatal illness. Additionally, maternal and intrauterine infections have been speculatively linked to congenital anomalies; prematurity, low birthweight, and intrauterine growth retardation; neurodevelopmental sequelae; unexplained neonatal illness and death; and increased risk of type 1 diabetes.

Neonatal infection may range from asymptomatic (the majority) to benign febrile illness to severe multisystem disease. Most affected newborns are full term and previously well; maternal history often reveals a recent viral illness, including fever and, frequently, abdominal pain. Neonatal symptoms may occur as early as day 1 of life, with onset of severe disease generally within the 1st 2 wk of life. Frequent findings include fever or hypothermia, irritability, lethargy, anorexia, rash (usually maculopapular, occasionally petechial or papulovesicular), jaundice, respiratory symptoms, apnea, hepatomegaly, abdominal distention, emesis, diarrhea, and decreased perfusion. Most patients have benign courses, with resolution of fever in an average of 3 days and of other symptoms in about 1 wk. A biphasic course may occur occasionally. A minority have severe disease dominated by any combination of sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and/or pneumonitis. Meningoencephalitis may be manifested by focal or complex seizures, bulging fontanelle, nuchal rigidity, or reduced level of consciousness. Myocarditis, most often associated with coxsackie B virus infection, may be suggested by tachycardia, dyspnea, cyanosis, and cardiomegaly. Hepatitis and pneumonitis are associated with echovirus infection, although they may occur with coxsackie B viruses. Gastrointestinal manifestations may predominate in premature neonates. Laboratory and radiographic evaluation may reveal leukocytosis, thrombocytopenia, CSF pleocytosis, CNS white matter damage, elevations of serum transaminases and bilirubin, coagulopathy, pulmonary infiltrates, and electrocardiographic changes.

Complications of severe neonatal disease include CNS necrosis and generalized or focal neurologic compromise; arrhythmias, congestive heart failure, myocardial infarction, and pericarditis; hepatic necrosis and failure; intracranial or other bleeding; adrenal necrosis and hemorrhage; and rapidly progressive pneumonitis and pulmonary hypertension. Myositis, arthritis, necrotizing enterocolitis, inappropriate antidiuretic hormone secretion, hemophagocytic lymphohistiocytosis-like presentation, bone marrow failure, and sudden death are rare events. Mortality with severe disease is significant and most often associated with hepatitis and bleeding complications, myocarditis, or pneumonitis.

Survivors of severe neonatal disease may have gradual resolution of hepatic and cardiac dysfunction, although persistent hepatic dysfunction and residual cardiac impairment, chronic calcific myocarditis, and ventricular aneurysm can occur. Meningoencephalitis may be associated with speech and language impairment; cognitive deficits; spasticity, hypotonicity, or weakness; seizure disorders; microcephaly or hydrocephaly; and ocular abnormalities. However, many survivors appear not to have long-term sequelae. Risk factors for severe disease include illness onset in the 1st few days of life, maternal illness just prior to or at delivery, prematurity, male sex, infection by echovirus 11 or a coxsackie B virus, positive serum viral culture, absence of neutralizing antibody to the infecting virus, and evidence of severe hepatitis and/or multisystem disease.

Transplant Recipients and Patients with Malignancies

Enterovirus infections in stem cell and solid organ transplant recipients may be severe and/or prolonged, causing progressive pneumonia, severe diarrhea, pericarditis, heart failure, meningoencephalitis, and disseminated disease. Enterovirus-associated hemophagocytic lymphohistiocytosis, meningitis, encephalitis, and myocarditis have been reported in children with malignancies and patients treated with anti-CD20 monoclonal antibody. Infections in these groups are associated with high fatality rates.

DIAGNOSIS

Clues to enterovirus infection include characteristic findings such as hand-foot-and-mouth disease or herpangina lesions, consistent seasonality, known community outbreak, and exposure to enterovirus-compatible disease. In the neonate, history of maternal fever, malaise, and/or abdominal pain near delivery during enterovirus season is suggestive.

Enterovirus infection can be confirmed with viral culture using a combination of cell lines. Sensitivity ranges from 50-75% and can be increased by sampling of multiple sites (e.g., CSF plus throat and rectum in children with meningitis). In neonates, yields of 30-70% are achieved when blood, urine, CSF, and mucosal swabs are cultured. A major limitation is the inability of most coxsackie A viruses to grow in culture. Yield may also be limited by neutralizing antibody in patient specimens, improper specimen handling, or insensitivity of the cell lines used. Culture is relatively slow, with 3-8 days usually required to detect growth. Centrifugation-enhanced antigen detection coupled with culture (shell vial techniques) can shorten the time to detection, but the sensitivity of this method has been limiting. Although cultivation of an enterovirus from any site can generally be considered evidence of recent infection, isolation from the rectum or stool can reflect more remote shedding. Similarly, recovery from a mucosal site may suggest an association with an illness, whereas recovery from a normally sterile site (e.g., CSF, blood, or tissue) is more conclusive evidence of causation. Serotype identification by type-specific antibody staining or neutralization of a viral isolate is generally required only for investigation of an outbreak or an unusual disease manifestation, surveillance, or to distinguish nonpoliovirus enteroviruses from vaccine or wild-type polioviruses.

Direct testing for nucleic acid overcomes the imperfect sensitivity and delayed results of culture. RT-PCR detection of highly conserved areas of the enterovirus genome can detect the majority of enteroviruses, including coxsackie A viruses (but generally *not* the parechoviruses) in CSF; serum; urine; conjunctival, nasopharyngeal, throat, tracheal, rectal, and stool specimens; dried blood spots; and tissues such as myocardium, liver, and brain. Sensitivity and specificity of RT-PCR are high, with results in as short as 2-3 hr. Real-time, quantitative PCR assays and nested PCR assays with enhanced sensitivity have been developed, as have enterovirus-containing multiplex PCR assays, nucleic acid sequence–based amplification assays, reverse transcription-loop-mediated isothermal amplification, culture-enhanced PCR assays, and PCR-based microarray assays. PCR testing of CSF from children with meningitis and from hypogammaglobulinemic patients with chronic meningoencephalitis is frequently positive despite negative cultures. Routine application of CSF PCR for infants and young children with

suspected meningitis decreases the number of diagnostic tests, duration of hospital stay, antibiotic use, and overall costs. PCR testing of tracheal aspirates of children with myocarditis has good concordance with testing of myocardial specimens. In ill neonates and young infants, PCR testing of serum and urine has higher yields than culture. Viral load in blood of neonates is correlated with disease severity, and viral nucleic acid may persist in blood of severely ill newborns for up to 2 mo.

Sequence analysis of amplified nucleic acid can be used for serotype identification and phylogenetic analysis and to establish a transmission link among cases. Serotype-specific (e.g., enterovirus 71 and coxsackie A virus 16) PCR assays have been developed, including assays that can be used in resource-poor regions. For enterovirus 71, the yield of specimens other than CSF and blood (throat, nasopharyngeal, rectal, and vesicle swabs and CNS tissue) is greater (by PCR or culture) than the yield of CSF and blood, which are infrequently positive. Antigen detection assays that target specific serotypes such as enterovirus 71 with monoclonal antibodies have also been developed.

Enterovirus infections can be detected serologically by a rise, in serum or CSF, of neutralizing, complement fixation, enzyme-linked immunosorbent assay, or other type-specific antibody or by detection of serotype-specific IgM antibody. However, serologic testing requires presumptive knowledge of the infecting serotype or an assay with sufficiently broad cross-reactivity. Sensitivity and specificity may be limiting, and cross-reactivity among serotypes may occur. Except for epidemiologic studies or cases characteristic of specific serotypes (e.g., enterovirus 71), serology is generally less useful than culture or nucleic acid detection.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of enterovirus infections varies with the clinical presentation (Table 250-2).

Human parechoviruses, members of the *Picornaviridae* family, produce many manifestations similar to the nonpolio enteroviruses. Human parechoviruses are small RNA viruses that were once mistakenly classified as echoviruses. Infections in older children are often unrecognized or cause nonspecific acute and benign febrile illnesses with very few specific findings. Neonates and young infants are often more severely affected, demonstrating aseptic meningitis, encephalitis, a sepsis-like picture, and hepatitis. The viral sepsis and the encephalitic presentations are the most common serious manifestations, often requiring intensive care treatment for shock, seizures, and other signs of encephalitis. Epidemics occur in the same season as enterovirus infections; in contrast to the enteroviruses there is a higher incidence of MRI abnormalities in those with encephalitis.

More frequently than with enteroviruses, those affected by parechovirus may have no CSF pleocytosis despite the presence of CNS infection. The diagnosis is confirmed by human parechovirus-specific PCR on CSF, stool, and nasopharyngeal secretions. Infants suspected of having an enteroviral infection should also be considered as possibly having a parechovirus infection because the two may be indistinguishable; nonetheless, parechovirus infections appear to be less common.

TREATMENT

In the absence of a proven antiviral agent for enterovirus infections, supportive care is the mainstay of treatment. Newborns and young infants with nonspecific febrile illnesses and children with meningitis frequently require diagnostic evaluations for bacterial and herpes simplex virus infection and hospitalization for presumptive treatment until tests rule out these diagnoses. Neonates with severe disease and infants and children with myocarditis or concerning neurologic diseases (e.g., enterovirus 71 neurologic and/or cardiopulmonary disease) may require intensive supportive care, including cardiorespiratory and blood product support. Milrinone has been suggested as a useful agent in severe enterovirus 71 cardiopulmonary disease. Liver and cardiac transplantation have been performed for neonates with progressive end-organ failure.

Immunoglobulin has been utilized to treat enterovirus infections based on the importance of the humoral immune response to enterovirus infection and the observation that absence of neutralizing antibody is a risk factor for symptomatic infection. Immunoglobulin products contain neutralizing antibodies to many commonly circulating serotypes, although titers vary with serotype and among products and lots. Anecdotal and retrospective, uncontrolled use of intravenous immunoglobulin or infusion of maternal convalescent plasma to treat newborns with severe disease has been associated with varying outcomes. The one randomized, controlled trial was too small to demonstrate significant clinical benefits, although neonates who received immunoglobulin containing high neutralizing titers to their own isolates had shorter periods of viremia and viruria. Immunoglobulin has been administered intravenously and intraventricularly to treat hypogammaglobulinemic patients with chronic enterovirus meningoencephalitis and intravenously in transplant and oncology patients with severe infections, with variable success. Intravenous immunoglobulin and corticosteroids have been used for patients with neurologic disease caused by enterovirus 71 and other enteroviruses; modulation of cytokine profiles after administration of intravenous immunoglobulin for enterovirus 71–associated brainstem encephalitis has been demonstrated. High-titer enterovirus 71 immunoglobulin appeared promising in animal models, and clinical trials in regions with epidemic enterovirus 71 disease are underway. Development of anti–enterovirus 71 monoclonal antibodies is also being pursued. A retrospective study suggested that treatment of presumed viral myocarditis with immunoglobulin was associated with improved outcome; however, virologic diagnoses were not made. Evaluation of corticosteroids and

Table 250-2 Differential Diagnosis of Enterovirus Infections

CLINICAL MANIFESTATION	BACTERIAL PATHOGENS	VIRAL PATHOGENS
Nonspecific febrile illness	*Streptococcus pneumoniae, Haemophilus influenzae* type b, *Neisseria meningitidis*	Influenza viruses, human herpesviruses 6 and 7, human parechoviruses
Exanthems/enanthems	Group A streptococcus, *Staphylococcus aureus, N. meningitidis*	Herpes simplex virus, adenoviruses, varicella-zoster virus, Epstein-Barr virus, measles virus, rubella virus, human herpesviruses 6 and 7, human parechoviruses
Respiratory illness/conjunctivitis	*S. pneumoniae, H. influenzae* (nontypeable and type b), *N. meningitidis, Mycoplasma pneumoniae, Chlamydia pneumoniae*	Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, human metapneumovirus, coronaviruses
Myocarditis/pericarditis	*S. aureus, H. influenzae* type b, *M. pneumoniae*	Adenoviruses, influenza virus, parvovirus, cytomegalovirus
Meningitis/encephalitis	*S. pneumoniae, H. influenzae* type b, *N. meningitidis, Mycobacterium tuberculosis, Borrelia burgdorferi, M. pneumoniae, Bartonella henselae, Listeria monocytogenes*	Herpes simplex virus, West Nile virus, influenza viruses, adenoviruses, Epstein-Barr virus, mumps virus, lymphocytic choriomeningitis virus, arboviruses, human parechoviruses
Neonatal infections	Group B streptococcus, Gram-negative enteric bacilli, *L. monocytogenes, Enterococcus*	Herpes simplex virus, adenoviruses, cytomegalovirus, rubella virus, human parechoviruses

cyclosporine and other immunosuppressive therapy for myocarditis has been inconclusive. Successful treatment of enterovirus myocarditis with interferon-α has been reported anecdotally, and interferon-β treatment was associated with viral clearance, improved cardiac function, and survival in chronic cardiomyopathy associated with persistence of enterovirus (or adenovirus) genome. Activity of interferon-α against enterovirus 71 has been demonstrated in in vitro and in animal models, but potency varies with interferon-α type.

Antiviral agents that act at various steps in the enterovirus life cycle—attachment, penetration, uncoating, translation, polyprotein processing, protease activity, replication, and assembly—are being evaluated. Candidates include pharmacologically active chemical compounds, small interfering RNAs and DNA-like antisense agents, purine nucleoside analogs, synthetic peptides, enzyme inhibitors of signal transduction pathways, interferon-inducers, and herbal compounds. **Pleconaril**, an inhibitor of attachment and uncoating, was associated with benefit in some controlled studies of enterovirus meningitis and picornavirus upper respiratory tract infections, and uncontrolled experience suggested possible benefits in high-risk infections; however, application for licensure was denied because of concern about potential medication interactions. A randomized, controlled trial of pleconaril in neonates with severe hepatitis, coagulopathy, and/or myocarditis suggested possible virologic and clinical benefits of treatment.

Design and evaluation of candidate agents active against enterovirus 71 is a priority. Of currently available agents, lactoferrin and ribavirin have demonstrated activity in vitro and/or in animal models. Challenges to development of antivirals for enterovirus 71 include limited cross-genotypic activity of candidate compounds and high viral mutagenicity that favors emergence of resistance.

COMPLICATIONS AND PROGNOSIS

The prognosis in the majority of enterovirus infections is excellent. Morbidity and mortality are associated primarily with myocarditis, neurologic disease, severe neonatal infections, and infections in immune compromised hosts.

PREVENTION

The first line of defense is hygiene, such as handwashing, to prevent fecal-oral and respiratory spread within families, schools, and institutional settings; avoidance of sharing utensils and drinking containers and other potential fomites; disinfection of contaminated surfaces; and avoiding community settings where exposures are likely to occur. Chlorination of drinking water and swimming pools may be important. Infection control techniques such as cohorting have proven effective in limiting nursery outbreaks. Prophylactic administration of immunoglobulin or convalescent plasma has been used in nursery epidemics; simultaneous use of infection control interventions makes it difficult to determine efficacy.

Pregnant women near term should avoid contact with individuals ill with possible enterovirus infections. If a pregnant woman experiences a suggestive illness, it is advisable not to proceed with emergency delivery unless there is concern for fetal compromise or obstetric emergencies cannot be excluded. Rather, it may be advantageous to extend pregnancy, allowing the fetus to passively acquire protective antibodies. A strategy of prophylactically administering immunoglobulin to neonates born to mothers with enterovirus infections is untested.

Maintenance antibody replacement with high-dose intravenous immunoglobulin for patients with hypogammaglobulinemia has reduced the incidence of chronic enterovirus meningoencephalitis, although breakthrough infections occur. Vaccines for nonpoliovirus enteroviruses are not available, but candidates for virulent serotypes such as enterovirus 71 are being investigated. Approaches include inactivated vaccines; VP1 capsid protein-based subunit, DNA, and vector vaccines; combined peptide vaccines; live-attenuated vaccines; virus-like particles; breast milk enriched with VP1 capsid protein or lactoferrin; and interferon-γ–expressing recombinant viral vectors. Several enterovirus 71 candidate vaccines have demonstrated protection in animal models and human clinical trials. Circulation of multiple enterovirus 71 types, antigenic drift, viral recombination, and potential immunologic cross-reactivity with brain tissue may pose challenges to vaccine development.

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Chapter 251

Parvoviruses

William C. Koch

The parvoviruses are small, single-stranded DNA viruses. They are common infectious agents of a variety of animal species, including mammals, birds, and insects. Parvoviruses as a group include a number of important animal pathogens. There are now 4 different types of parvoviruses known to infect humans: the dependoviruses also called adeno-associated viruses (AAVs), parvovirus B19 (B19), human bocaviruses (HBoV), and parvovirus 4. B19 and HBoV are the only 2 parvoviruses known to be pathogenic in humans. B19 is the most well studied and clinically important of the human parvoviruses and the cause of **erythema infectiosum** or **fifth disease**. *The more recently described human bocavirus is an emerging human pathogen.*

ETIOLOGY

The 4 human parvoviruses are distinct enough from each other to represent 4 different genera within the Parvoviridae family. B19 is a member of the genus *Erythrovirus*. The virus is composed of an icosahedral protein capsid without an envelope and contains a single-stranded DNA genome of approximately 5.5 kb. It is relatively heat and solvent resistant. It is antigenically distinct from other mammalian parvoviruses and has only 1 known serotype. The relatively short parvovirus genome does not encode a DNA polymerase, so all parvoviruses require either host cell factors present in late S phase or coinfection with another virus to replicate their DNA. B19 can be propagated effectively in vitro only in $CD36^+$ erythroid progenitor cells derived from human bone marrow, umbilical cord blood, or peripheral blood.

HBoV is a member of the genus *Bocavirus*. HBoV was first isolated from nasopharyngeal specimens from children with respiratory tract infection in 2005. It was identified using random polymerase chain reaction (PCR) amplification and sequencing methods specifically designed to detect previously unknown viral sequences. Analysis of the gene sequences showed similarities to both bovine and canine parvoviruses, and thus the virus was named human bocavirus. Later, 3 other HBoVs were identified in stool samples and named HBoV types 2, 3, and 4, with the initial respiratory isolate called HBoV1. The HBoV capsid structure and genome size are similar to those of B19, but the genomic organization and replication are different (though not fully characterized to date). HBoVs cannot be propagated in conventional cell culture but have been grown in a pseudostratified human airway epithelial cell culture system.

The AAVs are members of the genus *Dependovirus* and were the first parvoviruses to be found in humans. They were originally identified as contaminants in adenovirus preparations, resulting in the designation "adeno-associated viruses." They were later isolated directly from human tissue samples, and now several AAV serotypes are known to commonly infect humans. AAVs have a unique life cycle that can take 1 of 2 paths: (1) a lytic infection with replication of viral DNA and production of new virus, or (2) viral integration into the host cell DNA. In the presence of a "helper" virus, usually an adenovirus or a herpesvirus, AAV can replicate its DNA, produce capsids, and release new virions by cell lysis. In the absence of a helper virus infection, the AAV genome becomes integrated into the host cell DNA. This feature has drawn interest in AAVs as potential vectors for gene therapy. Although

human infection with AAVs is common, there is no known disease association and no evidence of pathogenicity, so this virus will not be discussed further in this chapter.

Parvovirus 4 was initially identified in 2005 from the blood of an adult patient with "acute viral syndrome," who was also an intravenous drug user coinfected with hepatitis C. Subsequently, this virus has been found in blood donors and donated plasma pools in many different countries. It appears to be present in approximately 3% of blood donors in the United States and 4% of plasma pools. There is, as of this writing, no known disease association or clinical symptoms associated with infection. The virus has not yet been assigned to a parvovirus genus and may represent a new genus once its virology is better characterized. The full epidemiology and clinical relevance of this virus await further study, and the reader is referred to the bibliography for further information.

EPIDEMIOLOGY

Parvovirus B19

Infections with B19 are common and occur worldwide. Clinically apparent infections, such as the rash illness of erythema infectiosum and transient aplastic crisis, are most prevalent in school-age children (70% of cases occur in patients between 5 and 15 yr of age). Seasonal peaks occur in the late winter and spring, with sporadic infections throughout the year. Seroprevalence increases with age, 40-60% of adults having evidence of prior infection.

Transmission of B19 is by the respiratory route, presumably via large-droplet spread from nasopharyngeal viral shedding. The transmission rate is 15-30% among susceptible household contacts, and mothers are more commonly infected than fathers. In outbreaks of erythema infectiosum in elementary schools, the secondary attack rates range from 10-60%. Nosocomial outbreaks also occur, with secondary attack rates of 30% among susceptible healthcare workers.

Although respiratory spread is the primary mode of transmission, B19 is also transmissible in blood and blood products, as documented among children with hemophilia receiving pooled-donor clotting factor. Given the resistance of the virus to solvents, fomite transmission could be important in childcare centers and other group settings, but this mode of transmission has not been established.

Human Bocaviruses

The majority of studies published have used molecular methods to detect HBoV DNA in respiratory secretions, fecal samples, blood, and other tissues. HBoV DNA (HBoV1) can be found commonly in respiratory secretions from children hospitalized with acute lower respiratory tract infections (LRTIs). It is more prevalent in children younger than 2 yr of age and seems to be associated with wheezing respiratory illness. However, it can be isolated from respiratory secretions from asymptomatic children and can often be found as a coinfection with other common respiratory pathogens of children this age, including respiratory syncytial virus, human metapneumovirus, and rhinoviruses. This has caused some confusion as to the pathogenic role of HBoV in acute LRTI, including whether it can persist in secretions long after a subclinical infection or requires a helper virus. A limited number of seroepidemiologic studies have been performed, and these suggest that infection is common in children younger than 5 yr of age. The most recent studies provide evidence that the virus is in fact pathogenic, especially in children younger than 2 with wheezing and LRTI, as HBoV1 is more likely to be the only virus isolated in these patients and more likely to have an acute antibody response when coupled with antibody testing. When quantitative PCR is used, the virus is found to be much higher in titer in these symptomatic cases.

HBoV DNA (HBoV2, HBoV3, and HBoV4) has also been found in fecal samples in studies from various countries, but its role as a cause of viral gastroenteritis is still undetermined.

PATHOGENESIS

Parvovirus B19

The primary target of B19 infection is the erythroid cell line, specifically erythroid precursors near the pronormoblast stage. Viral infection produces cell lysis, leading to a progressive depletion of erythroid precursors and a transient arrest of erythropoiesis. The virus has no apparent effect on the myeloid cell line. The tropism for erythroid cells is related to the erythrocyte P blood group antigen, which is the primary cell receptor for the virus and is also found on endothelial cells, placental cells, and fetal myocardial cells. Thrombocytopenia and neutropenia are often observed clinically, but the pathogenesis of these abnormalities is unexplained.

Experimental infection of normal volunteers with B19 revealed a biphasic illness. From 7-11 days after inoculation, subjects had viremia and nasopharyngeal viral shedding with fever, malaise, and rhinorrhea. Reticulocyte counts dropped to undetectable levels but resulted in only a mild, clinically insignificant fall in serum hemoglobin. With the appearance of specific antibodies, symptoms resolved and serum hemoglobin returned to normal. Several subjects experienced a rash associated with arthralgia 17-18 days after inoculation. Some manifestations of B19 infection, such as transient aplastic crisis, appear to be a direct result of viral infection, whereas others, including the exanthem and arthritis, appear to be **postinfectious phenomena** related to the immune response. Skin biopsy of patients with erythema infectiosum reveals edema in the epidermis and a perivascular mononuclear infiltrate compatible with an immune-mediated process.

Individuals with **chronic hemolytic anemia** and increased red blood cell (RBC) turnover are very sensitive to minor perturbations in erythropoiesis. Infection with B19 leads to a transient arrest in RBC production and a precipitous fall in serum hemoglobin, often requiring transfusion. The reticulocyte count drops to undetectable levels, reflecting the lysis of infected erythroid precursors. Humoral immunity is crucial in controlling infection. Specific immunoglobulin (Ig) M appears within 1-2 days of infection and is followed by anti-B19 IgG, which leads to control of the infection, restoration of reticulocytosis, and a rise in serum hemoglobin.

Individuals with **impaired humoral immunity** are at increased risk for more serious or persistent infection with B19, which usually manifests as chronic RBC aplasia, although neutropenia, thrombocytopenia, and marrow failure are also described. Children undergoing chemotherapy for leukemia or other forms of cancer, transplant recipients, and patients with congenital or acquired immunodeficiency states (including AIDS) are at risk for chronic B19 infections.

Infections in the **fetus** and **neonate** are somewhat analogous to infections in immunocompromised persons. B19 is associated with nonimmune fetal hydrops and stillbirth in women experiencing a primary infection but does not appear to be teratogenic. Like most mammalian parvoviruses, B19 can cross the placenta and cause fetal infection during primary maternal infection. Parvovirus cytopathic effects are seen primarily in erythroblasts of the bone marrow and sites of extramedullary hematopoiesis in the liver and spleen. Fetal infection can presumably occur as early as 6 wk of gestation, when erythroblasts are first found in the fetal liver; after the 4th mo of gestation, hematopoiesis switches to the bone marrow. In some cases, fetal infection leads to profound fetal anemia and subsequent high-output cardiac failure (see Chapter 103). **Fetal hydrops** ensues and is often associated with fetal death. There may also be a direct effect of the virus on myocardial tissue that contributes to the cardiac failure. However, most infections during pregnancy result in normal deliveries at term. Some of the asymptomatic infants from these deliveries have been reported to have chronic postnatal infection with B19 that is of unknown significance.

Human Bocaviruses

Mechanisms of HBoV replication and pathogenesis are poorly characterized to date. Growth of HBoV1 in tissue culture is difficult, though the virus has been cultured in primary respiratory epithelial cells as noted above. The primary site of viral replication appears to be the respiratory tract, as the virus has been detected most frequently and in highest copy numbers here. HBoV1 has also been found occasionally in the serum, suggesting the potential for systemic spread. HBoV1 has also been detected in stool, but copy numbers are very low. In contrast, HBoV types 2-4 are found predominantly in the stool, but host cell types are not known.

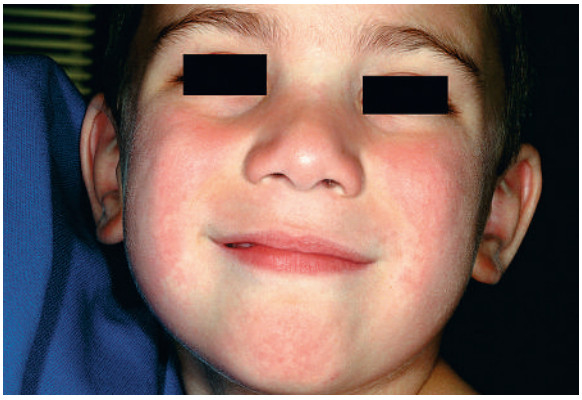

Figure 251-1 **Erythema infectiosum.** Erythema of the bilateral cheeks, which has been likened to a "slapped cheek" appearance. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3. Philadelphia, 2006, WB Saunders, p. 431.)*

CLINICAL MANIFESTATIONS

Parvovirus B19

Many infections are clinically inapparent. Infected children characteristically demonstrate the rash illness of erythema infectiosum. Adults, especially women, frequently experience acute polyarthropathy with or without a rash.

Erythema Infectiosum (Fifth Disease)

The most common manifestation of parvovirus B19 is erythema infectiosum, also known as *fifth disease*, which is a benign, self-limited exanthematous illness of childhood.

The incubation period for erythema infectiosum is 4-28 days (average: 16-17 days). The prodromal phase is mild and consists of low-grade fever in 15-30% of cases, headache, and symptoms of mild upper respiratory tract infection. The hallmark of erythema infectiosum is the characteristic rash, which occurs in 3 stages that are not always distinguishable. The initial stage is an erythematous facial flushing, often described as a **"slapped-cheek" appearance** (Fig. 251-1). The rash spreads rapidly or concurrently to the trunk and proximal extremities as a diffuse macular erythema in the 2nd stage. Central clearing of macular lesions occurs promptly, giving the rash a **lacy, reticulated appearance** (Fig. 251-2). The rash tends to be more prominent on extensor surfaces, sparing the palms and soles. Affected children are afebrile and do not appear ill. Some have petechiae. Older children and adults often complain of mild pruritus. The rash resolves spontaneously without desquamation, but tends to wax and wane over 1-3 wk. It can recur with exposure to sunlight, heat, exercise, and stress. Lymphadenopathy and atypical papular, purpuric, vesicular rashes are also described.

Arthropathy

Arthritis and arthralgia may occur in isolation or with other symptoms. Joint symptoms are much more common among adults and older adolescents with B19 infection. Females are affected more frequently than males. In 1 large outbreak of fifth disease, 60% of adults and 80% of adult women reported joint symptoms. Joint symptoms range from diffuse polyarthralgia with morning stiffness to frank arthritis. The joints most often affected are the hands, wrists, knees, and ankles, but practically any joint may be affected. The joint symptoms are self-limited and, in the majority of patients, resolve within 2-4 wk. Some patients may have a prolonged course of many months, suggesting rheumatoid arthritis. Transient rheumatoid factor positivity is reported in some of these patients but with no joint destruction.

Transient Aplastic Crisis

The transient arrest of erythropoiesis and absolute reticulocytopenia induced by B19 infection leads to a sudden fall in serum hemoglobin in individuals with chronic hemolytic conditions. This B19-induced RBC aplasia or transient aplastic crisis occurs in patients with all types of chronic hemolysis and/or rapid RBC turnover, including sickle cell disease, thalassemia, hereditary spherocytosis, and pyruvate kinase deficiency. In contrast to children with erythema infectiosum only, patients with aplastic crisis are ill with fever, malaise, and lethargy and have signs and symptoms of profound anemia, including pallor, tachycardia, and tachypnea. Rash is rarely present. The incubation period for transient aplastic crisis is shorter than that for erythema infectiosum because the crisis occurs coincident with the viremia. Children with sickle cell hemoglobinopathies may also have a concurrent vaso-occlusive pain crisis, further confusing the clinical presentation.

Figure 251-2 **Erythema infectiosum.** Reticulate erythema on the upper arm of a patient with erythema infectiosum. *(From Paller AS, Macini AJ:* Hurwitz clinical pediatric dermatology, *ed 3. Philadelphia, 2006, WB Saunders, p. 431.)*

Immunocompromised Persons

Persons with impaired humoral immunity are at risk for chronic parvovirus B19 infection. Chronic anemia is the most common manifestation, sometimes accompanied by neutropenia, thrombocytopenia, or complete marrow suppression. Chronic infections occur in persons receiving cancer chemotherapy or immunosuppressive therapy for transplantation and persons with congenital immunodeficiencies, AIDS, and functional defects in IgG production who are thereby unable to generate neutralizing antibodies.

Fetal Infection

Primary maternal infection is associated with nonimmune fetal hydrops and intrauterine fetal demise, with the risk for fetal loss after infection estimated at <5%. The mechanism of fetal disease appears to be a viral-induced RBC aplasia at a time when the fetal erythroid fraction is rapidly expanding, leading to profound anemia, high-output cardiac failure, and fetal hydrops. Viral DNA has been detected in infected abortuses. The 2nd trimester seems to be the most sensitive period, but fetal losses are reported at every stage of gestation. If maternal B19 infection is suspected, fetal ultrasonography and measurement of the peak systolic flow velocity of the middle cerebral artery are sensitive,

noninvasive procedures to diagnose fetal anemia and hydrops. Most infants infected in utero are born normally at term, including some who have had ultrasonographic evidence of hydrops. A small subset of infants infected in utero may acquire a chronic or persistent postnatal infection with B19 that is of unknown significance. Congenital anemia associated with intrauterine B19 infection has been reported in a few cases, sometimes following intrauterine hydrops. This process may mimic other forms of congenital hypoplastic anemia (e.g., Diamond-Blackfan syndrome). Fetal infection with B19 has been associated with bone lesions but has not been associated with other birth defects. B19 is only 1 of many causes of hydrops fetalis (see Chapter 103.2).

Myocarditis

B19 infection has been associated with myocarditis in fetuses, infants, children, and a few adults. Diagnosis has often been based on serologic findings suggestive of a concurrent B19 infection, but in many cases B19 DNA has been demonstrated in cardiac tissue. B19-related myocarditis is plausible because fetal myocardial cells are known to express P antigen, the cell receptor for the virus. In the few cases in which histology is reported, a predominantly lymphocytic infiltrate is described. Outcomes have varied from complete recovery to chronic cardiomyopathy to fatal cardiac arrest. Although B19-associated myocarditis seems to be a rare occurrence, there appears to be enough evidence to consider B19 as a potential cause of lymphocytic myocarditis, especially in infants and immunocompromised persons.

Other Cutaneous Manifestations

A variety of atypical skin eruptions have been reported with B19 infection. Most of these are petechial or purpuric in nature, often with evidence of vasculitis on biopsy. Among these rashes, the ***papular-purpuric "gloves-and-socks" syndrome (PPGSS)*** is well established in the dermatologic literature as distinctly associated with B19 infection (Fig. 251-3). PPGSS is characterized by fever, pruritus, and painful edema and erythema localized to the distal extremities in a distinct "gloves-and-socks" distribution, followed by acral petechiae and oral lesions. The syndrome is self-limited and resolves within a few weeks. Although PPGSS was initially described in young adults, a number of reports of the disease in children have since been published. In those cases linked to B19 infection, the eruption is accompanied by serologic evidence of acute infection.

Figure 251-3 Photographs revealing the petechial rash on the extremities **(A),** that was sharply demarcated on the ankles **(B)** in a 6 yr old child. *(From Parez N, Dehee A, Michel Y, et al: Papular-purpuric gloves and socks syndrome associated with B19V infection in a 6-year-old child.* J Clin Virol *44:167–169, 2009, Fig. 1.)*

Human Bocaviruses

Many studies have reported an association between respiratory tract infection and HBoV1 infection as detected by PCR of respiratory secretions, primarily nasopharyngeal secretions. Clinical manifestations in these studies have ranged from mild upper respiratory symptoms to pneumonia. However, the role of HBoV1 as a pathogen has been challenged by the detection of the virus in asymptomatic children and by the frequent detection of other respiratory viruses in the same samples. Nonetheless, studies that have included some combination of quantitative PCR, serum PCR, and serology have been more convincing about HBoV1 as a human pathogen. The use of a quantitative PCR method also seems to differentiate between HBoV1 infection (and wheezing) and prolonged viral shedding, as patients with higher viral titers were more likely to be symptomatic, to be viremic, and to have HBoV1 isolated without other viruses.

HBoV type 2 DNA has been found in the stool of 3-25% of children with gastroenteritis, but often with another enteric virus. DNA of HBoV types 2, 3, and 4 has also been found in the stool of healthy, asymptomatic individuals. At present, there are few data linking HBoV2, HBoV3, or HBoV4 to gastroenteritis or any clinical illness. Further studies are required to determine if any of the HBoVs are associated with some cases of childhood gastroenteritis.

DIAGNOSIS

Parvovirus B19 Infection

The diagnosis of erythema infectiosum is usually based on clinical presentation of the typical rash and rarely requires virologic confirmation. Similarly, the diagnosis of a typical transient aplastic crisis in a child with sickle cell disease is generally made on clinical grounds without specific virologic testing.

Serologic tests for the diagnosis of B19 infection are available. B19-specific IgM develops rapidly after infection and persists for 6-8 wk. Anti-B19 IgG serves as a marker of past infection or immunity. Determination of anti-B19 IgM is the best marker of recent/acute infection on a single serum sample; seroconversion of anti-B19 IgG antibodies in paired sera can also be used to confirm recent infection. Demonstration of anti-B19 IgG in the absence of IgM, even in high titer, is not diagnostic of recent infection.

Serologic diagnosis is unreliable in immunocompromised persons; diagnosis in these patients requires methods to detect viral DNA. Because the virus cannot be isolated by standard cell culture, methods to detect viral particles or viral DNA, such as PCR and nucleic acid hybridization, are necessary to establish the diagnosis. These tests are not widely available outside of research centers or reference laboratories. Prenatal diagnosis of B19-induced fetal hydrops can be accomplished by detection of viral DNA in fetal blood or amniotic fluid by these methods.

Human Bocavirus Infections

HBoV1 infections cannot be differentiated from other viral respiratory infections on clinical grounds. HBoV DNA can be readily detected by PCR methods and is now included in several commercially available multiplex respiratory virus PCR assays. As noted above, quantitative

PCR is useful to differentiate acute infection from persistent viral shedding, as higher viral copy numbers (>10(4) HBoV1 genomes/mL) correlate with acute illness, but this test is not widely available. Likewise, serologic methods to detect specific IgM and IgG antibodies have been developed, but these too are not routinely available and there are problems with cross-reactivity among antibodies to the various HBoV types. The most reliable method to diagnose HBoV1 infection would include detection of viral DNA in serum by PCR, and in respiratory tract samples by quantitative PCR, with concurrent detection of IgM or a diagnostic IgG response in paired samples.

DIFFERENTIAL DIAGNOSIS

Parvovirus B19

The rash of erythema infectiosum must be differentiated from rubella, measles, enteroviral infections, and drug reactions. Rash and arthritis in older children should prompt consideration of juvenile rheumatoid arthritis, systemic lupus erythematosus, serum sickness, and other connective tissue disorders.

Human Bocavirus

Respiratory illness and wheezing caused by HBoV1 cannot clinically be differentiated from other common viral respiratory infections, especially respiratory syncytial virus, human metapneumovirus, rhinoviruses, enterovirus 68, and parainfluenza viruses. HBoV1 infection in young children seems to most closely resemble that of respiratory syncytial virus and human metapneumovirus, as the clinical symptoms and age ranges will overlap.

TREATMENT

Parvovirus B19

There is no specific antiviral therapy for B19 infection. Commercial lots of intravenous immunoglobulin (IVIG) have been used with some success to treat B19-related episodes of anemia and bone marrow failure in immunocompromised children. Specific antibody may facilitate clearance of the virus; it is not always necessary, however, because cessation of cytotoxic chemotherapy with subsequent restoration of immune function often suffices. In patients whose immune status is not likely to improve, such as patients with AIDS, administration of IVIG may give only a temporary remission, and periodic reinfusions may be required. In patients with AIDS, clearance of B19 infection has been reported after initiation of highly active antiretroviral therapy without the use of IVIG.

No controlled studies have been published regarding dosing of IVIG for B19-induced RBC aplasia. Doses reported with good results in a limited number of cases include 200 mg/kg/day for 5-10 days and 1 g/kg/day for 3 days. IVIG should not be used for treatment of B19-induced arthropathy.

B19-infected fetuses with anemia and hydrops have been managed successfully with intrauterine RBC transfusions, but this procedure has significant attendant risks. Once fetal hydrops is diagnosed, regardless of the suspected cause, the mother should be referred to a fetal therapy center for further evaluation because of the high risk for serious complications (see Chapter 103.2).

Human Bocavirus

There is no specific antiviral therapy available. Appropriate supportive treatment for viral LRTI and pneumonia is recommended, as directed by clinical severity. For children with wheezing illness specifically caused by HBoV1 infection, there are no data examining their response to bronchodilator therapy.

COMPLICATIONS

Parvovirus B19

Erythema infectiosum is often accompanied by arthralgias or arthritis in adolescents and adults that may persist after resolution of the rash. B19 may rarely cause thrombocytopenic purpura. Neurologic conditions, including aseptic meningitis, encephalitis, and peripheral neuropathy, have been reported in both immunocompromised and healthy individuals in association with B19 infection. The incidence of stroke may be increased in children with sickle cell disease following B19-induced transient aplastic crisis. B19 is also a cause of infection-associated hemophagocytic syndrome, usually in immunocompromised persons.

Human Bocavirus

There are no studies reporting on complications of HBoV1 infection. Complications of wheezing and viral pneumonia would be possible, including hypoxemia and secondary bacterial infection, among others.

PREVENTION

Parvovirus B19

Children with erythema infectiosum are not likely to be infectious at presentation because the rash and arthropathy represent immune-mediated, postinfectious phenomena. Isolation and exclusion from school or child care are unnecessary and ineffective after diagnosis.

Children with B19-induced RBC aplasia, including the transient aplastic crisis, are infectious upon presentation and demonstrate a more intense viremia. Most of these children require transfusions and supportive care until their hematologic status stabilizes. They should be isolated in the hospital to prevent spread to susceptible patients and staff. Isolation should continue for at least 1 wk and until after resolution of fever. Pregnant caregivers should not be assigned to these patients. Exclusion of pregnant women from workplaces where children with erythema infectiosum may be present (e.g., primary and secondary schools) is not recommended as a general policy because it is unlikely to reduce their risk. There are no data to support the use of IVIG for postexposure prophylaxis in pregnant caregivers or immunocompromised children. No vaccine is currently available, though this is a topic of ongoing research.

Human Bocavirus

There are no studies that have addressed the prevention of transmission of this infection. In the hospital setting, standard precautions should be observed to limit spread of the virus. Since HBoV1 causes respiratory infection and can be detected in respiratory secretions sometimes in very high titer, measures to limit contact with respiratory secretions should be considered, including contact and droplet isolation for severely symptomatic young children. No vaccine is available, and no other preventive measures have been reported.

Bibliography is available at Expert Consult.

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Chapter 252

Herpes Simplex Virus

Lawrence R. Stanberry

The 2 closely related herpes simplex viruses (HSVs), HSV type 1 (HSV-1) and HSV type 2 (HSV-2), cause a variety of illnesses, depending on the anatomic site where the infection is initiated, the immune state of the host, and whether the symptoms reflect primary or recurrent infection. Common infections involve the skin, eye, oral cavity, and genital tract. Infections tend to be mild and self-limiting, except in the immunocompromised patient and newborn infant, in whom they may be severe and life-threatening.

Primary infection occurs in individuals who have not been infected previously with either HSV-1 or HSV-2. Because these individuals are HSV seronegative and have no preexisting immunity to HSV, primary infections can be severe. **Nonprimary 1st infection** occurs in individuals previously infected with 1 type of HSV (e.g., HSV-1) who have become infected for the 1st time with the other type of HSV (in this case, HSV-2). Because immunity to 1 HSV type provides some cross-protection against disease caused by the other HSV type, nonprimary 1st infections tend to be less severe than true primary infections.

During primary and nonprimary initial infections, HSV establishes latent infection in regional sensory ganglion neurons. Virus is maintained in this latent state for the life of the host but periodically can reactivate and cause **recurrent infection.** Symptomatic recurrent infections tend to be less severe and of shorter duration than 1st infections. Asymptomatic recurrent infections are extremely common. They cause no physical distress, although patients with recurrent infections are contagious and can transmit the virus to susceptible individuals. Reinfection with a new strain of either HSV-1 or HSV-2 at a previously infected anatomic site (e.g., the genital tract) can occur but is relatively uncommon, suggesting that host immunity, perhaps site-specific local immunity, resulting from the initial infection affords protection against exogenous reinfection. This observation suggests that it might be feasible to develop effective HSV vaccines.

ETIOLOGY

HSVs contain a double-stranded DNA genome of approximately 152 kb that encodes at least 84 proteins. The DNA is contained within an icosadeltahedral capsid, which is surrounded by an outer envelope composed of a lipid bilayer containing at least 12 viral glycoproteins. These glycoproteins are the major targets for humoral immunity, whereas other nonstructural proteins are important targets for cellular immunity. Two encoded proteins, viral DNA polymerase and thymidine kinase, are targets for antiviral drugs. HSV-1 and HSV-2 have a similar genetic composition with extensive DNA and protein homology. One important difference in the 2 viruses is their glycoprotein G genes, which have been exploited to develop a new generation of commercially available, accurate, type-specific serologic tests that can be used to discriminate whether a patient has been infected with HSV-1 or HSV-2, or both.

EPIDEMIOLOGY

HSV infections are ubiquitous, and there are no seasonal variations in risk for infection. The only natural host is humans, and the mode of transmission is direct contact between mucocutaneous surfaces. There are no documented incidental transmissions from inanimate objects such as toilet seats.

All infected individuals harbor latent infection and experience recurrent infections, which may be symptomatic or may go unrecognized, and thus are periodically contagious. This information helps explain the widespread prevalence of HSV.

HSV-1 and HSV-2 are equally capable of causing initial infection at any anatomic site but differ in their capacity to cause recurrent infections. HSV-1 has a greater propensity to cause recurrent oral infections, whereas HSV-2 has a greater proclivity to cause recurrent genital infections. For this reason, HSV-1 infection typically results from contact with contaminated oral secretions, whereas HSV-2 infection most commonly results from anogenital contact.

HSV seroprevalence rates are highest in developing countries and among lower socioeconomic groups, although high rates of HSV-1 and HSV-2 infections are found in developed nations and among persons of the highest socioeconomic strata. Incident HSV-1 infections are more common during childhood and adolescence but are also found throughout later life. Data from the U.S. population–based National Health and Nutrition Examination Survey conducted between 1999 and 2004 showed a consistent increase of HSV-1 prevalence with age, which rose from 39% in adolescents 14-19 yr of age to 65% among those 40-49 yr of age. HSV-1 seroprevalence was not influenced by gender but rates were highest in Mexican-Americans (80.8%), intermediate in non-Hispanic blacks (68.3%), and lowest in non-Hispanic whites (50.1%). The National Health and Nutrition Examination Survey study conducted between 2005 and 2008 found an overall HSV-2 prevalence of 16.2% with a steady increase with age from 1.4% in the 14-19 yr old age group to 26.1% in the 40-49 yr old group. The rate was higher among females than males (20.9% and 11.5%, respectively) and varied by race and ethnic group, with an overall seroprevalence of 39.2% in blacks, 10.1% in Mexican-Americans, and 12.3% in whites. Modifiable factors that predict HSV-2 seropositivity include less education, poverty, cocaine use, and a greater lifetime number of sexual partners. Studies show that only approximately 10-20% of HSV-2–seropositive subjects report a history of genital herpes, emphasizing the asymptomatic nature of most HSV infections.

A 3 yr longitudinal study of Midwestern adolescent girls 12-15 yr of age found that 44% were seropositive for HSV-1 and 7% for HSV-2 at enrollment. At the end of the study, 49% were seropositive for HSV-1 and 14% for HSV-2. The attack rates, based on the number of cases per 100 person-years, were 3.2 for HSV-1 infection among all girls and 4.4 for HSV-2 infection among girls who reported being sexually experienced. Findings of this study indicate that sexually active young women have a high attack rate for genital herpes and suggest that genital herpes should be considered in the differential diagnosis of any young woman who reports recurrent genitourinary complaints. In this study, participants with preexisting HSV-1 antibodies had a significantly lower attack rate for HSV-2 infection, and those who became infected were less likely to have symptomatic disease than girls who were HSV seronegative when they entered the study. Prior HSV-1 infection appears to afford adolescent girls some protection against becoming infected with HSV-2; in adolescent girls infected with HSV-2, the preexisting HSV-1 immunity appears to protect against development of symptomatic genital herpes.

Neonatal herpes is an uncommon but potentially fatal infection of the fetus or more likely the newborn. It is not a reportable disease in most states, and therefore there are no solid epidemiologic data regarding its frequency in the general population. In King County, Washington, the estimated incidence of neonatal herpes was 2.6 cases per 100,000 live births in the late 1960s, 11.9 cases per 1000,000 live births from 1978-1981, and 31 cases per 1,000,000 live births from 1982-1999. This increase in neonatal herpes cases parallels the increase in cases of genital herpes. The estimated rate of neonatal herpes is 1 per 3,000-5,000 live births, which is higher than reported for the reportable perinatally acquired sexually transmitted infections such as congenital syphilis and gonococcal ophthalmia neonatorum. More than 90% of the cases are the result of maternal-fetal transmission. The risk for transmission is greatest during a primary or nonprimary 1st infection (30-50%) and much lower when the exposure is during a recurrent infection (<2%). HSV viral suppression therapy in mothers does not consistently eliminate the possibility of neonatal infection. Infants born to mothers dually infected with HIV and HSV-2 are also at higher risk for acquiring HIV than infants born to HIV-positive mothers who are not HSV-2 infected. It is estimated that approximately 25% of pregnant women are HSV-2 infected and that approximately 2% of pregnant women acquire HSV-2 infection during pregnancy.

HSV is a leading cause of sporadic, fatal encephalitis in children and adults. In the United States it is estimated that there are 1,250 cases annually of HSV encephalitis.

PATHOGENESIS

In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes followed by replication and spread in neural tissue. Viral infection typically begins at a cutaneous **portal of entry** such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. Virus replicates locally, resulting in the death of the cell, and sometimes produces clinically apparent inflammatory responses that facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport. Virus replicates in some sensory neurons, and the progeny virions are sent via intraneuronal transport mechanisms back to the periphery, where they are released from nerve endings and replicate further in skin or mucosal surfaces. It is virus moving through this neural arc that is primarily responsible for the development of characteristic herpetic lesions, although most HSV infections do not reach a threshold necessary to cause clinically recognizable disease. Although many sensory neurons become productively infected during the initial infection, some infected neurons do not initially support viral replication. It is in these neurons that the virus establishes a **latent infection,** a condition in which the viral genome persists within the neuronal nucleus in a largely metabolically inactive state. Intermittently throughout the life of the host, undefined changes can occur in latently infected neurons that trigger the virus to begin to replicate.

This replication occurs despite the host's having established a variety of humoral and cellular immune responses that successfully controlled the initial infection. With reactivation of the latent neuron, progeny virions are produced and transported within nerve fibers back to cutaneous sites somewhere in the vicinity of the initial infection, where further replication occurs and causes recurrent infections. Recurrent infections may be symptomatic (with typical or atypical herpetic lesions) or asymptomatic. In either case, virus is shed at the site where cutaneous replication occurs and can be transmitted to susceptible individuals who come in contact with the site or with contaminated secretions. Latency and reactivation are the mechanisms by which the virus is successfully maintained in the human population.

Viremia, or hematogenous spread of the virus, does not appear to play an important role in HSV infections in the immunocompetent host but can occur in neonates, individuals with eczema, and severely malnourished children. It is also seen in patients with depressed or defective cell-mediated immunity, such as occurs with HIV infection or some immunosuppressive therapies. Viremia can result in dissemination of the virus to visceral organs, including the liver and adrenals. Hematogenous dissemination of virus to the central nervous system appears to only occur in neonates.

The pathogenesis of HSV infection in newborns is complicated by their relative immunologic immaturity. The source of virus in neonatal infections is typically but not exclusively the mother. Transmission generally occurs during delivery, although it is well documented to occur even with cesarean delivery with intact fetal membranes. The most common portals of entry are the conjunctiva, mucosal epithelium of the nose and mouth, and breaks or abrasions in the skin that occur with scalp electrode use or forceps delivery. With prompt antiviral therapy, virus replication may be restricted to the site of inoculation (the skin, eye, or mouth). However, virus may also extend from the nose to the respiratory tract to cause pneumonia, move via intraneuronal transport to the central nervous system to cause encephalitis, or spread by hematogenous dissemination to visceral organs and the brain. Factors that may influence neonatal HSV infection include the virus type, portal of entry, inoculum of virus to which the infant is exposed, gestational age of the infant, and presence of maternally derived antibodies specific to the virus causing infection. Latent infection is established during neonatal infection, and survivors may experience recurrent cutaneous and neural infections. Persistent central nervous system infection may impact the neurodevelopment of the infant.

CLINICAL MANIFESTATIONS

The hallmarks of common HSV infections are skin vesicles and shallow ulcers. Classic infections manifest as small, 2-4 mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers. The vesicular phase tends to persist longer when keratinized epithelia is involved and is generally brief and sometimes just fleeting when moist mucous membranes are the site of infection. Because HSV infections are common and their natural history is influenced by many factors, including portal of entry, immune status of the host, and whether it is an initial or recurrent infection, the typical manifestations are seldom classic. Most infections are asymptomatic or unrecognized, and nonclassic presentations, such as small skin fissures and small erythematous nonvesicular lesions, are common.

Acute Oropharyngeal Infections

Herpes gingivostomatitis most often affects children 6 mo to 5 yr of age but is seen across the age spectrum. It is an extremely painful condition with sudden onset, pain in the mouth, drooling, refusal to eat or drink, and fever of up to 40.0-40.6°C (104-105.1°F). The gums become markedly swollen, and vesicles may develop throughout the oral cavity, including the gums, lips, tongue, palate, tonsils, pharynx, and perioral skin (Fig. 252-1). The vesicles may be more extensively distributed than typically seen with enteroviral herpangina. During the initial phase of the illness there may be tonsillar exudates suggestive of bacterial pharyngitis. The vesicles are generally present only a few days before progressing to form shallow indurated ulcers that may be covered with a yellow-gray membrane. Tender submandibular, submaxillary, and cervical lymphadenopathy is common. The breath may be foul as a result of overgrowth of anaerobic oral bacteria. Untreated, the illness resolves in 7-14 days, although the lymphadenopathy may persist for several weeks.

Figure 252-1 Clustered perioral vesicles and erosions in an infant with primary herpetic gingivostomatitis. *(From Schachner LA, Hansen RC, editors:* Pediatric dermatology, *ed 3. Philadelphia, 1988, Mosby, p. 1078.)*

In older children, adolescents, and college students, the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis. The vesicular phase is often over by the time the patient presents to a healthcare provider, and signs and symptoms may be indistinguishable from those of streptococcal pharyngitis, consisting of fever, malaise, headache, sore throat, and white plaques on the tonsils. The course of illness is typically longer than for untreated streptococcal pharyngitis.

Herpes Labialis

Fever blisters (cold sores) are the most common manifestation of recurrent HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, chin, cheek, or oral mucosa. Older patients report experiencing burning, tingling, itching, or pain 3-6 hr (rarely as long as 24-48 hr) before the development of the herpes lesion. The lesion generally begins as a small grouping of erythematous papules that over a few hours progress to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab. Complete healing without scarring occurs with reepithelialization of the ulcerated skin, usually within 6-10 days. Some patients experience local lymphadenopathy but no constitutional symptoms.

Cutaneous Infections

In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macro or micro abrasions and

Figure 252-2 Herpes simplex infection of finger (whitlow). *(From Schachner LA, Hansen RC, editors:* Pediatric dermatology, *ed 3. Philadelphia, 1988, Mosby, p. 1079.)*

exposure to infectious secretions. This situation most often occurs in play or contact sports such as wrestling (**herpes gladiatorum**) and rugby (**scrum pox**). As with other HSV infections, an initial cutaneous infection establishes a latent infection that can subsequently result in recurrent infections at or near the site of the initial infection. Pain, burning, itching, or tingling often precedes the herpetic eruption by a few hours to a few days. Like herpes labialis, lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then heal without scarring in 6-10 days. Although herpes labialis typically results in a single lesion, a cutaneous HSV infection results in multiple discrete lesions and involves a larger surface area. Regional lymphadenopathy may occur but systemic symptoms are uncommon. Recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

Herpes whitlow is a term generally applied to HSV infection of fingers or toes, although strictly speaking it refers to HSV infection of the paronychia. Among children, this condition is most commonly seen in infants and toddlers who suck the thumb or fingers and who are experiencing either a symptomatic or a subclinical oral HSV-1 infection (Fig. 252-2). An HSV-2 herpes whitlow occasionally develops in an adolescent as a result of exposure to infectious genital secretions. The onset of the infection is heralded by itching, pain, and erythema 2-7 days after exposure. The cuticle becomes erythematous and tender and may appear to contain pus, although if it is incised, little fluid is present. Incising the lesion is discouraged, as this maneuver typically prolongs recovery and increases the risk for secondary bacterial infection. Lesions and associated pain typically persist for about 10 days, followed by rapid improvement and complete recovery in 18-20 days. Regional lymphadenopathy is common, and lymphangitis and neuralgia may occur. Unlike other recurrent herpes infections, recurrent herpetic whitlows are often as painful as the primary infection but are generally shorter in duration.

Cutaneous HSV infections can be severe or life-threatening in patients with disorders of the skin such as eczema (eczema herpeticum), pemphigus, burns, and Darier disease, and following laser skin resurfacing. The lesions are frequently ulcerative and nonspecific in appearance, although typical vesicles may be seen in adjacent normal skin (Fig. 252-3). If untreated, these lesions can progress to disseminated infection and death. Recurrent infections are common but generally less severe than the initial infection.

Figure 252-3 Widespread cutaneous herpes infection in a child with underlying eczema (eczema herpeticum).

Genital Herpes

Genital HSV infection is common in sexually experienced adolescents and young adults, but up to 90% of infected individuals are unaware they are infected. Infection may result from genital-genital transmission (usually HSV-2) or oral-genital transmission (usually HSV-1). Symptomatic and asymptomatic individuals periodically shed virus from anogenital sites and hence can transmit the infection to sexual partners or, in the case of pregnant women, to their newborns. Classic primary genital herpes may be preceded by a short period of local burning and tenderness before vesicles develop on genital mucosal surfaces or keratinized skin and sometimes around the anus or on the buttocks and thighs. Vesicles on mucosal surfaces are short lived and rupture to produce shallow, tender ulcers covered with a yellowish gray exudate and surrounded by an erythematous border. Vesicles on keratinized epithelium persist for a few days before progressing to the pustular stage and then crusting.

Patients may experience urethritis and dysuria severe enough to cause urinary retention and bilateral, tender inguinal and pelvic lymphadenopathy. Women may experience a watery vaginal discharge, and men may have a clear mucoid urethral discharge. Significant local pain and systemic symptoms such as fever, headache, and myalgia are common. Aseptic meningitis develops in an estimated 15% of cases. The course of classic primary genital herpes from onset to complete healing is 2-3 wk.

Most patients with symptomatic primary genital herpes experience at least 1 recurrent infection in the following year. Recurrent genital herpes is usually less severe and of shorter duration than the primary infection. Some patients experience a sensory prodrome with pain, burning, and tingling at the site where vesicles subsequently develop. Asymptomatic recurrent anogenital HSV infections are common, and all HSV-2–seropositive individuals appear to periodically shed virus from anogenital sites. Most sexual transmissions and maternal-neonatal transmissions of virus result from asymptomatic shedding episodes.

Genital infections caused by HSV-1 and HSV-2 are indistinguishable, but HSV-1 causes significantly fewer subsequent episodes of recurrent infection; hence, knowing which virus is causing the infection has important prognostic value. Genital HSV infection increases the risk for acquiring HIV infection.

Rarely, genital HSV infections are identified in young children and preadolescents. Although genital disease in children should raise concerns about possible sexual abuse, there are documented cases of autoinoculation, in which a child has inadvertently transmitted virus from contaminated oral secretions to his or her own genitalia.

Ocular Infections

HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and is often associated with blepharitis and tender preauricular lymphadenopathy. The conjunctiva appears edematous but there is rarely purulent discharge. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically have fever. Untreated infection generally resolves in 2-3 wk. Obvious corneal involvement is rare, but when it occurs it can produce ulcers that are described as appearing dendritic or geographic. Extension to the stroma is uncommon although more likely to occur in patients inadvertently treated with corticosteroids. When it occurs, it may be associated with corneal edema, scarring, and corneal perforation. Recurrent infections tend to involve the underlying stroma and can cause progressive corneal scarring and injury that can lead to blindness.

Retinal infections are rare and are more likely among infants with neonatal herpes and immunocompromised persons with disseminated HSV infections.

Central Nervous System Infections

HSV encephalitis is the leading cause of sporadic, nonepidemic encephalitis in children and adults in the United States. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may manifest as nonspecific findings, including fever, headache, nuchal rigidity, nausea, vomiting, generalized seizures, and alteration of consciousness. Injury to the frontal or temporal cortex or limbic system may produce findings more indicative of HSV encephalitis, including anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal seizures. The untreated infection progresses to coma and death in 75% of cases. Examination of the cerebrospinal fluid (CSF) typically shows a moderate number of mononuclear cells and polymorphonuclear leukocytes, a mildly elevated protein concentration, a normal or slightly decreased glucose concentration, and often a moderate number of erythrocytes.

HSV is also a cause of aseptic meningitis and is the most common cause of recurrent aseptic meningitis (**Mollaret meningitis**).

Infections in Immunocompromised Persons

Severe, life-threatening HSV infections can occur in patients with compromised immune functions, including neonates, the severely malnourished, those with primary or secondary immunodeficiency diseases, including AIDS, and those receiving some immunosuppressive regimens, particularly for cancer and organ transplantation. Mucocutaneous infections, including mucositis and esophagitis, are most common, although their presentations may be atypical and can result in lesions that slowly enlarge, ulcerate, become necrotic, and extend to deeper tissues. Other HSV infections include tracheobronchitis, pneumonitis, and anogenital infections. Disseminated infection can result in a sepsis-like presentation, with liver and adrenal involvement, disseminated intravascular coagulopathy, and shock.

Perinatal Infections

HSV infection may be acquired in utero, during the birth process, or during the neonatal period. Intrauterine and postpartum infections are well described but occur infrequently. Postpartum transmission may be from the mother or another adult with a nongenital (typically HSV-1) infection such as herpes labialis. Most cases of neonatal herpes result from maternal infection and transmission, usually during passage through an infected birth canal of a mother with asymptomatic genital herpes. Transmission is well documented in infants delivered by cesarean section. Fewer than 30% of mothers of an infant with neonatal herpes have a history of genital herpes. The risk for infection is higher in infants born to mothers with primary genital infection (>30%) than with recurrent genital infection (<2%). Use of scalp electrodes may also increase risk. There also have been rare cases of neonatal herpes associated with Jewish ritual circumcisions, but only with ritual oral contact with the circumcision site.

Neonatal HSV infection is thought to never be asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with intrauterine infection typically have skin vesicles or scarring, eye findings including chorioretinitis and keratoconjunctivitis, and microcephaly or hydranencephaly that are present at delivery. Few infants survive without therapy, and those who do generally have severe sequelae. Infants infected during delivery or the postpartum period present with 1 of the following 3 patterns of disease: (1) disease localized to the skin, eyes, or mouth; (2) encephalitis with or without skin, eye, and mouth disease; and (3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin.

Infants with **skin, eye, and mouth disease** generally present at 5-11 days of life and typically demonstrate a few small vesicles, particularly on the presenting part or at sites of trauma such as sites of scalp electrode placement. If untreated, skin, eye, and mouth disease in infants may progress to encephalitis or disseminated disease.

Infants with encephalitis typically present at 8-17 days of life with clinical findings suggestive of bacterial meningitis, including irritability, lethargy, poor feeding, poor tone, and seizures. Fever is relatively uncommon, and skin vesicles occur in only approximately 60% of cases (Fig. 252-4). If untreated, 50% of infants with HSV encephalitis die and most survivors have severe neurologic sequelae.

Infants with disseminated HSV infections generally become ill at 5-11 days of life. Their clinical picture is similar to that of infants with bacterial sepsis, consisting of hyperthermia or hypothermia, irritability, poor feeding, and vomiting. They may also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash, and evidence of central nervous system infection; seizures are common. Skin vesicles

Figure 252-4 Vesicular-pustular lesions on the face of a neonate with herpes simplex virus infection. *(From Kohl S: Neonatal herpes simplex virus infection,* Clin Perinatol *24:129–150, 1997.)*

are seen in approximately 75% of cases. If untreated, the infection causes shock and disseminated intravascular coagulation; approximately 90% of these infants die, and most survivors have severe neurologic sequelae.

Infants with neonatal herpes whose mothers received antiherpes antiviral drugs in the weeks prior to delivery may present later than their untreated counterparts; whether the natural history of the infection in these infants is different is an unanswered question.

DIAGNOSIS

The clinical diagnosis of HSV infections, particularly life-threatening infections and genital herpes, should be confirmed by laboratory test, preferably isolation of virus or viral DNA detection by polymerase chain reaction (PCR). Histologic findings or imaging studies may support the diagnosis but should not substitute for virus-specific tests. HSV immunoglobulin M tests are notoriously unreliable, and the demonstration of a 4-fold or greater rise in HSV-specific immunoglobulin G titers between acute and convalescent serum samples is useful only in retrospect.

Virus culture remains the gold standard for diagnosing HSV infections. The highest yield comes from rupturing a suspected herpetic vesicle and vigorously rubbing the base of the lesion to collect fluid and cells. Culturing dried, crusted lesions is generally of low yield. Although not as sensitive as viral culture, direct detection of HSV antigens in clinical specimens can be done rapidly and has very good specificity. The use of PCR for detection of HSV DNA is highly sensitive and specific and in some instances can be performed rapidly. It is the test of choice in examining CSF in cases of suspected HSV encephalitis.

Evaluation of the neonate with suspected HSV infection should include cultures of suspicious lesions as well as eye and mouth swabs and PCR of CSF and blood. In neonates testing for elevation of liver enzymes may provide indirect evidence of HSV dissemination to visceral organs. Culture or antigen detection should be used in evaluating lesions associated with suspected acute genital herpes. HSV-2 type-specific antibody tests are useful for evaluating sexually experienced adolescents or young adults who have a history of unexplained recurrent nonspecific urogenital signs and symptoms, but these tests are less useful for general screening in populations in which HSV-2 infections are of low prevalence.

Because most HSV diagnostic tests take at least a few days to complete, treatment should not be withheld but rather initiated promptly so as to ensure the maximum therapeutic benefit.

LABORATORY FINDINGS

Most self-limited HSV infections cause few changes in routine laboratory parameters. Mucocutaneous infections may cause a moderate polymorphonuclear leukocytosis. In HSV meningoencephalitis there can be an increase in mononuclear cells and protein in CSF, the glucose content may be normal or reduced, and red blood cells may be present. The electroencephalogram and MRI of the brain may show temporal lobe abnormalities in HSV encephalitis beyond the neonatal period. Encephalitis in the neonatal period tends to be more global and not limited to the temporal lobe (Fig. 252-5). Disseminated infection may cause elevated liver enzymes, thrombocytopenia, and abnormal coagulation.

TREATMENT

See Chapter 245 for more information about principles of antiviral therapy.

Three antiviral drugs are available in the United States for the management of HSV infections, namely acyclovir, valacyclovir, and

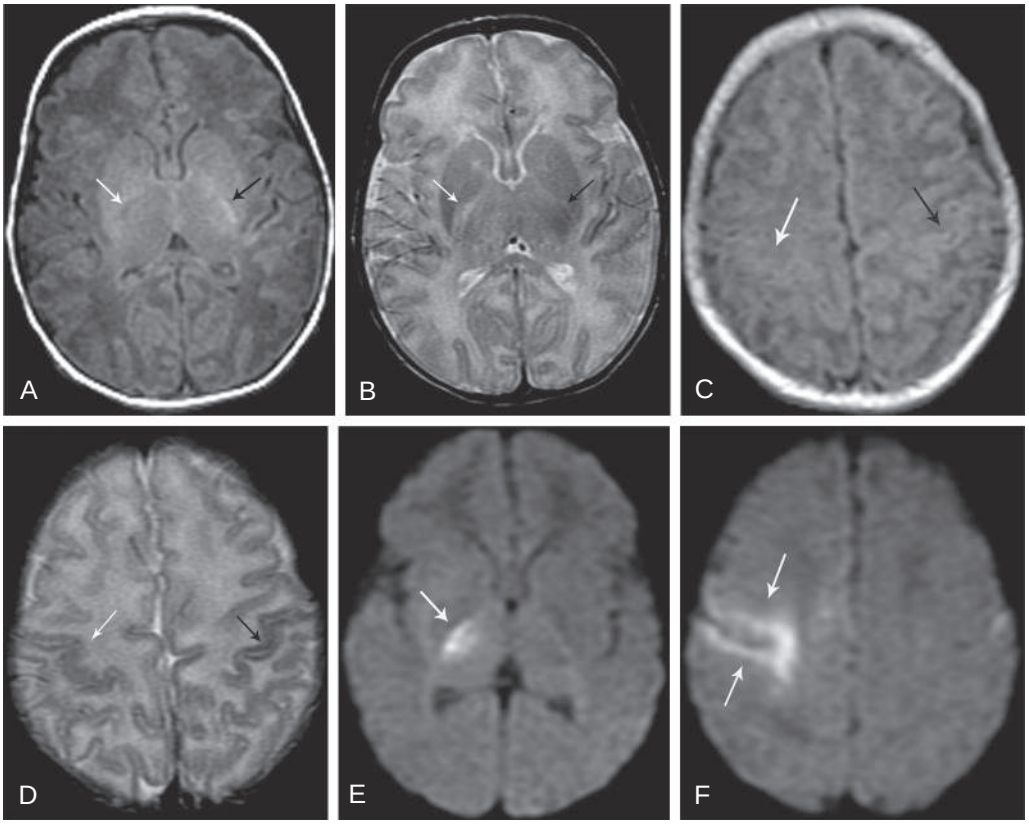

Figure 252-5 Involvement of corticospinal tract and thalamus in a 2 wk old infant. **A,** MRI with axial T1-weighted image demonstrating subtle loss of T1 hyperintensity corresponding to myelination in the posterior limb of the right internal capsule *(white arrow).* T1 hyperintensity in the left posterior limb of the internal capsule is maintained *(black arrow).* **B,** T2-weighted image showing findings similar to those seen on T1-weighted imaging. **C,** Axial T1- and **(D)** T2-weighted images through the vertex demonstrating subtle indistinct margins of the cortex around the right central sulcus *(white arrow)* compared with the normal appearance on the left side *(black arrow).* **E** and **F,** Diffusion-weighted images with more extensive diffusion restriction in the posterior limb of the right internal capsule and lateral thalamus *(arrows),* and in the right pre- and postcentral gyrus *(arrows). (From Bajaj M, Mody S, Natarajan G: Clinical and neuroimaging findings in neonatal herpes simplex virus infection.* J Pediatr *165:404–407, 2014, Fig. 1.)*

famciclovir. All 3 are available in oral form, but only acyclovir is available in a suspension form. Acyclovir has the poorest bioavailability and hence requires more frequent dosing. Valacyclovir, a prodrug of acyclovir, and famciclovir, a prodrug of penciclovir, both have very good oral bioavailability and are dosed once or twice daily. Acyclovir and penciclovir are also available in a topical form but these provide limited or no benefit to patients with recurrent mucocutaneous HSV infections. Only acyclovir has an intravenous formulation. Early initiation of therapy results in the maximal therapeutic benefit. All 3 drugs have exceptional safety profiles and are safe to use in pediatric patients. Doses should be modified in patients with renal impairment.

Resistance to acyclovir and penciclovir is rare in immunocompetent persons but does occur in immunocompromised persons. Virus isolates from immunocompromised persons whose HSV infection is not responding or is worsening with acyclovir therapy should be tested for drug sensitivities. Foscarnet and cidofovir have been used in the treatment of HSV infections caused by acyclovir-resistant mutants.

Topical trifluorothymidine, vidarabine, and idoxuridine are used in the treatment of herpes keratitis.

Patients with genital herpes also require counseling to address psychosocial issues, including possible stigma, and to help them understand the natural history and management of this chronic infection.

Acute Mucocutaneous Infections

For gingivostomatitis, oral acyclovir (15 mg/kg/dose 5 times a day PO for 7 days; maximum: 1 g/day) started within 72 hr of onset reduces the severity and duration of the illness. Pain associated with swallowing may limit oral intake of infants and children, putting them at risk for dehydration. Intake should be encouraged through the use of cold beverages, ice cream, and yogurt.

For **herpes labialis,** oral treatment is superior to topical antiviral therapy. For treatment of a recurrence in adolescents, oral valacyclovir (2,000 mg bid PO for 1 day), acyclovir (200-400 mg 5 times daily PO for 5 days), or famciclovir (1,500 mg once daily PO for 1 day) shortens the duration of the episode. Long-term daily use of oral acyclovir (400 mg bid PO) or valacyclovir (500 mg once daily PO) has been used to prevent recurrences in individuals with frequent or severe recurrences.

Anecdotal reports suggest that treatment of adolescents with **herpes gladiatorum** with oral acyclovir (200 mg 5 times daily PO for 7-10 days) or valacyclovir (500 mg bid PO for 7-10 days) at the first signs of the outbreak can shorten the course of the recurrence. For patients with a history of recurrent herpes gladiatorum, chronic daily prophylaxis with valacyclovir (500-1,000 mg daily) has been reported to prevent recurrences.

There are no clinical trials assessing the benefit of antiviral treatment for **herpetic whitlow.** High-dose oral acyclovir (1,600-2,000 mg/day divided in 2-3 doses PO for 10 days) started at the first signs of illness has been reported to abort some reoccurrences and reduce the duration of others in adults.

A clinical trial in adults has established the effectiveness of oral acyclovir (200 mg 5 times a day PO for 5 days) in the treatment of **eczema herpeticum;** however, serious infections should be treated with intravenous acyclovir. Oral-facial HSV infections can reactivate after cosmetic facial laser resurfacing, causing extensive disease and scarring. Treatment of adults beginning the day before the procedure with either valacyclovir (500 mg twice daily PO for 10-14 days) or famciclovir (250-500 mg bid PO for 10 days) has been reported to be effective in preventing the infections. HSV infections in **burn patients** can be severe or life-threatening and have been treated with intravenous acyclovir (10-20 mg/kg/day divided every 8 hr IV).

Antiviral drugs are not effective in the treatment of HSV-associated **erythema multiforme,** but their daily use as for herpes labialis prophylaxis prevents reoccurrences of erythema multiforme.

Genital Herpes

Pediatric patients, usually adolescents or young adults, with suspected 1st-episode genital herpes should be treated with antiviral therapy. Treatment of the initial infection reduces the severity and duration of the illness but has no effect on the frequency of subsequent recurrent infections. Treatment options for adolescents include acyclovir (400 mg tid PO for 7-10 days), famciclovir (250 mg tid PO for 7-10 days), or valacyclovir (1,000 mg bid PO for 7-10 days). The twice-daily valacyclovir option avoids treatment during school hours. For smaller children, acyclovir suspension can be used at a dose of 10-20 mg/kg/dose 4 times daily not to exceed the adult dose. The 1st episode of genital herpes can be extremely painful, and use of analgesics is generally indicated. All patients with genital herpes should be offered counseling to help them deal with psychosocial issues and understand the chronic nature of the illness.

There are 3 strategic options regarding the management of recurrent infections. The choice should be guided by several factors, including the frequency and severity of the recurrent infections, the psychologic impact of the illness on the patient, and concerns regarding transmission to a susceptible sexual partner. Option 1 is no therapy; option 2 is episodic therapy; and option 3 is long-term suppressive therapy. For **episodic therapy,** treatment should be initiated at the first signs of an outbreak. Recommended choices for episodic therapy in adolescents include famciclovir (1,000 mg bid PO for 1 day), acyclovir (800 mg tid PO for 2 days), or valacyclovir (500 mg bid PO for 3 days or 1,000 mg once daily for 5 days). Long-term suppressive therapy offers the advantage that it prevents most outbreaks, improves patient quality of life in terms of the psychosocial impact of genital herpes, and, with daily valacyclovir therapy, also reduces (but does not eliminate) the risk for sexual transmission to a susceptible sexual partner. Options for **long-term suppressive therapy** are acyclovir (400 mg bid PO), famciclovir (250 mg bid PO), and valacyclovir (500 or 1,000 mg qd PO).

Ocular Infections

HSV ocular infections can result in blindness. Management should involve consultation with an ophthalmologist.

Central Nervous System Infections

Patients older than neonates who have herpes encephalitis should be promptly treated with intravenous acyclovir (10 mg/kg every 8 hr given as a 1 hr infusion for 14-21 days). Treatment for increased intracranial pressure, management of seizures, and respiratory compromise may be required.

Infections in Immunocompromised Persons

Severe mucocutaneous and disseminated HSV infections in immunocompromised patients should be treated with intravenous acyclovir (5-10 mg/kg or 250 mg/m^2 every 8 hr) until there is evidence of resolution of the infection. Oral antiviral therapy with acyclovir, famciclovir, or valacyclovir has been used for treatment of less-severe HSV infections and for suppression of recurrences during periods of significant immunosuppression. Drug resistance does occur occasionally in immunocompromised patients, and in individuals whose HSV infection does not respond to antiviral drug therapy, viral isolates should be tested to determine sensitivity. Acyclovir-resistant viruses are often also resistant to famciclovir but may be sensitive to foscarnet or cidofovir.

Perinatal Infections

All infants with proven or suspected neonatal HSV infection should be treated immediately with high-dose intravenous acyclovir (60 mg/kg/day divided every 8 hr IV). Treatment may be discontinued in infants shown by laboratory testing not to be infected. Infants with HSV disease limited to skin, eyes, and mouth should be treated for 14 days, whereas those with disseminated or central nervous system disease should receive 21 days of therapy. Patients receiving high-dose therapy should be monitored for neutropenia.

Suppressive oral acyclovir therapy for 6 mo after completion of the intravenous therapy has been shown to improve the neurodevelopment of infants with central nervous system infection and to prevent cutaneous recurrences in infants regardless of disease pattern. Infants should receive 300 mg/m^2 per dose 3 times daily for 6 mo. The absolute

neutrophil count should be measured at weeks 2 and 4 after initiation treatment and then monthly.

PROGNOSIS

Most HSV infections are self-limiting, last from a few days (for recurrent infections) to 2-3 wk (for primary infections), and heal without scarring. Recurrent oral-facial herpes in a patient who has undergone dermabrasion or laser resurfacing can be severe and lead to scarring. Because genital herpes is a sexually transmitted infection, it can be stigmatizing, and its psychologic consequences may be much greater than its physiologic effects. Some HSV infections can be severe and may have grave consequences without prompt antiviral therapy. Life-threatening conditions include neonatal herpes, herpes encephalitis, and HSV infections in immunocompromised patients, burn patients, and severely malnourished infants and children. Recurrent ocular herpes can lead to corneal scarring and blindness.

PREVENTION

Transmission of infection occurs through exposure to virus either as the result of skin-to-skin contact or from contact with contaminated secretions. Good handwashing and, when appropriate, the use of gloves provide healthcare workers with excellent protection against HSV infection in the workplace. Healthcare workers with active oral-facial herpes or herpes whitlow should take precautions, particularly when caring for high-risk patients such as newborns, immunocompromised individuals, and patients with chronic skin conditions. Patients and parents should be advised about good hygienic practices, including handwashing and avoiding contact with lesions and secretions, during active herpes outbreaks. Schools and daycare centers should clean shared toys and athletic equipment such as wrestling mats at least daily after use. Athletes with active herpes infections who participate in contact sports such as wrestling and rugby should be excluded from practice or games until the lesions are completely healed. Genital herpes can be prevented by avoiding genital-genital and oral-genital contact. The risk for acquiring genital herpes can be reduced but not eliminated through the correct and consistent use of condoms. Male circumcision is associated with a reduced risk of acquiring genital HSV infection. The risk for transmitting genital HSV-2 infection to a susceptible sexual partner can be reduced but not eliminated by the daily use of oral valacyclovir by the infected partner.

For **pregnant women** with **active genital herpes** at the time of delivery, the risk for mother-to-baby transmission can be reduced but not eliminated by delivering the baby via a cesarean section (within 4-6 hr of rupture of membranes). The risk for recurrent genital herpes, and therefore the need for cesarean delivery, can be reduced but not eliminated in pregnant women with a history of genital herpes by the daily use of oral acyclovir, valacyclovir, or famciclovir during the last 4 wk of gestation, which is recommended by the American College of Obstetrics and Gynecology. There are documented cases of neonatal herpes occurring in infants delivered by cesarean section, as well as in infants born to mothers who have been appropriately treated with antiherpes antiviral drugs for the last month of gestation. Hence a history of cesarean delivery or antiviral treatment at term does not rule out consideration of neonatal herpes.

Infants delivered vaginally to women with 1st-episode genital herpes are at very high risk for acquiring HSV infection. The nasopharynx, mouth, conjunctivae, rectum, and umbilicus should be cultured (some add PCR surface testing) at delivery and on day 1-2 of life. Some also recommend HSV-PCR on blood. Some authorities recommend that these infants receive anticipatory acyclovir therapy for at least 2 wk, and others treat such infants if signs develop or if the 48 hr cultures have positive results. Infants delivered to women with a history of recurrent genital herpes are at low risk for development of neonatal herpes. In this setting, parents should be educated about the signs and symptoms of neonatal HSV infection and should be instructed to seek care without delay at the first suggestion of infection. When the situation is in doubt, infants should be evaluated and tested with surface culture (and PCR) for neonatal herpes as well as with PCR on blood *and* CSF; intravenous acyclovir is begun until culture results are negative or until another explanation can be found for the signs and symptoms.

Recurrent genital HSV infections can be prevented by the daily use of oral acyclovir, valacyclovir, or famciclovir, and these drugs have been used to prevent recurrences of oral-facial (labialis) and cutaneous (gladiatorum) herpes. Oral and intravenous acyclovir has also been used to prevent recurrent HSV infections in immunocompromised patients. Use of sun blockers is reported to be effective in preventing recurrent oral-facial herpes in patients with a history of sun-induced recurrent disease.

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Chapter 253

Varicella-Zoster Virus

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Varicella-zoster virus (VZV) causes primary, latent, and recurrent infections. The primary infection is manifested as varicella **(chickenpox)** and results in establishment of a lifelong latent infection of sensory ganglion neurons. Reactivation of the latent infection causes herpes zoster **(shingles).** Although often a mild illness of childhood, varicella can cause substantial morbidity and mortality in otherwise healthy children. Morbidity and mortality are higher in immunocompetent infants, adolescents, and adults as well as in immunocompromised persons. Varicella predisposes to severe group A *Streptococcus* and *Staphylococcus aureus* infections. A clinically modified disease can occur among vaccinated persons (breakthrough varicella), usually with milder presentation. Varicella and herpes zoster can be treated with antiviral drugs. Primary clinical disease can be prevented by immunization with live-attenuated VZV vaccine (varicella vaccine). Herpes zoster vaccine (zoster vaccine), which contains the same VZV strain used in the varicella vaccine but with a higher potency, is available for persons 50 yr of age and older to boost their immunity to VZV and prevent herpes zoster and its major complication, painful postherpetic neuralgia.

ETIOLOGY

VZV is a neurotropic human herpesvirus with similarities to herpes simplex virus. These enveloped viruses contain double-stranded DNA genomes that encode more than 70 proteins, including proteins that are targets of cellular and humoral immunity.

EPIDEMIOLOGY

Before the introduction of varicella vaccine in 1996, varicella was an almost universal communicable infection of childhood in the United States. Most children were infected by 15 yr of age, with fewer than 5% of adults remaining susceptible. This pattern of infection at younger ages remains characteristic in all countries in temperate climates. In contrast, in tropical areas, children acquire varicella at older ages and a higher proportion of young adults remain susceptible leading to a higher proportion of cases occurring among adults. In the United States, prior to introduction of varicella vaccination, annual varicella epidemics occurred in winter and spring, and there were about 4 million cases of varicella, 11,000-15,000 hospitalizations, and 100-150 deaths every year. Varicella is a more serious disease in young infants, adults, and immunocompromised persons, in whom there are higher rates of complications and deaths than in healthy children. Within households, transmission of VZV to susceptible individuals occurs at a rate of 65-86%; more casual contact, such as occurs in a

school classroom, is associated with lower attack rates among susceptible children. Persons with varicella are contagious 24-48 hr before the rash is evident and until vesicles are crusted, usually 3-7 days after onset of rash. Susceptible persons may also acquire varicella after close, direct contact with adults or children who have herpes zoster.

Since implementation of the varicella vaccination program in 1996, there have been substantial declines in varicella morbidity and mortality in the United States. By 2006, prior to implementation of the 2 dose program, 1 dose vaccination coverage had reached 90% and varicella incidence had declined 90-91% since 1995 in sites where active surveillance was being conducted; varicella-related hospitalizations had declined 84% from prevaccine years. Varicella-related deaths decreased by 88% from 1990-1994 to 2005-2007; in persons younger than 20 yr of age there was a 97% decline in deaths. Declines in morbidity and mortality were seen in all age groups, including infants younger than 12 mo of age who were not eligible for vaccination, indicating protection from exposure by indirect vaccination effects. Although the age-specific incidence has declined in all age groups, the median age at infection has increased, and cases occur predominantly in children in upper elementary school rather than in the preschool years. This change in varicella epidemiology highlights the importance of offering vaccine to every susceptible child, adolescent, and adult. The continued occurrence of breakthrough infections and of outbreaks in settings with high 1-dose varicella vaccine coverage, together with the evidence that 1 dose is only approximately 85% effective against all varicella, prompted adoption in 2006 of a routine 2 dose childhood varicella vaccination program with catch-up vaccination of all individuals without evidence of immunity. Between 2006 and 2010, varicella incidence declined further by approximately 70% and fewer outbreaks were reported.

Herpes zoster is caused by the reactivation of latent VZV. It is not common in childhood and shows no seasonal variation in incidence. Zoster is not caused by exposure to a patient with varicella; in fact, exposures to varicella boost the cell-mediated immune response to VZV in individuals with prior infection, decreasing the likelihood of reactivation of latent virus. The lifetime risk for herpes zoster for individuals with a history of varicella is 20-30%, with 75% of cases occurring after 45 yr of age. Herpes zoster is very rare in healthy children younger than 10 yr of age, with the exception of those infected with VZV in utero or in the 1st yr of life, who have an increased risk for development of zoster in the 1st few yr of life. Herpes zoster in children tends to be milder than herpes zoster in adults, is less frequently associated with acute pain, and postherpetic neuralgia generally does not occur in healthy children. In children receiving immunosuppressive therapy for malignancy or other diseases and in those who have HIV infection, herpes zoster occurs more frequently, occasionally multiple times, and may be severe. The attenuated VZV in the varicella vaccine can establish latent infection and reactivate as herpes zoster. However, the evidence to date indicates that the risk for development of subsequent herpes zoster is lower after vaccination than after natural VZV infection among both healthy and immunocompromised children. Vaccinated children who do develop zoster may have disease resulting from vaccine or wild-type VZV.

PATHOGENESIS

VZV is transmitted by contact with oropharyngeal secretions and the fluid of skin lesions of infected individuals, either by airborne spread or through direct contact. Primary infection (varicella) results from inoculation of the virus onto the mucosa of the upper respiratory tract and tonsillar lymphoid tissue. During the early part of the 10-21 day incubation period, virus replicates in the local lymphoid tissue, and then a brief subclinical viremia spreads the virus to the reticuloendothelial system. Widespread cutaneous lesions occur during a 2nd viremic phase that lasts 3-7 days. Peripheral blood mononuclear cells carry infectious virus, generating new crops of vesicles during this period of viremia. VZV is also transported back to the mucosa of the upper respiratory tract and oropharynx during the late incubation period, permitting spread to susceptible contacts 1-2 days before the appearance of rash. Host immune responses limit viral replication and facilitate recovery from infection. In the immunocompromised child, the failure of immune responses, especially cell-mediated immune responses, results in continued viral replication that may lead to prolonged and/or disseminated infection with resultant complications in the lungs, liver, brain, and other organs. Virus is transported in a retrograde manner through sensory axons to the dorsal root ganglia throughout the spinal cord, where the virus establishes latent infection in the neurons and satellite cells associated with these axons. Virus may also reach the ganglia by the hematogenous route. Subsequent **reactivation** of latent virus causes **herpes zoster,** a vesicular rash that usually is dermatomal in distribution. During herpes zoster, necrotic changes may be produced in the neurons and surrounding satellite cells in associated ganglia. The skin lesions of varicella and herpes zoster have identical histopathology, and infectious VZV is present in both. Varicella elicits humoral and cell-mediated immunity that is highly protective against symptomatic reinfection. Suppression of cell-mediated immunity to VZV correlates with an increased risk for VZV reactivation as herpes zoster.

CLINICAL MANIFESTATIONS

Varicella is an acute febrile rash illness that was common in children in the United States before the universal childhood vaccination program. It has variable severity but is usually self-limited. It may be associated with severe complications, including staphylococcal and streptococcal superinfection, pneumonia, encephalitis, bleeding disorders, congenital infection, and life-threatening perinatal infection. Herpes zoster, not common in children, causes localized cutaneous symptoms, but may disseminate in immunocompromised patients.

Varicella in Unvaccinated Individuals

The illness usually begins 14-16 days after exposure, although the incubation period can range from 10-21 days. Subclinical varicella is rare; almost all exposed, susceptible persons experience a rash, albeit so mild in some cases that it may go unnoticed. Prodromal symptoms may be present, particularly in older children and adults. Fever, malaise, anorexia, headache, and occasionally mild abdominal pain may occur 24-48 hr before the rash appears. Temperature elevation is usually 37.8-38.9°C (100-102°F) but may be as high as 41.1°C (106°F); fever and other systemic symptoms usually resolve within 2-4 days after the onset of the rash.

Varicella lesions often appear first on the scalp, face, or trunk. The initial exanthem consists of intensely pruritic erythematous macules that evolve through the papular stage to form clear, fluid-filled vesicles. Clouding and umbilication of the lesions begin in 24-48 hr. While the initial lesions are crusting, new crops form on the trunk and then the extremities; the simultaneous presence of lesions in various stages of evolution is characteristic of varicella (Fig. 253-1). The distribution of the rash is predominantly central or centripetal with the greatest concentration on the trunk and proximally on the extremities. Ulcerative lesions involving the mucosa of the oropharynx and vagina are also common; many children have vesicular lesions on the eyelids and conjunctivae, but corneal involvement and serious ocular disease are rare. The average number of varicella lesions is about 300, but healthy children may have fewer than 10 to more than 1,500 lesions. In cases resulting from secondary household spread and in older children, more lesions usually occur, and new crops of lesions may continue to develop for more than 7 days. The exanthem may be much more extensive in children with skin disorders, such as eczema or recent sunburn. Hypopigmentation or hyperpigmentation of lesion sites persists for days to weeks in some children, but severe scarring is unusual unless the lesions were secondarily infected.

The **differential diagnosis** of varicella includes vesicular rashes caused by other infectious agents, such as herpes simplex virus, enterovirus, monkey pox, rickettsial pox, and *S. aureus;* drug reactions; disseminated herpes zoster; contact dermatitis; and insect bites (especially for breakthrough varicella). Severe varicella was the most common illness confused with smallpox before the eradication of smallpox.

Varicelliform Rashes in Vaccinated Individuals

Varicelliform rashes that occur after vaccination could be a result of wild-type VZV, vaccine strain VZV, or other etiologies (e.g., insect bites, coxsackievirus). During days 0-42 after vaccination, the

Figure 253-1 **A,** Varicella lesions in unvaccinated persons display the characteristic "cropping" distribution, or manifest themselves in clusters; the simultaneous presence of lesions in various stages of evolution is characteristic. **B,** Breakthrough varicella lesions are predominantly maculopapular, and vesicles are less common; the illness is most commonly mild with <50 lesions. (***A*** *courtesy of the Centers for Disease Control and Prevention [CDC];* ***B*** *courtesy of the CDC and Dr. John Noble, Jr.)*

likelihood of rash from wild-type or vaccine strain VZV varies depending on the stage of a country's vaccination program. In the early stages of a vaccine program, rash within 1-2 wk is still most commonly caused by wild-type VZV, reflecting exposure to varicella before vaccination could provide protection. Rash occurring 14-42 days after vaccination is a result of either wild-type or vaccine strains, reflecting exposure and infection before protection from vaccination or an adverse event of vaccination (vaccine-associated rash), respectively. As wild-type varicella continues to decline as a consequence of the vaccination program, VZV circulation will also decline and rashes in the interval 0-42 days after vaccination will be less commonly caused by wild-type VZV.

Breakthrough varicella is disease that occurs in a person vaccinated more than 42 days before rash onset and is caused by **wild-type** virus**.** One dose of varicella vaccine is >97% effective in preventing moderate and severe varicella and is 85% (median; range: 44-100%) effective in preventing all disease after exposure to wild-type VZV. This means that after close exposure to VZV, as may occur in a household or an outbreak setting in a school or daycare center, about 1 of every 5 children who received one dose of vaccine may experience breakthrough varicella. Exposure to VZV may also result in asymptomatic infection in the previously immunized child. The rash in breakthrough disease is frequently atypical and predominantly maculopapular, vesicles are seen less commonly. The illness is most commonly mild with <50 lesions, shorter duration of rash, fewer complications, and little or no fever. However, approximately 25-30% of breakthrough cases in vaccinees who received one dose are not mild, with clinical features more similar to those of wild-type infection. Breakthrough cases are overall **less contagious** than wild-type infections within household settings, but contagiousness varies proportionally with the number of lesions; typical breakthrough cases (<50 lesions) is about one third as contagious as disease in unvaccinated cases, whereas breakthrough cases with ≥50 lesions are as contagious as wild-type cases. Consequently, children with breakthrough disease should be considered potentially infectious and excluded from school until lesions have crusted or, if there are no vesicles present, until no new lesions are occurring. Transmission has been documented to occur from breakthrough cases in household, childcare, and school settings.

Fewer studies have evaluated the performance of the 2 dose varicella vaccine regimen. One clinical trial estimated the 2 dose vaccine effectiveness for preventing all disease at 98%; the estimate is 95% (median; range: 88-98%) in conditions of everyday clinical practice. Breakthrough cases have been reported among 2 dose vaccinees, although recipients of 2 doses of varicella vaccine are less likely to have breakthrough disease than those who received 1 dose. Additionally, data suggest that disease may be further attenuated among 2 dose vaccine recipients.

Neonatal Varicella

Mortality is particularly high in neonates born to susceptible mothers who contracted varicella around the time of delivery. Infants whose mothers demonstrate varicella in the period from 5 days prior to delivery to 2 days afterward are at high risk for severe varicella. These infants acquire the infection transplacentally as a result of maternal viremia, which may occur up to 48 hr prior to onset of maternal rash. The infant's rash usually occurs toward the end of the 1st wk to the early part of the 2nd wk of life (although it may be as soon as 2 days). Because the mother has not yet developed a significant antibody response, the infant receives a large dose of virus without the moderating effect of maternal anti-VZV antibody. If the mother demonstrates varicella more than 5 days prior to delivery, she still may pass virus to the soon-to-be-born child, but infection is attenuated because of transmission of maternal VZV-specific antibody across the placenta. This moderating effect of maternal antibody is present if delivery occurs after about 30 wk of gestation, when maternal immunoglobulin (Ig) G is able to cross the placenta in significant amounts. The recommendations for use of human varicella-zoster immunoglobulin (VZIG) differ based on when the infant is exposed to varicella. Newborns whose mothers develop varicella during the period of 5 days before to 2 days after delivery should receive VZIG as soon as possible. Although neonatal varicella may occur in about half of these infants despite administration of VZIG, it is usually milder than in the absence of VZIG administration. All premature infants born <28 wk of gestation to a mother with active varicella at delivery (even if the maternal rash has been present for >1 wk) should receive VZIG. If VZIG is not available, intravenous immunoglobulin (IVIG) may provide some protection, although varicella-specific antibody titers may vary from lot to lot. Because perinatally acquired varicella may be life threatening, the infant should be treated with acyclovir (10 mg/kg every 8 hr IV) when lesions develop. Some experts might initiate treatment with oral acyclovir in infants who received VZIG. Neonatal varicella can also follow a postpartum exposure of an infant delivered to a mother who was susceptible to VZV, although the frequency of complications declines rapidly in the weeks after birth. Recommendations for VZIG administration for these infants are presented in the postexposure prophylaxis section. Neonates with community-acquired varicella who experience severe varicella, especially those who have a complication such as pneumonia, hepatitis, or encephalitis, should also receive treatment with intravenous acyclovir (10 mg/kg every 8 hr). Infants with neonatal varicella who receive prompt antiviral therapy have an excellent prognosis.

Congenital Varicella Syndrome

In utero transmission of VZV can occur; however, because most adults in temperate climates are immune, pregnancy complicated by varicella is unusual in these settings. When pregnant women do contract

varicella early in pregnancy, experts estimate that as many as 25% of the fetuses may become infected. Fortunately, clinically apparent disease in the infant is uncommon: The congenital varicella syndrome occurs in approximately 0.4% of infants born to women who have varicella during pregnancy before 13 wk of gestation and in approximately 2% of infants born to women with varicella between 13 and 20 wk of gestation. Rarely, cases of congenital varicella syndrome have been reported in infants of women infected after 20 wk of pregnancy, the latest occurring at 28 wk of gestation. Before availability of varicella vaccine in the United States, 44 cases of congenital varicella syndrome were estimated to occur each year. The congenital varicella syndrome is characterized by cicatricial skin scarring in a zoster-like distribution; limb hypoplasia; and abnormalities of the neurologic system (e.g., microcephaly, cortical atrophy, seizures, and mental retardation), eye (e.g., chorioretinitis, microphthalmia, and cataracts), renal system (e.g., hydroureter and hydronephrosis), and autonomic nervous system (neurogenic bladder, swallowing dysfunction, and aspiration pneumonia). Low birthweight is common among infants with congenital varicella syndrome. Most of the stigmata can be attributed to virus-induced injury to the nervous system, although there is no obvious explanation why certain regions of the body are preferentially infected during fetal VZV infection. The characteristic cutaneous lesion has been called a cicatrix, a zigzag scarring, in a **dermatomal** distribution, often associated with atrophy of the affected limb (Fig. 253-2). Many infants with severe manifestations of congenital varicella syndrome (atrophy and scarring of a limb) have significant neurologic deficiencies. Alternatively, there may be neither skin nor limb abnormalities but the infant may show cataracts or even extensive aplasia of the entire brain.

There are rare case reports of fetal abnormalities following the development of herpes zoster in the mother; whether or not these cases truly represent the congenital varicella syndrome is unclear. If it does occur, the congenital syndrome acquired as a result of maternal herpes zoster is exceedingly rare. Maternal herpes zoster was associated with typical congenital varicella syndrome in 1 case, but the mother had disseminated herpes zoster (at 12 wk of gestation).

The diagnosis of VZV fetopathy is based mainly on the history of gestational varicella combined with the presence of characteristic abnormalities in the newborn infant. Virus cannot be cultured from the affected newborn, but viral DNA may be detected in tissue samples by polymerase chain reaction (PCR). VZV-specific IgM antibody is detectable in the cord blood sample in some infants, although the IgM titer drops quickly in the postpartum period and can be nonspecifically positive. Chorionic villus sampling and fetal blood collection for the detection of viral DNA, virus, or antibody have been used in an attempt to diagnose fetal infection and embryopathy. The usefulness of these tests for patient management and counseling has not been defined. Because these tests may not distinguish between infection and disease, their utility may primarily be that of reassurance when the result is negative. A persistently positive VZV IgG antibody titer at 12-18 mo of age is a reliable indicator of prenatal infection in the asymptomatic child, as is the development of zoster in the 1st yr of life without evidence of postnatal infection.

Figure 253-2 Newborn with congenital varicella syndrome. The infant had severe malformations of both lower extremities and cicatricial scarring over his left abdomen.

VZIG has often been administered to the susceptible mother exposed to varicella to modify maternal disease severity; it is uncertain whether this step modifies infection in the fetus, although some evidence suggests that it may be beneficial for the fetus too. Similarly, acyclovir treatment may be given to the mother with severe varicella. A prospective registry of acyclovir use in the 1st trimester demonstrated that the occurrence of birth defects approximates that found in the general population. Acyclovir is a class B drug for pregnancy and should be considered when the benefit to the mother outweighs the potential risk to the fetus. The efficacy of acyclovir treatment of the pregnant woman in preventing or modifying the severity of congenital varicella is not known, but its use should be considered to protect the mother from severe disease. Because the damage caused by fetal VZV infection does not progress in the postpartum period, antiviral treatment of infants with congenital VZV syndrome is not indicated.

COMPLICATIONS

The complications of VZV infection occur with varicella or with reactivation of infection, more commonly in immunocompromised patients. In the otherwise healthy child, mild varicella hepatitis is relatively common but rarely clinically symptomatic. Mild thrombocytopenia occurs in 1-2% of children with varicella and may be associated with transient petechiae. Purpura, hemorrhagic vesicles, hematuria, and gastrointestinal bleeding are rare complications that may have serious consequences. Other complications of varicella, some of them rare, include acute cerebellar ataxia, encephalitis, pneumonia, nephritis, nephrotic syndrome, hemolytic-uremic syndrome, arthritis, myocarditis, pericarditis, pancreatitis, orchitis, and acute retinal necrosis. A reduction in the number and rates of varicella-related complications is seen with the use of the vaccine. Reports of serious varicella-related complications in vaccinated persons (breakthrough) have been rare (meningitis, 1 case of acute transverse myelitis, 1 fatal case of VZV encephalitis in an apparently immunocompetent child, and 4 fatal cases of breakthrough disease, 3 of which involved high-dose steroids or an underlying immunocompromising condition).

Declines in varicella-related hospitalizations and deaths in the United States since implementation of the varicella vaccination program provide supporting evidence that varicella vaccine reduces severe complications from varicella. Approximately 100 deaths (with varicella listed as the underlying cause of death) occurred in the United States annually before the introduction of the varicella vaccine; during 2005-2007 the annual average number of varicella deaths was 15. In both the pre- and postvaccine era, the majority of deaths (>80%) have been among persons without high-risk preexisting conditions.

Bacterial Infections

Secondary bacterial infections of the skin, usually caused by group A *Streptococcus* and *S. aureus,* may occur in up to 5% of children with varicella. These range from impetigo to cellulitis, lymphadenitis, and subcutaneous abscesses. An early manifestation of secondary bacterial infection is erythema of the base of a new vesicle. Recrudescence of fever 3-4 days after the initial exanthem may also herald a secondary bacterial infection. Varicella is a well-described risk factor for serious invasive infections caused by group A *Streptococcus*, which can have a fatal outcome. The more invasive infections, such as varicella gangrenosa, bacterial sepsis, pneumonia, arthritis, osteomyelitis, cellulitis, and necrotizing fasciitis, account for much of the morbidity and

mortality of varicella in otherwise healthy children. Bacterial toxin–mediated diseases (e.g., toxic shock syndrome) also may complicate varicella. A substantial decline in varicella-related invasive bacterial infections is associated with the use of the varicella vaccine.

Encephalitis and Cerebellar Ataxia

Encephalitis (1 per 50,000 cases of varicella in unvaccinated children) and acute cerebellar ataxia (1 per 4,000 cases of varicella in unvaccinated children) are well-described neurologic complications of varicella; morbidity from central nervous system complications is highest among patients younger than 5 yr and older than 20 yr. Nuchal rigidity, altered consciousness, and seizures characterize meningoencephalitis. Patients with cerebellar ataxia have a gradual onset of gait disturbance, nystagmus, and slurred speech. Neurologic symptoms usually begin 2-6 days after the onset of the rash but may occur during the incubation period or after resolution of the rash. Clinical recovery is typically rapid, occurring within 24-72 hr, and is usually complete. Although severe hemorrhagic encephalitis, analogous to that caused by herpes simplex virus, is very rare in children with varicella, the consequences are similar to those of herpes encephalitis. Reye syndrome (hepatic dysfunction with hypoglycemia and encephalopathy) associated with varicella and other viral illnesses such as influenza is rare now that salicylates are no longer used as antipyretics in these situations (see Chapter 361).

Pneumonia

Varicella pneumonia is a severe complication that accounts for most of the increased morbidity and mortality from varicella in adults and other high-risk populations, but pneumonia may also complicate varicella in young children. Respiratory symptoms, which may include cough, dyspnea, cyanosis, pleuritic chest pain, and hemoptysis, usually begin within 1-6 days after the onset of the rash. Smoking has been described as a risk factor for severe pneumonia complicating varicella. The frequency of varicella pneumonia may be greater in the parturient.

Progressive Varicella

Progressive varicella, with visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 7 days, is a severe complication of primary VZV infection. Severe abdominal pain, which may reflect involvement of mesenteric lymph nodes or the liver, or the appearance of hemorrhagic vesicles in otherwise healthy adolescents and adults, immunocompromised children, pregnant women, and newborns, may herald severe, and potentially fatal, disease. Although rare in healthy children, the risk for progressive varicella is highest in children with congenital cellular immune deficiency disorders and those with malignancy, particularly if chemotherapy, and especially corticosteroids, had been given during the incubation period and the absolute lymphocyte count is <500 cells/μL. The mortality rate for children who acquired varicella while undergoing treatment for malignancy and who were not treated with antiviral therapy approached 7%; varicella-related deaths usually occurred within 3 days after the diagnosis of varicella **pneumonia.** Children who acquire varicella after organ transplantation are also at risk for progressive VZV infection. Children undergoing long-term, low-dose systemic or inhaled corticosteroid therapy are not considered to be at higher risk for severe varicella, but progressive varicella does occur in patients receiving high-dose corticosteroids. There are case reports in patients receiving inhaled corticosteroids as well as in asthmatic patients receiving multiple short courses of systemic corticosteroid therapy. Unusual clinical findings of varicella, including lesions that develop a hyperkeratotic appearance and continued new lesion formation for weeks or months, have been described in children with untreated, late-stage **HIV infection.** Immunization of HIV-infected children who have a $CD4^+$ T-lymphocyte percent ≥15%, as well as children with leukemia and solid organ tumors who are in remission and whose chemotherapy can be interrupted for 2 wk around the time of immunization or has been terminated, have reduced frequency of severe disease. Moreover, since the advent of the universal immunization program in the United States, many children who would become immunocompromised later in life because of disease or treatment are protected before the immunosuppression occurs; also, as a result of reductions in varicella incidence, immunocompromised children are less likely to be exposed to varicella.

Figure 253-3 Herpes zoster involving the lumbar dermatome. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 6. Philadelphia, 2005, Elsevier, p. 1783.)*

Figure 253-4 Many groups of blisters occurring over the arm in a child with herpes zoster. *(From Weston WL, Lane AT, Morelli JG:* Color textbook of pediatric dermatology, *ed 3. Philadelphia, 2002, Mosby, Fig. 8-28.)*

Herpes Zoster

Herpes zoster manifests as vesicular lesions clustered within 1 or, less commonly, 2 adjacent dermatomes (Fig. 253-3). In the elderly, herpes zoster typically begins with burning pain followed by clusters of skin lesions in a dermatomal pattern. Almost half of the elderly with herpes zoster experience complications; the most frequent complication is postherpetic neuralgia, a painful condition that affects the nerves despite resolution of the skin lesions. Approximately 4% of patients suffer a 2nd episode of herpes zoster; 3 or more episodes are rare. Unlike herpes zoster in adults, zoster in children is infrequently associated with localized pain, hyperesthesia, pruritus, low-grade fever, or complications. In children, the rash is mild, with new lesions appearing for a few days (Fig. 253-4); symptoms of acute neuritis are minimal; and complete resolution usually occurs within 1-2 wk. Unlike in adults, postherpetic neuralgia is unusual in children. An increased risk for herpes zoster early in childhood has been described in children who acquire infection with VZV in utero or in the 1st yr of life.

Immunocompromised children may have more severe herpes zoster, similar to the situation in adults, including postherpetic neuralgia. Immunocompromised patients may also experience disseminated cutaneous disease that mimics varicella, with or without initial dermatomal rash, as well as visceral dissemination with pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy. Severely immunocompromised children, particularly those with advanced HIV infection, may have unusual, chronic, or relapsing cutaneous disease,

retinitis, or central nervous system disease without rash. The finding of a lower risk for herpes zoster among vaccinated children with leukemia than in those who have had varicella suggested that the vaccine virus reactivates less commonly than wild-type VZV. Studies to date indicate that the risk for herpes zoster in healthy children who have received one dose of vaccine is lower than in children who had wild-type varicella. Many more years of follow-up are needed to determine whether this lower risk is maintained among older persons who are at greatest risk for herpes zoster. The risk for herpes zoster in healthy children following 2 doses of varicella vaccine has not been evaluated.

DIAGNOSIS

Varicella and herpes zoster have been diagnosed primarily by their clinical appearance. Laboratory evaluation has not been considered necessary for diagnosis or management. However, as varicella disease has declined to low levels, laboratory confirmation has become increasingly useful. The atypical nature of breakthrough varicella, with a higher proportion of papular rather than vesicular rash, poses both clinical and laboratory diagnostic challenges.

Leukopenia is typical during the 1st 72 hr after onset of rash; it is followed by a relative and absolute lymphocytosis. Results of liver function tests are also usually (75%) mildly elevated. Patients with neurologic complications of varicella or uncomplicated herpes zoster have a mild lymphocytic pleocytosis and a slight to moderate increase in protein content of the cerebrospinal fluid; the cerebrospinal fluid glucose concentration is usually normal.

Rapid laboratory diagnosis of VZV is often important in high-risk patients and can be important for infection control, especially for breakthrough cases that have mild or atypical presentations. Confirmation of VZV infections can be accomplished by many referral hospital laboratories and all state health laboratories. VZV can be identified quickly by direct fluorescence assay of cells from cutaneous lesions (vesicular fluid) in 15-20 min, by PCR amplification testing (vesicular fluid, crusts) in hours to days, depending on availability, and by rapid culture with specific immunofluorescence staining (shell vial technique) in 48-72 hr. In the absence of vesicles or scabs, scrapings of maculopapular lesions can be collected for PCR or direct fluorescence assay testing. Infectious virus may be recovered by means of tissue culture methods; such methods require specific expertise, and virus may take days to weeks to grow. Of available tests, PCR is the most sensitive and allows for differentiation of wild-type and vaccine strains. Direct fluorescence assay is specific and less sensitive than PCR but when available allows for rapid diagnosis. Although multinucleated giant cells can be detected with nonspecific stains (Tzanck smear), they have poor sensitivity and do not differentiate VZV from herpes simplex virus infections. Strain identification (genotyping) can distinguish wild-type VZV from the vaccine strain in a vaccinated child; however, genotyping is available only at specialized reference laboratories. Laboratory tests of lesions cannot be used to distinguish between varicella and disseminated herpes zoster. VZV IgG antibodies can be detected by several methods, and a 4-fold or greater rise in IgG antibodies is confirmatory of acute infection (although this requires a 2-3 wk delay to collect a convalescent specimen); in vaccinated persons, commercially available tests are not sufficiently sensitive to always detect antibody following vaccination and a 4-fold rise in IgG antibody may not occur. VZV IgG antibody tests can also be valuable to determine the immune status of individuals whose clinical history of varicella is unknown or equivocal. Testing for VZV IgM antibodies is not useful for routine confirmation or ruling out of varicella because commercially available methods are unreliable and the kinetics of the IgM response have not been well defined. Reliable VZV-specific IgM assays are available in certain reference laboratories, including a capture-IgM assay available at the national VZV laboratory at the Centers for Disease Control and Prevention. Serologic tests are not useful for the initial diagnosis of herpes zoster, but a large rise in IgG titer in convalescent titer in the presence of an atypical zoster rash is confirmatory. As with any laboratory tests, a negative varicella test should be considered in the context of the clinical presentation. Clinicians should use clinical judgment to decide on the best course of therapy.

TREATMENT

Antiviral treatment modifies the course of both varicella and herpes zoster. Antiviral drug resistance is rare but has occurred, primarily in children with HIV infection and other immunocompromising conditions where frequent relapse of VZV infections has resulted in multiple courses of antiviral therapy. Foscarnet and cidofovir may be useful for the treatment of acyclovir-resistant VZV infections, but consultation of an infectious disease specialist is recommended.

Varicella

The only antiviral drug available in liquid formulation that is licensed for treatment of varicella for pediatric use is acyclovir. Given the safety profile of acyclovir and its demonstrated efficacy in the treatment of varicella, treatment of all children, adolescents, and adults with varicella is acceptable. However, acyclovir therapy is not recommended routinely by the American Academy of Pediatrics for treatment of uncomplicated varicella in the otherwise healthy child because of the marginal benefit, the cost of the drug, and the low risk for complications of varicella. Oral therapy with acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) given as 4 doses/day for 5 days can be used to treat uncomplicated varicella in individuals at increased risk for moderate to severe varicella: nonpregnant individuals older than 12 yr of age and individuals older than 12 mo of age with chronic cutaneous or pulmonary disorders; individuals receiving short-term, intermittent, or aerosolized corticosteroid therapy; individuals receiving long-term salicylate therapy; and possibly secondary cases among household contacts. To be most effective, treatment should be initiated as early as possible, preferably within 24 hr of the onset of the exanthem. There is less clinical benefit if treatment is initiated more than 72 hr after onset of the exanthem. Acyclovir therapy does not interfere with the induction of VZV immunity. Acyclovir has been used to treat varicella in pregnant women; its safety for the fetus has not been established (see congenital varicella syndrome section). Some experts recommend the use of famciclovir or valacyclovir in older children who can swallow tablets. These drugs are highly active against VZV by the same mechanism as acyclovir and are better absorbed by the oral route than acyclovir. Valacyclovir (20 mg/kg/dose; maximum: 1,000 mg/dose, administered 3 times daily for 5 days) is licensed for treatment of varicella in children 2 to <18 yr of age, and both valacyclovir and famciclovir are approved for treatment of herpes zoster in adults.

Intravenous therapy is indicated for severe disease and for varicella in immunocompromised patients (even if begun more than 72 hr after onset of rash). Any patient who has signs of disseminated VZV, including pneumonia, severe hepatitis, thrombocytopenia, or encephalitis, should receive immediate treatment. IV acyclovir therapy (500 mg/m^2 every 8 hr) initiated within 72 hr of development of initial symptoms decreases the likelihood of progressive varicella and visceral dissemination in high-risk patients. Treatment is continued for 7-10 days or until no new lesions have appeared for 48 hr. Delaying antiviral treatment in high-risk individuals until it is obvious that prolonged new lesion formation is occurring is not advisable because visceral dissemination occurs during the same period.

Acyclovir-resistant VZV has been identified primarily in children infected with HIV. These children may be treated with intravenous foscarnet (120 mg/kg/day divided every 8 hr for up to 3 wk). The dose should be modified in the presence of renal insufficiency. Resistance to foscarnet has been reported with prolonged use. Cidofovir is also useful in this situation. Because of the increased toxicity profile of foscarnet and cidofovir, these 2 drugs should be initiated in collaboration with an infectious disease specialist.

Herpes Zoster

Antiviral drugs are effective for treatment of herpes zoster. In healthy adults, acyclovir (800 mg 5 times a day PO for 5-7 days), famciclovir (500 mg tid PO for 7 days), and valacyclovir (1,000 mg tid PO for 7 days) reduce the duration of the illness and the risk for development of postherpetic neuralgia. In otherwise healthy children, herpes zoster is a less-severe disease, and postherpetic neuralgia usually does not occur. Therefore, treatment of uncomplicated herpes zoster in the child

with an antiviral agent may not always be necessary, although some experts would treat with oral acyclovir (20 mg/kg/dose; maximum: 800 mg/dose) to shorten the duration of the illness. It is important to start antiviral therapy as soon as possible. Delay beyond 72 hr from onset of rash limits its effectiveness.

In contrast, herpes zoster in **immunocompromised** children can be severe, and disseminated disease may be life-threatening. Patients at high risk for disseminated disease should receive IV acyclovir (500 mg/m^2 or 10 mg/kg every 8 hr). Oral acyclovir, famciclovir, and valacyclovir are options for immunocompromised patients with uncomplicated herpes zoster, who are considered at low risk for visceral dissemination. Neuritis with herpes zoster should be managed with appropriate analgesics.

Use of corticosteroids in the treatment of herpes zoster in children is not recommended.

PROGNOSIS

Primary varicella has a mortality rate of 2-3 per 100,000 cases, with the lowest case fatality rates among children 1-9 yr of age (~1 death per 100,000 cases). Compared with these age groups, infants have a 4 times greater risk of dying and adults have a 25 times greater risk of dying. The most common complications among people who died from varicella were pneumonia, central nervous system complications, secondary infections, and hemorrhagic conditions. The mortality rate of untreated primary infection is 7-14% in immunocompromised children and may approach 50% in untreated adults with pneumonia.

Herpes zoster among healthy children has an excellent prognosis and is usually self-limited. Severe presentation with complications and sometimes fatalities can occur in immunocompromised children.

PREVENTION

VZV transmission is difficult to prevent, especially from persons with varicella, because a person with varicella is contagious for 24-48 hr before the rash is apparent. Herpes zoster is less infectious than varicella; nonetheless, transmission has been reported even in the absence of direct contact with the patient. Infection control practices, including caring for patients with varicella in isolation rooms with filtered air systems, are essential. All healthcare workers should have evidence of varicella immunity (Table 253-1). Unvaccinated healthcare workers without other evidence of immunity who have had a close exposure to VZV should be furloughed for days 8-21 after exposure because they are potentially infectious during this period.

Table 253-1 | Evidence of Immunity to Varicella

Evidence of immunity to varicella consists of any of the following:
- Documentation of age-appropriate vaccination with a varicella vaccine:
  - Preschool-age children (i.e., age ≥12 mo): 1 dose
  - School-age children, adolescents, and adults: 2 doses*
  - Laboratory evidence of immunity† or laboratory confirmation of disease
  - Birth in the United States before 1980§
  - Diagnosis or verification of a history of varicella disease by a healthcare provider¶
  - Diagnosis or verification of a history of herpes zoster by a healthcare provider

*For children who received their 1st dose at younger than age 13 yr and for whom the interval between the 2 doses was 28 or more days, the 2nd dose is considered valid.

†Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might yield false-negative results).

§For healthcare personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.

¶Verification of history or diagnosis of typical disease can be provided by any healthcare provider (e.g., school or occupational clinic nurse, nurse practitioner, physician assistant, or physician). For persons reporting a history of, or reporting with, atypical or mild cases, assessment by a physician or his/her designee is recommended, and 1 of the following should be sought: (1) an epidemiologic link to a typical varicella case or to a laboratory-confirmed case or (2) evidence of laboratory confirmation if it was performed at the time of acute disease. When such documentation is lacking, persons should not be considered as having a valid history of disease, because other diseases might mimic mild atypical varicella.

Vaccine

Varicella is a vaccine-preventable disease. Varicella vaccine contains live, attenuated VZV (Oka strain) and is indicated for subcutaneous administration. In the United States, varicella vaccine is recommended for routine administration as a 2 dose regimen to healthy children at ages 12-15 mo and 4-6 yr. Catch-up vaccination with the 2nd dose is recommended for children and adolescents who received only 1 dose. Vaccination with 2 doses is recommended for all persons without evidence of immunity. The minimum interval between the 2 doses is 3 mo for persons 12 yr of age or younger and 4 wk for older children, adolescents, and adults. Administration of varicella vaccine within 4 wk of measles-mumps-rubella (MMR) vaccination is associated with a higher risk for breakthrough disease; therefore, it is recommended that the varicella and MMR vaccines either be administered simultaneously at different sites or be given at least 4 wk apart. Varicella vaccine can be administered as a monovalent vaccine (for all healthy persons ≥12 mo of age) or as the quadrivalent measles-mumps- rubella-varicella (MMRV) vaccine (for children age 12 mo through 12 yr only).

Varicella vaccine is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine; pregnant women; persons with cell-mediated immune deficiencies, including those with leukemia, lymphoma, and other malignant neoplasms affecting the bone marrow or lymphatic systems; persons receiving immunosuppressive therapy; and persons who have a family history of congenital or hereditary immunodeficiency in 1st-degree relatives unless the immune competence of the potential vaccine recipient is demonstrated. Children with isolated humoral immunodeficiencies may receive varicella vaccine. The monovalent varicella vaccine has been studied in clinical trial settings in children with acute lymphocytic leukemia and certain solid tumors who are in remission. Protocols are available that define the timing of vaccination in terms of the length of time a patient has been in remission while receiving maintenance chemotherapy; when to interrupt maintenance chemotherapy, including therapy with corticosteroids, before and after vaccination; and the minimal acceptable lymphocyte and platelet counts at the time of vaccination. Because of the risk of severe vaccine-related complications, use of the vaccine in these specific populations of children should only be considered in settings where these protocols can be followed, antiviral therapy with acyclovir is readily available, and physicians have expertise with use of the vaccine in these populations.

The vaccine should be considered for HIV-infected children with a $CD4^+$ T-lymphocyte percentage ≥15%. These children should receive 2 doses of vaccine, 3 mo apart. Specific guidelines for immunizing these children should be reviewed before vaccination. Data indicate that varicella vaccine is 100% effective in preventing herpes zoster among children infected with HIV. MMRV should not be administered as a substitute for the component vaccines in HIV-infected children.

Zoster vaccine is licensed for use as a single immunization for prevention of herpes zoster and to decrease the frequency of postherpetic neuralgia among individuals 50 yr of age and older. It is not indicated for the treatment of zoster or postherpetic neuralgia.

Vaccine-Associated Adverse Events

Varicella vaccine is safe and well tolerated. The incidence of injection site complaints observed ≤3 days after vaccination was slightly higher after dose 2 (25%) than after dose 1 (22%). A mild vaccine-associated varicelliform rash was reported in approximately 1-5% of healthy vaccinees, consisting of 6-10 papular-vesicular, erythematous lesions with peak occurrence 8-21 days after vaccination. Serious adverse reactions confirmed to be caused by the vaccine strain are rare and include pneumonia, hepatitis, meningitis, recurrent herpes zoster, severe rash, and 2 deaths. Transmission of vaccine virus to susceptible contacts is a very rare event (9 documented occurrences from healthy vaccine recipients, all in the presence of a rash in the vaccine recipient). MMRV vaccine is associated with a greater risk for febrile seizures 5-12 days after the 1st dose among children 12-23 mo of age compared with

simultaneous MMR and varicella vaccines (1 extra febrile seizure for every 2,500 children vaccinated).

Postexposure Prophylaxis

Vaccine given to healthy children within 3 or 5 days after exposure (as soon as possible is preferred) is effective in preventing or modifying varicella. Varicella vaccine is now recommended for postexposure use and for outbreak control. Oral acyclovir administered late in the incubation period may modify subsequent varicella in the healthy child; however, its use in this manner is not recommended until it can be further evaluated.

High-titer anti-VZV immune globulin as postexposure prophylaxis is recommended for immunocompromised children, pregnant women, and newborns exposed to varicella. Since 2012 the product licensed for use in the United States is VariZIG. VariZIG is distributed in the United States by FFF Enterprises, Temecula, California (1-800-843-7477) or ASD Healthcare, Frisco Texas (800-746-6273). The recommended dose is 1 vial (125 units) for each 10 kg increment of body weight (maximum: 625 units), except for infants weighing ≤2 kg who should receive 0.5 vial. VariZIG should be given intramuscularly as soon as possible but may be efficacious up to 10 days after exposure.

Newborns whose mothers demonstrate varicella 5 days before to 2 days after delivery should receive VariZIG (0.5 vial for those weighing ≤2 kg and 1 vial for those weighing >2 kg). VariZIG is also indicated for pregnant women and immunocompromised persons without evidence of varicella immunity; hospitalized premature infants born at <28 wks of gestation (or weight <1,000 g) who were exposed to varicella, regardless of maternal varicella immunity; and hospitalized premature infants born at ≥28 wk of gestation who were exposed to varicella and whose mothers have no evidence of varicella immunity. If possible, adults should be tested for VZV IgG antibodies before VariZIG administration, because many adults with no clinical history of varicella are immune. Anti-VZV antibody prophylaxis may ameliorate disease but does not eliminate the possibility of progressive disease and does not ensure that varicella is not transmitted to close susceptible contacts; patients should be monitored and treated with acyclovir if necessary once lesions develop.

Close contact between a susceptible high-risk patient and a patient with herpes zoster is also an indication for VariZIG prophylaxis. Passive antibody administration or treatment does not reduce the risk for herpes zoster or alter the clinical course of varicella or herpes zoster when given after the onset of symptoms.

Although licensed pooled IVIG preparations contain anti-VZV antibodies, the titer varies from lot to lot. In situations in which administration of VariZIG does not appear possible, IVIG can be administered (400 mg/kg administered once within 10 days of exposure). Immunocompromised patients who have received high-dose IVIG (>400 mg/kg) for other indications within 2-3 wk before VZV exposure can be expected to have serum antibodies to VZV.

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Chapter 254

Epstein-Barr Virus

Hal B. Jenson

Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as **glandular fever,** it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness. Other infections may cause infectious mononucleosis-like illnesses.

ETIOLOGY

EBV is a double-stranded DNA virus that is a member of the γ-herpesviruses and causes >90% of cases of infectious mononucleosis. Two distinct types of EBV, **type 1 and type 2 (also called type A and type B),** have been characterized and have 70-85% sequence homology. EBV-1 is more prevalent worldwide, although EBV-2 is more common in Africa than in the United States and Europe. Both types lead to persistent, lifelong, latent infection. Dual infections with both types have been documented among immunocompromised persons. EBV-1 induces in vitro growth transformation of B cells more efficiently than does EBV-2, but no type-specific disease manifestations or clinical differences have been identified. Coacquisition of multiple EBV genotypes has been shown by heteroduplex tracking assays to occur commonly in otherwise healthy patients with infectious mononucleosis. However, only a single genotype tends to be cultured. It is unknown if this represents isolation of a predominant strain or if the strains that are not able to be cultured, using the transformation assay, are defective.

As many as 5-10% of **infectious mononucleosis–like illnesses** are caused by primary infection with cytomegalovirus, *Toxoplasma gondii,* adenovirus, hepatitis virus, primary HIV, and possibly rubella virus. In the majority of EBV-negative infectious mononucleosis-like illnesses, the exact cause remains unknown.

EPIDEMIOLOGY

EBV infects more than 95% of the world's population. It is transmitted primarily via oral secretions and may be transmitted via penetrative sexual intercourse. Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home childcare. Nonintimate contact, environmental sources, or fomites do not contribute to spread of EBV.

EBV is shed in oral secretions consistently for more than 6 mo after acute infection and then intermittently for life. As many as 20-30% of healthy EBV-infected persons excrete virus at any particular time. Immunosuppression permits reactivation of latent EBV; 60-90% of EBV-infected immunosuppressed patients shed the virus. EBV is also found in male and female genital secretions and, especially for EBV-2, is spread through sexual contact.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations of developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 yr of age. Among more affluent populations in industrialized countries, half of the population is infected by 6-8 yr of age with approximately 30% of infections during adolescence and young adulthood. In the United States, seroprevalence increases with age, from approximately 54% for 6-8 yr olds to 83% for 18-19 yr olds. Seroprevalence at each age is substantially higher for Mexican-Americans and non-Hispanic blacks than non-Hispanic whites. Large differences are seen by family income, with highest seroprevalence in children of families with lowest income.

The epidemiology of the illness of infectious mononucleosis is related to the age of acquisition of EBV infection. Primary infection with EBV during childhood is usually asymptomatic or mild and indistinguishable from other childhood infections; the clinical syndrome of infectious mononucleosis is practically unknown in undeveloped regions of the world. Primary EBV infection in adolescents and adults manifests in 30-50% of cases as the **classic triad** of fatigue, pharyngitis, and generalized lymphadenopathy, which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages but is rarely apparent in children younger than 4 yr of age, when most EBV infections are asymptomatic, or in adults older than 40 yr of age, when most individuals have already been infected by EBV. The true incidence of the syndrome of infectious mononucleosis is unknown but is estimated to occur in 20-70 per 100,000 persons/yr; in young adults, the incidence increases to approximately 100 per 100,000 persons/yr. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

PATHOGENESIS

After acquisition in the oral cavity, EBV initially infects crypt epithelial cells, which may contribute to the symptoms of pharyngitis. After

intracellular viral replication and cell lysis with release of new virions, virus spreads to contiguous structures such as the salivary glands, with eventual viremia and infection of B lymphocytes in the peripheral blood and the entire lymphoreticular system, including the liver and spleen. The atypical lymphocytes that are characteristic of infectious mononucleosis are CD8 T lymphocytes, which exhibit both suppressor and cytotoxic functions that develop in response to the infected B lymphocytes. This relative as well as absolute increase in CD8 lymphocytes results in a transient reversal of the normal 2:1 CD4/CD8 (helper/suppressor) T-lymphocyte ratio. Many of the clinical manifestations of infectious mononucleosis may result, at least in part, from cytokine release from the host immune response, which is effective in reducing the EBV load to <1 copy/105 circulating B lymphocytes, equivalent to <10 copies/μg of DNA from whole blood. The EBV load is more variable among immunocompromised persons and can be >4,000 copies/μg of DNA.

Epithelial cells of the uterine cervix may become infected by sexual transmission of the virus, although local symptoms have been described after sexual transmission. EBV is consistently found intracellularly in smooth muscle cells of leiomyosarcomas of immunocompromised persons, but not in leiomyosarcomas of immunocompetent persons.

EBV, like the other herpesviruses, establishes lifelong latent infection after the primary illness. The latent virus is carried in oropharyngeal epithelial cells and systemically in memory B lymphocytes as multiple episomes in the nucleus. The viral episomes replicate with cell division and are distributed to both daughter cells. Viral integration into the cell genome is not typical. Only a few viral proteins, including the EBV-determined nuclear antigens (EBNAs), are produced during latency. These proteins are important in maintaining the viral episome during the latent state. Progression to viral replication begins with production of EBV early antigens (EAs), proceeds to viral DNA replication, is followed by production of viral capsid antigen (VCA), and culminates in cell death and release of mature virions. Reactivation with viral replication occurs at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. Reactivation is apparently asymptomatic and not recognized to be accompanied by distinctive clinical symptoms.

ONCOGENESIS

EBV was the first human virus to be associated with malignancy. EBV infection may result in a spectrum of proliferative disorders ranging from self-limited, usually benign disease such as infectious mononucleosis to aggressive, nonmalignant proliferations such as the virus-associated hemophagocytic syndrome to lymphoid and epithelial cell malignancies. Benign EBV-associated proliferations include oral hairy leukoplakia, primarily in adults with AIDS, and lymphoid interstitial pneumonitis, primarily in children with AIDS. Malignant EBV-associated proliferations include nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, lymphoproliferative disorders, and leiomyosarcoma in immunodeficient states, including AIDS. There is no firm evidence of development of EBV quasispecies that would contribute to the pathogenesis of EBV-positive malignancies.

Nasopharyngeal carcinoma occurs worldwide but is 10 times more common in persons in southern China, where it is the most common malignant tumor among adult men. It is also common among whites in North Africa and Inuits in North America. Patients usually present with cervical lymphadenopathy, eustachian tube blockage, and nasal obstruction with epistaxis. All malignant cells of undifferentiated nasopharyngeal carcinoma contain a high copy number of EBV episomes. Persons with undifferentiated and partially differentiated, nonkeratinizing nasopharyngeal carcinomas have elevated EBV antibody titers that are both diagnostic and prognostic. High levels of immunoglobulin (Ig) A antibody to EA and VCA may be detected in asymptomatic individuals and can be used to follow response to tumor therapy (Table 254-1). Cells of well-differentiated, keratinizing nasopharyngeal carcinoma contain a low number of or no EBV genomes; these persons have EBV serologic patterns similar to those of the general population.

CT and MR images are helpful in both identifying and defining masses in the head and neck. The diagnosis is established by biopsy of the mass or of a suspicious cervical lymph node. Surgery is important for staging and diagnosis. Radiation therapy is effective for control of the primary tumor and regional nodal metastases. Chemotherapy with 5-fluorouracil, cisplatin, and methotrexate is effective but not always curative. The prognosis is good if the tumor is localized.

Endemic (African) Burkitt lymphoma, often found in the jaw, is the most common childhood cancer in equatorial East Africa and New

Table 254-1 Correlation of Clinical Status and Serologic Responses to Epstein-Barr Virus Infection

	Serologic Response					
		EBV-Specific Antibody				
CLINICAL STATUS	HETEROPHILE ANTIBODIES (QUALITATIVE TEST)	IgM-VCA	IgG-VCA	EA-D	EA-R	EBNA
Negative reaction	–	<1:8*	<1:10*	<1:10*	<1:10*	<1:2.5*
Susceptible	–	–	–	–	–†	–
Acute primary infection: infectious mononucleosis	+	1:32 to 1:256	1:160 to 1:640	1:40 to 1:160	–†	– to 1:2.5
Recent primary infection: infectious mononucleosis	±	– to 1:32	1:320 to 1:1,280	1:40 to 1:160	–†	1:5 to 1:10
Remote infection	–	–	1:40 to 1:160	–‡	– to 1:40	1:10 to 1:40
Reactivation: immunosuppressed or immunocompromised	–	–	1:320 to 1:1,280	–‡	1:80 to 1:320	– to 1:160
Burkitt lymphoma	–	–	1:320 to 1:1,280	–‡	1:80 to 1:320	1:10 to 1:80
Nasopharyngeal carcinoma	–	–	1:320 to 1:1,280	1:40 to 1:160	–§	1:20 to 1:160

The data were obtained from numerous studies. Individual responses outside the characteristic range may occur.

*Or the lowest test dilution.

†In young children and adults with asymptomatic seroconversion, the anti–early antigen response may be mainly to the EA-R component.

‡A minority of individuals will have the anti–early antigen response mainly to the EA-D component.

§A minority of individuals will have the anti–early antigen response mainly to the EA-R component.

–, Negative; +, positive; EA-D, diffuse staining component of early antigen; EA-R, cytoplasmic restricted component of early antigen; EBNA, EBV-determined nuclear antigens; EBV, Epstein-Barr virus; IgG, immunoglobulin G; IgM, immunoglobulin M; VCA, viral capsid antigen.

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Guinea (see Chapter 496.2). The median age at onset is 5 yr. These regions are holoendemic for *Plasmodium falciparum* malaria and have a high rate of EBV infection early in life. The constant malarial exposure acts as a B-lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation with EBV infection, impairs T-lymphocyte surveillance of EBV-infected B lymphocytes, and increases the risk for developing Burkitt lymphoma. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of nonendemic (sporadic or American) Burkitt lymphoma cases. Individuals with Burkitt lymphoma have unusually and characteristically high levels of antibody to VCA and EA that correlate with the risk for developing tumor (see Table 254-1).

All cases of Burkitt lymphoma, including those that are EBV-negative, are monoclonal and demonstrate chromosomal translocation of the c-*myc* protooncogene to the constant region of the immunoglobulin heavy-chain locus, t(8;14), to the κ constant light-chain locus, t(2;8), or to the λ constant light-chain locus, t(8;22). This results in the deregulation and constitutive transcription of the c-*myc* gene with overproduction of a normal c-*myc* product that autosuppresses c-*myc* production on the untranslocated chromosome.

The incidence of **Hodgkin disease** peaks in childhood in developing countries and in young adulthood in developed countries. Levels of EBV antibodies are consistently elevated preceding development of Hodgkin disease; only a small minority of patients is seronegative for EBV. Infection with EBV increases the risk for Hodgkin disease by a factor of 2-4, with the risk of developing Hodgkin disease peaking at 2.4 yr following infectious mononucleosis. EBV is associated with more than half of cases of mixed cellularity Hodgkin disease and approximately one quarter of cases of the nodular sclerosing subtype, and is rarely associated with lymphocyte-predominant Hodgkin disease. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin disease.

Failure to control EBV infection may result from host immunologic deficits. The prototype is the **X-linked lymphoproliferative syndrome (Duncan syndrome),** an X chromosome–linked recessive disorder of the immune system associated with severe, persistent, and sometimes fatal EBV infection (see Chapter 123). Approximately 65% of these male patients die of disseminated and fulminating lymphoproliferation involving multiple organs at the time of primary EBV infection. Surviving patients acquire hypogammaglobulinemia, B-cell lymphoma, or both. Most patients die by 10 yr of age.

Numerous congenital and acquired immunodeficiency syndromes are associated with an increased incidence of EBV-associated B-lymphocyte lymphoma, especially central nervous system lymphoma, and leiomyosarcoma. The incidence of lymphoproliferative syndromes parallels the degree of immunosuppression. A decline in T-cell function evidently permits EBV to escape from immune surveillance. Congenital immunodeficiencies predisposing to EBV-associated lymphoproliferation include the X-linked lymphoproliferative syndrome, common-variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. Individuals with acquired immunodeficiencies resulting from anticancer chemotherapy, immunosuppression after solid organ or bone marrow transplantation, or HIV infection have a significantly increased risk for EBV-associated lymphoproliferation. The lymphomas may be focal or diffuse and are usually histologically polyclonal but may become monoclonal. Their growth is not reversed on cessation of immunosuppression.

EBV is found intracellularly in all of the smooth muscle cells of leiomyosarcomas occurring in immunocompromised persons, including HIV-infected patients and transplant recipients, but not in leiomyosarcomas occurring in immunocompetent persons.

EBV is also associated with carcinoma of the salivary glands. Other tumors putatively associated with EBV include some T-lymphocyte lymphomas (including lethal midline), angioimmunoblastic lymphadenopathy-like lymphoma, thymomas and thymic carcinomas derived from thymic epithelial cells, supraglottic laryngeal carcinomas, lymphoepithelial tumors of the respiratory tract and gastrointestinal tract, and gastric adenocarcinoma. The precise contribution of EBV to these various malignancies is not well defined.

CLINICAL MANIFESTATIONS

The incubation period of infectious mononucleosis in adolescents is 30-50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. In older patients, the onset of illness is usually insidious and vague. Patients may complain of malaise, fatigue, acute or prolonged (>1 wk) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1-2 wk. Lytic infection of B lymphocytes and crypt epithelial cells results in high salivary levels and oral shedding. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

The classic physical examination findings are generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy occurs most commonly in the anterior and posterior cervical nodes and the submandibular lymph nodes and less commonly in the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy is particularly suggestive of infectious mononucleosis. Symptomatic hepatitis or jaundice is uncommon, but elevated liver enzymes are very common. Splenomegaly to 2-3 cm below the costal margin is typical (15-65% of cases) and is seen in most cases by ultrasonography; massive enlargement is uncommon.

The sore throat is often accompanied by moderate to severe pharyngitis with marked tonsillar enlargement, occasionally with exudates (Fig. 254-1). Palatal petechiae at the junction of the hard and soft palate are frequently seen. The pharyngitis resembles that caused by streptococcal infection. Other clinical findings may include rashes and edema of the eyelids.

Rashes are usually maculopapular and have been reported in 3-15% of patients. Patients with infectious mononucleosis treated with ampicillin or amoxicillin may experience **"ampicillin rash,"** which may occur with other β-lactam antibiotics. This morbilliform, vasculitic rash is probably immune mediated and resolves without specific treatment. EBV is also associated with **Gianotti-Crosti syndrome,** a symmetric rash on the cheeks with multiple erythematous papules, which may coalesce into plaques and persist for 15-50 days. The rash has the appearance of atopic dermatitis and may appear on the extremities and buttocks.

Infants coinfected with HIV acquire EBV infection at an earlier age, have higher EBV plasma loads that are slower to resolve, and more frequently develop pneumonia and hepatosplenomegaly and require hospitalization compared to HIV-negative infants.

DIAGNOSIS

The diagnosis of infectious mononucleosis implies primary EBV infection. A presumptive diagnosis may be made by the presence of typical clinical symptoms with atypical lymphocytosis in the peripheral blood.

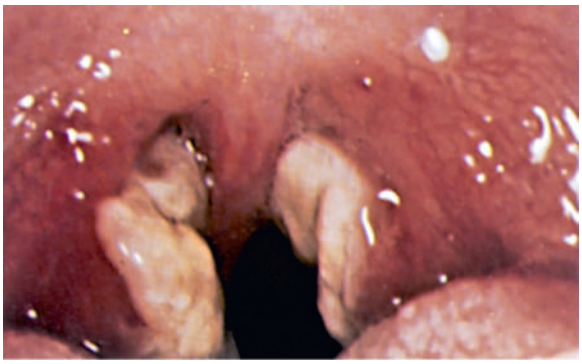

Figure 254-1 Tonsillitis with membrane formation in infectious mononucleosis. *(Courtesy of Alex J. Steigman, MD.)*

The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

Culture of EBV is tedious and requires 4-6 wk. The culture method is the **transformation assay,** which is performed by cocultivating oropharyngeal or genital secretions, peripheral blood (10-30 mL), or tumor with human umbilical cord lymphocytes. The cultures are observed for 6 wk for signs of **cell transformation:** proliferation and rapid growth, mitotic figures, large vacuoles, granular morphology, and cell aggregation. EBV **immortalizes** the umbilical cord cells, resulting in cell lines that harbor the EBV strain isolated from the patient and can be maintained in vitro in perpetuity.

Differential Diagnosis

Infectious mononucleosis-like illnesses may be caused by primary infection with cytomegalovirus, *T. gondii,* adenovirus, hepatitis virus, HIV, or possibly rubella virus. Cytomegalovirus infection is a particularly common cause in adults. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of infectious mononucleosis but is not associated with hepatosplenomegaly. Approximately 5% of cases of EBV-associated infectious mononucleosis have positive throat cultures for group A *Streptococcus*, representing pharyngeal streptococcal carriage. Failure of a patient with streptococcal pharyngitis to improve within 48-72 hr should evoke suspicion of infectious mononucleosis. The most serious problem in the diagnosis of acute illness arises in the occasional patient with extremely high or low white blood cell counts, moderate thrombocytopenia, and even hemolytic anemia. In these patients, bone marrow examination and hematologic consultation are warranted to exclude the possibility of leukemia.

Laboratory Tests

In >90% of cases there is leukocytosis of 10,000-20,000 cells/μL, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20-40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, **atypical lymphocytes** are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many of the infections usually causing lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Other syndromes associated with atypical lymphocytosis include acquired cytomegalovirus infection (in contrast to congenital cytomegalovirus infection), toxoplasmosis, viral hepatitis, rubella, roseola, mumps, tuberculosis, typhoid, *Mycoplasma* infection, and malaria, as well as some drug reactions. Mild thrombocytopenia to 50,000-200,000 platelets/μL occurs in more than 50% of patients, but only rarely is associated with purpura. Mild elevation of hepatic transaminases occurs in approximately 50% of uncomplicated cases, but is usually asymptomatic without jaundice.

Heterophile Antibody Test

Heterophile antibodies agglutinate cells from species different from those in the source serum. The transient heterophile antibodies seen in infectious mononucleosis, also known as **Paul-Bunnell antibodies**, are IgM antibodies detected by the Paul-Bunnell-Davidsohn test for sheep red cell agglutination. The heterophile antibodies of infectious mononucleosis agglutinate sheep or, for greater sensitivity, horse red cells but not guinea pig kidney cells. This adsorption property differentiates this response from the heterophile response found in patients with serum sickness, rheumatic diseases, and some normal individuals. Titers of >1 : 28 or >1 : 40, depending on the dilution system used, after absorption with guinea pig cells are considered positive.

Heterophile antibody tests are positive in 75% of cases in the 1st wk and 90-95% of cases in the 2nd wk. Results of the sheep red cell agglutination test are often positive for several months after infectious mononucleosis; those of the horse red cell agglutination test may be positive for as long as 2 yr. The most widely used method is the qualitative rapid slide test using horse erythrocytes. It detects heterophile antibody in 90% of cases of EBV-associated infectious mononucleosis in adolescents and adults but in only up to 50% of cases in children younger than 4 yr of age because they typically develop a lower titer. From 5-10% of cases of infectious mononucleosis syndromes are not caused by EBV and are not uniformly associated with a heterophile antibody response. The false-positive rate is <10%, usually resulting from erroneous interpretation. If the heterophile test result is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated. Nonetheless, a positive heterophile test, together with classic clinical manifestations of mononucleosis, helps confirm the diagnosis in adolescents and adults. Primary HIV infection may also be associated with a positive heterophile test and a mononucleosis-like clinical picture.

SPECIFIC EPSTEIN-BARR VIRUS ANTIBODIES

EBV-specific antibody testing is useful to confirm acute EBV infection, especially in heterophile-negative cases, or to confirm past infection and determine susceptibility to future infection. Several distinct EBV antigen systems have been characterized for diagnostic purposes (Fig. 254-2 and see Table 254-1). The EBNA, EA, and VCA antigen systems are most useful for diagnostic purposes. The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 wk and occasionally up to 3 mo. The laboratory must take steps to remove rheumatoid factor, which may cause a false-positive IgM VCA result. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

Anti-EA antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Antibodies to the diffuse-staining component of EA, EA-D, are found transiently in 80% of patients during the acute phase of infectious mononucleosis and reach high titers in patients with nasopharyngeal carcinoma. Antibodies to the cytoplasmic-restricted component of EA, EA-R, emerge transiently in the convalescence from infectious mononucleosis and often attain high titers in patients with EBV-associated Burkitt lymphoma, which in the terminal stage of the disease may be exceeded by antibodies to EA-D. High levels of antibodies to EA-D or EA-R may be found also in immunocompromised patients with persistent EBV infections and active EBV replication. Anti-EBNA antibodies are the last to develop in infectious mononucleosis and gradually

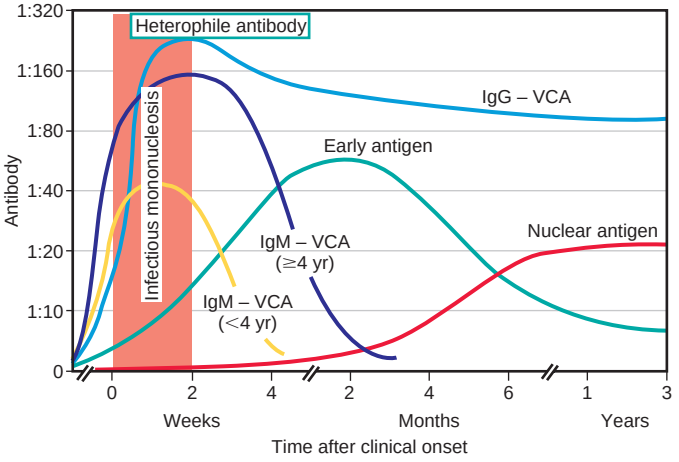

Figure 254-2 Schematic of the development of antibodies to various Epstein-Barr virus antigens in patients with infectious mononucleosis. Antibody titers are calculated as geometric mean values expressed as reciprocals of the serum dilution. The immunoglobulin M (IgM) response to viral capsid antigen (VCA) is divided because of the significant differences noted according to age of the patient. *IgG,* immunoglobulin G. *(Reprinted with permission from Jenson HB: Epstein-Barr virus. In Detrick B, Hamilton RG, Folds JD, editors:* Manual of molecular and clinical laboratory immunology, *ed 7. Washington, DC, 2006, American Society for Microbiology.)*

appear 3-4 mo after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3-4 mo previously. The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is the most valuable and specific serologic test for the diagnosis of acute EBV infection and is generally sufficient to confirm the diagnosis.

TREATMENT

There is no specific treatment for infectious mononucleosis. The mainstays of management are rest, encouraging adequate fluid and nutrition intake, and symptomatic treatment with acetaminophen or nonsteroidal antiinflammatory agents to manage fever, throat discomfort, and malaise. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be allowed to begin resumption of normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise against participation in contact sports and strenuous athletic activities during the 1st 2-3 wk of illness or while splenomegaly is present.

Short courses of corticosteroids (<2 wk) may be helpful for selected complications of infectious mononucleosis, but this use has not been evaluated critically. Some appropriate indications include incipient airway obstruction, thrombocytopenia with hemorrhaging, autoimmune hemolytic anemia, seizures, and meningitis. A recommended regimen is prednisone 1 mg/kg/day (maximum: 60 mg/day) or equivalent for 7 days and tapered over another 7 days. There are no controlled data showing efficacy of corticosteroids in any of these conditions. In view of the potential and unknown hazards of immunosuppression for a virus infection with oncogenic complications, corticosteroids should not be used in uncomplicated cases of infectious mononucleosis.

Antiviral therapy is not recommended. Therapy with high doses of acyclovir, with or without corticosteroids, decreases viral replication and oropharyngeal shedding during the period of administration but does not reduce the severity or duration of symptoms or alter the eventual outcome.

COMPLICATIONS

Very few patients with infectious mononucleosis experience complications. The most feared complication is subcapsular splenic hemorrhage or splenic rupture, which occurs most frequently during the 2nd wk of the disease at a rate of <0.5% of cases in adults; the rate in children is unknown but is probably much lower. Rupture is commonly related to trauma, which is often mild, and is rarely fatal. Swelling of the tonsils and oropharyngeal lymphoid tissue may be substantial and may cause airway obstruction that manifests as drooling, stridor, and interference with breathing. Airway compromise with progressive symptoms occurs in <5% of cases and is a common indication for hospitalization with infectious mononucleosis. It may be managed by elevating the head of the bed, intravenous hydration, humidified air, and systemic corticosteroids. Respiratory distress with incipient or actual airway occlusion should be managed by tonsilloadenoidectomy and endotracheal intubation for 12-24 hr in an intensive care setting.

Many uncommon and unusual neurologic conditions are reported to be associated with EBV infectious mononucleosis. Headache is present in about half of cases, with severe neurologic manifestations, such as seizures and ataxia, in 1-5% of cases. Perceptual distortions of sizes, shapes, and spatial relationships, known as the **Alice-in-Wonderland syndrome (metamorphopsia),** may be a presenting symptom. There may be meningitis with nuchal rigidity and mononuclear cells in the cerebrospinal fluid, facial nerve palsy, transverse myelitis, and encephalitis. Most patients with encephalitis from EBV, however, do not demonstrate the common symptoms of infectious mononucleosis.

Guillain-Barré syndrome or Reye syndrome may follow acute illness. Hemolytic anemia, often with a positive Coombs test result and with cold agglutinins specific for red cell antigen i, occurs in 3% of cases. The onset is typically in the 1st 2 wk of illness and lasts for <1 mo. Aplastic anemia is a rare complication that usually presents 3-4 wk after the onset of illness, usually with recovery in 4-8 days, but some cases do require bone marrow transplantation. Mild thrombocytopenia and neutropenia are common, but severe thrombocytopenia (<20,000 platelets/μL) or severe neutropenia (<1,000 neutrophils/μL) is rare. Myocarditis or interstitial pneumonia may occur, both resolving in 3-4 wk. Other rare complications include pancreatitis, parotitis, and orchitis.

PROGNOSIS

The prognosis for complete recovery is excellent. The major symptoms typically last 2-4 wk followed by gradual recovery within 2 mo of onset of symptoms. Individuals often harbor multiple strains of EBV and second infections with a different type of EBV (type 1 or type 2) have been demonstrated in immunocompromised persons, but symptoms or second clinical episodes of infectious mononucleosis have not been documented. Cervical lymphadenopathy and fatigue may resolve more slowly. Prolonged and debilitating fatigue, malaise, and some disability that may wax and wane for several weeks to 6 mo are common complaints even in otherwise unremarkable cases. Occasional persistence of fatigue for a few years after infectious mononucleosis is well recognized. There is no convincing evidence linking EBV infection or EBV reactivation to chronic fatigue syndrome (see Chapter 121).

PREVENTION

It is impractical to try to prevent EBV infection because the virus is ubiquitous and the majority of the population is EBV-positive. A recombinant EBV subunit glycoprotein 350 candidate vaccine in a 3 dose regimen shows promise to prevent infectious mononucleosis and potentially EBV-associated malignancies as well.

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Chapter 255

Cytomegalovirus

William J. Britt

Human cytomegalovirus (CMV) is ubiquitous in the population, and once infected, individuals remain persistently infected for life with intermittent excretion of infectious virus. Although CMV rarely causes symptoms in normal individuals, it is an important cause of morbidity, and in some cases death, in immunocompromised hosts. CMV remains a well-recognized cause of disease in the newborn infant following intrauterine infection (congenital CMV) and the allograft recipients undergoing posttransplantation immunosuppression. CMV has emerged as the most common opportunistic infection in HIV/AIDS patients prior to the advent of highly active retroviral therapy. Case reports also indicate that invasive CMV infections can be observed in patients treated with immunosuppressive biologics such as anti–tumor necrosis factor antibodies. In each of these clinical situations, the association of disease with CMV infection has been linked to high levels of virus replication and end-organ disease, usually following virus dissemination. In contrast, there is likely another group of disease states associated with chronic effects of persistent CMV infection that reflects the robust inflammatory response induced by this virus. Such associations have included coronary artery disease, transplant vasculopathy and cardiac allograft loss, tubular sclerosis and renal allograft loss, exacerbations of inflammatory bowel disease, and possibly some cancers such as glioblastoma.

THE VIRUS AND ITS INTERACTION WITH THE HOST

CMV is the largest of the human herpesvirus with an estimated size of 190 nm. The 230-kb double-stranded DNA genome is approximately

50% larger than the herpes simplex virus genome and encodes more than 100 unique virion proteins and an unknown number of nonstructural proteins. Viral DNA replication takes place in the nucleus of the infected cell followed by virus assembly in both the nucleus and cytoplasm. The structure of the virus is typical of herpesviruses and includes a complex envelope composed of host cell–derived membrane studded with virion glycoproteins, an amorphous area between the envelope and the capsid called the tegument layer, and an icosahedral capsid that contains the virion DNA. The tegument layer is highly immunogenic and induces strong adaptive immune responses, including CMV-specific $CD8^+$ cytotoxic T lymphocytes that are thought to play a pivotal role in controlling CMV replication in the infected host. Likewise, the protein components of the viral envelope are also immunogenic and believed to induce protective antibody responses that can be most closely correlated with virus neutralization. In vivo, CMV appears to replicate in nearly all tissue and cell types, whereas in vitro productive virus replication (production of infectious progeny) occurs in primary cells derived from epithelial tissue and the dermis. Literature from nearly 3 decades ago suggested that each strain of CMV isolated from epidemiologically unrelated individuals was genetically unique, a finding suggesting that an infinite number of distinct viruses existed in the human population. New evidence suggests that CMV exists as genetically diverse swarms within an individual because CMV DNA synthesis is fraught with error rates that are much higher than has been thought; alternately an individual may acquire a library of CMV variants during each exposure and infection. An important finding supportive of this latter possibility is that reinfection of previously infected individuals with new strains of CMV is commonplace. These observations have led many to argue that CMV must express an armamentarium of immune evasion functions that allow it to remain hidden from protective host immunity. This relationship between host and virus is best illustrated by the finding that a persistently infected individual over years can maintain a stable virus load, unwavering antiviral antibody responses, and, in some cases, up to 15% of a total peripheral blood $CD8^+$ cytotoxic T-lymphocyte activity dedicated to recognition of CMV-infected cells.

EPIDEMIOLOGY

CMV infections are acquired through several settings: (1) community exposure, (2) nosocomial transmission, and (3) intrauterine infection. Community acquisition occurs throughout life and is linked by exposure to CMV present in saliva and urine. Peaks in exposure occur during childhood and in adolescents and young adults, presumably in the latter cases secondary to sexual activity. Common routes of infection of the young infant include perinatal exposure to infected genital secretions during birth and ingestion of breast milk containing CMV. Breastfeeding is the most common route of CMV infection in early childhood. Ingestion of breast milk from seropositive women results in a rate of infection of approximately 60-70% in infants. Infection is most common during the 1st 6 mo of breastfeeding, but the risk continues for the duration of breastfeeding. Infants infected through breast milk excrete virus in the saliva and urine for prolonged periods of time measured in months to years and thus serve as a reservoir of virus for spread to other infants, children, and adults. After this period of intense exposure to CMV during the 1st yr of life, infection in the remainder of childhood and early teenage years depends on specific exposures, such as enrollment in group childcare facilities and/or exposure to infected, similarly aged siblings. Up to 50% of young infants and children attending group care facilities can be excreting CMV, a source of virus that can result in infection of uninfected children enrolled in the facility, and in some cases, the workers in the facility. Furthermore, once infected, infants can then readily transmit virus to their parents and siblings. Throughout childhood and early adulthood, CMV is transmitted by exposure to saliva and urine. However, in adolescence and early adulthood there is a spike in infection possibly associated with sexual exposure. CMV is considered a sexually transmitted infection.

Nosocomial infections with CMV are well described and follow exposure to blood products containing CMV and less commonly through allograft transplantation following transplantation of an organ from a CMV infected donor. Prior to improvements in blood banking that limited the number of leukocytes in red blood transfusions, transmission of CMV by blood transfusion was not uncommon and was closely related to the volume of blood that was transfused. Transfusion-acquired CMV infections often resulted in symptomatic illness, with laboratory findings including hepatitis and thrombocytopenia in children and adults. In newborn infants lacking antibodies to CMV secondary to being born to women without seroimmunity to CMV or extreme prematurity, severe, sometimes fatal infections have developed. Similarly, immunocompromised patients who received CMV containing blood were also at risk for severe infection. Current methodologies of leukocyte depletion and the use of blood products from CMV seronegative donors have greatly decreased the incidence of transfusion-associated CMV infections. Finally, CMV transmission through infected allografts is well described, and infections arising from CMV transferred in the allograft are a major cause of morbidity in the early and late period after transplantation. Severe infections and graft loss are more often associated with mismatches between the donor and recipient, for instance, if the donor has a history of CMV infection (and is therefore positive for CMV) and the recipient has not been exposed to CMV (and is therefore negative for CMV), there is a D+/R– mismatch. Even with effective antiviral therapy, CMV infection remains linked to long-term graft dysfunction and graft loss, a particularly important problem in cardiac and lung transplant recipients.

Congenital CMV infection (present at birth) occurs following intrauterine transmission of CMV. Rates of congenital infection between 0.5-1.0% have been routinely reported in the United States. Rates as high as 2% in some areas in Asia and Africa have also been described. CMV is thought to be transferred to the developing fetus following hematogenous spread of the virus to the placenta, presumably followed by cell-free transfer of virus to the fetal blood system. The rate of transmission to the fetus is approximately 30% in women undergoing primary infection during pregnancy, whereas in utero infections also occur in previously immune women (nonprimary infection) albeit at a reduced rate on the order of 1-2%. This later rate is an estimate because a precise rate following nonprimary maternal infection has not been established. It is important to note that although the rate of transmission of CMV is more frequent following primary maternal infection, the absolute number of congenitally infected infants born to women with nonprimary infections in most populations outnumber those resulting from primary maternal infection by 3-4–fold. This is particularly true in Africa, South America, and Asia, where maternal seroimmunity to CMV often exceeds 95%. Interestingly, these populations also have the highest rates of congenital CMV infections. The source of nonprimary infection is also somewhat controversial. Older reports suggested it followed reactivation (recurrence) of virus infection in seroimmune women, whereas more recent literature has demonstrated that reinfection by genetically distinct strains of CMV occurs in previously infected women and that these strains can be transmitted to the developing fetus. In some studies, the reinfection rates are approximately 15-20% with annualized rates as high as 25%. Thus, immunity to CMV is far from protective, although it appears to decrease the risk of transmission to the developing fetus.

Mechanisms of Disease Associated with Cytomegalovirus Infections

The mechanism(s) of disease associated with CMV infections remain undefined for most clinical syndromes that follow CMV infection. Several reasons have contributed to the overall lack of understanding of the pathogenesis of CMV infections and include (1) the asymptomatic nature of infections in almost all normal individuals, (2) the complexity of the underlying disease processes in immunocompromised hosts that often confounds the assignment of specific manifestations of CMV infection, (3) limitations of observational studies in humans, and (4) the species-specific tropism of human CMV. Although CMV replicates in a limited number of cell types in vitro, CMV inclusions, antigens, and nucleic acids can be demonstrated in almost organ systems and cell types in individuals with severe, disseminated infections. The virus does

not exhibit specific cellular or organ system tropism in vivo. Hematogenous dissemination is usually associated with cell-associated virus, and significant levels of plasma virus are usually detected only in severely immunocompromised hosts. Virus and viral DNA can be recovered from neutrophils, monocytes, and endothelial cells. High levels of virus replication can result in end-organ disease, presumably secondary to direct virus-mediated cellular damage. These manifestations of CMV infections are thought to result from uncontrolled virus replication and dissemination secondary to deficits in innate and adaptive immune responses to CMV. In some cases, clinical disease has been observed in patients without significant levels of virus replication, a finding suggesting indirect mechanisms of disease such as immunopathologic responses to CMV. Such a mechanism was clearly operative in patients with immune recovery vitreitis, a pathologic T-lymphocyte–mediated response to CMV in HIV/AIDS patients with CMV retinitis that closely followed the reconstitution of their virus-specific T-lymphocyte responses following active retroviral therapy. Likewise, the level of virus replication has not been closely correlated with several chronic diseases thought to be linked to CMV, an observation that is consistent with indirect mechanisms of disease such as immunopathologic responses.

From early observations in patients with invasive CMV infections in allograft recipients it was apparent that immunosuppressive therapies that resulted in altered T-lymphocyte function predisposed these patients to severe infections. Definitive evidence consistent with this mechanism was provided by a clinical study that demonstrated that in vitro expanded, CMV-specific cytotoxic T lymphocytes could limit invasive infection in hematopoietic cell transplant recipients. Invasive infections such as retinitis and colitis in HIV/AIDS patients with very low $CD4^+$ T-lymphocyte counts also clearly demonstrated the importance of T-lymphocyte responses and invasive CMV infections. Other studies in solid organ transplant recipients have demonstrated that the passive transfer of immune globulins containing high titers of anti-CMV antibodies could provide some degree of protection from invasive disease, a finding that was consistent with the proposed role of antiviral antibodies in limiting CMV dissemination and disease in animal models of invasive CMV infections. The importance of innate immune responses such as natural killer cells and γΔ T lymphocytes in limiting invasive infections has been well documented in representative animal models, but definitive evidence for a key role in resistance to CMV infections in humans is limited. Lastly, effector molecules such as γ-interferon appear to a play an important role in controlling local CMV infections in animal models, but evidence of a similar role in humans has not been shown experimentally.

The control of acute CMV infection is clearly dependent on an effective adaptive immune response; however, even a vigorous T-lymphocyte response is not sufficient to eliminate CMV from the infected host as CMV persists for the lifetime of the host either as a low-level chronic infection or as a latent infection with limited expression of its genome. The inability of the host to clear CMV remains incompletely understood, but the large array of immune evasion functions encoded by this virus likely contributes to the blunted innate and adaptive immune response. These functions include inhibition of apoptotic functions of infected cells, inhibition of interferon-regulated responses, inhibition of natural killer cell activation, downregulation of class I major histocompatibility complex expression, inhibition of class II major histocompatibility complex function, and mechanisms to limit antibody recognition of envelope proteins such as carbohydrate masking of antibody recognition sites and extensive variation in amino acid sequences in virion envelope proteins. Although each of these functions by itself could be expected to have limited effects on virus clearance by the immune system, when acting in concert they likely provide the virus an advantage that leads to its persistence.

CLINICAL MANIFESTATIONS

In the overwhelming majority of normal patients with acute CMV infections there are no specific symptoms or clinical findings. In patients with symptomatic, acute CMV infection, clinical findings are consistent with a mononucleosis-like syndrome, with fatigue and occasionally cervical adenopathy. Up to 20% of heterophile antibody negative cases of mononucleosis could be attributed to CMV. Laboratory findings could include mild elevation of hepatic transaminases and decreased platelet counts.

Immunocompromised Host

The clinical presentation of CMV infection in immunocompromised hosts often reflects the magnitude of the immunodeficiency. Profoundly immunocompromised hosts such as hematopoietic cell allograft recipients can present with disseminated infection and clinical manifestations reflecting the involvement of multiple organ systems including liver, lung, gastrointestinal tract, and rarely the central nervous system. Organ-threatening and life-threatening disease is not infrequent. In less-immunocompromised patients such as most solid organ transplant recipients, CMV infection can present with fever, hematologic abnormalities including leukopenia and thrombocytopenia, and mild hepatocellular dysfunction. In contrast to renal and liver solid organ transplant recipients, heart–lung and lung transplant recipients are at high risk for severe manifestations from CMV infection, presumably because the transplanted organ is a site of virus replication and disease. Prior to the use of antivirals for prophylaxis of allograft recipients, clinical disease usually developed between 30 and 60 days posttransplantation. More recently, prolonged antiviral prophylaxis has nearly eliminated CMV disease in most solid-organ transplants but late manifestations of CMV disease can be seen after discontinuation of the antiviral prophylaxis. These late manifestations are most worrisome in hematopoietic cell recipients, as they may signal deficits in graft function leading to invasive CMV infections. Finally, long-term graft function has been reported to be influenced by CMV infection. This has been most well studied in the renal allograft recipients but has been seen perhaps most dramatically in heart transplant recipients, where CMV is believed to play a major role in transplant vascular sclerosis, a vasculopathy of the coronary arteries in the allograft, leading to loss of the transplanted heart.

Congenital Infection

Congenital infection with CMV can present with symptomatic infections (Table 255-1) in approximately 10% of infected newborns, whereas 90% of infected infants will have no clinical manifestations of infection in the newborn period. Severe multiorgan disease is

Table 255-1 Findings in Infants with Symptomatic Congenital Cytomegalovirus Infection Identified Through Newborn Screening Program*

	PERCENTAGE (%) OF INFANTS
CLINICAL FINDINGS	
Prematurity (<37 wk)	24
Jaundice (direct bilirubin >2 mg/dL)	42
Petechiae	54
Hepatosplenomegaly	19
Purpura	3
Microcephaly	35
Small gestational age	28
1 Clinical finding	41
2 Clinical findings	59
LABORATORY FINDINGS	
Elevated alanine aminotransferase (>80 IU/mL)	71
Thrombocytopenia (<100,000/μL)	43
Direct hyperbilirubinemia (>2 mg/dL)	54
Head CT abnormalities	42

*Findings in 70 infants with symptomatic congenital CMV infection identified during the newborn screening program for infants with congenital CMV infection performed at the University of Alabama Hospitals over an approximate 20 yr interval.

infrequent and occurs in less than 5% of infants with congenital CMV infections. The clinical findings of infants with symptomatic congenital CMV infections can include hepatosplenomegaly, petechial rashes, jaundice, and in some cases microcephaly. These findings were utilized for natural history studies to classify infants as having symptomatic or asymptomatic infections; however, several authors have included intrauterine growth restriction as a finding of symptomatic congenital CMV infection. Laboratory findings include direct hyperbilirubinemia, elevation of hepatic transaminases, thrombocytopenia, anemia, and abnormal findings on cranial ultrasonography. If cerebrospinal fluid is obtained, there can be evidence of encephalitis with elevation of mononuclear cell number and in some cases, elevation of cerebrospinal fluid protein. A small number of symptomatically infected infants (<10%) will be found to have chorioretinitis. Finally, because hearing loss is the most common long-term sequela associated with congenital CMV infection, the failure of an infant to pass a newborn hearing screening exam should raise the possibility of congenital CMV infection. Hearing loss in the older infant and young child should also alert the clinician to the possibility of congenital CMV infection, as approximately 50% of infants with hearing loss associated with congenital CMV infection will pass an initial hearing screening exam but develop hearing loss in later infancy and early childhood.

An organized plan for follow-up is an important aspect in the clinical management of infants with congenital CMV infection. Because permanent sequelae are limited to disorders of the nervous system, long-term follow-up should include appropriate assessment of development and neuromuscular function in infected infants, with referral to specialized care if necessary. Hearing loss will develop in approximately 11% of infected infants, and in some infants hearing loss will progress during infancy. Thus, audiologic testing and follow-up are mandatory in these patients. Other sequelae such as vision loss are infrequent, but vision testing and comprehensive eye examinations should be included in the care plan.

Perinatal Infection

Perinatal infections can be acquired during birth or following ingestion of CMV-containing breast milk. In almost all cases, perinatal infections are not associated with any clinical manifestations of infection and, perhaps more importantly, have not been associated with any long-term sequelae. In rare cases, such as is seen in breast milk transmission of CMV to extremely premature infants or infants born to nonimmune women, perinatal infection can result in severe, disseminated infections associated with end-organ disease and death. These more severe infections are thought to develop in infants who lack transplacentally acquired antiviral antibodies either secondary to extreme prematurity or being the product of a mother lacking anti-CMV antibodies.

DIAGNOSIS

In the nonimmunocompromised individual, diagnosis of CMV infection requires evidence of a primary infection. Serologic reactivity for CMV is lifelong following primary infection; therefore, the presence of immunoglobulin (Ig) G antibody to CMV does not provide evidence of infection. In addition, IgM reactivity for CMV can be detected for prolonged periods after acute infection and cannot be used to reliably to estimate the duration of infection. Furthermore, recovery of virus from body fluids such as saliva or urine does not in itself permit diagnosis of CMV infection, because persistently infected individuals can intermittently shed virus. In the immunocompromised host, CMV can frequently be recovered from patients in the absence of evidence of invasive CMV infection. Thus, assignment of CMV as a cause of disease in this patient population must be made carefully, and other potential causes of symptoms and clinical findings in these patients must also be considered. Serologic assays are of limited value in the transplant recipient secondary to impact of immunosuppression on antibody responses in the allograft recipient. Furthermore, IgM antibodies can be produced following a nonprimary infection in these patients. Sequential viral load measurements by polymerase chain reaction in relevant body fluids such as blood and measurements of CMV DNA in biopsy tissue can be of great value in establishing CMV as a cause of disease in allograft recipients.

Congenital Infections

The diagnosis of congenital CMV infections requires the recovery of replicating virus and/or viral nucleic acids within the 1st 3 wk of life. Sources of virus and viral nucleic acids include urine, saliva, and blood. Methods of detection include routine virus culture combined with immunofluorescence and polymerase chain reaction. Although quantification of virus in various specimens can suggest the likelihood of long-term sequelae such as hearing loss for a population of infected newborns, the predictive value for the individual patient is limited. A considerable amount of effort has been devoted to identifying screening assays that would be suitable for populations of newborn infants. Newborn screening using saliva has proven sensitive and specific and is now performed for newborn screening in some institutions.

Early studies suggested that congenitally infected newborn infants could be identified by CMV-specific IgM reactivity and that elevated levels of CMV-specific IgM correlated with severity of disease. Subsequent studies have demonstrated that although of some value, the limited sensitivity of most assays employed to detect newborn IgM also limit their clinical utility.

Noncongenital Infections

In nonimmunocompromised patients, demonstration of CMV-specific IgG seroconversion or the presence of CMV-specific IgM antibodies represents evidence of a newly acquired CMV infection. IgM anti-CMV antibody reactivity can persist for months depending on the sensitivity of the particular assay. The use of the IgG avidity assays in which CMV-specific binding antibodies are eluted with increasing concentrations of chaotropic agents such as urea can be used to estimate the duration of infection. This assay has been used almost exclusively in the management of CMV infections during pregnancy to aid in defining primary maternal infections. Detection of CMV in urine, saliva, and blood and in tissue specimens obtained at biopsy can be most reliably accomplished by polymerase chain reaction–based methods, and because findings can be quantified, treatment responses can be monitored. However, conventional culture of CMV using human dermal fibroblasts often combined with immunofluorescence detection of CMV-encoded immediate early antigens also remains standard in many institutions. Routine histologic stains allow detection of characteristic nuclear (and cytoplasmic) inclusions (owl-eye inclusions) in tissue specimens.

TREATMENT

Treatment of immunocompromised hosts with invasive CMV disease limits both the morbidity and mortality in the patient with disseminated CMV infections with end-organ disease. This has been shown in allograft transplant recipients and patients with HIV/AIDS. Similarly, antiviral prophylaxis can limit the development of clinically important CMV disease in allograft recipients. Several agents are currently licensed for CMV infections, including ganciclovir and foscarnet. In some transplant centers, high-titered CMV immunoglobulins are included as a component of prophylaxis. Treatment with CMV immunoglobulins alters the natural history of CMV infection in renal and liver allograft recipients. Currently, the effectiveness of antiviral agents in prophylaxis has resulted in less-frequent use of these biologics.

Treatment of congenitally (symptomatic and asymptomatic but at risk for hearing loss) infected infants with ganciclovir has been studied in clinical trials; many infected infants have been treated off-label with this agent because of severe CMV infections. The study conducted by the Collaborative Antiviral Study Group sponsored by the National Institutes of Health suggested that 6 wk of ganciclovir treatment could limit hearing loss and possibly improve developmental outcome in symptomatically infected infants. In addition, infants with severe perinatal CMV infection following breast milk ingestion have been successfully treated with ganciclovir. Preliminary evidence suggests

that 6 mo of oral valganciclovir may be more effective and less toxic than intravenous ganciclovir in infants with symptomatic CMV infection.

PREVENTION

Passive Immunoprophylaxis

Passive transfer of anti-CMV antibodies has been utilized to limit disease but not infection in allograft recipients. A similar approach has also been considered for prevention of intrauterine disease. An uncontrolled trial of human immunoglobulin suggested that passive transfer of anti-CMV antibodies to pregnant women undergoing primary CMV infection may limit transmission and disease. Unfortunately, another study that was controlled failed to confirm this first study.

Active Immunoprophylaxis

A number of different vaccine platforms have been explored, including replicating attenuated CMV as vaccines, protein-based vaccines, heterologous virus vectored CMV vaccines, and DNA vaccines. In all cases, some level of immunity was induced in volunteers. Larger-scale trials have been carried out using replication competent, attenuated CMV vaccines and adjuvant recombinant protein vaccines. However, there has been little evidence that current approaches will be adequate to attenuate a replicating CMV and yet retain sufficient immunogenicity to induce protective responses. More progress has been made in use of adjuvant recombinant proteins. An adjuvant recombinant glycoprotein B, a major protein component of the envelope and target of neutralizing antibodies, has been shown to induce virus-neutralizing antibodies and $CD4^+$ T-lymphocyte proliferative responses. Moreover, this vaccine reduced virus acquisition by approximately 50% in a small trial carried out in young women. However, closer examination of this vaccine trial revealed that protection was very short-lived and that the effectiveness of the vaccine, although statistically significant, was not convincingly demonstrated because of the small numbers of subjects in the trial. Yet, this was perhaps the first evidence that active immunization could effect some level of protection. Because of the potentially large population that may be targeted by a successful vaccine, it should be anticipated that more candidate vaccines will be tested in the near future. Finally, a major question that will face all vaccine programs is whether existing immunity in seropositive women can be augmented to a level to prevent damaging infection in their offspring. The maternal population with existing immunity to CMV prior to childbearing age is responsible for the greatest number of congenitally infected infants in almost all regions of the world.

Counseling

Studies of the natural history of CMV repeatedly demonstrate that transmission requires close, often direct, contact with infected material, such as secretions from the oral or genitourinary tract. Although only limited data suggest that it can be transmitted on fomites, infectivity can persist for hours on surfaces such as toys. Limiting exposure to such secretions and attention to hygiene such as handwashing can drastically limit acquisition of CMV. Counseling is very effective in the prevention of CMV infection in women of childbearing age. In fact, counseling programs are more effective in limiting CMV infection during pregnancy than any vaccine that has been tested to date. Sexual transmission is an important route of infection, and CMV is considered to be a sexually transmitted infection. Limiting sexual transmission through education and counseling should be considered in sexually active individuals.

Acquisition of CMV by hospital workers and other healthcare providers was shown to be less than that of age-matched individuals in the general public. Importantly, these studies were carried out prior to universal precautions that are in place in most hospitals today. Thus, patient education with an emphasis on describing the sources of infectious virus in communities and attention to general hygiene could dramatically reduce CMV spread in the community.

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Chapter 256

Roseola (Human Herpesviruses 6 and 7)

Mary T. Caserta

Human herpesvirus 6 (HHV-6A and HHV-6B) and human herpesvirus 7 (HHV-7) cause ubiquitous infection in infancy and early childhood. HHV-6B is responsible for the majority of cases of **roseola infantum** (**exanthema subitum** or **sixth disease**) and is associated with other diseases, including encephalitis, especially in immunocompromised hosts. A small percentage of children with roseola have primary infection with HHV-7.

ETIOLOGY

HHV-6A, HHV-6B, and HHV-7 are the sole members of the *Roseolovirus* genus in the Betaherpesvirinae subfamily of human herpesviruses. Human cytomegalovirus, the only other β-herpesvirus, shares limited sequence homology with HHV-6 and HHV-7. Morphologically all human herpesviruses are composed of an icosahedral nucleocapsid, protein-dense tegument, and lipid envelope. Within the nucleocapsid, HHV-6 and HHV-7 both contain large, linear, double-stranded DNA genomes that encode more than 80 unique proteins.

Initially, 2 strain groups of HHV-6 were recognized, HHV-6 variant A and HHV-6 variant B. Despite sharing highly conserved genomes with approximately 90% sequence identity, the 2 variants could be distinguished by restriction fragment length polymorphisms, reactivity with monoclonal antibodies, differential cell tropism, and epidemiology. Because of these differences, the 2 were reclassified as separate species in the genus *Roseolovirus* by the International Committee on the Taxonomy of Viruses in 2012.

Although the frequency of detection of HHV-6A DNA differs among studies, HHV-6B is the overwhelmingly predominant virus found in both normal and immunocompromised hosts by both culture and polymerase chain reaction (PCR). Primary infection with HHV-6A has been detected by PCR in children in Africa. It is not clear whether the differences in the detection of HHV-6A DNA and HHV-6B DNA relate to different tissue tropism, differences in mode or age of acquisition, differences in the ability to cause human disease, or geographic location of the population studied.

EPIDEMIOLOGY

Primary infection with HHV-6B is acquired rapidly by essentially all children following the loss of maternal antibodies in the 1st few mo of infancy, 95% of children being infected with HHV-6 by 2 yr of age. The peak age of primary HHV-6B infection is 6-9 mo of life, with infections occurring sporadically and without seasonal predilection or contact with other ill individuals. Infection with HHV-7 is also widespread but occurs later in childhood and at a slower rate; only 50% of children have evidence of prior infection with HHV-7 by 3 yr of age. Seroprevalence reaches 75% at 3-6 yr of age. In a small study of children with primary HHV-7 infection, the mean age of the patients was 26 mo, significantly older than that of children with primary HHV-6 infection.

Preliminary data suggest that the majority of children acquire primary infection with HHV-6 from the saliva or respiratory droplets of asymptomatic adults or older children. However, congenital infection with HHV-6 occurs in 1% of newborns. Two mechanisms of vertical transmission of HHV-6 have been identified, transplacental infection and chromosomal integration. HHV-6 is unique among the human herpesviruses in that it is integrated at the telomere end of human chromosomes at a frequency of 0.2-2.2% of the population and is passed from parent to child via the germline. Chromosomal

integration has been identified as the major mechanism by which HHV-6 is vertically transmitted, accounting for 86% of congenital infections, with one third resulting from HHV-6A, a percentage much higher than in primary infection in the United States. The clinical consequences of chromosomal integration or transplacental infection with HHV-6 have yet to be determined. In 1 series of infants identified with HHV-6 congenital infection, no evidence of disease was present in the early neonatal period. Congenital infection with HHV-7 has not been demonstrated, and primary infection is presumed to be spread by the saliva of asymptomatic individuals. DNA of both HHV-6 and HHV-7 has been identified in the cervical secretions of pregnant women, suggesting an additional role for sexual or perinatal transmission of these viruses. Breast milk does not appear to play a role in transmission of either HHV-6 or HHV-7.

PATHOLOGY/PATHOGENESIS

Primary HHV-6B infection causes a viremia that can be demonstrated by coculture of the patient's peripheral blood mononuclear cells with mitogen-stimulated cord blood mononuclear cells. HHV-6 has a recognizable cytopathic effect, consisting of the appearance of large refractile mononucleated or multinucleated cells with intracytoplasmic and/or intranuclear inclusions. Infected cells exhibit a slightly prolonged life span in culture; however, lytic infection predominates. HHV-6 infection also induces apoptosis of T cells and may lead to cell expiration via loss of mitochondrial membrane potential as well as alteration of interferon and retinoic acid–induced cell death signals. In vitro, HHV-6 can infect a broad range of cell types, including primary T cells, monocytes, natural killer cells, dendritic cells, and astrocytes. HHV-6 has also been documented to infect B-cell, megakaryocytic, endothelial, and epithelial cell lines. Human astrocytes, oligodendrocytes, and microglia have been infected with HHV-6 ex vivo. The broad tropism of HHV-6 is consistent with the recognition that CD46, a complement regulatory protein present on the surface of all nucleated cells, is a cellular receptor for HHV-6. Recent data also suggest that CD134 is a selective receptor for HHV-6B and may explain some of the differences in tissue tropism noted between HHV-6A and HHV-6B. The CD4 molecule has been identified as a receptor for HHV-7. HHV-7 has been demonstrated to reactivate HHV-6 from latency in vitro. Whether this phenomenon occurs in vivo is not clear.

Primary infection with HHV-6 and HHV-7 is followed by lifelong latency or persistence of virus at multiple sites. HHV-6 exists in a true state of viral latency in monocytes and macrophages. The detection of replicating HHV-6 in cultures of primary $CD34^+$ hematopoietic stem cells has also been described, suggesting that cellular differentiation is a trigger of viral reactivation. This observation is clinically significant because HHV-6 may cause either primary or reactivated infection during hematopoietic stem cell transplantation (HSCT). Additionally, HHV-6 and HHV-7 infection may be persistent in salivary glands, and DNA of both HHV-6 and HHV-7 can be routinely detected in the saliva of both adults and children. HHV-7 can also be isolated in tissue culture from saliva, but HHV-6 cannot. HHV-6 DNA has been identified in the cerebrospinal fluid (CSF) of children, both during and subsequent to primary infection, as well as in brain tissue from immunocompetent adults at autopsy, implicating the central nervous system as an additional important site of either viral latency or persistence. HHV-7 DNA has also been found in adult brain tissue but at a significantly lower frequency.

CLINICAL MANIFESTATIONS

Roseola infantum (**exanthem subitum**, or **sixth disease)** is an acute, self-limited disease of infancy and early childhood. It is characterized by the abrupt onset of high fever, which may be accompanied by fussiness. The fever usually resolves acutely after 72 hr ("crisis") but may gradually fade over a day ("lysis") coincident with the appearance of a faint pink or rose-colored, nonpruritic, 2-3 mm morbilliform rash on the trunk (Fig. 256-1). The rash usually lasts 1-3 days but is often described as evanescent and may be visible only for hours, spreading

Figure 256-1 Roseola infantum. Erythematous, blanching macules and papules **(A)** in an infant who had high fever for 3 days preceding development of the rash. On closer inspection **(B),** some lesions reveal a subtle peripheral halo of vasoconstriction. *(From Paller AS, Mancinin AJ, editors:* Hurwitz clinical pediatric dermatology, *ed 3. Philadelphia, 2006, Elsevier, p. 434.)*

from the trunk to the face and extremities. Because the rash is variable in appearance, location, and duration, it is not distinctive. Associated signs are few but can include mild injection of the pharynx, palpebral conjunctivae, or tympanic membranes and enlarged suboccipital nodes. In Asian countries, ulcers at the uvulopalatoglossal junction (**Nagayama spots**) are commonly reported in infants with roseola.

High fever (mean: 39.7°C [103.5°F]) is the most consistent finding associated with primary HHV-6B infection. Rash detected either during the illness or following defervescence has been reported in approximately 20% of infected children in the United States. Additional symptoms and signs include irritability, inflamed tympanic membranes, rhinorrhea and congestion, gastrointestinal complaints, and encephalopathy. Symptoms of lower respiratory tract involvement such as cough are identified significantly less frequently in children with primary HHV-6B infection than in children with other febrile illnesses. The mean duration of illness caused by primary HHV-6B infection is 6 days, with 15% of children having fever for 6 or more days. Primary infection with HHV-6B accounts for a significant burden of illness on the healthcare system; 1 study found that 24% of visits to emergency departments by infants between 6 and 9 mo of age were because of primary HHV-6B infection. A population-based study of primary HHV-6B infection confirmed that 93% of infants had symptoms and were more likely to visit a physician than noninfected infants. Fever was less likely to be present with HHV-6B infection in children younger than 6 mo of age but was significantly more common in older infants and children.

Much less is known about the clinical manifestations of HHV-7 infection. Primary infection with HHV-7 has been identified in a small number of children with roseola in whom the illness is indistinguishable from that caused by HHV-6B. Secondary cases of roseola caused by infection with HHV-7 have also been reported. Additionally, primary infection with HHV-7 may be asymptomatic or may cause a nonspecific febrile illness lasting approximately 3 days.

LABORATORY FINDINGS

The most characteristic laboratory findings noted in children with primary HHV-6B infection are lower mean numbers of total white blood cells (8,900/μL), lymphocytes (3,400/μL), and neutrophils (4,500/μL), than in febrile children without primary HHV-6B infection. Similar hematologic findings have been reported during primary infection with HHV-7. Thrombocytopenia, elevated serum transaminase values, and atypical lymphocytes have also been noted sporadically in children with primary HHV-6B infection.

Results of CSF analyses reported in patients with encephalitis thought to be caused by HHV-6 have been normal or demonstrated only minimal CSF pleocytosis with mild elevations of protein, especially early in the course of the disease, which may progress with time. Areas of hyperintense signal on T2-weighted and fluid attenuation inversion recovery images of the hippocampus, uncus, and amygdala have been found on MRI, as well as increased metabolism within the hippocampus on positron emission tomography scanning.

DIAGNOSIS

Although roseola is generally a benign self-limited disease, its diagnosis can exclude other, more serious disorders that cause fever and rash. A history of 3 days of high fever in an otherwise nontoxic 10 mo old infant with a blanching maculopapular rash on the trunk suggests a diagnosis of roseola. Likewise, a specific diagnosis of HHV-6 is not usually necessary except in situations in which the manifestations of the infection are severe or unusual and might benefit from antiviral therapy.

The diagnosis of primary infection with either HHV-6 or HHV-7 is confirmed by demonstrating the presence of actively replicating virus in the patient's blood sample coupled with seroconversion. Viral culture is the gold standard method to document active viral replication. Unfortunately, culture is expensive, time-consuming, and available only in research laboratories. Two other methods used to identify active HHV-6 replication are the detection of viral DNA by PCR on *acellular fluids* such as plasma or reverse transcriptase PCR on peripheral blood mononuclear cell samples designed to detect viral transcription and protein production. Quantitative PCR for HHV-6 genome copy numbers on various specimens is also frequently reported and is commercially available. However, the role of this methodology is not clear, as a specific value of DNA that can discriminate between patients with viremia and those who are culture negative has not been determined. *Complicating the use of molecular assays for the detection of active replication of HHV-6 is the recognition that individuals with chromosomally integrated HHV-6 have persistent HHV-6 DNA in plasma, peripheral blood mononuclear cells, and CSF in the absence of disease and replicating virus.*

Serologic methods including indirect immunofluorescence assays, enzyme-linked immunosorbent assays, neutralization assays, and immunoblot have been described for the measurement of concentrations of antibodies to HHV-6 and HHV-7 in serum or plasma and are commercially available. Although immunoglobulin M antibody is produced early in infection with HHV-6, assays designed to measure this response have not proved useful in the diagnosis of primary or reactivated infection. The absence of immunoglobulin G antibody in an infant older than 6 mo of age combined with the presence of replicating virus is strong evidence of primary infection with either HHV-6 or HHV-7. Alternatively, the demonstration of seroconversion between acute and convalescent samples also confirms primary infection but is not clinically useful in the acute care setting. Unfortunately, serologic assays have not been found reliable in the detection of HHV-6 reactivation and cannot be used to differentiate between infection with HHV-6A and HHV-6B. Additionally, limited antibody cross-reactivity has been demonstrated between HHV-6 and HHV-7, complicating the interpretation of serologic assays, especially if low titers are reported.

Differential Diagnosis

Primary infection with either HHV-6B or HHV-7 usually causes an undifferentiated febrile illness that may be very difficult to distinguish from other common viral infections of childhood. This difficulty also applies to the early stages of roseola, before the development of rash. Once the rash is present, roseola may be confused with other exanthematous diseases of childhood, especially measles and rubella. Children with **rubella** often have a prodrome characterized by mild illness with low-grade fever, sore throat, arthralgia, and gastrointestinal complaints, unlike those with roseola. On physical examination, suboccipital and posterior auricular lymph nodes are prominent up to 1 wk before the rash of rubella is evident and persist during the exanthematous phase. Additionally, the rash of rubella usually begins on the face and spreads to the chest, like that in measles. The associated symptoms of **measles** virus infection include cough, coryza, and conjunctivitis, with high fever coincident with the development of rash, unlike in roseola. Roseola may also be confused with scarlet fever, though the latter is rare in children younger than 2 yr of age and causes a characteristic sandpaper-like rash concurrent with fever.

Roseola may be confused with illness caused by enterovirus infections, especially in the summer and fall months. Drug hypersensitivity reactions may also be difficult to distinguish from roseola. Antibiotics are frequently prescribed for children with fever from roseola before the appearance of rash. A child who then demonstrates rash after the resolution of fever may erroneously be labeled as being drug allergic.

COMPLICATIONS

Convulsions are the most common complication of roseola and are recognized in up to one third of patients. Seizures are also the most common complication of children with primary HHV-6B infection, occurring in approximately 15%, with a peak age of 12-15 mo. Children with primary HHV-6B infection are also reported to have a higher frequency of partial seizures, prolonged seizures, postictal paralysis, and repeated seizures than are children with febrile seizures

not associated with HHV-6. In a study limited to children with primary HHV-6B infection and seizures, 30% of patients had prolonged seizures, 29% had focal seizures, and 38% had repeated seizures. A prospective study of children 2-35 mo of age with suspected encephalitis or severe febrile illness with convulsions found that 17% had primary infection with either HHV-6 or HHV-7, and status epilepticus was the most common presentation. Among children with febrile status epilepticus (FSE), primary or reactivated infection with HHV-6B or HHV-7 has been identified in approximately one third.

An association between recurrent seizures and reactivated or persistent infection of the central nervous system by HHV-6 has also been suggested. Studies evaluating brain tissue specimens implicate HHV-6 in as many as 35% of patients with temporal lobe epilepsy, high viral loads being found in the hippocampus or lateral temporal lobe regions. HHV-6 protein production has also been identified in a small number of resected tissue specimens. Primary astrocytes obtained from these samples had undetectable levels of a glutamate transporter, suggesting the loss of ability to control glutamate levels as a possible mechanism for the development of recurrent seizures. Contrary to these findings, limited clinical data suggest that there may be a decreased risk of recurrent seizures after primary infection with HHV-6 and febrile seizures than of febrile seizures from other causes. Additionally, children with FSE associated with HHV-6B and HHV-7 had similar seizure characteristics and a similar proportion of electroencephalography and MRI hippocampal abnormalities as children with FSE not associated with HHV-6B or HHV-7, suggesting a shared pathogenesis to other etiologies of FSE. Further study is needed to determine if there is a link between HHV-6 and HHV-7 infection and epilepsy.

Case reports and small patient series have described additional complications in children with primary HHV-6B infection, including encephalitis, acute disseminated demyelination, autoimmune encephalitis, acute cerebellitis, hepatitis, and myocarditis. Late-developing long-term sequelae, including developmental disabilities and autistic-like features, are reported rarely in children who have central nervous system symptoms during primary HHV-6B infection.

Reactivation of HHV-6 has been reported in several different populations with and without disease with the use of various methods of detection. The best documentation of HHV-6 reactivation has been in immunocompromised hosts, especially those patients who have undergone HSCT. Such reactivation occurs in approximately 50% of patients, typically at 2-4 wk after transplantation. Many of the clinical complications seen following HSCT have been associated with HHV-6B reactivation, including fever, rash, delayed engraftment of platelets or monocytes, and graft-versus-host disease with variable degrees of support in the literature for each.

HHV-6B reactivation has also been reported as a cause of encephalitis in both normal and immunocompromised hosts. A distinct syndrome of *posttransplant acute limbic encephalitis (PALE)* has been described primarily in patients following HSCT, especially cord blood stem cell transplantation; it is characterized by short-term memory dysfunction, confusion, and insomnia with seizures noted either clinically or on prolonged electroencephalography monitoring. HHV-6B DNA has been identified in the CSF in the majority of these patients with additional evidence of reactivation by detection of HHV-6B DNA in plasma. HHV-6 proteins were identified in the astrocytes of the hippocampus in 1 postmortem specimen, consistent with active HHV-6B infection at the time of death. The development of PALE is associated with increased mortality and long-term neurocognitive sequelae.

TREATMENT

Supportive care is usually all that is needed for infants with roseola. Parents should be advised to maintain hydration and may use antipyretics if the child is especially uncomfortable with the fever. Specific antiviral therapy is not recommended for routine cases of primary HHV-6B or HHV-7 infection. Unusual or severe manifestations of primary or presumed reactivated HHV-6B infection such as encephalitis/PALE, especially in immunocompromised patients, may benefit from treatment. Ganciclovir, foscarnet, and cidofovir all demonstrate inhibitory activity against HHV-6 in vitro similar to their activity against cytomegalovirus. Case reports suggest that all 3 drugs, alone or in combination, can decrease HHV-6 viral replication, as evidenced by decreased viral loads in plasma and CSF. However, clinical data regarding efficacy are sparse and contradictory, with no randomized trials to guide use. Additionally, in vitro resistance of HHV-6 to all 3 drugs has been described. Despite these drawbacks, treatment with ganciclovir or foscarnet as first-line agents has been recommended for a minimum of 3 wk in patients with PALE. Foscarnet appears to be most likely to have activity against HHV-7 on the basis of in vitro testing, but no clinical data are available.

PROGNOSIS

Roseola is generally a self-limited illness associated with complete recovery. The majority of children with primary infections with HHV-6B and HHV-7 also recover uneventfully without sequelae. Although seizures are a common complication of primary infection with HHV-6B and HHV-7, the risk of recurrent seizures does not appear to be higher than that associated with other causes of simple febrile seizures.

PREVENTION

Primary infections with HHV-6 and HHV-7 are widespread throughout the human population with no current means of interrupting transmission.

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Chapter 257

Human Herpesvirus 8

Mary T. Caserta

Human herpesvirus 8 (HHV-8) was first identified in tissue specimens from patients with **Kaposi sarcoma (KS)**. Because of this association, it is also known as **Kaposi sarcoma–associated herpesvirus**. HHV-8 has since been recognized as the etiologic agent of 2 additional lymphoproliferative disorders: **primary effusion–based lymphoma (PEL)** and **multicentric Castleman disease**.

ETIOLOGY

HHV-8 is a γ_2-human herpesvirus similar to Epstein-Barr virus. The virus contains a large DNA genome encoding 85-95 unique proteins. Infection is followed by both lytic and latent viral states with different degrees of viral replication associated with distinct disease manifestations.

EPIDEMIOLOGY

The prevalence of infection with HHV-8 varies both geographically and by population and roughly matches the epidemiology of KS. HHV-8 infection is endemic in Africa and parts of South America, with infection rates of up to 30-60% by adolescence. Seroprevalence >20% has also been found in regions bordering the Mediterranean. In contrast, infection rates <5% are noted in North America, central Europe, and Asia. However, within geographic regions, the prevalence

of infection varies with risk behaviors, rates of 30-75% being found among men who have sex with men in North America and Europe. HHV-8 DNA can be detected in saliva, blood, and tissues. Based upon large-scale epidemiologic studies, the current consensus is that saliva is the major mode of transmission. Other less-common routes of HHV-8 transmission include blood transfusion, bone marrow transplantation, and solid organ transplantation. Vertical transmission may occur in regions where HHV-8 is highly endemic, but the risk appears low.

PATHOLOGY AND PATHOGENESIS

HHV-8 contains multiple genes that impact cell-cycle regulation and the host immune response. Viral proteins interfere with the function of the tumor suppressor molecules p53 and retinoblastoma protein, induce the expression of proangiogenesis factors vascular endothelial growth factor A and vascular endothelial growth factor receptor-2, and lead to upregulation of the human mammalian target of rapamycin pathway, which is instrumental in the control of cell growth and metabolism. HHV-8 also encodes a homolog of human interleukin-6, which can bind and activate cytokine receptors and serve as a host cell autocrine growth factor. Additionally, viral proteins are associated with the constitutive expression of the transcription factor nuclear factor-κB. All of these proteins may be potential targets for therapeutic intervention.

CLINICAL MANIFESTATIONS

Although subclinical infection appears to be common, symptomatic primary HHV-8 infection has been described in immunocompetent children. Patients commonly had fever and a maculopapular rash or a mononucleosis-like syndrome, with full recovery the rule. In immunocompromised patients, primary infection has been associated with fever, rash, splenomegaly, pancytopenia, and lymphoid hyperplasia, and may be quite severe. Additionally, preliminary data suggest that transfusion-associated primary infection with HHV-8 is associated with an increased risk of mortality.

KS has several different clinical forms; each includes multifocal, angiogenic lesions arising from vascular endothelial cells infected with HHV-8. Classic KS is an indolent disorder seen in elderly men with limited involvement of the skin of the lower extremities. Endemic KS is more aggressive, occurring in children and young people, primarily in Africa, and can include visceral involvement as well as widespread cutaneous lesions (patches, plaques, or nodules). Posttransplantation KS and AIDS-related KS are the most severe forms, with disseminated lesions, often in the gastrointestinal tract and lungs, in addition to the skin.

Primary effusion–based lymphoma is a rare disease caused by HHV-8 that is seen most commonly in HIV-infected individuals. It consists of lymphomatous invasion of the serosal surfaces of the pleura, pericardium, and peritoneum. Similarly, **multicentric Castleman disease** is an unusual lymphoproliferative disorder characterized by anemia, thrombocytopenia, generalized lymphadenopathy, and constitutional symptoms and frequently associated with HHV-8 infection and a high degree of viral replication.

DIAGNOSIS

Serologic assays, including immunofluorescence and enzyme-linked immunosorbent assays, are the primary methods of diagnosing infection with HHV-8. However, testing has limited sensitivity, specificity, and reproducibility and is primarily a research tool with no universally recognized standard assays. Additionally, the loss of antibodies over time, referred to as *seroreversion,* has been described, further complicating serodiagnosis. Immunohistochemistry and molecular methods are available for the detection of the HHV-8 genome in tissue samples and are utilized in the diagnosis of KS, PEL, and multicentric Castleman disease.

TREATMENT

Treatment for KS, PEL, and multicentric Castleman disease is multifaceted and includes attempts to control malignant proliferations with traditional chemotherapeutic regimens and biologic agents as well as agents aimed at specific cellular pathways targeted by HHV-8 proteins. Highly active antiretroviral treatment (HAART) is a mainstay of both prevention and therapy for HHV-8 related disease in HIV-infected patients. In HIV associated KS, treatment with HAART alone is often used for the control of mild disease, while HAART plus chemotherapy is utilized for more severe disease. In transplantation-associated KS, the first line of treatment includes decreasing immunosuppression, often in association with a switch from calcineurin inhibitors to sirolimus (rapamycin) to block the mammalian target of rapamycin pathway. Severe disease frequently requires the use of traditional chemotherapy as well. The role of specific antiherpesvirus antiviral treatment is unclear. Oral valganciclovir decreases both the quantity and frequency of detection of HHV-8 in saliva, and ganciclovir treatment has been associated with decreased rates of development of KS in HIV-infected individuals. However, results of using antivirals in the treatment of established disease have been generally disappointing. The prognosis for PEL tends to be poor despite the use of traditional chemotherapy, while rituximab (anti-CD20) shows promise in the treatment of multicentric Castleman disease, both alone and in combination with chemotherapy. Rituximab treatment may worsen concurrent KS.

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Chapter 258

Influenza Viruses

Fiona P. Havers and Angela J.P. Campbell

Influenza viral infections cause a broad array of respiratory illnesses that are responsible for significant morbidity and mortality in children. Influenza A viruses also have the potential to cause periodic global pandemics with even higher penetrance of illness than seasonal epidemics.

ETIOLOGY

Influenza viruses are large, single-stranded RNA viruses belonging to the family Orthomyxoviridae, which includes 3 genera (or types): A, B, and C. Influenza A and B viruses are the primary human pathogens, causing seasonal epidemics, while influenza virus type C is a sporadic cause of predominantly mild upper respiratory tract illness. Influenza A viruses are further divided into subtypes based on 2 surface proteins that project as spikes from the lipid envelope, the hemagglutinin (HA) and neuraminidase (NA) proteins (Fig. 258-1). Strain variants are identified by antigenic differences in their HA and NA and are designated by the geographic area from which they were originally isolated, isolate number, and year of isolation—for example, influenza A/Victoria/361/2011(H3N2). The HA and NA antigens from influenza B and C viruses do not receive subtype designations, as there is less variation among influenza B and C antigens.

EPIDEMIOLOGY

Influenza has generally been thought to be transmitted primarily via respiratory droplets, but transmission via contact with secretions and small-particle aerosols may also occur. The incubation period is short, ranging from 12-72 hr. Seasonal influenza incidence peaks during colder months in temperate climates and circulates throughout

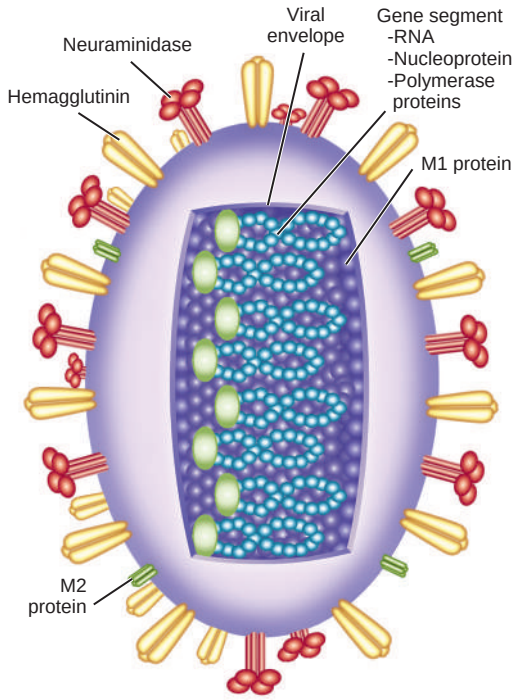


Figure 258-1 Schematic of influenza A virus. *(From Treanor JJ: Influenza viruses, including avian influenza and swine influenza. In Mandell GL, Bennet JE, Dolin R, editors:* Mandell, Douglas, and Bennet's principles and practice of infectious diseases, *ed 7. Philadelphia, 2009, WB Saunders,* Fig. 165-2.*)*

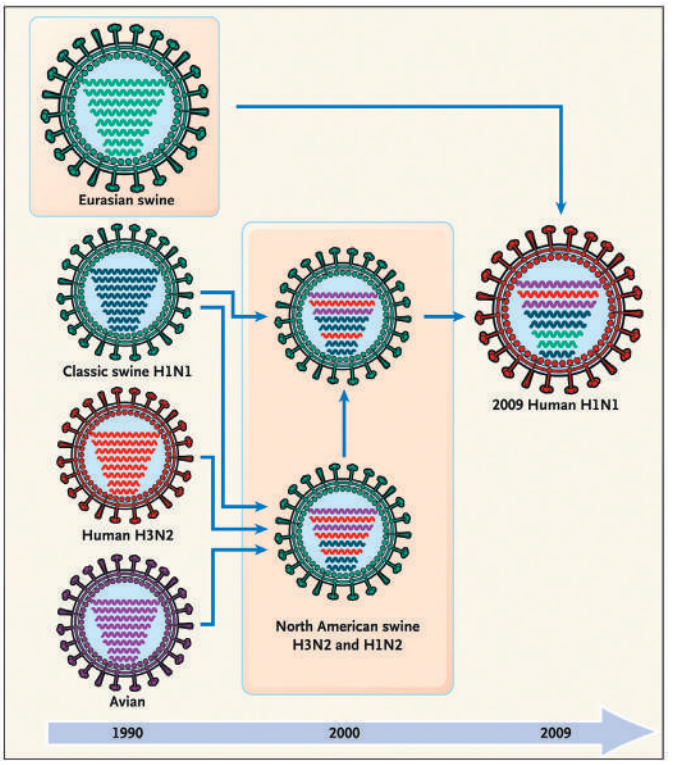


Figure 258-2 History of reassortment events in the evolution of the 2009 influenza A (H1N1) virus. The 8 segments shown within each virus code for the following proteins of the influenza A virus *(top to bottom):* polymerase PB2, polymerase PB1, polymerase PA, hemagglutinin, nuclear protein, neuraminidase, matrix proteins, and nonstructural proteins. The segments of the human 2009 influenza A (H1N1) virus have coexisted in swine influenza A virus strains for more than 10 yr. *(From Trifonov V, Khiabanian H, Rabadan R. Geographic dependence, surveillance, and origins of the 2009 influenza A [H1N1] virus.* N Engl J Med *361(2):115–119, 2009, Fig. 1.)*

the year in the tropics. Transmission through a community is rapid, with the highest incidence of illness occurring within 2-3 wk of introduction.

Antigenic Variation

Influenza A and B viruses contain a genome consisting of 8 single-strand RNA segments. Minor changes within a subtype continually occur through point mutations during viral replication, particularly in the HA gene, and result in new influenza strains of the same HA type. This phenomenon, termed *antigenic drift*, occurs in both influenza A and B viruses. Variation in antigenic composition of influenza virus surface proteins occurs almost yearly, which confers a selective advantage to a new strain and results in annual epidemics.

Major changes in subtype, less frequent but more dramatic, can occur through reassortment of viral gene segments when there is simultaneous infection by more than 1 strain of influenza in a single host. This process is called *antigenic shift,* and can occur in humans or animal hosts, resulting in emergence of novel subtypes. This occurs in influenza A viruses, which have multiple avian and mammalian hosts acting as reservoirs for diverse strains.

Through the process of reassortment, potentially any of 18 HA and 10 NA proteins currently known to reside in influenza A viruses of nonhuman hosts could be introduced into humans, who may have little existing immunologic cross protection to emerging viruses. A global pandemic can result if an influenza A virus with a novel HA or NA enters a nonimmune human population and acquires the capacity for sustained and efficient transmission between people. In the last 100 yr, 4 major global pandemics have occurred: in 1918 (caused by an influenza A[H1N1] virus), 1957 (A[H2N2]), 1968 (A[H3N2]), and 2009 (caused by an influenza A[H1N1] virus designated (A[H1N1]pdm09). The most severe pandemic in recorded history occurred in 1918, when the virus was estimated to have killed an estimated 50 million people. The 1918 pandemic virus was likely the result of direct adaptation of an avian influenza virus to the human host, rather than from reassortment. The 2009 pandemic stemmed from reassortment of genes from swine, avian, and human viruses (Fig. 258-2). This resulted in the emergence of a novel influenza A(H1N1) virus that spread quickly from North America across the globe, and has replaced the previously circulating seasonal H1N1 viruses.

In addition to the 2009 H1N1 pandemic, several other novel influenza strains, all originating in animals, have recently caused outbreaks of human infections. Avian influenza A(H5N1), a virulent avian influenza strain that was first identified in 1997, has caused more than 600 documented cases in 15 countries, with a 60% mortality rate. Another novel avian influenza, A(H7N9)—which first caused an outbreak of human infections in China during the spring of 2013 and second larger outbreak beginning fall 2014—also appears highly virulent; it has been fatal in more than one third of cases. In addition, a novel influenza A(H3N2v) virus caused more than 300 confirmed human infections in the United States from 2011-2013. Influenza viruses that normally circulate in swine are designated variant ("v") viruses when detected in humans. In contrast to avian influenza A(H5N1) and A(H7N9), this H3N2v influenza virus caused generally mild illness, primarily in children with swine contact at agricultural fairs. However, none of these viruses has exhibited sustained, efficient human-to-human transmission.

Seasonal Influenza

An estimated 20,000 children younger than 5 yr of age are hospitalized annually in the United States as a result of seasonal influenza-associated

complications, with hospitalization and mortality rates greatest in infants. Since 2004, the annual number of reported influenza-associated pediatric deaths in the United States has ranged from 34-149 during regular influenza seasons (it was 348 during the 2009 H1N1 pandemic). Influenza disproportionately affects children with specific chronic conditions, such as underlying pulmonary, cardiac, or neurologic and neuromuscular disorders. Very young children, especially those younger than 2 yr of age, and children with chronic medical conditions are more likely to develop severe influenza-related complications, including viral and bacterial pneumonia, respiratory failure, and death. However, while children with underlying medical conditions are at higher risk of complications, many healthy children are hospitalized with influenza, and nearly half of pediatric influenza-associated deaths are in children that have no known underlying medical condition.

Hospitalizations represent a small fraction of influenza-associated healthcare use; the proportion of outpatient visits resulting from influenza ranges from 10-25% annually in children younger than 5 yr of age. Influenza may also be underdiagnosed. Many who seek medical care for influenza do not have laboratory testing performed and do not receive a diagnosis of influenza. Children with primary influenza infection have higher influenza viral loads and more prolonged viral shedding than adults, making children extremely effective transmitters of infection. Nosocomial outbreaks of influenza can cause significant morbidity.

Every year, 3-4 influenza virus types or subtypes typically cocirculate, including H3N2, H1N1, and B viruses. Although 1 subtype usually predominates in any given season, it is difficult to predict which will be predominant. Thus, the influenza vaccine varies annually and contains 3 or 4 antigens representing the expected circulating types.

PATHOGENESIS

Influenza viruses infect the respiratory tract epithelium, primarily the ciliated columnar epithelial cells, by using the HA to attach to sialic acid residues. Virus is then adsorbed and virus replication occurs, usually within 4-6 hr. Infectious virus is then released, infecting neighboring cells and allowing the virus to spread rapidly. Influenza virus is rarely detected in extrapulmonary sites. With primary infection, virus replication continues for 10-14 days. Influenza virus causes a lytic infection of the respiratory epithelium with loss of ciliary function, decreased mucus production, and desquamation of the epithelial layer. These changes permit secondary bacterial invasion, either directly through the epithelium or, in the case of the middle ear space, through obstruction of the normal drainage through the eustachian tube.

The exact immune mechanisms involved in termination of primary infection and protection against reinfection are complex. Induction of cytokines that inhibit viral replication, such as interferon and tumor necrosis factor, as well as other host defenses, such as cell-mediated immune responses and local and humoral antibody defenses, all likely play a role. Secretory antibodies produced by the respiratory mucosa immunoglobulin A antibodies are thought to be an effective and immediate response generated during influenza infection. Serum antibody levels inhibiting HA activity can usually be detected by the 2nd wk after infection. These antibodies are also generated by vaccines, and high HA inhibition titers correlate with protection.

CLINICAL MANIFESTATIONS

The onset of influenza illness is often abrupt, with a predominance of systemic symptoms including fever, myalgias, chills, headache, malaise, and anorexia. Coryza, pharyngitis, and dry cough are also usually present at the onset of illness but may be less prominent than systemic symptoms. Respiratory manifestations can include isolated upper respiratory tract illness, including croup, or progression to lower tract disease, such as bronchiolitis or pneumonia. More than any other respiratory virus, influenza virus causes systemic manifestations such as high temperature, myalgia, malaise, and headache.

Abdominal pain, vomiting, and diarrhea may also occur in children; in some studies, diarrhea was reported to be more often associated with 2009 H1N1 compared with seasonal influenza. Influenza is a less-distinct illness in younger children and infants. The infected young infant or child may be highly febrile and toxic in appearance, prompting a full diagnostic work-up. The typical duration of the febrile illness is 2-4 days. Cough may persist for longer periods, and evidence of small airway dysfunction is often found weeks later. Owing to the high transmissibility of influenza, other family members or close contacts of an infected person often experience a similar illness.

COMPLICATIONS

Otitis media and pneumonia are common complications of influenza in young children. Acute otitis media may be seen in up to 25% of cases of documented influenza. Pneumonia accompanying influenza may be a primary viral process or a secondary bacterial infection (usually *Staphylococcus aureus*) facilitated through damaged respiratory epithelium. Unusual clinical manifestations of influenza include acute myositis seen with influenza type B, marked by muscle weakness and pain, particularly in the calf muscles, and myoglobinuria. Influenza types A and B are reported to cause myocarditis. Toxic shock syndrome can be associated with toxin-producing staphylococcal colonization. Central nervous system complications, such as encephalitis, myelitis, and Guillain-Barré syndrome, can occur and are seen more commonly in children than adults. Although it has essentially disappeared in the United States, Reye syndrome can result with the use of salicylates during influenza type B infection (see Chapter 361). Influenza is particularly severe in children with underlying cardiopulmonary disease, including congenital and acquired valvular disease, cardiomyopathy, bronchopulmonary dysplasia, asthma, cystic fibrosis, and neuromuscular diseases affecting the accessory muscles of breathing. Pregnant women are at special risk for severe influenza. In children receiving cancer chemotherapy and children with immunodeficiency, virus is shed for longer periods, with higher risk of complications.

LABORATORY FINDINGS

The clinical laboratory abnormalities associated with influenza are nonspecific. Relative leukopenia is frequently seen. Chest radiographs may show evidence of atelectasis or infiltrate.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of influenza depends on epidemiologic, clinical, and laboratory considerations. In the context of an epidemic, the clinical diagnosis of influenza in a young child who has fever without a focus, malaise, and respiratory symptoms may be made with some certainty; however, clinical presentation is often indistinguishable from other respiratory viruses, including respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, and even rhinovirus. Although confirmation of influenza virus infection by diagnostic testing is not required for clinical decisions to prescribe antiviral medications, prompt suspicion or diagnosis of influenza may allow for early antiviral therapy to be initiated and may reduce inappropriate use of antibiotics. A number of diagnostic tests may be used for laboratory confirmation of influenza (Table 258-1).

Although rapid influenza diagnostic tests are often employed because of their ease of use and fast results, they can have suboptimal sensitivity to detect influenza virus infection, particularly for novel influenza viruses. Sensitivities of rapid diagnostic tests are generally 50-70%, although a range of 10-80% has been reported, compared to viral culture or reverse-transcription polymerase chain reaction. Specificities are higher, approximately 95-100%. Therefore, false-negative results occur more often than false-positive results. The interpretation of negative results should take into account the clinical characteristics and the patient's risk for complications. If there is clinical suspicion for influenza in a patient at high risk for complications (Table 258-2), early empiric treatment should be given regardless of a negative rapid diagnostic test result, and another type of test (e.g., reverse-transcription

Table 258-1 Influenza Virus Testing Methods

METHOD	ACCEPTABLE SPECIMENS	TEST TIME	COMMENTS
Rapid influenza diagnostic tests	Nasopharyngeal (NP) swab, throat swab, nasal wash, nasal aspirate	<30 min	Rapid turnaround; suboptimal sensitivity
Immunofluorescence, direct (DFA) or indirect (IFA) antibody staining	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 hr	Relatively rapid turnaround; requires laboratory expertise and experience
RT-PCR* (single and multiplex; real-time and other RNA-based) and other molecular assays	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varied (generally 1-6 hr)	Excellent sensitivity, relatively rapid turnaround
Rapid cell culture (shell vials culture)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	1-3 days	Culture isolates important for strain information and antiviral resistance monitoring
Viral cell culture (conventional)	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 days	
Serologic tests (antibody detection)	Paired acute and convalescent sera	N/A (not performed during acute infection)	Not generally recommended for routine patient diagnosis

*Reverse transcription polymerase chain reaction

Adapted from Centers for Disease Control and Prevention (CDC): Rapid diagnostic testing for influenza: information for health care professionals; *available at http://www.cdc.gov/flu/professionals/diagnosis/rapidclin.htm#table*

Table 258-2 Children and Adolescents Who Are at Higher Risk for Influenza Complications*

Children younger than 2 yr of age†
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Persons with immunosuppression, including that caused by medications or by HIV infection
Adolescents who are pregnant or postpartum (within 2 wk after delivery)
Persons younger than 19 yr of age who are receiving long-term aspirin therapy
American Indians/Alaska Natives
Persons who are morbidly obese
Residents of long-term care facilities

Current for 2014-2015 influenza season.

*Antiviral treatment is recommended for high-risk children with confirmed or suspected influenza; antivirals are also recommended for children who are hospitalized or have severe or progressive disease.

†Although all children younger than 5 yr of age are considered at higher risk for complications from influenza, the highest risk is for those younger than 2 yr of age, with the highest hospitalization and death rates among infants younger than 6 mo of age.

Adapted from Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. *Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at http://www.cdc.gov/flu*

polymerase chain reaction, direct fluorescent antibody, or viral culture) may be performed for confirmation.

TREATMENT

Two classes of antiviral drugs are licensed for treatment of influenza in children. The NA inhibitors, oseltamivir and zanamivir, may be used for treatment of children from the ages of 2 wk and 7 yr, respectively (Table 258-3). These drugs are generally given either by inhalation (zanamivir) or oral administration (oseltamivir). In December 2012, the FDA approved the use of oseltamivir for the treatment of influenza in infants as young as 2 wk of age, and the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics recommend its use in all infants. Investigational intravenous zanamivir is also available for compassionate use under an emergency investigational new drug request.

The second class of drugs, adamantanes, includes amantadine and rimantadine, which are effective only against influenza A viruses. These 2 antivirals are not effective against influenza type B strains and are not approved for use in children younger than 5 yr of age. Genetic mutations have conferred widespread adamantane resistance among circulating influenza A (H3N2) and A(H1N1)pdm09 viruses; therefore, this class of antivirals is not currently recommended for use. Many H5N1 viruses and the H7N9 avian influenza viruses detected in 2013 and 2014 are also resistant to amantadine and rimantadine. It is important to review annual recommendations and updates published by the CDC before prescribing influenza antiviral medications.

When initiated early in the course of uncomplicated influenza illness, antiviral agents can reduce the duration of symptoms and the likelihood of complications. Among hospitalized patients, observational studies suggest that early treatment reduces disease severity and mortality. Most data regarding potential benefit are for adults; however, a few studies support the use of antiviral agents in children. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hr of influenza illness onset. Although early treatment is desired, treatment as early as possible, even more than 48 hr from onset, is recommended for hospitalized patients, patients with complicated or progressive illness, and patients at high risk for

Table 258-3 Centers for Disease Control and Prevention Recommended Dosage and Schedule of Influenza Antiviral Medications for Treatment and Chemoprophylaxis

ANTIVIRAL AGENT	USE	CHILDREN	ADULTS*
Oseltamivir (Tamiflu)	Treatment (5 days)	**If child is younger than 1 yr old**[†]: 3 mg/kg/dose twice daily[‡] **If child is 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **twice** a day >15-23 kg, the dose is 45 mg **twice** a day >23-40 kg, the dose is 60 mg **twice** a day >40 kg, the dose is 75 mg **twice** a day	75 mg twice daily
	Chemoprophylaxis (7 days)	If child is younger than 3 mo old, use of oseltamivir for chemoprophylaxis is not recommended unless situation is judged critical because of limited data in this age group **If child's age is 3 mo or older and younger than 1 yr old**[†]: 3 mg/kg/dose **once** daily[‡] **If child is 1 yr or older, dose varies by child's weight:** 15 kg or less, the dose is 30 mg **once** a day >15-23 kg, the dose is 45 mg **once** a day >23-40 kg, the dose is 60 mg **once** a day >40 kg, the dose is 75 mg **once** a day	75 mg once daily
Zanamivir[¶] (Relenza)	Treatment (5 days)	**For children age 7 yr and older:** 10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) **twice** daily
	Chemoprophylaxis (7 days)	**For children age 5 yr and older:** 10 mg (two 5-mg inhalations) once daily	10 mg (two 5-mg inhalations) **once** daily

Current for 2013-2014 influenza season, United States.

*Intravenous peramivir (Rapivab) was approved on December 19, 2014, for use in the treatment of acute uncomplicated influenza in people 18 years and older.

[†]Oral oseltamivir is approved by the FDA for treatment of acute uncomplicated influenza with twice-daily dosing in persons older than 14 days of age, and for prophylaxis with once-daily dosing in persons 1 yr and older. Although not part of the FDA-approved indications, use of oral oseltamivir for treatment of influenza in infants younger than 14 days old, and for prophylaxis in infants 3 mo to 1 yr of age, is recommended by the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics.

[‡]This is the FDA-approved oral and CDC-recommended oseltamivir treatment dose for infants 14 days and older and less than 1 yr old, and provides oseltamivir exposure in children similar to that achieved by the approved dose of 75 mg orally twice daily for adults, as shown in 2 studies of oseltamivir pharmacokinetics. The American Academy of Pediatrics recommends an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants ages 9-11 mo for the 2013-2014 season, on the basis of data that indicated that the higher dose of 3.5 mg/kg was needed to achieve the protocol-defined targeted exposure for this cohort as defined in the Collaborative Antiviral Study Group (CASG) 114 study. It is unknown whether this higher dose will improve efficacy or prevent the development of antiviral resistance. However, there is no evidence that the 3.5 mg/kg dose is harmful or causes more adverse events to infants in this age group.

[¶]Inhaled zanamivir is approved for treatment of acute uncomplicated influenza with twice-daily dosing in persons age 7 yr and older, and for prophylaxis with once-daily dosing in persons age 5 yr and older.

Adapted from Centers for Disease Control and Prevention (CDC): Influenza antiviral medications: summary for clinicians. *Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. For current details, consult annually updated recommendations at http://www.cdc.gov/flu*

influenza complications (see Table 258-2). **Decisions about starting antiviral treatment should not wait for laboratory confirmation of influenza.** Currently, for hospitalized patients and patients with severe or complicated illness, treatment with oral or enterically administered oseltamivir (and not inhaled zanamivir) is recommended. The recommended treatment course for uncomplicated influenza is 2 doses per day of an NA inhibitor medication for 5 days; however, the optimal duration and dose are uncertain for severe or complicated influenza and longer courses of treatment (e.g., 10 days of treatment) may be considered.

Clinical judgment, on the basis of the patient's disease severity, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important when making antiviral treatment decisions for outpatients at high risk for complications. Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hr of illness onset.

Drug resistance can develop commonly during a course of amantadine or rimantadine therapy and has also been reported to emerge in patients receiving oseltamivir treatment. Antiviral medications should be considered an adjunct to vaccination.

SUPPORTIVE CARE

Adequate fluid intake and rest are important components in the management of influenza. Bacterial superinfections are relatively common and should be appropriately treated with antibiotic therapy. Bacterial superinfection should be suspected with recrudescence of fever, prolonged fever, or deterioration in clinical status. With uncomplicated influenza, children should start to feel better after the 1st 48-72 hr of symptoms.

PROGNOSIS

The prognosis for recovery from uncomplicated influenza is generally excellent, although full return to normal level of activity and freedom from cough usually requires weeks rather than days. Fatigue may also persist for weeks. However, severe influenza disease can be associated with hospitalizations and death, even among previously healthy children.

PREVENTION

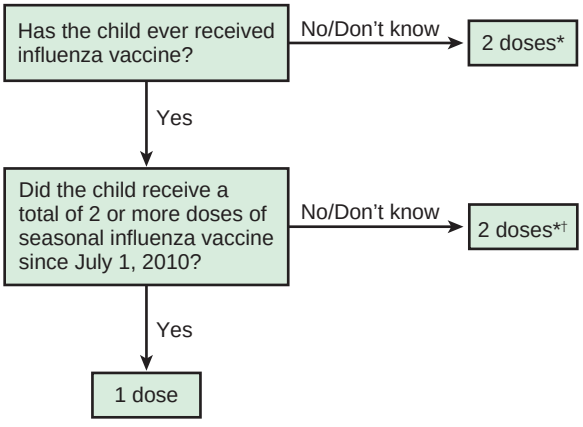
Influenza vaccination is the best means of preventing severe disease caused by influenza. In studies of children who are fully vaccinated, influenza vaccine was approximately 50-80% effective in reducing the risk of laboratory-confirmed influenza illness. Vaccine effectiveness can vary from year to year and among different age and risk groups. Recommendations for use of the influenza vaccine have broadened as the impact of influenza is appreciated in such groups as *pregnant women* and *young infants*. Starting in the 2008-2009 influenza season, the Advisory Committee on Immunization Practices (ACIP) recommended that all children from 6 mo to 18 yr of age be vaccinated for influenza unless they have a specific contraindication to receiving the

vaccine. In 2012, the Department of Health in the United Kingdom announced plans to extend their influenza vaccination program at no charge to include all children between the ages of 2 and 17 yr. In addition, household contacts and out-of-home caregivers of children 0-6 mo of age are a targeted group so as to protect infants who are too young to receive vaccine. Chemoprophylaxis with antiviral medications is a secondary means of prevention, and not a substitute for vaccination.

Vaccines

There are 2 main categories of seasonal influenza vaccines available for children, inactivated influenza vaccine (IIV) and live-attenuated influenza vaccine (LAIV). Previously referred to as the trivalent inactivated vaccine, IIV is given intramuscularly; it uses killed virus components and cannot cause influenza virus infection. The LAIV vaccine uses weakened influenza virus and is administered as an intranasal spray. Starting in 2014-2015, ACIP and CDC recommended the use of the LAIV nasal spray vaccine for healthy children 2 through 8 yr of age, when it is immediately available and when no contraindications or precautions to that vaccine exist. LAIV is not recommended for children younger than 2 yr of age or children who are at higher risk of developing influenza complications. In addition, special vaccination instructions for children 6 mo to 8 yr of age should be followed: depending on vaccination history, some children will require 2 doses of seasonal influenza vaccine (administered a minimum of 4 wk apart) to optimize immune response (Fig. 258-3). Influenza vaccines have an excellent safety profile, with the most common side effects being soreness, redness, tenderness, or swelling from the injection, and nasal congestion after the nasal spray.

Inactivated and live-attenuated seasonal influenza vaccines become available in the late summer and early fall of each year. The formulation reflects the strains of influenza viruses that are expected to circulate in the coming winter. Beginning in the 2013-2014 season, IIVs were available in both trivalent and quadrivalent formulations. The trivalent vaccine (IIV3) contains 2 influenza A strains and 1 influenza B strain; the quadrivalent vaccine (IIV4) contains a second influenza B strain of an antigenically distinct lineage. In addition to IIV and LAIV vaccines, a third vaccine category, recombinant hemagglutinin influenza vaccine, became available as a trivalent formulation in the 2013-2014 season.



* Doses should be administered at least 4 wk apart.

Figure 258-3 Influenza vaccine dosing algorithm for children 6 mo through 8 yr of age. *(From Centers for Disease Control and Prevention (CDC):* Summary recommendations: prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices–United States, 2014-15. *Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6332a3.htm.)*

Vaccination should be given as soon as vaccine is available, preferably before the onset of influenza circulation in the community, so that there is time for antibodies to reach protective levels. The ACIP publishes guidelines for vaccine use each year when the vaccines are formulated and released. These guidelines are widely publicized but appear initially in the *Morbidity and Mortality Weekly Report* published by the CDC.

Chemoprophylaxis

Routine use of antiviral medications for chemoprophylaxis is not recommended. Examples for which the use of chemoprophylaxis may be considered to prevent influenza after exposure to an infectious person include (1) unvaccinated persons at high risk of influenza complications, (2) persons for whom vaccine is contraindicated or expected to have low effectiveness, and (3) residents/patients in care facilities during institutional influenza outbreaks. NA inhibitors or adamantanes may be used for chemoprophylaxis of influenza; however, adamantanes are not currently recommended because of widespread adamantane resistance. Table 258-3 shows the recommendations for dosage and duration of treatment and chemoprophylaxis for the 2012-2013 influenza season, but updated recommendations from the ACIP and CDC should be consulted every season (http://www.cdc.gov/flu). In general, if chemoprophylaxis can be started within 48 hr of exposure to an infectious person, postexposure chemoprophylaxis for persons at high risk of influenza complications (see Table 258-2) is recommended for at least 7 days after the most recent exposure. An alternative to chemoprophylaxis for some persons after a suspected exposure is close monitoring and early initiation of antiviral treatment if symptoms develop. For control of outbreaks with seasonal influenza in long-term care facilities and hospitals, antiviral chemoprophylaxis should be considered for exposed vaccinated and unvaccinated high-risk patients, as well as unvaccinated healthcare providers. The CDC and the Infectious Disease Society of America recommend chemoprophylaxis for a minimum of 2 wk and up to 1 wk after the last known case is identified, whichever is longer.

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Chapter 259

Parainfluenza Viruses

Angela J.P. Campbell

Parainfluenza viruses (PIVs) are common causes of acute respiratory illness in infants and children and are important causes of lower respiratory tract disease in young children and immunocompromised persons. These viruses cause a spectrum of upper and lower respiratory tract illnesses but are particularly associated with croup (laryngotracheitis or laryngotracheobronchitis), bronchiolitis, and pneumonia.

ETIOLOGY

The PIVs are members of the Paramyxoviridae family. Four PIVs cause illness in humans, classified as types 1-4, with diverse manifestations of infection. Type 4 is divided into 2 antigenic subgroups, A and B. PIVs have a nonsegmented, single-stranded RNA genome with a lipid-containing envelope derived from budding through the cell membrane. The major antigenic moieties are the HN and F envelope spike glycoproteins, which exhibit hemagglutinin-neuraminidase and fusion functions, respectively.

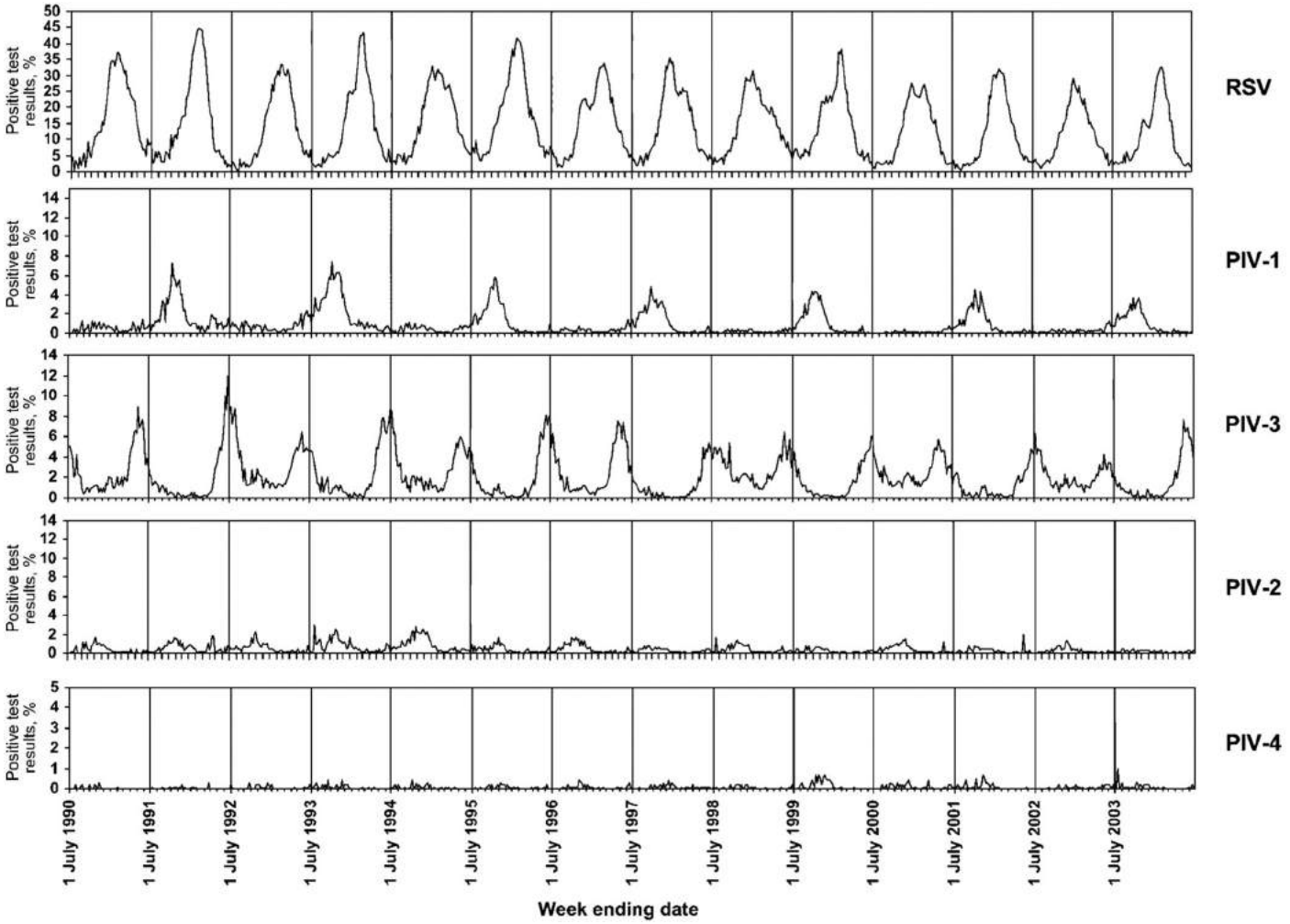

Figure 259-1 The percentage of tests positive for parainfluenza virus (PIV) serotypes 1, 3, 2, and 4 reported to the National Respiratory and Enteric Viruses Surveillance System (NREVSS), by week, July 1990-June 2004. The percentage of antigen detection tests positive for respiratory syncytial virus (RSV) reported to NREVSS is shown for comparison. (Note that RSV and PIV-4 have different axis scales than the other human PIV serotypes.) *(From Fry AM, Curns AT, Harbour K, Hutwagner L, Holman RC, Anderson LJ. Seasonal trends of human parainfluenza viral infections: United States, 1990-2004.* Clin Infect Dis *43:1016–1022, 2006, Fig. 1.)*

EPIDEMIOLOGY

By 5 yr of age, most children have experienced primary infection with PIV types 1, 2, and 3. PIV-3 infections often occur in the 1st 6 mo of life, with half of children estimated to be infected by age 1 year, and 90-100% by age 5 yr. PIV-1 and PIV-2 are more common after infancy, with 60-75% infected by age 5 yr. Although PIV-4 is not recognized as often, about half of children have antibody by the age of 5 yr. In the United States and temperate climates, PIV-1 has typically been reported to have biennial epidemics in the fall, sometimes noted to alternate years in which the serotype is most prevalent with PIV-2 (Fig. 259-1). PIV-2 has also been reported to cause yearly outbreaks. PIV-3 is endemic throughout the year but typically peaks in late spring. In years with less PIV-1 activity, the PIV-3 season has been observed to extend longer or to have a second peak in the fall (Fig. 259-1). The epidemiology of PIV-4 is less-well defined, because it is difficult to grow in tissue culture and was often excluded from previous studies, but newer studies show it to have an irregular epidemic pattern.

PIVs are spread primarily from the respiratory tract by inhalation of large respiratory droplets or contact with infected secretions. PIVs are notable for causing outbreaks of respiratory infections in hospital wards, clinics, neonatal nurseries, and other institutional settings. The incubation period from exposure to symptom onset is 2-6 days. Children are likely to excrete virus from the oropharynx for 2-3 wk, but excretion can be more prolonged even in immunocompetent children; in immunocompromised patients, excretion may persist for months. Primary infection does not confer permanent immunity, and reinfections are common throughout life. Reinfections are generally mild and self-limited.

PATHOGENESIS

PIVs replicate in the respiratory epithelium. The propensity to cause illness in the upper large airways is presumably related to preferential replication in the larynx, trachea, and bronchi in comparison with other viruses. Some PIVs induce cell-to-cell fusion. During the budding process, cell membrane integrity is lost, and viruses can induce cell death through the process of apoptosis. In children, the most severe illness coincides with the time of maximal viral shedding. However, disease severity is likely related to the host immune response to infection as much as to direct cytopathic effects of the virus.

Virus-specific immunoglobulin A antibody levels correlate with protection from PIV infection. Circulating serum antibody is also likely to play a role in protection against PIV acquisition and progression to severe infection. Patients with compromised cellular immunity have severe, prolonged disease, suggesting that T cells are critical to controlling and terminating PIV infection.

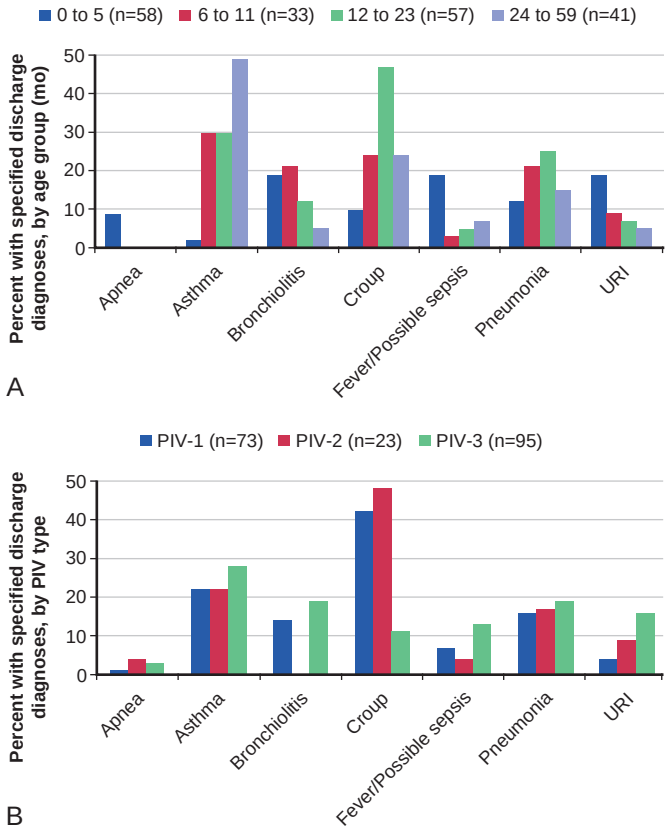

Figure 259-2 Selected discharge diagnoses of hospitalized children with parainfluenza (PIV) infection, by **(A)** age in months and **(B)** virus type. *(Adapted with data from Weinberg GA, Hall CB, Iwane MK, et al. Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization.* J Pediatr *154:694–699, 2009, Table II.)*

CLINICAL MANIFESTATIONS

The most common type of illness caused by PIV infection consists of some combination of low-grade fever, rhinorrhea, cough, pharyngitis, and hoarseness, and may be associated with vomiting or diarrhea. Rarely, PIV infection is associated with parotitis. Illness usually lasts 4-5 days. The generally mild illness pattern is belied by a spectrum of rarer but more serious illnesses that result in hospitalization (Fig. 259-2). PIVs account for 50% of hospitalizations for croup and at least 15% of cases of bronchiolitis and pneumonia. PIV-1, and to a lesser extent PIV-2, cause more cases of croup, whereas PIV-3 is more likely to infect the small air passages and cause pneumonia, bronchiolitis, or bronchitis. PIV-4 causes a similar range of illness as the other PIV types. Any PIV can cause lower respiratory tract disease, particularly during primary infection or in immunosuppressed patients. In children and adult patients with hematologic malignancies and undergoing hematopoietic stem cell transplantation, lymphopenia has repeatedly been shown to be an independent risk factor for progression from upper to lower respiratory tract disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of PIV infection in children is often based only on clinical and epidemiologic criteria. Croup is a clinical diagnosis and must be distinguished from foreign body aspiration, epiglottitis, pharyngeal abscess, and subglottic hemangioma. Although the radiographic "steeple sign," consisting of progressive narrowing of the subglottic region, is characteristic of croup, differential considerations include acute epiglottitis, thermal injury, angioedema, and bacterial tracheitis. Manifestation of PIV lower respiratory tract disease may be similar to that of a number of other respiratory viral infections; therefore, identification of virus should be specifically sought by the most sensitive diagnostic means available for certain severe illnesses, such as pneumonia in immunocompromised children.

Conventional laboratory diagnosis of infection is accomplished by PIV isolation in tissue culture. Direct immunofluorescent staining is available in some centers for rapid identification of virus antigen in respiratory secretions. Many laboratories now use sensitive and specific multiplex polymerase chain reaction assays, which greatly increase sensitivity of PIV detection. For immunocompromised patients, these highly sensitive platforms provide the critical ability to make a diagnosis by detecting a wide range of viral pathogens, including PIVs, thus allowing for early implementation of infection prevention measures and potential treatment.

TREATMENT

There are no specific antiviral medications approved for the treatment of PIV infections. For croup, the possibility of rapid respiratory compromise should influence the acuity of care given (see Chapter 385). Humidified air has not been shown to be effective. Corticosteroids, including dexamethasone orally or by injection and budesonide via nebulizer, improve symptoms within 6 hr after treatment, lessen the need for other medications, and shorten hospital stays. *In general, because of its safety, efficacy, and cost-effectiveness, a single dose of oral dexamethasone (0.6 mg/kg) is preferred as part of the management of croup in the office or emergency room setting.* A single dose of intramuscular dexamethasone or budesonide (2 mg [2 mL solution] via nebulizer) may provide an alternative to dexamethasone for children with severe respiratory distress or vomiting. The dose may be repeated, but this should not necessary on a routine basis, and there are no guidelines to compare outcomes of single- and multiple-dose treatment schedules. Moderate to severe symptoms that persist for more than a few days should prompt investigation for other causes of airway obstruction.

For obstructive airway symptoms associated with moderate to severe croup, nebulized epinephrine (either racemic epinephrine 2.25%, 0.5 mL in 2.5 mL of saline, or L-epinephrine, 1:1,000 dilution in 5 mL of saline) is recommended and may also provide temporary symptomatic improvement. Children should be observed for at least 2 hr after receiving epinephrine treatment for return of obstructive symptoms. Repeated treatments may be provided, depending on the duration of symptoms. Oxygen should be administered for hypoxia, and supportive care with analgesics and antipyretics is reasonable for fever and discomfort associated with PIV infections. The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ear(s) or lower respiratory tract.

Ribavirin has some antiviral activity against PIVs in vitro and in animal models. Inhaled ribavirin has been given to severely immunocompromised children with PIV pneumonia, although the majority of data indicate that it is not effective, particularly for PIV pneumonia when given late in the course of illness. It is unclear whether treatment given early to prevent progression to pneumonia may be beneficial, although there have been anecdotal reports of successful use of aerosolized ribavirin for this purpose in children with severe combined immunodeficiency and transplant recipients. DAS181, a novel sialidase fusion protein inhibitor, has shown clinical potential when used for treatment of PIV lower respiratory tract disease among solid organ and hematopoietic stem cell transplant recipients, with reported improvement in viral load and symptoms following initiation of therapy. Other promising strategies for drug development include hemagglutinin-neuraminidase inhibitors, transcription inhibitors, and synthetic small interfering RNAs.

COMPLICATIONS

Eustachian tube obstruction can lead to secondary bacterial invasion of the middle ear space and acute otitis media in 30-50% of PIV

infections. Similarly, obstruction of the paranasal sinuses can lead to sinusitis. The destruction of cells in the upper airways can lead to secondary bacterial invasion and resultant bacterial tracheitis, and antecedent PIV infection of lower airways may predispose to bacterial pneumonia. Nonrespiratory complications of PIV are rare but include aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, rhabdomyolysis, myocarditis, and pericarditis.

PROGNOSIS

The prognosis for full recovery from PIV infection in the normal child is excellent, with no long-term pulmonary sequelae.

PREVENTION

Vaccine development has focused largely on live-attenuated intranasal PIV-3 vaccines. The candidates include a cold-adapted virus of human origin (cp45), an attenuated bovine PIV-3, and newer constructs using the bovine PIV-3 vaccine with insertion of human PIV-3 HN and F genes and the F and G proteins of respiratory syncytial virus. Reverse genetics technology has led to development of a live-attenuated investigational PIV-3 vaccine virus (rcp45) derived from complementary DNA, as well as complementary DNA–derived chimeric bovine/human PIV-3 virus constructs; these candidates are well tolerated and immunogenic in infants and young children. Although less advanced, candidate PIV-1 and PIV-2 vaccines have been developed and are undergoing phase 1 clinical studies in children (www.clinicaltrials.gov). The measure of protection afforded by vaccines will be difficult to assess, because symptomatic reinfection occurs and the frequency of serious infection in the general population is low. Nonetheless, it is clear that prevention of acute respiratory illness caused by PIVs, particularly lower respiratory tract infections among infants and young children, is a worthwhile goal.

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Chapter 260

Respiratory Syncytial Virus

James E. Crowe Jr.

Respiratory syncytial virus (RSV) is the major cause of bronchiolitis (see Chapter 391) and viral pneumonia in children younger than 1 yr of age and is the most important respiratory tract pathogen of early childhood.

ETIOLOGY

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane. Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do. The virus belongs to the family Paramyxoviridae, along with parainfluenza and measles viruses, and is in the subfamily Pneumovirinae, which also contains the human metapneumovirus (see Chapter 261). It is the only member of the genus *Pneumovirus* that infects humans. There are 2 antigenic subgroups of RSV, distinguished based primarily on variation in 1 of the 2 surface proteins, the G glycoprotein that is responsible for attachment. This antigenic variation caused by point mutations from infidelity of the virus RNA polymerase may to some degree contribute to the frequency with which RSV reinfects children and adults.

RSV replicates in a wide variety of cell line monolayer cultures in vitro, and in HeLa or HEp-2 cells produces characteristic syncytial cytopathology, from which the virus derives its name. Interestingly, it is now known that the virus does not cause large syncytia in polarized epithelial cells in vitro, and it is not clear whether syncytium formation occurs to any significant degree in vivo.

EPIDEMIOLOGY

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over 4-5 mo. During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June. Some areas in the United States, such as Florida, report a moderate incidence year-round. In the Southern hemisphere, outbreaks also occur during winter months in that hemisphere. RSV outbreaks often overlap with outbreaks of influenza and human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 mo of age. In the tropics, the epidemic pattern is less clear. This pattern of widespread annual outbreaks and the high incidence of infection during the 1st 3-4 mo of life are unique among human viruses.

Transplacentally acquired anti-RSV maternal immunoglobulin G serum antibodies, if present in high concentration, appear to provide partial but incomplete protection. These immunoglobulin Gs may account for the lower severity of RSV infections during the 1st 4-6 wk of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides substantial protection against severe disease, an effect that may pertain only to female infants and not male infants. RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their 2nd birthday. Reinfection occurs at a rate of at least 10-20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60-80% for second and subsequent infections.

Reinfection may occur as early as a few weeks after recovery, but usually takes place during subsequent annual outbreaks. Antigenic variation is not required for reinfection, as shown by the fact that a proportion of adults inoculated repeatedly with the same experimental preparation of wild-type virus could be reinfected multiple times. The immune response of infants is poor in quality, magnitude, and durability. The severity of illness during reinfection in childhood is usually lower and appears to be a function of partial acquired immunity, more robust airway physiology, and increased age.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by a virus in the middle ear or bacterial superinfection following eustachian tube dysfunction. The lower respiratory tract is involved to a varying degree with bronchiolitis and bronchopneumonia in about a third of children. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5-4%, depending on region, gender, socioeconomic status, exposure to cigarette smoke, gestational age, and family history of atopy. The admitting diagnosis is usually bronchiolitis with hypoxia, although this condition is often indistinguishable from RSV pneumonia in infants, and, indeed, the 2 processes frequently coexist. All RSV diseases of the lower respiratory tract (excluding croup) have their highest incidence at 6 wk to 7 mo of age and decrease in frequency thereafter. The syndrome of bronchiolitis is much less common after the 1st birthday. The terminology used for diagnosis of virus-associated wheezing illnesses in toddlers is confusing, as these illnesses are variably termed *wheezing-associated respiratory infection, "wheezy bronchitis," exacerbation of reactive airways disease,* or *asthma attack*. Because many toddlers wheeze during RSV infection but do not go on to have lifelong asthma, it is best to use the diagnostic term *asthma* only later in life. Acute viral

pneumonia is a recurring problem throughout childhood, although RSV becomes less prominent as the etiologic agent after the 1st yr. RSV plays a causative role in an estimated 40-75% of cases of hospitalized bronchiolitis, 15-40% of cases of childhood pneumonia, and 6-15% of cases of croup.

Bronchiolitis and pneumonia resulting from RSV are more common in boys than in girls by a ratio of approximately 1.5:1. Other risk factors with similar impact include 1 or more siblings in the home, white race, rural residence, maternal smoking, and maternal education <12 yr. The medical factors in infants associated with highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity. Still, most infants admitted to the hospital because of RSV infection do not have strong, easily identifiable risk factors. Therefore, any strategy for prophylaxis focused only on individuals with strong risk factors probably could prevent only approximately 10% of hospitalizations, even if the prophylaxis was 100% effective in treated high-risk individuals.

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious virus for 1-2 wk after hospital admission. Excretion for 3 wk, and even longer, has been documented. Spread of infection occurs when large, infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject. RSV is probably introduced into most families by young schoolchildren undergoing reinfection. Typically, in the space of a few days, 25-50% of older siblings and 1 or both parents acquire upper respiratory tract infections, but infants become more severely ill with fever, otitis media, or lower respiratory tract disease.

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults undergoing reinfection also have been implicated in spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, as the virus is not usually spread by small particle aerosol. In practice, however, adherence to isolation procedures by caregivers often is not complete.

PATHOGENESIS

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Infants are particularly apt to experience small airway obstruction because of the small size of their normal bronchioles; airway resistance is proportional to $1/\text{radius}^4$. There has been relatively little pathologic examination of RSV disease in the lower airways of otherwise healthy subjects. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, the infiltration is more generalized, and epithelial shedding may extend to both the bronchi and the alveoli. In older subjects, smooth muscle hyperreactivity may contribute to airway narrowing, but the airways of young infants typically do not exhibit a high degree of reversible smooth muscle hyperreactivity during RSV infection.

Several facts suggest that elements of the host response may cause inflammation and contribute to tissue damage. The immune response required to eliminate virus-infected cells is a double-edged sword, reducing the cells producing virus but causing host cell death in the process. A large number of soluble factors, such as cytokines, chemokines, and leukotrienes, are released in the process, and skewing of the patterns of these responses may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.

Children who received a formalin-inactivated, parenterally administered RSV vaccine in the 1960s experienced more severe and more frequent bronchiolitis upon subsequent natural exposure to wild-type RSV than did their age-matched controls. Several children died during naturally acquired RSV infection after vaccination. This event has greatly inhibited progress in RSV vaccine development, because of both an incomplete understanding of the mechanism and a reluctance to test new experimental vaccines that might induce the same type of response.

Some studies have identified the presence of both RSV and human metapneumovirus viral RNA in airway secretions in a significant proportion of infants requiring assisted ventilation and intensive care. It may be that coinfection is associated with more severe disease. Positive results of polymerase chain reaction (PCR) analysis must be interpreted carefully because this positivity can remain for prolonged periods after infection, even when infectious virus can no longer be detected.

It is not clear how often superimposed bacterial infection plays a pathogenic role in RSV lower respiratory tract disease. RSV bronchiolitis in infants is probably exclusively a viral disease, although there is evidence that bacterial pneumonia can be triggered by respiratory viral infection, including with RSV. A large clinical study of pneumococcal vaccine showed that childhood vaccination reduced the incidence of viral pneumonia by approximately 30%, suggesting viral-bacterial interactions that we currently do not fully understand.

CLINICAL MANIFESTATIONS

Typically, the first sign of infection in infants with RSV is rhinorrhea. Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

If the illness progresses, cough and wheezing worsen and air hunger ensues, with increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual and pleural effusion is rare.

In some infants, the course of the illness may resemble that of pneumonia, the prodromal rhinorrhea and cough being followed by dyspnea, poor feeding, and listlessness, with a minimum of wheezing and hyperexpansion. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently and the chest radiographs may show air trapping.

Fever is an inconstant sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. Apnea is not necessarily caused by respiratory exhaustion, but rather appears to be a consequence of alterations in central control of breathing.

RSV infections in profoundly immunocompromised hosts may be severe at any age of life. The mortality rates associated with RSV pneumonia in the 1st few wk after hematopoietic stem cell or solid organ transplantation in both children and adults are high. RSV infection does not seem to be more severe in HIV-infected patients with reasonable control of HIV disease, although these patients may shed virus for prolonged periods.

DIAGNOSIS

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty on the basis of the season of the year and the presence of the virus in the community. Other epidemiologic features that

may be helpful are the presence of colds in older household contacts and the age of the child. The other respiratory viruses that attack infants frequently during the 1st few mo of life are parainfluenza virus type 3, human metapneumovirus, enteroviruses, coronaviruses, and influenza viruses. Rhinovirus is frequently found in the respiratory tract of children, and there is growing evidence that this virus may contribute significantly to lower respiratory tract disease.

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV. The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood CO_2 value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

The most important diagnostic concern is to identify bacterial or chlamydial involvement. When bronchiolitis is not accompanied by infiltrates on chest radiographs, there is little likelihood of a bacterial component. In infants 1-4 mo of age, interstitial pneumonitis may be caused by *Chlamydia trachomatis* (see Chapter 226). With *C. trachomatis* pneumonia there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing and inspiratory crackles may be prominent; wheezing is not. Fever is usually absent.

Lobar consolidation without other signs or with pleural effusion should be considered of bacterial etiology until proved otherwise. Other signs suggesting bacterial pneumonia are neutrophilia, neutropenia in the presence of severe disease, ileus or other abdominal signs, high temperature, and circulatory collapse. In such instances, antibiotics should be initiated.

Definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. The antigen test is less sensitive than culture, whereas reverse transcription PCR analysis is more sensitive than culture. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. Nasopharyngeal or throat swabs are less preferable but acceptable. A tracheal aspirate is unnecessary, but endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis. The virus is thermolabile, so it degrades over relatively short periods of time unless frozen at a low temperature such as −80°C (−112°F) in freezers used in research settings.

TREATMENT

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Humidified oxygen and suctioning are usually indicated for hospitalized infants who are hypoxic. Many infants are slightly to moderately dehydrated, and therefore fluids should be carefully administered in amounts somewhat greater than those for maintenance. Often, intravenous or tube feeding is helpful when sucking is difficult because of tachypnea.

There is disagreement among experts regarding the usefulness of aerosolized saline or hypertonic saline, epinephrine or β_2-agonists in RSV bronchiolitis. Most patients do not receive lasting benefit from prolonged therapy, which is associated with a relatively high frequency of side effects. Corticosteroid therapy is not indicated except in older children with an established diagnosis of asthma, because its use is associated with prolonged virus shedding and is of no proven clinical benefit.

In nearly all instances of bronchiolitis, antibiotics are not useful, and their inappropriate use contributes to development of antibiotic resistance. Interstitial pneumonia in infants 1-4 mo old may be caused by *C. trachomatis,* and macrolide therapy may be indicated for that infection.

Ribavirin is an antiviral agent delivered through an oxygen hood, face mask, or endotracheal tube with use of a small-particle aerosol generator most of the day for 3-5 days. Early small trials of its use suggested a modest beneficial effect on the course of RSV pneumonia, with some reduction in the duration of both mechanical ventilation and hospitalization. However, subsequent studies failed to document a clear beneficial effect of ribavirin, and therefore this drug is no longer used for routine therapy of RSV disease. The monoclonal antibody palivizumab is licensed for prophylaxis in high-risk infants during the RSV season, and does prevent about half of the expected hospitalizations in that population. Small clinical trials using the palivizumab as a therapy during established infection have not shown benefit to date.

PROGNOSIS

The mortality rate of hospitalized infants with RSV infection of the lower respiratory tract is very low in the developed world. Almost all deaths occur among young, premature infants or infants with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system. It is estimated, however, that more than 100,000 children worldwide in resource-poor settings die each year from RSV. In addition, thousands of elderly patients die of RSV infection each year in the United States.

Many children with asthma have a history of bronchiolitis in infancy. There is recurrent wheezing in 30-50% of children with severe RSV bronchiolitis in infancy. The likelihood of recurrence is increased in the presence of an allergic diathesis (e.g., eczema, hay fever, or a family history of asthma). With a clinical presentation of bronchiolitis in a patient older than 1 yr of age, there is an increasing probability that, although the episode may be virus induced, this is likely the first of multiple wheezing attacks that will later be diagnosed as hyperreactive airways disease or asthma. Asthma is difficult to diagnose in the 1st yr of life. It is not fully clear at this time whether early, severe RSV wheezing disease causes some cases of asthma or whether subjects destined to suffer asthma present with symptoms first when provoked by RSV infection during infancy. However, results from a recent long-term follow-up study of infants who received palivizumab prophylaxis suggested that prevention of severe RSV infection reduces the incidence of reactive airways disease later in life.

PREVENTION

In the hospital, the most important preventive measures are aimed at blocking nosocomial spread. During RSV season, high-risk infants should be separated from all infants with respiratory symptoms. Gowns, gloves, and careful handwashing should be used for the care of all infants with suspected or established RSV infection. A high level of compliance with contact isolation is essential. Viral laboratory tests are adequate for diagnosis in the setting of acute disease when levels of virus are high, but they are not designed to detect low levels of virus. Therefore, contact precaution isolation should be observed for most patients admitted for acute disease assigned for the duration of hospitalization; rapid antigen tests should not be used to determine whether or not a patient still requires isolation. Ideally, patients with RSV or metapneumovirus infections are housed separately, because coinfection may be associated with more severe disease.

Passive Immunoprophylaxis

Administration of palivizumab (15 mg/kg IM once a month), a neutralizing humanized murine monoclonal antibody against RSV, is recommended for protecting high-risk children against serious complications from RSV disease. Immunoprophylaxis reduces the frequency and total days of hospitalization for RSV infections in high-risk infants in about half of cases. Palivizumab is administered monthly from the beginning to the end of the RSV season. The American Academy of Pediatrics Committee on Infectious Diseases issued "Modified Recommendations for Use of Palivizumab for Prevention of Respiratory Syncytial Virus Infections" in 2014. Palivizumab prophylaxis may be considered for the following infants and children

- Infants born before 29 wk of gestation in the 1st yr of life
- Infants born before 32 wk of gestation, who have chronic lung disease of prematurity (required >21% FIO_2 [fraction of inspired oxygen] for ≥28 days after birth), in the 1st yr of life

- Infants younger than 1 yr of age with hemodynamically significant congenital heart disease
- Children 24 mo of age or younger with profound immunocompromising conditions during RSV season
- Infants in the 1st yr of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises handling of respiratory secretions
- Administration in the 2nd yr of life is recommended for children who required 28 or more days of oxygen after birth and who have ongoing treatment for chronic pulmonary disease (oxygen, steroids, diuretics)

The American Academy of Pediatrics 2012 *Red Book* recommendations also give the following specific guidelines on implementation of prophylaxis. Recommendations for initiation and termination of prophylaxis reflect current descriptions from the Centers for Disease Control and Prevention of RSV seasonality in different geographic locations within the United States. Typically, prophylaxis is initiated July 1 in southeast Florida, September 15 in north-central and southwest Florida, and November 1 in most other areas of the United States. Regardless of the month in which the 1st dose is administered, the recommendation for a maximal number of 5 doses for all geographic locations is emphasized for infants with hemodynamically significant congenital heart disease, chronic lung disease of prematurity, or birth before 32 wk, 0 days of gestation. A maximal number of 3 doses is recommended for infants with a gestational age of 32 wk, 0 days to 34 wk, 6 days without hemodynamically significant congenital heart disease or chronic lung disease of prematurity who qualify for prophylaxis. Infants born from 32 wk, 0 days through 34 wk, 6 days of gestation who qualify for prophylaxis under the new recommendations should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first).

Vaccine

There is no licensed vaccine against RSV. The challenge for development of live virus vaccines has been to produce attenuated vaccine strains that infect infants in the nasopharynx after topical inoculation without producing unacceptable symptoms, that remain genetically stable during shedding, and that induce protection against severe disease following reinfection. The most promising live-attenuated virus candidates have been engineered in the laboratory from cold-passaged strains of RSV, according to a basic strategy that yielded the live poliovirus and influenza virus vaccine strains. A variety of nonreplicating experimental vaccines are being tested in early clinical trials. Plans are underway to study some of the new vaccine candidates in maternal immunization trials. The rationale of such studies is to test whether boosting the serum level of RSV-neutralizing antibodies in the mother can enhance immunity in neonates following transplacental transfer of maternal antibodies to the infant.

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Chapter 261

Human Metapneumovirus

James E. Crowe Jr.

Human metapneumovirus (HMPV) is a respiratory virus that was first identified in 2001 and has emerged as one of the most common causes of serious lower respiratory tract illness in children throughout the world.

ETIOLOGY

HMPV is an enveloped, single-stranded nonsegmented negative-sense RNA genome of the Paramyxoviridae family, which is divided into 2 subfamilies, Pneumovirinae and Paramyxovirinae. The Pneumovirinae subfamily includes the 2 genera *Metapneumovirus* and *Pneumovirus,* which includes respiratory syncytial virus (RSV). HMPV and the avian pneumoviruses are highly related and are separated into the separate genus *Metapneumovirus* because the gene order in the nonsegmented genome is slightly altered and because avian pneumoviruses/HMPVs lack the genes for 2 nonstructural proteins, NS1 and NS2, that are encoded at the 3′ end of RSV genomes. These proteins are thought to counteract host type I interferons. The absence of NS1/NS2 in the metapneumoviruses may contribute to an overall slightly reduced pathogenicity relative to wild-type RSV strains.

Full-length sequences of a number of HMPV genomes have been determined. The genome encodes 9 proteins in the order 3′-N-P-M-F-M2-(orf1 and 2)-SH-G-L-5′. The genome also contains noncoding 3′ leader, 5′ trailer, and intergenic regions, consistent with the organization of most paramyxoviruses, with a viral promoter contained in the 3′ end of the genome. The F (fusion), G (glycosylated), and SH (short hydrophobic) proteins are integral membrane proteins on the surfaces of infected cells and virion particles. The F protein is a classic type I integral membrane viral fusion protein that contains 2 heptad repeats in the extracellular domain that facilitate membrane fusion. There is a predicted protein cleavage site near a hydrophobic fusion peptide that likely is cleaved by an extracellular protease, activating the F protein for fusion. The predicted attachment (G) protein of HMPV exhibits the basic features of a glycosylated type II mucin-like protein. The HMPV G protein differs from the RSV G protein in that it lacks a cysteine noose structure. This protein may inhibit innate immune responses. The internal proteins of the virus appear similar in function to those of other paramyxoviruses.

EPIDEMIOLOGY

HMPV outbreaks occur in annual epidemics during late winter and early spring in temperate climates, often overlapping with the second half of the annual RSV epidemic (Fig. 261-1). Sporadic infections occur year round. The usual period of viral shedding is likely to be many days or even several weeks after primary infection in infants. The incubation period is approximately 3-5 days. Humans are the only source of virus, as there is no known animal or environmental reservoir. Transmission occurs by close or direct contact with contaminated secretions involving large-particle aerosols, droplets, or contaminated surfaces. Nosocomial infections have been reported, and contact isolation with excellent handwashing for healthcare providers is critical in medical settings. This virus affects the elderly, immunocompromised patients, and patients with reactive airways disease more severely than otherwise healthy individuals.

PATHOLOGY

Infection is usually limited to the superficial layer of airway epithelial cells and is associated with a local inflammatory infiltrate consisting of lymphocytes and macrophages. Immunocompromised individuals have evidence of both acute and organizing injuries during prolonged infection.

PATHOGENESIS

Infection occurs via inoculation of the upper respiratory tract. Infection can spread rapidly to the lower respiratory tract, but it is not clear whether the dissemination is mediated by cell-to-cell spread or aspiration of infected materials from the upper tract. Severe lower respiratory tract illness, especially wheezing, occurs mainly during the 1st yr of life, at a time when the airways are of a small diameter and high resistance. Maternal serum neutralizing antibodies that cross the placenta may afford a relative protection against severe disease for several weeks or months after birth. Once infection is established, it is likely that cytotoxic T cells recognize and eliminate virus-infected cells, thus terminating the infection but also causing some cytopathology. The virus appears to have specific mechanisms for inhibiting T-cell responses during acute infection. Individuals with an underlying predisposition to reactive airways disease (including adults) are susceptible to severe wheezing during reinfection later in life, suggesting that HMPV may cause smooth muscle hyperactivity, inflammation, or increased mucus

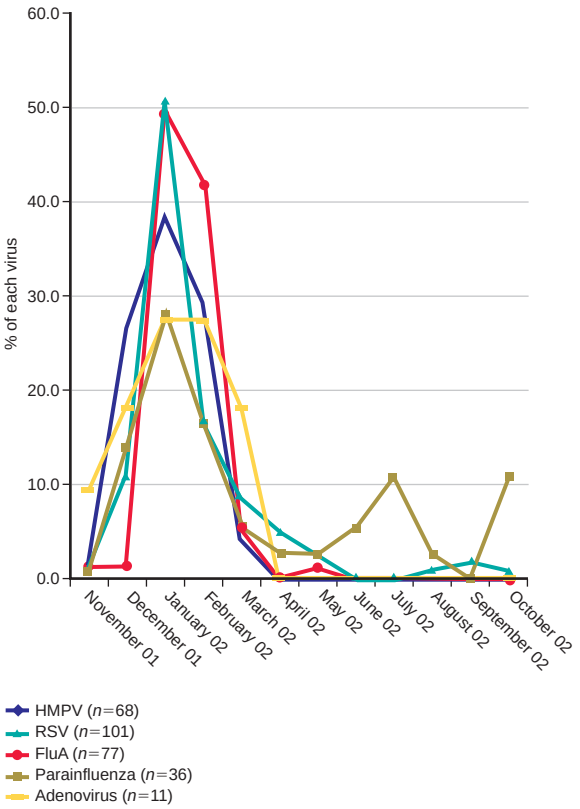

Figure 261-1 Temporal distribution of respiratory viruses among children hospitalized with lower respiratory tract infections from November 2001 through October 2002. Data are displayed as the proportion of each virus detected monthly. *FluA,* influenza A; *HMPV,* human metapneumovirus; *RSV,* respiratory syncytial virus. *(From Wolf DG, Greenberg D, Kalkstein D, et al: Comparison of human metapneumovirus, respiratory syncytial virus and influenza A virus lower respiratory tract infections in hospitalized young children,* Pediatr Infect Dis J *25:320–324, 2006.)*

production in such individuals. Infection in otherwise healthy individuals resolves without apparent long-term consequences in most cases. HMPV infection is associated with exacerbations of asthma later in life.

CLINICAL MANIFESTATIONS

HMPV is associated with the common cold (complicated by otitis media in approximately 30% of cases) and with lower respiratory tract illnesses such as bronchiolitis, pneumonia, croup, and exacerbation of reactive airways disease. The profile of signs and symptoms caused by HMPV is very similar to that caused by RSV (Table 261-1). Approximately 5-10% of outpatient lower respiratory tract illnesses in otherwise healthy young children is associated with HMPV infection, which is second in incidence only to RSV. Children with RSV or HMPV infection require supplemental oxygen and medical intensive care at similar frequencies.

About half of the cases of HMPV lower respiratory tract illness in children occur in the 1st 6 mo of life, suggesting that young age is a major risk factor for severe disease. Both young adults and the elderly can have HMPV infection that requires medical care including hospitalization, but severe disease occurs at much lower frequencies in adults than in young children. Severe disease in older subjects is most common in immunocompromised patients and can be fatal. A significant number of both adult and pediatric patients with asthma exacerbations have HMPV infection; it is not clear whether the virus causes long-term wheezing. RSV and HMPV coinfections have been reported; coinfections may be more severe than infection with a single virus, resulting in pediatric intensive care unit admissions. It is difficult to define true coinfections because these viral genomes can be detected

Table 261-1 Clinical Manifestations of Human Metapneumovirus in Children

COMMON (>50%)
Fever >38°C (100.4°F)
Cough
Rhinitis, coryza
Wheezing
Tachypnea, retractions
Hypoxia (O_2 saturation <94%)
Chest radiograph demonstration of infiltrates or hyperinflation
LESS COMMON
Otitis media
Pharyngitis
Rales
RARE
Conjunctivitis
Hoarseness
Encephalitis
Fatal respiratory failure in immunocompromised children

by reverse transcriptase polymerase chain reaction (PCR) in respiratory secretions for at least several weeks after illness, even when virus shedding has terminated.

LABORATORY FINDINGS

The virus can be visualized only with electron microscopy. The virus grows in primary monkey kidney cells or LLC-MK2 cell or Vero cell-line monolayer cultures, but efficient isolation of the virus requires an experienced laboratory technician. Conventional bright-field microscopy of infected cell monolayer cultures often reveals cytopathic effect only after multiple passages in cell culture. The characteristics of the cytopathic effect are not sufficiently distinct to allow identification of the virus on this basis alone, even by a trained observer. Direct antigen tests for identification of HMPV antigens in nasopharyngeal secretions are available but are less efficient than nucleic acid–based detection. Some laboratories have success with the use of immunofluorescence staining with monoclonal or polyclonal antibodies to detect HMPV in nasopharyngeal secretions and shell vial cultures or in monolayer cultures in which virus has been cultivated. The most sensitive test for identification of HMPV in clinical samples is reverse transcriptase PCR, usually performed with primers directed to conserved viral genes. Detection by this modality is also available in some multiplex PCR tests for panels of respiratory viruses. Real-time reverse transcriptase PCR tests offer enhanced sensitivity and specificity, including assays designed to detect viruses from the 4 known genetic lineages.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In temperate areas, the diagnosis should be suspected during the late winter in infants or young children with wheezing or pneumonia and a negative RSV diagnostic test result. The diseases caused by RSV and HMPV cannot be distinguished clinically. Many other common respiratory viruses, such as parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, enteroviruses, and coronaviruses, can cause similar disease in young children. Some of these viruses can be identified by PCR genetic testing or conventional cell culture means.

COMPLICATIONS

Bacterial superinfection of the lower airways is unusual but does occur. The local complication of otitis media is common, likely a result of eustachian tube dysfunction caused by the virus.

TREATMENT

There is no specific treatment at this time for HMPV infection. Management consists of supportive care. The rate of bacterial lung infection or bacteremia associated with HMPV infection is not fully defined but is suspected to be low. Antibiotics are usually not indicated in treatment of infants hospitalized for HMPV bronchiolitis or pneumonia.

SUPPORTIVE CARE

Treatment is supportive and includes careful attention to hydration, monitoring of respiratory status by physical examination and measurement of oxygen saturation, use of supplemental oxygen, and, if necessary, mechanical ventilation.

PROGNOSIS

Most infants and children recover from acute HMPV infection without apparent long-term consequences. Many experts believe an association exists between severe HMPV infections in infancy and risk for recurrent wheezing or the development of asthma; however, it is not clear whether the virus causes these conditions or precipitates their first manifestations.

PREVENTION

The only method of prevention of HMPV infection is reduction of exposure. Contact precautions are recommended for the duration of HMPV-associated illness among hospitalized infants and young children. Patients known to have HMPV infection should be housed in single rooms or with a cohort of HMPV-infected patients. When feasible, it is wise to care for patients with RSV infection in a separate cohort from HMPV-infected patients, so as to prevent coinfection. Preventive measures include limiting exposure to contagious settings during annual epidemics (such as daycare centers) as much as possible and emphasis on hand hygiene in all settings, including the home, especially during periods when the contacts of high-risk children have respiratory infections. However, providers should keep in mind that infection is universal in the 1st several years of life. Therefore, reduction of exposure makes most sense during the 1st 6 mo of life, when infants are at highest risk for severe disease.

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Chapter 262

Adenoviruses

Jason B. Weinberg and John V. Williams

Human adenoviruses (HAdVs) are a common cause of human disease. Conjunctivitis is a familiar illness associated with HAdVs, but these viruses also cause upper and lower respiratory disease, pharyngitis, gastroenteritis, and hemorrhagic cystitis. HAdVs can cause severe disease in immunocompromised hosts. Outbreaks of HAdV infection occur in communities and closed populations, notably the military. No specific antivirals that are highly effective against HAdVs are available. Vaccines are available for HAdV types 4 and 7, but are used only for military populations.

ETIOLOGY

Adenoviruses were first isolated from human adenoidal surgical specimens in 1953. They are nonenveloped viruses with an icosahedral protein capsid. The double-stranded DNA genome is contained within the particle complexed with several viral proteins. Antigenic variability in surface proteins of the virion defines more than 50 serotypes grouped into 8 species. Species differ in their tissue tropism and target organs, causing distinct clinical infections (Table 262-1). HAdVs can be shed from the gastrointestinal tract for prolonged periods and can establish chronic low-level infection of the tonsils and adenoids.

EPIDEMIOLOGY

HAdVs circulate worldwide and cause endemic infections year-round in immunocompetent hosts. Asymptomatic infections are also common. Only about one third of all known HAdV types are associated with clinically apparent disease. The most prevalent types in recent surveillance studies are HAdV types 3, 2, 1, and 5. Epidemics of conjunctivitis (often severe), pharyngitis, and respiratory disease occur, especially in schools and military settings. Outbreaks of febrile respiratory illness caused by HAdV-4 and HAdV-7 are a major source of morbidity in military barracks, with attack rates ranging from 25% to >90%. Spread of HAdV occurs by respiratory and fecal-oral routes. An important factor in HAdV transmission, especially in epidemics, is the ability of the nonenveloped particle to survive on inanimate objects in the environment. Nosocomial outbreaks have been reported.

Table 262-1 Adenovirus Types with Associated Infections

SPECIES	TYPE	PREFERRED SITE OF INFECTION
A	12, 18, 31	Gastrointestinal
B1	3, 7, 16, 21, 50	Respiratory
B2	11, 14, 34, 35	Renal/urinary tract epithelium
C	1, 2, 5, 6	Respiratory
D	8, 9, 10, 13, 15, 17, 19a, 19p, 20, 22-30, 32, 33, 36, 37, 38, 39, 42-48, 49, 51	Ocular
E	4	Respiratory
F	40, 41	Gastrointestinal
G	52	Gastrointestinal

PATHOGENESIS

HAdVs bind to cell surface receptors and trigger internalization by endocytosis. Acidification of the endosome induces conformational changes in the capsid, leading to eventual translocation of the genome to the cell nucleus. Viral messenger RNA transcription and genomic replication occur in the nucleus. Progeny virion particles assemble in the nucleus. Lysis of the cell releases new infectious particles and causes damage to epithelial mucosa, sloughing of cell debris, and inflammation. Host responses to HAdV infection include the recruitment of neutrophils, macrophages, and natural killer cells to the site of infection and the elaboration by these cells of a number of cytokines and chemokines. This host immune response is likely to contribute to the symptoms of HAdV infection, but specific mechanisms of pathogenesis are poorly understood. The strict species specificity of the adenoviruses precludes the development of an animal model for HAdVs; consequently, mouse adenovirus is used to study adenovirus pathogenesis using a murine model.

CLINICAL MANIFESTATIONS

HAdVs cause a variety of common clinical syndromes in both immunocompetent and immunocompromised hosts. These syndromes are difficult to distinguish reliably from similar illnesses caused by other pathogens, such as respiratory syncytial virus, human metapneumovirus, human rhinovirus, rotavirus, group A streptococcus, and other common viral and bacterial pathogens.

Acute Respiratory Disease

Respiratory tract infections are common manifestations of HAdV infections in children and adults. HAdVs cause an estimated 5-10% of all childhood respiratory disease. Primary infections in infants may manifest as bronchiolitis or pneumonia. HAdV pneumonia may manifest as features more typical of bacterial disease (lobar infiltrates, high fever, parapneumonic effusions). HAdV-14 has recently emerged as a significant cause of severe acute respiratory disease in military and civilian populations, in some cases leading to hospitalization and death. Pharyngitis caused by HAdV typically includes symptoms of coryza, sore throat, and fever. The virus can be identified in 15-20% of

children with isolated pharyngitis, mostly in preschool children and infants.

Ocular Infections

Common follicular conjunctivitis caused by HAdV is self-limiting and requires no specific treatment. A more severe form, called *epidemic keratoconjunctivitis*, involves the cornea and conjunctiva. Pharyngoconjunctival fever is a distinct syndrome that includes a high temperature, pharyngitis, nonpurulent conjunctivitis, and preauricular and cervical lymphadenopathy.

Gastrointestinal Infections

HAdV can be detected in the stools of 5-10% of children with acute diarrhea. Most cases of acute diarrhea are self-limiting, although severe disease can occur. Enteric infection with HAdV is often asymptomatic, so the causative role in these episodes is frequently uncertain. HAdV may also cause mesenteric adenitis.

Hemorrhagic Cystitis

Hemorrhage cystitis consists of a sudden onset of hematuria, dysuria, frequency, and urgency with negative urine bacterial culture results. Urinalysis may show sterile pyuria in addition to red blood cells. This illness occurs more frequently in young males and typically resolves on its own in 1-2 wk.

Other Complications

Rarely, HAdVs are associated with myocarditis, hepatitis, or meningoencephalitis in immunocompetent individuals.

Adenoviruses in Immunocompromised Patients

Immunocompromised persons are at high risk for severe disease caused by HAdV, particularly recipients of hematopoietic stem cell transplants (HSCTs) and solid organ transplants. These patients may experience primary HAdV infection, but reactivation of endogenous virus in a transplant recipient, as well as transmission of virus from a donor organ, may also occur. Organ failure as a consequence of pneumonia, hepatitis, gastroenteritis, and disseminated infection occurs primarily in these patients. HAdV infection in HSCT recipients commonly manifests as pulmonary or disseminated disease and is most likely to occur in the 1st 100 days after transplantation. Hemorrhagic cystitis can be severe in HSCT recipients. Infections caused by HAdV in solid organ transplant recipients usually involve the transplanted organ. Immunocompromised children are at greater risk than immunocompromised adults for complicated HAdV infection, presumably because of a lack of preexisting immunity. Additional risk factors are T-cell–depleted grafts, high-level immunosuppression, and presence of graft-versus-host disease. Some experts advocate a preemptive screening approach to detect and treat HAdV infection early in immunocompromised patients, with the intent to prevent dissemination and severe illness in this vulnerable population.

DIAGNOSIS

HAdV may be suspected as the etiology of an illness on the basis of epidemiologic or clinical features; neither of these categories is specific enough to firmly establish the diagnosis. The frequency of asymptomatic shedding of HAdV makes assigning causality to this pathogen difficult at times. Most HAdV serotypes grow well in culture, although this method requires 2-7 days and thus is not helpful for early identification. Cells from respiratory or ocular specimens can be tested using immunofluorescent staining with antibodies to detect HAdV protein. Commercially available enzyme-linked immunoassays can be used to rapidly detect HAdV in patient specimens, usually in stool. Molecular techniques, such as polymerase chain reaction, offer rapid, sensitive, and specific diagnosis of HAdV infections and are most useful clinically for the management of suspected HAdV infections in immunocompromised hosts. In these patients, measurement of *HAdV genome copy number* using quantitative real-time polymerase chain reaction can facilitate diagnosis, and repeated measurements can aid in assessing a patient's response to treatment. Serology is generally useful only in epidemiologic investigations.

COMPLICATIONS

HAdV pneumonia can lead to respiratory failure requiring mechanical ventilation, especially in the immunocompromised patient. Secondary bacterial pneumonias do not appear to be as common following HAdV infection as they are after influenza infection, but data for this issue are limited. Severe HAdV pneumonia has been linked to chronic lung disease and bronchiolitis obliterans in a minority of cases. Epidemic keratoconjunctivitis is a sight-threatening form of HAdV infection. Nearly any form of HAdV infection can be fatal in an HSCT or solid organ transplant recipient. Refractory severe anemia requiring repeated blood transfusions can develop in HSCT recipients with hemorrhagic cystitis. Mortality rates of up to 60-80% have been reported in transplant recipients with disseminated HAdV or HAdV pneumonia.

TREATMENT

Supportive care is the mainstay of HAdV treatment in most cases. Patients with severe HAdV conjunctivitis should be referred for ophthalmologic consultation. No specific antiviral therapy produces a definite clinical benefit against HAdV infection. The nucleoside analog cidofovir has in vitro activity against most HAdV serotypes. Cidofovir is used topically to treat epidemic keratoconjunctivitis, often in conjunction with topical steroids or other immunosuppressive agents to limit the inflammatory component. Cidofovir may be used intravenously for HAdV infections in immunocompromised patients. Cidofovir is highly nephrotoxic; however, prehydration, concomitant administration of probenecid, and weekly dosing may alleviate renal toxicity. Clinical studies suggest benefit from cidofovir, but there are no prospective, randomized controlled trials of cidofovir for HAdV. In addition, no formal guidelines or recommendations for treatment exist. There are anecdotal descriptions of benefit from intravenous immunoglobulin. Adoptive immunotherapy involving the infusion of HAdV-specific T cells may also provide some benefit for immunocompromised patients with life-threatening HAdV infections, but this intervention is not yet considered standard therapy.

PREVENTION

Environmental and fomite transmission of HAdV occurs readily; therefore, simple measures such as handwashing and cleaning reduce spread. Live-attenuated HAdV-4 and HAdV-7 vaccines were used effectively in the United States military from the 1970s until 1999. Cessation of their use led to widespread outbreaks in barracks, and these vaccines have been reintroduced into military use. HAdVs are highly immunogenic and have been used as gene therapy vectors and vaccine vectors for other pathogens, including malaria and HIV, but no HAdV-specific vaccines are commercially available.

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Chapter 263

Rhinoviruses

E. Kathryn Miller and John V. Williams

Human rhinoviruses (HRVs) are the most frequent cause of the **common cold** in both adults and children. Although rhinoviruses were once thought to cause only the common cold, it is now known that they are associated with lower respiratory infections in adults and children. Many HRVs do not grow in culture; studies using molecular diagnostic tools such as polymerase chain reaction (PCR) have revealed that HRVs are leading causes of both mild and serious respiratory illnesses in children.

ETIOLOGY

HRVs are members of the Picornaviridae family ("pico" = small; "rna" = RNA genome). Traditional methods of virus typing using immune

antiserum have identified approximately 100 serotypes, classified into HRVA and HRVB species on the basis of genetic sequence similarity. A novel group of HRVs, designated HRVCs, has been detected by reverse transcriptase PCR but has not been cultivated using conventional methods. Virus gene sequence analysis demonstrates that HRVCs are a genetically distinct and diverse species. The increased proportions of HRV reported in recent PCR-based studies are likely the result of detection of these previously unknown HRVC viruses in addition to improved detection of known HRVA and HRVB strains.

EPIDEMIOLOGY

Rhinoviruses are distributed worldwide. There is no proven correlation between serotypes and epidemiologic or clinical characteristics, although several studies suggest that HRVC may be more strongly associated with lower respiratory infection and asthma than other HRVs. Multiple serotypes circulate in a community simultaneously, and particular HRV strains may be isolated during consecutive epidemic seasons, suggesting persistence in a community over an extended period. In temperate climates the incidence of HRV infection peaks in fall, with another peak in spring, but HRV infections occur year-round. HRVC appears to circulate with seasonal variation, exchanging dominance with HRVA. Rhinoviruses are the major infectious trigger for asthma among young children, and numerous studies have described a sharp increase in asthmatic attacks in this age group when school opens in the fall. Peak HRV incidence in the tropics occurs during the rainy season, from June to October.

Rhinoviruses are present in high concentrations in nasal secretions and can be detected in the lower airways. Rhinovirus particles are nonenveloped and quite hardy, persisting for hours to days in secretions on hands or other surfaces such as telephones, light switches, doorknobs, and stethoscopes. Transmission occurs when infected secretions carried on contaminated fingers are rubbed onto the nasal or conjunctival mucosa. Rhinoviruses are present in aerosols produced by talking, coughing, and sneezing. Children are the most important reservoir of the virus.

PATHOGENESIS

The majority of HRVs infect respiratory epithelial cells via intercellular adhesion molecule-1, but some HRV strains utilize the low-density lipoprotein receptor. The receptor for HRVCs is not known. Infection begins in the nasopharynx and spreads to the nasal mucosa and, in some cases, to bronchial epithelial cells in the lower airway. Rhinoviruses do not appear to cause significant direct cellular damage, so it is thought that many of the pathogenic effects are produced by the host immune response. Rhinovirus infection of bronchial epithelial cells in vitro induces the secretion of many inflammatory chemokines and cytokines. Both innate and adaptive immune mechanisms are important in HRV pathogenesis and clearance. HRV-specific nasal immunoglobulin (Ig) A can be detected on day 3 after infection, followed by the production of serum IgM and IgG after 7-8 days. Neutralizing IgG to HRVs may prevent or limit the severity of illness following reinfection. Cross protection between antibodies to different HRV serotypes is limited in breadth and duration. Both allergen exposure and elevated IgE values predispose patients with asthma to more severe respiratory symptoms in response to HRV infection. Abnormalities in the host cellular response to HRV infection that result in impaired apoptosis and increased viral replication may be responsible for the severe and prolonged symptoms in individuals with asthma.

CLINICAL MANIFESTATIONS

Most HRV infections produce clinical symptoms, but approximately 15% are asymptomatic. Typical symptoms of sneezing, nasal congestion, rhinorrhea, and sore throat develop following an incubation period of 1-4 days. Cough and hoarseness are present in one third of cases. Fever is less common with HRV than with other common respiratory viruses, including influenza virus, respiratory syncytial virus, and human metapneumovirus. Symptoms are frequently more severe and last longer in children, with 70% of children still reporting symptoms by day 10, compared with 20% of adults. Virus can be shed for as long as 3 wk.

HRVs are the most prevalent agents associated with acute wheezing, otitis media, and hospitalization for respiratory illness in children and are an important cause of severe pneumonia and exacerbation of asthma or chronic obstructive pulmonary disease in adults. HRV-associated hospitalizations are more frequent in young infants than in older children and in children with a history of wheezing or asthma. HRV infection in immunocompromised hosts may be life threatening. Certain strains or species of HRV, namely HRVC, may be more pathogenic than others.

DIAGNOSIS

Culturing HRV is labor intensive and of relatively low yield; HRVC has only been cultivated in polarized primary airway epithelial cell culture, a highly specialized method. Sensitive and specific diagnostic methods based on reverse transcriptase PCR are commercially available. However, because reverse transcriptase PCR tests do not identify the HRV types, it can be difficult to distinguish prolonged shedding from newly acquired infection. An important caveat of HRV detection is the fact that HRV infection can be asymptomatic, and thus the presence of the virus does not prove causality in all cases. Serology is impractical because of the great number of HRV serotypes. Presumptive clinical diagnosis based on symptoms and seasonality is not specific, because many other viruses cause similar clinical illnesses. Bacterial culture or antigen testing may exclude streptococcal pharyngitis. Rapid detection techniques for HRV might lessen the use of unnecessary antibiotics or procedures.

COMPLICATIONS

Possible complications of HRV infection include sinusitis, otitis media, asthma exacerbation, bronchiolitis, pneumonia, and, rarely, death. HRV-associated wheezing during infancy is a significant risk factor for the development of childhood asthma. This effect appears to remain until adulthood, but the mechanisms have not been elucidated. One large study determined that genetic variants at the 17q21 locus were associated with asthma in children who had experienced HRV wheezing illnesses during infancy. Further studies are required to determine the likely multiple genetic and environmental factors that contribute to HRV-related asthma.

TREATMENT

Supportive care is the mainstay of HRV treatment. The symptoms of HRV infection are commonly treated with analgesics, decongestants, antihistamines, or antitussives. Data are limited on the effectiveness of such nonprescription cold medications for children. If bacterial superinfections are highly suspected or diagnosed, antibiotics may be appropriate. Antibiotics are not indicated for uncomplicated viral upper respiratory infection. Vaccines have not been successfully developed because of the numerous HRV serotypes and limited cross protection between serotypes.

PREVENTION

Good handwashing remains the mainstay of prevention of HRV infection and should be reinforced frequently, especially in young children, the predominant "vectors" for disease.

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Chapter 264

Coronaviruses

Megan Culler Freeman and Mark R. Denison

Coronaviruses are increasingly recognized as important human pathogens. They cause up to 15% of common colds and have been implicated in more serious diseases, including croup, asthma exacerbations, bronchiolitis, and pneumonia. Evidence also suggests that coronaviruses may cause enteritis or colitis in neonates and infants and may be

underappreciated as agents of meningitis or encephalitis. Four coronaviruses are endemic in humans: human coronaviruses **(HCoVs) 229E**, **OC43**, **NL63**, and **HKU1**. In addition, 2 epidemics of previously unknown coronaviruses caused significant respiratory distress and high mortality rates among infected individuals. The discoveries of **SARS-associated coronavirus (SARS-CoV)** in 2003, the cause of **severe acute respiratory syndrome (SARS)**, and of **Middle East respiratory syndrome coronavirus (MERS-CoV)** in 2012, support the potential for coronaviruses to emerge from animal hosts such as bats and become important human pathogens.

ETIOLOGY

Coronaviruses are enveloped viruses of medium to large size (80-220 nm) that possess the largest known single-stranded positive-sense RNA genomes. These viruses encode the protein nsp14-ExoN, which is the first known RNA proofreading enzyme and is likely responsible for the evolution of the large and complex coronavirus genome. Coronaviruses derive their name from the characteristic surface projections of spike protein, which give a corona or crown-like appearance on negative-stain electron microscopy. Coronaviruses are organized taxonomically by a lettering system based on genomic phylogenetic relationships. Alphacoronaviruses include human coronavirus 229E (HCoV-229E) and HCoV-NL63. Betacoronaviruses include 4 human pathogens and are commonly divided into 4 lineages, without formal taxonomic recognition. HCoV-OC43 and the HCoV-HKU1 are in lineage A, while SARS-CoV falls in lineage B. Lineages C and D were exclusively comprised of bat coronaviruses until the discovery of MERS-CoV, which aligns with lineage C. Gammacoronaviruses and deltacoronaviruses presently include exclusively nonhuman pathogens.

In 2002-2003, coronaviruses received international attention during the SARS outbreak, which was responsible for more than 800 deaths in 30 countries. SARS-CoV, a novel coronavirus at the time of the epidemic, was found to be the causative agent of SARS. The detection of SARS-like coronaviruses in a live animal market in the Guangdong province in Southern China, along with serologic evidence of exposure in food handlers in the same market, suggest that these markets may have facilitated the spread of SARS-CoV to humans from an animal reservoir. Subsequent studies identified SARS-like coronaviruses in fecal specimens from asymptomatic Chinese horseshoe bats that are very closely related, but not direct precursors to, SARS-CoV. Thus, although bats are thought to be a reservoir for SARS-like precursors, the precise antecedent to SARS-CoV remains to be identified.

In June 2012, another novel coronavirus, **MERS-CoV**, was isolated from a man with acute pneumonia and renal failure in Saudi Arabia. To date, more than 500 cases have been confirmed in Saudi Arabia, Qatar, Jordan, United Arab Emirates, Oman, Kuwait, Yemen, United States (imported), and the United Kingdom; 145 of these patients died from their infection. **MERS-CoV** differs from SARS in that it seems to be less communicable, although human-to-human transmission has been confirmed. **MERS-CoV** has been shown to use dipeptidyl peptidase 4 as its cellular receptor, a difference compared to SARS-CoV, which utilizes ACE-2. With this receptor specificity, **MERS-CoV** is able to infect cells from several animal lineages, including human, pig, and bat, suggesting the possibility of movement between multiple species.

EPIDEMIOLOGY

Seroprevalence studies have demonstrated that antibodies against 229E and OC43 increase rapidly during early childhood, so that by adulthood 90-100% of persons are seropositive. Although less information is available for HKU1 and NL63, available studies demonstrate similar patterns of seroconversion to these viruses during early childhood. Although some degree of strain-specific protection may be afforded by recent infection, reinfections are common and occur despite the presence of strain-specific antibodies. Attack rates are similar in different age groups. Although infections occur throughout the year, there is a peak during the winter and early spring for each of these HCoVs. In the United States, outbreaks of OC43 and 229E have occurred in 2- to 3-yr alternating cycles. Independent studies of viral etiologies of upper and lower respiratory infections during the same period, but from different countries, have confirmed that all known HCoVs have a worldwide distribution. Studies using both viral culture and polymerase chain reaction (PCR) multiplex assays demonstrate that coronaviruses often occur as coinfections with other respiratory viruses, including respiratory syncytial virus, adenovirus, rhinovirus, or human metapneumovirus. Volunteer studies demonstrated that OC43 and 229E are transmitted predominantly through the respiratory route. Droplet spread appears to be most important, although aerosol transmission may also occur.

There have been no identified natural or laboratory-acquired cases of SARS-CoV since 2004, but the mechanisms of introduction, spread, and disease remain important for potential animal-to-human transmission and disease. The primary mode of SARS-CoV transmission occurred through direct or indirect contact of mucous membranes with infectious droplets or fomites. Aerosol transmission was less common, occurring primarily in the setting of endotracheal intubation, bronchoscopy, or treatment with aerosolized medications. Fecal-oral transmission did not appear to be an efficient mode of transmission, but may have occurred because of the profuse diarrhea observed in some patients. The seasonality of SARS-CoV remains unknown. SARS-CoV is not highly infectious, with generally only 2-4 secondary cases resulting from a single infected adult. During the SARS epidemic, a small number of infected individuals, "superspreaders," transmitted infection to a much larger number of persons, but the mechanism for this high degree of spread remains unknown. In contrast, persons with mild disease, such as children younger than 12 yr of age, rarely transmitted the infection to others. Infectivity correlated with disease stage; transmission occurred almost exclusively during symptomatic disease. During the 2003 outbreak, most individuals with SARS-CoV infection were hospitalized within 3-4 days of symptom onset. Consequently, most subsequent infections occurred within hospitals and involved either healthcare workers or other hospitalized patients. MERS-CoV may begin in an animal vector (camel, bat); although person-to-person contagion has been reported, it is thought to be a minor mechanism for acquisition of the MERS-CoV.

PATHOGENESIS

Coronaviruses are reported to cause minimal cytopathology. Studies with SARS-CoV in human airway epithelial cell cultures indicate that ciliated cells are principal targets for infection and that infected ciliated cells may be directly extruded or lost from the infected monolayer. Thus, the cytopathology from other HCoVs may be from direct cell infection and loss, although symptoms may also be from the host immune response. Infection with OC43 and 229E is associated with the elaboration of cytokines, including interleukin-8 and interferon-γ. In experimentally infected volunteers, serum-specific immunoglobulin A and immunoglobulin G antibody levels peak 12-14 days after infection but decline rapidly thereafter. At 1 year following experimental infection, there is only partial protection against reinfection with the homologous strain, suggesting a challenge for the development of successful vaccines against HCoVs.

CLINICAL MANIFESTATIONS

While all known HCoVs cause respiratory disease, the role of HCoVs in gastrointestinal and neurologic disease is less clear and remains to be proven. In addition to causing severe respiratory pathology, both SARS-CoV and MERS-CoV can cause renal failure, although this symptom is observed less frequently during SARS-CoV infections.

Respiratory Infections

Even though up to 50% of respiratory tract infections with OC43 and 229E are asymptomatic, coronaviruses are still responsible for up to 15% of common colds. Cold symptoms caused by HCoVs are indistinguishable from those caused by rhinoviruses and other respiratory viruses. The average incubation period is 2-4 days, with symptoms typically lasting 4-7 days. Rhinorrhea, cough, sore throat, malaise, and headache are the most common symptoms. Fever occurs in up to 60% of cases. Coronavirus NL63 is a cause of croup in children younger than 3 yr of age. Coronavirus infections are linked to episodes of wheezing in asthmatic children, albeit at a lower frequency and

severity than observed with rhinovirus and respiratory syncytial virus infections. Lower respiratory tract infections, including bronchiolitis and pneumonia, are also reported in immunocompetent and immunocompromised children and adults. As with respiratory syncytial virus or rhinovirus, coronavirus detection in upper respiratory infections is frequently associated with acute otitis media and can be isolated from middle ear fluid.

Nonrespiratory Sequelae

There is some evidence to support a role for coronaviruses in human gastrointestinal disease, particularly in young children. Coronavirus-like particles have been detected by electron microscopy in the stools of infants with nonbacterial gastroenteritis. In addition, several outbreaks in neonatal intensive care units of gastrointestinal disease characterized by diarrhea, bloody stools, abdominal distention, bilious gastric aspirates, and classic necrotizing enterocolitis have also been associated with the presence of coronavirus-like particles in stools. In older children and adults, coronavirus-like viruses have been observed with similar frequency in symptomatic and asymptomatic individuals, making it difficult to discern if they are pathogenic in the gastrointestinal tract. Coronaviruses are well-known causes of neurologic disease in animals, including demyelinating encephalitis, but their role in causing human neurologic disease remains unclear. They have been detected by culture, in situ hybridization, and reverse transcriptase PCR (RT-PCR) in brain tissue from a few patients with multiple sclerosis. However, coronavirus RNA has also been recovered from the spinal fluid and brain tissue of adults without neurologic disease. HCoV-OC43 has been detected by RT-PCR in the spinal fluid and nasopharynx of one child with acute disseminated encephalomyelitis.

Severe Acute Respiratory Syndrome–Associated Coronavirus

SARS-CoV infections in teenagers and adults included a viral replication phase and an immunologic phase. During the viral replication phase there was a progressive increase in viral load that reached its peak during the 2nd wk of illness. The appearance of specific antibodies coincided with peak viral replication. The clinical deterioration that typified the 2nd and 3rd wk of illness was characterized by a decline in the viral load and evidence of tissue injury likely from cytokine-mediated immunity. The explanation for milder clinical disease in children younger than 12 yr of age has not been determined. Seroepidemiologic studies suggest that asymptomatic SARS-CoV infections were uncommon. The incubation period ranged from 1-14 days, with a median of 4-6 days. The clinical manifestations were nonspecific, most commonly consisting of fever, cough, malaise, coryza, chills or rigors, headache, and myalgia. Coryza was more common in children younger than 12 yr of age, whereas systemic symptoms were seen more often in teenagers. Some young children had no respiratory symptoms. Gastrointestinal symptoms, including diarrhea and nausea or vomiting, occurred in up to one third of cases. The clinical course of SARS-CoV infection varied with age. Adults were most severely affected, with initial onset of fever, cough, chills, myalgia, malaise, and headache. Following an initial improvement at the end of the 1st wk, fever recurred and respiratory distress developed, with dyspnea, hypoxemia, and diarrhea. These symptoms progressed in 20% of patients to acute respiratory distress syndrome and respiratory failure. Acute renal failure with histologic acute tubular necrosis was present in 6.9% of patients, likely a result of hypoxic kidney damage. Of SARS patients, 28.8% had abnormal urinalysis, with viral genome detectable by quantitative RT-PCR. In contrast, children younger than 12 yr of age had a relatively mild nonspecific illness, with only a minority experiencing significant lower respiratory tract disease and illness typically lasting less than 5 days. There were no deaths or acute respiratory distress syndrome in children younger than 12 yr of age from SARS-CoV infection. Adolescents manifested increasing severity in direct correlation to increasing age; respiratory distress and hypoxemia were observed in 10-20% of patients, one third of whom required ventilator support. The case fatality rate from SARS-CoV infection during the 2003 outbreak was 10-17%. No pediatric deaths were reported. The estimated case fatality rate according to age varied from <1% for those younger than 20 yr of age to >50% for those older than 65 yr of age.

Middle East Respiratory Syndrome Coronavirus

The incubation period of HCoV-EMC infection is thought to be approximately 10 days. Because most healthcare workers caring for patients with HCoV-EMC infection have not been infected, this virus is considered to be less transmissible from person to person than SARS-CoV. Two clusters of patients have been diagnosed with confirmed cases, although it is difficult to determine if their infections were spread from person to person or if they shared a common environmental exposure. A third cluster in the United Kingdom confirmed person-to-person transmission, as only 1 of the individuals had traveled to the Arabian Peninsula. Because the method of transmission is presently unknown, appropriate airborne and contact precautions are required when treating infected patients. Patients have presented with acute respiratory infection, a fever higher than 38°C (100.4°F), cough, and pulmonary parenchymal disease such as pneumonia or acute respiratory distress syndrome. Lymphopenia, neutrophilia, and late thrombocytopenia occurred in the index-case patient. This patient also had progressive renal impairment, beginning on the ninth day of symptoms which continued to progress until the patient's death at day 11. The case fatality rate is presently >65% for the limited number of confirmed cases. Most patients have been adults, although children as young as 1 yr of age have been infected. Approximately 65% of patients have severe disease requiring hospitalization; approximately 5% had mild disease, and the remainder may have been asymptomatic.

DIAGNOSIS

In the past, specific diagnostic tests for coronavirus infections were not available in most clinical settings. The use of conserved PCR primers for coronaviruses in multiplex RT-PCR viral diagnostic panels now allows widely available and sensitive detection of the viruses. Virus culture of primary clinical specimens remains a challenge for HCoVs HKU1, OC43, 229E, and NL63, even though both SARS-CoV and MERS-CoV can successfully be grown in culture from respiratory samples. Serodiagnosis with complement fixation, neutralization, hemagglutination inhibition, enzyme immunoassay, and Western blots have been used in the research setting. The diagnosis of SARS-CoV infection can be confirmed by serologic testing, detection of viral RNA using RT-PCR, or isolation of the virus in cell culture. Even though serology for SARS-CoV has sensitivity and specificity approaching 100%, antibodies are not detectable until 10 days after the onset of symptoms, and immunoglobulin G seroconversion may be delayed for up to 4 wk. In addition, the SARS epidemic resulted in the inclusion of coronavirus-conserved primers in many diagnostic PCR multiplex assays such that coronaviruses may be more readily detected. For emerging coronaviruses, such as HCoV-EMC, highly conserved primers were used for initial detection, with confirmatory assays using specific primers. Thus, the mainstay of early diagnosis is RT-PCR. For all known endemic and emerging HCoVs, respiratory specimens (nasopharyngeal swabs or aspirates) are most likely to be positive, but in a setting of a possible novel coronavirus, serum or stool may be positive. Two highly sensitive real-time RT-PCR assays are currently available for testing for MERS-CoV RNA in addition to utilizing immunofluorescence microscopy for the detection of antibody response.

TREATMENT AND PREVENTION

Coronavirus infections of humans are acute and self-limited, although persistent infection and shedding may occur in multiple animal models in the setting of minimal or no symptomology. There are no available antiviral agents for clinical use against coronaviruses, although strategies targeting conserved coronavirus proteases have been shown to block replication of the virus in vitro. Challenges for development of effective vaccines targeted against OC43, 229E, HKU1, and NL63 include the fact that infections are rarely life-threatening and reinfection is the rule, even in the presence of natural immunity from previous infections. Treatment of SARS-CoV and MERS-CoV infections is primarily supportive. The role of antiviral and immune-modulating

agents remains inconclusive, largely because none of these therapies have been evaluated in properly conducted randomized controlled trials. Ribavirin was extensively used during the 2003 SARS-CoV outbreak, but is of questionable benefit given its poor in vitro activity against SARS-CoV at clinically relevant concentrations. The identification of the proofreading nsp14-exonuclease suggests that this activity may be important in resistance to antiviral nucleosides and RNA mutagens such as ribavirin. Systemic corticosteroid therapy was temporally associated with clinical improvement in some patients. In another small, open-label, nonrandomized pilot study, interferon-α was associated with more rapid resolution of oxygen requirements and radiographic abnormalities. Human monoclonal antibodies derived from SARS patients demonstrate broad neutralization against early and late epidemic strains of SARS-CoV and could potentially be therapeutic.

An effective vaccine for SARS-CoV and MERS-CoV is highly desirable but not yet available. A potential vaccine target is the viral spike protein, which could be delivered as a recombinant protein or via viral or DNA vectors. This approach appears to be effective against closely related strains of SARS-CoV but not necessarily early animal or human variants. A SARS-CoV vaccine approach that recently has shown success in animal models utilized a live-engineered SARS-CoV mutant with inactivated ExoN, demonstrating attenuation and protection in a variety of aged, immunocompromised mice. Approaches for rapid development of stably attenuated live viruses or broadly immunogenic and cross-protective protein immunogens continues to be a key area for future research. Although SARS-CoV demonstrated characteristics of symptomatic transmission that made it controllable by public health measures like quarantine, these characteristics cannot be assumed for future novel HCoVs. The recent outbreak of MERS-CoV serves as a reminder that coronavirus emergence is both likely and unpredictable, making it very important to continue studies of the coronavirus replication, emergence, and transmission of coronaviruses. Additionally, strategies for rapid recovery, testing, and development of vaccines and neutralizing human monoclonal antibodies may be essential to prevent the high morbidity and mortality associated with previous epidemics.

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Chapter 265

Rotaviruses, Caliciviruses, and Astroviruses

Dorsey M. Bass

Diarrhea is a leading cause of childhood mortality in the world, accounting for 5-10 million deaths/yr. In early childhood, the single most important cause of severe dehydrating diarrhea is rotavirus infection. Rotavirus and other gastroenteric viruses not only are major causes of pediatric mortality but also lead to significant morbidity. Children in the United States, before vaccine was available, were estimated to have a risk of hospitalization for rotavirus diarrhea of 1:43, corresponding to 80,000 hospitalizations annually.

ETIOLOGY

Rotaviruses, astroviruses, caliciviruses such as the **Norwalk agent,** and enteric adenoviruses are the medically important pathogens of human viral gastroenteritis (see Chapter 340).

Rotaviruses are in the Reoviridae family and cause disease in virtually all mammals and birds. These viruses are wheel-like, triple-shelled icosahedrons containing 11 segments of double-stranded RNA. The diameter of the particles on electron microscopy is approximately 80 nm. Rotaviruses are classified by serogroup (A, B, C, D, E, F, and G) and subgroup (I or II). Rotavirus strains are species specific and do not cause disease in heterologous hosts. Group A includes the common human pathogens as well as a variety of animal viruses. Group B rotavirus is reported as a cause of severe disease in infants and adults in China only. Occasional human outbreaks of group C rotavirus are reported. The other serogroups infect only nonhumans.

Subgrouping of rotaviruses is determined by the antigenic structure of the inner capsid protein, VP6. Serotyping of rotaviruses, described for group A only, is determined by classic cross-neutralization testing and depends on the outer capsid glycoproteins, VP7 and VP4. The VP7 serotype is referred to as the *G type* (for glycoprotein). There are 10 G serotypes, of which 4 cause most illness and vary in occurrence from year to year and region to region. The VP4 serotype is referred to as the P type. There are 11 P serotypes. Although both VP4 and VP7 elicit neutralizing immunoglobulin G antibodies, the relative role of these systemic antibodies compared with that of mucosal immunoglobulin A antibodies and cellular responses in protective immunity remains unclear.

Caliciviruses, which constitute the Caliciviridae family, are small 27-35 nm viruses that are the most common cause of gastroenteritis outbreaks in older children and adults. Caliciviruses also cause a rotavirus-like illness in young infants. They are positive-sense, single-stranded RNA viruses with a single structural protein. Human caliciviruses are divided into 2 genera, the noroviruses and sapoviruses. Caliciviruses have been named for locations of initial outbreaks: Norwalk, Snow Mountain, Montgomery County, Sapporo, and others. Caliciviruses and astroviruses are sometimes referred to as **small, round viruses** on the basis of appearance on electron microscopy.

Astroviruses, which constitute the Astroviridae family, are important agents of viral gastroenteritis in young children, with a high incidence in both the developing and developed worlds. Astroviruses are positive-sense, single-stranded RNA viruses. They are small particles, approximately 30 nm in diameter, with a characteristic central 5- or 6-pointed star when viewed on electron microscopy. The capsid consists of 3 structural proteins. There are 8 known human serotypes.

Enteric adenoviruses are a common cause of viral gastroenteritis in infants and children. Although many adenovirus serotypes exist and are found in human stool, especially during and after typical upper respiratory tract infections (see Chapter 262), only serotypes 40 and 41 cause gastroenteritis. These strains are very difficult to grow in tissue culture. The virus consists of an 80 nm-diameter icosahedral particle with a relatively complex double-stranded DNA genome.

Aichi virus is a picornavirus that is associated with gastroenteritis and was initially described in Asia. Several other viruses that may cause diarrheal disease in animals have been postulated but are not well established as human gastroenteritis viruses. These include coronaviruses, toroviruses, and pestiviruses. The **picobirnaviruses** are an unclassified group of small (30 nm), single-stranded RNA viruses that have been found in 10% of patients with HIV-associated diarrhea.

EPIDEMIOLOGY

Worldwide, rotavirus is estimated to cause more than 111 million cases of diarrhea annually in children younger than 5 yr of age. Of these, 18 million cases are considered at least moderately severe, with approximately 500,000 deaths per year. Rotavirus causes 3 million cases of diarrhea, 80,000 hospitalizations, and 20-40 deaths annually in the United States.

Rotavirus infection is most common in winter months in temperate climates. In the United States, the annual winter peak historically spread from west to east. Unlike the spread of other winter viruses, such as influenza, this wave of increased incidence was not caused by a single prevalent strain or serotype. Since widespread adoption of vaccine, this geographic phenomenon has vanished. Typically, several serotypes predominate in a given community for 1 or 2 seasons, while nearby locations may harbor unrelated strains. Disease tends to be most severe in patients 3-24 mo of age, although 25% of the cases of severe disease occur in children older than 2 yr of age, with serologic evidence of infection developing in virtually all children by 4-5 yr of age. Infants younger than 3 mo are relatively protected by transplacental antibody and possibly breastfeeding. Infections in neonates and in adults in close

contact with infected children are generally asymptomatic. Some rotavirus strains have stably colonized newborn nurseries for years, infecting virtually all newborns without causing any overt illness.

Rotavirus and the other gastrointestinal viruses spread efficiently via a fecal-oral route, and outbreaks are common in children's hospitals and childcare centers. The virus is shed in stool at very high concentration before and for days after the clinical illness. Very few infectious virions are needed to cause disease in a susceptible host.

The epidemiology of **astroviruses** is not as thoroughly studied as that of rotavirus, but these viruses are a common cause of mild to moderate watery winter diarrhea in children and infants and an uncommon pathogen in adults. Hospital outbreaks are common. **Enteric adenovirus** gastroenteritis occurs year-round, mostly in children younger than 2 yr of age. Nosocomial outbreaks occur but are less common than with rotavirus and astrovirus. **Calicivirus** is best known for causing large, explosive outbreaks among older children and adults, particularly in settings such as schools, cruise ships, and hospitals. Often a single food, such as shellfish or water used in food preparation, is identified as a source. Like astrovirus and rotavirus, caliciviruses are also commonly found in winter infantile gastroenteritis.

PATHOGENESIS

Viruses that cause human diarrhea selectively infect and destroy villus tip cells in the small intestine. Biopsies of the small intestines show variable degrees of villus blunting and round cell infiltrate in the lamina propria. Pathologic changes may not correlate with the severity of clinical symptoms and usually resolve before the clinical resolution of diarrhea. The gastric mucosa is not affected despite the commonly used term *gastroenteritis,* although delayed gastric emptying has been documented during Norwalk virus infection.

In the small intestine, the upper villus enterocytes are differentiated cells, which have both digestive functions, such as hydrolysis of disaccharides, and absorptive functions, such as the transport of water and electrolytes via glucose and amino acid cotransporters. Crypt enterocytes are undifferentiated cells that lack the brush-border hydrolytic enzymes and are net secretors of water and electrolytes. Selective viral infection of intestinal villus tip cells thus leads to (1) decreased absorption of salt and water and an imbalance in the ratio of intestinal fluid absorption to secretion, and (2) diminished disaccharidase activity and malabsorption of complex carbohydrates, particularly lactose. Most evidence supports altered absorption as the more important factor in the genesis of viral diarrhea. It has been proposed that a rotavirus nonstructural protein (NSP4) functions as an enterotoxin.

Viremia may occur often in severe, primary infections, but symptomatic **extraintestinal infection** is extremely rare in immunocompetent persons—although immunocompromised patients may rarely experience hepatic and renal involvement. The increased vulnerability of infants (compared with older children and adults) to severe morbidity and mortality from gastroenteritis viruses may relate to a number of factors, including decreased intestinal reserve function, lack of specific immunity, and decreased nonspecific host defense mechanisms such as gastric acid and mucus. Viral enteritis greatly enhances intestinal permeability to luminal macromolecules and has been postulated to increase the risk for food allergies.

CLINICAL MANIFESTATIONS

Rotavirus infection typically begins after an incubation period of <48 hr (range: 1-7 days) with mild to moderate fever as well as vomiting, followed by the onset of frequent, watery stools. All 3 symptoms are present in about 50-60% of cases. Vomiting and fever typically abate during the 2nd day of illness, but diarrhea often continues for 5-7 days. The stool is without gross blood or white blood cells. Dehydration may develop and progress rapidly, particularly in infants. The most severe disease typically occurs among children 4-36 mo of age. Malnourished children and children with underlying intestinal disease, such as short-bowel syndrome, are particularly likely to acquire severe rotavirus diarrhea. Rarely, immunodeficient children experience severe and prolonged illness. Although most newborns infected with rotavirus are asymptomatic, some outbreaks of necrotizing enterocolitis have been associated with the appearance of a new rotavirus strain in the affected nurseries.

The clinical course of **astrovirus** infection appears to be similar to that of rotavirus gastroenteritis, with the notable exception that the disease tends to be milder, with less significant dehydration. **Adenovirus enteritis** tends to cause diarrhea of longer duration, often 10-14 days. The **Norwalk virus** has a short (12-hr) incubation period. Vomiting and nausea tend to predominate in illness associated with the Norwalk virus, and the duration is brief, usually consisting of 1-3 days of symptoms. The clinical and epidemiologic picture of Norwalk virus often closely resembles so-called food poisoning from preformed toxins such as *Staphylococcus aureus* and *Bacillus cereus.*

DIAGNOSIS

In most cases, a satisfactory diagnosis can be made on the basis of the clinical and epidemiologic features. Enzyme-linked immunosorbent assays, which offer >90% specificity and sensitivity, are available for detection of group A rotavirus, caliciviruses, and enteric adenovirus in stool samples. Latex agglutination assays are also available for group A rotavirus and are less sensitive than enzyme-linked immunosorbent assay. Research tools include electron microscopy of stools, RNA polymerase chain reaction analysis to identify G and P antigens, and culture. The diagnosis of viral gastroenteritis should always be questioned in patients with persistent or high fever, blood or white blood cells in the stool, or persistent severe or bilious vomiting, especially in the absence of diarrhea.

LABORATORY FINDINGS

Isotonic dehydration with acidosis is the most common finding in children with severe viral enteritis. The stools are free of blood and leukocytes. Although the white blood cell count may be moderately elevated secondary to stress, the marked left shift seen with invasive bacterial enteritis is absent.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes other infectious causes of enteritis, such as bacteria and protozoa. Occasionally, surgical conditions such as appendicitis, bowel obstruction, and intussusception may initially mimic viral gastroenteritis.

TREATMENT

Avoiding and treating dehydration are the main goals in treatment of viral enteritis. A secondary goal is maintenance of the nutritional status of the patient (see Chapters 58 and 340).

There is no routine role for antiviral drug treatment of viral gastroenteritis. Controlled studies show no benefit from antiemetics or antidiarrheal drugs, and there is a significant risk for serious side effects with both types of agents. Antibiotics are similarly of no benefit. Immunoglobulins have been administered orally to both normal and immunodeficient patients with severe rotavirus gastroenteritis, but this treatment is currently considered experimental. Therapy with probiotic organisms such as *Lactobacillus* species has been shown to be helpful only in mild cases and not in dehydrating disease.

Supportive Treatment

Rehydration via the oral route can be accomplished in most patients with mild to moderate dehydration (see Chapters 58 and 340). Severe rehydration requires immediate intravenous therapy followed by oral rehydration. Modern oral rehydration solutions containing appropriate quantities of sodium and glucose promote optimum absorption of fluid from the intestine. There is no evidence that a particular carbohydrate source (rice) or addition of amino acids improves the efficacy of these solutions for children with viral enteritis. Other clear liquids, such as flat soda, fruit juice, and sports drinks, are inappropriate for rehydration of young children with significant stool loss. Rehydration via the oral (or nasogastric) route should be done over 6-8 hr, and feedings should be initiated immediately thereafter. Providing the rehydration fluid at a slow, steady rate, typically 5 mL/min, reduces vomiting and improves the success of oral therapy. Rehydration

solution should be continued as a supplement to make up for ongoing excessive stool loss. Initial intravenous fluids are required for the infant in shock or the occasional child with intractable vomiting.

After rehydration has been achieved, resumption of a normal diet for age has been shown to result in a more rapid recovery from viral gastroenteritis. Prolonged (>12 hr) administration of exclusive clear liquids or dilute formula is without clinical benefit and actually prolongs the duration of diarrhea. Breastfeeding should be continued even during rehydration. Selected infants may benefit from lactose-free feedings (such as soy formula and lactose-free cow's milk) for several days, although this step is not necessary for most children. Hypocaloric diets low in protein and fat such as BRAT (*b*ananas, *r*ice, cereal, *a*pplesauce, and *t*oast) have not been shown to be superior to a regular diet.

PROGNOSIS

Most fatalities occur in infants with poor access to medical care and are attributed to dehydration. Children may be infected with rotavirus each year during the 1st 5 yr of life, but each subsequent infection decreases in severity. Primary infection results in a predominantly serotype-specific immune response, whereas reinfection, which is usually with a different serotype, induces a broad immune response with cross-reactive heterotypic antibody. After the initial natural infection, children have limited protection against subsequent asymptomatic infection (38%) and greater protection against mild diarrhea (73%) and moderate to severe diarrhea (87%). After the second natural infection, protection increases against subsequent asymptomatic infection (62%) and mild diarrhea (75%) and is complete (100%) against moderate to severe diarrhea. After the third natural infection, there is even higher protection against subsequent asymptomatic infection (74%) and near-complete protection against even mild diarrhea (99%).

PREVENTION

Good hygiene reduces the transmission of viral gastroenteritis, but even in the most hygienic societies, virtually all children become infected as a result of the efficiency of infection of the gastroenteritis viruses. Good handwashing and isolation procedures can help control nosocomial outbreaks. The role of breastfeeding in prevention or amelioration of rotavirus infection may be small, given the variable protection observed in a number of studies. Vaccines offer the best hope for control of these ubiquitous infections.

Vaccines

A trivalent rotavirus vaccine was licensed in the United States in 1998 and was subsequently linked to an increased risk for intussusception, especially during the 3-14 day period after the 1st dose and the 3-7 day period after the 2nd dose. The vaccine was withdrawn from the market in 1999. Subsequently 2 new live, oral rotavirus vaccines have been approved in the United States after extensive safety and efficacy testing.

A live, oral, pentavalent rotavirus vaccine was approved in 2006 for use in the United States. The vaccine contains 5 reassortant rotaviruses isolated from human and bovine hosts. Four of the reassortant rotaviruses express 1 serotype of the outer protein VP7 (G1, G2, G3, or G4), and the 5th expresses the protein P1A (genotype P[8]) from the human rotavirus parent strain. The pentavalent vaccine protects against rotavirus gastroenteritis when administered as a 3 dose series at 2, 4, and 6 mo of age. The 1st dose should be administered between 6 and 12 wk of age, with all 3 doses completed by 32 wk of age. The vaccine provides substantial protection against rotavirus gastroenteritis, with primary efficacy of 98% against severe rotavirus gastroenteritis caused by G1-G4 serotypes and 74% efficacy against rotavirus gastroenteritis of any severity through the first rotavirus season after vaccination. It provides a 96% reduction in hospitalizations for rotavirus gastroenteritis through the 1st 2 yr after the 3rd dose. In a study of more than 70,000 infants, the pentavalent vaccine did not increase the risk for intussusception, although other studies suggest a slight increased risk.

Another new monovalent rotavirus vaccine was licensed in the United States and also appears to be safe and effective. It is an attenuated monovalent human rotavirus and is administered as 2 oral doses at 2 and 4 mo of age. The vaccine has 85% efficacy against severe gastroenteritis and was found to reduce hospital admissions for all diarrhea by 42%. Despite being monovalent, the vaccine is effective in prevention of all 4 common serotypes of human rotavirus.

Preliminary surveillance data on rotavirus incidence from the U.S. Centers for Disease Control and Prevention suggest that rotavirus vaccination greatly reduced the disease burden in the United States during the 2007-2008 rotavirus season. Given the incomplete vaccine coverage during this period, the results suggest a degree of "herd immunity" from rotavirus immunization. Studies from several developed countries show greater than 90% protection against severe rotavirus disease. Studies from developing countries show 50-60% protection from severe disease. Vaccine-associated disease has been reported in vaccine recipients who have severe combined immunodeficiency disease (a contraindication). In addition, vaccine-derived virus may undergo reassortment and become more virulent, producing diarrhea in unvaccinated siblings.

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Chapter 266

Human Papillomaviruses

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See also Chapter 667.

Human papillomaviruses (HPVs) cause a variety of proliferative cutaneous and mucosal lesions, including common skin warts, benign and malignant anogenital tract lesions, oral pharyngeal cancers, and life-threatening respiratory papillomas. Most HPV-related infections in children and adolescents are benign.

ETIOLOGY

The papillomaviruses are small (55 nm), DNA-containing viruses that are ubiquitous in nature, infecting most mammalian and many non-mammalian animal species. Strains are almost always species specific. More than 100 different types of HPVs have been identified through comparison of sequence homologies. The different HPV types typically cause disease in specific anatomic sites; more than 30 HPV types have been identified from genital tract specimens.

EPIDEMIOLOGY

HPV infections of the skin are common, and most individuals are probably infected with 1 or more HPV types at some time. There are no animal reservoirs for HPV; all transmission is presumably from person to person. There is little evidence to suggest that HPV is transmitted by fomites. Common warts, including palmar and plantar warts, are frequently seen in children and adolescents and typically infect the hands and feet, common areas of frequent minor trauma.

Human papillomavirus is the most prevalent viral sexually transmitted infection in the United States. Up to 80% of sexually active women will acquire HPV through sexual transmission; most have their first infection within 3 yr of beginning sexual intercourse. The greatest risks for HPV in sexually active adolescents is exposure to new sexual partners or having more than 1 partner, underscoring the ease of transmission of this virus through sexual contact. It is estimated that after 11 acts of sexual intercourse 100% of all HPV types will be transmitted to the other sexual partner. Couple studies show that there is high concordance in the genital area as well as between the hand and the genital area in the other partner. Whether the DNA detected in the hand is capable of transmitting infectious particles is unknown. Unlike other sexually transmitted infections, female-to-male transmission appears greater than male-to-female transmission. This may be because males in general have superficial transient infections or deposition. In turn, males do not develop an adequate immune response, so reinfections

are quite common. The prevalence of HPV in women decreases with time, suggesting immune protection, whereas in men, the prevalence of HPV remains high across all ages.

As with many other genital pathogens, perinatal transmission to newborns also occurs, but infections appear transient. Transmission from caregiver to the child during the early childhood years has also been documented but is generally transient, as with perinatal detection. It remains unclear whether these HPV DNA detections are simply deposition of caregiver DNA or true infections. Detection of HPV DNA in older preadolescent children is rare. HPV DNA detection in nonsexually active adolescents has been reported, but the reports of no sexual activity in adolescent populations can be difficult to confirm. If lesions are detected in a child older than 3 yr of age, the possibility of sexual transmission should be raised.

In adolescents, HPV DNA is most commonly detected without evidence of any lesion. Some of these detections are thought to be the result of partner deposition and hence do not represent a true infection. In older women, detection of HPV DNA is more commonly associated with a lesion. This is because the HPV DNA detected in older women reflects those HPV infections that became established persistent infections. Persistence is now the known necessary prerequisite for the development of significant precancerous lesions and cervical cancer. Approximately 15-20% of sexually active adolescents have detectable HPV at any given time and have normal cytologic findings. External genital warts are much less common, occurring in <1% of adolescents. The most common clinically detected lesion in adolescent women is the cervical lesion termed **low-grade squamous intraepithelial lesion (LSIL)** (Table 266-1). LSILs can be found in 25-30% of adolescents infected with HPV. LSIL is a cytologic and histologic term to reflect the benign changes caused by an active viral infection and is likely present in most, if not all, women with HPV infection. The majority of women, however, have very minute or subtle lesions not easily detected by cytology. As with HPV DNA detection, most LSILs regress spontaneously in young women and do not require any intervention or therapy. Less commonly, HPV can induce more severe cellular changes, termed **high-grade squamous intraepithelial lesions (HSILs)** (see Chapter 553).

Although HSILs are considered precancerous lesions, they rarely progress to invasive cancer. HSILs occur in approximately 0.4-3% of sexually active women, whereas invasive cervical cancer occurs in 8 cases per 100,000 adult women. In true virginal populations, including children who are not sexually abused, rates of clinical disease are close to zero. In the United States, there are approximately 12,000 new cases and 3,700 deaths from cervical cancer each year. Worldwide, cervical cancer is the second most common cause of cancer deaths among women.

Some infants may acquire papillomaviruses during passage through an infected birth canal, leading to recurrent **juvenile laryngeal papillomatosis** (also referred to as *respiratory papillomatosis*). Cases also have been reported after cesarean section. The incubation period for emergence of clinically apparent lesions (genital warts or laryngeal papillomas) after perinatally acquired infection is unknown but is estimated to be around 3-6 mo (see Chapter 390.2). It may be that infections can also occur during hygienic care from an infected parent.

Genital warts appearing in childhood may result from sexual abuse, with HPV transmission during the abusive contact. Genital warts may represent a sexually transmitted infection even in some very young children. Their presence is cause to suspect that possibility. A child with genital warts should therefore be provided with a complete evaluation for evidence of possible abuse (see Chapter 40.1), including the presence of other sexually transmitted infections (see Chapter 120). Presence of genital warts in a child does not confirm sexual abuse, because perinatally transmitted genital warts may go undetected until the child is older. Typing for specific genital HPV types in children is not helpful in diagnosis or to confirm sexual abuse status, because the same genital types occur in both perinatal transmission and abuse.

PATHOGENESIS

Initial HPV infection of the cervix is thought to begin by viral invasion of the basal cells of the epithelium, a process that is enhanced by disruption of the epithelium caused by trauma or inflammation. It is thought that the virus initially remains relatively dormant because virus is present without any evidence of clinical disease. The life cycle of HPV depends on the differentiation program of keratinocytes. The pattern of HPV transcription varies throughout the epithelial layer as well as through different stages of disease (LSIL, HSIL, invasive cancer). Understanding of HPV transcription enhances understanding of its ability to behave as an oncovirus. Early region proteins, E6 and E7, function as transactivating factors that regulate cellular transformation. Complex interactions between E6- and E7-transcribed proteins and host proteins result in the perturbation of normal processes that regulate cellular DNA synthesis. The perturbations caused by E6 and E7 are primarily disruption of the antioncoprotein p53 and retinoblastoma protein (Rb), respectively, contributing to the development of anogenital cancers. Disruption of these proteins results in continued cell proliferation, even under the circumstances of DNA damage, which leads to basal cell proliferation, chromosomal abnormalities,

Table 266-1 Terminology for Reporting Cervical Cytology and Histology

DESCRIPTIVE DIAGNOSIS OF EPITHELIAL CELL ABNORMALITIES	EQUIVALENT TERMINOLOGY
SQUAMOUS CELL	
Atypical squamous cells of undetermined significance (ASC-US)	Squamous atypia
Atypical squamous cells, cannot exclude HSIL (ASC-H)	
Low-grade squamous intraepithelial lesion (LSIL)	Mild dysplasia, condylomatous atypia, HPV-related changes, koilocytic atypia, cervical intraepithelial neoplasia (CIN) 1
High-grade squamous intraepithelial lesion (HSIL)	Moderate dysplasia, CIN 2, severe dysplasia, CIN 3, carcinoma in situ
GLANDULAR CELL	
Endometrial cells, cytologically benign, in a postmenopausal woman	
Atypical	
• Endocervical cells, NOS	
• Endometrial cells, NOS	
• Glandular cells, NOS	
• Endocervical cells, favor neoplastic	
• Glandular cells, favor neoplastic	
Endocervical adencocarinoma in situ	
Adenocarcinoma	
• Endocervical	
• Endometrial	
• Extrauterine	
• NOS	

NOS, not otherwise specified.

and aneuploidy, hallmarks of squamous intraepithelial lesion (SIL) development.

Evidence of productive viral infection occurs in benign lesions such as external genital warts and LSILs, with the abundant expression of viral capsid proteins in the superficial keratinocytes. The appearance of the HPV-associated koilocyte is a result of the expression of E4, a structural protein that causes collapse of the cytoskeleton. Low-level expression of E6 and E7 proteins results in cell proliferation seen in the basal cell layer of LSILs. LSILs are a manifestation of active viral replication and protein expression. In HSILs, expression of E6 and E7 predominates throughout the epithelium with little expression of the structural proteins L1 and L2. This results in the chromosomal abnormalities and aneuploidy characteristic of the higher-grade lesions. The critical events that lead to cancer have not been verified; however, several mechanisms are thought to be critical, including viral integration into the host chromosome and activation of telomerase to lengthen chromosomes and avoid physiologic cell senescence. Over 150 HPV types have been documented and are classified by extent of their DNA homology into 5 genera, with the different types having different life-cycle and disease characteristics. The predominant group is α HPV types, which are associated with cutaneous and mucosal anogenital infections and cancers. β, γ, μ, and ν cause predominantly benign cutaneous lesions but can be difficult to manage in severely immunocompromised individuals. β Types are commonly detected on the skin without any apparent lesions but are associated with the development of skin cancers in those with epidermodysplasia verruciformis or other forms of immunodeficiencies. Genital lesions caused by the α HPV types may be broadly grouped into those with little to no malignant potential (low risk) and those with greater malignant potential (high risk). **Low-risk HPV types** 6 and 11 are most commonly found in genital warts and are rarely found isolated in malignant lesions. **High-risk HPV types are those types that are associated with anogenital cancers, specifically cervical cancer. HPV 16 and 18 are thought to be more oncogenic than other HPV types because they comprise 70% of cervical cancers, whereas each of the other 13 high-risk types (**31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73) **contributes less than 1-9%.** HPV 16 appears to be even more important in anal and HPV-associated oropharyngeal cancers, comprising close to 90% of these cancers. HPV 16 is also commonly found in women without lesions or in those with LSILs, making the connection with cancer confusing. Genital warts and SIL are commonly associated with the detection of multiple HPV types, including a combination of low- and high-risk HPV types. Recent data show that it is likely that a single lesion arises from a single HPV type. Detection of multiple HPV types reflects the presence of cervical and anal coexisting lesions. Almost all (95%) incident low-risk and high-risk HPV DNA detection, with or without detectable SIL, will spontaneously resolve within 1-3 yr. Although HPV 16 has a slower rate of regression than some of the other high-risk types, the majority of incident HPV 16 detection also will resolve. Data suggest that clearance of an HPV type results in natural immune protection against reinfection with that same type. Redetections of the same type are not common and when found are often associated with a history of a new sexual partner, suggesting that these are not reactivated infections but are due to new exposures. These redetections rarely result in high-grade disease. Persistent high-risk–type infections are associated with increased risk for development of HSILs and invasive cancer. Progression of HSIL to invasive cancer is still rare, with only 5-15% showing progression. Approximately 50% of HPV 16–associated HSILs and 80% of non–HPV 16 HSILs will spontaneously regress in young women. Genital and common warts in general also resolve without therapy but may take years to do so. Genital warts in only extremely rare conditions can become malignant.

Most infants with recognized genital warts are infected with the low-risk types. In contrast, children with a history of sexual abuse have a clinical picture more like that of adult genital warts, consisting of mixed low- and high-risk types. There are rare reports of HPV-associated genital malignancies occurring in preadolescent children and adolescents. On the other hand, precancerous HSILs do occur in sexually active adolescents. There is a concern that younger age of sexual debut has contributed to the increase in invasive cervical cancers seen in women younger than 50 yr of age in the United States, specifically cervical adenocarcinomas. Persistent HPV infections are considered necessary but not sufficient for the development of invasive cancers. Other risk factors for which there is relatively strong suggestive evidence of association include smoking cigarettes, prolonged oral contraceptive use, greater parity, and *Chlamydia trachomatis* and herpes simplex virus infections.

CLINICAL MANIFESTATIONS

The clinical findings in HPV infection depend on the site of epithelial infection.

Skin Lesions

The typical HPV-induced lesions of the skin are proliferative, papular, and hyperkeratotic. Common warts are raised circinate lesions with a keratinized surface (Fig. 266-1). Plantar and palmar warts are practically flat. Multiple warts are common and may create a mosaic pattern. Flat warts appear as small (1-5 mm), flat, flesh-colored papules.

Genital Warts

Genital warts may be found throughout the perineum around the anus, vagina, and urethra, as well as in the cervical, intravaginal, and intraanal areas (Fig. 266-2). Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts, which may occur in men and women without a history of anal sex. Although rare, lesions caused by genital genotypes can also be found on other mucosal surfaces, such as the conjunctivae, tongue, gingivae, and nasal mucosa. They may be single or multiple lesions and are frequently found in multiple anatomic sites, including the cervix. External genital warts can be flat, dome shaped, keratotic, pedunculated, and cauliflower shaped and may occur singly, in clusters, or as plaques. On mucosal epithelium, the lesions are softer. Depending on the size and anatomic location, lesions may be pruritic and painful, may cause burning with urination, may be friable and bleed, or may become superinfected. Adolescents are frequently disturbed by the development of genital lesions. Other rarer lesions caused by HPV of the external genital area include Bowen disease, bowenoid papulosis, squamous cell carcinomas, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Squamous Intraepithelial Lesions and Cancers

Squamous intraepithelial lesions detected with cytology are usually invisible to the naked eye and require the aid of colposcopic magnification and acetic acid. With aid, the lesions appear white and show evidence of neovascularity. SILs can occur on the cervix, vagina, vulva, penis, and intraanus. Invasive cancers tend to be more exophytic, with aberrant-appearing vasculature. These lesions are rarely found in non–sexually active individuals.

Figure 266-1 Common warts of the left hand and the chest wall. *(From Meneghini CL, Bonifaz E:* An atlas of pediatric dermatology, *Chicago, 1986, Year Book Medical Publishers, p. 45.)*

Figure 266-2 Common warts of the hand in a mother and perianal condylomata acuminata in her son. *(From Meneghini CL, Bonifaz E:* An atlas of pediatric dermatology, *Chicago, 1986, Year Book Medical Publishers, p. 44.)*

Laryngeal Papillomatosis

The median age at diagnosis of recurrent laryngeal papillomatosis is 3 yr. Children present with hoarseness, an altered cry, and sometimes stridor. Rapid growth of respiratory papillomas can occlude the upper airway, causing respiratory compromise. These lesions may recur within weeks of removal, requiring frequent surgery. The lesions do not become malignant unless treated with irradiation.

DIAGNOSIS

The diagnosis of external genital warts and common warts may be reliably determined by visual inspection of a lesion by an experienced observer and does not require additional tests for confirmation. A biopsy should be considered if the diagnosis is uncertain, the lesions do not respond to therapy, or the lesions worsen during therapy.

Screening for cervical cancer in young women begins with cytology, which is either performed by Papanicolaou smear or liquid-based cytology. Screening guidelines, which were updated in 2012 by the American Cancer Society and the U.S. Preventive Services Task Force, recommend to start screening at age 21 yr. Screening earlier is more likely to result in unnecessary referrals for colposcopy, because most lesions, both LSILs and HSILs in this group, are likely to regress. Updated guidelines now recommend screening with cytology every 3 yr. At 30 yr of age, screening can also include cotesting with HPV DNA. This is not recommended earlier, because HPV infections are extremely common in young women, resulting in a very-low positive-predictive value in this age group. The recommended terminology used for cytologic evaluation is based on the Bethesda system (see Table 266-1). Recent updates to terminology used for histology uses similar terms. Many clinicians still prefer the World Health Organization terminology using cervical intraepithelial neoplasia (CIN) 1, 2, and 3 (see Table 266-1). Although the purpose of screening is to identify CIN 3+ lesions, the majority of these lesions are found in women who were referred for **atypical squamous cells of undetermined significance (ASC-US)** or LSILs on cytology. On the other hand, few CIN 3 or cancers exist in women younger than 24 yr of age. For women 21-24 yr of age, ASC-US and LSILs are treated the same. The current preferred recommendation for young women with ASC-US or LSILs is to repeat cytology every 12 mo for up to 24 mo. For persistent ASC-US or LSILs at 2 yr of follow-up, referral for colposcopy is recommended. Women 21-24 yr of age with HSIL at any visit should be referred for colposcopy and biopsy. In adult women, HSIL can be treated without histologic confirmation. However, this approach should be avoided in those 21-24 yr of age, because HSIL is often misdiagnosed in this group or will resolve spontaneously.

In women older than 21 yr of age, high-risk HPV testing is acceptable to assist in ASC-US triage. This recommendation is based on the observations that adult women with ASC-US and a positive HPV test result for high-risk types are more likely to have CIN 2/3 than women with a negative HPV test result. However, in women with ASC-US and a positive HPV test for high-risk types, repeat cytology is recommended. In women 21-24 yr of age referred for colposcopy and found to have no lesion or biopsy-confirmed LSIL after ASC-US or LSIL cytology, repeat cytology is recommended at 12 mo intervals. If ASC-US or LSIL has persisted after 2 yr or if HSIL is present at any time, referral for colposcopy is recommended. In women with biopsy-confirmed LSIL after atypical squamous cells of high grade (ASC-H) or HSIL, observation with cytology and colposcopy is recommended at 6 mo intervals for up to 2 yr. For persistent ASC-H or HSIL at 2 yr or progression at any time, treatment is recommended. Any young woman with histology-confirmed HSIL can be followed by colposcopy and cytology at 6 mo intervals if the patient is compliant. If HSIL continues to persist after 2 yr of follow-up, treatment is recommended. When CIN 3 is specified, treatment is recommended. These guidelines and updates can be found at http://www.asccp.org.

Very sensitive tests for the presence of HPV DNA, RNA, and proteins are becoming generally available, although they are not required for the diagnosis of external genital warts or related conditions. There are no indications for HPV DNA testing in women younger than 21 yr of age or children. HPV DNA testing is not recommended in women 21-24 yr of age but is acceptable for ASC-US triage.

Diagnosis of juvenile laryngeal papillomatosis (JRP) is made based on laryngeal examination.

DIFFERENTIAL DIAGNOSIS

A number of other conditions should be considered in the differential diagnosis of genital warts, including condyloma latum, seborrheic keratoses, dysplastic and benign nevi, molluscum contagiosum, pearly penile papules, neoplasms, Bowen disease, bowenoid papulosis, Buschke-Löwenstein tumors, and vulvar intraepithelial neoplasias.

Condyloma latum is caused by secondary syphilis and can be diagnosed with darkfield microscopy and standard serologic tests for syphilis. Seborrheic keratoses are common, localized, hyperpigmented lesions that are rarely associated with malignancy. Molluscum contagiosum is caused by a poxvirus, is highly infectious, and is often umbilicated. Pearly penile papules occur at the penile corona and are normal variants that require no treatment.

TREATMENT

Most common (plantar, palmar, skin) warts eventually resolve spontaneously (see Chapter 667). Symptomatic lesions should be removed. Removal includes a variety of self-applied therapies, including salicylic acid preparations and provider-applied therapies (cryotherapy, laser therapy, electrosurgery). Genital warts are benign and usually remit, but only over an extended period. It is recommended that genital lesions be treated if the patient or the parent requests therapy. Treatments for genital warts are categorized into self-applied and provider-applied. No one therapy has been shown to be more efficacious than any other. Recommended patient-applied treatment regimens for external genital warts include topical podofilox, imiquimod, and sinecatechins. Podofilox 0.5% solution (using a cotton swab) or gel (using a finger) is applied to visible warts in a cycle of applications twice a day for 3 days followed by 4 days of no therapy, repeated for up to a total of 4 cycles. Imiquimod 5% cream is applied at bedtime, 3 times a week, every other day, for up to 16 wk; the treated area should be washed with mild soap and water 6-10 hr after treatment. Sinecatechins (15% ointment) is a topical product from green tea extract used for external genital wart treatment that can be used 3 times daily for up to 16 wk. Provider-applied therapies include surgical treatments (electrosurgery, surgical excision, laser surgery) and office-based treatment (cryotherapy with liquid nitrogen or a cryoprobe, podophyllin resin 10-25%, and bichloroacetic or trichloroacetic acid). Office-based treatments are usually applied once a week for 3-6 wk. Podophyllin resins have lost favor to other methods because of the variability in preparations. Intralesional interferon is associated with significant adverse effects and is reserved for treatment of recalcitrant cases.

Many therapies are painful, and children should not undergo painful genital treatments unless adequate pain control is provided. Parents and

patients should not be expected to apply painful therapies themselves. None of the patient-applied therapies are approved for use during pregnancy, and podophyllin resin is contraindicated in pregnancy. For any of the nonsurgical treatments, prescription is contraindicated in a patient with any history of hypersensitivity to any product constituents.

If HPV exposure as a result of sexual abuse is suspected or known, the clinician should ensure that the child's safety has been achieved and is maintained.

When indicated, the most common treatments for CIN 2/3 are ablative and excisional treatments, including cryotherapy, laser, and loop electrosurgical excisional procedures. Once confirmed by histology with CIN 1, LSILs can be observed indefinitely. The decision to treat a persistent CIN 1 rests between the provider and patient. Risks of treatment, including premature delivery in a future pregnancy, should be discussed prior to any treatment decision. Treatment in pregnancy is not recommended unless invasive cancer is present.

JRP is commonly treated with surgical removal of lesions, but laser and microdebriders are also used.

COMPLICATIONS

The presence of HPV lesions in the genital area may be a cause of profound embarrassment to a child or parent. Complications of therapy are uncommon; chronic pain (vulvodynia) or hypoesthesia may occur at the treatment site. Lesions may heal with hypopigmentation or hyperpigmentation and less commonly with depressed or hypertrophic scars. Surgical therapies can lead to infection and scarring. Premature delivery and low birthweight in future pregnancies are complications of excisional therapy for CIN.

It is estimated that 5-15% of untreated CIN 3 lesions will progress to cervical cancer. Most cancer is prevented by early detection and treatment of these lesions. Despite screening, cervical cancer develops rapidly in a few adolescents and young women. The reason for the rapid development of cancer in these rare cases remains unknown, but host genetic defects are likely underlying causes. Juvenile laryngeal papillomas rarely become malignant, unless they have been treated with irradiation. Vulvar condylomas rarely become cancerous. HPV-associated cancers of the vagina, vulva, anus, penis, and oral cavity are much rarer than cervical tumors, and therefore screening for them is not currently recommended. However, anal, vaginal, and vulvar cancers are more common in women with cervical cancer; hence, it is recommended to screen women with cervical cancer for these tumors with visual and/or digital inspection.

PROGNOSIS

With all forms of therapy, genital warts commonly recur, and approximately half of children and adolescents require a 2nd or 3rd treatment. Recurrence is also evident in patients with Juvenile laryngeal papillomatosis. Patients and parents should be warned of this likelihood. Combination therapy for genital warts (imiquimod and podofilox) does not improve response and may increase complications. Prognosis of cervical disease is better, with 85-90% cure rates after a single treatment with the loop electrosurgical excision procedure. Cryotherapy has a slightly lower cure rate. Recalcitrant disease should prompt an evaluation and is common in immunocompromised individuals, specifically men and women infected with HIV.

PREVENTION

The only means of preventing HPV infection is to avoid direct contact with lesions. Condoms may reduce the risk for HPV transmission; condoms also prevent other sexually transmitted infections, which are risk factors associated with SIL development. In addition, condoms appear to hasten the regression of LSILs in women. Avoiding smoking cigarettes is important in preventing cervical cancer. Prolonged oral contraceptive use and parity have been shown to be risks for cervical cancer. However, the mechanisms associated with these factors have not been identified, and consequently no change in counseling is recommended.

HPV vaccines show efficacy against type-specific persistence and development of type-specific disease, including the cervix, vagina, vulva, and anus. A quadrivalent HPV vaccine containing types 6, 11, 16, and 18 was licensed in the United States in 2006, and a bivalent HPV vaccine containing types 16 and 18 was licensed in the United States in 2009. A 9-valent vaccine containing types 6, 11, 16, 18, 31, 33, 45, 52, and 58 has recently been approved. The efficacy of these vaccines is mediated by the development of neutralizing antibodies. Data from Sweden and Australia show a decrease in national rates of genital warts within 4 yr of implementing vaccination programs. Vaccination in the United States is recommended routinely for all girls at 11-12 yr of age and is administered intramuscularly in the deltoid region in a 3 dose series at 0, 1-2, and 6 mo. It is important that vaccination take place in children before they become sexually active, because the rate of HPV acquisition is high shortly after the onset of sexual activity. Vaccine can be given to girls as young as 9 yr of age, and a catch-up vaccination is recommended in girls 13-26 yr. Individuals who are already infected with 1 or more vaccine-related HPV types prior to vaccination are protected from clinical disease caused by the remaining vaccine HPV types. However, the vaccines are not therapeutic. The quadrivalent vaccine is also licensed to be administered in a 3 dose series to males 9 through 26 yr of age to reduce their likelihood of acquiring genital warts and developing anal dysplasia and cancer. Two doses of the vaccines have shown similar levels of immunogenicity as 3 doses. A vaccine that will cover 9 HPV high-risk types has been approved.

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Chapter 267

Arboviral Infections in North America

Scott B. Halstead

The arthropod-borne viral infections in North America are a group of mosquito-transmitted pathogens of several taxa causing neurologic infections or acute viral exanthems. Neuroviruses are transmitted during warmer weather in overlapping regions across most the United States and much of southern Canada.

ETIOLOGY

The principal causes of the arthropod-borne infections (with or without encephalitis) of North America are West Nile encephalitis (WNE), St. Louis encephalitis (StLE), Powassan (POW), a complex of California encephalitis group viruses, and, less frequently, western equine encephalitis (WEE), eastern equine encephalitis (EEE), and Colorado tick fever. Chikungunya virus is an emerging pathogen in the Western Hemisphere including the United States. The etiologic agents belong to different viral taxa: alphaviruses of the family Togaviridae (chikungunya virus, EEE, and WEE), Flaviviridae (WNE, STLE, POW), the California complex of the family Bunyaviridae (California encephalitis), and Reoviridae (Colorado tick fever virus). Alphaviruses are 69 nm, enveloped, positive-sense RNA viruses that evolved from a common Venezuelan equine encephalitis–like viral ancestor in the Western hemisphere. Flaviviruses are 40-50 nm, enveloped, positive-sense RNA viruses that evolved from a common ancestor. They are mosquito-borne (WNE, STLE) and tick-borne (POW) agents, globally distributed, and responsible for many important human viral diseases. The California serogroup, 1 of 16 Bunyavirus groups, are 75-115 nm enveloped viruses possessing a 3-segment, negative-sense RNA genome. Reoviruses are 60-80 nm double-stranded RNA viruses.

EPIDEMIOLOGY

Eastern Equine Encephalitis

In the United States, EEE is a very low incidence disease, with a median of 8 cases occurring annually in the Atlantic and Gulf States from 1964-2007 (Fig. 267-1). Transmission occurs often in focal endemic

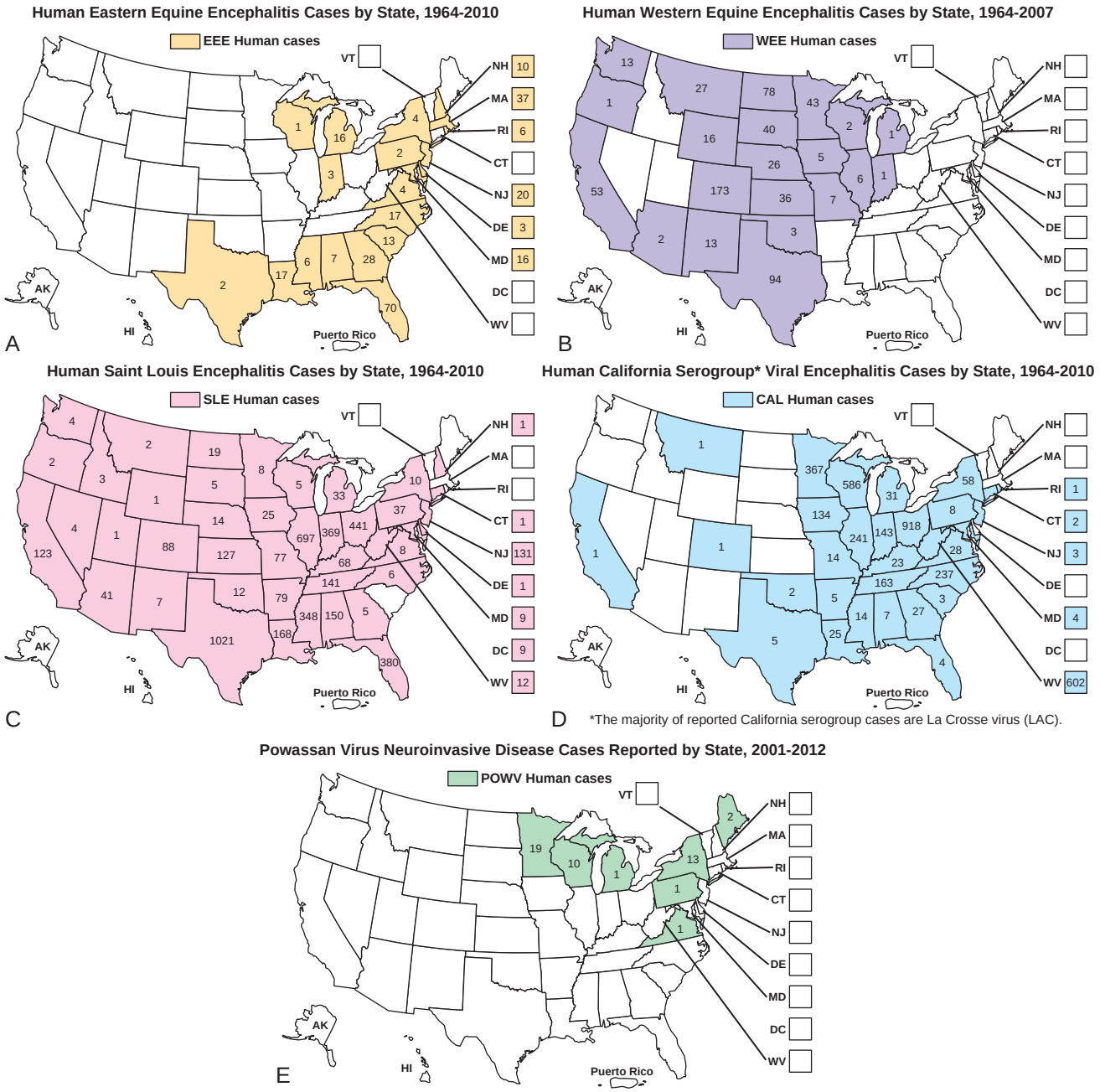

Figure 267-1 The distribution and incidence of reported cases of eastern equine encephalitis **(A),** western equine encephalitis **(B),** St. Louis encephalitis **(C),** California serogroup encephalitis **(D),** and Powassan encephalitis **(E)** reported by state to the Centers for Disease Control and Prevention, 1964–2010. *(From Division of Vector-Borne Diseases, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/ncidod/dvbid/arbor/arbocase/htm)*

areas of the coast of Massachusetts, the 6 southern counties of New Jersey, and northeastern Florida. In North America, the virus is maintained in freshwater swamps in a zoonotic cycle involving *Culiseta melanura* and birds. Various other mosquito species obtain viremic meals from birds and transmit the virus to horses and humans. Virus activity varies markedly from year to year in response to still unknown ecologic factors. Most infections in birds are silent, but infections in pheasants are often fatal, and epizootics in these species are used as sentinels for periods of increased viral activity. Cases have been recognized on Caribbean islands. The case : infection ratio is lowest in children (1 : 8) and somewhat higher in adults (1 : 29).

Western Equine Encephalitis

WEE infections occur principally in the United States and Canada west of the Mississippi River (see Fig. 267-1), mainly in rural areas where water impoundments, irrigated farmland, and naturally flooded land provide breeding sites for *Culex tarsalis.* The virus is transmitted in a cycle involving mosquitoes, birds, and other vertebrate hosts. Humans and horses are susceptible to encephalitis. The case : infection ratio varies by age, having been estimated at 1 : 58 in children younger than 4 yr of age and 1 : 1,150 in adults. Infections are most severe at the extremes of life; one third of cases occur in children younger than 1 yr of age. Recurrent human epidemics have been reported from the Yakima Valley in Washington State and the Central Valley of California; the largest outbreak on record resulted in 3,400 cases and occurred in Minnesota, North and South Dakota, Nebraska, and Montana as well as Alberta, Manitoba, and Saskatchewan, Canada. Epizootics in horses precede human epidemics by several weeks. For the past 20 yr, only 3 cases of WEE have been reported, presumably reflecting successful mosquito abatement.

St. Louis Encephalitis

Cases of STLE are reported from nearly all states; the highest attack rates occur in the Gulf and central states (see Fig. 267-1). Epidemics frequently occur in urban and suburban areas; the largest, in 1975, involved 1,800 persons living in Houston, Chicago, Memphis, and Denver. Cases often cluster in areas where there is ground water or septic systems, which support mosquito breeding. The principal vectors are *Culex pipiens* and *Culex quinquefasciatus* in the central Gulf States, *Culex nigripalpus* in Florida, and *C. tarsalis* in California. STLE virus is maintained in nature in a bird–mosquito cycle. Viral amplification occurs in bird species abundant in residential areas (e.g., sparrows, blue jays, and doves). Virus is transmitted in the late summer and early fall. The case : infection ratio may be as high as 1 : 300. Age-specific attack rates are lowest in children and highest in individuals older than age 60 yr. The most recent small outbreaks were in Florida in 1990 and Louisiana in 2001. For the past 15 yr there have been a mean of 18 cases annually.

West Nile Encephalitis

West Nile (WN) virus has been implicated as the cause of sporadic summertime cases of human encephalitis and meningitis in Israel, India, Pakistan, Romania, Russia, and the United States. All American WN viruses are genetically similar and are related to a virus recovered from a goose in Israel in 1998. WN virus was imported into the United States in 1999 and now survives in a broad enzootic cycle across the United States. Every state in the continental United States plus 9 provinces in Canada have reported mosquito, bird, mammalian, or human WN virus infection, most frequently during the summer or fall months (Fig. 267-2). Through the end of 2012, 35,941 total cases had been reported, 40-50% of which were neuroinvasive, with 1,439 deaths. WN virus transmission cycles appear to resemble those of Japanese encephalitis with large epizootics and human cases every 5-10 yr. WN virus has entered the blood supply through asymptomatic viremic potential blood donors. Blood banks screen for WN virus RNA. In 2012, 597 viremic potential blood donors were identified and the donation was rejected (Fig. 267-2). WN virus has also been transmitted to humans via the placenta, breast milk, and organ transplantation. Throughout its range, the virus is maintained in nature by transmission between mosquitoes of the *Culex* genus and various species of birds. In the United States, human infections are largely acquired from *C. pipiens.* Horses are the nonavian vertebrates most likely to exhibit disease with WN virus infection. During the 2002 transmission season, 14,000 equine cases were reported, with a mortality rate of 30%. Disease occurs predominantly in individuals >50 yr of age.

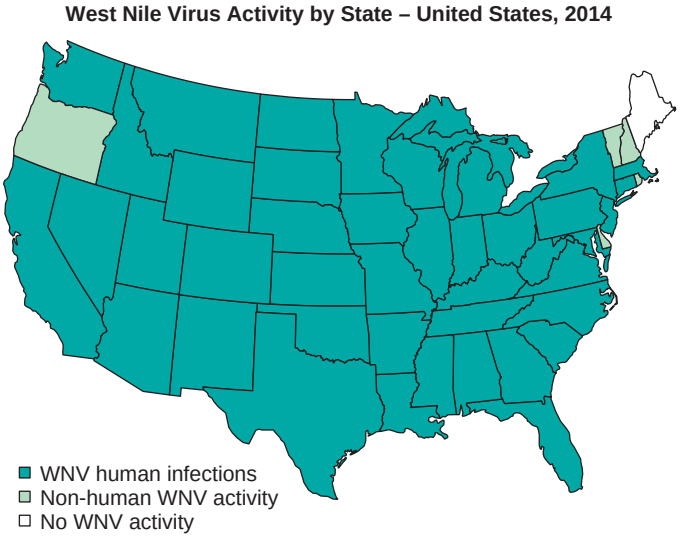

Figure 267-2 West Nile virus activity reported to ArboNET by state, United States, 2014. (Preliminary data as of October 28, 2014.) *(From ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/westnile/statsMaps/preliminaryMapsData/activitystatedate.html)*

Powassan Encephalitis

POW virus is transmitted by *Ixodes cookei* among small mammals in eastern Canada and the United States; it has been responsible for 39 deaths in the United States since 2008 (see Fig. 267-1). Other ticks may transmit the virus in a wider geographic area, and there is some concern that *Ixodes scapularis* (also called *Ixodes dammini*), a competent vector in the laboratory, may become involved as it becomes more prominent in the United States.

La Crosse/California Encephalitis

La Crosse viral infections are endemic in the United States, occurring annually from July to September, principally in the north-central and central states (see Fig. 267-1). Infections occur in peridomestic environments as the result of bites from *Aedes triseriatus* mosquitoes, which often breed in tree holes. The virus is maintained vertically in nature by transovarial transmission and can be spread between mosquitoes by copulation and amplified in mosquito populations by viremic infections in various vertebrate hosts. Amplifying hosts include chipmunks, squirrels, foxes, and woodchucks. A case : infection ratio of 1 : 22-300 has been surmised. La Crosse encephalitis is principally a disease of children, who may account for up to 75% of cases. A mean of 100 cases has been reported annually for the past 10 yr.

Colorado Tick Fever

Colorado tick fever virus is transmitted by the wood tick *Dermacentor andersoni,* which inhabits high-elevation areas of states extending from the central plains to the Pacific coast. The tick is infected with the virus at the larval stage and remains infected for life. Squirrels and chipmunks serve as primary reservoirs. Human infections typically occur in hikers and campers in indigenous areas during the spring and early summer.

Chikungunya Virus

Chikungunya virus is endemic in Africa and Asia as well as parts of Latin America. It is an emerging pathogen in areas of the United States inhabited by day biting mosquitos (*Aedes aegyti, Aedes albopictus*).

CLINICAL MANIFESTATIONS

The arboviruses produce symptoms of viral meningitis or encephalitis. WN virus and Colorado tick fever illnesses more commonly manifest as flulike diseases and only occasionally as encephalitides.

Eastern Equine Encephalitis

EEE virus infections result in fulminant encephalitis with a rapid progression to coma and death in one third of cases. In infants and children, abrupt onset of fever, irritability, and headache are followed by lethargy, confusion, seizures, and coma. High temperature, bulging fontanel, stiff neck, and generalized flaccid or spastic paralysis are observed. There may be a brief prodrome of fever, headache, and dizziness. Unlike most other viral encephalitides, the peripheral white blood cell count usually demonstrates a marked leukocytosis, and the cerebrospinal fluid (CSF) may show marked pleocytosis. Pathologic changes are found in the cortical and gray matter, with viral antigens localized to neurons. There is necrosis of neurons, neutrophilic infiltration, and perivascular cuffing by lymphocytes.

Western Equine Encephalitis

In WEE, there may be a prodrome with symptoms of an upper respiratory tract infection. The onset is usually sudden with chills, fever, dizziness, drowsiness, increasing headache, malaise, nausea and vomiting, stiff neck, and disorientation. Infants typically present with the sudden cessation of feeding, fussiness, fever, and protracted vomiting. Convulsions and lethargy develop rapidly. On physical examination, patients are somnolent, exhibit meningeal signs, and have generalized motor weakness and reduced deep tendon reflexes. In infants, a bulging fontanel, spastic paralysis, and generalized convulsions may be observed. On pathologic examination, disseminated small focal abscesses, small focal hemorrhages, and patchy areas of demyelination are distinctive.

St. Louis Encephalitis

Clinical manifestations of STLE vary from a mild flulike illness to fatal encephalitis. There may be a prodrome of nonspecific symptoms with subtle changes in coordination or mentation of several days to 1 wk in duration. Early signs and symptoms include fever, photophobia, headache, malaise, nausea, vomiting, and neck stiffness. About half of patients exhibit abrupt onset of weakness, incoordination, disturbed sensorium, restlessness, confusion, lethargy, and delirium or coma. The peripheral white blood cell count is modestly elevated, with 100-200 cells/μL found in the CSF. On autopsy, the brain shows scattered foci of neuronal damage and perivascular inflammation.

West Nile Encephalitis

WNE may be asymptomatic, but when clinical features appear, they include an abrupt onset of high fever, headache, myalgias, and nonspecific signs of emesis, rash, abdominal pain, or diarrhea. Most infections manifest as a flulike febrile illness, whereas a minority of patients demonstrate meningitis or encephalitis, or both. Rarely there may be cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, retinitis, orchitis, pancreatitis, or hepatitis. WN virus disease in the United States has been accompanied by prolonged lymphopenia and an acute asymmetric polio-like paralytic illness with CSF pleocytosis involving the anterior horn cells of the spinal cord. A striking but uncommon feature has been parkinsonism and movement disorders (with tremor and myoclonus). WN virus infections have been shown to lead to chronic kidney disease in a small group of patients.

Powassan Encephalitis

POW encephalitis has occurred mostly in adults living in enzootic areas with vocational or recreational exposure; it is associated with significant long-term morbidity and has a case-fatality rate of 10-15%.

Lacrosse/California Encephalitis

The clinical spectrum includes a mild febrile illness, aseptic meningitis, and fatal encephalitis. Children typically present with a prodrome of 2-3 days with fever, headache, malaise, and vomiting. The disease evolves with clouding of the sensorium, lethargy, and, in severe cases, focal or generalized seizures. On physical examination, children are lethargic but not disoriented. Focal neurologic signs, including weakness, aphasia, and focal or generalized seizures, have been reported in 16-25% of cases. CSF shows low to moderate leukocyte counts. On autopsy, the brain shows focal areas of neuronal degeneration, inflammation, and perivascular cuffing.

Colorado Tick Fever

Colorado tick fever begins with the abrupt onset of a flulike illness, including high temperature, malaise, arthralgia and myalgia, vomiting, headache, and decreased sensorium. Rash is uncommon. The symptoms rapidly disappear after 3 days of illness. However, in approximately half of patients, a second identical episode reoccurs 24-72 hr after the first, producing the typical "saddleback" temperature curve of Colorado tick fever. Complications, including encephalitis, meningoencephalitis, and a bleeding diathesis, develop in 3-7% of infected persons and may be more common in children younger than 12 yr of age.

Chikungunya Virus

Clinical manifestations begin 3-7 days after a mosquito bite and begin abruptly with high fever and severe joint symptoms (hands, feet, ankles, wrists) that include symmetric bilateral polyarthralgia or arthritis. Most patients are symptomatic, and all ages are vulnerable. In addition, there may be headache, myalgias, conjunctivitis, weakness, lymphopenia, and a maculopapular rash. Mortality is rare; some develop prolonged joint symptoms (tenosynovitis, arthritis) lasting over a year. The acute episode lasts 7-10 days. The differential diagnosis includes dengue, West Nile, enterovirus diseases, leptospirosis, rickettsial disease, measles, parvovirus disease, rheumatologic diseases, and other alphavirus diseases in endemic areas. Figure 267-3 lists the diagnostic criteria.

DIAGNOSIS

The etiologic diagnosis of a specific arboviral infection is established by testing an acute-phase serum ≥5 days after onset of illness for the presence of virus-specific immunoglobulin (Ig) M antibodies using an indirect immunofluorescence test or an enzyme-linked immunosorbent assay IgM capture test. Alternatively, acute and convalescent sera can be tested for a 4-fold or greater increase in enzyme-linked immunosorbent assay, hemagglutination inhibition, or neutralizing IgG antibody titers. Commercial serologic diagnostic kits are marketed, especially for WN viral infections. Serum and CSF should be tested for WN virus–specific IgM. However, IgM may reflect past infection, because it may be present up to 12 mo after infection. The diagnosis may also be established by isolation in cell cultures of virus in brain tissue, obtained by brain biopsy or at autopsy, or by identification of viral RNA reverse transcriptase polymerase chain reactions.

The diagnosis of encephalitis may be aided by CT or MRI and by electroencephalography. Focal seizures or focal findings on CT or MRI or electroencephalography should suggest the possibility of herpes simplex encephalitis, which should be treated with acyclovir (see Chapter 252).

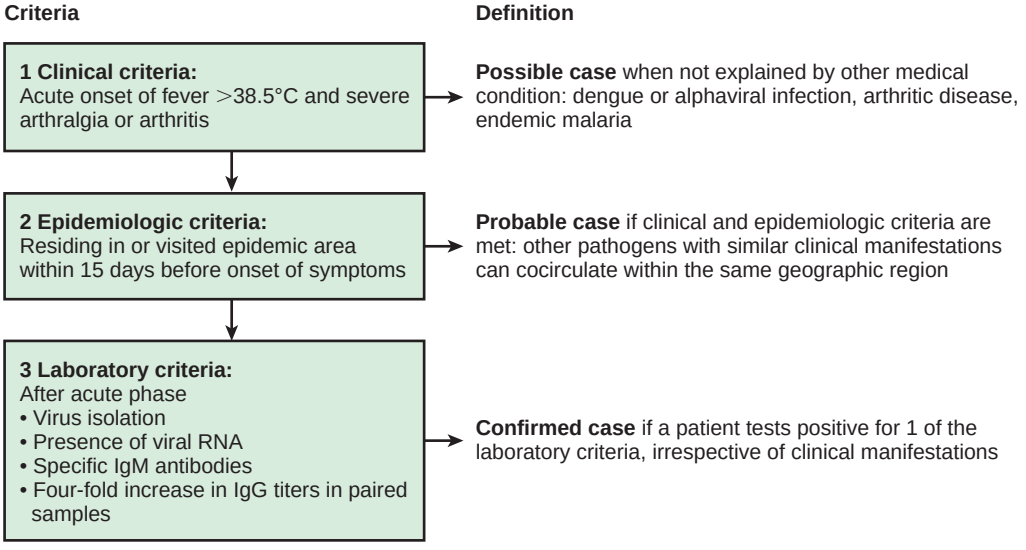

Figure 267-3 Diagnostic criteria for chikungunya virus fever. *(From Burt FJ, Rolph MS, Rulli NE, et al: Chikungunya: a re-emerging virus,* Lancet *379:662–668, 2012, Fig. 6.)*

TREATMENT

There is no specific treatment for arboviral encephalitides, although oral ribavirin may have been of benefit in a case of La Crosse encephalitis. The treatment of acute arboviral encephalitis is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

Fatalities occur with all arboviral encephalitides. With the exception of EEE, most resolve without residua.

Eastern Equine Encephalitis

The prognosis in EEE is better for patients with a prolonged prodrome; the occurrence of convulsions conveys a poor prognosis. Patient fatality rates are 33-75% and are highest in the elderly. Residual neurologic defects are common, especially in children.

Western Equine Encephalitis

Patient fatality rates in WEE are 3-9% and highest in the elderly. Major neurologic sequelae have been reported in up to 13% of cases and may be as high as 30% in infants. Parkinsonian syndrome has been reported as a residual in adult survivors.

St. Louis Encephalitis

The principal risk factor for fatal outcome of STLE is advanced age, with patient fatality rates being as high as 80% in early outbreaks. In children, mortality rates are 2-5%. In adults, underlying hypertensive cardiovascular disease has been a risk factor for fatal outcome. Recovery from STLE is usually complete, but the rate of serious neurologic sequelae has been reported to be as high as 10% in children.

West Nile Encephalitis

Cases and deaths caused by WNE occur mainly in the elderly, although many serologic surveys show that persons of all ages are infected. In 2012, among a total of 5,387 human cases, 2,734 were neuroinvasive disease, which resulted in 243 deaths, an 8.9% mortality rate (Fig. 267-4). Paralysis may result in permanent weakness.

Powassan Encephalitis

In a limited experience, POW encephalitis has occurred mainly in adults with vocational or recreational exposure and has a high fatality rate.

La Crosse or California Encephalitis

Recovery from California encephalitis is usually complete. The case fatality rate is approximately 1%.

West Nile virus neuroinvasive disease incidence reported to ArboNET, by state, United States, 2013

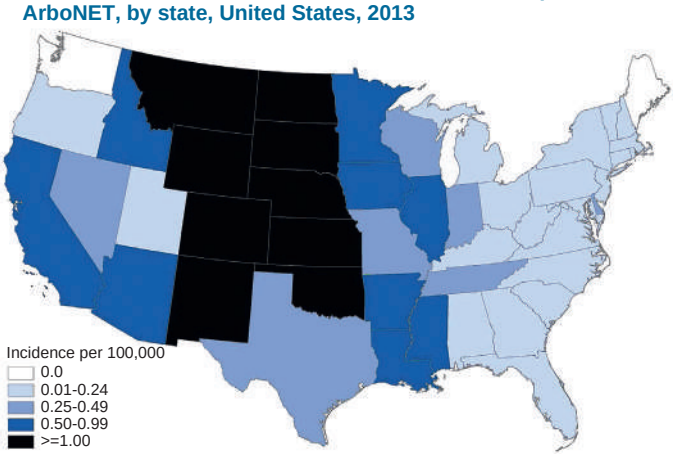

Figure 267-4 West Nile virus neuroinvasive disease incidence reported to ArboNET by state, United States, 2013. *(From ArboNET, Arboviral Diseases Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/westnile/statsMaps/finalMapsData/data/2013StateIncidenceMap.pdf)*

Colorado Tick Fever

Recovery from Colorado tick fever is usually complete. Three deaths have been reported, all in persons with hemorrhagic signs.

Chikungunya

The incidence of febrile convulsions is high in infants. Prognosis is generally good, although in large outbreaks in Africa and India severe disease and deaths have been attributed to chikungunya infections, predominantly in adults.

PREVENTION

Killed EEE, WEE, and WNE vaccines are available for horses, and an experimental killed vaccine is administered to human laboratory workers who handle EEE virus. Flocks of sentinel chickens or pheasants have been stationed at various locations along the Atlantic coast during the late summer or early fall to obtain early warning of increased transmission of EEE virus. No human vaccine is licensed for arboviral encephalitides, although several WNE vaccines are in late-stage development. Killed WNE vaccines are licensed for veterinary use. Protection against CHIK is attained by avoiding bites by vector mosquitoes. These bite during daytime hours in and around human habitations (see Chapter 269).

Extensive water management and mosquito abatement programs in California have reduced transmission of WEE and the incidence of human infections. Urban WNE and STLE outbreaks in the eastern United States, Texas, and the Midwest have been controlled by the application of ultra-low-volume adulticide chemicals applied from trucks or low-flying aircraft. Because mosquito biting may occur in and around residential areas, sealing mosquito breeding sites, using insect repellents, and instructing children to play in open, sunny areas away from forest fringe may help prevent disease.

Because there is no vaccine or specific therapy for POW encephalitis, the best means of prevention is protection from tick bite. This includes using insect repellents, wearing light-colored clothing with long sleeves and pants tucked into socks or boots, avoiding or clearing brushy areas, and removing ticks before they attach or soon after attachment. Checking family pets also can prevent ticks from entering the home. Because *I. cookei* are often found on woodchucks and skunks and may be the primary vector of POW virus, reducing human contact with small and medium-sized mammals may reduce risk of exposure to POW virus-infected ticks. Areas around homes in enzootic areas should be kept clear of brush, weeds, trash, and other elements that could support small and medium-sized mammals. When removing rodent nests, avoid direct contact with nesting materials and use sealed plastic bags for disposal and to prevent direct contact with ticks.

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Chapter 268

Arboviral Infections Outside North America

Scott B. Halstead

Globally, the principal causes of arboviral encephalitis are Venezuelan equine encephalitis (VEE), Japanese encephalitis (JE), West Nile fever (WN), and tickborne encephalitis (TBE) (Table 268-1). Other widespread arboviral infections include chikungunya (CHIK) and dengue (DEN) (see Chapter 269).

Table 268-1 Vectors and Geographic Distribution of Arboviral Encephalitis Outside North America

GENUS	VIRUS AND DISEASE	VECTOR	GEOGRAPHIC DISTRIBUTION
Flavivirus	Japanese encephalitis	*Culex tritaeniorhynchus*	Asia/Japan to Sri Lanka
	Murray Valley encephalitis	*Culex annulirostris*	Eastern Australia
	Rocio	*Psorophora* or *Aedes*	Sao Paulo, Brazil
	West Nile	*Culex* and others	Europe to Australia
	Tick-borne encephalitis	*Ixodes ricinus*	Europe
		Ixodes persulcatus	Russia
Togavirus	Venezuelan equine encephalitis	*Culex* and others	Northern South America

268.1 Venezuelan Equine Encephalitis

Scott B. Halstead

The VEE virus was isolated from an epizootic in Venezuelan horses in 1938. Human cases were first identified in 1943. Hundreds of thousands of equine and human cases have occurred over the past 70 yr. During 1971, epizootics moved through Central America and Mexico to southern Texas. After 2 decades of quiescence, epizootic disease emerged again in Venezuela and Colombia in 1995.

ETIOLOGY

VEE is an alphavirus of the family Togaviridae. VEE circulates in nature in 6 subtypes. Virus types I and III have multiple antigenic variants. Types IAB and IC have caused epizootics and human epidemics.

EPIDEMIOLOGY

The majority of epizootics resulting from types IAB and IC have occurred in Venezuela and Colombia. The virus resides in ill-defined sylvatic reservoirs in the South American rain forests. Known hosts include rodents and aquatic birds with transmission by *Culex melanoconion* species. Vectors for horse-to-horse and horse-to-human transmission include *Aedes taeniorhynchus* and *Psorophora confinnis*. Epizootics move rapidly, up to several miles per day. Human cases are proportional to and follow epizootic occurrences. Viremia levels in human blood are high enough to infect mosquitoes. Because virus can be recovered from human pharyngeal swabs, and household attack rates are often as high as 50%, it is widely believed that person-to-person transmission occurs, although direct evidence is lacking. Virus types II-VI are restricted to relatively small foci; each has a unique vector–host relationship and rarely results in human infections.

CLINICAL MANIFESTATIONS

The incubation period is 2-5 days, followed by the abrupt onset of fever, chills, headache, sore throat, myalgia, malaise, prostration, photophobia, nausea, vomiting, and diarrhea. In 5-10% of cases, there is a biphasic illness; the 2nd phase is heralded by seizures, projectile vomiting, ataxia, confusion, agitation, and mild disturbances in consciousness. There is cervical lymphadenopathy and conjunctival suffusion. Cases of meningoencephalitis may demonstrate **cranial nerve palsy,** motor weakness, paralysis, seizures, and coma. Microscopic examination of tissues reveals inflammatory infiltrates in lymph nodes, spleen, lung, liver, and brain. Lymph nodes show cellular depletion, necrosis of germinal centers, and lymphophagocytosis. The liver shows patchy hepatocellular degeneration, the lungs demonstrate a diffuse interstitial pneumonia with intraalveolar hemorrhages, and the brain shows patchy cellular infiltrates.

DIAGNOSIS

The etiologic diagnosis of VEE is established by testing an acute-phase serum collected early in the illness for the presence of virus-specific immunoglobulin (Ig) M antibodies or, alternatively, demonstrating a 4-fold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by isolation in tissue cultures or recovery of viral RNA by polymerase chain reaction.

TREATMENT

There is no specific treatment for VEE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

In patients with VEE meningoencephalitis, the fatality rate ranges from 10-25%. Sequelae include nervousness, forgetfulness, recurrent headache, and easy fatigability.

PREVENTION

Several veterinary vaccines are available to protect equines. VEE virus is highly infectious in laboratory settings, and biosafety level 3 containment should be used. An experimental vaccine is available for use in laboratory workers. Several vaccine constructs are in the pipeline for potential use in humans.

Bibliography is available at Expert Consult.

268.2 Japanese Encephalitis

Scott B. Halstead

Epidemics of encephalitis were reported in Japan from the late 1800s.

ETIOLOGY

JE virus is a positive-sense, single-stranded RNA virus of the family Flaviviridae.

EPIDEMIOLOGY

JE is a mosquito-borne viral disease of humans as well as horses, swine, and other domestic animals that causes human infections and acute disease in a vast area of Asia, northern Japan, Korea, China, Taiwan, the Philippines, and the Indonesian archipelago and from Indochina through the Indian subcontinent. *Culex tritaeniorhynchus summarosus,* a night-biting mosquito that feeds preferentially on large domestic animals and birds but only infrequently on humans, is the principal vector of zoonotic and human JE in northern Asia. A more complex ecology prevails in southern Asia. From Taiwan to India, *C. tritaeniorhynchus* and members of the closely related *Culex vishnui* group are vectors. Before the introduction of JE vaccine, summer outbreaks of JE occurred regularly in Japan, Korea, China, Okinawa, and Taiwan. Over the past decade, there has been a pattern of steadily enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with small outbreaks in the Philippines, Indonesia, and the northern tip of Queensland, Australia. Seasonal rains are accompanied by increases in mosquito populations and JE transmission. Pigs serve as an amplifying host.

The annual incidence in endemic areas ranges from 1-10 per 10,000 population. Children younger than 15 yr of age are principally affected, with nearly universal exposure by adulthood. The case : infection ratio for JE virus has been variously estimated at 1 : 25 to 1 : 1,000. Higher ratios have been estimated for populations indigenous to enzootic areas. JE occurs in travelers visiting Asia; therefore, a travel history in the diagnosis of encephalitis is critical.

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CLINICAL MANIFESTATIONS

After a 4-14 day incubation period, cases typically progress through the following 4 stages: prodromal illness (2-3 days), acute stage (3-4 days), subacute stage (7-10 days), and convalescence (4-7 wk). Onset may be characterized by abrupt onset of fever, headache, respiratory symptoms, anorexia, nausea, abdominal pain, vomiting, and sensory changes, including psychotic episodes. Grand mal seizures are seen in 10-24% of children with JE; parkinsonian-like nonintention tremor and cogwheel rigidity are seen less frequently. Particularly characteristic are **rapidly changing central nervous system** signs (e.g., hyperreflexia followed by hyporeflexia or plantar responses that change). The sensory status of the patient may vary from confusion through disorientation and delirium to somnolence, progressing to coma. There is usually a mild pleocytosis (100-1,000 leukocytes/μL) in the cerebrospinal fluid, initially polymorphonuclear but in a few days predominantly lymphocytic. Albuminuria is common. Fatal cases usually progress rapidly to coma, and the patient dies within 10 days.

DIAGNOSIS

JE should be suspected in patients reporting exposure to night-biting mosquitoes in endemic areas during the transmission season. The etiologic diagnosis of JE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a fourfold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction.

TREATMENT

There is no specific treatment for JE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

Patient fatality rates for JE are 24-42% and are highest in children 5-9 yr of age and in adults older than 65 yr of age. The frequency of sequelae is 5-70% and is directly related to the age of the patient and severity of disease. Sequelae are most common in patients younger than 10 yr at the onset of disease. The more common sequelae are mental deterioration, severe emotional instability, personality changes, motor abnormalities, and speech disturbances.

PREVENTION

Travelers to endemic countries who plan to be in rural areas of the endemic region during the expected period of seasonal transmission and travelers in rural areas experiencing endemic transmission should receive JE vaccine. An inactivated vaccine manufactured in Japan by intracerebral injection of young mice and available throughout the world has been taken off the market owing to a high incidence of adverse events. In 2008-2009, tissue culture–based JE vaccine (Ixiaro) was licensed in Europe, Australia, and the United States. In the United States, this vaccine (also called IC51) is licensed for use in children and adults and is distributed by Novartis (Basel). For this vaccine, JE virus is grown in Vero cells, then formalin inactivated and administered intramuscularly as 2 doses of 0.5 mL each, 28 days apart. The final dose should be completed at least 1 wk prior to the patient's expected arrival in a JE endemic area. This vaccine contains alum and protamine sulfate and has exhibited only mild adverse events. A highly efficacious live-attenuated single-dose JE vaccine developed in China for children is licensed and marketed in some Asian countries. This vaccine can be coadministered with live-attenuated measles vaccine without altering the immune responses to either vaccine. In humans, prior dengue virus infection provides partial protection from clinical JE.

Personal measures should be taken to reduce exposure to mosquito bites, especially for short-term residents in endemic areas. They consist of avoiding evening outdoor exposure, using insect repellents, covering the body with clothing, and using bed nets or house screening.

Commercial pesticides, widely used by rice farmers in Asia, are effective in reducing populations of *C. tritaeniorhynchus*. Fenthion, fenitrothion, and phenthoate are effectively adulticidal and larvicidal. Insecticides may be applied from portable sprayers or from helicopters or light aircraft.

Bibliography is available at Expert Consult.

268.3 Tickborne Encephalitis

Scott B. Halstead

TBE is widespread in Europe, where it has also been identified as the cause of milkborne encephalitis.

ETIOLOGY

TBE virus is a positive-sense, single-stranded RNA virus of the family Flaviviridae.

EPIDEMIOLOGY

TBE refers to neurotropic tick-transmitted flaviviral infections occurring across the Eurasian land mass. In the Far East, the disease is called *Russian spring-summer encephalitis*; the milder, often biphasic form in Europe is simply called TBE. TBE is found in all countries of Europe except Portugal and the Benelux countries. The incidence is particularly high in Austria, Poland, Hungary, Czech Republic, Slovakia, former Yugoslavia, and Russia. The incidence tends to be very focal. Seroprevalence is as high as 50% in farm and forestry workers. The majority of cases occur in adults, but even young children may be infected while playing in the woods or on picnics or camping trips. The seasonal distribution of cases is midsummer in southern Europe, with a longer season in Scandinavia and the Russian Far East. TBE can be excreted from the milk of goats, sheep, or cows. Before World War II, when milk was consumed unpasteurized, milkborne cases of TBE were common.

Viruses are transmitted principally by hard ticks of *Ixodes ricinus* in Europe and *Ixodes persulcatus* in the Far East. Viral circulation is maintained by a combination of transmission from ticks to birds, rodents, and larger mammals and transtadial transmission from larval to nymphal and adult stages. In some parts of Europe and Russia, ticks feed actively during the spring and early fall, giving rise to the name "spring-summer encephalitis."

CLINICAL MANIFESTATIONS

After an incubation period of 7-14 days, the European form begins as an acute nonspecific febrile illness that is followed in 5-30% of cases by meningoencephalitis. The Far Eastern variety more often results in encephalitis with higher case fatality and sequelae rates. The 1st phase of illness is characterized by fever, headache, myalgia, malaise, nausea, and vomiting for 2-7 days. Fever disappears and after 2-8 days may return accompanied by vomiting, photophobia, and signs of meningeal irritation in children and more severe encephalitic signs in adults. This phase rarely lasts more than 1 wk.

DIAGNOSIS

The diagnosis of TBE should be suspected in any patient reporting a tick bite in an endemic area during the transmission season. The etiologic diagnosis of TBE is established by testing acute-phase serum collected early in the illness for the presence of virus-specific IgM antibodies or, alternatively, demonstrating a 4-fold or greater increase in IgG antibody titers by testing paired acute and convalescent sera. The virus can also be identified by polymerase chain reaction. With widespread use of vaccines, an IgM titer of >500 arbitrary units in early convalescent serum has been recommended for the diagnosis of acute TBE.

TREATMENT

There is no specific treatment for TBE. The treatment is intensive supportive care (see Chapter 67), including control of seizures (see Chapter 593).

PROGNOSIS

The main risk for fatal outcome is advanced age; the fatality rate in adults is approximately 1%, but sequelae in children are rare. Transient

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unilateral paralysis of an upper extremity is a common finding in adults. Common sequelae include chronic fatigue, headache, sleep disorders, and emotional disturbances.

PREVENTION

Specific immunoglobulin has been given to persons with seasonal tick bite exposure, although efficacy of this preventive therapy is not well studied. Effective inactivated vaccines for human use, made from virus grown in tissue culture, are licensed in Russia and Europe. They are administered in a 3 dose series.

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268.4 West Nile Encephalitis

See Chapter 267.

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Chapter 269

Dengue Fever and Dengue Hemorrhagic Fever

Scott B. Halstead

Dengue fever is a benign syndrome caused by several arthropod-borne viruses and is characterized by biphasic fever, myalgia or arthralgia, rash, leukopenia, and lymphadenopathy. **Dengue hemorrhagic fever** (Philippine, Thai, or Singapore hemorrhagic fever; hemorrhagic dengue; acute infectious thrombocytopenic purpura) is a severe, often fatal, febrile disease caused by 1 of 4 dengue viruses. It is characterized by capillary permeability, abnormalities of hemostasis, and, in severe cases, a protein-losing shock syndrome **(dengue shock syndrome),** which is thought to have an immunopathologic basis.

ETIOLOGY

There are at least 4 distinct antigenic types of dengue virus (dengue 1, 2, 3, and 4), members of the family Flaviviridae. In addition, 3 other arthropod-borne viruses (arboviruses) cause similar or identical febrile diseases with rash (Table 269-1).

EPIDEMIOLOGY

Dengue viruses are transmitted by mosquitoes of the Stegomyia family. *Aedes aegypti,* a daytime biting mosquito, is the principal vector, and all 4 virus types have been recovered from it. In most tropical areas, *A. aegypti* is highly urbanized, breeding in water stored for drinking or bathing and in rainwater collected in any container. Dengue viruses have also been recovered from *Aedes albopictus,* as in the 2001 Hawaiian epidemic, whereas outbreaks in the Pacific area have been attributed to several other *Aedes* species. These species breed in water trapped in vegetation. In Southeast Asia and West Africa, dengue virus may be maintained in a cycle involving canopy-feeding jungle monkeys and *Aedes* species, which feed on monkeys.

Epidemics were common in temperate areas of the Americas, Europe, Australia, and Asia until early in the 20th century. Dengue fever and dengue-like disease are now endemic in tropical Asia, the South Pacific Islands, northern Australia, tropical Africa, the Arabian Peninsula, the Caribbean, and Central and South America. Dengue fever occurs frequently among travelers to these areas. Locally acquired disease has been reported in Florida and Texas, and imported cases in the United States occur in travelers to endemic areas. More than 390 million dengue infections occur annually; approximately 96 million have clinical disease.

Dengue outbreaks in urban areas infested with *A. aegypti* may be explosive; up to 70-80% of the population may be involved. Most overt disease occurs in older children and adults. Because *A. aegypti* has a limited flight range, spread of an epidemic occurs mainly through viremic human beings and follows the main lines of transportation. Sentinel cases may infect household mosquitoes; a large number of nearly simultaneous secondary infections give the appearance of a contagious disease. Where dengue is endemic, children and susceptible foreigners may be the only persons to acquire overt disease, as adults have become immune.

Table 269-1 Vectors and Geographic Distribution of Dengue-Like Diseases

VIRUS	GEOGRAPHIC GENUS AND DISEASE	VECTOR	DISTRIBUTION
Togavirus	Chikungunya	*Aedes aegypti* *Aedes africanus* *Aedes albopictus*	Africa, India, Southeast Asia, Latin America, United States
Togavirus	O'nyong-nyong	*Anopheles funestus*	East Africa
Flavivirus	West Nile fever	*Culex molestus* *Culex univittatus*	Europe, Africa, Middle East, India

Dengue-Like Diseases

Dengue-like diseases may occur in epidemics. Epidemiologic features depend on the vectors and their geographic distribution (see Table 269-1). Chikungunya virus is enzootic throughout much of West, Central, and South Africa as well as Central America and recently the southern United States. Periodic introductions of virus into the urban transmission cycle have led to pandemics, resulting in widespread endemicity in the most populous areas of Asia. In Asia, *A. aegypti* is the principal vector; in Africa, other Stegomyia species may be important vectors. In Southeast Asia, dengue and chikungunya outbreaks occur concurrently. Outbreaks of o'nyong-nyong fever usually involve villages or small towns, in contrast to the urban outbreaks of dengue and chikungunya. West Nile virus is enzootic in Africa. Chikungunya is now endemic in urban cycles in tropical countries throughout the world. Intense transmission in Caribbean countries presages emergence of chikungunya into the United States.

Dengue Hemorrhagic Fever

Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted. It is endemic in all of tropical America and Asia, where warm temperatures and the practices of water storage in homes plus outdoor breeding sites result in large, permanent populations of *A. aegypti.* Under these conditions, infections with dengue viruses of all types are common. A first infection, referred to as a primary infection, may be followed by infection with a different dengue virus, referred to as a secondary infection. In areas of high endemicity secondary infections are frequent.

Secondary dengue infections are relatively mild in the majority of instances, ranging from an inapparent infection through an undifferentiated upper respiratory tract or dengue-like disease, but may also progress to dengue hemorrhagic fever. Nonimmune foreigners, both adults and children, who are exposed to dengue virus during outbreaks of hemorrhagic fever have classic dengue fever or even milder disease. The differences in clinical manifestations of dengue infections between natives and foreigners in Southeast Asia are related more to immunologic status than to racial susceptibility. Dengue hemorrhagic fever can occur during primary dengue infections, most frequently in infants whose mothers are immune to dengue. Dengue hemorrhagic fever or severe dengue occurs rarely in individuals of African ancestry because of an as yet

undiscovered resistance gene that would explain the low incidence of severe dengue throughout much of Africa and among African populations in the American tropics despite high rates of dengue infection.

PATHOGENESIS

Fatalities with chikungunya and West Nile fever infections are not common but have been ascribed to viral encephalitis.

The pathogenesis of dengue hemorrhagic fever is incompletely understood, but epidemiologic studies suggest that it is usually associated with second heterotypic infections with dengue types 1-4. Retrospective studies of sera from human mothers whose infants acquired dengue hemorrhagic fever and prospective studies in children acquiring sequential dengue infections have shown that the circulation of infection-enhancing antibodies at the time of infection is the strongest risk factor for development of severe disease. Absence of cross-reactive neutralizing antibodies and presence of enhancing antibodies from passive transfer or active production are the best correlates of risk for dengue hemorrhagic fever. Monkeys that are infected sequentially or are receiving small quantities of enhancing antibodies have enhanced viremias. In humans studied early during the course of secondary dengue infections, viremia levels directly predicted disease severity. When dengue virus immune complexes attach to macrophage Fc receptors, a signal is sent that suppresses innate immunity, resulting in enhanced viral production. In the Americas, dengue hemorrhagic fever and dengue shock syndrome have been associated with dengue types 1-4 strains of recent Southeast Asian origin. Recent occurrences of sizable dengue hemorrhagic fever outbreaks in India, Pakistan, and Bangladesh also appear to be related to imported dengue strains.

Early in the acute stage of secondary dengue infections, there is rapid activation of the complement system. Shortly before or during shock, blood levels of soluble tumor necrosis factor receptor, interferon-γ, and interleukin-2 are elevated. C1q, C3, C4, C5-C8, and C3 proactivators are depressed, and C3 catabolic rates are elevated. These factors, the virus itself, or viral nonstructural protein 1 (NS1) may interact with endothelial cells, blood clotting factors, and platelets to produce increased vascular permeability. The blood clotting and fibrinolytic systems are activated, and levels of factor XII (Hageman factor) are depressed. The mechanism of bleeding in dengue hemorrhagic fever is not known, but a mild degree of disseminated intravascular coagulopathy, liver damage, and thrombocytopenia may operate synergistically. Capillary damage allows fluid, electrolytes, small proteins, and, in some instances, red blood cells to leak into extravascular spaces. This internal redistribution of fluid, together with deficits caused by fasting, thirsting, and vomiting, results in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis, and hyponatremia.

Usually no pathologic lesions are found to account for death. In rare instances, death may be a result of gastrointestinal or intracranial hemorrhages. Minimal to moderate hemorrhages are seen in the upper gastrointestinal tract, and petechial hemorrhages are common in the interventricular septum of the heart, on the pericardium, and on the subserosal surfaces of major viscera. Focal hemorrhages are occasionally seen in the lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged, often with fatty changes. Yellow, watery, and at times blood-tinged effusions are present in serous cavities in approximately 75% of patients at autopsy.

Dengue virus is frequently absent in tissues at the time of death; viral antigens or RNA have been localized to hepatocytes and macrophages in liver, spleen, lung, and lymphatic tissues.

CLINICAL MANIFESTATIONS

Dengue Fever

The incubation period is 1-7 days. The clinical manifestations are variable and are influenced by the age of the patient. In infants and young children, the disease may be undifferentiated or characterized by fever for 1-5 days, pharyngeal inflammation, rhinitis, and mild cough. A majority of infected older children and adults experience sudden onset of fever, with temperature rapidly increasing to 39.4-41.1°C (103-106°F), usually accompanied by frontal or retroorbital pain, particularly when pressure is applied to the eyes. Occasionally, severe back pain precedes the fever (back-break fever). A transient, macular, generalized rash that blanches under pressure may be seen during the 1st 24-48 hr of fever. The pulse rate may be slow relative to the degree of fever. Myalgia and arthralgia occur soon after the onset of fevers and increase in severity over time. Joint symptoms may be particularly severe in patients with chikungunya or o'nyong-nyong infection. From the 2nd-6th day of fever, nausea and vomiting are apt to occur, and generalized lymphadenopathy, cutaneous hyperesthesia or hyperalgesia, taste aberrations, and pronounced anorexia may develop.

Approximately 1-2 days after defervescence, a generalized, morbilliform, maculopapular rash appears that spares the palms and soles. It disappears in 1-5 days; desquamation may occur. Rarely there is edema of the palms and soles. About the time this second rash appears, the body temperature, which has previously decreased to normal, may become slightly elevated and demonstrate the characteristic biphasic temperature pattern.

Dengue Hemorrhagic Fever

Differentiation between dengue fever and dengue hemorrhagic fever is difficult early in the course of illness. A relatively mild 1st phase with abrupt onset of fever, malaise, vomiting, headache, anorexia, and cough may be followed after 2-5 days by rapid clinical deterioration and collapse. In this 2nd phase, the patient usually has cold, clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability, midepigastric pain, and decreased urinary output. Frequently, there are scattered petechiae on the forehead and extremities; spontaneous ecchymoses may appear, and easy bruising and bleeding at sites of venipuncture are common. A macular or maculopapular rash may appear, and there may be circumoral and peripheral cyanosis. Respirations are rapid and often labored. The pulse is weak, rapid, and thready, and the heart sounds are faint. The liver may enlarge to 4-6 cm below the costal margin and is usually firm and somewhat tender. Approximately 20-30% of cases of dengue hemorrhagic fever are complicated by shock (dengue shock syndrome). Dengue shock can be subtle, arising in patients who are fully alert, and is accompanied by increased peripheral vascular resistance and raised diastolic blood pressure. Shock is not from congestive heart failure but from venous pooling. With increasing cardiovascular compromise, diastolic pressure rises toward the systolic level and the pulse pressure narrows. Fewer than 10% of patients have gross ecchymosis or gastrointestinal bleeding, usually after a period of uncorrected shock. After a 24-36 hr period of crisis, convalescence is fairly rapid in the children who recover. The temperature may return to normal before or during the stage of shock. Bradycardia and ventricular extrasystoles are common during convalescence.

DIAGNOSIS

A clinical diagnosis of dengue fever derives from a high index of suspicion and knowledge of the geographic distribution and environmental cycles of causal viruses. Because clinical findings vary and there are many possible causative agents, the term *dengue-like disease* should be used until a specific diagnosis is established. A case is confirmed by isolation of the virus, viral antigen, or genome by polymerase chain reaction analysis, as well as demonstration of a 4-fold or greater increase in antibody titers. A probable case is a typical acute febrile illness with supportive serology and occurrence at a location where there are confirmed cases.

The World Health Organization criteria for **dengue hemorrhagic fever** are fever (2-7 days in duration or biphasic), minor or major hemorrhagic manifestations, thrombocytopenia (≤100,000/μL), and objective evidence of increased capillary permeability (hematocrit increased by ≥20%), pleural effusion or ascites (by chest radiography or ultrasonography), or hypoalbuminemia. **Dengue shock syndrome** criteria include those for dengue hemorrhagic fever as well as hypotension, tachycardia, narrow pulse pressure (≤20 mm Hg), and signs of poor perfusion (cold extremities).

In 2009, the World Health Organization promulgated new guidelines for the diagnosis of probable dengue, dengue with warning signs, and a category called "severe dengue." Occurrence of warning signs in an individual with probable dengue should alert the physician to the need for hospitalization. Severe dengue is a mixture of syndromes associated

with dengue infection. This includes classical dengue hemorrhagic fever and dengue shock syndrome, but also rare instances of encephalitis or encephalopathy associated with dengue infection. Severe dengue also includes respiratory distress that may be a harbinger of pulmonary edema caused by overhydration, an all too common outcome of inexpert treatment (see "Treatment" and "Complications" sections).

Virologic diagnosis can be established by serologic tests, by detection of viral proteins or viral RNA, or by the isolation of the virus from blood leukocytes or acute-phase serum. Following primary and secondary dengue infections, there is a relatively transient appearance of antidengue (immunoglobulin [Ig] M) antibodies. These disappear after 6-12 wk, a feature that can be used to time a dengue infection. In secondary dengue infections, most antibody is of the IgG class. Serologic diagnosis depends on a 4-fold or greater increase in IgG antibody titer in paired sera by hemagglutination inhibition, complement fixation, enzyme immunoassay, or neutralization test. Carefully standardized IgM and IgG capture enzyme commercial immunoassays are now widely used to identify acute-phase antibodies from patients with primary or secondary dengue infections in single-serum samples. Usually such samples should be collected not earlier than 5 days and not later than 6 wk after onset. It may not be possible to distinguish the infecting virus by serologic methods alone, particularly when there has been prior infection with another member of the same arbovirus group. Virus can be recovered from acute-phase serum after inoculating tissue culture or living mosquitoes. Viral RNA can be detected in blood or tissues by specific complementary RNA probes or amplified first by polymerase chain reaction or by real-time polymerase chain reaction. A viral nonstructural protein, NS1, is released by infected cells into the circulation and can be detected in acute-stage blood samples using monoclonal or polyclonal antibodies. The detection of NS1 is the basis of commercial tests, including rapid lateral flow tests. These tests offer reliable point of care diagnosis of acute dengue infection.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of dengue fever includes dengue-like diseases, viral respiratory and influenza-like diseases, the early stages of malaria, mild yellow fever, scrub typhus, viral hepatitis, and leptospirosis.

Four arboviral diseases have dengue-like courses but without rash: Colorado tick fever, sandfly fever, Rift Valley fever, and Ross River fever. Colorado tick fever occurs sporadically among campers and hunters in the western United States; sandfly fever in the Mediterranean region, the Middle East, southern Russia, and parts of the Indian subcontinent; and Rift Valley fever in North, East, Central, and South Africa. Ross River fever is endemic in much of eastern Australia, with epidemic extension to Fiji. In adults, Ross River fever often produces protracted and crippling arthralgia involving weight-bearing joints.

Because meningococcemia, yellow fever (see Chapter 270), other viral hemorrhagic fevers (see Chapter 271), many rickettsial diseases, and other severe illnesses caused by a variety of agents may produce a clinical picture similar to dengue hemorrhagic fever, the etiologic diagnosis should be made only when epidemiologic or serologic evidence suggests the possibility of a dengue infection.

LABORATORY FINDINGS

In dengue fever, pancytopenia may develop after the 3-4 days of illness. Neutropenia may persist or reappear during the latter stage of the disease and may continue into convalescence, with white blood cell counts <2,000/μL. Platelet counts rarely fall below 100,000/μL. Venous clotting, bleeding and prothrombin times, and plasma fibrinogen values are within normal ranges. The tourniquet test result may be positive. Mild acidosis, hemoconcentration, increased transaminase values, and hypoproteinemia may occur during some primary dengue virus infections. The electrocardiogram may show sinus bradycardia, ectopic ventricular foci, flattened T waves, and prolongation of the P-R interval.

The most common hematologic abnormalities during dengue hemorrhagic fever and dengue shock syndrome are hemoconcentration with an increase of >20% in hematocrit, thrombocytopenia, prolonged bleeding time, and a moderately decreased prothrombin level that is seldom <40% of control. Fibrinogen levels may be subnormal, and fibrin split-product values are elevated. Other abnormalities include moderate elevations of serum transaminase levels, consumption of complement, mild metabolic acidosis with hyponatremia, occasionally hypochloremia, slight elevation of serum urea nitrogen, and hypoalbuminemia. Roentgenograms of the chest reveal pleural effusions (right > left) in nearly all patients with dengue shock syndrome. Ultrasonography can be used to detect serosal effusions of the thorax or abdomen. Thickening of gallbladder wall and presence of perivesicular fluid are characteristic signs of increased vascular permeability.

TREATMENT

Treatment of uncomplicated dengue fever is supportive. Bed rest is advised during the febrile period. Antipyretics should be used to keep body temperature <40°C (104°F). Analgesics or mild sedation may be required to control pain. Aspirin is contraindicated and should not be used because of its effects on hemostasis. Fluid and electrolyte replacement is required for deficits caused by sweating, fasting, thirsting, vomiting, and diarrhea.

Dengue Hemorrhagic Fever and Dengue Shock Syndrome

Dengue shock syndrome is a medical emergency that may occur in any child with a recent travel history to a tropical destination. Management begins with diagnostic suspicion and the understanding that shock often occurs during defervescence. Detailed instructions for case management are available at the Geneva or New Delhi World Health Organization websites: http://www.who.int/csr/don/archive/disease/dengue_fever/dengue.pdf. Management of dengue hemorrhagic fever and dengue shock syndrome includes immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance. Close monitoring is essential for at least 48 hr, because shock may occur or recur precipitously early in the disease. Patients who are cyanotic or have labored breathing should be given oxygen. Rapid intravenous replacement of fluids and electrolytes can frequently sustain patients until spontaneous recovery occurs. Normal saline is more effective than the more expensive Ringer lactated saline in treating shock. When pulse pressure is ≤10 mm Hg or when elevation of the hematocrit persists after replacement of fluids, plasma or colloid preparations are indicated.

Care must be taken to avoid overhydration, which may contribute to cardiac failure. Transfusions of fresh blood or platelets suspended in plasma may be required to control bleeding; they should not be given during hemoconcentration but only after evaluation of hemoglobin or hematocrit values. Salicylates are contraindicated because of their effect on blood clotting.

Sedation may be required for children who are markedly agitated. Use of vasopressors has not resulted in a significant reduction of mortality over that observed with simple supportive therapy. Disseminated intravascular coagulation may require treatment (see Chapter 483). Corticosteroids do not shorten the duration of disease or improve prognosis in children receiving careful supportive therapy.

COMPLICATIONS

Hypervolemia during the fluid reabsorptive phase may be life-threatening and is heralded by a decrease in hematocrit with wide pulse pressure. Diuretics and digitalization may be necessary.

Primary infections with dengue fever and dengue-like diseases are usually self-limited and benign. Fluid and electrolyte losses, hyperpyrexia, and febrile convulsions are the most frequent complications in infants and young children. Epistaxis, petechiae, and purpuric lesions are uncommon but may occur at any stage. Blood from epistaxis that is swallowed, vomited, or passed by rectum may be erroneously interpreted as gastrointestinal bleeding. In adults and possibly in children, underlying conditions may lead to clinically significant bleeding. Convulsions may occur during high temperature, especially with chikungunya fever. Infrequently, after the febrile stage, prolonged asthenia, mental depression, bradycardia, and ventricular extrasystoles may occur in children.

In endemic areas, dengue hemorrhagic fever should be suspected in children with a febrile illness suggestive of dengue fever who experience hemoconcentration and thrombocytopenia.

PROGNOSIS

Dengue Fever

The prognosis is good. Care should be taken to avoid use of drugs that suppress platelet activity.

Dengue Hemorrhagic Fever

The prognosis of dengue hemorrhagic fever is adversely affected by late diagnosis and delayed or improper treatment. Death has occurred in 40-50% of patients with shock, but with adequate intensive care, deaths should occur in <1% of cases. Infrequently, there is residual brain damage as a consequence of prolonged shock or occasionally of intracranial hemorrhage. Many fatalities are caused by overhydration.

PREVENTION

Several types of dengue type 1-4 vaccines are under development, and a killed vaccine for chikungunya is efficacious but not licensed. Large-scale Phase III clinical evaluations of a chimeric yellow fever/dengue tetravalent vaccine manufactured by Sanofi Pasteur reveal only moderate protection against individual dengue viruses but a reduction in hospitalization and severe disease. Other major vaccine manufacturers, GlaxoSmithKline, Takeda and Merck, have other tetravalent dengue vaccines in human clinical trials. Sanofi plans to license their vaccine first in dengue-endemic countries. The possibility exists that incomplete dengue immunization may sensitize recipients, with the potential that ensuing dengue infections could result in dengue hemorrhagic fever. Prophylaxis consists of avoiding daytime household-based **mosquito bites** through the use of insecticides, repellents, body covering with clothing, screening of houses, and destruction of *A. aegypti* breeding sites. If water storage is mandatory, a tight-fitting lid or a thin layer of oil may prevent egg laying or hatching. A larvicide, such as Abate (O,O′-[thiodi-*p*-phenylene] O,O,O,O′-tetramethyl phosphorothioate), available as a 1% sand-granule formation and effective at a concentration of 1 ppm, may be added safely to drinking water. Ultra-low-volume spray equipment effectively dispenses the adulticide malathion from truck or airplane for rapid intervention during an epidemic. Only mosquito repellants and other personal antimosquito measures are effective against mosquitoes in the field, forest, or jungle.

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Chapter 270

Yellow Fever

Scott B. Halstead

Yellow fever is an acute infection characterized in its most severe form by fever, jaundice, proteinuria, and hemorrhage. The virus is mosquito-borne and occurs in epidemic or endemic form in South America and Africa. Seasonal epidemics occurred in cities located in temperate areas of Europe and the Americas until 1900, and epidemics continue in West, Central, and East Africa.

ETIOLOGY

Yellow fever is the prototype of the *Flavivirus* genus of the family Flaviviridae, which are enveloped single-stranded RNA viruses 35-50 nm in diameter.

Yellow fever circulates zoonotically as 5 genotypes: type IA in West Central Africa, type IB in South America, type II in West Africa, type III in East Central Africa, and type IV in East Africa. Types IA and IB virus are capable of urban transmission between human beings by *Aedes aegypti.* Sometime in the 1600s yellow fever virus was brought to the American tropics through the African slave trade. Subsequently, yellow fever caused enormous coastal and riverine epidemics in the Atlantic and Caribbean basins until the 20th century, when the virus and its urban and sylvan mosquito cycles were identified, mosquito control methods were perfected, and a vaccine was developed. The East and East/Central African genotypes have not fully entered the urban cycle and have not spread to the East Coast of Africa or to the countries of Asia.

EPIDEMIOLOGY

Human and nonhuman primate hosts acquire the yellow fever infection by the bite of infected mosquitoes. After an incubation period of 3-6 days, virus appears in the blood and may serve as a source of infection for other mosquitoes. The virus must replicate in the gut of the mosquito and pass to the salivary gland before the mosquito can transmit the virus. Yellow fever virus is transmitted in an urban cycle—human to *A. aegypti* to human—and a jungle cycle—monkey to jungle mosquitoes to monkey. Classic yellow fever epidemics in the United States, South America, the Caribbean, and parts of Europe were of the urban variety. Since 2000, West Africa has experienced 5 urban epidemics, including in the capital cities of Abidjan (Cote d'Ivoire), Conakry (Guinea), and Dakar (Senegal). In 2012-2013, large outbreaks of East and East/Central yellow fever occurred across a large, predominantly rural area of war-ravaged Darfur in southwestern Sudan and in adjacent areas of northern Uganda. Most of the approximately 200 cases reported each year in South America are jungle yellow fever. In colonial times, urban yellow fever attack rates in white adults were very high, suggesting that subclinical infections are uncommon in this age group. Yellow fever may be less severe in children, with subclinical infection : clinical case ratios ≥2 : 1. In areas where outbreaks of urban yellow fever are common, most cases involve children because many adults are immune. Transmission in West Africa is highest during the rainy season, from July to November. The migration of nonimmune laborers into endemic regions is a significant factor in some outbreaks.

In tropical forests, yellow fever virus is maintained in a transmission cycle involving monkeys and tree hole–breeding mosquitoes (*Haemagogus* in Central and South America; the *Aedes africanus* complex in Africa). In the Americas, most cases involve tourists, campers, and men who work in forested areas and are exposed to infected mosquitoes. In Africa, the virus is prevalent in moist savanna and savanna transition areas, where other tree hole–breeding *Aedes* vectors transmit the virus between monkeys and humans and between humans.

PATHOGENESIS

Pathologic changes seen in the liver include: (1) coagulative necrosis of hepatocytes in the midzone of the liver lobule, with sparing of cells around the portal areas and central veins; (2) eosinophilic degeneration of hepatocytes **(Councilman bodies);** (3) microvacuolar fatty change; and (4) minimal inflammation. The kidneys show acute tubular necrosis. In the heart, myocardial fiber degeneration and fatty infiltration are seen. The brain may show edema and petechial hemorrhages. Direct viral injury to the liver results in impaired ability to perform functions of biosynthesis and detoxification; this is the central pathogenic event of yellow fever. Hemorrhage is postulated to result from decreased synthesis of vitamin K–dependent clotting factors and, in some cases, disseminated intravascular clotting. However, because the pathogenesis of shock in patients with yellow fever appears similar to that described for dengue shock syndrome and the other viral hemorrhagic fevers, viral damage to platelets and endothelial cells resulting in release of prohemorrhagic factors may be the central mechanism of hemorrhage in yellow fever.

Renal dysfunction has been attributed to hemodynamic factors (prerenal failure progressing to acute tubular necrosis).

CLINICAL MANIFESTATIONS

In Africa, inapparent, abortive, or clinically mild infections are frequent; some studies suggest that children experience a milder disease than adults do. Abortive infections, characterized by fever and headache, may be unrecognized except during epidemics.

In its classic form, yellow fever begins with sudden onset of fever, headache, myalgia, lumbosacral pain, anorexia, nausea, and vomiting. Physical findings during the early phase of illness, when virus is present in the blood, include prostration, conjunctival injection, flushing of

face and neck, reddening of the tongue at the tip and edges, and relative bradycardia. After 2-3 days, there may be a brief period of remission, followed in 6-24 hr by reappearance of fever with vomiting, epigastric pain, jaundice, dehydration, gastrointestinal and other hemorrhages, albuminuria, hypotension, renal failure, delirium, convulsions, and coma. Death may occur after 7-10 days, with the fatality rate in severe cases approaching 50%. Some patients who survive the acute phase of illness later succumb to renal failure or myocardial damage. Laboratory abnormalities include leukopenia; prolonged clotting, prothrombin, and partial thromboplastin times; thrombocytopenia; hyperbilirubinemia; elevated serum transaminase values; albuminuria; and azotemia. Hypoglycemia may be present in severe cases. Electrocardiogram abnormalities such as bradycardia and ST-T changes are described.

DIAGNOSIS

Yellow fever should be suspected when fever, headache, vomiting, myalgia, and jaundice appear in residents of enzootic areas or in unimmunized visitors who have recently traveled (within 2 wk before onset of symptoms) to endemic areas. Clinically, yellow fever is quite similar to dengue hemorrhagic fever. In contrast to the gradual onset of acute viral hepatitis resulting from hepatitis A, B, C, D, or E virus, jaundice in yellow fever appears after 3-5 days of high temperature and is often accompanied by severe prostration. Mild yellow fever is dengue-like and cannot be distinguished from a wide variety of other infections. Jaundice and fever may occur in any of several other tropical diseases, including malaria, viral hepatitis, louse-borne relapsing fever, leptospirosis, typhoid fever, rickettsial infections, certain systemic bacterial infections, sickle cell crisis, Rift Valley fever, Crimean-Congo hemorrhagic fever, and other viral hemorrhagic fevers. Outbreaks of yellow fever always include cases with severe gastrointestinal hemorrhage.

Specific diagnosis depends on detection of virus or viral antigen in acute-phase blood samples or antibody assays. The immunoglobulin M enzyme immunoassay is particularly useful. Sera obtained during the 1st 10 days after onset of symptoms should be kept in an ultra-low-temperature freezer (−70°C [−94°F]) and shipped on dry ice for virus testing. Convalescent-phase samples for antibody tests are managed by conventional means. In handling acute-phase blood specimens, medical personnel must take care to avoid contaminating themselves or others on the evacuation trail (laboratory personnel and others). Postmortem diagnosis is based on virus isolation from liver or blood, identification of Councilman bodies in liver tissue, or detection of antigen or viral genome in liver tissue.

TREATMENT

It is customary to keep patients with yellow fever in a mosquito-free area, with use of mosquito nets if necessary. Patients are viremic during the febrile phase of the illness. Although there is no specific treatment for yellow fever, medical care is directed at maintaining physiologic status with the following measures: (1) sponging and acetaminophen to reduce high temperature, (2) vigorous fluid replacement of losses resulting from fasting, thirsting, vomiting, or plasma leakage, (3) correcting acid–base imbalance, (4) maintaining nutritional intake to lessen the severity of hypoglycemia, and (5) avoiding drugs that are either metabolized by the liver or toxic to the liver, kidney, or central nervous system.

COMPLICATIONS

Complications of acute yellow fever include severe hemorrhage, liver failure, and acute renal failure. Bleeding should be managed by transfusion of fresh whole blood or fresh plasma with platelet concentrates if necessary. Renal failure may require peritoneal dialysis or hemodialysis.

PREVENTION

Yellow fever 17D is a live-attenuated vaccine with a long record of safety and efficacy. It is administered as a single 0.5 mL subcutaneous injection at least 10 days before arrival in a yellow fever–endemic area. With the exceptions noted later, individuals traveling to endemic areas in South America and Africa should be considered for vaccination, but length of stay, exact locations to be visited, and environmental or occupational exposure may determine the specific risk and individual need for vaccination. Persons traveling from yellow fever–endemic to yellow fever–receptive countries may be required by national authorities to obtain a yellow fever vaccine (e.g., from South America or Africa to India). Usually countries that require travelers to obtain a yellow fever immunization do not issue a visa without a valid immunization certificate. Vaccination is valid for 10 yr for international travel certification, although immunity lasts at least 40 yr and probably for life. Immunoglobulin M antibodies circulate for years after administration of yellow fever vaccine.

Since 1996, there have been a number of reports of **yellow fever vaccine–associated viscerotropic disease** with higher risk in elderly vaccine recipients and in persons with previous thymectomies. Yellow fever vaccine should not be administered to persons who have symptomatic immunodeficiency diseases, are taking immunosuppressant drugs, or have a history of thymectomy. A recent study has shown that individuals on maintenance corticosteroids may be successfully vaccinated. Although the vaccine is not known to harm fetuses, its administration during pregnancy is not advised. The vaccine virus may be rarely transmitted through breastfeeding. In very young children, there is a small risk of encephalitis and death after yellow fever 17D vaccination. The 17D vaccine should not be administered to infants younger than 4 mo. Residence in or travel to areas of known or anticipated yellow fever activity (e.g., forested areas in the Amazon basin), which puts an individual at high risk, warrants immunization of infants 4-9 mo of age. Immunization of children 9 mo of age and older is routinely recommended before entry into endemic areas. Immunization of persons older than 60 yr of age should be weighed against their risk for sylvatic yellow fever in the American tropics and for urban or sylvatic yellow fever in Africa. Vaccination should be avoided in persons with a history of egg allergy. Alternatively, a skin test can be performed to determine whether a serious allergy exists that would preclude vaccination.

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Chapter 271

Ebola and Other Viral Hemorrhagic Fevers

Scott B. Halstead

Viral hemorrhagic fevers are a loosely defined group of clinical syndromes in which hemorrhagic manifestations are either common or especially notable in severe illness. Both the etiologic agents and clinical features of the syndromes differ, but disseminated intravascular coagulopathy may be a common pathogenetic feature.

ETIOLOGY

Six of the viral hemorrhagic fevers are caused by arthropod-borne viruses (arboviruses) (Table 271-1). Four are caused by togaviruses of the family Flaviviridae: Kyasanur Forest disease, Omsk hemorrhagic fever, dengue (see Chapter 269), and yellow fever (see Chapter 270) viruses. Three are caused by viruses of the family Bunyaviridae: Congo fever, Hantaan fever, and Rift Valley fever (RVF) viruses. Four are caused by viruses of the family Arenaviridae: Junin fever, Machupo fever, Guanarito fever, and Lassa fever. Two are caused by viruses of the family Filoviridae: Ebola and Marburg disease. The Filoviridae are enveloped, filamentous RNA viruses that are sometimes branched, unlike any other known virus.

EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS

With some exceptions, the viruses causing viral hemorrhagic fevers are transmitted to humans via a nonhuman entity. The specific ecosystem

Table 271-1 Viral Hemorrhagic Fevers

MODE OF TRANSMISSION	DISEASE	VIRUS
Tick-borne	Crimean-Congo hemorrhagic fever (HF)*	Congo
	Kyasanur Forest disease	Kyasanur Forest disease
	Omsk HF	Omsk
Mosquito-borne†	Dengue HF	Dengue (4 types)
	Rift Valley fever	Rift Valley fever
	Yellow fever	Yellow fever
Infected animals or materials to humans	Argentine HF	Junin
	Bolivian HF	Machupo
	Lassa fever*	Lassa
	Marburg disease*	Marburg
	Ebola HF*	Ebola
	HF with renal syndrome	Hantaan

*Patients may be contagious; nosocomial infections are common.
†Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.

required for viral survival determines the geographic distribution of disease. Although it is commonly thought that all viral hemorrhagic fevers are arthropod borne, 7 may be contracted from environmental contamination caused by animals or animal cells or from infected humans (see Table 271-1). Laboratory and hospital infections have occurred with many of these agents. Lassa fever and Argentine and Bolivian hemorrhagic fevers are reportedly milder in children than in adults.

Crimean-Congo Hemorrhagic Fever

Sporadic human infection with Crimean-Congo hemorrhagic fever in Africa provided the original virus isolation. Natural foci are recognized in Bulgaria, western Crimea, and the Rostov-on-Don and Astrakhan regions; disease occurs in Central Asia from Kazakhstan to Pakistan. Index cases were followed by nosocomial transmission in Pakistan and Afghanistan in 1976, in the Arabian Peninsula in 1983, and in South Africa in 1984. In the Russian Federation, the vectors are ticks of the species *Hyalomma marginatum* and *Hyalomma anatolicum,* which, along with hares and birds, may serve as viral reservoirs. Disease occurs from June to September, largely among farmers and dairy workers.

Kyasanur Forest Disease

Human cases of Kyasanur Forest disease occur chiefly in adults in an area of Mysore State, India. The main vectors are 2 Ixodidae ticks, *Haemaphysalis turturis* and *Haemaphysalis spinigera.* Monkeys and forest rodents may be amplifying hosts. Laboratory infections are common.

Omsk Hemorrhagic Fever

Omsk hemorrhagic fever occurs throughout south-central Russia and northern Romania. Vectors may include *Dermacentor pictus* and *Dermacentor marginatus,* but direct transmission from moles and muskrats to humans seems well established. Human disease occurs in a spring-summer-autumn pattern, paralleling the activity of vectors. This infection occurs most frequently in persons with outdoor occupational exposure. Laboratory infections are common.

Rift Valley Fever

The virus causing RVF is responsible for epizootics involving sheep, cattle, buffalo, certain antelopes, and rodents in North, Central, East, and South Africa. The virus is transmitted to domestic animals by *Culex theileri* and several *Aedes* species. Mosquitoes may serve as reservoirs by transovarial transmission. An epizootic in Egypt in 1977-1978 was accompanied by thousands of human infections, principally among veterinarians, farmers, and farm laborers. Smaller outbreaks occurred in Senegal in 1987, Madagascar in 1990, and Saudi Arabia and Yemen in 2000-2001. Humans are most often infected during the slaughter or skinning of sick or dead animals. Laboratory infection is common.

Argentine Hemorrhagic Fever

Before introduction of vaccine, hundreds to thousands of cases of Argentine hemorrhagic fever occurred annually from April through July in the maize-producing area northwest of Buenos Aires that reaches to the eastern margin of the Province of Cordoba. Junin virus has been isolated from the rodents *Mus musculus, Akodon arenicola,* and *Calomys laucha laucha*. It infects migrant laborers who harvest the maize and who inhabit rodent-contaminated shelters.

Bolivian Hemorrhagic Fever

The recognized endemic area of Bolivian hemorrhagic fever consists of the sparsely populated province of Beni in Amazonian Bolivia. Sporadic cases occur in farm families who raise maize, rice, yucca, and beans. In the town of San Joaquin, a disturbance in the domestic rodent ecosystem may have led to an outbreak of household infection caused by Machupo virus transmitted by chronically infected *Calomys callosus,* ordinarily a field rodent. Mortality rates are high in young children.

Venezuelan Hemorrhagic Fever

In 1989, an outbreak of hemorrhagic illness occurred in the farming community of Guanarito, Venezuela, 200 miles south of Caracas. Subsequently, in 1990-1991, there were 104 cases reported with 26 deaths caused by Guanarito virus. Cotton rats *(Sigmodon alstoni)* and cane rats *(Zygodontomys brevicauda)* have been implicated as likely reservoirs of Venezuelan hemorrhagic fever.

Lassa Fever

Lassa virus has an unusual potential for human-to-human spread, which has resulted in many small epidemics in Nigeria, Sierra Leone, and Liberia. In 2012, an outbreak of more than 1,000 cases of Lassa fever occurred in east-central Nigeria. Medical workers in Africa and the United States have also contracted the disease. Patients with acute Lassa fever have been transported by international aircraft, necessitating extensive surveillance among passengers and crews. The virus is probably maintained in nature in a species of African peridomestic rodent, *Mastomys natalensis.* Rodent-to-rodent transmission and infection of humans probably operate via mechanisms established for other arenaviruses.

Marburg Disease

Until recently, the world experience of Marburg disease had been limited to 26 primary and 5 secondary cases in Germany and Yugoslavia in 1967, and to small outbreaks in Zimbabwe in 1975, Kenya in 1980 and 1988, and South Africa in 1983. However, in 1999 a large outbreak occurred in Congo Republic and in 2005 a still larger outbreak occurred in Uige Province, Angola, with 252 cases and 227 deaths. In laboratory and clinical settings, transmission occurs by direct contact with tissues of the African green monkey or with infected human blood or semen. A reservoir in bats has been demonstrated. It appears that the virus is transmitted by close contact between fructivorous bats and from bats by aerosol to humans.

Ebola Hemorrhagic Fever

Ebola virus was isolated in 1976 from a devastating epidemic involving small villages in northern Zaire and southern Sudan; smaller outbreaks have occurred subsequently. Outbreaks have initially been nosocomial. Attack rates have been highest in the birth-1 yr old and 15-50 yr old age groups. The virus is closely related to Marburg virus. Ebola virus epidemics have occurred in Kikwit, Zaire, in 1995, followed by scattered outbreaks in Uganda and Central and West Africa. The virus has been recovered from chimpanzees, and antibodies have been found in other subhuman primates, which apparently acquire infection from a zoonotic reservoir in bats. The mode of transmission to humans is unknown. Reston virus, related to Ebola virus, has been recovered from Philippine monkeys and pigs and has caused subclinical infections in workers in monkey colonies in the United States.

West Africa in 2014 has experienced the largest number of cases of Ebola virus disease (EVD), with more than 17,900 cases reported as of December 2014 (Fig. 271-1). Countries primarily affected are Liberia, Sierra Leone, and Guinea, with imported cases reported in Nigeria,

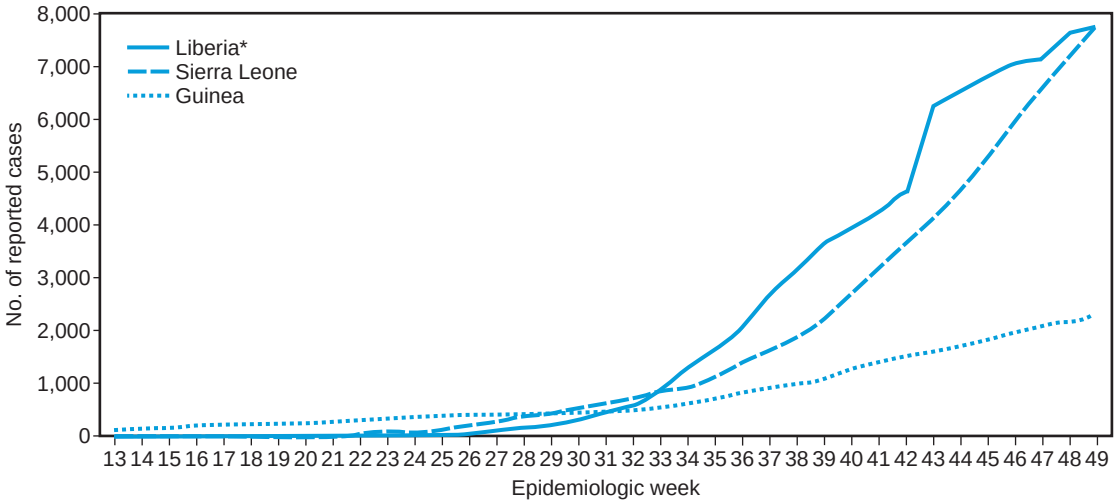

Figure 271-1 Cumulative number of Ebola virus disease cases reported—three countries, West Africa, March 29–September 20, 2014. The highest reported case counts were from Sierra Leone (7,897 cases) and Liberia (7,719), followed by Guinea (2,292). *A change in reporting source data at week 43 resulted in an adjustment of cumulative cases in Liberia. *(From Centers for Disease Control and Prevention (CDC): Ebola virus disease epidemic–West Africa, December 2014.* MMWR *63:1199–1201, 2014.)*

Mali, and Senegal as well as Europe and the United States. Of the 3 strains of EVD (Zaire, Sudan, Bundibugyo), the new strain in Zaire has a mortality rate of approximately 55-65%.

EVD may occur following exposure to fruit bats or bushmeat but most often occurs through exposure to body fluids (blood, sweat, saliva, vomitus, diarrhea, and less often human milk or semen). Patients are infectious once they are symptomatic; the incubation period is 2-21 days (mean: 11 days). The age range in the West African epidemic is broad but most patients are between 15 and 44 yr old.

Manifestations of EVD may come in stages, but most EVD begins with the sudden onset of fever accompanied by fatigue, weakness, myalgias, headache, and sore throat. This is followed by gastrointestinal involvement including anorexia, nausea, abdominal pain, vomiting, and diarrhea. Hemorrhage (defined by any evidence of bleeding) is seen in more than 50% and is a serious later phase often accompanied by vascular leakage, multiorgan failure, and death. Those who survive improve on approximately days 6-11 of EVD.

The diagnosis is confirmed by enzyme-linked immunosorbent assay immunoglobulin M and polymerase chain reaction (which may need to be repeated if initially negative). The differential diagnosis includes malaria, typhoid, Lassa fever, influenza, and meningococcemia. Criteria to aid in the diagnosis of EVD include temperature >38.6°C (101.5°F) plus symptoms; contact with an affected patient, the patient's body fluids, or the funeral; residence in or travel to an endemic region; or a history of handling bats, rodents, or primates from an endemic area.

Treatment of EVD often requires an intensive care unit and management of multiorgan system dysfunction, including fluid replacement and ventilation support. Convalescent serum and monoclonal antibodies have been employed on an experimental basis. Strict isolation and appropriate barrier protection of healthcare workers is mandatory. There is no vaccine, and epidemic control measures, isolation, and quarantine have been used to attempt to decrease the spread of the West African epidemic.

Hemorrhagic Fever with Renal Syndrome

The endemic area of hemorrhagic fever with renal syndrome (HFRS), also known as *epidemic hemorrhagic fever* and *Korean hemorrhagic fever*, includes Japan, Korea, far eastern Siberia, north and central China, European and Asian Russia, Scandinavia, Czechoslovakia, Romania, Bulgaria, Yugoslavia, and Greece. Although the incidence and severity of hemorrhagic manifestations and the mortality are lower in Europe than in northeastern Asia, the renal lesions are the same. Disease in Scandinavia, **nephropathia epidemica,** is caused by a different although antigenically related virus, Puumala virus, associated with the bank vole, *Clethrionomys glareolus.* Cases occur predominantly in the spring and summer. There appears to be no age factor in susceptibility, but because of occupational hazards, young adult men are most frequently attacked. Rodent plagues and evidence of rodent infestation have accompanied endemic and epidemic occurrences. Hantaan virus has been detected in lung tissue and excreta of *Apodemus agrarius coreae.* Antigenically related agents have been detected in laboratory rats and in urban rat populations around the world, including Prospect Hill virus in the wild rodent *Microtus pennsylvanicus* in North America and *sin nombre* virus in the deer mouse in the southern and southwestern United States; these viruses are causes of hantavirus pulmonary syndrome (see Chapter 273). Rodent-to-rodent and rodent-to-human transmission presumably occurs via the respiratory route.

CLINICAL MANIFESTATIONS

Dengue hemorrhagic fever (see Chapter 269) and yellow fever (see Chapter 270) cause similar syndromes in children in endemic areas.

Crimean-Congo Hemorrhagic Fever

The incubation period of 3-12 days is followed by a febrile period of 5-12 days and a prolonged convalescence. Illness begins suddenly with fever, severe headache, myalgia, abdominal pain, anorexia, nausea, and vomiting. After 1-2 days, fever may subside until the patient experiences an erythematous facial or truncal flush and injected conjunctivae. A second febrile period of 2-6 days then develops, with a hemorrhagic enanthem on the soft palate and a fine petechial rash on the chest and abdomen. Less frequently, there are large areas of purpura and bleeding from the gums, nose, intestines, lungs, or uterus. Hematuria and proteinuria are relatively rare. During the hemorrhagic stage, there is usually tachycardia with diminished heart sounds and occasionally hypotension. The liver is usually enlarged, but there is no icterus. In protracted cases, central nervous system signs include delirium, somnolence, and progressive clouding of consciousness. Early in the disease, leukopenia with relative lymphocytosis, progressively worsening thrombocytopenia, and gradually increasing anemia occur. In convalescence there may be hearing and memory loss. The mortality rate is 2-50%.

Kyasanur Forest Disease and Omsk Hemorrhagic Fever

After an incubation period of 3-8 days, both Kyasanur Forest disease and Omsk hemorrhagic fever begin with sudden onset of fever and headache. Kyasanur Forest disease is characterized by severe myalgia, prostration, and bronchiolar involvement; it often manifests without hemorrhage but occasionally with severe gastrointestinal bleeding. In Omsk hemorrhagic fever, there is moderate epistaxis, hematemesis,

and a hemorrhagic enanthem but no profuse hemorrhage; bronchopneumonia is common. In both diseases, severe leukopenia and thrombocytopenia, vascular dilation, increased vascular permeability, gastrointestinal hemorrhages, and subserosal and interstitial petechial hemorrhages occur. Kyasanur Forest disease may be complicated by acute degeneration of renal tubules and focal liver damage. In many patients, recurrent febrile illness may follow an afebrile period of 7-15 days. This 2nd phase takes the form of a meningoencephalitis.

Rift Valley Fever

Most RVF infections have occurred in adults with signs and symptoms resembling those of dengue fever (see Chapter 269). Onset is acute, with fever, headache, prostration, myalgia, anorexia, nausea, vomiting, conjunctivitis, and lymphadenopathy. The fever lasts 3-6 days and is often biphasic. Convalescence is often prolonged. In the 1977-1978 outbreak many patients died after showing signs that included purpura, epistaxis, hematemesis, and melena. RVF affects the uvea and posterior chorioretina; macular scarring, vascular occlusion, and optic atrophy occur, resulting in permanent visual loss in a high proportion of patients with mild to severe RVF. At autopsy extensive eosinophilic degeneration of the parenchymal cells of the liver has been observed.

Argentine, Venezuelan, and Bolivian Hemorrhagic Fevers and Lassa Fever

The incubation period in Argentine, Venezuelan, and Bolivian hemorrhagic fevers and Lassa fever is commonly 7-14 days; the acute illness lasts for 2-4 wk. Clinical illnesses range from undifferentiated fever to the characteristic severe illness. **Lassa fever** is most often clinically severe in white persons. Onset is usually gradual, with increasing fever, headache, diffuse myalgia, and anorexia (Table 271-2). During the 1st wk, signs frequently include a sore throat, dysphagia, cough, oropharyngeal ulcers, nausea, vomiting, diarrhea, and pains in the chest and abdomen. Pleuritic chest pain may persist for 2-3 wk. In Argentine and Bolivian hemorrhagic fevers and less frequently in Lassa fever, a petechial enanthem appears on the soft palate 3-5 days after onset and at about the same time on the trunk. The tourniquet test may be positive. The clinical course of Venezuelan hemorrhagic fever has not been well described.

In 35-50% of all patients, these diseases may become severe, with persistent high temperature, increasing toxicity, swelling of the face or neck, microscopic hematuria, and frank hemorrhages from the stomach, intestines, nose, gums, and uterus. A syndrome of **hypovolemic shock** is accompanied by pleural effusion and renal failure. **Respiratory distress** resulting from airway obstruction, pleural effusion, or congestive heart failure may occur. A total of 10-20% of patients experience late neurologic involvement, characterized by intention tremor of the tongue and associated speech abnormalities. In severe cases, there may be intention tremors of the extremities, seizures, and delirium. The cerebrospinal fluid is normal. In Lassa fever, nerve deafness occurs in early convalescence in 25% of cases.

Table 271-2 Clinical Stages of Lassa Fever

STAGE	SYMPTOMS
1 (days 1-3)	General weakness and malaise. High fever, >39°C (102.2°F), constant with peaks of 40-41°C (104-105.8°F)
2 (days 4-7)	Sore throat (with white exudative patches) very common; headache; back, chest, side, or abdominal pain; conjunctivitis; nausea and vomiting; diarrhea; productive cough; proteinuria; low blood pressure (systolic <100 mm Hg); anemia
3 (after 7 days)	Facial edema; convulsions; mucosal bleeding (mouth, nose, eyes); internal bleeding; confusion or disorientation
4 (after 14 days)	Coma and death

From Richmond JK, Baglole DJ: Lassa fever: epidemiology, clinical features, and social consequences, BMJ *327: 1271–1275, 2003.*

Prolonged convalescence is accompanied by alopecia and, in Argentine and Bolivian hemorrhagic fevers, by signs of autonomic nervous system lability, such as postural hypotension, spontaneous flushing or blanching of the skin, and intermittent diaphoresis.

Laboratory studies reveal marked leukopenia, mild to moderate thrombocytopenia, proteinuria, and, in Argentine hemorrhagic fever, moderate abnormalities in blood clotting, decreased fibrinogen, increased fibrinogen split products, and elevated serum transaminases. There is focal, often extensive eosinophilic necrosis of liver parenchyma, focal interstitial pneumonitis, focal necrosis of the distal and collecting tubules, and partial replacement of splenic follicles by amorphous eosinophilic material. Usually bleeding occurs by diapedesis with little inflammatory reaction. The mortality rate is 10-40%.

Marburg Disease and Ebola Hemorrhagic Fever

After an incubation period of 4-7 days, illness begins abruptly with severe frontal headache, malaise, drowsiness, lumbar myalgia, vomiting, nausea, and diarrhea. A **maculopapular** eruption begins 5-7 days later on the trunk and upper arms. It becomes generalized and often hemorrhagic and exfoliates during convalescence. The exanthem is accompanied by a dark red enanthem on the hard palate, conjunctivitis, and scrotal or labial edema. Gastrointestinal hemorrhage occurs as the severity of illness increases. Late in the illness, the patient may become tearfully depressed with marked hyperalgesia to tactile stimuli. In fatal cases, patients become hypotensive, restless, and confused and lapse into coma. Convalescent patients may experience alopecia and may have paresthesias of the back and trunk. There is a marked leukopenia with necrosis of granulocytes. **Disseminated intravascular coagulopathy** and thrombocytopenia are universal and correlate with severity of disease; there are moderate abnormalities in concentrations of clotting proteins and elevations of serum transaminases and amylase. Pregnant women and young children are at high risk of severe disease with fatal outcome. The mortality rate of Marburg disease is 25-85%, and the mortality rate of Ebola hemorrhagic fever 50-90%. High viral loads in acute-phase blood samples convey a poor prognosis.

Hemorrhagic Fever with Renal Syndrome

In most cases, HFRS is characterized by fever, petechiae, mild hemorrhagic phenomena, and mild proteinuria, followed by relatively uneventful recovery. In 20% of recognized cases, the disease may progress through 4 distinct phases. The febrile phase is ushered in with fever, malaise, and facial and truncal flushing. It lasts 3-8 days and ends with thrombocytopenia, petechiae, and proteinuria. The hypotensive phase, of 1-3 days, follows defervescence. Loss of fluid from the intravascular compartment may result in marked hemoconcentration. Proteinuria and ecchymoses increase. The oliguric phase, usually 3-5 days in duration, is characterized by a low output of protein-rich urine, increasing nitrogen retention, nausea, vomiting, and dehydration. Confusion, extreme restlessness, and hypertension are common. The diuretic phase, which may last for days or weeks, usually initiates clinical improvement. The kidneys show little concentrating ability, and rapid loss of fluid may result in severe dehydration and shock. Potassium and sodium depletion may be severe. Fatal cases manifest as abundant protein-rich retroperitoneal edema and marked hemorrhagic necrosis of the renal medulla. The mortality rate is 5-10%.

DIAGNOSIS

Diagnosis of these viral hemorrhagic fevers depends on a high index of suspicion in endemic areas. In nonendemic areas, histories of recent travel, recent laboratory exposure, or exposure to an earlier case should evoke suspicion of a viral hemorrhagic fever.

In all viral hemorrhagic fevers, the viral agent circulates in the blood at least transiently during the early febrile stage. Togaviruses and bunyaviruses can be recovered from acute-phase serum samples by inoculation into tissue culture or living mosquitoes. Argentine, Bolivian, and Venezuelan hemorrhagic fever viruses can be isolated from acute-phase blood or throat washings by intracerebral inoculation into guinea pigs, infant hamsters, or infant mice. Lassa virus may be isolated from acute-phase blood or throat washings by inoculation into tissue cultures. For Marburg disease and Ebola hemorrhagic fever,

acute-phase throat washings, blood, and urine may be inoculated into tissue culture, guinea pigs, or monkeys. The viruses are readily identified on electron microscopy, with a filamentous structure differentiating them from all other known agents. Specific complement-fixing and immunofluorescent antibodies appear during convalescence. The virus of HFRS is recovered from acute-phase serum or urine by inoculation into tissue culture. A variety of antibody tests using viral subunits is becoming available. Serologic diagnosis depends on demonstration of seroconversion or a 4-fold or greater increase in immunoglobulin G antibody titer in acute and convalescent serum specimens collected 3-4 wk apart. Viral RNA may also be detected in blood or tissues with use of reverse transcriptase polymerase chain reaction analysis.

Handling blood and other biologic specimens is hazardous and must be performed by specially trained personnel. Blood and autopsy specimens should be placed in tightly sealed metal containers, wrapped in absorbent material inside a sealed plastic bag, and shipped on dry ice to laboratories with biocontainment safety level 4 facilities. Even routine hematologic and biochemical tests should be done with extreme caution.

Differential Diagnosis

Mild cases of hemorrhagic fever may be confused with almost any self-limited systemic bacterial or viral infection. More severe cases may suggest typhoid fever; epidemic, murine, or scrub typhus; leptospirosis; or a rickettsial spotted fever, for which effective chemotherapeutic agents are available. Many of these disorders may be acquired in geographic or ecologic locations endemic for a viral hemorrhagic fever.

TREATMENT

Ribavirin administered intravenously is effective in reducing mortality rates in Lassa fever and HFRS. Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Special Pathogens Branch, Atlanta, Georgia 30333 (404-639-1115).

The therapeutic principle involved in all of these diseases, especially HFRS, is the reversal of dehydration, hemoconcentration, renal failure, and protein, electrolyte, or blood losses. The contribution of disseminated intravascular coagulopathy to the hemorrhagic manifestations is unknown, and the management of hemorrhage should be individualized. Transfusions of fresh blood and platelets are frequently given. Good results have been reported in a few patients after the administration of clotting factor concentrates. The efficacy of corticosteroids, ε-aminocaproic acid, pressor amines, and α-adrenergic blocking agents has not been established. Sedatives should be selected with regard to the possibility of kidney or liver damage. The successful management of HFRS may require renal dialysis.

Although whole-blood transfusions from Ebola virus–immune donors are thought to be therapeutic, studies in a monkey model were unable to confirm this outcome.

Patients suspected of having Lassa fever, Ebola fever, Marburg fever, or Congo Crimean hemorrhagic fever should be placed in a private room on standard contact and droplet precautions. Caretakers should use barrier precautions to prevent skin or mucous membrane exposure. All persons entering the patient's room should wear gloves and gowns and face shields. Before exiting the patient's room, caretakers should safely remove and dispose of all protective gear and should clean and disinfect shoes. Protocols require two-person clinical care teams, one observer and one caregiver. (see CDC website: www.cdc.gov/vhf/ebola/hcp).

PREVENTION

A live-attenuated vaccine (Candid-I) for Argentine hemorrhagic fever (Junin virus) is highly efficacious. A form of inactivated mouse brain vaccine is reported to be effective in preventing Omsk hemorrhagic fever. Inactivated RVF vaccines are widely used to protect domestic animals and laboratory workers. HFRS inactivated vaccine is licensed in Korea, and killed and live-attenuated vaccines are widely used in China. A vaccinia-vector glycoprotein vaccine provides protection against Lassa fever in monkeys. A single dose of a recombinant vesicular stomatitis virus vaccine containing surface glycoproteins from Ebola and Marburg viruses is effective in preventing virus hemorrhagic fevers due to several strains of filovirus in a monkey model.

Prevention of **mosquito-borne** and **tick-borne infections** includes use of repellents, wearing of tight-fitting clothing that fully covers the extremities, and careful examination of the skin after exposure, with removal of any vectors found. Diseases transmitted from a rodent-infected environment can be prevented through methods of rodent control; elimination of refuse and breeding sites is particularly successful in urban and suburban areas.

Patients should be isolated until they are virus-free or for 3 wk after illness. Patient urine, sputum, blood, clothing, and bedding should be disinfected. Disposable syringes and needles should be used. Prompt and strict enforcement of barrier nursing may be lifesaving. The mortality rate among medical workers contracting these diseases is 50%. A few entirely asymptomatic Ebola infections result in strong antibody production.

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Chapter 272

Lymphocytic Choriomeningitis Virus

Daniel J. Bonthius

Lymphocytic choriomeningitis virus (LCMV) is a prevalent human pathogen and an important cause of meningitis in children and adults. Capable of crossing the placenta and infecting the fetus, LCMV is also an important cause of neurologic birth defects and encephalopathy in the newborn.

ETIOLOGY

LCMV is a member of the family Arenaviridae, which are enveloped, negative-sense single-stranded RNA viruses. The name of the arenaviruses is derived from *arenosus*, the Latin word for "sandy," because of the fine granularities observed within the virion on ultrathin electron microscopic sections.

EPIDEMIOLOGY

Like all arenaviruses, LCMV utilizes rodents as its reservoir. The common house mouse, *Mus musculus,* is both the natural host and primary reservoir for the virus, which is transferred vertically from 1 generation of mice to the next via intrauterine infection. Hamsters and guinea pigs are also potential reservoirs. Although heavily infected with LCMV, rodents that acquire the virus transplacentally often remain asymptomatic because congenital infection provides rodents with immunologic tolerance for the virus. Infected rodents shed the virus in large quantities in nasal secretions, urine, feces, saliva, and milk throughout their lives.

Humans typically acquire LCMV by contacting fomites contaminated with infectious virus or by inhaling aerosolized virus. Most human infections occur during the fall and early winter, when mice move into human habitations. Humans can also acquire the virus via organ transplantation. Congenital LCMV infection occurs when a woman acquires a primary LCMV infection during pregnancy. The virus passes through the placenta to the fetus during maternal viremia. The fetus may also acquire the virus during passage through the birth canal from exposure to infected vaginal secretions. Outside of organ transplantation and vertical transmission during pregnancy, there have been no cases of human-to-human transmission of LCMV.

LCMV is prevalent in the environment, has a great geographic range, and infects large numbers of humans. The virus is found throughout the world's temperate regions and probably occurs wherever the genus *Mus* has been introduced (which is every continent but

Antarctica). An epidemiologic study found that 9% of house mice are infected and that substantial clustering occurs, where the prevalence is higher. Serologic studies demonstrate that approximately 5% of adult humans possess antibodies to LCMV, indicating prior exposure and infection.

PATHOGENESIS

LCMV is not a cytolytic virus. Thus, unlike many other nervous system pathogens that directly damage the brain by killing host brain cells, LCMV pathogenesis involves other underlying mechanisms. Furthermore, the pathogenic mechanisms are different in postnatal (acquired) infection than in prenatal (congenital) infection. A critical difference in the pathogenesis of postnatal vs prenatal infection is that the virus infects brain parenchyma in the case of prenatal infection, but is restricted to the meninges and choroid plexus in postnatal cases.

In postnatal infections, LCMV replicates to high titers in the choroid plexus and meninges. Viral antigen within these tissues becomes the target of an acute mononuclear cell infiltration driven by $CD8^+$ T lymphocytes. The presence of lymphocytes in large numbers within the meninges and cerebrospinal fluid leads to the symptoms of meningitis that mark acquired LCMV infection. As the lymphocytes clear the virus from the meninges and cerebrospinal fluid, the density of lymphocytes declines, and the symptoms of meningitis resolve. Thus, symptoms of acquired (postnatal) LCMV infection are immune mediated and are a result of the presence of large numbers of lymphocytes.

Prenatal infection likewise inflames the tissues surrounding the brain parenchyma, and this inflammation leads to some of the signs of congenital LCMV. In particular, within the ventricular system, congenital LCMV infection often leads to ependymal inflammation, which may block the egress of cerebrospinal fluid (CSF) at the cerebral aqueduct and lead to hydrocephalus. However, unlike postnatal cases, prenatal infection with LCMV includes infection of the substance of the brain rather than just the meninges or ependyma. This infection of brain parenchyma leads to the substantial neuropathologic changes typically accompanying congenital LCMV infection. In particular, LCMV infects the mitotically active neuroblasts, located at periventricular sites. Through an unknown mechanism, presence of the virus kills these periventricular cells, leading to periventricular calcifications, a radiographic hallmark of this disorder. Within the fetal brain, LCMV infection of neurons and glial cells also disrupts neuronal migration, leading to abnormal gyral patterns, and interferes with neuronal mitosis, leading to microcephaly and cerebellar hypoplasia.

CLINICAL MANIFESTATIONS

The clinical manifestations of LCMV infection depend on whether the infection occurs prenatally or postnatally. Congenital infection with LCMV is unique, as it involves both the postnatal infection of a pregnant woman and the prenatal infection of a fetus.

Acquired (Postnatal) Lymphocytic Choriomeningitis Virus Infection

LCMV infection during postnatal life (during childhood or adulthood) typically consists of a brief febrile illness, from which the patient fully recovers. The illness classically consists of 2 clinical phases. In the 1st phase, the symptoms are those of a nonspecific viral syndrome and include fever, myalgia, malaise, nausea, anorexia, and vomiting. These symptoms usually resolve after several days but are followed by a 2nd phase, consisting of central nervous system disease. The symptoms of this 2nd phase are those of aseptic meningitis, including headache, fever, nuchal rigidity, photophobia, and vomiting. The entire course of the biphasic disease is typically 1-3 wk.

The clinical spectrum of LCMV infection is broad. One third of postnatal infections are asymptomatic. Other patients develop extraneural disease that extends beyond the usual symptoms and may include orchitis, pneumonitis, myocarditis, parotitis, dermatitis, alopecia, and pharyngitis. In others, the neurologic disease may be considerably more severe than usual and may include transverse myelitis, Guillain-Barré syndrome, hydrocephalus, and encephalitis. Recovery from acquired LCMV infection is usually complete, but fatalities occasionally occur.

LCMV infections acquired via solid organ transplantation always induce severe disease. Several weeks posttransplantation, recipients of infected organs develop fever, leukopenia, and lethargy. Following these nonspecific symptoms, the course of disease rapidly progresses to multiorgan system failure and shock. These cases are almost always fatal.

Congenital Lymphocytic Choriomeningitis Virus Infection

LCMV infection during pregnancy can kill the fetus and induce spontaneous abortion. Among surviving fetuses, the 2 clinical hallmarks of congenital LCMV infection are vision impairment and brain dysfunction.

The vision impairment in congenital LCMV infection is a result of chorioretinitis and the formation of chorioretinal scars. The scarring is usually bilateral and most commonly located in the periphery of the fundus, but involvement of the macula also occurs.

Although the retinal injuries from congenital LCMV infection are often severe, it is the *brain* effects that cause the greatest disability. Prenatal infection with LCMV commonly induces either macrocephaly or microcephaly. Macrocephaly following LCMV infection is almost invariably caused by noncommunicating hydrocephalus, stemming from inflammation within the ventricular system. Microcephaly is a result of virus-induced failure of brain growth. In addition to disturbances of head size, periventricular calcifications are also cardinal features of congenital LCMV infection.

Although hydrocephalus, microencephaly, and periventricular calcifications are by far the most commonly observed abnormalities of the brain in congenital LCMV, other forms of neuropathology, alone or in combination, can also occur. These include periventricular cysts, porencephalic cysts, encephalomalacia, intraparenchymal calcifications, cerebellar hypoplasia, and neuronal migration disturbances.

Infants with congenital LCMV infection typically present during the newborn period with evidence of brain dysfunction. The most common signs are lethargy, seizures, irritability, and jitteriness.

Within the fetus, LCMV has a specific tropism for the brain. Thus, unlike many other congenital infections, LCMV usually does not induce systemic manifestations. Birthweight is typically appropriate for gestational age. Skin rashes and thrombocytopenia, which are common in several other prominent congenital infections, are unusual in congenital LCMV infection. Hepatosplenomegaly is only rarely observed, and serum liver enzyme levels are usually normal. Auditory deficits are unusual.

LABORATORY FINDINGS

In acquired (postnatal) LCMV infection, the hallmark laboratory abnormality occurs during the 2nd (central nervous system) phase of the disease and is CSF pleocytosis. The CSF typically contains hundreds to thousands of white blood cells, almost all of which are lymphocytes. However, CSF eosinophilia may also occur. Mild elevations of CSF protein and hypoglycorrhachia are common.

In congenital LCMV infection, laboratory findings in the newborn depend on whether the infant is still infected or not. If the infant still harbors the infection, then examination of the CSF may reveal a lymphocytic pleocytosis. Unlike many other congenital infections, LCMV does not typically induce elevations in liver enzymes, thrombocytopenia, or anemia. In many cases, the most reliably abnormal test is the head CT scan, which typically reveals a combination of microencephaly, hydrocephalus, and periventricular calcifications (Fig. 272-1).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Acute LCMV infections can be diagnosed by isolating the virus from CSF. Polymerase chain reaction has also been used to detect LCMV RNA in patients with active infections. However, by the time of birth, a baby prenatally infected with LCMV may no longer harbor the virus. Thus, congenital LCMV infection is more commonly diagnosed by serologic testing. The immunofluorescent antibody test detects both immunoglobulin (Ig) M and IgG and has greater sensitivity than the more widely available complement fixation method. The immunofluorescent antibody test is commercially available, and its specificity and sensitivity make it an acceptable diagnostic tool. A more sensitive test for detecting congenital LCMV infection is the enzyme-linked

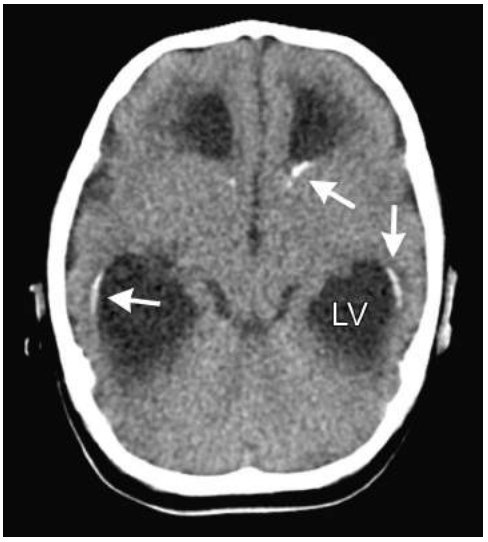

Figure 272-1 Head CT scan from a 2 mo old microcephalic baby with congenital lymphocytic choriomeningitis virus infection. The scan reveals enlargement of the lateral ventricles *(LV)* and periventricular calcifications *(arrows)*.

immunosorbent assay, which measures titers of LCMV IgG and IgM and is performed at the Centers for Disease Control and Prevention.

For acquired (postnatal) LCMV infection, the principal items in the differential diagnosis are the other infectious agents that can induce meningitis. These include bacteria, fungi, viruses, and some other forms of pathogens. The most common viral causes of meningitis are the enteroviruses, including coxsackieviruses and echoviruses, and the arboviruses, including La Crosse encephalitis virus and equine encephalitis virus. Unlike LCMV, which is most common in winter, the enteroviruses and arboviruses are most commonly acquired in summer and early fall.

The principal items in the differential diagnosis of congenital LCMV infection are the other infectious pathogens that can cross the placenta and damage the developing fetus. These infectious agents are linked by the acronym "TORCHS" and include *Toxoplasma gondii*, rubella virus, cytomegalovirus, herpes simplex virus, and syphilis. Toxoplasmosis and cytomegalovirus infection are particularly difficult to differentiate from LCMV because all 3 of these infectious agents can produce microcephaly, intracerebral calcifications, and chorioretinitis. Although clinical clues may aid in distinguishing 1 congenital infection from another, definitive identification of the causative infectious agent usually requires laboratory data, including cultures and serologic studies.

COMPLICATIONS

Complications in children with congenital LCMV infection are nonspecific and include the medical problems that commonly arise in scenarios involving ventriculoperitoneal shunts, severe seizure disorders, and static encephalopathy. These complications include shunt failure or infection, aspiration pneumonia, injuries from falls, and joint contractures.

TREATMENT

There is no specific treatment for acquired or congenital LCMV infection. An effective antiviral therapy for LCMV infection has not yet been developed. Ribavirin is active against LCMV and other arenaviruses in vitro, but its utility in vivo is unproven. Immunosuppressive therapy, if present, should be reduced.

SUPPORTIVE CARE

Children with hydrocephalus from congenital LCMV infection often require placement of a ventriculoperitoneal shunt during infancy for treatment of hydrocephalus. Seizures often begin during early postnatal life, are often difficult to control, and require administration of multiple antiepileptic medications. The mental retardation induced by congenital LCMV infection is often profound. In most cases, affected children should be referred for educational intervention during early life. The spasticity accompanying congenital LCMV infection is often severe. Although physical therapy can help to maintain range of motion and minimize painful spasms and contractures, implantation of a baclofen pump is often helpful.

PROGNOSIS

The great majority of patients with postnatally acquired LCMV infection have a full recovery with no permanent sequelae. Rarely, postnatal infections induce hydrocephalus and require shunting. Rarer yet, postnatal LCMV infection is fatal.

In contrast to the usual benign outcome of postnatal infections, prenatal infections typically lead to severe and permanent disability. In children with congenital LCMV infection, brain function is nearly always impaired and chorioretinitis is invariably present. Mental retardation, cerebral palsy, ataxia, epilepsy, and blindness are common neurologic sequelae. However, children with congenital LCMV infection have diverse outcomes. All children with the combination of microencephaly and periventricular calcifications are profoundly neurologically impaired. Blindness, medically refractory epilepsy, spastic quadriparesis, and mental retardation are typical of this group. However, other children with congenital LCMV infection who do not have the combination of microencephaly and periventricular calcifications often have a more favorable outcome, with less severe motor, mental, and vision impairments. Children with isolated cerebellar hypoplasia may be ataxic but have only mild or moderate mental retardation and vision loss.

PREVENTION

No vaccine exists to prevent LCMV infection. However, measures can be taken to reduce the risk of infection. Because rodents, especially house mice, are the principal reservoir of LCMV, people can reduce their risk of contracting LCMV by minimizing their exposure to the secretions and excretions of mice. This can be accomplished most effectively by eliminating cohabitation with mice. Congenital LCMV infection will not occur unless a woman contracts a primary infection with LCMV during pregnancy. Thus, women should be especially careful to avoid contact or cohabitation with mice during pregnancy. Pregnant women should also avoid contact with pet rodents, especially mice and hamsters. These facts should be stressed during prenatal visits.

Acquisition of LCMV from solid organ transplantation represents a substantial risk to organ recipients. Prospective donors with LCMV meningitis or encephalitis pose a clear risk for transmitting a fatal infection to recipients. Healthcare providers, transplantation centers, and organ procurement organizations should be aware of the risks posed by LCMV and should consider LCMV in any potential donor with signs of aseptic meningitis but no identified infectious agent. The risks and benefits of offering and receiving organs from donors with possible LCMV infection should be carefully considered.

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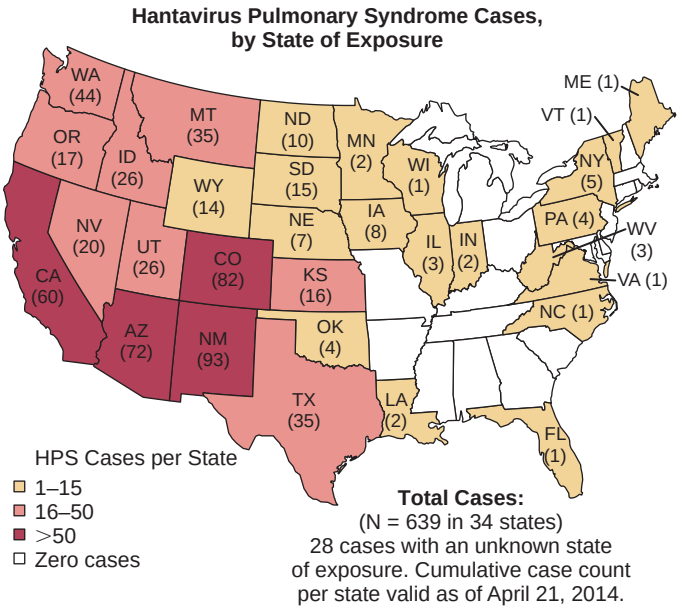
Chapter 273

Hantavirus Pulmonary Syndrome

Scott B. Halstead

The hantavirus pulmonary syndrome (HPS) is caused by multiple closely related hantaviruses that have been identified from the western United States, with sporadic cases reported from the eastern United States (Fig. 273-1) and Canada and important foci of disease in several countries in South America. HPS is characterized by a febrile



Source: Viral Special Pathogens Branch, CDC

Figure 273-1 Total number of confirmed cases of Hantavirus pulmonary syndrome, by state of exposure—United States, 1993-2014. N = 639 as of April 21, 2014. *(From Viral Special Pathogens Branch, Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/hantavirus/surveillance/reporting-state.html).*

prodrome followed by the rapid onset of noncardiogenic pulmonary edema and hypotension or shock. Sporadic cases in the United States caused by related viruses may manifest with renal involvement. Cases in Argentina and Chile sometimes include severe gastrointestinal hemorrhaging; nosocomial transmission has been documented in this geographic region only.

ETIOLOGY

Hantaviruses are a genus in the family Bunyaviridae, which are lipid-enveloped viruses with a negative-sense RNA genome composed of 3 unique segments. Several pathogenic viruses that have been recognized within the genus include Hantaan virus, which causes the most severe form of hemorrhagic fever with renal syndrome (HFRS) seen primarily in mainland Asia (see Chapter 271); Dobrava virus, which causes the most severe form of HFRS seen primarily in the Balkans; Puumala virus, which causes a milder form of HFRS with a high proportion of subclinical infections and is prevalent in northern Europe; and Seoul virus, which results in moderate HFRS and is transmitted predominantly in Asia by urban rats or worldwide by laboratory rats. Prospect Hill virus, a hantavirus that is widely disseminated in meadow voles in the United States, is not known to cause human disease. There are an increasing number of case reports of European hantaviruses causing HPS.

HPS is associated with *sin nombre* virus, isolated from deer mice, *Peromyscus maniculatus,* in New Mexico. Multiple HPS-like agents in the American hemisphere isolated to date belong to a single genetic group of hantaviruses and are associated with rodents of the family Muridae, subfamily Sigmodontinae. These rodent species are restricted to the Americas, suggesting that HPS may be a Western hemisphere disease.

EPIDEMIOLOGY

Persons acquiring HPS generally have a history of recent outdoor exposure or live in an area with large populations of deer mice. Clusters of cases have occurred among individuals who have cleaned houses that were rodent infested. *P. maniculatus* is one of the most common North American mammals and, where found, is frequently the dominant member of the rodent community. About half of the average of 30+ cases seen annually occurs between the months of May and July. Patients are almost exclusively 12-70 yr of age; 60% of patients are 20-39 yr of age. Rare cases are reported in children younger than 12 yr of age. Two thirds of patients are male, probably reflecting their greater outdoor activities. It is not known whether almost complete absence of disease in young children is a reflection of innate resistance or simply lack of exposure. Evidence of human-to-human transmission has been reported in Argentine outbreaks.

Hantaviruses do not cause apparent illness in their reservoir hosts, which remain asymptomatically infected for life. Infected rodents shed virus in saliva, urine, and feces for many weeks, but the duration of shedding and the period of maximum infectivity are unknown. The presence of infectious virus in saliva, the sensitivity of these animals to parenteral inoculation with hantaviruses, and field observations of infected rodents indicate that biting is important for rodent-to-rodent transmission. Aerosols from infective saliva or excreta of rodents are implicated in the transmission of hantaviruses to humans. Persons visiting animal care areas housing infected rodents have been infected after exposure for as little as 5 min. It is possible that hantaviruses are spread through contaminated food and breaks in skin or mucous membranes; transmission to humans has occurred by rodent bites. Person-to-person transmission is distinctly uncommon but has been documented in Argentina.

PATHOGENESIS

HPS is characterized by sudden and catastrophic pulmonary edema, resulting in anoxia and acute heart failure. The virus is detected in pulmonary capillaries, suggesting that pulmonary edema is the consequence of T-cell attack on virus-infected capillaries. Disease severity is predicted by the level of acute-phase viremia titer. A useful hamster model of HPS is available.

CLINICAL MANIFESTATIONS

HPS is characterized by a prodrome and a cardiopulmonary phase. The mean duration after the onset of prodromal symptoms to hospitalization is 5.4 days. The mean duration of symptoms to death is 8 days (median: 7 days; range: 2-16 days). The most common **prodromal symptoms** are fever and myalgia (100%); cough or dyspnea (76%); gastrointestinal symptoms, including vomiting, diarrhea, and midabdominal pain (76%); and headache (71%). The **cardiopulmonary phase** is heralded by progressive cough and shortness of breath. The most common initial physical findings are tachypnea (100%), tachycardia (94%), and hypotension (50%). Rapidly progressive acute pulmonary edema, hypoxia, and shock develop in most severely ill patients. Pulmonary vascular permeability is complicated by cardiogenic shock associated with increased vascular resistance. The clinical course of the illness in patients who die is characterized by pulmonary edema accompanied by severe hypotension, frequently terminating in sinus bradycardia, electromechanical dissociation, ventricular tachycardia, or fibrillation. Hypotension may be progressive even with adequate oxygenation. HPS virus is excreted in the urine during the acute illness phase, and survivors may demonstrate evidence of chronic renal damage.

DIAGNOSIS

The diagnosis of HPS should be considered in a previously healthy patient presenting with a febrile prodrome and acute respiratory distress. Occurrence of thrombocytopenia with the febrile prodrome and outdoor exposure in the spring and summer months are strongly suggestive of HPS. Specific diagnosis of HPS is made by serologic tests that detect hantavirus immunoglobulin M antibodies. Early appearance of immunoglobulin G antibodies signals probable recovery. Hantavirus antigen can be detected in tissue by immunohistochemistry and amplification of hantavirus nucleotide sequences detected by reverse transcriptase polymerase chain reaction. The state health department or the Centers for Disease Control and Prevention should be consulted to assist in diagnosis, epidemiologic investigations, and outbreak control.

Laboratory Findings

Laboratory findings include leukocytosis (median: 26,000 cells/μL), elevated hematocrit resulting from hemoconcentration, thrombocytopenia (median: 64,000 cells/μL), prolonged prothrombin and partial

thromboplastin times, elevated serum lactate dehydrogenase concentration, decreased serum protein concentrations, proteinuria, and microscopic hematuria. Patients who die often experience disseminated intravascular coagulopathy including frank hemorrhage and exceptionally high leukocyte counts.

Differential Diagnosis

The differential diagnosis includes adult respiratory distress syndrome, pneumonic plague, psittacosis, severe mycoplasmal pneumonia, influenza, leptospirosis, inhalation anthrax, rickettsial infections, pulmonary tularemia, atypical bacterial and viral pneumonial diseases, legionellosis, meningococcemia, and other sepsis syndromes. The key determinant in the diagnosis of HPS is thrombocytopenia.

TREATMENT

Management of patients with hantavirus infection requires maintenance of adequate oxygenation and careful monitoring and support of cardiovascular function. The pathophysiology of HPS somewhat resembles that of dengue shock syndrome (see Chapter 269). Pressor or inotropic agents, such as dobutamine, should be administered in combination with judicious volume replacement to treat symptomatic hypotension or shock while avoiding exacerbation of the pulmonary edema. Intravenous ribavirin, which is lifesaving if given early in the course of HFRS and is effective in preventing death in the hamster model, has not yet been demonstrated to be of value in HPS.

Further information and advice about management, control measures, diagnosis, and collection of biohazardous specimens can be obtained from the Centers for Disease Control and Prevention, National Center for Infectious Diseases, Special Pathogens Branch, Atlanta, Georgia 30333 (404-639-1115).

PROGNOSIS

In some geographic areas fatality rates for HPS have been 50%. Severe abnormalities in hematocrit, white blood cell count, lactate dehydrogenase value, and partial thromboplastin time, and a high viral load predict death with high specificity and sensitivity. Early appearance of immunoglobulin G antibodies may signal a hopeful prognosis.

PREVENTION

Avoiding contact with rodents is the only preventive strategy against HPS. Rodent control in and around the home is important. Barrier nursing is advised, and biosafety level 3 facilities and practices are recommended for laboratory handling of blood, body fluids, and tissues from suspect patients or rodents, because the virus may be aerosolized.

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Chapter 274

Rabies

Rodney E. Willoughby Jr.

Rabies virus is a bullet-shaped, negative-sense, single-stranded, enveloped RNA virus from the family Rhabdoviridae, genus *Lyssavirus*. There currently are 12 known genotypes of *Lyssavirus*, and more are under taxonomic consideration. The classic rabies virus (genotype 1) is distributed worldwide and naturally infects a large variety of animals. The other 6 genotypes are more geographically confined, with none found in the Americas. Seven *Lyssavirus* genotypes are associated with rabies in humans, although genotype 1 accounts for the great majority of cases. Within genotype 1, a number of genetic variants have been defined. Each variant is specific to a particular animal reservoir, although cross-species transmission can occur.

EPIDEMIOLOGY

Rabies is present on all continents except Antarctica. Rabies predominantly afflicts underaged, poor, and geographically isolated populations. Approximately 50,000 cases of human rabies occur in Africa and Asia annually. Theoretically, rabies virus can infect any mammal (which then can transmit disease to humans), but true animal reservoirs that maintain the presence of rabies virus in the population are limited to terrestrial carnivores and bats. Worldwide, transmission from dogs accounts for >90% of human cases. In Africa and Asia, other animals serve as prominent reservoirs, such as jackals, mongooses, and raccoon dogs. In industrialized nations, canine rabies has been largely controlled through the routine immunization of pets. In the United States, raccoons are the most commonly infected wild animal along the eastern seaboard. Three phylogenies of skunk rabies are endemic in the Midwest (north and south) and California, and gray foxes harbor rabies in Arizona and Texas and mongooses in Puerto Rico. Rabies occurs infrequently in livestock. Among American domestic pets, infected cats outnumber infected dogs, probably because cats frequently prowl unsupervised and are not uniformly subject to vaccine laws. Rabies is rare in small mammals, including mice, squirrels, and rabbits; to date, no animal-to-human transmission from these animals has been documented.

The epidemiology of human rabies in the United States is dominated by cryptogenic bat rabies. Bats are migratory in the spring and fall; rabid bats are identified in every state of the union except Hawaii. In 1 study, the largest proportion of cases of human rabies were infected with a bat variant, and in almost all cases of bat-associated human rabies there was no history of a bat bite. Among inhabitants of the Peruvian Amazon region who have exposure to rabies infected vampire bats, there are some who have rabies virus neutralizing antibodies and have survived. Antibody-positive patients remember bat bites but do not recall symptoms of rabies.

In the United States, 30,000 episodes of rabies postexposure prophylaxis (PEP) occur annually. Between 1 and 3 endemic human cases are diagnosed annually, half postmortem. There have been 3 outbreaks of rabies associated with solid-organ and corneal transplantations.

TRANSMISSION

Rabies virus is found in large quantities in the saliva of infected animals, and transmission occurs almost exclusively through inoculation of the infected saliva through a bite or scratch from a rabid mammal. Approximately 35-50% of people bitten by a known rabies-infected animal and receiving no PEP contract rabies. The transmission rate is increased if the victim has suffered multiple bites and if the inoculation occurs in highly innervated parts of the body such as the face and the hands. Infection does not occur after exposure of intact skin to infected secretions, but virus may enter the body through intact mucous membranes. Claims that spelunkers may experience rabies after inhaling bat excreta have come under doubt, although inhalational exposure can occur during laboratory accidents.

No case of nosocomial transmission to a healthcare worker has been documented to date, but caregivers of a patient with rabies are advised to use full barrier precautions. The virus is rapidly inactivated in the environment, and contamination of fomites is not a mechanism of spread.

PATHOGENESIS

After inoculation, rabies virus replicates slowly and at low levels in muscle or skin. This slow initial step likely accounts for the disease's long incubation period. Virus then enters the peripheral motor nerve, utilizing the nicotinic acetylcholine receptor and possibly several other receptors for entry. Once in the nerve, the virus travels by fast axonal transport, crossing synapses roughly every 12 hr. Rapid dissemination occurs throughout the brain and spinal cord before symptoms appear. Infection of the dorsal root ganglia is apparently futile but causes characteristic radiculitis. Infection concentrates in the brainstem, accounting for autonomic dysfunction and relative sparing of cognition. Despite severe neurologic dysfunction with rabies, histopathology reveals limited damage, inflammation, or apoptosis. The pathologic

hallmark of rabies, the Negri body, is composed of clumped viral nucleocapsids that create cytoplasmic inclusions on routine histology. Negri bodies can be absent in documented rabies virus infection. Rabies may be a metabolic disorder of neurotransmission; tetrahydrobiopterin deficiency in human rabies causes severe deficiencies in dopamine, norepinephrine, and serotonin metabolism.

After infection of the central nervous system, the virus travels anterograde through the peripheral nervous system to virtually all innervated organs. It is through this route that the virus infects the salivary glands. Many victims of rabies die from uncontrolled cardiac dysrhythmia.

Deficiency of tetrahydrobiopterin, an essential cofactor for neuronal nitric oxide synthase, is predicted to lead to spasm of the basilar arteries. Onset of vasospasm has been confirmed in a few patients within 5-8 days of first hospitalization, at about the time coma supervenes in the natural history. Increased intracranial pressure is regularly measured early in rabies in association with elevated *N*-acetylaspartate in cerebrospinal fluid (CSF), but is rarely radiologically apparent. Metabolites in CSF consistent with ketogenesis are associated with demise.

CLINICAL MANIFESTATIONS

The incubation period for rabies is 1-3 mo, but is variable. In severe wounds to the head, symptoms may occur within 5 days after exposure, and occasionally the incubation period can extend to longer than 6 mo. Rabies has 2 principal clinical forms. **Encephalitic** or **"furious" rabies** begins with nonspecific symptoms, including fever, sore throat, malaise, headache, nausea and vomiting, and weakness. These symptoms are often accompanied by paresthesia and pruritus at or near the site of the bite that then extend along the affected limb. Soon thereafter the patient begins to demonstrate symptoms of encephalitis, with agitation, depressed mentation, and, occasionally, seizures. Characteristically, patients with rabies encephalitis initially have periods of lucidity alternating with periods of profound encephalopathy. Hydrophobia and aerophobia are the cardinal signs of rabies; they are unique to humans and are not universal or specific. Phobic spasms are manifested by agitation and fear created by being offered a drink or fanning of air in the face, which in turn produce choking and aspiration through spasms of the pharynx, neck, and diaphragm. The illness is relentlessly progressive. There is a dissociation of electrophysiologic or encephalographic activity with findings of brainstem coma caused by anterograde denervation. Death almost always occurs within 1-2 days of hospitalization in developing countries and by 18 days of hospitalization with intensive care.

A second form of rabies known as **paralytic** or **"dumb" rabies** is seen much less frequently and is characterized principally by fevers and ascending motor weakness affecting both the limbs and the cranial nerves. Most patients with paralytic rabies also have some element of encephalopathy as the disease progresses subacutely.

Case reports suggest that milder forms of rabies encephalitis may exist, and 16 rabies survivors are known. Rabies should be considered earlier and more frequently in the diagnosis than current practice.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of rabies encephalitis includes all forms of severe cerebral infections, tetanus, and some intoxications and envenomations. Rabies can be confused with autoimmune (anti–*N*-methyl-D-aspartate receptor) encephalitis, other infectious encephalitis, psychiatric illness, drug abuse, and conversion disorders. Paralytic rabies is most frequently confused with Guillain-Barré syndrome. The diagnosis of rabies is frequently delayed in Western countries because of its rarity and the unfamiliarity of the medical staff with the infection. These considerations highlight the need to pursue a history of contact with an animal belonging to 1 of the known reservoirs for rabies or to establish a travel history to a rabies-endemic region.

DIAGNOSIS

The Centers for Disease Control and Prevention (CDC) require a number of tests to confirm a clinically suspected case of rabies. Reverse transcription polymerase chain reaction is the most sensitive available assay for the diagnosis of rabies when done iteratively. Rabies virus RNA has been detected in saliva, skin, and brain by the reverse transcription polymerase chain reaction. The virus can be grown both in cell culture and after animal injection, but identification of rabies by these methods is slow. Rabies antigen is detected through immunofluorescence of saliva or biopsies of hairy skin or brain. Corneal impressions are not recommended. Rabies-specific antibody can be detected in serum or CSF samples, but most patients die while seronegative. Antirabies antibodies are present in the sera of patients who have received an incomplete course of the rabies vaccine, precluding a meaningful interpretation in this setting. Antibody in CSF is rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status. CSF abnormalities in cell count, glucose, and protein content are minimal and are not diagnostic. MRI findings in the brain are late.

TREATMENT AND PROGNOSIS

Rabies is generally fatal. Conventional critical care yielded 1 survivor from 74 attempts since 1990. Five of 16 patients survived without use of critical care (including 3 milder cases) and 7 with use of the Milwaukee Protocol (http://www.mcw.edu/rabies). Survival using the Milwaukee Protocol is estimated at 20%; neurologic outcomes are poor in one third of patients. Neither rabies immunoglobulin (RIG) nor rabies vaccine provides benefit once symptoms have appeared. Among 11 survivors of rabies after use of biologics, 6 had poor neurologic outcomes. Among 5 vaccine-naïve survivors, 1 had a poor outcome. Antiviral treatments have not been effective. Ribavirin delays the immune response and should be avoided during early management. In contrast, appearance of the normal antibody response by 7 days is associated with clearance of salivary viral load and survival.

PREVENTION

Primary prevention of rabies infection includes vaccination of domestic animals and education to avoid wild animals, stray animals, and animals with unusual behavior.

Immunization and Fertility Control of Animal Reservoirs

The introduction of routine rabies immunization for domestic pets in the United States and Europe during the middle of the 20th century virtually eliminated infection in dogs, which prior to that time had been the principal transmitter of rabies to humans in developed, as well as nonindustrialized, countries. In the 1990s, control efforts in Europe and North America shifted to immunization of wildlife reservoirs of rabies, where rabies was newly emerging. These programs employed bait laced with either an attenuated rabies vaccine or a recombinant rabies surface glycoprotein inserted into vaccinia, distributed by air or hand into areas inhabited by rabid animals. Human contact with vaccine-laden bait has been infrequent. Adverse events after such contact have been rare, but the vaccinia vector poses a threat to the same population at risk for vaccinia itself, namely, pregnant women, immunocompromised patients, and people with atopic dermatitis. Mass culling of endemic reservoirs has never worked; vaccination and fertility control stop outbreaks. Bats are ubiquitous and very important for insect control. Less than 1% of free-flying bats but >8% of downed bats and bats found in dwellings are rabid.

Postexposure Prophylaxis

The relevance of rabies for most pediatricians centers on evaluating whether an animal exposure warrants PEP (Table 274-1). No case of rabies has been documented in a person receiving the recommended schedule of PEP since introduction of modern cellular vaccines in the 1970s.

Given the incubation period for rabies, PEP is a medical urgency, not emergency. Algorithms have been devised to aid practitioners in deciding when to initiate rabies PEP (Fig. 274-1). The decision to proceed ultimately depends on the local epidemiology of animal rabies

as determined by active surveillance programs, information that can be obtained from local and state health departments. In general, bats, raccoons, skunks, coyotes, and foxes should be considered rabid unless proven otherwise through euthanasia and testing of brain tissue, whereas bites from small herbivorous animals (squirrels, hamsters, gerbils, chipmunks, rats, mice, and rabbits) can be discounted. The response to bites from a pet, particularly a dog, cat, or ferret, depends on local surveillance statistics and on whether the animal is available for observation.

The approach to nonbite bat exposures is controversial. In response to the observation that most cases of rabies in the United States have been caused by bat variants and that the majority of affected patients had no recollection of a bat bite, the CDC has recommended that rabies PEP be considered after any physical contact with bats and when a bat is found in the same room as persons who may not be able to accurately report a bite, assuming that the animal is unavailable for testing. Such people include young children, the mentally disabled, and intoxicated individuals. Other nonbite contacts (e.g., handling a carcass, exposure to an animal playing with a carcass, or coming into contact with blood or excreta from a potentially rabid animal) usually do not require PEP.

In all instances of a legitimate exposure, effort should be made to recover the animal for quarantine and observation or brain examination after euthanasia. Testing obviates the need for PEP more than half the time. In most instances, PEP can be deferred until the results of observation or brain histology are known. In dogs, cats, and ferrets, symptoms of rabies always occur within several days of viral shedding; therefore, in these animals a 10-day observation period is sufficient to eliminate the possibility of rabies.

No duration of time between exposure and onset of symptoms should preclude rabies prophylaxis. Rabies PEP is most effective when applied expeditiously. Nevertheless, the series should be initiated in the asymptomatic person as soon as possible, regardless of the length of time since the bite. *The vaccine and RIG are contraindicated once symptoms develop.*

The first step in rabies PEP is to cleanse the wound thoroughly. Soapy water is sufficient to inactivate an enveloped virus, and its effectiveness is supported by broad experience. Other commonly used

Table 274-1 Rabies Postexposure Prophylaxis Guide

ANIMAL TYPE	EVALUATION AND DISPOSITION OF ANIMAL	POSTEXPOSURE PROPHYLAXIS RECOMMENDATIONS
Dogs, cats, and ferrets	Healthy and available for 10 days of observation Rabid or suspected of being rabid[†] Unknown (escaped)	Prophylaxis only if animal shows signs of rabies[*] Immediate immunization and RIG Consult public health officials for advice
Bats, skunks, raccoons, foxes, and most other carnivores; woodchucks	Regarded as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests[†]	Immediate immunization and RIG
Livestock, rodents, and lagomorphs (rabbits, hares, and pikas)	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice and other rodents, rabbits, hares, and pikas almost never require antirabies treatment

*During the 10-day observation period, at the first sign of rabies in the biting dog, cat, or ferret, treatment of the exposed person with RIG (human) and vaccine should be initiated. The animal should be euthanized immediately and tested.

[†]The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Immunization is discontinued if immunofluorescent test result for the animal is negative.

RIG, rabies immunoglobulin.

From American Academy of Pediatrics: Red book 2012: report of the Committee on Infectious Diseases, *ed 29. Elk Grove Village, IL, 2012, American Academy of Pediatrics.*

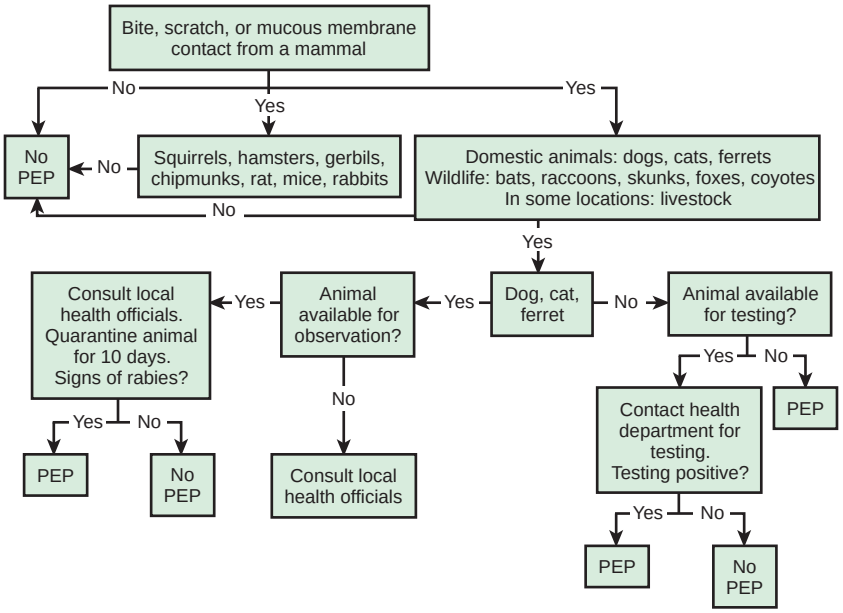

Figure 274-1 **Algorithm for evaluating a child for rabies postexposure prophylaxis.** This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

disinfectants, such as iodine-containing preparations, are virucidal and should be used in addition to soap when available. Probably the most important aspect of this component is that the wound is cleansed with copious volumes of disinfectant. Primary closure is avoided; wounds may be bacterially infected as well, so cosmetic repair should follow. Antibiotics and tetanus prophylaxis (see Chapter 211) should be applied with the use of usual wound care criteria.

The second component of rabies PEP consists of passive immunization with RIG. Most failures of PEP are attributed to not using RIG. Human RIG, the formulation used in industrialized countries, is administered at a dose of 20 IU/kg. As much of the dose is infused around the wound as possible, and the remainder is injected intramuscularly in a limb distant from the 1 injected with the killed vaccine. Like other immunoglobulin preparations, RIG interferes with the take of live viral vaccines for at least 4 mo after administration of the RIG dose. Human RIG is not available in many parts of the developing world. Equine RIG serves as a substitute for the human immunoglobulin preparation in some areas. Modern preparations of equine RIG are associated with fewer side effects than prior products composed of crude horse serum. Regrettably, for a large segment of the world's population, no passive immunization product is available at all. Monoclonal antibody products are in clinical trials and may alleviate this deficiency.

The third component of rabies PEP is immunization with inactivated vaccine. In most of the world, cell-based vaccines have replaced previous preparations. Two formulations currently are available in the United States, namely, RabAvert (Chiron Behring Vaccines, Maharashtra, India), a purified chick-embryo cell cultivated vaccine, and Imovax Rabies (Aventis Pasteur, Bridgewater, NJ), cultivated in human diploid cell cultures. In both children and adults, both vaccines are administered intramuscularly in a 1 mL volume in the deltoid or anterolateral thigh on days 0, 3, 7, and 14 after presentation. Injection into the gluteal area is associated with a blunted antibody response, so this area should not be used. The rabies vaccines can be safely administered during pregnancy. In most persons the vaccine is well tolerated; most adverse effects are related to booster doses. Pain and erythema at the injection site occur commonly, and local adenopathy, headache, and myalgias occur in 10-20% of patients. Approximately 5% of patients who receive the human diploid cell vaccine experience an immune complex–mediated allergic reaction, including rash, edema, and arthralgias, several days after a booster dose. The World Health Organization has approved schedules using smaller amounts of vaccine, administered intradermally, that are immunogenic and protective (http://www.who.int/rabies/human/postexp/en/), but none is approved for use in the United States. Other cell culture–derived rabies virus vaccines are available in the developing world. A few countries still produce nerve tissue–derived vaccines; these preparations are poorly immunogenic, and cross reactivity with human nervous tissue may occur with their use, producing severe neurologic symptoms even in the absence of rabies infection.

Preexposure Prophylaxis

The killed rabies vaccine can be given to prevent rabies in persons at high risk for exposure to wild-type virus, including laboratory personnel working with rabies virus, veterinarians, and others likely to be exposed to rabid animals as part of their occupation. Preexposure prophylaxis should be considered for persons traveling to a rabies-endemic region where there is a credible risk for a bite or scratch from a rabies-infected animal, particularly if there is likely to be a shortage of RIG or cell culture–based vaccine (see Chapter 175). Rabies vaccine as part of the routine vaccine series is under investigation in some countries. The schedule for preexposure prophylaxis consists of 3 intramuscular injections on days 0, 7, and 21 or 28. PEP in the patient who has received preexposure prophylaxis or a prior full schedule of PEP consists of 2 doses of vaccine (1 each on days 0 and 3) and does not require RIG. Immunity from preexposure prophylaxis wanes after several years and requires boosting if the potential for exposure to rabid animals recurs.

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Chapter 275

Polyomaviruses

Gregory A. Storch

The polyomaviruses are small (45 nm), nonenveloped, circular, double-stranded DNA viruses with genomes of approximately 5,000 bp. Because of the association of animal polyomaviruses with tumors in the animals they infect, there has also been concern for a relationship to neoplasia in humans; however, the only virus for which there is strong evidence for an etiologic role in neoplasia is Merkel cell polyomavirus (see below). Among the polyomaviruses, the traditional human pathogens are JC virus and BK viruses. In recent years the number of human polyomaviruses has expanded dramatically, with discovery in humans of 10 additional viruses. Two of the newer polyomaviruses, designated KI virus and WU virus, can be detected in respiratory samples from children; however, a pathogenic role for these viruses has not been proven to date. Merkel cell polyomavirus is associated with Merkel cell carcinoma, an unusual neuroectodermal tumor of the skin that occurs primarily in elderly and immunocompromised individuals. Clonal integration of Merkel cell polyomavirus DNA is present in Merkel cell carcinoma cells, supporting an etiologic role for the virus in the development of the tumor. Another human polyomavirus has been isolated from patients with the dermatologic condition trichodysplasia spinulosa and has been named trichodysplasia spinulosa–associated polyomavirus. Trichodysplasia spinulosa is a condition of the skin that occurs in immunocompromised individuals and involves the development of follicular papules and keratin spines, usually involving the face. Two other viruses, designated human polyomaviruses 6 and 7, have also been found in human skin samples, but are not presently known to cause disease. Human polyomavirus 9 was detected in serum from a renal transplant recipient. The most recently discovered viruses, named Malawi virus and St. Louis virus, were first detected in stool samples, but a role in gastrointestinal or other disease has not been established at this time.

JC and BK viruses are tropic for renal epithelium; JC virus also infects brain oligodendrocytes and is the etiologic agent of **progressive multifocal leukoencephalopathy,** a rare and fatal demyelinating disease of immunocompromised persons, especially those with AIDS. Progressive multifocal leukoencephalopathy is now known to occur in individuals receiving the immunomodulatory agents natalizumab (Tysabri), used to treat multiple sclerosis and Crohn disease, and efalizumab (Raptiva), used to treat psoriasis. It has also been reported in individuals receiving the anti-CD20 monoclonal antibody rituximab (Rituxan) and the anti-CD52 monoclonal antibody alemtuzumab (Campath). BK virus is the cause of transplant nephropathy in renal transplant recipients and of hemorrhagic cystitis in hematopoietic stem cell and bone marrow transplant recipients. Several million persons in the United States were exposed to simian virus 40 (SV40), an oncogenic polyomavirus of Asian macaques, from contaminated poliovirus vaccines administered during 1955-1963. There were no recognized sequelae and no demonstrable increased risk for cancer.

Seroepidemiologic studies have shown that infection with all of the human polyomaviruses appears to be widespread, often occurring during childhood. Primary infection with these viruses is not recognized clinically. Approximately half of children in the United States are infected with BK virus by 3-4 yr of age and with JC virus by 10-14 yr of age, and approximately 60-80% of adults are seropositive for 1 or both viruses. Infection with polyomaviruses is thought to persist throughout life, with JC and BK viruses remaining latent in renal epithelium, oligodendrocytes, and peripheral blood mononuclear cells. The site of latency of the other human polyomaviruses is not currently known. Approximately 30-50% of healthy persons have detectable BK or JC virus in renal tissue at autopsy. Reactivation and viruria occur

with increased frequency with advancing age and are more common in immunocompromised persons. On the basis of polymerase chain reaction results, BK and JC viruria occur in 2.6% and 13.2%, respectively, of persons younger than 30 yr of age and in approximately 9% and 50%, respectively, of persons older than 60 yr of age.

Reactivation of BK and JC viruses with asymptomatic viruria occurs in 10-50% of hematopoietic stem cell and bone marrow transplant recipients and in 30% of renal transplant recipients. Of those renal transplant recipients who demonstrate BK viruria, approximately one third also have plasma viremia. Recipients with plasma viremia are at risk for development of nephropathy, which can clinically mimic allograft rejection and can result in failure of the allograft. Reduction of immunosuppression has been effective in preventing progression from viremia to nephropathy, and thus posttransplantation monitoring of either urine or plasma by polymerase chain reaction is important. It is particularly important to distinguish BK nephropathy from rejection because the treatments are different—increase in immunosuppression for rejection but decrease in immunosuppression for BK nephropathy.

Polymerase chain reaction is the preferred means to detect the BK and JC viruses. The high seroprevalence in the general population and lack of clear relationship to clinical illness limit the usefulness of serologic testing. There are no proven antiviral treatments for BK or JC virus infection, although cidofovir may be effective in some cases of BK-related transplant nephropathy. Effective treatment of AIDS with antiretroviral therapy can prevent the progression of progressive multifocal leukoencephalopathy.

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Chapter 276

Acquired Immunodeficiency Syndrome (Human Immunodeficiency Virus)

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Advances in research and major improvements in the treatment and management of HIV infection have brought about a substantial decrease in the incidence of new HIV infections and AIDS in children. Globally, there has been an estimated 58% decline in newly infected children since 2001, largely the result of antiretroviral treatment of HIV-infected pregnant women for the prevention of mother-to-child transmission. More than 90% of adults and children with HIV infection live in sub-Saharan Africa, where the disease continues to have a devastating impact (Fig. 276-1). Children experience more rapid disease progression than adults, with up to half of untreated children dying within the 1st 2 yr of life. This rapid progression is correlated with a higher viral burden and faster depletion of infected CD4 lymphocytes in infants and children than in adults. Accurate diagnostic tests and the early initiation of potent drugs to inhibit HIV replication have dramatically increased the ability to prevent and control this disease.

ETIOLOGY

HIV-1 and HIV-2 are members of the Retroviridae family and belong to the *Lentivirus* genus, which includes cytopathic viruses causing diverse diseases in several animal species. The HIV-1 genome contains 2 copies of single-stranded RNA that is 9.2 kb in size. At both ends of the genome there are identical regions, called **long terminal repeats,** which contain the regulation and expression genes of HIV. The remainder of the genome includes 3 major sections: the **GAG** region, which encodes the viral core proteins (p24 [capsid protein: CA], p17 [matrix protein: MA], p9, and p6, which are derived from the precursor p55); the **POL** region, which encodes the viral enzymes (i.e., reverse transcriptase [p51], protease [p10], and integrase [p32]); and the **ENV** region, which encodes the viral envelope proteins (gp120 and gp41, which are derived from the precursor gp160). Other regulatory proteins, such as transactivator of transcription (tat: p14), regulator of virion (rev: p19), negative regulatory factor (nef: p27), viral protein r (vpr: p15), viral infectivity factor (vif: p23), viral protein u (vpu in HIV-1: P16), and viral protein x (vpx in HIV-2: P15) are involved in transactivation, viral messenger RNA expression, viral replication, induction of cell cycle arrest, promotion of nuclear import of viral reverse transcription complexes, downregulation of CD4 receptors and class I major histocompatibility complex, proviral DNA synthesis, and virus release and infectivity (Fig. 276-2).

The HIV tropism to the target cell is determined by its envelope glycoprotein (Env). Env consists of 2 components, namely the surface heavily glycosylated subunit gp120 protein and the associated transmembrane subunit glycoprotein gp41. Both gp120 and gp41 are produced from the precursor protein gp160. The glycoprotein gp41 is very immunogenic and is used to detect HIV-1 antibodies in diagnostic assays; gp120 is a complex molecule that includes the highly variable **V3 loop.** This region is immunodominant for neutralizing antibodies. The heterogeneity of gp120 presents major obstacles in establishing an effective HIV vaccine. The gp120 glycoprotein also carries the binding site for the CD4 molecule, the most common host cell surface receptor of T lymphocytes. This tropism for $CD4^+$ T cells is beneficial to the virus because of the resulting reduction in the effectiveness of the host immune system. Other CD4-bearing cells include macrophages and microglial cells. The observations that $CD4^-$ cells are also infected by HIV and that some $CD4^+$ T cells are resistant to such infections suggests that other cellular attachment sites are needed for the interaction between HIV and human cells. Several chemokines serve as coreceptors for the envelope glycoproteins, permitting membrane fusion and entry into the cell. Most HIV strains have a specific tropism for 1 of the chemokines, including the fusion-inducing molecule **CXCR-4**, which acts as a coreceptor for HIV attachment to lymphocytes, and **CCR-5**, a β chemokine receptor that facilitates HIV entry into macrophages. Several other chemokine receptors (CCR-3) have also been shown in vitro to serve as virus co-receptors. Other mechanisms of attachment of HIV to cells use nonneutralizing antiviral antibodies and complement receptors. The Fab portion of these antibodies attaches to the virus surface, and the Fc portion binds to cells that express Fc receptors (macrophages, fibroblasts), thus facilitating virus transfer into the cell. Other cell-surface receptors, such as mannose-binding protein on macrophages or DC-specific C-type lectin (DC-SIGN) on dendritic cells, also bind to the HIV-1 envelope glycoprotein and increase the efficiency of viral infectivity. Cell-to-cell transfer of HIV without formation of fully formed particles is a more rapid mechanism of spreading the infection to new cells than is direct infection by the virus.

Following viral attachment, gp120 and the CD4 molecule undergo conformational changes, and gp41 interacts with the fusion receptor on the cell surface (Fig. 276-3). Viral fusion with the cell membrane allows entry of viral RNA into the cell cytoplasm. This process involves accessory viral proteins (nef, vif) and binding of cyclophilin A (a host cellular protein) to the capsid protein (p24). The p24 protein is involved in virus uncoating, recognition by restriction factors, and nuclear importation and integration of the newly created viral DNA. Viral DNA copies are then transcribed from the virion RNA through viral reverse transcriptase enzyme activity, which builds the 1st DNA strand from the viral RNA and then destroys the viral RNA and builds a 2nd DNA strand to produce double-stranded circular DNA. The HIV-1 reverse transcriptase is error prone and lacks error-correcting mechanisms. Thus, many mutations arise, creating wide genetic variation in

Figure 276-1 Estimated number of people living with HIV in 2012 and trends in the incidence of new infections from 2001 to 2012 by global region. Data from UNAIDS 2013 report. *(From Maartens G, Celum C, Lewin SR: HIV infection: epidemiology, pathogenesis, treatment, and prevention.* Lancet *384:258–268, 2014, Fig. 1).*

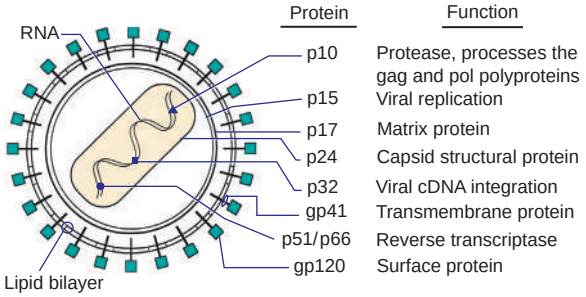

Figure 276-2 The human immunodeficiency virus and associated proteins and their functions.

HIV-1 isolates even within an individual patient. Many of the drugs used to fight HIV infection were designed to block the reverse transcriptase action. The circular DNA is transported into the cell nucleus, using viral accessory proteins like vpr, where it is integrated (with the help of the virus integrase) into the host chromosomal DNA and referred to as the *provirus*. The provirus has the advantage of latency, as it can remain dormant for extended periods, making it extremely difficult to eradicate. The infected $CD4^+$ T cells that survive long enough to revert to resting memory state become the HIV latent reservoir where the virus persists indefinitely even in patients who respond favorably to potent antiretroviral therapy. The molecular mechanisms of this latency are complex and involve unique biologic properties of the latent provirus (e.g., absence of tat, epigenetic changes inhibiting HIV gene expression) and the nature of the cellular host (e.g., absence of transcription factors like nuclear factor κB). Integration usually occurs near active genes, which allow a high level of viral production in response to various external factors such as an increase in inflammatory cytokines (by infection with other pathogens) and cellular activation. Anti-HIV drugs that block the integrase enzyme activity have been developed. Depending on the relative expression of the viral regulatory genes (tat, rev, nef), the proviral DNA may encode production of the viral RNA genome, which, in turn, leads to production of viral proteins necessary for viral assembly.

HIV-1 transcription is followed by translation. A capsid polyprotein is cleaved to produce, the virus-specific protease (p10), among other products. This enzyme is critical for HIV-1 assembly because it cleaves the long polyproteins into the proper functional pieces. Several HIV-1 antiprotease drugs have been developed, targeting the increased sensitivity of the viral protease, which differs from the cellular proteases. The regulatory protein vif is active in virus assembly and Gag processing. The RNA genome is then incorporated into the newly formed viral capsid that requires zinc finger domains (p7) and the matrix protein (MA: p17). The matrix protein forms a coat on the inner surface of the viral membrane, which is essential for the budding of the new virus from the host cell's surface. As new virus is formed, it buds through specialized membrane areas, known as *lipid rafts*, and is released. The virus release is facilitated by the viroporin vpu, which induces rapid degradation of newly synthesized CD4 molecules that impede viral budding. In addition, vpu counteracts host innate immunity (e.g., hampering natural killer T-cell activity).

Full-length sequencing of the HIV-1 genome demonstrated 3 different groups (M [main], O [outlier], and N [non-M, non-O]), probably occurring from multiple zoonotic infections from primates in different geographic regions. The same technique identified 8 groups of HIV-2 isolates. Group M diversified to 9 subtypes (or clades A to D, F to H, J and K). In each region of the world, certain clades predominate, for example, clade A in Central Africa, clade B in the United States and South America, clade C in South Africa, clade E in Thailand, and clade F in Brazil. Although some subtypes were identified within group O, none was found in any of the HIV-2 groups. Clades are mixed in some patients as a result of HIV recombination, and some crossing between groups (i.e., M and O) has been reported.

HIV-2 has a similar life cycle to HIV-1 and is known to cause infection in several monkey species. Subtypes A and B are the major causes of infection in humans, but rarely cause infection in children. HIV-2 differs from HIV-1 in its accessory genes (e.g., it has no *vpu* gene but contains the *vpx* gene, which is not found in HIV-1). It is most prevalent in western Africa, but increasing numbers of cases are reported from Europe and southern Asia. The diagnosis of HIV-2 infection is more difficult because of major differences in the genetic sequences between HIV-1 and HIV-2. Thus, several of the standard confirmatory assays (immunoblot), which are HIV-1 specific, may give indeterminate results with HIV-2 infection. If HIV-2 infection is suspected, a combination screening test that detects antibody to HIV-1 and HIV-2 peptides should be used. In addition, the rapid HIV detection tests have been less reliable in patients suspected to be dually infected with HIV-1 and HIV-2, because of lower antibody concentrations against HIV-2.

EPIDEMIOLOGY

The World Health Organization (WHO) estimated that in 2013, 3.2 million children younger than 15 yr of age worldwide were living with

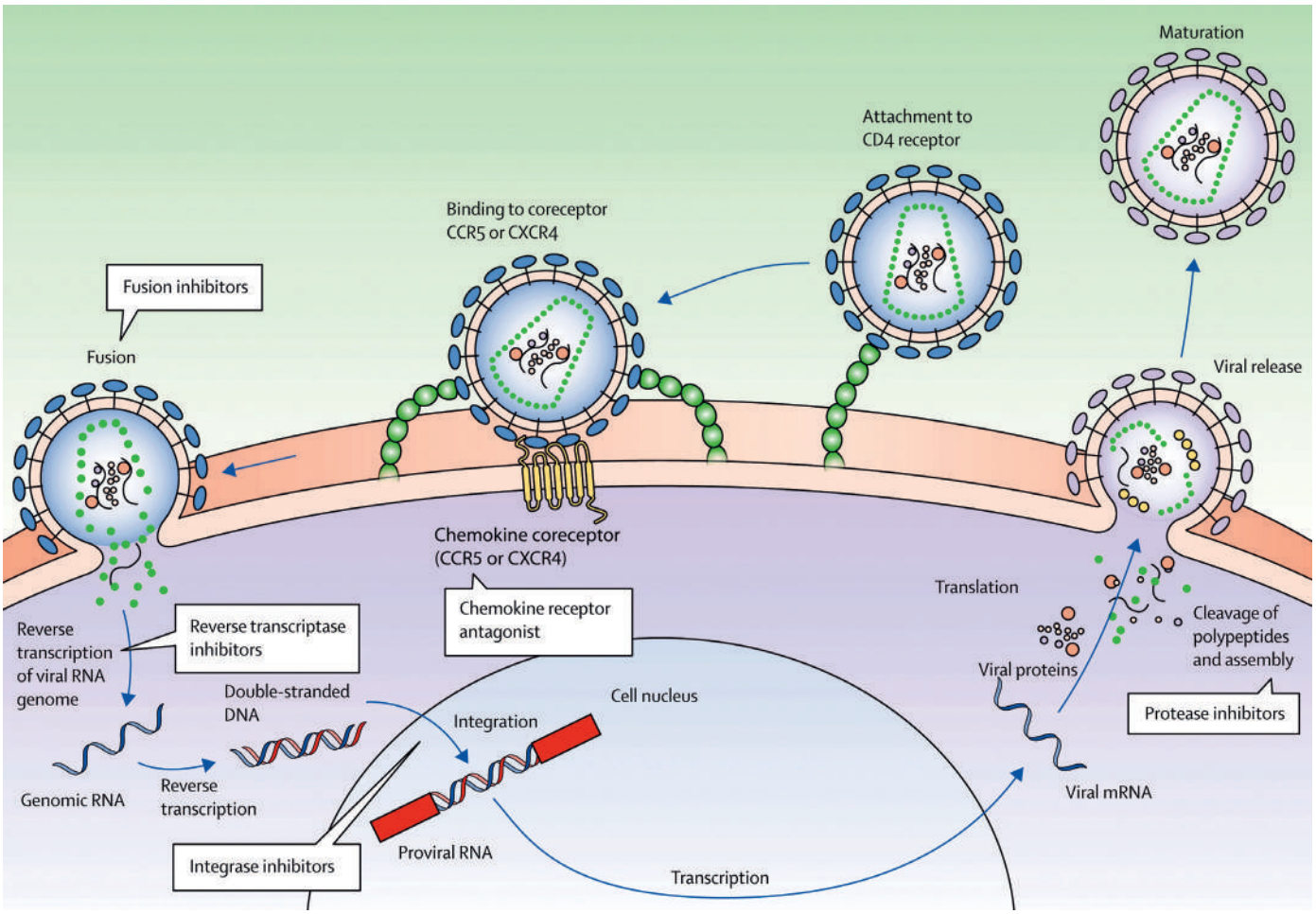

Figure 276-3 HIV life cycle showing the sites of action and different classes of antiretroviral drugs. *(Adapted from Walker BN, Colledge NR, Ralston SH, Penman I, editors:* Davidson's principles and practice of medicine, *ed 22. London, 2014, Churchill Livingstone.)*

HIV-1 infection, 90% of whom were from sub-Saharan Africa. Although the number of children born with HIV in this region decreased by 43% between 2009 and 2013, still 199,000 children were newly infected with HIV in 2013 alone. These trends reflect the slow but steady expansion of services to prevent perinatal transmission of HIV to infants. Unfortunately, through 2011, an estimated 16.6 million children have been orphaned by AIDS, defined as having 1 or both parents die from AIDS.

The vast majority of HIV infections in childhood are the result of **vertical transmission** from an HIV-infected mother. In the United States, approximately 10,800 children, adolescents, or young adults were reported to be living with perinatally acquired HIV infection in 2010. The number of U.S. children with AIDS diagnosed each year increased from 1984-1992 but then declined by more than 95% to <100 cases annually by 2003, largely from the success of prenatal screening and perinatal antiretroviral treatment of HIV-infected mothers and infants. Children of racial and ethnic minority groups are disproportionately overrepresented, particularly non-Hispanic African-Americans and Hispanics. Race and ethnicity are not risk factors for HIV infection but more likely reflect other social factors that may be predictive of increased risk for HIV infection, such as lack of educational and economic opportunities. New York, Florida, Texas, and California are the states with the highest number of cases of HIV in children in the United States.

Although adolescents (13-24 yr of age) represent a minority of U.S. AIDS cases (approximately 4%), they constitute a growing population of newly infected individuals; in 2011, almost 10,500 new cases of HIV were diagnosed in this age group, representing 21% of all new HIV infections in the United States. In 2009, 69% of all new youth infections occurred in young males who have sex with males (MSM), with a 48% increase in new infections in black MSM between 2006 and 2009. More than 50% of HIV-positive youth report being unaware of their diagnosis. Considering the long latency period between the time of infection and the development of clinical symptoms, reliance on AIDS case definition surveillance data significantly underrepresents the impact of the disease in adolescents. Based on a median incubation period of 8-12 yr, it is estimated that 15-20% of all AIDS cases were acquired between 13 and 19 yr of age.

Risk factors for HIV infection vary by gender in adolescents. For example, 91-93% of males between the ages of 13 and 24 yr with HIV acquire infection through sex with males. In contrast, 91-93% of adolescent females with HIV are infected through heterosexual contact. As in the pediatric population, adolescent racial and ethnic minority populations are overrepresented, especially among females.

Transmission

Transmission of HIV-1 occurs via sexual contact, parenteral exposure to blood, or vertical transmission from mother to child. The primary route of infection in the pediatric population is vertical transmission. Rates of transmission of HIV from mother to child have varied in high- and low-resource countries; the United States and Europe have documented transmission rates in untreated women between 12% and 30%, whereas transmission rates in Africa and Haiti have been higher (25-52%), likely because of more advanced maternal disease and the presence of coinfections. Perinatal treatment of HIV-infected pregnant women with antiretroviral drugs has dramatically decreased the rate to <2%.

Vertical transmission of HIV can occur before **(intrauterine),** during **(intrapartum),** or after delivery (through **breastfeeding**). Although intrauterine transmission has been suggested by identification of HIV by culture or polymerase chain reaction (PCR) in fetal tissue as early as 10 wk, statistical modeling data suggest that the majority of in utero transmissions likely occur in late gestation, when the vascular integrity of the placenta weakens and microtransfusions across the maternal–fetal circulation occur. It is generally accepted that 20-30% of infected newborns are infected in utero, because this percentage of infants has laboratory evidence of infection (positive viral culture or PCR) within the 1st wk of life. Some studies have found that viral detection soon after birth also correlates with early onset of symptoms and rapid progression to AIDS, consistent with more long-standing infection during gestation.

A higher percentage of HIV-infected children acquire the virus intrapartum, evidenced by the fact that 70-80% of infected infants do not demonstrate detectable virus until after 1 wk of age. The mechanism of transmission appears to be mucosal exposure to infected blood and cervicovaginal secretions in the birth canal, and intrauterine contractions during active labor/delivery could also increase the risk of late microtransfusions. Breastfeeding is the least-common route of vertical transmission in industrialized nations, but is responsible for as much as 40% of perinatal infections in resource-limited countries. Both free and cell-associated viruses have been detected in breast milk from HIV-infected mothers. The risk for transmission through breastfeeding is approximately 9-16% in women with established infection, but is 29-53% in women who acquire HIV postnatally, suggesting that the viremia experienced by the mother during primary infection at least triples the risk for transmission. Where replacement feeding is readily available and safe, it seems reasonable for women to substitute infant formula for breast milk if they are known to be HIV infected or are at risk for ongoing sexual or parenteral exposure to HIV. However, the WHO recommends that in low-resource countries where other diseases (diarrhea, pneumonia, malnutrition) substantially contribute to a high infant mortality rate, the benefit of breastfeeding outweighs the risk for HIV transmission, and HIV-infected women in developing countries should breastfeed their infants for at least the 1st 6 mo of life (see "Prevention" below).

Several risk factors influence the rate of vertical transmission: maternal viral load at delivery, preterm delivery (<34 wk gestation), and low maternal antenatal CD4 count. The most important variable appears to be the level of maternal viremia; the odds of transmission may be increased more than 2-fold for every $\log_{10}$ increase in viral load at delivery. Elective cesarean delivery was shown to decrease transmission by 87% if used in conjunction with zidovudine therapy in the mother and infant. However, because these data predated the advent of **combined antiretroviral therapy (cART, also called HAART),** the additional benefit of cesarean section appears to be negligible if the mother's viral load is <1,000 copies/mL. It should be noted that rarely (≤0.1%) transmission may occur with maternal viral loads <50 copies/mL.

Transfusions of infected blood or blood products have accounted for 3-6% of all pediatric AIDS cases. The period of highest risk was between 1978 and 1985, before the availability of HIV antibody-screened blood products. Whereas the prevalence of HIV infection in individuals with hemophilia treated before 1985 was as high as 70%, heat treatment of factor VIII concentrate and HIV antibody screening of donors has virtually eliminated HIV transmission in this population. Donor screening has dramatically reduced, but not eliminated, the risk for blood transfusion–associated HIV infection: nucleic acid amplification testing of "minipools" (pools of 16-24 donations) performed on antibody-nonreactive blood donations (to identify donations made during the window period before seroconversion) reduced the residual risk of transfusion-transmitted HIV-1 to approximately 1 in 2 million blood units. However, in many resource-limited countries, screening of blood is not uniform, and the risk for transmitting HIV infection via transfusion remains.

Although HIV can be isolated rarely from saliva, it is in very low titers (<1 infectious particle/mL) and has not been implicated as a transmission vehicle. Studies of hundreds of household contacts of HIV-infected individuals have found that the risk for household HIV transmission is practically nonexistent. Only a few cases have been reported in which urine or feces (possibly devoid of visible blood) have been proposed as a possible vehicle of HIV transmission.

In the pediatric population, sexual transmission is infrequent, but a small number of cases resulting from sexual abuse have been reported. Sexual contact is a major route of transmission in the adolescent population, accounting for most of the cases.

PATHOGENESIS

HIV infection affects most of the immune system and disrupts its homeostasis (see Fig. 276-3). In most cases, the initial infection is caused by low amounts of a single virus. Therefore, disease may be prevented by prophylactic drug(s) or vaccine. When the mucosa serves as the portal of entry for HIV, the 1st cells to be affected are the dendritic cells. These cells collect and process antigens introduced from the periphery and transport them to the lymphoid tissue. HIV does not infect the dendritic cell but binds to its DC-SIGN surface molecule, allowing the virus to survive until it reaches the lymphatic tissue. In the lymphatic tissue (e.g., lamina propria, lymph nodes), the virus selectively binds to cells expressing CD4 molecules on their surface, primarily helper T lymphocytes ($CD4^+$ T cells) and cells of the monocyte-macrophage lineage. Other cells bearing CD4, such as microglia, astrocytes, oligodendroglia, and placental tissue containing villous Hofbauer cells, may also be infected by HIV. Additional factors (coreceptors) are necessary for HIV fusion and entry into cells. These factors include the chemokines CXCR4 (fusion) and CCR5. Other chemokines (CCR1, CCR3) may be necessary for the fusion of certain HIV strains. Several host genetic determinants affect the susceptibility to HIV infection, the progression of disease, and the response to treatment. These genetic variants vary in different populations. A deletion in the CCR5 gene that is protective against HIV infection (CCR5Δ32) is relatively common in whites but is rare in blacks. Several other genes that regulate chemokine receptors, ligands, the histocompatibility complex, and cytokines also influence the outcome of HIV infection. Usually, $CD4^+$ lymphocytes migrate to the lymphatic tissue in response to viral antigens and then become activated and proliferate, making them highly susceptible to HIV infection. This antigen-driven migration and accumulation of CD4 cells within the lymphoid tissue may contribute to the generalized lymphadenopathy characteristic of the acute retroviral syndrome in adults and adolescents. HIV preferentially infects the very cells that respond to it (HIV-specific memory CD4 cells), accounting for the progressive loss of these cells and the subsequent loss of control of HIV replication. The continued destruction of memory $CD4^+$ cells in the gastrointestinal tract leads to reduced integrity of the gastrointestinal epithelium followed by leakage of bacterial particles into the blood and increased inflammatory response, which cause further $CD4^+$ cell loss. When HIV replication reaches a threshold (usually within 3-6 wk from the time of infection), a burst of plasma viremia occurs. This intense viremia causes **flu or mononucleosis-like symptoms** (fever, rash, lymphadenopathy, arthralgia) in 50-70% of infected adults. With establishment of a cellular and humoral immune response within 2-4 mo, the viral load in the blood declines substantially, and patients enter a phase characterized by a lack of symptoms and a return of CD4 cells to only moderately decreased levels.

The HIV rapidly responds to the immune system pressure by developing a genetically complex population (quasispecies) that successfully evade it. In addition, inappropriate use of antiretroviral treatment increases the ability of the virus to diverge even further. Early HIV-1 replication in children has no apparent clinical manifestations. Whether tested by virus isolation or by PCR for viral nucleic acid sequences, fewer than 40% of HIV-1–infected infants demonstrate evidence of the virus at birth. The virus load increases by 1-4 mo, and almost all HIV-infected infants have detectable HIV-1 in peripheral blood by 4 mo of age.

In adults, the long period of clinical latency (8-12 yr) is not indicative of viral latency. In fact, there is a very high turnover of virus and CD4 lymphocytes (more than a billion cells per day), gradually causing deterioration of the immune system, marked by depletion of CD4 cells.

Several mechanisms for the depletion of CD4 cells in adults and children have been suggested, including HIV-mediated single cell killing, formation of multinucleated giant cells of infected and uninfected CD4 cells **(syncytia formation),** virus-specific immune responses (natural killer cells, antibody-dependent cellular cytotoxicity), superantigen-mediated activation of T cells (rendering them more susceptible to infection with HIV), autoimmunity, and programmed cell death (apoptosis). The viral burden is greater in the lymphoid organs than in the peripheral blood during the asymptomatic period. As HIV virions and their immune complexes migrate through the lymph nodes, they are trapped in the network of dendritic follicular cells. Because the ability of HIV to replicate in T cells depends on the state of activation of the cells, the immune activation that takes place within the microenvironment of the lymph nodes in HIV disease serves to promote infection of new CD4 cells as well as subsequent viral replication within these cells. Monocytes and macrophages can be productively infected by HIV yet resist the cytopathic effect of the virus and, with their long lifespan, explain their role as reservoirs of HIV and as effectors of tissue damage in organs such as the brain. In addition, they reside in anatomic viral sanctuaries where current treatment agents are less effective.

The innate immune system responds almost immediately following HIV infection by recognizing the viral nucleic acids, once the virus fuses into the infected cell, by the toll-like receptor 7. This engagement leads to activation of proinflammatory cytokines and interferon (IFN-α), which blocks virus replication and spread. The virus uses its Nef protein to downregulate the expression of major histocompatibility complex (MHC) and non-MHC ligands to reduce the natural killing (NK) cell–mediated anti-HIV activity. It also modulates NK cell differentiation and maturation, dysregulates cytokine production, and increases apoptosis. While the mechanism by which the innate system triggers the adaptive immune responses is not yet fully understood, cell-mediated and humoral responses occur early in the infection. CD8 T cells play an important role in containing the infection. These cells produce various ligands (macrophage inflammatory proteins 1α and 1β, RANTES), which suppress HIV replication by blocking the binding of the virus to the coreceptors (CCR5). HIV-specific cytotoxic T lymphocytes (CTLs) develop against both the structural (ENV, POL, GAG) and regulatory (tat) viral proteins. The CTLs appear at the end of the acute infection, as viral replication is controlled by killing HIV-infected cells before new viruses are produced and by secreting potent antiviral factors that compete with the virus for its receptors (CCR5). Neutralizing antibodies appear later in the infection and seem to help in the continued suppression of viral replication during clinical latency. There are at least 2 possible mechanisms that control the steady-state viral load level during the chronic clinical latency. One mechanism may be the limited availability of activated CD4 cells, which prevent further increase in viral load. The other mechanism is development of an active immune response, which is influenced by the amount of viral antigen and limits viral replication at a steady state. There is no general consensus about which of these 2 mechanisms is more important. The CD4 cell limitation mechanism accounts for the effect of antiretroviral therapy, whereas the immune response mechanism emphasizes the importance of immune modulation treatment (cytokines, vaccines) to increase the efficiency of immune-mediated control. A group of cytokines that includes tumor necrosis factor TNF-α, TNF-β, interleukin IL-1, IL-2, IL-3, IL-6, IL-8, IL-12, IL-15, granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor plays an integral role in upregulating HIV expression from a state of quiescent infection to active viral replication. Other cytokines such as IFN-γ, IFN-β, and IL-13 exert a suppressive effect on HIV replication. Certain cytokines (IL-4, IL-10, IFN-γ, transforming growth factor-β) reduce or enhance viral replication depending on the infected cell type. The interactions among these cytokines influence the concentration of viral particles in the tissues. Plasma concentrations of cytokines need not be elevated for them to exert their effect, because they are produced and act locally in the tissues. The activation of virtually all the cellular components of the immune system (i.e., T and B cells, natural killer cells, and monocytes) plays a significant role in the pathologic aspects of HIV infection. Further understanding of their interactions during the infection will expand our treatment options. Commonly, HIV isolated during the clinical latency period grows slowly in culture and produces low titers of reverse transcriptase. These isolates use CCR5 as their coreceptor. By the late stages of clinical latency, the isolated virus is phenotypically different. It grows rapidly and to high titers in culture and uses CXCR4 as its coreceptor. The switch from CCR5 receptor to CXCR4 receptor increases the capacity of the virus to replicate, to infect a broader range of target cells (CXCR4 is more widely expressed on resting and activated immune cells), and to kill T cells more rapidly and efficiently. As a result, the clinical latency phase is over and progression toward AIDS is noted. The **progression of disease** is related temporally to the gradual disruption of lymph node architecture and degeneration of the follicular dendritic cell network with loss of its ability to trap HIV particles. The virus is freed to recirculate, producing high levels of viremia and an increased disappearance of CD4 T cells during the later stages of disease.

The clinical course of the HIV infection shows a substantial heterogenicity. This variation is determined by both viral and host factors. HIV viruses that use coreceptor CXCR4 in the course of the infection are associated with an accelerated deterioration of the immune system and more rapid progression to AIDS. In addition, several host genetic determinants (e.g., variants in the human leukocyte antigen region, polymorphisms in the CCR5 region like CCR5Δ32) were already identified as affecting the disease course. **Three distinct patterns of disease** were described in children. Approximately 15-25% of HIV-infected newborns in developed countries present with a **rapid disease course**, with onset of AIDS and symptoms during the 1st few months of life and a median survival time of 6-9 mo if untreated. In resource-poor countries, the majority of HIV-infected newborns will have this rapidly progressing disease. It has been suggested that if intrauterine infection coincides with the period of rapid expansion of CD4 cells in the fetus, the virus could effectively infect the majority of the body's immunocompetent cells. The normal migration of these cells to the marrow, spleen, and thymus would result in efficient systemic delivery of HIV, unchecked by the immature immune system of the fetus. Thus, infection would be established before the normal ontogenic development of the immune system, causing more-severe impairment of immunity. Most children in this group have a positive HIV-1 culture and/or detectable virus in the plasma (median level: 11,000 copies/mL) in the 1st 48 hr of life. This early evidence of viral presence suggests that the newborn was infected in utero. The viral load rapidly increases, peaking by 2-3 mo of age (median: 750,000 copies/mL) and staying high for at least the 1st 2 yr of life.

From 60-80% of perinatally infected newborns in developed countries present with a much **slower progression** of disease, with a median survival time of 6 yr representing the 2nd pattern of disease. Many patients in this group have a negative viral culture or PCR in the 1st wk of life and are therefore considered to be infected intrapartum. In a typical patient, the viral load rapidly increases, peaking by 2-3 mo of age (median: 100,000 copies/mL) and then slowly declines over a period of 24 mo. The slow decline in viral load is in sharp contrast to the rapid decline after primary infection seen in adults. This observation can be explained only partially by the immaturity of the immune system in newborns and infants.

The 3rd pattern of disease occurs in <5% of perinatally infected children, referred to as **long-term survivors,** who have minimal or no progression of disease with relatively normal CD4 counts and very low viral loads for longer than 8 yr. Mechanisms for the delay in disease progression include effective humoral immunity and/or CTL responses, host genetic factors (e.g., human leukocyte antigen profile), and infection with attenuated (defective gene) virus. A subgroup of the long-term survivors called "elite survivors" has no detectable viruses in the blood and may reflect different or greater mechanisms of protection from disease progression.

HIV-infected children have changes in the immune system that are similar to those in HIV-infected adults. CD4 cell depletion may be less dramatic because infants normally have a relative lymphocytosis. A value of 1,500 CD4 cells/μL in children younger than 1 yr of age is indicative of severe CD4 depletion and is comparable to <200 CD4

cells/μL in adults. Lymphopenia is relatively rare in perinatally infected children and is usually only seen in older children or those with end-stage disease. Although cutaneous anergy is common during HIV infection, it is also frequent in healthy children younger than 1 yr of age, and thus its interpretation is difficult in infected infants. The depletion of CD4 cells also decreases the response to soluble antigens such as in vitro mitogens phytohemagglutinin and concanavalin A.

Polyclonal activation of B cells occurs in most children early in the infection, as evidenced by elevation of immunoglobulin (Ig) A, IgM, IgE, and particularly IgG **(hypergammaglobulinemia)**, with high levels of anti–HIV-1 antibody. This response may reflect both dysregulation of T-cell suppression of B-cell antibody synthesis and active CD4 enhancement of B-lymphocyte humoral response. As a result, antibody response to routine childhood vaccinations may be abnormal. The B-cell dysregulation precedes the CD4 depletion in many children, and may serve as a surrogate marker of HIV infection in symptomatic children in whom specific diagnostic tests (PCR, culture) are not available or are too expensive. Despite the increased levels of immunoglobulins, some children lack specific antibodies or protective antibodies. Hypogammaglobulinemia is very rare (<1%).

Central nervous system (CNS) involvement is more common in pediatric patients than in adults. Macrophages and microglia play an important role in HIV neuropathogenesis, and data suggest that astrocytes may also be involved. Although the specific mechanisms for encephalopathy in children are not yet clear, the developing brain in young infants is affected by at least 2 mechanisms. The virus itself may directly infect various brain cells or cause indirect damage to the nervous system by the release of cytokines (IL-1α, IL-1β, TNF-α, IL-2) or reactive oxygen from HIV-infected lymphocytes or macrophages.

Appropriate therapy with antiretroviral agents may result in **immune reconstitution inflammatory syndrome (IRIS)**, which is characterized by an increased inflammatory response from the recovered immune system to subclinical opportunistic infections (e.g., *Mycobacterium*, herpes simplex virus [HSV] infection, toxoplasmosis, cytomegalovirus [CMV] infection, *Pneumocystis*, cryptococcal infection). This condition is more commonly observed in patients with progressive disease and severe CD4+ T-lymphocyte depletion. Patients with IRIS develop fever and worsening of the clinical manifestations of the opportunistic infection or new manifestations (e.g., enlargement of lymph nodes, pulmonary infiltrates), typically within the 1st few weeks after initiation of antiretroviral therapy. Determining whether the symptoms represent IRIS, worsening of a current infection, a new opportunistic infection, or drug toxicity is often very difficult. If the syndrome does represent IRIS, adding nonsteroidal antiinflammatory agents or corticosteroids may alleviate the inflammatory reaction, although the use of corticosteroids is controversial. The inflammation may take weeks or months to subside. In most cases, continuation of anti-HIV treatment while treating the opportunistic infection (with or without antiinflammatory agents) is sufficient. If opportunistic infection is suspected prior to initiation of antiretroviral therapy, appropriate antimicrobial treatment should be given 1st.

CLINICAL MANIFESTATIONS

The clinical manifestations of HIV infection vary widely among infants, children, and adolescents. In most infants, physical examination at birth is normal. Initial symptoms may be subtle, such as lymphadenopathy and hepatosplenomegaly, or nonspecific, such as failure to thrive, chronic or recurrent diarrhea, respiratory symptoms, or oral thrush and may be distinguishable only by their persistence. Whereas systemic and pulmonary findings are common in the United States and Europe, chronic diarrhea, pneumonia, wasting, and severe malnutrition predominate in Africa. Clinical manifestations found more commonly in children than adults with HIV infection include recurrent bacterial infections, chronic parotid swelling, lymphocytic interstitial pneumonitis (LIP), and early onset of progressive neurologic deterioration.

The CDC Surveillance Case Definition for HIV infection was revised in 2014 and has consolidated the staging system for children with adolescents and adults. It is based on age-specific CD4+ T-lymphocyte count or CD4+ T-lymphocyte percentage of total lymphocytes (Table 276-1), except when a stage 3-defining opportunistic illness (Table 276-2) supersedes the CD4 data. Age adjustment of the absolute CD4 count is necessary because counts that are relatively high in normal infants decline steadily until age 6 yr, when they reach adult norms. The CD4 count takes precedence over the CD4 T-lymphocyte percentage, and the percentage is considered only if the count is missing.

Infections

Approximately 20% of AIDS-defining illnesses in children are recurrent bacterial infections caused primarily by encapsulated organisms such as *Streptococcus pneumoniae* and *Salmonella* as a result of disturbances in humoral immunity. Other pathogens, including *Staphylococcus, Enterococcus, Pseudomonas aeruginosa, Haemophilus influenzae,* and other Gram-positive and Gram-negative organisms, may also be seen. The most common serious infections in HIV-infected children are bacteremia, sepsis, and bacterial pneumonia, accounting for more than 50% of infections in these patients. Meningitis, urinary tract infections, deep-seated abscesses, and bone/joint infections occur less frequently. Milder recurrent infections, such as otitis media, sinusitis, and skin and soft tissue infections, are very common and may be chronic with atypical presentations.

Opportunistic infections are generally seen in children with severe depression of the CD4 count. In adults, these infections usually represent reactivation of a latent infection acquired early in life. In contrast, young children generally have primary infection and often have a more fulminant course of disease reflecting the lack of prior immunity. This principle is best illustrated by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, the most common opportunistic infection in the pediatric population (see Chapter 244). The peak incidence of *Pneumocystis* pneumonia occurs at age 3-6 mo in the setting of undiagnosed perinatally acquired disease, with the highest mortality rate in children younger than 1 yr of age. Aggressive approaches to treatment have improved the outcome substantially. While the overall

Table 276-1 HIV Infection Stage* Based on Age-Specific CD4+ T-Lymphocyte Count or CD4+ T-Lymphocyte Percentage of Total Lymphocytes

	Age on Date of CD4+ T-Lymphocyte Test					
	<1 Yr		1-5 Yr		≥6 Yr	
Stage	CELLS/μL	%	CELLS/μL	%	CELLS/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750-1,499	26-33	500-999	22-29	200-499	14-25
3	<750	<26	<500	<22	<200	<14

*Stage is based primarily on the CD4+ T-lymphocyte count. The CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage, and the percentage is considered only if the count is missing.

From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014. MMWR 63(No RR-3):1-10, 2014.

Table 276-2 Stage 3—Defining Opportunistic Illnesses in HIV Infection

Bacterial infections, multiple or recurrent*
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive†
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 mo duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 mo
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy attributed to HIV‡
Herpes simplex: chronic ulcers (>1 mo duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 mo)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 mo duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary,† disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jiroveci (previously known as *Pneumocystis carinii*) pneumonia
Pneumonia, recurrent†
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 mo
Wasting syndrome attributed to HIV‡

*Only among children aged <6 yr.
†Only among adults, adolescents, and children aged ≥6 yr.
‡Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in the following references: Centers for Disease Control and Prevention: 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 43(No. RR-12), 1994. Centers for Disease Control and Prevention: 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 41(No. RR-17), 1992.
From Centers for Disease Control and Prevention: Revised surveillance case definition for HIV infection—United States, 2014. MMWR 63(No RR-3):1-10, 2014.

incidence of opportunistic infections has markedly declined since the era of combination antiretroviral therapy, opportunistic infections still occur in patients with severe immunodepletion as the result of unchecked viral replication, which often accompanies poor antiretroviral therapy adherence.

The classic clinical presentation of *Pneumocystis* pneumonia includes acute onset of fever, tachypnea, dyspnea, and marked hypoxemia; in some children, more indolent development of hypoxemia may precede other clinical or x-ray manifestations. Chest x-ray findings most commonly consist of interstitial infiltrates or diffuse alveolar disease, which rapidly progresses. Nodular lesions, streaky or lobar infiltrates, or pleural effusions may occasionally be seen. Diagnosis is established by demonstration of *P. jiroveci* with appropriate staining of induced sputum or bronchoalveolar fluid lavage; rarely, an open lung biopsy is necessary.

The 1st-line therapy for *Pneumocystis* pneumonia is intravenous trimethoprim-sulfamethoxazole (TMP-SMZ) (15-20 mg/kg/day of the TMP component every 6 hr IV) with adjunctive corticosteroids if the Pa_{O_2} is <70 mm Hg while breathing room air. When the patient has improved, therapy with oral TMP-SMZ should be continued for a total of 21 days while the corticosteroids are weaned. Alternative therapy for *Pneumocystis* pneumonia includes intravenous administration of pentamidine (4 mg/kg/day). Other regimens such as TMP plus dapsone, clindamycin plus primaquine, or atovaquone are used as alternatives in adults but have not been widely used in children to date.

Nontuberculous mycobacterial infection, with *Mycobacterium avium-intracellulare* complex (MAC), may cause disseminated disease in HIV-infected children who are severely immunosuppressed. The incidence of MAC infection in antiretroviral therapy–naïve children with <100 CD4 cells/mm^3 is estimated to be as high as 10%, but effective cART that results in viral suppression makes MAC infections rare. Disseminated MAC infection is characterized by fever, malaise, weight loss, and night sweats; diarrhea, abdominal pain, and, rarely, intestinal perforation or jaundice (a result of biliary tract obstruction by lymphadenopathy) may also be present. Diagnosis is made by isolation of MAC from blood, bone marrow, or tissue; the isolated presence of MAC in the stool does not confirm a diagnosis of disseminated MAC. Treatment can reduce symptoms and prolong life but is at best only capable of suppressing the infection if severe CD4 depletion persists. Therapy should include at least 2 drugs: clarithromycin or azithromycin and ethambutol. A 3rd drug (rifabutin, rifampin, ciprofloxacin, levofloxacin, or amikacin) is generally added to decrease the emergence of drug-resistant isolates. Careful consideration of possible drug interactions with antiretroviral agents is necessary before initiation of disseminated MAC therapy. Drug susceptibilities should be ascertained, and the treatment regimen should be adjusted accordingly in the event of inadequate clinical response to therapy. Because of the great potential for toxicity with most of these medications, surveillance for adverse effects should be ongoing.

Oral candidiasis is the most common **fungal infection** seen in HIV-infected children. Oral nystatin suspension (2-5 mL qid) is often effective. Clotrimazole troches or fluconazole (3-6 mg/kg PO qd) are an effective alternative. Oral thrush progresses to involve the esophagus in as many as 20% of children with severe CD4 depletion, presenting with symptoms such as anorexia, dysphagia, vomiting, and fever. Treatment with oral fluconazole for 7-14 days generally results in rapid improvement in symptoms. Fungemia rarely occurs, usually in the setting of indwelling venous catheters, and up to 50% of cases may be caused by non–albicans species. Disseminated histoplasmosis, coccidioidomycosis, and cryptococcosis are rare in pediatric patients but may occur in endemic areas. Parasitic infections such as intestinal cryptosporidiosis and microsporidiosis and rarely isosporiasis or giardiasis are other opportunistic infections that cause significant morbidity. Although these intestinal infections are usually self-limiting in healthy hosts, they cause severe chronic diarrhea in HIV-infected children with low CD4 counts, often leading to malnutrition. Nitazoxanide therapy is partially effective at improving cryptosporidia diarrhea, but immune reconstitution with cART is the most important factor for clearance of the infection. Albendazole has been reported to be effective against some microsporidia, and TMP-SMZ appears to be effective for isosporiasis.

Viral infections, especially with the herpesvirus group, pose significant problems for HIV-infected children. HSV causes recurrent gingivostomatitis, which may be complicated by local and distant cutaneous dissemination. Primary varicella-zoster virus infection (chickenpox) may be prolonged and complicated by bacterial infections or visceral dissemination, including pneumonitis. Recurrent, atypical, or chronic episodes of herpes zoster are often debilitating and require prolonged therapy with acyclovir; in rare instances, varicella-zoster virus has developed resistance to acyclovir, requiring the use of foscarnet. Disseminated CMV infection occurs in the setting of severe CD4 depletion (<50 CD4 cells/μL) and may involve single or multiple organs. Retinitis, pneumonitis, esophagitis, gastritis with pyloric obstruction, hepatitis, colitis, and encephalitis have been reported, but these complications are rarely seen if cART is given. Ganciclovir (6 mg/kg bid IV) and foscarnet (60 mg/kg tid IV) are the drugs of choice and are often given together in children with sight-threatening CMV retinitis. Intraocular injections of foscarnet or intraocular ganciclovir implants plus oral valganciclovir have also been efficacious in adults and older children with CMV retinitis. Measles may occur despite immunization and may present without the typical rash. It often disseminates to the lung or brain with a high mortality rate.

Respiratory viruses such as respiratory syncytial virus and adenovirus may present with prolonged symptoms and persistent viral shedding. In parallel with the increased prevalence of genital tract human papillomavirus infection, cervical intraepithelial neoplasia and anal intraepithelial neoplasia also occur with increased frequency among HIV-1–infected adult women compared with HIV-seronegative women. The relative risk for cervical intraepithelial neoplasia is 5-10 times higher for HIV-1 seropositive women. Multiple modalities are used to treat human papillomavirus infection (see Chapter 266), although none is uniformly effective and the recurrence rate is high among HIV-1–infected persons.

Central Nervous System

The incidence of CNS involvement in perinatally infected children is as high as 50-90% in resource-limited countries but significantly lower in developed countries, with a median onset at 19 mo of age. Manifestations may range from subtle developmental delay to progressive encephalopathy with loss or plateau of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetric motor dysfunction. **Encephalopathy** may be the initial manifestation of the disease or may present much later when severe immune suppression occurs. With progression, marked apathy, spasticity, hyperreflexia, and gait disturbance may occur, as well as loss of language and oral, fine, and/or gross motor skills. The encephalopathy may progress intermittently, with periods of deterioration followed by transiently stable plateaus. Older children may exhibit behavioral problems and learning disabilities. Associated abnormalities identified by neuroimaging techniques include cerebral atrophy in up to 85% of children with neurologic symptoms, increased ventricular size, basal ganglia calcifications, and, less frequently, leukomalacia.

Fortunately, since the advent of cART, the incident rate of encephalopathy has dramatically declined to as low as 0.08% in 2006. However, as HIV-infected children progress through adolescence and young adulthood, other subtle manifestations of CNS disease are evident, such as cognitive deficits, attention problems, and psychiatric disorders. Living with a chronic, often stigmatizing, disease, parental loss, and the requirement for lifelong pristine medication adherence compounds these issues, making it challenging for these youth as they inherit responsibility for managing their disease as adults.

Focal neurologic signs and seizures are unusual and may imply a comorbid pathologic process such as a CNS tumor, opportunistic infection, or stroke. **CNS lymphoma** may present with new onset focal neurologic findings, headache, seizures, and mental status changes. Characteristic findings on neuroimaging studies include a hyperdense or isodense mass with variable contrast enhancement or a diffusely infiltrating contrast-enhancing mass. **CNS toxoplasmosis** is exceedingly rare in young infants, but may occur in HIV-infected adolescents and is typically associated with serum antitoxoplasma IgG as a marker of infection. Other opportunistic infections of the CNS are rare and include infection with CMV, JC virus **(progressi*ve multifocal leukoencephalopathy*),** HSV, *Cryptococcus neoformans*, and *Coccidioides immitis.* Although the true incidence of cerebrovascular disorders (both hemorrhagic and nonhemorrhagic strokes) is unclear, 6-10% of children from large clinical series have been affected.

Respiratory Tract

Recurrent upper respiratory tract infections such as otitis media and sinusitis are very common. Although the typical pathogens *(S. pneumoniae, H. influenzae, Moraxella catarrhalis)* are most common, unusual pathogens such as *P. aeruginosa,* yeast, and anaerobes may be present in chronic infections and result in complications such as invasive sinusitis and mastoiditis.

LIP is the most common chronic lower respiratory tract abnormality reported to the Centers for Disease Control and Prevention (CDC); historically this occurred in approximately 25% of HIV-infected children, although the incidence has declined in the cART era. LIP is a chronic process with nodular lymphoid hyperplasia in the bronchial and bronchiolar epithelium, often leading to progressive alveolar capillary block over months to years. It has a characteristic chronic diffuse reticulonodular pattern on chest radiography rarely accompanied by hilar lymphadenopathy, allowing a presumptive diagnosis to be made radiographically before the onset of symptoms. There is an insidious onset of tachypnea, cough, and mild to moderate hypoxemia with normal auscultatory findings or minimal rales. Progressive disease presents with symptomatic hypoxemia, which usually resolves with oral corticosteroid therapy, accompanied by digital clubbing. Several studies suggest that LIP is a lymphoproliferative response to a primary Epstein-Barr virus infection in the setting of HIV infection.

Most symptomatic HIV-infected children experience at least 1 episode of pneumonia during the course of their disease. *S. pneumoniae* is the most common bacterial pathogen, but *P. aeruginosa* and other Gram-negative bacterial pneumonias may occur in end-stage disease and are often associated with acute respiratory failure and death. Rarely, severe recurrent bacterial pneumonia results in bronchiectasis. *Pneumocystis* pneumonia is the most common opportunistic infection, but other pathogens, including CMV, *Aspergillus, Histoplasma,* and *Cryptococcus,* can cause pulmonary disease. Infection with common respiratory viruses, including respiratory syncytial virus, parainfluenza, influenza, and adenovirus, may occur simultaneously and have a protracted course and period of viral shedding from the respiratory tract. Pulmonary and extrapulmonary tuberculosis (TB) has been reported with increasing frequency in HIV-infected children in low-resource countries, although it is considerably more common in HIV-infected adults. Because of drug interactions between rifampin and ritonavir-based antiretroviral therapy and poor tolerability of the combination of multiple drugs required, treatment of TB/HIV coinfection is particularly challenging in children.

Cardiovascular System

Cardiac dysfunction, including left ventricular hypertrophy, left ventricular dilation, reduced left ventricular fractional shortening, and/or heart failure occurred in 18-39% of HIV-infected children in the pre-cART era; among those affected, lower nadir CD4 percent and a higher viral load were associated with lower cardiac function. However, a more recent evaluation of HIV-infected children taking long-term cART found that echocardiographic findings were closer to normal and none had symptomatic heart disease, suggesting that cART has a cardioprotective effect. What is still unclear is whether an increased rate of premature cardiovascular disease that has been seen in adults will be seen in children who have disease- or treatment-related hyperlipidemia, and prospective studies will be needed to assess this risk.

Gastrointestinal and Hepatobiliary Tract

Oral manifestations of HIV disease include erythematous or pseudomembranous candidiasis, periodontal disease (e.g., ulcerative gingivitis or periodontitis), salivary gland disease (i.e., swelling, xerostomia), and rarely ulcerations or oral hairy leukoplakia. Gastrointestinal tract involvement is common in HIV-infected children. A variety of pathogens can cause gastrointestinal disease, including bacteria (*Salmonella, Campylobacter,* MAC), protozoa (*Giardia, Cryptosporidium, Isospora,* microsporidia), viruses (CMV, HSV, rotavirus), and fungi *(Candida).* MAC and the protozoal infections are most severe and protracted in patients with severe CD4 cell depletion. Infections may be localized or disseminated and affect any part of the gastrointestinal tract from the oropharynx to the rectum. Oral or esophageal ulcerations, either viral in origin or idiopathic, are painful and often interfere with eating. AIDS enteropathy, a syndrome of malabsorption with partial villous atrophy not associated with a specific pathogen, has been postulated to be a result of direct HIV infection of the gut. Disaccharide intolerance is common in HIV-infected children with chronic diarrhea.

The most common symptoms of gastrointestinal disease are chronic or recurrent diarrhea with malabsorption, abdominal pain, dysphagia, and failure to thrive. Prompt recognition of weight loss or poor growth velocity in the absence of diarrhea is critical. Linear growth impairment often correlates with the level of HIV viremia. Supplemental enteral feedings should be instituted, either by mouth or with nighttime nasogastric tube feedings in cases associated with more severe chronic

growth problems; placement of a gastrostomy tube for nutritional supplementation may be necessary in severe cases. The wasting syndrome, defined as a loss of >10% of body weight, is not as common as failure to thrive in pediatric patients, but the resulting malnutrition is associated with a grave prognosis. Chronic liver inflammation evidenced by fluctuating serum levels of transaminases with or without cholestasis is relatively common, often without identification of an etiologic agent. Cryptosporidial cholecystitis is associated with abdominal pain, jaundice, and elevated γ-glutamyltransferase. In some patients, chronic hepatitis caused by CMV, hepatitis B, hepatitis C, or MAC may lead to portal hypertension and liver failure. Several of the antiretroviral drugs or other drugs such as didanosine, protease inhibitors, nevirapine, and dapsone may also cause reversible elevation of transaminases.

Pancreatitis with increased pancreatic enzymes with or without abdominal pain, vomiting, and fever may be the result of drug therapy (e.g., with pentamidine, didanosine, or lamivudine) or, rarely, opportunistic infections such as MAC or CMV.

Renal Disease

Nephropathy is an unusual presenting symptom of HIV infection, more commonly occurring in older symptomatic children. A direct effect of HIV on renal epithelial cells has been suggested as the cause, but immune complexes, hyperviscosity of the blood (secondary to hyperglobulinemia), and nephrotoxic drugs are other possible factors. A wide range of histologic abnormalities has been reported, including focal glomerulosclerosis, mesangial hyperplasia, segmental necrotizing glomerulonephritis, and minimal change disease. Focal glomerulosclerosis generally progresses to renal failure within 6-12 mo, but other histologic abnormalities in children may remain stable without significant renal insufficiency for prolonged periods. Nephrotic syndrome is the most common manifestation of pediatric renal disease, with edema, hypoalbuminemia, proteinuria, and azotemia with normal blood pressure. Cases resistant to steroid therapy may benefit from cyclosporine therapy. Polyuria, oliguria, and hematuria have also been observed in some patients.

Skin Manifestations

Many cutaneous manifestations seen in HIV-infected children are inflammatory or infectious disorders that are not unique to HIV infection. These disorders tend to be more disseminated and respond less consistently to conventional therapy than in the uninfected child. Seborrheic dermatitis or eczema that is severe and unresponsive to treatment may be an early nonspecific sign of HIV infection. Recurrent or chronic episodes of HSV, herpes zoster, molluscum contagiosum, flat warts, anogenital warts, and candidal infections are common and may be difficult to control.

Allergic drug eruptions are also common, in particular related to nonnucleoside reverse transcription inhibitors, and generally respond to withdrawal of the drug but also may resolve spontaneously without drug interruption: rarely, progression to Stevens-Johnson syndrome has been reported. Epidermal hyperkeratosis with dry, scaling skin is frequently observed, and sparse hair or hair loss may be seen in the later stages of the disease.

Hematologic and Malignant Diseases

Anemia occurs in 20-70% of HIV-infected children, more commonly in children with AIDS. The anemia may be a result of chronic infection, poor nutrition, autoimmune factors, virus-associated conditions (hemophagocytic syndrome, parvovirus B19 red cell aplasia), or the adverse effect of drugs (zidovudine).

Leukopenia occurs in almost 30% of untreated HIV-infected children, and neutropenia often occurs. Multiple drugs used for treatment or prophylaxis for opportunistic infections, such as *Pneumocystis* pneumonia, MAC, and CMV, or antiretroviral drugs (zidovudine) may also cause leukopenia and/or neutropenia. In cases in which therapy cannot be changed, treatment with subcutaneous granulocyte colony-stimulating factor may be necessary.

Thrombocytopenia has been reported in 10-20% of patients. The etiology may be immunologic (i.e., circulating immune complexes or antiplatelet antibodies) or, less commonly, from drug toxicity, or the cause may be unknown. Antiretroviral (ARV) therapy may also reverse thrombocytopenia in ARV-naïve patients. In the event of sustained severe thrombocytopenia (<10,000 platelets/μL), treatment with intravenous immunoglobulin or anti-D offers temporary improvement in most patients already taking ARVs. If ineffective, a course of steroids may be an alternative, but consultation with a hematologist should be sought. Deficiency of clotting factors (factors II, VII, IX) is not rare in children with advanced HIV disease and is often easy to correct with vitamin K. A novel disease of the thymus has been observed in a few HIV-infected children. These patients were found to have characteristic anterior mediastinal multilocular thymic cysts without clinical symptoms. Histologic examination shows focal cystic changes, follicular hyperplasia, and diffuse plasmacytosis and multinucleated giant cells. Treatment with cART may result in resolution, or spontaneous involution occurs in some cases.

In contrast to the more frequent occurrence in adults, malignant diseases have been reported infrequently in HIV-infected children, representing only 2% of AIDS-defining illnesses. Non-Hodgkin lymphoma, primary CNS lymphoma, and leiomyosarcoma are the most commonly reported neoplasms among HIV-infected children. Epstein-Barr virus is associated with most lymphomas and with all leiomyosarcomas (see Chapter 254). Kaposi sarcoma, which is caused by human herpesvirus 8, occurs frequently among HIV-infected adults but is exceedingly uncommon among HIV-infected children in resource-rich countries (see Chapter 257).

DIAGNOSIS

All infants born to HIV-infected mothers test antibody-positive at birth because of passive transfer of maternal HIV antibody across the placenta during gestation. Most uninfected infants without ongoing exposure (i.e., who are not breastfed) lose maternal antibody between 6 and 12 mo of age and are known as **seroreverters.** Because a small proportion of uninfected infants continue to test HIV antibody-positive for up to 18 mo of age, positive IgG antibody tests, including the rapid tests, cannot be used to make a definitive diagnosis of HIV infection in infants younger than this age. The presence of IgA or IgM anti-HIV in the infant's circulation can indicate HIV infection, because these immunoglobulin classes do not cross the placenta; however, IgA and IgM anti-HIV assays have been both insensitive and nonspecific and therefore are not valuable for clinical use. In any child older than 18 mo of age, demonstration of IgG antibody to HIV by a repeatedly reactive enzyme immunoassay and confirmatory Western blot test establishes the diagnosis of HIV infection. Breastfed infants should have antibody testing performed 12 wk following cessation of breastfeeding to identify those who became infected at the end of lactation by the HIV-infected mother. Certain diseases (e.g., syphilis, autoimmune diseases) may cause false-positive or indeterminate results. In such cases specific viral diagnostic tests (see later) have to be done.

Several rapid HIV tests are currently available with sensitivity and specificity better than those of the standard enzyme immunoassay. Many of these tests require only a single step that allows test results to be reported within less than 30 min. Incorporating rapid HIV testing during delivery or immediately after birth is crucial for the care of HIV-exposed newborns whose HIV status was unknown during pregnancy. A positive rapid test has to be confirmed by Western blot testing. However, if 2 different rapid tests (testing different HIV-associated antibodies) are positive, there is no need for further verification with Western blot testing. In infants who are at risk of exposure to HIV-2 infection (e.g., born to an HIV-infected woman from West Africa), a rapid test that can detect both HIV-1 and HIV-2 should be used. However, if the HIV testing is negative or the Western blot test reveals an unusual pattern, further diagnostic tests should be considered. In addition, they should be tested with HIV-2 specific DNA PCR assay.

Viral diagnostic assays, such as HIV DNA or RNA PCR or HIV culture, are considerably more useful in young infants, allowing a definitive diagnosis in most infected infants by 1-6 mo of age (Table 276-3). By 3-4 mo of age, the HIV culture and/or PCR identifies all infected infants. HIV DNA PCR is the preferred virologic assay in

Table 276-3 Laboratory Diagnosis of HIV Infection

TEST	COMMENT
HIV DNA PCR	Preferred test to diagnose HIV-1 subtype B infection in infants and children younger than 18 mo of age; highly sensitive and specific by 2 wk of age and available; performed on peripheral blood mononuclear cells. False negatives can occur in non-B subtype HIV-1 infections
HIV culture	Expensive, not easily available, requires up to 4 wk to do test; not recommended
HIV RNA PCR	Preferred test to identify non-B subtype HIV-1infections. Similar sensitivity and specificity to HIV DNA PCR in infants and children younger than 18 mo of age, but DNA PCR is generally preferred because of greater clinical experience with that assay

PCR, polymerase chain reaction.

Data from American Academy of Pediatrics, Committee of Pediatric AIDS: Diagnosis of HIV-1 infection in children younger than 18 months in the United States, Pediatrics *120:e1547–e1562, 2007.*

developed countries. Almost 40% of infected newborns have positive test results in the 1st 2 days of life, with >90% testing positive by 2 wk of age. Plasma HIV RNA assays, which detect viral replication, are as sensitive as the DNA PCR for early diagnosis. HIV culture has similar sensitivity to HIV DNA PCR but is more technically complex and expensive, and results are often not available for several weeks compared with 2-3 days for PCR. The commercially available HIV-1 assays are not designed for quantification of HIV-2 RNA and thus should not be used to monitor patients with this infection.

Viral diagnostic testing should be performed within the 1st 12-24 hr of life. Almost 40% of HIV-infected children can be identified at this time. It seems that many of these children have a more rapid progression of their disease and deserve more aggressive therapy. Data suggest that if anti-HIV treatment will start at this point, the outcome will be much better. In exposed children with negative virologic testing at 1-2 days of life, additional testing should be done at 1-2 mo of age and at 4-6 mo of age; some also favor testing at age 14 days as almost 90% of the infected infants can be identified and ARV therapy can be initiated earlier. A positive virologic assay (i.e., detection of HIV by PCR, culture, or p24 antigen) suggests HIV infection and should be confirmed by a repeat test on a second specimen as soon as possible. A diagnosis of HIV infection can be made with 2 positive virologic test results obtained from different blood samples.

The perinatal use of ARV prophylaxis (either single drug or combination) to prevent vertical transmission has not affected the predictive value of viral diagnostic testing. In addition, the intensive antiviral combinations (protease inhibitors) in pregnant women do not affect the DNA PCR; however, these combinations may have an effect on the RNA PCR. HIV infection can be reasonably excluded if an infant has had at least 2 negative virologic test results with at least 1 test performed at ≥4 mo of age. In some parts of the world where non–subtype B strains are common (i.e., outside of the United States), interpretation of a negative PCR test result should be done with caution because the assay may not detect the particular subtype (e.g., group O). Close clinical monitoring with serologic testing (by 18 mo of age) or culture (if possible) is recommended. In older infants, 2 or more negative HIV antibody tests performed at least 1 mo apart past 6 mo of age in the absence of hypogammaglobulinemia or clinical evidence of HIV disease can reasonably exclude HIV infection. The infection can be excluded definitively if the same parameters are met when the infant is at least 18 mo of age.

Few surrogate markers (e.g., neopterin, β_2-microglobin) were shown to improve the predictive information of $CD4^+$ T-cell counts. These markers may be useful in places where $CD4^+$ T-cell counts are not available. Neopterin is an early marker of HIV infection and its level rises further as the disease progress to AIDS. β_2-Microglobin, which can be measured both in blood and urine, spikes in the acute phase of the disease, declines during the asymptomatic phase, and rises again as the disease progresses.

TREATMENT

The currently available therapy does not eradicate the virus and cure the patient; instead it suppresses the virus for extended periods of time and changes the course of the disease to a chronic process. Decisions about ARV therapy for pediatric HIV-infected patients are based on the magnitude of viral replication (viral load), CD4 lymphocyte count or percentage, and clinical condition. Because ARV therapy changes as new drugs become available, decisions regarding therapy should be made in consultation with an expert in pediatric HIV infection. Plasma viral load monitoring and measurement of CD4 values have made it possible to implement rational treatment strategies for viral suppression as well as to assess the efficacy of a particular drug combination. The following principles form the basis for ARV treatment: (1) uninterrupted HIV replication causes destruction of the immune system and progression to AIDS; (2) the magnitude of the viral load predicts the rate of disease progression, and the CD4 cell count reflects the risk of opportunistic infections and HIV infection complications; (3) cART, which includes at least 3 drugs with at least 2 different mechanisms of action, should be the initial treatment. Potent combination therapy that suppresses HIV replication to an undetectable level restricts the selection of ARV-resistant mutants; drug-resistant strains are the major factor limiting successful viral suppression and delay of disease progression; (4) the goal of sustainable suppression of HIV replication is best achieved by the simultaneous initiation of combinations of ARV agents to which the patient has not been exposed previously and that are not crossresistant to drugs with which the patient has been treated previously; (5) drug-related interactions and toxicities should be minimal; and (6) adherence to the complex drug regimens is crucial for a successful outcome.

Combination Therapy

As of 2014, 21 ARV drugs were approved by the FDA for use in HIV-infected adults and adolescents and 19 of them (Table 276-4) for the pediatric population (most of them available as liquid, powder, or small tablet/capsules). ARV drugs are categorized by their mechanism of action, such as preventing viral entrance into $CD4^+$ T cells, inhibiting the HIV reverse transcriptase or protease enzymes, or inhibiting integration of the virus into the human DNA. Within the reverse transcriptase inhibitors, a further subdivision can be made: **nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs)** and **nonnucleoside reverse transcriptase inhibitors (NNRTIs)** (see Fig. 276-3). The NRTIs have a similar structure to the building blocks of DNA (e.g., thymidine, cytosine). When incorporated into DNA, they act like chain terminators and block further incorporation of nucleosides, preventing viral DNA synthesis. Among the NRTIs, thymidine analogs (e.g., stavudine, zidovudine [ZDV]) are found in higher concentrations in activated or dividing cells producing >99% of the HIV virions population) and nonthymidine analogs (e.g., didanosine, lamivudine) have more activity in resting cells, which account for <1% of the HIV virions but may serve as a reservoir for HIV. Suppression of replication in both populations is thought to be an important component of long-term viral control. NNRTIs (i.e., nevirapine, efavirenz, etravirine, rilpivirine) act differently than the NRTIs. They attach to the reverse transcriptase and restrict its motility, reducing the activity of the enzyme. The **protease inhibitors** are potent agents that act farther along the viral replicative cycle. They bind to the site where the viral long polypeptides are cut to individual, mature, and functional core proteins that produce the infectious virions before they leave the cell. The virus entry into the cell is a complex process that involves several cellular receptors and fusion. Several drugs have been developed to prevent this process. The **fusion inhibitor,** enfuvirtide, which binds to viral gp41, causes conformational changes that prevent fusion of the virus with the $CD4^+$ cell and entry into the cell. Maraviroc is an example of a selective CCR5 coreceptor antagonist that blocks the attachment of the virus to this chemokine (an essential process in the viral binding and fusion to the

Text continued on p. 1660

Table 276-4 Summary of Antiretroviral Therapies Available in 2014

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Lactic acidosis with hepatic steatosis	
Abacavir (ABC) Ziagen, ABC Tablet: 300 mg Oral solution: 20 mg/mL Trizivir: combination of zidovudine (ZDV), lamivudine, ABC (300, 150, 300 mg) Epzicom: combination of lamivudine, ABC (300, 600 mg)	Children: ≥3 mo to 13 yr: 8 mg/kg bid (maximum dose 300 mg bid) >30 kg: 300 mg bid Children with viral load <40 copies/mm^3:16 mg/kg once daily (max 600 mg) Adolescents >16 yr and adults: 600 mg once daily Trizivir (>40 kg): 1 tablet bid Epzicom (>16 yr of age): 1 tablet bid	Common: nausea, vomiting, anorexia, fever, headache, diarrhea, rash Less common: hypersensitivity, lactic acidosis with hepatic steatosis, pancreatitis, elevated triglycerides, myocardial infarction	Can be given with food Genetic screening for HLAB*5701 is recommended prior to initiation of ABC-containing treatment. If test is positive avoid ABC. Do not restart ABC in patients who had hypersensitivity-like symptoms (e.g., flu-like symptoms)
Didanosine Videx, ddI Powder for oral solution (prepared with solution containing antacid): 10 mg/mL	2 wk to <3 mo: 50 mg/m^2 bid 3-8 mo: 100 mg/m^2 bid >8 mo: 120 mg/m^2 (maximum 200 mg per dose) bid Adolescents (>13 yr) and adults <60 kg: 250 mg once daily >60 kg: 400 mg once daily (to increase adherence) If combined with tenofovir <60 kg–200 mg once daily >60 kg–250 mg once daily	Common: diarrhea, abdominal pain, nausea, vomiting Less common: pancreatitis, peripheral neuropathy, electrolyte abnormalities, lactic acidosis with hepatic steatosis, hepatomegaly, retinal depigmentation	Food decreases bioavailability up to 50%. Take 30 min before or 2 hr after meal. Tablets dissolved in water are stable for 1 hr (4 hr in buffered solution) Drug interactions: antacids/gastric acid antagonists may increase bioavailability; possible decreased absorption of fluoroquinolones, ganciclovir, ketoconazole, itraconazole, dapsone, and some protease inhibitors. Combination with d4T enhances toxicity, also common if combined with tenofovir
Videx EC Capsule, delayed release: 125, 200, 250, 400 mg Generic: 200, 250, 400 mg	Children: not established 20-25 kg: 200 mg once daily 25-60 kg: 250 mg once daily ≥60 kg: 400 mg once daily	Same as for ddI	Same as for ddI
Emtricitabine Emtriva, FTC Capsules: 200 mg Oral solution: 10 mg/mL Truvada: combination FTC, tenofovir disoproxil fumarate (TDF) (200, 300 mg) Atripla: Combination FTC, TDF, efavirenz (EFV) (200, 300, 600 mg) Complera: combination of FTC, TDF, rilpivirine (RPV) (200, 300, 25mg) Stribild: combination of FTC, TDF, elvitegravir (EVG), cobicistat (COBI) (200, 300, 150, 150 mg)	Infants: 0-3 mo: 3 mg/kg once daily Children ≥3 mo to 17 yr: 6 mg/kg (maximum 240 mg) once daily >33 kg, adolescent and adult: 200 mg capsule or 240 mg solution once daily Truvada or Atripla or Complera or Stribild adult dose: 1 tablet once daily	Common: headache, insomnia, diarrhea, nausea, skin discoloration Less common: lactic acidosis with hepatic steatosis, neutropenia	Closely monitor patients with hepatitis B coinfection Can be given without regard to food. Oral solution should be refrigerated if temperature above 25°C (77°F)
Lamivudine Epivir, Epivir HBV, 3TC Tablet: 150 (scored), 300 mg (Epivir) 100 mg (Epivir HBV) Solution: 5 mg/mL (Epivir HBV), 10 mg/mL (Epivir) Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir and Epzicom combination (see abacavir)	Neonates (<30 days): 2 mg/kg bid >1 mo: 4 mg/kg bid (maximum 150 mg bid) ≥30 kg: 150 mg bid or 300 mg once daily Children with VL <40 copies/mL: 8-10 mg/kg qd Combivir, Trizivir (>30 kg): 1 tablet bid Epzicom (>16 yr): 1 tablet qd	Common: headache, nausea Less common: pancreatitis, peripheral neuropathy, lactic acidosis with hepatic steatosis, lipodystrophy	No food restrictions Combination with ZDV may prevent ZDV resistance. Patient should be screened for hepatitis B virus (HBV) and if positive watched for HBV exacerbation when lamivudine is discontinued
Stavudine Zerit, d4T Capsule: 15, 20, 30, 40 mg Solution: 1 mg/mL	Neonates (0-13 days): 0.5 mg/kg bid 14 days to 30 kg: 1 mg/kg bid >30 kg: 30 mg bid	Common: headache, nausea, hyperlipidemia, fat maldistribution Less common: peripheral neuropathy, pancreatitis, lactic acidosis, hepatic steatosis	No food restrictions. Should not be administered with ZDV because of virologic antagonism. Higher incidence of lactic acidosis. Increased toxicity if combined with ddI

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Tenofovir Viread, TDF Tablet: 150, 200, 250, 300 mg Powder: 40 mg per 1 gr powder Truvada: combination of FTC, TDF (200, 300 mg) Atripla: Combination of FTC, TDF, EFV (200, 300, 600 mg) Complera: combination of FTC, TDF, RPV (200, 300, 25 mg) Stribild: combination of FTC, TDF, EVG, COBI (200, 300, 150, 150 mg)	2 to <12 yr: 8 mg/kg qd >12 yr and 35 kg, adolescent >12 yr and 35 kg and adult: 300 mg once daily Truvada, Atripla, Complera, and Stribild (see FTC)	Common: nausea, vomiting, diarrhea Less common: lactic acidosis with hepatic steatosis, hepatomegaly, reduced bone density, renal toxicity	High-fat meal increases absorption; coadministration with ddI may increase ddI toxicity, decrease atazanavir (ATV) levels (therefore boosting ATV with ritonavir is required). ATV and lopinavir (LPV) increase TDF levels and potential toxicity. Screen for HBV before TDF given, as exacerbation of hepatitis may occur when TDF is discontinued
Zidovudine Retrovir, AZT, ZDV Capsule: 100 mg Tablet: 300 mg Syrup: 10 mg/mL Injection: 10 mg/mL Combivir: combination of ZDV, lamivudine (300, 150 mg) Trizivir: Combination of ZDV, lamivudine, ABC (300, 150, 300 mg)	**Prophylaxis:** 0-6 wk: Premature infants: 1.5 mg/kg IV every 12 hr *or* 2 mg/kg orally every 12 hr for 2 wk (for gestational age 30 to 35 wk) or 4 wk (for gestational age <30 wk); then increase to 3 mg/kg every 12 hr to complete 6 wk (if needed) For gestational age >35 wk: 3 mg/kg/dose IV every 12 hr *or* 4 mg/kg orally every 12 hr **Treatment:** 6 wk to 18 yr: 240 mg/m^2 every 12 hr *or* 4 kg to <9 kg: 12 mg/kg bid 9 kg to <30 kg: 9 mg/kg bid >30 kg, adolescent and adult: 200 mg tid or 300 mg bid Combivir *or* Trizivir: 1 tablet bid	Common: bone marrow suppression (e.g., macrocytic anemia, leukopenia), headache, nausea, vomiting, anorexia Less common: liver toxicity, lactic acidosis with hepatic steatosis, myopathy, fat redistribution	No food restrictions Drug interactions: should not be given with d4T or doxorubicin Rifampin may increase metabolism Cimetidine, fluconazole, valproic acid may decrease metabolism Ganciclovir, IFN-α, ribavirin increase ZDV toxicity
NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS		Class adverse effects: Rash is mild to severe, usually within 1st 6 wk. Discontinue the drug if severe rash (with blistering, desquamation, muscle involvement, or fever)	
Efavirenz Sustiva, EFV Capsule: 50, 200 mg Tablet: 600 mg Atripla combination of EFV, FTC, TDF (600, 200, 300 mg)	Children <3 yr: consult with expert Children ≥3 yr: 10 to <15 kg: 200 mg qd 15 to <20 kg: 250 mg qd 20 to <25 kg: 300 mg qd 25 to <32.5 kg: 350 mg qd 32.5 to <40 kg: 400 mg qd ≥40 kg: 600 mg qd or 370 mg/m^2 body surface area Atripla (see FTC)	Common: skin rashes, CNS abnormalities (e.g., abnormal dreams, impaired concentration, insomnia, depression, hallucination) Less common: increased liver enzymes; potentially teratogenic	Capsules can be opened for mixing in food. Can be given without regard to food except fatty foods (because absorption is increased 50%) Drug interactions: Efavirenz induces/inhibits CYP3A4 enzymes. Increase clearance of drugs metabolized by this pathway (e.g., antihistamines, sedatives and hypnotics, cisapride, ergot derivatives, warfarin, ethinyl estradiol) and several other ARVs (i.e., protease inhibitors). Drugs that induce CYP3A4 (e.g., phenobarbital, rifampin, rifabutin) decrease efavirenz levels. Clarithromycin levels decrease with EFV and azithromycin should be considered
Etravirine (ETR), Intelence, ETR, tablet: 25, 100, 200 mg	Children <6 yr: consult with expert 16 to <20 kg: 100 mg bid 20 to <25 kg: 125 mg bid 25 to <30 kg: 150 mg bid >30 kg, adolescent and adult: 200 mg bid	Common: nausea, rash, diarrhea Less common: hypersensitivity reactions	Given only with food. Tablets can be dispensed in water Inducer of CYP3A4 enzymes and inhibitor of CYP2C9 and CYP2C19, causing multiple interactions that should be checked before initiating ETR. Should not be given in combination with TPV, Fos-APV, ATZ, or other nonnucleoside reverse transcriptase inhibitors

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Nevirapine Viramune, NVP Tablet: 200 mg Extended-release (XR) tablet: 100, 400 mg Suspension: 10 mg/mL	**Prophylaxis:** For infant of woman with no antepartum ARV treatment: 2 mg/kg birth to 48 hr 2 mg/kg 48 hr after 1st dose 2 mg/kg 96 hr after 2nd dose **Treatment:** <8 yr: 200 mg/m^2 once daily for 14 days; then same dose bid (maximum 200 mg per dose) or XR 400 mg qd >8 yr: 120-150 mg/m^2 once daily for 14 days; then bid (maximum 200 mg per dose) Adolescent and adult: 200 mg once daily for 14 days; then 200 mg bid *or* XR 400 mg qd	Common: skin rash, headache, fever, nausea, abnormal liver function tests Less common: hepatotoxicity (rarely life-threatening), hypersensitivity reactions	No food restrictions Drug interactions: induces hepatic CYP450A enzymes (including CYP3A and CYP2B6) activity and decreases protease inhibitor concentrations (e.g., IND, SQV, LPV). Should not be given with ATV. Reduces ketoconazole concentrations (fluconazole should be used as an alternative). Rifampin decreases nevirapine serum levels. Anticonvulsants and psychotropic drugs using same metabolic pathways as NVP should be monitored. Oral contraceptives may also be affected
Rilpivirine Edurant, RPV Tablet: 25 mg Complera combination of RPV, FTC, TDF (25, 200, 300 mg)	Pediatrics: consult with expert Adolescent (>18 yr) and adult: 25 mg	Headache, insomnia, rash, depression, mood changes	Given with food only Should not be used if viral load >100,000 copies/mm^3 or drugs that induce CYP3A or with proton pump inhibitors
PROTEASE INHIBITORS		Class adverse effects: hyperglycemia, hyperlipidemia (except atazanavir), lipodystrophy, increased transaminases, increased bleeding disorders in hemophiliacs. Can induce metabolism of ethinyl estradiol; use alternate contraception (other than estrogen-containing oral contraceptives). All undergo hepatic metabolism, mostly by CYP3A4, with many drug interactions	
Atazanavir Reyataz, ATV Capsules: 100, 150, 200, 300 mg	<6 yr: consult with expert 6-18 yr: 15 to <20 kg: 150 mg + 100 RTV qd 20 to 40 kg: 200 mg + 100 RTV qd >40 kg, adolescent and adult: 300 mg + 100 RTV qd *or* 400 mg if unboosted with food If given with EFV (600 mg) or TDF (300 mg): 400 mg + 100 RTV qd	Common: elevation of indirect bilirubin; headache, arthralgia, depression, insomnia, nausea, vomiting, diarrhea, paresthesias Less common: prolongation of PR interval on electrocardiogram (ECG); rash, rarely Stevens-Johnson syndrome, diabetes mellitus, nephrolithiasis	Administer with food to increase absorption. Review drug interactions before initiating because ATV inhibits CYP3A4, CYP1A2,CYP2C9, and UGT1A1 enzymes. Use with caution with cardiac conduction disease or liver impairment. Combination with EFV should not be used in treatment-experienced patients because it decreases ATV levels. TDF, antacids, H_2-receptor antagonists, and proton-pump inhibitors decreases ATV concentrations. Patients taking buffered ddI should take it at least 2 hr before ATV
Darunavir Prezista, DRV Tablets: 75, 150, 400, 600, 800 mg Suspension: 100 mg/mL	<3 yr: consult with expert 3 to <18 yr: 10 to <15 kg: 20 mg/kg DRV + 3 mg/kg RTV 15 to <30 kg: 375 mg DRV + 50 mg RTV bid 30 to <40 kg: 450 DRV mg + 100 mg RTV bid >40 kg, adolescent and adult: 600 mg DRV + 100 mg RTV bid *or* Adolescent (>12 yr and 40 kg) and adult: 800 mg DRV + 100 mg RTV qd with food If any DRV resistance is found: 600 mg DRV = 100 mg RTV bid	Common: diarrhea, nausea, vomiting, abdominal pain, fatigue, headache Less common: skin rashes (including Stevens-Johnson syndrome), lipid and liver enzyme elevations, hyperglycemia, fat maldistribution	DRV should not be given without food. Contraindicated for concurrent therapy with cisapride, ergot alkaloids, benzodiazepines, pimozide, or any major CYP3A4 substrates. Use with caution in patients taking strong CYP3A4 inhibitors, or moderate/strong CYP3A4 inducers. Adjust dose with concurrent rifamycin therapy. Contains sulfa moiety: potential for cross-sensitivity with sulfonamide class

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Fosamprenavir Lexiva, FPV Tablets: 700 mg Suspension: 50 mg/mL	6 mo to 18 yr: <11 kg: 45 mg/kg FPV + 7 mg/kg RTV bid 11 to <15 kg: 30 mg/kg + 3 mg/kg RTV bid 15 to <20 kg: 23 mg/kg + 3 mg/kg RTV bid >20 kg: 18 mg/kg (max 700 mg) + 3 mg/kg (max: 100 mg) RTV bid Adolescent >18 yr and adult: FPV 700 mg + RTV 100 mg bid *or* FPV 1,400 mg + RTV 200 mg qd For protease inhibitor (PI)-experienced, the once daily dose is not recommended	Common: nausea, vomiting, perioral paresthesias, headache, rash, lipid abnormalities Less common: Stevens-Johnson syndrome, fat redistribution, neutropenia, elevated creatine kinase, hyperglycemia, diabetes mellitus, elevated liver enzymes, angioedema, nephrolithiasis	Should be given with food. FPV is an inhibitor of the CYP450 system and an inducer, inhibitor, and substrate of CYP3A4, which can cause multiple drug interactions. Use with caution in sulfa-allergic individuals
Indinavir Crixivan, IDV Capsule: 100, 200, 400 mg	Infants: not approved Children: 500 mg/m^2 every 8 hr (max dose: 800 mg per dose) *or* 400 mg/m^2 + RTV 100 mg/m^2 bid Adolescent and adult: 800 mg IDV + 100 *or* 200 mg RTV bid	Common: nausea, abdominal pain, hyperbilirubinemia, headache, dizziness, lipid abnormalities, nephrolithiasis, metallic taste Less common: fat redistribution, hyperglycemia, diabetes mellitus, hepatitis, acute hemolytic anemia	Administer on empty stomach if given without RTV. Reduce dose (600 mg IDV every 8 hr) with mild to moderate liver dysfunction. Adequate hydration (at least 48 oz fluid/day in adults) necessary to minimize risk of nephrolithiasis. IDV is cytochrome P450 3A4 inhibitor and substrate, which can cause multiple drug interactions: rifampin reduces levels; ketoconazole, ritonavir, and other protease inhibitors increase IDV levels. Do not coadminister with EFV, astemizole cisapride, terfenadine
Lopinavir/Ritonavir Kaletra, LPV/r Tablets: 100/25 mg, 200/50 mg Solution: 80/20 mg per/mL (contains 42% alcohol)	14 days to 18 yr: 300 mg/m^2 LPV +75 mg/m^2 RTV bid Adolescent (>18 yr) and adult: 400 mg LPV +100 mg RTV bid *or* 800 mg LPV +200 mg RTV qd If taken with NVP, EFV, FPV, or NFV: LPV 600 mg + RTV 150 mg bid	Common: diarrhea, headache, nausea and vomiting, lipid elevation Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation	No food restrictions. High-fat meal and flavoring of solution to increase palpability are recommended if oral solution is used. Interacts with drugs using CYP3A4, which can cause multiple drug interactions
Nelfinavir Viracept, NFV Tablet: 250, 625 mg	<2 yr: not recommended Children 2-13 yr: 45-55 mg/kg bid Adolescents and adults: 1,250 mg bid	Common: diarrhea asthenia, abdominal pain, skin rashes, lipid abnormalities Less common: exacerbation of liver disease, fat redistribution, hyperglycemia, diabetes mellitus, elevation of liver enzymes	Administer with a meal to optimize absorption; avoid acidic food or drink (e.g., orange juice). Tablet can be crushed or dissolved in water to administer as a solution Drug interactions: Nelfinavir inhibits CYP3A4 activity, which may cause multiple drug interactions. Rifampin, phenobarbital, and carbamazepine reduce levels. Ketoconazole, ritonavir, indinavir, and other protease inhibitors increase levels. Do not coadminister astemizole, cisapride, terfenadine. RTV boosting has no effect. Because of very high variation in plasma levels, TDM should be used for dose adjustment

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
Ritonavir Norvir, RTV Capsule: 100 mg Tablet: 100 mg Solution: 80 mg/mL (contains 43% alcohol)	Only use is to enhance other PIs; dose varies (see information for specific PI)	Common: nausea, headache, vomiting, abdominal pain, diarrhea, taste aversion, lipid abnormalities, perioral paresthesias Less common: fat redistribution, hyperglycemia, diabetes mellitus, pancreatitis, hepatitis, PR interval prolongation, allergic reactions	Administration with food enhances bioavailability and reduces gastrointestinal symptoms. RTV solution should not be refrigerated RTV is potent inhibitor of CYP3A4 and CYP2D6 and inducer of CYP3A4 and CYP1A2 that leads to many drug interactions (e.g., protease inhibitors, antiarrhythmics, antidepressants, cisapride). Use cautiously with inhaled steroids
Saquinavir Invirase, SQV Hard gel: 200 mg Film-coated tablets: 500 mg	Infants and children <2 yr: not established SQV must be boosted with RTV >2 yr: 5 to <15 kg: 50 mg/kg + 3 mg/kg RTV bid 15-40 kg: 50 mg/kg + 2.5 mg/kg RTV bid >40: 50 mg/kg + 100 RTV bid Adolescent and adult: SQV 1,000 mg + 100 mg RTV bid	Common: diarrhea, abdominal pain, headache, nausea, skin rashes, lipid abnormalities Less common: exacerbation of chronic liver disease, diabetes mellitus, pancreatitis, elevated liver transaminases, fat maldistribution, increase in both QT and PR in ECG	Administration with a high-fat meal to enhance bioavailability. Use only in combination with ritonavir boosting dose. SQV is metabolized by CYP3A4, which may cause many drug interactions): rifampin, phenobarbital, and carbamazepine decrease serum levels. Saquinavir may decrease metabolism of calcium channel antagonists, azoles (e.g., ketoconazole), macrolides
Tipranavir Aptivus, TPV Capsule: 250 mg Solution 100 mg/mL (contains 116 IU vitamin E/mL)	<2 yr: not established. 2-18 yr: 375 mg/m^2 TPV + 150 mg/m^2 RTV (maximum 500 mg TPV + 200 mg RTV) bid *or* 14 mg TPV + 6 mg RTV per kg (maximum-same) bid Adolescent (>18 yr) and adult: 500 mg TPV +200 mg RTV bid	Common: diarrhea, nausea, vomiting, fatigue, headache, skin rashes, elevated liver enzymes, lipid abnormalities Less common: fat redistribution, hepatitis, hyperglycemia, diabetes mellitus, intracranial hemorrhage	No food restrictions. Better tolerated with meal. TPV must be boosted with RTV. Can inhibit human platelet aggregation: use with caution in patients at risk for increased bleeding (trauma, surgery, etc.) or in patients receiving concurrent medications that may increase the risk of bleeding. TPV is metabolized by CYP3A4, which may cause many drug interactions. Contraindicated in patients with hepatic insufficiency or receiving concurrent therapy with amiodarone, cisapride, ergot alkaloids, benzodiazepines, pimozide. TPV contains sulfonamide moiety and caution should be taken in patients with sulfonamide allergy
FUSION INHIBITORS			
Enfuvirtide Fuzeon, ENF Injection: lyophilized powder of 108 mg reconstituted in 1.1 mL of sterile water delivers 90 mg/mL	<6 yr: not established Children >6 yr to 16 yr: 2 mg/kg SQ (maximum 90 mg) bid Adolescent and adult: 90 mg SQ bid	Common: Local injection site reactions in 98% (e.g., erythema, induration nodules, cysts, ecchymoses) Less common: increased incidence of bacterial pneumonia, hypersensitivity, fever, nausea, vomiting, chills, elevated liver enzymes, hypotension, immune-mediated reactions (e.g., glomerulonephritis, Guillain-Barré syndrome, respiratory distress)	Must be given subcutaneously. Severity of reactions increased if given intramuscularly. Apply ice after injection and massage the area to reduce local reactions. Injection sites should be rotated

Continued

Table 276-4 Summary of Antiretroviral Therapies Available in 2014—cont'd

DRUG (TRADE NAMES, FORMULATIONS)	DOSING	SIDE EFFECTS	COMMENTS
ENTRY INHIBITORS			
Maraviroc Selzentry, MVC Tablets: 150, 300 mg	Not approved for children or adolescents <16 yr Adolescents >16 yr and adults: 150 mg bid if given with potent CYP3A inhibitor (e.g., protease inhibitor except TPV) 300 mg bid if given with not potent CYP3A4 inhibitors (e.g., NRTI, TPV, NVP, ENF, RAL) 600 mg bid if given with potent CYP3A4 inducer (e.g., EFV, ETR, rifampin, phenobarbital)	Common: fever, upper respiratory infection–like symptoms, rash, abdominal pain, musculoskeletal symptoms, dizziness Less common: cardiovascular abnormalities, cholestatic jaundice, rhabdomyolysis, myositis, osteonecrosis	No food restrictions. MVC is a CYP3A4 and P-glycoprotein (Pgp) substrate, which may cause many drug interactions Tropism assay to exclude the presence of CXCR4 HIV is required before using MVC. Caution should be used when given to patients with hepatic impairment or cardiac disease or receiving CYP3A4 or Pgp modulating drugs
INTEGRASE INHIBITORS			
Dalutegravir Tivicay, DTG Tablet: 50 mg	Children <12 yr: consult with expert >12 yr and 40 kg, adolescents, and adults: 50 mg qd If taken with EFV, FPV, TPV, or rifampin: 50 mg bid	Insomnia Headache	No food restrictions UGT1A1 and CYP450 (CYP) 3A substrate Should be taken 2 hr before or 6 hr after taking laxatives, sucralfate, iron or calcium supplements, or buffered medications
Elvitegravir EVG Only as Stribild combination of EVG, FTC, TDF, cobicistat (COBI) (150, 200, 300, 150 mg)	Children and adolescents (<18 yr): not established Adolescent (>18 yr) and adult: 1 tablet qd	Common: nausea, diarrhea Less common: increased serum creatinine, urea, and phosphate, decreased bone density; lactic acidosis, hepatomegaly with stenosis	Administer with food EVG is metabolized by CYP3A4 and modestly induces CYP2D6 that can cause multiple drug interactions. Cautiously use with nephrotoxic drugs. Stribild should not be used with ritonavir
Raltegravir Isentress, RAL Film-coated tablet: 400 mg Chewable tablet: 25, 100 mg Solution: 20 mg/ml	Oral solution: 3 to <4 kg: 20 mg bid 4 to <6 kg: 30 mg bid 6 to <8 kg: 40 mg bid 8 to <11 kg: 60 mg bid 11 to <14 kg: 80 mg bid 14 to <20 kg: 100 mg bid Chewable tablet: 10 to <14 kg: 75 mg bid 14 to <20 kg: 100 mg bid 20 to <28 kg: 150 mg bid 28 to <40 kg: 200 mg bid Adolescent (>12 yr) and adult: 400 mg bid	Common: nausea, headache, dizziness, diarrhea, fatigue Less common: abdominal pain, vomiting, itching, creatine phosphokinase elevation, myopathy, rhabdomyolysis, depression, hypersensitivity	No food restrictions Film-coated tablet and chewable tablet are not interchangeable RAL is metabolized by UGT1A1 glucuronidation, and inducers of this system (e.g., rifampin, TPV) will reduce RGV levels, whereas inhibitors (e.g., ATV) will increase it

Antiretroviral drugs often have significant drug–drug interactions, with each other and with other classes of medicines, which should be reviewed before initiating any new medication.

The information in this table is not all-inclusive. Updated and additional information on dosing, drug–drug interactions, and toxicities is available on the AIDSinfo website at http://www.aidsinfo.nih.gov

Modified from the Guidelines for use of antiretroviral agents in pediatric HIV infection. *http://aidsinfo.nih.gov/contentFiles/PediatricGuidelines.pdf*

$CD4^+$ cells). **Integrase inhibitors** like raltegravir block the enzyme that catalyzes the incorporation of the viral genome into the host's DNA.

While the principal site of viral replication is lymphoid tissue, sanctuary sites such as the CNS may harbor residual virions with the potential to be a source of local or persistent disease. Impaired penetration of drugs to these compartments could result in development of resistance. Although data on CNS penetration of antiviral agents are presently limited, ZDV, stavudine, and lamivudine appear to achieve inhibitory concentrations in the CNS. Nevirapine and efavirenz also penetrate the cerebrospinal fluid, but protease inhibitors are actively transported out of the CNS, thereby limiting their potential efficacy at this site.

By targeting different points in the viral life cycle and stages of cell activation and by delivering drug to all tissue sites, maximal viral suppression may be feasible. Combinations of 3 drugs, a thymidine analog NRTI (abacavir or ZDV) and a nonthymidine analog NRTI (lamivudine) to suppress replication in both active and resting cells and a protease inhibitor (atazanavir or lopinavir/ritonavir) or an NNRTI (efavirenz) produce prolonged viral suppression. Less-potent combinations, such as triple NRTIs (abacavir, zidovudine, lamivudine), may be considered in special situations (e.g., children <3 yr with concomitant tuberculosis when nevirapine-based cART is unacceptable or in rare cases when there are concerns about significant drug interactions or adherence to a complex drug regimen). The use of 3 drugs from 3 different classes should be avoided as it has the potential to cause resistance to 3 drug classes. Combination treatment increases the rate of toxicities (see Table 276-4), and complex drug–drug interactions exist among many of the antiretroviral drugs. Many protease inhibitor drugs are inducers or inhibitors of the cytochrome P450 system and are therefore likely to have serious interactions with multiple drug classes, including nonsedating antihistamines and psychotropic, vasoconstrictor, antimycobacterial, cardiovascular, analgesic, and gastrointestinal drugs (cisapride). Whenever new medications are added

to an antiretroviral treatment regimen, especially a protease inhibitor–containing regimen, a pharmacist and/or HIV specialist should be consulted to address possible drug interactions. The inhibitory effect of ritonavir (a protease inhibitor) on the cytochrome P450 system has been exploited, and small doses of the drug are added to several other protease inhibitors (e.g., lopinavir, tipranavir, atazanavir, darunavir) to slow their metabolism by the P450 system and to improve their pharmacokinetic profile. This strategy provides more effective drug levels with less toxicity and less-frequent dosing. Recently, the development of cobicistat provides an alternative to ritonavir. Although cobicistat is a potent inhibitor of cytochrome P450 3A, it is a weak inhibitor of CYP2D6 and other CYP isoforms (e.g., CYP1A2), making pharmacologic interactions with many drugs more predictable than for ritonavir, which is also active against these isoforms. Preliminary studies with cobicistat suggest that it has a good tolerability profile and less effect on adipocytes (resulting in milder accumulation of lipid and response to insulin). The better solubility of cobicistat compared to ritonavir may foster the availability of more single-tablet combination regimens with cobicistat.

Adherence

Adherence to the medication schedules and dosages is fundamental to ARV therapy success. Therefore, assessment of the likelihood of adherence to treatment is an important factor in deciding whether and when to initiate therapy. Numerous studies show that compliance of <90% results in less-successful suppression of the viral load. In addition, several studies document that almost half of the pediatric patients surveyed were nonadherent to their regimen. Poor adherence to prescribed medication regimens results in subtherapeutic drug concentrations and enhances development of resistance. Several barriers to adherence are unique to children with HIV infection. Combination antiretroviral regimens are often unpalatable and require extreme dedication on the part of the caregiver and child; a reluctance to disclose the child's disease to others reduces social support; there may be a tendency to skip doses if the caregiver is not around or when the child is in school. Adolescents have other issues that reduce adherence. Denial and/or fear of their infection, unstructured lifestyle, conduct or emotional disorder, wishing to be the same as their peers, depression, fatigue from taking a lifelong regimen, anxiety, and alcohol and substance abuse are just a few of the barriers for a long-term adherence in this growing population. These and other barriers make participation of the family in the decision to initiate therapy essential. Intensive education on the relationship of drug adherence to viral suppression, training on drug administration, frequent follow-up visits, peer support, pager messaging, and commitment of the caregiver and the patient (despite the inconvenience of adverse effects, dosing schedule) are critical for successful antiviral treatment. Multiple methods such as viral load response, self-reporting of missed doses during the last 3-7 days, and pharmacy/pill counting or monitoring drugs' concentrations in the blood should be used to assess adherence.

Initiation of Therapy

The decision on when to initiate cART is controversial and keeps evolving. Even the recent adult guidelines that recommend initiation of cART in individuals with CD4 cell counts <500 cells/μL acknowledges that treatment of individuals with higher CD4 cell counts may be beneficial. Therefore, the following recommendations for pediatric patients are only accurate for the time they were written (August 2014), and physicians providing care to few HIV-exposed or infected children should periodically consult physicians with expertise in pediatric HIV infection as well as the U.S. pediatric guidelines for treatment of HIV-infected children found at http://aidsinfo.nih.gov.

Children younger than 1 yr of age are at high risk for disease progression, and immunologic and virologic tests to identify those likely to develop rapidly progressive disease are less predictive than in older children. Therefore, HIV-infected infants younger than 1 yr of age should be treated with ARV agents as soon as the diagnosis of HIV infection has been confirmed, regardless of clinical or immunologic status or viral load. Data suggest that HIV-infected infants who are treated before the age of 3 mo control their HIV infection better than infants whose ARV therapy started later than 3 mo of age. Some of these infants even become HIV seronegative and lose their HIV specific immune response.

There is still a debate on when to start therapy in children older than 1 yr of age. The 2014 U.S. Pediatric Guidelines Panel recommends, with varying strength of the recommendations, treating all children ≥1 year of age with Stage 3 CD4 counts, significant clinical symptoms, or HIV RNA >100,000 copies/mL. Children 1-<6 years of age should be treated with CD4 counts between 500-999 cells/mm^3, and treatment should be considered if the child has minimal/no symptoms and a CD4 count ≥1000 cells/mm^3. Children ≥6 years of age should be treated with CD4 counts between 200-499 cells/mm^3, and treatment should be considered if the child has minimal/no symptoms and a CD4 count ≥500 cells/mm^3. These guidelines are reviewed yearly, and care providers should check for revisions at http://aidsinfo.nih.gov. Some clinicians advocate treating all HIV-infected children regardless of their clinical stage, viral load, or CD4$^+$ T-cell status to prevent the inevitable immunologic deterioration that will otherwise occur.

Dosing

Children are usually treated with higher doses (per kg weight) than adults because of reduced absorption or increased elimination. Data on ARV drug dosages for neonates, especially premature infants, are often limited. Because of the immaturity of the neonatal liver, there must often be an increase in the dosing interval of drugs primarily cleared through hepatic glucuronidation. In addition, drug absorption from the gastrointestinal tract may be problematic. Therefore, monitoring of drugs plasma levels should be considered, if available.

Adolescents should have ARV dosages prescribed on the basis of Tanner staging of puberty rather than on the basis of age. Pediatric dosing ranges should be used during early puberty (Tanner stages I, II, and III), whereas adult dosing schedules should be followed in adolescents in late puberty (Tanner stages IV and V). Efavirenz should be avoided in females who may become pregnant and do not use effective contraception because of its potential teratogenicity. Because some protease inhibitors may change the metabolism of oral contraceptives and decrease their effectiveness, monthly injections of medroxyprogesterone (DMPA) or use of an intrauterine device should be considered, or the protease inhibitor can be changed, if needed, to an integrase inhibitor, which has no interaction with estrogen-based contraceptives.

Changing Antiretroviral Therapy

Therapy should be changed when the current regimen is judged ineffective as evidenced by increase in viral load, deterioration of the CD4 cell count, or clinical progression. Development of toxicity or intolerance to drugs is another reason to consider a change in therapy. When a change is considered, the patient and family should be reassessed for adherence problems. Because adherence is a major issue in this population, resistance testing (while on ARV medications) is important in identifying adherence issues (e.g., detectable virus sensitive to current drugs will suggest lack of adherence) or development of resistance (e.g., evidence of resistance mutations to given drugs). In both situations, other contributing factors such as poor absorption, incorrect dose, or drug–drug interactions should be carefully reviewed. While considering possible new drug choices, potential cross-resistance should be addressed. In addition, few patients who have virologic failure may still demonstrate improved CD4 cell counts (discordant response). Impaired replication ability of the resistant virus (also called reduced viral fitness) and enhanced CTL effects are some of the reasons for this discordant response. In these patients, delay in changing therapy should be considered as long as the immunologic benefit is evident. Ideally, when a decision is made to change the ARV therapy, all drugs should be changed. However, in many situations (previous ARV experience, intolerance, toxicity) this is not possible, thus at least 2 drugs should be changed based on the resistance mutation genotype or phenotype (if available) or evaluation of the drugs used in the previous regimen.

Monitoring Antiretroviral Therapy

To ensure proper monitoring, the CD4 cells count, viral load, complete blood count, chemistries, urinalysis, and serum lipids should be done before initiation or change in cART to have a baseline for comparisons while on treatment. Children need to be seen within 1-2 wk after initiation of new ARV therapy to ensure compliance and to screen for potential side effects. Virologic and immunologic surveillance (using HIV RNA copy number and CD4 lymphocyte count or percentage) as well as clinical assessment should be performed regularly during ARV therapy. Initial virologic response (i.e., at least a 5-fold [0.7 $\log_{10}$] reduction in viral load) should be achieved within 4-8 wk of initiating antiretroviral therapy. The maximum response to therapy usually occurs within 12-16 wk, but may be later (24 wk) in very young infants. Thus, HIV RNA levels should be measured at 4 wk and 3-4 mo after therapy initiation. Once an optimal response has occurred, viral load should then be measured at least every 3-6 mo. If the response is unsatisfactory, another viral load should be performed as soon as possible to verify the results before a change in therapy is considered. The CD4 cells respond more slowly to successful treatment and, therefore, can be monitored less frequently. Potential toxicity should be monitored closely for the 1st 8-12 wk (including complete blood count, serum chemistries, urinalysis, and lipids), and if no clinical or laboratory toxicity is documented, a follow-up visit every 3-4 mo is adequate. Monitoring for potential toxicity should be tailored to the drugs taken. These toxicities include but are not limited to hematologic complications (e.g., ZDV); hypersensitivity rash (e.g., efaviranz); lipodystrophy (e.g., redistribution of body fat seen with NRTIs, protease inhibitors); hyperlipidemia (elevation of cholesterol and triglyceride concentrations); hyperglycemia, and insulin resistance (e.g., protease inhibitors); mitochondrial toxicity leading to severe lactic acidosis (e.g., stavudine, didanosine); electrocardiogram abnormalities (e.g., atazanavir, lopinavir); abnormal bone mineral metabolism (e.g., tenofovir); and hepatic toxicity, including severe hepatomegaly with steatosis.

Resistance to Antiretroviral Therapy

Young children usually are at greater risk than adults for developing resistance because they have higher viral loads than adults and are more limited by which ARV options are available. The high mutation rate of HIV (mainly as a result of the absence of error-correcting mechanisms) severely impairs the success of ARV therapy. Failure to reduce the viral load to <40 copies/mL increases the risk for developing resistance. Even effectively treated patients do not completely suppress viral replication, and persistence of HIV transcription and evolution of envelope sequences continues in the latent cellular reservoirs. The accumulation of resistance mutations progressively diminishes the potency of the ARV therapy and challenges the physician to find new regimens. For some drugs (e.g., nevirapine, lamivudine) a single mutation is associated with resistance, whereas for other drugs (e.g., ZDV, lopinavir) several mutations are needed before resistance develops. Testing for drug resistance, especially when devising a new regimen, is becoming the standard of care. Two types of tests are available: (1) The **phenotypic assay** measures the virus susceptibility in various concentrations of the drug that allows calculation of the drug concentration that inhibits viral replication by 50% (IC_{50}). The ratio of the IC_{50} and a reference virus IC_{50} is reported as fold resistance change. (2) The **genotypic assay** predicts the virus susceptibility from mutations identified in the HIV genome isolated from the patient. Several online sites (e.g., http://hivdb.stanford.edu) can assist in interpreting the test's results. Several studies show that treatment success is higher in patients whose ARV therapy was guided by genotype or phenotype testing. Neither method may detect drug resistance if the amount of the resistant virus is <10% of the circulating population or if it is present only in the latent reservoir.

It is recommended to test for drug resistance before initiating therapy and before changing treatment because of failure. When changing therapy, the resistance test results should be considered in the context of previous resistance tests results, if done, and drugs used in previous regimens.

Supportive Care

Even before ARV drugs were available, a significant impact on the quality of life and survival of HIV-infected children was achieved when supportive care was given. A multidisciplinary team approach is desirable for successful management. Following initiation or change of cART, more frequent visits or contacts with the patient/caregivers for support and education will help in their acceptance and adjustment to the new regimen and will contribute to a better adherence. Close attention should be paid to nutritional status, which is often delicately balanced and may require aggressive supplementation. Painful oropharyngeal lesions and dental caries may interfere with eating, and thus routine dental evaluations and careful attention to oral hygiene should be encouraged. Paradoxically, an increasing number of adolescents with perinatally acquired or behavioral risk-acquired disease are obese. Some teens experience ARV-related central lipo-accumulation, but others have poor dietary habits and inactivity as the cause of their obesity, in parallel to epidemic obesity in the United States. Development should be evaluated regularly with provision of necessary physical, occupational, and/or speech therapy. Recognition of pain in the young child may be difficult, and effective nonpharmacologic and pharmacologic protocols for pain management should be instituted.

All infants born to HIV-infected mothers should receive ZDV prophylaxis for 4-6 wk. Additional ARV therapy should be considered if the risk of acquiring HIV by the newborn is high. For example, if the mother has not received cART during pregnancy, 3 doses of nevirapine (at birth, 48 hr, and 144 hr of life) should be added. If the mother's HIV status is unknown, rapid HIV-testing of either the mother or the newborn should be done immediately after delivery and if positive, ARV prophylaxis should be started as soon as possible without waiting for the confirmatory test results. Guidelines for prophylaxis in newborns are updated at least yearly and can be accessed at http://www.aidsinfo.nih.gov. A complete blood count, differential leukocyte count, and platelet count should be performed at 4 wk of age to monitor ZDV toxicity. These tests should be continued every 1-3 mo to assess the hematologic effect of ZDV and prophylactic trimethoprim-sulfamethoxazole (TMP-SMZ), if given. If the child is found to be HIV infected, baseline laboratory assessment (e.g., CD4 count, HIV RNA, complete blood count, chemistries) should be done and cART should be started as soon as possible. Viral load and CD4 lymphocyte counts should be performed at 1 and 3 mo of age and should be repeated every 3 mo. All HIV-exposed and infected children should receive standard pediatric immunizations. In general, live oral polio vaccine should not be given (Fig. 276-4). The risk and benefits of rotavirus vaccination should be considered in infants born to HIV-infected mothers. Because <1% of these infants in resource-rich countries will develop HIV infection, the vaccine should be given. In other situations, the considerable attenuation of the vaccine's strains should be taken into account and unless the infant has clinical symptoms of AIDS or CD4 <15%, vaccination seems to be appropriate. Other live bacterial vaccines (e.g., bacillus Calmette-Guérin) should be avoided because of the high incidence of bacillus Calmette-Guérin–related disease in HIV-infected infants. Varicella and measles-mumps-rubella vaccines are recommended for children who are not severely immunosuppressed (i.e., CD4 cell percentage ≥15%), but these vaccines should not be given to severely immunocompromised children (i.e., CD4 cell <15%). Of note, prior immunizations do not always provide protection, as evidenced by outbreaks of measles and pertussis in immunized HIV-infected children. Durability of vaccine-induced titers is often short, especially if vaccines are administered when the child's CD4 cell is <15%, and re-immunization when the CD4 count has increased (i.e., >15%) may be indicated.

Prophylactic regimens are integral for the care of HIV-infected children. All infants between 4-6 wk and 1 yr of age who are proven to be HIV-infected should receive prophylaxis to prevent *P. carinii* (also called *P. jiroveci*) infection regardless of the CD4 count or percentage (Tables 276-5 and 276-6). Infants exposed to HIV-infected mothers should receive the same prophylaxis until they are proven to be noninfected; however, prophylaxis does not have to be initiated if there is strong presumptive evidence of noninfection (i.e., non–breastfed

Vaccine	Birth	1 mo	2 mo	4 mo	6 mo	12 mo	15 mo	18 mo	24 mo	4-6 yr	11-12 yr	14-16 yr
Hepatitis B	Hep B	Hep B			Hep B							
Measles, Mumps, Rubella*						MMR†	MMR†					
Influenza					Influenza‡							
Pneumococcal Conjugate and Hemophilus b			PCV Hib	PCV Hib	PCV Hib	PCV Hib					Pneumococcal§	
Diphtheria, Tetanus, Pertussis			DTap	DTap	DTap		DTap					
Polio (inactivated)			Polio	Polio	Polio							
Varicella						Varicella						
Hepatitis A						Hep A{}						
Rotavirus*			RV¶	RV	RV							

* See text.
† Contraindicated in children with AIDS or CD4+ <15%. Give 2 doses 1-3 mo apart.
‡ Revaccination is recommended every year. Attenuated vaccine can be used >2 yr of age only if CD4+ >15%.
§ Revaccination with pneumococcal polysaccharide vaccine (PPV) every 5 yr.
{} Two doses at least 6 mo apart.
¶ First dose 6 through 14 wk of age and final dose no later than 8 mo 0 days of age. If using Rotarix, only 2 doses (2 and 4 mo) are needed.

Figure 276-4 Routine childhood immunization schedule for HIV-infected children.

Table 276-5 Recommendations for PCP Prophylaxis and CD4 Monitoring for HIV-Exposed Infants and HIV-Infected Children, by Age and HIV Infection Status

AGE/HIV INFECTION STATUS	PCP PROPHYLAXIS	CD4 MONITORING
Birth to 4-6 wk, HIV exposed	No prophylaxis	None
HIV infection reasonably excluded*	No prophylaxis	None
<1 yr, HIV-infected or indeterminate	Prophylaxis regardless of CD4 count or percentage	According to local practice for initiation or follow-up of cART
1-5 yr, HIV infected	Prophylaxis if: CD4 <500 cells/μL or <15%†	According to local practice for initiation or follow-up of cART
>6 yr, HIV infected	Prophylaxis if: CD4 <200 cells/μL or <15%†‡	According to local practice for initiation or follow-up of cART

The National Perinatal HIV Hotline (1-888-448-8765) provides consultation on all aspects of perinatal HIV care.
*See text.
†More frequent monitoring (e.g., monthly) is recommended for children whose CD4 counts or percentages are approaching the threshold at which prophylaxis is recommended.
‡Prophylaxis should be considered on a case-by-case basis for children who might otherwise be at risk for PCP, such as children with rapidly declining CD4 counts or percentages or children with category C conditions. Children who have had PCP should receive PCP prophylaxis until their CD4 count is >20% (for >6 yr of age) or >25% (for 2-5 yr of age) on continuous cART.
cART, combined antiretroviral therapy; PCP, *Pneumocystis carinii* (also called *P. jirovecii*) pneumonia.

infant with 2 negative HIV PCR tests at older than 14 days and 4 wk of age, respectively). When the HIV-infected child is older than 1 yr of age, prophylaxis should be given according to the CD4 lymphocyte count (Table 276-5). The best prophylactic regimen is 150 mg/m^2/day of TMP and 750 mg/m^2/day of SMZ (maximum: 320/1,600 mg) given as 1-2 daily doses 3 days (consecutively or every other day) per wk. For severe adverse reactions to TMP-SMZ, alternative therapies include dapsone, atovaquone, and aerosolized pentamidine.

Prophylaxis against MAC should be offered to HIV-infected children with advanced immunosuppression (i.e., CD4 lymphocyte count <750 cells/μL in children younger than 1 yr of age, <500 cells/μL in children 1-2 yr of age, <75 cells/μL in children 2-5 yr of age, and <50 cells/μL in children >6 yr of age) (see Table 276-6). The drugs of choice are azithromycin (20 mg/kg [maximum: 1,200 mg] once a week PO or 5 mg/kg [maximum: 250 mg] once daily PO) or clarithromycin (7.5 mg/kg bid PO). In rare situations, rifabutin 300 mg qd can be an alternative for children older than 6 yr of age.

Based on adult data, primary prophylaxis against opportunistic infections may be discontinued if patients have experienced sustained (>6 mo duration) immune reconstitution with cART, even if they had previous opportunistic infections such as *Pneumocystis* pneumonia or disseminated MAC. HIV-infected children are at higher risk for TB and thus should have tuberculin skin testing (5 tuberculin units purified protein derivation) for TB at least once per year; an induration of 5 mm or more should be considered positive. If the child is living in close contact with a person with TB, the child should be tested more frequently. Of note, the sensitivity of purified protein derivation is reduced in severely immunocompromised patients and other laboratory tests should be used. For example, assays that determine IFN-γ release from lymphocytes following stimulation by specific *Mycobacterium tuberculosis* antigens were found to be more specific than the skin testing in adults. Limited data suggest that they are less sensitive in diagnosing TB in children, and therefore caution should be used in interpreting negative results of such tests in children. The "Guidelines for Prevention and Treatment of

Table 276-6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States*

PATHOGEN	Preventive Regimen: INDICATION	FIRST CHOICE	ALTERNATIVE
STRONGLY RECOMMENDED AS STANDARD OF CARE			
Pneumocystis pneumonia†	HIV-infected or HIV-indeterminate infants aged 1-12 mo; HIV-infected children aged 1-5 yr with CD4 count of <500 cells/μL or CD4 percentage of <15%; HIV-infected children aged 6-12 yr with CD4 count of <200 cells/μL or CD4 percentage of <15%	**TMP-SMX**, 150/750 mg/m^2 body surface area per day (max: 320/1600 mg) orally qd or bid 3 times weekly on consecutive days *or* qd or bid orally 3 times weekly on alternate days	**Dapsone**: age ≥1 mo: 2 mg/kg (max: 100 mg) orally qd; *or* 4 mg/kg (max: 200 mg) orally once a week **Atovaquone**: age 1-3 mo and >24 mo: 30 mg/kg orally qd; age 4-24 mo: 45 mg/kg orally qd **Aerosolized pentamidine**: age ≥5 yr: 300 mg once a month by Respirgard II (Marquest, Englewood, CO) nebulizer **Doxycycline** age >8 yr: 2.2 mg/kg qd
Malaria	Living or traveling to area in which malaria is endemic	Same for HIV-infected and HIV-uninfected children. Refer to http://www.cdc.gov/malaria/ for the most recent recommendations. **Mefloquine**, 5 mg/kg orally 1 time weekly (max: 250 mg) **Atovaquone/proguanil** (Malarone) qd 11-20 kg: 62.5 mg/25 mg (1 pediatric tablet) 21-30 kg: 2 pediatric tablets 31-40 kg: 3 pediatric tablets >40 kg: 1 adult tablet (250 mg/100 mg)	**Doxycycline**, 100 mg orally qd for children >8 yr **Chloroquine**, 5 mg/kg base (equal 7.5 mg/kg chloroquine phosphate) orally up to 300 mg weekly (only for regions where the parasite is sensitive)
Mycobacterium tuberculosis			
Isoniazid-sensitive	TST reaction ≥5 mm *or* Prior positive TST result without treatment *or* Close contact with any person who has contagious TB. TB disease must be excluded before start of treatment	**Isoniazid**, 10-15 mg/kg body weight (max: 300 mg) qd for 9 mo *or* 20-30 mg/kg body weight (max: 900 mg) orally 2 times weekly for 9 mo	**Rifampin**, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant TB	**Rifampin**, 10-20 mg/kg body weight (max: 600 mg) orally daily for 4-6 mo	Uncertain
Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant TB	Choice of drugs requires consultation with public health authorities and depends on susceptibility of isolate from source patient	
Mycobacterium avium complex‡	For children age ≥6 yr with CD4 count of <50 cells/μL; age 2-5 yr with CD4 count of <75 cells/μL; age 1-2 yr with CD4 count of <500 cells/μL; age <1 yr with CD4 count of <750 cells/μL	**Clarithromycin**, 7.5 mg/kg (max: 500 mg) orally bid *or* **Azithromycin**, 20 mg/kg (max: 1,200 mg) orally once a week	**Azithromycin**, 5 mg/kg body weight (max: 250 mg) orally qd *or* Children age ≥6 yr *or* **Rifabutin**, 300 mg orally qd
Varicella-zoster virus§	Exposure to varicella or shingles with no history of varicella *or* Zoster or seronegative status for VZV *or* Lack of evidence for age-appropriate vaccination	Varicella-zoster immunoglobulin (VariZIG), 125 IU per 10 kg (max: 625 IU) IM, administered within 96 hr after exposure‖	If VariZIG is not available and <96 hr from exposures, **acyclovir** 20 mg/kg (max: 800 mg) 4 times a day for 5-7 days *or* IVIG, 400 mg/kg, administered once
Vaccine-preventable pathogens	Standard recommendations for HIV-exposed and HIV-infected children	Routine vaccinations (see Fig. 276-3)	

Table 276-6 Prophylaxis to Prevent First Episode of Opportunistic Infections Among HIV-Exposed and HIV-Infected Infants and Children, United States—cont'd

PATHOGEN	Preventive Regimen		
	INDICATION	FIRST CHOICE	ALTERNATIVE
USUALLY RECOMMENDED			
Toxoplasma gondii¶	Seropositive IgG to *Toxoplasma* and severe immunosuppression: age <6 yr with CD4 <15%; age ≥6 yr with CD4 <100 cells/μL	TMP-SMZ, 150/750 mg/m^2 orally bid *or* Same dosage qd 3 times weekly on consecutive days *or* bid 3 times weekly on alternate days	**Dapsone,** age ≥1 mo: 2 mg/kg or 15 mg/m^2 (max: 25 mg) orally qd *plus* **Pyrimethamine,** 1 mg/kg (max: 25 mg) orally qd *plus* **Leucovorin,** 5 mg orally twice a week *or* **Atovaquone,** age 1-3 mo and >24 mo, 30 mg/kg orally qd; children age 4-24 mo, 45 mg/kg orally qd with or without **pyrimethamine,** 1 mg/kg (or 15 mg/m^2) (max: 25 mg) qd *plus* **Leucovorin,** 5 mg orally twice a week (3 days apart)
Invasive bacterial infections	Hypogammaglobulinemia (i.e., IgG <400 mg/dL)	IVIG 400 mg/kg body weight every 2-4 wk	
Cytomegalovirus	CMV antibody positivity and severe immunosuppression (CD4 <50 cells/μL)	**Valganciclovir,** 900 mg orally qd with food for older children who can receive adult dosing	

*Information in these guidelines might not represent FDA approval or FDA-approved labeling for products or indications. Specifically, the terms "safe" and "effective" might not be synonymous with the FDA-defined legal standards for product approval.

†Daily trimethoprim-sulfamethoxazole (TMP-SMZ) reduces the frequency of certain bacterial infections. Compared with weekly dapsone, daily dapsone is associated with lower incidence of PCP but higher hematologic toxicity and mortality. Patients receiving therapy for toxoplasmosis with sulfadiazine-pyrimethamine are protected against PCP and do not need TMP-SMZ. TMP-SMZ, dapsone-pyrimethamine, and possibly atovaquone (with or without pyrimethamine) protect against toxoplasmosis; however, data have not been prospectively collected.

‡Substantial drug interactions can occur between rifamycins (i.e., rifampin and rifabutin) and protease inhibitors and nonnucleoside reverse transcriptase inhibitors. A specialist should be consulted.

§Children routinely being administered intravenous immunoglobulin (IVIG) should receive VariZIG if the last dose of IVIG was administered more than 21 days before exposure.

‖As of 2007, VariZIG can be obtained only under a treatment Investigational New Drug protocol (1-800-843-7477, FFF Enterprises, Temecula, CA).

¶Protection against toxoplasmosis is provided by the preferred anti-*Pneumocystis* regimens and possibly by atovaquone.

CMV, cytomegalovirus; FDA, U.S. Food and Drug Administration; HIV, human immunodeficiency virus IgG, immunoglobulin G; IM, intramuscularly; IVIG, intravenous immunoglobulin; PCP, *Pneumocystis* pneumonia; TMP-SMZ, trimethoprim-sulfamethoxazole; TB, tuberculosis; TST, tuberculin skin test;; VZV, varicella-zoster virus.

From Centers for Disease Control and Prevention (CDC): Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children, MMWR Recomm Rep *58(RR-11):127–128, 2009, Table 1.*

Opportunistic Infections Among HIV-Exposed and HIV-Infected Children" (http://aidsinfo.nih.gov) should be consulted for these and other opportunistic infections that may occur in these populations. To reduce the incidence of opportunistic infections, parents should be counseled about (1) the importance of good hand washing, (2) avoiding raw or undercooked food *(Salmonella)*, (3) avoiding drinking or swimming in lake or river water or being in contact with young farm animals *(Cryptosporidium)*, and (4) the risk of playing with pets (*Toxoplasma* and *Bartonella* from cats, *Salmonella* from reptiles).

PROGNOSIS

The improved understanding of the pathogenesis of HIV infection in children and the availability of more effective antiretroviral drugs has changed the prognosis considerably. The earlier cART is started, the better the prognosis; a clinical trial aims to start treatment as close to delivery as possible will test the possibility of curing perinatally infected newborns. In settings with ready access to early diagnosis and antiretroviral therapy, progression of the disease to AIDS has significantly diminished. Since the advent of cART in the mid-1990s, mortality in perinatally infected children has declined more than 90% and many of the children survive to adolescence and adulthood. Even with only partial reduction of viral load, children may have both significant immunologic and clinical benefits. In general, the best prognostic indicators are the sustained suppression of plasma viral load and restoration of a normal CD4$^+$ lymphocyte count. If determinations of viral load and CD4 lymphocytes are available, the results can be used to evaluate prognosis. It is unusual to see rapid progression in an infant with a viral load <100,000 copies/mL. In contrast, a high viral load (>100,000 copies/mL) over time is associated with greater risk for disease progression and death. CD4 lymphocyte percentage is another prognostic indicator, and the mortality rate is higher in patients with a CD4 lymphocyte percentage <15%. To define prognosis more accurately, the use of changes in both markers (CD4 lymphocyte percentage and plasma viral load) is recommended.

Even in resource-limited countries where ARV therapy and molecular diagnostic tests are less available, the use of cART had a substantial benefit on the survival of HIV-infected children and reduced the hazard of mortality by 75%. Children with opportunistic infections (e.g., *Pneumocystis* pneumonia, MAC), encephalopathy and regressing developmental milestones, or wasting syndrome have the worst prognosis, with 75% dying before 3 yr of age. A higher risk of mortality was documented in children who did not receive TMP-SMZ preventive therapy. Persistent fever and/or oral thrush, serious bacterial infections (meningitis, pneumonia, sepsis), hepatitis, persistent anemia (<8 g/dL), and/or thrombocytopenia (<100,000/μL) also suggest a poor outcome, with >30% of such children dying before 3 yr of age. In contrast, lymphadenopathy, splenomegaly, hepatomegaly, lymphoid interstitial pneumonitis, and parotitis are indicators of a better prognosis.

PREVENTION

Use of antiretroviral therapy for interruption of perinatal transmission from mother-to-child has been one of the greatest achievements of HIV research. Maternal cART is documented to decrease the rate of

perinatal HIV-1 transmission to <2%, and <1% if the mother's viral RNA level is <1,000 copies/mL at delivery. Therefore, it is recommended that **all** pregnant women be tested for HIV and if positive, treated with a cART regimen, irrespective of viral load or CD4 count during pregnancy. This should be in conjunction with 4-6 wk of ZDV prophylaxis for the infant and with collaboration between the HIV-specialist and the obstetrician. Cesarean section (C-section) as a prevention strategy was examined in a multinational meta-analysis, which showed that the combination of elective C-section and maternal ZDV treatment reduced transmission by 87%. However, these data were obtained prior to the advent of cART, and the additional benefit of elective C-section to the cART-treated mother whose viral load is <1,000 copies/mL is negligible. Thus, elective C-section at 38 wk of gestation should be considered only for women whose viral load is >1,000 copies/mL in late gestation, to further reduce the risk of vertical transmission.

A multinational randomized, controlled trial in non-breastfed neonates whose mothers received no ARVs during pregnancy showed that prophylaxis with a two- or three-drug ARV regimen is superior to ZDV alone for the prevention of intrapartum HIV transmission. Based on these data, the U.S. Guidelines Panel recommends that infants born to HIV-infected women who have received no antepartum or only intrapartum ARVs, or who have HIV RNA >1000 copies/mL near delivery, should receive prophylaxis with ZDV for 6 wk combined with three doses of NVP in the 1st wk of life (i.e., at birth, 48 hr later, and 96 hr after the second dose), begun as soon after birth as possible (see Table 276-4).

The WHO recommends that all pregnant women receive a cART regimen appropriate for their own health, which should be continued at least throughout breastfeeding (in resource-limited areas) and for the remainder of their lives. This approach has the potential to reduce transmission during breastfeeding and future pregnancies, lowers the transmission risk to sexual partners, improves maternal survival, and promotes simplified universal treatment regimens. Breastfed infants should receive NVP for 6 wk if the mother is receiving cART, or NVP for the duration of breastfeeding if the mother is not on therapy. Formula-fed infants in resource-limited countries should receive ZDV bid or NVP qd for 6 wk.

Although the most effective way to prevent postpartum transmission of HIV is to eliminate breastfeeding altogether and substitute replacement feeding, there is evidence that early weaning may not be safe in resource-limited settings because of the high risk of malnutrition and diarrhea in formula-fed infants without a consistent source of clean water. Furthermore, exclusive breastfeeding (no additional solids or fluids other than water) results in less transmission than mixed feeding. Guidelines have evolved to recommend that HIV-infected mothers living in resource-limited settings should breastfeed their infants until at least 12 mo of age, with exclusive breastfeeding for the 1st 6 mo, and ARVs should continue to be provided, either to the mother or to the infant, at least until 1 wk after all breastfeeding has ceased. In settings where there are safe alternatives to breastfeeding, formula feeding is recommended. U.S. guidelines for prevention of mother-to-child transmission are regularly updated at http://aidsinfo.nih.gov/ and the international guidelines are regularly updated at the WHO website (http://www.who.int/hiv/topics/mtct/en/).

Now that it is clear that perinatal transmission can be reduced dramatically by treating pregnant mothers, a compelling argument can be made for prenatal identification of HIV-1 infection in the mother. The benefit of therapy both for the mother's health and to prevent transmission to the infant cannot be overemphasized. The recommended universal prenatal HIV-1 counseling and HIV-1 testing for all pregnant women has reduced the number of new infections dramatically in many areas of the United States and Europe. For women not tested during pregnancy, the use of rapid HIV antibody testing during labor or on the 1st day of the infant's life is a way to provide perinatal prophylaxis to an additional group of at-risk infants.

Prevention of sexual transmission involves avoiding the exchange of bodily fluids. In sexually active adolescents, condoms should be an integral part of programs to reduce sexually transmitted diseases, including HIV-1. Unprotected sex with older partners or with multiple partners and use of recreational drugs is common among HIV-1–infected adolescents, increasing their risk. Educational efforts about avoidance of risk factors are essential for older school-age children and adolescents and should begin before the onset of sexual activity. In addition, promising research for sexually active adults may translate to increased prevention for adolescents. Three African trials demonstrated that male circumcision was associated with a 50-60% reduction in risk of HIV acquisition in young men. For women, use of a 1% vaginal gel formulation of tenofovir during intercourse was found to reduce HIV acquisition by nearly 40%. Other topical microbicides are being investigated. A double-blind study of preexposure prophylaxis in MSM using once daily dosing of coformulated tenofovir and emtricitabine resulted in a 44% reduction in the incidence of HIV (95% confidence interval, 15-63; P = 0.005). Of interest, the incidence of HIV transmission was reduced by 73% when participants took the drug on 90% or more days. In addition, a large randomized multinational clinical trial of HIV serodiscordant adults demonstrated that effective ARV therapy in the HIV-infected partner reduced secondary transmission to an uninfected sexual partner by 96%. However, none of the studies that have shown promise for prevention in at-risk populations has included adequate representation in youth, making it difficult to interpret the effect on this population.

Despite prolonged suppression of viremia, it is obvious that cART may not fully restore health and may be associated with long-term toxicity. In addition, adherence is a major challenge and constrained resources will limit the ability to expand cART to all patients who need it. However, recent discoveries of new antiretroviral drugs, new vaccines, and advances in our understanding of HIV latency are encouraging developments on the long road to a cure.

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Chapter 277

Human T-Lymphotropic Viruses (1 and 2)

Hal B. Jenson

ETIOLOGY

Human T-lymphotropic viruses 1 (HTLV-1) and 2 (HTLV-2) are members of the *Deltaretrovirus* genus of the Retroviridae family, which are single-stranded RNA viruses that encode reverse transcriptase, an RNA-dependent DNA polymerase that transcribes the single-stranded viral RNA into a double-stranded DNA copy. HTLV-1 was the first human retrovirus to be associated with cancer, as the cause of adult T-cell leukemia/lymphoma (ATL).

HTLV-1 and -2 share a genome homology of approximately 65% and infect T cells, B cells, and synovial cells via the ubiquitous glucose transporter type 1, which serves as the virus receptor. The genome contains *gag, pol,* and *env* genes and the pX region, which encodes nonstructural proteins. The nonstructural proteins include the Tax and Rex regulatory proteins, the novel proteins essential for virus spread (p30, p12, and p13), and the antisense-encoded HTLV-1 basic leucine zipper factor. Circular viral DNA is transported into the nucleus where it is integrated into chromosomal DNA (provirus), evading the typical mechanisms of immune surveillance and facilitating lifelong infection. The host response is mediated by cytotoxic T lymphocytes, resulting in lysis of infected cells. An exuberant inflammatory response with overproduction of cytokines contributes to developing nonmalignant disease.

EPIDEMIOLOGY

HTLV-1 infects 15-20 million persons globally. It is endemic in southwestern Japan (where >10% of adults are seropositive), areas of the

Caribbean, including Jamaica and Trinidad (up to 6%), and in parts of sub-Saharan Africa (up to 5%). Lower seroprevalence rates are found in South America (up to 2%) and Taiwan (0.1-1%). There is microclustering with marked variability within geographic regions.

The seroprevalence of HTLV-1 and HTLV-2 in the United States in the general population is 0.01-0.03% for each virus, with higher rates with increasing age. The prevalence of HTLV-1 infection is highest in babies born in endemic areas or in persons who have had sexual contact with persons from endemic areas. The prevalence of HTLV-2 infection correlates with intravenous illicit drug use. A prevalence of approximately 18% was found in a study of illicit drug users in the United States, often with concomitant HIV infection.

HTLV-1 and -2 are transmitted as cell-associated viruses by **vertical transmission** from mother to child and **horizontal transmission** through genital secretions, contaminated blood products, and intravenous illicit drug use. Higher maternal HTLV-1 proviral load may be associated with greater risk of vertical transmission, which occurs primarily via breastfeeding from infected mothers with a 3-fold increased risk of transmission with breastfeeding for longer than 6 mo. Intrauterine and intrapartum transmissions account for <5% of vertical transmissions. In Japan, approximately 20-25% of children born to infected mothers become infected, and more than 90% of HTLV-1–infected children have HTLV-1–infected mothers. HTLV-2 may also be transmitted via breastfeeding, but it has a slightly lower reported transmission rate via breast milk of approximately 14%.

DIAGNOSIS

HTLV-1 and HTLV-2 infections are diagnosed by screening using 2nd-generation enzyme immunoassay with confirmation by immunoblot, indirect immunofluorescence, or line immunoassays. Polymerase chain reaction can also be used to distinguish HTLV-1 from HTLV-2 infection.

CLINICAL MANIFESTATIONS

The lifetime risk of disease associated with HTLV-1 infection is estimated at 5-10% and is highest following vertical transmission. HTLV-1 is associated with ATL and several nonmalignant conditions, including the neurodegenerative disorder HTLV-1–associated myelopathy (HAM), also known as tropical spastic paraparesis and sometimes termed HAM/tropical spastic paraparesis. The geographic epidemiologic characteristics of ATL and HAM are similar. **HTLV-1–associated arthropathy** mimics rheumatoid arthritis, including a positive rheumatoid factor. Treatment is with antiinflammatory agents. **HTLV-1–associated uveitis** may be unilateral or bilateral, is more common among women, and resolves spontaneously, although it often recurs within 1-3 yr. Topical corticosteroids hasten recovery. **HTLV-1–associated infective dermatitis** is a chronic and recurrent eczematous disease occurring during childhood and adolescence. HTLV-1 infection predisposes to disseminated and recurrent *Strongyloides stercoralis* infection, increased risk of developing tuberculosis disease following latent infection, and severe scabies.

Adult T-Cell Leukemia/Lymphoma

The age distribution of ATL peaks at approximately 50 yr, underscoring the long latent period of HTLV-1 infection. HTLV-1–infected persons remain at risk for ATL even if they move to an area of low HTLV-1 prevalence, with a lifetime risk for ATL of 2-4%. Most cases of ATL are associated with monoclonal integration of HTLV-1 provirus into the cellular genome of CD4 lymphocytes, resulting in unchecked proliferation of CD4 T cells. There is a spectrum of disease that is categorized into different forms: acute, lymphomatous, chronic, primary cutaneous smoldering, and primary cutaneous tumoral. The acute form of ATL comprises 55-75% of all cases. Smoldering, subclinical lymphoproliferation may spontaneously resolve, in approximately half of cases, or progress to chronic leukemia or lymphomatous or even acute ATL. **Chronic, low-grade, HTLV-1–associated lymphoproliferation (pre-ATL)** may persist for years with abnormal lymphocytes with or without peripheral lymphadenopathy before progressing to the acute form. Acute ATL is characterized by hypercalcemia, lytic bone lesions, lymphadenopathy that spares the mediastinum, hepatomegaly, splenomegaly, cutaneous lymphomas, and opportunistic infections. Leukemia may develop with circulating polylobulated malignant lymphocytes, called **flower cells**, possessing mature T-cell markers. Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) is often the initial therapy for ATL, although chemotherapy is not curative and relapses are common. The median survival after diagnosis is 6-13 mo.

Human T-Cell Lymphotropic Virus-1–Associated Myelopathy

HAM is more common in women than in men and has a relatively short incubation period after HTLV-1 infection, of 1-4 yr compared with 40-60 yr for ATL. HAM occurs in up to 4% of persons with HTLV-1 infection, usually developing during middle age. It is characterized by infiltration of mononuclear cells into the gray and white matter of the thoracic spinal cord, leading to severe white matter degeneration and fibrosis. HTLV-1 is found near but not directly within the lesions, suggesting that reactive inflammation is a major mechanism of disease. The cerebrospinal fluid typically shows a mildly elevated protein and a modest monocytic pleocytosis, along with anti–HTLV-1 antibodies. Neuroimaging studies are normal or show periventricular lesions in the white matter. Clinical manifestations include gradual onset of slowly progressive, symmetric neurologic degeneration of the corticospinal tracts and, to a lesser extent, the sensory system that leads to lower-extremity spasticity or weakness, lower back pain, and hyperreflexia of the lower extremities with an extensor plantar response. The bladder and intestines may become dysfunctional, and men may become impotent. Some patients develop dysesthesias of the lower extremities with diminished sensation to vibration and pain. Upper-extremity function and sensation, cranial nerves, and cognitive function are usually preserved. Treatment regimens have included corticosteroids, danazol, interferon, plasmapheresis, high-dose vitamin C, and antivirals, all with minimal effects.

Human T-Cell Lymphotropic Virus-2

HTLV-2 was originally identified in patients with hairy cell leukemia, although most patients with hairy cell leukemia are seronegative for HTLV-2 infection. HTLV-2 has been rarely isolated from patients with leukemias or with myelopathies resembling HAM, and there is limited evidence of disease specifically associated with HTLV-2 infection.

PREVENTION

Routine antibody testing of all blood products using HTLV-1 viral lysate began in the United States in 1988 and missed 30-58% of HTLV-2 infections. Combination HTLV-1/2 antibody testing was implemented in 1997. Formula feeding in lieu of breastfeeding of infants of HTLV-1–infected mothers is an effective means of controlling endemic HTLV-1 transmission. No vaccine is available.

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Chapter 278

Transmissible Spongiform Encephalopathies

David M. Asher

The transmissible spongiform encephalopathies (TSEs) are slow infections of the human nervous system, consisting of at least 4 diseases of humans (Table 278-1): kuru; Creutzfeldt-Jakob disease (CJD) with its variants—sporadic CJD (sCJD), familial CJD (fCJD), iatrogenic CJD (iCJD), and new-variant or variant CJD (vCJD); Gerstmann-Sträussler-Scheinker syndrome (GSS); and fatal familial insomnia (FFI), or the even more rare sporadic fatal insomnia syndrome. TSEs also affect

Table 278-1 Clinical and Epidemiologic Features of Human Transmissible Spongiform Encephalopathies (Prion Diseases)

DISEASE	CLINICAL FEATURES	SOURCE OF INFECTION	GEOGRAPHIC DISTRIBUTION AND PREVALENCE	USEFUL ANCILLARY TESTS	DURATION OF ILLNESS
sCJD	Dementia, myoclonus, ataxia	Unknown	Worldwide; ≈1/1 million/yr; 85-95% of all CJD cases in U.S.	EEG—PSWCs; CSF 14-3-3; MRI/DWI	1-24 mo (mean: 4-6 mo)
fCJD	Dementia, myoclonus, ataxia	Genetic association (*PRNP* mutations) ?? Possible exogenous source of infection	Worldwide—geographic clusters; >100 known families; 5-15% of CJD cases	Gene testing; EEG—PSWC rare; MRI/DWI (?)	Mean ≈15 mo
iCJD	Incoordination, dementia (late)	Cadaver dural grafts, human pituitary hormones, corneal transplantation, neurosurgical instruments, EEG depth electrodes	≈1% of CJD cases in toto (cadaver dural grafts), >100 cases (human pituitary hormones), >100 cases; corneal transplantation 3 cases; neurosurgical instruments, 6 cases, including 2 from cortical depth electrodes; RBC transfusions, 4 cases of vCJD infection, 3 clinical, 1 preclinical (U.K.); human plasma–derived factor VIII, 1 preclinical case of vCJD (U.K.)		1 mo-10 yr
vCJD	Mood and behavioral abnormalities, paresthesias, dementia	Linked to BSE in cattle, transfusion plasma products	>220 clinical cases (see iatrogenic vCJD above)	Tonsil biopsy may show PrP^{TSE} MRI/FLAIR	8-36 mo (mean 14 mo)
Kuru	Incoordination, ataxia, tremors, dementia (late)	Linked to cannibalism	Fore people of Papua New Guinea (≈2,600 known cases)	EEG—no PSWCs; CSF 14-3-3 often negative; MRI (?)	3-24 mo
GSS	Incoordination, chronic progressive ataxia, corticospinal tract signs, dementia (late), myoclonus (rare)	90% genetic (*PRNP* mutations)	Worldwide; >50 families; ≈1-10/100 million/yr	*PRNP* gene sequencing	2-12 yr (mean ≈ 57 mo)
FFI	Disrupted sleep, intractable insomnia; autonomic hyperactivation; myoclonus, ataxia; corticospinal tract signs; dementia	*PRNP* gene mutation (D 178L); very rare sporadic cases	≈27 families in Europe, U.K., U.S., Finland, Australia, China, Japan	EEG—PSWCs only rarely positive; MRI—no DWI abnormalities; CSF 14-3-3 positive in ≈ 50%	8 mo–6 yr (mean: *PRNP* 129 MM 12 ± 4 mo 129 MV 21 ± 15 mo)

BSE, bovine spongiform encephalopathy; CSF, cerebrospinal fluid; CJD, Creutzfeldt-Jakob disease; DWI, diffusion-weighted image; EEG, electroencephalography; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FLAIR, fluid attenuation inversion recovery MRI; GSS, Gerstmann-Sträussler-Scheinker syndrome; iCJD, iatrogenic Creutzfeldt-Jakob disease; *PRNP*, prion protein encoding gene; PrP^{TSE}, abnormal prion protein; PSWCs, periodic sharp wave complexes; RBC, red blood cell; sCJD, sporadic Creutzfeldt-Jakob disease; vCJD, variant Creutzfeldt-Jakob disease.

NOTE: PRNP 129 MM, homozygous, encoding the amino acid methionine at both codons 129 of the prion-protein-encoding (PRNP) gene on chromosome 20; 129 MV, heterozygous at PRNP codon 129, encoding methionine on one chromosome 20 and valine on the other.

Modified from Mandell GL, Bennett JE, Dolin R, editors: Principles and practice of infectious diseases, *vol 2, ed 6, Philadelphia, 2005, Elsevier, p. 2222; Love S, Louis DN, Ellison DW, editors:* Greenfield's neuropathology, *vol 2, ed 8, London, 2008, Hodder Arnold, p. 1239.*

animals; the most common and best-known TSEs of animals are scrapie in sheep, bovine spongiform encephalopathy (BSE or mad cow disease) in cattle, and a chronic wasting disease (CWD) of deer, elk, and moose found in parts of the United States and Canada. All TSEs have similar clinical manifestations and histopathology, and all are "slow" infections with very long asymptomatic incubation periods (often years), durations of several months or more, and overt disease affecting only the nervous system. TSEs are relentlessly progressive after illness begins and invariably fatal. The most striking neuropathologic change that occurs in each TSE, to a greater or lesser extent, is spongy degeneration of the cerebral cortical gray matter.

ETIOLOGY

The TSEs are transmissible to susceptible animals by inoculation of tissues from affected subjects. Although the infectious agents replicate in some cell cultures, they do not achieve the high titers of infectivity found in brain tissues or cause recognizable cytopathic effects in cultures. Most studies of TSE agents have used in vivo assays, relying on the transmission of typical neurologic disease to animals as evidence that the agent was present and intact. Inoculation of susceptible recipient animals with small amounts of infectious TSE agent results, months later, in the accumulation in tissues of large amounts of agent with the same physical and biologic properties as the original agent. The TSE agents display a spectrum of extreme resistance to inactivation by a variety of chemical and physical treatments that is unknown among conventional pathogens. This characteristic, as well as their partial sensitivity to protein-disrupting treatments and their consistent association with abnormal isoforms of a normal host-encoded protein (prion protein or PrP), stimulated the hypothesis that the TSE agents are probably subviral in size, composed of protein, and devoid of nucleic acid.

The term **prion** (for proteinaceous infectious agent) is now widely used for such agents. The prion hypothesis proposes that the molecular mechanism by which the pathogen-specific information of TSE agents is propagated involves a self-replicating change in the folding host-encoded PrP associated with a transition from an α-helix–rich structure in the native protease-sensitive conformation (cellular PrP or

PrP^C) to a β-sheet–rich structure in the protease-resistant conformation associated with infectivity. The existence of a second host-encoded protein—termed "protein X"—that participates in the transformation was also postulated to explain certain otherwise puzzling findings but never identified.

The prion hypothesis is still not universally accepted; it relies on the postulated existence of a genome-like coding mechanism based on differences in protein folding that have not been satisfactorily explained at a molecular level. In addition, it has yet to account convincingly for the many biologic strains of TSE agent that have been observed, although strain-specific differences in the abnormal forms of the PrP have been found and proposed as providing a plausible molecular basis for the coding. It fails to explain why pure PrP uncontaminated with nucleic acid from an infected host has not transmitted a convincingly typical spongiform encephalopathy associated with a serially self-propagating agent. Also troubling, in several experimental models and human illnesses, abnormal PrP and infectivity were not consistently associated. Particularly problematic is the finding that some illnesses associated with mutations in the *PRNP* gene and accompanied by abnormal PrP failed to transmit infection to animals. If the TSE agents ultimately prove to consist of protein and only protein, without any obligatory nucleic acid component, then the term *prion* will indeed be appropriate and the early proponents of the prion hypothesis will prove to have been prescient. If the agents are ultimately found to contain small nucleic acid genomes, then they might better be considered atypical viruses, for which the term *virino* has been suggested. Until the actual molecular structure of the infectious TSE pathogens and the presence or absence of a nucleic acid genome are rigorously established, it seems less contentious to continue calling them TSE agents, although many authorities now use the term *prion* (sometimes referring to the agent of a TSE and sometimes to the abnormal protein, even when nontransmissible).

The earliest evidence that abnormal proteins are associated with the TSE was morphologic: scrapie-associated fibrils were found in extracts of tissues from patients and animals with spongiform encephalopathies but not in normal tissues. Scrapie-associated fibrils resemble but are distinguishable from the amyloid fibrils that accumulate in the brains of patients with Alzheimer disease. A group of antigenically related protease-resistant proteins (PrPs) proved to be components of scrapie-associated fibril and to be present in the amyloid plaques found in the brains of patients and animals with TSEs. The abnormal forms of PrP are variously designated PrP^{Sc} (scrapie-type PrP), PrP-res (protease-resistant PrP), PrP^{TSE} (TSE-associated PrP), or PrP^D (disease-associated PrP) by different authorities.

It remains unclear whether abnormal PrP constitutes the complete infectious particle of spongiform encephalopathies, is a component of those particles, or is a pathologic host protein not usually separated from the actual infectious entity by currently used techniques. The demonstration that PrP is encoded by a normal host gene seemed to favor the last possibility. Several studies suggest that agent-specific pathogenic information can be transmitted and replicated by different conformations of a protein with the same primary amino acid sequence in the absence of agent-specific nucleic acids. Properties of 2 fungal proteins were found to be heritable without encoding in nucleic acid, although those properties have not been transmitted to recipient fungi as infectious elements. Whatever its relationship to the actual infectious TSE particles, PrP clearly plays a central role in susceptibility to infection, because the normal PrP must be expressed in mice and cattle if they are to acquire a TSE or to sustain replication of the infectious agents. Furthermore, inherited normal variations in PrP phenotype are associated with increased susceptibility to vCJD and (to a lesser extent) to sCJD and with occurrence of fCJD.

PrPs are glycoproteins; protease-resistant PrPs, when aggregated, have the physical properties of amyloid proteins. The PrPs of different species of animals are very similar in their amino acid sequences and antigenicity but are not identical in structure. The primary structure of PrP is encoded by the host and is not altered by the source of the infectious agent provoking its formation. The function of the ubiquitous protease-sensitive PrP precursor (designated PrP^C, for "cellular" PrP, or PrP-sen, for protease-sensitive PrP) in normal cells is unknown; it binds copper and may play some role in normal synaptic transmission, but it is not required for life or for relatively normal cerebral function in mice and cattle. As noted, expression of PrP is required both for development of scrapie disease and for replication of the transmissible scrapie agent in animals. The degree of homology between amino acid sequences of PrPs in different animal species may correlate with the "species barrier" that affects susceptibility of animals of 1 species to infection with a TSE agent adapted to grow in another species.

Attempts to find particles resembling those of viruses or virus-like agents in brain tissues of humans or animals with spongiform encephalopathies have been unsuccessful. Peculiar tubulovesicular structures reminiscent of some viruses have been seen in thin sections of TSE-infected brain tissues and cultured cells but not in normal cells. It has never been convincingly established that those structures are associated with infectivity.

EPIDEMIOLOGY

Kuru once affected many children of both sexes ≥4 yr of age, adolescents, and young adults (mainly women) living in 1 limited area of Papua New Guinea. The complete disappearance of kuru among people born after 1957 suggests that the practice of ritual cannibalism (thought to have ended that year) was probably the only mechanism by which the infection was spread in Papua New Guinea.

CJD, the most common human spongiform encephalopathy, was formerly thought to occur only in older adults; however, iCJD and, much more rarely, sCJD (to date, 7 reports in adolescents—1 a 14 yr old girl) have affected young people. A single case of sporadic fatal insomnia was recognized in a U.S. adolescent. GSS has not been diagnosed in children or adolescents. vCJD, however, has a peculiar predilection for younger people. Of 174 cases of vCJD reported through 2010 in the United Kingdom, all except 23 were in people younger than 40 yr of age and 22 were younger than 20 yr of age; the youngest age at onset was 12 yr. sCJD has been recognized worldwide, at yearly rates of 0.25-2 cases/million population (not age-adjusted), with CJD foci of considerably higher incidence among Libyan Jews in Israel, in isolated villages of Slovakia, and in other limited areas. Sporadic CJD has not been convincingly linked to any common exposure, and the source of infection remains unknown. Proponents of the prion hypothesis are convinced that PrP can spontaneously misfold, becoming self-replicating and causing sCJD; skeptics favor infection with some ubiquitous TSE agent which, fortunately, has a very low attack rate except in persons with certain mutations in the *PRNP* gene. Neither of those possible etiologies has been proven. Person-to-person spread has been confirmed only for iatrogenic cases. Spouses and household contacts of patients are at very low risk of acquiring CJD, although 2 instances of conjugal CJD have been reported. However, medical personnel exposed to brains of patients with CJD may be at some increased risk; at least 20 healthcare workers have been recognized with the disease.

The striking resemblance of CJD to scrapie prompted a concern that infected sheep tissues might be a source of spongiform encephalopathy in humans. No reliable epidemiologic evidence suggests that exposure to potentially scrapie-contaminated animals, meat, meat products, or experimental preparations of the scrapie agent have transmitted a TSE to humans. The potential of the CWD agent to infect human beings has also not been demonstrated but remains under investigation; deer, elk, and moose in 15 U.S. states and 2 Canadian provinces have been naturally infected; monkeys have been experimentally infected by injections with deer tissues containing the CWD agent. Exposure to contaminated meat, including venison from animals infected with the CWD agent, has not been implicated as a risk factor for sCJD.

The outbreak of BSE among cattle (possibly infected by eating scrapie-agent–contaminated meat-and-bone meal added to feed) was first recognized in the United Kingdom in 1986 and later reported in native cattle of 24 other countries, including Canada and the United States. The finding of a new TSE in ungulate and feline animals in British zoos and later in domestic cats raised a fear that some TSE agent (probably a strain of the scrapie agent), having crossed the species barrier from sheep to cattle, had acquired a broadened range

of susceptible hosts, posing a potential danger for humans. That remains a plausible explanation for the occurrence of vCJD, first described in adolescents in Britain in 1996 and as of November 2013 affecting at least 177 people in the United Kingdom (not counting a disturbing number of people with evidence of possible asymptomatic or "preclinical" vCJD infection) and more than 50 in other countries: 27 in France, 5 in Spain, 4 in Ireland, 3 in the Netherlands, 2 each in Italy and Portugal, and single cases in Japan and Saudi Arabia. Variant CJD has also occurred in former U.K. residents living in Ireland (2 cases), France (1 case), Canada (1 case), Taiwan (1 case), and the United States (2 cases); 2 additional cases of vCJD—1 in the United States and 1 in Canada—have been reported in former long-time residents of Saudi Arabia, a country that has not recognized BSE but might have imported contaminated meat products from the United Kingdom. A third case of vCJD was previously confirmed in a Saudi citizen residing in Saudi Arabia. Examination of resected appendixes in the United Kingdom for evidence of subclinical infection with prions suggested that many more people than expected had subclinical infection than those recognized with actual vCJD.

Iatrogenic transmissions of CJD have been recognized for more than 30 yr (Table 278-2). Such accidental transmissions of CJD have been attributed to use of contaminated neurosurgical instruments (no case reported since 1980) or operating facilities, use of cortical electrodes contaminated during epilepsy surgery, injections of human cadaveric pituitary growth hormone and gonadotropin (no longer marketed in the United States), and transplantation of contaminated corneas and allografts of human dura mater used as a surgical patching material. Pharmaceuticals and tissue grafts derived from or contaminated with human neural tissues, particularly when obtained from unselected donors and large pools of donors, pose special risks.

Studies of animals experimentally infected with TSE agents first suggested that blood and blood components from humans with preclinical CJD infections might pose a risk of transmitting disease to recipients, and since the 1980s such blood components have been withdrawn as a precaution in the United States when a donor was later found to have CJD and blood products were still in-date. While no epidemiologic study identified any subject exposed to such products obtained from donors later diagnosed with sporadic or fCJD, a surveillance program in the United Kingdom has already reported vCJD in 3 recipients of nonleukoreduced red blood cells from donors later diagnosed with vCJD; there was autopsy evidence of a preclinical vCJD infection in a fourth red cell recipient who died of another disease. Evidence of a preclinical vCJD infection was also found at autopsy in a patient with hemophilia A who was treated with human plasma–derived coagulation factor VIII to which at least 1 vCJD-infected donor contributed; the coagulation factor involved was never licensed in the United States.

Table 278-2 Iatrogenic Transmission of Creutzfeldt-Jakob Disease by Products of Human Origin

PRODUCT	NO. OF PATIENTS	INCUBATION TIME	
		Mean	Range
Cornea	3	17 mo	16-18 mo
Dura mater allograft	>100	7.4 yr	1.3-16 yr
Pituitary extract			
Growth hormone	>100*	12 yr	5-38.5 yr
Gonadotropin	4	13 yr	12-16 yr
Red blood cells	4	? 6 yr	6.3-8.5 yr†
Plasma-derived coagulation factor VIII	1	? > 11 yr‡	

*There have been 28 cases reported among approximately 8,000 recipients of human cadaveric growth hormone in the United States; the remaining cases have been reported in other countries.

†The second transfusion-transmitted case of vCJD (Peden AH, Head MW, Ritchie DL, et al: Preclinical vCJD after blood transfusion in a *PRNP* codon 129 heterozygous patient, *Lancet* 364:527–529, 2004) died of unrelated causes about 5 yr after transfusion but was found to have accumulations of abnormal PrP in spleen and cervical lymph node—a finding unique to vCJD and interpreted as probable preclinical infection.

‡The diagnosis of vCJD infection attributed to treatment with human plasma–derived coagulation factor VIII (UK Health Protection Agency vCJD abnormal prion protein found in a patient with haemophilia at post mortem. Press release 17 February 2009. http://webarchive.nationalarchives.gov.uk/20140714084352/http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1234859690542?p=1231252394302) was also supported by immunohistochemical testing for abnormal PrP in the spleen of a person who died of other causes. Both patients with "preclinical" infections are thought to have died during the asymptomatic incubation period of vCJD.

PATHOGENESIS AND PATHOLOGY

The probable portal of entry for the TSE agent in kuru is thought to have been either through the gastrointestinal tract or lesions in the mouth or integument incidentally exposed to the agent during cannibalism. Patients with vCJD (and animals with BSE and BSE-related TSEs) are thought to have been similarly infected with the BSE agent through exposure to a contaminated beef product, possibly through the intestinal tract. Except after direct introduction into the nervous system, the first site of replication of TSE agents appears to be in tissues of the reticuloendothelial system. TSE agents have been detected in low titers in blood of experimentally infected animals (mice, monkeys, hamsters, and sheep and in the blood of persons with vCJD and perhaps sCJD); infectivity was mainly associated with nucleated cells, although plasma contained a substantial portion of total infectivity in blood. Circulating lymphoid cells seem to be required to infect mice by peripheral routes. Limited evidence suggests that TSE agents also spread to the central nervous system by ascending peripheral nerves. Several researchers claim to have developed tests that detected the CJD agent in human blood, although most attempts have failed. To date no blood-based test has been validated for antemortem testing of either humans or animals.

In human kuru, it seems probable that the only portal of exit of the agent from the body, at least in quantities sufficient to infect others, was through infected tissues exposed during cannibalism. In iatrogenically transmitted CJD, the brains and eyes of patients with CJD have been the probable sources of contamination. Experimental transmission of the agent to animals from kidney, liver, lung, lymph node, and spleen showed that those tissues as well as cerebrospinal fluid (CSF) sometimes contain the CJD agent; none of those sources has been implicated in accidental transmission of CJD to humans. At no time during the course of any TSE have antibodies or cell-mediated immunity to the infectious agents been convincingly demonstrated in either patients or animals. However, mice must be immunologically competent to be infected with the scrapie agent by peripheral routes of inoculation.

Typical changes in TSE include vacuolation and loss of neurons with hypertrophy and proliferation of glial cells, most pronounced in the cerebral cortex in patients with CJD and in the cerebellum in those with kuru. The central nervous system lesions are usually most severe in or even confined to gray matter, at least early in the disease. Loss of myelin appears to be secondary to degeneration of neurons. There generally is no inflammation, but a marked increase in the number and size of astrocytes is usual. Spongiform changes are not a striking autopsy finding in patients with FFI, and neuronal degeneration and gliosis are largely restricted to thalamic nuclei.

Amyloid plaques are found in the brains of all patients with GSS and in at least 70% of those with kuru. These plaques are less common in patients with CJD. Amyloid plaques are most common in the cerebellum but occur elsewhere in the brain as well. In brains of patients with vCJD, plaques surrounded by halos of vacuoles (described as flower-like or florid plaques) have been a consistent finding. TSE amyloid plaques react with antiserum prepared against PrP. Even in the absence of plaques, extracellular PrP can be detected in the brain parenchyma by immunostaining.

CLINICAL MANIFESTATIONS

Kuru, no longer seen, is a progressive degenerative disease of the cerebellum and brainstem with less obvious involvement of the cerebral cortex. The first sign of kuru was usually cerebellar ataxia followed by progressive incoordination. Coarse, shivering tremors were characteristic. Variable abnormalities in cranial nerve function appeared, frequently with impairment in conjugate gaze and swallowing. Patients died of inanition and pneumonia or of burns from cooking fires, usually within 1 yr after onset. Although changes in mentation were common, there was no frank dementia or progression to coma, as in CJD. There were no signs of acute encephalitis such as fever, headaches, and convulsions.

CJD occurs throughout the world. Patients initially have either sensory disturbances (most often visual) or confusion and inappropriate behavior, progressing over weeks or months to frank dementia, akinetic mutism, and ultimately coma. Some patients have cerebellar ataxia early in disease, and most patients experience myoclonic jerking movements. Mean survival of patients with sCJD has been <1 yr from the earliest signs of illness, although approximately 10% live for 2 yr. Variant CJD (Table 278-3) differs from the more common sCJD: patients with vCJD are much younger at onset (as young as 12 yr) and more often present with complaints of dysesthesia and subtle behavioral changes, often mistaken for psychiatric illness. Severe mental deterioration occurs later in the course of vCJD. Patients with vCJD have survived substantially longer than those with sCJD. (Attempts have been made to subclassify cases of CJD based on electrophoretic differences in PrP^{TSE} and variation in its sensitivity to digestion with the proteolytic enzyme proteinase (PK); the different variants are said to have somewhat different clinical features, including duration of illness, though all are ultimately fatal.)

GSS is a familial disease resembling CJD but with more prominent cerebellar ataxia and amyloid plaques. Dementia may appear only late in the course, and the average duration of illness is longer than typical sCJD. Progressively severe insomnia and dysautonomia as well as ataxia, myoclonus, and other signs resembling those of CJD and GSS characterize FFI and sporadic fatal insomnia. A case of sporadic fatal insomnia has been described in a young adolescent. GSS has not been diagnosed in children or adolescents.

A novel "prion disease" has been reported that is expressed in several generations with an autosomal dominant pattern associated with a unique mutation in the *PRNP* gene. The affected persons were middle-aged with a history of chronic diarrhea for years plus autonomic neuropathy and modest mental impairment but without full-blown dementia; PK-resistant PrP deposits with amyloid properties occurred in the brain, lymphoid tissues, kidney, spleen, and intestinal tract. The disease was not successfully transmitted to 3 lines of mice susceptible to several TSEs. It is not clear that such a syndrome—not a spongiform encephalopathy and apparently not associated with an infectious agent—should be lumped together with TSEs. It might well result from the abnormal *PRNP* gene product itself; if so, it would not pose the same potential threat to public health as do the TSEs.

DIAGNOSIS

Diagnosis of spongiform encephalopathies is most often determined on clinical grounds after excluding other diseases. The presence of 14-3-3 protein (see "Laboratory Findings") in CSF may aid in distinguishing between CJD and Alzheimer disease, although this is not a consideration in children. Elevations of 14-3-3 protein levels in CSF are not specific to TSEs and are common in viral encephalitis and other conditions causing rapid necrosis of brain tissue. Brain biopsy may be diagnostic of CJD, but it can be recommended only if a potentially treatable disease remains to be excluded or if there is some other compelling reason to make an antemortem diagnosis. Definitive diagnosis usually requires microscopic examination of brain tissue obtained at autopsy. The demonstration of protease-resistant PrP proteins in brain extracts can be useful to augment histopathologic diagnosis. Accumulation of the abnormal PrP in lymphoid tissues, even before the onset of neurologic signs, is typical of vCJD. Tonsil biopsy may avoid the need for brain biopsy when antemortem diagnosis of vCJD is indicated. Transmission of disease to susceptible animals by inoculation of brain suspension must be reserved for cases of special research interest.

LABORATORY FINDINGS

Virtually all patients with typical sporadic, iatrogenic, and familial forms of CJD have abnormal electroencephalograms (EEGs) as the disease progresses; the background becomes slow and irregular with diminished amplitude. A variety of paroxysmal discharges such as slow waves, sharp waves, and spike-and-wave complexes may also appear, and these may be unilateral or focal or bilaterally synchronous. Paroxysmal discharges may be precipitated by loud noise. Many patients have typical periodic suppression-burst complexes of high-voltage slow activity on EEG at some time during the illness. Patients with vCJD have had only generalized slowing, without periodic bursts of high-voltage discharges on EEG. CT or MRI may show cortical atrophy and large ventricles late in the course of CJD. Many patients with vCJD have an increase in density of the pulvinar on MRI. Reliable interpretation of the images might best be left to experienced radiologists.

Table 278-3 Clinical and Histopathologic Features of Patients with Variant and Typical Sporadic Creutzfeldt-Jakob Disease

FEATURE	VARIANT CJD (FIRST 10 PATIENTS)	SPORADIC CJD (185 PATIENTS)
Years of age at death* (range)	29 (19-74)	65
Duration of illness, mo (range)	12 (8-23)	4
Presenting signs	Abnormal behavior, dysesthesia	Dementia
Later signs	Dementia, ataxia, myoclonus	Ataxia, myoclonus
Periodic complexes on EEG	Rare	Most
PRNP 129 Met/Met	All tested (except 1 transfusion-transmitted case, 1 plasma-derivative transmitted case; 1 possible clinical case in United Kingdom where no tissue was available to confirm)	83%
Histopathologic changes	Vacuolation, neuronal loss, astrocytosis, plaques (100%)	Vacuolation, neuronal loss, astrocytosis, plaques (≤15%)
Florid PrP plaques†	100%	0
PrP^{TSE} glycosylation pattern	BSE-like‡	Not BSE-like

*Median age and duration for variant CJD; averages for typical sporadic CJD.

†Dense plaques with a pale periphery of surrounding vacuolated cells.

‡Characterized by an excess of high molecular mass band (diglycosylated) and 19 kDa nonglycosylated band glycoform of PrP-res (Collinge J, Sidle KC, Meads J, et al: Molecular analysis of prion strain variation and the aetiology of "new variant" CJD, *Nature* 383:685–690, 1996).

BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; EEG, electroencephalogram; Met, codon 129 of one *PRNP* gene encoding for methionine; *PRNP*, prion protein–encoding gene; PrP, prion protein.

Modified from Will RG, Ironside JW, Zeidler M, et al: A new variant of Creutzfeldt-Jakob disease in the UK, Lancet *347:921–925, 1996.*

There may be modest elevation of CSF protein content in patients with TSE. Unusual protein spots were observed in CSF specimens after 2-dimensional separation in gels and silver staining; the spots were identified as 14-3-3 proteins, normal proteins (not related to PrP) abundant in neurons but not ordinarily detected in CSF. However, the finding of 14-3-3 protein in CSF has also been detected in CSF specimens from some patients with acute viral encephalitides and recent cerebral infarctions, and thus is not specific to CJD. Finding the 14-3-3 protein in CSF is neither sensitive nor specific but has been of some help in confirming the diagnosis of vCJD, especially when accompanied by increases in other cellular proteins. Diagnosis usually rests on recognizing the typical constellation of clinical findings, clinical course, and testing (CSF examination, CT or MRI, EEG), confirmed by histopathology and detection of PrP^{TSE} in brain tissues at autopsy (or, less often, by tonsil or brain biopsy).

TREATMENT

No treatment has proven effective. Studies of cell cultures and rodents experimentally infected with TSE agents suggested that treatment with chlorpromazine, quinacrine, and tetracyclines might be of benefit, especially during the incubation period. Early reports of clinical trials based on those studies have been discouraging, and it seems unlikely that the severe brain damage found in late disease can be reversed by such treatment. Infusions with pentosan polysulfate directly into the cerebral ventricles appear to have delayed the progression of vCJD in a least 1 patient but did not reverse earlier brain damage. Appropriate supportive care should be provided to all CJD patients as for other progressive fatal neurologic diseases. On the basis of experimental studies in animals, several prophylactic postexposure treatment regimens have been suggested, but none has been widely accepted.

GENETIC COUNSELING

TSE sometimes occurs in families in a pattern consistent with an autosomal dominant mode of inheritance. In patients with a family history of CJD, the clinical and histopathologic findings are similar to those seen in sporadic cases. In the United States, only approximately 10% of cases of CJD are familial. GSS and FFI are always familial. In some affected families, approximately 50% of siblings and children of a patient with a familial TSE eventually acquire the disease; in other families, the "penetrance" of illness may be less.

The gene coding for PrP is closely linked if not identical to that controlling the incubation periods of scrapie in sheep and both scrapie and CJD in mice. The gene encoding PrP in humans is designated the *PRNP* gene and is located on the short arm of chromosome 20. It has an open reading frame of about 759 nucleotides (253 codons), in which more than 20 different point mutations and a variety of inserted sequences encoding extra tandem-repeated octapeptides are linked to the occurrence of spongiform encephalopathy in families with a pattern consistent with autosomal dominance of variable penetrance.

The same nucleotide substitution at codon 178 of the *PRNP* gene associated with CJD in some families has been found in all patients with FFI. Homozygosity for valine and especially for methionine at codon 129 seems to increase susceptibility to iCJD and sCJD. Almost all patients with vCJD to be genotyped have been homozygous for methionine at codon 129 of the *PRNP* gene. A few probable preclinical vCJD infections and 1 clinically typical case of vCJD have been reported in persons with other genotypes. It is of interest that when the *PRNP* genes from appendices containing accumulations of what appears to be PrP^{TSE} in the United Kingdom were sequenced, a surprising number were homozygous for valine—the genotype of only approximately 10% of U.K. subjects and never found in a case of vCJD. The significance of this finding is not clear. U.K. authorities have adopted the precautionary assumption that some persons with PrP^{TSE} in lymphoid tissues may have latent infections. Whether the blood and tissues of such persons are infectious is unknown.

Although the interpretation of these findings in regard to the prion hypothesis is in dispute, persons from families with CJD or GSS who have the associated mutations in the *PRNP* gene have a high probability of eventually acquiring spongiform encephalopathy. The significance of mutations in the *PRNP* genes of individuals from families with no history of spongiform encephalopathy is not known. It seems wise to avoid alarming those from unaffected families who have miscellaneous mutations in the *PRNP* gene, because the implications are not yet clear; in the United States, such persons are deferred from donating blood if a blood relative has been diagnosed with a TSE.

PROGNOSIS

The prognosis of all spongiform encephalopathies is uniformly poor. Approximately 10% of patients may survive for longer than 1 yr, but the quality of life is poor.

FAMILY SUPPORT

The CJD Foundation (http://www.cjdfoundation.org), organized and maintained by family members and friends of patients with CJD and related disorders, working closely with the Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/dvrd/prions) and with the National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, Ohio (http://www.cjdsurveillance.com), is a support and educational group and a useful source of information regarding available resources for those dealing with the diseases.

PREVENTION

Exposure to the BSE agent in meat products clearly poses a special danger. Authorities in Canada, the United States, and other countries have responded by implementing progressively more stringent agricultural and public health measures during the past 20 yr, with elimination of most bovine-derived materials from animal feeds probably the most effective measure. Three cases of BSE in native cattle have been recognized in the United States since 2004—the last in 2012; a case was also recognized in a Canadian cow imported into the United States in 2003. Canada found 19 native cattle with BSE between 2003 and 2010 (and imported a case from the United Kingdom in 1993). In spite of encouraging epidemiologic studies that failed to implicate exposure to scrapie or CWD agents in human TSEs, it seems prudent to avoid exposing children to meat and other products likely to be contaminated with any TSE agent.

The safety of human blood, blood components, and plasma derivatives in the United States and Canada is protected by deferring those donors with histories suggesting an increased risk of TSEs: persons treated with cadaveric pituitary hormones (no longer used) or dura mater allografts, patients with a family history of CJD (unless sequencing shows that the TSE-affected blood relative or the donor has revealed no TSE-related mutation in either *PRNP* gene), and persons who spent substantial periods of time in specified countries during years when BSE was prevalent. Persons transfused with blood in the United Kingdom and France after 1980 should be deferred from donating blood (similar deferral policies are in place for donors of human cells and tissues). U.K. authorities have warned persons treated with U.K.-sourced pooled coagulation factor concentrates or antithrombin between 1989 and 2001 that they may be "at risk of vCJD for public health purposes" and that "special infection control precautions" apply to them.

In principle, it would be better to identify the few blood and tissue donors actually infected with a TSE rather than deferring all those at increased risk of exposure, because most of them are unlikely to have been infected. Accordingly, antemortem donor screening tests that might identify persons with preclinical TSE infections are currently under development but have not been clinically validated. Another attractive approach would be to remove TSE agents from blood. Along these lines, a committee of expert advisors to the U.K. government recommended considering the use of an investigational device to filter red cells intended to transfuse children, because some unknown but possibly substantial number of U.K. blood donors might be incubating vCJD; authorities in the United Kingdom (and Ireland) evaluated, but have not adopted, that advice.

Standard precautions should be used to handle all human tissues, blood, and body fluids. Materials and surfaces contaminated with tissues or fluids from patients suspected of having CJD must be treated with great care. Whenever possible, discard contaminated instruments

by careful packaging and incineration. Contaminated tissues and biologic products probably cannot be completely freed of infectivity without destroying their structural integrity and biologic activity; therefore, the medical and family histories of individual tissue donors should be carefully reviewed to exclude a diagnosis of TSE. Histopathologic examination of brain tissues of cadaveric donors and testing for abnormal PrP might be performed where feasible to provide an additional assurance of safety. Although no method of sterilization can be relied on to remove all infectivity from contaminated surfaces, exposures to moist heat, sodium hydroxide, chlorine bleach, concentrated formic acid, acidified detergent, and guanidine salts markedly reduced infectivity in experimental studies.

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Section 14

Antiparasitic Therapy

Chapter 279

Principles of Antiparasitic Therapy

Mark R. Schleiss

Parasites are divided into 2 main groups taxonomically: **protozoans,** which are unicellular, and **helminths**, which are multicellular. Chemotherapeutic agents appropriate for 1 group may not be appropriate for the other, and not all drugs are readily available (Table 279-1). Some drugs are available only from the manufacturer, some are not available in the United States, and some are available through the Centers for Disease Control and Prevention (CDC). Availability of drugs can be ascertained by contacting the Parasitic Diseases Public Inquiries Branch (1-404-718-4745; e-mail INTER REF chagas@cdc.gov). For after-hours emergencies, practitioners can contact the CDC Emergency Operations Center (770-488-7100) and ask for the on-call parasitic diseases physician. For assistance in the management of malaria, healthcare should call the CDC Malaria Hotline: 770-488-7788 or 855-856-4713 toll-free (M-F, 9 AM-5 PM, Eastern time). For emergency consultation after hours, clinicians can phone 770-488-7100 and request to speak with a CDC Malaria Branch clinician.

SELECTED ANTIPARASITIC DRUGS FOR PROTOZOANS

Nitazoxanide (Alinia)

Nitazoxanide is a nitrothiazole benzamide, initially developed as a veterinary anthelmintic. Nitazoxanide inhibits pyruvate-ferredoxin oxidoreductase, which is an enzyme necessary for anaerobic energy metabolism. In humans, nitazoxanide is effective against many protozoans and helminths. Nitazoxanide is approved for the treatment of diarrhea caused by *Cryptosporidium* species in children 1-11 yr of age and by *Giardia intestinalis* in children 1 yr of age and older.

Nitazoxanide is available as an oral suspension, which has a pink color and strawberry flavor. The bioavailability is doubled with food. The drug is well absorbed from the gastrointestinal tract. One third is excreted in urine, and two thirds is excreted in feces as the active metabolite, tizoxanide. Although in vitro metabolism studies have not demonstrated cytochrome P450 enzyme effects, no pharmacokinetic studies have been performed yet in patients with compromised renal or hepatic function. In addition, no studies have been performed in pregnant or lactating women. Common adverse effects include abdominal pain, diarrhea, and nausea. Rare side effects include anorexia, flatulence, increased appetite, fever, pruritus, and dizziness. Intriguingly, nitazoxanide has activity against both hepatitis C and rotavirus, although the use of the agent against these viruses is investigational.

Tinidazole (Tindamax)

Tinidazole is a synthetic nitroimidazole with a chemical structure similar to metronidazole. It is FDA approved for treatment of trichomoniasis and for giardiasis and amebiasis in children 3 yr of age and older. In the treatment of giardiasis, it has the advantages of very few side effects and only requiring a single dose. Its mechanism of action against *Trichomonas* may be secondary to the generation of free nitro radicals by the protozoan. The mechanism of action against *Giardia lamblia* and *Entamoeba histolytica* is unknown. After oral administration, tinidazole is rapidly and completely absorbed and distributes into almost all tissues and body fluids, including crossing the blood–brain barrier and placental barrier. It is excreted via urine and feces. Hemodialysis increases clearance of drug. No studies have been performed for patients undergoing peritoneal dialysis or for patients with compromised hepatic function. Tinidazole carries a pregnancy category C classification and can be detected in breast milk. Breastfeeding should be interrupted during treatment and for 3 days after treatment.

Atovaquone/Proguanil (Malarone)

Atovaquone is a hydroxynaphthoquinone and has been used in the past predominantly against *Pneumocystis* pneumonia in AIDS patients. Its mechanism of action is via disruption of mitochondria membrane potential through interaction with cytochrome B. Atovaquone can also effectively inhibit liver stages of all *Plasmodium* species.

Proguanil is approved for use in the United States. Its mechanism of action is inhibition of the parasite dihydrofolate reductase enzyme by the active form, cycloguanil. When used alone, it has poor efficacy for prophylaxis.

Proguanil acts in synergy with atovaquone on the cytochrome B enzyme in *Plasmodia* mitochondria. The exact mechanism of synergy is unknown. In 2000, the FDA approved atovaquone/proguanil for the prevention and treatment of acute, uncomplicated *Plasmodium falciparum* malaria. Atovaquone alone and in combination with proguanil is the only drug to completely inhibit the liver stage, which provides the advantage of only needing to use the drug for 7 days after departing a malaria-endemic area (compared to several weeks).

Two double-blind, randomized clinical trials assessing malaria prophylaxis demonstrated that atovaquone/proguanil was at least comparable to (and perhaps better than) chloroquine plus proguanil, and that atovaquone/proguanil was comparable to mefloquine. Atovaquone/proguanil was better tolerated than chloroquine plus proguanil and mefloquine. Atovaquone/proguanil treatment of acute uncomplicated *P. falciparum* infection has demonstrated higher or comparable cure rates when compared with other *P. falciparum* treatment drugs. Compared with other antimalaria treatment therapies, atovaquone/proguanil treatment has the highest cost.

Artemisinin Derivatives and Artemether/Lumefantrine (Coartem, Artemether, Artesunate)

Artemisinin is a sesquiterpene lactone isolated from the weed *Artemisia annua.* It was developed in China where it is known as qinghaosu. Artemisinins act very rapidly against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant *P. falciparum.* Artemisinins are also rapidly eliminated. Emerging resistance to artemisinins has been seen in Cambodia, but not all of Southeast Asia. Coartem is the first artemisinin-containing drug approved for use by the FDA. It is a fixed-dose combination of 2 novel antimalarials, artemether (20 mg) and lumefantrine (120 mg). It is a highly effective 3 day malaria treatment with cure rates of >96%, even in areas of multidrug resistance.

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Table 279-1 Drugs for Parasitic Infections

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of AIDS, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Acanthamoeba keratitis			
Drug of choice:	See footnote 1		
Amebiasis *(Entamoeba histolytica)*			
Asymptomatic			
Drug of choice:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day (max 2 g) in 3 doses PO × 20 days
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Alternative:	Diloxanide furoate[2]	500 mg tid PO × 10 days	20 mg/kg/day PO in 3 doses × 10 days
Mild to moderate intestinal disease[3]			
Drug of choice[4]:	Metronidazole	500-750 mg tid PO × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[5]	2 g PO once daily × 3 days	50 mg/kg/day PO (max 2 g) in 1 dose × 3 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Severe intestinal and extraintestinal disease[3]			
Drug of choice:	Metronidazole	750 mg PO tid × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole[5]	2 g PO once daily × 5 days	50 mg/kg/day PO (max 2 g) × 5 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Amebic meningoencephalitis, primary and granulomatous			
Naegleria			
Drug of choice:	Amphotericin B[6,7]	1.5 mg/kg/day IV in 2 doses × 3 days, then 1.5 mg/kg/day IV × 6 days	1.5 mg/kg/day IV in 2 doses × 3 days, then 1 mg/kg/d IV × 6 days
or		1 mg/kg IV once/day plus 0.5 mg/day intraventricularly (max of 1.5 mg/kg by both routes)	1 mg/kg IV once/daily plus 0.5 mg/d intraventricularly (max of 1.5 mg/kg by both routes)
or			
	Rifampin	10 mg/kg IV once/daily (max 600 mg/d)	10 mg/kg IV once/daily (max 600 mg/d)
	Fluconazole	12 mg/kg IV once/daily	12 mg/kg IV once/daily
	Azithromycin	500 mg IV once/daily	20 mg/kg IV once/daily (max 500 mg/d)
Acanthamoeba			
Drug of choice:	See footnote 8		

[1]For treatment of keratitis caused by *Acanthamoeba*, concurrent topical use of 0.1% propamidine isethionate (Brolene) plus neomycin-polymyxin B-gramicidin ophthalmic solution has been successful (Hargrave SL, et al: *Ophthalmology* 106:952, 1999). In some European countries, propamidine is not available and hexamidine (Desmodine) has been used (Seal DV: *Eye* 17:893, 2003). In addition, 0.02% topical polyhexamethylene biguanide (PHMB) and/or chlorhexidine has been used successfully in a large number of patients (Tabin G, et al: *Cornea* 20:757, 2001; Wysenbeek YS, et al: *Cornea* 19:464, 2000). PHMB is available from Leiter's Park Avenue Pharmacy, San Jose, CA (800-292-6773; www.leiterrx.com). The combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al: *Jpn J Ophthalmol* 47:616, 2003).

[2]The drug is not available commercially, but as a service can be compounded by Panorama Compounding Pharmacy, 6744 Balboa Blvd, Van Nuys, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-6816).

[3]Treatment should be followed by a course of iodoquinol or paromomycin in the dosage used to treat asymptomatic amebiasis.

[4]Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of *Cryptosporidium* in immunocompetent children younger than 12 yr old and for *Giardia* (*Med Lett* 2003;45:29). It may also be effective for mild to moderate amebiasis (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

[5]A nitroimidazole similar to metronidazole, tinidazole was recently approved by the FDA and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (Humco, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Ornidazole, a similar drug, is also used outside the United States.

[6]*Naegleria* infection has been treated successfully with intravenous and intrathecal use of both amphotericin B and miconazole plus rifampin and with amphotericin B, rifampin, and ornidazole (Seidel J, et al: *N Engl J Med* 306:346, 1982; Jain R, et al: *Neurol India* 50:470, 2002). Other reports of successful therapy are less-well documented.

[7]An approved drug, but considered investigational for this condition by the FDA.

[8]Strains of *Acanthamoeba* isolated from fatal granulomatous amebic encephalitis are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and (less so) to amphotericin B. Chronic *Acanthamoeba* meningitis has been successfully treated in 2 children with a combination of oral trimethoprim-sulfamethoxazole, rifampin, and ketoconazole (Singhal T, et al: *Pediatr Infect Dis J* 20:623, 2001), and in an AIDS patient with fluconazole, sulfadiazine, and pyrimethamine combined with surgical resection of the CNS lesion (Seijo Martinez M, et al: *J Clin Microbiol* 38:3892, 2000). Disseminated cutaneous infection in an immunocompromised patient has been treated successfully with IV pentamidine isethionate, topical chlorhexidine, and 2% ketoconazole cream, followed by oral itraconazole (Slater CA, et al: *N Engl J Med* 331:85, 1994).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Balamuthia mandrillaris			
Drug of choice:	See footnote 9		
Sappinia diploidea			
Drug of choice:	See footnote 10		
Ancylostoma caninum (eosinophilic enterocolitis)			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
or	Pyrantel pamoate[7]	11 mg/kg PO (max 1 g) × 3 days	11 mg/kg PO (max 1 g) × 3 days
or	Endoscopic removal		
Ancylostoma duodenale, see Hookworm			
Angiostrongyliasis *(Angiostrongylus cantonensis, Angiostrongylus costaricensis)*			
Drug of choice:	See footnote 11		
Anisakiasis (*Anisakis* spp.)			
Treatment of choice[12]:	Surgical or endoscopic removal		
Ascariasis (*Ascaris lumbricoides*, roundworm)			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg PO once	100 mg PO bid × 3 days or 500 mg PO once
or	Ivermectin[7]	150-200 µg/kg PO once	150-200 µg/kg PO once
Babesiosis *(Babesia microti)*			
Drugs of choice[13]:	Atovaquone[7] **plus** azithromycin[7]	750 mg PO bid × 7-10 days 600 mg PO daily × 7-10 days	20 mg/kg PO bid × 7-10 days 10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/d (max 250 mg/dose) PO days 2-10
or	Clindamycin[7] **plus** quinine[7]	300-600 mg IV qid or 600 mg tid PO × 7-10 days 650 mg tid PO × 7-10 days	20-40 mg/kg/day IV or PO in 3 or 4 doses × 7-10 days (max 600 mg/dose) 24 mg/kg/day PO in 3 doses × 7-10 days
Balamuthia mandrillaris, see Amebic meningoencephalitis, primary			
Balantidiasis *(Balantidium coli)*			
Drug of choice:	Tetracycline[7,14]	500 mg PO qid × 10 days	40 mg/kg/day PO (max 2 g) in 4 doses × 10 days
Alternatives:	Metronidazole[7] Iodoquinol[7]	750 mg PO tid × 5 days 650 mg PO tid × 20 days	35-50 mg/kg/day PO in 3 doses × 5 days 40 mg/kg/day PO in 3 doses × 20 days

[9]A free-living leptomyxid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of *Balamuthia* encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deetz TR, et al: *Clin Infect Dis* 37:1304, 2003; Jung S, et al: *Arch Pathol Lab Med* 128:466, 2004). Miltefosine is another option currently being evaluated but it is not approved for any indication in the United States at this time. Case reports and in vitro data suggest it may have some antiamebic activity (AC Aichelburg et al., *Emerg Infect Dis* 2008; 14:1743; DY Martinez et al., *Clin Infect Dis* 2010; 51:e7; FL Schuster et al., *J Eukaryot Microbiol* 2006; 53:121). Miltefosine (Impavido) is manufactured in 10 or 50 mg capsules by Paladin (Canada) and is available in the United States from the CDC for treatment of infections with free-living amebas.

[10]A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al: *J Neuropathol Exp Neurol* 62:990, 2003).

[11]Most patients have a self-limited course and recover completely. Analgesics, corticosteroids, and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ: *Am J Med* 114:217, 2003). No anthelmintic drug is proven to be effective, and some patients have worsened with therapy (Slom TJ, et al: *N Engl J Med* 346:668, 2002). Mebendazole or albendazole and a corticosteroid appeared to shorten the course of infection (K Sawanyawisuth and K Sawanyawisuth, *Trans R Soc Trop Med Hyg* 2008; 102:990; V Chotmongkol et al. *Am J Trop Med Hyg* 2009;81:443).

[12](Repiso Ortega A, et al: *Gastroenterol Hepatol* 26:341, 2003.) Successful treatment of a patient with *Anisakiasis* with albendazole has been reported (Moore DA, et al *Lancet* 360:54, 2002).

[13]Exchange transfusion has been used in severely ill patients and those with high (>10%) parasitemia (Hatcher JC, et al *Clin Infect Dis* 32:1117, 2001). In patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al: *N Engl J Med* 343:1454, 2000). Highly immunosuppressed patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (PJ Krause et al., *Clin Infect Dis* 2008; 46:370). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (LM Weiss et al., *N Engl J Med* 2001; 344:773). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcurative course of this regimen (GP Wormser et al., *Clin Infect Dis* 2010; 50:381).

[14]Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Baylisascariasis *(Baylisascaris procyonis)*			
Drug of choice:	See footnote 15		
Blastocystis hominis infection			
Drug of choice:	See footnote 16		
Capillariasis *(Capillaria philippinensis)*			
Drug of choice:	Mebendazole[7]	200 mg PO bid × 20 days	200 mg PO bid × 20 days
Alternatives:	Albendazole[7]	400 mg PO daily × 10 days	400 mg PO daily × 10 days
Chagas disease, see Trypanosomiasis			
Clonorchis sinensis, see Fluke infection			
Cryptosporidiosis *(Cryptosporidium)*			
Immunocompetent			
Drug of choice:	Nitazoxanide[4]	500 mg PO bid × 3 days[7]	1-3 yr: 100 mg PO bid × 3 days
			4-11 yr: 200 mg PO bid × 3 days
HIV infected			
Drug of choice:	See footnote 17		
Cutaneous larva migrans (creeping eruption, dog and cat hookworm)			
Drug of choice[18]:	Albendazole[7]	400 mg PO daily × 3 days	400 mg PO daily × 3 days
or	Ivermectin[7]	200 μg/kg PO daily × 1-2 days	200 μg/kg PO daily × 1-2 days
Alternative:	Thiabendazole	Topically	Topically
Cyclosporiasis *(Cyclospora cayetanensis)*			
Drug of choice[19]:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days	TMP 5 mg/kg, SMX 25 mg/kg bid PO × 7-10 days
Alternative:	Ciprofloxacin	500 mg PO bid × 7 days	-
Cysticercosis, see Tapeworm infection			
Drug of choice:			
Cystoisosporiasis *(Cystoisospora belli, formerly known as Isospora)*			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)[7]	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days	TMP 5 mg/kg, SMX 25 mg/kg PO bid × 10 days
Dientamoeba fragilis infection[20]			
	Paromomycin[7]	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
or	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO (max 2 g) in 3 doses × 20 days
or	Metronidazole	500-750 mg tid × 10 days	20-40 mg/kg/day in 3 doses × 10 days
Diphyllobothrium latum, see Tapeworm infection			

[15]No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/d PO and high-dose steroids has been used successfully (JM Peters et al., *Pediatrics* 2012; 129:e806; S Haider, *Emerg Infect Dis* 2012; 18:347). Albendazole 25 mg/kg/d PO × 20 d started as soon as possible (up to 3 d after possible infection) might prevent clinical disease and is recommended for children with known exposure, such as in the setting of ingestion of raccoon stool or contaminated soil (WJ Murray and KR Kazacos, *Clin Infect Dis* 2004; 39:1484). Mebendazole, levamisole, or ivermectin could be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae.

[16]Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days or trimethoprim-sulfamethoxazole 1 DS tab bid × 7 days have been reported to be effective (Stenzel DJ, Borenam PFL: *Clin Microbiol Rev* 9:563, 1996; Ok UZ, et al: *Am J Gastroenterol* 94:3245, 1999). Metronidazole resistance may be common (Haresh K, et al: *Trop Med Int Health* 4:274, 1999). Nitazoxanide has been effective in children (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003).

[17]Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al: *Lancet* 360;1375, 2002). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide (treatment duration of 5-21 days), paromomycin, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (B Pantenburg et al., *Expert Rev Anti Infect Ther* 2009; 7:385).

[18]Albanese G, et al: *Int J Dermatol* 40:67, 2001.

[19]HIV-infected patients may need higher dosage and long-term maintenance (Kansouzidou A, et al: *J Trav Med* 11:61, 2004).

[20]Norberg A, et al: *Clin Microbiol Infect* 9:65, 2003.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Dracunculus medinensis (guinea worm) infection			
Drug of choice:	See footnote 21		
Echinococcus, see Tapeworm Infection			
Entamoeba histolytica, see Amebiasis			
Enterobius vermicularis (pinworm) infection			
Drug of choice[22]:	Albendazole[7]	400 mg PO once; repeat in 2 wk	400 mg PO once; repeat in 2 wk
or	Mebendazole	100 mg PO once; repeat in 2 wk	100 mg PO once; repeat in 2 wk
or	Pyrantel pamoate	11 mg/kg base PO once (max 1 g); repeat in 2 wk	11 mg/kg base PO once (max 1 g); repeat in 2 wk
Fasciola hepatica, see Fluke infection			
Filariasis[23]			
Wuchereria bancrofti, Brugia malayi, Brugia timori			
Drug of choice[24]:	Diethylcarbamazine	6 mg/kg PO in 3 doses × 14 days[25]	6 mg/kg PO in 3 doses × 14 days[25]
Loa loa			
Drug of choice[26]:	Diethylcarbamazine	9 mg/kg PO in 3 doses × 14 days[25]	9 mg/kg PO in 3 doses × 14 days[25]
Mansonella ozzardi			
Drug of choice:	See footnote 27		
Mansonella perstans			
Drug of choice:	Doxycycline[7,14]	100 mg bid PO × 7 days	4 mg/kg/day in 2 doses PO × 7 days
Mansonella streptocerca[28]			
Drug of choice:	Diethylcarbamazine Ivermectin[7]	6 mg/kg/day PO × 14 days 150 μg/kg PO once	6 mg/kg/day PO × 14 days 150 μg/kg PO once
Tropical pulmonary eosinophilia (TPE)[29]			
Drug of choice:	Diethylcarbamazine	6 mg/kg/day in 3 doses × 12-21 days	6 mg/kg/day in 3 doses × 12-21 days
Onchocerca volvulus (river blindness)			
Drug of choice:	Invermectin[30]	150 μg/kg PO once, repeated every 6-12 mo until asymptomatic	150 μg/kg PO once, repeated every 6-12 mo until asymptomatic
Fluke, hermaphroditic, infection			

[21]Treatment of choice is slow extraction of worm combined with wound care (*MMWR Morbid Mortal Wkly Rep* 2011; 60:1450). 10 days' treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day × 6 days has been reported to kill the worm directly.

[22]Since all family members are usually infected, treatment of the entire household is recommended.

[23]Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa*. Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response, and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day × 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent block of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (Hoerauf A, et al: *Med Microbiol Immunol* 192:211, 2003; Hoerauf A, et al: *BMJ* 326:207, 2003).

[24]Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 μg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilaria but does not kill the adult forms (Addiss D, et al: *Cochrane Database Syst Rev* 2004;CD003753).

[25]For patients with microfilaria in the blood, *Medical Letter* consultants would start with a lower dosage and scale up: day 1, 50 mg; day 2, 50 mg tid; day 3, 100 mg tid; day 4-14, 6 mg/kg in 3 doses (for *Loa loa* day 4-14, 9 mg/kg in 3 doses). Multidose regimens have been shown to provide more rapid reduction in microfilaria than single-dose diethylcarbamazine, but microfilaria levels are similar 6-12 mo after treatment (Andrade LD, et al: *Trans R Soc Trop Med Hyg* 89:319, 1995; Simonsen PE, et al: *Am J Trop Med Hyg* 53:267, 1995). A single dose of 6 mg/kg is used in endemic areas for mass treatment (Figueredo-Silva J, et al: *Trans R Soc Trop Med Hyg* 90:192, 1996; Noroes J, et al: *Trans R Soc Trop Med Hyg* 91:78, 1997).

[26]In heavy infections with *Loa loa*, rapid killing of microfilariae can provoke an encephalopathy. Apheresis has been reported to be effective in lowering microfilarial counts in patients heavily infected with *Loa loa* (Ottesen ES: *Infect Dis Clin North Am* 7:619, 1993). Albendazole or ivermectin have also been used to reduce microfilaremia; albendazole is preferred because of its slower onset of action and lower risk for encephalopathy (Klion AD, et al: *J Infect Dis* 168:202, 1993; Kombila M, et al: *Am J Trop Med Hyg* 58:458, 1998). Albendazole may be useful for treatment of loiasis when diethylcarbamazine is ineffective or cannot be used, but repeated courses may be necessary (Klion AD, et al: *Clin Infect Dis* 29:680, 1999). Diethylcarbamazine, 300 mg once/wk, has been recommended for prevention of loiasis (Nutman TB, et al: *N Engl J Med* 319:752, 1988).

[27]Diethylcarbamazine has no effect. Ivermectin 200 μg/kg once has been effective.

[28]Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (The Medical Letter: *Drugs for parasitic infections*, ed 2, 2010).

[29]Relapse occurs and can be treated with diethylcarbamazine.

[30]Annual treatment with ivermectin, 150 μg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al: *Ophthalmology* 103:1001, 1996). Diethylcarbamazine should not be used for treatment of this disease.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Clonorchis sinensis (Chinese liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
or	Albendazole[7]	10 mg/kg PO × 7 days	10 mg/kg PO × 7 days
Fasciola hepatica (sheep liver fluke)			
Drug of choice[31]:	Triclabendazole	10 mg/kg PO once or twice[32]	10 mg/kg PO once or twice[32]
Alternative:	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Nitazoxanide	500 mg PO bid × 7 days	1-3 yr: 100 mg PO bid 4-11 yr: 200 mg PO bid
Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai (intestinal flukes)			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
Metorchis conjunctus (North American liver fluke)[33]			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
Nanophyetus salmincola			
Drug of choice:	Praziquantel[7]	60 mg/kg/day PO in 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
Opisthorchis viverrini (Southeast Asian liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or	Albendazole	10 mg/kg/day PO × 7 days	10 mg/kg/day PO × 7 days
Paragonimus westermani (lung fluke)			
Drug of choice:	Praziquantel[7]	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or[34]	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Triclabendazole	10 mg/kg PO once or twice	10 mg/kg PO once or twice
Giardiasis *(Giardia duodenalis)*			
Drugs of choice:	Metronidazole[7] Nitazoxanide[4] Tinidazole[5]	250 mg PO tid × 5 days 500 mg PO bid × 3 days 2 g PO once	15 mg/kg/day PO in 3 doses × 5 days 1-3 yr: 100 mg PO every 12 hr × 3 days 4-11 yr: 200 mg PO every 12 hr × 3 days 50 mg/kg PO once (max 2 g)
Alternatives[35]:	Paromomycin[7,36] Furazolidone Quinacrine[2]	25-35 mg/kg/day PO in 3 doses × 7 days 100 mg PO qid × 7-10 days 100 mg PO tid × 5 days	25-35 mg/kg/day PO in 3 doses × 7 days 6 mg/kg/day PO in 4 doses × 7-10 days 2 mg/kg tid PO × 5 days (max 300 mg/day)
Gnathostomiasis *(Gnathostoma spinigerum)*			
Treatment of choice[37]:	Albendazole[7]	400 mg PO bid × 21 days	400 mg PO bid × 21 days
or	Ivermectin[7]	200 μg/kg/day PO × 2 days	200 μg/kg/day PO × 2 days
±	Surgical removal		
Gongylonemiasis (*Gongylonema* sp.)[38]			
Treatment of choice:	Surgical removal		
or	Albendazole[7]	10 mg/kg/day PO × 3 days	10 mg/kg/day PO × 3 days

[31]Unlike infections with other flukes, *Fasciola hepatica* infections may not respond to praziquantel. Triclabendazole (Egaten, Novartis) may be safe and effective but data are limited (Graham CS, et al: *Clin Infect Dis* 33:1, 2001). It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com; 41-1-211-24-32) and should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al: *Aliment Pharmacol Ther* 17:265, 2003).

[32]Richter J, et al: *Curr Treat Options Infect Dis* 2002;4:313.

[33]MacLean JD, et al: *Lancet* 347:154, 1996.

[34]Triclabendazole may be effective in a dosage of 5 mg/kg once/day × 3 days or 10 mg/kg bid + 1 day (Calvopiña M, et al: *Trans R Soc Trop Med Hyg* 92:566, 1998). See footnote 31 for availability.

[35]Albendazole 400 mg daily × 5 days alone or in combination with metronidazole may also be effective (Hall A, Nahar Q: *Trans R Soc Trop Med Hyg* 87:84, 1993; Dutta AK, et al: *Indian J Pediatr* 61:689, 1994; Cacopardo B, et al: *Clin Ter* 146:761, 1995). Combination treatment with standard doses of metronidazole and quinacrine given for 3 wk has been effective for a small number of refractory infections (Nash TE, et al: *Clin Infect Dis* 33:22, 2001). In 1 study, nitazoxanide was used successfully in high doses to treat a case of *Giardia* resistant to metronidazole and albendazole (Abboud P, et al: *Clin Infect Dis* 32:1792, 2001).

[36]Not absorbed; may be useful for treatment of giardiasis in pregnancy.

[37]de Gorgolas M, et al: *J Travel Med* 10:358, 2003. All patients should be treated with a medication regardless of whether surgery is attempted.

[38]Eberhard ML, Busillo C: *Am J Trop Med Hyg* 61:51, 1999; Wilson ME, et al: *Clin Infect Dis* 32:1378, 2001.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Hookworm infection *(Ancylostoma duodenale, Necator americanus)*			
Drug of choice:	Albendazole[7]	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg once	100 mg PO bid × 3 days or 500 mg once
or	Pyrantel pamoate[7]	11 mg/kg (max 1 g) PO × 3 days	11 mg/kg (max 1 g) PO × 3 days
Hydatid cyst, see Tapeworm infection			
Hymenolepis nana, see Tapeworm infection			
***Leishmania* infection**			
Visceral[39, 40]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days[41]	20 mg Sb/kg/day IV or IM × 28 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]
or	Amphotericin B[7]	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Liposomal amphotericin B[42]	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21[43]	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21[43]
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternative[44]:	Pentamidine[7]	4 mg/kg IV or IM daily or every 2 days for 15-30 doses	4 mg/kg IV or IM daily or every 2 days for 15-30 doses
Cutaneous[45]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 20 days[41]	20 mg Sb/kg/day IV or IM × 20 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 20 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 20 days[41]
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternatives[46]:	Pentamidine[7]	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses[47]	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses[47]
or	Paromomycin[7,48]	Topically 2×/day × 10-20 days	Topically 2×/day × 10-20 days

[39]Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (HW Murray, Lancet 2005; 366:1561). Some of the listed drugs and regimens are effective only against certain *Leishmania* species/strains and only in certain areas of the world (S Sundar and J Chakravarty, Expert Opin Pharmacother 2013; 14:53).

[40]Visceral infection is most commonly caused by the Old World species *Leishmania donovani* (kala-azar) and *Leishmania infantum* and the New World species. *Leishmania chagasi*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[41]May be repeated or continued; a longer duration may be needed for some patients (Herwaldt BL: *Lancet* 354:1191, 1999).

[42]Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *Leishmania infantum*, the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A, *Clin Infect Dis* 1999;28:42). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesteryl sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

[43]The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day (days 1-5) and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, Nigro LC, Minniti S, et al: Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B [AmBisome], *J Infect* 32:133-137, 1996).

[44]For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (~205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al: *N Engl J Med* 341:1795, 1999; Sangraula H, et al: *J Assoc Physicians India* 51:686, 2003). Gastrointestinal adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al: *Clin Infect Dis* 38:217, 2004). Miltefosine (Impavido) is available from the manufacturer (Zentaris, Frankfurt, Germany at Impavido@zentaris.de).

[45]Cutaneous infection is most commonly caused by the Old World species *Leishmania major* and *Leishmania tropica* and the New World species *Leishmania mexicana, Leishmania (Viannia) braziliensis* and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[46]In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) panamensis* in Colombia but not *L. (V.) braziliensis* in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. "Motion sickness," nausea, headache and increased creatinine were the most frequent adverse effects (Soto J, et al: *Clin Infect Dis* 38:1266, 2004). See footnote 44 regarding miltefosine availability. For treatment of *L. major* cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al: *N Engl J Med* 346:891, 2002).

[47]At this dosage pentamidine has been effective against leishmaniasis in Colombia where the likely organism was *L. (V.) panamensis* (Soto-Mancipe J, et al: *Clin Infect Dis* 16:417, 1993; Soto J, et al: *Am J Trop Med Hyg* 50:107, 1994); its effect against other species is not well established.

[48]Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread. A formulation of 15% paromomycin/12% methylbenzethonium chloride (Leshcutan) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *L. major* in Israel and against *L. mexicana* and *L. (V.) braziliensis* in Guatemala, where mucosal spread is very rare (Arana BA, et al: *Am J Trop Med Hyg* 65:466, 2001). The methylbenzethonium is irritating to the skin; lesions may worsen before they improve.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mucosal[49]			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days[41]	20 mg Sb/kg/day IV or IM × 28 days[41]
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]	20 mg pentavalent antimony/kg/day IV or IM × 28 days[41]
or	Amphotericin B[7]	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Lice infestation *(Pediculus humanus, Pediculus capitis, Phthirus pubis)*[50]			
Drugs of choice:	0.5% Malathion[51]	Topically	Topically
or	1% Permethrin[52]	Topically	Topically
or	Pyrethrins with piperonyl butoxide[52]	Topically	Topically
or	0.5% Ivermectin lotion	Topically, once	Topically, once
or	0.9% Spinosad susp	Topically, 2 × at least 7 days apart	Topically, 2 × at least 7 days apart
or	Ivermectin[7,53]	200 μg/kg PO × 3 doses, on days 1, 2, and 10	200 μg/kg PO × 3 doses, on days 1, 2, and 10
Loa loa, see Filariasis			
Malaria, treatment of *(Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax,* and *Plasmodium malariae)*			
P. falciparum[54] acquired in areas of **chloroquine resistance**			
Oral[55]			
Drugs of choice:	Atovaquone/proguanil[56]	2 adult tabs PO bid[58] or 4 adult tabs PO once daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days
or	Quinine sulfate	650 mg PO every 8 hr × 3-7 days[57]	30 mg/kg/day PO in 3 doses × 3-7 days[57]
	plus doxycycline[7,14]	100 mg PO bid × 7 days	4 mg/kg/day PO in 2 doses × 7 days
	or plus tetracycline[7,14]	250 mg PO qid × 7 days	6.25 mg/kg PO qid × 7 days
	or plus clindamycin[7,59]	20 mg/kg/day PO in 3 doses × 7 days[60]	20 mg/kg/day PO in 3 doses × 7 days

[49]Mucosal infection is most commonly due to the New World species *L. (V.) braziliensis, L. (V.) panamensis,* or *L. (V.) guyanensis*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

[50]For infestation of eyelashes with *Phthirus pubis* lice, use petrolatum; TMP-SMX has also been used (Meinking TL: *Curr Probl Dermatol* 24:157, 1996). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective together with permethrin for head lice (Hipolito RB, et al: *Pediatrics* 107:E30, 2001).

[51]Yoon KS, et al: *Arch Dermatol* 139:994, 2003.

[52]A second application is recommended 1 wk later to kill hatching progeny. Some lice are resistant to pyrethrins and permethrin (Meinking et al: *Arch Dermatol* 2002;138:220).

[53]Ivermectin is effective against adult lice but has no effect on nits (Jones KN, JC English III: *Clin Infect Dis* 36:1355, 2003).

[54]Chloroquine-resistant *P. falciparum* occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant. *P. falciparum* in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artemether plus mefloquine may be used (Luxemburger JC, et al: *Trans R Soc Trop Med Hyg* 88:213, 1994; Karbwang J, et al: *Trans R Soc Trop Med Hyg* 89:296, 1995).

[55]Uncomplicated or mild malaria may be treated with oral drugs.

[56]Atovaquone/proguanil is available as a fixed-dose combination tablet: adult tablets (Malarone; atovaquone 250 mg/proguanil 100 mg) and pediatric tablets (Malarone Pediatric; atovaquone 62.5 mg/proguanil 25 mg). To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown and use is generally not recommended. In a few small studies outcomes were normal in women treated with the combination in the 2nd and 3rd trimester (B Paternak et al., *Arch Intern Med* 2011; 171:259; AK Boggild et al., *Am J Trop Med Hyg* 2007; 76:208). The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min). There have been isolated case reports of resistance in *P. falciparum* in Africa, but *Medical Letter* consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (E Schwartz et al., *Clin Infect Dis* 2003; 37:450; A Farnert et al., *BMJ* 2003; 326:628; S Kuhn et al., *Am J Trop Med Hyg* 2005; 72:407; CT Happi et al., *Malar J* 2006; 5:82).

[57]In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

[58]Although approved for once daily dosing, *Medical Letter* consultants usually divide the dose in 2 to decrease nausea and vomiting.

[59]For use in pregnancy.

[60]Lell B, Kremsner PG: *Antimicrob Agents Chemother* 46:2315, 2002.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Coartem (Artemether-lumefantrine)	1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of six oral doses is recommended for both adult and pediatric patients based on weight. These six doses should be administered over 3 days (4 tabs/dose at 0, 8, 24, 36, 48, and 60 hr)	5 to <15 kg: 1 tablet PO per dose 15 to <25 kg: 2 tablets PO per dose 25 to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose
Alternative:	Mefloquine[61,62]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
P. vivax[63] acquired in areas of **chloroquine resistance**			
Oral[55]			
Drug of choice:	Quinine sulfate **plus** doxycycline[7,14] **plus** primaquine[64]	650 mg PO every 8 hr × 3-7 days[57] 100 mg PO bid × 7 days 30 mg base PO daily × 14 days	30 mg/kg/day PO in 3 doses × 3-7 days[57] 4 mg/kg/day PO in 2 doses × 7 days 0.5 mg/kg/day PO × 14 days
or	Mefloquine[61]	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
Alternatives:	Chloroquine **plus** primaquine[64]	25 mg base/kg PO in 3 doses over 48 hr 30 mg base PO daily × 14 days	25 mg base/kg PO in 3 doses over 48 hr 0.5 mg/kg/day PO × 14 days
All *Plasmodium* except **chloroquine-resistant *P. falciparum***[54] and **chloroquine-resistant *P. vivax***[63] **(areas without chloroquine resistance)**			
Oral[55]			
Drug of choice:	Chloroquine phosphate[65]	1 g (600 mg base), then 500 mg (300 mg base) 6 hr later PO, then 500 mg (300 mg base) at 24 and 48 hr	10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 hr later PO, then 5 mg base/kg at 24 and 48 hr
All *Plasmodium*			
Parenteral (severe infection; chloroquine-sensitive and resistant)			
Drugs of choice[66]:	Quinidine gluconate[67]	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started
or	Quinine dihydrochloride[67]	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started

[61]At this dosage, adverse effects including nausea, vomiting, diarrhea, dizziness, disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option because of increased risk for stillbirth (Nosten F, et al: *Clin Infect Dis* 28:808, 1999). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[62]*P. falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

[63]*P. vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia, and Peru.

[64]Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primaquine should not be used during pregnancy.

[65]If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

[66]Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications (Miller KD, et al: *N Engl J Med* 321:65, 1989).

[67]Continuous ECG, blood pressure, and glucose monitoring are recommended, especially in pregnant women and young children. For problems with quinidine availability, call the manufacturer (Eli Lilly, 800-545-5979) or the CDC Malaria Hotline (770-488-7788). Quinidine may have greater antimalarial activity than quinine. The loading dose should be decreased or omitted in those patients who have received quinine or mefloquine. If more than 48 hr of parenteral treatment is required, the quinine or quinidine dose should be reduced by 30-50%.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Alternative:	Artesunate[68] Plus a second oral drug	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr
Prevention of relapses: *P. vivax* and *P. ovale* only			
Drug of choice:	Primaquine phosphate[64]	30 mg base/day PO × 14 days	0.6 mg base/kg/day PO × 14 days
Malaria, prevention of[69]			
Chloroquine-sensitive areas[54]			
Drug of choice	Chloroquine phosphate[70,71]	500 mg (300 mg base), PO once/wk[72]	5 mg/kg base once/wk, up to adult dose of 300 mg base[72]
Chloroquine-resistant areas[54]			
Drug of choice:	Atovaquone/proguanil[56,71]	1 adult tab PO q day[73]	11-20 kg: 1 pediatric tab PO/day[56,73] 21-30 kg: 2 pediatric tabs PO/day[56,73] 31-40 kg: 3 pediatric tabs PO/day[56,73] >40 kg: 1 adult tab PO/day[56,73]
or	Mefloquine[61,71,74]	250 mg PO once/wk[72]	<9 kg: 5 mg/kg salt once/wk[72] 9-19 kg: ¼ tab once/wk[72] 19-30 kg: ½ tab once/wk[72] 31-45 kg: ¾ tab once/wk[72] >45 kg: 1 tab once/wk[72]
or	Doxycycline[7,71]	100 mg PO daily[75]	2 mg/kg/day, up to 100 mg/day[75]
Alternatives:	Primaquine[7]	30 mg base PO daily[76]	0.6 mg/kg base daily
Malaria, self-presumptive treatment[77]			
Drug of choice:	Atovaquone/proguanil[7,56, 78]	4 adult tabs PO daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days

[68]Oral artesunate is not available in the United States; the IV formulation is available through the CDC Malaria branch under an investigational new drug (IND) for patients with severe disease who do not have timely access or cannot tolerate, or fail to respond to IV quinidine (*Med Lett Drugs Ther* 2008; 50:37). To avoid development of resistance, adults treated with artesunate must also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin, or mefloquine; children should take either atovaquone/proguanil, clindamycin, or mefloquine (F Nosten et al., *Lancet* 2000; 356:297; M van Vugt, *Clin Infect Dis* 2002; 35:1498; F Smithuis et al., *Trans R Soc Trop Med Hyg* 2004; 98:182). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group, *Lancet* 2005; 366:717; PE Duffy and CH Sibley, *Lancet* 2005;366:1908). Reduced susceptibility to artesunate characterized by slow parasitic clearance has been reported in Cambodia (WO Rogers et al., *Malar J* 2009; 8:10; AM Dundorp et al., *N Engl J Med* 2009; 361:455).

[69]No drug regimen guarantees protection against malaria. If fever develops within a year (particularly within the first 2 mo) after travel to malarious areas, travelers should be advised to seek medical attention. Insect repellents, insecticide-impregnated bed nets, and proper clothing are important adjuncts for malaria prophylaxis (*Med Lett* 45:41, 2003). Malaria in pregnancy is particularly serious for both mother and fetus; therefore, prophylaxis is indicated if exposure cannot be avoided.

[70]In pregnancy, chloroquine prophylaxis has been used extensively and safely.

[71]For prevention of attack after departure from areas where *P. vivax* and *P. ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some experts prescribe in addition primaquine phosphate 30 mg base/day or, for children, 0.6 mg base/kg/day during the last 2 wk of prophylaxis. Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 64.

[72]Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone. Most adverse events occur within 3 doses. Some *Medical Letter* consultants favor starting mefloquine 3 wk prior to travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water. For pediatric doses less than ½ tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There are no data for use in children weighing <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.

[73]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al: *Clin Infect Dis* 33:1015, 2001).

[74]Mefloquine has not been approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the 2nd or 3rd trimester of pregnancy and possibly during early pregnancy as well. Mefloquine is not recommended for patients with cardiac conduction abnormalities, and patients with a history of depression, seizures, psychosis, or psychiatric disorders should avoid mefloquine prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders; in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.

[75]Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause gastrointestinal disturbances, vaginal moniliasis, and photosensitivity reactions.

[76]Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malaria area provides effective prophylaxis against chloroquine-resistant *P. falciparum* (Baird JK, et al: *Clin Infect Dis* 37:1659, 2003). Some studies have shown less efficacy against *P. vivax*. Nausea and abdominal pain can be diminished by taking with food.

[77]A traveler can be given a course of atovaquone/proguanil, mefloquine, or quinine plus doxycycline for presumptive self-treatment of febrile illness. The drug given for self-treatment should be different from that used for prophylaxis. This approach should be used only in very rare circumstances when a traveler cannot promptly get to medical care.

[78]Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving malarious zone. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (D Overbosch et al., *Clin Infect Dis* 2001; 33:1015). The protective efficacy of Malarone against *P. vivax* is variable ranging from 84% in Indonesian New Guinea (J Ling et al., *Clin Infect Dis* 2002; 35:825) to 100% in Colombia (J Soto et al., *Am J Trop Med Hyg* 2006; 75:430). Some *Medical Letter* consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate plus doxycycline[7,14]	650 mg PO every 8 hr × 3-7 days[57] 100 mg bid PO × 7 days	30 mg/kg/day PO in 3 doses × 3-7 days[57] 4 mg/kg/day in 2 PO doses × 7 days
or	Mefloquine[61]	750 mg PO followed 12 hr later by 500 mg	15 mg/kg followed 12 hr later by 10 mg/kg
Microsporidiosis			
Ocular *(Encephalitozoon hellem, Encephalitozoon cuniculi, Vittaforma corneae [Nosema corneum])*			
Drug of choice:	Albendazole[7] **plus** fumagillin[79]	400 mg PO bid	
Intestinal *(Enterocytozoon bieneusi, Encephalitozoon [Septata] intestinalis)*			
E. bieneusi[80]			
Drug of choice:	Fumagillin	60 mg/day PO × 14 days in 3 divided doses	
E. intestinalis			
Drug of choice	Albendazole[7]	400 mg PO bid × 21 days	
Disseminated *(E. hellem, E. cuniculi, E. intestinalis, Pleistophora* sp., *Trachipleistophora* sp., and *Brachiola vesicularum)*			
Drug of choice[81]:	Albendazole[7]	400 mg PO bid	
Mites, see Scabies			
Moniliformis *moniliformis* infection			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg PO once, repeat twice, 2 wk apart	11 mg/kg PO once, repeat twice, 2 wk apart
***Naegleria* species,** see Amebic meningoencephalitis, primary			
Necator americanus, see Hookworm infection			
Oesophagostomum *bifurcum*			
Drug of choice:	See footnote 82		
Onchocerca volvulus, see Filariasis			
Opisthorchis viverrini, see Fluke infection			
Paragonimus westermani, see Fluke infection			
Pediculus capitis, Pediculus humanus, Phthirus pubis, see Lice			
Pinworm, see *Enterobius*			
Pneumocystis jiroveci (formerly *Pneumocystis carinii*) pneumonia (PCP)[83]			
Moderate to severe disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days
Alternatives:	Pentamidine *or* Primaquine **plus** clindamycin[7]	3-4 mg IV daily × 21 days 30 mg base PO daily × 21 days 600-900 mg IV tid or qid × 21 days, or 300-450 mg PO tid or qid × 21 days (change to PO after clinical improvement)	3-4 mg IV daily × 21 days 0.3 mg/kg base PO (max 30 mg) daily × 21 days 15-25 mg/kg IV tid or qid × 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days (change to PO after clinical improvement)

[79]Ocular lesions caused by *E. hellem* in HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC: *Am J Ophthalmol* 115:293, 1993), available from Leiter's Park Avenue Pharmacy (see footnote 1). For lesions caused by *V. corneae*, topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al: *Ophthalmology* 97:953, 1990).

[80]Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating *E. bieneusi* (Molina J-M, et al: *N Engl J Med* 346:1963, 2002), but has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.

[81]Molina J-M, et al: *J Infect Dis* 171:245, 1995. There is no established treatment for *Pleistophora*. For disseminated disease caused by *Trachipleistophora* or *Brachiola*, itraconazole 400 mg PO once/day plus albendazole may also be tried (Coyle CM, et al: *N Engl J Med* 351:42, 2004).

[82]Albendazole or pyrantel pamoate may be effective (Ziem JB, et al: *Ann Trop Med Parasitol* 98:385, 2004).

[83]*Pneumocystis* has been reclassified as a fungus. In severe disease with room air P_{O_2} ≤70 mm Hg or A-aO_2 gradient ≥35 mm Hg, prednisone should also be used (Gagnon S, et al: *N Engl J Med* 323:1444, 1990; Caumes E, et al: *Clin Infect Dis* 18:319, 1994).

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mild to moderate disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	2 DS tablets (160 mg/800 mg each) PO tid × 21 days	TMP 15-20 mg/kg/day SMX 75-100 mg/kg/day PO in 3 or 4 doses × 21 days
Alternative:	Dapsone	100 mg PO daily × 21 days	2 mg/kg/day (max 100 mg) PO × 21 days
	plus trimethoprim	15 mg/kg/day PO in 3 doses	15 mg/kg/day PO in 3 doses
	or primaquine	30 mg base PO daily × 21 days	0.3 mg/kg base PO daily (max 30 mg) × 21 days
	plus clindamycin	300-450 mg PO tid or qid × 21 days	10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days
	or atovaquone	750 mg PO bid × 21 days	1-3 mo: 30 mg/kg/day PO in 2 doses × 21 days 4-24 mo: 45 mg/kg/day PO in 2 doses × 21 days >24 mo: 30 mg/kg/day PO in 2 doses × 21 days
Primary and secondary prophylaxis[84]			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	1 tab (single or double strength) PO daily or 1 DS tab PO 3 doses/wk	TMP 150 mg/m^2, SMX 750 mg/m^2 PO in 2 doses on 3 consecutive days per wk
Alternatives[85]:	Dapsone[7]	50 mg PO bid, or 100 mg PO daily	2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk
or	Dapsone[7] **plus** pyrimethamine[86]	50 mg PO daily or 200 mg PO each wk 50 mg PO or 75 mg PO each wk	
or	Pentamidine aerosol	300 mg inhaled monthly via *Respirgard II* nebulizer	≥5 yr: 300 mg inhaled monthly via *Respirgard II* nebulizer
or	Atovaquone[7]	1,500 mg/d PO in 1 or 2 doses	1-3 mo: 30 mg/kg/day PO 4-24 mo: 45 mg/kg/day PO >24 mo: 30 mg/kg/day PO
Roundworm, see Ascariasis			
Sappinia diploidea, see Amebic meningoencephalitis, primary			
Scabies *(Sarcoptes scabiei)*			
Drug of choice:	5% Permethrin	Topically, 2× at least 7 days apart[87]	Topically, 2× at least 7 days apart[87]
Alternatives[88]:	Ivermectin[7,89] 10% Crotamiton	200 μg/kg PO 2× at least 7 days apart [87] Topically overnight on days 1, 2, 3, 8	200 μg/kg PO 2× at least 7 days apart [87] Topically overnight on days 1, 2, 3, 8
Schistosomiasis *(Bilharziasis)*			
Schistosoma haematobium			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Schistosoma intercalatum			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Schistosoma japonicum			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day

[84]Primary/secondary prophylaxis in patients with HIV can be discontinued after CD4 count increases to >200 × 10^6/L for longer than 3 mo.

[85]An alternative trimethoprim-sulfamethoxazole regimen is 1 DS tab 3×/wk. Weekly therapy with sulfadoxine 500 mg/pyrimethamine 25 mg/leucovorin 25 mg was effective *Pneumocystis carinii* pneumonia (PCP) prophylaxis in liver transplant patients (Torre-Cisneros J, et al: *Clin Infect Dis* 29:771, 1999).

[86]Plus leucovorin 25 mg with each dose of pyrimethamine.

[87]In some cases, treatment may need to be repeated in 10-14 days. BJ Currie and JS McCarthy, *N Engl J Med* 2010; 362:717. A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (V Usha et al., *J Am Acad Dermatol* 2000; 42:236). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (P del Giudice, *Curr Opin Infect Dis* 2004; 15:123).

[88]Lindane (γ-benzene hexachloride; Kwell) should be reserved as a second-line agent. The FDA has recommended it should not be used for immunocompromised patients, young children, the elderly, and patients who weigh <50 kg.

[89]Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P: *Curr Opin Infect Dis* 15:123, 2004). The safety of oral ivermectin in pregnancy and young children has not been established.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Schistosoma mansoni			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Alternative:	Oxamniquine[90]	15 mg/kg PO once[91]	20 mg/kg/day PO in 2 doses × 1 day[91]
Schistosoma mekongi			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
Sleeping sickness, see Trypanosomiasis			
Strongyloidiasis *(Strongyloides stercoralis)*			
Drug of choice[92]:	Ivermectin	200 μg/kg/day PO × 2 days	200 μg/kg/day PO × 2 days
Alternative:	Albendazole[7, 93]	400 mg PO bid × 7 days	400 mg bid PO × 7 days
Tapeworm infection			
Adult (intestinal stage)			
Diphyllobothrium latum **(fish),** ***Taenia saginata*** **(beef),** ***Taenia solium*** **(pork),** ***Dipylidium caninum*** **(dog)**			
Drug of choice:	Praziquantel[7]	5-10 mg/kg PO once	5-10 mg/kg PO once
Alternative:	Niclosamide	2 g PO once	50 mg/kg PO once
Hymenolepis nana **(dwarf tapeworm)**			
Drug of choice:	Praziquantel[7]	25 mg/kg PO once	25 mg/kg PO once
Alternative:	Niclosamide	2 g PO daily × 7 days	11-34 kg: 1 g PO on day 1 then 500 mg/day PO × 6 days[94] >34 kg: 1.5 g PO on day 1 then 1 g/d PO × 6 days[94]
Larval (tissue stage)			
Echinococcus granulosus (hydatid cyst)			
Drug of choice[95]:	Albendazole	400 mg PO bid × 1-6 mo	15 mg/kg/day PO (max 800 mg) × 1-6 mo
Echinococcus multilocularis			
Treatment of choice:	See footnote 96		
Taenia solium (cysticercosis)			
Treatment of choice		See footnote 97	
Alternative:	Albendazole	400 mg bid PO × 8-30 days; can be repeated as necessary	15 mg/kg/day PO (max 800 mg) in 2 doses × 8-30 days; can be repeated as necessary
or	Praziquantel[7]	50 mg/kg/day PO in 3 doses × 15 days	50 mg/kg/day PO × 15 day
Toxocariasis, see Visceral larva migrans			

[90]Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al: *J Infect Dis* 176:304, 1997). Oxamniquine is contraindicated in pregnancy.

[91]In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC: *Drugs* 42:379, 1991).

[92]In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy, or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiodini PL, et al: *Lancet* 355:43, 2000; Orem J, et al: *Clin Infect Dis* 37:152, 2003; Tarr PE: *Am J Trop Med Hyg* 68:453, 2003).

[93]Albendazole must be taken with food; a fatty meal increases oral bioavailability.

[94]Niclosamide must be thoroughly chewed or crushed and swallowed with a small amount of water. Nitazoxanide may be an alternative (JJ Ortiz et al., *Trans R Soc Trop Med Hyg* 2002; 96:193; JC Chero et al., *Trans R Soc Trop Med Hyg* 2007; 101:203; E Diaz et al., *Am J Trop Med Hyg* 2003; 68:384).

[95]Patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Percutaneous aspiration-injection-reaspiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al: *Clin Infect Dis* 37:1073, 2003).

[96]Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P: *Curr Opin Infect Dis* 16:437, 2003).

[97]Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JM: *N Engl J Med* 350:215, 2004). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (Garcia HH, et al: *N Engl J Med* 350:249, 2004). Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days (Proaño JV, et al: *N Engl J Med* 345:879, 2001). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Arachnoiditis, vasculitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White Jr AC: *Annu Rev Med* 51:187, 2000). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Toxoplasmosis *(Toxoplasma gondii)*[98]			
Drugs of choice[99,100]:	Pyrimethamine[101]	200 mg PO × 1, then 50-75 mg/day × 3-6 wk	2 mg/kg/d × 3 days, then 1 mg/kg/day (max 25 mg/day) × 4 wk[102]
	plus Sulfadiazine	1-1.5 g PO qid × 3-6 wk	100-200 mg/kg/day × 3-4 wk
	or **plus** Clindamycin	1.8-2.4 g/day IV or PO in 3 or 4 doses	5-7.5 mg/kg/day IV or PO in 3 or 4 doses (max 600 mg/dose)
	or **plus** Atovaquone	1,500 mg PO bid	1,500 mg PO bid
Alternative:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses
Trichinellosis *(Trichinella spiralis)*			
Drugs of choice:	Steroids for severe symptoms **plus** Albendazole[7]	Prednisone 30-60 mg PO daily × 10-15 days; 400 mg PO bid × 8-14 days	400 mg PO bid × 8-14 days
Alternative:	Mebendazole[7]	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days
Trichomoniasis *(Trichomonas vaginalis)*			
Drug of choice[103]:	Metronidazole	2 g PO once or 500 mg PO bid × 7 days	15 mg/kg/day PO in 3 doses × 7 days
or	Tinidazole[5]	2 g PO once	50 mg/kg PO once (max 2 g)
Trichostrongylus infection			
Drug of choice:	Pyrantel pamoate[7]	11 mg/kg base PO once (max 1 g)	11 mg/kg PO once (max 1 g)
Alternative:	Mebendazole[7]	100 mg PO bid × 3 days	100 mg PO bid × 3 days
or	Albendazole[7]	400 mg PO once	400 mg PO once
Trichuriasis (*Trichuris trichiura*, whipworm)			
Drug of choice:	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
Alternative:	Albendazole[7] Ivermectin[7]	400 mg PO × 3 days 200 μg/kg PO × 3 days	400 mg PO × 3 days 200 μg/kg PO × 3 days
Trypanosomiasis[104]			
Trypanosoma cruzi (American trypanosomiasis, Chagas disease)			
Drug of choice:	Benznidazole	5-7 mg/kg/day PO in 2 divided doses × 60 days	≤12 yr: 10 mg/kg/day PO in 2 or 3 doses × 60 days
or	Nifurtimox[105]	8-10 mg/kg/day PO in 3-4 doses × 90 days	1-10 yr: 15-20 mg/kg/day PO in 4 doses × 90 days 11-16 yr: 12.5-15 mg/kg/day in 4 doses × 90 days

[98]In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.

[99]To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al: *Clin Infect Dis* 34:1243, 2002). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with $<100 \times 10^6$/L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to $>200 \times 10^6$/L for more than 3 mo (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004).

[100]Women who develop toxoplasmosis during the 1st trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the 1st trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, Liesenfeld O: *Lancet* 363:1965, 2004). Pyrimethamine is a potential teratogen and should be used only after the 1st trimester.

[101]Plus leucovorin 10-25 mg with each dose of pyrimethamine.

[102]Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, Klein JO, editors: *Infectious disease of the fetus and newborn infant*, ed 5, Philadelphia, 2001, WB Saunders, p. 290).

[103]Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day × 7-14 days) or with tinidazole (Hager WD: *Sex Transm Dis* 31:343, 2004).

[104]Barrett MP, et al: *Lancet* 362:1469, 2003.

[105]The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al: *J Infect Dis* 163:912, 1991).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Trypanosoma brucei gambiense (West African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice[106]:	Pentamidine isethionate[7]	4 mg/kg/day IM × 7 days	4 mg/kg/day IM or IV × 7 days
Alternative:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol[107]	2.2 mg/kg/day IV × 10 days	2.2 mg/kg/day IV × 10 days
or	Eflornithine[108]	400 mg/kg/day IV in 4 doses × 14 d	400 mg/kg/day in 4 doses × 14 days
Trypanosoma brucei rhodesiense (East African trypanosomiasis, sleeping sickness)			
Hemolymphatic stage			
Drug of choice:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol[107]	2.2 mg/kg/day × 10 days	2.2 mg/kg/day × 10 days
Visceral larva migrans[109] (Toxocariasis)			
Drugs of choice:	Albendazole[7] Mebendazole[7]	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days
Whipworm, see Trichuriasis			
Wuchereria bancrofti, see Filariasis			

[106]For treatment of *T. b. gambiense*, pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

[107]In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy (Pepin J, et al: *Trans R Soc Trop Med Hyg* 89:92, 1995). Up to 20% of patients with *T. b. gambiense* fail to respond to melarsoprol (Barrett MP: *Lancet* 353:1113, 1999).

[108]Eflornithine is highly effective in *T. b. gambiense* but not against *T. b. rhodesiense* infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 d when used in conjunction with nifurtimox at a dose of 15 mg/kg/d PO in 3 doses × 10 d.

[109]Optimum duration of therapy is not known; some *Medical Letter* consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.

CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DS, double strength; ECG, electrocardiography; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; SMX, sulfamethoxazole; TMP, trimethoprim; WHO, World Health Organization.

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SELECTED ANTIPARASITIC DRUGS FOR HELMINTHS

Albendazole (Albenza)

Albendazole is a benzimidazole carbamate structurally related to mebendazole and has similar anthelmintic activity. Its absorption from the gastrointestinal tract is poor but improved with a concomitant high-fat meal. Albendazole sulfoxide, the principal metabolite with anthelmintic activity, has a plasma half-life of 8.5 hr. It is widely distributed in the body, including the bile and cerebrospinal fluid. It is eliminated by bile. Albendazole is FDA approved for treatment of neurocysticercosis and hydatid diseases *(Echinococcus granulosus)*. It is not FDA approved but is used for *Ancylostoma caninum*, ascariasis, Chinese liver fluke, cutaneous larva migrans, pinworms, filariasis, gnathostomiasis, hookworms, microsporidiosis, and visceral larva migrans. Albendazole is generally well tolerated. Common adverse effects include headache, nausea, vomiting, and abdominal pain. Serious adverse effects include elevated liver enzymes and leukopenia, which have occurred in a few patients with treatment of hydatid disease. Rare adverse effects include acute renal failure, pancytopenia, granulocytopenia, and thrombocytopenia.

Ivermectin (Stromectol, Mectizan)

Ivermectin is a semisynthetic derivative of 1 of the avermectins, which is a group of macrocyclic lactones produced by *Streptomyces avermitilis*. After oral administration, ivermectin has peak plasma concentrations after approximately 4 hr and a plasma elimination half-life of approximately 12 hr. It is excreted as metabolites over a 2 wk period via feces. It is FDA approved for treatment of onchocerciasis and intestinal strongyloidiasis. It may have some effect in treating cutaneous larva migrans, intestinal nematode infections, loiasis, lymphatic filariasis, *Mansonella* infections, and scabies. Combination therapies of ivermectin with albendazole or diethylcarbamazine are being used to treat lymphatic filariasis. Common adverse events include dizziness, headache, pruritus, and gastrointestinal effects. Serious adverse events include Mazzotti reactions, including arthralgia, synovitis, enlarged lymph nodes, rash, and fever secondary to microfilaria death in patients with onchocerciasis.

Praziquantel (Biltricide)

Praziquantel achieves its antiparasitic activity via the pyrazino isoquinoline ring system and was originally synthesized as a potential tranquillizer. After oral administration, praziquantel is rapidly absorbed with peak levels in 1-2 hr and plasma half-life of about 1-3 hr. Elimination via the urine and feces is >80% complete after 24 hr. Praziquantel is metabolized in the liver by the microsomal cytochrome P450 (especially 2B1 and 3A). Bioavailability of praziquantel is increased with concomitant administration of agents that inhibit cytochrome P450. Praziquantel is FDA approved for treatment of Chinese liver fluke, Southeast Asian liver fluke, and schistosomiasis. It is used for treatment of intestinal flukes, North American liver fluke, *Nanophyetus salmincola*, lung fluke, and tapeworm infections but is not FDA approved for these indications. Adverse effects can be seen in 30-60% of patients,

although most are mild and disappear within 24 hr. Common adverse effects include headache, abdominal pain, dizziness, and malaise. Serious but rare adverse effects include arrhythmias, heart block, and convulsions.

Section 15

Protozoan Diseases

Chapter 280

Primary Amebic Meningoencephalitis

Matthew D. Eberly and Martin E. Weisse

Naegleria, Acanthamoeba, Balamuthia, and *Sappinia* are small, free-living amebas that cause human amebic meningoencephalitis, which has 2 distinct clinical presentations. The more common is an acute, fulminant, and usually fatal **amebic meningitis** caused by *Naegleria* that occurs in previously healthy children and young adults. **Granulomatous amebic meningoencephalitis,** which is caused by *Acanthamoeba, Balamuthia,* and *Sappinia,* is a more indolent infection that typically occurs in immunocompromised hosts.

ETIOLOGY

Naegleria is an ameboflagellate that can exist as cysts, trophozoites, and transient flagellate forms. Temperature and environmental nutrient and ion concentrations are the major factors that determine the stage of the ameba. Trophozoites are the only stages that are invasive, although cysts are potentially infective, because they can convert to the vegetative form very quickly under the proper environmental stimuli. Although there are some 30 species of *Naegleria,* only *Naegleria fowleri* has been shown to be pathogenic for humans.

Acanthamoeba exist in cyst and motile trophozoite forms; only the trophozoite form is invasive. Cases of *Acanthamoeba* **keratitis** usually follow incidents of trivial corneal trauma followed by flushing with contaminated tap water. Infections can also occur among contact lens wearers who come in contact with contaminated water during swimming or using contact lenses cleaned or stored in contaminated tap water. Granulomatous amebic encephalitis from *Acanthamoeba* occurs worldwide and is associated with an immunocompromising condition such as HIV infection, diabetes mellitus, chronic liver disease, renal failure, immunosuppressive therapy, or radiation therapy.

Balamuthia mandrillaris has been implicated as an etiology of granulomatous amebic encephalitis. Although the clinical presentation is similar to infection with *Acanthamoeba,* most patients are not immunocompromised.

Other free-living amebas can also cause infection, as illustrated by case reports of *Sappinia diploidea* granulomatous encephalitis.

EPIDEMIOLOGY

The free-living amebas have a worldwide distribution. *Naegleria* species have been isolated from a variety of freshwater sources, including ponds and lakes, domestic water supplies, hot springs and spas, thermal discharge of power plants, groundwater, and, occasionally, from the nasal passages of healthy children. *Acanthamoeba* species have been isolated from soil, mushrooms, vegetables, brackish water, and seawater, as well as most of the freshwater sources for *Naegleria.* It can also be found in tap water, as chlorination does not kill *Acanthamoeba. Balamuthia* is present in soil and may be transmitted by inhalation or contamination of preexisting skin lesions.

Naegleria meningoencephalitis has been reported from every continent. Most of the cases occur during the summer months in previously healthy individuals who have a history of swimming in or contact with freshwater before their illness. Only 1-2 cases are reported in the United States per year, but 8 cases were reported in 2001-2002, and 6 cases were reported in 2007. Most of the reports have come from the southern and southwestern states, particularly Florida and Texas, with occasional infections occurring in the Midwest and East. Of note, 2 cases from Louisiana in 2011 were linked to sinus irrigation with neti pots, which contained contaminated tap water.

PATHOGENESIS

The free-living amebas enter the nasal cavity by inhalation or aspiration of dust or water contaminated with trophozoites or cysts. *Naegleria* gains access to the central nervous system through the olfactory epithelium and migrates via the olfactory nerve to the olfactory bulbs located in the subarachnoid space and bathed by the cerebrospinal fluid (CSF). This space is richly vascularized and is the route of spread to other areas of the central nervous system. Grossly, there is widespread cerebral edema and hyperemia of the meninges. The olfactory bulbs are necrotic, hemorrhagic, and surrounded by a purulent exudate. Microscopically, the gray matter is the most severely affected, with severe involvement in all cases. Fibrinopurulent exudate may be found throughout the cerebral hemispheres, brainstem, cerebellum, and upper portions of the spinal cord. Pockets of trophozoites may be seen in necrotic neural tissue, usually in the perivascular spaces of arteries and arterioles.

The route of invasion and penetration in cases of granulomatous amebic meningoencephalitis caused by *Acanthamoeba* and *Balamuthia* may be by direct spread through olfactory epithelium or hematogenous from a primary focus in the skin or lungs. Pathologic examination reveals granulomatous encephalitis, with multinucleated giant cells mainly in the posterior fossa structures, basal ganglia, bases of the cerebral hemispheres, and cerebellum. Both trophozoites and cysts may be found in the central nervous system lesions, primarily located in the perivascular spaces and invading blood vessel walls. The olfactory bulbs and spinal cord are usually spared. The single case of *Sappinia* encephalitis followed a sinus infection, and evaluation revealed a solitary 2 cm temporal lobe mass with mild ring enhancement.

CLINICAL MANIFESTATIONS

The incubation of ***Naegleria* infection** may be as short as 2 days or as long as 15 days. Symptoms have an acute onset and progress rapidly. Infection is characterized by a sudden onset of severe headache, fever, pharyngitis, nasal congestion or discharge, and nausea and vomiting, followed by altered mental status, confusion, somnolence, seizures, and ultimately coma. Most cases end in death within 3-10 days after onset of symptoms.

Granulomatous amebic meningoencephalitis may occur weeks to months after initial infection. The presenting signs and symptoms are often those of single or multiple central nervous system space-occupying lesions and include hemiparesis, ataxia, personality changes, seizures, and drowsiness. Altered mental status is often a prominent symptom. Headache and fever occur only sporadically, but stiff neck is seen in a majority of cases. Cranial nerve palsies, especially of cranial nerves III and VI, may be present. There is also 1 report of acute hydrocephalus and fever with *Balamuthia.* Granulomatous amebic meningoencephalitis is usually fatal after 4-6 wk of illness. Results of neuroimaging studies of the brain usually demonstrate multiple low-density lesions resembling infarcts or enhancing lesions of granulomas (Fig. 280-1).

DIAGNOSIS

The CSF in *Naegleria* infection may mimic that of herpes simplex encephalitis early in the disease and that of acute bacterial meningitis later in the disease, with a neutrophilic pleocytosis, elevated protein level, and hypoglycorrhachia. Motile amebas may be visualized on a wet mount of freshly drawn CSF using Wright or Giemsa stains, but are often mistaken for lymphocytes or macrophages. Because *Naegleria* are the only amebas that differentiate into the flagellate state in a

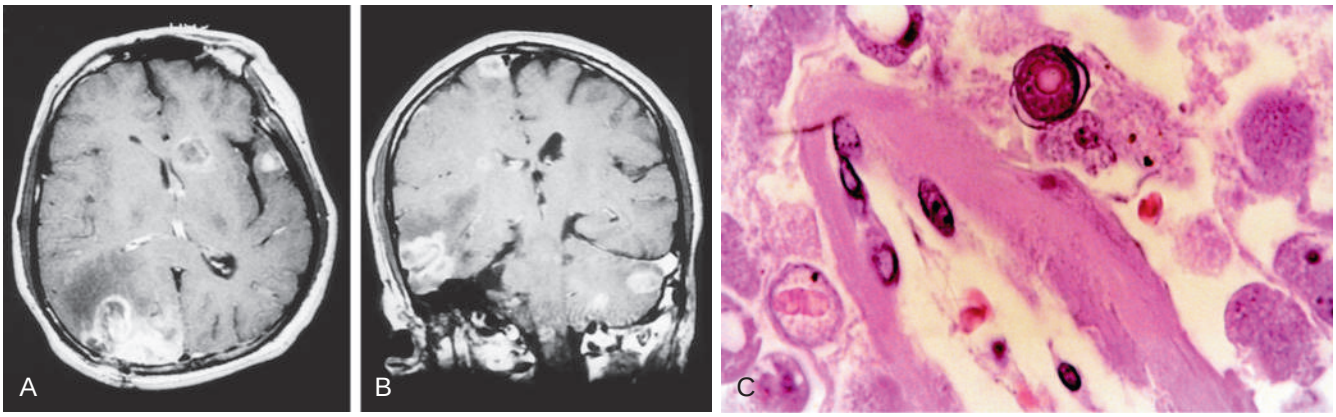

Figure 280-1 **A** and **B,** MRIs of the brain of a patient with *Balamuthia mandrillaris* granulomatous amebic encephalitis. Multiple enhancing lesions are seen in the right hemisphere, left cerebellum, midbrain, and brainstem. **C,** Photomicrograph of the brain lesion from the same patient showing perivascular amebic trophozoites. A round amebic cyst with a characteristic double wall is seen in the top center (hematoxylin-and-eosin, original magnification ×100). *(From Deol I, Robledo L, Meza A, et al: Encephalitis due to a free-living amoeba* [Balamuthia mandrillaris]*: case report with literature review,* Surg Neurol *53:611–616, 2000.)*

hypotonic environment, placing a drop of fresh CSF in 1 mL of distilled water and watching for development of swimming flagellates after 1-2 hr can confirm the diagnosis of *Naegleria*. *Naegleria* can also be grown on a nonnutrient agar plate coated with *Escherichia coli*, on which they feed.

The diagnosis of granulomatous amebic meningoencephalitis relies on the isolation or histologic identification of *Acanthamoeba* trophozoites or cysts from brain tissue specimens. The CSF findings of granulomatous meningoencephalitis reveal lymphocytic pleocytosis, moderately elevated protein, and low glucose concentrations. Motile trophozoites of *Acanthamoeba,* however, are more difficult to isolate than *Naegleria* and the CSF is typically sterile. *Acanthamoeba* may be cultured from the same agar used for growing *Naegleria,* but *Balamuthia* must be grown on mammalian cell cultures. Pediatric cases of *Balamuthia* meningoencephalitis have been diagnosed antemortem by brain biopsy as well as postmortem. Immunofluorescence staining of brain tissue can differentiate *Acanthamoeba* and *Balamuthia.*

TREATMENT

Naegleria infection is nearly always fatal, and early recognition and early treatment are crucial to successful therapy. There are several reports of treatment survivors, most of whom recovered fully. *Naegleria* infections have been successfully treated using amphotericin B, either alone or in combination with rifampin, chloramphenicol, fluconazole, or ketoconazole. The early use of dexamethasone may be considered, as steroid treatment was used in the few cases of survivors (as well as nonsurvivors). The optimal duration of treatment is unknown, but at least 10 days of therapy has been used in survivors. In 2013, the U.S. Centers for Disease Control and Prevention made available miltefosine for the treatment of primary amebic meningoencephalitis. In 2013, two children with *Naegleria* infection survived; both received miltefosine as part of their treatment; one received therapeutic hypothermia.

The optimal therapy for granulomatous amebic meningoencephalitis is also uncertain. Miltefosine has been used to successfully treat patients with *Balamuthia* and disseminated *Acanthamoeba* infections. Strains of *Acanthamoeba* isolated from fatal cases are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and less so to amphotericin B. One patient was successfully treated with sulfadiazine and fluconazole, and another was successfully treated with intravenous pentamidine followed by oral itraconazole. *Acanthamoeba* keratitis responds to long courses of topical propamidine–polymyxin B sulfate or topical polyhexamethylene biguanide or chlorhexidine gluconate, and antifungal azoles plus topical steroids. Limited success has been demonstrated in *Balamuthia* infection with systemic azole therapy combined with flucytosine. More recently, the combination of flucytosine, pentamidine, fluconazole, sulfadiazine, a macrolide, and phenothiazines resulted in the survival of 2 patients with *Balamuthia* meningoencephalitis, although both were left with mild neuromotor and cognitive impairment. Corticosteroids prior to initiating effective therapy appear to have a detrimental effect, contributing to rapid progression of disease.

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Chapter 281

Amebiasis

Edsel Maurice T. Salvana and Robert A. Salata

Entamoeba species infects or colonizes up to 10% of the world's population, particularly in resource-limited settings. In most infected individuals, *Entamoeba histolytica* or a related species parasitizes the lumen of the gastrointestinal tract and causes few symptoms or sequelae. *E. histolytica* is the only invasive species and can cause **amebic colitis** with parasitic invasion of the intestinal mucosa and **amebic liver abscess** with dissemination of the parasite to the liver.

ETIOLOGY

Three morphologically identical but genetically distinct species of *Entamoeba* commonly infect humans. *Entamoeba dispar,* the most prevalent species, does not cause symptomatic disease. *Entamoeba moshkovskii*, previously thought to be nonpathogenic, has been shown to cause diarrhea in infants. *E. histolytica,* the main pathogenic species, causes a spectrum of disease and can become invasive in 4-10% of infected patients. Patients previously described as asymptomatic carriers of *E. histolytica* based on microscopy findings were likely harboring *E. dispar.* Four other species of nonpathogenic *Entamoeba* are known to colonize the human gastrointestinal tract: *E. coli, E. hartmanni, E. gingivalis,* and *E. polecki.*

Infection is acquired through the ingestion of parasite cysts, which measure 10-18 μm in diameter and contain 4 nuclei. Cysts are resistant to harsh environmental conditions, including chlorine concentrations commonly used in water purification, but can be killed by heating to 55°C (131°F). After ingestion, cysts are resistant to gastric acidity and digestive enzymes and germinate in the small intestine to form trophozoites. These large, actively motile organisms colonize the lumen of the large intestine and may invade the mucosal lining. Infection is not

usually transmitted by trophozoites, as these rapidly degenerate outside the body and are unable to survive the low pH of the stomach if swallowed.

EPIDEMIOLOGY

Prevalence of infection with *E. histolytica* varies greatly depending on region and socioeconomic status. Most prevalence studies have not distinguished between *E. histolytica* and *E. dispar,* and thus the true prevalence of *E. histolytica* infection is not known. It is estimated that infection with *E. histolytica* leads to 50 million cases of symptomatic disease and 40,000-110,000 deaths annually. Amebiasis is the second leading parasitic cause of death worldwide, after malaria. Prospective studies show that 4-10% of individuals infected with *E. histolytica* develop amebic colitis and that <1% of infected individuals develop disseminated disease, including amebic liver abscess. These numbers vary by region; for example, in South Africa and Vietnam, liver abscesses form a disproportionately large number of the cases of invasive disease caused by *E. histolytica.* Amebic liver abscesses are rare in children and occur equally in male and female children; in adults, amebic liver abscesses occur predominantly in men.

Amebiasis is endemic to Africa, Latin America, India, and Southeast Asia. In the United States, amebiasis is seen most frequently in immigrants from and in travelers to developing countries. Residents of mental health institutions and men who have sex with men are also at increased risk for invasive amebiasis. Food or drink contaminated with *Entamoeba* cysts and oral-anogenital sex are the most common means of infection. Untreated water and night soil (human feces used as fertilizer) are important sources of infection. Food handlers shedding amebic cysts play a role in spreading infection. Direct contact with infected feces can also result in person-to-person transmission.

PATHOGENESIS

Trophozoites are responsible for tissue invasion and destruction. These attach to colonic epithelial cells by a galactose and *N*-acetyl-D-galactosamine–specific lectin. This lectin is also thought to be responsible for resistance to complement-mediated lysis. Once attached to the colonic mucosa, amebas release proteases that allow for penetration through the epithelial layer. Host cells are destroyed by cytolysis and apoptosis. Cytolysis is mediated by trophozoite release of **amoebapores** (pore-forming proteins), phospholipases, and hemolysins. Amoebapores, which cause a massive influx of extracellular calcium, may also be partially responsible for the induction of apoptosis that occurs with amebic liver disease and colitis. Once host cells are partially digested by amebic proteases, the degraded material is internalized through phagocytosis. Early invasive amebiasis produces significant inflammation, due in part to parasite-mediated activation of nuclear factor-κB. Once *E. histolytica* trophozoites invade the intestinal mucosa, the organisms multiply and spread laterally underneath the intestinal epithelium to produce the characteristic **flask-shaped ulcers.** Amebas produce similar lytic lesions if they reach the liver. These lesions are commonly called *abscesses*, although they contain no granulocytes. Well-established ulcers and amebic liver abscesses demonstrate little local inflammatory response.

Immunity to infection is associated with a mucosal secretory IgA response against the galactose/*N*-acetyl-D-galactosamine lectin. Neutrophils appear to be important in initial host defense, but *E. histolytica*–induced epithelial cell damage releases neutrophil chemoattractants, and *E. histolytica* is able to kill neutrophils, which then release mediators that further damage epithelial cells. The disparity between the extent of tissue destruction by amebas and the absence of a local host inflammatory response in the presence of systemic humoral (antibody) and cell-mediated responses may reflect both parasite-mediated apoptosis and the ability of the trophozoite to kill not only epithelial cells but neutrophils, monocytes, and macrophages. Studies show a protective role of the hormone leptin in mucosal resistance. A malnourished state, in which leptin levels are low, and a genetic polymorphism in the leptin receptor can increase susceptibility to invasive disease.

The sequencing of the *E. histolytica* genome has led to further insights into the pathogenesis of *E. histolytica* disease. The genome is functionally tetraploid and contains evidence of lateral gene transfer from bacteria. It has been demonstrated that the **amoebapore-A** *(Ap-A)* gene, along with other important genes, can be epigenetically silenced using plasmids with specifically engineered sequences or short hairpin RNAs. Transcriptional profiling using proteomics and microarrays has likewise identified several candidate virulence factors. Several classes of proteases that may be associated with pathogenesis have been identified, including the cysteine proteases binding family proteins (CPBF8), which modulate lysosome and phagosome function, and M8 metalloprotease EhMSP-1, which likely has a key role in amebic invasion and is notably absent in *E. dispar*.

CLINICAL MANIFESTATIONS

Clinical presentations range from asymptomatic cyst passage to amebic colitis, amebic dysentery, ameboma, and extraintestinal disease. Up to 10% of infected persons develop invasive disease within a year. Thus, asymptomatic carriers should be treated. Severe disease is more common in young children, pregnant women, malnourished individuals, and persons taking corticosteroids, and invasive disease is more common in men. Extraintestinal disease usually involves the liver, but less common extraintestinal manifestations include amebic brain abscess, pleuropulmonary disease, ulcerative skin, and genitourinary lesions.

Amebic Colitis

Amebic colitis may occur within 2 wk of infection or may be delayed for months. The onset is usually gradual, with colicky abdominal pains and frequent bowel movements (6-8/day). Diarrhea is frequently associated with tenesmus. Almost all stool is heme-positive, but most patients do not present with grossly bloody stools. Generalized constitutional symptoms and signs are characteristically absent, with fever documented in only one third of patients. Amebic colitis affects all age groups but is strikingly common in children 1-5 yr of age. Severe amebic colitis in infants and young children tends to be rapidly progressive with more frequent extraintestinal involvement and high mortality rates, particularly in tropical countries. Amebic dysentery can result in dehydration and electrolyte disturbances.

Amebic Liver Abscess

Amebic liver abscess, a serious manifestation of disseminated infection, is uncommon in children. Although diffuse liver enlargement has been associated with intestinal amebiasis, liver abscesses occur in <1% of infected individuals and may appear in patients with no clear history of intestinal disease. Amebic liver abscess may occur months to years after exposure, so obtaining a careful travel history is critical. In children, fever is the hallmark of amebic liver abscess and is frequently associated with abdominal pain, abdominal distention, and enlargement and tenderness of the liver. Changes at the base of the right lung, such as elevation of the diaphragm and atelectasis or effusion, may also occur.

Men Who Have Sex with Men and HIV Coinfection

Epidemiologic studies from both developed and developing countries have shown an increased risk for *E. histolytica* infection among men who have sex with men. This risk is further increased in HIV because of increased host susceptibility, and is particularly pronounced in men who have sex with men with HIV infection.

LABORATORY FINDINGS

Laboratory examination findings are often unremarkable in uncomplicated amebic colitis. Laboratory findings in amebic liver abscess are a slight leukocytosis, moderate anemia, high erythrocyte sedimentation rate, and elevations of hepatic enzyme (particularly alkaline phosphatase) levels. Stool examination for amebas is negative in more than half of patients with documented amebic liver abscess. Ultrasonography, CT, or MRI can localize and delineate the size of the abscess cavity (Fig. 281-1). The most common finding is a single abscess in the right hepatic lobe in about one half of these cases. Higher-resolution

ultrasound and CT studies show that left lobe abscess and multiple abscesses occur more often than previously recognized.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A diagnosis of amebic colitis is made in the presence of compatible symptoms with detection of *E. histolytica* antigens in stool. This approach has a >95% sensitivity and specificity and coupled with a positive serology test is the most accurate means of diagnosis in developed countries. The *E. histolytica* II stool antigen detection test (TechLab, Blacksburg, VA) is able to distinguish *E. histolytica* from *E. dispar* infection. Microscopic examination of stool samples has a sensitivity of 60%. Sensitivity can be increased to 85-95% by examining 3 stools, as excretion of cysts can be intermittent. However, microscopy cannot differentiate between *E. histolytica* and *E. dispar* unless phagocytosed erythrocytes (specific for *E. histolytica*) are seen. In highly endemic areas, trophozoites without phagocytosed erythrocytes may reflect coinfection with *E. dispar* in a patient with another cause of colitis, such as shigellosis. Endoscopy and biopsies of suspicious areas should be performed when stool sample results are negative and suspicion for amebiasis remains high.

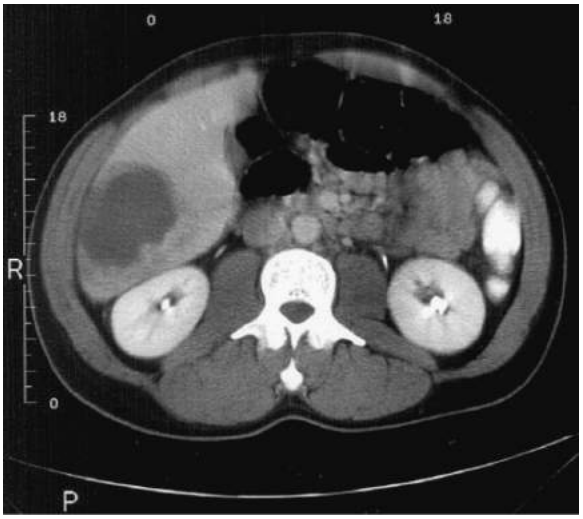

Figure 281-1 Abdominal CT scan of a patient with an amebic liver abscess. *(From Miller Q, Kenney JM, Cotlar AM: Amebic abscess of the liver presenting as acute cholecystitis,* Curr Surg *57:476–479, 2000, Fig. 1, p. 477.)*

Various serum antiamebic antibody tests are available. Serologic results are positive in 70-80% of patients with invasive disease (colitis or liver abscess) at presentation and in >90% of patients after 7 days of disease symptoms. The most sensitive serologic test, indirect hemagglutination, yields a positive result even years after invasive infection. Therefore, many uninfected adults and children in highly endemic areas demonstrate antibodies to *E. histolytica.* Polymerase chain reaction detection in stool of *E. histolytica* is also able to distinguish *E. histolytica* from *E. dispar* but is less sensitive (72%) than the stool antigen test. Rapid antigen and antibody tests for bedside diagnosis in the developing world have been developed and are currently being tested. A high-throughput Luminex technique for simultaneous detection and differentiation of *Entamoeba* species has also been developed. In addition, a loop-mediated isothermal amplification assay that can be optimized for field use is under development.

The **differential diagnosis** for amebic colitis includes colitis caused by bacterial (*Shigella, Salmonella,* enteropathogenic *Escherichia coli, Campylobacter, Yersinia, Clostridium difficile*), mycobacterial (tuberculosis and atypical mycobacteria), and viral (cytomegalovirus) pathogens, as well as noninfectious causes such as inflammatory bowel disease. Pyogenic liver abscess from bacterial infection, hepatoma, and echinococcal cysts are in the differential diagnosis for amebic liver abscess. However, echinococcal cysts are rarely associated with systemic symptoms such as fever unless there is cyst rupture or leakage.

COMPLICATIONS

Complications of amebic colitis include acute necrotizing colitis, ameboma, toxic megacolon, extraintestinal extension, or local perforation and peritonitis. Less commonly, a chronic form of amebic colitis develops, often recurring over several years. Amebomas are nodular foci of proliferative inflammation that sometimes develop in the wall of the colon. Chronic amebiasis should be excluded before initiating corticosteroid treatment for inflammatory bowel disease, as corticosteroid therapy given during active amebic colitis is associated with high mortality rates.

An amebic liver abscess may rupture into the peritoneum, pleural cavity, skin, and pericardium. Cases of amebic abscesses in extrahepatic sites, including the lung and brain, have been reported.

TREATMENT

Invasive amebiasis is treated with a nitroimidazole such as **metronidazole** or **tinidazole** and then a **luminal amebicide** (Table 281-1).

Table 281-1 Drug Treatment for Amebiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
INVASIVE DISEASE		
Metronidazole	Colitis or liver abscess: 750 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
or		
Diloxanide furoate†	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
or		
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
ASYMPTOMATIC INTESTINAL COLONIZATION		
Paromomycin (preferred)	As for invasive disease	As for invasive disease
or		
Diloxanide furoate†		
or		
Iodoquinol		

*All pediatric dosages are up to a maximum of the adult dose.
†Not available in the United States.

Tinidazole has similar efficacy to metronidazole with shorter and simpler dosing and less-frequent adverse effects. These adverse effects include nausea, abdominal discomfort, and a metallic taste that disappears after completion of therapy. Therapy with a nitroimidazole should be followed by treatment with a luminal agent, such as paromomycin (which is preferred) or iodoquinol. Diloxanide furoate can also be used in children older than 2 yr of age, but it is no longer available in the United States. Paromomycin should not be given concurrently with metronidazole or tinidazole, because diarrhea is a common side effect of paromomycin and may confuse the clinical picture. Asymptomatic intestinal infection with *E. histolytica* should be treated preferably with paromomycin or alternatively with either iodoquinol or diloxanide furoate. For fulminant cases of amebic colitis, some experts suggest adding dehydroemetine (1 mg/kg/day subcutaneously or IM, never IV), available only through the Centers for Disease Control and Prevention. Patients should be hospitalized for monitoring if dehydroemetine is administered. Dehydroemetine should be discontinued if tachycardia, T-wave depression, arrhythmia, or proteinuria develops.

Broad-spectrum antibiotic therapy may be indicated in fulminant colitis to cover possible spillage of intestinal bacteria into the peritoneum and translocation into the bloodstream. Intestinal perforation and toxic megacolon are indications for surgery. In amebic liver abscess, image-guided aspiration of large lesions or left lobe abscesses may be necessary if rupture is imminent or if the patient shows a poor clinical response 4-6 days after administration of amebicidal drugs. A Cochrane metaanalysis comparing metronidazole and metronidazole plus aspiration in uncomplicated amebic liver abscess showed that there is insufficient evidence to make any recommendation for or against this approach. Chloroquine, which concentrates in the liver, may also be a useful adjunct to nitroimidazoles in the treatment of amebic liver abscess. To confirm cure, stool examination should be repeated every 2 wk following completion of therapy until clear.

PROGNOSIS

Most infections evolve to either an asymptomatic carrier state or eradication. Extraintestinal infection carries about a 5% mortality rate.

PREVENTION

Control of amebiasis can be achieved by exercising proper sanitation and avoiding fecal-oral transmission. Regular examination of food handlers and thorough investigation of diarrheal episodes may help identify the source of infection. No prophylactic drug or vaccine is currently available for amebiasis. Immunization with a combination of galactose/*N*-acetyl-D-galactosamine lectin and CpG oligodeoxynucleotides is protective against amebic trophozoite challenge in animals, and an intranasal galactose-lectin subunit vaccine is protective in baboons.

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Chapter 282

Giardiasis and Balantidiasis

282.1 *Giardia lamblia*

Chandy C. John

Giardia lamblia is a flagellated protozoan that infects the duodenum and small intestine. Infection results in clinical manifestations that range from asymptomatic colonization to acute or chronic diarrhea and malabsorption. Infection is more prevalent in children than in adults. *Giardia* is endemic in areas of the world with poor levels of sanitation. It is also an important cause of morbidity in developed countries, where it is associated with urban childcare centers, residential institutions for the developmentally delayed, and waterborne and foodborne outbreaks. *Giardia* is a particularly significant pathogen in people with malnutrition, certain immunodeficiencies, and cystic fibrosis.

ETIOLOGY

The life cycle of *G. lamblia* (also known as *Giardia intestinalis* or *Giardia duodenalis*) is composed of 2 stages: trophozoites and cysts. *Giardia* infects humans after ingestion of as few as 10-100 cysts (which measure 8-10 µm in diameter). Each ingested cyst produces 2 trophozoites in the duodenum. After excystation, trophozoites colonize the lumen of the duodenum and proximal jejunum, where they attach to the brush border of the intestinal epithelial cells and multiply by binary fission. The body of the trophozoite is teardrop shaped, measuring 10-20 µm in length and 5-15 µm in width. *Giardia* trophozoites contain 2 oval nuclei anteriorly, a large ventral disk, a curved median body posteriorly, and 4 pairs of flagella. As detached trophozoites pass down the intestinal tract, they encyst to form oval cysts that contain 4 nuclei. Cysts are passed in stools of infected individuals and may remain viable in water for as long as 2 mo. Their viability often is not affected by the usual concentrations of chlorine used to purify water for drinking.

Giardia strains that infect humans are diverse biologically, as shown by differences in antigens, restriction endonuclease patterns, DNA fingerprinting, isoenzyme patterns, and pulsed-field gel electrophoresis. Studies suggest that different *Giardia* genotypes may cause unique clinical manifestations, but these findings appear to vary according to the geographic region tested.

EPIDEMIOLOGY

Giardia occurs worldwide and is the most common intestinal parasite identified in public health laboratories in the United States, where it is estimated that up to 2 million cases of giardiasis occur annually. *Giardia* infection usually occurs sporadically, but *Giardia* is a frequently identified etiologic agent of outbreaks associated with drinking water. The age-specific prevalence of giardiasis is high during childhood and begins to decline after adolescence. The asymptomatic carrier rate of *G. lamblia* in the United States is as high as 20-30% in children younger than 36 mo of age attending childcare centers. Asymptomatic carriage may persist for several months.

Transmission of *Giardia* is common in certain high-risk groups, including children and employees in childcare centers, consumers of contaminated water, travelers to certain areas of the world, men who have sex with men, and persons exposed to certain animals. The major reservoir and vehicle for spread of *Giardia* appears to be water contaminated with *Giardia* cysts, but foodborne transmission occurs. The seasonal peak in age-specific case reports coincides with the summer recreational water season and might be a result of the extensive use of communal swimming venues by young children, the low infectious dose, and the extended periods of cyst shedding that can occur. In addition, *Giardia* cysts are relatively resistant to chlorination and to ultraviolet light irradiation. Boiling is effective for inactivating cysts.

Person-to-person spread also occurs, particularly in areas of low hygiene standards, frequent fecal-oral contact, and crowding. Individual susceptibility, lack of toilet training, crowding, and fecal contamination of the environment all predispose to transmission of enteropathogens, including *Giardia,* in childcare centers. Childcare centers play an important role in transmission of urban giardiasis, with secondary attack rates in families as high as 17-30%. Children in childcare centers may pass cysts for several months. Campers who drink untreated stream or river water, particularly in the western United States, and residents of institutions for the developmentally delayed are also at increased risk for infection.

Humoral immunodeficiencies, including common variable hypogammaglobulinemia and X-linked agammaglobulinemia, predispose

humans to chronic symptomatic *Giardia* infection, suggesting the importance of humoral immunity in controlling giardiasis. Selective immunoglobulin A deficiency is also associated with *Giardia* infection. Although many individuals with AIDS have relatively mild *Giardia* infections, some reports suggest that severe *Giardia* infection, often refractory to treatment, may occur in a subset of individuals with AIDS. There is a higher incidence of *Giardia* infection in patients with cystic fibrosis, probably owing to local factors such as the increased amount of mucus, which may protect the organism against host factors in the duodenum. Human milk contains glycoconjugates and secretory immunoglobulin A antibodies that may provide protection to nursing infants against *Giardia*.

CLINICAL MANIFESTATIONS

The incubation period of *Giardia* infection usually is 1-2 wk but may be longer. A broad spectrum of clinical manifestations occurs, depending on the interaction between *G. lamblia* and the host. Children who are exposed to *G. lamblia* may experience asymptomatic excretion of the organism, acute infectious diarrhea, or chronic diarrhea with persistent gastrointestinal tract signs and symptoms, including failure to thrive and abdominal pain or cramping. *Giardia* was the cause of 15% of nondysenteric diarrhea illnesses in children examined in U.S. outpatient clinics in 1 study. Most infections in both children and adults are asymptomatic. There usually is no extraintestinal spread, but occasionally trophozoites may migrate into bile or pancreatic ducts.

Symptomatic infections occur more frequently in children than in adults. Most symptomatic patients usually have a limited period of acute diarrheal disease with or without low-grade fever, nausea, and anorexia; in a small proportion of patients, an intermittent or more protracted course characterized by diarrhea, abdominal distention and cramps, bloating, malaise, flatulence, nausea, anorexia, and weight loss develops (Table 282-1). Stools initially may be profuse and watery and later become greasy and foul smelling and may float. Stools do not contain blood, mucus, or fecal leukocytes. Varying degrees of malabsorption may occur. Abnormal stool patterns may alternate with periods of constipation and normal bowel movements. Malabsorption of sugars, fats, and fat-soluble vitamins is well documented and may be responsible for substantial weight loss. *Giardia* has been associated with iron deficiency in internationally adopted children. Giardiasis has been associated with growth stunting, and repeated *Giardia* infections correlate with a decrease in cognitive function in children in endemic areas.

Table 282-1 Clinical Signs and Symptoms of Giardiasis

SYMPTOM	FREQUENCY (%)
Diarrhea	64-100
Malaise, weakness	72-97
Abdominal distention	42-97
Flatulence	35-97
Abdominal cramps	44-81
Nausea	14-79
Foul-smelling, greasy stools	15-79
Anorexia	41-73
Weight loss	53-73
Vomiting	14-35
Fever	0-28
Constipation	0-27

DIAGNOSIS

Giardiasis should be considered in children who have acute nondysenteric diarrhea, persistent diarrhea, intermittent diarrhea and constipation, malabsorption, chronic crampy abdominal pain and bloating, failure to thrive, or weight loss. It should be particularly high in the differential diagnosis of children in child care, children in contact with an index case, children with a history of recent travel to an endemic area, and children with humoral immunodeficiencies. Testing for giardiasis should be standard for internationally adopted children from *Giardia*-endemic areas, and screening for iron deficiency should be considered in internationally adopted children with giardiasis.

Stool enzyme immunoassay (EIA) or direct fluorescent antibody tests for *Giardia* antigens are the tests of choice for giardiasis in most situations. EIA is less reader dependent and more sensitive for detection of *Giardia* than microscopy. Some studies report that a single stool is sufficiently sensitive for detection of *Giardia* by EIA, whereas others suggest that sensitivity is increased with testing of 2 samples. A diagnosis of giardiasis was traditionally established by microscopy documentation of trophozoites or cysts in stool specimens, but 3 stool specimens are required to achieve a sensitivity of >90% using this approach. In patients in whom other parasitic intestinal infections are in the differential diagnosis, microscopy examination of stool allows evaluation for these infections in addition to *Giardia*. Laboratories can reduce reagent and personnel costs by pooling specimens submitted for detection of *Giardia* before evaluation by microscopy or EIA. Polymerase chain reaction and gene probe–based detection systems specific for *Giardia* have been used in environmental monitoring but at present remain research tools. Multiplex polymerase chain reaction testing for multiple parasitic pathogens may become a viable option for testing in the future.

In patients with chronic symptoms in whom giardiasis is suspected but in whom testing of stool specimens for *Giardia* yields a negative result, aspiration or biopsy of the duodenum or upper jejunum should be considered. In a fresh specimen, trophozoites usually can be visualized by direct wet mount. An alternate method of directly obtaining duodenal fluid is the commercially available Entero-Test (Hedeco Corp, Mountain View, CA), but this method is less sensitive than aspiration or biopsy. The biopsy can be used to make touch preparations and tissue sections for identification of *Giardia* and other enteric pathogens and also to visualize changes in histology. Biopsy of the small intestine should be considered in patients with characteristic clinical symptoms, negative stool and duodenal fluid specimen findings, and 1 or more of the following: abnormal radiographic findings (such as edema and segmentation in the small intestine); abnormal lactose tolerance test result; absent secretory immunoglobulin A level; hypogammaglobulinemia; and achlorhydria. Duodenal biopsy may show findings consistent with chronic inflammation, including eosinophilic infiltration of the lamina propria.

Radiographic contrast studies of the small intestine may show nonspecific findings such as irregular thickening of the mucosal folds. Blood cell counts usually are normal. Giardiasis is not tissue invasive and is not associated with peripheral blood eosinophilia.

TREATMENT

Children with acute diarrhea in whom *Giardia* organisms are identified should receive therapy. In addition, children who manifest failure to thrive or exhibit malabsorption or gastrointestinal tract symptoms such as chronic diarrhea should be treated.

Asymptomatic excreters generally are not treated except in specific instances such as outbreak control, prevention of household transmission by toddlers to pregnant women and patients with hypogammaglobulinemia or cystic fibrosis, and situations requiring oral antibiotic treatment where *Giardia* may produce malabsorption of the antibiotic.

The FDA has approved tinidazole and nitazoxanide for the treatment of *Giardia* in the United States. Both medications have been used to treat *Giardia* in thousands of patients in other countries and have excellent safety and efficacy against *Giardia* (Table 282-2). Tinidazole

Table 282-2 Drug Treatment for Giardiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
RECOMMENDED		
Tinidazole	2 g once	>3 yr: 50 mg/kg once
Nitazoxanide	500 mg bid for 3 days	1-3 yr: 100 mg (5 mL) bid for 3 days 4-11 yr: 200 mg (10 mL) bid for 3 days >12 yr: 500 mg bid for 3 days
Metronidazole	250 mg tid for 5-7 days	15 mg/kg/day in 3 divided doses for 5-7 days
ALTERNATIVE		
Albendazole	400 mg once a day for 5 days	>6 yr: 400 mg once a day for 5 days
Paromomycin	25-35 mg/kg/day in 3 divided doses for 5-10 days	Not recommended
Quinacrine†	100 mg tid for 5-7 days	6 mg/kg/day in 3 divided doses for 5 days

*All pediatric dosages are up to a maximum of the adult dose.
†Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-6816) or Panorama Compounding Pharmacy in Van Nuys, CA (800-247-9767).

has the advantage of single-dose treatment and very high efficacy (>90%), while nitazoxanide has the advantage of a suspension form, high efficacy (80-90%), and very few adverse effects. Metronidazole, though never approved by the FDA for treatment of *Giardia,* is also highly effective (80-90% cure rate), and the generic form is considerably less expensive than tinidazole or nitazoxanide. Frequent adverse effects are seen with metronidazole therapy, and it requires 3 times a day dosing for 5-7 days. Suspension forms of tinidazole and metronidazole must be compounded by a pharmacy; neither drug is sold in suspension form.

Second-line alternatives for the treatment of patients with giardiasis include albendazole, paromomycin, and quinacrine (see Table 282-2). Albendazole may be of similar efficacy to metronidazole. Albendazole has few adverse effects and is effective against many helminths, making it useful for treatment when multiple intestinal parasites are identified or suspected. Paromomycin is a nonabsorbable aminoglycoside and is less effective than other agents but is recommended for treatment of pregnant women with giardiasis because of potential teratogenic effects of other agents. Quinacrine is effective and inexpensive but is not available commercially and must be obtained from compounding pharmacies (see Table 282-2). Quinacrine can also rarely have serious side effects, including hallucinations and psychosis. Refractory cases of giardiasis have been successfully treated with nitazoxanide, prolonged courses of tinidazole, or a 3 wk course of metronidazole and quinacrine.

PROGNOSIS

Symptoms recur in some patients in whom reinfection cannot be documented and in whom an immune deficiency such as an immunoglobulin abnormality is not present, despite use of appropriate therapy. Several studies have demonstrated that variability in antimicrobial susceptibility exists among strains of *Giardia,* and in some instances resistant strains have been demonstrated. Combined therapy may be useful for infection that persists after single-drug therapy, assuming reinfection has not occurred and the medication was taken as prescribed.

PREVENTION

Infected persons and persons at risk should practice strict handwashing after any contact with feces. This point is especially important for caregivers of diapered infants in childcare centers, where diarrhea is common and *Giardia* organism carriage rates are high.

Methods to purify public water supplies adequately include chlorination, sedimentation, and filtration. Inactivation of *Giardia* cysts by chlorine requires the coordination of multiple variables such as chlorine concentration, water pH, turbidity, temperature, and contact time. These variables cannot be appropriately controlled in all municipalities and are difficult to control in swimming pools. Individuals, especially children in diapers, should avoid swimming if they have diarrhea. Individuals should also avoid swallowing recreational water and drinking untreated water from shallow wells, lakes, springs, ponds, streams, and rivers.

Travelers to endemic areas are advised to avoid uncooked foods that might have been grown, washed, or prepared with water that was potentially contaminated. Purification of drinking water can be achieved by a filter with a pore size of <1 μm or that has been National Sanitation Foundation rated for cyst removal, or by brisk boiling of water for at least 1 min. Treatment of water with chlorine or iodine is less effective but may be used as an alternate method when boiling or filtration is not possible.

Bibliography is available at Expert Consult.

282.2 Balantidiasis

Chandy C. John

Balantidium coli is a ciliated protozoan and is the largest protozoan that parasitizes humans. Both trophozoites and cysts may be identified in feces. Disease caused by this organism is uncommon in the United States and generally is reported where there is a close association of humans with pigs, which are the natural hosts of *B. coli.* Because the organism infects the large intestine, symptoms are consistent with large bowel disease, similar to those associated with amebiasis and trichuriasis, and include nausea, vomiting, lower abdominal pain, tenesmus, and bloody diarrhea. Symptoms associated with chronic infection include abdominal cramps, watery diarrhea with mucus, occasionally bloody diarrhea, and colonic ulcers similar to those associated with *Entamoeba histolytica.* Extraintestinal spread of *B. coli* is rare and usually occurs only in immunocompromised patients. Most infections are asymptomatic.

Diagnosis using direct saline mounts is established by identification of trophozoites (50-100 μm long) or spherical or oval cysts (50-70 μm in diameter) in stool specimens. Trophozoites usually are more numerous than cysts. The recommended treatment regimen is metronidazole (45 mg/kg/day divided tid PO; maximum: 750 mg/dose) for 5 days, or tetracycline (40 mg/kg/day divided qid PO; maximum: 500 mg/dose) for 10 days for persons older than 8 yr of age. An alternative is iodoquinol (40 mg/kg/day divided tid PO; maximum: 650 mg/dose) for 20 days. Prevention of contamination of the environment by pig feces is the most important means for control.

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Chapter 283

Cryptosporidium, Isospora, Cyclospora, and Microsporidia

Patricia M. Flynn

The spore-forming intestinal protozoa *Cryptosporidium, Isospora,* and *Cyclospora* are important intestinal pathogens in both immunocompetent and immunocompromised hosts. *Cryptosporidium, Isospora,* and *Cyclospora* are coccidian parasites that predominantly infect the epithelial cells lining the digestive tract. Microsporidia were formerly considered spore-forming protozoa but have been reclassified as fungi. Microsporidia are ubiquitous, obligate intracellular parasites that infect many other organ systems in addition to the gastrointestinal tract and cause a broader spectrum of disease.

CRYPTOSPORIDIUM

Cryptosporidium is recognized as a leading protozoal cause of diarrhea in children worldwide and is a common cause of outbreaks in childcare centers; it is also a significant pathogen in immunocompromised patients.

Etiology

Cryptosporidium hominis and *Cryptosporidium parvum* cause most cases of cryptosporidiosis in humans. Disease is initiated by ingestion of infectious oocysts that release 4 sporozoites that invade enterocytes, primarily in the small intestine. The cysts are immediately infectious to other hosts or can reinfect the same host.

Epidemiology

Cryptosporidiosis is associated with diarrheal illness worldwide and is more prevalent in developing countries and among children younger than 2 yr of age. It has been implicated as an etiologic agent of persistent diarrhea in the developing world and as a cause of significant morbidity and mortality from malnutrition, including permanent effects on growth.

Transmission of *Cryptosporidium* to humans can occur by close association with infected animals, via person-to-person transmission, or from environmentally contaminated water. Although zoonotic transmission, especially from cows, occurs in persons in close association with animals, person-to-person transmission is probably responsible for cryptosporidiosis outbreaks within hospitals and childcare centers where transmission rates as high as 67% have been reported. Recommendations to prevent outbreaks in childcare centers include strict handwashing, use of protective clothes or diapers capable of retaining liquid diarrhea, and separation of diapering and food-handling areas and responsibilities.

Outbreaks of cryptosporidial infection are associated with contaminated community water supplies and recreational waters, including lakes and chlorinated swimming pools. Wastewater in the form of raw sewage and runoff from dairies and grazing lands can contaminate both drinking and recreational water sources. It is estimated that *Cryptosporidium* oocysts are present in 65-97% of the surface water in the United States. The organism's small size (4-6 µm in diameter), resistance to chlorination, and ability to survive for long periods outside a host creates problems in public water supplies.

Clinical Manifestations

The incubation period is 2-14 days. Infection with *Cryptosporidium* is associated with profuse, watery, nonbloody diarrhea that can be accompanied by diffuse crampy abdominal pain, nausea, vomiting, and anorexia. Although less common in adults, vomiting occurs in more than 80% of children with cryptosporidiosis. Nonspecific symptoms such as myalgia, weakness, and headache also may occur. Fever occurs in 30-50% of cases. Malabsorption, lactose intolerance, dehydration, weight loss, and malnutrition often occur in severe cases. Recently, the clinical spectrum and disease severity has been linked with both the infecting species and host human leukocyte antigen class I and class II alleles.

In immunocompetent persons, the disease is usually self-limiting, typically 5-10 days, although diarrhea may persist for several weeks and oocyst shedding may persist many weeks after symptoms resolve. Chronic diarrhea is common in individuals with immunodeficiency, such as congenital hypogammaglobulinemia or HIV infection. Symptoms and oocyst shedding can continue indefinitely and may lead to severe malnutrition, wasting, anorexia, and even death.

Cryptosporidiosis in **immunocompromised hosts** is often associated with biliary tract disease, characterized by fever, right upper quadrant pain, nausea, vomiting, and diarrhea. It also is associated with pancreatitis. Respiratory tract disease, with symptoms of cough, shortness of breath, wheezing, croup, and hoarseness, is very rare.

Diagnosis

Infection can be diagnosed by microscopy using modified acid-fast stain or polymerase chain reaction, but immunodetection of antigens on the surface of the organism in stool samples using monoclonal antibody–based assays is the current diagnostic method of choice. In stool, oocysts appear as small, spherical bodies (2-6 µm) and stain red with modified acid-fast staining. Because *Cryptosporidium* does not invade below the epithelial layer of the mucosa, fecal leukocytes are not found in stool specimens. Oocyst shedding in feces can be intermittent, and several fecal specimens (at least 3 for an immunocompetent host) should be collected for microscopic examination. Serologic diagnosis is not helpful in acute cryptosporidiosis.

In tissue sections, *Cryptosporidium* organisms can be found along the microvillus region of the epithelia that line the gastrointestinal tract. The highest concentration usually is detected in the jejunum. Histologic section results reveal villus atrophy and blunting, epithelial flattening, and inflammation of the lamina propria.

Treatment

Often the diarrheal illness attributable to cryptosporidiosis is self-limited in immunocompetent patients and requires no specific antimicrobial therapy. Treatment should focus on supportive care, including rehydration orally or, if fluid losses are severe, intravenously. Nitazoxanide (100 mg bid PO for 3 days for children 1-3 yr of age; 200 mg bid PO for children 4-11 yr of age; 500 mg bid PO for children ≥12 yr of age) is approved for treatment of diarrhea caused by *Cryptosporidium.* Clinical studies have not definitively demonstrated that nitazoxanide is superior to placebo in trials of HIV-infected (with low CD4 counts) or immunocompromised patients. However, given the severity of the infection in these populations, nitazoxanide treatment is usually initiated. In patients with HIV infection, treatment with combination antiretroviral therapy should also be administered to improve immune function. Other agents that have been suggested for treatment in clinical reports or small studies include orally administered human serum immunoglobulin or bovine colostrum, paromomycin, spiramycin, azithromycin, and roxithromycin or a combination of antibiotics.

ISOSPORA

Like *Cryptosporidium, Isospora belli* (also called *Cystoisospora*) is implicated as a cause of diarrhea in institutional outbreaks and in travelers and has also been linked with contaminated water and food. *Isospora* appears to be more common in tropical and subtropical climates and in developing areas, including South America, Africa, and Southeast Asia. *Isospora* has not been associated with animal contact. It is also an infrequent cause of diarrhea in patients with AIDS in the United States but may infect up to 15% of AIDS patients in Haiti.

The life cycle and pathogenesis of infection with *Isospora* species are similar to those of *Cryptosporidium* organisms except that oocysts excreted in the stool are not immediately infectious and must undergo further maturation at temperatures below 37°C (98.6°F). Thus, direct person-to-person transmission is unlikely. The most common clinical manifestation is watery, nonbloody diarrhea. Symptoms of infection are indistinguishable from those of cryptosporidiosis, although fever may be a more common finding. Eosinophilia may be present in up to 50% of cases, contrasting with other enteric protozoan infections. The diagnosis is established by detecting the oval, 22-33 μm long by 10-19 μm wide, oocysts by using modified acid-fast staining of the stool. Each oocyst contains 2 sporocysts with 4 sporozoites in each. Fecal leukocytes are not detected. Oocysts are shed in low number, underscoring the need for repeated stool examinations. Presence of oocysts in the gastrointestinal track is almost always associated with clinical symptoms. Histologic appearance of gastrointestinal epithelium reveals blunting and atrophy of the villi, acute and chronic inflammation, and crypt hyperplasia.

Isosporiasis responds promptly to **treatment** with oral trimethoprim-sulfamethoxazole (TMP-SMZ) (5 mg TMP and 25 mg SMZ/kg/dose; maximum: 160 mg TMP and 800 mg SMZ/dose bid for 10 days). In patients with AIDS, relapses are common and often necessitate higher doses of trimethoprim-sulfamethoxazole and/or maintenance therapy. Combination antiretroviral therapy associated with immune recovery may also result in improved symptoms. Ciprofloxacin, nitazoxanide, or a regimen of pyrimethamine alone or with folinic acid is effective in patients intolerant of sulfonamide drugs.

CYCLOSPORA

Cyclospora cayetanensis is a coccidian parasite similar to but larger than *Cryptosporidium.* The organism infects both immunocompromised and immunocompetent individuals and is more common in children younger than 18 mo of age. The pathogenesis and pathologic findings of cyclosporiasis are similar to those of isosporiasis. Asymptomatic carriage of the organism has been found, but travelers who harbor the organism almost always have diarrhea. Outbreaks of cyclosporiasis are linked with contaminated food and water. Implicated foods include raspberries, lettuce, snow peas, basil, and other fresh food items. After fecal excretion, the oocysts must sporulate outside the host to become infectious. This finding explains the lack of person-to-person transmission.

The **clinical manifestations** of cyclosporiasis are similar to those of cryptosporidiosis and isosporiasis and follow an incubation period of approximately 7 days. Moderate *Cyclospora* illness is characterized by a median of 6 stools/day with a median duration of 10 days (range: 3-25 days). The duration of diarrhea in immunocompetent persons is characteristically longer in cyclosporiasis than in the other intestinal protozoan illnesses. Associated symptoms frequently include anorexia; fatigue; abdominal bloating or gas; abdominal cramps or pain; nausea; muscle, joint, or body aches; low-grade fever; chills; headache; and weight loss. Vomiting may occur. Bloody stools are uncommon. Biliary disease has been reported. Intestinal pathology includes inflammation with villus blunting.

The diagnosis is established by identification of oocysts in the stool. Oocysts are wrinkled spheres, measure 8-10 μm in diameter, and resemble large *Cryptosporidium* organisms. Each oocyst contains 2 sporocysts, each with 2 sporozoites. The organisms can be seen by using modified acid-fast, auramine-phenol, or modified trichrome staining, but stain less consistently than *Cryptosporidium.* They can also be detected with phenosafranin stain and by autofluorescence using strong green or intense blue under ultraviolet epifluorescence. Multiple stool samples enhance identification of the pathogen. New molecular diagnostic testing, including real-time polymerase chain reaction, is currently under investigation. Fecal leukocytes are not present.

The **treatment** of choice for cyclosporiasis is TMP-SMZ (5 mg TMP and 25 mg SMZ/kg/dose bid PO for 7 days; maximum: 160 mg TMP and 800 mg SMZ/dose). Ciprofloxacin or nitazoxanide is effective in patients intolerant of sulfonamide drugs.

MICROSPORIDIA

Microsporidia are ubiquitous and infect most animal groups, including humans. They are classified as fungi and multiple species of the phylum Microsporidia have been linked with human disease in both immunocompetent and immunocompromised hosts. The species most commonly associated with gastrointestinal disease are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis.*

Although still not definitive, the source of human infections is likely zoonotic. Like *Cryptosporidium,* there is concern for waterborne transmission through occupational and recreational contact with contaminated water sources. There is also the potential for foodborne outbreaks; the organisms have been identified on vegetables as a consequence of contaminated irrigation water. Vector-borne transmission is hypothesized because 1 species, *Brachiola algerae*, typically infects mosquitoes. Finally, transplacental transmission has been reported in animals but not in humans. Once infected, intracellular division produces new spores that can spread to nearby cells, disseminate to other host tissues, or be passed into the environment via feces. Spores also have been detected in urine and respiratory epithelium, suggesting that some body fluids may also be infectious. Once in the environment, microsporidial spores remain infectious for up to 4 mo.

Initially, microsporidial intestinal infection had been almost exclusively reported in patients with AIDS, but there is increasing evidence that immunocompetent individuals are also commonly infected. Microsporidia-associated diarrhea is intermittent, copious, watery, and nonbloody. Abdominal cramping and weight loss may be present; fever is unusual. Stromal keratitis and encephalitis may also be associated with microsporidia infections. Disseminated disease involving most organs, including liver, heart, kidney, bladder, biliary tract, lung, bone, skeletal muscle, and sinuses, has been reported.

Microsporidia stain with modified trichrome, hematoxylin-eosin, Giemsa, Gram, periodic acid–Schiff, and acid-fast stains, but are often overlooked because of their small size (1-5 μm) and the absence of associated inflammation in surrounding tissues. Electron microscopy remains the reference method of detection. Multiple research laboratories report success with polymerase chain reaction technology in detecting microsporidia, both in human and environmental samples.

There is no proven **therapy** for microsporidial intestinal infections. Albendazole (adult dose 400 mg bid PO for 3 wk) is usually effective against *E. intestinalis* infection, but is ineffective against infection caused by some microsporidial species. Fumagillin (adult dose 20 mg tid PO for 2 wk) was effective in a small controlled study of adults with *E. bieneusi* infection and topical therapy with this agent was also demonstrated to be effective in HIV-infected adults with keratoconjunctivitis. Supportive care with hydration, correction of electrolyte imbalances, and nutrition should be used in gastrointestinal infection when clinically indicated. Improvement in underlying HIV infection with combination antiretroviral therapy also improves microsporidiosis symptoms.

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Chapter 284

Trichomoniasis (*Trichomonas vaginalis*)

Edsel Maurice T. Salvana and Robert A. Salata

Trichomoniasis, caused by the protozoan parasite *Trichomonas vaginalis,* is the most common nonviral sexually transmitted disease worldwide. It primarily causes vulvovaginitis in women but has been implicated in pelvic inflammatory disease, adverse outcomes in pregnancy, chronic prostatitis, and an increased risk of transmission of HIV.

EPIDEMIOLOGY

More than 170 million new cases of trichomoniasis occur yearly, the majority in resource-limited settings. Prevalence and incidence rates are likely underestimated, as most men and up to 30% of women are asymptomatic. Diagnostic accuracy using wet mount microscopy, the mainstay of diagnosis, is less sensitive than previously assumed. While the disease is easily treated, sequelae of untreated infection remain a significant cause of morbidity as a result of high reinfection rates from untreated partners, underrecognition of asymptomatic cases, and insensitive diagnostics.

Trichomoniasis is the most common parasitic infection in the United States, with approximately 7.4 million cases occurring each year. A population-based study conducted in 2005 showed a prevalence of 2.8% in women and 1.7% in men, and an overall prevalence of 2.3%. The incidence of trichomoniasis is highest among females with multiple sexual partners and in groups with the highest rates of other sexually transmitted infections. *T. vaginalis* is recovered from more than 60% of female partners of infected men and 70% of male sexual partners of infected women. Vaginal trichomoniasis is rare until menarche. Its presence in a younger child should raise the possibility of **sexual abuse.**

Trichomoniasis may be transmitted to neonates during passage through an infected birth canal. Infection in this setting is usually self-limited, but rare cases of neonatal vaginitis and respiratory infection have been reported.

PATHOGENESIS

T. vaginalis is an anaerobic, flagellated protozoan parasite. Infected vaginal secretions contain 10^1 to 10^5 or more protozoa/mL. *T. vaginalis* is pear shaped and exhibits characteristic twitching motility in wet mount (Fig. 284-1). Reproduction is by binary fission. It exists only as **vegetative cells;** cyst forms have not been described. *T. vaginalis* damages host cells and tissues by a number of mechanisms. Adhesion molecules allow attachment of *T. vaginalis* to host cells, and hydrolases, proteases, and cytotoxic molecules act to destroy or impair the integrity of host cells. An iron-upregulated cysteine proteinase legumain-1 (TvLEGU-1) has been characterized as a major factor in cytoadherence. There is increasing evidence that *T. vaginalis* is associated with low levels of *Lactobacillus* spp. and high levels of *Mycoplasma* spp. in the vaginal microbiota. However, whether trichomoniasis alters the bacterial flora or whether altered bacterial flora predisposes to trichomoniasis is uncertain. Parasite-specific antibodies and lymphocyte priming occur in response to infection, but durable protective immunity does not occur.

CLINICAL MANIFESTATIONS

The **incubation period** in females is 5-28 days. Symptoms may begin or exacerbate with menses. Most infected women eventually develop symptoms, although up to one third remain asymptomatic. Common signs and symptoms include a copious malodorous gray, frothy vaginal discharge, vulvovaginal irritation, dysuria, and dyspareunia. Physical examination may reveal a frothy discharge with vaginal erythema and cervical hemorrhages ("strawberry cervix"). The discharge usually has a pH of >4.5. Abdominal discomfort is unusual and should prompt evaluation for pelvic inflammatory disease (see Chapter 120).

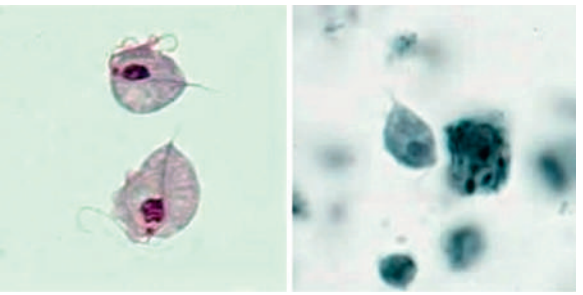

Figure 284-1 *Trichomonas vaginalis* trophozoites stained with Giemsa *(left)* and iron hematoxylin *(right). (From the Centers for Disease Control and Prevention [CDC]: Laboratory identification of parasites of public health concern. Trichomoniasis. Available at:* http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Trichomoniasis_il.htm*)*

Most infections in males are asymptomatic. Symptomatic males usually have dysuria and scant urethral discharge. Trichomonads occasionally cause epididymitis, prostatic involvement, and superficial penile ulceration. Infection is often self-limited, spontaneously resolving in 36% of men. *Trichomonas* has been implicated as a cause of recurrent or relapsing urethritis and can be isolated in 3-20% of men with **nongonococcal urethritis.** Treatment failures with standard therapy for gonorrhea and *Chlamydia* are frequently treated with antitrichomonal therapy.

DIAGNOSIS

Trichomonads may be recognized in vaginal secretions by using the wet mount technique. This technique has been estimated to have a sensitivity of 60-70%; studies using more sensitive assays with nucleic acid probes and polymerase chain reaction suggest that this is closer to 35-60%. Although *Trichomonas* is sometimes seen on Papanicolaou smears and in urine, these methods are not considered reliable tests for disease. Wet mount examination of material obtained by platinum loop from the anterior urethra may reveal the organism in 50-90% of infected men. Microscopic examination of urine sediment after prostatic massage is also useful in infected men. Culture of the organism is the gold standard for detection, and commercial culture media are available. Enzyme-linked immunosorbent assay and direct fluorescent antigen testing of vaginal secretions are more sensitive than wet mount testing but less sensitive than culture for detection of *T. vaginalis* infection. In women, DNA immunoblot and polymerase chain reaction testing of vaginal secretions have similar sensitivity and specificity to culture. In men, these methods appear to be more sensitive at detection of infection than culture. Nucleic acid amplification testing and immunologic diagnostic kits for diagnosis of *Trichomonas* alone and in combination with other gynecologic diseases, such as *Candida* and *Gardnerella,* have been evaluated by multiple studies and have been found to be accurate and easy to use. The APTIMA TV (Gen-Probe Incorporated, CA) assay is an FDA-approved commercial nucleic acid amplification test that is highly sensitive and specific, particularly in asymptomatic patients. Two point-of-care kits for rapid testing, Affirm VP III (BD Diagnostic Systems, Sparks, MD) and OSOM *Trichomonas* Rapid Test (Genzyme Diagnostics, Cambridge, MA), have received approval by the FDA but are less sensitive than the APTIMA TV. Patients with *T. vaginalis* should be screened for other sexually transmitted infections, including *Chlamydia* and gonorrhea.

COMPLICATIONS

Untreated trichomoniasis is associated with pelvic inflammatory disease, premature delivery, low birthweight, tubal infertility, and vaginal cuff cellulitis. *T. vaginalis* infection increases the risk of acquisition and transmission of HIV. *Trichomonas*-induced inflammation of the genital mucosa recruits greater numbers of $CD4^+$ cells in the epithelium and provides greater access to the bloodstream for HIV. In HIV-infected individuals, trichomoniasis is associated with higher viral loads in cervical secretions and semen, as well as higher levels of infected lymphocytes in urogenital fluids. HIV-1 shedding in vaginal fluids decreases following treatment for trichomoniasis.

TREATMENT

In the United States, **metronidazole** and **tinidazole** are used; in other countries ornidazole is also used. Both metronidazole (single-dose regimen of 2 g orally as a single dose for adolescents and adults; alternative regimen, 500 mg orally bid for 7 days) and tinidazole (single 2 g dose orally in adolescents and adults) are used as first-line treatment. For children infected prior to adolescence, the recommended regimen is metronidazole 15 mg/kg/day divided in 3 doses orally for 7 days; tinidazole is not approved for dosing in younger children. Topical metronidazole gel is not efficacious when used as the sole therapy for *T. vaginalis* infection, but it may decrease symptoms in individuals with severe infection when used in conjunction with oral therapy. Sexual partners should be treated simultaneously to prevent reinfection. Multiple head-to-head trials comparing the efficacy between single-dose/short courses of metronidazole and single-dose tinidazole have shown either noninferiority or superior efficacy for tinidazole. A Cochrane metaanalysis demonstrated that single dose tinidazole was superior compared to short-course metronidazole in clinical efficacy and parasitologic cure rates and had significantly fewer side effects. Tinidazole is more expensive than metronidazole and is generally reserved for treatment failures or metronidazole intolerance.

Treatment failures have been reported with metronidazole, although poor response can usually be overcome by higher doses of drugs. Second-line treatment recommendations include either a 7-day course of metronidazole 500 mg twice daily or a single dose of tinidazole. If this treatment fails, either metronidazole or tinidazole at 2 g daily for 5 days is recommended. Further treatment failure should be referred to an infectious diseases specialist and may require susceptibility testing, which is available from the Centers for Disease Control and Prevention. Metronidazole has not been shown to be teratogenic during pregnancy in humans but is currently classified as a category C drug. A Cochrane metaanalysis showed an association (RR = 1.78 [1.19, 2.66]) between premature births with metronidazole treatment of asymptomatic *T. vaginalis* infection in pregnancy. Further studies are needed to confirm this finding. Treatment of symptomatic trichomoniasis in pregnancy should be weighed against possible risks, while treatment of asymptomatic disease should be delayed as much as possible to near term.

PREVENTION

Prevention of *T. vaginalis* infection is best accomplished by treatment of all sexual partners of an infected person and by programs aimed at prevention of all sexually transmitted infections (see Chapter 120). No vaccine is available, and drug prophylaxis is not recommended.

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Chapter 285

Leishmaniasis (*Leishmania*)

Peter C. Melby

The leishmaniases are a diverse group of diseases caused by intracellular protozoan parasites of the genus *Leishmania,* which are transmitted by phlebotomine sand flies. Multiple species of *Leishmania* are known to cause human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs. Cutaneous disease is generally mild but may cause cosmetic disfigurement. Mucosal and visceral leishmaniasis is associated with significant morbidity and mortality.

ETIOLOGY

Leishmania organisms are members of the Trypanosomatidae family and include 2 subgenera, *Leishmania (Leishmania)* and *Leishmania (Viannia)*. The parasite is dimorphic, existing as a flagellate promastigote in the insect vector and as an aflagellate amastigote that resides and replicates within mononuclear phagocytes of the vertebrate host. Within the sandfly vector, the promastigote changes from a noninfective procyclic form to an infective metacyclic stage. Fundamental to this transition are changes that take place in the terminal polysaccharides of the surface lipophosphoglycan, which allow forward migration of the infective parasites from the sandfly midgut to the mouth parts and inoculation of the host during a blood meal. Metacyclic lipophosphoglycan also plays an important role in the entry and survival of *Leishmania* in the mammalian host by conferring complement resistance and by facilitating entry into the macrophage by way of multiple receptors, including complement receptors 1 and 3. Once within the macrophage, the promastigote transforms to an amastigote and resides and replicates within a phagolysosome. The parasite is resistant to the acidic, hostile environment of the macrophage and eventually ruptures the cell and goes on to infect other macrophages. Infected macrophages have a diminished capacity to initiate and respond to an inflammatory response, thus providing a safe haven for the intracellular parasite.

EPIDEMIOLOGY

The leishmaniases are estimated to affect 10-20 million people in endemic tropical and subtropical regions on all continents except Australia and Antarctica. The different forms of the disease are distinct in their causes, epidemiologic characteristics, transmission, and geographic distribution. The leishmaniases may occur sporadically throughout an endemic region or may occur in epidemic focuses. With only rare exceptions, the *Leishmania* organisms that primarily cause cutaneous disease do not cause visceral disease.

Localized cutaneous leishmaniasis (LCL) in the Old World is caused by *L. (Leishmania) major* and *L. (L.) tropica* in North Africa, the Middle East, central Asia, and the Indian subcontinent. *L. (L.) aethiopica* is a cause of LCL and diffuse cutaneous leishmaniasis (DCL) in Kenya and Ethiopia. **Visceral leishmaniasis (VL)** in the Old World is caused by *L. (L.) donovani* in Kenya, Sudan, India, Pakistan, and China and by *L. (L.) infantum* in the Mediterranean basin, Middle East, and central Asia. *L. infantum* is also a cause of LCL (without visceral disease) in this same geographic distribution. *L. tropica* also has been recognized as an uncommon cause of visceral disease in the Middle East and India. In the New World, *L. (L.) mexicana* causes LCL in a region stretching from southern Texas through Central America. *L. (L.) amazonensis, L. (L.) pifanoi, L. (L.) garnhami,* and *L. (L.) venezuelensis* cause LCL in South America, the Amazon basin, and northward. Members of the *Viannia* subgenus (*L. [V.] braziliensis, L. [V.] panamensis, L. [V.] guyanensis,* and *L. [V.] peruviana*) cause LCL from the northern highlands of Argentina northward to Central America.

Members of the *Viannia* subgenus also cause **mucosal leishmaniasis (ML)** in a similar geographic distribution. VL in the New World is caused by *L. (L.) chagasi* (now considered to be the same organism as *L. infantum*), which is distributed from Mexico (rare) through Central and South America. *L. infantum/chagasi* can also cause LCL in the absence of visceral disease.

The maintenance of *Leishmania* in most endemic areas is through a zoonotic transmission cycle. In general, the dermotropic strains in both the Old and New Worlds are maintained in rodent reservoirs, and the domestic dog is the usual reservoir for *L. infantum/chagasi.* The transmission between reservoir and sandfly is highly adapted to the specific ecologic characteristics of the endemic region. Human infections occur when human activities bring them in contact with the zoonotic cycle. Anthroponotic transmission, in which humans are the presumed reservoir, occurs with *L. tropica* in some urban areas of the Middle East and Central Asia, and with *L. donovani* in India and Sudan. Congenital transmission of *L. donovani* or *L. infantum/chagasi* has been reported.

There is a resurgence of leishmaniasis in long-standing endemic areas as well as in new foci. Tens of thousands of cases of LCL occurred in an outbreak in Kabul, Afghanistan, and severe epidemics with more than 100,000 deaths from VL have occurred in India and Sudan. VL is most prevalent among the poorest of the poor, with substandard housing contributing to the vector-borne transmission and undernutrition leading to increased host susceptibility. The emergence of the leishmaniases in new areas is the result of (1) movement of a susceptible population into existing endemic areas, usually because of agricultural or industrial development or timber harvesting; (2) increase in vector and/or reservoir populations as a result of agriculture development projects; (3) increase in anthroponotic transmission owing to rapid urbanization in some focuses; and (4) increase in sandfly density resulting from a reduction in vector control programs.

PATHOLOGY

Histopathologic analysis of the LCL lesion shows intense chronic granulomatous inflammation involving the epidermis and dermis. Occasionally, neutrophils and even microabscesses can be seen. The lesions of DCL are characterized by dense infiltration with vacuolated macrophages containing abundant amastigotes. ML is characterized by an intense granulomatous reaction with prominent tissue necrosis, which may include adjacent cartilage or bone. In VL there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes. Amastigotes are abundant in the histiocytes and Kupffer cells. Late in the course of disease, splenic infarcts are common, centrilobular necrosis and fatty infiltration of the liver occur, the normal marrow elements are replaced by parasitized histiocytes, and erythrophagocytosis is present.

PATHOGENESIS

Cellular immune mechanisms determine resistance or susceptibility to infection with *Leishmania.* Resistance is mediated by interleukin (IL)-12–driven generation of a T helper 1 cell response, with interferon-γ inducing classical macrophage (M1) activation and parasite killing. Susceptibility is associated with expansion of IL-4–producing Th2 cells and/or the production of IL-10 and transforming growth factor-β, which are inhibitors of macrophage-mediated parasite killing, and the generation of regulatory T cells and alternatively activated (M2) macrophages. Patients with ML exhibit a hyperresponsive cellular immune reaction that may contribute to the prominent tissue destruction seen in this form of the disease. Patients with DCL or active VL demonstrate reduced or altered *Leishmania*-specific cellular immune responses, with prominent generation of IL-10, but these responses recover after successful therapy.

Within endemic areas, people who have had a subclinical infection can be identified by a positive delayed-type hypersensitivity skin response to leishmanial antigens **(Montenegro skin test)** or by antigen-induced production of interferon-γ in a whole blood assay**.** Subclinical infection occurs considerably more frequently than does active cutaneous or visceral disease. Host factors (genetic background, concomitant disease, nutritional status), parasite factors (virulence, size of the inoculum), and possibly vector-specific factors (vector genotype, immunomodulatory salivary constituents) influence the expression as either subclinical infection or active disease. Within endemic areas the prevalence of skin test result positivity increases with age and the incidence of clinical disease decreases with age, indicating that immunity is acquired in the population over time. Individuals with prior active disease or subclinical infection are usually immune to a subsequent clinical infection; however, latent infection can lead to active disease if the patient is immunosuppressed.

CLINICAL MANIFESTATIONS

The different forms of the disease are distinct in their causes, epidemiologic features, transmission, and geographic distribution.

Localized Cutaneous Leishmaniasis

LCL **(Oriental sore)** can affect individuals of any age, but children are the primary victims in many endemic regions. It may present as 1 or a few papular, nodular, plaquelike, or ulcerative lesions that are usually located on exposed skin, such as the face and extremities (Fig. 285-1). Rarely, more than 100 lesions have been recorded. The lesions typically begin as a small papule at the site of the sandfly bite, which enlarges to 1-3 cm in diameter and may ulcerate over the course of several weeks to months. The shallow ulcer is usually nontender and surrounded by a sharp, indurated, erythematous margin. There is no drainage unless a bacterial superinfection develops. Lesions caused by *L. major* and *L. mexicana* usually heal spontaneously after 3-6 mo, leaving a depressed scar. Lesions on the ear pinna caused by *L. mexicana,* called **chiclero ulcer** because they were common in chicle harvesters in Mexico and Central America, often follow a chronic, destructive course. In general, lesions caused by *L. (Viannia)* species tend to be larger and more chronic. Regional lymphadenopathy and palpable subcutaneous nodules or lymphatic cords, the so-called sporotrichoid appearance, are also more common when the patient is infected with organisms of the *Viannia* subgenus. If lesions do not become secondarily infected, there are usually no complications aside from the residual cutaneous scar.

Diffuse Cutaneous Leishmaniasis

DCL is a rare form of leishmaniasis caused by organisms of the *L. mexicana* complex in the New World and *L. aethiopica* in the Old World. DCL manifests as large nonulcerating macules, papules,

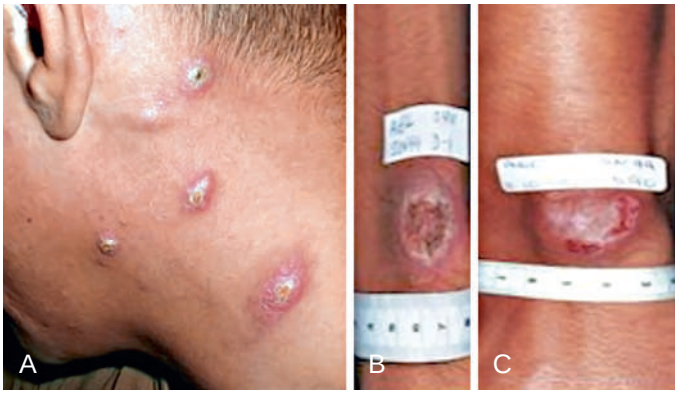

Figure 285-1 Cutaneous disease. **A,** Old World infection *(Leishmania major)* acquired in Iraq; note 5 papular and nodular lesions on neck. **B,** New World infection *(Leishmania panamensis)* in Colombia; purely ulcerative lesion is characteristic of New World disease. **C,** Healed infection in patient shown in **B** 70 days after 20 days of meglumine antimonate treatment; note paper-thin scar tissue over flat reepithelialized skin. *(**A** courtesy of P. Weina. **B** courtesy of J. Soto. **A-C** modified from Murray HW, Berman JD, Davies CR, et al: Advances in leishmaniasis,* Lancet *366:1561–1577, 2005.)*

nodules, or plaques that often involve large areas of skin and may resemble lepromatous leprosy. The face and extremities are most commonly involved. Dissemination from the initial lesion usually takes place over several years. It is thought that an immunologic defect underlies this severe form of cutaneous leishmaniasis.

Mucosal Leishmaniasis

ML **(espundia)** is an uncommon but serious manifestation of leishmanial infection resulting from hematogenous metastases to the nasal or oropharyngeal mucosa from a cutaneous infection. It is usually caused by parasites in the *L. (Viannia)* complex. Approximately half of the patients with mucosal lesions have had active cutaneous lesions within the preceding 2 yr, but ML may not develop until many years after resolution of the primary lesion. ML occurs in <5% of individuals who have, or have had, LCL caused by *L. (V.) braziliensis*. Patients with ML most commonly have nasal mucosal involvement and present with nasal congestion, discharge, and recurrent epistaxis. Oropharyngeal and laryngeal involvement is less common but associated with severe morbidity. Marked soft tissue, cartilage, and even bone destruction occurs late in the course of disease and may lead to visible deformity of the nose or mouth, nasal septal perforation, and tracheal narrowing with airway obstruction.

Visceral Leishmaniasis

VL **(kala-azar)** typically affects children younger than 5 yr of age in the New World and Mediterranean region (*L. infantum/chagasi*) and older children and young adults in Africa and Asia (*L. donovani*). After inoculation of the organism into the skin by the sandfly, the child may have a completely asymptomatic infection or an oligosymptomatic illness that either resolves spontaneously or evolves into active kala-azar. Children with asymptomatic infection are transiently seropositive but show no clinical evidence of disease. Children who are oligosymptomatic have mild constitutional symptoms (malaise, intermittent diarrhea, poor activity tolerance) and intermittent fever; most will have a mildly enlarged liver. In most of these children the illness will resolve without therapy, but in approximately 25% it will evolve to active kala-azar within 2-8 mo. Extreme incubation periods of several years have rarely been described. During the first few wk to months of disease evolution the fever is intermittent, there is weakness and loss of energy, and the spleen begins to enlarge. The classic clinical features of high fever, marked splenomegaly, hepatomegaly, and severe cachexia typically develop approximately 6 mo after the onset of the illness, but a rapid clinical course over 1 mo has been noted in up to 20% of patients in some series (Fig. 285-2). At the terminal stages of kala-azar the hepatosplenomegaly is massive, there is gross wasting, the pancytopenia is profound, and jaundice, edema, and ascites may be present. Anemia may be severe enough to precipitate heart failure. Bleeding episodes, especially epistaxis, are frequent. The late stage of the illness is often complicated by secondary bacterial infections, which frequently are a cause of death. A younger age at the time of infection and underlying malnutrition may be risk factors for the development and more rapid evolution of active VL. Death occurs in more than 90% of patients without specific antileishmanial treatment.

VL is an opportunistic infection associated with HIV infection. Most cases have occurred in southern Europe and Brazil, often as a result of needle sharing associated with illicit drug use, with the potential for many more cases as the endemic regions for HIV and VL converge. Leishmaniasis may also result from reactivation of a long-standing subclinical infection. Frequently there is an atypical clinical presentation of VL in HIV-infected individuals with prominent involvement of the gastrointestinal tract and absence of the typical hepatosplenomegaly.

A small percentage of patients previously treated for VL develop diffuse skin lesions, a condition known as **post–kala-azar dermal leishmaniasis.** These lesions may appear during or shortly after therapy (Africa) or up to several years later (India). The lesions of post–kala-azar dermal leishmaniasis are hypopigmented, erythematous, or nodular and commonly involve the face and torso. They may persist for several months or for many years.

LABORATORY FINDINGS

Patients with cutaneous leishmaniasis or ML generally do not have abnormal laboratory results unless the lesions are secondarily infected with bacteria. Laboratory findings associated with classic kala-azar include anemia (hemoglobin 5-8 mg/dL), thrombocytopenia, leukopenia (2,000-3,000 cells/μL), elevated hepatic transaminase levels, and hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G.

DIFFERENTIAL DIAGNOSIS

Diseases that should be considered in the differential diagnosis of LCL include sporotrichosis, blastomycosis, chromomycosis, lobomycosis, cutaneous tuberculosis, atypical mycobacterial infection, leprosy, ecthyma, syphilis, yaws, and neoplasms. Infections such as syphilis, tertiary yaws, histoplasmosis, paracoccidioidomycosis, as well as sarcoidosis, Wegener granulomatosis, midline granuloma, and carcinoma may have clinical features similar to those of ML. VL should be strongly suspected in the patient with prolonged fever, weakness, cachexia, marked splenomegaly, hepatomegaly, cytopenias, and hypergammaglobulinemia who has had potential exposure in an endemic area. The clinical picture may also be consistent with that of malaria, typhoid

Figure 285-2 Visceral leishmaniasis *(Leishmania donovani)* in Bihar State, India. **A,** Hepatosplenomegaly and wasting in a young man. **B,** Children with burn marks over enlarged spleen or liver—local shaman's unsuccessful remedy. *(**A** courtesy of D. Sacks. **B** courtesy of R. Kenney. **A** and **B** modified from Murray HW, Berman JD, Davies CR, et al: Advances in leishmaniasis,* Lancet *366:1561–1577, 2005.)*

fever, miliary tuberculosis, schistosomiasis, brucellosis, amebic liver abscess, infectious mononucleosis, lymphoma, and leukemia.

DIAGNOSIS

The development of 1 or several slowly progressive, nontender, nodular, or ulcerative lesions in a patient who had potential exposure in an endemic area should raise suspicion of LCL.

Serologic tests for diagnosis of ML or LCL generally have low sensitivity and specificity and offer little for diagnosis. Serologic testing by enzyme immunoassay, indirect fluorescence assay, or direct agglutination is very useful in VL because of the very high level of antileishmanial antibodies. An immunochromatographic strip test using a recombinant antigen (K39) has a diagnostic sensitivity and specificity for VL of 80-90% and 95%, respectively. Serodiagnostic tests have positive findings in only about half of the patients who are coinfected with HIV.

Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture. Amastigotes can be identified in Giemsa-stained tissue sections, aspirates, or impression smears in about half of the cases of LCL but only rarely in the lesions of ML. Culture of a tissue biopsy or aspirate, best performed by using Novy-McNeal-Nicolle biphasic blood agar medium, yields a positive finding in only approximately 65% of cases of cutaneous leishmaniasis. Identification of parasites in impression smears, histopathologic sections, or culture medium is more readily accomplished in DCL than in LCL. In patients with VL, smears or cultures of material from splenic, bone marrow, or lymph node aspirations are usually diagnostic. In experienced hands, **splenic aspiration** has a higher diagnostic sensitivity, but it is rarely performed in the United States because of the risk for bleeding complications. A positive culture result allows speciation of the parasite, usually by isoenzyme analysis by a reference laboratory, which may have therapeutic and prognostic significance.

TREATMENT

Specific antileishmanial therapy is not routinely indicated for uncomplicated LCL caused by strains that have a high rate of spontaneous resolution and self-healing *(L. major, L. mexicana).* Lesions that are extensive, severely inflamed, or located where a scar would result in disability (near a joint) or cosmetic disfigurement (face or ear), that involve the lymphatics, or that do not begin healing within 3-4 mo should be treated. Cutaneous lesions suspected or known to be caused by members of the *Viannia* subgenus (New World) should be treated because of the low rate of spontaneous healing and the potential risk for development of mucosal disease. Similarly, patients with lesions caused by *L. tropica* (Old World), which are typically chronic and nonhealing, should be treated. All patients with VL or ML should receive therapy.

The pentavalent antimony compounds (sodium stibogluconate [Pentostam, GlaxoSmithKline, Uxbridge, UK] and meglumine antimoniate [Glucantime, Aventis, Strasbourg, France]) have been the mainstay of antileishmanial chemotherapy for more than 40 yr. These drugs have similar efficacies, toxicities, and treatment regimens. Currently, for sodium stibogluconate (available in the United States from the Centers for Disease Control and Prevention, Atlanta, Georgia), the recommended regimen is 20 mg/kg/day intravenously or intramuscularly for 20 days (for LCL and DCL) or 28 days (for ML and VL). Repeated courses of therapy may be necessary in patients with severe cutaneous lesions, ML, or VL. An initial clinical response to therapy usually occurs in the 1st wk of therapy, but complete clinical healing (reepithelialization and scarring for LCL and ML, and regression of splenomegaly and normalization of cytopenias for VL) is usually not evident for weeks to a few months after completion of therapy. Cure rates with this regimen of 90-100% for LCL, 50-70% for ML, and 80-100% for VL were common in the 1990s, but treatment failures, especially in children, have become common in parts of India, East Africa, and Latin America. Relapses are common in patients who do not have an effective antileishmanial cellular immune response (DCL or HIV coinfection). Adverse effects of antimony therapy are dose and duration dependent and commonly include fatigue, arthralgias and myalgias (50%), abdominal discomfort (30%), elevated hepatic transaminase level (30-80%), elevated amylase and lipase levels (almost 100%), mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count) (10-30%), and nonspecific T-wave changes on electrocardiography (30%). Sudden death from cardiac toxicity has rarely been reported with use of very high doses of pentavalent antimony.

Amphotericin B desoxycholate and the amphotericin lipid formulations are very useful in the treatment of VL or ML and in some regions have replaced antimony as first-line therapy. However, the prohibitively high cost of these drugs precludes their use in many resource-poor regions of the world. Amphotericin B desoxycholate at doses of 0.5-1.0 mg/kg every day or every other day for 14-20 doses achieved a cure rate for VL of close to 100%, but the renal toxicity associated with amphotericin B was common. The lipid formulations of amphotericin B are especially attractive for treatment of leishmaniasis because the drugs are concentrated in the reticuloendothelial system and are less nephrotoxic. Liposomal amphotericin B is highly effective, with a 90-100% cure rate for VL in immunocompetent children, some of whom were refractory to antimony therapy. Liposomal amphotericin B (AmBisome, Gilead Sciences, Foster City, CA) is approved by the U.S. Food and Drug Administration for treatment of VL at a recommended dose for immunocompetent patients of 3 mg/kg on days 1-5, 14, and 21 and should be considered for first-line therapy in the United States. Therapy for immunocompromised patients may need to be prolonged. A single high dose of liposomal amphotericin B (10 mg/kg) was found to be noninferior to conventional amphotericin (15 doses of 1 mg/kg) in India and offers a less-cost-prohibitive approach. Parenteral treatment of VL with the aminoglycoside paromomycin (aminosidine) has efficacy (~95%) similar to that of amphotericin B in India. Miltefosine, a membrane-activating alkylphospholipid, has been approved as the first oral treatment for VL and has a cure rate of 80-90% in Indian patients with VL when administered orally at 50-100 mg/day (or 2.5 mg/kg for children younger than 12 yr of age) for 28 days. Miltefosine is indicated for cutaneous infection caused by *L. braziliensis*, *L. guyanensis,* and *L. panamensis*; mucosal disease caused by *L. braziliensis*; and visceral disease caused by *L. donovani*. Gastrointestinal adverse effects were frequent but did not require discontinuation of the drug. An increased rate of relapse (up to 20%) has been seen in children treated with miltefosine. Dose-sparing combination regimens are being actively investigated for treatment of VL. Treatment of LCL with oral drugs has had only modest success. Ketoconazole has been effective in treating adults with LCL caused by *L. major, L. mexicana,* and *L. panamensis,* but not *L. tropica* or *L. braziliensis*. Fluconazole in high doses (up to 8 mg/kg/day) for 4-8 wk was demonstrated to be effective in treating LCL in studies in both the Old and New World; however, the experience in young children is limited. Miltefosine 2.5 mg/kg/day orally for 20-28 days was effective in 70-90% of patients with LCL in the Americas. Topical treatment of LCL with paromomycin ointment has been effective in selected areas in the both Old and New World. Enhanced drug development efforts and clinical trials of new drugs are clearly needed, especially in children.

PREVENTION

Personal protective measures should include avoidance of exposure to the nocturnal sandflies and, when necessary, the use of insect repellent and permethrin-impregnated mosquito netting. Where peridomiciliary transmission is present, community-based residual insecticide spraying has had some success in reducing the prevalence of leishmaniasis, but long-term effects are difficult to maintain. Control or elimination of infected reservoir hosts (e.g., seropositive domestic dogs) has had limited success. Where anthroponotic transmission is thought to occur, early recognition and treatment of cases are essential. Several vaccines have been demonstrated to have efficacy in experimental models, and vaccination of humans or domestic dogs may have a role in the control of the leishmaniases in the future.

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Chapter 286

African Trypanosomiasis (Sleeping Sickness; *Trypanosoma brucei* Complex)

Edsel Maurice T. Salvana and Robert A. Salata

Seventy million people in 36 countries are at risk for infection with *Trypanosoma brucei* complex, the causative agent of sleeping sickness. Also known as **human African trypanosomiasis (HAT)**, this disease is restricted to sub-Saharan Africa, the range of the tsetse fly vector. It is a disease of extreme poverty, with an increased burden observed in remote rural areas. HAT comes in 2 geographically and clinically distinct forms. *T. brucei gambiense* causes a chronic infection lasting years and mostly affects people who live in Western and Central Africa **(West African sleeping sickness, Gambian trypanosomiasis).** *T. brucei rhodesiense* is a zoonosis that presents as an acute illness lasting several weeks and usually occurs in residents of eastern and southern Africa **(East African sleeping sickness, Rhodesian trypanosomiasis).**

ETIOLOGY

HAT is a vector-borne disease caused by parasitic, flagellated kinetoplastid protozoans of 2 subspecies of *T. brucei*. It is transmitted to humans through the bite of *Glossina*, commonly known as the **tsetse fly.**

The vector feeds on the blood of humans and wild game animals and penetrates intact mucous membranes and skin. Humans usually contract East African HAT when they venture from towns to rural areas to visit woodlands or livestock, highlighting the importance of zoonotic reservoirs in this disease. West African HAT is contracted closer to settlements and only requires a small vector population, making it difficult to eradicate. Low rates of infection in tsetse flies of this form necessitates close and repeated contact between humans and insects to permit frequent biting. While animal reservoirs occur, these are less important than for East African HAT, and the main source of infection remains chronically infected human hosts.

LIFE CYCLE

T. brucei undergoes several stages of development in the insect and mammalian host. Upon ingestion with a blood meal, nonproliferative stumpy forms of the parasite, which are optimally adapted to surviving in *Glossina,* transform into procyclic forms in the insect's midgut. These procyclic forms proliferate and undergo further development into epimastigotes, which then become infective metacyclic forms that migrate to the insect's salivary glands. The life cycle within the tsetse fly takes 15-35 days. On inoculation into the mammalian host, the metacyclic stage transforms into proliferative long and slender forms in the bloodstream and the lymphatics, eventually penetrating the central nervous system. These slender forms appear in waves in the peripheral blood, with each wave followed by a febrile crisis and heralding the formation of a new antigenic variant. The slender forms transform into intermediate forms, which become nonproliferative stumpy forms that are ingested by *Glossina* and start the cycle anew.

Direct transmission to humans has been reported, either mechanically through contact with the contaminated mouth parts of tsetse flies with viable slender forms during feeding or vertically to infants.

EPIDEMIOLOGY

HAT is a major public health problem in sub-Saharan Africa. It occurs in the region between latitudes 14 degrees north and 29 degrees south, corresponding roughly to the area where the annual rainfall creates optimal climatic conditions for *Glossina* flies to thrive. More than 70% of reported cases are from the Democratic Republic of Congo. In 2009, as a result of intensive control efforts spearheaded by the World Health Organization (WHO), the number of new HAT cases annually fell below 10,000 for the first time in 50 yr. In 2011, this further fell to 6,743 cases. As a result, the disease has been targeted by the international community for elimination as a public health problem.

T. brucei rhodesiense infection is restricted to the eastern third of the endemic area in tropical Africa, stretching from Ethiopia to the northern boundaries of South Africa. *T. brucei gambiense*, which accounts for 97% of HAT cases, occurs mainly in the western half of the continent's endemic region. *Glossina* captured in endemic foci show a low rate of infection, usually <5%. Rhodesian HAT, which has an acute and often fatal course, greatly reduces chances of transmission to tsetse flies. The ability of *T. brucei rhodesiense* to multiply rapidly in the bloodstream and infect other species of mammals helps maintain its life cycle. The insect vector is able to transmit disease for up to 6 mo.

PATHOGENESIS

The initial entry site of the organisms develops a hard, painful, red nodule known as a trypanosomal **chancre.** It contains long, thin trypanosomes multiplying beneath the dermis and is surrounded by a lymphocytic cellular infiltrate. Dissemination into the blood and lymphatic systems follows, with subsequent localization to the central nervous system (CNS). Histopathologic findings in the brain are consistent with meningoencephalitis, with lymphocytic infiltration and perivascular cuffing of the membranes. The appearance of **morular** cells (large, strawberry-like cells, supposedly derived from plasma cells) is a characteristic finding in chronic disease.

Antigenic variation of **variant surface glycoproteins** on the trypanosome's surface enables evasion of acquired immunity during infection. Both *T. brucei gambiense* and *T. brucei rhodesiense* have acquired resistance to trypanolytic factors in human serum, the most well-studied of which is **apolipoprotein L-1** (APOL1), through the expression of a protein known as *serum resistance-associated protein*. A frameshift mutation in the APOL1 gene in 1 patient enabled infection with a nonhuman trypanosome, *Trypanosoma evansi*, and treatment with recombinant APOL1 restored trypanolytic activity. Mechanisms underlying virulence in HAT are still incompletely understood, although severity of disease seems to be dependent on the host inflammatory response, particularly interferon-γ production in the CNS and blood.

CLINICAL MANIFESTATIONS

Clinical presentations vary not only because of the 2 subspecies of organisms but also because of differences in host response in the indigenous population of endemic areas and in newcomers or visitors. Visitors usually suffer more from the acute symptoms, but in untreated cases death is inevitable for natives and visitors alike. Symptoms usually occur within 1-4 wk of infection. The clinical syndromes of HAT are trypanosomal chancre, hemolymphatic stage, and meningoencephalitic stage.

Trypanosomal Chancre

The site of the tsetse fly bite may be the first presenting feature. A nodule or chancre develops in 2-3 days and becomes a painful, hard, red nodule surrounded by an area of erythema and swelling within 1 wk. Nodules are commonly seen on the lower limbs and sometimes also on the head. They subside spontaneously in about 2 wk, leaving no permanent scar.

Hemolymphatic Stage (Stage 1)

The most common presenting features of acute HAT occur at the time of invasion of the bloodstream by the parasites, 2-3 wk after infection.

Patients usually present with irregular episodes of fever, each lasting up to 7 days, accompanied by headache, sweating, and generalized lymphadenopathy. Attacks may be separated by symptom-free intervals of days or even weeks. Painless, nonmatted lymphadenopathy, most commonly of the posterior cervical and supraclavicular nodes, is one of the most constant signs, particularly in the Gambian form. A common feature of trypanosomiasis in Caucasians is the presence of blotchy, irregular, nonpruritic, erythematous macules, which may appear any time after the first febrile episode, usually within 6-8 wk. The majority of macules have a normal central area, giving the rash a circinate outline. This rash is seen mainly on the trunk and is evanescent, fading in 1 place only to appear at another site. Examination of the blood during this stage may show anemia, leukopenia with relative monocytosis, and elevated levels of immunoglobulin M. Cardiac manifestations of HAT have also been reported but are generally limited to nonspecific ST-T wave electrocardiographic abnormalities. Histopathologic characterization shows a lymphomonohistiocytic infiltrate in the interstitium and no penetration of the myocardial cells, unlike that for American trypanosomiasis (see Chapter 287). Progression of cardiac pathology to congestive heart failure has not been reported, and the perimyocarditis is usually self-limited and/or readily resolves with treatment.

Meningoencephalitic Stage (Stage 2)

Neurologic symptoms and signs are nonspecific, including irritability, insomnia, and irrational and inexplicable anxieties with frequent changes in mood and personality. Neurologic symptoms may precede invasion of the CNS by the organisms. In untreated *T. brucei rhodesiense* infections, CNS invasion occurs within 3-6 wk and is associated with recurrent bouts of headache, fever, weakness, and signs of acute toxemia. Tachycardia may be evidence of myocarditis. Death occurs in 6-9 mo as a result of secondary infection or cardiac failure.

In Gambian HAT, cerebral symptoms appear within 2 yr after the acute symptoms. An increase in drowsiness during the day and insomnia at night reflect the continuous progression of infection and may be accompanied by anemia, leukopenia, and muscle wasting. Patients are also at increased risk for infection.

The chronic, diffuse meningoencephalitis without localizing symptoms is the form referred to as **sleeping sickness.** Drowsiness and an uncontrollable urge to sleep are the major features of this stage of the disease and become almost continuous in the terminal stages. Tremor or rigidity with stiff and ataxic gait, suggest involvement of the basal ganglia. Psychotic changes occur in almost one third of untreated patients. Although untreated disease has been thought to be uniformly fatal, there is prospective evidence that, in rare cases, some individuals remain asymptomatic, are able to clear parasitemia, and occasionally become seronegative.

DIAGNOSIS

Definitive diagnosis can be established during the early stages by examination of a fresh, thick blood smear, which permits visualization of the motile active forms (Fig. 286-1). HAT can also be detected from blood using a variety of sensitive techniques: quantitative buffy coat smears and mini anion exchange resins are common examples. The **card agglutination trypanosomiasis test** is of value for epidemiologic purposes and in screening for *T. brucei gambiense.* Dried, Giemsa-stained smears should be examined for the detailed morphologic features of the organisms. If a thick blood or buffy coat smear is negative, concentration techniques may help. Aspiration of an enlarged lymph node can also be used to obtain material for parasitologic examination. If positive, cerebrospinal fluid should also be examined for the organisms. The presence of trypanosomes, or 5 white blood cells/μL, or both, is indicative of stage 2 disease. If trypanosomes are absent in the cerebrospinal fluid, some authorities use a count of 20 white blood cells/μL as a cutoff for diagnosing late-stage disease. Because the white blood cell count in the cerebrospinal fluid is critical in making treatment decisions, methods for improving cell counting, such as the use of disposable cell counters and combining multiple counts, have been proposed.

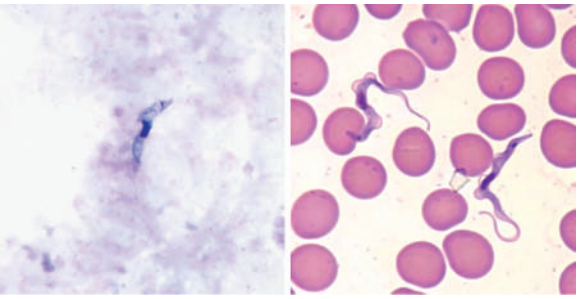

Figure 286-1 *Trypanosoma brucei* sp. trypomastigotes in thick blood smear stained with Giemsa *(left)* and thin blood smear stained with Wright-Giemsa *(right). (From the Centers for Disease Control and Prevention [CDC]: Laboratory identification of parasites of public health concern. Trypanosomiasis, African. Available at: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAfrican_il.htm)*

Polymerase chain reaction–based tests have been shown to be highly sensitive and specific, but these require advanced laboratory facilities. Field-based loop-mediated isothermal amplification tests have been developed but need further validation. Low cost, stable, but highly specific rapid tests such as the HAT Sero-Strip and HAT Sero-K-SeT that detect trypanosome-specific antibodies have been developed, and may prove to be useful for point-of-care diagnosis as the focus shifts from control to elimination.

TREATMENT

The choice of chemotherapeutic agents for treatment is dependent upon the stage of the infection and the causative organisms.

Stage 1 Treatment

Hematogenous forms of both Rhodesian and Gambian HAT can be treated with either suramin or pentamidine, which are better tolerated than drugs for stage 2 or CNS disease but are associated with substantial risks of toxicity. **Suramin** is a polysulphonated symmetrical naphthalene derivative given as a 10% solution for intravenous administration. A **test dose** (10 mg for children; 100-200 mg for adults) is initially administered to detect rare idiosyncratic reactions of shock and collapse. The dose for subsequent IV injections is 20 mg/kg (maximum: 1 g) administered on days 1, 3, 7, 14, and 21. Suramin is nephrotoxic, and thus a urinalysis should be performed before each dose. Marked proteinuria, blood, or casts is a contraindication to continuation of suramin. Resistance is rare but has been reported.

Pentamidine isethionate (4 mg/kg/day IM for 7-10 days daily or on alternate days) concentrates to high levels in trypanosomes and is highly trypanocidal. It is better tolerated than suramin but carries significant risk of hypoglycemia, nephrotoxicity, hypotension, leukopenia, and liver enzyme elevation. Because of its potency, long half-life, and toxicity, short course treatment is desirable and is being investigated.

Stage 2 Treatment

The treatment of late stage *T. brucei gambiense* has substantially changed as a result of programmatic efforts of the WHO and the donation of large quantities of trypanosomicidal drugs, including eflornithine, pentamidine, suramin, and nifurtimox. **Combination eflornithine and nifurtimox** is the treatment of choice for *T. brucei gambiense* CNS infection. This regimen is noninferior to eflornithine monotherapy, and the duration of treatment is shorter. For combination therapy eflornithine is given at 400 mg/kg/day every 12 hr IV for 7 days, along with nifurtimox 15 mg/kg/day every 8 hr PO for 10 days. If nifurtimox is unavailable, eflornithine monotherapy can be given at a dose of 400 mg/kg/day, every 6 hr IV for 14 days. Adverse reactions to these regimens include fever, hypertension and seizures, with combination eflornithine and nifurtimox having less-frequent events.

Melarsoprol is an arsenical compound and is the only effective treatment for late *T. brucei rhodesiense* disease. Treatment of children is initiated at 0.36 mg/kg once daily IV, with gradually escalating doses every 1-5 days to 3.6 mg/kg once daily IV; treatment is usually 10 doses (18-25 mg/kg total dose). Treatment of adults is with melarsoprol 2-3.6 mg/kg once daily IV for 3 days; and after 1 wk, 3.6 mg/kg once daily IV for 3 days, which is repeated after 10-21 days. An alternative regimen is 2.2 mg/kg once daily for 10 days. Guidelines recommend 18-25 mg/kg total over 1 mo. Reactions such as fever, abdominal pain, and chest pain are rare but may occur during or shortly after administration. Serious toxic effects include encephalopathy and exfoliative dermatitis.

Because of the inherent logistic difficulties in administering intravenous therapy for late stage HAT, an active area of research is finding effective oral agents for late-stage HAT. Several promising agents are due to enter phase 2 trials. Efforts to decrease the toxicity of melarsoprol by making it more water soluble are also underway.

PREVENTION

A vaccine or consistently effective prophylactic therapy is not available and is particularly challenging because of the antigenic variation resulting from variant surface glycoproteins. A single injection of pentamidine (3-4 mg/kg IM) provides protection against Gambian trypanosomiasis for at least 6 mo, but the effectiveness against the Rhodesian form is uncertain.

While the progress in controlling HAT has been impressive, the increasing cost of treatment per case as the overall number of patients decline may lead to premature termination of intensive control efforts. Underreporting of cases remains a challenge. Vector control programs to control *Glossina* have been essential in controlling disease, coupled with the use of screens, traps, and sanitary measures. Encouraging neutral-colored clothing that is not attractive to the tsetse fly may reduce bites.

Using serology and parasitologic methods, mobile medical surveillance of the population at risk by specialized staff has been done, and strong collaboration between WHO, Medecins sans Frontieres, and African governments has shifted the burden of treatment to well-organized and funded national control programs. Ground spraying of insecticides, aerial spraying, and the use of cloth and live animal baits have proven successful. Transgenic techniques to restrict the ability of the tsetse fly to survive and transmit pathogens are also being developed.

The full genome of *T. brucei* with approximately 9,000 genes has been sequenced. Approximately 10% of these genes encode variant surface glycoproteins. This advance has helped identify genes relevant to the disease and its possible prevention, as well as the design of new antitrypanosomal drugs, including those that target specific metabolic pathways.

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Chapter 287

American Trypanosomiasis (Chagas Disease; *Trypanosoma cruzi*)

Edsel Maurice T. Salvana and Robert A. Salata

American trypanosomiasis or Chagas disease is a vector-borne disease caused by the protozoan *Trypanosoma cruzi*. Its natural vectors are the bloodsucking insects of the family Reduviidae. It can also be transmitted orally from contaminated food, vertically from mother to child, and through blood transfusion and organ transplantation. While acute American trypanosomiasis usually manifests as a nonspecific febrile illness, chronic Chagas disease is associated with cardiomyopathy and severe gastrointestinal abnormalities.

ETIOLOGY

American trypanosomiasis is a caused by *T. cruzi*, a parasitic, flagellated kinetoplastid protozoan (Fig. 287-1). The main vectors for *T. cruzi* are insects of the order Triatominae, which includes *Triatoma infestans* (free roaming kissing bugs), *Rhodnius prolixus,* and *Panstrongylus megistus.*

LIFE CYCLE

T. cruzi has 3 recognizable morphogenetic phases: amastigotes, trypomastigotes, and epimastigotes (see Figs. 287-1 and 287-2). **Amastigotes** are intracellular forms found in mammalian tissues that are spherical and have a short flagellum but form clusters of oval shapes (pseudocysts) within infected tissues. **Trypomastigotes** are spindle-shaped, extracellular, nondividing forms that are found in blood and are responsible for both transmission of infection to the insect vector and cell-to-cell spread of infection. **Epimastigotes** are found in the midgut of the vector insect and multiply in the midgut and rectum of arthropods, differentiating into **metacyclic trypomastigotes.** Metacyclic trypomastigotes are the infectious form for humans and are released onto the skin of a human when the insect defecates close to the site of a bite, entering via the damaged skin or mucous membranes. Once in the host, these multiply intracellularly as amastigotes and are

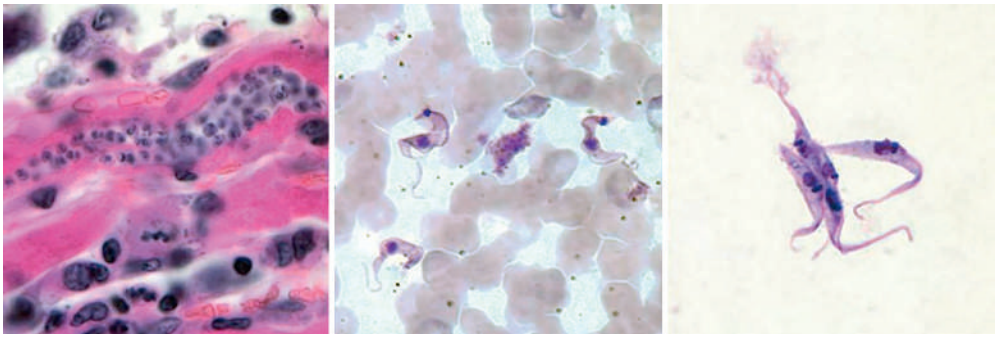

Figure 287-1 Stages of *Trypanosoma cruzi.* From *left* to *right:* amastigote, trypomastigote, and epimastigote. *(From the Centers for Disease Control and Prevention [CDC]: Laboratory identification of parasites of public health concern. Trypanosomiasis, American. Available at: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAmerican_il.htm)*

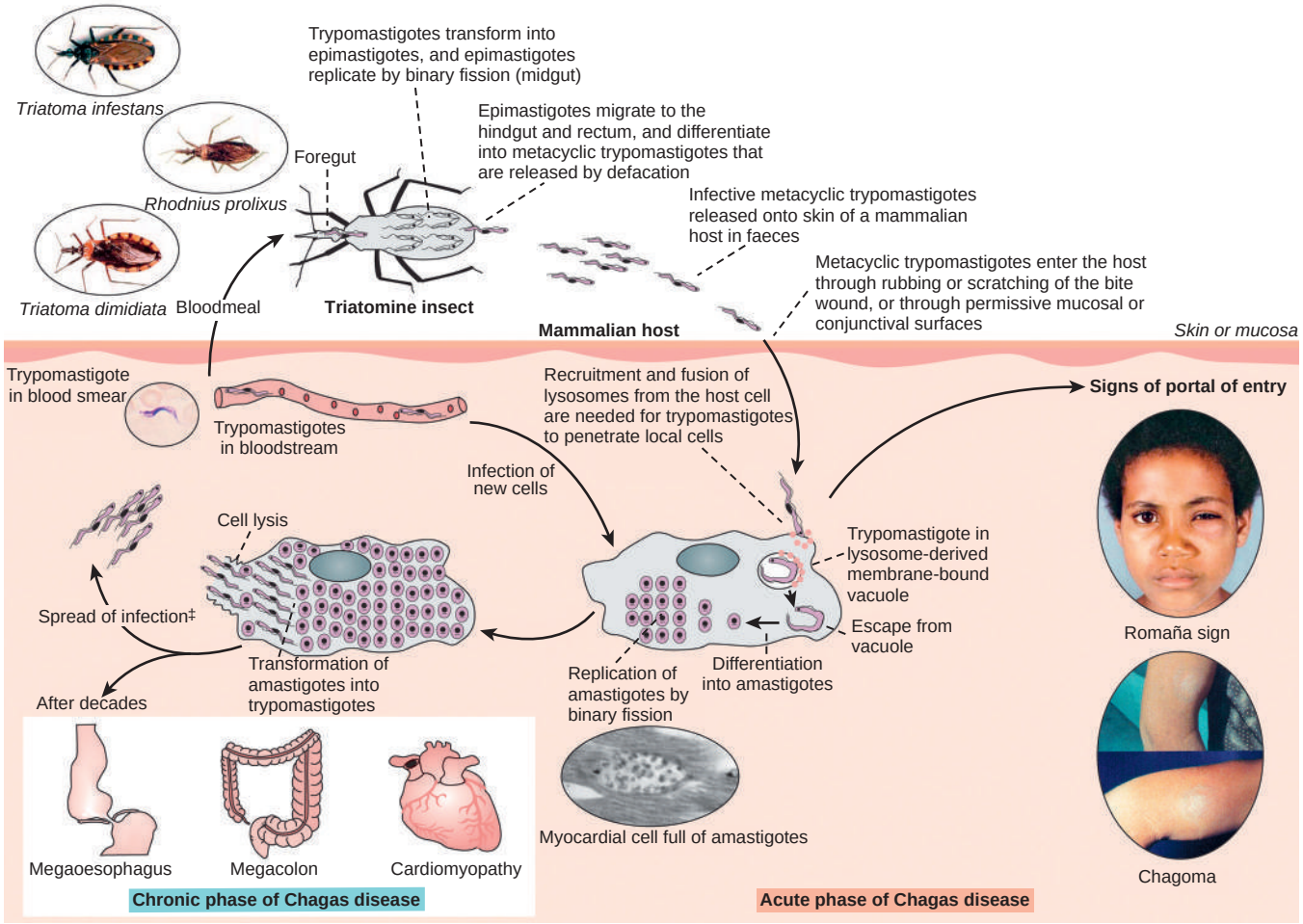

Figure 287-2 Vector-borne transmission and life cycle of *Trypanosoma cruzi*. *(From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease,* Lancet *375:1388–1400, 2010, Fig. 1, p. 1389.)*

released into the circulation when the cell dies. Bloodborne trypomastigotes circulate until they enter another host cell or are taken up by the bite of another insect, completing the life cycle.

EPIDEMIOLOGY

Chagas disease is found only in the Western hemisphere, specifically the Americas, particularly in southern Patagonia (Fig. 287-3). Natural transmission only occurs within this region, but the disease may arise elsewhere as a consequence of migration and transmission through contaminated blood. Multilateral efforts coordinated by the World Health Organization and the Pan-American Health Organization in large-scale vector control, blood donor screening to prevent transmission through transfusion, and case-finding and treatment of chronically infected mothers and newborn infants have effectively halted transmission in a number of areas of South America. In the Brazilian Amazon, vectorial transmission from *T. infestans* has been effectively interrupted through multicountry programs involving vector control, housing design improvements, and health education. The number of cases has dropped from a peak of 24 million in 1984 to a current estimate of 8-10 million. Vectorial transmission continues to drop in other regions, although challenges remain, including the emergence of disease in new areas thought to be Chagas-free, along with occasional re-emergence in previously controlled areas.

Infection is divided into 3 main phases: acute (Table 287-1), indeterminate, and chronic. Acute infection is the most amenable to treatment. Indeterminate infection is asymptomatic but associated with a positive antibody titer. Up to 30% of infected persons proceed to chronic *T. cruzi* infection and develop symptoms. While it was initially believed that chronic infection without treatment does not clear, at least 3 well-documented cases of spontaneous resolution without treatment have been reported. It is still unclear how this parasitic protozoan escapes the immune system because, unlike African trypanosomiasis (see Chapter 286), antigenic variation is not observed. The *T. cruzi* genome has been fully sequenced and contains 12,000 genes, the most widely expanded among trypanosomatids, possibly reflect the ability of *T. cruzi* to invade a wide variety of host tissues. Significant strain-to-strain genome variability and extensive epigenetic modification of surface proteins have been found, likely contributing to immune evasion.

T. cruzi infection is primarily a zoonosis, and humans are incidental hosts. *T. cruzi* has a large sylvan reservoir and has been isolated from numerous animal species. The presence of reservoirs and vectors of *T. cruzi* and the socioeconomic and educational levels of the population are the most important risk factors for vector-borne transmission to humans. The arthropod vectors for *T. cruzi* are the **reduviid insects** or **triatomines,** variably known as **wild bedbugs, assassin bugs,** or **kissing bugs.** Insect vectors are found in rural, wooded areas and acquire infection through ingestion of blood from humans or animals with circulating trypomastigotes. Free roaming kissing bugs in the southwestern United States have been found to have fed on humans; some bugs contained *T. cruzi*.

Housing conditions are very important in the transmission chain. Incidence and prevalence of infection depends on the adaptation of the triatomines to human dwellings as well as the vector capacity of the species. Animal reservoirs of reduviid bugs include dogs, cats, rats, opossums, guinea pigs, monkeys, bats, and raccoons. Humans often

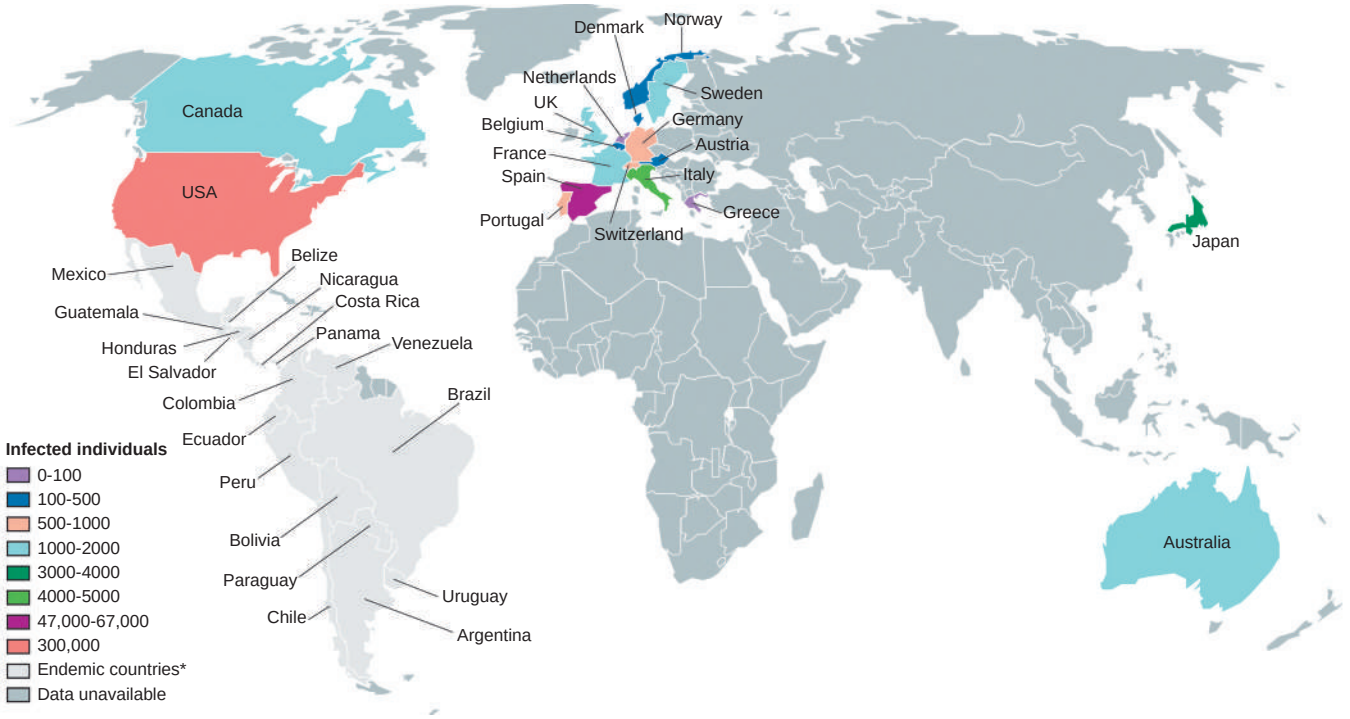

Figure 287-3 Estimated number of immigrants with *Trypanosoma cruzi* infection living in nonendemic countries. Data are supplied for Canada, Australia, and Japan in 2006; the United States in 2005; Spain in 2008; and other European countries in 2004–2006. *(From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease,* Lancet *375:1388–1400, 2010, Fig. 2, p. 1391.)*

become infected when land in enzootic areas is developed for agricultural or commercial purposes. Although reduviid insects can be found in warmer regions of the United States as far north as Maryland, Chagas disease is extremely rare owing to the higher standard of domestic housing. Most acute cases in the United States are associated with laboratory accidents. An estimated 300,000 immigrants from endemic countries living in the United States are likely infected with *T. cruzi,* 30,000 to 45,000 of whom have cardiomyopathy.

Humans can be infected transplacentally, occurring in 10.5% of infected mothers and causing congenital Chagas disease. Transplacental infection is associated with premature birth, fetal wastage, and placentitis. Previously, up to 1,000 neonates infected with *T. cruzi* were born every year in Argentina; this number has substantially decreased since widespread control programs were initiated. Disease transmission can occur through blood transfusions in endemic areas from asymptomatic blood donors. Seropositivity rates in endemic areas are as high as 20%. The risk for transmission through a single blood transfusion from a chagasic donor is 13-23%. Blood screening for Chagas disease in the United States was started in 2006 and has demonstrated a prevalence of slightly over 1 in 13,000 donors. Risk factors in these donors were consistent with exposure to Chagas disease, including travel to endemic areas and a history of a reduviid bug bite.

Percutaneous injection as a result of laboratory accidents is also a documented mode of transmission. Oral transmission through contaminated food is an increasingly important method of transmission as vector transmission is successfully interrupted by control programs. Although breastfeeding is a very uncommon mode of transmission, women with acute infections should not nurse until they have been treated.

PATHOGENESIS

Acute Disease

At the site of entry or puncture site, neutrophils, lymphocytes, macrophages, and monocytes infiltrate. *T. cruzi* organisms are engulfed by macrophages and are sequestered in membrane-bound vacuoles. Trypanosomes lyse the phagosomal membrane, escape into the cytoplasm, and replicate. A local tissue reaction, the **chagoma,** develops, and the process extends to a local lymph node (see Fig. 287-2). Blood forms appear, and the process disseminates. Initial immune recognition of parasites is through innate pathways involving activation of multiple Toll-like receptors (TLRs) by different parasite substrates, including TLR 2/6, TLR 4, and TLR 9. Adaptive immunity is mediated by interferon-γ and interleukin-12 activation of T-cells and is modulated by interleukin-10 and transforming growth factor-β, which downregulates macrophage activity. The interplay of these cytokines is probably responsible, in part, for the variability in disease manifestations and the progression to chronic disease. Acute myocarditis likely occurs in all patients with acute disease but is frequently asymptomatic and may only be apparent on biopsy.

Chronic Disease

The pathophysiology of chronic Chagas disease is incompletely understood. Two main mechanisms are likely involved, although other factors may come into play. The first mechanism involves direct tissue destruction by low-level parasite persistence mediated by lymphocytic infiltration and fibrosis. The second mechanism involves molecular mimicry of host antigens by the parasite, resulting in autoantibodies that produce (1) an inflammatory reaction associated with direct damage to host tissue, and/or (2) direct stimulation of adrenergic and muscarinic cholinergic receptors associated with dysautonomia and increased risk of arrhythmia.

T. cruzi strains demonstrate selective parasitism for certain tissues. Most strains are myotropic and invade smooth, skeletal, and heart muscle cells. Attachment is mediated by specific receptors on the trypomastigotes that attach to complementary glycoconjugates on the host cell surface. Attachment to cardiac muscle results in inflammation of the endocardium and myocardium, edema, focal necrosis in the contractile and conducting systems, periganglionitis, and lymphocytic inflammation. The heart becomes enlarged, and endocardial thrombosis or aneurysm may result. Right bundle-branch block is also common. Trypanosome parasites also attach to neural cells and reticuloendothelial cells. In patients with gastrointestinal tract involvement, myenteric plexus destruction leads to pathologic organ dilation. Immunologic mechanisms for control of parasitism and resistance are not fully

Table 287-1 Vector-Borne Transmission and Life Cycle of *Trypanosoma Cruzi*

	GEOGRAPHICAL DISTRIBUTION	PREDOMINANT POPULATION	INCUBATION TIME	CLINICAL PRESENTATION	DIAGNOSIS	MORTALITY
Vectorial	Endemic countries	Children and adolescents	1-2 wk	Asymptomatic; fever, malaise, lymphadenopathy, hepatosplenomegaly, subcutaneous edema; signs of portal of entry (Romaña sign, chagoma); myocarditis, meningoencephalitis	Parasite detection by microscopy; fresh blood specimen; stained blood smears; buffy coat preparation (microhematocrit technique); or serum precipitate (Strout technique)	Low (<5-10%*)
Transfusion-based	Endemic and nonendemic countries	Adults	8-120 days	Same as for vectorial but excluding signs of portal of entry	Same as for vectorial	Variable†
Congenital	Endemic and nonendemic countries	Neonates and children younger than 1 yr	Up to a few weeks	Asymptomatic; abortion, neonatal death, prematurity, low birthweight, low Apgar score; hypotonicity, fever, hepatosplenomegaly, respiratory distress, anemia; myocarditis, meningoencephalitis, megaviscera, edema	Microhematocrit with cord blood or peripheral blood from neonate; 2 or more samples in the 1st mo of life; immunoglobulin G serology at 6-9 mo of age is microhematocrit negative or not done	Unknown
Oral	Amazon basin and regional outbreaks	Individuals of any age from the same family or community	3-22 days	Same as for transfusion-based plus headache, myalgia, vomiting, abdominal pain, jaundice, diarrhea, and digestive hemorrhage	Same as for vectorial	High (8-35%)
Reactivation-based	Endemic and nonendemic countries	Patients with associated immunosuppressive states	Variable	Same as for transfusion-based plus panniculitis, subcutaneous parasite-containing nodules, and skin ulcers	Same as for vectorial, and parasites can also be detected in tissues by microscopy or polymerase chain reaction	Variable†

*Refers to symptomatic cases; because 95% of acute infections from vectorial transmission are asymptomatic and 5-10% of patients with acute symptoms die, estimated mortality in this phase of infection is between 1 in 200 and 1 in 400.

†Depends on the underlying disease and the patient's clinical condition.

From Rassi A Jr, Rassi A, Marin-Neto JA: Chagas disease, Lancet *375:1388–1400, 2010, Table 2, p. 1393.*

understood. Despite strong acquired immunity, parasitologic cure in chronic infection is exceedingly rare. Antibodies involved with resistance to *T. cruzi* are related to the phase of infection. Immunoglobulin G antibodies, probably to several major surface antigens, mediate immunophagocytosis of *T. cruzi* by macrophages. Conditions that depress cell-mediated immunity increase the severity of *T. cruzi* infection. There is increasing evidence that host genetic factors play a significant role in progression and severity of chronic disease.

CLINICAL MANIFESTATIONS

Acute Chagas disease in children is usually asymptomatic or is associated with a mild febrile illness characterized by malaise, facial edema, and lymphadenopathy (see Table 287-1). Infants often demonstrate local signs of inflammation at the site of parasite entry, which is then referred to as a **chagoma.** Approximately 50% of children come to medical attention with the **Romaña sign** (unilateral, painless eye swelling), conjunctivitis, and preauricular lymphadenitis. Patients complain of fatigue and headache. Fever can persist for 4-5 wk. More severe systemic presentations can occur in children younger than 2 yr old and may include lymphadenopathy, hepatosplenomegaly, and meningoencephalitis. A cutaneous morbilliform eruption can accompany the acute syndrome. Anemia, lymphocytosis, hepatitis, and thrombocytopenia have also been described.

The heart, central nervous system, peripheral nerve ganglia, and reticuloendothelial system are often heavily parasitized. The heart is the primary target organ. The intense parasitism can result in acute inflammation and in 4-chamber cardiac dilation. Diffuse myocarditis and inflammation of the conduction system can lead to the development of fibrosis. Histologic examination reveals the characteristic **pseudocysts,** which are the intracellular aggregates of amastigotes.

Intrauterine infection in pregnant women can cause spontaneous abortion or premature birth. In children with congenital infection, severe anemia, hepatosplenomegaly, jaundice, and convulsions can mimic congenital cytomegalovirus infection, toxoplasmosis, and erythroblastosis fetalis. *T. cruzi* can be visualized in the cerebrospinal fluid in meningoencephalitis. Children usually undergo spontaneous remission in 8-12 wk and enter an indeterminate phase with lifelong low-grade parasitemia and development of antibodies to many *T. cruzi* cell

surface antigens. The mortality rate is 5-10%, with deaths caused by acute myocarditis with resultant heart failure, or meningoencephalitis. Acute Chagas disease should be differentiated from malaria, schistosomiasis, visceral leishmaniasis, brucellosis, typhoid fever, and infectious mononucleosis.

Autonomic dysfunction and peripheral neuropathy can occur. Central nervous system involvement in Chagas disease is uncommon. If granulomatous encephalitis occurs in the acute infection, it is usually fatal.

Chronic Chagas disease may be asymptomatic or symptomatic. The most common presentation of chronic *T. cruzi* infection is **cardiomyopathy,** manifested by congestive heart failure, arrhythmia, and thromboembolic events. Electrocardiographic abnormalities include partial or complete atrioventricular block and right bundle-branch block. Left bundle-branch block is unusual. Pathologic examination of infected heart muscle reveals muscle atrophy, myonecrosis, myocytolysis, fibrosis, and lymphocytic infiltration. Myocardial infarction has been reported and may be secondary to left apical aneurysm embolization or necrotizing arteriolitis of the microvasculature. Left ventricular apical aneurysms are pathognomonic of chronic chagasic cardiomyopathy.

Gastrointestinal manifestations of chronic Chagas disease occur in 8-10% of patients and involve a diminution in the Auerbach plexus and Meissner plexus. There are also preganglionic lesions and a reduction in the number of dorsal motor nuclear cells of the vagus nerve. Characteristically, this involvement presents clinically as **megaesophagus** and **megacolon.** Sigmoid dilation, volvulus, and fecalomas are often found in megacolon. Loss of ganglia in the esophagus results in abnormal dilation; the esophagus can reach up to 26 times its normal weight and hold up to 2 L of excess fluid. Megaesophagus presents as dysphagia, odynophagia, and cough. Esophageal body abnormalities occur independently of lower esophageal dysfunction. Megaesophagus can lead to esophagitis and cancer of the esophagus. Aspiration pneumonia and pulmonary tuberculosis are also more common in patients with megaesophagus.

Immunocompromised Persons

T. cruzi infections in immunocompromised persons may be caused by transmission from an asymptomatic donor of blood products or reactivation of prior infection. Organ donation to allograft recipients can result in a devastating form of the illness. Cardiac transplantation for Chagas cardiomyopathy has resulted in reactivation, despite prophylaxis and postoperative treatment with benznidazole. HIV infection also leads to reactivation in approximately 20% of cases; cerebral lesions are more common in these patients and can mimic those of toxoplasmic encephalitis. Myocarditis is also commonly observed, and secondary prophylaxis may be of benefit in some HIV coinfected patients. In immunocompromised patients at risk for reactivation, serologic testing and close monitoring are necessary.

DIAGNOSIS

A careful history with attention to geographic origin and travel is important. A **peripheral blood smear** or a Giemsa-stained smear during the acute phase of illness may show motile trypanosomes, which is diagnostic for Chagas disease (see Fig. 287-1). These are only seen in the 1st 6-12 wk of illness. Buffy coat smears may improve yield.

Most persons seek medical attention during the chronic phase of the disease, when parasites are not found in the bloodstream and clinical symptoms are not diagnostic. Serologic testing is used for diagnosis, most commonly enzyme-linked immunosorbent assay, indirect hemagglutination, and indirect fluorescent antibody testing. No single serology test is sufficiently reliable to make the diagnosis, so repeat or parallel testing using a different method or antigen is required to confirm the result of an initial positive serologic test. In the case of discordant results, a third test may be employed. Confirmatory tests used typically include the radiologic immunoprecipitation assay (used as a confirmatory test in blood donors in the United States) and Western blot assays based on trypomastigote excreted-secreted antigens.

Nonimmunologic methods of diagnosis are also available. Mouse inoculation and xenodiagnosis (allowing uninfected reduviid bugs to feed on a patient's blood and examining the intestinal contents of those bugs 30 days after the meal) are quite sensitive. Parasites may also be cultured in Novy-MacNeal-Nicolle media. Polymerase chain reaction of nuclear and kinetoplast DNA sequences have been developed and can be highly sensitive in acute disease, but are less reliable for the detection of chronic disease. Polymerase chain reaction is not sufficiently sensitive for blood screening and was only positive in 1 of 22 radiologic immunoprecipitation assay–confirmed donors in the United States. Moreover, there is significant variability among methods and parasite strains. An international collaborative study has validated 4 methods that have the best performance characteristics for widespread use. Diagnosis of congenital transmission in newborns cannot be made at birth with serology because of the presence of maternal antibodies in the 1st 6 mo of life. Microscopic examination, parasite culture, or polymerase chain reaction can be used. However, a serologic test at 6-12 mo is recommended to completely exclude infection.

TREATMENT

Biochemical differences between the metabolism of American trypanosomes and that of mammalian hosts have been exploited for chemotherapy. Trypanosomes are very sensitive to oxidative radicals and do not possess catalase or glutathione reductase/glutathione peroxidase, which are key enzymes in scavenging free radicals. All trypanosomes also have an unusual reduced nicotinamide adenine dinucleotide phosphate–dependent disulfide reductase. Drugs that stimulate H_2O_2 generation or prevent its use are potential trypanosomicidal agents. Other biochemical pathways that have been targeted include ergosterol synthesis using azole compounds and the hypoxanthine-guanine phosphoribosyltransferase pathway using allopurinol.

Drug treatment for *T. cruzi* infection is currently limited to nifurtimox and benznidazole. Both are effective against trypomastigotes and amastigotes and have been used to eradicate parasites in the acute stages of infection. Treatment responses vary according to the phase of Chagas disease, duration of treatment, dose, age of the patient, and geographic origin of the patient. For acute disease, the average cure rate is approximately 60-80%, while for chronic cases, the cure rate is less than 20%. Neither drug is safe in pregnancy.

Benznidazole is a nitroimidazole derivative that may be slightly more effective than nifurtimox. Although benznidazole is capable of inducing the production of free oxide radicals, the dose at which it is given is not effective for this mode of action. Instead, its nitro reduction intermediates may form covalent bonds or interact in other ways with parasitic DNA, lipids, and proteins and cause damage to parasite components. The recommended treatment regimen for children younger than 12 yr of age is 10 mg/kg/day divided twice daily PO for 60 days, and for those older than 12 yr of age, it is 5-7 mg/kg/day divided twice daily PO for 60 days. This drug is associated with significant toxicity, including rash, photosensitivity, peripheral neuritis, granulocytopenia, and thrombocytopenia.

Nifurtimox generates highly toxic oxygen metabolites through the action of nitroreductases, which produce unstable nitro anion radicals, which, in turn, react with oxygen to produce peroxide and superoxide free radicals. The treatment regimen for children 1-10 yr of age is 15-20 mg/kg/day divided 4 times a day PO for 90 days; for children 11-16 yr of age, 12.5-15 mg/kg/day divided 4 times a day PO for 90 days; and for children older than 16 yr of age, 8-10 mg/kg/day divided 3 or 4 times a day PO for 90-120 days. Nifurtimox is associated with weakness, anorexia, gastrointestinal disturbances, toxic hepatitis, tremors, and seizures (hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency).

Although treatment is generally recommended for acute Chagas disease and is effective in the early stages of infection, the treatment of asymptomatic (or indeterminate) infection and symptomatic chronic disease is controversial. Multiple trials with long-term follow-up have yielded mixed results, with an estimated response rate of 6-20% for chronic disease. The definition of response in itself is

problematic, and parasitologic cure is nearly impossible to demonstrate given the limitations of the sensitivity and specificity of detection methods. Instead, serologic conversion is seen as an appropriate treatment response, although some patients who achieve this still eventually develop symptoms. Recommendations from authorities are mixed, with some advocating for treatment regardless of disease phase and others recommending against treatment because of uncertain benefit and the toxicity of the drugs involved. Proponents of the latter approach instead advocate symptomatic treatment of disease manifestations.

Treatment of congestive heart failure is generally in line with recommendations for management of dilated cardiomyopathy from other causes. β-Blockers have been validated in the management of these patients. Digitalis toxicity occurs frequently in patients with Chagas cardiomyopathy. Pacemakers may be necessary in cases of severe heart block. Although cardiac transplantation has been used successfully in chagasic patients, it is reserved for those with the most severe disease manifestations. Plasmapheresis to remove antibodies with adrenergic activity has been proposed for refractory patients, as this approach has been tried and has worked in patients with dilated cardiomyopathy from other causes. However, its application to Chagas disease is unproven.

A light, balanced diet is recommended for megaesophagus. Surgery or dilation of the lower esophageal sphincter treats megaesophagus; pneumatic dilation is the superior mode of therapy. Nitrates and nifedipine have been used to reduce lower esophageal sphincter pressure in patients with megaesophagus. Treatment of megacolon is surgical and symptomatic. Treatment of meningoencephalitis is also supportive.

In accidental infection when parasitic penetration is certain, treatment should be initiated immediately and continued for 10-15 days. Blood is usually collected and tested for seroconversion at 15, 30, and 60 days.

PREVENTION

Massive coordinated vector control programs under the auspices of the World Health Organization and Pan-American Health Organization and the institution of widespread blood donor screening and targeted surveillance of chronically infected mothers and infants at risk have effectively eliminated or at least drastically reduced transmission in most endemic countries. As Chagas disease remains linked to poverty, improvement of living conditions is likewise essential to successful control and eradication. Education of residents in endemic areas, use of bed nets, use of insecticides, and destruction of adobe houses that harbor reduviid bugs are effective methods to control the bug population. Synthetic pyrethroid insecticides help keep houses free of vectors for up to 2 yr and have low toxicity for humans. Paints incorporating insecticides have also been used. A therapeutic vaccine composed of bivalent recombinant *T. cruzi* antigens has been shown to be effective in preclinical proof-of-concept animal models and is currently undergoing further development.

Blood transfusions in endemic areas are a significant risk. Gentian violet, an amphophilic cationic agent that acts photodynamically, has been used to kill the parasite in blood. Photoirradiation of blood containing gentian violet and ascorbate generates free radicals and superoxide anions that are trypanosomicidal. Mepacrine and maprotiline have also been used to eradicate the parasite in blood transfusions.

Because immigrants can carry this disease to nonendemic areas, serologic testing should be performed in blood and organ donors from endemic areas. Potential seropositive donors can be identified by determining whether they have been or have spent extensive time in an endemic area. Questionnaire-based screening of potentially infected blood and organ donors from areas endemic for infection can reduce the risk for transmission. Seropositivity should be considered a contraindication to organ donation, particularly for heart transplantation.

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Chapter 288

Malaria (*Plasmodium*)

Chandy C. John

Malaria is an acute and chronic illness characterized by paroxysms of fever, chills, sweats, fatigue, anemia, and splenomegaly. It has played a major role in human history, causing harm to more people than perhaps any other infectious disease. Malaria is of overwhelming importance in the developing world today, with an estimated 300-500 million cases and more than 1 million deaths each year. Most malarial deaths occur among infants and young children. Although malaria is not endemic in the United States, approximately 1,000 imported cases are recognized in the United States each year. Physicians practicing in nonendemic areas should consider the diagnosis of malaria in any febrile child who has returned from a malaria-endemic area within the previous year, because delay in diagnosis and treatment can result in severe illness or death.

ETIOLOGY

Malaria is caused by intracellular *Plasmodium* protozoa transmitted to humans by female *Anopheles* mosquitoes. Prior to 2004, only 4 species of *Plasmodium* were known to cause malaria in humans: *P. falciparum, P. malariae, P. ovale*, and *P. vivax*. In 2004 *P. knowlesi* (a primate malaria species) was also shown to cause human malaria, and cases of *P. knowlesi* infection have been documented in Malaysia, Indonesia, Singapore, and the Philippines. Malaria also can be transmitted through blood transfusion, use of contaminated needles, and transplacentally from a pregnant woman to her fetus. The risk for blood transmission is small and decreasing in the United States, but may occur by way of whole blood, packed red blood cells, platelets, leukocytes, and organ transplantation.

EPIDEMIOLOGY

Malaria is a major worldwide problem, occurring in more than 100 countries with a combined population of more than 1.6 billion people (Fig. 288-1). The principal areas of transmission are Africa, Asia, and South America. *P. falciparum* and *P. malariae* are found in most malarious areas. *P. falciparum* is the predominant species in Africa, Haiti, and New Guinea. *P. vivax* predominates in Bangladesh, Central America, India, Pakistan, and Sri Lanka. *P. vivax* and *P. falciparum* predominate in Southeast Asia, South America, and Oceania. *P. ovale* is the least-common species and is transmitted primarily in Africa. Transmission of malaria has been eliminated in most of North America (including the United States), Europe, and the Caribbean, as well as Australia, Chile, Israel, Japan, Korea, Lebanon, and Taiwan.

Most cases of malaria in the United States occur among previously infected visitors to the United States from endemic areas and among U.S. citizens who travel to endemic areas without appropriate chemoprophylaxis. The most common regions of acquisition of the 10,100 cases of malaria reported to the Centers for Disease Control and Prevention (CDC) among U.S. citizens between 1985 and 2001 were sub-Saharan Africa (58%), Asia (18%), and the Caribbean and Central or South America (16%). Most of the fatal cases were caused by *P. falciparum* (94% or 66 of the 70 cases), of which 47 (71%) were acquired in sub-Saharan Africa. More than 60% of imported cases of *P. vivax* come from Asia; the remaining species usually come from Africa, Rare cases of apparent locally transmitted malaria have been reported since the 1950s. These cases are likely a result of transmission from untreated and often asymptomatic infected individuals from malaria endemic countries who travel to the United States and infect local mosquitoes or to infected mosquitoes from malaria endemic areas that are transported to the United States on airplanes.

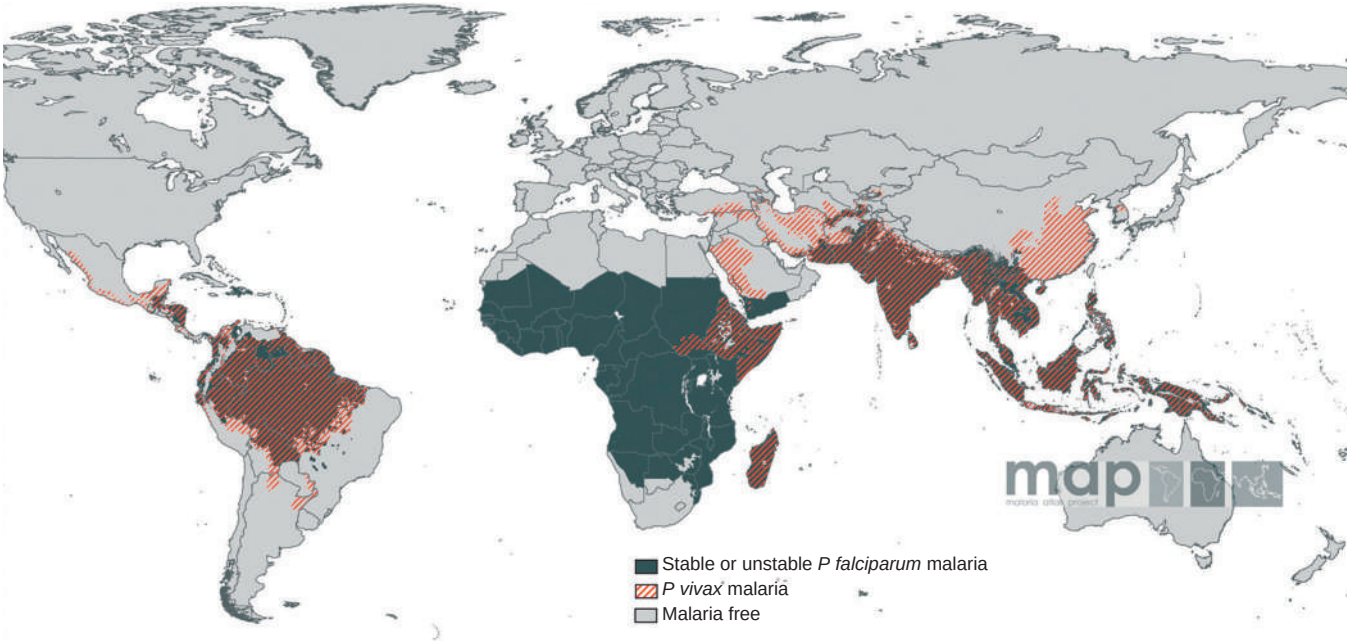

Figure 288-1 Global spatial distribution of *Plasmodium falciparum* malaria in 2007 and preliminary global distribution of *Plasmodium vivax* malaria. *(From Crawley J, Chu C, Mtove G, et al: Malaria in children,* Lancet *375:1468–1478, 2010, Fig. 1, p. 1469.)*

PATHOGENESIS

Plasmodium species exist in a variety of forms and have a complex life cycle that enables them to survive in different cellular environments in the human host (asexual phase) and the mosquito (sexual phase) (Fig. 288-2). A marked amplification of *Plasmodium*, from approximately 10^2 to as many as 10^{14} organisms, occurs during a 2-step process in humans, with the first phase in hepatic cells (exoerythrocytic phase) and the second phase in the red cells (erythrocytic phase). The **exoerythrocytic phase** begins with inoculation of sporozoites into the bloodstream by a female *Anopheles* mosquito. Within minutes, the sporozoites enter the hepatocytes of the liver, where they develop and multiply asexually as a schizont. After 1-2 wk, the hepatocytes rupture and release thousands of merozoites into the circulation. The tissue schizonts of *P. falciparum, P. malariae,* and apparently *P. knowlesi* rupture once and do not persist in the liver. There are 2 types of tissue schizonts for *P. ovale* and *P. vivax*. The primary type ruptures in 6-9 days, and the secondary type remains dormant in the liver cell for weeks, months, or as long as 5 yr before releasing merozoites and causing relapse of infection. The **erythrocytic phase** of *Plasmodium* asexual development begins when the merozoites from the liver penetrate erythrocytes. Once inside the erythrocyte, the parasite transforms into the **ring form,** which then enlarges to become a **trophozoite.** These latter 2 forms can be identified with Giemsa stain on blood smear, the primary means of confirming the diagnosis of malaria (Fig. 288-3). The trophozoite multiplies asexually to produce a number of small erythrocytic **merozoites** that are released into the bloodstream when the erythrocyte membrane ruptures, which is associated with fever. Over time, some of the merozoites develop into male and female gametocytes that complete the *Plasmodium* life cycle when they are ingested during a blood meal by the female anopheline mosquito. The male and female gametocytes fuse to form a **zygote** in the stomach cavity of the mosquito. After a series of further transformations, sporozoites enter the salivary gland of the mosquito and are inoculated into a new host with the next blood meal.

Four important pathologic processes have been identified in patients with malaria: fever, anemia, immunopathologic events, and tissue anoxia. Fever occurs when erythrocytes rupture and release merozoites into the circulation. Anemia is caused by hemolysis, sequestration of erythrocytes in the spleen and other organs, and bone marrow suppression. Immunopathologic events that have been documented in patients with malaria include excessive production of proinflammatory cytokines, such as tumor necrosis factor, that may be responsible for most of the pathology of the disease, including tissue anoxia; polyclonal activation resulting in both hypergammaglobulinemia and the formation of immune complexes; and immunosuppression. Cytoadherence of infected erythrocytes to vascular endothelium occurs in *P. falciparum* malaria and may lead to obstruction of blood flow and capillary damage, with resultant vascular leakage of blood, protein, and fluid and tissue anoxia. In addition, hypoglycemia and lactic acidemia are caused by anaerobic metabolism of glucose. The cumulative effects of these pathologic processes may lead to cerebral, cardiac, pulmonary, intestinal, renal, and hepatic failure.

Immunity after *Plasmodium* species infection is incomplete, preventing severe disease but still allowing future infection. In some cases, parasites circulate in small numbers for a long time but are prevented from rapidly multiplying and causing severe illness. Repeated episodes of infection occur because the parasite has developed a number of immune evasive strategies, such as intracellular replication, vascular cytoadherence that prevents infected erythrocytes from circulating through the spleen, rapid antigenic variation, and alteration of the host immune system resulting in partial immune suppression. The human host response to *Plasmodium* infection includes natural immune mechanisms that prevent infection by other *Plasmodium* species, such as those of birds or rodents, as well as several alterations in erythrocyte physiology that prevent or modify malarial infection. Erythrocytes containing hemoglobin S (sickle erythrocytes) resist malaria parasite growth, erythrocytes lacking Duffy blood group antigen are resistant to *P. vivax*, and erythrocytes containing hemoglobin F (fetal hemoglobin) and ovalocytes are resistant to *P. falciparum*. In hyperendemic areas, newborns rarely become ill with malaria, in part because of passive maternal antibody and high levels of fetal hemoglobin. Children 3 mo to 2-5 yr of age have little specific immunity to malaria species and therefore suffer yearly attacks of debilitating and potentially fatal disease. Immunity is subsequently acquired, and severe cases of malaria become less common. Severe disease may occur during pregnancy, particularly first pregnancies or after extended residence outside the endemic region. In general, extracellular *Plasmodium* organisms are targeted by antibody, whereas intracellular organisms are targeted by cellular defenses such as T lymphocytes, macrophages, polymorphonuclear leukocytes, and the spleen.

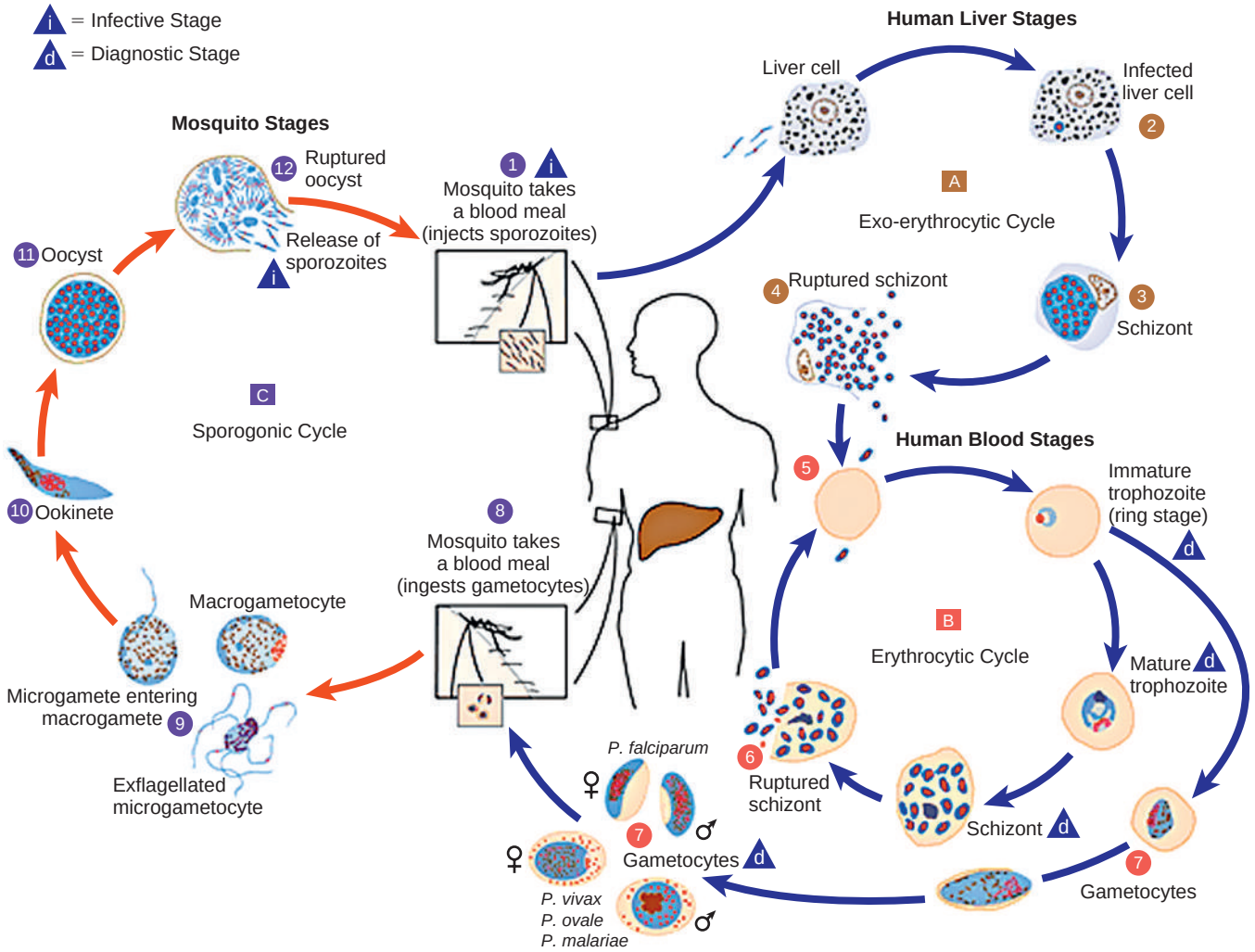

Figure 288-2 Life cycle of *Plasmodium* spp. *(From Centers for Disease Control and Prevention [CDC]: Laboratory diagnosis of malaria:* Plasmodium *spp. Available at: http://www.dpd.cdc.gov/dpdx/HL/ImageLibrary/M-R/Malaria/body_Malaria_il1.h)*

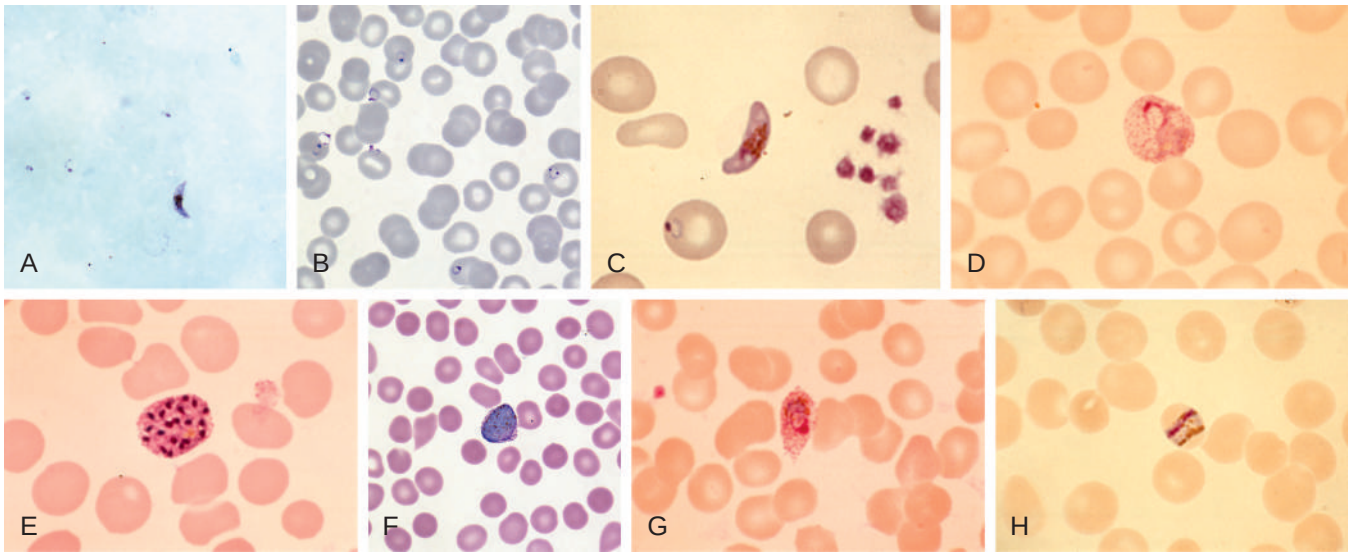

Figure 288-3 Giemsa-stained thick (A) and thin (B-H) smears used for the diagnosis of malaria and the speciation of *Plasmodium* parasites. **A,** Multiple signet-ring *Plasmodium falciparum* trophozoites, which are visualized outside erythrocytes. **B,** A multiply infected erythrocyte containing signet-ring *P. falciparum* trophozoites, including an accolade form positioned up against the inner surface of the erythrocyte membrane. **C,** Banana-shaped gametocyte unique to *P. falciparum*. **D,** Ameboid trophozoite characteristic of *Plasmodium vivax*. Both *P. vivax*– and *Plasmodium ovale*–infected erythrocytes exhibit Schüffner dots and tend to be enlarged compared with uninfected erythrocytes. **E,** *P. vivax* schizont. Mature *P. falciparum* parasites, by contrast, are rarely seen on blood smears because they sequester in the systemic microvasculature. **F,** *P. vivax* spherical gametocyte. **G,** *P. ovale* trophozoite. Note Schüffner dots and ovoid shapes of the infected erythrocyte. **H,** Characteristic band form trophozoite of *Plasmodium malariae*, containing intracellular pigment hemozoin. *(**A, B,** and **F** from Centers for Disease Control and Prevention [CDC]: DPDx: laboratory identification of parasites of public health concern. Available at: http://www.dpd.cdc.gov/dpdx/. **C, D, E, G,** and **H** courtesy of David Wyler, Newton Centre, MA.)*

CLINICAL MANIFESTATIONS

Children and adults are asymptomatic during the initial phase of infection, the incubation period of malaria infection. The usual incubation periods are 9-14 days for *P. falciparum*, 12-17 days for *P. vivax*, 16-18 days for *P. ovale,* and 18-40 days for *P. malariae*. The incubation period can be as long as 6-12 mo for *P. vivax* and can also be prolonged for patients with partial immunity or incomplete chemoprophylaxis. A prodrome lasting 2-3 days is noted in some patients before parasites are detected in the blood. Prodromal symptoms include headache, fatigue, anorexia, myalgia, slight fever, and pain in the chest, abdomen, and joints.

The classic presentation of malaria is seldom noted with other infectious diseases and consists of **paroxysms** of fever alternating with periods of fatigue but otherwise relative wellness. Febrile paroxysms are characterized by high fever, sweats, and headache, as well as myalgia, back pain, abdominal pain, nausea, vomiting, diarrhea, pallor, and jaundice. Paroxysms coincide with the rupture of schizonts that occurs every 48 hr with *P. vivax* and *P. ovale,* resulting in fever spikes every other day. Rupture of schizonts occurs every 72 hr with *P. malariae*, resulting in fever spikes every third or fourth day. Periodicity is less apparent with *P. falciparum* and mixed infections and may not be apparent early on in infection, when parasite broods have not yet synchronized. Patients with primary infection, such as travelers from nonendemic regions, also may have irregular symptomatic episodes for 2-3 days before regular paroxysms begin. Children with malaria often lack typical paroxysms and have nonspecific symptoms, including fever (may be low-grade but is often greater than 40°C [104°F]), headache, drowsiness, anorexia, nausea, vomiting, and diarrhea. Distinctive physical signs may include splenomegaly (common), hepatomegaly, and pallor as a consequence of anemia. Typical laboratory findings include anemia, thrombocytopenia, and a normal or low leukocyte count. The erythrocyte sedimentation rate is often elevated.

P. falciparum is the most severe form of malaria and is associated with higher density parasitemia and a number of complications (Fig. 288-4). The most common serious complication is severe anemia, which also is associated with other malaria species. Serious complications that appear unique to *P. falciparum* include cerebral malaria, acute renal failure, respiratory distress from metabolic acidosis, algid malaria and bleeding diatheses (see "Complications of *Plasmodium falciparum* Malaria" below and Table 288-1). The diagnosis of *P. falciparum* malaria in a nonimmune individual constitutes a medical emergency. Severe complications and death can occur if appropriate therapy is not instituted promptly. In contrast to malaria caused by *P. ovale, P. vivax,* and *P. malariae,* which usually results in parasitemias of less than 2%, malaria caused by *P. falciparum* can be associated with parasitemia levels as high as 60%. The differences in parasitemia reflect the fact that *P. falciparum* infects both immature and mature erythrocytes, whereas *P. ovale* and *P. vivax* primarily infect immature erythrocytes and *P. malariae* infects only mature erythrocytes. Like *P. falciparum, P. knowlesi* has a 24 hr replication cycle and can also lead to very-high-density parasitemia.

P. vivax malaria has long been considered less severe than *P. falciparum* malaria, but recent reports suggest that in some areas of Indonesia it is as frequent a cause of severe disease and death as P. *falciparum*. Severe disease and death from *P. vivax* are usually a consequence of severe anemia and sometimes of splenic rupture. *P. ovale* malaria is the least-common type of malaria. It is similar to *P. vivax* malaria and commonly is found in conjunction with *P. falciparum* malaria. *P. malariae* is the mildest and most chronic of all malaria infections. Nephrotic syndrome is a rare complication of *P. malariae* infection that is not observed with any other human malaria species. Nephrotic syndrome associated with *P. malariae* infection is poorly responsive to steroids. Low-level, undetected *P. malariae* infection may be present for years and is sometimes unmasked by immunosuppression or physiologic stress such as splenectomy or corticosteroid treatment.

Recrudescence after a primary attack may occur from the survival of erythrocyte forms in the bloodstream. Long-term relapse is caused by release of merozoites from an exoerythrocytic source in the liver, which occurs with *P. vivax* and *P. ovale*, or from persistence within the

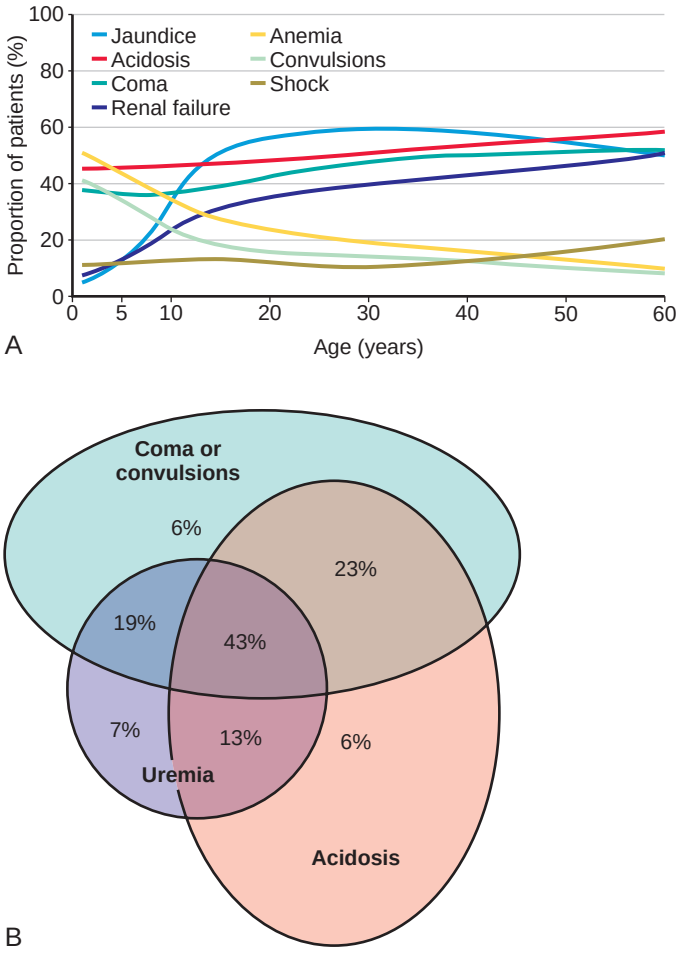

Figure 288-4 Manifestations of severe falciparum malaria by age **(A)** and mortality in children associated with central nervous system involvement, acidosis, and uremia **(B).** Data from 3,228 prospectively studied African children with severe falciparum malaria. Uremia here is defined as a blood urea nitrogen higher than 7.14 mmol/L. Surface areas denote the relative prevalence of the different severity signs, which frequently coexist. The percentages denote the observed mortality associated with the presenting signs. *(From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria.* Lancet *383:723–735, 2014; based on data from von Seidlein L, Olaosebikan R, Hendriksen ICE, et al: Predicting the clinical outcome of severe falciparum malaria in African children: findings from a large randomized trial.* Clin Infect Dis *54:1080–1090, 2012.)*

Table 288-1 World Health Organization Criteria for Severe Malaria, 2000

Impaired consciousness
Prostration
Respiratory distress
Multiple seizures
Jaundice
Hemoglobinuria
Abnormal bleeding
Severe anemia
Circulatory collapse
Pulmonary edema

erythrocyte, which occurs with *P. malariae* and rarely with *P. falciparum*. A history of typical symptoms in a person more than 4 wk after return from an endemic area is therefore more likely to be *P. vivax, P. ovale,* or *P. malariae* infection than *P. falciparum* infection. In the most recent survey of malaria in the United States among individuals in whom a malaria species was identified, 48.6% of cases were caused by *P. falciparum,* 22.1% by *P. vivax,* 3.5% by *P. malariae,* and 2.5% by *P. ovale.* Ninety-four percent of *P. falciparum* infections were diagnosed within 30 days of arrival in the United States, and 99% within 90 days of arrival. In contrast, 50.7% of *P. vivax* cases occurred more than 30 days after arrival in the United States.

Congenital malaria is acquired from the mother prenatally or perinatally and is a serious problem in tropical areas but is rarely reported in the United States. In endemic areas, congenital malaria is an important cause of abortions, miscarriages, stillbirths, premature births, intrauterine growth retardation, and neonatal deaths. Congenital malaria usually occurs in the offspring of a nonimmune mother with *P. vivax* or *P. malariae* infection, although it can be observed with any of the human malaria species. The first sign or symptom most commonly occurs between 10 and 30 days of age (range: 14 hr to several months of age). Signs and symptoms include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly. Malaria is often severe during pregnancy and may have an adverse effect on the fetus or neonate, resulting in intrauterine growth retardation and low birthweight, even in the absence of transmission from mother to child.

DIAGNOSIS

Any child who presents with fever or unexplained systemic illness and has traveled or resided in a malaria-endemic area within the previous year should be assumed to have life-threatening malaria until proven otherwise. Malaria should be considered regardless of the use of chemoprophylaxis. Important criteria that suggest *P. falciparum* malaria include symptoms occurring less than 1 mo after return from an endemic area, more than 2% parasitemia, ring forms with double chromatin dots, and erythrocytes infected with more than 1 parasite.

The diagnosis of malaria is established by identification of organisms on Giemsa-stained smears of peripheral blood (see Fig. 288-3) or by rapid immunochromatographic assay (rapid diagnostic test). Giemsa stain is superior to Wright stain or Leishman stain. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a **thick smear** is 20-40 times that on a thin smear and is used to quickly scan large numbers of erythrocytes. The **thin smear** allows for positive identification of the malaria species and determination of the percentage of infected erythrocytes and is useful in following the response to therapy. Identification of the species is best made by an experienced microscopist and checked against color plates of the various *Plasmodium* species (see Fig. 288-3). Morphologically it is impossible to distinguish *P. knowlesi* from *P. malariae*, so polymerase chain reaction detection by a reference lab or the CDC is required. Although *P. falciparum* is most likely to be identified from blood just after a febrile paroxysm, the timing of the both thick and thin smears is less important than their being obtained several times a day over a period of 3 successive days. A single negative blood smear does not exclude malaria. Most symptomatic patients with malaria will have detectable parasites on thick blood smears within 48 hr. For nonimmune persons, symptoms typically occur 1-2 days before parasites are detectable on blood smear.

The BinaxNOW Malaria test is approved by the FDA for rapid diagnosis of malaria. This immunochromatographic test for *P. falciparum* histidine-rich protein (HRP2) and aldolase is approved for testing for *P. falciparum* and *P. vivax.* Aldolase is present in all 5 of the malaria species that infect humans. Thus, a positive result for *P. vivax* could be because of *P. ovale* or *P. malariae* infection. Sensitivity and specificity for *P. falciparum* (94-99% and 94-99%, respectively) and *P. vivax* (87-93% and 99%, respectively) are good, but sensitivity for *P. ovale* and *P. malariae* is lower. Sensitivity for *P. falciparum* decreases at lower levels of parasitemia, so microscopy is still advised in areas where expert microscopy is available. The test is simple to perform and can be done in the field or laboratory in 10 min. Polymerase chain reaction is even more sensitive than microscopy but is technically more complex. It is available in some reference laboratories, but the time delay in availability of results generally precludes its use for acute diagnosis of malaria.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of malaria is broad and includes viral infections such as influenza and hepatitis, sepsis, pneumonia, meningitis, encephalitis, endocarditis, gastroenteritis, pyelonephritis, babesiosis, brucellosis, leptospirosis, tuberculosis, relapsing fever, typhoid fever, yellow fever, viral hemorrhagic fevers, amebic liver abscess, Hodgkin disease, and collagen vascular disease.

TREATMENT

Physicians caring for patients with malaria or traveling to endemic areas need to be aware of current information regarding malaria because resistance to antimalarial drugs has complicated therapy and prophylaxis. The best source for such information is the CDC Malaria webpage (http://www.cdc.gov/malaria/diagnosis_treatment/treatment.hl), which provides up-to-date guidelines for malaria treatment, and an algorithm for an approach to malaria treatment (Fig. 288-5). In cases in which treatment is unclear or complex, the CDC Malaria Hotline, which is available to physicians 24 hr a day (770-488-7788 from 8:00 AM to 4:30 PM Eastern Standard Time [EST] and 770-488-7100 from 4:30 PM to 8:00 AM EST, and on weekends and holidays; ask the operator to page the person on call for the Malaria Epidemiology Branch), is an excellent resource.

Fever without an obvious cause in any patient who has left a *P. falciparum* endemic area within 30 days and is nonimmune should be considered a medical emergency. Thick and thin blood smears should be obtained immediately, and all children with symptoms of severe disease should be hospitalized. If blood films are negative, they should be repeated every few hours. If the patient is severely ill, antimalarial therapy should be initiated immediately. Outpatient therapy generally is not given to nonimmune children but may be considered in immune or semi-immune children who have low-level parasitemia (<1%), no evidence of complications defined by the World Health Organization, no vomiting, and a lack of toxic appearance; who are able to contact the physician or emergency department at any time; and in whom follow-up within 24 hr is assured.

Plasmodium Falciparum Malaria

Malarious regions considered chloroquine-sensitive include Central America west of the Panama Canal, Haiti, the Dominican Republic, and most of the Middle East except Iran, Oman, Saudi Arabia, and Yemen. The CDC website (http://www.cdc.gov/MALARIA/) should be consulted for updated information on chloroquine susceptibility in an area, and current treatment options. Individuals traveling from areas with chloroquine-susceptible *P. falciparum* can be treated with chloroquine if they do not have severe malaria. Malaria acquired in *P. falciparum* areas with chloroquine resistance or where there is any doubt about chloroquine sensitivity after conferring with the CDC should be treated with drugs other than chloroquine (Table 288-2). Trials in Asia and Africa have definitively proven that artesunate treatment of severe malaria is associated with decreased mortality when compared to quinine treatment. However, artesunate is still not FDA approved in the United States for treatment of malaria, or available outside of special request indications from the CDC, so intravenous quinidine gluconate remains first-line therapy for severe malaria in the United States (Table 288-2). Monotherapy with artesunate agents is discouraged because of the development of resistance and treatment failures. Nonetheless in endemic countries, artesunate derivatives in combination with other antimalarial agents have become the treatment of choice (Tables 288-3 and 288-4). Children with severe malaria should be admitted to the intensive care unit for monitoring of complications, plasma quinidine levels, and adverse effects during quinidine administration. During administration of quinidine, blood pressure monitoring for hypotension and cardiac monitoring for widening of the QRS

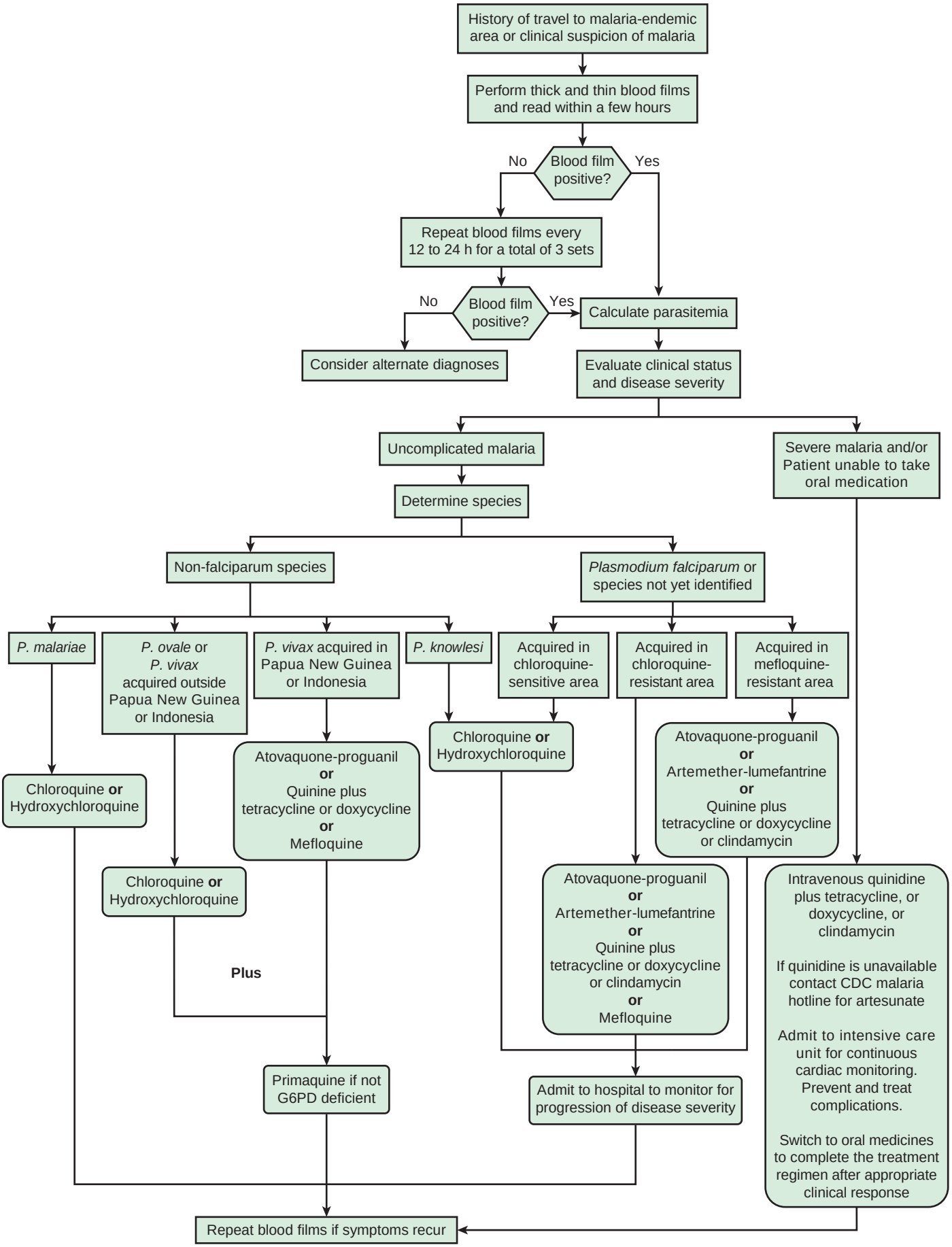

Figure 288-5 Algorithm for approach to patient with malaria in the United States. *(From Centers for Disease Control and Prevention [CDC]. Available at: http://www.cdc.gov/malaria/resources/pdf/algorithm.pdf)*

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)

(CDC Malaria Hotline: [770] 488-7788 or [855] 856-4713 toll-free Monday-Friday 9 AM to 5 PM EST; [770] 488-7100 after hours, weekends, and holidays)

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Uncomplicated malaria/ *P. falciparum* *or* Species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P. ovale:* see *P. vivax* and *P. ovale* (below) regarding treatment with primaquine	Chloroquine-resistant or unknown resistance[2] (All malarious regions except those specified as chloroquine-sensitive listed in the box below)	A. Atovaquone-proguanil (Malarone)[3] Adult tab = 250 mg atovaquone/100 mg proguanil 4 adult tabs PO qd × 3 days	A. Atovaquone-proguanil (Malarone)[3] Adult tab = 250 mg atovaquone/100 mg proguanil Pediatric (ped) tab = 62.5 mg atovaquone/25 mg proguanil 5-8 kg: 2 ped tabs PO qd × 3 days 9-10 kg: 3 ped tabs PO qd × 3 days 11-20 kg: 1adult tab PO qd × 3 days 21-30 kg: 2 adult tabs PO qd × 3 days 31-40 kg: 3 adult tabs PO qd × 3 days > 40 kg: 4 adult tabs PO qd × 3 days
		B. Artemether-lumefantrine (Coartem)[3] 1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hr later, then 1 dose PO bid for the following 2 days 5-<15 kg: 1 tablet per dose 15-<25 kg: 2 tablets per dose 25-<35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		C. Quinine sulfate plus 1 of the following: doxycycline, tetracycline, or clindamycin Quinine sulfate: 542 mg base (=650 mg salt)[4] PO tid × 3 or 7 days[5] Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg base/kg/day PO divided tid × 7 days	C. Quinine sulfate[4] plus 1 of the following: doxycycline[6], tetracycline,[6] or clindamycin Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) PO tid × 3 or 7 days[5] Doxycycline: 2.2 mg/kg PO every 12 hr × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg base/kg/day PO divided tid × 7 days
		D. Mefloquine (Lariam and generics)[7] 684 mg base (=750 mg salt) PO as initial dose, followed by 456 mg base (=500 mg salt) PO given 6-12 hr after initial dose Total dose = 1,250 mg salt	D. Mefloquine (Lariam and generics)[7] 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) PO given 6-12 hr after initial dose. Total dose = 25 mg salt/kg
Uncomplicated malaria/ *P. falciparum* *or* Species not identified	Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	Chloroquine phosphate (Aralen and generics)[8] 600 mg base (=1,000 mg salt) PO immediately, followed by 300 mg base (=500 mg salt) PO at 6, 24, and 48 hr Total dose: 1,500 mg base (=2,500 mg salt) *or* Hydroxychloroquine (Plaquenil and generics) 620 mg base (=800 mg salt) PO immediately, followed by 310 mg base (=400 mg salt) PO at 6, 24, and 48 hr Total dose: 1,550 mg base (=2,000 mg salt)	Chloroquine phosphate (Aralen and generics)[8] 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg *or* Hydroxychloroquine (Plaquenil and generics) 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg

[1]If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use 1 of the other options instead.

[2]NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

[3]Take with food or whole milk. If patient vomits within 30 min of taking a dose, then patient should repeat the dose.

[4]U.S. manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult because of unavailability of noncapsule forms of quinine.

[5]For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

[6]Doxycycline and tetracycline are not indicated for use in children younger than 8 yr old. For children younger than 8 yr old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children younger than 8 yr old with chloroquine-resistant *P. vivax,* mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

[7]Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia as a consequence of drug resistance.

[8]When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

Continued

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Uncomplicated malaria/*P. malariae* or *P. knowlesi*	All regions	**Chloroquine phosphate:**[8] treatment as above *or* **Hydroxychloroquine:** treatment as above	**Chloroquine phosphate:**[8] treatment as above *or* **Hydroxychloroquine:** treatment as above
Uncomplicated malaria/*P. vivax* or *P. ovale*	All regions Note: for suspected chloroquine-resistant *P. vivax*, see row below	**Chloroquine phosphate**[8] **plus primaquine phosphate**[9] **Chloroquine phosphate:** treatment as above **Primaquine phosphate:** 30 mg base PO qd × 14 days *or* **Hydroxychloroquine plus primaquine phosphate**[9] **Hydroxychloroquine:** treatment as above **Primaquine phosphate:** 30 mg base PO qd × 14 days	**Chloroquine phosphate**[8] **plus primaquine phosphate**[9] **Chloroquine phosphate:** treatment as above **Primaquine:** 0.5 mg base/kg PO qd × 14 days *or* **Hydroxychloroquine plus primaquine phosphate**[9] **Hydroxychloroquine:** treatment as above **Primaquine phosphate:** 0.5 mg base/kg PO qd × 14 days
Uncomplicated malaria/*P. vivax*	**Chloroquine-resistant**[10] (Papua New Guinea and Indonesia)	A. **Quinine sulfate plus either doxycycline or tetracycline plus primaquine phosphate**[9] **Quinine sulfate:** treatment as above **Doxycycline or tetracycline:** Treatment as above **Primaquine phosphate:** treatment as above B. **Atovaquone-proguanil plus primaquine phosphate**[9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above C. **Mefloquine plus primaquine phosphate**[9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above	A. **Quinine sulfate plus either doxycycline**[6] **or tetracycline**[6] **plus primaquine phosphate**[9] **Quinine sulfate:** treatment as above **Doxycycline or tetracycline:** treatment as above **Primaquine phosphate:** treatment as above B. **Atovaquone-proguanil plus primaquine phosphate**[9] **Atovaquone-proguanil:** treatment as above **Primaquine phosphate:** treatment as above C. **Mefloquine plus primaquine phosphate**[9] **Mefloquine:** treatment as above **Primaquine phosphate:** treatment as above
Uncomplicated malaria: alternatives for pregnant women[11-13]	**Chloroquine-sensitive** (See uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate:** treatment as above *or* **Hydroxychloroquine:** treatment as above	Not applicable
	Chloroquine-resistant (See sections above for regions with chloroquine-resistant *P. falciparum* and *P. vivax*)	**Quinine sulfate plus clindamycin** **Quinine sulfate:** treatment as above **Clindamycin:** treatment as above *or* **Mefloquine:** treatment as above	Not applicable

[9]Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally 1 time per week for 8 wk; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

[10]NOTE: There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates as a result of chloroquine-resistant *P. vivax* are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* are also documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

[11]For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

[12]Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the 1st trimester because of a lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

[13]For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States–Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ *PLASMODIUM* SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE[1]	RECOMMENDED DRUG AND PEDIATRIC DOSE[1] PEDIATRIC DOSE SHOULD *NEVER* EXCEED ADULT DOSE
Severe malaria[14-16]	All regions	Quinidine gluconate[14] plus 1 of the following: doxycycline, tetracycline, or clindamycin **Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hr, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hr. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hr, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hr every 8 hr, starting 8 hr after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; =3 days in Africa or South America **Doxycycline:** treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hr and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days *Investigational new drug (contact CDC for information):* Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), doxycycline (clindamycin in pregnant women), or mefloquine	Quinidine gluconate[14] plus one of the following: doxycycline[4], tetracycline[4], or clindamycin **Quinidine gluconate:** same mg/kg dosing and recommendations as for adults **Doxycycline:** treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hr and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children >45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days **Tetracycline:** treatment as above **Clindamycin:** treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. *Investigational new drug (contact CDC for information):* Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), clindamycin, or mefloquine

[14]Persons with a positive blood smear *or* history of recent possible exposure and no other recognized pathology who have 1 or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum.*

[15]Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hr or if they have received mefloquine within the preceding 12 hr. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

[16]Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

From the Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf

complex or lengthening of the QTc interval should be performed continuously, and blood glucose monitoring for hypoglycemia should be performed periodically. Cardiac adverse events may require temporary discontinuation of the drug or slowing of the intravenous infusion. Parenteral therapy should be continued until the parasitemia is less than 1%, which usually occurs within 48 hr, and the patient can tolerate oral medication. Quinidine gluconate (United States) or quinine sulfate (other countries) is administered for a total of 3 days for malaria acquired in Africa or South America and for 7 days for malaria acquired in Southeast Asia. Doxycycline, tetracycline, or clindamycin is then given orally to complete the therapeutic course (see Tables 288-2 and 288-4). Although there are no data to support the use of sequential quinine and atovaquone-proguanil, the difficulty of maintaining compliance with oral quinine has led many clinicians to complete oral therapy after IV quinine with a complete course of atovaquone-proguanil.

Parenterally administered artesunate or artemether can be substituted for quinine for treatment of severe malaria in children and adults (see Table 288-2). Artesunate is now available on special request from the CDC (770-488-7788) for treatment of severe malaria, but empirical therapy should not be delayed while awaiting delivery of artesunate. Children who do receive artesunate can follow up with

Table 288-3 Treatment of Uncomplicated Malaria

	REGIMENS
All *Plasmodium falciparum* malaria	Artemether-lumefantrine 1.5 mg/kg-9 mg/kg twice daily for 3 days with food or milk Artesunate 4 mg/kg daily for 3 days and mefloquine 25 mg base per kg (8 mg/kg/daily for 3 days*)† Dihydroartemisinin-piperaquine 2.5 mg/kg-20 mg/kg daily for 3 days
Sensitive *P. falciparum* malaria	Artesunate 4 mg/kg daily for 3 days and a single dose of sulfadoxine-pyrimethamine 25 mg/kg-1.25 mg/kg Artesunate 4 mg/kg and amodiaquine* 10 mg base per kg daily for 3 days
Chloroquine-sensitive *Plasmodium vivax*‡, *Plasmodium malariae*‡, *Plasmodium ovale*‡, *Plasmodium knowlesi*‡	Chloroquine 10 mg base per kg immediately, followed by 10 mg/kg at 24 hr and 5 mg/kg at 48 hr

*World Health Organization prequalified fixed dose formulations are preferable to loose tablets. A taste masked dispersible pediatric tablet formulation of artemether-lumefantrine is available.

†High failure rates with artesunate-mefloquine have been reported on the Thailand–Myanmar border.

‡Any of the artemisinin combination treatments can be given except for artesunate-sulfadoxine-pyrimethamine where *P. vivax* is resistant. Patients with *P. vivax* or *P. ovale* infections should also be given a 14 day course of primaquine to eradicate hypnozoites (radical cure). However, severe glucose-6-phosphate dehydrogenase deficiency is a contraindication because a 14 day course of primaquine can cause severe hemolytic anemia in this group.

From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria. Lancet *383:723–732, 2014.*

Table 288-4 Treatment of Severe Malaria in Adults and Children

- Artesunate 2·4 mg/kg by intravenous or intramuscular* injection, followed by 2.4 mg/kg at 12 hr and 24 hr; continue injection once daily if necessary†
- Artemether 3.2 mg/kg by immediate intramuscular* injection, followed by 1.6 mg/kg daily
- Quinine dihydrochloride 20 mg salt per kg infused during 4 hr, followed by maintenance of 10 mg salt per kg infused during 2-8 hr every 8 hr (can also be given by intramuscular injection* when diluted to 60-100 mg/mL)

Artesunate is the treatment of choice. Artemether should only be used if artesunate is unavailable. Quinine dihydrochloride should be given only when artesunate and artemether are unavailable.

*Intramuscular injections should be given to the anterior thigh.

†Young children with severe malaria have lower exposure to artesunate and its main biologically active metabolite dihydroartemisinin than do older children and adults. Revised dose regimens to ensure similar drug exposures have been suggested.

From White NJ, Pukrittayakamee S, Hien TT, et al: Malaria. Lancet *383:723–732, 2014.*

artemether-lumefantrine oral therapy. Oral and rectal administration of these artemisinin-based antimalarial drugs is effective in treatment of malaria, but such formulations are not indicated or approved in the United States.

Patients from areas with chloroquine-resistant *P. falciparum* who have mild infection, parasitemia less than 1%, no evidence of complications, and no vomiting and who can take oral medication can be considered for oral therapy with either oral atovaquone-proguanil (Malarone), oral artemether-lumefantrine (Coartem), or oral quinine plus doxycycline, tetracycline, or clindamycin (see Table 288-2). However, as noted in Figure 288-5, all children with clinical malaria, even those started on oral therapy, should be admitted to evaluate for progression of disease. Coartem is approved by the FDA for the treatment of uncomplicated malaria and is an appealing choice because it is highly effective and well-tolerated. Pediatric dosing is well established, but pediatric dispersible tablets, available in some other countries, are not yet available in the United States. Coartem should not be used in children with known QT interval prolongation. Patients who acquire *P. falciparum* in Thailand, Myanmar, or Cambodia should receive 7 days of quinine therapy if they are prescribed quinine. Mefloquine is contraindicated for use in patients with a known hypersensitivity to mefloquine or with a history of epilepsy or severe psychiatric disorders. Mefloquine is not recommended for persons with cardiac conduction abnormalities but may be administered to persons concurrently receiving β-blockers if they have no underlying arrhythmia. Quinidine or quinine may exacerbate the adverse effects of mefloquine and should generally not be given to patients who have received mefloquine unless there are no other alternatives.

Patients with uncomplicated *P. falciparum* malaria acquired in areas without chloroquine resistance should be treated with oral chloroquine phosphate. If the parasite count does not drop rapidly (within 24-48 hr) and become negative after 4 days, chloroquine resistance should be assumed and the patient started on a different antimalarial regimen.

Supportive therapy is very important and may include red blood cell transfusion(s) to maintain the hematocrit at more than 20%, exchange transfusion in *P. falciparum* malaria with parasitemia greater than 10% and evidence of severe complications (e.g., severe malarial anemia, cerebral malaria), supplemental oxygen and ventilatory support for pulmonary edema or cerebral malaria, careful intravenous rehydration for severe malaria, intravenous glucose for hypoglycemia, anticonvulsants for cerebral malaria with seizures, and dialysis for renal failure. Exchange transfusion is thought to be useful in severe malaria with high-level parasitemia, but no randomized clinical trial has ever been conducted to assess its utility, and some groups, including the Centers for Disease Control and Prevention, no longer advocate its use for severe malaria. Corticosteroids are not recommended for cerebral malaria.

Plasmodium Vivax, P. Ovale, P. Malariae, or *P. Knowlesi* Malaria

Uncomplicated infection caused by *P. vivax*, *P. ovale*, or *P. malariae* can usually be treated with chloroquine (see Table 288-2). Chloroquine remains the initial drug of choice for *P. vivax* malaria in the absence of good data on drug alternatives. Indications for using alternative therapy are worsening or new symptoms, persistent *P. vivax* parasitemia after 72 hr, and possibly acquisition of infection in Oceania or India. Patients with *P. vivax* or *P. ovale* malaria should also be given primaquine once daily for 14 days to prevent relapse from the hypnozoite forms that remain dormant in the liver. Some strains may require 2 courses of primaquine. Testing for glucose-6-phosphate dehydrogenase deficiency must be performed before initiation of primaquine, because it can cause hemolytic anemia in such patients. Unfortunately, no alternatives to primaquine currently exist for eradication of the hypnozoite forms of *P. vivax* or *P. ovale*. Patients with any type of malaria must be monitored for possible recrudescence with repeat blood smears at the end of therapy because recrudescence may occur more than 90 days after therapy with low-grade resistant organisms. If vomiting precludes oral administration, chloroquine can be given by nasogastric tube. Based on limited evidence, chloroquine plus sulfadoxine-pyrimethamine should be used to treat *P. knowlesi* infections. For cases of severe malaria caused by any *Plasmodium* species, intravenous quinidine or quinine along with a second drug (clindamycin, doxycycline, or tetracycline) should be used, as for *P. falciparum*. Patients with any type of malaria must be monitored for possible recrudescence with repeat blood smears at the end of therapy, because recrudescence may occur more than 90 days after therapy with low-grade resistant organisms. For children living in endemic areas, mothers should be encouraged to seek evaluation for malaria any time the child has a fever, as many clinics in endemic areas now have accurate rapid diagnostic tests available. If such children are severely ill, they should be given the same therapy as nonimmune children.

COMPLICATIONS OF *PLASMODIUM FALCIPARUM* MALARIA

The World Health Organization has identified 10 complications of *P. falciparum* malaria that define severe malaria (see Table 288-1 and Fig. 288-4). The most common complications in children are severe anemia, impaired consciousness (including cerebral malaria), respiratory distress (a result of metabolic acidosis), multiple seizures, prostration, and jaundice.

Severe malarial anemia (hemoglobin level <5 g/dL) is the most common severe complication of malaria in children and is the leading cause of anemia leading to hospital admission in African children. Anemia is associated with hemolysis, but removal of infected erythrocytes by the spleen and impairment of erythropoiesis likely play a greater role than hemolysis in the pathogenesis of severe malarial anemia. The primary treatment for severe malarial anemia is blood transfusion. With appropriate and timely treatment, severe malarial anemia usually has a relatively low mortality (~1%).

Cerebral malaria is defined as the presence of coma in a child with *P. falciparum* parasitemia and an absence of other reasons for coma. Children with altered mental status who are not in coma fall into the larger category of impaired consciousness. Cerebral malaria is most common in children in areas of midlevel transmission and in adolescents or adults in areas of very low transmission. It is less frequently seen in areas of very high transmission. Cerebral malaria often develops after the patient has been ill for several days but may develop precipitously. Cerebral malaria has a fatality rate of 15-20% and is associated with long-term cognitive impairment in children. Repeated seizures are frequent in children with cerebral malaria. Hypoglycemia is common, but children with true cerebral malaria fail to arouse from coma even after receiving a dextrose infusion that normalizes their glucose level. Physical findings may include high fever, seizures, muscular twitching, rhythmic movement of the head or extremities, contracted or unequal pupils, retinal hemorrhages, hemiplegia, absent or exaggerated deep tendon reflexes, and a positive Babinski sign. Lumbar puncture reveals increased pressure and cerebrospinal fluid protein with no pleocytosis and normal glucose and protein concentrations. Studies suggest that funduscopic findings of malaria retinopathy (retinal hemorrhages, peripheral whitening, macular whitening, vessel changes) are specific for cerebral malaria and may identify children in whom malaria is the reason for coma, as opposed to children with coma and incidental *P. falciparum* parasitemia. Treatment of cerebral malaria other than antimalarial medications is largely supportive and includes evaluation of and treatment of seizures and hypoglycemia. Although increased intracranial pressure has been documented in some children with cerebral malaria, treatment with mannitol and corticosteroids has not improved outcomes in these children.

Respiratory distress is a poor prognostic indicator in severe malaria and appears to be caused by metabolic acidosis rather than intrinsic pulmonary disease. To date, no successful interventions for treatment of metabolic acidosis in children with severe malaria have been described, but trials of dichloroacetate treatment and fluid expansion are ongoing.

Seizures are a common complication of severe malaria, particularly cerebral malaria. Benzodiazepines are first-line therapy for seizures, and intrarectal diazepam has been used successfully in children with malaria and seizures. Many seizures resolve with a single dose of diazepam. For persistent seizures, phenobarbital or phenytoin are the standard medications used. Phenytoin may be preferred for seizure treatment, particularly in hospitals or clinics where ventilatory support is not available. However, no comparative trials of the 2 drugs have been performed, and phenytoin is considerably more expensive than phenobarbital. There are currently no drugs recommended for seizure prophylaxis in children with severe malaria. Phenobarbital prophylaxis decreased seizure activity but increased mortality in 1 major study of children with severe malaria, probably because of the respiratory depression associated with phenobarbital that may have been exacerbated by benzodiazepine therapy.

Hypoglycemia is a complication of malaria that is more common in children, pregnant women, and patients receiving quinine therapy. Patients may have a decreased level of consciousness that can be confused with cerebral malaria. Any child with impaired consciousness and malaria should have a glucose level checked, and if glucometers are not available, an empirical bolus of dextrose should be given. Hypoglycemia is associated with increased mortality and neurologic sequelae.

Circulatory collapse (algid malaria) is a rare complication that manifests as hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. Death may occur within hours. Severe malaria is occasionally accompanied by bacteremia, which may have been the cause of some of the cases previously referred to as algid malaria. Any child with severe malaria and hypotension or hypoperfusion should have a blood culture obtained and be treated empirically for bacterial sepsis.

Long-term cognitive impairment occurs in 25% of children with cerebral malaria and also occurs in children with repeated episodes of uncomplicated disease. Prevention of attacks in these children improves educational attainment.

Tropical splenomegaly syndrome is a chronic complication of *P. falciparum* malaria in which massive splenomegaly persists after treatment of acute infection. The syndrome is characterized by marked splenomegaly, hepatomegaly, anemia, and an elevated immunoglobulin M level. Tropical splenomegaly syndrome is thought to be caused by an impaired immune response to *P. falciparum* antigens. Prolonged antimalarial prophylaxis (for at least several years) is required to treat this syndrome if the child remains in a malaria endemic area. Spleen size gradually regresses on antimalarial prophylaxis but often increases again if prophylaxis is stopped.

Other complications in children include jaundice, which is associated with a worse outcome, and prostration. Prostration is defined as the inability to sit, stand, or eat without support, in the absence of impaired consciousness. Prostration also has been associated with increased mortality in some studies, but the pathophysiology of this process is not well understood. Uncommon complications include hemoglobinuria, abnormal bleeding, pulmonary edema, and renal failure. These are uncommon complications in children with severe malaria and are more common in adults, particularly pulmonary edema and renal failure. Although frank renal failure is uncommon in children, uremia (when defined as an elevation in blood urea nitrogen levels) is not, particularly in older children. It remains unclear whether BUN elevation reflects a degree of renal failure or primarily dehydration.

PREVENTION

Malaria prevention consists of reducing exposure to infected mosquitoes and chemoprophylaxis. The most accurate and current information on areas in the world where malaria risk and drug resistance exist can be obtained by contacting local and state health departments or the CDC or consulting *Health Information for International Travel*, which is published by the U.S. Public Health Service.

Travelers to endemic areas should remain in well-screened areas from dusk to dawn, when the risk for transmission is highest. They should sleep under permethrin-treated mosquito netting and spray insecticides indoors at sundown. During the day the travelers should wear clothing that covers the arms and legs, with trousers tucked into shoes or boots. Mosquito repellent should be applied to thin clothing and exposed areas of the skin, with applications repeated every 1-2 hr. A child should not be taken outside from dusk to dawn, but if at risk for exposure, a solution with 25-35% *N,N*-diethyl-3-methylbenzamide (DEET) (not greater than 40%) should be applied to exposed areas except for the eyes, mouth, or hands. Hands are excluded because they are often placed in the mouth. DEET should then be washed off as soon as the child comes back inside. The American Academy of Pediatrics recommends that DEET solutions be avoided in children less than 2 mo of age. Adverse reactions to DEET include rashes, toxic encephalopathy, and seizures, but these reactions occur almost exclusively with inappropriate application of high concentrations of DEET. Picaridin is an alternative and sometimes better tolerated repellent. Even with these precautions, a child should be taken to a physician immediately if the child develops illness when traveling to a malarious area.

Table 288-5 Chemoprophylaxis of Malaria for Children

AREA	DRUG	DOSAGE (ORAL)	ADVANTAGES	DISADVANTAGES	BEST USE
Chloroquine-resistant area	Mefloquine*†	<10 kg: 4.6 mg base (5 mg salt)/kg/wk 10-19 kg: ¼ tab/wk 20-30 kg: ½ tab/wk 31-45 kg: ¾ tab/wk >45 kg: 1 tab/wk (228 mg base)	Once weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria endemic area for 4 wk or more Children unlikely to take daily medication
	Doxycycline‡	2 mg/kg daily (max 100 mg)	Inexpensive	Cannot give to children <8 yr Daily dosing Must take with food or causes stomach upset Photosensitivity	Children going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone/proguanil§ (Malarone)	Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil Adult tabs: 250 mg proguanil/100 mg proguanil 5-8 kg: pediatric tab once daily (off-label) 9-10 kg: pediatric tab once daily (off-label) 11-20 kg: 1 pediatric tab once daily 21-30 kg: 2 pediatric tabs once daily 31-40 kg: 3 pediatric tabs once daily >40 kg: 1 adult tab once daily	Pediatric formulation Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria endemic area for <4 wk
Chloroquine-susceptible area	Chloroquine phosphate	5 mg base/kg/wk (max: 300 mg base)	Once weekly dosing Inexpensive Generally well tolerated	Bitter taste No pediatric formulation	Best medication for children traveling to areas with *Plasmodium falciparum* or *Plasmodium vivax* that is chloroquine susceptible
	Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas				

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.

†Mefloquine resistance exists in western Cambodia and along the Thailand–Cambodia and Thailand–Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.

‡Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children younger than 8 yr of age or in pregnant women.

§Atovaquone/proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children weighing <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

Chemoprophylaxis is necessary for all visitors to and residents of the tropics who have not lived there since infancy, including children of all ages (Table 288-5). Healthcare providers should consult the latest information on resistance patterns before prescribing prophylaxis for their patients. Chloroquine is given in the few remaining areas of the world free of chloroquine-resistant malaria strains. In areas where chloroquine-resistant *P. falciparum* exists, atovaquone-proguanil, mefloquine, or doxycycline may be given as chemoprophylaxis. Atovaquone-proguanil is generally recommended for shorter trips (up to 2 wk) because it must be taken daily. Pediatric tablets are available and are generally well tolerated, although the taste is sometimes unpleasant to very young children. For longer trips, mefloquine is preferred, as it is given only once a week. Mefloquine does not have a pediatric formulation and has an unpleasant taste that usually requires that the cut tablet be "disguised" in another food, such as chocolate syrup. Mefloquine should not be given to children if they have a known hypersensitivity to mefloquine, are receiving cardiotropic drugs, have a history of convulsive or certain psychiatric disorders, or travel to an area where mefloquine resistance exists (the borders of Thailand with Myanmar and Cambodia, the western provinces of Cambodia, and the eastern states of Myanmar). Atovaquone-proguanil is started 1-2 days before travel, and mefloquine is started 2 wk before travel. It is important that these doses are given, both to allow therapeutic levels of the drugs to be achieved and to be sure that the drugs are tolerated. Doxycycline is an alternative for children older than 8 yr of age. It must be given daily and should be given with food. Side effects of doxycycline include photosensitivity and vaginal yeast infections. Primaquine is a daily prophylaxis option for children who cannot tolerate any of the other options, but it should be provided in consultation with a travel medicine specialist if needed, and all children should be checked for glucose-6-phosphate dehydrogenase deficiency prior to prescribing this medication, which is contraindicated in children with glucose-6-phosphate dehydrogenase deficiency. Provision of medication can be considered in individuals who refuse to take prophylaxis or will be in very remote areas without accessible medical care. Provision of medication for self-treatment of malaria should be done in

consultation with a travel medicine specialist, and the medication provided should be different than that used for prophylaxis.

A number of other efforts are currently underway to prevent malaria in malaria endemic countries. Some have been highly successful, leading to a significant decrease in malaria incidence in many countries in Africa, Asia, and South America in the last decade. These interventions include the use of insecticide-treated bed nets (which have decreased all-cause mortality in children under 5 yr of age in several highly malaria endemic areas by ~20%), indoor residual spraying with long-lasting insecticides, and the use of artemisinin-combination therapy for first-line malaria treatment. The first malaria vaccine to have any degree of efficacy is the RTS,S vaccine, which is based on the circumsporozoite protein of *P. falciparum*. In various clinical trials, this vaccine has shown an efficacy of 17-56% against uncomplicated malaria and 38-50% against severe malaria in young children in malaria endemic areas for periods as long as 48 mo after vaccination. The vaccine is in large phase III trials. Given the relatively low efficacy of this vaccine, it is unclear if it will be implemented as part of a combination strategy that includes the already successful interventions mentioned. Numerous other vaccines are also in current clinical trials, and it is hoped that future vaccines will improve upon the efficacy of the RTS,S vaccine. There is currently no vaccine with sufficient efficacy to be considered for prevention of malaria in travelers.

Intermittent prevention treatment during infancy has been particularly successful in reducing the incidence of malaria in sub Saharan Africa. Sulfadoxine-pyrimethamine given to infants at the second and third doses of the diphtheria, tetanus toxoid, and pertussis and measles vaccinations is safe and relatively effective. Intermittent prevention treatment has also been given to pregnant women; 3 doses of sulfadoxine-pyrimethamine have resulted in a reduction of low birthweight infants.

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Chapter 289

Babesiosis *(Babesia)*

Peter J. Krause

Babesiosis is an emerging disease caused by intraerythrocytic protozoa that are transmitted by hard body (ixodid) ticks. The clinical manifestations of babesiosis range from subclinical illness to fulminant disease resulting in death.

ETIOLOGY

There are more than 100 species of *Babesia* that infect a wide variety of wild and domestic animals throughout the world. Only a few of these species have been reported to infect humans, including *Babesia microti* (and *B. microti*-like species), *Babesia divergens* (and *B. divergens*-like species), *Babesia duncani*, *Babesia venatorum*, and KO1.

EPIDEMIOLOGY

Babesia are transmitted to humans from vertebrate reservoir hosts by the *Ixodes* species of ticks. *B. microti* is the most common cause of babesiosis in humans. The primary reservoir for *B. microti* is the white-footed mouse, *Peromyscus leucopus*, and the primary vector is *Ixodes scapularis*, the black legged tick. *I. scapularis* ticks also transmit the causative agents of Lyme disease, human granulocytic anaplasmosis, *Borrelia miyamotoi*, and Powassan virus and may simultaneously transmit 2 or more microorganisms. White-tailed deer (*Odocoileus virginianus*) serve as the host on which adult ticks most abundantly feed but are incompetent reservoirs. Babesiosis may be transmitted through blood transfusion, and *B. microti* is the most frequently reported transfusion-transmitted microbial agent in the United States. Rarely, babesiosis is acquired by transplacental transmission.

Human *B. microti* infection is endemic (most cases occurring in June, July, and August) in the northeastern and upper midwestern United States and has been sporadically reported in China, Taiwan, and Europe (Fig. 289-1). Human babesial infections caused by the cattle parasite, *B. divergens*, have been described in many countries in Europe, while *B. divergens*-like infections have been described in Kentucky, Missouri, and Washington State. *B. duncani* infects humans along the northern Pacific coast. *B. venatorum* infects people in Austria, Germany, China, and Italy. Human babesiosis cases also have been documented in Africa, Australia, and South America.

In certain sites and in certain years of high transmission, babesiosis constitutes a significant public health burden. On Nantucket Island, case rates as high as 280 per 100,000 population have been recorded, placing the community burden of disease in a category with gonorrhea as "moderately common." Comparable incidence rates have been described elsewhere on the southern New England coast.

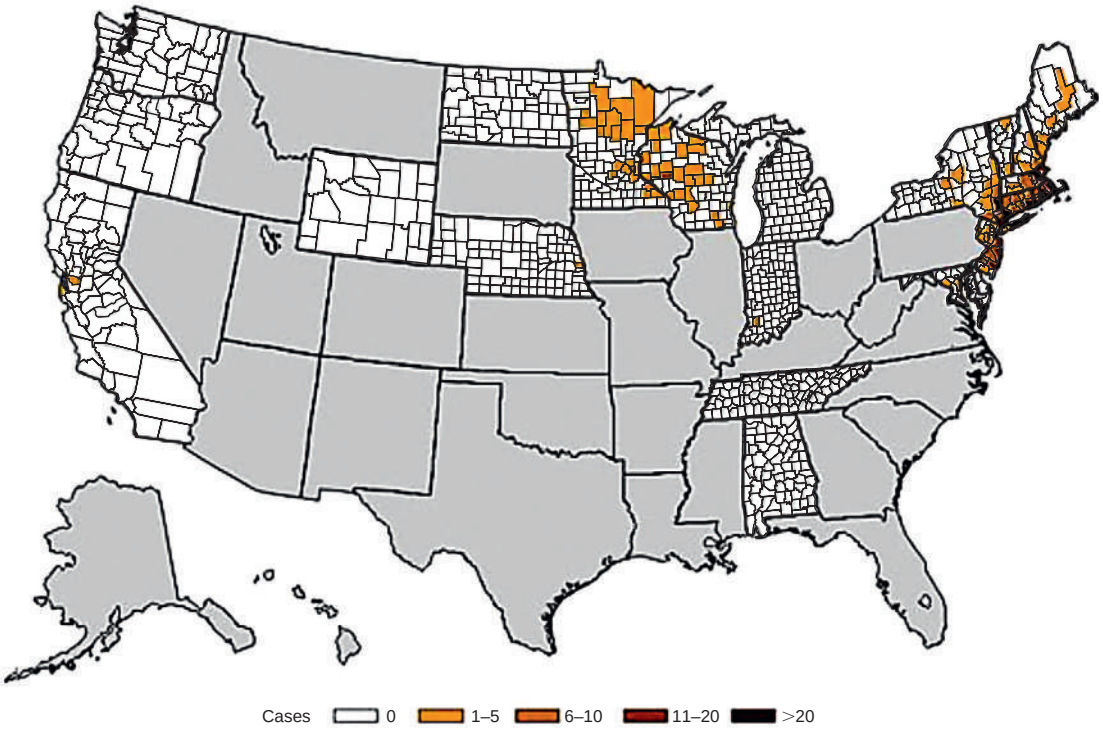
PATHOGENESIS

The pathogenesis of human babesiosis is not well understood. Cytoadherence and lysis of infected erythrocytes and excessive production of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 may account for most of the clinical manifestations and complications of the disease. The spleen has an important role in clearing parasitemia as do T and B cells, macrophages, polymorphonuclear leukocytes, cytokines, antibody, and complement.

CLINICAL MANIFESTATIONS

The clinical severity of babesiosis ranges from subclinical infection to fulminating disease and death. In clinically apparent cases, symptoms of babesiosis begin after an incubation period of 1-4 wk from the beginning of tick feeding or 1 wk to 6 mo after transfusion. Typical symptoms in moderate to severe infection include intermittent fever to as high as 40.9°C (105.6°F) accompanied by any combination of fatigue, chills, sweats, myalgias, headache, and anorexia. Less commonly noted are emotional lability, hyperesthesia, headache, sore throat, abdominal pain, conjunctival injection, photophobia, weight loss, and nonproductive cough. The findings on physical examination generally are minimal, often consisting only of fever. Splenomegaly, hepatomegaly, or both are noted occasionally, but rash seldom is reported. Abnormal laboratory findings include moderately severe hemolytic anemia, elevated reticulocyte count, thrombocytopenia, proteinuria, and elevated bilirubin, blood urea nitrogen, and creatinine levels. The leukocyte count is normal to slightly decreased, with increased bands. Babesiosis symptoms usually last for 1 to 2 weeks, with prolonged recovery of up to a year or more in severe cases. Complications include respiratory failure, disseminated intravascular coagulation, congestive heart failure, renal failure, liver failure, and coma. A prolonged relapsing course of illness has been described in highly immunocompromised hosts, such as those with cancer, with asplenia, and on treatment with immunosuppressive agents, even though they received multiple courses of antibabesial therapy. About a quarter of these patients died, while the remainder were cured after an average of 3 mo (range: 1-24 mo) of antibabesial therapy.

Risk factors for severe disease include anatomic or functional asplenia, concomitant malignancy or HIV infection, immunosuppressive drugs, age of more than 50 yr, acquisition of infection through blood transfusion, or infection with *B. divergens* or *B. duncani*. Concurrent babesiosis and Lyme disease occurs in 3-11% of patients experiencing Lyme disease depending upon location in southern New England and the northern Midwest. Such coinfection results in more severe acute Lyme disease illness. Moderate to severe babesiosis may occur in children, but infection generally is less severe than in adults. About half of infected children are asymptomatic or experience minimal symptoms. Neonates may develop severe illness and usually are infected from blood transfusion.



N = 1,750; county of residence was unknown for 12 of the 1,762 patients. Cases are mapped to the patients' county of residence, which was notnecessarily where they became infected.

For 2013, 22 of the 27 states that conducted surveillance for babesiosis reported at least 1 case: California, Connecticut, Delaware, Indiana, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Nebraska, New Hampshire, New Jersey, New York, North Dakota, Rhode Island, South Carolina, South Dakota, Texas, Vermont, Washington, and Wisconsin. Five (5) states reported 0 cases: Alabama, Oregon, Tennessee, West Virginia, and Wyoming. In 2013, babesiosis was not a reportable disease in the gray states, and health departments in those states did not notify CDC of cases.

Figure 289-1 Number of reported cases of babesiosis, by county of residence–27 states, 2013. *(Adapted from Centers for Disease Control and Prevention, Data and Statistics, Babesiosis: http://www.cdc.gov/parasites/babesiosis/data-statistics/index.html.)*

DIAGNOSIS

The diagnosis of babesiosis should be considered in any patient with an unexplained febrile illness who has resided in or traveled to an endemic area within the previous 2 mo or received a blood transfusion within the previous 6 mo. The diagnosis is confirmed by microscopic identification of parasites on blood smear or amplifiable Babesia DNA in blood and antibacteral antibody in serum. Babesia are identified on blood smear using Giemsa or Wright staining. Parasitemia may be exceedingly low, especially early in the course of illness. Thick blood smears may be examined, but the organisms may be mistaken for stain precipitate or iron inclusion bodies. The polymerase chain reaction is a sensitive and specific test for detection of *Babesia* DNA. Subinoculation of blood into hamsters or gerbils and in vitro cultivation are too specialized for all but the most experienced laboratories. Serologic testing is useful, particularly for diagnosing *B. microti* infection. The indirect immunofluorescence serologic assay for both immunoglobulin G and immunoglobulin M antibodies is sensitive and specific and can help confirm a diagnosis of babesiosis when parasites are scarce or undetectable. The diagnosis of active babesial infection based on seropositivity alone is unreliable.

TREATMENT

The combination of clindamycin (7-10 mg/kg given every 6-8 hr [up to a maximum of 600 mg per dose] intravenously or orally) and quinine (8 mg/kg given every 8 hr [up to a maximum of 650 mg per dose] orally) for 7-10 days was the first effective therapeutic combination for the treatment of babesiosis and remains the treatment of choice for severe disease. Adverse reactions are common, however, especially tinnitus and abdominal distress. The combination of atovaquone (20 mg/kg every 12 hr [up to a maximum of 750 mg per dose]) and azithromycin (10 mg/kg per day once per day on day 1 [up to a maximum of 500 mg per dose] and 5 mg/kg once per day [up to a maximum of 250 mg per dose] thereafter orally) for 7-10 days is as effective as clindamycin and quinine but has fewer adverse effects. Combination atovaquone and azithromycin has been used successfully to treat babesiosis in infants and should be considered for initial use in children experiencing mild to moderate infection. Treatment failure with clindamycin and quinine and with atovaquone and azithromycin may occur in highly immunocompromised hosts. Consultation with an infectious diseases expert is recommended in these cases. Exchange blood transfusion can decrease parasitemia rapidly and remove toxic by-products of infection. It should be considered for all patients experiencing severe babesiosis.

PROGNOSIS

Moderate to severe disease is frequently observed in some highly endemic areas. The case fatality rate was estimated at 5% in a retrospective study of 136 New York cases but may be as high as 21% in immunocompromised hosts. Immunity is sometimes incomplete with low-level asymptomatic parasitemia persisting for as long as 26 mo after symptoms have resolved or with relapsing symptomatic disease in immunocompromised hosts.

PREVENTION

Prevention of babesiosis can be accomplished by avoiding areas where ticks, deer, and mice are known to thrive. Use of clothing that covers the lower part of the body and that is sprayed or impregnated with diethyltoluamide (DEET), dimethyl phthalate, or permethrin (Permanone) is recommended for those who travel in the foliage of endemic areas. A search for ticks on people and pets should be carried out and the ticks removed using tweezers. Prospective blood donors with a history of babesiosis are excluded from giving blood to prevent transfusion-related cases.

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Chapter 290

Toxoplasmosis (*Toxoplasma gondii*)

Rima Mcleod, Christine VanTubbergen, and Kenneth M. Boyer

Toxoplasma gondii, an obligate intracellular protozoan, is acquired perorally, transplacentally, or, rarely, parenterally in laboratory accidents; by transfusion; or from a transplanted organ. In immunologically normal children, acute acquired infection may be asymptomatic, cause lymphadenopathy, or affect almost any organ. Once acquired, latent encysted organisms persist in the host throughout life. In immunocompromised persons either initial acquisition or recrudescence of latent organisms often causes signs or symptoms related to the central nervous system (CNS) and can result in systemic disease in bone marrow transplant recipients. If untreated, congenital infection often causes disease either perinatally or later in life, most frequently chorioretinitis and CNS lesions. Other manifestations, such as intrauterine growth retardation, prematurity, being small for gestational age, cognitive and motor deficits, fever, lymphadenopathy, rash, hearing loss, pneumonitis, hepatitis, thrombocytopenia, and cerebrospinal fluid (CSF) inflammatory changes such as pleocytosis, elevated CSF protein, and low CSF glucose, may also occur. Congenital toxoplasmosis in infants with HIV infection may be fulminant.

ETIOLOGY

T. gondii is a coccidian protozoan that multiplies only in living cells. The tachyzoites are oval or crescent-like, measuring 2-4 × 4-7 µm. Tissue cysts, which are 10-100 µm in diameter, may contain thousands of parasites, and will remain in tissues, especially the CNS and skeletal and heart muscle, for the life of the host. *Toxoplasma* can multiply in all tissues of mammals and birds.

Newly infected cats and other Felidae species excrete infectious *Toxoplasma* oocysts in their feces. *Toxoplasma* organisms are transmitted to cats by ingestion of infected meat containing encysted bradyzoites or by ingestion of oocysts excreted by other recently infected cats. The parasites then multiply through schizogonic and gametogonic cycles in the distal ileal epithelium of the cat intestine. Oocysts containing 2 sporocysts are excreted, and, under proper conditions of temperature and moisture, each sporocyst matures into 4 sporozoites. For approximately 2 wk the cat excretes 10^5-10^7 oocysts/day, which may retain their viability for longer than 1 yr in a suitable environment. Oocysts sporulate 1-5 days after excretion and are then infectious. Oocysts are killed by drying or boiling but not exposure to bleach. Oocysts have been isolated from soil and sand frequented by cats, and outbreaks associated with contaminated food and water have been reported. Oocysts and tissue cysts are sources of animal and human infections (Fig. 290-1). There are genetically distinct types of *T. gondii* that have different virulence for mice (and perhaps for humans) and form different numbers of cysts in the brains of outbred mice. In the United States, there are 4 predominant clonal lineages called types I, II, III, and IV (haplogroup XII) in addition to atypical, recombinant types. Virulence differs based on parasite genetics. There is 1 predominant clonal type in France, Austria, and Poland, and nonarchetypal parasites in Brazil, Guyana, French Guiana, and Central America.

EPIDEMIOLOGY

Toxoplasma infection is ubiquitous in animals and is one of the most common latent infections of humans throughout the world. Incidence varies considerably among people and animals in different geographic areas. In many areas of the world, approximately 3-35% of pork, 7-60% of lamb, and 0-9% of beef contain *T. gondii* organisms. Significant antibody titers are detected in 50-80% of residents of some localities, such as France, Brazil, and Central America, and in <5% in other areas. There is a higher prevalence of infection in warmer, more humid climates. Non-II genetic type parasites are more common in mothers of congenitally infected infants in warm, moist southern climates, in rural areas with lower socioeconomic status, and in places with Hispanic ethnicity in the United States.

Human infection is usually acquired orally by eating undercooked or raw meat that contains cysts or food or other material contaminated with oocysts from acutely infected cats. Freezing meat to −20°C (−4°F) or heating meat to 66°C (150.8°F) renders the cysts noninfectious. Outbreaks of acute acquired infection have occurred in families, at social gatherings, and in restaurants where people have consumed the same infected food. *Toxoplasma* organisms are not known to be transmitted from person to person except for transplacental infection from mother to fetus and, rarely, by organ transplantation or transfusion.

Seronegative transplant recipients who receive an organ or bone marrow from seropositive donors have experienced life-threatening illness requiring therapy. Seropositive recipients may have increased serologic titers without associated disease. Laboratory accidents have resulted in infections, including fatalities.

Congenital Toxoplasmosis

Transmission to the fetus usually follows acquisition of primary infection by an immunologically normal pregnant woman during gestation. Congenital transmission from mothers infected before pregnancy is extremely rare except for immunocompromised women who are chronically infected. The incidence of congenital infection in the United States ranges from 1 in 1,000 to 1 in 8,000 live births. The incidence of infection among pregnant women depends on the general risk for infection in the specific locale and the proportion of the population that has not been infected previously.

PATHOGENESIS

T. gondii is acquired by children and adults from ingesting food that contains cysts or that is contaminated with oocysts from acutely infected cats. Oocysts also may be transported to food by flies and cockroaches or be carried on the fur of dogs. When the organism is ingested, bradyzoites are released from cysts or sporozoites from oocysts. The organisms enter gastrointestinal cells where they multiply, rupture cells, infect contiguous cells, enter the lymphatics, and disseminate hematogenously throughout the body. Tachyzoites proliferate, producing necrotic foci surrounded by a cellular reaction. With development of a normal immune response that is both humoral and cell mediated, tachyzoites disappear from tissues. In immunocompromised persons and also some apparently immunocompetent persons, acute infection progresses and may cause potentially lethal disease, including pneumonitis, myocarditis, or encephalitis.

Alterations of T-lymphocyte populations during acute *T. gondii* infection are common and include lymphocytosis, increased CD8 count, and decreased CD4:CD8 ratio. Depletion of CD4 cells in patients with AIDS may contribute to severe manifestations of toxoplasmosis. Characteristic lymph node changes include reactive follicular hyperplasia with irregular clusters of epithelioid histiocytes that encroach on and blur margins of germinal centers, and focal distention of sinuses with monocytoid cells.

Cysts form as early as 7 days after infection and remain for the life of the host. During latent infection they produce little or no inflammatory response but can cause recrudescent disease in immunocompromised persons. Recrudescent chorioretinitis occurs in children with postnatal infection and in older children and adults with congenital infection. Host and parasite genetics influence outcome.

Congenital Toxoplasmosis

When a mother acquires infection during gestation, organisms may disseminate hematogenously to the placenta. Infection may be transmitted to the fetus transplacentally or during vaginal delivery. Of

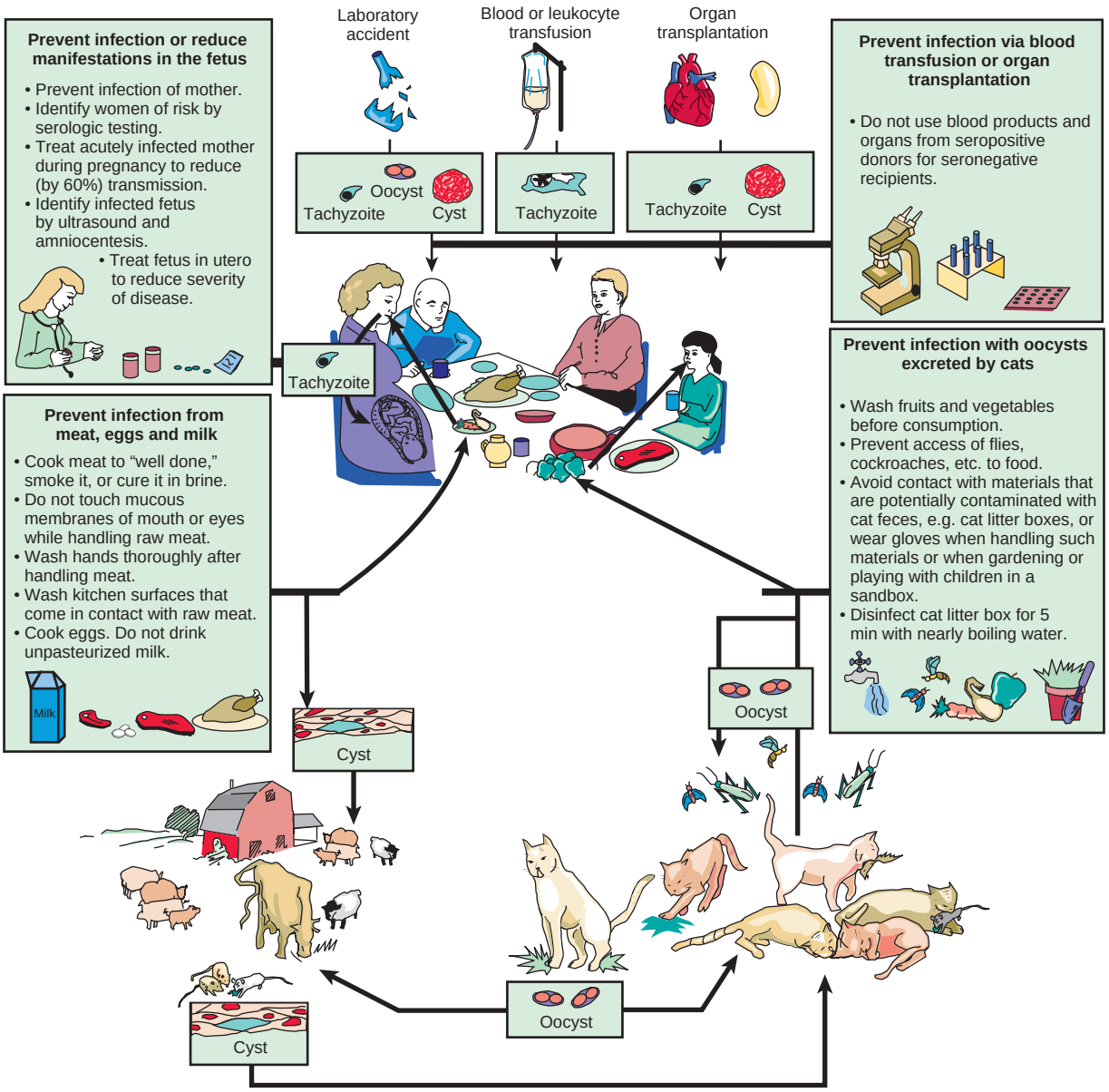


Figure 290-1 Life cycle of *Toxoplasma gondii* and prevention of toxoplasmosis by interruption of transmission to humans.

untreated maternal infections acquired in the 1st trimester, approximately 17% of fetuses are infected, usually with severe disease. Of untreated maternal infection acquired in the 3rd trimester, approximately 65% of fetuses are infected, usually with disease that is more mild or inapparent at birth. These different rates of transmission and outcomes are most likely related to placental blood flow, virulence, inoculum of *T. gondii,* and immunologic capacity of the mother and fetus to limit parasitemia.

Examination of the placenta of infected newborns may reveal chronic inflammation and cysts. Tachyzoites can be seen with Wright or Giemsa stains but are best demonstrated with immunoperoxidase technique. Tissue cysts stain well with periodic acid–Schiff and silver stains as well as with the immunoperoxidase technique. Gross or microscopic areas of necrosis may be present in many tissues, especially the CNS, choroid and retina, heart, lungs, skeletal muscle, liver, and spleen. Areas of calcification occur in the brain.

Almost all congenitally infected individuals who are not treated manifest signs or symptoms of infection, such as chorioretinitis, by adolescence. Some severely involved infants with congenital infection appear to have *Toxoplasma* antigen–specific cell-mediated anergy, which may be important in the pathogenesis of disease.

CLINICAL MANIFESTATIONS

Manifestations of primary infection with *T. gondii* are highly variable and are influenced primarily by host immunocompetence. There may be no signs or symptoms or severe disease. Reactivation of previously asymptomatic congenital toxoplasmosis usually manifests as ocular toxoplasmosis.

Acquired Toxoplasmosis

Immunocompetent children who acquire infection postnatally generally do not have clinically recognizable symptoms. When clinical manifestations are apparent, they may include almost any combination of fever, stiff neck, myalgia, arthralgia, maculopapular rash that spares the palms and soles, localized or generalized lymphadenopathy, hepatomegaly, hepatitis, reactive lymphocytosis, meningitis, brain abscess, encephalitis, confusion, malaise, pneumonia, polymyositis, pericarditis, pericardial effusion, and myocarditis. Chorioretinitis is usually

unilateral and is estimated to occur in approximately 1% of cases in the United States. Approximately 10% of mothers of congenitally infected infants also have eye lesions. Acquired chorioretinal lesions cannot be distinguished from congenital infection based on their appearance. In some areas of Brazil, 80% of the population is infected and, of these, 20% have retinal involvement. Ocular symptoms may be present for a few days only or may persist for many months. The most common manifestation of acute acquired toxoplasmosis is enlargement of 1 or a few cervical lymph nodes. Cases of *Toxoplasma* lymphadenopathy can resemble infectious mononucleosis, lymphoma, or other lymphadenopathies (see Chapter 490). In the pectoral area in older girls and women, enlarged nodes may be confused with breast neoplasms. Mediastinal, mesenteric, and retroperitoneal lymph nodes may be involved. Involvement of intraabdominal lymph nodes may be associated with fever, mimicking appendicitis. Nodes may be tender but do not suppurate. Lymphadenopathy may wax and wane for as long as 1-2 yr. However, almost all patients with lymphadenopathy recover spontaneously without antimicrobial therapy. Significant organ involvement in immunologically normal persons is uncommon, although some individuals have suffered significant morbidity, including rare cases of encephalitis, brain abscesses, hepatitis, myocarditis, pericarditis, and polymyositis. In persons acquiring *T. gondii* in Guyana and along Amazon tributaries, a severe form of multivisceral involvement with fever has occurred.

Ocular Toxoplasmosis

In the United States and Western Europe, *T. gondii* is estimated to cause 35% of cases of chorioretinitis (Fig. 290-2). In Brazil, *T. gondii* retinal lesions are common. Clinical manifestations include blurred vision, visual floaters, photophobia, epiphora, and, with macular involvement, loss of central vision. Ocular findings of congenital toxoplasmosis also include strabismus, microphthalmia, microcornea, cataracts, anisometropia, nystagmus, glaucoma, optic neuritis, and optic atrophy. Episodic recurrences are common, but precipitating factors have not been defined. Recurrent, active disease occurs most commonly at school-entry age and during adolescence. Anecdotally, stress or trauma seems to precipitate symptoms. Recurrences are most common closest to the time of acquisition of infection, and treatment leads to resolution of activity.

Immunocompromised Persons

Disseminated *T. gondii* infection among older children who are immunocompromised by AIDS, malignancy, cytotoxic therapy, corticosteroids, or immunosuppressive drugs given for organ transplantation involves the CNS in 50% of cases and may also involve the heart, lungs, and gastrointestinal tract. Stem cell transplant recipients present a special problem, because active infection is difficult to diagnose serologically. After transplantation, *T. gondii*-specific antibody levels may remain the same, increase, or decrease, and can even become undetectable. Toxoplasmosis in transplantation patients almost always results from transplantation from a seropositive donor to a seronegative recipient. Active infection is often fulminant and rapidly fatal without treatment.

Congenital *T. gondii* infection in infants with HIV infection is rare and can be a severe and fulminant disease with substantial CNS involvement. Alternatively, it may be more indolent in presentation, with focal neurologic deficits or systemic manifestations such as pneumonitis occurring with CD4 depletion.

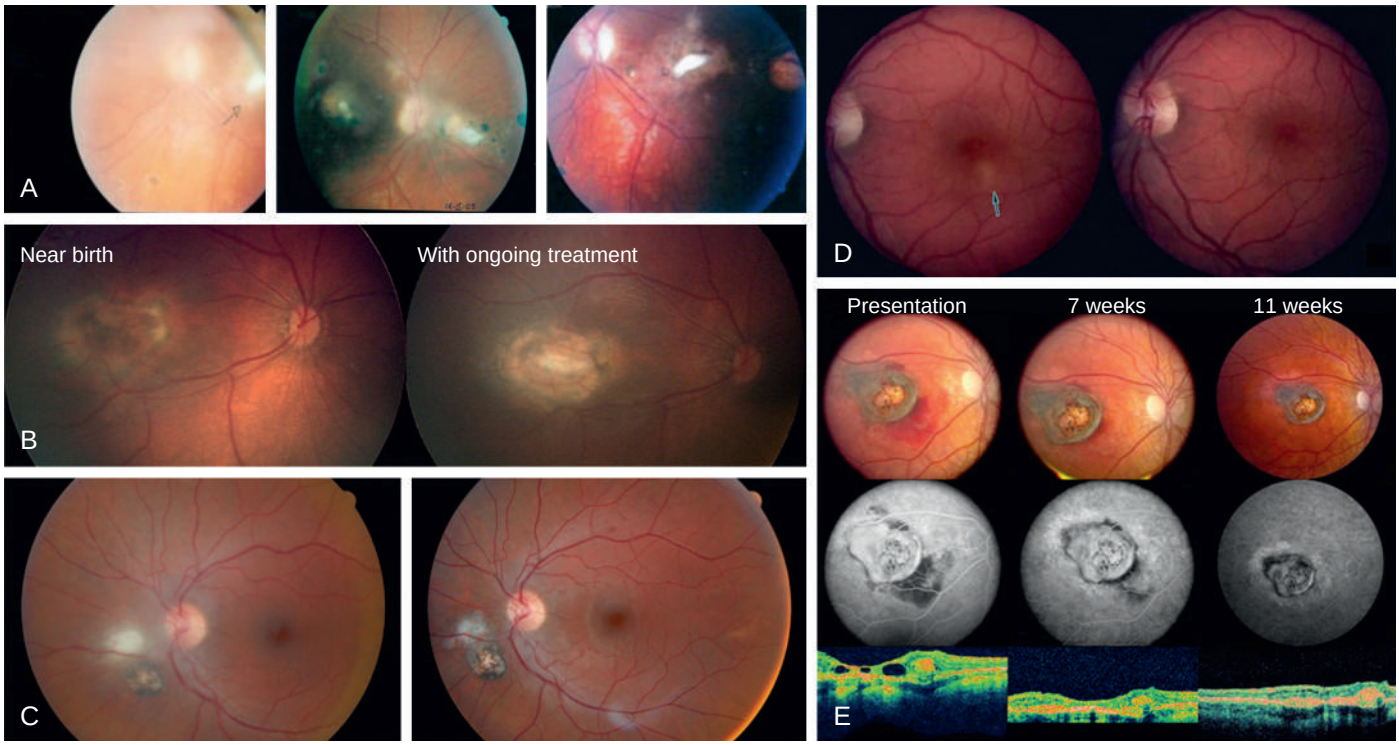


Figure 290-2 **Toxoplasmic chorioretinitis. A,** Retinal photographs of a child with severe vitreitis that is less intense than the classic "headlight in fog" appearance *(left)*. Resolving vitreitis caused by underlying active lesion *(middle)*. Resolved healed lesion without vitreitis *(right)*. **B,** Retina photographs for a newborn infant with active vitreitis (*left*, labeled "near birth") with clearing of vitreitis and marked, but not complete, resolution of activity of the lesion 3 wk later (*right*, labeled "with ongoing treatment"). **C,** Retinal photographs of a child showing an active lesion at presentation *(left)*, and scarred lesion *(right)*. **D,** Retinal photographs showing an active retinal lesion before treatment *(left)* and a completely resolved normal appearing retina within 1 mo of initiating treatment *(right)*. **E,** Example of active choroidal neovascular membranes (CNVMs) in a child. Fundus photographs *(top row)*, fluorescein angiogram (FA; *middle row*), and ocular coherence tomography (OCT; *bottom row*) of a child at presentation *(first column)*, 7 wk after first ranibizumab (Lucentis, antibody to VEGF) injection *(second column)*, and 11 wk after first ranibizumab injection *(third column)*. (***A*** *to* ***D*** *adapted from Delair E, Latkany P, Noble AG, et al: Clinical manifestations of ocular toxoplasmosis,* Ocul Immunol Inflamm *19:91–102, 2011;* ***E*** *adapted from Benevento JD, Jager RD, Noble AG, et al: Toxoplasmosis-associated neovascular lesions treated successfully with ranibizumab and antiparasitic therapy,* Arch Ophthalmol *126:1152–1156, 2008.)*

From 25-50% of persons with *T. gondii* antibodies and **HIV infection** without antiretroviral treatment eventually experience toxoplasmic encephalitis, which is fatal if not treated. Highly active antiretroviral therapy and trimethoprim-sulfamethoxazole prophylaxis have diminished the incidence of toxoplasmosis in patients with HIV infection, but toxoplasmic encephalitis remains a presenting manifestation in adult patients with AIDS. Typical findings include fever, headache, altered mental status, psychosis, cognitive impairment, seizures, and focal neurologic defects, including hemiparesis, aphasia, ataxia, visual field loss, cranial nerve palsies, and dysmetria or movement disorders. In adult patients with AIDS, toxoplasmic retinal lesions are often large with diffuse necrosis and contain many organisms but little inflammatory cellular infiltrate. Diagnosis of presumptive toxoplasmic encephalitis based on neuroradiologic studies in patients with AIDS necessitates a prompt therapeutic trial of medications effective against *T. gondii*. Clear clinical improvement within 7-14 days and improvement of neuroradiologic findings within 3 wk makes the presumptive diagnosis almost certain.

Congenital Toxoplasmosis

Congenital toxoplasmosis usually occurs when a woman acquires primary infection while pregnant. Most often, maternal infection is asymptomatic or without specific symptoms or signs. As with other adults with acute toxoplasmosis, lymphadenopathy is the most common symptom.

In monozygotic twins the clinical pattern of involvement is most often similar, whereas in dizygotic twins the manifestations often differ, including cases of congenital infection in only 1 twin. The major histocompatibility complex class II gene DQ3 appears to be more frequent among HIV-infected persons seropositive for *T. gondii* who develop toxoplasmic encephalitis, and in children with congenital toxoplasmosis who develop hydrocephalus. These findings suggest that the presence of HLA-DQ3 is a risk factor for severity of toxoplasmosis. Other allelic variants of genes, including *COL2A*, *ABC4R*, *P2X7R*, *NALP1*, *TLR9*, and *ERAAP*, are also associated with susceptibility.

Congenital infection may present as a mild or severe neonatal disease. It may also present with sequelae or relapse of a previously undiagnosed and untreated infection later in infancy or even later in life. There is a wide variety of manifestations of congenital infection, ranging from hydrops fetalis and perinatal death to small size for gestational age, prematurity, peripheral retinal scars, persistent jaundice, mild thrombocytopenia, CSF pleocytosis, and the characteristic triad of chorioretinitis, hydrocephalus, and cerebral calcifications. More than 50% of congenitally infected infants are considered normal in the perinatal period, but almost all such children develop ocular involvement later in life if they are not treated during infancy. Neurologic signs such as convulsions, setting-sun sign with downward gaze, and hydrocephalus with increased head circumference may be associated with substantial cerebral damage or with relatively mild inflammation obstructing the aqueduct of Sylvius. If affected infants are treated and shunted promptly, signs and symptoms may resolve and development may be normal.

The spectrum and frequency of neonatal manifestations of 210 newborns with congenital *Toxoplasma* infection identified by a serologic screening program of pregnant women were described in 1984. In this study, 10% had severe congenital toxoplasmosis with CNS involvement, eye lesions, and general systemic manifestations; 34% had mild involvement with normal clinical examination results other than retinal scars or isolated intracranial calcifications; and 55% had no detectable manifestations. These numbers represent an underestimation of the incidence of severe congenital infection for several reasons: the most-severe cases, including most of those individuals who died, were not referred; therapeutic abortion sometimes was performed when acute acquired infection of the mother was diagnosed early during pregnancy; in utero spiramycin therapy prevented or diminished the severity of infection; only 13 of the 210 congenitally infected newborns had brain CT, and only 77% of these 210 infants had a CSF examination. Routine newborn examinations often yield normal findings for congenitally infected infants, but more careful evaluations may reveal significant abnormalities. In a 2012 analysis of the National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2009) data, it was found that 72% of children at or near birth had chorioretinal scars, 70% had CNS calcifications, 12% had microcephalus, 37% had hydrocephalus, 41% had thrombocytopenia, 39% had hepatomegaly, 32% had splenomegaly, and 41% were born prematurely (Fig. 290-3). In 1 study of 28 infants identified by a universal state-mandated serologic screening program for *T. gondii*–specific immunoglobulin (Ig) M, 26 had normal findings on routine newborn examination but 14 had significant abnormalities detected with more careful evaluation. The abnormalities included retinal scars (7 infants), active chorioretinitis (3 infants), and CNS abnormalities (8 infants). In Fiocruz, Belo Horizonte, Brazil, infection is common, occurring in 1 in 600 live births. Half of these infected infants have active chorioretinitis at birth. When the infection is acquired in utero and the fetus is treated by treatment of the pregnant woman with pyrimethamine, sulfadiazine, and leucovorin, signs and symptoms in the infant may be prevented. The newborn infant may appear normal with no CSF abnormalities and no brain or eye disease. In utero treatment initiated rapidly results in a reduction of ocular and neurologic sequelae.

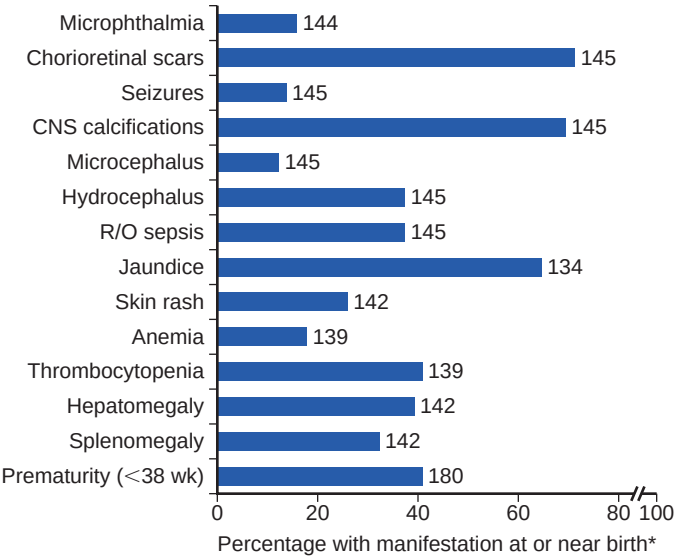


Figure 290-3 Manifestations at presentation, National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2009). *Infants diagnosed with congenital toxoplasmosis in the newborn period and referred to the NCCCTS during the first yr of life. Number in parenthesis represents number of infants with this manifestation and is based on information in birth records; R/O, rule out sepsis. Sample size dependent on available birth records/diagnoses at birth. *(Adapted from McLeod R, Boyer KM, Lee D, et al: Prematurity and severity are associated with* Toxoplasma gondii *alleles [NCCCTS, 1981-2009],* Clin Infect Dis *54:1595-1605, 2012.)*

There is also a wide spectrum of symptoms of untreated congenital toxoplasmosis that presents later in the 1st yr of life (Table 290-1). More than 80% of these children have IQ scores of <70, and many have convulsions and severely impaired vision.

SYSTEMIC SIGNS

From 25% to >50% of infants with clinically apparent disease at birth are born prematurely. Parasite clonal types other than type II are more often associated with prematurity and more-severe disease. Intrauterine growth retardation, low Apgar scores, and temperature instability are common. Other manifestations may include lymphadenopathy, hepatosplenomegaly, myocarditis, pneumonitis, nephrotic syndrome, vomiting, diarrhea, and feeding problems. Bands of metaphyseal lucency and irregularity of the line of provisional calcification at the epiphyseal plate may occur without periosteal reaction in the ribs, femurs, and vertebrae. Congenital toxoplasmosis may be confused with erythroblastosis fetalis resulting from isosensitization, although

Table 290-1 Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed 4 Yr or More (B)

SIGNS AND SYMPTOMS	Frequency of Occurrence in Patients with "Neurologic" Disease*	Frequency of Occurrence in Patients with "Generalized" Disease†
A. INFANTS	108 PATIENTS (%)	44 PATIENTS (%)
Chorioretinitis	102 (94)	29 (66)
Abnormal cerebrospinal fluid	59 (55)	37 (84)
Anemia	55 (51)	34 (77)
Convulsions	54 (50)	8 (18)
Intracranial calcification	54 (50)	2 (4)
Jaundice	31 (29)	35 (80)
Hydrocephalus	30 (28)	0 (0)
Fever	27 (25)	34 (77)
Splenomegaly	23 (21)	40 (90)
Lymphadenopathy	18 (17)	30 (68)
Hepatomegaly	18 (17)	34 (77)
Vomiting	17 (16)	21 (48)
Microcephalus	14 (13)	0 (0)
Diarrhea	7 (6)	11 (25)
Cataracts	5 (5)	0 (0)
Eosinophilia	6 (4)	8 (18)
Abnormal bleeding	3 (3)	8 (18)
Hypothermia	2 (2)	9 (20)
Glaucoma	2 (2)	0 (0)
Optic atrophy	2 (2)	0 (0)
Microphthalmia	2 (2)	0 (0)
Rash	1 (1)	11 (25)
Pneumonitis	0 (0)	18 (41)
B. CHILDREN ≥4 YR OF AGE	70 PATIENTS (%)	31 PATIENTS (%)
Mental retardation	62 (89)	25 (81)
Convulsions	58 (83)	24 (77)
Spasticity and palsies	53 (76)	18 (58)
Severely impaired vision	48 (69)	13 (42)
Hydrocephalus or microcephalus	31 (44)	2 (6)
Deafness	12 (17)	3 (10)
Normal	6 (9)	5 (16)

*Patients with otherwise undiagnosed central nervous system disease in the 1st yr of life.

†Patients with otherwise undiagnosed nonneurologic diseases during the 1st 2 mo of life.

Adapted from Eichenwald H: A study of congenital toxoplasmosis. In Slim JC, editor: Human toxoplasmosis, *Copenhagen, 1960, Munksgaard, pp. 41–49. Study performed in 1947. The most severely involved institutionalized patients were not included in the later study of 101 children.*

the Coombs test result is usually negative with congenital *T. gondii* infection.

Skin

Cutaneous manifestations among newborn infants with congenital toxoplasmosis include rashes and jaundice and/or petechiae secondary to thrombocytopenia, but ecchymoses and large hemorrhages secondary to thrombocytopenia also occur. Rashes may be fine punctate, diffuse maculopapular, lenticular, deep blue-red, sharply defined macular, or diffuse blue and papular. Macular rashes involving the entire body including the palms and soles, exfoliative dermatitis, and cutaneous calcifications have been described. Jaundice with hepatic involvement and/or hemolysis, cyanosis due to interstitial pneumonitis from congenital infection, and edema secondary to myocarditis or nephrotic syndrome may be present. Jaundice and conjugated hyperbilirubinemia may persist for months.

Endocrine Abnormalities

Endocrine abnormalities may occur secondary to hypothalamic or pituitary involvement or end-organ involvement but are not common. Occasionally reported endocrinopathies include myxedema, persistent hypernatremia with vasopressin-sensitive diabetes insipidus, sexual precocity, and partial anterior hypopituitarism.

Central Nervous System

Neurologic manifestations of congenital toxoplasmosis vary from massive acute encephalopathy to subtle neurologic syndromes. Toxoplasmosis should be considered as a potential cause of any undiagnosed neurologic disease in children younger than 1 yr of age, especially if retinal lesions are present.

Hydrocephalus may be the sole clinical neurologic manifestation of congenital toxoplasmosis and almost always requires shunt placement. Hydrocephalus may present prenatally and progress during the perinatal period, or, much less commonly, may present later in life. Patterns of seizures are protean and have included focal motor seizures, petit and grand mal seizures, muscular twitching, opisthotonus, and hypsarrhythmia. Spinal or bulbar involvement may be manifested by paralysis of the extremities, difficulty swallowing, and respiratory distress. Microcephaly usually reflects severe brain damage, but some children with microcephaly caused by congenital toxoplasmosis who have been treated have normal or superior cognitive function. Untreated congenital toxoplasmosis that is symptomatic in the 1st yr of life can cause substantial diminution in cognitive function and developmental delay. Intellectual impairment also occurs in some children with subclinical infection without or despite treatment with pyrimethamine and sulfonamides. Seizures and focal motor defects may become apparent after the newborn period, even when infection is subclinical at birth.

CSF abnormalities occur in at least 50% of infants with congenital toxoplasmosis. A CSF protein level of >1 g/dL is characteristic of severe CNS toxoplasmosis and is usually accompanied by hydrocephalus. Local production of *T. gondii*–specific IgG and IgM antibodies may be demonstrated. CT of the brain is useful to detect calcifications, determine ventricular size, and demonstrate porencephalic cystic structures (Fig. 290-4). Calcifications occur throughout the brain, but there is a propensity for development of calcifications in the caudate nucleus and basal ganglia, choroid plexus, and subependyma. MRI and contrast-enhanced CT brain scans are useful for detecting active inflammatory lesions. MRIs that take only a brief time (<45 sec) for imaging or ultrasonography may be useful for following ventricular size. Treatment in utero and in the 1st yr of life results in improved neurologic outcomes.

Eyes

Almost all untreated congenitally infected infants develop chorioretinal lesions by adulthood, and may have severe visual impairment. *T. gondii* causes a focal necrotizing retinitis in congenitally infected individuals (see Fig. 290-2). Retinal detachment may occur. Any part of the retina may be involved, either unilaterally or bilaterally, including the maculae. The optic nerve may be involved, and toxoplasmic lesions that involve projections of the visual pathways in the brain or the visual cortex also may lead to visual impairment. In association with severe retinal lesions and vitreitis, secondary anterior uveitis may develop and occasionally lead to erythema of the external eye. Other ocular findings include cells and protein in the anterior chamber, large keratic precipitates, posterior synechiae, nodules on the iris, and neovascular formation on the surface of the iris, sometimes with increased intraocular pressure and glaucoma. Rarely, the extraocular musculature may also be involved directly. Other manifestations include strabismus, nystagmus, visual impairment, and microphthalmia. Enucleation has been required for a blind, phthisic, painful eye. The differential diagnosis of ocular toxoplasmosis includes congenital coloboma and inflammatory lesions caused by cytomegalovirus, *Treponema pallidum, Mycobacterium tuberculosis,* or vasculitis. Ocular toxoplasmosis may be a recurrent and progressive disease that requires multiple courses of therapy.

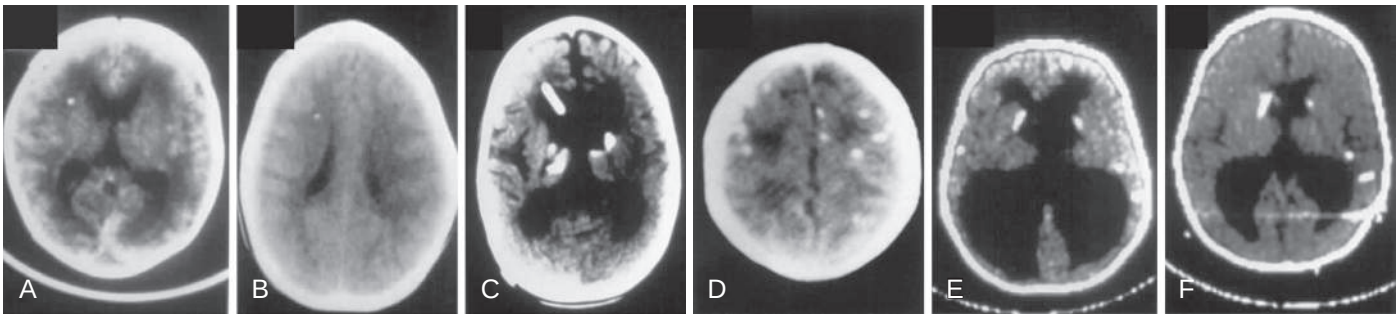


Figure 290-4 Head CT scans of infants with congenital toxoplasmosis. **A,** CT scan at birth that shows areas of hypolucency, mildly dilated ventricles, and small calcifications. **B,** CT scan of the same child at 1 yr of age (after antimicrobial therapy for 1 yr). This scan is normal with the exception of 2 small calcifications. This child's Mental Development Index (MDI) at 1 yr of age was 140 by the Bayley Scale of Infant Development. **C,** CT scan from a 1 yr old infant who was normal at birth. His meningoencephalitis became symptomatic in the 1st few wk of life but was not diagnosed correctly and remained untreated during his 1st 3 mo of life. At 3 mo of age, development of hydrocephalus and bilateral macular chorioretinitis led to the diagnosis of congenital toxoplasmosis, and antimicrobial therapy was initiated. This scan shows significant residual atrophy and calcifications. This child had substantial motor dysfunction, development delays, and visual impairment. **D,** CT scan obtained during the 1st mo of life of a microcephalic child. Note the numerous calcifications. This child's IQ scores using the Stanford-Binet Intelligence Scale for children when she was 3 yr of age and the Wechsler Preschool and Primary Scale Intelligence when she was 5 yr of age were 100 and 102, respectively. She received antimicrobial therapy during her 1st yr of life. **E,** CT scan with hydrocephalus owing to aqueductal obstruction, before shunt. **F,** Scan from the same patient as the scan in **E,** after shunt. This child's IQ scores using the Stanford-Binet Intelligence Scale for children were approximately 100 when she was 3 and 6 yr of age. (***A*** *to* ***F*** *adapted from McAuley J, Boyer K, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial,* Clin Infect Dis *18:38–72, 1994.)*

Limited data suggest that occurrence of lesions in the early years of life may be prevented by instituting antimicrobial treatment with pyrimethamine and sulfonamides during the 1st yr of life and that treatment of the infected fetus in utero followed by treatment in the 1st yr of life with pyrimethamine, sulfadiazine, and leucovorin reduces the incidence and the severity of the retinal disease.

Ears

Sensorineural hearing loss, both mild and severe, may occur. It is not known whether this is a static or progressive disorder. Treatment in the 1st yr of life is associated with decreased frequency of hearing loss.

DIAGNOSIS

Diagnosis of acute *Toxoplasma* infection can be established by a number of methods (Table 290-2). For example, isolation of *T. gondii* from blood or body fluids; identification of tachyzoites in sections or preparations of tissues and body fluids, amniotic fluid, or placenta; identification of cysts in the placenta or tissues of a fetus or newborn; and characteristic lymph node histologic features establish the diagnosis. Serologic tests are very useful for diagnosis. Polymerase chain reaction (PCR) is useful to identify *T. gondii* DNA in CSF and amniotic fluid, and has been reported to be useful with infant peripheral blood and urine to definitively establish the diagnosis.

Isolation

Organisms are isolated by inoculation of body fluids, leukocytes, or tissue specimens into mice or tissue cultures. Body fluids should be processed and inoculated immediately, but *T. gondii* has been isolated from tissues and blood that have been stored overnight or even for 4-5 days at 4°C (39.2°F). Freezing or treatment of specimens with formalin kills *T. gondii.* From 6-10 days after inoculation into mice, or earlier if mice die, peritoneal fluids should be examined for tachyzoites. If inoculated mice survive for 6 wk and seroconvert, definitive diagnosis is made by visualization of *Toxoplasma* cysts in mouse brain. If cysts are not seen, subinoculations of mouse tissue into other mice are performed.

Microscopic examination of tissue culture inoculated with *T. gondii* shows necrotic, heavily infected cells with numerous extracellular tachyzoites. Isolation of *T. gondii* from blood or body fluids reflects acute infection. Except in the fetus or neonate, it is usually not possible to distinguish acute from past infection by isolation of *T. gondii* from tissues such as skeletal muscle, lung, brain, or eye obtained by biopsy or at autopsy.

Diagnosis of acute infection can be established by visualization of tachyzoites in biopsy tissue sections, bone marrow aspirate, or body fluids such as CSF or amniotic fluid. Immunofluorescent antibody and immunoperoxidase staining techniques may be necessary, because it is often difficult to distinguish the tachyzoite using ordinary stains. Tissue cysts are diagnostic of infection but do not differentiate between acute and chronic infection, although the presence of many cysts suggests recent acute infection. Cysts in the placenta or tissues of the newborn infant establish the diagnosis of congenital infection. Characteristic histologic features strongly suggest the diagnosis of toxoplasmic lymphadenitis.

Serologic Testing

Serologic tests are useful in establishing the diagnosis of congenital or acutely acquired *Toxoplasma* infection. Each laboratory that reports serologic test results must have established values for their tests that diagnose infection in specific clinical settings, provide interpretation of their results, and ensure appropriate quality control before therapy is based on serologic test results. Serologic test results used as the basis for therapy should be confirmed in a reference laboratory.

The **Sabin-Feldman dye test** is sensitive and specific. It measures primarily IgG antibodies. Results should be expressed in international units (IU/mL), based on international standard reference sera available from the World Health Organization.

The **IgG indirect fluorescent-antibody (IgG-IFA) test** measures the same antibodies as the dye test, and the titers tend to be parallel. These antibodies usually appear 1-2 wk after infection, reach high titers (≥1:1,000) after 6-8 wk, and then decline over months to years. Low titers (1:4 to 1:64) usually persist for life. Antibody titer does not correlate with severity of illness.

An **agglutination test** (Bio-Mérieux, Lyon, France) that is available commercially in Europe uses formalin-preserved whole parasites to detect IgG antibodies. This test is accurate, simple to perform, and inexpensive.

The **IgM-IFA test** is useful for the diagnosis of acute acquired infection with *T. gondii* in the older child because IgM antibodies appear earlier, often by 5 days after infection, and diminish more quickly than IgG antibodies. In most instances, IgM antibodies rise rapidly (1:50 to <1:1,000) and then fall to low titers (1:10 or 1:20) or disappear after weeks or months. However, some patients continue to have positive IgM results with low titers for several years. The IgM-IFA test detects *Toxoplasma*-specific IgM in only approximately 25% of congenitally infected infants at birth. IgM antibodies may not be present in sera of

Table 290-2 Generalizations Concerning Clinical Presentations, *Toxoplasma*-Specific Diagnostic Tests, and Treatment

CLINICAL SETTING & MANIFESTATION	SAMPLE SOURCE	*Toxoplasma*-Specific Diagnostic Tests								Treatment				
		G	M	A	E	AV	AC/HS	PCR	SUBINOCULATION	SP	PSL*	CO	LU	NONE
PRENATAL														
Acute infection in pregnant woman ≤18 wk gestation *and* no clinical evidence of fetal infection	Mother	+	+	+	+	L	Acute	AF (17-18 wk)	NS					
Acute infection in pregnant woman ≤18 wk gestation *and* signs of fetal infection	Mother	+	+	+	+	L	Acute	AF (may not be necessary)	NS		†No P 1st trimester			
Acute infection in pregnant woman at >21 wk gestation	Mother	+	+	+	+	L	Acute	AF	NS					
Congenital infection in infant	Infant	+	+	+	+	L	Acute	Placenta/buffy coat	placenta/buffy coat			‡		
POSTNATAL														
Acute, symptomatic	Child	+	+	+	+	L	Acute	NS	NS					
Acute, self-limited symptoms														
Chronic, asymptomatic	Child	+	–	–	–	H	Chronic	NS	NS					
Acute, severely symptomatic	Child	+	+	+	+	L	Acute	§	Body fluids/buffy coat					
Immune compromised¶	Child	+/–	+/–	+/–	+/–	+/–	+/–	§	Body fluids/buffy coat					
Laboratory accident‖	Child	+/–	+/–	+/–	+/–	+/–	+/–	NS	NS		‖			
Eye Disease														
Quiescent scar**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS					
Active chorioretinitis**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS					
Active CNVM**	Child	+	+/–	+/–	+/–	+/–	+/–	NS	NS				††	

*Pyrimethamine and leucovorin should be adjusted for granulocytopenia; complete blood counts, including platelets, should be monitored each Monday and Thursday. If there is sulfonamide allergy, alternative medicines include clindamycin, azithromycin, or clarithromycin in place of sulfadiazine.

†*DO NOT* use pyrimethamine in the 1st 14 wk gestation.

‡Occasionally, corticosteroids (prednisone) have been used when CSF protein is ≥1 g/dL or when active chorioretinitis threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

§Utility of PCR depends on clinical setting. For example, the following may be useful to establish the diagnosis: PCR of body fluids such as amniotic fluid or CSF; cells from bronchoalveolar lavage from a patient with pneumonia; or tissue such as placenta where presence of parasites or parasite DNA would support a diagnosis of infection.

¶In some cases, in immune compromised persons, there is no detectable serologic response to *T. gondii*. However, if clinical presentation is indicative of infection in the absence of positive serologic results, then CSF, buffy coat of peripheral blood, histopathology of tissue samples, or body fluids tested with PCR or subinoculation may be useful. If PCR demonstrates the presence of *T. gondii* DNA in the sample, it is useful for diagnosis. However, the sensitivity of PCR has been variable in this setting. In some circumstances, presumptive treatment may be warranted.

‖Whether a person should be treated for a laboratory accident depends on the nature of the accident, the serology of the person before the accident, and other factors. When there is risk of infection, treatment is given.

**Serologic results depend on whether infection is acute (recently acquired) or chronic. When testing serum from persons with ocular toxoplasmosis, *T. gondii*-specific IgG may be demonstrable only in an undiluted serum sample.

††Corticosteroids (prednisone) are used if inflammation or edema due to infection threatens vision and should be continued until signs of inflammation or active chorioretinitis that threatens vision have subsided; then dosage can be tapered and the steroids discontinued.

+, positive; –, negative; +/–, equivocal; A, *T. gondii*–specific IgA; AC/HS, direct agglutination; AF, amniotic fluid; Av, *T. gondii*–specific IgG avidity; CNVM, choroidal neovascular membrane; Co, corticosteroids (prednisone); CSF, cerebrospinal fluid; E, *T. gondii*–specific IgE; G, *T. gondii*–specific IgG; IG, immunoglobulin; Lu, Lucentis (antibody to vascular endothelial growth factor); M, *T. gondii*–specific IgM; NS, not standard to obtain; PCR, polymerase chain reaction; PSL, pyrimethamine, sulfadiazine, leucovorin (folinic acid); Sp, spiramycin.

Adapted from Remington JS, McLeod R, et al: Toxoplasmosis. In Remington JS, Klein JO, editors: Infectious diseases of the fetus and newborn infant, *ed 6, Philadelphia, 2006, WB Saunders.*

immunocompromised patients with acute toxoplasmosis or in patients with reactivation of ocular toxoplasmosis. The IgM-IFA test may yield false-positive results as a result of rheumatoid factor.

The **double-sandwich IgM enzyme-linked immunosorbent assay (IgM-ELISA)** is also useful for detection of *Toxoplasma* IgM antibodies. In the older child, serum IgM-ELISA *Toxoplasma* antibodies of >2 (a value of 1 reference laboratory; each laboratory must establish its own value for positive results) indicates that *Toxoplasma* infection most likely has been acquired recently. The IgM-ELISA identifies approximately 50-75% of infants with congenital infection. IgM-ELISA avoids both the false-positive results from rheumatoid factor and the false-negative results from high levels of passively transferred maternal

IgG antibody in fetal serum, as may occur in the IgM-IFA test. Results obtained with commercial kits must be interpreted with caution, because false-positive reactions are not infrequent. Care must also be taken to determine whether kits have been standardized for diagnosis of infection in specific clinical settings, such as in the newborn infant. The **IgA-ELISA** also is a sensitive test for detection of maternal and congenital infection, and results may be positive when those of the IgM-ELISA are not.

The **immunosorbent agglutination assay (ISAGA)** combines trapping of a patient's IgM to a solid surface and use of formalin-fixed organisms or antigen-coated latex particles. It is read as an agglutination test. There are no false-positive results from rheumatoid factor or antinuclear antibodies. The IgM-ISAGA is more sensitive than the IgM-ELISA and may detect specific IgM antibodies before and for longer periods than the IgM-ELISA.

At present, the IgM-ISAGA and the **IgA-ELISA** are the most useful tests for diagnosis of congenital infection in the newborn. The **IgE-ELISA** and **IgE-ISAGA** are also sometimes useful in establishing the diagnosis of congenital toxoplasmosis or acute acquired *T. gondii* infection. The presence of IgM antibodies in the older child or adult can never be used alone to diagnose acute acquired infection.

The **differential agglutination test (HS/AC)** compares antibody titers obtained with formalin-fixed tachyzoites **(HS antigen)** with titers obtained using acetone- or methanol-fixed tachyzoites **(AC antigen)** to differentiate recent and remote infections in adults and older children. This method may be particularly useful in differentiating remote infection in pregnant women, because levels of IgM and IgA antibodies detectable by ELISA or ISAGA may remain elevated for months to years in adults and older children.

The **avidity test** can be helpful to establish time of acquisition of infection. A high-avidity test result indicates that infection began more than 12-16 wk earlier, which is especially useful in determining time of acquisition of infection in the 1st or final 16 wk of gestation. A low-avidity test result may be present for many months and is not diagnostic of recent acquisition of infection.

A relatively higher level of *Toxoplasma* antibody in the aqueous humor or in CSF demonstrates local production of antibody during active ocular or CNS toxoplasmosis. This comparison is performed, and a coefficient [C] is calculated as follows:

$$C = \frac{\text{Antibody titer in body fluid}}{\text{Antibody titer in serum}} \times \frac{\text{Concentration of IgG in serum}}{\text{Concentration of IgG in body fluid}}$$

Significant coefficients [C] are >8 for ocular infection, >4 for CNS for congenital infection, and >1 for CNS infection in patients with AIDS. If the serum dye test titer is >300 IU/mL, it is not possible to demonstrate significant local antibody production using this formula with either the dye test or the IgM-IFA test titer. IgM antibody may be detectable in CSF.

Comparative **Western immunoblot** tests of sera from a mother and infant may detect congenital infection. Infection is suspected when the mother's serum and her infant's serum contain antibodies that react with different *Toxoplasma* antigens.

The **enzyme-linked immunofiltration assay** using micropore membranes permits simultaneous study of antibody specificity by immunoprecipitation and characterization of antibody isotypes by immunofiltration with enzyme-labeled antibodies. This method is capable of detecting 85% of cases of congenital infection in the 1st few days of life.

PCR is used to amplify the DNA of *T. gondii,* which then can be detected by using a DNA probe. Detection of repetitive *T. gondii* genes, the B1 or 529 bp, 300 copy gene, in amniotic fluid is the PCR target of choice for establishing the diagnosis of congenital *Toxoplasma* infection in the fetus. Sensitivity and specificity of this test in amniotic fluid obtained to diagnose infections acquired between 17 and 21 wk of gestation are approximately 95%. Before and after that time, PCR with the 529 bp, 300 copy repeat gene as the template is 92% sensitive and 100% specific for detection of congenital infection. PCR of vitreous or aqueous fluids also has been used to diagnose ocular toxoplasmosis. PCR of peripheral white blood cells, CSF, and urine has been reported to detect congenital infection.

Lymphocyte blastogenesis to *Toxoplasma* antigens has been used to diagnose congenital toxoplasmosis when the diagnosis is uncertain and other test results are negative. However, a negative result does not exclude the diagnosis because peripheral blood lymphocytes of infected newborns may not respond to *T. gondii* antigens.

Acquired Toxoplasmosis

Recent infection is diagnosed by seroconversion from a negative to a positive IgG antibody titer (in the absence of transfusion); a 2 tube increase in *Toxoplasma*-specific IgG titer when serial sera are obtained 3 wk apart and tested in parallel; or the detection of *Toxoplasma*-specific IgM antibody in conjunction with other tests, but never alone.

Ocular Toxoplasmosis

IgG antibody titers of 1:4 to 1:64 are usual in older children with active *Toxoplasma* chorioretinitis. Even the presence of antibodies measurable only when serum is tested undiluted is helpful in establishing the diagnosis. The diagnosis is likely with characteristic retinal lesions and positive serologic tests. PCR of aqueous or vitreous fluid has been used to diagnose ocular toxoplasmosis but is infrequently performed because of the risks associated with obtaining intraocular fluid.

Immunocompromised Persons

IgG antibody titers may be low, and *Toxoplasma*-specific IgM is often absent in immunocompromised stem cell transplant recipients, but not in kidney or heart transplant recipients with toxoplasmosis. Demonstration of *Toxoplasma* DNA in serum, blood, and CSF may identify disseminated *Toxoplasma* infection in immunocompromised persons. Resolution of CNS lesions during a therapeutic trial of pyrimethamine and sulfadiazine has been useful to diagnose toxoplasmic encephalitis in patients with AIDS. Brain biopsy has been used to establish the diagnosis if there is no response to a therapeutic trial and to exclude other likely diagnoses such as CNS lymphoma.

Congenital Toxoplasmosis

Fetal ultrasound examination, performed every 2 wk during gestation, beginning at the time acute acquired infection is diagnosed in a pregnant woman, and PCR analysis of amniotic fluid are used for prenatal diagnosis. *T. gondii* may also be isolated from the placenta at delivery.

Serologic tests are also useful in establishing a diagnosis of congenital toxoplasmosis. Either persistent or rising titers in the dye test or IFA test, or a positive IgM-ELISA or IgM-ISAGA result is diagnostic of congenital toxoplasmosis. The half-life of IgM is approximately 2 days, so if there is a placental leak, the level of IgM antibodies in the infant's serum decreases significantly, usually within 1 wk. Passively transferred maternal IgG antibodies may require many months to a year to disappear from the infant's serum, depending on the magnitude of the original titer. The half-life of passively transferred maternal IgG is approximately 30 days, so the titer diminishes by half each 30 days. Synthesis of *Toxoplasma* antibody is usually demonstrable by the 3rd mo of life if the infant is untreated, although the rate of IgG synthesis varies considerably in infants younger than 1 year of age. If the infant is treated, synthesis may be delayed for as long as the 9th mo of life and, infrequently, may not occur at all. When an infant begins to synthesize IgG antibody, infection may be documented serologically even without demonstration of IgM antibodies by an increase in the ratio of specific serum IgG antibody titer to the total IgG, whereas the ratio will decrease if the specific IgG antibody has been passively transferred from the mother.

Newborns suspected of having congenital toxoplasmosis should be evaluated by general, ophthalmologic, and neurologic examinations; head CT scan; attempt to isolate *T. gondii* from the placenta and infant's leukocytes from peripheral blood buffy coat; measurement of serum *Toxoplasma*-specific IgG, IgM, IgA, and IgE antibodies, and the levels

of total serum IgM and IgG; lumbar puncture including analysis of CSF for cells, glucose, protein, *Toxoplasma*-specific IgG and IgM antibodies, and level of total IgG; and testing of CSF for *T. gondii* by PCR and inoculation into mice. Presence of *Toxoplasma*-specific IgM in CSF that is not contaminated with blood or confirmation of local antibody production of *Toxoplasma*-specific IgG antibody in CSF establishes the diagnosis of congenital *Toxoplasma* infection.

Many manifestations of congenital toxoplasmosis are similar to findings that occur in other perinatal infections, especially congenital cytomegalovirus infection. Thus, neither cerebral calcification nor chorioretinitis is pathognomonic. The clinical picture in the newborn infant may also be compatible with sepsis, aseptic meningitis, syphilis, or hemolytic disease. Some children younger than 5 yr of age with chorioretinitis have postnatally acquired *T. gondii* infection.

TREATMENT

Pyrimethamine and sulfadiazine act synergistically against *Toxoplasma,* and combination therapy is indicated for many of the forms of toxoplasmosis. Use of pyrimethamine is contraindicated during the 1st trimester of pregnancy. Spiramycin should be used to attempt to prevent vertical transmission of infection to the fetus of acutely infected pregnant women. Pyrimethamine inhibits the enzyme dihydrofolate reductase, and thus the synthesis of folic acid, and therefore produces a dose-related, reversible, and usually gradual depression of the bone marrow. Neutropenia is most common but rarely treatment has been reported to result in thrombocytopenia and anemia. Reversible neutropenia is the most common adverse effect in treated infants. All patients treated with pyrimethamine should have platelet and leukocyte counts twice weekly. Seizures may occur with overdosage of pyrimethamine. Folinic acid, as calcium leucovorin, should always be administered concomitantly and for 1 wk after treatment with pyrimethamine is discontinued to prevent bone marrow suppression. Potential toxic effects of sulfonamides (e.g., crystalluria, hematuria, and rash) should be monitored. Hypersensitivity reactions occur, especially in patients with AIDS.

Acquired Toxoplasmosis

Patients with acquired toxoplasmosis and lymphadenopathy usually do not need specific treatment unless they have severe and persistent symptoms or evidence of damage to vital organs (see Table 290-2). If such signs and symptoms occur, treatment with pyrimethamine, sulfadiazine, and leucovorin should be initiated. Patients who appear to be immunocompetent but have severe and persistent symptoms or damage to vital organs (e.g., chorioretinitis, myocarditis) need specific therapy until these specific symptoms resolve, followed by therapy for an additional 2 wk. Therapy often is administered for at least 4-6 wk. The optimal duration of therapy is unknown. A loading dose of pyrimethamine for older children is 2 mg/kg/day divided bid (maximum: 50 mg/bid), given for the 1st 2 days of treatment. The maintenance dose begins on the 3rd day and is 1 mg/kg/day (maximum: 50 mg/day). Sulfadiazine is administered at a dosage of 100 mg/kg/day divided bid (maximum: 4 g/day). Leucovorin is administered orally at a dosage of 5-20 mg 3 times a week (or even daily depending on the leukocyte count).

Ocular Toxoplasmosis

Patients with active ocular toxoplasmosis are treated with pyrimethamine, sulfadiazine, and leucovorin (see Table 290-2). They are treated while disease is active and then for approximately 1 wk after the lesion has developed a quiescent appearance (i.e., sharp borders, pigmentation at margins of the lesion, and resolution of associated inflammatory cells in the vitreous), which usually occurs in 2-4 wk when treatment is initiated promptly. Within 7-10 days the borders of the retinal lesions sharpen, and visual acuity usually returns to that noted before development of the acute lesion. Systemic corticosteroids have been administered concomitantly with antimicrobial treatment when lesions involve the macula, optic nerve head, or papillomacular bundle. Corticosteroids are never given alone and are begun after loading doses of pyrimethamine and sulfadiazine have been administered (2 days). With recurrences, new lesions often appear contiguous to old ones. Very rarely, vitrectomy and removal of the lens are needed to restore visual acuity. Suppressive treatment has prevented frequent recurrences of vision-threatening lesions.

Active choroidal neovascular membranes as a result of toxoplasmic chorioretinitis have been treated successfully in children with intravitreal injection of antibody to vascular endothelial growth factor in addition to oral anti-*Toxoplasma* medicines.

Immunocompromised Persons

Serologic evidence of acute infection in an immunocompromised patient, regardless of whether signs and symptoms of infection are present or tachyzoites are demonstrated in tissue, are indications for therapy similar to that described for immunocompetent persons with symptoms of organ injury (see Table 290-2). It is important to establish the diagnosis as rapidly as possible and institute treatment early. In immunocompromised patients other than those with AIDS, therapy should be continued for at least 4-6 wk beyond complete resolution of all signs and symptoms of active disease and resolution of cause for immune suppression. Careful follow-up observation of these patients is imperative because relapse may occur, requiring prompt reinstitution of therapy. Relapse used to be frequent in patients with AIDS without antiretroviral treatment, and suppressive therapy with pyrimethamine and sulfonamides, or trimethoprim-sulfamethoxazole, was continued for life. Now it is possible to discontinue maintenance therapy when the CD4 count remains at >200 cells/μL for 4 mo and all lesions have resolved. Therapy usually induces a beneficial response clinically, but it does not eradicate cysts. Treatment of *T. gondii*–seropositive patients with AIDS should be continued as long as CD4 counts remain at <200 cells/μL. Prophylactic treatment with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia significantly reduces the incidence of toxoplasmosis in patients with AIDS.

Congenital Toxoplasmosis

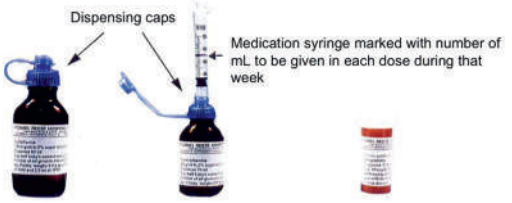
All fetuses and newborns infected with *T. gondii* should be treated whether or not they have clinical manifestations of the infection because treatment may be effective in interrupting acute disease that damages vital organs (see Table 290-2 and Fig. 290-5). The fetus is treated by treating the pregnant woman with pyrimethamine and sulfadiazine (with leucovorin). Infants should be treated for 1 yr with pyrimethamine (2 mg/kg/day divided bid for 2 days, then beginning on the 3rd day, 1 mg/kg/day for 2 or 6 mo, and then 1 mg/kg given on Monday, Wednesday, and Friday, PO), sulfadiazine (100 mg/kg/day divided bid PO), and leucovorin (5-10 mg given on Monday, Wednesday, and Friday, or more often depending on neutrophil count, PO). The relative efficacy in reducing sequelae of infection and the safety of treatment with 2 vs 6 mo of the higher dosage of pyrimethamine are being compared in the U.S. National Collaborative Study. Updated information about this study and these regimens is available from Dr. Rima McLeod (773-834-4131). Pyrimethamine and sulfadiazine are available only in tablet form and can be prepared as suspensions. Prednisone (1 mg/kg/day divided bid PO) has been used in addition when active chorioretinitis involves the macula or otherwise threatens vision or the CSF protein is >1,000 mg/dL at birth, but the efficacy is not established. Prednisone is continued only for as long as the active inflammatory process in the posterior pole of the eye is vision threatening or CSF protein is >1,000 mg/dL and then tapered rapidly if the duration of treatment has been brief.

Pregnant Women with *Toxoplasma gondii* Infection

The immunologically normal pregnant woman who acquired *T. gondii* more than 6 mo before conception does not need treatment to prevent congenital infection of her fetus. Although data are not available to allow for a definitive time interval, if infection occurs during or shortly before the pregnancy, it is reasonable to evaluate the fetus by use of PCR with amniotic fluid and ultrasonography and treat to prevent congenital infection in the fetus (see Table 290-2).

Treatment of a pregnant woman who acquires infection at any time during pregnancy reduces the chance of congenital infection in her

Oral Suspension Formulations	
Sulfadiazine 100mg/mL suspension 1. Crush ten 500mg sulfadiazine tablets in a mortar to a fine powder 2. Add enough sterile water to make a smooth paste 3. Slowly triturate syrup vehicle close to 50mL final volume 4. Transfer mixture to an amber bottle 5. Add enough syrup vehicle to q.s. to 50mL final volume 6. Shake very well. 7. Label and give a 7 day expiration 8. Store refrigerated	**Pyrimethamine** 2mg/mL suspension 1. Crush four 25mg pyrimethamine tablets in a mortar to a fine powder 2. Add 10cc of syrup vehicle 3. Transfer mixture to an amber bottle 4. Rinse motor with 10cc sterile water and transfer to bottle 5. Add enough syrup vehicle to q.s. to 50mL final volume 6. Shake very well. 7. Label and give 7 day expiration 8. Store refrigerated



Medication:	Sulfadiazine	Pyrimethamine	Folinic acid (calcium leukovorin)
Concentration:	100mg/mL	2mg/mL	5mg tablets
Dispense:	50mL*	25mL*	30 tablets
Dosage:	Half of infant's current weight in kg equals number of mL given in AM and PM†	Half of infant's current weight in kg equals number of mL given once daily‡§	10mg (two 5mg tablets) on Monday, Wednesday, and Friday. Crush and give with formula, water, milk, or juice in one dosage. May adjust based on neutrophil count.

* Suspended in 2% sugar solution. Suspension at usual concentration must be made each week. Store refrigerated.
† e.g. If infant weighs 5kg, give 2.5mL at 7AM and 7 PM.
‡ e.g. If infant weighs 5kg, give 2.5mL daily.
§ *For pyrimethamine*, first loading dose is 1mg/kg given BID for 2 days. Beginning third day, dose is 1mg/kg per day.

Figure 290-5 Compounding and administration of medications to treat congenital toxoplasmosis in infants. *(Adapted from Remington JS, McLeod R, et al: Toxoplasmosis. In Remington JS, Klein JO, editors:* Infectious diseases of the fetus and newborn infant, *ed 6, Philadelphia, 2006, WB Saunders; and McAuley J, Boyer K, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial,* Clin Infect Dis *18:38–72, 1994.)*

infant. Spiramycin (1 g every 8 hr PO without food) is recommended for prevention of fetal infection if the mother develops acute toxoplasmosis during pregnancy. Spiramycin is available in the United States upon an "emergency use" request by a physician through the FDA Division of Anti-Infective Drugs (301-796-1400) after the diagnosis of acute infection is confirmed in a reference laboratory (Palo Alto Medical Facility Toxoplasma Serology Lab 650-853-4828). With this approval, the physician can then contact the spiramycin manufacturer, Sanofi Pasteur (1-800-822-2463), to obtain spiramycin for the patient. Adverse reactions are infrequent and include paresthesia, rash, nausea, vomiting, and diarrhea. Following a loading dose of pyrimethamine (50 mg divided bid) for 2 days, beginning on the 3rd day, pyrimethamine is administered at a dose of 50 mg once daily. Beginning on the 1st day of treatment with pyrimethamine, sulfadiazine (1.5-2.0 g bid PO), and leucovorin (10 mg once daily PO) are recommended for treatment of the pregnant woman whose fetus has confirmed or probable fetal infection except in the 1st trimester. In the 1st trimester, when there is definite infection, sulfadiazine alone is recommended because pyrimethamine is potentially teratogenic at that time. Spiramycin treatment is used for infection acquired early in gestation when it is uncertain whether there is fetal infection. Treatment of the mother of an infected fetus with pyrimethamine and sulfadiazine reduces infection in the placenta and the severity of disease in the newborn. Delay in maternal treatment during gestation results in greater brain and eye disease in the infant. Diagnostic amniocentesis should be performed at >17-18 wk of gestation in pregnancies when there is high suspicion of fetal infection. Overall sensitivity of PCR for amniotic fluid is at 85% between 17 and 21 wk of gestation. The sensitivity of PCR using amniotic fluid for diagnosis of fetal infection is 92% in early and late gestation when amniotic fluid is tested for presence of the 529 bp, 300 copy gene. After 24 wk gestation, incidence of transmission is relatively high and pregnant women who are infected acutely after that time are treated with pyrimethamine and sulfadiazine to treat the fetus.

The approach in France to congenital toxoplasmosis includes systematic serologic screening of all women of childbearing age and again intrapartum each month during gestation beginning at ≤11 wk gestational age, at birth, and 1 mo after birth. Mothers with acute infection early in gestation and without evidence of involvement of the fetus are treated with spiramycin, which decreases the transmission. Ultrasonography and amniocentesis for PCR at approximately 18 wk of gestation are used for fetal diagnosis and have 97% sensitivity and 100% specificity. Confidence intervals for sensitivity are largest early and late in gestation. Fetal infection is treated with pyrimethamine and sulfadiazine. Termination of pregnancy is very rare at present. Prompt initiation of treatment with pyrimethamine and sulfadiazine during pregnancy usually has an excellent outcome, with normal development of children. Only 19% have subtle findings of congenital infection, including intracranial calcifications (13%) and chorioretinal scars (6%), although 39% have chorioretinal scars detected at follow-up observation during later childhood. Several studies have demonstrated improved outcomes with shorter times between diagnosis and initiation of treatment.

Chronically infected pregnant women who are immunocompromised have transmitted *T. gondii* to their fetuses. Such women should be treated with spiramycin throughout gestation. The optimal management for prevention of congenital toxoplasmosis in the fetus of a pregnant woman with HIV infection with a CD4 count <200 cells/μL and inactive *T. gondii* infection is unknown. If the pregnancy is not terminated, some investigators suggest that the mother should be treated with spiramycin during the 1st 14 wk of gestation and thereafter with pyrimethamine and sulfadiazine until term. There are no universally accepted guidelines at present. In a study of adult patients with AIDS and toxoplasmic encephalitis, pyrimethamine (75 mg once daily PO) combined with high dosages of intravenously administered clindamycin (1,200 mg every 6 hr IV) appeared equal in efficacy to sulfadiazine and pyrimethamine in the treatment of the toxoplasmic encephalitis. Other experimental agents include the macrolides clarithromycin and azithromycin.

PROGNOSIS

Early institution of specific treatment for congenitally infected infants usually cures the active manifestations of toxoplasmosis, including active chorioretinitis, meningitis, encephalitis, hepatitis, splenomegaly, and thrombocytopenia. Rarely, hydrocephalus resulting from aqueductal obstruction may develop or become worse during therapy. Treatment appears to reduce the incidence of some sequelae such as diminished cognitive and abnormal motor function. Without therapy and in some treated patients as well, chorioretinitis often recurs. Children with extensive involvement at birth may function normally later in life or have mild to severe impairment of vision, hearing, cognitive

function, and other neurologic functions. Delays in diagnosis and therapy, perinatal hypoglycemia, hypoxia, hypotension, repeated shunt infections, and severe visual impairment are associated with a poorer prognosis. The prognosis is not necessarily poor for infected babies. It should be understood, however, that treatment with pyrimethamine and sulfadiazine does not eradicate encysted parasites.

Studies in Lyon and Paris, France, demonstrated that outcome of treated fetal toxoplasmosis, even when infection is acquired early in gestation, is usually favorable if no hydrocephalus is detected on ultrasound, and treatment with pyrimethamine and sulfadiazine is initiated promptly. The SYROCOT (Systematic Review on Congenital Toxoplasmosis) study in Europe indicated that neurologic outcome is improved with shorter times between diagnosis and initiation of treatment of fetal toxoplasmosis. Work in Lyon, France, has indicated a low incidence of recurrent eye disease in children with congenital toxoplasmosis who had been treated in utero and in their 1st yr of life. The National Collaborative Chicago-Based Congenital Toxoplasmosis Study (NCCCTS) (1981-2004) in the United States found that neurologic, developmental, audiologic, and ophthalmologic outcomes are considerably better for most, but not all, children who were treated in their 1st yr of life with pyrimethamine and sulfadiazine (with leucovorin) when compared to children who had not been treated or were treated for only 1 mo in earlier decades described in the literature. The mean age of the children in this study was 10.8 yr at the time of this analysis, when most of the children had not yet entered their teenage years. Recurrent disease, if it occurs, appears most commonly during adolescence.

PREVENTION

Counseling pregnant women about the methods of preventing transmission of *T. gondii* (see Fig. 290-1) during pregnancy can reduce acquisition of infection during gestation. Women who do not have specific antibody to *T. gondii* before pregnancy should only eat well-cooked meat during pregnancy and avoid contact with oocysts excreted by cats. Cats that are kept indoors, maintained on prepared food, and not fed fresh, uncooked meat should not contact encysted *T. gondii* or shed oocysts. Serologic screening, ultrasound monitoring, and treatment of pregnant women during gestation can also reduce the incidence and manifestations of congenital toxoplasmosis. No protective vaccine is available.

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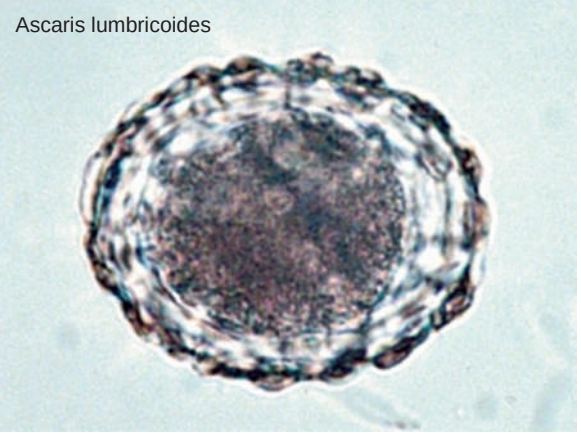

Figure 291-1 Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

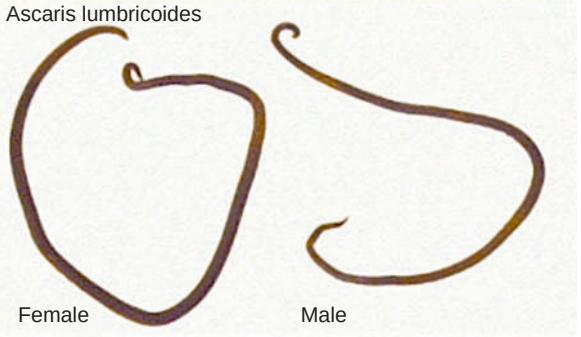

Figure 291-2 Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

Section 16

Helminthic Diseases

Chapter 291

Ascariasis (*Ascaris lumbricoides*)

Arlene E. Dent and James W. Kazura

ETIOLOGY

Ascariasis is caused by the nematode, or roundworm, *Ascaris lumbricoides.* Adult worms of *A. lumbricoides* inhabit the lumen of the small intestine and have a life span of 10-24 mo. The reproductive potential of *Ascaris* is prodigious; a gravid female worm produces 200,000 eggs per day. The fertile ova are oval in shape with a thick mammillated covering measuring 45-70 µm in length and 35-50 µm in breadth (Fig. 291-1). After passage in the feces, the eggs embryonate and become infective in 5-10 days under favorable environmental conditions. Adult worms can live for 12-18 mo (Fig. 291-2).

EPIDEMIOLOGY

Ascariasis occurs globally and is the most prevalent human helminthiasis in the world. It is most common in tropical areas of the world where environmental conditions are optimal for maturation of ova in the soil. Approximately 1 billion persons are estimated to be infected. Although the number of cases in the United States is not known precisely, the highest prevalence is thought to be in high poverty areas of the South and Appalachia. Pig farming in Maine is also associated with *Ascaris* species. Key factors linked with a higher prevalence of infection include poor socioeconomic conditions, use of human feces as fertilizer, and geophagia. Even though infection can occur at any age, the highest rate is in preschool or early school-age children. Transmission is primarily hand to mouth, but may also involve ingestion of contaminated raw fruits and vegetables. Transmission is enhanced by the high output of eggs by fecund female worms and resistance of ova to the outside environment. *Ascaris* eggs can remain viable at 5-10°C (41-50°F) for as long as 2 yr.

PATHOGENESIS

Ascaris ova hatch in the small intestine after ingestion by the human host. Larvae are released, penetrate the intestinal wall, and migrate to

the lungs by way of the venous circulation. The parasites then cause **pulmonary ascariasis** as they enter into the alveoli and migrate through the bronchi and trachea. They are subsequently swallowed and return to the intestines, where they mature into adult worms. Female *Ascaris* begin depositing eggs in 8-10 wk.

CLINICAL MANIFESTATIONS

The clinical presentation depends on the intensity of infection and the organs involved. Most individuals have low to moderate worm burdens and have no symptoms or signs. The most common clinical problems are from **pulmonary disease** and **obstruction of the intestinal or biliary tract**. Larvae migrating through these tissues may cause allergic symptoms, fever, urticaria, and granulomatous disease. The pulmonary manifestations resemble Loeffler syndrome and include transient respiratory symptoms such as cough and dyspnea, pulmonary infiltrates, and blood eosinophilia. Larvae may be observed in the sputum. Vague abdominal complaints have been attributed to the presence of adult worms in the small intestine, although the precise contribution of the parasite to these symptoms is difficult to ascertain. A more serious complication occurs when a large mass of worms leads to acute bowel obstruction. Children with heavy infections may present with vomiting, abdominal distention, and cramps. In some cases, worms may be passed in the vomitus or stools. *Ascaris* worms occasionally migrate into the biliary and pancreatic ducts, where they cause cholecystitis or pancreatitis. Worm migration through the intestinal wall can lead to peritonitis. Dead worms can serve as a nidus for stone formation. Studies show that chronic infection with *A. lumbricoides* (often coincident with other helminth infections) impairs growth, physical fitness, and cognitive development.

DIAGNOSIS

Microscopic examination of fecal smears can be used for diagnosis because of the high number of eggs excreted by adult female worms (see Fig. 291-1). A high index of suspicion in the appropriate clinical context is needed to diagnose pulmonary ascariasis or obstruction of the gastrointestinal tract. Ultrasound examination of the abdomen is capable of visualizing intraluminal adult worms.

TREATMENT

Although several chemotherapeutic agents are effective against ascariasis, none has documented utility during the pulmonary phase of infection. Treatment options for gastrointestinal ascariasis include albendazole (400 mg PO once, for all ages), mebendazole (100 mg PO bid for 3 days or 500 mg once for all ages), or ivermectin (150-200 μg/kg PO once). Piperazine citrate (75 mg/kg/day for 2 days; maximum: 3.5 g/day), which causes neuromuscular paralysis of the parasite and rapid expulsion of the worms, is the treatment of choice for intestinal or biliary obstruction and is administered as syrup through a nasogastric tube. Surgery may be required for cases with severe obstruction. Nitazoxanide (100 mg PO bid for 3 days for children 1-3 yr of age, 200 mg bid for 3 days for children 4-11 yr, and 500 mg bid for 3 days for adolescents and adults) produces cure rates comparable to single-dose albendazole. Drug resistance has not been reported, but repeated treatment for ascariasis may be necessary because reinfection is common.

PREVENTION

Although ascariasis is the most prevalent worm infection in the world, little attention has been given to its control. Anthelmintic chemotherapy programs can be implemented in 1 of 3 ways: (1) offering universal treatment to all individuals in an area of high endemicity; (2) offering treatment targeted to groups with high frequency of infection, such as children attending primary school; or (3) offering individual treatment based on intensity of current or past infection. Improving education about and practices of sanitary conditions and sewage facilities, discontinuing the practice of using human feces as fertilizer, and education are the most effective long-term preventive measures.

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Chapter 292

Hookworms (*Necator americanus* and *Ancylostoma* Spp.)

Peter J. Hotez

ETIOLOGY

Two major genera of hookworms, which are nematodes or roundworms, infect humans. *Necator americanus,* the only representative of its genus, is a major anthropophilic hookworm and is the most common cause of human hookworm infection. Hookworms of the genus *Ancylostoma* include the anthropophilic hookworm *Ancylostoma duodenale* that also causes classic hookworm infection and the less common zoonotic species *Ancylostoma ceylanicum, Ancylostoma caninum,* and *Ancylostoma braziliense.* Human zoonotic infection with the dog hookworm *A. caninum* is associated with an eosinophilic enteritis syndrome. The larval stage of *A. braziliense,* whose definitive hosts include dogs and cats, is the principal cause of cutaneous larva migrans.

The infective larval stages of the anthropophilic hookworms live in a developmentally arrested state in warm, moist soil. Larvae infect humans either by penetrating through the skin (*N. americanus* and *A. duodenale*) or when they are ingested *(A. duodenale).* Larvae entering the human host by skin penetration undergo **extraintestinal migration** through the venous circulation and lungs before they are swallowed, whereas orally ingested larvae may undergo extraintestinal migration or remain in the gastrointestinal tract. Larvae returning to the small intestine undergo 2 molts to become adult, sexually mature, male and female worms ranging in length from 5-13 mm. The buccal capsule of the adult hookworm is armed with cutting plates *(N. americanus)* or teeth *(A. duodenale)* to facilitate attachment to the mucosa and submucosa of the small intestine. Hookworms can remain in the intestine for 1-5 yr, where they mate and produce eggs. Although up to 2 mo is required for the larval stages of hookworms to undergo extraintestinal migration and develop into mature adults, *A. duodenale* larvae may remain developmentally arrested for many months before resuming development in the intestine. Mature *A. duodenale* female worms produce about 30,000 eggs per day; daily egg production by *N. americanus* is <10,000/day (Fig. 292-1). The eggs are thin shelled and ovoid, measuring approximately 40-60 μm. Eggs that are deposited on soil with adequate moisture and shade develop into first-stage larvae and hatch. Over the ensuing several days and under appropriate conditions, the larvae molt twice to the infective stage. Infective larvae are developmentally arrested and nonfeeding. They migrate vertically in the soil until they either infect a new host or exhaust their lipid metabolic reserves and die.

EPIDEMIOLOGY

Hookworm infection is one of the most prevalent infectious diseases of humans, affecting an estimated 600-700 million individuals worldwide. New information from the Global Burden of Disease 2010 Study indicates that hookworm infection leads all neglected tropical diseases in years lost through disability. In the case of hookworm infection, all of the years lost through disability are attributed to anemia from intestinal blood loss.

Because of the requirement for adequate soil moisture, shade, and warmth, hookworm infection is usually confined to rural areas, especially where human feces are used for fertilizer or where sanitation is inadequate. Hookworm is an infection associated with economic underdevelopment and poverty throughout the tropics and subtropics. Sub-Saharan Africa, East Asia, and tropical regions of the Americas

Figure 292-1 Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367: 1521–1532, 2006.)*

Figure 292-2 Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

have the highest prevalence of hookworm infection. High rates of infection are often associated with cultivation of certain agricultural products such as tea in India; sweet potato, corn, cotton, and mulberry trees in China; coffee in Central and South America; and rubber in Africa. It is not uncommon to find dual *N. americanus* and *A. duodenale* infections. *N. americanus* predominates in Central and South America as well as in southern China and southeast Asia, whereas *A. duodenale* predominates in North Africa, in northern India, in China north of the Yangtze River, and among aboriginal people in Australia. The ability of *A. duodenale* to withstand somewhat harsher environmental and climatic conditions may reflect its ability to undergo arrested development in human tissues. *A. ceylanicum* infection occurs in India and Southeast Asia.

Eosinophilic enteritis caused by *A. caninum* was first described in Queensland, Australia, with 2 reported cases in the United States. Because of its global distribution in dogs, it was initially anticipated that human *A. caninum* infections would be identified in many locales, but this has not been found.

PATHOGENESIS

The major morbidity of human hookworm infection is a direct result of intestinal blood loss. Adult hookworms adhere tenaciously to the mucosa and submucosa of the proximal small intestine by using their cutting plates or teeth and a muscular esophagus that creates negative pressure in their buccal capsules. At the attachment site, host inflammation is downregulated by the release of antiinflammatory polypeptides by the hookworm. Rupture of capillaries in the lamina propria is followed by blood extravasation, with some of the blood ingested directly by the hookworm. After ingestion, the blood is anticoagulated, the red blood cells are lysed, and the hemoglobin released and digested. Each adult *A. duodenale* hookworm causes loss of an estimated 0.2 mL of blood/day; blood loss is less for *N. americanus.* Individuals with light infections suffer from very little blood loss and, consequently, may have hookworm infection but not hookworm disease. There is a direct correlation between the number of adult hookworms in the gut and the volume of fecal blood loss. Hookworm disease results only when individuals with moderate and heavy infections experience sufficient blood loss to develop iron deficiency and anemia. Hypoalbuminemia and consequent edema and anasarca from the loss of intravascular oncotic pressure can also occur. These features depend heavily on the dietary reserves of the host.

CLINICAL MANIFESTATIONS

Chronically infected children with moderate and heavy hookworm infections suffer from intestinal blood loss that results in **iron deficiency** and can lead to **anemia** as well as protein malnutrition. Prolonged iron deficiency associated with hookworms in childhood can lead to physical growth retardation and cognitive and intellectual deficits.

Anthropophilic hookworm larvae elicit dermatitis sometimes referred to as **ground itch** when they penetrate human skin. The vesiculation and edema of ground itch are exacerbated by repeated infection. Infection with a zoonotic hookworm, especially *A. braziliense,* can result in lateral migration of the larvae to cause the characteristic cutaneous tracts of **cutaneous larva migrans** (see Chapter 292.1). Cough subsequently occurs in *A. duodenale* and *N. americanus* hookworm infection when larvae migrate through the lungs to cause laryngotracheobronchitis, usually about 1 wk after exposure. Pharyngitis also can occur. The onset of eosinophilia coincides with the entry of hookworm larvae into the gastrointestinal tract. Upper abdominal pain can occur during this period, but it eventually subsides.

Chronic intestinal hookworm infection is not typically associated with specific gastrointestinal complaints, although pain, anorexia, and diarrhea have been attributed to the presence of hookworms. The major clinical manifestations are related to intestinal blood loss. Heavily infected children exhibit all of the signs and symptoms of iron deficiency anemia and protein malnutrition. In some cases, children with chronic hookworm disease acquire a yellow-green pallor known as **chlorosis.**

An infantile form of ancylostomiasis resulting from heavy *A. duodenale* infection has been described. Affected infants experience diarrhea, melena, failure to thrive, and profound anemia. Infantile ancylostomiasis has significant mortality.

Eosinophilic enteritis caused by *A. caninum* is associated with colicky abdominal pain that begins in the epigastrium and radiates outward and is usually exacerbated by food. Extreme cases may mimic acute appendicitis.

DIAGNOSIS

Children with hookworm release eggs that can be detected by direct fecal examination (Fig. 292-2). Quantitative methods are available to determine whether a child has a heavy worm burden that can cause hookworm disease. The eggs of *N. americanus* and *A. duodenale* are morphologically indistinguishable. Species identification typically requires egg hatching and differentiation of third-stage infective larvae; newer methods using polymerase chain reaction methods have been developed but are not generally used in clinical practice.

In contrast, eggs are generally not present in the feces of patients with eosinophilic enteritis caused by *A. caninum.* Eosinophilic enteritis is often diagnosed by demonstrating ileal and colonic ulcerations by colonoscopy in the presence of significant blood eosinophilia. An adult canine hookworm may occasionally be recovered during colonoscopic biopsy. Patients with this syndrome develop immunoglobulin G and immunoglobulin E serologic responses.

TREATMENT

The goal of **deworming** is removal of the adult hookworms with an anthelmintic drug. The benzimidazole anthelmintics, mebendazole and albendazole, are effective at eliminating hookworms from the

intestine, although multiple doses are sometimes required. Albendazole (400 mg PO once, for all ages) usually achieves high cure rates, although *N. americanus* adult hookworms are sometimes more refractory and require additional doses. Mebendazole (100 mg bid PO for 3 days, for all ages) is also effective. In many developing countries, mebendazole is administered as a single dose of 500 mg; however, the cure rates with this regimen can be as low as 10% or less. According to the World Health Organization, children should be encouraged to chew tablets of albendazole or mebendazole because forcing very young children to swallow large tablets may cause choking or asphyxiation. Mebendazole is recommended for *A. caninum*–associated eosinophilic enteritis, although recurrences are common. Because the benzimidazoles have been reported to be embryotoxic and teratogenic in laboratory animals, their safety during pregnancy and in young children is a potential concern and the risks vs benefits must be carefully considered. The World Health Organization currently support the use of benzimidazoles in infected children ≥1 yr of age but at a reduced dose (200 mg for albendazole) in the youngest age group (1-2 yr old). Pyrantel pamoate (11 mg/kg PO once daily for 3 days; maximum dose: 1 g) is available in liquid form and is an effective alternative to the benzimidazoles. Replacement therapy with oral iron is not usually required to correct hookworm-associated iron deficiency in children.

PREVENTION

In 2001, the World Health Assembly urged its member states to implement programs of periodic deworming so as to control the morbidity of hookworm and other soil-transmitted helminth infections. Although anthelmintic drugs are effective at eliminating hookworms from the intestine, the high rates of drug failure from single-dose mebendazole and posttreatment reinfection among children suggest that mass drug administration alone is not effective for controlling hookworm in highly endemic areas. Moreover, data suggest that the efficacy of mebendazole decreases with frequent, periodic use, leading to concerns about the possible emergence of anthelmintic drug resistance. To reduce the reliance exclusively on anthelmintic drugs, a recombinant human hookworm vaccine has been developed and is undergoing clinical testing. Economic development and associated improvements in sanitation, health education, and avoidance of human feces as fertilizer remain critical for reducing hookworm transmission and endemicity.

Bibliography is available at Expert Consult.

292.1 Cutaneous Larva Migrans

Peter J. Hotez

ETIOLOGY

Cutaneous larva migrans **(creeping eruption)** is caused by the larvae of several nematodes, primarily hookworms, which are not usually parasitic for humans. *A. braziliense,* a hookworm of dogs and cats, is the most common cause, but other animal hookworms may also produce the disease.

EPIDEMIOLOGY

Cutaneous larva migrans is usually caused by *A. braziliense,* which is endemic to the southeastern United States and Puerto Rico. Travelers account for a significant percentage of the cases.

CLINICAL MANIFESTATIONS

After penetrating the skin, larvae localize at the epidermal-dermal junction and migrate in this plane, moving at a rate of 1-2 cm/day. The response to the parasite is characterized by raised, erythematous, serpiginous tracks, which occasionally form bullae (Fig. 292-3). These lesions may be single or numerous and are usually localized to an extremity, although any area of the body may be affected. As the organism migrates, new areas of involvement may appear every few days. Intense localized pruritus, without any systemic symptoms, may be associated with the lesions. Bacterial superinfection can occur.

Figure 292-3 Creeping eruption of cutaneous larva migrans. *(From Korting GW:* Hautkrankheiten bei kindern und jugendlichen, *Stuttgart, Germany, 1969, FK Schattauer Verlag.)*

DIAGNOSIS

Cutaneous larva migrans is diagnosed by clinical examination of the skin. Patients are often able to recall the exact time and location of exposure, because the larvae produce intense itching at the site of penetration. Eosinophilia may occur but is uncommon.

TREATMENT

If left untreated, the larvae die, and the syndrome resolves within a few weeks to several months. Treatment with ivermectin (200 μg/kg daily PO for 1-2 days; considered the drug of choice by some investigators), albendazole (400 mg daily PO for 3 days, for all ages), or topical thiabendazole hastens resolution, if symptoms warrant treatment. Nausea and vomiting frequently preclude repeated administration of oral thiabendazole. The safety of ivermectin in young children (weighing <15 kg) and pregnant women remains to be established. Ivermectin should be taken on an empty stomach with water, whereas albendazole should be taken with a fatty meal.

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Chapter 293

Trichuriasis *(Trichuris trichiura)*

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ETIOLOGY

Trichuriasis is caused by the **whipworm,** *Trichuris trichiura,* a nematode, or roundworm, that inhabits the cecum and ascending colon. The principal hosts of *T. trichiura* are humans who acquire infection by ingesting embryonated, barrel-shaped eggs (Fig. 293-1). The larvae escape from the shell in the upper small intestine and penetrate the intestinal villi. The worms slowly move toward the cecum, where the

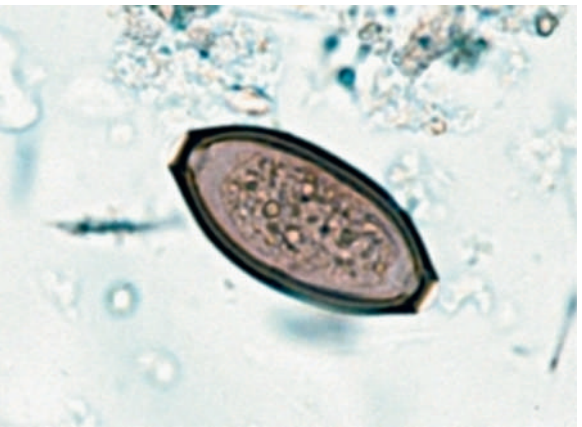

Figure 293-1 *Trichuris trichiura.* Soil-transmitted helminth eggs. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367: 1521–1532, 2006.)*

Figure 293-2 *Trichuris trichiura.* Adult male and female soil-transmitted helminths. *(From Bethony J, Brooker S, Albonico M, et al: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm,* Lancet *367:1521–1532, 2006.)*

anterior three quarters whiplike portion remains within the superficial mucosa and the short posterior end is free in the lumen (Fig. 293-2). In 1-3 mo, the adult female worm begins producing 5,000-20,000 eggs per day. After excretion in the feces, embryonic development occurs in 2-4 wk with optimal temperature and soil conditions. The adult worm life span is approximately 2 yr.

EPIDEMIOLOGY

Trichuriasis occurs throughout the world and is especially common in poor rural communities with inadequate sanitary facilities and soil contaminated with human or animal feces. Trichuriasis is one of the most prevalent human helminthiases, with an estimated 1 billion infected individuals worldwide. In many parts of the world, where protein-energy malnutrition and anemia are common, the prevalence of *T. trichiura* infection can be as high as 95%. Although trichuriasis occurs in the rural southeastern United States, its prevalence has not been reported. The highest rate of infection occurs among children 5-15 yr of age. Infection develops after ingesting embryonated ova by direct contamination of hands, food (raw fruits and vegetables fertilized with human feces), or drink. Transmission can also occur indirectly through flies or other insects.

CLINICAL MANIFESTATIONS

Most persons harbor low worm burdens and do not have symptoms. Some individuals may have a history of right-lower-quadrant or vague periumbilical pain. Adult *Trichuris* suck approximately 0.005 mL of blood per worm per day. Children, who are most likely to be heavily infected, frequently suffer from disease. Clinical manifestations include chronic dysentery, rectal prolapse, anemia, poor growth, as well as developmental and cognitive deficits. There is no significant eosinophilia, even though a portion of the worm is embedded in the mucosa of the large bowel.

DIAGNOSIS

Because egg output is so high, fecal smears frequently reveal the characteristic barrel-shaped ova of *T. trichiura.*

TREATMENT

Albendazole (400 mg PO for 3 days for all ages) is the drug of choice and is safe and effective, in part because it is poorly absorbed from the gastrointestinal tract. It reduces egg output by 90-99% and has cure rates of 70-90%, although reinfection and resumption of egg production by live worms that presumably survive after treatment may occur. Alternatives include mebendazole (100 mg PO bid for 3 days) and ivermectin (200 μg/kg PO for 3 days). Single-day treatment with albendazole, nitazoxanide, or albendazole plus nitazoxanide lead to cure rates that are low and short-lived. Combination treatment with oxantel pamoate (20 mg/kg) plus 400 mg albendazole on consecutive days may have the highest cure rate.

PREVENTION

Disease can be prevented by personal hygiene, improved sanitary conditions, and eliminating the use of human feces as fertilizer.

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Chapter 294

Enterobiasis *(Enterobius vermicularis)*

Arlene E. Dent and James W. Kazura

ETIOLOGY

The cause of enterobiasis, or **pinworm** infection, is *Enterobius vermicularis,* which is a small (1 cm in length), white, threadlike nematode, or roundworm, that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon. Gravid females migrate at night to the perianal and perineal regions, where they deposit up to 15,000 eggs. Ova are convex on 1 side and flattened on the other and have diameters of approximately 30×60 µm. Eggs embryonate within 6 hr and remain viable for 20 days. Human infection occurs by the fecal-oral route typically by ingestion of embryonated eggs that are carried on fingernails, clothing, bedding, or house dust. After ingestion, the larvae mature to form adult worms in 36-53 days.

EPIDEMIOLOGY

Enterobiasis infection occurs in individuals of all ages and socioeconomic levels. It is prevalent in regions with temperate climates and is the most common helminth infection in the United States. It infects 30% of children worldwide, and humans are the only known host. Infection occurs primarily in institutional or family settings that include children. The prevalence of pinworm infection is highest in children 5-14 yr of age. It is common in areas where children live, play, and sleep close together, thus facilitating egg transmission. Because the life span of the adult worm is short, chronic parasitism is likely due to repeated cycles of reinfection. Autoinoculation can occur in individuals who habitually put their fingers in their mouth.

Figure 294-1 Eggs of *Enterobius vermicularis*. *(From Guerrant RL, Walker DH, Weller PF, et al:* Tropical infectious diseases, *Philadelphia, 2006, Churchill Livingstone, p. 1248.)*

PATHOGENESIS

Enterobius infection may cause symptoms by mechanical stimulation and irritation, allergic reactions, and migration of the worms to anatomic sites where they become pathogenic. *Enterobius* infection has been associated with concomitant *Dientamoeba fragilis* infection, which causes diarrhea.

CLINICAL MANIFESTATIONS

Pinworm infection is innocuous and rarely causes serious medical problems. The most common complaints include itching and restless sleep secondary to nocturnal perianal or perineal pruritus**.** The precise cause and incidence of pruritus are unknown but may be related to the intensity of infection, psychologic profile of the infected individual and his or her family, or allergic reactions to the parasite. Eosinophilia is not observed in most cases, because tissue invasion does not occur. Aberrant migration to ectopic sites occasionally may lead to appendicitis, chronic salpingitis, pelvic inflammatory disease, peritonitis, hepatitis, and ulcerative lesions in the large or small bowel.

DIAGNOSIS

A history of nocturnal perianal pruritus in children strongly suggests enterobiasis. Definitive diagnosis is established by identification of parasite eggs or worms. Microscopic examination of adhesive cellophane tape pressed against the perianal region early in the morning frequently demonstrates eggs (Fig. 294-1). Repeated examinations increase the chance of detecting ova; a single examination detects 50% of infections, 3 examinations 90%, and 5 examinations 99%. Worms seen in the perianal region should be removed and preserved in 75% ethyl alcohol until microscopic examination can be performed. Digital rectal examination may also be used to obtain samples for a wet mount. Routine stool samples rarely demonstrate *Enterobius* ova.

TREATMENT

Anthelmintic drugs should be administered to infected individuals and their family members. Albendazole (400 mg PO with a repeat dose 2 wk later for all age groups) is the treatment of choice and results in cure rates exceeding 90%. Alternatives include mebendazole (100 mg PO with a repeat dose 2 wk later) and pyrantel pamoate (11 mg/kg base PO 3 times for 1 day up to a maximum of 1 g; repeat at 2 wk). Morning bathing removes a large portion of eggs. Frequent changing of underclothes, bed clothes, and bed sheets decreases environmental egg contamination and may decrease the risk for autoinfection.

PREVENTION

Household contacts can be treated at the same time as the infected individual. Repeated treatments every 3-4 mo may be required in circumstances with repeated exposure, such as with institutionalized children. Good hand hygiene is the most effective method of prevention.

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Chapter 295

Strongyloidiasis (*Strongyloides stercoralis*)

Arlene E. Dent and James W. Kazura

ETIOLOGY

Strongyloidiasis is caused by the nematode, or roundworm, *Strongyloides stercoralis.* Only adult female worms inhabit the small intestine. The nematode reproduces in the human host by parthenogenesis and releases eggs containing mature larvae into the intestinal lumen. Rhabditiform larvae immediately emerge from the ova and are passed in feces, where they can be visualized by stool examination. Rhabditiform larvae either differentiate into free-living adult male and female worms or metamorphose into the infectious filariform larvae. Sexual reproduction occurs only in the free-living stage. Humans are usually infected through skin contact with soil contaminated with infectious larvae. Larvae penetrate the skin, enter the venous circulation and then pass to the lungs, break into alveolar spaces, and migrate up the bronchial tree. They are then swallowed and pass through the stomach, and adult female worms develop in the small intestine. Egg deposition begins approximately 28 days after initial infection.

The **hyperinfection syndrome** occurs when large numbers of larvae transform into infective organisms during their passage in feces and then reinfect (autoinfect) the host by way of the lower gastrointestinal tract or perianal region. This cycle may be accelerated in immunocompromised persons, particularly those with depressed T-cell function.

EPIDEMIOLOGY

S. stercoralis infection is prevalent in tropical and subtropical regions of the world and is endemic in several areas of Europe, the southern United States, and Puerto Rico. Transmission requires appropriate environmental conditions, particularly warm, moist soil. Poor sanitation and crowded living conditions are conducive to high levels of transmission. Dogs and cats can act as reservoirs. The highest prevalence of infection in the United States (4% of the general population) is in impoverished rural areas of Kentucky and Tennessee. Infection may be especially common among residents of mental institutions, veterans who were prisoners of war in areas of high endemicity, and refugees and immigrants. Because of internal autoinfection, individuals may remain infected for decades. Infection may be transmitted by organ transplantation. Individuals with hematologic malignancies, autoimmune diseases, malnutrition, and drug-induced immunosuppression (especially corticosteroids) are at high risk for the **hyperinfection syndrome**. Patients with AIDS may experience a rapid course of disseminated strongyloidiasis with a fatal outcome.

PATHOGENESIS

The initial host immune response to infection is production of immunoglobulin E and eosinophilia in blood and tissues, which presumably prevents dissemination and hyperinfection in the immunocompetent host. Adult female worms in otherwise healthy and asymptomatic individuals may persist in the gastrointestinal tract for years. If infected persons become immunocompromised, the reduction in cellular and humoral immunity may lead to an abrupt and dramatic increase in parasite load with systemic dissemination.

CLINICAL MANIFESTATIONS

Approximately 30% of infected individuals are asymptomatic. The remaining patients have symptoms that correlate with the 3 stages of infection: invasion of the skin, migration of larvae through the lungs, and parasitism of the small intestine by adult worms. **Larva currens** is

the manifestation of an allergic reaction to filariform larvae that migrate through the skin, where they leave pruritic, tortuous, urticarial tracks. The lesions may recur and are typically found over the lower abdominal wall, buttocks, or thighs, resulting from larval migration from defecated stool. Pulmonary disease secondary to larval migration through the lung rarely occurs and may resemble **Loeffler syndrome** (cough, wheezing, shortness of breath, transient pulmonary infiltrates accompanied by eosinophilia). Gastrointestinal strongyloidiasis is characterized by indigestion, crampy abdominal pain, vomiting, diarrhea, steatorrhea, protein-losing enteropathy, protein-caloric malnutrition, and weight loss. Edema of the duodenum with irregular mucosal folds, ulcerations, and strictures can be seen radiographically. Infection may be chronic in nature and is associated with **eosinophilia.**

Strongyloidiasis is potentially lethal because of the ability of the parasite to replicate within the host and cause overwhelming hyperinfection in immunocompromised persons. The **hyperinfection syndrome** is characterized by an exaggeration of the clinical features that develop in symptomatic immunocompetent individuals. The onset is usually sudden, with generalized abdominal pain, distention, and fever. Multiple organs can be affected as massive numbers of larvae disseminate throughout the body and introduce bowel flora. The latter may result in bacteremia and septicemia. Cutaneous manifestations may include petechiae and purpura. Cough, wheezing, and hemoptysis are indicative of pulmonary involvement. Whereas eosinophilia is a prominent feature of strongyloidiasis in immunocompetent persons, this sign may be absent in immunocompromised persons. Because of the low incidence of strongyloidiasis in industrialized countries, it is often misdiagnosed, resulting in a significant delay in treatment.

DIAGNOSIS

Intestinal strongyloidiasis is diagnosed by examining feces or duodenal fluid for the characteristic larvae (Fig. 295-1). Several stool samples should be examined either by direct smear, the Koga agar plate method, or the Baermann test. Alternatively, duodenal fluid can be sampled by the **enteric string test** (Entero-Test) or aspiration via endoscopy. In children with the hyperinfection syndrome, larvae may be found in sputum, gastric aspirates, and, rarely, in small intestinal biopsy specimens. An enzyme-linked immunosorbent assay for immunoglobulin G antibody to *Strongyloides* may be more sensitive than parasitologic methods for diagnosing intestinal infection in the immunocompetent host. The utility of the assay in diagnosing infection in immunocompromised subjects with the hyperinfection syndrome has not been determined. Eosinophilia is common.

TREATMENT

Treatment is directed at eradication of infection. Ivermectin (200 μg/kg/day once daily PO for 2 days) is the drug of choice for uncomplicated strongyloidiasis. Alternatively, albendazole (400 mg PO twice daily for 7 days) may be used. Patients with the hyperinfection syndrome should be treated with ivermectin for 7-10 days and may require repeated courses. Reducing the dose of immunosuppressive therapy and treatment of concomitant bacterial infections are essential in the management of the hyperinfection syndrome. Close follow-up with repeated stool examination is necessary to ensure complete elimination of the parasite. *Strongyloides* antibodies decrease within 6 mo after successful treatment.

PREVENTION

Sanitary practices designed to prevent soil and person-to-person transmission are the most effective control measures. Wearing shoes is a main preventive strategy. Reduction in transmission in institutional settings can be achieved by decreasing fecal contamination of the environment such as by the use of clean bedding. Because infection is uncommon in most settings, case detection and treatment are advisable. Individuals who will be given prolonged high-dose corticosteroids, immunosuppressive drugs before organ transplantation, or cancer chemotherapy should have a screening examination for *S. stercoralis*. If infected, they should be treated before immunosuppression is initiated.

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Figure 295-1 Larvae of intestinal strongyloidiasis.

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Chapter 296

Lymphatic Filariasis (*Brugia malayi, Brugia timori,* and *Wuchereria bancrofti*)

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ETIOLOGY

The filarial worms *Brugia malayi* **(Malayan filariasis),** *Brugia timori,* and *Wuchereria bancrofti* **(bancroftian filariasis)** are threadlike nematodes that cause similar infections. Infective larvae are introduced into humans during blood feeding by the mosquito vector. Over a period of 4-6 mo, the larval forms develop into sexually mature adult worms. Once an adequate number of male and female worms accumulate in the afferent lymphatic vessels, adult female worms release large numbers of microfilariae that circulate in the bloodstream. The life cycle of the parasite is completed when mosquitoes ingest microfilariae

in a blood meal, which molt to form infective larvae over a period of 10-14 days. Adult worms have a 5-7 yr life span.

EPIDEMIOLOGY

More than 120 million people living in tropical Africa, Asia, and Latin America are infected; approximately 10-20% of these individuals have clinically significant morbidity attributable to filariasis. *W. bancrofti* is transmitted in Africa, Asia, and Latin America and accounts for 90% of lymphatic filariasis. *B. malayi* is restricted to the South Pacific and Southeast Asia, and *B. timori* is restricted to several islands of Indonesia. Travelers from nonendemic areas of the world who spend brief periods of time in endemic areas are rarely infected. Global elimination has been targeted for 2020.

CLINICAL MANIFESTATIONS

The clinical manifestations of *B. malayi, B. timori,* and *W. bancrofti* infection are similar; manifestations of acute infection include transient, recurrent lymphadenitis and lymphangitis. The early signs and symptoms include episodic fever, lymphangitis of an extremity, lymphadenitis (especially the inguinal and axillary areas), headaches, and myalgias that last a few days to several weeks. These symptoms are caused by an acute inflammatory response triggered by death of adult worms. Initial damage to lymphatic vessels may remain subclinical for years. The syndrome is most frequently observed in persons 10-20 yr of age. Manifestations of chronic lymphatic filariasis occur mostly in adults 30 yr of age or older and result from anatomic and functional obstruction to lymph flow. This obstruction results in lymphedema of the legs, arms, breasts, and/or genitalia. Male genital involvement, such as hydrocele, is very common in *W. bancrofti* infection, but uncommon in *Brugia* species infection. Chronic lymphedema predisposes affected extremities to bacterial superinfections, sclerosis, and verrucous skin changes, resulting in elephantiasis, which may involve 1 or more limbs, the breasts, or genitalia. It is uncommon for children to have overt signs of chronic filariasis.

Tropical Pulmonary Eosinophilia

The presence of microfilariae in the body has no apparent pathologic consequences except in persons with tropical pulmonary eosinophilia, a syndrome of filarial etiology in which microfilariae are found in the lungs and lymph nodes but not the bloodstream. It occurs only in individuals who have lived for years in endemic areas. Men 20-30 yr of age are most likely to be affected, although the syndrome occasionally occurs in children. The presentation includes paroxysmal nocturnal cough with dyspnea, fever, weight loss, and fatigue. Rales and rhonchi are found on auscultation of the chest. The x-ray findings may occasionally be normal, but increased bronchovascular markings, discrete opacities in the middle and basal regions of the lung, or diffuse miliary lesions are usually present (Fig. 296-1). Recurrent episodes may result in interstitial fibrosis and chronic respiratory insufficiency in untreated individuals. Hepatosplenomegaly and generalized lymphadenopathy are often seen in children. The diagnosis is suggested by residence in a filarial endemic area, eosinophilia (>2,000/μL), compatible clinical symptoms, increased serum immunoglobulin E (>1,000 IU/mL), and high titers of antimicrofilarial antibodies in the absence of microfilaremia. Although microfilariae may be found in sections of lung or lymph node, biopsy of these tissues is unwarranted in most situations. The clinical response to diethylcarbamazine (2 mg/kg/dose tid PO for 12-21 days) is the final criterion for diagnosis; the majority of patients improve with this therapy. If symptoms recur, a second course of the anthelmintic should be administered. Patients with chronic symptoms are less likely to show improvement than those who have been ill for a short time.

DIAGNOSIS

Demonstration of microfilariae in the blood is the primary means for confirming the diagnosis of lymphatic filariasis. Because microfilaremia is **nocturnal** in most cases, blood samples should be obtained between 10 PM and 2 AM Anticoagulated blood is passed through a Nuclepore filter that is stained and examined microscopically for microfilariae. Adult worms or microfilariae can be identified in tissue specimens obtained at biopsy. Infection with *W. bancrofti* in the absence of bloodborne microfilariae may be diagnosed by detection of parasite antigen in the serum. Adult worms in lymphatic vessels can be visualized by ultrasonography.

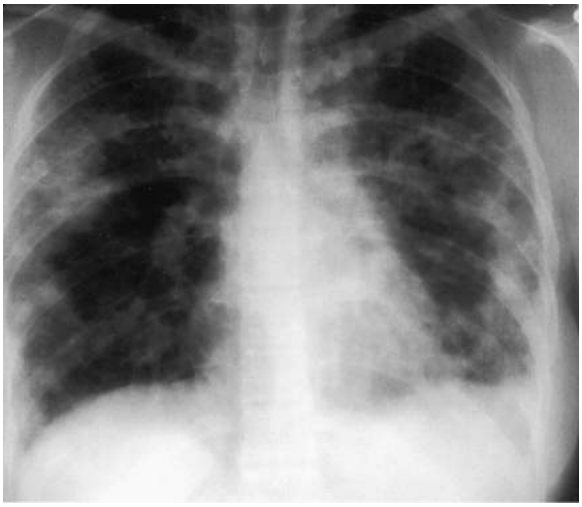

Figure 296-1 Chest radiograph of a woman with tropical pulmonary eosinophilia. Reticulonodular opacities are scattered throughout both lungs. *(From Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *vol 2, ed 6, Philadelphia, 2006, Elsevier, p. 3274.)*

TREATMENT

The use of antifilarial drugs in the management of acute lymphadenitis and lymphangitis is controversial. No controlled studies demonstrate that administration of drugs such as diethylcarbamazine modifies the course of acute lymphangitis. Diethylcarbamazine may be given to asymptomatic microfilaremic persons to lower the intensity of parasitemia. The drug also kills a proportion of the adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypotension, and even death may occur, especially with high microfilarial levels, the dose of diethylcarbamazine should be increased gradually (children: 1 mg/kg PO as a single dose on day 1, 1 mg/kg tid PO on day 2, 1-2 mg/kg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4-14; adults: 50 mg PO on day 1, 50 mg tid PO on day 2, 100 mg tid PO on day 3, and 6 mg/kg/day divided tid PO on days 4-14). For patients with no microfilaria in the blood, the full dose (6 mg/kg/day divided tid PO) can be given beginning on day 1. Repeat doses may be necessary to further reduce the microfilaremia and kill lymph-dwelling adult parasites. *W. bancrofti* is more sensitive than *B. malayi* to diethylcarbamazine.

Global programs to control and ultimately eradicate lymphatic filariasis from endemic populations currently recommend a single annual dose of diethylcarbamazine (6 mg/kg PO once) in combination with albendazole (400 mg PO once) for 5 yr (mass drug administration). In coendemic areas of filariasis and onchocerciasis, mass drug applications with single-dose ivermectin (150 μg/kg PO once) and albendazole are used because of severe adverse reactions with diethylcarbamazine in onchocerciasis-infected individuals. Five years of annual mass treatment is thought to be necessary to stop transmission. Adjuvant medicines (e.g., doxycycline) that target endosymbiont bacteria *(Wolbachia)* in filarial parasites may accelerate eradication.

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Chapter 297

Other Tissue Nematodes

Arlene E. Dent and James W. Kazura

ONCHOCERCIASIS *(ONCHOCERCA VOLVULUS)*

Infection with *Onchocerca volvulus* leads to onchocerciasis or **river blindness.** Onchocerciasis occurs primarily in West Africa but also in Central and East Africa and is the world's second leading infectious cause of blindness. There have been scattered foci in Central and South America, but the infection is now thought to be eliminated in the Americas with the exception of isolated populations living in the border area of Venezuela and Brazil. *O. volvulus* larvae are transmitted to humans by way of the bite of *Simulium* black flies that breed in fast-flowing streams. The larvae penetrate the skin and migrate through the connective tissue and eventually develop into adult worms that can be found tangled in fibrous tissue. Adult worms can live in the human body for up to 14 yr. Female worms produce large numbers of microfilariae that migrate through the skin, connective tissue, and eye. Most infected individuals are asymptomatic. In heavily infected subjects, clinical manifestations are a result of localized host inflammatory reactions to dead or dying microfilariae and subcutaneous adult worms surrounded by a palpable fibrous capsule. Cutaneous and ocular reactions to microfilaria produce pruritic dermatitis, punctate keratitis, corneal pannus formation, and chorioretinitis. Adult worms in **subcutaneous nodules** are not painful and tend to occur over bony prominences of the hip. The **diagnosis** can be established by obtaining snips of skin covering the scapulae, iliac crests, buttocks, or calves. The snips are immersed in saline for several hours and examined microscopically for microfilariae that have emerged into the fluid. The diagnosis can also be established by demonstrating microfilariae in the cornea or anterior chamber on slit-lamp examination or finding adult worms on a nodule biopsy specimen. Ophthalmology consultation should be obtained before treatment of eye lesions. A single dose of ivermectin (150 μg/kg PO) is the drug of choice and clears *O. volvulus* microfilariae from the skin for several months but has no effect on the adult worm. Treatment with ivermectin should be repeated every 6-12 mo until the patient is asymptomatic or has no evidence of eye infection. Adverse effects of ivermectin therapy include fever, urticaria, and pruritus, which are more frequent in individuals not born in endemic areas who acquired the infection following periods of intense exposure, such as Peace Corps volunteers. Patients with concurrent high-density microfilaremia from loiasis may develop encephalopathy with ivermectin therapy. Treatment with ivermectin should be withheld until *Loa loa* microfilaremia can be reduced by cytapheresis or the use of doxycycline, which kills endosymbiont bacteria *(Wolbachia)* of *O. volvulus*. Personal protection includes avoiding areas where biting flies are numerous, wearing protective clothing, and using insect repellent. Programs of mass treatment with ivermectin have been implemented in Africa in an effort to reduce the prevalence of onchocerciasis.

Although an etiologic link has not been established, epidemiologic studies have reported an association between onchocerciasis and a nodding syndrome of children living in focal areas of Uganda, Tanzania and South Sudan. The syndrome is characterized by the head dropping forward, convulsions, and periods of staring. A meta-analysis suggests an association between *O. volvulus* infection and epilepsy.

LOIASIS *(LOA LOA)*

Loiasis is caused by infection with the tissue nematode *Loa loa.* The parasite is transmitted to humans via diurnally biting flies *(Chrysops)* that live in the rain forests of West and Central Africa. Migration of adult worms through skin, subcutaneous tissue, and subconjunctival area can lead to transient episodes of pruritus, erythema, and localized edema known as **Calabar swellings,** which are nonerythematous areas of subcutaneous edema 10-20 cm in diameter typically found around joints such as the wrist or the knee (Fig. 297-1). They resolve over several days to wk and may recur at the same or different sites. Lifelong residents of *L. loa* endemic regions may have microfilaremia and eosinophilia but are often asymptomatic. In contrast, travelers to endemic regions may have a hyperreactive response to *L. loa* infection characterized by frequent recurrences of swelling, high level eosinophilia, debilitation, and serious complications such as glomerulonephritis and encephalitis. Diagnosis is usually established on clinical grounds, often assisted by the infected individual reporting a worm being seen crossing the conjunctivae. Microfilariae may be detected in blood smears collected between 10 AM and 2 PM. Adult worms should be surgically excised when possible. Diethylcarbamazine is the agent of choice for eradication of microfilaremia, but the drug does not kill adult worms. Because treatment-associated complications such as pruritus, fever, generalized body pain, hypertension, and even death may occur, especially with high microfilaria levels, the dose of diethylcarbamazine should be increased gradually in such cases (children: 1 mg/kg PO on day 1, 1 mg/kg tid on day 2, 1-2 mg/kg tid on day 3, 6 mg/kg in 3 doses on days 4-21; adults: 50 mg PO on day 1, 50 mg tid on day 2, 100 mg tid on day 3, 6 mg/kg in 3 doses on days 4-21). Full doses can be instituted on day 1 in persons without microfilaremia (9 mg/kg/day PO divided tid for 12 days). A single dose of ivermectin (150 μg/kg) decreases microfilarial densities in the blood in persons with high density microfilaremia. A 3 wk course of albendazole can also be used to slowly reduce *L. loa* microfilarial levels as a result of embryotoxic effects on the adult worms. Antihistamines or corticosteroids may be used to limit allergic reactions secondary to killing of microfilariae. Personal protective measures include avoiding areas where biting flies are present, wearing protective clothing, and using insect repellents. Diethylcarbamazine (300 mg PO once weekly) prevents infection in travelers who spend prolonged periods of time in endemic areas. *L. loa* do not harbor *Wolbachia* endosymbionts, and therefore doxycycline has no effect on infection.

Figure 297-1 Calabar swelling of the right hand. *(From Guerrant RL, Walker DH, Weller PF, et al:* Tropical infectious diseases, *Philadelphia, 2006, Churchill Livingstone, p. 1165.)*

INFECTION WITH ANIMAL FILARIAE

The most commonly recognized zoonotic filarial infections are caused by members of the genus *Dirofilaria.* The worms are introduced into humans by the bites of mosquitoes containing third-stage larvae. The most common filarial zoonosis in the United States is *Dirofilaria tenuis,* a parasite of raccoons. In Europe, Africa, and Southeast Asia, infections are most commonly caused by the dog parasite *Dirofilaria repens.* The **dog heartworm,** *Dirofilaria immitis,* is the second most commonly

encountered filarial zoonosis worldwide. Other genera, including *Dipetalonema*-like worms, *Onchocerca,* and *Brugia,* are rare causes of zoonotic filarial infections.

Animal filariae do not undergo normal development in the human host. The clinical manifestations and pathologic findings correspond to the anatomic site of infection and can be categorized into 4 major groups: subcutaneous, lung, eye, and lymphatic. Pathologic examination of affected tissue reveals a localized foreign-body reaction around a dead or dying parasite. The lesion consists of granulomas with eosinophils, neutrophils, and tissue necrosis. *D. tenuis* does not leave the subcutaneous tissues, whereas *Brugia beaveri* eventually localizes to superficial lymph nodes. Infections may be present for up to several months. *D. immitis* larvae migrate for several months in subcutaneous tissues and most frequently result in a well-circumscribed coinlike lesion in a single lobe of the lung. The chest x-ray typically reveals a solitary pulmonary nodule 1-3 cm in diameter. Definitive diagnosis and cure depend on surgical excision and identification of the nematode within the surrounding granulomatous response. *D. tenuis* and *B. beaveri* infections present as painful 1-5 cm rubbery nodules in the skin of the trunk, of the extremities, and around the orbit. Patients often report having been engaged in activities predisposing to exposure to infected mosquitoes, such as working or hunting in swampy areas. Diagnosis and management is by surgical excision.

ANGIOSTRONGYLUS CANTONENSIS

Angiostrongylus cantonensis, the **rat lungworm,** is the most common cause of eosinophilic meningitis worldwide. Rats are the definitive host. Human infection follows ingestion of third-stage larvae in raw or undercooked intermediate hosts such as snails and slugs, or transport hosts such as freshwater prawns, frogs, and fish. Most cases are sporadic, but clusters have been reported, including clusters related to consumption of lettuce contaminated with intermediate or transport hosts. Even though most infections have been described in Southeast Asia, the South Pacific, and Taiwan, shipboard travel of infected rats has spread the parasite to Madagascar, Africa, the Caribbean, and, most recently, Australia and North America. Larvae penetrate the vasculature of the intestinal tract and migrate to the meninges, where they usually die but induce eosinophilic aseptic meningitis. Patients present 2-35 days after ingestion of larvae with severe headache, neck pain or nuchal rigidity, hyperesthesias and paresthesias (often migrating), fatigue, fever, rash, pruritus, nausea, and vomiting. Neurologic involvement varies from asymptomatic to paresthesias, severe pain, weakness, and focal neurologic findings such as cranial nerve palsies. Symptoms can last for several weeks to months, especially headache. Coma and death from hydrocephalus occur rarely in heavy infections. Peripheral blood eosinophilia is not always present on initial examination but peaks about 5 wk after exposure, often when symptoms are improving. Cerebrospinal fluid analysis reveals pleocytosis with >10% eosinophils in more than half of patients, with mildly elevated protein, a normal glucose level, and an elevated opening pressure. Head CT or MRI is usually unremarkable. The diagnosis is established clinically with supporting travel and diet history. A sensitive and specific enzyme-linked immunosorbent assay is available on a limited basis from the Centers for Disease Control and Prevention for testing either cerebrospinal fluid or serum. Treatment is primarily supportive because the majority of infections are mild and most patients recover within 2 mo without neurologic sequelae. Analgesics should be given for headache. Careful, repeated lumbar punctures should be performed to relieve hydrocephalus. Anthelmintic drugs have not been shown to influence the outcome and may exacerbate neurologic symptoms. The use of corticosteroids may shorten the duration of persistent and severe headaches. There is a higher incidence of permanent neurologic sequelae and mortality among children than among adults. Infection can be avoided by not eating raw or undercooked crabs, prawns, or snails.

ANGIOSTRONGYLUS COSTARICENSIS

Angiostrongylus costaricensis is a nematode that infects several species of rodents and causes abdominal angiostrongyliasis, which has been described predominantly in Latin America and the Caribbean. The mode of transmission to humans, who are accidental hosts, is unknown. It is speculated that infectious larvae from a molluscan intermediate host, such as the slug *Vaginulus plebeius,* contaminate water or vegetation that is inadvertently consumed (chopped up in salads or on vegetation contaminated with the slug's mucus secretions). Although this slug is not indigenous to the continental United States, it has been found on imported flowers and produce. The incubation period for abdominal angiostrongyliasis is unknown, but limited data suggest that it ranges from 2 wk to several months after ingestion of larvae. Third-stage larvae migrate from the gastrointestinal tract to the mesenteric arteries, where they mature into adults. These eggs degenerate and elicit an eosinophilic granulomatous reaction. The clinical findings of abdominal angiostrongyliasis **mimic appendicitis,** although the former are typically more indolent. Children can have fever, right lower quadrant pain, a tumor-like mass, abdominal rigidity, and a painful rectal examination. Most patients have leukocytosis with eosinophilia. Radiologic examination may show bowel wall edema, spasticity, or filling defects in the ileocecal region and the ascending colon. Examination of stool for ova and parasites is not useful for *A. costaricensis* but is useful for evaluating the presence of other intestinal parasites. An enzyme-linked immunosorbent assay is available for diagnosis on a limited basis from the Centers for Disease Control and Prevention, but the test has a low specificity and is known to cross react with *Toxocara, Strongyloides,* and *Paragonimus.* Many patients undergo laparotomy for suspected appendicitis and are found to have a mass in the terminal ileum to the ascending colon. No specific treatment is known for abdominal angiostrongyliasis. Even though the use of anthelmintic therapy has not been studied systematically, thiabendazole or diethylcarbamazine has been suggested. The prognosis is generally good. Most cases are self-limited, although surgery may be required in some patients. Cornerstones of prevention include avoidance of slugs and not ingesting raw food and water that may be contaminated with imperceptible slugs or slime from slugs. Rat control is also important in preventing the spread of infection.

DRACUNCULIASIS *(DRACUNCULUS MEDINENSIS)*

Dracunculiasis is caused by the guinea worm, *Dracunculus medinensis.* The World Health Organization has targeted dracunculiasis for eradication. As of 2012, the transmission of the infection was confined to Chad, Ethiopia, Mali, and South Sudan. Humans become infected by **drinking contaminated stagnant water** that contains immature forms of the parasite in the gut of tiny crustaceans (copepods or water fleas). Larvae are released in the stomach, penetrate the mucosa, mature, and mate. Approximately 1 yr later, the adult female worm (1-2 mm in diameter and up to 1 m long) migrates and partially emerges through the human host skin, usually of the legs. Thousands of immature larvae are released when the affected body part is immersed in the water. The cycle is completed when larval forms are ingested by the crustaceans. Infected humans have no symptoms until the worm reaches the subcutaneous tissue, causing a **stinging papule** that may be accompanied by urticaria, nausea, vomiting, diarrhea, and dyspnea. The lesion vesiculates, ruptures, and forms a painful ulcer in which a portion of the worm is visible. Diagnosis is established clinically. Larvae can be identified by microscopic examination of the discharge fluid. Metronidazole (25 mg/kg/day PO divided into 3 doses for 10 days; maximum dose: 750 mg) decreases local inflammation. Although the drug does not kill the worm, it facilitates its removal. The worm must be physically removed by rolling the slowly emerging 1 m long parasite onto a thin stick over a week. Topical corticosteroids shorten the time to complete healing while topical antibiotics decrease the risk of secondary bacterial infection. Dracunculiasis can be prevented by boiling or chlorinating drinking water or passing the water through a cloth sieve before consumption. Eradication is dependent on behavior modification and education.

GNATHOSTOMA SPINIGERUM

Gnathostoma spinigerum is a dog and cat nematode endemic to Southeast Asia, Japan, China, Bangladesh, and India, but has been identified

in Mexico and parts of South America. Infection is acquired by ingesting intermediate hosts containing larvae of the parasite such as raw or undercooked freshwater fish, chickens, pigs, snails, or frogs. Penetration of the skin by larval forms and prenatal transmission has also been described. Nonspecific signs and symptoms such as generalized malaise, fever, urticaria, anorexia, nausea, vomiting, diarrhea, and epigastric pain develop 24-48 hr after ingestion of *G. spinigerum*. Ingested larvae penetrate the gastric wall and migrate through soft tissue for up to 10 yr. Moderate to severe eosinophilia can develop. Cutaneous gnathostomiasis manifests as intermittent episodes of localized, migratory nonpitting edema associated with pain, pruritus, or erythema. Central nervous system involvement in gnathostomiasis is suggested by focal neurologic findings, initially neuralgia followed within a few days by paralysis or changes in mental status. Multiple cranial nerves may be involved, and the cerebrospinal fluid may be xanthochromic but typically shows an eosinophilic pleocytosis. Diagnosis of gnathostomiasis is based on clinical presentation and epidemiologic background. Brain and spinal cord lesions may be seen on CT or MRI. Serologic testing varies in sensitivity and specificity and is available through the Centers for Disease Control and Prevention. There is no well-documented effective chemotherapy, although albendazole (400 mg PO bid for 21 days) as first-line therapy or ivermectin (200 μg/kg for 2 days) as an alternative is recommended without or with surgical removal. Multiple courses may be needed. Corticosteroids have been used to relieve focal neurologic deficits. Surgical resection of the *Gnathostoma* is the major mode of therapy and the treatment of choice. Blind surgical resection of subcutaneous areas of diffuse swelling is not recommended because the worm can rarely be located. Prevention through the avoidance of ingestion of poorly cooked or raw fish, poultry, or pork should be emphasized for individuals living in or visiting endemic areas.

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Chapter 298

Toxocariasis (Visceral and Ocular Larva Migrans)

Arlene E. Dent and James W. Kazura

ETIOLOGY

Most cases of human toxocariasis are caused by the **dog roundworm,** *Toxocara canis.* Adult female *T. canis* worms live in the intestinal tracts of young puppies and their lactating mothers. Large numbers of eggs are passed in the feces of dogs and embryonate under optimal soil conditions. *Toxocara* eggs can survive relatively harsh environmental conditions and are resistant to freezing and extremes of moisture and pH. Humans ingest embryonated eggs contaminating soil, hands, or fomites. The larvae hatch and penetrate the intestinal wall and travel via the circulation to the liver, lung, and other tissues. Humans do not excrete *T. canis* eggs because the larvae are unable to complete their maturation to adult worms in the intestine. The **cat roundworm,** *Toxocara cati,* is responsible for far fewer cases of visceral larva migrans (VLM) than *T. canis.* Ingestion of infective larvae of the raccoon ascarid *Baylisascaris procyonis* rarely leads to VLM but can cause neural larva migrans resulting in fatal eosinophilic meningitis. Ingestion of larvae from the opossum ascarid *Lagochilascaris minor* leads to VLM rarely.

EPIDEMIOLOGY

Human *T. canis* infections have been reported in nearly all parts of the world, primarily in temperate and tropical areas where dogs are popular household pets. Young children are at highest risk because of their unsanitary play habits and tendency to place fingers in the mouth. Other behavioral risk factors include pica, contact with puppy litters, and institutionalization. In North America, the highest prevalences of infection are in the southeastern United States and Puerto Rico, particularly among socially disadvantaged African-American and Hispanic children. In the United States, serosurveys show that 4.6-7.3% of children are infected. Assuming an unrestrained and untreated dog population, toxocariasis is prevalent in settings where other geohelminth infections, such as ascariasis, trichuriasis, and hookworm infections, are common.

PATHOGENESIS

T. canis larvae secrete large amounts of immunogenic glycosylated proteins. These antigens induce immune responses that lead to eosinophilia and polyclonal and antigen-specific immunoglobulin E production. The characteristic histopathologic lesions are granulomas containing eosinophils, multinucleated giant cells (histiocytes), and collagen. Granulomas are typically found in the liver but may also occur in the lungs, central nervous system, and ocular tissues. Clinical manifestations reflect the intensity and chronicity of infection, anatomic localization of larvae, and host granulomatous responses.

CLINICAL MANIFESTATIONS

There are 3 major clinical syndromes associated with human toxocariasis: VLM, ocular larva migrans (OLM), and covert toxocariasis (Table 298-1). The classic presentation of VLM includes eosinophilia, fever, and hepatomegaly, and occurs most commonly in toddlers with a history of pica and exposure to puppies. The findings include fever, cough, wheezing, bronchopneumonia, anemia, hepatomegaly, leukocytosis, eosinophilia, and positive *Toxocara* serology. Cutaneous manifestations such as pruritus, eczema, and urticaria can be present. OLM tends to occur in older children without signs or symptoms of VLM. Presenting symptoms include unilateral visual loss, eye pain, white pupil, or strabismus that develops over a period of weeks. Granulomas occur on the posterior pole of the retina and may be mistaken for retinoblastoma. Serologic testing for *Toxocara* has allowed the identification of individuals with less obvious or covert symptoms of infection. These children may have nonspecific complaints that do not constitute a recognizable syndrome. Common findings include hepatomegaly, abdominal pain, cough, sleep disturbance, failure to thrive, and headache with elevated *Toxocara* antibody titers. Eosinophilia may be present in only 50-75% of cases. The prevalence of positive *Toxocara* serology in the general population supports the notion that most children with *T. canis* infection are asymptomatic and will not develop overt clinical sequelae over time. A correlation between positive *Toxocara* serology and allergic asthma has also been described.

DIAGNOSIS

A presumptive diagnosis can be established in a young child with **eosinophilia** (>20%), leukocytosis, hepatomegaly, fevers, wheezing, and a history of geophagia and exposure to puppies or unrestrained dogs. Supportive laboratory findings include hypergammaglobulinemia and elevated isohemagglutinin titers to A and B blood group antigens. Most patients with VLM have an absolute eosinophil count of >500/μL. Eosinophilia is less common in subjects with OLM. Biopsy confirms the diagnosis. When biopsies cannot be obtained, an enzyme-linked immunosorbent assay using excretory-secretory proteins harvested from *T. canis* larvae maintained in vitro is the standard serologic test used to confirm toxocariasis. A titer of 1:32 is associated with a sensitivity of approximately 78% and a specificity of approximately 92%. The sensitivity for OLM is significantly less. The diagnosis of OLM can be established in patients with typical clinical findings of a retinal or peripheral pole granuloma or endophthalmitis with elevated antibody titers. Vitreous and aqueous humor fluid anti-*Toxocara* titers are usually greater than serum titers. The diagnosis of covert toxocariasis should be considered in individuals with chronic weakness, abdominal pain, or allergic signs with eosinophilia and increased immunoglobulin E. In temperate regions of the world, nonparasitic causes of eosinophilia that should be considered in the differential diagnosis include allergies,

Table 298-1 Clinical Syndromes of Human Toxocariasis

SYNDROME	CLINICAL FINDINGS	AVERAGE AGE	INFECTIOUS DOSE	INCUBATION PERIOD	LABORATORY FINDINGS	ELISA
Visceral larva migrans	Fevers, hepatomegaly, asthma	5 yr	Moderate to high	Weeks to months	Eosinophilia, leukocytosis, elevated IgE	High (≥1:16)
Ocular larva migrans	Visual disturbances, retinal granulomas, endophthalmitis, peripheral granulomas	12 yr	Low	Months to years	Usually none	Low
Covert toxocariasis	Abdominal pain, gastrointestinal symptoms, weakness, hepatomegaly, pruritus, rash	School-age to adult	Low to moderate	Weeks to years	±Eosinophilia, ±elevated IgE	Low to moderate

ELISA, enzyme-linked immunosorbent assay; IgE, immunoglobulin E; ±, with or without.

Adapted from Liu LX: Toxocariasis and larva migrans syndrome. In Guerrant RL, Walker DH, Weller PF, editors: Tropical infectious diseases: principles, pathogens & practice, *Philadelphia, 2006, Churchill-Livingstone, p. 1209.*

drug hypersensitivity, lymphoma, vasculitis, and the idiopathic hypereosinophilic syndrome (see Chapter 129).

TREATMENT

Most cases do not require treatment because signs and symptoms are mild and subside over a period of weeks to months. Several anthelmintic drugs have been used for symptomatic cases, often with adjunctive corticosteroids to limit inflammatory responses that presumably result from release of *Toxocara* antigens by dying parasites. Albendazole (400 mg PO bid for 5 days for all ages) has demonstrated efficacy in both children and adults. Mebendazole (100-200 PO mg bid for 5 days for all ages) is also useful. Anthelmintic treatment of central nervous system and ocular disease should be extended (3-4 wk). Even though there are no clinical trials regarding therapy of OLM, a course of oral corticosteroids such as prednisone (1 mg/kg/day PO for 2-4 wk) has been recommended to suppress local inflammation while treatment with anthelmintic agents is initiated.

PREVENTION

Transmission can be minimized by public health measures that prevent dog feces from contaminating the environment. These include keeping dogs on leashes and excluding pets from playgrounds and sandboxes that toddlers use. Children should be discouraged from putting dirty fingers in their mouth and eating dirt. Vinyl covering of sandboxes reduces the viability of *T. canis* eggs. Widespread veterinary use of broad-spectrum anthelmintics effective against *Toxocara* may lead to a decline in parasite transmission to humans.

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Chapter 299

Trichinellosis *(Trichinella spiralis)*

Arlene E. Dent and James W. Kazura

ETIOLOGY

Human trichinellosis (also called trichinosis) is caused by consumption of meat containing encysted larvae of *Trichinella spiralis,* a tissue-dwelling nematode with a worldwide distribution. After ingestion of raw or inadequately cooked meat from pigs (or other commercial meat sources such as horses) containing viable *Trichinella* larvae, the organisms are released from the cyst by acid-pepsin digestion of the cyst walls in the stomach and then pass into the small intestine. The larvae invade the small intestine columnar epithelium at the villi base and develop into adult worms. The adult female worm produces about 500 larvae over 2 wk and is then expelled in the feces. The larvae enter the bloodstream and seed striated muscle by burrowing into individual muscle fibers. Over a period of 3 wk, they coil as they increase about 10 times in length and become capable of infecting a new host if ingested. The larvae eventually become encysted and can remain viable for years. Sylvatic *Trichinella* spp. (*T. brivoti, T. nativa, T. pseudospiralis,* and *T. murrelli*) present in traditional native foods such as walrus meat and game meat may also cause disease similar to that caused by *T. spiralis*.

EPIDEMIOLOGY

Despite public health efforts to control trichinellosis by eliminating the practice of feeding garbage to domestic swine, epidemics and isolated cases of *Trichinella* spp. infection continue to be a health problem in many areas of the world. It is most common in Asia, Latin America, and Central Europe. Swine fed with garbage may become infected when given uncooked trichinous scraps, usually pig meat, or when the carcasses of infected wild animals such as rats are eaten. Prevalence rates of *T. spiralis* in domestic swine range from 0.001% in the United States to ≥25% in China. The resurgence of this disease can be attributed to translocations of animal populations, human travel, and export of food as well as ingestion of sylvatic *Trichinella* (*T. brivoti, T. nativa, T. pseudospiralis,* and *T. murrelli*) through game meat. In the United States from 1997 to 2001, wild game meat (especially bear meat) was the most common source of infection. Most outbreaks occur from the consumption of *T. spiralis*–infected pork (or horse meat in areas of the world where horse is eaten) obtained from a single source.

PATHOGENESIS

During the 1st 2-3 wk after infection, pathologic reactions to infection are limited to the gastrointestinal tract and include a mild, partial villous atrophy with an inflammatory infiltrate of neutrophils, eosinophils, lymphocytes, and macrophages in the mucosa and submucosa. Larvae are released by female worms and disseminate over the next several weeks. Skeletal muscle fibers show the most striking changes with edema and basophilic degeneration. The muscle fiber may contain the typical coiled worm, the cyst wall derived from the host cell, and the surrounding lymphocytic and eosinophilic infiltrate.

CLINICAL MANIFESTATIONS

The development of symptoms depends on the number of viable larvae ingested. Most infections are asymptomatic or mild, and children often show milder symptoms than adults who consumed the same amount of infected meat. Watery diarrhea is the most common symptom corresponding to maturation of the adult worms in the gastrointestinal tract, which occurs during the 1st 1-2 wk after ingestion. Patients may also complain of abdominal discomfort and vomiting. Fulminant

enteritis may develop in individuals with extremely high worm burdens. The classic symptoms of facial and periorbital edema, fever, weakness, malaise, and myalgia peak approximately 2-3 wk after the infected meat is ingested as the larvae migrate and then encyst in the muscle. Headache, cough, dyspnea, dysphagia, subconjunctival and splinter hemorrhages, and a macular or petechial rash may occur. Patients with high-intensity infection may die from myocarditis, encephalitis, or pneumonia. In symptomatic patients, eosinophilia is common and may be dramatic.

DIAGNOSIS

The Centers for Disease Control and Prevention diagnostic criteria for trichinellosis require positive serology or muscle biopsy for *Trichinella* with 1 or more compatible clinical symptoms (eosinophilia, fever, myalgia, facial or periorbital edema). To declare a discrete outbreak, at least 1 person must have positive serology or muscle biopsy. Antibodies to *Trichinella* are detectable approximately 3 wk after infection. Severe muscle involvement results in elevated serum creatine phosphokinase and lactic dehydrogenase levels. Muscle biopsy is not usually necessary, but if needed, a sample should be obtained from a tender swollen muscle. A history of eating undercooked meat supports the diagnosis. The cysts may calcify and be visible by radiograph.

TREATMENT

Recommended treatment of trichinellosis diagnosed at the gastrointestinal phase is albendazole (400 mg PO bid for 8-10 days for all ages) to eradicate the adult worms if a patient has ingested contaminated meat within the previous 1 wk. An alternative regimen is mebendazole (200-400 mg PO tid for 3 days followed by 400-500 mg tid for 10 days). There is no consensus for treatment of muscle-stage trichinellosis. Corticosteroids may be used, although evidence for efficacy is anecdotal.

PREVENTION

Trichinella larvae can be killed by cooking meat (≥55°C [131°F]) until there is no trace of pink fluid or flesh, or by storage in a freezer (−15°C [5°F]) for ≥3 wk. Freezing to kill larvae should only be applied to pork meat, as larvae in horse, wild boar, or game meat can remain viable even after 4 wk of freezing. Smoking, salting, and drying meat are unreliable methods of killing *Trichinella.* Strict adherence to public health measures, including garbage feeding regulations, stringent rodent control, prevention of exposure of pigs and other livestock to animal carcasses; constructing barriers between livestock, wild animals, and domestic pets; and proper handling of wild animal carcasses by hunters, can reduce infection with *Trichinella.* Current meat inspection for trichinellosis is by direct digestion and visualization of encysted larvae in meat samples. Serologic testing does not have a role in meat inspection.

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Chapter 300

Schistosomiasis *(Schistosoma)*

Charles H. King and Amaya L. Bustinduy

The term *schistosomiasis* **(bilharzia)** encompasses the acute and chronic inflammatory disorders caused by human infection with *Schistosoma* spp. parasites. Disease is related to both the systemic and focal effects of schistosome infection and its consequent host immune responses triggered by parasite eggs deposited in the tissues. For the affected individuals, this frequently manifests as disabling chronic morbidity.

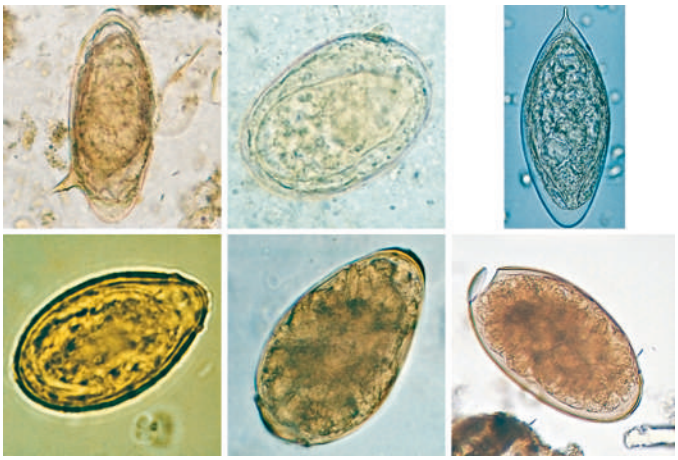

Figure 300-1 Eggs of common human trematodes. Clockwise from upper left: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma haematobium, Clonorchis sinensis, Paragonimus westermani*, and *Fasciola hepatica* (note the partially open operculum). *(From Centers for Disease Control and Prevention [CDC]:* DPDx: laboratory identification of parasites of public health concern. *Available at: http://www.cdc.gov/dpdx/az.html)*

ETIOLOGY

Schistosoma organisms are the trematodes, or flukes, that parasitize the bloodstream. Five schistosome species infect humans: *Schistosoma haematobium, S. mansoni, S. japonicum, S. intercalatum,* and *S. mekongi*. Humans are infected through contact with water contaminated with cercariae, the free-living infective stage of the parasite. These motile, forked-tail organisms emerge from infected snails and are capable of penetrating intact human skin. As they reach maturity, adult worms migrate to specific anatomic sites characteristic of each schistosome species: *S. haematobium* adults are found in the perivesical and periureteral venous plexus, *S. mansoni* in the inferior mesenteric veins, and *S. japonicum* in the superior mesenteric veins. *S. intercalatum* and *S. mekongi* are usually found in the mesenteric vessels. Adult schistosome worms (1-2 cm long) are clearly adapted for an intravascular existence. The female accompanies the male in a groove formed by the lateral edges of its body. On fertilization, female worms begin oviposition in the small venous tributaries. The eggs of the 3 main schistosome species have characteristic morphologic features: *S. haematobium* has a terminal spine, *S. mansoni* has a lateral spine, and *S. japonicum* has a smaller size with a short, curved spine (Fig. 300-1). Parasite eggs provoke a significant granulomatous inflammatory response, which allows them to ulcerate through host tissues to reach the lumen of the urinary tract or intestines. They are carried to the outside environment in urine or feces (depending on the species), where they will hatch if deposited in freshwater. Motile miracidia emerge, infect specific freshwater snail intermediate hosts, and divide asexually. After 4-12 wk, the infective cercariae are released by the snails into the contaminated water.

EPIDEMIOLOGY

Schistosomiasis infects more than 207 million people worldwide, primarily children and young adults. Prevalence is increasing in many areas as population density increases and new irrigation projects provide broader habitats for vector snails. Humans are the main definitive hosts for the 5 clinically important species of schistosomes, although *S. japonicum* is also a zoonosis, infecting animals such as dogs, rats, pigs, and cattle. *S. haematobium* is prevalent in Africa and the Middle East; *S. mansoni* is prevalent in Africa, the Middle East, the Caribbean, and South America; and *S. japonicum* is prevalent in China, the Philippines, and Indonesia, with some sporadic foci in parts of Southeast Asia. The other 2 species are less prevalent. *S. intercalatum*

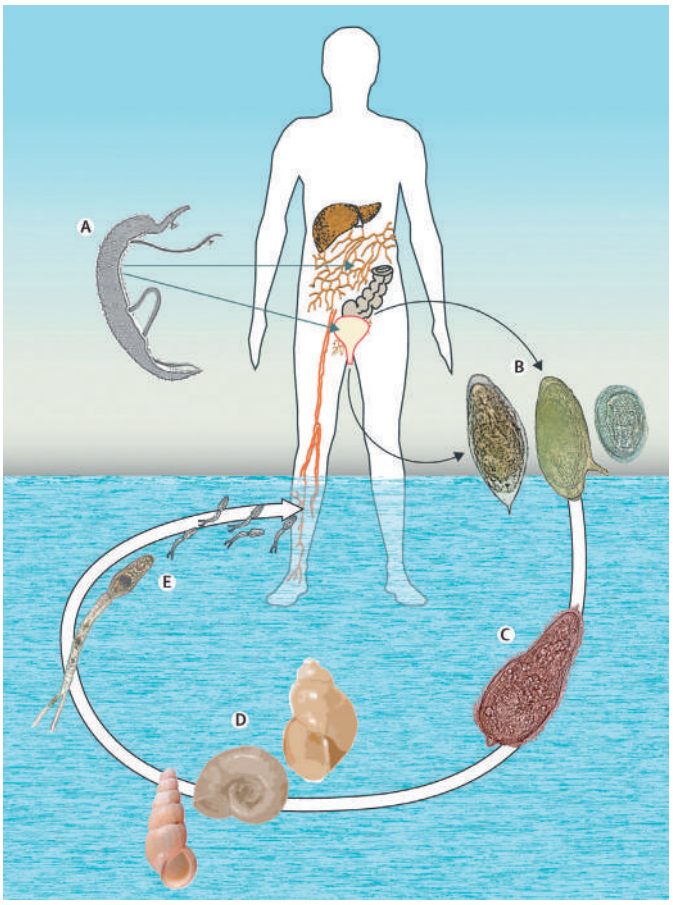

Figure 300-2 Lifecycles of *Schistosoma mansoni, Schistosoma haematobium*, and *Schistosoma japonicum*. *A*, Paired adult worms (larger male enfolding slender female). *B*, Eggs *(left to right, S. haematobium, S. mansoni, S. japonicum)*. *C*, Ciliated miracidium. *D*, Intermediate host snails *(left to right, Oncomelania, Biomphalaria, Bulinus)*. *E*, Cercariae. *(From Colley DG, Bustinduy AL, Secor WE, King CH: Human schistosomiasis.* Lancet *383:2253–2264, 2014, Fig. 1.)*

is found in West and Central Africa, and *S. mekongi* is found only along the upper Mekong River in the Far East.

Transmission depends on disposal of excreta, the presence of specific intermediate snail hosts, and the patterns of water contact and social habits of the population (Fig. 300-2). The distribution of infection in endemic areas shows that prevalence increases with age, to a peak at 10-20 yr of age. Exposure to infected water starts early in life for children living in endemic areas. Passive water contact by infants (accompanying mothers in their daily household activities) evolves to more active water contact as school age children pursue recreational activities such as swimming and wading.

Measuring intensity of infection (by quantitative egg count in urine or feces) demonstrates that the heaviest worm loads are found in school-age and adolescent children. Therefore, schistosomiasis is most prevalent and most severe in children and young adults, who are at maximal risk for suffering from its acute and chronic sequelae.

PATHOGENESIS

Both the early and late manifestations of schistosomiasis are immunologically mediated. Acute schistosomiasis, known as snail fever or Katayama syndrome, is a febrile illness that represents an immune complex disease associated with early infection and oviposition. The major pathology of infection occurs later, with chronic schistosomiasis, in which retention of eggs in the host tissues is associated with chronic granulomatous injury. Eggs may be trapped at sites of deposition (urinary bladder, ureters, intestine) or be carried by the bloodstream to other organs, most commonly the liver and less often the lungs and central nervous system. The host response to these eggs involves local as well as systemic manifestations. The cell-mediated immune response leads to granulomas composed of lymphocytes, macrophages, and eosinophils that surround the trapped eggs and add significantly to the degree of tissue destruction. Granuloma formation in the bladder wall and at the ureterovesical junction results in the major disease manifestations of schistosomiasis haematobia: hematuria, dysuria, and obstructive uropathy. Intestinal as well as hepatic granulomas underlie the pathologic sequelae of the other schistosome infections: ulcerations and fibrosis of intestinal wall, hepatosplenomegaly, and portal hypertension due to presinusoidal obstruction of blood flow. In terms of systemic disease, antischistosome inflammation increases circulating levels of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6, associated with elevated levels of C-reactive protein. These responses are associated with hepcidin-mediated inhibition of iron uptake and use, leading to anemia of chronic inflammation. Schistosomiasis-related undernutrition may be the result of similar pathways of chronic inflammation. Acquired partial protective immunity against schistosomiasis has been demonstrated in some animal species and may occur in humans.

CLINICAL MANIFESTATIONS

Most chronically infected individuals experience mild symptoms and may not seek medical attention; the more severe symptoms of schistosomiasis occur mainly in those who are heavily infected or who have been infected over longer periods of time. In addition to organ-specific morbidities, infected patients frequently demonstrate anemia, chronic pain, diarrhea, exercise intolerance, and chronic undernutrition manifesting as growth stunting. Cercarial penetration of human skin may result in a papular pruritic rash known as schistosomal dermatitis or swimmer's itch. It is more pronounced in previously exposed individuals and is characterized by edema and intense cellular infiltrates in the dermis and epidermis. Acute schistosomiasis, Katayama syndrome, may occur, particularly in heavily infected individuals 4-8 wk after exposure; this is a serum sickness–like syndrome manifested by the acute onset of fever, cough, chills, sweating, abdominal pain, lymphadenopathy, hepatosplenomegaly, and eosinophilia. Acute schistosomiasis most commonly presents in first-time visitors to endemic areas who experience primary infection at an older age.

Symptomatic children with chronic schistosomiasis haematobia usually complain of frequency, dysuria, and hematuria. Urine examination shows erythrocytes, parasite eggs, and occasional eosinophiluria. In endemic areas, moderate to severe pathologic lesions have been demonstrated in the urinary tract of >20% of infected children. The extent of disease correlates with the intensity of infection, but significant morbidity can occur even in lightly infected children. The advanced stages of schistosomiasis haematobia are associated with chronic renal failure, secondary infections, and cancer of the bladder.

An important complication of *S. haematobium* infection is female genital schistosomiasis. Eggs migrate from the vesical plexus to lodge in the female genital tract where they induce a granulomatous inflammatory response that can manifest as contact bleeding, pain, and eventual infertility. Symptoms start as early as 10 yr of age with an apparent 3-4–fold greater risk of HIV transmission. Pathognomonic lesions can be visualized in the cervix by photocolposcopy.

Children with chronic schistosomiasis *mansoni, japonica, intercalatum*, or *mekongi* may have intestinal symptoms; colicky abdominal pain and bloody diarrhea are the most common. However, the intestinal phase may remain subclinical, and the late syndrome of hepatosplenomegaly, portal hypertension, ascites, and hematemesis may then be the first clinical presentation. Liver disease is caused by granuloma formation and subsequent fibrosis; no appreciable liver cell injury occurs, and hepatic function may be preserved for a long time. Schistosome eggs may escape into the lungs, causing pulmonary hypertension and cor pulmonale. *S. japonicum* worms may migrate to the brain vasculature and produce localized lesions that cause seizures. Transverse myelitis, spinal compression, and other central nervous system involvement (meningoencephalitis) are rare but well known

complications in children or young adults with either acute or chronic *S. haematobium* or *S. mansoni* infection.

Although end-organ scarring is pathognomonic, affected children may also have persistent long-term systemic effects of infection, including poor growth, anemia, decreased aerobic capacity, and cognitive impairment.

DIAGNOSIS

Schistosome eggs are found in the excreta of infected individuals; quantitative methods should be used to provide an indication of the burden of infection. For diagnosis of schistosomiasis haematobia, a volume of 10 mL of urine should be collected around midday, which is the time of maximal egg excretion, and filtered for microscopic examination. Stool examination by the Kato-Katz thick smear procedure and detection of parasite antigen in patient serum or urine are the methods of choice for diagnosis and quantification of other schistosome infections.

TREATMENT

Treatment of children with schistosomiasis should be based on an appreciation of the intensity of infection and the extent of disease. The recommended treatment for schistosomiasis is praziquantel (40 mg/kg/day divided bid PO for 1 day for schistosomiasis *haematobia, mansoni,* and *intercalatum*; 60 mg/kg/day divided tid PO for 1 day for schistosomiasis *japonica* and *mekongi*). For *S. mansoni*, oxamniquine has been effective in some areas where praziquantel has been less effective.

PREVENTION

Transmission in endemic areas may be decreased by reducing the parasite load in the human population. The availability of oral, single-dose, effective chemotherapeutic agents may help achieve this goal. When added to national control drug-based programs, other measures such as improved sanitation, focal application of molluscicidals, and animal vaccination may prove useful in breaking the cycle of transmission. Ultimately, control of schistosomiasis is closely linked to economic and social development.

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Chapter 301

Flukes (Liver, Lung, and Intestinal)

Charles H. King and Amaya L. Bustinduy

Several different trematodes, or flukes, can parasitize humans and cause disease. Flukes are endemic worldwide but are more prevalent in the less-developed parts of the world. They include *Schistosoma,* or the blood flukes (see Chapter 300), as well as fluke species that cause infection in the human biliary tree, lung tissue, and intestinal tract. These latter trematodes are characterized by complex life cycles (Fig. 301-1). Sexual reproduction of adult worms in the definitive host produces eggs that are passed in the stool. Larvae, called **miracidia**, develop in freshwater. These, in turn, infect certain species of mollusks (aquatic snails or clams), in which asexual multiplication by parasite larvae produces **cercariae**. Cercariae then seek a second intermediate host, such as an insect, crustacean, or fish, or attach to vegetation to produce infectious **metacercariae**. Humans acquire liver, lung, and intestinal fluke infections by eating uncooked, lightly cooked, pickled, or smoked foods containing these infectious parasite cysts. The "alternation of generations" requires that flukes parasitize more than 1 host (often 3) to complete their life cycle. Because parasitic flukes are dependent on these nonhuman species for transmission, the distribution of human fluke infection closely matches the ecologic range of the flukes' intermediate hosts.

LIVER FLUKES

Fascioliasis *(Fasciola Hepatica)*

Fasciola hepatica, the sheep liver fluke, infects cattle, other ungulates, and occasionally humans. This infection affects approximately 17 million people worldwide and has been reported in many different

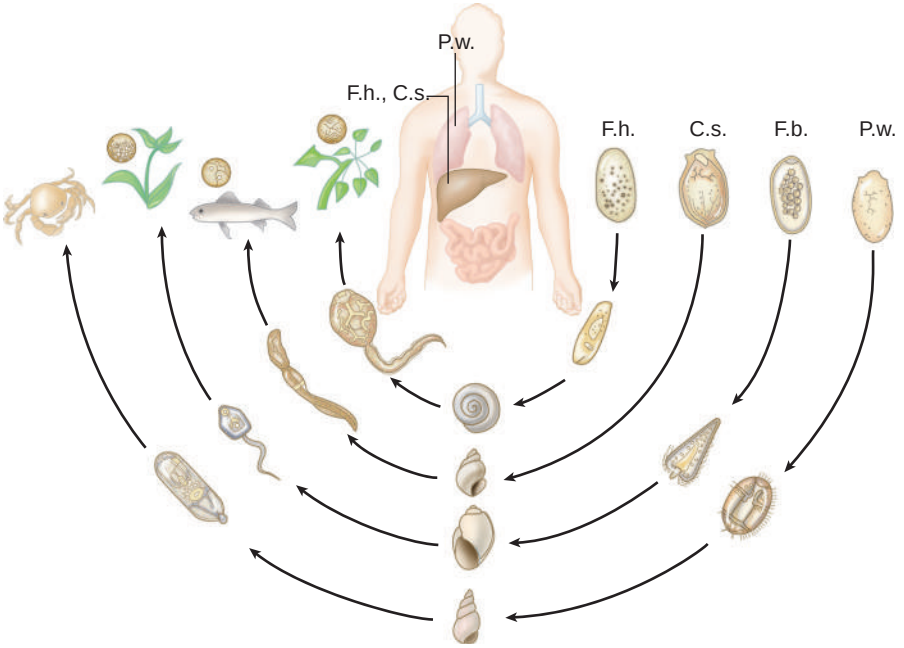

Figure 301-1 Life cycle of parasitic liver, lung, and intestinal flukes. *(Adapted from Mandell GL, Bennett JE, Dolin R, editors:* Principles and practice of infectious diseases, *ed 7. Philadelphia, 2010, Elsevier, Fig. 289-2.)*

parts of the world, particularly South America, Europe, Africa, China, Australia, and Cuba. Although *F. hepatica* is enzootic in North America, reported cases are extremely rare. Humans are infected by ingestion of metacercariae attached to vegetation, especially wild watercress, lettuce, and alfalfa. In the duodenum, the parasites excyst and penetrate the intestinal wall, liver capsule, and parenchyma. They wander for a few weeks before entering the bile ducts, where they mature. Adult *F. hepatica* (1-2.5 cm) commence oviposition approximately 12 wk after infection; the eggs are large (75-140 μm) and operculated. They pass to the intestines with bile and exit the body in the feces (see Fig. 301-1). On reaching freshwater, the eggs mature and hatch into miracidia, which infect specific snail intermediate hosts to multiply into many cercariae. These then emerge from infected snails and encyst on aquatic grasses and plants.

Clinical manifestations usually occur either during the liver migratory phase of the parasites or after their arrival at their final habitat in upper bile ducts. Fever, right upper quadrant pain, and hepatosplenomegaly characterize the first phase of illness. Peripheral blood eosinophilia is usually marked. As the worms enter bile ducts, most of the acute symptoms subside. On rare occasions, patients may suffer from obstructive jaundice or biliary cirrhosis, with signs of cholestasis, ascending cholangitis, cholelithiasis and jaundice with elevation in liver enzymes, direct bilirubin, and γ-glutamyl transpeptidase. *F. hepatica* infection is diagnosed by identifying the characteristic eggs in fecal smears or duodenal aspirates. Diagnosis can be suggested by positive serology and imaging that reveals acute hypodense liver lesions that change over time. Presentation can be dramatic in children, with features including generalized edema, hepatic cirrhosis with esophageal varices, and, in severe cases, death from generalized organ failure.

The recommended treatment of fascioliasis is triclabendazole (10 mg/kg once or twice PO) or bithionol (30-50 mg/kg once daily PO on alternate days for a total of 10-15 doses). In the United States, bithionol is available from the Centers for Disease Control and Prevention (telephone: 404-639-3670).

Clonorchiasis (*Clonorchis Sinensis*)

Infection of bile passages with *Clonorchis sinensis,* the Chinese or oriental liver fluke, is endemic in China, other parts of East Asia, and Japan, affecting more than 35 million people. Humans acquire infection by ingestion of raw or inadequately cooked freshwater fish carrying the encysted metacercariae of the parasite under their scales or skin. Metacercariae excyst in the duodenum and pass through the ampulla of Vater to the common bile duct and bile capillaries, where they mature into hermaphroditic adult worms (3-15 mm). *C. sinensis* worms deposit small operculated eggs (14-30 μm), which are discharged by way of the bile duct to the intestine and feces (see Fig. 301-1). The eggs mature and hatch outside the body, releasing motile miracidia into local freshwater streams, rivers, or ponds. If these are taken up by the appropriate snails, they develop into cercariae, which are in turn released from the snail to encyst under the skin or scales of freshwater fish.

Most individuals with *C. sinensis* infection, particularly those with few organisms, are minimally symptomatic. In heavily infected individuals, who tend to be older (>30 yr of age), localized obstruction of a bile duct results from repeated local trauma and inflammation. In these cases, cholangitis and cholangiohepatitis may lead to liver enlargement and jaundice. In Hong Kong, Korea, and other parts of Asia, cholangiocarcinoma is associated with chronic *C. sinensis* infection.

Clonorchiasis is diagnosed by examination of feces or duodenal aspirates for the parasite eggs. The recommended treatment of clonorchiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days). An alternative, used in adults, is albendazole (10 mg/kg once daily PO for 7 days).

Opisthorchiasis (*Opisthorchis* Spp.)

Infections with species of *Opisthorchis* are clinically similar to those caused by *C. sinensis. Opisthorchis felineus* and *Opisthorchis viverrini* are liver flukes of cats and dogs that infect humans through ingestion of metacercariae in freshwater fish. Infection with *O. felineus* is endemic in Eastern Europe and Southeast Asia, and *O. viverrini* is found mainly in Thailand, affecting an estimated 10 million people. Most individuals are minimally symptomatic; liver enlargement, relapsing cholangitis, and jaundice may occur in heavily infected individuals. Diagnosis is based on recovering eggs from stools or duodenal aspirates. The recommended treatment of opisthorchiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days).

LUNG FLUKES

Paragonimiasis (*Paragonimus* Spp.)

Human infection by the lung fluke *Paragonimus westermani,* and less frequently other species of *Paragonimus,* occurs throughout the Far East, in localized areas of West Africa, and in several parts of Central and South America, affecting approximately 20 million people. The highest incidence of paragonimiasis occurs in older children and adolescents 11-15 yr of age. Although *P. westermani* is found in many carnivores, human cases are relatively rare and seem to be associated with specific dietary habits, such as eating raw freshwater crayfish or crabs. These crustaceans contain the infective metacercariae in their tissues. After ingestion, the metacercariae excyst in the duodenum, penetrate the intestinal wall, and migrate to their final habitat in the lungs. Adult worms (5-10 mm) encapsulate within the lung parenchyma and deposit brown operculated eggs (60-100 μm), which pass into the bronchioles and are expectorated by coughing (see Fig. 301-1). Ova can be detected in the sputum of infected individuals or in their feces. If eggs reach freshwater, they hatch and undergo asexual multiplication in specific snails. The cercariae encyst in the muscles and viscera of crayfish and freshwater crabs.

Most individuals infected with *P. westermani* harbor low or moderate worm loads and are minimally symptomatic. The clinical manifestations include cough, production of rust-colored sputum, and hemoptysis (mimicking tuberculosis), which is the principal manifestation and occurs in 98% of symptomatic children. There are no characteristic physical findings, but laboratory examination usually demonstrates marked eosinophilia. Chest x-rays often reveal small patchy infiltrates or radiolucencies in the middle lung fields; however, radiographs may appear normal in one-fifth of infected individuals. In rare circumstances, lung abscess, pleural or pericardial effusion, or bronchiectasis may develop. Extrapulmonary localization of *P. westermani* in the brain, peritoneum, intestines, or pericardium may rarely occur. Cerebral paragonimiasis occurs primarily in heavily infected individuals living in highly endemic areas of the Far East. The clinical presentation resembles Jacksonian epilepsy or the symptoms of cerebral tumors.

Definitive diagnosis of paragonimiasis is established by identification of eggs in fecal or sputum smears. The recommended treatment of paragonimiasis is praziquantel (75 mg/kg/day divided tid PO for 2 days). Triclabendazole can also be used (5 mg/kg PO daily for 3 days).

INTESTINAL FLUKES

Several wild and domestic animal intestinal flukes, including *Fasciolopsis buski, Nanophyetus salmincola,* and *Heterophyes heterophyes,* may accidentally infect humans who eat uncooked or undercooked fish or water plants. For example, *F. buski* is endemic in the Far East, where humans who ingest metacercariae encysted on aquatic plants become infected. These develop into large flukes (1-5 cm) that inhabit the duodenum and jejunum. Mature worms produce operculated eggs that pass with feces; the organism completes its life cycle through specific snail intermediate hosts. Individuals with *F. buski* infection are usually asymptomatic; heavily infected subjects complain of abdominal pain and diarrhea and show signs of malabsorption. Diagnosis of fasciolopsiasis and other intestinal fluke infections is established by fecal examination and identification of the eggs (see Fig. 301-1). As for other fluke infections, praziquantel (75 mg/kg/day divided tid PO for 2 days) is the drug of choice.

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Chapter 302

Adult Tapeworm Infections

Philip R. Fischer and A. Clinton White Jr.

Tapeworms are adult forms of cestodes, multicellular helminth parasites, that live in human intestines and cause non–life-threatening illness. Invasive larval forms of cestodes are associated with cysts that lead to severe human disease such as neurocysticercosis (*Taenia solium*, discussed in Chapter 303) and echinococcosis (mostly *Echinococcus granulosa* and *Echinococcus multilocularis*, discussed in Chapter 304). The worms are flat and multisegmented, varying in length from 8 mm to 10 meters. Table 302-1 summarizes the key features of tapeworms that affect children.

ETIOLOGY

The **beef tapeworm** *(Taenia saginata)*, the **pork tapeworm** *(T. solium)*, and the Asian tapeworm *(Taenia asiatica)* are long worms (4-10 m) named for their intermediate hosts (*T. saginata*, *T. solium*) or geographic distribution (*T. asiatica*; larval host is the pig). The adult worms are found only in the human intestine. Like the adult stage of all tapeworms, their body is a series of hundreds or thousands of flattened segments **(proglottids)** with an anterior attachment organ **(scolex)** that anchors the parasite to the bowel wall. New segments arise from the distal aspect of the scolex with progressively more mature segments attached distally. The gravid terminal segments contain 50,000-100,000 eggs, and the eggs or even detached intact proglottids pass out of the child via the anus (with or separate from defecation). These tapeworms differ most significantly in that the intermediate stage of the pork tapeworm (cysticercus) can also infect humans and cause significant morbidity (see Chapter 303), whereas the larval stage of *T. saginata* does not cause human disease. *T. asiatica* is similar to and often confused with the beef tapeworm.

EPIDEMIOLOGY

The pork and beef tapeworms are distributed worldwide, with the highest risk for infection in Central America, Africa, India, Southeast Asia, and China where the relevant intermediate host is raised domestically. The prevalence in adults may not reflect the prevalence in young children, because cultural practices may dictate how well meat is cooked and how much is served to children.

PATHOGENESIS

When children ingest raw or undercooked meat containing larval cysts, gastric acid and bile facilitate release of immature scolices that attach to the lumen of the small intestine. The parasite grows, adding new segments at the base of the scolex. The terminal segments mature and after 2-3 mo produce eggs that are released in stool. The surface of proglottids serves as an absorptive organ to "steal" nutritional elements from the child's small bowel for use by the parasite. There is sometimes a transient eosinophilia prior to the parasite maturing enough to release eggs.

CLINICAL MANIFESTATIONS

Nonspecific abdominal symptoms have been reported with beef and pork tapeworm infections, but the most bothersome symptom is the psychologic distress caused by seeing proglottids in the stool or undergarments. The released segments of the worms are motile (especially those of *T. saginata)* and sometimes lead to anal pruritus. The adult beef and pork tapeworms are only rarely associated with other symptoms.

DIAGNOSIS

Identification of the infecting tapeworm species facilitates understanding of risk for invasive disease. Carriers of adult pork tapeworms are at increased risk for transmitting eggs with the pathogenic intermediate stage **(cysticercus)** to themselves or others, whereas children infected with the beef tapeworm or *T. asiatica* are a risk only to livestock. Because proglottids are generally passed intact, visual examination for gravid proglottids in the stool is a sensitive test; these segments may be used to identify species. Eggs, by contrast, are often absent from stool and cannot distinguish between *T. saginata* and *T. solium* (Fig. 302-1). If the parasite is completely expelled, the scolex of each species is diagnostic. The scolex of *T. saginata* has only a set of 4 anteriorly oriented suckers, whereas *T. solium* is armed with a double row of hooks in addition to suckers. The proglottids of *T. saginata* have more than 20 branches from a central uterine structure, and those of *T. solium* have 10 or fewer. Expelled proglottid segments are usually about 0.5 × 1-2 × 0.1 cm in size. Molecular methods can distinguish *T. saginata* from *T. asiatica*. Antigen detection tests are increasingly available.

Table 302-1 Key Features of Common Tapeworms in Children

PARASITE SPECIES	GEOGRAPHY	SOURCE	SYMPTOMS	TREATMENT
Taenia saginata	Asia, Africa, Latin America	Cysts in beef	Abdominal discomfort, motile proglottid migration, passing segments	Praziquantel or niclosamide, possibly nitazoxanide
Taenia solium	Asia, Africa, Latin America	Cysticerci in pork	Minimal, proglottids in stool	Praziquantel or niclosamide, possibly nitazoxanide
Taenia asiatica	Asia	Pigs	Minimal	Praziquantel or niclosamide, possibly nitazoxanide
Diphyllobothrium species	Worldwide, often northern areas	Plerocercoid cysts in fresh water fish	Usually minimal; with prolonged or heavy infection with *Diphyllobothrium latum*, vitamin B_{12} deficiency	Praziquantel or niclosamide
Hymenolepis	Worldwide, often northern areas	Infected humans, rodents	Mild abdominal discomfort	Praziquantel, niclosamide, or nitazoxanide
Dipylidium caninum	Worldwide	Domestic dogs and cats	Eosinophilia, anal pruritus confused with pinworm, proglottids in stool	Praziquantel or niclosamide

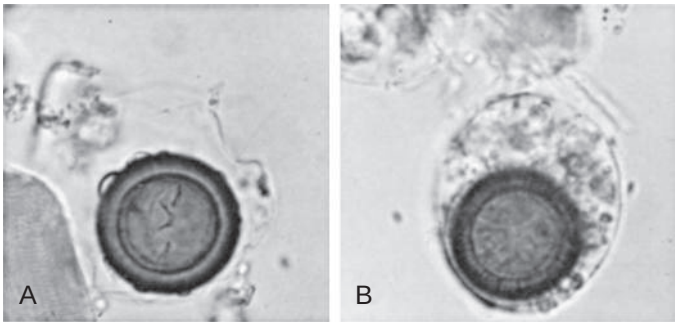

Figure 302-1 A and B, Eggs of *Taenia saginata* recovered from feces (original magnification ×400). The eggs are generally bile stained, dark, and prismatic. There is occasionally some surrounding cellular material from the proglottid in which the egg develops, which is more evident in **B** than in **A.** The larva within the egg shows 3 pairs of hooklets **(A),** which may occasionally be observed in motion.

DIFFERENTIAL DIAGNOSIS

Anal pruritus may mimic symptoms of pinworm *(Enterobius vermicularis)* infection. *Diphyllobothrium latum* and *Ascaris lumbricoides* (a long round worm) may be mistaken for *T. saginata* or *T. solium* in stools.

TREATMENT

Infections with all adult tapeworms respond to praziquantel (25 mg/kg PO once). When available, an alternative treatment for taeniasis is niclosamide (50 mg/kg PO once for children, 2 g PO once for adults). Nitazoxanide is sometimes effective as well. The parasite is usually expelled on the day of administration. Treatment with electrolyte-polyethylene glycol bowel preparations can increase the yield of passage of scolices.

PREVENTION

Prolonged freezing or thorough cooking of beef and pork kills the larval cystic forms of the parasite. Appropriate human sanitation can interrupt transmission by preventing infection in livestock.

DIPHYLLOBOTHRIASIS (*DIPHYLLOBOTHRIUM* SPECIES)

Etiology

The **fish tapeworms** of the genus *Diphyllobothrium* are the longest human tapeworms, reaching more than 10 meters in length, and have an anatomic organization similar to that of other adult cestodes. An elongated scolex equipped with slits **(bothria)** along each side but no suckers or hooks is followed by thousands of segments looped in the small bowel. Gravid terminal proglottids detach periodically but tend to disintegrate before expulsion, thus releasing eggs rather than intact worm segments in the feces. In contrast to taeniids, the life cycle of *Diphyllobothrium* species requires 2 intermediate hosts. Small fresh water crustaceans (copepods) take up the larvae that hatch from parasite eggs. The parasite passes up the food chain as small fish eat the copepods and are in turn eaten by larger fish. In this way, the juvenile parasite becomes concentrated in pike, walleye, perch, burbot, and perhaps salmon associated with aquaculture of this species. Consumption of raw or undercooked fish leads to human infection with adult fish tapeworms.

Epidemiology

The fish tapeworm is most prevalent in the temperate climates of Europe, North America, and Asia but may be found along the Pacific coast of South America and in Africa. In North America, the prevalence is highest in Alaska, Canada, and northern areas of continental United States. The tapeworm is found in fish from those areas that are then taken to market. Persons who prepare raw fish for home or commercial use or who sample fish before cooking are particularly at risk for infection.

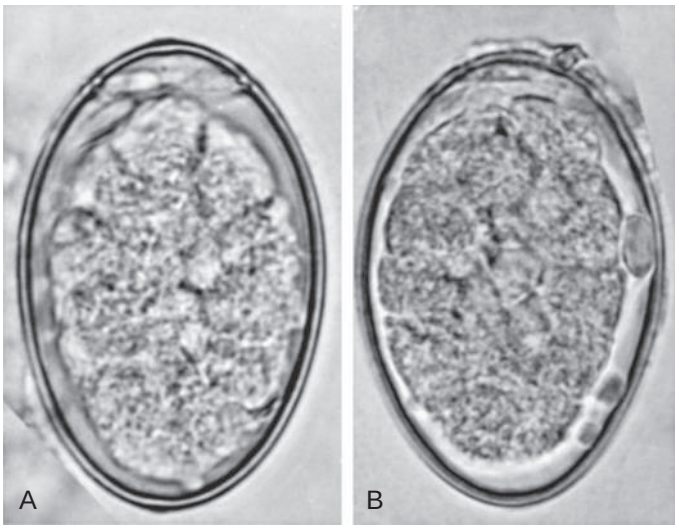

Figure 302-2 A and B, Eggs of *Diphyllobothrium latum* as seen in feces (original magnification ×400). The caplike operculum is at the upper end of the egg here.

Pathogenesis

The adult worm of *D. latum* (found in northern Europe) has high affinity receptors and efficiently scavenges vitamin B_{12} for its own use in the constant production of large numbers of segments and as many as 1 million eggs per day. As a result, diphyllobothriasis causes megaloblastic anemia in 2-9% of infections. Interestingly, other *Diphyllobothrium* species do not out-compete the host for vitamin B_{12}. Children with other causes of vitamin B_{12} or folate deficiency, such as chronic infectious diarrhea, celiac disease, or congenital malabsorption, are more likely to develop symptomatic infection.

Clinical Manifestations

Infection is largely asymptomatic. Segments may be noted in stool. Those who develop vitamin B_{12} or folate deficiency present with megaloblastic anemia with leukopenia, thrombocytopenia, glossitis, and/or signs of spinal cord posterior column dysfunction (loss of vibratory sense, proprioception, and coordination).

Diagnosis

Parasitologic examination of the stool is useful because eggs are abundant in the feces and have morphology distinct from that of all other tapeworms. The eggs are ovoid and have an operculum, which is a cap structure at 1 end that opens to release the embryo (Fig. 302-2). The worm itself has a distinct scolex and proglottid morphology; however, these are not likely to be passed spontaneously.

Differential Diagnosis

A segment or a whole section of the worm might be confused with *Taenia* or *Ascaris* after it is passed. Pernicious anemia, bone marrow toxins, and dietary restriction may contribute to or mimic the nutritional deficiencies associated with diphyllobothriasis.

Treatment

As with all adult tapeworms, *D. latum* infections respond to praziquantel (5-10 mg/kg PO once). Niclosamide (50 mg/kg in a single oral dose) is also effective.

Prevention

The intermediate stage is easily killed by brief cooking or prolonged freezing of fish prior to ingestion. Because humans are the major reservoir for adult worms, health education is one of the most important tools for preventing transmission, together with improved human sanitation.

HYMENOLEPIASIS *(HYMENOLEPIS)*

Infection with *Hymenolepis nana,* the **dwarf tapeworm,** is very common in developing countries. It is a major cause of eosinophilia, and although it rarely causes overt disease, the presence of *H. nana* eggs in stool may serve as a marker for exposure to poor hygienic conditions and the risk of additional fecal-oral contamination. The intermediate stage of *Hymenolepis diminuta* develop in various hosts (e.g., rodents, ticks, and fleas), but the entire life cycle of *H. nana* is completed in humans. Therefore, hyperinfection with thousands of small adult worms in a single child may occur. A similar infection may occur less commonly with the species *H. diminuta.* Eggs but not segments may be found in the stool. *H. nana* infection responds to praziquantel (25 mg/kg PO once). Nitazoxanide is effective in about three-fourths of children (100 mg by mouth twice daily for 3 days for children 1-3 yr of age, 200 mg by mouth twice daily for 3 days for children 4-11 yr of age, and 500 mg by mouth twice daily for 3 days for older children).

DIPYLIDIASIS *(DIPYLIDIUM CANINUM)*

Dipylidium caninum is a common tapeworm of domestic dogs and cat. Human infection is relatively rare. Direct transmission between pets and humans does not occur; human infection requires ingestion of the parasite's intermediate host, the dog or cat flea. Infants and small children are particularly susceptible because of their level of hygiene, generally more intimate contact with pets, and activities in areas where fleas can be encountered. Thus, children are most at risk of inadvertent ingestion of fleas infected with the larvae. The most common symptoms is passage of proglottids in stool. The proglottids are similar in size and shape to white rice grains. Anal pruritus, vague abdominal pain, and diarrhea have at times been associated with dipylidiasis, which is thus sometimes confused with pinworm *(E. vermicularis).* Dipylidiasis responds to treatment with praziquantel (5-10 mg/kg PO once) and niclosamide (50 mg/kg orally as a single dose). Deworming of pets and flea control are the best preventive measures.

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Chapter 303

Cysticercosis

A. Clinton White Jr. and Philip R. Fischer

ETIOLOGY

Taenia solium, also known as the **pork tapeworm**, causes 2 different infections in children. In its normal lifecycle, children can acquire the tapeworm form by ingestion of undercooked pork containing the larvae cysts (see Chapter 302). In the intestines, the cyst converts into the tapeworm form. Children are also susceptible to infection by the eggs shed by tapeworm carriers. After the eggs are ingested, the larvae are released from the eggs, invade through the intestines, and migrate through the bloodstream to the muscles (and other organs), where they form tissue cysts (0.2-2.0 cm fluid-filled bladders containing a single invaginated **scolex**). Infection with the cystic form is termed cysticercosis, and involvement of the central nervous system is termed **neurocysticercosis.** The tapeworm form only develops after ingestion of undercooked pork. Ingestion of pork is not necessary to develop cysticercosis, but individuals harboring an adult worm may infect themselves with the eggs by the fecal-oral route.

EPIDEMIOLOGY

The pork tapeworm is widely distributed wherever pigs are raised and have contact with human fecal material. Intense transmission occurs in Central and South America, southern and Southeast Asia, and much of sub-Saharan Africa. In these areas, approximately 30% of cases of seizures may be a result of cysticercosis. Most cases of cysticercosis in the United States are imported; however local transmission has been rarely documented.

PATHOGENESIS

Living, intact cystic stages usually suppress the host immune and inflammatory responses. Intact cysts can be associated with disease when they obstruct the flow of cerebrospinal fluid. Most cysts remain asymptomatic for a few years. Symptoms typically develop as the cysticerci begin to degenerate, associated with a host inflammatory response. The natural history of cysts is to eventually resolve by complete resorption or calcification, but this process make take years. Cysticerci can also present as subcutaneous nodules, ocular infection, or spinal lesions with myelopathy or radiculopathy.

CLINICAL MANIFESTATIONS

Seizures are the presenting finding in the vast majority of children with neurocysticercosis. Less-common manifestations include hydrocephalus, diffuse cerebral edema, or focal neurologic findings. It is important to classify neurocysticercosis as parenchymal, intraventricular, subarachnoid, spinal, or ocular on the basis of anatomic location, clinical presentation, and radiologic appearance since the prognosis and management vary with location.

Parenchymal neurocysticercosis typically presents with seizures. The seizures are usually focal, but often generalize. Children may present with a single seizure or recurrent epilepsy. Mild neurocognitive defects have been documented from cysticerci alone, but are more commonly associated with poorly controlled seizures. A fulminant encephalitis-like presentation may rarely occur, after a massive initial infection associated with cerebral edema. Intraventricular neurocysticercosis (up to 20% of cases) is associated with obstructive hydrocephalus and acute, subacute, or intermittent signs of increased intracranial pressure, usually without localizing signs. Subarachnoid neurocysticercosis is rare in children. It can be associated with basilar arachnoiditis that can present with signs of meningeal irritation, communicating hydrocephalus, cerebral infarction, or spinal disease with radiculitis or transverse myelitis. Cysticerci in the tissues may present with focal findings from mass effect. Ocular neurocysticercosis causes decreased visual acuity because of cysticerci in the retina or vitreous, retinal detachment, or iridocyclitis.

DIAGNOSIS

Neurocysticercosis should be suspected in a child with onset of seizures or hydrocephalus and who also has a history of residence in an endemic area or a care provider from an endemic area. The most useful diagnostic study for parenchymal disease is MRI of the head. MRI provides the most information about cyst location, viability, and associated inflammation. The protoscolex is sometimes visible within the cyst, which provides a pathognomonic sign for cysticercosis (Fig. 303-1*A*). The MRI also better detects basilar arachnoiditis (Fig. 303-1*B*), intraventricular cysts (Fig. 303-1*C*), and cysts in the spinal cord. CT is best for identifying calcifications. A solitary parenchymal cyst, with or without contrast enhancement, and central nervous system calcifications are the most common findings in children (Fig. 303-2). Plain films may reveal calcifications in muscle or brain consistent with cysticercosis. In children from endemic regions, the presentation with a single enhancing lesion that is round and <2 cm in diameter, absence of symptoms or signs of other diseases (e.g., no fever or lymph nodes), no focal findings, and no evidence of increased intracranial pressure is highly specific for neurocysticercosis.

Serologic diagnosis using the enzyme-linked immunotransfer blot is available commercially in the United States and through the Centers for Disease Control and Prevention. Serum antibody testing is highly specific, but is frequently negative in children with single lesions or just calcifications. Antigen-detection assays and polymerase chain reaction assays show promise as diagnostic procedures but are currently not commercially available.

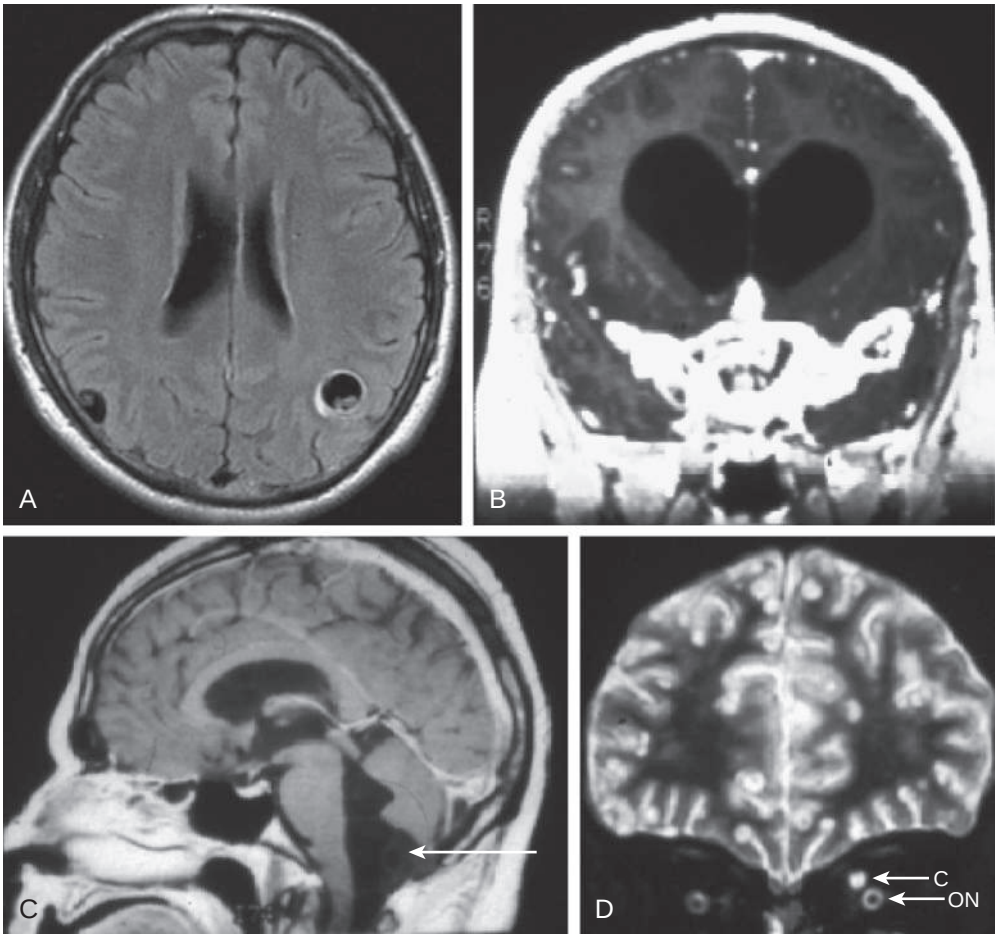

Figure 303-1 **A,** MRI (T1 weighted) demonstrating 2 parenchymal cysts with protoscoleces. **B,** MRI (T1 weighted) of cysticercal basilar arachnoiditis. **C,** MRI (T1 weighted) showing a cyst below the fourth ventricle *(arrow)*. **D,** MRI (T2 weighted) showing a cysticercus **(C)** above the optic nerve *(ON)*.

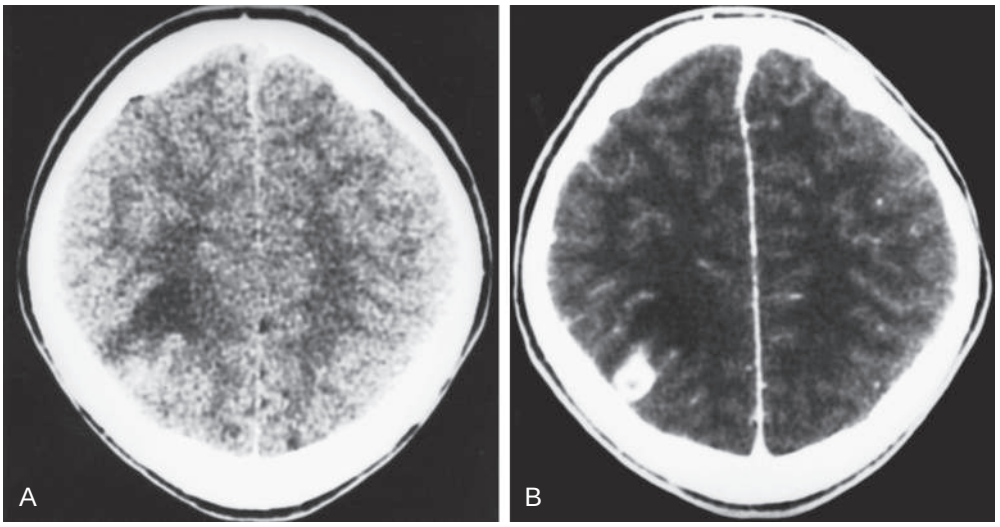

Figure 303-2 CT image of a solitary lesion of neurocysticercosis with **(A)** and without **(B)** contrast, showing contrast enhancement. *(Courtesy of Dr. Wendy G. Mitchell and Dr. Marvin D. Nelson, Children's Hospital, Los Angeles.)*

DIFFERENTIAL DIAGNOSIS

Neurocysticercosis is often confused clinically with other seizure disorders. Clinical suspicion is based on travel history, a history of contact with an individual who might carry an adult tapeworm, or suggestive imaging studies. The imaging appearance can be confused with brain abscess, granulomas (including tuberculomas, fungal infections, Langerhans histiocytosis, and toxoplasmosis), and tumors.

TREATMENT

The initial management of cysticercosis should focus on symptomatic therapy for seizures and/or hydrocephalus. Seizures can usually be controlled using standard antiepileptic drugs. If the lesions resolve, antiepileptic drugs can often be tapered off. Frequent seizures or the development of calcified lesions are risk factors for recurrent seizures and indications for prolonged or lifelong antiepileptic therapy.

The natural history of parenchymal lesions is to resolve spontaneously with or without antiparasitic drugs, but this process is often prolonged (months to years). Solitary parenchymal cysts resolve slightly more rapidly with antiparasitic therapy. Antiparasitic drugs also decrease the frequency of recurrent seizures. Other forms of the disease are less common in children. In adults with cystic lesions, randomized, controlled trials suggested an overall 2-fold decrease in recurrence of generalized seizures with albendazole treatment. The benefit to children was significantly less, perhaps because most of these infections were with only 1-2 cysts. Corticosteroids likely also decrease seizure frequency.

Albendazole is the most commonly used antiparasitic (15 mg/kg/day PO divided bid). It can be taken with a fatty meal to improve absorption. The most common duration of therapy is 7 days for parenchymal lesions. However, longer duration (months), higher doses (up to 30 mg/kg/day), or combination therapy with praziquantel is often required for multiple lesions or subarachnoid disease. Praziquantel (50-100 mg/kg/day PO divided tid for 28 days) can be used with albendazole or as an alternative to it. First-pass metabolism is common with corticosteroids or antiepileptic drugs. Cimetidine can be used in conjunction with praziquantel to blunt the first-pass metabolism. A worsening of symptoms can follow the use of either drug based on the host's inflammatory response to the dying parasite. Patients should be medicated with prednisone 1-2 mg/kg per day or oral dexamethasone 0.15 mg/kg per day beginning before the first dose of antiparasitic drugs and continuing for at least 2 wk. Methotrexate can be used as a steroid-sparing agent in patients requiring prolonged antiinflammatory therapy

Most patients with hydrocephalus require neurosurgical interventions. Some cases require emergent placement of a ventriculostomy, but most can be managed by cystectomy alone. For obstructive hydrocephalus caused by ventricular cysticercosis, many patients can be cured by minimally invasive surgery. Neuroendoscopy is the preferred approach to cysticerci in the lateral or third ventricle. Cysticerci in the fourth ventricle can be removed by either flexible endoscopy or via a suboccipital craniotomy Adherent cysticerci that cannot be removed can be treated by placement of a ventriculoperitoneal shunt. However, there is a high rate of shunt failure, which can be minimized somewhat by treatment with antiparasitic drugs plus corticosteroids.

Subarachnoid disease has a poor prognosis. However, recent studies suggest that the prognosis is much improved by aggressive therapy, including antiparasitic drugs, antiinflammatory treatment, and neurosurgical procedures for hydrocephalus (e.g., placement of a ventriculoperitoneal shunt). However, the dose and duration of antiparasitic and antiinflammatory therapy often need to be prolonged. Ocular cysticercosis is usually treated surgically, although there are reports of cure using medical therapy alone.

PREVENTION

In areas with evolved public health systems, cysticercosis can largely be eliminated by meat inspection, condemnation of infected meat, and thorough cooking of pork. This approach has not worked in countries where most meat is butchered informally. Mass chemotherapy for tapeworm carriers, mass treatment of pigs, and improved personal hygiene have decreased or eliminated transmission in some areas. Screening family members and those preparing food for index cases for cysticercosis has a very low yield, in part because of the poor sensitivity of current tests. Those who have noted passing material consistent with taeniasis should be treated with praziquantel regardless of the results of stool studies. Veterinary vaccines for several cestode infections have a high degree of efficacy and have a potential role in decreasing parasite transmission.

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Chapter 304

Echinococcosis (*Echinococcus granulosus* and *Echinococcus multilocularis*)

Philip R. Fischer, Miguel M. Cabada, and A. Clinton White Jr.

ETIOLOGY

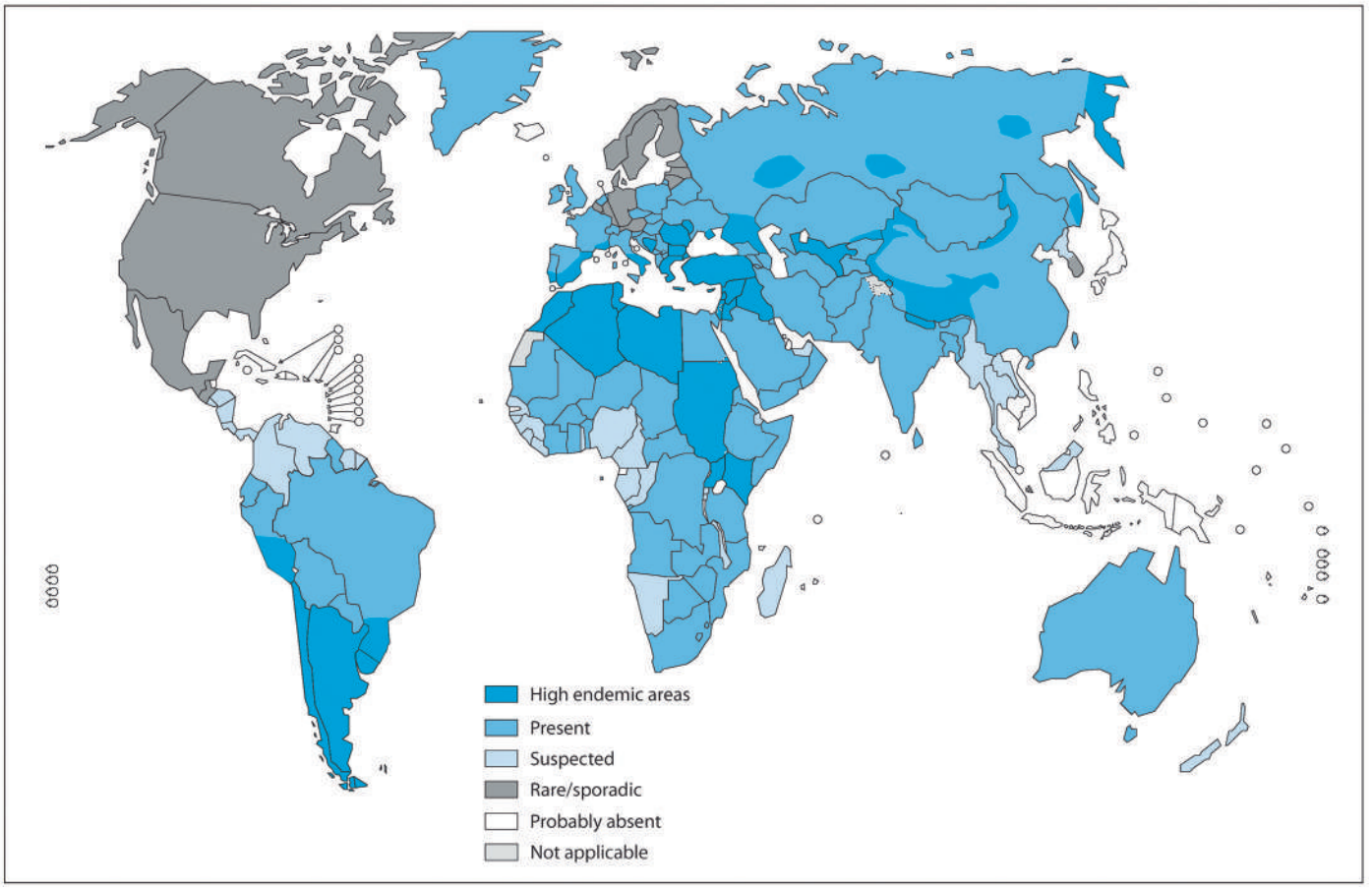
Echinococcosis (**hydatid disease** or **hydatidosis**) is a widespread, serious human cestode infection (Fig. 304-1). Two major *Echinococcus* groups of species are responsible for distinct clinical presentations. *Echinococcus granulosus* and related species cause **cystic hydatid disease.** The organisms were, until recently, thought to be a single species, but recent molecular data have confirmed that there are a number of different species and genotypes in what was formally thought to be a single species. *Echinococcus multilocularis* causes **alveolar hydatid disease.** The adult parasites are a small (2-7 mm) tapeworm with only 2-6 segments that inhabit the intestines of dogs, wolves, dingoes, jackals, coyotes, and foxes. These carnivores pass the eggs in their stool, which contaminates the soil, pasture, and water, as well as their own fur. Domestic animals, such as sheep, goats, cattle, and camels, ingest *E. granulosus* complex eggs while grazing. Humans are also infected by consuming eggs by direct contact with infected dogs or from ova in the environment. The larvae hatch, penetrate the gut, and are carried by the vascular or lymphatic systems to the liver, lungs, and less commonly bones, brain, or heart.

The different species within the *E. granulosus* complex show significant variation in both ecology and genetics. One distinct variant is found in a sylvatic wolf/moose cycle in North America and Siberia. For *E. multilocularis*, the main intermediate hosts are small rodents. The rodents are consumed by foxes, wolves, and other natural predators. In Europe, contamination of gardens by fox excrement is a major risk factor for transmission. Ingestion of infected rodents by dogs can also facilitate transmissions to children.

EPIDEMIOLOGY

There is potential for transmission of this parasite to humans wherever dogs are allowed to ingest the entrails of herd animals. Cysts have been detected in up to 10% of the human population in northern Kenya and western China. Disease is highly endemic in the Middle East and Central Asia. In South America, the disease is prevalent in sheepherding areas of the Andes, the beef-herding areas of the Brazilian/Argentine Pampas, and Uruguay. Among developed countries, the disease is recognized in Italy, Greece, Portugal, Spain, and Australia,

Distribution of *Echinococcus granulosus* and cystic echinococcosis (hydatidosis), worldwide, 2009



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2010. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)
World Health Organization

World Health Organization

Figure 304-1 Worldwide distribution of cystic echinococcosis. *(From Control of Neglected Tropical Diseases. © World Health Organization, 2011. Available at: http://gamapserver.who.int/mapLibrary/Files/Maps/Global_echinococcosis_2009.png)*

and is reemergent in dogs in Great Britain. In North America, transmission rarely occurs through a sylvatic cycle in the Arctic, as well as in foci of the domestic cycle in sheep raising areas of western United States.

Transmission of *E. multilocularis* occurs primarily in Central Europe, Siberia, Turkey, and China. Transmission is now rare in the Arctic regions of North America. Separate species, *Echinococcus vogel* and *Echinococcus oligarthurus,* cause polycystic disease similar to alveolar hydatidosis in northern South America.

PATHOGENESIS

E. granulosus complex parasites are often acquired in childhood, but liver cysts require many years to become large enough to detect or cause symptoms. In children, the lung is a common site, whereas in adults 70% of cysts develop in the liver. Cysts can also develop in bone, the genitourinary system, spleen, subcutaneous tissues, and brain. The host surrounds the primary cyst with a tough, fibrous capsule. Inside this capsule, the parasite produces a thick lamellar layer with the consistency of a soft-boiled egg white. Inside of the lamellar layer is the thin germinal layer of cells responsible for production of thousands of **protoscoleces** that remain attached to the wall or float free in the cyst fluid (Video 304-1). Smaller internal daughter cysts may develop within the primary cyst capsule. The fluid in a healthy cyst is clear, colorless, and watery. Rupture of the cyst, which can occur with trauma or during surgery, can be associated with an anaphylactic reaction. Protoscoleces released into the tissues can also develop into new cysts.

E. multilocularis almost always involves the liver. The lesions grow very slowly and rarely present in children. The secondary reproductive units bud externally and are not confined within a single well-defined structure. Thus, the lesions are often confused with a malignancy. Furthermore, the cyst tissues are poorly demarcated from those of the host, making surgical removal difficult. The secondary cysts are also capable of distant metastatic spread. The growing cyst mass eventually replaces a significant portion of the liver and compromises adjacent tissues and structures.

CLINICAL MANIFESTATIONS

In the liver, cysts may remain asymptomatic, may regress spontaneously, or may produce nonspecific symptoms. Symptomatic cysts can cause increased abdominal girth, hepatomegaly, a palpable mass, vomiting, or abdominal pain. Serious complications result from compression of adjacent structures or spillage of cyst contents. Mass effects can be noted in the brain and bone. Anaphylaxis can occur with cyst rupture or spontaneous spillage, from trauma or intraoperatively.

Spillage can also be catastrophic long-term, because each protoscolex can form a new cyst. Jaundice from cystic hydatid disease is rare. In the lung, cysts produce chest pain, cough, or hemoptysis. Fluid from partially ruptured cysts is often noted to be salty.

In alveolar hydatid disease, the proliferating mass may compromise hepatic tissue or the biliary system and causes progressive obstructive jaundice and hepatic failure. Symptoms also occur from expansion of extrahepatic foci.

DIAGNOSIS

Symptoms and signs are usually nonspecific (e.g., hepatomegaly or a palpable abdominal mass). Ultrasonography is the most valuable tool for both the diagnosis and treatment of cystic hydatid disease of the liver. The presence of internal membranes or echogenic cyst material (**protoscoleces,** termed **hydatid sand**) can be observed in real time to aid in the diagnosis. Ultrasonography can also be used for disease staging used to define optimal therapy (Fig. 304-2). Chest radiographs frequently reveal characteristic rounded masses (Fig. 304-3). Alveolar disease resembles a diffuse solid tumor. CT findings are similar to those of ultrasonography and may at times be useful in distinguishing alveolar from cystic hydatid disease in geographic regions where both occur (Fig. 304-4). CT or MRI is also important in planning a surgical intervention. Lung hydatid disease is usually apparent on chest radiograph (Fig. 304-3).

Serologic studies may be useful in confirming a diagnosis of cystic echinococcosis. The sensitivity is high for hepatic or bone disease, but the false-negative rate may be >50% with pulmonary or central nervous system infection.

DIFFERENTIAL DIAGNOSIS

Benign hepatic cysts are common but can be distinguished from cystic hydatid disease by the absence of a distinct wall, internal membranes, and hydatid sand. The density of bacterial hepatic abscesses is distinct from the watery cystic fluid characteristic of *E. granulosus* infection, but hydatid cysts may also be complicated by secondary bacterial infection. Alveolar echinococcosis is often confused with hepatoma or metastatic tumor.

TREATMENT

Management of cystic hydatid disease should be individualized and guided by disease stage. Approaches range from surgical resection for complicated disease to watchful waiting for cysts that are already degenerating. For small cystic lesions (cystic echinococcosis [CE] types 1 or 3; see Fig. 304-2) that are <5 cm in diameter, albendazole chemotherapy alone (15 mg/kg/day divided bid PO for 1-6 mo; maximum: 800 mg/day) may result in a high rate of cure. Adverse effects include occasional alopecia, mild gastrointestinal disturbance, and elevated transaminases on prolonged use. Because of leukopenia, the FDA recommends that blood counts be monitored at the beginning and every 2 wk during therapy. Chemotherapy may also be used for cysts that are not suitable to **PAIR** (***p***ercutaneous ***a***spiration, ***i***nstillation, and ***r***easpiration) or operative management.

For larger CE1 and CE3 lesions, ultrasound- or CT-guided PAIR is the preferred therapy. Compared with surgical treatment alone, PAIR plus albendazole results in similar cyst disappearance with fewer adverse events and fewer days in the hospital. Spillage with PAIR is surprisingly uncommon, but prophylactic albendazole therapy is routinely administered more than 1 wk prior to PAIR and should be continued for at least 1 mo afterward. PAIR is contraindicated in pregnancy and for bile-stained cysts, which should not be injected with a scolicidal agent because of increased risk for biliary complications. In experienced centers, cysts with thick internal septation (CE2) can be managed using a trochar to break up the membranes and external drainage or with surgery.

Surgery is the treatment of choice for complicated cysts, including ruptured cysts, cysts communicating with the biliary tract, large pulmonary cysts, or cysts of the central nervous system or bones.

For conventional surgery, the inner cyst wall (only laminate and germinal layers are of parasite origin) can be easily peeled from the

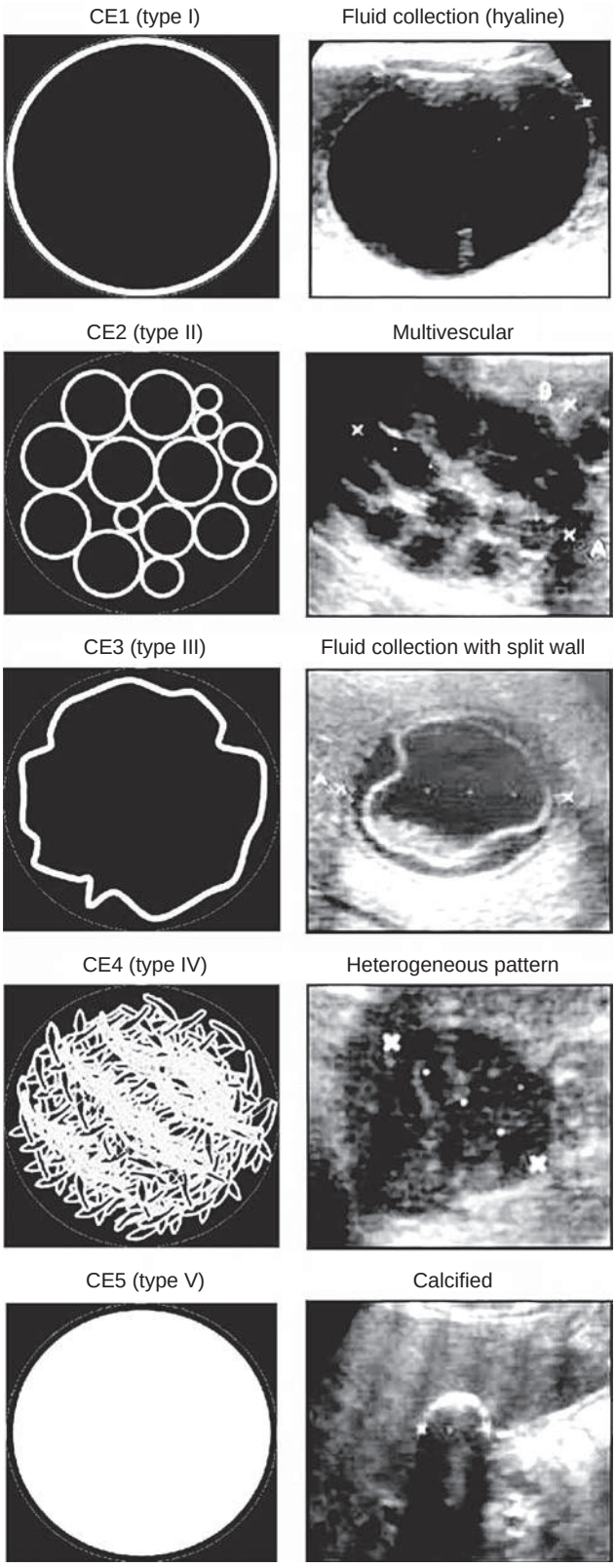


Figure 304-2 Ultrasound classification of cystic echinococcosis (CE) cysts. The WHO informal working group on echinococcosis classification differs from that of Gharbi and colleagues by the addition of a "cystic lesion" (CL) stage (undifferentiated) (not shown), and by reversing the order of CE types 2 and 3. CE3 transitional cysts may be differentiated into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). CE1 and CE3a are early stage cysts and CE4 and CE5 late stage cysts. *(From McManus DP, Gray DJ, Zhang W, Yang Y: Diagnosis, treatment, and management of echinococcosis.* BMJ *344:e3866, 2012, Fig. 4.)*

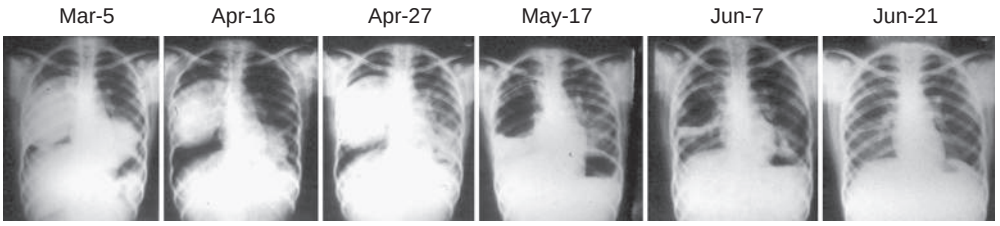


Figure 304-3 **Serial chest x-rays of a young Kenyan woman with bilateral hydatid cysts.** After 2 mo of albendazole therapy, sudden rupture of the right cyst was associated with massive aspiration and acute respiratory distress.

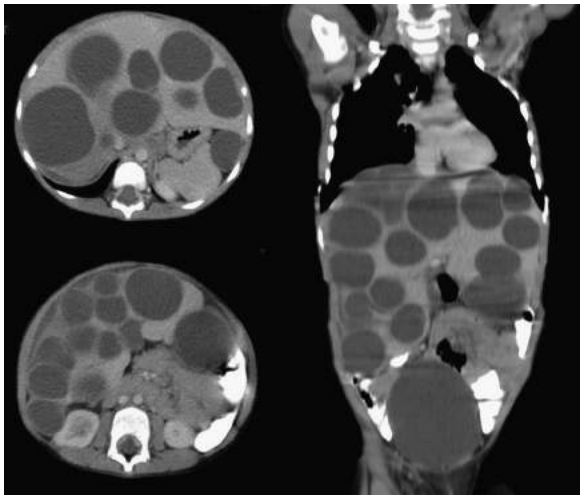


Figure 304-4 **Abdominal CT revealed hepatomegaly and multiple (>20) liver cysts.** *(From Ben-Shimol S, Zelcer I: Liver hydatid cysts.* J Pediatr *163:1792, 2013.)*

fibrous layer, although some studies suggest that removal of the whole capsule has a better outcome. Considerable care must be taken to avoid spillage of cyst contents and surgical drapes should be soaked in hypertonic saline because cyst fluid contains viable protoscoleces, each capable of producing secondary cysts. An additional risk is anaphylaxis because of spilled cyst fluid, making it useful to employ a surgeon experienced in this surgery. For hepatic cysts, patients should begin therapy with albendazole (ideally in combination with praziquantel) for several days to weeks preoperatively. Antiparasitic drugs should be continued for 6-8 wk postoperatively. CE4 and CE5 cysts are in the process of degeneration and usually do not require specific therapy. They can be managed with serial imaging studies to document resolution (watch and wait). Small thoracic cysts may resolve with chemotherapy, but most cysts require operative removal.

Alveolar hydatidosis frequently requires radical surgery, including partial hepatectomy, lobectomy, or liver transplantation. Medical therapy with albendazole should be continued for 2 yr after presumably curative surgery. In patients who are not operative candidates or whose lesions are not amenable to surgical cure, albendazole long-term suppressive therapy should be used to slow the progression, but the infection generally recurs if albendazole is stopped.

PROGNOSIS

Factors predictive of success with chemotherapy are age of the cyst (<2 yr), low internal complexity of the cyst, and small size. The site of the cyst is not important, although cysts in bone respond poorly. For alveolar hydatidosis, if surgical removal is unsuccessful, the average mortality is 92% by 10 yr after diagnosis.

PREVENTION

Important measures to interrupt transmission include, above all, thorough handwashing, avoiding contact with dogs in endemic areas, boiling or filtering water when camping, proper disposal of animal carcasses, and proper meat inspection. Strict procedures for proper disposal of refuse from slaughterhouses must be instituted and followed so that dogs and wild carnivores do not have access to entrails. Other useful measures are control or treatment of the feral dog population and regular praziquantel treatment of pets and working dogs in endemic areas. Vaccines have been developed to prevent infection in grazing animals but are not widely used.

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